

Heavier Alkaline Earth Metal Catalysis and Application to Organic Synthesis

New Routes to C–O and C–N Bond Formation

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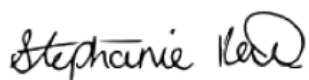
A thesis submitted for the Doctorate of Philosophy

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Declaration

The work described in this thesis was carried out in the Department of Chemistry at Imperial College London and in the laboratory of Prof. M. S. Hill in the Department of Chemistry at the University of Bath between September 2011 and July 2015. Except where specific reference is made to the contrary, it is original work produced by the author and neither the whole nor any part had been submitted before for a degree in any other institution.



Stephanie Reid, November 2015

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Abstract

This thesis describes the application of complexes of heavier alkaline earth metals to the intramolecular hydroalkoxylation/cyclisation of alkynyl and allenyl alcohols and in addition, to the hydroamination of polyunsaturated arenes.

Cyclisation of alkynyl alcohols was achieved using $[\text{Ae}\{\text{N}(\text{SiMe}_3)_2\}_2]$ (Ae = Ca, Sr, Ba) in the formation of five- and six-membered enol ethers. The cyclisations produced mixtures of the possible endo- and exocyclic enol ether products, rationalised as a consequence of alkyne/allene isomerisation. Although a 'catalyst of choice' could not be deduced, $[\text{Ba}\{\text{N}(\text{SiMe}_3)_2\}_2]$ proved highly effective in these cyclisations.

Extension of the hydroalkoxylation towards tandem C–O/C–C formation was attempted with dialkynyl alcohols but in all cases led to monocyclisation of the substrates.

Catalytic tandem C–N bond-forming reactions have been successfully applied to the double hydroamination of polyunsaturated arenes using heteroleptic complexes of the type $[\text{LAe}\{\text{N}(\text{SiMe}_3)_2\}(\text{THF})_n]$ (Ae = Ca, Sr, Ba). Chemo- and regioselective hydroamination reactions are coupled in sequence to construct tetrahydroisoquinoline frameworks. The amine scope of these reactions was determined and results have shown that these regioselective transformations occur under significant stereoelectronic control.

Table of Contents

1.0 Introduction	1
1.1 Background of Alkaline Earth Metals	1
1.2 σ -Bond metathesis and insertion pathways	3
1.3 The Schlenk Equilibrium.....	6
1.4 Alkaline Earth Catalysis.....	9
1.4.1 Group 2 catalysed heterofunctionalisation reactions.....	10
1.4.1.1 <i>Intramolecular Hydroamination</i>	10
1.4.1.2 <i>Intermolecular Hydroamination of Activated Alkenes and Alkynes</i>	14
1.4.1.3 <i>Intermolecular Hydroamination of Carbodiimides and Isocyanates</i>	18
1.4.1.4 <i>Intermolecular Hydrophosphination of Activated Alkenes and Alkynes</i>	19
1.4.1.5 <i>Alkene Hydrosilylation</i>	21
1.5 Polymerisation.....	24
1.5.1 <i>Polymerisation of Cyclic Esters</i>	24
1.5.2 <i>Polymerisation of Activated Alkenes</i>	34
2a Aims and Objectives	37
2.0 Results and Discussion	38
2.1 Heavier Alkaline Earth Catalysed Hydroalkoxylation/Cyclisation of Alkynyl Alcohols	38
2.1.1 <i>Alkynyl Alcohol Hydroalkoxylation</i>	43
2.1.2 <i>Attempted Double and Cascade Hydroalkoxylation of Dialkynyl Alcohols</i>	62
2.1.3 <i>Substrate Synthesis</i>	76
2.1.4 <i>Conclusion</i>	80
2.1.5 <i>Future Work</i>	81
2.2 Hydroamination of Functionalised Arenes.....	82
2.2.1 Heavier Alkaline Earth Catalysed Tandem C–N Bond Forming Reactions.....	83
2.2.1.2 <i>Inter/Intramolecular Hydroamination of polyvinyl arenes</i>	86
2.2.1.2 <i>Heavier Alkaline Earth Catalysed Ene-yne Cyclisations</i>	98
2.2.2 Attempted Hydroaminations	117
2.2.2.1 <i>Attempted intermolecular hydroamination of strained alkenes</i>	117
2.2.2 <i>Conclusion</i>	120
2.2.3 <i>Future Work</i>	121
3.0 Experimental	122
3.1 General Experimental Procedures	122
3.1.1 Analytical Methods	122

3.1.2 General Experimental Methods.....	123
3.1.3 Solvents and Reagents	124
3.2 Alkynyl Alcohol Hydroalkoxylation/Cyclisation	127
3.2.1 Preparation of Substrates.....	127
3.2.2 Catalytic Hydroalkoxylation Reactions	139
3.3 Attempted Cascade Reactions of Dialkynyl Alcohols.....	146
3.3.1 Preparation of Dialkynyl Alcohol Substrates	146
3.3.2 Attempted Cascade Reactions.....	174
3.4 Heavier Alkaline Earth Catalysed polyunsaturated arene hydraomination	179
Future Directions of Group 2 Catalysis	208
4.0 Literature	209

Abbreviations

Ae	alkaline earth
Ar	aryl group
bp	boiling point
Bn	benzyl
<i>t</i> Bu	<i>tert</i> -butyl
<i>n</i> Bu	normal butyl
BOX	bisoxazoline ligand
C _{Ar}	aromatic carbon
CI	chemical ionisation
COD	1,5-cyclooctadiene
conc.	concentrated
Cp	cyclopentadienyl
Cp [*]	<i>tetra</i> -methyl cyclopentadienyl
Cp ^{''}	[1,2,4-(Me ₃ C) ₃ C ₅ H ₂]
C _q	quaternary carbon
Cy	C ₆ H ₁₁ (cyclohexyl)
dd	doublet of doublets
DIPP	2,6-di-iso-propylphenyl
DMF	dimethylformamide
EI	electron ionisation
EtOAc	ethyl acetate
ESI	electrospray-ionisation
Eq.	equation
equiv	equivalents
Et	ethyl
Et ₂ O	diethyl ether
h	hour
hex	hexane
HRMS	high resolution mass spectrometry
IR	infrared
<i>k</i>	rate constant
KIE	kinetic isotope effect
KHMDS	potassium hexamethyldisilazide
L	ligand
LA	lactide
L [*]	non-racemic ligand
Ln	lanthanide
M	molar/metal
MS	mass spectrometry
Me	methyl
mp	melting point
NacNac	{(2,6-di-iso-propylphenyl)NC(Me)CHC(Me)N(2,6-di-iso-propylphenyl)}
NMR	nuclear magnetic resonance
OR	alkoxide group
min	minutes

pent	pentane
PDI	polydispersity index
Ph	phenyl, C ₆ H ₅
PLLA	poly(L-lactide)
<i>i</i> Pr	isopropyl
<i>n</i> Pr	normal propyl
pz	pyrazolyl
ROP	ring opening polymerisation
<i>i</i> ROP	immortal ring opening polymerisation
RT	room temperature
sat.	saturated
t	time
T	temperature
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
THP	tetrahydropyranyl ether
TOF	turnover frequency
TMS	trimethylsilyl
Tp	<i>tris</i> (pyrazolyl)borate
Y	σ-bonded reactive substituent
X	monoanionic spectator ligand

1.0 Introduction

1.1 Background of Alkaline Earth Metals

The heavier group 2 metals Ca, Sr and Ba constitute a relatively underexploited and yet inexpensive and benign series of elements. Several rock-forming minerals comprise magnesium and calcium and these metals are among the most abundant in the earth's crust.¹ Less abundant elements like beryllium, strontium and barium have accomplished many important niche applications in synthetic chemistry.²

However, the organometallic chemistry of the alkaline earth metals is still largely dominated by stoichiometric organomagnesium reagents, whilst the reaction chemistry encompassing the heavier elements of Group 2 has remained unreported.³ After the arrival of Grignard reagents in 1900, the first reports of analogous compounds of the heavier alkaline earth metals began to appear. Consistently, the 'RMX' derivatives of calcium, strontium and barium were more difficult to prepare, less thermally stable and less selective in chemical reactions than their magnesium counterparts.⁴ Hence, these compounds cannot merely be prepared through Grignard-type synthetic routes but do require special synthetic methods.^{5,6,7} Furthermore, syntheses of heavier alkaline earth complexes are also hindered by their general poor solubility. The reason for this imbalance could be that upon descending the group, the divalent alkaline earth cations display a striking increase in ionic radius from magnesium to barium (six-coordinate radii: Mg^{2+} , 0.72 Å; Ca^{2+} , 1.00 Å; Sr^{2+} , 1.18 Å; Ba^{2+} , 1.35 Å),⁸ which is accompanied by a marked decrease in electronegativity.⁹ As a result, metal-ligand bonding becomes increasingly ionic and non-directional interactions between the metal and auxiliary ligands arise, whereas organometallic compounds of magnesium show a degree of covalency in metal-ligand interactions.¹⁰ Their ionic radii also indicate that coordinative saturation is increasingly difficult and this often results in insoluble coordination polymers.¹¹

It has been noted that the heavier alkaline earth metals display a similar coordination behaviour with that of the isoelectronic 4f-elements.¹² Similarly to the alkaline earth metals, Ln^{3+} complexes are characterised by their d^0 configuration, redox inactivity and ionic metal ligand bonding resulting from high electropositivity and low polarisability.¹³ Further features common to both groups include the large yet similar ionic radii and the availability of a single, common oxidation state. Alkaline earth metals commonly exist in the M^{2+} oxidation state, whereas the most stable oxidation state for the lanthanide elements is +3. Hence, unlike the transition metals, access to multiple oxidation states prevents oxidative addition and reductive elimination pathways in organolanthanide and heavier alkaline earth catalysis and likewise parallels between mechanistic studies have frequently been drawn. A striking difference exhibited by group 2 metals in comparison with the lanthanide series is the vast increase in ionic radius from magnesium to barium. This is an 88% increase in comparison to the 17% range of the lanthanide contraction from La^{3+} to Lu^{3+} (Tables 1 and 2).

Table 1. Comparison of the ionic radii of the Ae $^{2+}$ ions.⁸

Ion	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
IR in Å	0.72	1.00	1.18	1.35
(CN)	(6)	(6)	(6)	(6)

IR = Ionic radius, CN = coordination number

Table 2. Comparison of the ionic radii of some Ln $^{3+}$ ions.¹⁴

Ion	La^{3+}	Ce^{3+}	Nd^{3+}	Eu^{3+}	Dy^{3+}	Yb^{3+}	Lu^{3+}
IR in Å	1.06	1.03	0.99	0.95	0.91	0.86	0.85
(CN)	(6)	(6)	(6)	(6)	(6)	(6)	(6)

IR = Ionic radius, CN = coordination number

Consequently, despite the many parallels in chemistry that can be drawn between magnesium or calcium and the trivalent lanthanide metal ions, the vast difference in ionic radii between magnesium and barium results in a significant difference in

reactivity and kinetic stability of the heavier alkaline earth metals, compared to the trivalent lanthanides.

Several lanthanide ions, however, are also accessible in the +2 and +4 oxidation states and display close charge/size ratio with that of Ca^{2+} and Sr^{2+} (Table 3).⁸

Table 3. Comparison of the Ionic Radii of Ln^{2+} ions versus Ae^{2+} ions.

Ion	Mg^{2+}	Ca^{2+}	Yb^{2+}	Sr^{2+}	Sm^{2+}	Eu^{2+}	Ba^{2+}
IR in Å	0.72	1.00	1.02	1.21	1.22	1.20	1.35
(CN)	(6)	(6)	(6)	(7)	(7)	(7)	(6)

IR = Ionic radii, CN = coordination number

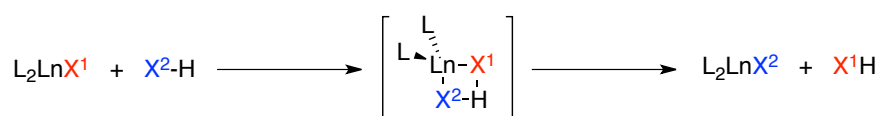
Despite displaying structural similarities, Ln^{2+} complexes are one-electron reductants and therefore react in adversely different reaction mechanisms to Ae^{2+} complexes. Furthermore, the more negative redox potentials for the alkaline earth metals ($E^\circ = -2.87 \text{ V}(\text{Ca}^{2+})$; $E^\circ = -2.89 \text{ V}(\text{Sr}^{2+})$; $E^\circ = -2.90 \text{ V}(\text{Ba}^{2+})$) make them more reactive than their lanthanide counterparts ($E^\circ = -2.22 \text{ V}(\text{Yb}^{2+})$; $E^\circ = -2.30 \text{ V}(\text{Sm}^{2+})$; $E^\circ = -1.99 \text{ V}(\text{Eu}^{2+})$).¹⁵

1.2 σ -Bond metathesis and insertion pathways

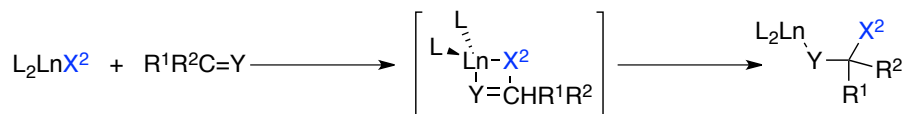
From the pioneering work of Marks it has been shown that the reactivity of trivalent organolanthanide catalysts of the form L_2MX^1 , where L is a mono-anionic spectator ligand and X^1 is a mono-anionic σ -bonded substituent, are founded upon two fundamental reaction pathways. These are (i) σ -bond metathesis and (ii) insertion of unsaturated carbon-carbon or carbon-heteroatom bonds into Ln-X bonds.

16,17,18,19

i) σ -bond metathesis



ii) insertion

**Scheme 1.** Fundamental reactions of trivalent lanthanide complexes.

The mechanism of the σ -bond metathesis or protonolysis involves precoordination of X^2H ($\text{X}^2 = \text{H}, \text{N}, \text{P}, \text{Si}, \text{B}$) followed by a rapid four-centred metathesis transition state forming the active catalytic species L_2LnX^2 . The outcome of the σ -bond metathesis is dependent upon the polarisation of the σ -bond. The reaction (i) may be considered to be a deprotonation and should occur if $\text{p}K_{\text{a}}(\text{X}^2\text{---H}) < \text{p}K_{\text{a}}(\text{X}^1\text{---H})$. These simple scenarios however, do not take into account the complexity of the reaction that occurs within the group 2 coordination sphere, where polarisation and stereoelectronic effects play important roles. In the case where $\text{X}^2 = \text{SiH}_2\text{Ph}$, SiHPh_2 or BR_2 , the σ -bond metathesis will tentatively yield an alkaline hydride species.

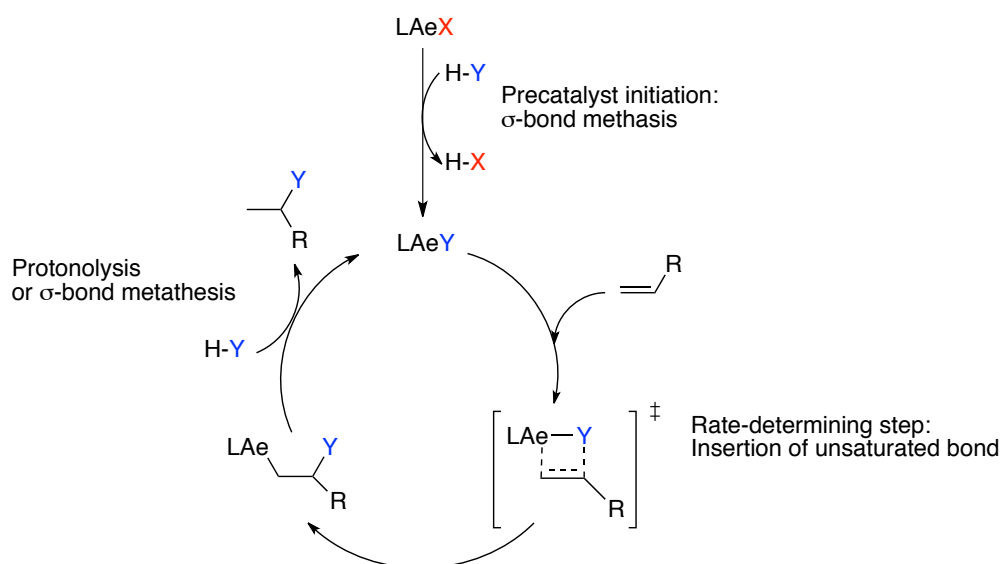
Unsaturated substrates containing π -systems can undergo a rate-determining insertion into Ln---X^2 σ -bonds via a cyclic four-membered transition state. The resulting highly reactive lanthanide-alkyl species is rapidly protonated to liberate the functionalised product and regenerate the active catalytic species. These steps permit a variety of heterofunctionalisation reactions to be achieved such as hydroamination, hydrophosphination and hydrosilylation.

Highly substituted, *ansa*-bridged cyclopentadienyl ligands initially proved to be the ligand of choice for such transformations.²⁰ Highly encumbered ligands are important for kinetic stabilisation of the active species in order to avoid ligand redistribution and dimerization. These two processes lead to unreactive homoleptic complexes and as a result reactivity is significantly decreased. In the last twenty years, the choice of ligand has ranged from bulky cyclopentadienyl spectator ligands to σ -bonded alkyl-calcium complexes, and furthering to chiral, non-cyclopentadienyl ligands for stereoselective induction.²¹ Catalytic activity is greatly impeded in the presence of Lewis donor solvents such as THF, which may block potential coordination

sites within the L_2LnX coordination sphere and inhibit substrate access, which is a prerequisite for catalysis.²²

Given the parallels between the bonding with group 2 and trivalent lanthanide compounds, it has been shown that these complexes can be employed as homogeneous catalytic reagents using σ -bond metathesis and insertion reaction chemistries to construct catalytic cycles which have been incorporated into an even wider range of catalytic processes (often analogous to those encountered in trivalent lanthanide chemistry) (Scheme 2).¹⁰

These two reaction pathways have been incorporated into catalytic cycles employing heavier alkaline earth metal complexes for a vast number of synthetic transformations.²³



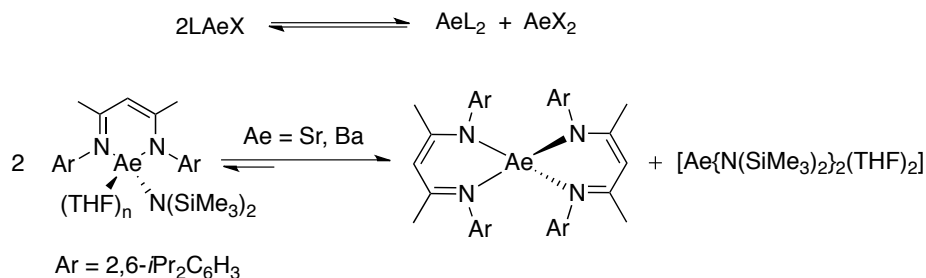
Scheme 2. General catalytic cycle for the alkaline earth-mediated heterofunctionalisation of carbon-carbon double bonds.

This introduction will describe recent synthetic advances in the area of group 2 chemistry that have resulted not only in the preparation of heavy organoalkaline earth compounds, but the application and impact of synthetic variables on the chemistry of the heavy alkaline earth metals. These advances in synthetic methodologies, which include competitive product purity and yields, provide the

basis for further exploration and development of heavier alkaline earth metal chemistry.

1.3 The Schlenk Equilibrium

An underlying challenge in the development of catalytic reagents based upon the heavier alkaline earth metal compounds is the propensity of heteroleptic compounds of the form $LAeX$ to undergo Schlenk-like solution redistribution reactions to homoleptic compounds L_2Ae and AeX_2 . Depending upon the nature of X , the latter product is usually polymeric and of poor solubility in non-coordinating solvents, while the former product is potentially kinetically stabilised and unreactive. This solution redistribution can result in mixtures of potentially catalytically active species and may cause the loss of any ligand control over turnover-, stereo- and regio-determining steps in the catalytic cycle. This problem becomes increasingly important for the heavier alkaline earth metals, as ionic radius increases and Lewis acidity decreases on descending the group. Given this, the tendency towards solution redistribution for the heteroleptic group 2 organometallics increases across the series $Ae = Mg < Ca < Sr < Ba$.^{24,25}



Scheme 3. Schlenk redistribution for heavier alkaline earth β -diketiminate complexes.

The displacement of $HN(SiMe_3)_2$ from $[Ae\{N(SiMe_3)_2\}_2]$ complexes with substrates of lower pK_a than that of hexamethyldisilazane is a well established synthetic method and has been applied to the synthesis of a great number of homoleptic alkaline earth acetylides, chalcogenolates and pnictides.²⁶

In order to overcome this problem, sterically demanding monoanionic spectator ligands have been applied to such complexes to enhance kinetic stabilisation. This in turn slows down the rate of the competing redistribution reaction and allows the subsequent study of the group 2 complex in catalysis. During the past decade, catalyst development has centred upon addressing the Schlenk equilibrium. Efforts to achieve suppression of Schlenk equilibria by use of appropriate ancillary ligands have gained considerable interest.

Work by Chisholm made use of β -diketiminate ligands as well as tris(pyrazolylborate) stabilized analogues (e.g. **1**, figure 1) in the synthesis of a number of group 2 derivatives. These were applied to the ring-opening polymerisation of *rac*-lactide to form heterotactic polylactide and presented a breakthrough in heteroleptic group 2 chemistry, demonstrating controlled reactivity at alkaline earth metal centres supported by a mono-anionic spectator ligand.^{27,28} Substituted fluorenyl ligands have been reported by Harder and co-workers for the stereocontrolled polymerisation of styrene to yield highly syndiotactic polystyrene.²⁹ Kinetic stabilisation of heavier alkaline earth metal complexes has been achieved through such spectator ligand design, a few of which are outlined in figure 1.

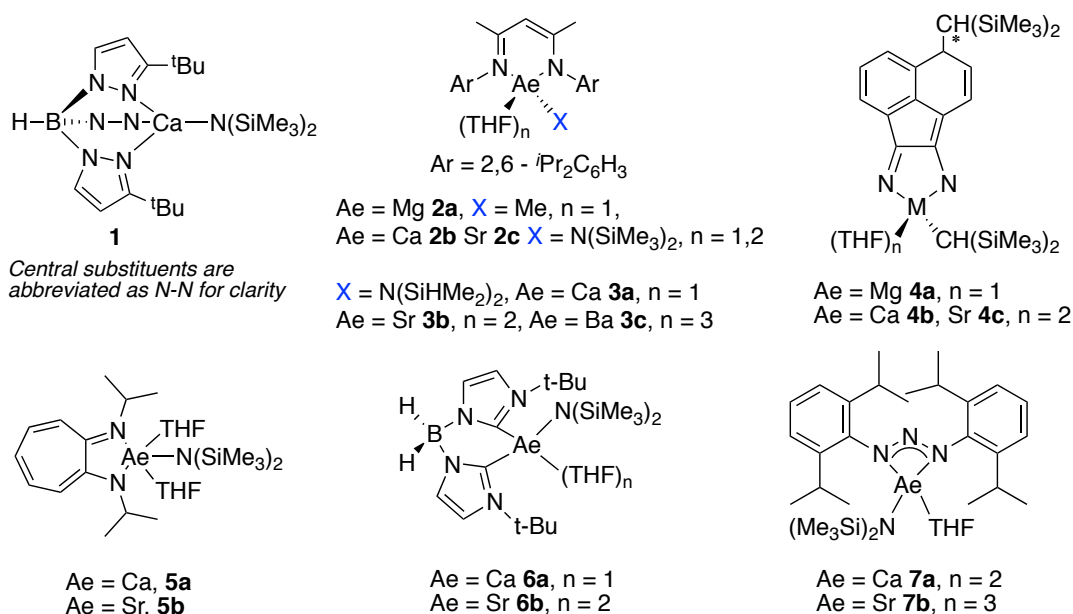
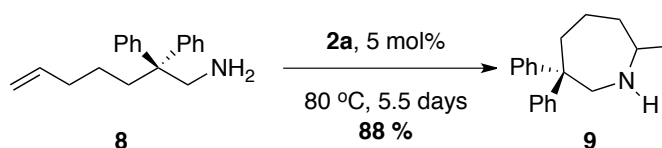


Figure 1. Examples of stabilised heteroleptic alkaline earth precatalysts.

While the activities of the catalyst systems in figure 1 are broadly comparable with one another, the tris(imidazolin-2-ylidene-1-yl)borate complexes (**1a–c**) are noteworthy as they are susceptible to B–N bond cleavage and are thermally unstable above 50 °C.³⁰ Catalyst lifetimes were also depleted due to the competing Schlenk equilibrium and in some cases the magnesium analogue proved to be more thermally robust. For example, the cyclisation of 1-amino-2,2-diphenylhept-6-ene to the corresponding hexahydroazepine (Scheme 4) was achieved with 5 mol% of the magnesium precatalyst (**2a**) after 5.5 days at 80 °C but no reaction was observed when the calcium complex (**2b**) was employed.³¹



Scheme 4. Intramolecular hydroamination of 1-amino-2,2-diphenylhept-6-ene **8** catalysed by **2a**.

Despite these precatalysts incorporating bulky, monoanionic spectator ligands being applied to intramolecular hydroamination transformations, a homologous series of complexes, which increase in catalytic activity and are kinetically stable from Mg–Ba have not been developed in this ligand set. Furthermore, depending on the ligand set, catalyst activities were different and followed different trends.

Carpentier and co-workers have recently reported the use of three families of kinetically stabilised complexes of the type $[\{L\}AeN(SiMe_3)_2(THF)_n]$ for calcium, strontium and less known barium analogues (Figure 2).³² These heteroleptic complexes supported by congested imino anilide ligands were isolated via a one-pot reaction of the ligand precursor, AeI_2 and two equivalents of $KN(SiMe_3)_2$. These products showed no evidence for ligand redistribution and proved stable in C_6D_6 solutions up to 60 °C.

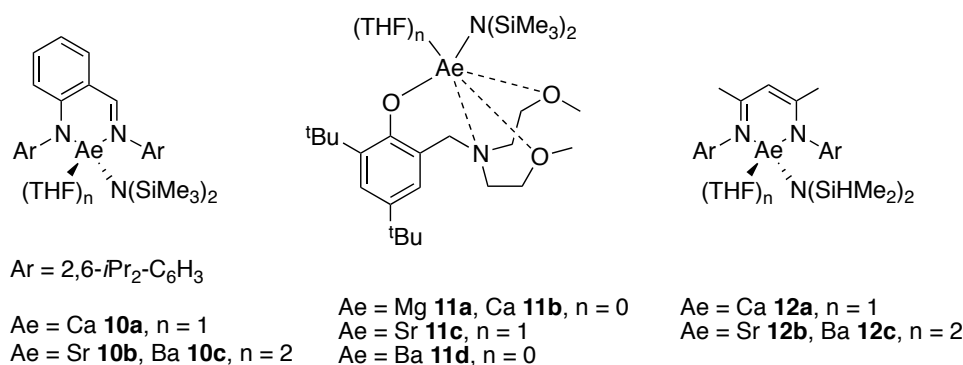


Figure 2. Examples of stable heteroleptic alkaline earth complexes synthesised by Carpentier *et al.*

Complexes **10a–c** displayed notably higher activities in the intermolecular hydroamination and hydrophosphination than previously studied group 2 complexes (Figure 1). Catalyst loadings as low as 2 mol% could be employed and 85% conversion to the phenylethylamine product was achieved in as little as 2 hours. By contrast, the same reaction of pyrrolidine with styrene using 2 mol% [Ca{N(SiMe₃)₂}₂(THF)₂] afforded the product in <1% yield.³²

1.4 Alkaline Earth Catalysis

The field of group 2 catalysis is rapidly growing.^{10,11} This is partially driven by the non-toxicity and low prices of the metals but also strongly accelerated by academic interest in this neglected and underexplored chemistry of the heavier congeners.

Striking progress, notably in the work of Harder, has shown that the highly reactive organocalcium compounds are suitable initiators for the polymerisation of styrene.^{33,34,35} These reactions occur through multiple insertions of the alkene into the metal-carbon σ -bond of the intermediate organometallic species.

Various other organocalcium-catalysed alkene transformations include hydroamination,^{12,36,37,38} hydrophosphination,³⁹ hydrosilylation⁴⁰ and hydrogenation⁴¹.

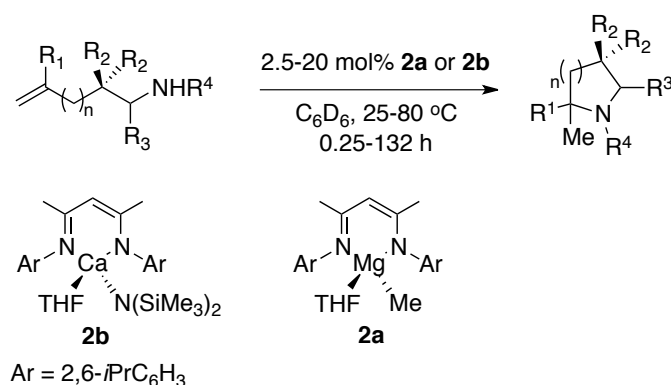
The next section provides details of the recent progress in heavier group 2 catalysed small molecule transformations mediated by well-defined heteroleptic and homoleptic complexes of the form LAeX or AeX₂, where L is a monoanionic

spectator ligand and X is a reactive σ -bonded substituent. A comparison of the alkaline earth metals, Ae = Mg, Ca, Sr, Ba has also been documented.

1.4.1 Group 2 catalysed heterofunctionalisation reactions

1.4.1.1 Intramolecular Hydroamination

Hydroamination is by definition, the formal addition of an N-H bond across C-C unsaturation, an attractive and atom-efficient route to nitrogen-containing molecules. Since 2005, the intramolecular hydroamination of a number of aminoalkenes catalysed by heteroleptic β -diketiminate calcium and magnesium compounds **2a** and **2b** has been reported by the Barrett and Hill groups (Scheme 5).^{12,31,38}



Scheme 5. Reaction scope of calcium and magnesium mediated intramolecular hydroamination of aminoalkenes.

The reaction scope is currently limited to the hydroamination cyclization of primary and secondary terminal aminoalkenes. The reaction was greatly influenced by the substitution pattern of the aminoalkene. Reactions were shown to proceed in high yield under mild conditions (25–80 °C, 0.25–132 h), constructing pyrrolidines, piperidines and hexahydroazepines from the intramolecular cyclisation of the respective aminoalkenes (Scheme 5). Reactions carried out at higher temperatures were found to proceed with Schlenk redistribution of calcium complex **2b** to the homoleptic [Ca{N(SiMe₃)₂}(THF)₂] and [{ArNC(Me)CHC(Me)NAr}₂Ca] species in solution. These preliminary results lay the foundation for further exploration and

development of heterofunctionalisation catalysis with heavier group 2 metal complexes.

Comparison of the kinetics of the magnesium versus the calcium complexes (**2a** and **2b**) revealed that the calcium precatalyst was more active than the magnesium analogues for the cyclisation of (1-allylcyclohexyl)methylamine. Although the cyclisation of 2,2-disubstituted 1-amino-5-hexene substrates was accompanied by alkene isomerisation products when calcium complex **2b** was used, the cyclisation of 1-amino-2,2-diphenyl-6-heptene could not be achieved with this catalyst.^{10,31}

Substrates that are kinetically activated *via* geminal disubstitution gave the fastest reaction times and could be cyclised using just 2 mol% of **2b** or 2–5 mol% of **2a**. Substitution about the C=C bond required longer reaction times and internal olefins failed to cyclise. It is not surprising that similar observations have been made in organolanthanide chemistry where a number of coordinatively unsaturated *ansa*-bridged metallocene and half-sandwich organolanthanide catalysts have been designed to effect the hydroamination/cyclisation of highly substituted aminoalkenes.⁴²

The cyclisation of aminoalkenes possessing two pro-chiral centres can result in the formation of four diastereoisomeric products (Figure 3).

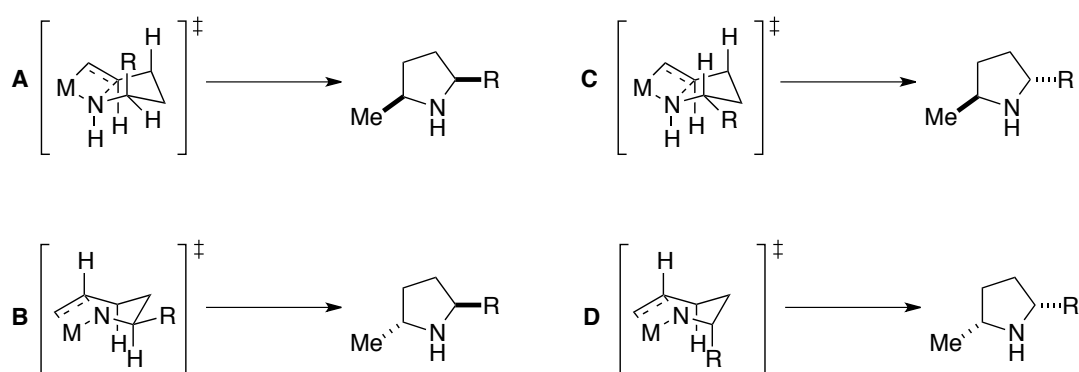


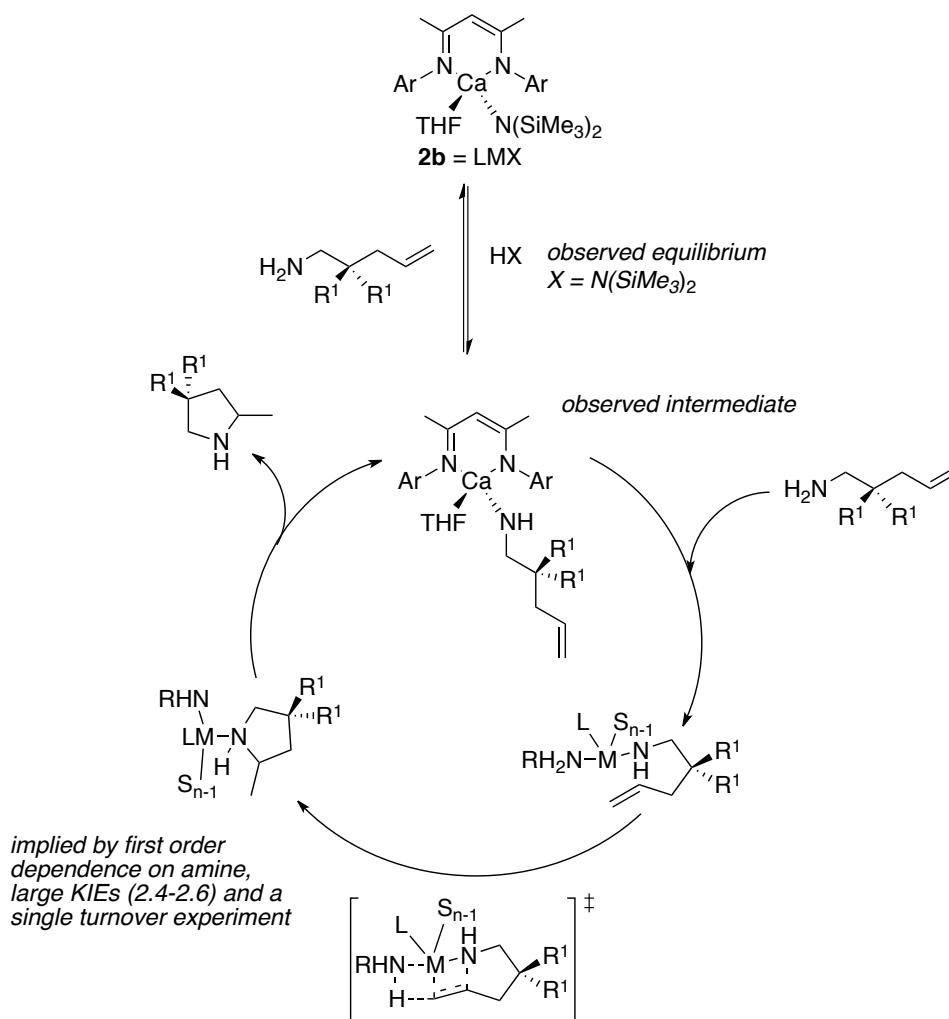
Figure 3. Diastereoselectivity in the intramolecular hydroamination of pro-chiral aminoalkenes.

Disubstitution at the β -position was found to have little affect on the diastereoselectivity of the reaction, but α -substituted aminoalkenes such as 1-amino-1-phenylpent-4-ene underwent a diastereoselective cyclisation with catalysts **2a** and **2b** to yield the corresponding *trans*-pyrrolidines in a diastereoisomeric

excess of 98 and 90%, respectively. Likewise, cyclisation of 2-aminohept-5-ene by 20 mol% of **2b** yielded the *trans*-pyrrolidine in 78% de (Figure 3). Similar selectivity observations have been reported in the organolanthanide series whereby cyclisation of 2-aminohept-5-ene with $[(C_5Me_4)_2SiMe_2]La\{CH(SiMe_3)_2\}$ yielded an 8:1 mixture of *trans*:*cis* heterocycles at 0 °C.¹⁶

The observed diastereoselectivity can be explained by considering the diastereoisomeric transition states in figure 3. Transition states **A** and **D**, leading to the *cis*-pyrrolidine products possess potentially destabilizing 1,3-diaxial steric interactions. These conformations may raise the energy barrier for the insertion step and consequently, the *trans*-diastereoisomers which proceed via transition states **B** and **C** are favoured. As a point of comparison, improved diastereoselectivity with the magnesium catalyst **2a** can be attributed to the shorter M–N and M–C bond lengths thereby tightening the transition state of the insertion reaction and increasing any effects exerted by non-bonding interactions.¹⁰

A mechanism proposed by Hill *et al.* for the intramolecular hydroamination of a generalized α - ω -aminoalkene catalyzed by the β -diketiminato calcium bis(trimethylsilyl)amide **2b** is presented in scheme 6. Mechanistic studies carried out by the Barrett and Hill groups revealed a first order dependence on aminoalkene and catalyst concentration accompanied by large KIEs (2.4–2.6). This led to the interpretation of a turnover-limiting transition state involving a six-membered metallocycle with alkene insertion into the M–N bond being assisted by a coordinated substrate molecule. This coordinated aminoalkene substrate can then transfer a proton to the newly forming M–C bond, resulting in N–H cleavage. This N–H cleavage is encountered in the rate-limiting insertion step and accounts for the large primary KIEs. Furthermore, these results ruled out the presumption of a long-lived, high-energy group 2 alkyl complex, a species that has limited precedent in group 2 coordination chemistry. Coordinating solvents such as THF and high substrate concentrations inhibited the catalytic turnover as the metal becomes coordinatively saturated and substrate coordination is prevented.^{31,38}



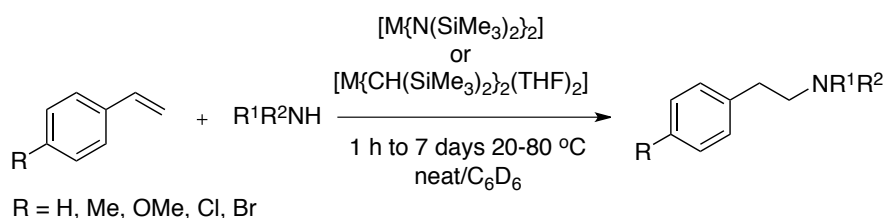
Scheme 6. Proposed mechanism for group 2 mediated hydroamination of aminoalkenes.

Initial attempts to achieve a stereocontrolled intramolecular hydroamination of 1-amino-2,2-diphenyl-4-pentene utilising a chiral calcium amide catalyst, based upon the (S)-Ph-pybox ligand, provided non-racemic products, but in poor enantioselectivity (less than 10% ee). It is proposed that the calcium complex L^*MX ($\text{X} = \text{N}(\text{SiMe}_3)_2$) is unstable with respect to Schlenk-like solution redistribution which provides homoleptic complexes of the type $(\text{L}^*)_2\text{M}$ and MX_2 . Additionally, the latter bis(trimethylsilyl) amide complex $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2(\text{THF})_2]$ can be catalytically active, giving rise to an achiral background reaction.⁴⁰

1.4.1.2 Intermolecular Hydroamination of Activated Alkenes and Alkynes

Few examples of intermolecular hydroamination reactions catalysed by alkaline earth complexes are known, and they involve activated alkenes, that is, vinyl arenes and conjugated dienes.

The reaction of benzylamine, pyrrolidine and piperidine with styrene, 4-methylstyrene, 4-methoxystyrene and 4-chlorostyrene catalysed by 5–10 mol% $[M\{N(SiMe_3)_2\}_2]$ or $[M\{CH(SiMe_3)_2\}_2(THF)_2]$ ($M = Ca, Sr$) has been reported to proceed under mild, solvent-free conditions at 60 °C (Scheme 7).^{43,44}



Scheme 7. Intermolecular hydroamination mediated by homoleptic group 2 complexes.

The vinyl arene hydroamination proceeded with good isolated yields and excellent *anti*-Markovnikov regioselectivity. In every case, the strontium catalyst was found to display a higher activity than the calcium complex and in general, comparable conversions were achieved in approximately half the reaction time. Kinetic studies suggested that the increased rate with the strontium catalyst was attributed to an influential entropic advantage, with the calcium catalyst providing data consistent with a much tighter and more ordered transition state in the insertion step than the strontium system ($\Delta S = -167.8 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ and $-22.0 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ for calcium and strontium respectively).

The hydroamination reactions proved more challenging with styrene systems such as α -methylstyrene and dihydronaphthalene with primary and secondary amines. In these cases, higher catalyst loadings and longer reaction times of up to one week were required.

A combined computational and experimental study of the intermolecular hydroamination of alkenes catalyzed by group 2 complexes was reported by Barrett

and Hill in 2009 and provided considerable insight into the observed reactivity and regioselectivity (figure 4).⁴³ All reactions were reported to proceed with *anti*-Markovnikov selectivity or 2,1-addition of the amine to the alkene. This preferential 2,1-addition to styrene can be attributed to the organization of the transition state during alkene insertion and N–C bond formation. Stabilisation of the developing anionic charge on the incipient benzylic carbon atom, adjacent to the metal centre is expected to lower the activation energy of the insertion (**A**). In this instance, the phenyl ring may stabilise the adjacent anionic centre through interaction with the aromatic π -system. In the case of the 1,2-addition, no such stabilization exists.

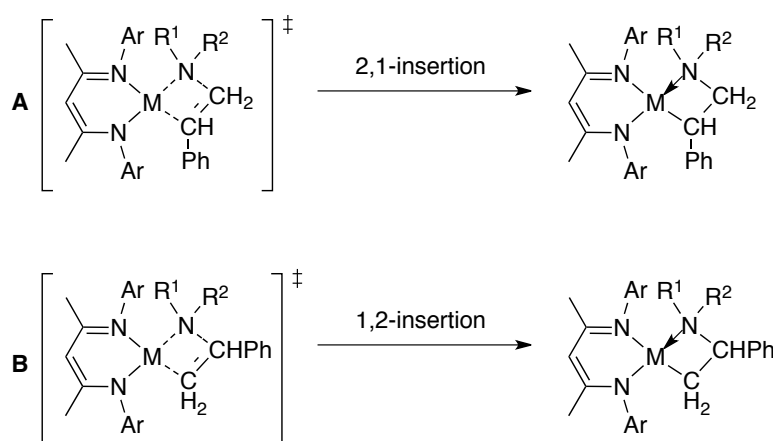


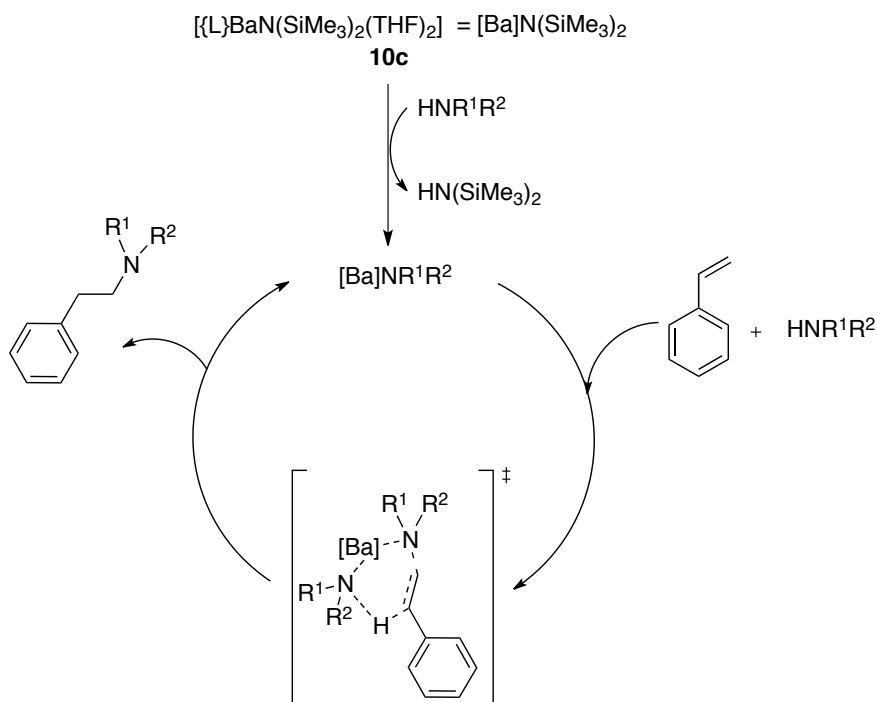
Figure 4. Possible transition states for the intermolecular hydroamination of styrene.

The new heteroleptic complexes **10a–c** published by Sarazin (Figure 2) have been applied to the *anti*-Markovnikov intermolecular hydroamination of vinyl arenes and isoprene.³² In all cases, the activity trend varied in the order (Mg<)Ca < Sr < Ba, that is, the catalytic activity increases linearly with the size of the metal. The barium complexes are not only the most active in the series, but also reported was the first example of complexes of this metal that are capable of catalyzing intermolecular hydrofunctionalisations of alkenes without Schlenk redistribution. The fastest reaction rates were achieved with pyrrolidine and high conversions could be achieved with as little as 0.1 mol%. Likewise, electron-donating substituents on the aromatic ring led to a marked decrease in catalytic activity. Kinetic studies on the hydroamination of styrene with pyrrolidine catalyzed by **10c** using a variety of

amine, styrene and catalyst concentrations are represented by the empirically determined rate law, Eq. (1).

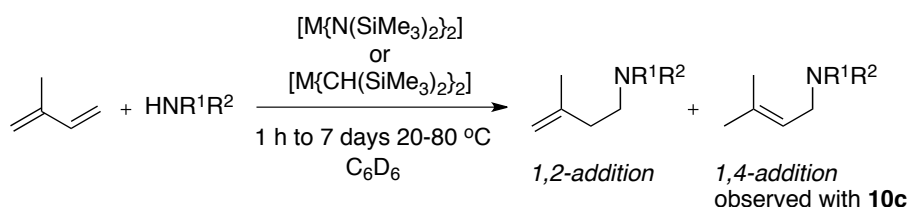
$$v = k[\text{styrene}]^{1.0}[\text{pyrrolidine}]^{1.0}[\mathbf{10c}]^{1.0} \quad (1)$$

This differs from that established for rare-earth catalysts and for the group 2 bis(amide)-mediated intermolecular hydroamination reaction, which showed a second order dependence on catalyst concentration.⁴⁴ In the case of the organolanthanide catalysed reaction, the overall rate law was summed up as zero order in amine and first order in catalyst and alkene concentrations.⁴⁵ The rate law determined for **10c** led to the proposal of a different mechanism than that based on the alkaline earth systems whereby the rate-limiting step is not that of insertion of the alkene into the Ba–N bond, but a concerted proton transfer onto the unsaturation, activated towards attack of the nucleophile which proceeds via a six-centred transition state (Scheme 8).

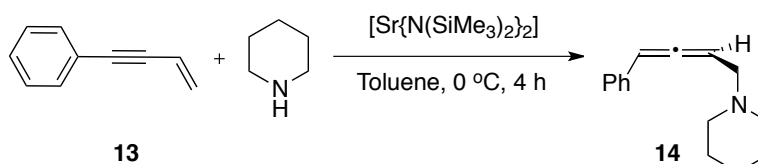


Scheme 8. Possible six-centred concerted mechanistic pathway proposed by Sarazin and coworkers for the intermolecular hydroamination of styrene catalysed by **10c**.

Dienes have also been reported to undergo intermolecular hydroamination. The barium catalyst **10c** resulted in the selective 1,4-addition of pyrrolidine to isoprene, while homoleptic precatalysts $[M\{N(SiMe_3)_2\}_2]$ ($M = Ca, Sr$) yielded a mixture of 1,4-addition and 1,2-addition regioisomers for the hydroamination of isoprene and myrcene with piperidine (Scheme 9).^{32,44} Efforts to achieve the hydroamination of 1,3-cyclohexadiene with the homoleptic precatalysts led to aromatisation to form benzene, whereas the addition of piperidine to but-3-en-1-ynylbenzene selectively formed the corresponding allene at 0 °C in toluene (Scheme 10).

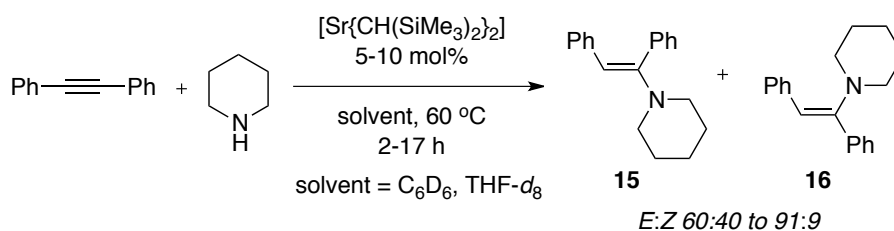


Scheme 9. Intermolecular hydroamination of isoprene with group 2 precatalysts.



Scheme 10. Intermolecular hydroamination of an ene-yne with strontium bis(amide).

The hydroamination of diphenylacetylene is noteworthy. This is the only example of group 2 catalysed intermolecular hydroamination of alkynes. It was found that both phenyl groups were essential in order to electronically activate the alkyne, giving rise to a mixture of *E* and *Z* products. Thus, piperidine undergoes addition to diphenylacetylene in the presence of 10 mol% $[Sr\{CH(SiMe_3)_2\}_2(THF)_2]$ at 60 °C in C_6D_6 solution after 17 h (Scheme 11).



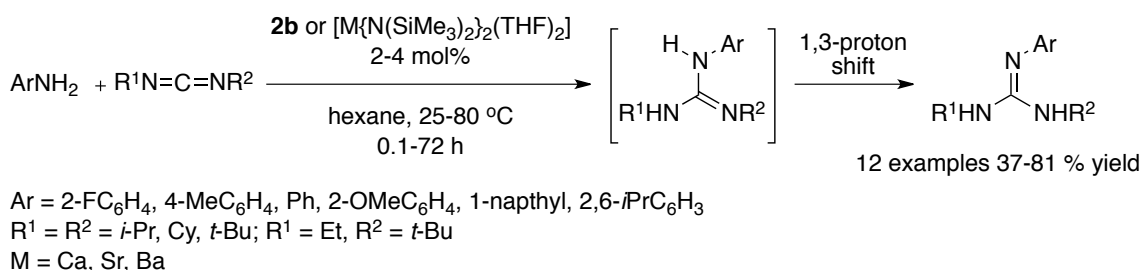
Scheme 11. Group 2 catalysed intermolecular hydroamination of diphenylacetylene.

A 6:4 mixture of *E* and *Z* addition products were isolated, consistent with an isomerisation pathway occurring during the reaction.⁴⁶ Interestingly, the reaction proved highly solvent dependent as different selectivities were observed, accompanied by a rate enhancement when the solvent was switched to THF. In this case, full conversion was achieved after 2 h at 60 °C using only 5 mol% of $[\text{Sr}\{\text{CH}(\text{SiMe}_3)_2\}_2(\text{THF})_2]$; a 91:9 mixture of *E:Z* products were detected.

1.4.1.3 Intermolecular Hydroamination of Carbodiimides and Isocyanates

The intermolecular group 2 catalysed hydroamination has been successfully extended to carbodiimide and isocyanate substrates to yield the corresponding guanidine and urea products (Schemes 12 and 13).

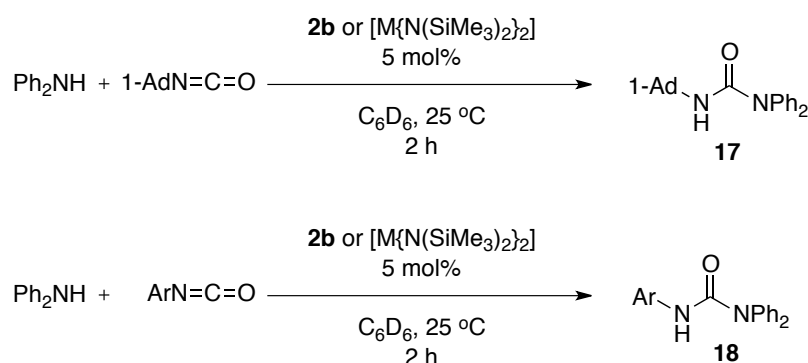
The intermolecular hydroamination of carbodiimides was reported to proceed with primary aryl amines catalysed by **2b** or 2–4 mol% $[\text{M}\{\text{N}(\text{SiMe}_3)_2\}_2(\text{THF})_2]$ ($\text{M} = \text{Ca}, \text{Sr}, \text{Ba}$).⁴⁷



Scheme 12. Scope of intermolecular hydroamination of carbodiimides catalyzed by group 2 complexes.

Electron-deficient and electron-rich primary arylamines could be employed as well as sterically encumbered amines (e.g. 2,6-di-*isopropyl*aniline) with reactions proceeding in good isolated yields. However, the reaction scope does not extend to aliphatic amines.

In related studies, the hydroamination of 2,6-di-*isopropyl*phenylisocyanate and 1-adamantyl isocyanate with diphenylamine has been reported by Hill and co-workers.⁴⁸ The reactions are catalysed by 5–6 mol% **2b** or $[M\{N(SiMe_3)_2\}_2(THF)_2]$ ($M = Ca, Sr, Ba$) in benzene or toluene solution to give the corresponding ureas in 48–93% isolated yield.



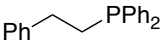
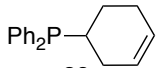
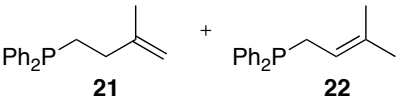
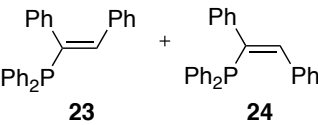
Scheme 13. Reaction scope of group 2 mediated hydroamination of isocyanates.

Although the arylsubstituted isocyanate was reported to undergo hydroamination at room temperature, the adamantyl substituted analogue required more forcing conditions (60 °C). Unfortunately, the reaction scope could not be developed beyond these substrate combinations.

1.4.1.4 Intermolecular Hydrophosphination of Activated Alkenes and Alkynes

By analogy to the Ca-mediated intramolecular hydroamination of aminoalkenes, the Barrett and Hill groups developed a procedure for alkene hydrophosphination.³⁹ Reactions were conducted at 25–80 °C in C_6D_6 solution catalysed by $[ArNCMe)_2CH]Ca\{N(SiMe_3)_2\}(THF)]$ (**2b**).

Table 4. Intermolecular Hydrophosphination of Activated Alkenes with Ph₂PH and Catalyst **2b** (10 mol%, C₆D₆).

Substrate	Product	Temp/°C	Time/h	Conversion/%
Styrene	 19	75	20	95
Cyclohexadiene	 20	75	24	78
Isoprene	 21 + 22	25	24	95
Diphenylacetylene	 23 + 24	75	13	94

More sterically hindered alkenes such as α -methylstyrene or *E* and *Z* stilbene did not undergo hydrophosphination. It is noteworthy that lanthanide(III) complexes have only been reported for intramolecular hydrophosphination and the phosphine-terminated polymerisation of alkenes.^{19,49}

The regioselectivity in the hydrophosphination of styrene originates from the preferred formation of a stabilized benzylcalcium intermediate (2,1-addition). For dienes, precatalyst **2b** was found to be highly selective for the 1,2-addition product. Hydrophosphination of the internal alkyne diphenylacetylene gave predominantly *syn*-addition. It was essential that the heteroleptic calcium catalyst was employed as conversion with the homoleptic [Ca{N(SiMe₃)₂}(THF)₂] complex met with limited success and the reaction was reported to be accompanied by the precipitation of a small amount of a yellow insoluble solid, which was later confirmed to be [Ca(PPh₂)₂(THF)₄] by independent synthesis.⁵⁰

In related studies, Hill and co-workers isolated the heteroleptic calcium phosphide [{ArNCMe)₂CH}Ca{PPh₂}(THF)] from the reaction of precatalyst **2b** with HPPH₂. The resting state in the catalytic cycle was found to be the calcium phosphide [{ArNCMe)₂CH}Ca{PPh₂}(THF)] which proved catalytically competent in hydrophosphination catalysis.

Subsequent to this study, Westerhausen and co-workers reported the use of $[\text{Ca}(\text{PPh}_3)_2(\text{THF})_4]$ as a precatalyst for the hydrophosphination of diphenylacetylene amongst other internal alkynes with HPPH_2 in THF at 25 °C,^{51,52} while Cui and co-workers detailed the hydrophosphination of a wider range of substrates including terminal and internal alkenes and alkynes as well as dienes with diphenylphosphine, catalysed by a calcium hexamethyldisilazide complex supported by a tridentate imino-amidinate ligand.⁵³

Although reports of organomagnesium, -strontium and -barium catalysed hydrophosphinations are more scarce, at 2 mol% catalyst loading Sarazin and co-workers demonstrated the ability of three different homologous series of heavier alkaline earth silazide complexes to promote the addition of HPPH_2 (<96% conversion) and HPCy_2 (<42% conversion) to neat styrene at 60 °C.³² In line with hydroamination studies, activities increased across the series $\text{Ba} > \text{Sr} > \text{Ca}$ where the barium analogue **10c** showed TOFs of 192 h^{-1} for the addition of HPPH_2 to styrene.

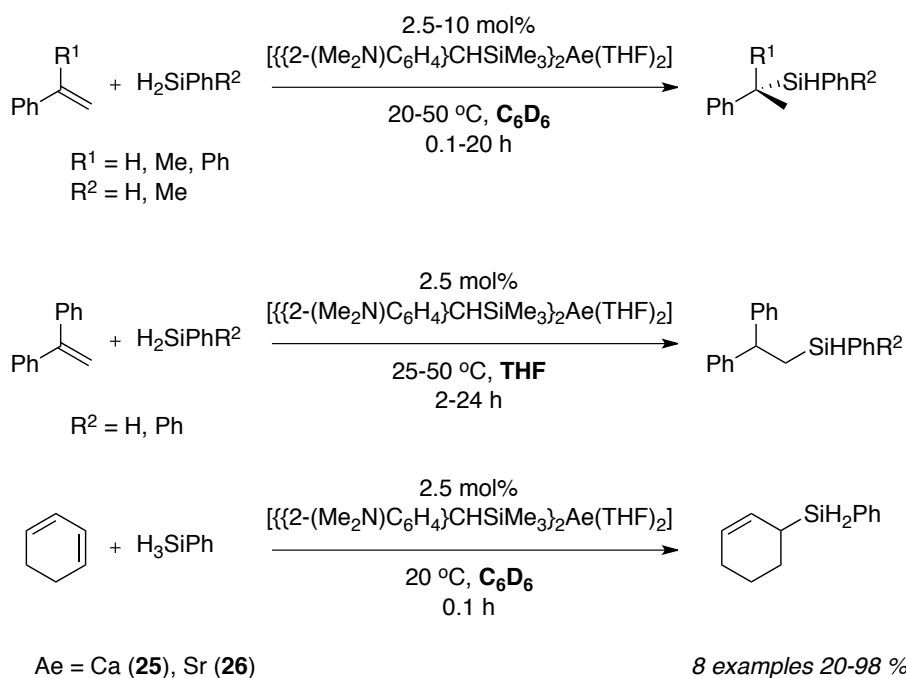
1.4.1.5 Alkene Hydrosilylation

Harder and co-workers introduced the first well-defined early main group metal catalysts for hydrosilylation of alkenes. The application of the heavier alkaline earth complexes, $[\{2-(\text{Me}_2\text{N})\text{C}_6\text{H}_4\}\text{CHSiMe}_3\}_2\text{Ae}(\text{THF})_2]$ ($\text{Ae} = \text{Ca}$ (**25**), Sr (**26**)) to the intermolecular hydrosilylation of vinylarenes and dienes with phenylsilane and phenylmethylsilane was reported. In addition, the isolation of the first calcium-hydride complex $[\{\text{ArNCMe}_2\text{CH}\}\text{Ca}\{\mu\text{-H}\}(\text{THF})_2]$ (**27**) and its relevance to the catalytic reaction has been documented.^{40,54}

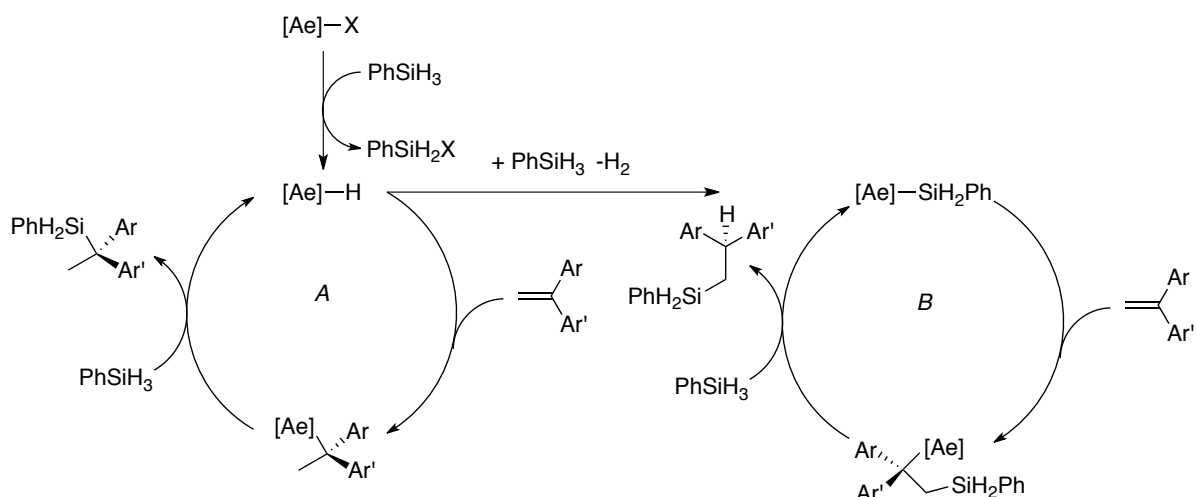
Reactions proceeded with low catalyst loadings (0.5–10 mol%) under relatively mild conditions (50 °C, 0.5–16 h) with the strontium catalyst giving shorter reaction times than the calcium analogue.⁴⁰ The reaction scope was limited to activated alkenes such as vinylarenes and dienes but norbornene and allylbenzene failed to undergo intermolecular hydrosilylation.

The regiochemistry of the reaction proved solvent dependent for the hydrosilylation of diphenylethene. Benzene gave products deriving from 2,1-insertions of the

alkene into the M–H σ -bond whereas switching the solvent to THF resulted in products derived from a similar 2,1-insertion, however, into a M–Si σ -bond (Scheme 14a). This result led the authors to postulate two contrasting reaction cycles (Scheme 14b).



Scheme 14a. Scope of heavier alkaline earth catalysed hydrosilylation of alkenes and dienes.



Scheme 14b. Solvent dependent catalytic cycles proposed by Harder and co-workers for the hydrosilylation of activated alkenes.⁴⁰

Potassium hydride is also an active catalyst for the hydrosilylation of 1,1-diphenylethylene in hydrocarbon solvents. This reaction gave rise to *anti*-Markovnikov products, but was inactive or showed polymerisation of the alkene for other substrates. Despite the proposal that CaH_2 could be formed upon catalyst initiation via reaction of complexes **25** and **26** with the appropriate silane, commercially available CaH_2 proved inactive for the hydrosilylation of alkenes under the same reaction conditions.⁴⁰

The calcium complexes **25** and $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2(\text{THF})_2]$ have been reported to react with silica, to afford catalytically active species for the hydrosilylation of styrene, 1,3-cyclohexadiene and 1,1-diphenylethene with PhSiH_3 . Lower catalyst activities were observed in comparison to those reported for homogeneous catalysis, in particular the hydrosilylation of 1,1-diphenylethene. Whilst it is still unclear whether the active catalyst is bound to the silica surface, the authors have made several observations that point towards a heterogeneous process.⁵⁵

Attempts to extend this reactivity to enantioselective group 2 amide hydrosilylation catalysts have so far been unsuccessful with the use of C_2 -symmetric ligands such as (*S*)-Ph-pybox. These complexes catalysed the addition of phenylsilane to neat styrene at 50 °C giving a maximum of 9% ee. As in the case of intramolecular hydroamination catalysis, these results can be explained by loss of ligand control due to the facile ligand redistribution reactions under the catalytic reaction conditions.⁵⁶

1.5 Polymerisation

This section describes the use of complexes of the alkaline earth metals (magnesium, calcium, strontium and barium) in homogeneous polymerisation catalysis. The latest developments in the polymerisation of unsaturated monomers such as styrene and dienes and in the ring-opening polymerisation (ROP) of cyclic esters are also covered.

The past decade has seen rapid progress in the use of well-defined organo-group 2 complexes as polymerisation catalysts. In view of the current issues related to the depletion of hydrocarbon sources, several efficient catalyst systems based on the biocompatible metal Ca and biodegradable polymers are currently attracting considerable interest. Biodegradable polymers are used in medical applications such as sutures, screws for bone fixation, drug delivery systems and tissue engineering.^{57,58,59,60} Hence, it is important that current ROP processes for example, are not accompanied by problematic removal of catalyst residues from the final polymers. The search for increasingly efficient catalyst systems able to mediate the controlled $\bar{R}OP$ of cyclic esters in addition to achieving high levels of stereocontrol in the ROP of optically active monomers remains at the forefront of catalyst development in this area.

1.5.1 Polymerisation of Cyclic Esters

The earliest polymerisation studies with alkaline earth catalysts date back to the early 1970s. In 1974, Lindsell and co-workers reported the highly syndiotactic polymerisation of MMA with bis(cyclopentadienyl)calcium precatalysts, however in very poor yield (8%).⁶¹

The group of Chisholm has reported extensive studies on the development of single-site catalysts of the type LM(OR) where M = Mg, Ca, Zn and recorded a detailed study and comparison of the metal complexes.^{27,28,62,63,64,65,66} The magnesium alkoxide complex supported by the bulky *tris*(pyrazolyl) or *tris*(indazolyl)borate

ligands (Figure 5) such as $\{HB(^tBupz)_3\}Mg(OEt)\}$ proved effective for the fast, stereoselective, ring-opening polymerisation of L,L -dilactide via an acyl-cleavage mechanism yielding isotactic poly(L,L -dilactide) with $PDI \approx 1.2$. The catalyst activity increased with the steric bulk of the ligand scaffold in these systems.

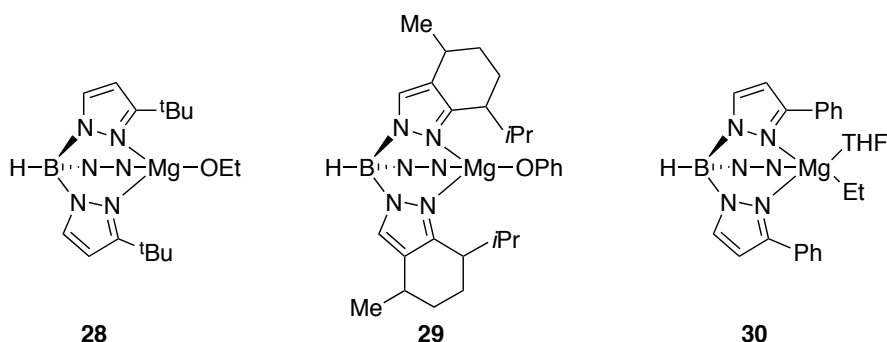
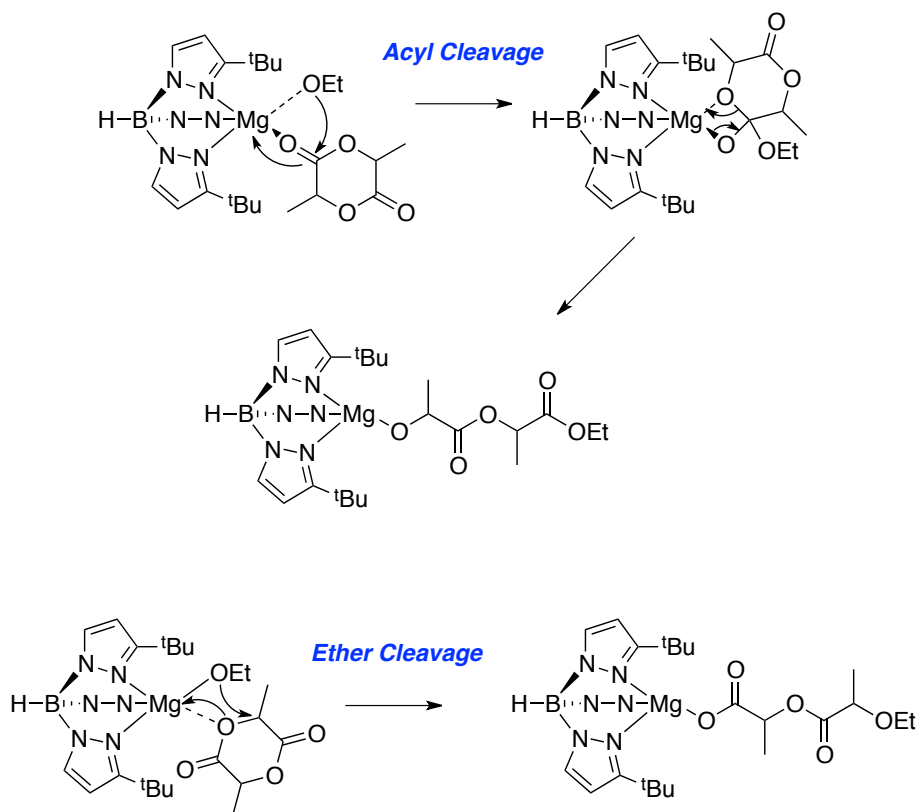


Figure 5. *Tris*(pyrazolyl) and *tris*(indazolyl) heteroleptic Mg complexes synthesised by Chisholm. Central substituents are abbreviated as N–N for clarity.

The ring-opening polymerisation of lactide can occur via two routes, by either acyl cleavage or ether cleavage (Scheme 15).⁶³ In the former process, the carbonyl group is attacked, leading to an ester-terminated chain and an alkoxy group bound to the metal, while in the latter the end group is an ether and an ester group is bound to the metal. Reactions employing **28** have clearly identified the end group as the ester, detectable through NMR spectroscopy.

In other studies, competition experiments of the precursor Mg, Ca and Zn amides incorporating the DIPP-nacnac ligand framework with a stoichiometric amount of L -LA showed the reactivity order $Ca > Mg > Zn$.²⁸ Likewise, in the former ring-opening polymerisation of lactide, the zinc complexes displayed a significant decrease in reactivity than their magnesium counterparts. The authors attribute this difference in reactivity to the difference in polarity of the $M-OR$ bond. The metal centre thereby activates the ketonic carbon to nucleophilic attack by the accompanying RO^- ligand more for $M = Mg$ than for $M = Zn$ which has a more covalent and less highly polarised $M-OR$ bond.⁶³



Scheme 15. Mechanism of Ring-Opening of Lactide.

The calcium complex $\text{Tp}^{\text{tBu}}\text{CaOAr}$ incorporating the bulky tridentate scorpionate ligand is an extremely fast and efficient catalyst for lactide polymerisation. It has been suggested that the bulky nature of the supporting ligand prevents aggregation of the catalytically active Ca species. Polymerisation of *rac*-LA gave a high degree of heterotactic polylactide. Chisholm has also reported chiral enantiopure scorpionate complexes of magnesium which polymerise *rac*-lactide with a slight enantioselectivity.⁶³

Monomers such as ϵ -caprolactone (CL) and glycolide (GL) have long been employed by polymer chemists, but more recently monomers such as lactide (LA) and trimethylene carbonate (TMC) have emerged as particularly attractive green monomers since they are derived from renewable resources (Figure 6).

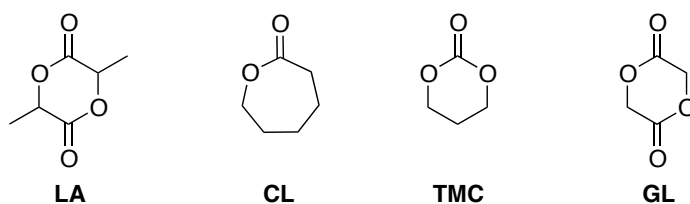
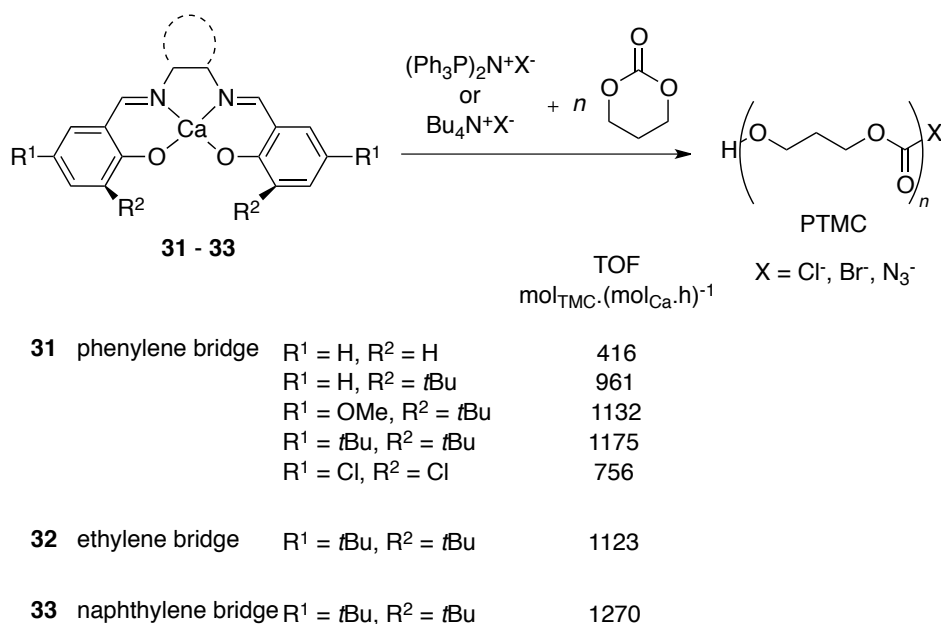


Figure 6. Examples of lactone monomers used for the preparation of linear aliphatic poly(ester)s in ring-opening polymerisation (ROP).

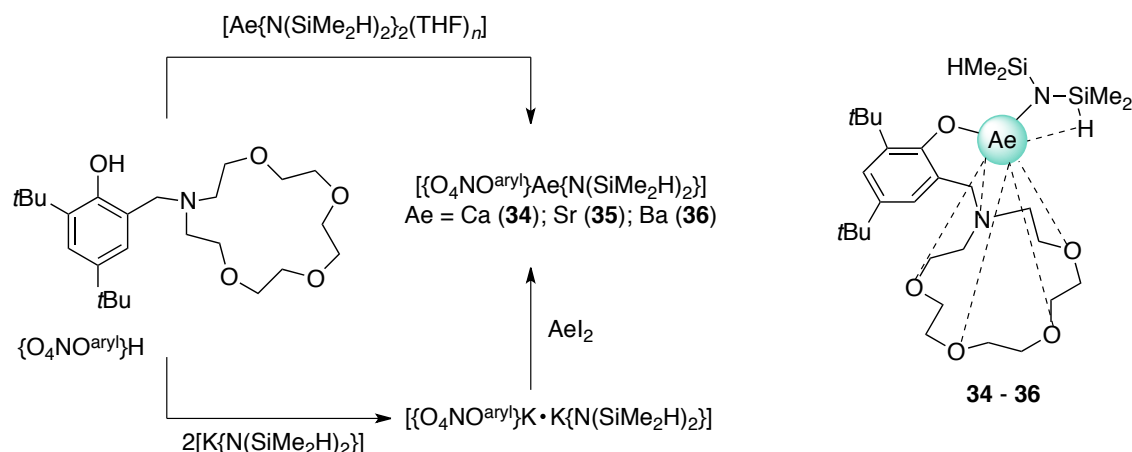
In light of Chisholm's pioneering work with discrete complexes of divalent zinc and magnesium, Westerhausen and Feijen jointly established well-defined Ca-based initiators for the ROP of cyclic esters. A simple combination of $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2(\text{THF})_2]$ and 2 equivalents of alcohol (MeOH, *i*PrOH, or hydroxyl end-capped PEO) effected the living ROP of L-LA and CL in THF.⁶⁷ These binary systems led to well-controlled and fast reactions, taking approx. 25–30 min and 10 min to quantitatively convert 100 equiv of L-LA ($M_w/M_n \approx 1.03\text{--}1.05$) or CL ($M_w/M_n \approx 1.24\text{--}1.29$), respectively, to afford polyesters with predictable molecular weights. In the case of *i*PrOH, each polymer chain end was found to contain isopropoxy end groups, suggesting that the initiation occurred via insertion of the monomer into the Ca–O*i*Pr bond.

Darensbourg and co-workers reported several calcium catalysts supported by a variety of Schiff base derivatives **31–33**, where the nature of the bridge and electronic and steric properties were tuned (Scheme 16).⁶⁸ Polymerisations are initiated by either a salen–Ca complex with an $\text{R}_4\text{N}^+\text{X}^-$ cocatalyst ($\text{X} = \text{Cl}, \text{Br}$ or N_3) or by well-defined single site catalysts.^{69,70} The latter calcium single-site catalysts showed excellent activities for the ROP of LA and TMC. The former Schiff base derivatives promoted the controlled ROP of TMC (275–700 equiv) in neat, melted monomer (86 °C; TOFs = 400–1300 $\text{mol}_{\text{TMC}} (\text{mol}_{\text{Ca}\cdot\text{h}})^{-1}$). The nature of the bridge was reported to have little impact, but the presence of bulky and/or electron-donating groups on the aromatic ring was advantageous.



Scheme 16. Binary Ca {salen}/X⁻ catalyst systems for the ROP of TMC.

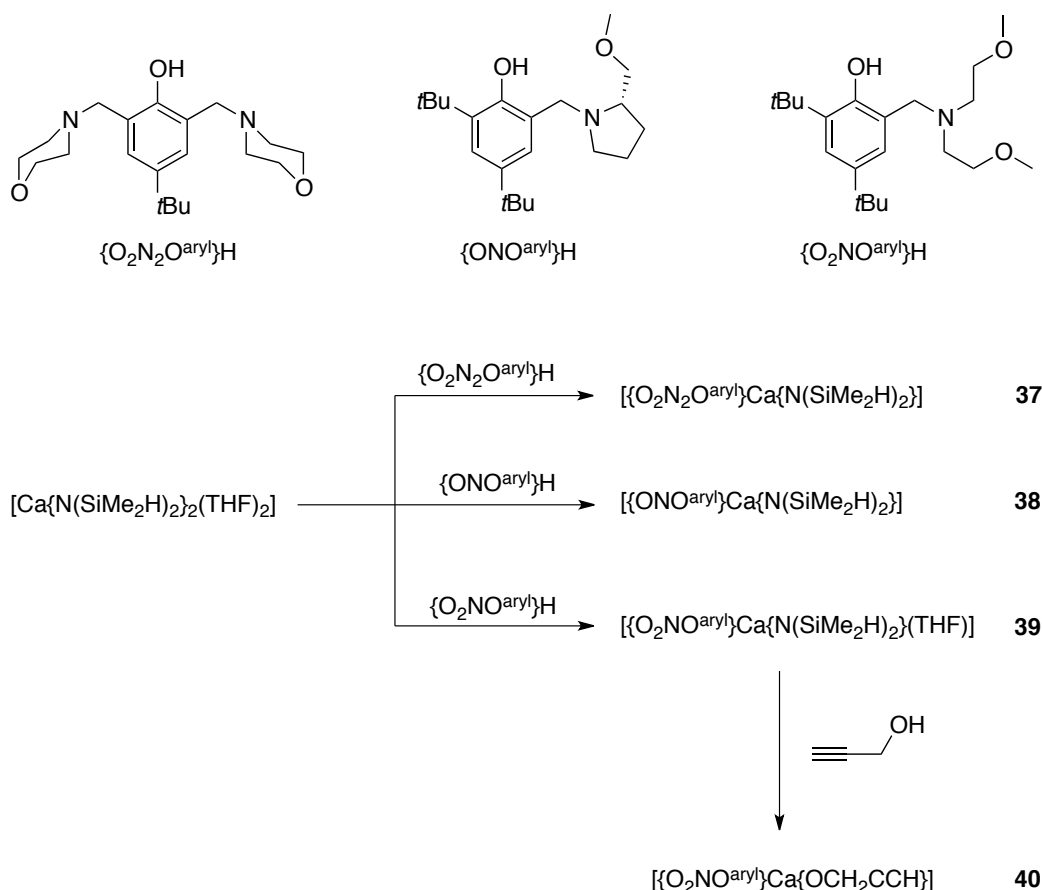
Carpentier and co-workers have exploited the use of the N(SiMe₂H)₂⁻ amido moiety instead of N(SiMe₃)₂⁻, which is much more common in the chemistry of the larger Ae metals, to provide a convenient and relatively general way to stabilize such complexes against ligand scrambling reactions due to the presence of internal β-agostic Ae...H–Si interactions.⁷¹ By reaction of the homoleptic complexes [Ae{N(SiMe₂H)₂}₂(THF)_n] (Ae = Ca, *n* = 1; Sr, *n* = 2,3; Ba, *n* = 0) with the electron-rich amino-ether phenol proligand {O₄NO^{aryl}}H, the desired [{O₄NO^{aryl}}Ae{N(SiMe₂H)₂}] complexes (Ae = Ca, **34**; Sr, **35**; Ba, **36**) were formed and were stable in solution (Scheme 17). These complexes could also be synthesised by treatment of AeI₂ with the homobimetallic heteroleptic precursor [{O₄NO^{aryl}}K·K{N(SiMe₂H)₂}].



Scheme 17. Synthesis of $\{[O_4NO^{aryl}]Ae\{N(SiMe_2H)_2\}_2\}$ complexes **34–36** by Carpentier *et al.*

In a following study, Carpentier and co-workers developed a large family of heteroleptic alkaline earth metal complexes of the type $\{[LO]Ae-Nu\}$ supported by phenolate ligands of various chelating ability and flexibility.⁷² Hence, the approach using intramolecular $Ae \cdots H-Si$ interactions to stabilise the metal complexes was further exploited to prepare a series of stable calcium complexes $\{[O_2N_2O^{aryl}]Ca\{N(SiMe_2H)_2\}_2\}$ (**37**), $\{[ONO^{aryl}]Ca\{N(SiMe_2H)_2\}_2\}$ (**38**) and $\{[O_2NO^{aryl}]Ca\{OCH_2C\equiv CH\}\}$ (**40**) in good yields (Scheme 18).

Complexes **34–40** mediated the *l*ROP of L -LA readily, converting up to 5,000 equiv of monomer at 0–30 °C in a controlled fashion. Employing up to 100 equiv of alcohol (9-anthracenylmethanol or benzyl, isopropyl or propargyl alcohol) as a transfer agent resulted in the activity of the catalyst increasing linearly with the size of the metal (**34** < **35** < **36**). High TOFs were reported in the range of 2,000–27,000 $\text{mol}_{L-LA} (\text{mol}_{\text{metal}} \cdot \text{h})^{-1}$. A satisfactory match between calculated and observed molecular weight was also obtained as well as narrow polydispersities ($M_w/M_n \approx 1.10\text{--}1.20$) for the resulting PLLAs.

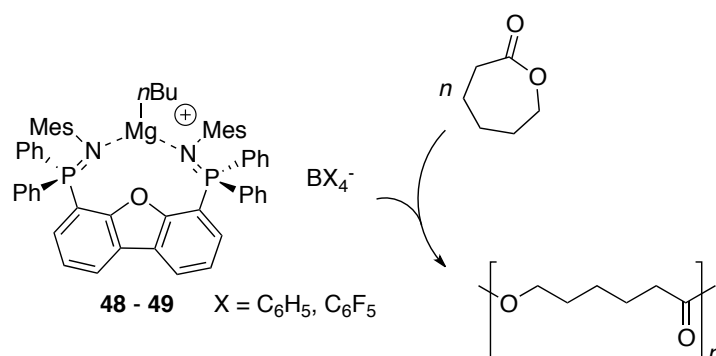


Scheme 18. Synthesis of Ca complexes **37–40** for the *ROP* of ϵ -LA by Carpentier and coworkers.

Recently, well-defined cationic complexes of the type $[\{L_nX\}Ae]^+ \cdot [X]^-$ ($Ae = Ca, Sr, Ba$) stabilised by a bulky ligand ($\{L_nX\}^-$) and a weakly coordinating counterion (X^-) have attracted interest. Furthermore, it has been credited that the positive charge on the metal centre should result in a strong increase in Lewis acidity and therefore produce highly active ROP catalysts.⁷³

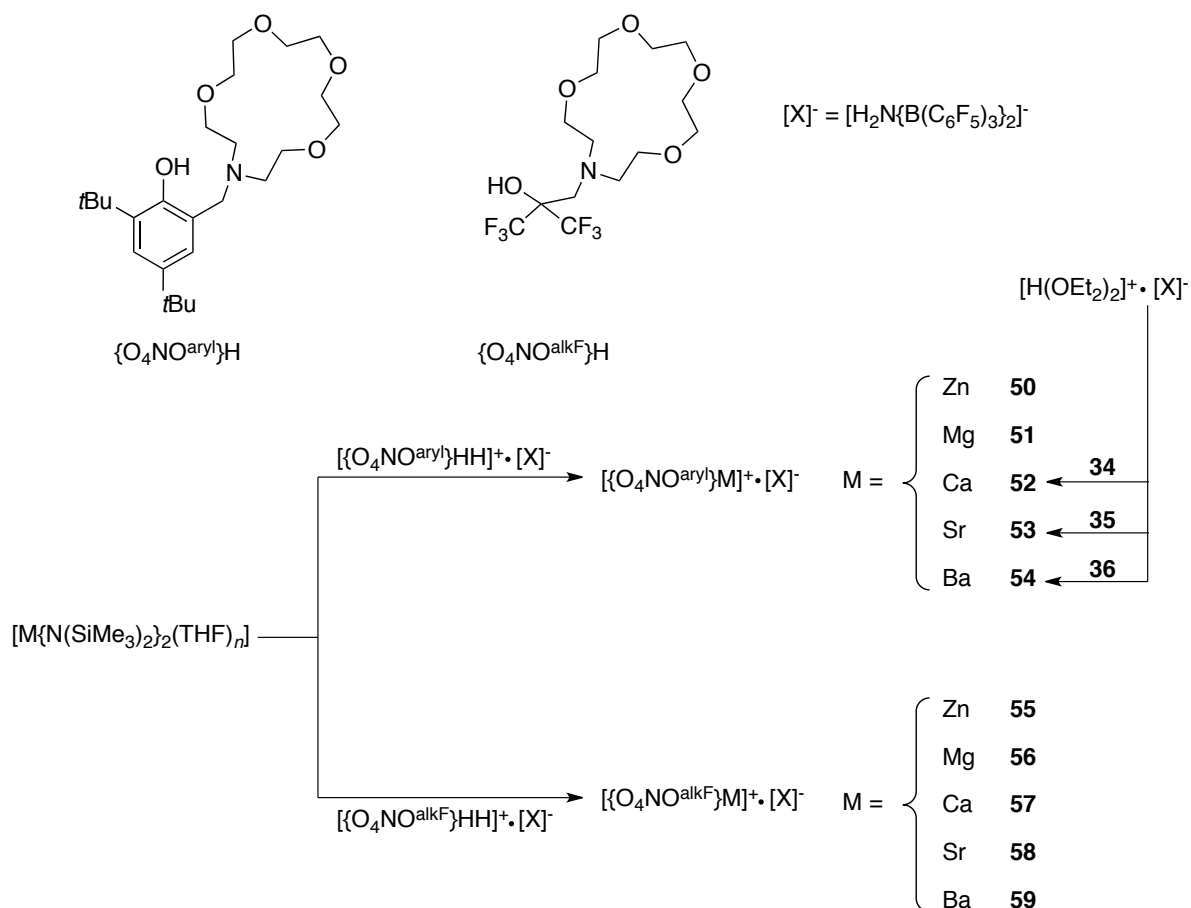
Primary work in this area was accomplished by Bochmann and co-workers in 2002–2005, who prepared a series of magnesium and zinc complexes of the type $[(Et_2O)_3M(X)]^+ \cdot [B(C_6F_5)_4]^-$ ($M = Zn, X = Et$ (**41**), $N(SiMe_3)_2$ (**42**); $M = Mg, X = Bu$ (**43**), $N(SiMe_3)_2$ (**44**) or $[\{DAD\}Zn(X)]^+ \cdot [B(C_6F_5)_4]^-$ ($DAD = iPr_2C_6H_3NC(Me)C(Me)N iPr_2C_6H_3$; $X = Me$ (**45**), Et (**46**), $N(SiMe_3)_2$ (**47**)). These complexes effectively catalysed the ring opening polymerisation of epoxides and ϵ -caprolactone.^{74,75,76}

In 2010, Hayes and co-workers introduced the cationic solvent-free organomagnesium complexes $[\{\text{pidbf}\}\text{Mg}(n\text{Bu})]^+ \cdot [\text{BX}_4]^-$ ($\text{X} = \text{C}_6\text{H}_5$ (**48**), C_6F_5 (**49**)) supported by a *bis*(phosphininime) ligand (Scheme 19). These complexes were active in the ROP of CL, yielding at room temperature excellent conversion of ca. 100–500 equiv in 4 min.⁷⁷



Scheme 19. Organomagnesium $[\{\text{pidbf}\}\text{Mg}(n\text{Bu})]^+ \cdot [\text{BX}_4]^-$ cationic complexes **48** and **49** prepared by Hayes and co-workers as initiators for ROP of CL.

At the same time, Carpentier and co-workers published synthetic routes to access complete families of well-defined, solvent-free cationic complexes of the type $[\{\text{O}_4\text{NO}^{\text{aryl}}\}\text{M}]^+ \cdot [\text{H}_2\text{N}\{\text{B}(\text{C}_6\text{F}_5)_3\}_2]^-$ ($\text{M} = \text{Zn}$, **50**; Mg , **51**; Ca , **52**; Sr , **53**; Ba , **54**) and $[\{\text{O}_4\text{NO}^{\text{alkF}}\}\text{M}]^+ \cdot [\text{H}_2\text{N}\{\text{B}(\text{C}_6\text{F}_5)_3\}_2]^-$ ($\text{M} = \text{Zn}$, **55**; Mg , **56**; Ca , **57**; Sr , **58**; Ba , **59**), where the supporting ligands $[\{\text{O}_4\text{NO}^{\text{aryl}}\}\text{H}]$ and $[\{\text{O}_4\text{NO}^{\text{alkF}}\}\text{H}]$ are electron-rich amino-ether phenol and fluorinated alcohols, respectively (Scheme 20).^{78,79}



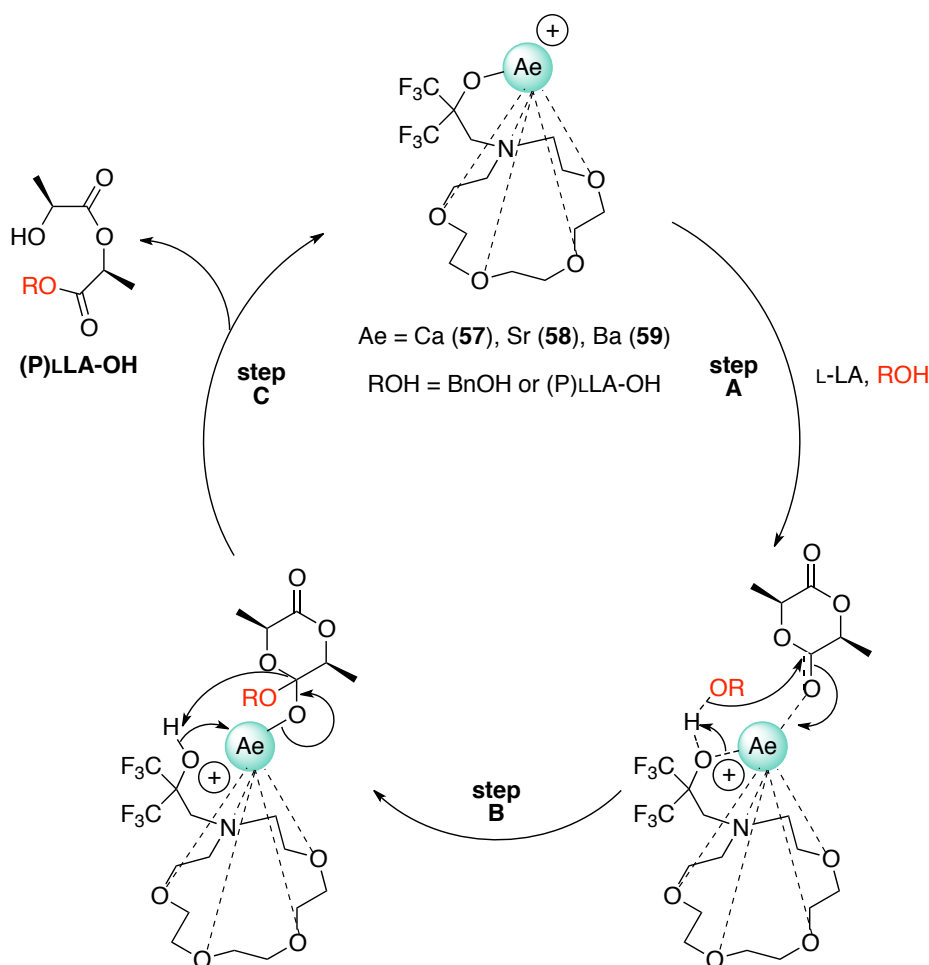
Scheme 20. Synthesis of well-defined cationic complexes $[\{O_4NO^{aryl}\}M]^+ \cdot [H_2N\{B(C_6F_5)_3\}_2]^-$ (**50–54**) and $[\{O_4NO^{alkF}\}M]^+ \cdot [H_2N\{B(C_6F_5)_3\}_2]^-$ (**55–59**) by Carpentier.

While the ligand $[\{O_4NO^{aryl}\}H]$ supporting complexes **50–54** have previously been highlighted as synthetically useful in the preparation of complexes **34–36** (Scheme 17),^{80,72} complexes **55–59** established the first examples of a whole family of Zn and Ae cationic complexes supported by an alkoxide ligand. The highly fluorinated tertiary alkoxide ligands $[\{O_4NO^{alkF}\}]^-$ with bulky, electron withdrawing CF_3 groups in the α position to the alkoxide are much weaker π -donors than conventional alkoxides. The authors suggested the similar nature of these ligands to the versatile phenolate ligands.

The cationic complexes **50–59** were synthesised by reaction of the amido precursors with the acids $[\{O_4NO^{aryl}\}HH]^+ \cdot [H_2N\{B(C_6F_5)_3\}_2]^-$ and $[\{O_4NO^{alkF}\}HH]^+ \cdot [H_2N\{B(C_6F_5)_3\}_2]^-$. Regarding complexes **52–54**, Bochmann's acid

$[\text{H}(\text{OEt}_2)_2]^+ \cdot [\text{H}_2\text{N}\{\text{B}(\text{C}_6\text{F}_5)_3\}_2]^-$ could also be used to prepare these complexes by reaction with heteroleptic complexes **34–36**.

In conjunction with BnOH or $i\text{PrOH}$ (5–50 equiv), complexes **50–59** were able to promote the very controlled $i\text{ROP}$ of L -LA (1,000–3,000 equiv) in toluene. Reaction times were typically 12–24 h to reach near-quantitative conversion. In the case of both families of cationic species the order of reactivity increased according to $\text{Mg} < \text{Zn} < \text{Ca} < \text{Sr} \approx \text{Ba}$. In all cases, a match between calculated and observed molecular weights and end-group fidelity were both excellent, and the polydispersity was very narrow ($M_w/M_n \approx 1.04\text{--}1.20$). Complexes **52–54** were superior to **57–59** in terms of activity, leading the authors to propose that the reactivity in the latter series was diminished by the presence of secondary $\text{Ae}\cdots\text{F}\cdots\text{C}$ internal interactions, observed during close examination of the X-ray structures of **57–59**.



Scheme 21. Proposed ligand-assisted activated monomer mechanism for the $i\text{ROP}$ of L -LA.

Carpentier, Sarazin and co-workers have revealed the exact mechanism of the *̳*ROP catalysed by these systems in combination with DFT and experimental investigations. Taking into account that excess alcohol necessary for the *̳*ROP catalysis could displace the ancillary fluoroalkoxide ligand from the metal cation under polymerisation conditions, they proposed the concept of a ligand-assisted activated monomer mechanism (Scheme 21).⁷³

In this system, the monomer is classically activated by coordination onto the cationic metal centre, while the nucleophile (the initiator BnOH for the first ring opening or the growing macro-alcohol after this) is activated through hydrogen bonding with the fluoroalkoxide (step A). Addition of RO[−] onto the activated carbonyl occurs simultaneously with the release of fluoroalcohol (step B), and acyl cleavage with recapture of the proton regenerates the initial metal species, releasing the ring-opened (macro)molecule (P)-_L-LA-OH (step C).

The same research group also investigated the solvent-free barium cations **54** and **59** further as *̳*ROP catalysts.⁸¹ In combination with 10–100 equiv of co-initiator (BnOH, 1,3-propanediol, BnNH₂ or a hydroxyl-functionalised alkoxy-amine), the Ba cationic complex **54** proved effective for the *̳*ROP of _L-LA at 0–30 °C. The barium complex **54** converted up to 1,000–5,000 equiv of monomer within 6 h (TOF up to 2,000 mol_{_L-LA} (mol_{Ba·h})^{−1}) in a controlled fashion, yielding end-functionalised PLAAs suitable for further application.

1.5.2 Polymerisation of Activated Alkenes

The first benzyl functionalised heavier alkaline earth metal complexes were reported by Harder in 2000.^{82,83} Among these, homoleptic *bis*(1,1,3-triphenylpropyl)barium, [Ba(Ph₂CCH₂CH₂Ph)₂(THF)₂] (**60**) initiated the anionic polymerisation of styrene to essentially atactic poly(styrene). Molecular weights were in close agreement to calculated values and presented relatively narrow molecular weight distributions (*M_w*/*M_n* ≈ 1.2–1.4). The heteroleptic complex **61** also prepared by Harder showed similar reactivity to **60** (Figure 7).

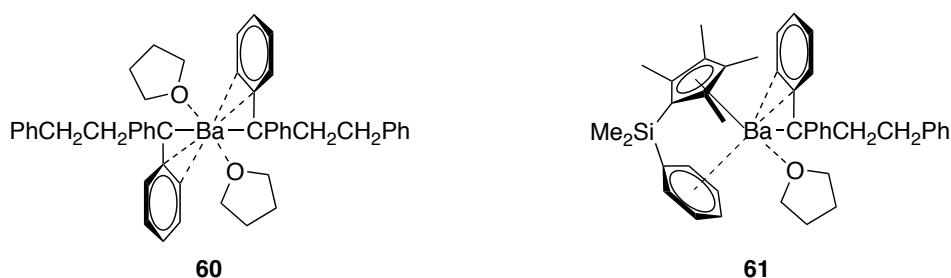


Figure 7. Homoleptic and heteroleptic benzyl barium complexes (**60–61**) used in the polymerisation of styrene by Harder and co-workers.

In a subsequent publication, Harder reported the benzylcalcium complex [α,α -bis(trimethylsilyl)benzyl]₂calcium(THF)₂ (**62**) which failed to polymerise styrene.⁸³ By replacing one of the trimethylsilyl groups with a hydrogen atom and introduction of a dimethylamino group on the aromatic ring which provided intramolecular coordination and hence stabilisation of the reactive calcium centre, the new complex efficiently promoted the anionic polymerisation of styrene, again affording essentially atactic poly(styrene) due to racemisation in solution (Figure 8).⁸⁴

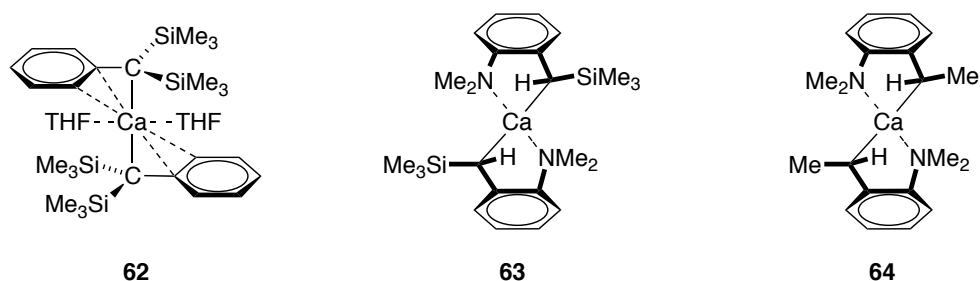


Figure 8. Examples of dibenzylcalcium complexes prepared by Harder and co-workers.

A significant advancement was made with the heteroleptic fluorenylbenzyl calcium complex **65** (Figure 9), which was obtained by reaction of the benzylcalcium complex **63** with 9-Me₃Si-fluorene. Complex **65** promoted the syndiospecific polymerisation of neat styrene whereby monomer precoordination and stereoselective insertion are key steps.³³

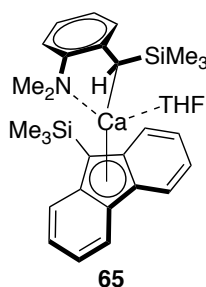


Figure 9. Heteroleptic fluorenyl-benzylcalcium complex (**65**) as an initiator for the syndiospecific styrene polymerisation by Harder and co-workers.

In addition to these well-defined benzylcalcium complexes, strontium complexes have also been shown to polymerise styrene in a living syndiospecific fashion.⁸⁵ The more ionic strontium initiator gave a faster polymerisation but was less selective than Ca initiators. It is thought that this is due to the more ionic and weaker Sr–C bond that causes fast chain-end inversion. Harder has attributed the successful application of organocalcium species as initiators for the syndiospecific and living styrene polymerisation to the right balance of Lewis-basic and Lewis-acidic properties. Even though organomagnesium complexes would be more Lewis-acidic than the calcium analogues, they are however, less ionic and are reported not to polymerise styrene.¹¹

2a Aims and Objectives

Catalytic reactions that are widely used in organic synthesis occur with a broad substrate scope, a high tolerance of auxiliary functional groups in the reaction, fast rates, inexpensive reagents and minimal side products. Although recent years have seen major developments in new reactivities of heavier alkaline earth metal complexes, further progress is still needed to address some of these points. An underlying challenge in the development of catalytic reagents based on heavier alkaline earth metals is the competing Schlenk equilibrium present in solution. The design of sterically demanding, monoanionic ligand sets in heteroleptic complexes of the type $[\text{LAe}\{\text{N}(\text{SiMe}_3)_2\}(\text{THF})_n]$ have been shown to slow down the rate of redistribution reactions and kinetically stabilise group 2 complexes. Studies of supporting ligands of heavier alkaline earth metal catalysts are therefore desirable.

The backbone on many organic molecules is composed of C–C bonds, but the main function of these molecules often contain C–heteroatom bonds, such as nitrogen, oxygen and sulphur. For example, pharmaceuticals and conductive polymers often contain amine C–N bonds, and almost all natural products contain ether, ketone or ester C–O bonds. Furthermore, useful intermediates in organic synthesis often contain C–B or C–Si bonds that are later converted into C–C or C–heteroatom bonds in the final products.

The aim of this work is to further investigate new small molecule transformations and in turn, construct new C–O bond-forming reactions through intramolecular hydroalkoxylation reactions. The hydroamination chemistry of heavier alkaline earth complexes has been thoroughly studied by the Barrett and Hill groups in the last decade. However, the construction of multiple C–N and C–C bonds through tandem, intramolecular hydroamination sequences has not yet been achieved by group 2 complexes and this needs to be further investigated. Such reactions produce synthetically challenging and valuable heterocycles in a single catalytic step.

2.0 Results and Discussion

2.1 Heavier Alkaline Earth Catalysed Hydroalkoxylation/Cyclisation of Alkynyl Alcohols

The metal catalysed addition of nucleophiles to activated C–C bonds such as alkenes, allenes, and 1,3-dienes is one of the most important processes in organic synthesis.^{86,87} The addition of alcohol nucleophiles across unsaturation is referred to as hydroalkoxylation. These processes are very important from a synthetic point of view because, in principle, the addition reactions can be performed with 100% atom efficiency, without any waste formation.⁸⁸ The products of these, tetrahydrofuranyl ethers, occur in a variety of natural products that possess diverse biological activities (Figure 10).^{89,90} These include cytotoxic Vernolide-A (**66a**) and the methoxylated protolimonoid (**66b**).

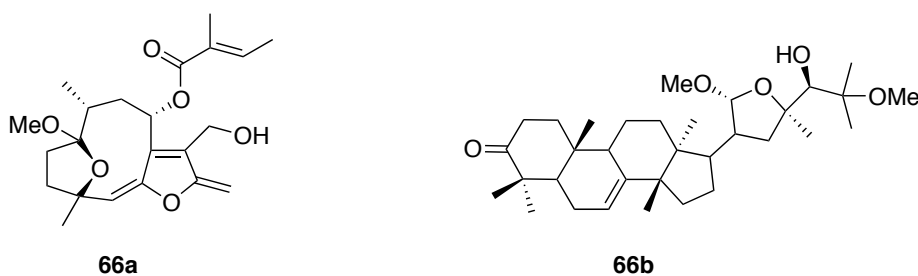


Figure 10. Naturally occurring tetrahydrofuranyl ethers.

Although tremendous work has been carried out in the fields of hydrocarbonation and hydroamination reactions, very few reports are known for hydroalkoxylation reactions partly due to the diminished nucleophilicity and the weaker Lewis base character of oxygen nucleophiles compared to those of amines. Although some progress has been made in this area, reports on asymmetric versions of these processes are scarce.⁹¹ Yamamoto was able to extend this methodology to the first transition metal catalysed asymmetric hydroalkoxylation, with good yields and good enantioselectivities.⁹²

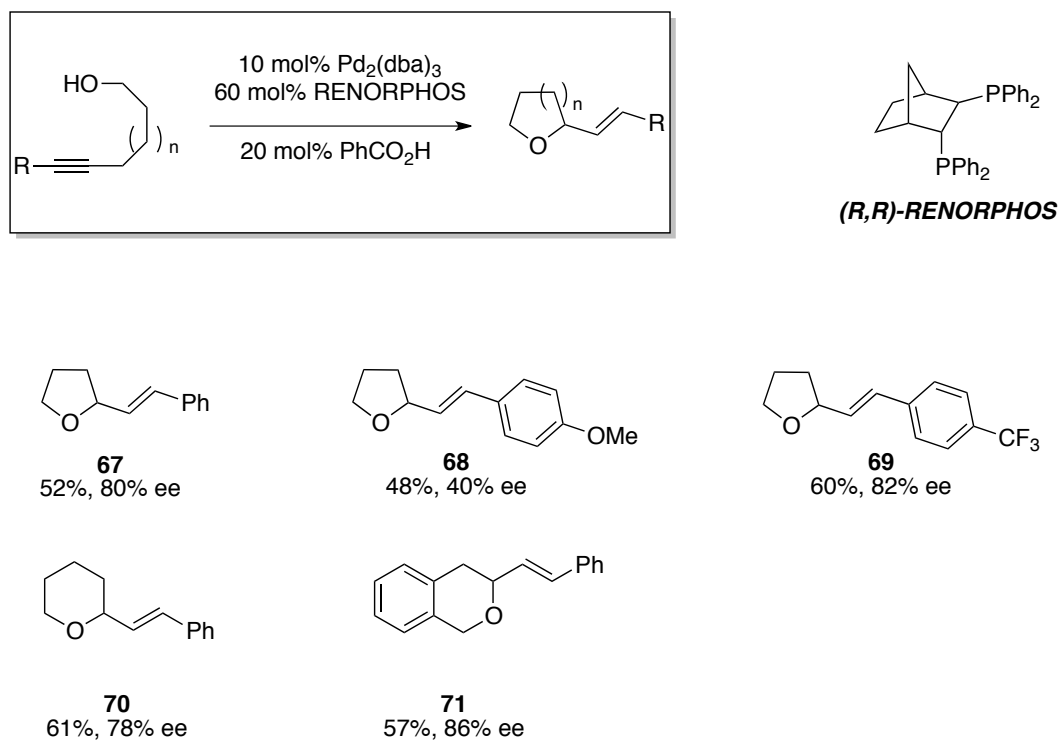
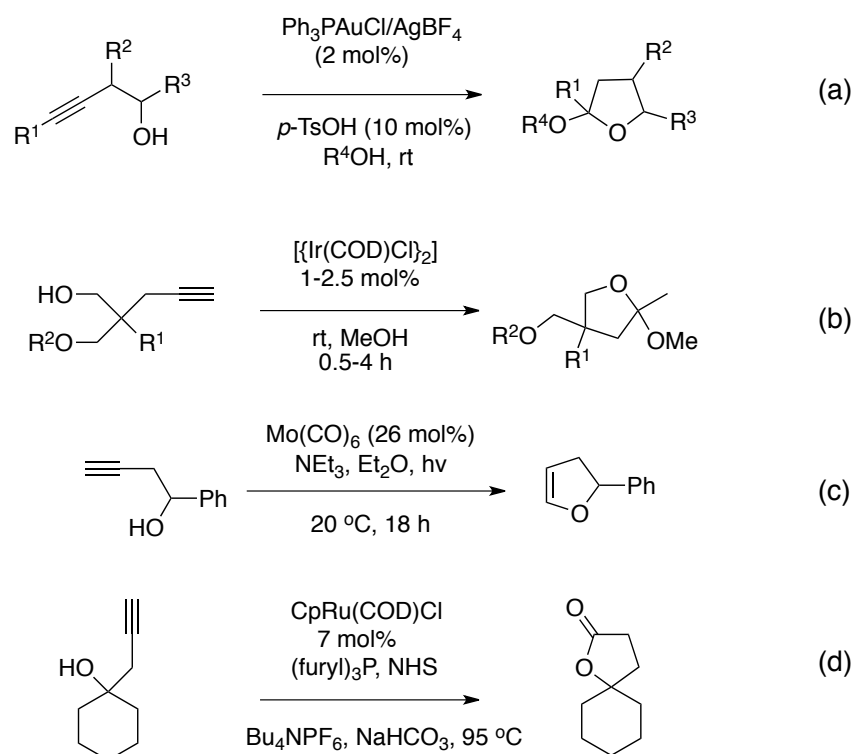


Figure 11. Catalytic intramolecular asymmetric hydroalkoxylation of alkynes.

It was found that a chiral palladium catalyst, derived from $Pd_2(dba)_3CHCl_3$ and (R,R) -renorphos, is highly effective for catalysing asymmetric intramolecular hydroalkoxylations. Intramolecular hydroalkoxylations of the phenyl-terminated alkynol gave the desired heterocycle in 52% yield and 80% ee (Figure 11). Electronic effects became pronounced in the aromatic substituted alkynols where the yield and ee values were significantly diminished in the presence of electron donating groups such as the 4-methoxy group. The yield with the electron withdrawing $-CF_3$ group increased which was accompanied with higher ee values. The reaction, however, has some limitations in that high catalyst loading, high temperature and long reaction times were required. Nevertheless, these studies provide a versatile platform for the development of catalysts for asymmetric intramolecular hydroalkoxylations.

The cycloisomerisation/hydroalkoxylation of alkynyl alcohols to enol ethers can be carried out in the presence of an alcohol and a dual catalyst system, consisting of a gold precatalyst and a Brønsted acid. This method was applied to the cyclisation of

the bis-homopropargylic alcohols (Scheme 22, a).⁹³ Transformation to 5-*exo* enol ethers via metal vinylidenes was introduced by Genet and coworkers via $[\text{Ir}(\text{COD})\text{Cl}]_2$ (Scheme 22, b).⁹⁴ This cyclisation proceeded under mild, base-free conditions and with low catalyst loadings to allow the formation of *exo*-selective five- and six-membered cyclic ethers. Focus is made on the 5-*exo* selectivity of the Ir(I) catalyst in comparison to other transition metals like W, Ru, Rh and Mo whereby 6-*endo* cyclisation products are obtained. McDonald first introduced the cycloisomerisation of alkynyl alcohols to endocyclic enol ethers employing $\text{Mo}(\text{CO})_6$ and $\text{W}(\text{CO})_6$ (Scheme 22, c).⁹⁵ These catalysts form a metal vinylidene intermediate which subsequently generates the isomerised endocyclic enol ether.⁹⁶ Trost's group utilized $\text{CpRu}(\text{COD})\text{Cl}$ to produce γ -lactones via intramolecular hydroalkoxylation and oxidation (Scheme 22, d). A range of conventional oxidants and catalyst ligands were explored in their work.⁹⁷



Scheme 22. Examples of transition metal complexes in intramolecular hydroalkoxylations of alkynyl alcohols.

In work of most relevance to our current study, organolanthanide complexes are known to be highly active hydrofunctionalisation catalysts. Among these catalysts homoleptic $\text{Ln}[\text{N}(\text{SiMe}_3)_2]_3$ amido complexes have successfully been shown to catalyse the intramolecular hydroalkoxylation transformation.^{98,99} Thermodynamic considerations of the large $\text{Ln}-\text{O}$ bond enthalpy firstly provide a challenge for the rate limiting insertion step. Estimation of the bond enthalpy values for typical insertions into different types of unsaturation are outlined in table 5.⁹⁸

Table 5. Estimated $\Delta H_{\text{insertion}}$ into an $\text{L}_2\text{Ln}-\text{OR}$ bond.

Unsaturatation	$\Delta H_{\text{insertion}}/\text{kcal}\cdot\text{mol}^{-1}$
Alkyne	-13
Allene	+6
Alkene	+22

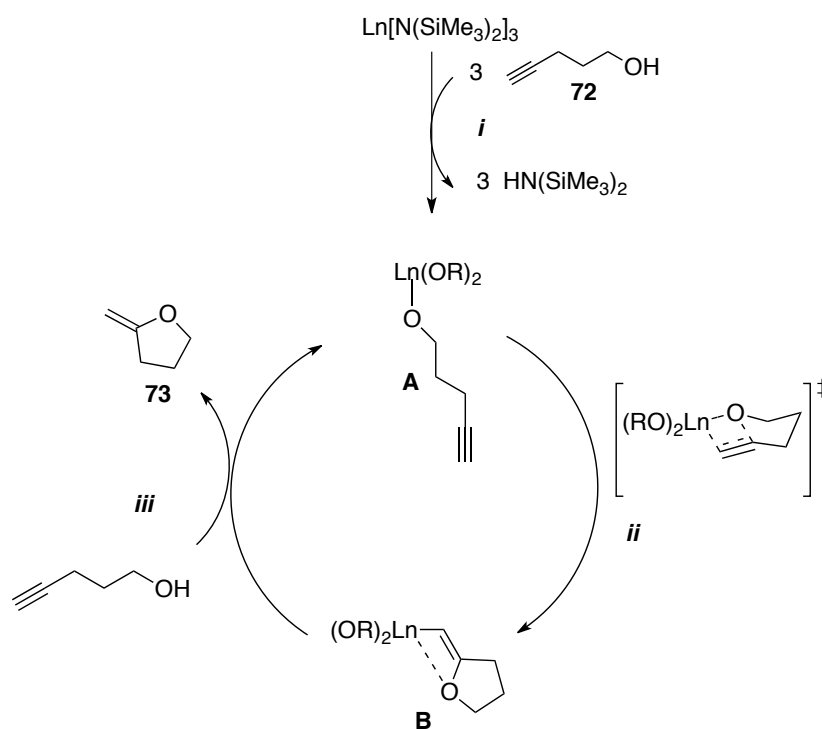
Because of the large barrier for insertion of alkenes into $\text{Ln}-\text{OR}$ bonds, this transformation has not been observed, and it is likely that this insertion will require activated or strained alkenes.

The reaction mechanism for trivalent lanthanide tris(amide) mediated hydroalkoxylation/cyclisation reactions is considerably different from that in operation for the previous reported transition metal catalysed hydroalkoxylation of alkynyl alcohols (Scheme 22, a–d).

Consistent with the observed kinetics (eq 1), the reaction is represented by the following equation:

$$\text{Rate} = k_{\text{obs}}[\text{Catalyst}]^1[\text{Substrate}]^0 \quad (1)$$

The reaction proceeds through the insertion/protonolysis pathway (Scheme 23, step *i–iii*) similar to that established for intramolecular lanthanide mediated hydroamination.^{16,17}

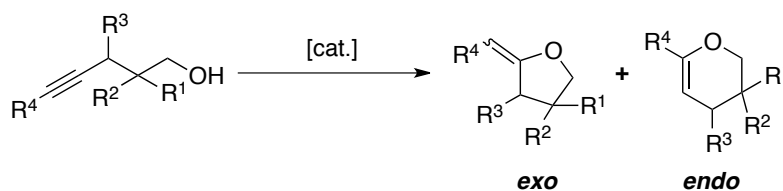


Scheme 23. Proposed mechanism for lanthanide mediated hydroalkoxylation of alkynyl alcohols.

The protonolysis is followed by turnover-limiting insertion (step *ii*) of the alkyne into the Ln–OR bond. The vinyl ether is then rapidly protonolysed from the metal centre to regenerate the catalyst and yield the cyclic product (step *iii*). These present hydroalkoxylation reactions proceed with high *exo* and *E* selectivities, resulting from the stereochemistry of the alkyne insertion into the Ln–OR bond. The reactions proceeded cleanly at 25–130 °C to provide furans, pyrans, benzofurans and isochromans in excellent conversions.^{98,99}

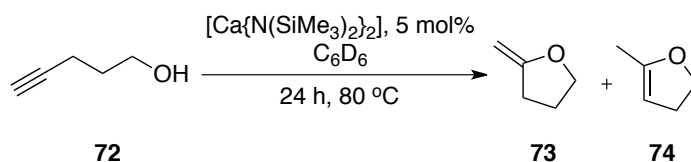
2.1.1 Alkynyl Alcohol Hydroalkoxylation

For the intramolecular hydroalkoxylation/cyclisation of alkynyl alcohols, two possible regioisomers can be anticipated as reaction products (Scheme 24). These are the *exo*-dig and the *endo*-dig cyclisations which yield tetrahydrofurans or dihydropyran products according to Baldwin's rules.¹⁰⁰



Scheme 24. Possible enol ether products from hydroalkoxylation/cyclisation of alkynyl alcohols.

As described previously, the hydroalkoxylation of alkynyl alcohols is a challenging and attractive reaction and therefore worth studying. In preliminary attempts, 4-pentyn-1-ol and 5 mol% [Ca{N(SiMe₃)₂]₂] were dissolved in *d*₆-benzene and the mixture analysed by ¹H NMR spectroscopy. Initial analysis of the spectrum showed full catalyst initiation by liberation of HN(SiMe₃)₂ at room temperature and a broadening of the hydroxyl as well as the alkynyl proton peaks, indicating the rapid formation of the anticipated calcium alkoxide and a calcium alkyl intermediate. Although no further reaction occurred after several hours at room temperature, heating the reaction mixture to 80 °C for 24 h converted the alkynyl alcohol selectively to the corresponding five membered enol ethers, prompting further investigation (Scheme 25).



Scheme 25. Hydroalkoxylation of 4-pentyn-1-ol (**72**) catalysed by [Ca{N(SiMe₃)₂]₂].

The reaction mediated by [Ca{N(SiMe₃)₂]₂] proceeded with quantitative conversion under the reaction conditions stated. In addition to the expected exocyclic enol

ether product **73** about 10% of its isomerised form, the dihydrofuran **74**, was produced as confirmed by 2D-NMR spectroscopic experiments and by comparison with literature data.¹⁰¹

The reaction progress was conveniently monitored by ^1H NMR spectroscopy, using evolved $\text{HN}(\text{SiMe}_3)_2$ or added ferrocene as internal NMR standards (Figure 12).

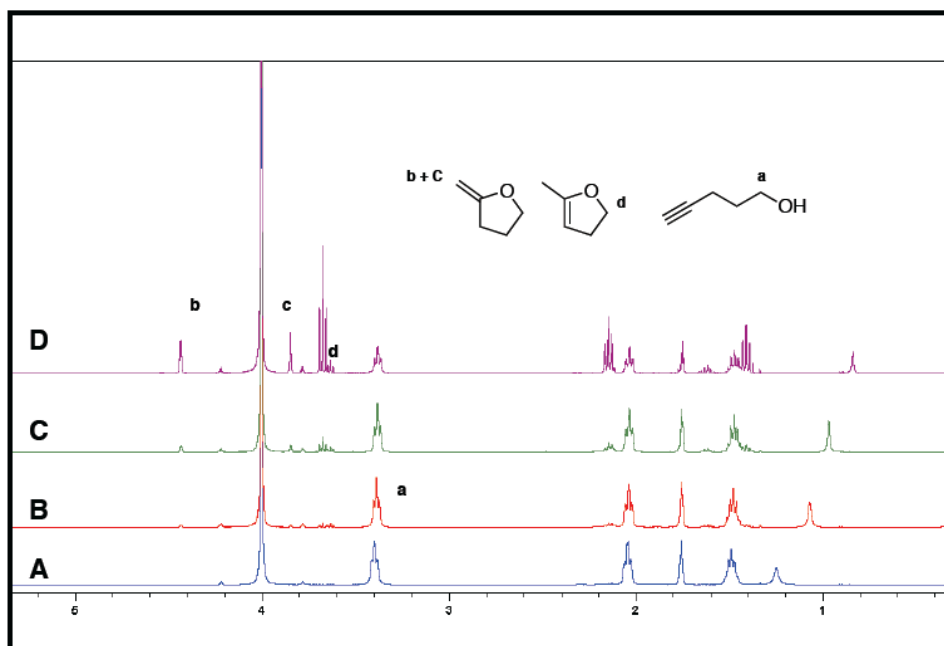
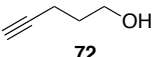
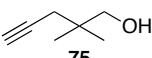
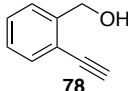
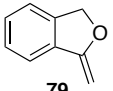
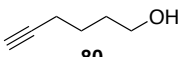
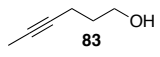


Figure 12. ^1H NMR spectra during monitoring of the cyclisation of 4-pentyn-1-ol **72** mediated by $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ in C_6D_6 at $70\text{ }^\circ\text{C}$ with ferrocene as an internal standard. A) Room temperature, $t = 0$ h; B) $t = 5$ h; C) $t = 24$ h; D) $t = 48$ h.

The intramolecular hydroalkoxylation of a diverse series of substituted alkynyl alcohols mediated by homoleptic heavier alkaline earth metal bis(amides) proceeded selectively with high conversions to yield the corresponding furan, pyran and benzofuran heterocycles as summarised in table 6.

Table 6. Catalytic heavier alkaline earth mediated intramolecular hydroalkoxylation/cyclisation of primary terminal alkynyl alcohols.

Entry	Substrate ^a	Product ^b	Catalyst	Time/ h	Product Ratio ^c
1			[Ca{N(SiMe ₃) ₂] ₂]	24	92:8
2			[Sr{N(SiMe ₃) ₂] ₂]	16	90:10
3			[Ba{N(SiMe ₃) ₂] ₂]	40	97:3
4			[Ca{N(SiMe ₃) ₂] ₂]	<1	100:0
5			[Sr{N(SiMe ₃) ₂] ₂]	<1	91:9
6			[Ba{N(SiMe ₃) ₂] ₂]	<1	92:8
7			[Ca{N(SiMe ₃) ₂] ₂]	<0.5	-
8			[Sr{N(SiMe ₃) ₂] ₂]	<0.5	-
9			[Ba{N(SiMe ₃) ₂] ₂]	<0.5	-
10			[Ca{N(SiMe ₃) ₂] ₂]	30 ^d	66:34:0
11			[Sr{N(SiMe ₃) ₂] ₂]	24 ^e	49:7:44
12			[Ba{N(SiMe ₃) ₂] ₂]	24 ^d	10:11:79

(a) Reaction Conditions: 5 mol% [Ae{N(SiMe₃)₂]₂] (Ae = Ca **75a**, Sr **75b**, Ba **75c**), [substrate] = 0.35 M in C₆D₆ at 80 °C; (b) Yields ≥ 95% by ¹H NMR spectroscopy; (c) Ratio of major exocyclic enol ether product:isomerised product(s) at given time, *t*; (d) 110 °C, 10 mol% of precatalyst; (e) 120 °C, 10 mol% of precatalyst.

In general, the catalytic hydroalkoxylation/cyclisation reactions of the terminal alkynyl alcohols proceeded at 80–120 °C under inert atmosphere, at 5 mol% catalyst loading in 1 h to approximately 1 day. Unlike the trend observed with that of the trivalent lanthanide catalysed alkynyl alcohol hydroalkoxylation of 4-pentyn-1-ol whereby increasing the Ln³⁺ radius increased the turnover frequencies,⁹⁹ this was not the case with that of the group 2 bis(amides). Hence, the conversion of 4-pentyn-1-ol to 2-methylenetetrahydrofuran and 2,3-dihydrofuran (**72** → **73** and **74**) took 16 h and 40 h to reach completion when the strontium and barium bis(amide) precatalysts were employed. [Ba{N(SiMe₃)₂]₂] unexpectedly showed good activity

towards 4-pentyn-1-ol where the cyclised products (**73** and **74**) were obtained after 40 h at 80 °C. This observation of the notable reactivity of the barium species (**75c**) towards **72** was significant in comparison to its inability to effect intra- or intermolecular hydroamination.¹⁰ $[\text{Ba}\{\text{N}(\text{SiMe}_3)_2\}_2]$ can slowly catalyse the intermolecular hydroamination of styrene and in this case the intramolecular hydroalkoxylation reaction. The rate of cyclisation proceeded in the order $\text{Sr} > \text{Ca} > \text{Ba}$ whereas the selectivity for the major exocyclic enol ether product decreased in the reverse order $\text{Ba} > \text{Ca} > \text{Sr}$.

It has previously been reported that exocyclic enol ethers are extremely unstable and undergo isomerisation to the thermodynamically more stable dihydrofuran.¹⁰² Addition of an extra 5–10 mol% of $[\text{Sr}\{\text{N}(\text{SiMe}_3)_2\}_2]$ to the reaction mixture in transformation **72** $\rightarrow$ **73** and **74** did not change the ratio of isomers observed. This may indicate that the endocyclic enol ether product **74** is formed before the formation of the highly labile enol ether **73** during the catalytic cycle. Several reaction conditions were employed such as varying the precatalyst loading (2–20 mol%), temperature (60–120 °C) and initial substrate concentration (0.1–0.6 M) but it was not possible to completely avoid the formation of the dihydrofuran **74** and in all runs between 3 and 10% of the dihydrofuran was formed.

The reaction scope in table 6 was designed initially to probe a variety of structural effects on terminal alkynyl alcohols, including five- and six-membered ring formation. It was found that the ease of ring size formation was $5 > 6$, consistent with a classical, stereoelectronically controlled cyclisation process.^{103,104} In contrast to the cyclisation of 4-pentyn-1-ol, isomerisation to the internal alkyne **83** occurred with 5-hexyn-1-ol which was isolated and identified by comparison of NMR spectroscopy data with literature reported data.¹⁰⁵ The internal alkyne remained unaffected by the catalytic conditions employed. The formation of **83** is most likely ascribed to a competing isomerisation pathway of the alkyne via an allene, which emerges as an intermediate during the cyclisation of 5-hexyn-1-ol **80**. Such alkyne/allene isomerisation was evident by *in situ* ^1H NMR monitoring during the

reaction course. This was especially distinctive when the barium bis(amide) precatalyst **75c** was used (Table 6, entry 12; Figure 13).

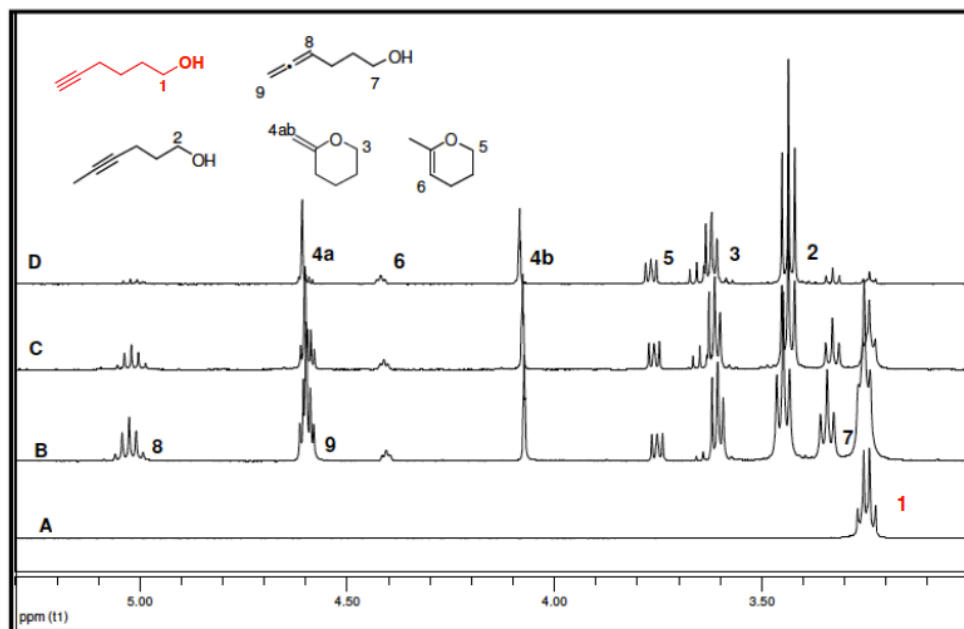


Figure 13. ^1H NMR monitoring of the hydroalkoxylation/cyclisation of 5-hexyn-1-ol (**80**) mediated by 5 mol% $[\text{Ba}\{\text{N}(\text{SiMe}_3)_2\}_2]$ in C_6D_6 at 120°C . (a) 5-hexyn-1-ol at rt, $t = 0$ h; (b) $t = 6.5$ h; (c) $t = 11$ h; (d) $t = 16$ h

During the monitoring of the intramolecular hydroalkoxylation/cyclisation of 5-hexyn-1-ol **80** by ^1H NMR spectroscopy, the appearance of an intermediate reminiscent of the analogous allene could be observed as a multiplet at 5.10 and 4.70 ppm, although only present in very small concentrations.

The best result for this reaction was obtained with the calcium bis(amide) precatalyst **75a**. Heating the reaction mixture at 110°C for 30 h revealed no internal alkyne by-product as a result of isomerisation (Table 6, entry 10). By analysis of table 6, no clear trend in catalyst activity of the heavier alkaline earth metal bis(amides) could be concluded. Previous studies of the intramolecular hydroamination of aminoalkenes with varying electronic and steric properties have demonstrated that in the case of magnesium, calcium and strontium bis(amides), in all cases $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ showed the best activity in comparison to the analogous

magnesium and strontium complexes, while the barium complex showed no catalytic turnover at all.^{12,31,106,107,38}

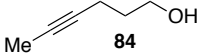
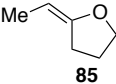
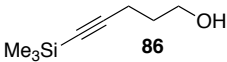
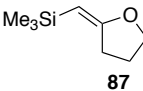
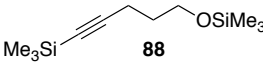
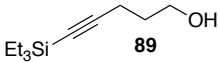
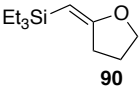
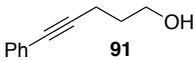
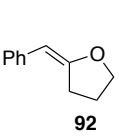
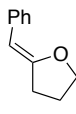
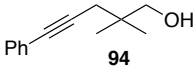
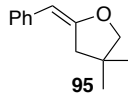
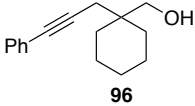
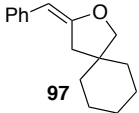
Previously reported barium-catalysed heterofunctionalisation processes have highlighted that the necessary polarisation of C–C unsaturation is prevented by the large size and diffuse nature of the Ba²⁺ centre.^{43,44}

The reaction rate proved to be greatly influenced by the substitution pattern of the alkynyl alcohol substrates. Geminal dialkyl substitution led to a pronounced rate acceleration of more than one order of magnitude in the case of five-membered ring formation. Thus, the transformation **75** → **76** was significantly more facile than **72** → **73** and **74**. This can be attributed to the Thorpe-Ingold effect, central to many intramolecular processes. These substrates benefit from a favourable kinetic effect through which the conformational freedom of the alkynyl alcohol substrate is decreased, favouring reactive conformations during the insertive transition state.¹⁰⁸ Although minor quantities of the dihydrofuran **77** was formed when [Sr{N(SiMe₃)₂}]₂ and [Ba{N(SiMe₃)₂}]₂ were employed (Table 6, entries 5 and 6), complete selectivity to the exocyclic product **76** was achieved by [Ca{N(SiMe₃)₂}]₂. At a lower temperature of 60 °C the calcium species showed the highest reactivity as full conversion of **75** → **76** was achieved after 1.5 h. In contrast, the strontium and barium precatalysts achieved the same conversion in 3.5 and 8.5 h, respectively.

Likewise, arene substitution displayed a marked rate acceleration (**78** → **79** vs **72** → **73** and **74**). The heavier alkaline earth metal bis(amide) precatalysts catalysed the cyclisation efficiently, providing selective conversion to the *exo* product in less than half an hour and even at 60 °C. A combination of electronic factors and the Thorpe-Ingold effect can describe this observed transformation. The electronic effect exerted by the arene group has been proposed to provide some level of stabilisation of the incipient negative charge that is induced in the C≡C/M–O insertion transition state, analogous to that proposed for the key C–N bond-forming step in the intermolecular hydroamination of styrene.^{43,44}

Extension of the substrate scope to internal alkynyl alcohols proved more challenging when precatalysts **75a–c** were studied. In this case, the substituent can be positioned in two orientations giving rise to the *E* or *Z* enol ether product. In all cases except one, the homoleptic heavier alkaline earth amido precatalysts [Ae{N(SiMe₃)₂}]₂ selectively yielded the *E* exocyclic enol ether. The results are outlined in table 7.

Table 7. Intramolecular hydroalkoxylation/cyclisation of internal alkynyl alcohols mediated by 5 mol% [Ca{N(SiMe₃)₂}]₂ **75a**.

Entry	Substrate	Product ^a	Ratio ^b	Time/ h	Temp/ °C	Conversion/ % ^c
1			-	168	120	13
2		  	1:38:61	24	80	82
3			47:53	48	100	4
4		 	56:44	14	90	12
5			-	4	70	99
6			-	4	70	99

(a) Determined by ¹H NMR spectroscopy; (b) Ratio of major exocyclic enol ether product:isomerised product(s) at given time, *t*; (c) Determined by ¹H NMR spectroscopy at given time, *t*.

The cyclisation rates of internal alkynyl alcohols (Table 7) were significantly diminished in comparison to the terminal alkynyl alcohols (Table 6). Elevated reaction temperatures of $> 80\text{ }^{\circ}\text{C}$ were required to achieve conversions comparable to that of the terminal alkynyl alcohols. The relative rates of linear internal alkynyl alcohol conversion as a function of substituent are $-\text{H} > -\text{SiMe}_3 > -\text{Ph} > -\text{Me}$ (Table 6, entry 1 versus Table 7, entries 1–2, entry 4). This is comparable to that observed by lanthanide mediated hydroalkoxylations whereby the fastest reactions were observed for the terminal alkyne 4-pentyn-1-ol (**72**). The cyclisation of the methyl-terminated alcohol **84** only showed emergence of the cyclised product by ^1H NMR in a yield of 13% after 7 days. Increasing the catalyst loading to 10 mol% increased the yield to 19% after a further 7 days at $120\text{ }^{\circ}\text{C}$. The reaction was mediated at $120\text{ }^{\circ}\text{C}$ for three weeks and no further cyclisation occurred. Although the phenyl-terminated alkynyl alcohols (**94** and **96**) benefitted from β -disubstitution, cyclisation of 5-phenylpent-4-yn-1-ol (**91** $\rightarrow$ **92** and **93**) yielded a mixture of products with poor conversion.

Additional to the anticipated (*E*)-2-benzylidenetetrahydrofuran **92**, the *Z*-isomer was also observed during the reaction course. The formation of the (*Z*)-2-benzylidenetetrahydrofuran can be rationalised by a subsequent thermal isomerisation step during the catalytic cycle. The predominant *E* exocyclic ether product supports a reaction mechanism involving insertion of the alkyne into the M–O bond of the intermediate metal alkoxide. Trace amounts of the dihydrofuran could be observed during ^1H NMR monitoring but further conversion of **91** could not be achieved at elevated temperatures and longer reaction times. This high *E*-selectivity can be attributed to the insertive transition state in which the terminal R substituent occupies the less sterically hindered position via a four-centred transition state, in analogy to that proposed for the intramolecular hydroamination of aminoalkenes.^{12,31} The hydroalkoxylation/cyclisation reaction kinetics are governed by a combination of non-bonded repulsions and electronic effects. Due to the greater ease of cyclisation of terminal alkynyl alcohols *versus* internal substrates, it is most likely that these steric demands dictate the rate of catalysis during the initial

cyclisation process and hence the initial stereoselective formation of the *E*-exocyclic enol ether product (Figure 14).

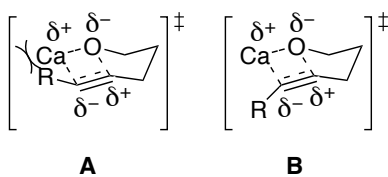
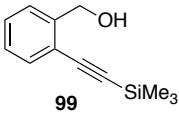
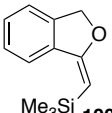
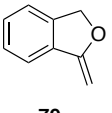
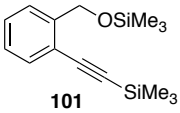
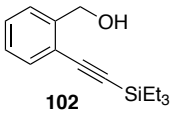
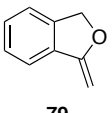
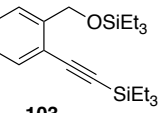
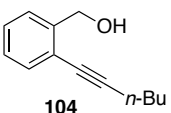
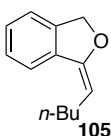
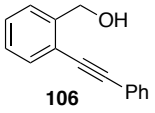
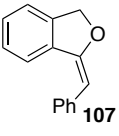


Figure 14. Steric effects encountered during insertive transition state.

A surprising observation was the difficulty of cyclisation of arene substituted internal alkynes (Table 8).

Table 8. Intramolecular hydroalkoxylation/cyclisation of internal alkynyl alcohols mediated by 5 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ **75a**.

Entry	Substrate	Product ^a	Ratio ^b	Time/ h	Temp/ °C	Conversion/ % ^c
1		  	48:47:5	<1	80	100
2		 	42:58	1	80	100
3			-	120	80	15
4			-	120	80	15

(a) Determined by ^1H NMR spectroscopy; (b) Ratio of major exocyclic enol ether product:isomerised product(s) at given time, t ; (c) Determined by ^1H NMR spectroscopy at given time, t .

Although aromatic substitution was found to increase the cyclisation rate of **78**, the same outcome could not be achieved when alkyl and phenyl terminated substrates **104** and **106** were employed. This may reflect configurations in which the arene-functionalised substrates **104** and **106** may experience non-bonded repulsions between the Ca^{2+} centre and the $n\text{-Bu}$ /Ph group, resulting in slower rates. This interplay of steric and electronic factors is rather complex in several cases as demonstrated by the relative ease of cyclisation of Me_3Si -terminated substrates. Likewise, the cyclisation of the aromatic Me_3Si -substituted internal alkynyl alcohol **99** was significantly greater than that observed for the linear alkynyl alcohol derivative **86** (Table 6, entry 2 versus Table 8, entry 1). While this trend may be

justified by the activating effects that the SiMe_3 group exhibits in which the hyperconjugative $\beta\text{-Si-C}$ bond interactions stabilise electrophilic metal centres,^{109,110} it is noteworthy that the ease of cyclisation of the more sterically demanding but electronically similar triethylsilyl substituted substrate **90** was considerably diminished (Table 7, entry 3). In the case of substrates **99** and **102**, the aryl structural backbone can potentially facilitate preorganised structures and electrophilic Ca^{2+} centre-arene π system interactions (Figure 15).

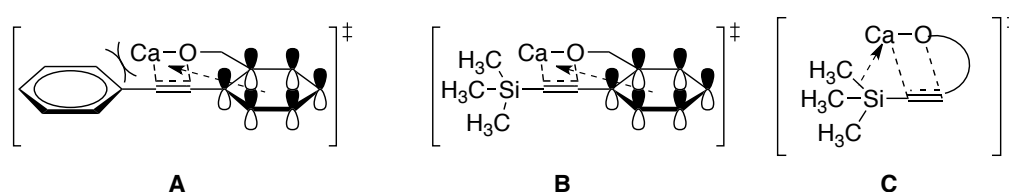
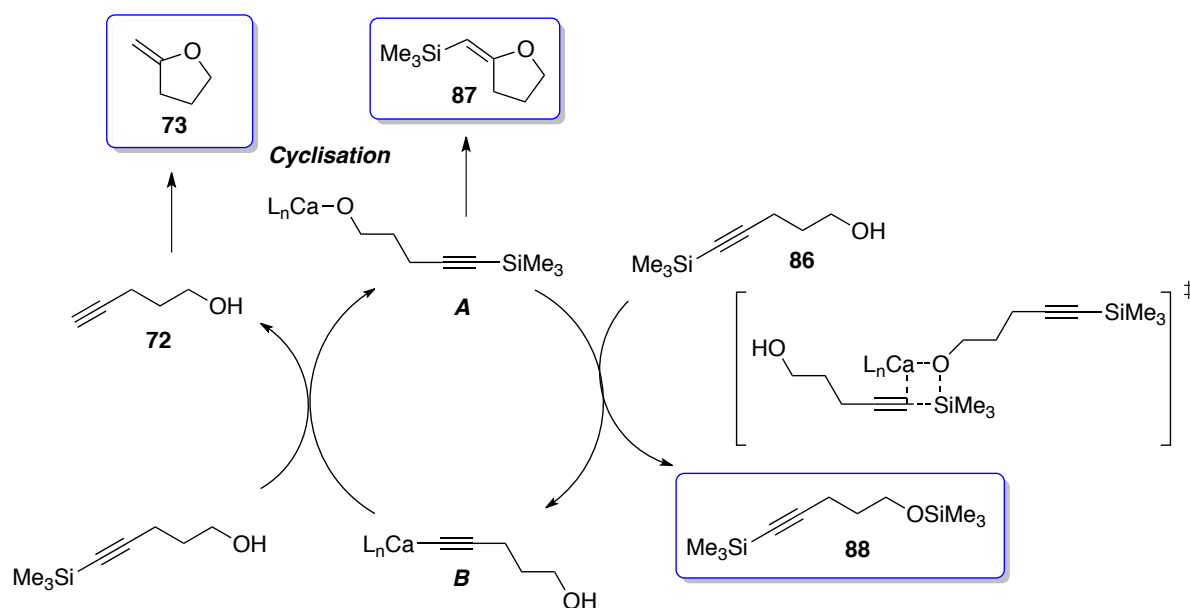


Figure 15. Insertive transition states illustrating electronic and steric effects during cyclisation.

Another instructive observation in the hydroalkoxylation of the Me_3Si -terminated alkynyl alcohols is the variety of reaction products detected in the ^1H NMR spectrum in addition to the accelerated rate (Table 7 entry 2 and Table 8, entry 1). Through ^1H , ^{13}C spectroscopy and MS techniques the reaction was found to consist of a mixture of three products. Unexpectedly, these transformations suffered from Si-C cleavage during the catalytic reaction. Careful monitoring by ^1H NMR spectroscopy during the reaction time did not reveal any formation of the endocyclic enol ether as the characteristic peak for the internal vinylic proton failed to appear. At a given time t , products **87**, **88**, and **89** (Table 7, entry 2) were found to appear simultaneously. In the case of **99** $\rightarrow$ **100**, **79** and **101** (Table 8, entry 1), the expected *E* *exo*-product was produced in the cyclisation in an almost 1:1 ratio to the terminal *exo*-enol ether.

The Me_3Si -terminated alkynyl alcohols are proposed to undergo a process involving cross metathesis (Scheme 26).



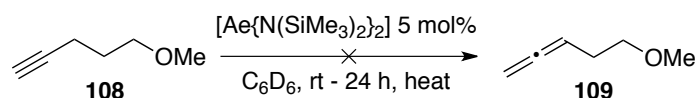
Scheme 26. Proposed catalytic cycle for heavier alkaline earth mediated hydroalkoxylation/cyclisation of Me_3Si -terminated alkynyl alcohol **86**.

In a simple scenario, the catalytic calcium alkoxide species **A** undergoes a $SiMe_3$ group transfer to the alcohol oxygen of substrate **86**, driven by the large Si–O bond enthalpy, generating the silyl ether **88** and complex **B**. Complex **B** can revert to **A** via cross metathesis or be transformed to 4-pentyn-1-ol **72** and hence further generate the catalytically active species, i.e. the calcium alkoxide complex which cyclises to form the *exo*-product **73**. A comparable process has been previously described in lanthanide- and actinide-mediated silylalkyne chemistry.^{99,111,112,113}

Addition of a further 5 mol% to the reaction mixture (Table 7. **86** → **87**, **73** and **88**) followed by heating at 80–120 °C for a further 18 h did not result in isomerisation of **87**.

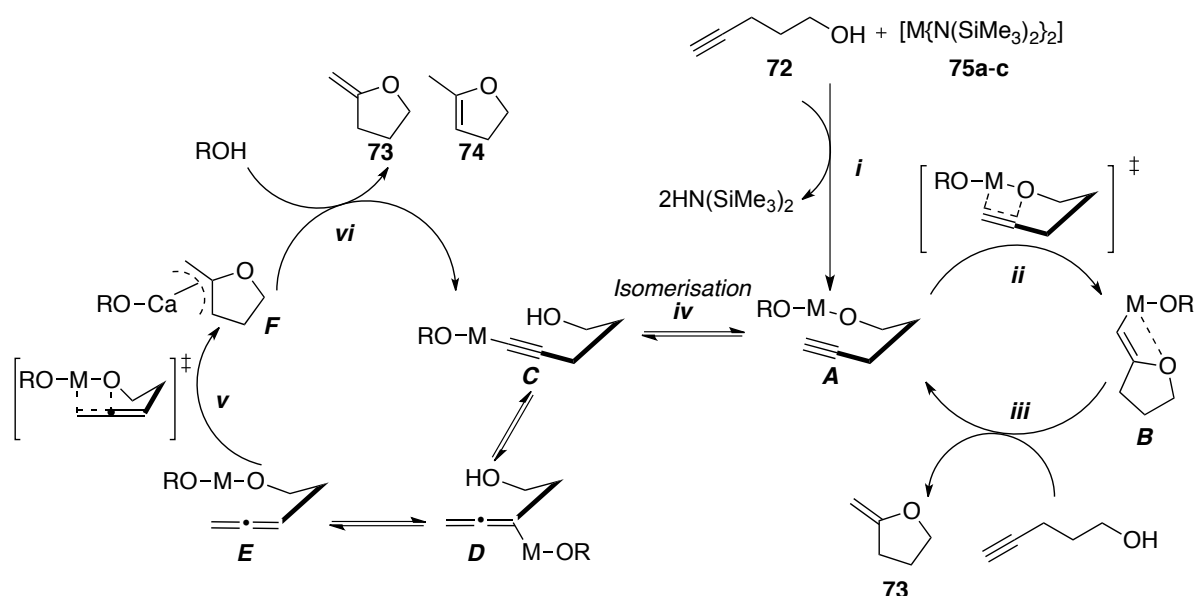
In initial experiments to test the plausibility of the alkyne/allene isomerisation, a non-hydroxylated alkyne such as 1-methoxy-4-pentyne (**108**) was subjected to the same catalytic reaction conditions as used in the cyclisation of 4-pentyn-1-ol **72**. The reaction resulted in the immediate precipitation of a highly insoluble alkynyl metal complex, due to the acidity of the alkynyl proton. Furthermore, when heated at comparable temperatures no isomerisation from the alkyne to the allene could be detected by NMR spectroscopy (Scheme 27). This has frequently been observed

with heavier alkaline earth metal bis(amides), for example, the reaction with $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ and phenylacetylene.⁴⁶ It has also been observed that group 2 complexes catalyse the isomerisation of less activated alkenes such as 1-pentene and 1,3-cyclohexadiene,⁴⁴ as well as the facile isomerisation to the cumulated $\text{C}=\text{C}=\text{C}$ unit of a hexatrienyl moiety as a result of coupling two terminal acetylenes.¹¹⁴



Scheme 27. Attempted alkyne/allene isomerisation with methoxy ether **108**.

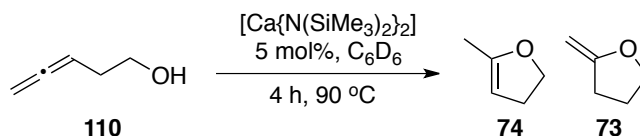
It is thus proposed that under the catalytic reaction conditions, 4-pentyn-1-ol **72** could undergo isomerisation to the allene 3,4-pentadien-1-ol **110**, which would further undergo hydroalkoxylation/cyclisation and account for the formation of the endocyclic enol ether **74**. A proposed reaction mechanism is outlined in Scheme 26 (*vide infra*).



Scheme 28. Proposed mechanism for the hydroalkoxylation of 4-pentyn-1-ol (**72**), mediated by group 2 bis(amides) (**75a-c**).

The reaction mechanism in scheme 28 shows the formation of the two enol ether products, **73** and **74** via the alkyne/allene isomerisation and subsequent cyclisation. The catalyst initiation step *i* yields the catalytically active metal alkoxide and the free amine $\text{HN}(\text{SiMe}_3)_2$, which is visible in the ^1H NMR spectrum at room temperature. The metal alkoxide can directly form the five-membered ether ring via a concerted, most likely rate-determining, insertion of the M–O bond into the triple bond of the alkyne (Scheme 28, step *ii*), followed by protonolysis by another equivalent of 4-pentyn-1-ol to liberate the exocyclic enol ether **73** (step *iii*). The mechanistic steps *i–iii* are analogous to the actinide- and lanthanide-mediated intramolecular hydroalkoxylation and to intra- and intermolecular hydroamination reactions catalysed by group 2 metals.^{99,10,98,113} A second possible scenario would involve the isomerisation of 4-pentyn-1-ol to 3,4-pentadien-1-ol initiated by the formation of a metal alkynyl intermediate (Scheme 28, steps *iv–vi*). The *in situ* formed allene could then undergo cyclisation via a concerted M–O insertion (step *v*) to yield an allyl metal complex **F**. The subsequent protonolysis (step *vi*) could form both the *exo*- and endocyclic enol ethers **73** and **74** respectively.

In order to support this hypothesis, the allenyl alcohol **110** was synthesised and subjected to the reaction conditions with precatalysts **75a–c**. After 4 hours the cyclisation afforded the endocyclic enol ether as the major product and the exocyclic enol ether in a minor quantity.



Scheme 29. Intramolecular hydroalkoxylation of 3,4-pentadien-1-ol (**110**) mediated by Group 2 precatalysts.

The cyclisation of the allenyl alcohol proceeded 6–10 times faster than that of the alkyne analogue. The higher reactivity of the allene in the hydroalkoxylation reaction is unexpected as it has been reported that the intramolecular hydroalkoxylation of **110** catalysed by the lanthanide amide complexes proved to be

almost one order of magnitude slower than that of the alkyne cyclisations.⁹⁹ Furthermore, this also suggests that the rate-determining step may not be that of insertion but indeed the isomerisation of the alkyne to the allene (Scheme 28, step *iv*).

To rule out the possibility that the *exo*-methylene tetrahydrofuran was being isomerised to the 2,3-dihydrofuran by the group 2 bis(amide) catalysts, **73** was synthesised individually and subjected to the catalytic reaction conditions. Taking the exocyclic enol ether **73** and 5 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$, no isomerisation to the endocyclic product **74** could be seen by ^1H NMR spectroscopy when heated at 80–120 °C for 24 h. It has been reported that isomerisation of **73** to **74** occurs under acidic conditions at temperatures above 300 °C.¹¹⁵ Likewise, commercially available 2,3-dihydrofuran **74** did not show any change in the ^1H NMR when subjected to the same catalytic conditions.

During the ^1H NMR monitoring of the allenyl alcohol hydroalkoxylation **110** $\rightarrow$ **73** and **74**, the appearance of a peak analogous to that of the CH_2OH peak of 4-pentyn-1-ol could be observed as a broad multiplet at 3.51 ppm (Figure 16, B and C). A similar isomerisation could be observed for the corresponding hydroalkoxylation mediated by $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ albeit in very low concentration. This alkyne/allene isomerisation was most apparent during the ^1H NMR monitoring of 5-hexyn-1-ol mediated by $[\text{Ba}\{\text{N}(\text{SiMe}_3)_2\}_2]$ as discussed previously (Figure 13). It is apparent that under these catalytic reaction conditions an alkyne/allene isomerisation pathway operates for terminal, non-activated alkynes and hence the interconversion of 4-pentyn-1-ol to 3,4-pentadien-1-ol in the proposed reaction mechanism in scheme 28 is feasible. This explains the formation of the dihydrofuran **74** in the hydroalkoxylation of 4-pentyn-1-ol (Scheme 25), a product not observed during lanthanide hydroalkoxylation. Increasing amounts of the endocyclic enol ether products in the hydroalkoxylation of alkynyl alcohols can be attributed to a greater degree of isomerisation.

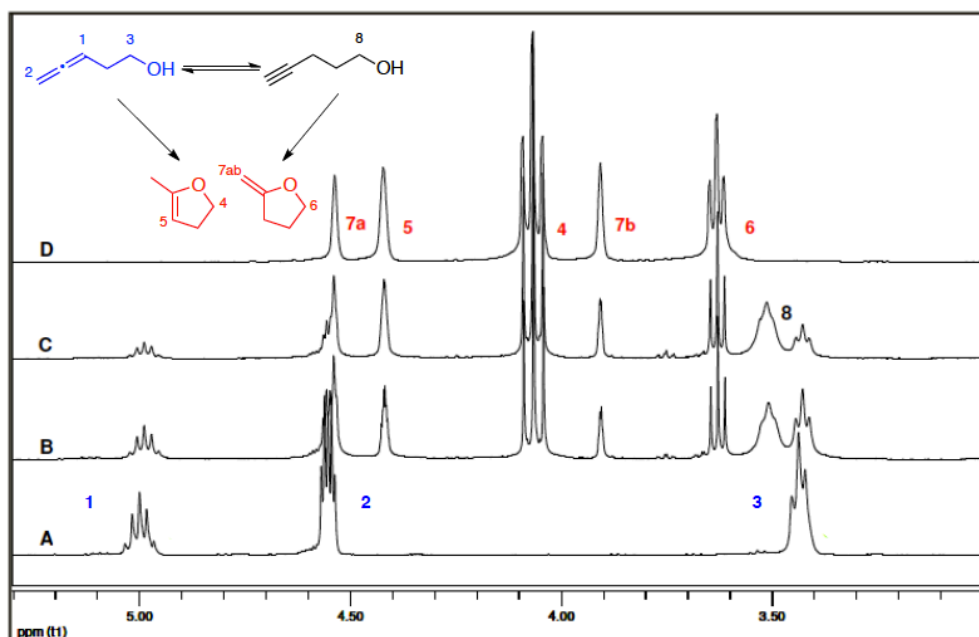
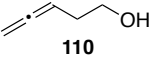
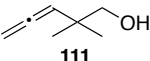
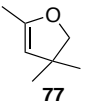
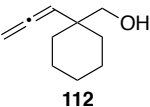
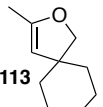
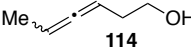
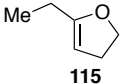
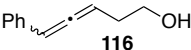
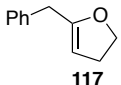


Figure 16. ^1H NMR monitoring of the cyclisation of 3,4-pentadien-1-ol **110** catalyzed by 5 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ **75a** in C_6D_6 at 80°C . A) 3,4-pentadien-1-ol at room temperature, $t = 0$ h; B) $t = 1$ h; C) $t = 2$ h; D) $t = 3$ h.

Given the interesting results displayed by the allene hydroalkoxylation/cyclisation, a small range of allenyl alcohols were synthesised and tested under the same reaction conditions. The results are outlined in table 9.

Table 9. Allenyl alcohol hydroalkoxylation/cyclisation mediated by 5 mol% precatalysts **75a–c** in C_6D_6 .

Entry	Substrate	Product ^a	Catalyst	Time/h	Temp/ $^\circ\text{C}$	Ratio ^b
1			$[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$	3.0	80	59:41
2	 110	 74	$[\text{Sr}\{\text{N}(\text{SiMe}_3)_2\}_2]$	2.5	80	61:39
3		 73	$[\text{Ba}\{\text{N}(\text{SiMe}_3)_2\}_2]$	3.5	80	70:30
4	 111	 77	$[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$	0.5	70	-
5	 112	 113	$[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$	0.5	70	-

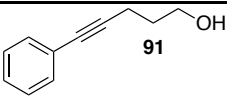
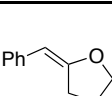
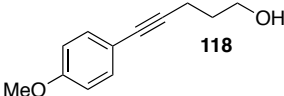
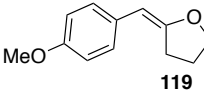
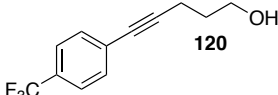
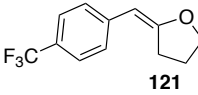
6^c			$[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$	72	110	-
7^c			$[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$	24	100	-

(a) Determined by ^1H NMR spectroscopy, conversion >99%; (b) Ratio of major endocyclic enol ether product:exocyclic enol ether product at given time, t ; (c) Yield less than 8% at given time, t .

Each allene substrate was found to cyclise more rapidly than the corresponding alkyne isomer, giving the endocyclic enol ethers as the major products, opposite to that of the alkynyl alcohols. The reactivity order for the cyclisation of 3,4-pentadien-1-ol **110** followed the same reactivity pattern of $\text{Sr} > \text{Ca} > \text{Ba}$ as that for the hydroalkoxylation of 4-pentyn-1-ol **72**. Likewise, the barium precatalyst **75c** proved to be most selective for the thermodynamically more stable *endo*-product **74** (entry 3). The calcium and strontium bis(amides) yielded the two regioisomers in almost the exact same ratio (Table 9, entries 1–2). This transformation of **110** $\rightarrow$ **74** and **73** yielded the enol ethers in the same ratio, i.e. 61:39.⁹⁸ The β -disubstituted substrates were found to cyclise more rapidly than the corresponding alkynol alcohols (Table 9, entry 4 vs Table 1, entry 4), a rate acceleration again attributed to the Thorpe-Ingold effect. For the internal allenyl alcohols **114** and **116** bearing methyl and phenyl substituents at the terminal allenyl carbon, harsher reaction conditions were necessary to achieve catalyst turnover (Table 9, entries 6–7), commensurate with the corresponding alkynyl alcohol substrates.

The electronic effect of substituents on the aromatic ring in phenyl substituted linear alkynyl alcohols was also examined. A similar study has been performed on *p*-substituted styrene substrates in the intermolecular hydroamination reactions, whereby increasing the electron withdrawing power of the aromatic ring led to a rate enhancement.⁴⁶ Likewise, introducing the electron-rich methoxy group deactivated the aromatic ring and most likely resulted in a higher activation barrier for insertion. As mentioned previously, stabilization of the incipient negative charge on the carbon atom adjacent to the metal centre is necessary to achieve such transformations.^{43,44} Likewise, analogues **118** and **120** were synthesised and reacted with the $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ precatalyst (Table 10).

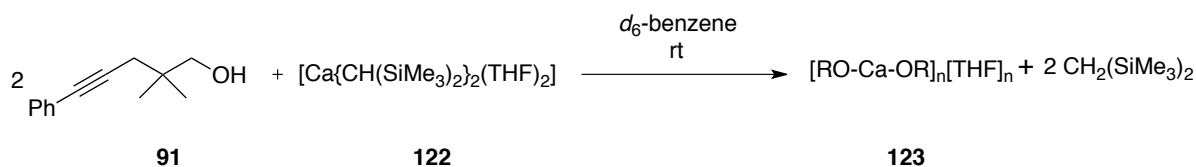
Table 10. Effect of *p*-substitution on the phenyl group in group 2 catalysed hydroalkoxylation.^a

Entry	Substrate	Product ^b	Ratio ^c	Conversion/% ^d
1		 	56:44	12
2			-	<8
3			-	16

(a) Reactions carried out with 5 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ in C_6D_6 , $[\text{substrate}] = 0.35 \text{ M}$ at 90°C ; (b) Determined by ^1H NMR; (c) Ratio of major exocyclic enol ether product:isomerised product at given time, t ; (d) Determined by ^1H NMR spectroscopy at given time, t .

It was evident that by running the reactions side-by-side at 90°C for a period of 24 h, the substrate with the *para*-trifluoromethyl electron withdrawing group, i.e. **120** cyclised more easily than **91** and **118**. Unfortunately, these reactions occurred too slowly to study further. Furthermore, polymerisation side reactions took place due to the formation of an insoluble precipitate after heating at temperatures of $100\text{--}140^\circ\text{C}$. The hydroalkoxylation reaction yields could not be improved further. No thermal isomerisation to the *Z* isomers of **119** and **121** occurred during the reaction course (Table 10, entries 2–3). It can be further concluded that the electronic nature of the aromatic ring during the insertive transition state is also important in determining the ease of cyclisation.

In order to establish the properties and reactivity of the potential alkoxide intermediates, the reactions of calcium alkyl $[\text{Ca}\{\text{CH}(\text{SiMe}_3)_2\}_2(\text{THF})_2]$ **122** with an alkynyl alcohol were investigated (Scheme 30). An initial NMR scale reaction between two equivalents of alkynyl alcohol **91** and $[\text{Ca}\{\text{CH}(\text{SiMe}_3)_2\}_2(\text{THF})_2]$ **122** led to the formation of a colourless solution with no evidence of any precipitation in d_6 -benzene at room temperature. The formation of alkoxide complex **123** was evident by ^1H NMR spectroscopy with the release of alkyl silane $\text{CH}_2(\text{SiMe}_3)_2$.

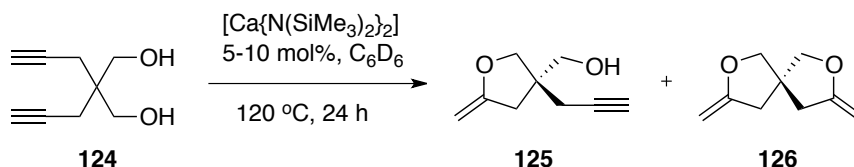


Scheme 30. Stoichiometric reaction between alkynol alcohol **91** and Ca bis(alkyl) precatalyst **122**.

Attempts to isolate complex **123** as a crystalline solid proved extremely difficult. Furthermore, initial attempts at these stoichiometric reactions were also tested with heteroleptic calcium and magnesium β -diketiminate complexes **2b** and **2a**. In this case all reactions led to the protonation of the β -diketiminate ligand with the immediate formation of a highly insoluble and most likely polymeric species in solution. Different stoichiometric ratios of substrate to catalyst were examined and in all cases insoluble polymeric material was recovered along with starting alkynyl alcohol, resulting in extremely broad ^1H NMR spectra.

2.1.2 Attempted Double and Cascade Hydroalkoxylation of Dialkynyl Alcohols

There have been growing efforts to develop catalysts capable of effecting tandem hydroalkoxylation reactions. Substrates bearing a dialkyne dialcohol functionality cyclise to produce useful scaffolds with a variety of applications in natural and pharmaceutical product synthesis.¹¹⁶ Such transformations have been achieved with organolanthanide complexes.¹¹² Hence, to test the plausibility of such sequences and compare the catalytic activity and selectivity, the following substrate was synthesised and subjected to the catalytic reaction conditions.



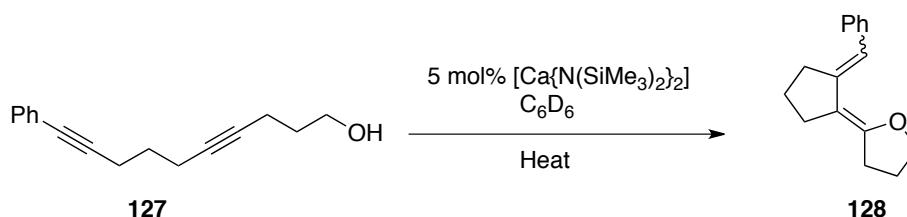
Scheme 31. Dialkynyl diol hydroalkoxylation/cyclisation mediated by $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$.

The intramolecular hydroalkoxylation/cyclisation of the terminal dialkynyl dialcohol substrate **124** proceeded at 120°C to give a conversion of 69% to the substituted 2-methylenetetrahydrofuran **125** after 24 h, with trace amounts of spirofuran heterocycle **126** visible by ^1H NMR spectroscopy. In the present study, substrate **124** first underwent cyclisation to give the monocyclised intermediate **125** which in turn was predicted to subsequently cyclise to give spirofuran **126**. At the conclusion of turnover, full conversion to the bicyclic product **126** could not be achieved under the reaction conditions and a yield more than 5% could not be obtained when harsher reaction conditions were employed. In all cases, a mixture of the mono- and trace amounts of bicycled product were synthesised. The opposite effect was obtained in lanthanide catalysed systems whereby substrate **124** was quantitatively cyclised by 5 mol% $[\text{La}\{\text{N}(\text{SiMe}_3)_2\}_3]$ to produce **126** after 12 h at 120°C .¹¹² Moreover, no isomerisation to the endocyclic spirofuran was observed by both processes, unlike that observed in the hydroalkoxylation of 4-pentyn-1-ol.¹¹⁷ Due to the difficulty of double cyclisation of doubly functionalised substrate **124**, this process was not studied further.

Reactions involving dialkynyl monoalcohol substrates whereby an intramolecular hydroalkoxylation/cyclisation is achieved followed by a subsequent insertion to make a new C–C bond has not been reported in the literature so far. Such compounds would undergo an intramolecular hydroalkoxylation/cyclisation involving insertion of the internal alkyne into the M–O bond to produce the exocyclic enol ether, followed by a second intramolecular cyclisation involving insertion of the distant alkyne into the metal alkenyl species to produce highly reactive enol ethers of the structure **128**.

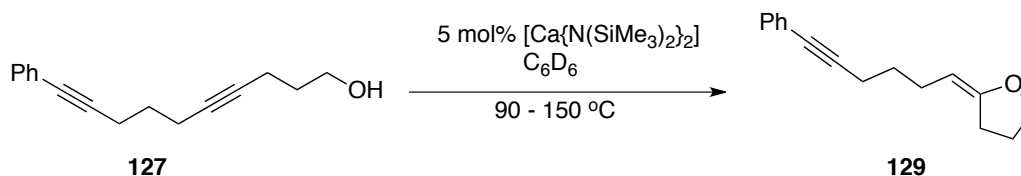
To date, this type of heterofunctionalisation process whereby a new carbon–heteroatom bond is formed followed by intramolecular C–C bond formation, has only been achieved in this sense by Marks and Molander in the cascade cyclisations of dialkenyl amines catalysed by lanthanide tris(amides).^{18,118,119}

To envisage a plausible catalytic cyclisation involving these steps, the initial substrate **127** was developed and contacted with the heavier alkaline earth bis(amides).



Scheme 32. Double cyclisation envisaged that could occur with substrate **127**.

However, when dialkynyl alcohol **127** was reacted with 5 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ in d_6 -benzene at 90 °C, monocyclised enol ether **129** was the only product in the catalytic reaction (Scheme 33).



Scheme 33. Cyclisation of **127** to afford exocyclic enol ether **129**.

Cyclisation proceeded at 90 °C and elevated temperatures of up to 150 °C were required to drive product formation. Like the cyclisation of alkyl terminated alkynyl alcohols,¹¹⁷ the rate of reaction was severely diminished. Therefore, taking into account the activating effects exerted by geminal disubstituted and aromatic substituted substrates in the hydroalkoxylation/cyclisation of alkynyl alcohols mediated by heavier alkaline earth metal bis(amides), substrates bearing these functionalities were synthesised and subjected to the reaction conditions to test the double cyclisation. The preliminary results are summarised in table 11.

Table 11. Attempted double hydroalkoxylation of dialkynyl alcohol substrates.^a

Entry	Substrate	Product	Time/h	Conversion/% ^b	Ratio ^c
1			45	15 (120 °C)	100:0
2	127	129 + Z Isomer 130	72 ^d	31 (150 °C)	50:1
3			24	22 (110 °C)	100:0
4		132	48	62 (130 °C)	33:1
5	131	132 + Z Isomer 133	48	99 (150 °C)	33:1
6			2	30 (150 °C)	-
7	134	135	44	86 (150 °C)	-

(a) Reactions carried out with 5 mol% [Ca{N(SiMe₃)₂}₂] in C₆D₆, [substrate] = 0.35 M; (b) Determined by ¹H NMR spectroscopy; (c) Ratio of major *E* enol ether:isomerised *Z* enol ether at given time, *t*; (d) 10 mol% catalyst used.

Substrates that were activated by the Thorpe-Ingold effect (Table 11 entries 3–5), cyclised under the reaction conditions in almost quantitative yield, accompanied by the formation of the *Z* isomer **133** in a minor yield (Figure 17). The product distribution of the reaction proved highly temperature dependent as no *Z* isomer was present at lower temperatures (entry 3). At forcing temperatures above 120 °C, the minor *Z* isomer appeared in a 3% yield and a ratio of *E*:*Z* products of 33:1 remained constant throughout the reaction progress. The reaction products remained stable up to temperatures of 165 °C.

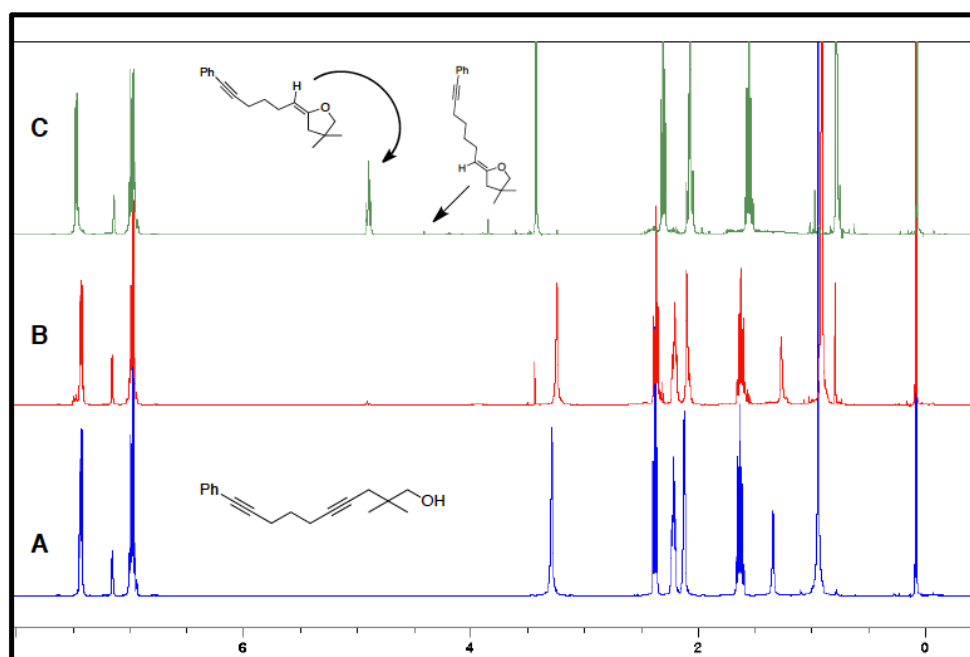
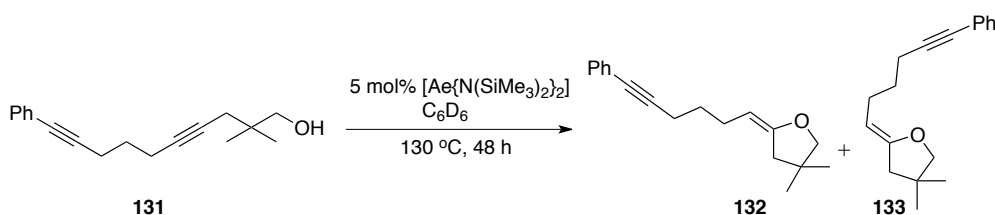


Figure 17. ^1H NMR monitoring of the cyclisation of **131** mediated by 5 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ at 150 °C. A) RT, $t = 0$ h; B) $t = 5$ h; C) $t = 48$ h.

Further heating of non-activated substrate **127** at 150 °C for a number of days did not increase the yield beyond 40%. Interestingly, the conversion of alkyl functionalised internal alkyne **127** $\rightarrow$ **129** was greater than that observed in the hydroalkoxylation of the methyl and phenyl terminated alkynyl alcohols (Table 7, entries 1 and 4) and likewise, the conversion of the aromatic substituted dialkynyl alcohol **134** $\rightarrow$ **135** proceeded to 86% conversion after 44 h at 150 °C. When more forcing conditions were employed for the conversions of the *n*-butyl and phenyl terminated aromatic alkynyl alcohols **104** and **106**, i.e. increased catalyst loading to 10 mol% and elevated temperatures up to 150 °C, comparable conversions could not be achieved. These substrates may have more accessible, pre-organised structures than the linear and aromatic internal alkynyl alcohols (Tables 7 and 8 versus Table 11). This suggests that the ease of cyclisation is not completely dominated by steric factors, but rather reflects an interplay of preorganisational advantages provided by a rigid backbone during the insertive, rate-limiting transition state.

Another instructive observation was the complex mixture of reaction products detected when the cyclisation of **131** was performed with $[\text{Sr}\{\text{N}(\text{SiMe}_3)_2\}_2]$ and $[\text{Ba}\{\text{N}(\text{SiMe}_3)_2\}_2]$. This included both monocyclised *E* and *Z* exocyclic enol ethers **132** and **133** in varying ratios in contrast to that observed by $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ (Table 12).

Table 12. Effect of metal ion on hydroalkoxylation/cyclisation of dialkynyl alcohol **131**.

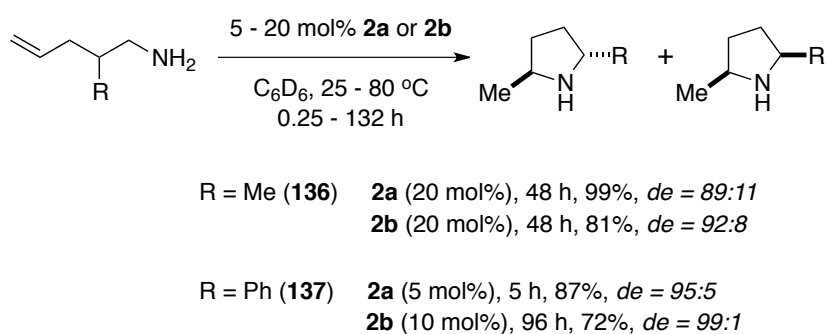


Entry	Catalyst	<i>E/Z</i> Product Ratio ^a	Conversion/% ^b
1	$[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$	33:1	62
2	$[\text{Sr}\{\text{N}(\text{SiMe}_3)_2\}_2]$	9:1	24
3	$[\text{Ba}\{\text{N}(\text{SiMe}_3)_2\}_2]$	4:1	22

(a) Determined by ^1H NMR spectroscopy; (b) Determined by ^1H NMR using $\text{Si}(\text{SiMe}_3)_4$ as an internal standard.

Increasing the size of the heavier alkaline earth metal cation did not result in an increased yield or better selectivity for the major *E* product. In contrast, the opposite trend was observed in the mono-cyclisation of 4-pentyn-1-ol (**72**) and previously studied alkynyl alcohols (Table 6 and Table 9). Catalyst structural effects are also operative in the present cyclisation whereby the size of the larger Ba^{2+} cation may be consistent with a more open and less ordered transition state, resulting in the formation of multiple by-products and isomers (Figure 18). Consequently, the yield is affected by the change in size of the metal centre with increasing amounts of the *Z* enol ether product **133** forming as the size of the metal cation increases. In accordance with the hydroalkoxylation/cyclisation of alkynyl alcohols, the reaction produces the *E* exocyclic enol ether **132** as the initial and major product in these reactions, reflecting steric impact during the insertion step. The formation of the *Z* isomer can be attributed to an isomerisation pathway, induced by increasing the temperature of the reaction vessel and also by employing the larger Sr^{2+} and Ba^{2+}

complexes. The improved selectivity in the case of the Ca catalyst may be attributed to the shorter M–O and M–C bond lengths relative to the strontium- and barium-containing complexes. This would therefore lead to a tightening of the transition state of the insertion reaction thereby preventing the formation of isomerised product mixtures (note that the *Z* isomer (**133**) was only visible at temperatures above 120 °C (Table 11, entries 4–5)). A comparable effect of cation size has previously been studied in group 2 hydroamination chemistry in the cyclisation of α -substituted aminoalkenes.³¹ In this case, improved diastereoselectivities were observed when the smaller Mg^{2+} cation was employed (Scheme 34).



Scheme 34. Diastereoselectivity in the intramolecular hydroamination of pro-chiral aminoalkenes catalysed by complexes **2a** and **2b**.

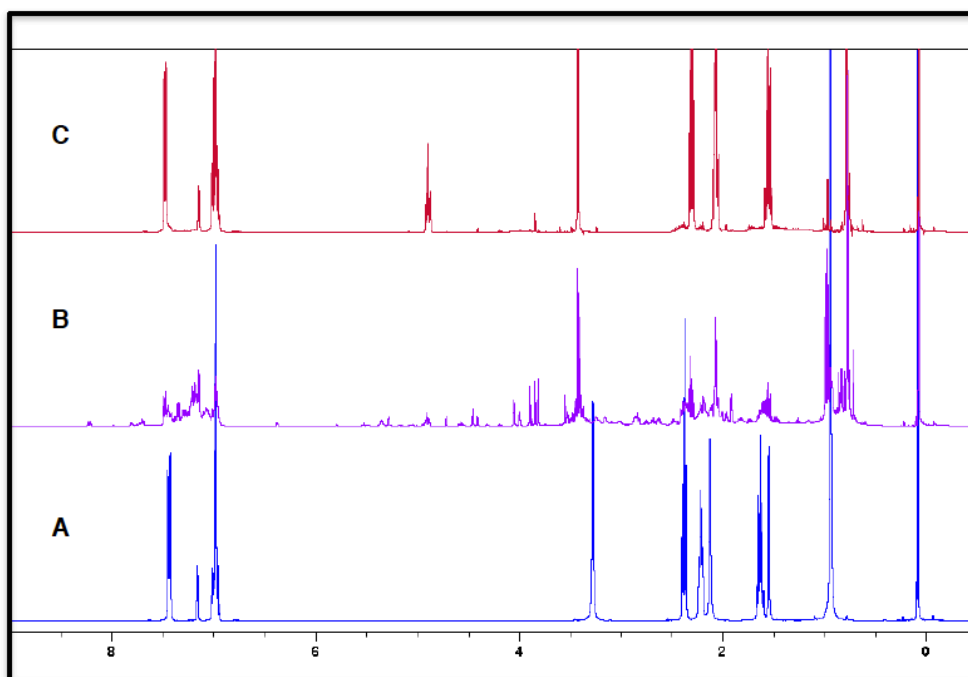
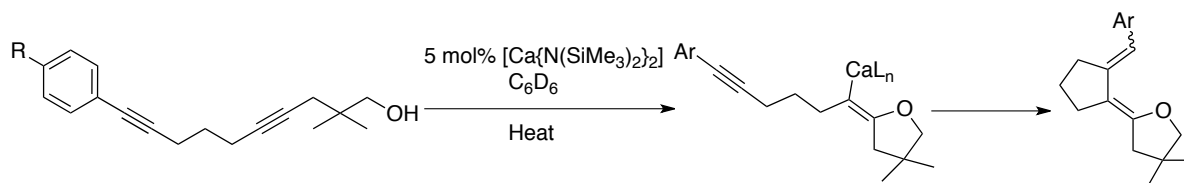


Figure 18. ^1H NMR spectra illustrating the different reaction product mixture for **131** $\longrightarrow$ **132** employing 5 mol% $[\text{Ba}\{\text{N}(\text{SiMe}_3)_2\}_2]$ versus $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$. A) **131** at RT, $t = 0$ h; B) 5 mol% $[\text{Ba}\{\text{N}(\text{SiMe}_3)_2\}_2]$, 150 $^\circ\text{C}$, $t = 48$ h; C) 5 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$, 150 $^\circ\text{C}$, $t = 48$ h

This envisioned tandem intramolecular hydroalkoxylation/cyclisation of the dialkynyl alcohols could, in principle, produce a number of distinct regioisomers resulting from mono- and double cyclisations, i.e. a mixture of *exo*- and *endo*-products. During the monitoring of the hydroalkoxylation/cyclisation of dialkynyl substrates **127**, **131** and **134**, no formation of the endocyclic enol ether could be observed. This further supports the alkyne/allene isomerisation pathway shown in scheme 28 and is in good agreement with steric impediments experienced during the insertive step of the mechanistic pathway.

Prompted by these preliminary results, functionalisation of the aromatic ring on the alkyne terminus of more unsaturated substrates was explored. Only electron withdrawing groups in the *para* position of the phenyl ring were included as previous studies indicated a significant rate enhancement when these substrates were examined. The idea was to achieve the second intramolecular ring closure and subsequent C–C bond formation more readily. Additionally, only the *gem*-dimethyl

substituents were synthesised as the reaction only proceeds to completion with such activating effects. A reaction scheme is shown in scheme 35 below.

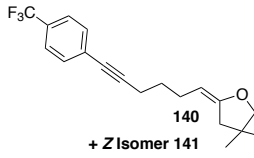
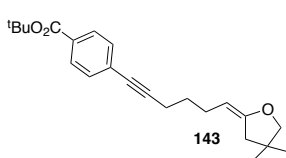


Scheme 35. Attempted tandem C–O and C–C bond formation with $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$.

Each of the substrates investigated comprised aromatic substituents of varying electron withdrawing strengths and are presented in table 13. A minimum temperature of 80 °C was essential for catalytic turnover and forcing conditions of up to 150 °C were necessary in order for the reactions to approach completion.

As shown in table 13, the undesired mono-cyclisation occurred in all cases with 100% *exo*-selectivity.

Table 13. Attempted double cyclisation with different electron withdrawing R groups *para* in the aromatic ring.

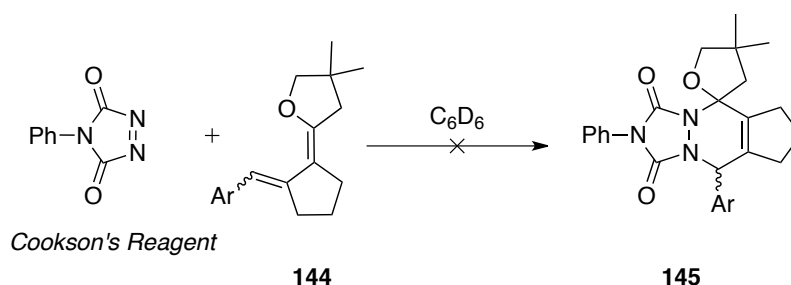
Entry	R	Catalyst (loading)	Time/h (Temp/°C)	Product ^a	Ratio ^c
1	NO ₂	[Ca{N(SiMe ₃) ₂ } ₂] (5 mol%)	48 (80-120)	Unidentified ^b	-
2	(138)	[Sr{N(SiMe ₃) ₂ } ₂] (5 mol%)	48 (80-120)	Unidentified ^b	-
3	CF ₃	[Ca{N(SiMe ₃) ₂ } ₂] (5 mol%)	72 (130)	 + Z Isomer 141	1.4:1
4 ^d	(139)	[Sr{N(SiMe ₃) ₂ } ₂] (5 mol%)	72 (90)		100:0
5 ^d		[Ba{N(SiMe ₃) ₂ } ₂] (5 mol%)	72 (90)		100:0
6		[Ca{CH ₂ (SiMe ₃) ₂ } ₂][THF] ₂ (100%)	24 (100)		100:0
7	CO ₂ ^t Bu (142)	[Ca{N(SiMe ₃) ₂ } ₂] (5 mol%)	48 (100)	 143	-

(a) Determined by ¹H NMR spectroscopy; (b) Immediate precipitation occurred at rt. The dark brown precipitate could not be characterised further and the solution gave rise to an unidentifiable product mixture that was not cyclic; (c) Ratio of major *E* exocyclic enol ether:Z isomer, determined by ¹H NMR at given time, *t*; (d) Mixture of inseparable, isomerised by-products formed during the catalysis.

The reactions were found to proceed to > 25% completion (Table 13, entries 3–6) at 150 °C after 4 days. At temperatures below 100 °C for transformation **139** → **140** the reaction affords exclusively the *E* *exo*-enol ether **140**. In analogy to table 11, higher temperatures (> 100 °C) resulted in a mixture of *E*:*Z* isomers, with their ratios remaining constant throughout the reaction progress. Using stoichiometric amounts resulted in only product **140** at 100 °C. In this case, no evidence of a double cyclisation was visible by ¹H NMR spectroscopy. Interestingly, when substrate **139** bearing R = CF₃ was subjected to 5 mol% [Ca{N(SiMe₃)₂}₂] precatalyst, not only does the mono-cyclised product appear in a roughly 1:1 *E*:*Z* ratio at 130 °C (Table 13, entry 3) but a distinctive singlet peak at 6.15 ppm appeared in the ¹H NMR spectrum of **140**.

Further monitoring of the ¹H NMR spectrum of **140** (Table 13, entry 3) revealed multiple peaks, one of which would be expected to correspond to the expected new

alkenyl proton, resulting from the second cyclisation, i.e. 6–6.5 ppm. This peak integrated for one proton as a singlet at 6.15 ppm, which also corresponded with other cyclic proton peaks further upfield. However, the product that gave rise to these peaks formed in a yield too low to be identified unambiguously and for its structure to be determined conclusively by ^{13}C NMR and 2D NMR experiments. Confirmation of a double cyclisation occurring is inconclusive at this stage. Furthermore, this suspected highly reactive enol ether was subjected in the same pot to Cookson's reagent, in order to attempt a Diels-Alder reaction and isolate any products, which could verify the formation of this doubly cyclised compound (Scheme 36).¹²⁰



Scheme 36. Attempted Diels-Alder cyclisation to confirm double cyclisation of dialkynyl alcohol substrate **139**.

Unfortunately, this led to a complex mixture of products, none of which could be characterised. Employing the Sr and Ba bis(amide) precatalysts **75b–c** for the same transformation **139** $\rightarrow$ **140** enabled catalytic turnover to be achieved more readily at lower temperatures in comparison to the Ca bis(amide) complex. These precatalysts indeed gave rise to a mixture of *E* and *Z* isomers, which the Ca bis(amide) precatalyst did not give. When elevated temperatures were examined, the reaction gave a complex product mixture with poor yields of the *exo*-enol ethers (< 10%). Where catalysis was effected with the strontium and barium bis(amides) (Table 13, entries 4–5), this singlet peak at 6.15 ppm resembling the *exo*-vinyl proton of a double cyclisation did not appear in either case.

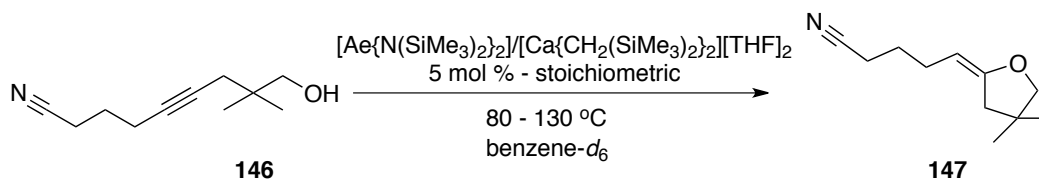
The results shown in entry 1 (Table 13) where R = NO₂ provide a unique case in which the reaction does not afford any cyclic products resembling the enol ethers

obtained so far. Several unidentified side products were detectable by ^1H NMR spectroscopy. Upon addition of 5 mol% of the precatalyst to a C_6D_6 solution of the substrate at room temperature the reaction mixture immediately turned bright red with the majority of the reaction components falling out of solution as a dark brown precipitate. Attempts to solubilise this precipitate failed with all organic solvents and by heating, as did attempted solubilisation with acetic acid, which resulted in decomposition of the reaction mixture at room temperature. Further attempts to obtain a crystal structure were also unsuccessful, mainly due to solubility issues. It is suggested that the calcium bis(amide) precatalyst coordinates very strongly to the powerful electron withdrawing NO_2 group, most likely through the oxygen atom(s) resulting in the observed insolubility. Therefore, the NO_2 group was replaced with CF_3 of comparable electron withdrawing strength and further studies continued with this substrate. This observation is not unique to these types of substrates with heavier alkaline earth precatalysts, but is consistent with processes identified for heavier alkaline earth catalysis whereby the NO_2 group proved problematic in other substrates such as aromatic amines during hydroamination studies.^{46,121}

The reaction utilising the *para-tert* butyl ester aryl substrate **142** (Table 13, entry 7) afforded likewise, the undesired monocyclised exocyclic enol ether at 100 °C. Less than 20% of the enol ether **143** formed and the product yield could not be improved to a desirable quantity at higher temperatures. No evidence of a double cyclisation was detectable in the ^1H NMR spectra for this substrate.

Previous successful amine functionalisation has been achieved using β -diketiminato-stabilised calcium amide complexes with carbodiimides.¹²² These observations highlighted the possibility that the phenyl-terminated alkyne could be replaced with a nitrile functional group. This could, in principle, effect the insertion of the more polarised $\text{C}\equiv\text{N}$ into the $\text{M}-\text{C}$ bond due to the electronegative nitrogen atom and hence a more feasible insertion may occur. However, when substrate **146** was subjected to the catalytic reaction conditions used for the dialkynyl alcohol substrates (Table 11 and Table 13), the envisaged tandem $\text{C}-\text{O}/\text{C}-\text{C}$ bond formation was not observed. In this case, the monocyclisation occurred to give

product **147** in 29% yield after 48 h at 130 °C. This reaction was additionally, accompanied by isomerised and multiple by-products.



Scheme 37. Monocyclisation of 9-hydroxy-8,8-dimethylnon-5-ynenitrile (**146**) with heavier alkaline earth metal precatalysts **75a–c**, **122**.

Although a yellow precipitate formed upon mixing stoichiometric amounts of the precatalyst $[Ca\{CH_2(SiMe_3)_2\}_2(THF)_2]$ (**122**) with substrate **146** at room temperature, *in situ* 1H NMR spectroscopy indicated that the hydroalkoxylation reaction ensued, and that the reaction did not proceed to insert again after the initial cyclisation. A second insertive transition state could be visualised to proceed as depicted in Figure 19 below.

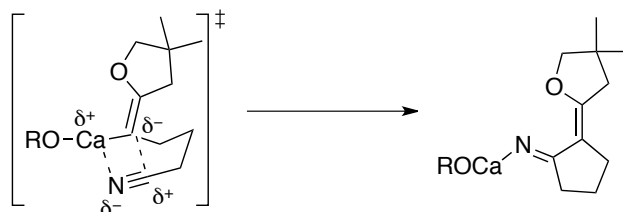
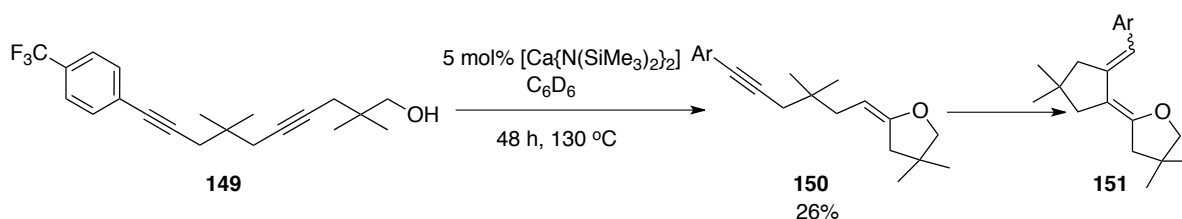


Figure 19. Proposed insertive transition state for a second cyclisation to occur.

The outcome of this reaction is likely to produce an imine species that would undergo subsequent protonolysis by the alcohol substrate and lead to the desired bicyclic imine product. The 1H NMR spectrum for this reaction showed indicative signs of the imine formation due to peaks observed between 9–10 ppm (and possible isomerised enamine product). In the same manner as the previously suspected double cyclisation of substrate **139**, the compounds detected were present in very limited amounts to be further studied. This reaction did indeed give rise to multiple product formation, confirmed by TLC analysis. Attempts to isolate

these compounds via column chromatography were also unsuccessful. Only product **147** was likewise quantifiable by NMR spectroscopy. In accordance with the previously studied dialkynyl alcohol substrates (Table 11 and Table 13), the *E* isomer was the sole product at temperatures of 90–100 °C and the formation of the *Z* exocyclic enol ether (**148**) took place at higher temperatures. This consisted of a 10:1 mixture of the *E*:*Z* isomers being formed, mediated by 5 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ at 130 °C. This ratio remained unchanged over a period of 7 days.

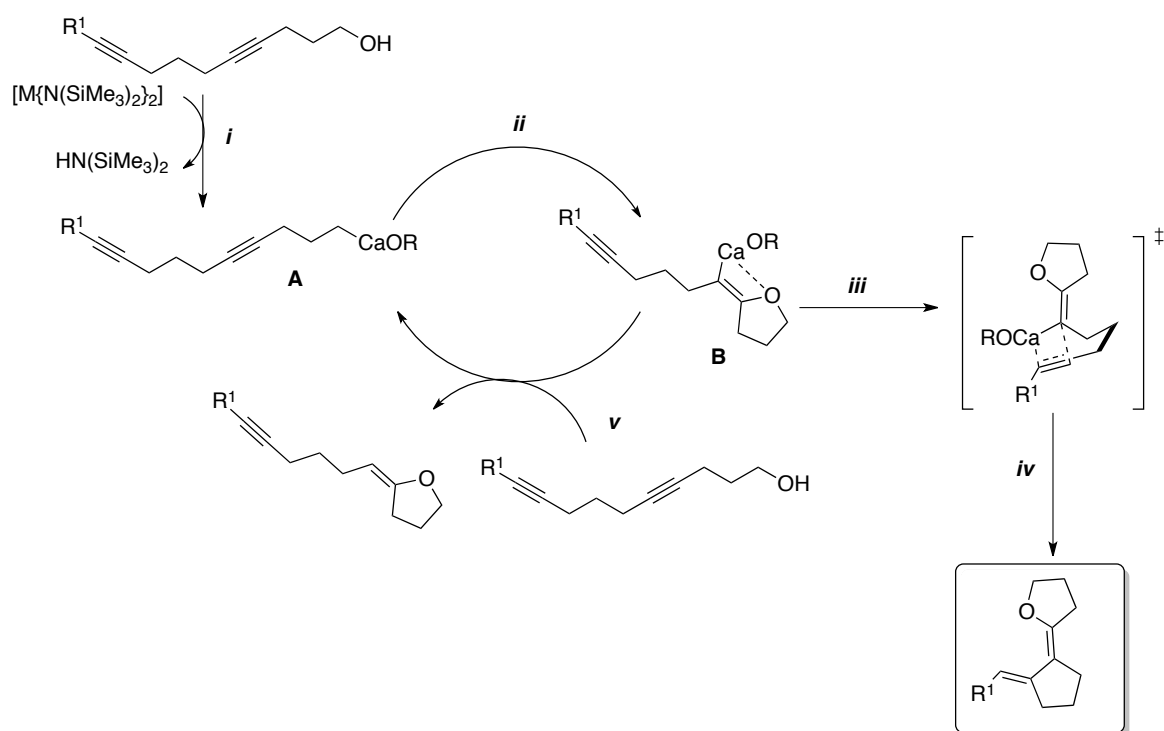
New efforts to induce the second insertion (Scheme 39, step *iii*) took further advantage of the Thorpe-Ingold effect, through the synthesis of a substrate with a second *gem*-dimethyl group on the distant alkynyl chain. This would, in principle, provide simultaneous kinetic activation of the substrate and at the same time permit the second insertion reaction by allowing more favourable, pre-organised conformations than the substrates previously studied. Thus substrate **149** (Scheme 38) was tested against the reaction conditions.



Scheme 38. Attempted cascade cyclisation of dialkynyl alcohol **149** with two *gem*-dimethyl groups.

Substrate **149** cyclised to give monocyclic product **150** and the resultant ^1H NMR spectrum did indeed reveal the appearance of the same singlet peak at around 6.2 ppm, expected to arise from the double cyclisation, along with the presence of multiple singlet peaks further upfield. A 26% conversion to the anticipated monocyclised product **150** was achieved after 48 h at 130 °C and the yield could not be improved further under a variety of forcing conditions including variation in the substrate concentration. Using 20 mol% to stoichiometric catalyst loadings did not show an increase in resonances attributed to the suspected double cyclisation.

The double cyclisation reaction could be envisaged to proceed by the following reaction mechanism proposed in Scheme 39 below.

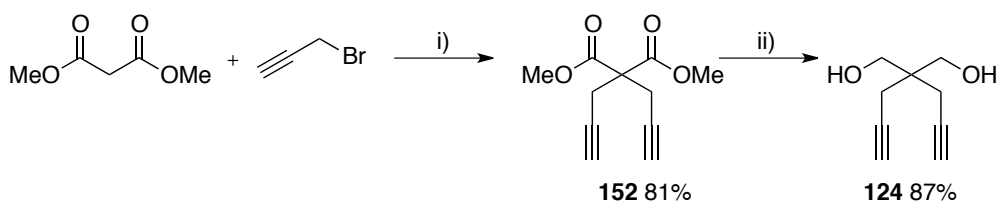


Scheme 39. Proposed catalytic cycle for the formation of the bicyclic enol ether product mediated by heavier alkaline earth metal bis(amides).

The present mono-cyclised products follow the same mechanistic pathway (Scheme 28, steps *i–iii*) as that for the previously studied alkynyl alcohols and reported lanthanide hydroalkoxylation/cyclisation reactions,^{98,99,117} by which the key steps involve protonolysis (Step *i*) to make the calcium alkoxide catalyst (**A**), rate-limiting insertion of the alkyne into the calcium alkoxide bond (Step *ii*) to produce a vinyl calcium intermediate (**B**) followed by fast protonolysis to afford the cyclised enol ether (step *v*). However, it is apparent from the results in tables 11 and 13 that the protonolysis of the alkenyl calcium species **B** occurs at a much faster rate than a possible second cyclisation/insertion (step *iii*) and hence quenching of the alkenyl calcium intermediate **B** was unavoidable. Consequently, monocyclisation predominated in all cases. In the study of *gem*-dimethyl substituted substrates bearing the CF_3 electron withdrawing arene group, trace amounts of the suspected tandem cyclisation may have occurred.

2.1.3 Substrate Synthesis

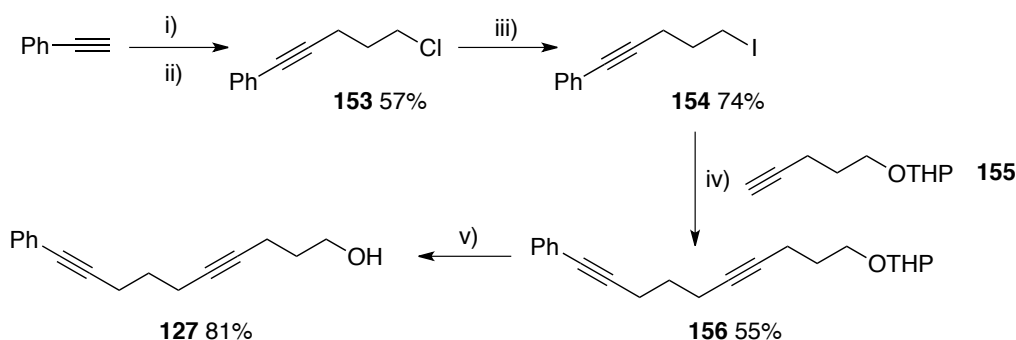
To explore the effects of the new dialkynyl dialcohol and dialkynyl alcohol substrates on the proposed group 2 mediated tandem C–O and C–O/C–C bond forming reactivity, a variety of new compounds were synthesised and characterised. Compound **124** was synthesised through adaptation of published procedures, as outlined in Scheme 40.



Scheme 40. Synthesis of dialkynyl dialcohol substrate **124**. i) NaOEt, EtOH, RT, 12 h; ii) LiAlH₄, Et₂O, 0 °C – RT, 3 h.

Addition of propargyl bromide to commercially available dimethyl malonate, followed by reduction using LiAlH₄ afforded substrate **124** in good yield.

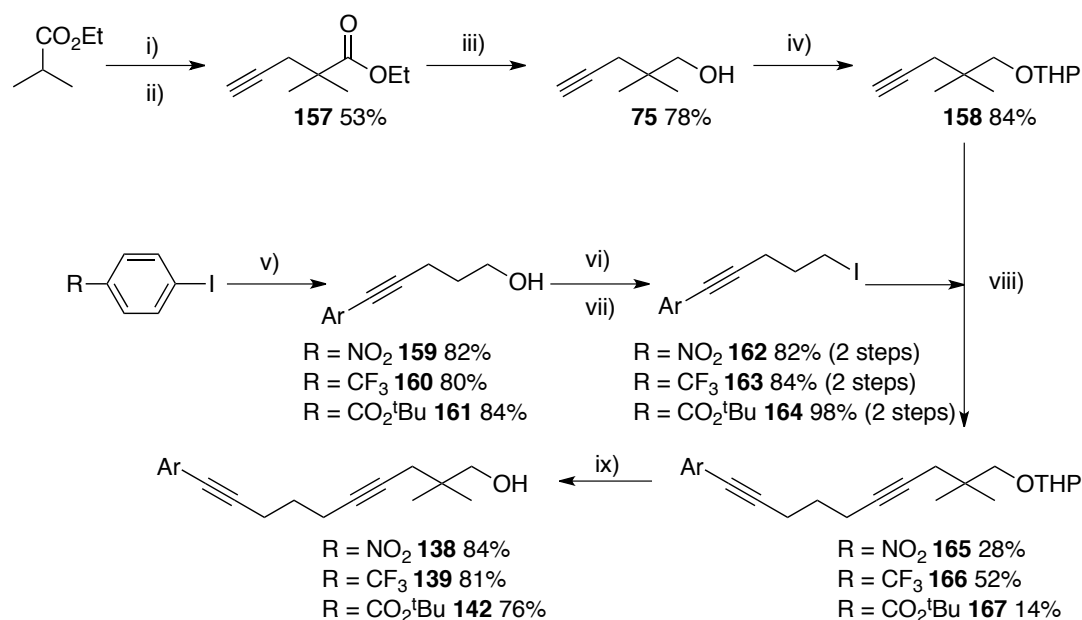
A synthetic scheme for dialkynyl alcohol **127** is shown below.



Scheme 41. Synthesis of dialkynyl alcohol **127**. i) *n*-BuLi, THF, –78 °C, 10 min; ii) 1-Bromo-3-chloropropane, –78 °C then RT, 1 h then reflux, 12 h; iii) NaI, Me₂CO, 60 °C, 15 h; iv) **155**, *n*-BuLi, THF, –78 °C, 10 min then **154**, –78 °C, 1 h then RT, 14 h; v) PTSA, MeOH, reflux, 2 h.

Thus, substrates **156** and **127** were synthesised via alkylation of phenylacetylene using *n*-BuLi and 1-bromo-3-chloropropane, followed by conversion of the alkyl chloride to the corresponding iodide **154**. This substrate was then coupled with the THP protected 4-pentyn-1-ol **155** by a second alkylation via the lithium alkynyl species of **155** to afford the protected dialkyne **156**. Deprotection of the acetal functionality using PTSA in refluxing methanol afforded the alcohol **127** in good yield.

Gem-dimethyl substituted substrates **138**, **139** and **142** were obtained according to Scheme 42 below.

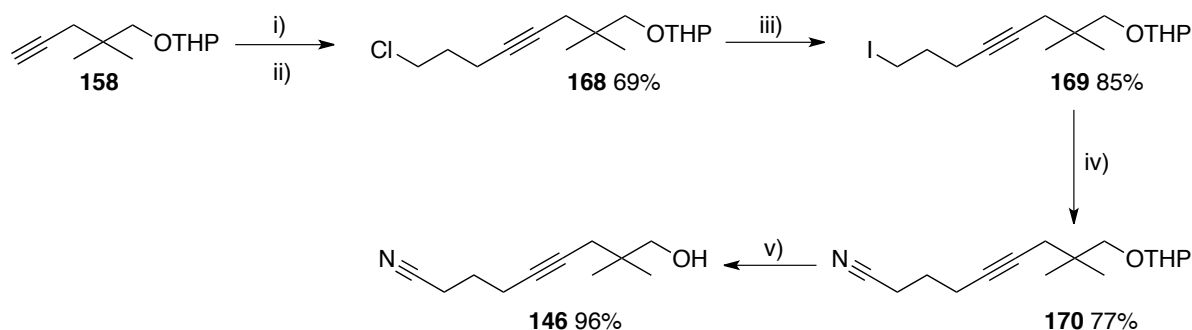


Scheme 42. Synthesis of substrates **138**, **139**, **142**. i) LDA, THF, $-78 - 0$ °C; ii) Propargyl bromide, -78 °C – RT, 14 h; iii) LiAlH₄, Et₂O, 0 °C, 1 h; iv) 3,4-Dihydro-2*H*-pyran, PTSA, CH₂Cl₂, RT, 12 h; v) 4-pentyn-1-ol, ArI, Pd(PPh₃)₂Cl₂, CuI, NEt₃, 0 °C – RT, 14 h; vi) NEt₃, MsCl, THF, 0 °C – RT, 12 h; vii) NaI, Me₂CO, reflux, 15 h; viii) *n*-BuLi, THF, -78 °C – reflux, 48 h; ix) PTSA, MeOH, reflux, 3 h.

Substrates **138**, **139** and **142** were obtained via a similar alkylation pathway to that described in scheme 41. The best overall reaction yields were obtained via a Sonagashira cross-coupling of the corresponding aryl iodides with 4-pentyn-1-ol, followed by conversion of the primary alcohol to the alkyl iodides **162–164** via a mesylate intermediate. These intermediates (**162–164**) were then reacted with the

lithium alkyne of **158** to produce **165–167** and likewise, deprotection was achieved using the same conditions employed for substrate **156** (Scheme 41).

In the case of alkynyl nitrile substrate **146**, the synthesis involved reaction of **158** with *n*-BuLi, followed by addition of 1-bromo-3-chloropropane to produce intermediate **168**. Likewise, conversion to the iodide was achieved by a Finkelstein reaction in refluxing NaI and acetone. The corresponding alkyl iodide **169** was transformed into the nitrile functional group by reaction with NaCN in DMSO at 70 °C and gave a 77% yield of **170**. The synthesis is outlined in Scheme 43.

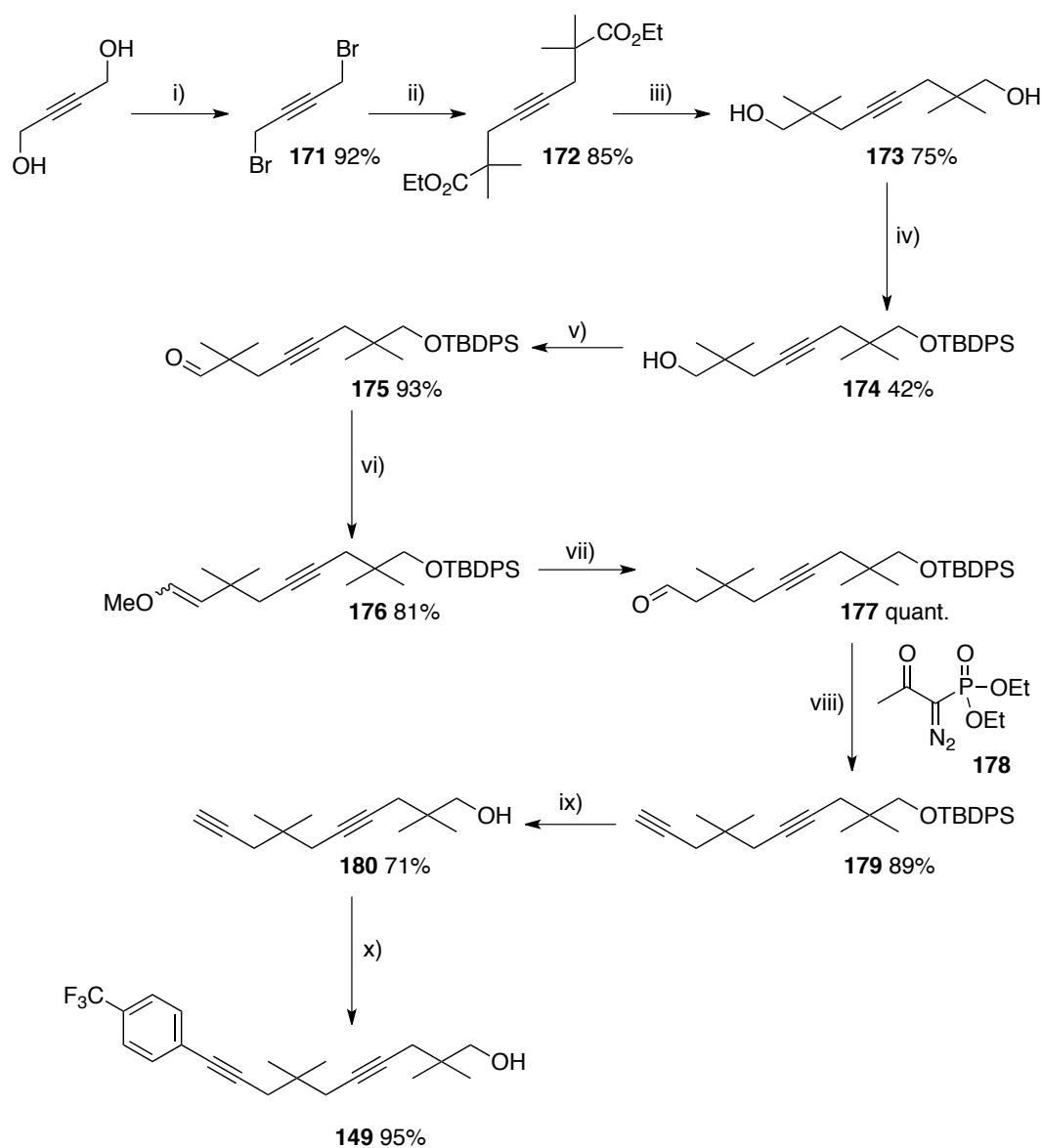


Scheme 43. Synthesis of 9-hydroxy-8,8-dimethylnon-5-ynenitrile **146**. i) *n*-BuLi, THF, –78 °C, 15 min; ii) 1-Bromo-3-chloropropane, –78 °C then RT, 1 h then reflux, 22 h; iii) NaI, Me₂CO, reflux, 24 h; iv) NaCN, DMSO, 70 °C, 3 h; v) PTSA, MeOH, reflux, 3 h.

A synthetic scheme for the preparation of the di-*gem*-disubstituted substrate **149** is outlined in scheme 44 below.

2-Butyne-1,4-diol is converted to the corresponding dibromide via reaction with PBr₃. Commercially available ethyl isobutyrate was used to alkylate dibromide **171** via the organolithium generated species of ethyl isobutyrate using LDA, followed by reduction of the corresponding diester (**172**) using LiAlH₄. Mono-protection and oxidation, followed by a Wittig reaction and subsequent hydrolysis of enol ether **176** revealed the aldehyde **177**. Next, a carbon homologation using the synthesised diethyl 1-diazo-2-oxopropylphosphonate **178**¹²³ produced alkyne **179**. Deprotection of the silyl ether using TBAF and finally Sonagashira cross-coupling was conducted to afford the di-*gem*-dimethyl dialkynyl alcohol **149**.

All substrates were then distilled via Kugelrohr distillation, degassed and subjected to the catalytic reaction conditions.



Scheme 44. Synthesis of double kinetically activated dialkynyl alcohol **149**. i) PBr_3 , pyridine, Et_2O , 0 °C, 30 min then reflux, 4 h; ii) Ethyl isobutyrate, LDA, -78 °C – 0 °C, 1 h then **171**, -78 °C – RT, 12 h; iii) LiAlH_4 , Et_2O , 0 °C, 1 h; iv) NaH, THF, 0 °C, 45 min then TBDPSCI, RT, 1 h; v) $(\text{COCl})_2$, DMSO, NEt_3 , CH_2Cl_2 , -78 °C – RT, 1.5 h; vi) KHMDS, $\text{PPh}_3\text{CH}_2\text{OMe}\cdot\text{Cl}$, THF, -78 °C – RT, 2 h; vii) 2N HCl, 1,4-dioxane, RT, 3 h; viii) K_2CO_3 , MeOH, 0 °C – RT, 60 h; ix) TBAF, THF, 0 °C – RT, 14 h; x) 4-iodobenzotrifluoride, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI, NEt_3 , 0 °C – RT, 12 h.

2.1.4 Conclusion

The application of organocalcium, strontium and barium complexes to the intramolecular hydroalkoxylation/cyclisation of alkynyl and allenyl alcohols for the formation of five- and six-membered enol ether heterocycles has proven successful. For non-activated substrates, the formation of the endocyclic enol ether was observed due to an isomerisation pathway of the alkynyl alcohol to the corresponding allenyl alcohol, detectable by ^1H NMR spectroscopy. Allenyl alcohols gave rise to the endocyclic enol ether as the major product, with activated allenyl alcohols producing the dihydrofuran as the sole product. All three alkaline earth bis(amides) $[\text{Ae}\{\text{N}(\text{SiMe}_3)_2\}_2]$ ($\text{Ae} = \text{Ca}, \text{Sr}, \text{Ba}$) showed high reactivity and good selectivity for the intramolecular hydroalkoxylation reactions. Although a “catalyst of choice” was not directly determined from these studies as different group 2 bis(amide) complexes gave rise to different rates and selectivities with varying substitution patterns of the substrates, $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ was used to further explore and extend the substrate scope of the hydroalkoxylation study.

Further attempts were made to achieve a tandem hydroalkoxylation reaction using a dialkynyl dialcohol. In contrast to the outcome observed by Marks with lanthanide tris(amide) complexes, the reaction was demonstrated to be less effective for the quantitative double cyclisation to produce the bicyclic spirofuran. The concept of achieving double cyclisations with group 2 precatalysts led to the design and synthesis of several dialkynyl alcohol substrates. These were found to cyclise with better ease in comparison to linear internal alkynyl alcohols. Of these, it is shown that the absence of a second cyclisation occurring under the specified reaction conditions is due to a faster protonolysis of the calcium alkenyl species rather than a second insertion. It was envisaged that the synthesis of a doubly kinetically activated substrate could achieve an energetically lower pathway and permit the second cyclisation to occur, producing the highly reactive bicyclic enol ether as the major product. Of the substrates examined, only substrates with the *para*- CF_3 aryl groups (**139** and **149**) in the presence of 5–10 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ showed promising signs of a second cyclisation by the appearance of a small singlet peak at

6.1–6.2 ppm, along with other peaks consistent with the desired process further upfield. However, these compounds formed in a yield too low to be examined further. When the Sr and Ba bis(amide) precatalysts (**75b** and **75c**) were investigated, the reactions in all instances led to complex product mixtures.

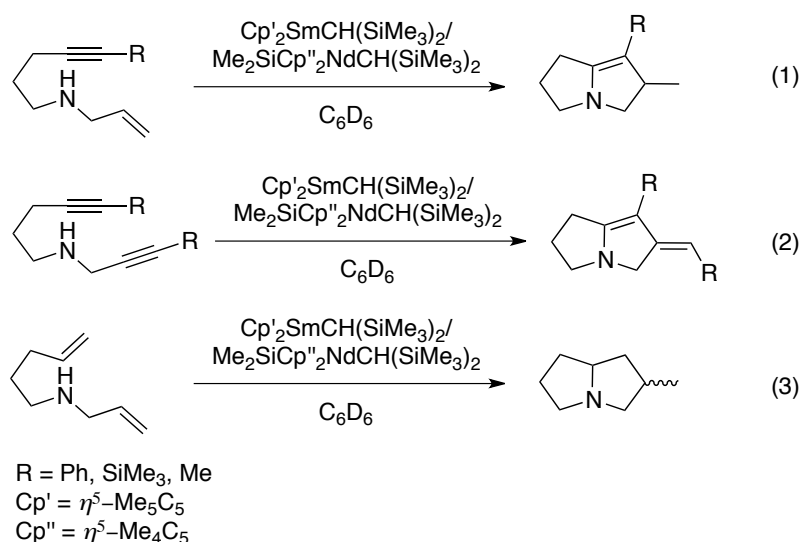
2.1.5 Future Work

While demonstrating that group 2 heavier alkaline earth metal bis(amides) effectively catalyse the intramolecular hydroalkoxylation/cyclisation of alkynyl alcohols, further exploration into more complicated C–O bond forming processes presents a challenging task. To this end, the extension towards the intermolecular hydroalkoxylation of allenes may be feasible. It has been previously demonstrated that the ligand(s) bound to the metal centre has a profound effect on the reactivity and catalytic activity of the group 2 precatalysts.¹²⁴ In addition, Sarazin has recently established the difference in catalytic nature of newly developed anilido amide complexes which were found to increase in catalytic activity with increasing size of the metal centre.^{32,125} The study of group 2 complexes based on these ligand systems or similar presents an interesting study for the hydroalkoxylation reactions, namely the cyclisation of the dialkynyl alcohols. Due to the high M–O bond enthalpy hydroalkoxylation is considered a very challenging transformation. Its successful achievement by heavier alkaline earth metal bis(amides) is supportive for further kinetic and computational studies to help support experimental results.

2.2 Hydroamination of Functionalised Arenes

Carbon–carbon bond forming reactions are important methods for the preparation of the main skeleton of organic molecules.^{126,127} While several kinds of C–C bond-forming reactions have been developed and successfully applied to organic synthesis, the development of reactions that are 100% atom efficient and are accompanied by the formation of less chemical waste are highly desirable. In the past few decades, such transformations have been achieved by Marks and Molander in lanthanide-catalysed systems.^{19,23}

Alkyne, alkene; alkyne, alkyne and alkene, alkene bicyclisations have been employed to yield a variety of pyrrolizidine and indolizidine skeletons.^{18,118,119}

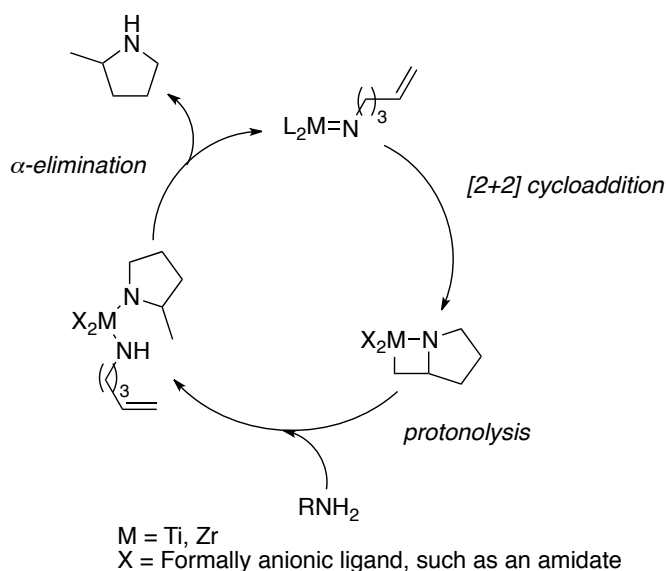


Scheme 45. Intermolecular hydroamination/bicyclisation mediated by Sm and Nd complexes.

In lanthanide-mediated intra- and intermolecular hydroamination reactions, the influence of different sized metal ions and the steric impediments exerted by the ligands have been thoroughly studied.^{45,19}

An alternative approach to the hydroamination of multiple C–C bonds exploits the use of zirconium (IV) and titanium (IV) imido complexes which undergo [2+2] cycloadditions with unsaturated substrates.¹²⁸ The catalytic cycle for such

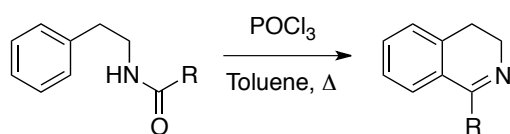
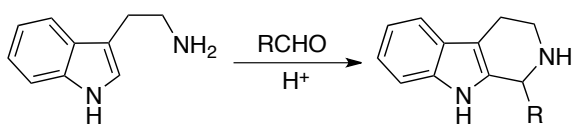
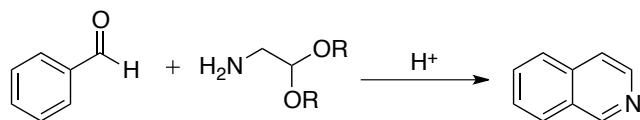
transformations proceeds via a four-membered metallocycle, similar to that of the [2+2] cycloadditions between alkenes and carbene complexes that occur during olefin metathesis. Protonation of the M–C bond in the resultant metallocycle by the amine, followed by elimination of the organic product regenerates the M–imido complex and releases the hydroamination product (Scheme 46).



Scheme 46. Group 4 catalysed intramolecular hydroamination.

2.2.1 Heavier Alkaline Earth Catalysed Tandem C–N Bond Forming Reactions

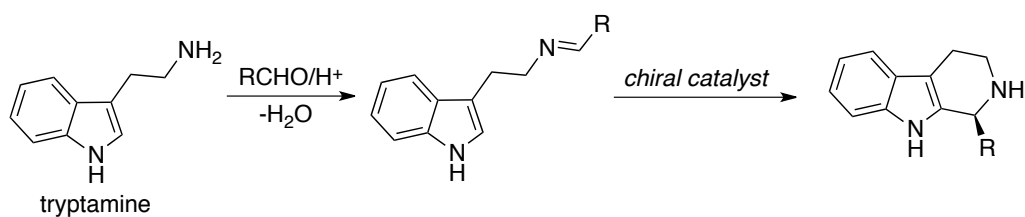
Tetrahydroisoquinoline ring systems are displayed across a wide range of naturally occurring alkaloids and useful synthetic organic compounds. Due to their important biological activities, such as use for antibiotics, anti-tumour and antimicrobial agents^{129,130,131}, methods of preparation for such systems have become increasingly desirable over the past few decades.¹³² The Bischler-Napieralksi, Pictet-Spengler and Pomeranz-Fritsch reactions are amongst the most notable synthetic methods for preparation of isoquinoline derivatives.¹³³ These methods allow the construction of the tetrahydroisoquinoline (THIQ) skeletons via an imine intermediate followed by cyclization. However, the Pictet-Spengler reaction permits the formation of the THIQ creating the stereogenic centre at C-1 in one step.

Bischler-Napieralski Reaction*Pictet-Spengler Reaction**Pomeranz-Fritsch Reaction*

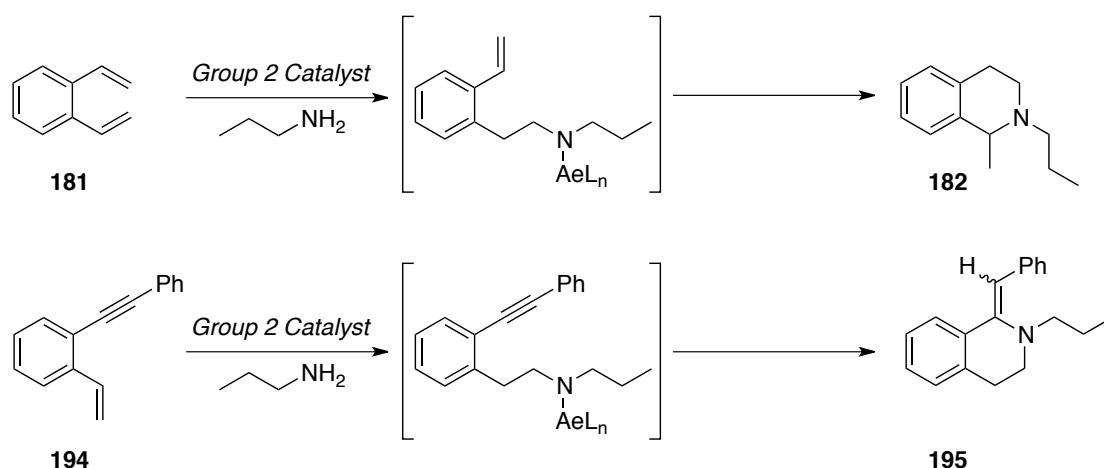
Scheme 47. Bischler-Napieralski, Pictet-Spengler and Pomeranz-Fritsch reactions frequently employed in organic synthesis.

Recently, various research groups have employed chiral Brønsted acid catalysts for establishing the THIQ skeleton via various synthetic pathways. These include: intramolecular oxetane ring opening,¹³⁴ multicatalytic three component coupling reactions with gold complexes,¹³⁵ oxetane directed aza-Diels-Alder reaction of indoles¹³⁶ and a reductive amination/aza-Michael sequence.¹³⁷ Likewise, the development of enantioselective, catalytic acyl-Pictet-Spengler reactions¹³⁸ has been achieved as well as calcium-catalysed Pictet-Spengler reactions.¹³⁹ In these cases, the reactions tend to proceed via multi-step reactions and/or by initial condensation reactions to firstly synthesise the imine intermediate. In contrast to these synthetic routes, heavier alkaline earth catalysed intermolecular hydroamination followed by intramolecular insertion into C–C unsaturation affords the THIQ framework in one single step.

Enantioselective Pictet-Spengler Reaction



Group 2 catalysed inter/intramolecular hydroamination sequences



Scheme 48. A conventional method for tetrahydroisoquinoline formation versus new approach catalysed by group 2 complexes.

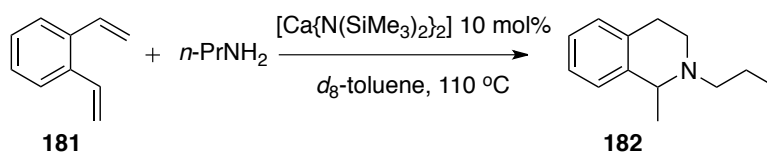
The newly developed routes described herein bypass harsh acidic conditions and the need for imine intermediates, most of which are required for these routes. The afforded exocyclic enamine can be enantioselectively reduced using Ir-catalysed hydrogenation.^{140,141,142} Recently, the Barrett and Hill group reported a detailed study of group 2 catalysed intermolecular hydroamination of styrene, 1,3-dienes and alkynes with a broad scope of amines including primary, secondary and *N*-heterocyclic amines.⁴⁴ In this chapter, an atom economical route employing heteroleptic heavier alkaline earth metal complexes to allow access to the tetrahydroisoquinoline series has been studied in detail.¹⁴³

2.2.1.2 Inter/Intramolecular Hydroamination of polyvinyl arenes

The concept of tandem C–N/C–C bond formation was introduced in styrene systems because of the remarkable kinetic ease with which group 2 metal–heteroatom bonds undergo inter- and intramolecular insertion reactions. These include activated alkene, alkyne and diene functionalities⁴⁴ as well as non-activated alkenes.³¹ The principal goal of this study was to construct amine-containing, synthetically useful heterocycles from readily synthesised substrates, in addition to the development of catalytic hydroamination methods possible with group 2 complexes.

A compound comprising multiple functional groups such as divinylbenzene (**181**) was tested with *n*-propylamine and the calcium bis(amide) [Ca{N(SiMe₃)₂]₂ (**75a**). To provide a comparison to the organolanthanide-catalysed hydroamination of divinylbenzene,⁴⁵ the same reaction conditions were first tested.

It was not only found that the simple, non-ligand supported calcium and strontium bis(amide) complexes were able to catalyse the reaction, but also that the reaction proved to be highly regio- and chemoselective whereby intermolecular hydroamination of one styrenyl unit was effected followed by intramolecular insertion of the second pendent double bond into the M–N bond to afford the *N*-propyl-1-methyltetrahydroisoquinoline (**182**) structure in a single catalytic step.



Scheme 49. Heavier alkaline earth catalysed hydroamination of divinylbenzene.

The success of the present process is based on the excellent regioselectivity of the intermolecular styrene hydroamination reactions. Consistent with our previous studies, the intermolecular alkene insertion step provided a single regioisomer intermediate, rationalised to occur via a four-membered transition state.^{10,43,44}

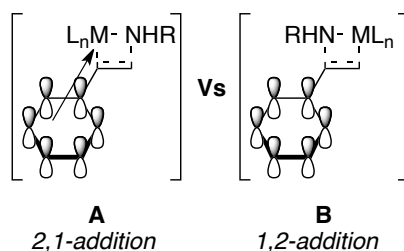
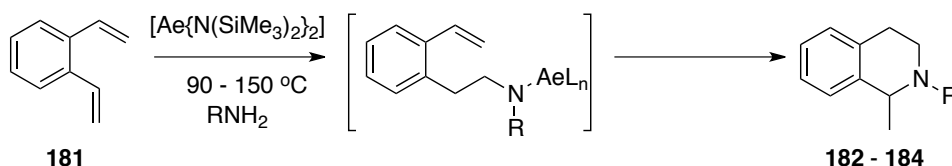


Figure 20. Transition states for 2,1- versus 1,2-addition.

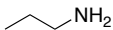
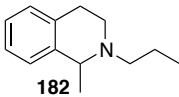
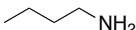
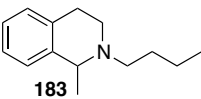
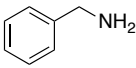
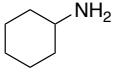
Regioselective M–N bond insertion through aryl-directed 2,1-addition provided the *anti*-Markovnikov intermediate products in excellent yields, and this process was subsequently coupled with intramolecular hydroamination of the arylethylamine intermediate (Scheme 50). The single regioisomer could be recovered under the reaction conditions by quenching and separation by column chromatography. An explanation for the selectivity can be derived from the two possible transition states (Figure 20). The metal amide can approach the alkene from two different directions, thereby polarising the alkene, resulting in a highly charge-separated transition state. The phenyl group can stabilise both the anionic and cationic centres. For the reason that electronegativity values between the group 2 metal and carbon differs much more than that between nitrogen and carbon, the anionic charge adjacent to the metal centre is much more significant. Thus, for an energetically low-lying transition state, stabilisation of the anionic centre is essential. Such stabilisation is achieved through the 2,1-addition of the M–N bond to the alkene. Similar studies and observations are well-documented and displayed by lanthanide and s-block-mediated hydroamination catalysis.^{45,144,145,146,147,148,149}



Scheme 50. Heavier alkaline earth metal catalysed intermolecular hydroamination/cyclisation.

The divinylarene intermolecular hydroamination/cyclisation was then tested over a narrow amine scope and the results are outlined in table 14.

Table 14. $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ catalysed intermolecular hydroamination/cyclisation of divinylbenzene.

Entry	Amine	Product	Time/h (Temp/°C)	Yield/% ^a
1		 182	18 (100)	28,
2			48 (120)	31
3			72 (150)	38 ^b
4		 183	33 (100)	11, 15 ^b
5			72 (120–140)	<5 ^c
6			72 (120–150)	No conversion
7		-	72 (120–150)	No conversion

(a) Yields determined by ^1H NMR spectroscopy at given time t in C_7D_8 . NMR reaction conditions: $[\text{cat}]:[\text{amine}]:[\text{divinylbenzene}] = 1:10:20$, $[\text{amine}] = 0.3 \text{ M}$; (b) Isolated yield after preparative scale reaction. Preparative reaction conditions: $[\text{cat}]:[\text{amine}]:[\text{divinylbenzene}] = 1:20:40$, $[\text{amine}] = 1 \text{ M}$; (c) extra 10 mol% of catalyst added and temperature increased to 140 °C resulted in no further reaction.

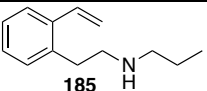
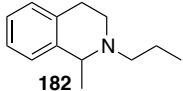
It can be seen that, depending on the structural features of the amine used, a significant difference in reactivity was observed with the homoleptic bis(amide) pre-catalyst. The simple aliphatic primary amines added cleanly without any detectable polymerisation side reactions of any reaction components. However, the reactivity of this system suggests a steric dependent nature of the amine employed. Hence, *tert*-butylamine and cyclohexylamine failed to undergo the cyclization (Table 14, entries 6–7). The ease of intermolecular hydroamination by sterically demanding amines was difficult as after 5 days at 140 °C only trace amounts of the

arylethylamine intermediate product had formed with *tert*-butylamine (Table 14, entry 6).

Contrastingly, benzylamine, which benefits from the proximity of the electron rich benzene ring, added to the styrene readily but only trace amounts of cyclohydroamination product could be detected by ^1H NMR spectroscopy after several days at 140 °C. From these initial results, it was evident that the cyclization to construct substituted tetrahydroisoquinolines was very sensitive to the steric nature of the primary amine involved and furthermore, suggested a rate-determining intramolecular insertion.

Kinetic studies of the reaction were not thoroughly investigated, but the reaction proved concentration dependent as the yields of the arylethylamine intermediate and the enamine product varied. In this sense, the divinylarene:amine ratio was significant in obtaining conversion to the *N*-propyl-1-methyltetrahydroisoquinoline product.

Table 15. ^1H NMR product distribution employing different substrate ratios for the reaction between divinylbenzene and *n*-propyl amine catalysed by 10 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$.

Entry	Ratio divinylbenzene:amine	Concentration of divinylbenzene/M	Major Product ^a
1	1:1	0.3	 185
2	2:1	0.6	 182
3	10:1	3	Polymerisation

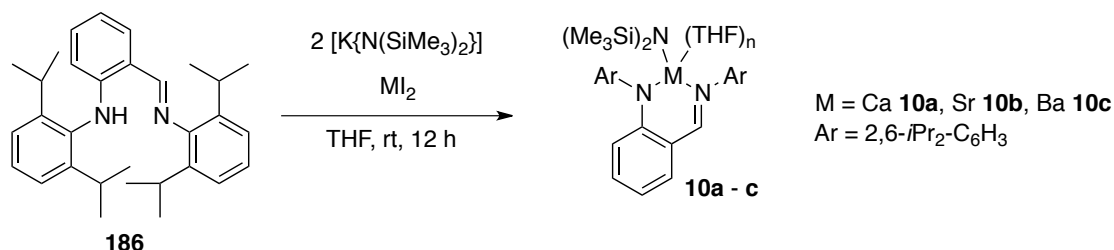
(a) Determined by ^1H NMR spectroscopy in C_7D_8 . NMR reaction conditions: $[\text{cat}]:[\text{amine}] = 1:10$, $[\text{amine}] = 0.3 \text{ M}$, heated at 130 °C for 12 h.

In the above-described experiment, the amine concentration was constant, but kept low at all times during the experiment. When a 1:1 mixture of divinylbenzene:*n*-propylamine was used at the lower concentration of 0.3 M, very little intramolecular insertion product could be detected. Significant conversion to the arylethylamine intermediate was observed. Presumably, in the case where the intermolecular hydroamination is relatively slow, a significant portion of the catalyst may be

involved in the first catalytic cycle and therefore delay the intramolecular step. It was found that when using 1:10:100 of [cat]:[amine]:[divinylbenzene], comparable to the conditions used by Marks in the lanthanide-catalysed system,⁴⁵ the competing polymerisation of divinylbenzene resulted in an insoluble polymeric solid that could not be characterised and consequently, shut down catalysis. From this point onwards, therefore a ratio of 1:2 [amine]:[divinylbenzene] was used ([amine] = ca. 0.3 M) where, dependent on the structural features of the amine, 5–10 mol% catalyst loading was applied.

Given the low conversions with the homoleptic heavier alkaline earth pre-catalysts, further exploration into the catalyst was prompted. A recent advancement in alkaline earth-based catalysts by Sarazin and co-workers explored the use of a new family of heteroleptic complexes supported by the congested imino anilide ligand $[\{L\}AeN(SiMe_3)_2(THF)_n]$ (**10a–c**) (Scheme 51).³² Their results indicated superiority over the β -diketiminates and the homoleptic metal bis(trimethylsilylamides) for hydroamination catalysis. Furthermore, they found that the catalytic activity increased down group 2. These pre-catalysts represent the first example of a stable barium complex providing the most active of the series and also capable of promoting the intermolecular hydroamination of aminoalkenes. This increased activity may be due to a number of factors, but it is thought that the extra rigidity and consequent stability of these complexes hinders solution redistribution and increases the catalytic activity in comparison to our previously studied precatalysts.¹⁰

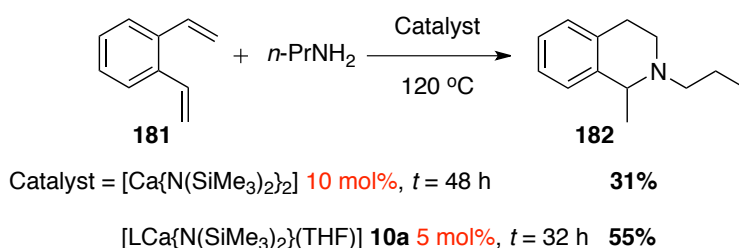
The Sr and Ca catalysts were isolated in 65 and 70% yield after the one-pot reaction of ligand **186**, Ml_2 , and 2 equivalents of KHMDS (Scheme 51).³²



Scheme 51. Heteroleptic complexes $[L]AeN(SiMe_3)_2(THF)_n$ ($Ae = Ca$ ($n = 1$, **10a**); Sr ($n = 2$, **10b**); Ba ($n = 2$, **10c**)) reported to be superior hydroamination catalysts to group 2 bis(amides).

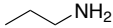
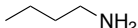
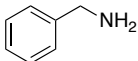
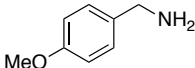
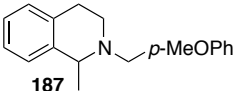
The ability of these new heteroleptic heavier alkaline earth metal complexes to catalyse tetrahydroisoquinoline formation was investigated.

As expected, **10a** and **10b** promoted the intermolecular hydroamination followed by subsequent cyclisation with a range of non-sterically demanding primary amines. It was observed that the activity improved greatly when calcium complex **10a** was utilised in comparison to calcium bis(trimethylsilyl)amide whereby a 55% conversion was seen with **10a** after 32 hours at 120 °C using 5 mol% catalyst (Table 16, entry 3 versus Table 14, entry 2). Likewise, the catalytic activity improved moving from calcium to strontium. These catalysts also permitted a larger amine scope with different substitution on the aromatic ring of the amines (Table 16).



Scheme 52. Comparison of product conversion using homoleptic calcium bis(amide) versus heteroleptic calcium complex **10a** in the double hydroamination of divinylbenzene.

Table 16. New heteroleptic heavier alkaline earth metal catalysed tandem C–N bond formation to construct 1-methyl tetrahydroisoquinoline skeletons.

Entry	Amine	Product	Catalyst	Temp/ ^o C	Time/h	Yield/% ^a
1		182	75a	120	44	13
2			75b	120	44	15
3			10a	120	32	55
4			10a	120	48	78
5			10b	120	32	61
6		183	75a	120	44	12
7			75b	120	44	13
8			10a	120	32	53
9			10b	120	32	59
10		184	10a^b	150	45	37
11			10a^c	130	16 ^d	57
12			10b^b	140	44	46
13			10b^b	150	68	24

(a) Yields determined by ¹H NMR spectroscopy in C₇D₈ at given time *t*, NMR reaction conditions: [cat]:[amine]:[divinylbenzene] = 1:20:40, [amine] = 0.3 M; (b) 10 mol% catalyst; (c) 20 mol% catalyst; (d) Heated under specified reaction conditions for further 16 hours (in addition to entry 10).

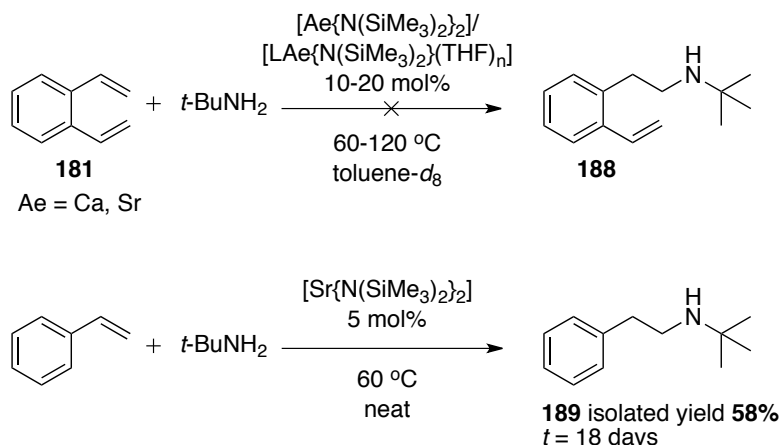
These results show a substantial increase in catalyst activity with catalysts **10a** and **10b**. After 32 h and 5 mol% catalyst loading, a 55% yield of the tetrahydroisoquinoline product **182** was observed by ¹H NMR spectroscopy. After 48 h, the reaction had proceeded to 78% conversion (Table 16, entry 4). No further conversion to the tetrahydroisoquinoline product was achieved after prolonged heating and increased catalyst loadings. In all cases, full conversion to the tetrahydroisoquinoline was not achieved and the intermolecular hydroamination product remained uncyclised in the reaction mixture. The activity of calcium and strontium precatalysts **10a** and **10b** was especially noteworthy in the case of benzylamine (entries 10–12) as [Ca{N(SiMe₃)₂]₂] failed to catalyse the double

transformation. In comparison to alkyl amines, benzylamine presented a diminished ease of cyclisation and required a catalyst loading of at least 10 mol%. In the case of entry 10, 29% of benzylamine still remained in solution. Where the catalyst loading was increased to 20 mol%, full consumption of benzylamine occurred, leaving 43% of the uncyclised intermolecular hydroamination product in solution.

Considering the divinylbenzene concentration dependence, the first hydroamination process was notably more efficient using a ratio of 1:10:100 of [cat]:[amine]:[divinylbenzene] when catalysed by **10a** and **10b**. The tetrahydroisoquinoline product **184** formed in a 50% yield with benzylamine *versus* a 37% conversion when a ratio of 1:20:40 was employed (Table 16, entry 10). Likewise, the competing polymerisation of divinylbenzene interfered with the rate of catalysis and product formation could not be driven further.

In contrast to the lanthanide-catalysed cascade reaction, it was found that the first intermolecular step of the cycle was faster than that of the styrene system under the same reaction conditions. In particular, Marks and co-workers attributed this notably enhanced rate to additional electron withdrawing alkene substitution at the *ortho*-position which decreases the electron density at the other olefin and in turn, reduces the electrostatic repulsion between the Ln–N and C=C functionalities.⁴⁵

However, upon comparison of the [Ca{N(SiMe₃)₂}₂] catalysed intermolecular addition of divinylbenzene (Table 14) versus styrene⁴⁴ and that of the anilido imine complexes **10a** and **10b** (Table 16), in contrast to the observations of Sarazin and coworkers,³² the intermolecular addition was notably slower and more difficult in both cases. Furthermore, the intermolecular addition using **10b** and [Ca{N(SiMe₃)₂}₂] was unachievable with sterically hindered *tert*-butylamine (Table 14, entry 6). A 58% conversion to the arylethylamine product was obtained after 18 days at 60 °C with styrene (Scheme 53).⁴⁴



Scheme 53. Comparison of the intermolecular hydroamination of divinylbenzene with *tert*-butylamine versus reaction with styrene.

Another informative observation with the use of *tert*-butylamine (Table 14, entry 6) was the incomplete catalyst initiation. Formation of the active catalytic species could not be accomplished when heated to 120–150 °C for 12 h. At this point, only 50% liberation of $\text{HN}(\text{SiMe}_3)_2$ was observed to have occurred. On the basis of steric reasons, *tert*-butylamine may be too bulky to effectively undergo free amine-amide exchange with the strontium complex **10b**. This was not the case with cyclohexylamine (Table 14, entry 7) as full liberation of $\text{HN}(\text{SiMe}_3)_2$ was achieved instantaneously at room temperature.

The present hydroamination process likely involves a significant stereoelectronic control via metal-induced positive polarisation of the evolving carbon skeleton, which ultimately leads to alkene insertion products. Using the more electron-rich 4-methoxy substituted benzylamine (Table 16, entry 13), a significant decrease in conversion was observed for both processes and no further increase in yield could be achieved even after prolonged heating for several days.

The marked regio- and chemoselectivity demonstrates that important factors other than simple sterics are operative, as previously observed in group 2-mediated hydroalkoxylation/cyclisation.¹¹⁷

These transformations were first reported by Marks in 2003 with organolanthanide complexes of the type $[\text{Cp}'_2\text{LnCH}(\text{SiMe}_3)_2]$.⁴⁵ By comparison of product conversion,

the lanthanide system shows greater activity towards tetrahydroisoquinoline formation as isolated yields of up to 87% were achieved (in comparison to 77% in the case of *n*-propylamine).

From the ^1H NMR spectrum it can be seen that the cyclized product begins to appear after approx. 50% consumption of the *n*-propylamine and approx. 50% generation of the intermolecular addition intermediate (Figure 21). The intramolecular cyclization appears to take place before the intermolecular hydroamination of divinylbenzene and *n*-propyl amine is complete.

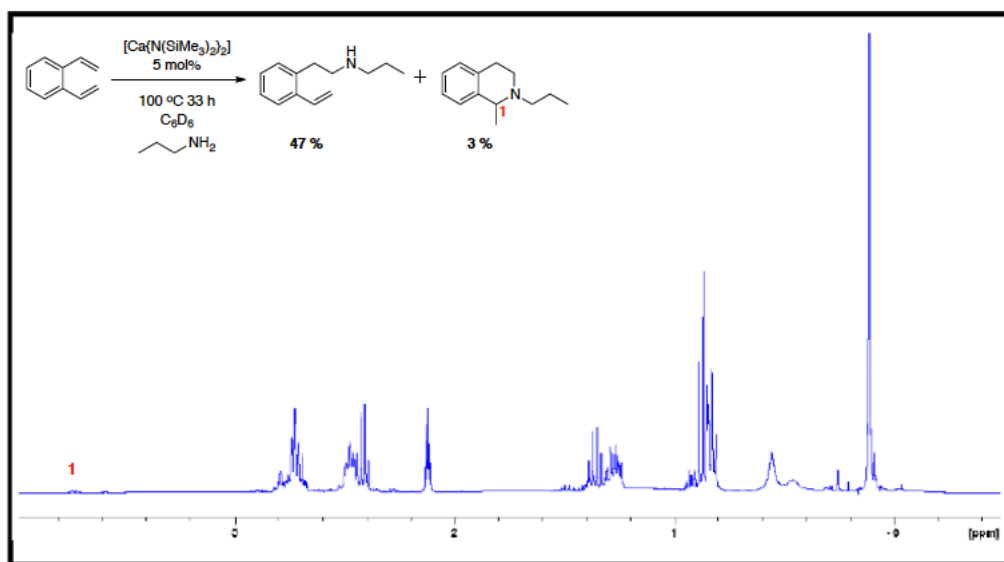
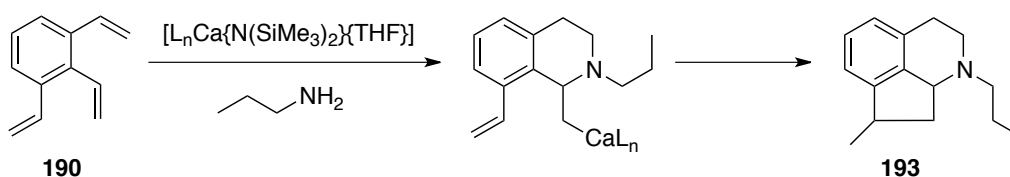


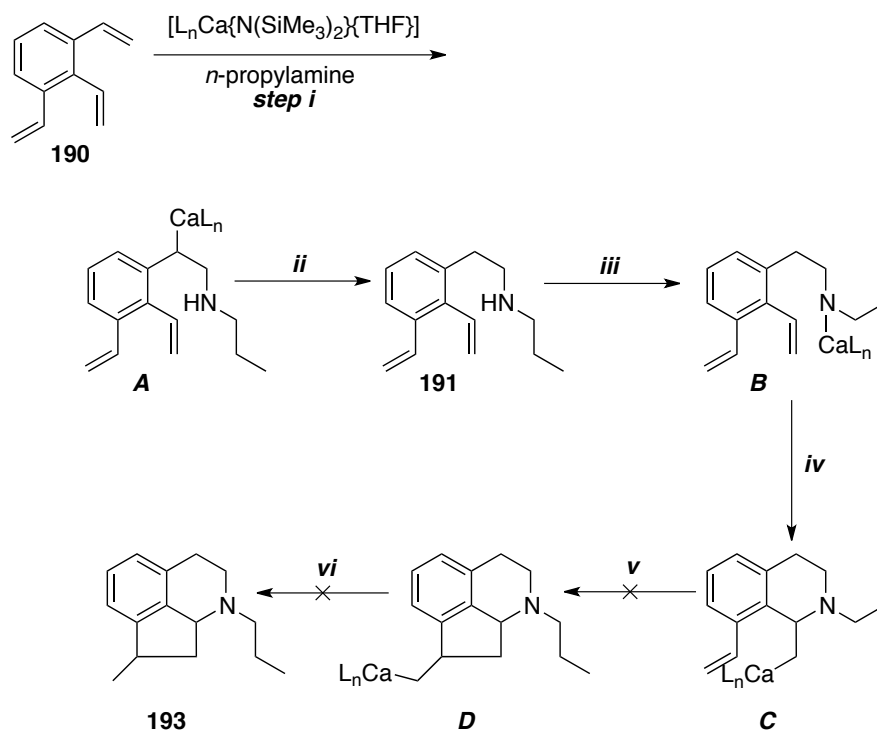
Figure 21. ^1H NMR spectrum during *in situ* monitoring of the hydroamination of divinylbenzene (**181**) with *n*-propylamine using 5 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ at $100\text{ }^\circ\text{C}$, $t = 33\text{ h}$. NMR reaction conditions: $[\text{cat}]:[\text{amine}]:[\text{divinylbenzene}] = 1:20:40$, $[\text{amine}] = 0.3\text{ M}$

An attempt was made to effect the intermolecular hydroamination followed by subsequent bicyclisation of trivinylbenzene (Scheme 54).



Scheme 54. Anticipated bicyclisation of trivinylbenzene with organo-group 2 complexes.

Intermolecular hydroamination with *n*-propylamine proceeded chemoselectively at the exterior vinyl moiety rather than at the sterically hindered, interior alkene. This alkene is effectively blocked by the two ortho vinyl substituents. Following the rapid protonolysis of the Ca–C bond by the amine (Scheme 55, step *ii*), the single intermediate **191** was observed by 1H NMR spectroscopy. The ensuing intramolecular cyclisation of **191** affords the Ca alkyl species **C** by analogy to the transformation of divinylbenzene **181** $\rightarrow$ **182**. The intramolecular cyclisation was observed by 1H NMR spectroscopy after 18% consumption of the amine (*vide infra*). In stark contrast to that observed with the organolanthanum-catalysed process,⁴⁵ low conversions to the intermediate **191** (17%) and tetrahydroisoquinoline product **192** (1%) were obtained. Consequently, the higher concentration of *n*-propylamine remaining effected the protonolysis of intermediates **B** and **C** rapidly. In this case, this would prevent the second insertion reaction, i.e. the insertion of the C=C bond into the Ca–C bond to afford the hexahydrocyclopentisoquinoline product **193**. Moreover, trivinylbenzene polymerised rapidly under these conditions, which prevented further catalyst turnover and contributed to the slow intermolecular and subsequent cyclohydroamination.



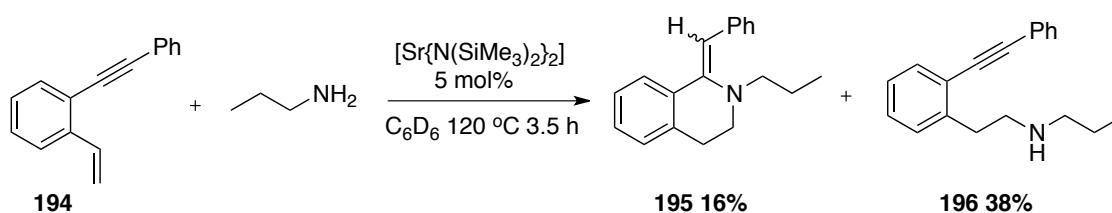
Scheme 55. Attempted bicyclisation of trivinylbenzene with organocalcium complexes.

While many heavier alkaline earth mediated heterofunctionalisation reactions such as hydroamination of alkenes and alkynes have been compared to the trivalent lanthanide processes, it is apparent that the catalytic route for such transformations studied may be more complex than anticipated. Considering the ability of the group 2 bis(amides) to catalyse the polymerisation of styrene⁴⁶ among other activated dienes, group 2 catalysed C–C bond formation presents a difficult challenge on such activated systems. Consideration of the nature of the metal and the supporting ligand may be necessary to achieve such transformations.

2.2.1.2 Heavier Alkaline Earth Catalysed Ene-yne Cyclisations

Due to the present success of heavier alkaline earth metal complexes in the intermolecular hydroamination of vinylarenes and diphenylacetylene, a multiple C–N bond forming process was envisaged whereby a molecule containing both styrene and diphenylacetylene functionality was incorporated into the one substrate. The hydroamination of alkynes is generally viewed as being more facile than that of alkenes because of the higher reactivity and electron density of alkyne bonds.¹⁵⁰ Moreover, the more entropically demanding intermolecular hydroamination of alkenes is much more difficult to achieve and far less developed than intramolecular reactions, which are kinetically and thermodynamically favoured.³¹

Initial attempts utilised the ene-yne compound **194**, 5 mol% $[\text{Sr}\{\text{N}(\text{SiMe}_3)_2\}_2]$ with *n*-propylamine in C_6D_6 and the mixture analysed by ^1H NMR spectroscopy. The ^1H NMR spectrum showed full liberation of $\text{HN}(\text{SiMe}_3)_2$ at room temperature. Heating to 90 °C for 14 hours showed 37% of the arylethylamine intermediate **196**. At 120 °C and after 3.5 hours, conversion to the exocyclic enamine product **195** was visible by ^1H NMR spectroscopy.



Scheme 56. Double hydroamination of **194** catalysed by 5 mol% $[\text{Sr}\{\text{N}(\text{SiMe}_3)_2\}_2]$.

When a 40:20:1 mixture of substrate:amine:catalyst was employed based on previous studies with divinylbenzene, intermolecular hydroamination proceeded chemoselectively at the styrene moiety rather than the more sterically hindered and electronically activated diphenylacetylene. For these types of alkynyl substrates, it appears that these chemoselective transformations occur under significant steric

control. The reaction mediated by $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ proved even less active than the Sr analogue and did not result in a significant yield of the cyclised product (< 5%).

The initial chemoselective, and aryl-directed 2,1-addition of the amine to the alkene component of the ene-yne substrate and the subsequent predominance of the *E* alkene isomer of the THIQ product correspondingly reflected the steric impediments during the alkyne insertion into the Sr–N bond, as observed in the hydroalkoxylation/cyclisation of alkynyl alcohols.¹¹⁷ Furthermore, the intramolecular insertion step of the alkyne versus the alkene in divinylbenzene was achieved much more readily and gave rise to much better conversions of the resulting enamine products.

The greater alkyne insertion rates can be associated with the sterically more accessible, cylindrical alkyne π system, more nucleophilic sp-hybridised carbon atoms,¹⁵¹ greater alkyne π -donating capacity, greater thermodynamic driving force and a greater stabilisation of the insertive transition state (Figure 22).⁴⁵

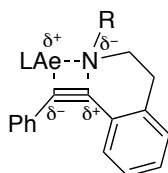


Figure 22. Stereoelectronic controlled intramolecular insertion of alkyne into Ae–N bond.

At this stage, further exploration into the catalyst was prompted. Inspired by the recent advancement in alkaline earth-based catalysts by Sarazin and co-workers, the use of complexes **10a–c** of the type $[\{\text{L}\}\text{AeN}(\text{SiMe}_3)_2(\text{THF})_n]$ was attractive. The heteroleptic Mg complex of the type $[\{\text{L}\}\text{Mg}(n\text{-Bu})(\text{THF})]$ **10d** was also synthesised and studied for comparison.

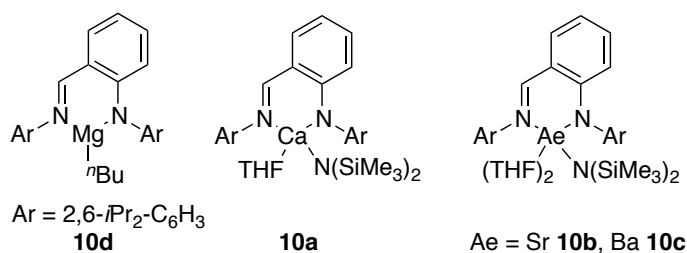
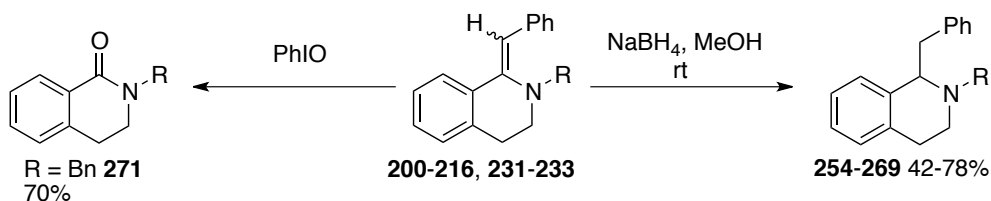


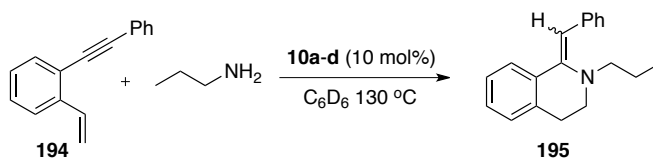
Figure 23. Heavier alkaline earth complexes used to catalyse the formation of *N*-substituted 1-benzyltetrahydroisoquinolines.

The reaction of complexes **10a–d** with the amine substrates resulted in a distinct colour change concurrent with catalytic initiation. The original yellow solutions of **194** and precatalysts **10a–d** in C_6D_6 instantaneously turned to the characteristic red/orange colour of the corresponding amine–amido complex. These complexes effectively catalysed the intermolecular hydroamination of the styrene unit followed by cyclohydroamination to afford the 6-membered exocyclic enamine product in good to excellent yields using a moderate catalyst loading of 10 mol%. Likewise, a trend was observed whereby the catalytic activity increased with the size of the metal. The results are summarised in table 17.

These enamine products could be effectively reduced to the corresponding *N*-alkyl-1-benzyltetrahydroisoquinolines using NaBH_4 or oxidised using iodosobenzene to the corresponding benzolactam.



Scheme 57. Synthesis of tetrahydroisoquinolines and benzolactams from exocyclic enamines.

Table 17. Heavier alkaline earth catalysed ene-yne hydroamination with *n*-propylamine.^a

Entry	Catalyst	Loading	Time/h	Conversion/% ^b
				X:int:amine
1	10d	10 mol%	12	6:4:90
2	10d	10 mol%	43 ^c	23:12:65
3	10a	5 mol%	16	32:68
4	10b	5 mol%	16	43:57
5	10a	10 mol%	15	71:29
6	10b	10 mol%	14	99
7	10c	10 mol%	12	99
8	$[Ca\{N(SiMe_3)_2\}_2]$	5 mol%	16 ^d	16:44:40
9	$[Sr\{N(SiMe_3)_2\}_2]$	5 mol%	16 ^d	22:59:19

(a) Reaction conditions: substrate:amine = 2:1, 5–10 mol% of catalyst, C_6D_6 , [amine] = 0.33 M, 130 °C; (b) Determined by 1H NMR spectroscopy at given time *t*, int = intermolecular addition intermediate; (c) Temperature 140 °C; (d) Reaction conducted in C_7D_8 .

The Sr complex **10b** quantitatively produced **195** after 14 h at 130 °C. Due to the ease of preparation and high yielding synthesis of complex **10b**, this was used as the catalyst of choice over the Ba complex **10c** throughout the study.

The Mg complex **10d** was the least active and was ineffective at cyclising the *N*-propylarylethylamine intermediate and in addition, displayed very low activity in performing the first intermolecular step (Table 17, entries 1–2). A comparable observation has previously been made with $(nBu)_2Mg$ which showed poor activity towards the hydroamination of styrene with piperidine.⁴⁶

Asymmetric hydrogenation of the enamine products is also possible using $[\text{Ir}(\text{cod})\text{Cl}]_2$ and provides a direct method to access optically pure *N*-alkyl-1-benzyltetrahydroisoquinolines.^{141,142,152} Of particular note, Laudanosine¹⁵³, Coclaurine¹⁵⁴ and Norcoclaurine¹⁵⁵ are examples of naturally occurring compounds containing the 1-benzyltetrahydroisoquinoline skeleton.

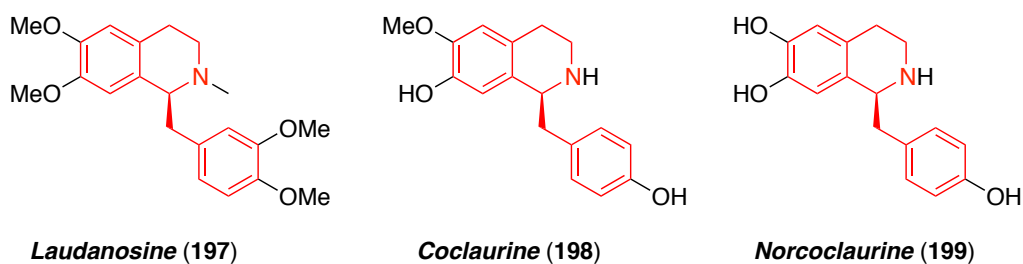


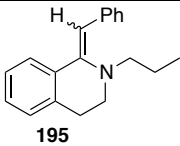
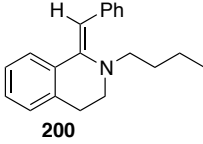
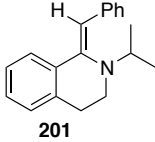
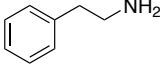
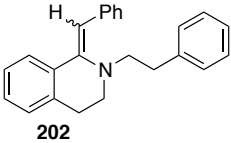
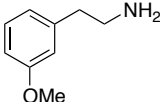
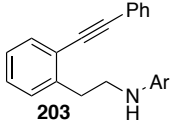
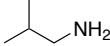
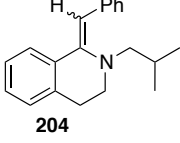
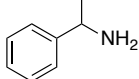
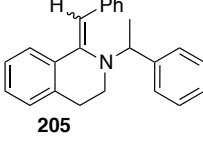
Figure 24. Naturally occurring 1-benzyltetrahydroisoquinolines.

Given the prevalence of the chiral 1,2,3,4-tetrahydroisoquinoline motif in natural alkaloids and pharmaceutical molecules,^{131,156} these methods to directly access such frameworks are highly desirable.

Encouraged by these promising results, we began our investigation into substrate scope by first analysing a range of readily available alkyl amines (Table 18). Although cyclisations could effectively be achieved using 5 mol% of the $[\{\text{L}\}\text{Sr}(\text{N}(\text{SiMe}_3)_2)(\text{THF})_2]$ complex (**10b**), use of 10 mol% of the catalyst considerably increased the conversion, especially with sterically hindered alkyl amines.

The results outlined in table 18 demonstrate that the C–N bond forming processes are chemo- and regioselectively coupled in sequence to assemble the tetrahydroisoquinoline skeleton. Regioselective insertion of the styrene unsaturation into the Sr–N bond occurs through aryl directed 2,1-addition providing the *anti*-Markovnikov product followed by insertion of the alkyne into the resulting Sr–N bond.

Table 18. Strontium catalysed ene-yne hydroamination with primary alkyl amines.^a

Entry	Amine	Product	Time/h	% Conversion ^b	<i>E:Z</i> Ratio ^b
1		 195	15	99	3:1
2		 200	15	24	-
3			22 ^c	99	-
4		 201	15	25, 18, 57	-
5			17 ^c	64	-
6			4 ^d	73	-
7		 202	13	56	1.1:1
8			12.5 ^c	65	1:1.6
9			24 ^c	70	1:2.6
10		 203	12.5 ^c	10	-
11		 204	15 ^c	64	4.5:1
12		 205	13 ^c	20	1:2.5
13			74 ^d	69	1:2.5

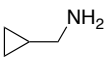
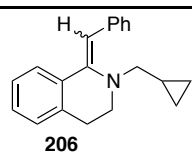
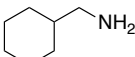
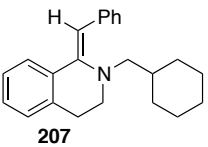
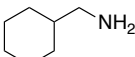
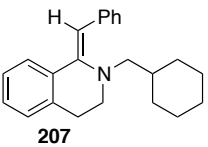
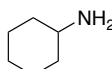
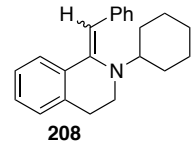
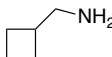
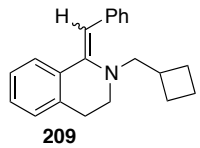
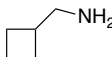
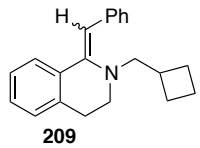
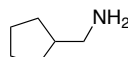
(a) Reaction conditions: [cat]:[amine]:[substrate] = 1:10:20 in C₆D₆ at 130 °C. [amine] = 0.33 M. Catalyst = [(L)SrN(SiMe₃)₂(THF)₂] (**10b**); (b) Determined by ¹H NMR spectroscopy at given time, *t*; (c) Temperature 140 °C; (d) Extra 5 mol% of catalyst added and heated further for amount of time specified.

The fastest reaction was achieved using *n*-propylamine. Quantitative conversion was achieved with *n*-propyl amine in less than 15 h (Table 18 entry 1). Under the same conditions almost quantitative conversion of the cyclopropylmethylamine to the exocyclic enamine product occurred (Table 19 entry 1).

Products from additions/cyclisations of amines containing bulky substituents near the C–NH₂ moiety were generally formed in lower yields than those from linear primary alkyl amines. In these reactions, significant amounts of the intermolecular addition product were formed which incorporated the rest of the reaction mixture in most cases. Good conversions with more bulky amines were obtained when the temperature was increased from 130 to 140 °C, which allowed characterisation of the products (Table 18 entries 5, 8, 11). The difference in activity between the *n*-propylamine and *n*-butylamine is noteworthy (Table 18 entry 1 versus entry 2). Under the same conditions, intramolecular insertion of the alkyne into the Sr–N bond of the *N*-butylarylethylamine intermediate showed comparable activity to that of isopropylamine (Table 18 entry 4).

With regard to the decreased product conversion with *n*-butylamine, a similar observation was made by Marks during the intermolecular hydroamination of terminal alkynes whereby the turnover number (*N_t*) decreased in the order *n*-propyl > *n*-butyl > isobutyl.⁴⁵ It is clear from this point that the intramolecular insertion step is highly sterically dependent and the yield of the cyclised product reflects the steric encumbrance of the amine used.

Table 19. Strontium catalysed ene-yne hydroamination with primary cycloalkyl- and cycloalkylmethylamines.^a

Entry	Amine	Product	Time/h	% Conversion ^b	<i>E:Z</i> Ratio ^b
1		 206	15	97	2:1
2		-	15 ^d	-	-
3		 207	12.5 ^c	38	-
4		 207	4 ^e	50	-
5		 208	15	25	1:2.6
6		 209	12.5	26	1:0.28
7		 209	13 ^c	36	1:1.2
8		-	12.5 ^d	-	-

(a) Reaction conditions: [cat]:[amine]:[substrate] = 1:10:20 in C₆D₆ at 130 °C. [amine] = 0.33 M. Catalyst = [{L}SrN(SiMe₃)₂(THF)₂] (**10b**); (b) Determined by ¹H NMR spectroscopy at given time, *t*; (c) Temperature 140 °C; (d) No conversion of amine to intermolecular addition intermediate nor subsequent cyclisation; (e) Extra 5 mol% of catalyst added and heated further for amount of time specified.

Analysis of the cycloalkylmethylamines revealed a slight trend in relation to the steric demands and internal bond angles of the cyclopropane, cyclobutane and cyclohexanemethylamines (Table 19, entries 1, 3–4, 6–7). Under comparable reaction conditions to that used to examine cyclopropanemethylamine (Table 19, entry 1), addition/cyclisation of cyclopentanemethylamine was unsuccessful and even under more forcing conditions (extra 5–10 mol% of catalyst added, higher

temperatures) no products could be detected by ^1H NMR spectroscopy (entry 8). Additionally, when the reaction mixture was cooled to room temperature small amounts of precipitate could be observed in the NMR tube.

A plausible explanation for these observations relates to factors including both steric considerations and ring strain of each of the cycloalkanes.¹⁵⁷ Whilst the cyclopropane ring suffers from most angular strain, the steric demands of this amine are lowest in comparison to amines in entries 3, 6 and 8 (Table 19). In this case, the strain on the cyclopropane ring seems to have no effect on the rate of cyclisation. However, when moving to the 4 and 5 membered analogues, ring strain appears to outweigh any steric drawbacks due to the ease of cyclisation of cyclohexanemethylamine versus the four-membered ring and also the dramatic decrease in yield observed when increasing the ring size in entry 1 versus entry 6 (Table 19). The cyclobutane ring also suffers from 1,3 destabilizing interactions and even more so in the cyclopentane ring, being the most strained out of the four. This does not occur in the cyclohexane ring.

Presumably, the rate of cyclisation of cycloalkanemethylamines depends on a balance between steric factors, ring strain and destabilizing effects encountered within the ring to allow a favourable conformation during insertion reactions in generating the tetrahydroisoquinoline framework. In analogy to these observations, attempts to cyclise cyclopropylamine (Table 19 entry 2) were unsuccessful in comparison to cyclohexylamine (entry 5). By further comparison with isobutylamine (Table 18, entries 4–6) branched alkylamines like isobutylamine may carry more conformational freedom, which is important in the sterically sensitive nature of the insertive transition state.

In regard to the geometry of the exocyclic enamine product, the *E:Z* product distribution is affected by sterically encumbered amines. When the reaction was monitored at lower conversions of **195**, **205** and **206** (Table 18, entries 1 and 12; Table 19 entry 1) the *E* isomer was observed as the major product, while the *Z* isomer was observed by thermal isomerization under the reaction conditions. In the

cases of the bulkier amines, the *Z* isomer prevails as the major product, again reflecting the likely significance of steric bulk in the rate determining transition state, which, in turn, also determines the *E:Z* product distribution. This becomes more apparent upon investigation into the benzylamines (Table 20).

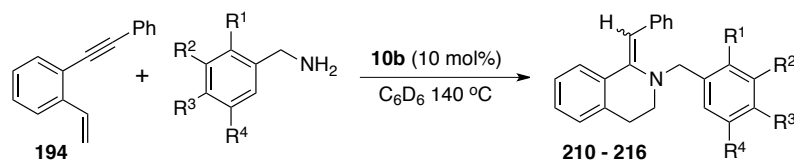


Table 20. Strontium catalysed ene-yne hydroamination with aryl substituted benzylamines.^a

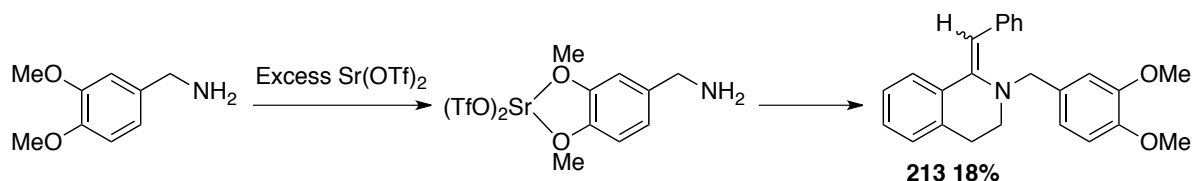
Entry	R ¹	R ²	R ³	R ⁴	Time/h	% Conversion ^b	<i>E:Z</i> ^b
1	H	H	H	H	12.5	99	1.2:1
					29	99	1:2
2	H	H	OMe	H	10	68	1:1.1
					15	72	1:1.8
3	H	H	O ^t Bu	H	13	55	1:0.9
					28	63	1:2
					12 ^c	85	1:2
4	H	OMe	OMe	H	12.5 ^d	-	-
					16 ^e	18	1:0
5	H	OMe	H	OMe	15	77	1:1.3
					32	85	1:2.6
6	H	OMe	H	H	12.5	83	1:0.67
					27	90	1:1.3
7	OMe	H	H	OMe	10	80	1:1
					15	82	1:1.5

(a) Reaction conditions: [cat]:[amine]:[substrate] = 1:10:20 in C₆D₆ at 140 °C, [amine] = 0.33 M; (b) Determined by ¹H NMR spectroscopy at given time *t*; (c) Extra 5 mol% of catalyst added and heated further for amount of time specified; (d) No conversion of amine to intermolecular addition intermediate nor subsequent cyclisation; (e) Reaction conditions: [cat]:[Sr(OTf)₂]:[amine]:[substrate] = 1:20:10:20 in C₆D₆ at 115 °C, [amine] = 0.33 M, Sr(OTf)₂ premixed with a solution of amine in C₆D₆ and added to catalyst followed by substrate addition.

The coupled intermolecular hydroamination and intramolecular cyclisations, mediated by the strontium precatalyst **10b** could be used for a wide range of

substituted benzylamines. A 10 °C increase in temperature produced the *N*-benzyl cyclic enamine products in good to excellent yields.

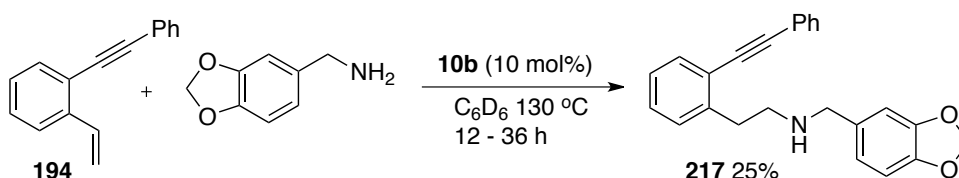
The above comparison of results presented in table 20 versus table 18–19 suggests kinetic advantages of benzyl amines versus alkyl amines. However, these advantages become diminished according to the position of ligating substituents on the aromatic ring, whereby a decrease in conversion to the cyclised product was observed in some cases (Table 20, entry 4). Note that for ligating substituents in the 3,4 position, hydroamination was unsuccessful most likely due to the coordinating nature of the dimethoxy group with the catalyst. In order to try and avoid this initial coordination, an excess of Lewis acidic $\text{Sr}(\text{OTf})_2$ was added to a solution of the 3,4-dimethoxybenzylamine in order to potentially block this site from ligating with the catalyst via pre-coordination (Scheme 58). This was followed by addition of the substrate and catalyst in C_6D_6 and heated at 115 °C for 11 hours.



Scheme 58. Addition of excess $\text{Sr}(\text{OTf})_2$ to 3,4-dimethoxybenzylamine in attempts to block pre-coordination by group 2 complexes.

At this point, 18% of the cyclised product was produced along with quantitative intermolecular hydroamination, observed by ^1H NMR spectroscopy. Further heating at 115–140 °C and higher catalyst loadings did not increase the yield of the cyclised product. This is possibly due to solubility issues of the $\text{Sr}(\text{OTf})_2$ in C_6D_6 .

Piperonyl amine was also tested under the reaction conditions and 25% of the intermolecular hydroamination product was produced after 16 hours. The oxygen bridging methylene did not perturb coordination of the catalyst and likewise, the intermolecular yield could not be improved further. No cyclohydroamination occurred with this substrate molecule.



Scheme 59. Attempted cyclohydroamination with piperonylamine.

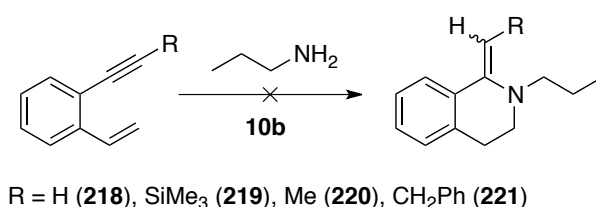
During the course of heating the reaction mixture containing piperonylamine, the initial light yellow/orange solutions turned dark brown with copious amounts of precipitation. Analysis of the reaction mixture after workup revealed that extensive polymerisation side reactions were also occurring for this substrate, which impeded the cyclisation of the arylethylamine intermediate. Unfortunately, the arylethylamine intermediate **217** could not be isolated from polymeric by-products.

The rationale that the diminished yield with 3,4-dimethoxybenzylamine (Table 20 entry 4), was a consequence of ligation with the strontium complex **10b** was further supported when 3,5-dimethoxybenzylamine was used (entry 5). In this case a significant ease of cyclisation occurred and the enamine product was obtained in good yield (77%, 15 h). Due to the larger bite angle of the methoxy substituents on the 3 and 5 positions on the aromatic ring of the amine, the catalytic strontium complex **10b** should coordinate less readily. Likewise, the yield of the exocyclic enamine product for 2,5-dimethoxybenzylamine was 80% after 10 hours (entry 7).

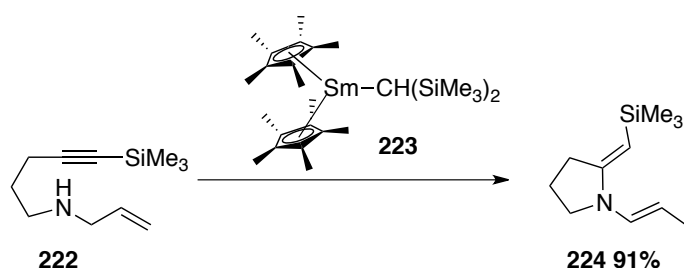
A further explanation for the observed results may also reflect steric demands in addition to ligating ability of the alkoxy substituents, and, to a less extent, electronic considerations. Diminished reactivity is evident when using the bulky *tert*-butoxy analogue (entry 3) in comparison to 4-methoxybenzylamine (entry 2). The results in table 18–20 suggest an insertive transition state, which may benefit from extra stabilisation from the benzylamine through unrestricted rotation when unsubstituted on the aryl ring. This freedom of rotation may become more restricted with groups present in the 2–5 positions due to the sterically sensitive nature of the accompanying unsaturated carbon–carbon bond insertion at the strontium centre.

Consequently, this may reduce any favourable interactions of the aromatic amine with the metal centre.

In contrast, no cyclohydroamination products were observed when the phenyl group of the diphenylacetylene moiety was replaced by a hydrogen, methyl, trimethylsilyl or benzyl group. This highlighted the necessity of stabilisation from the terminal phenyl group on the alkyne functionality. Surprisingly, no activating effects were observed for the $-\text{SiMe}_3$ terminated alkyne, in stark contrast to earlier reports relating to the insertion of alkynes into lanthanide–nitrogen bonds (Scheme 61).^{18,118}



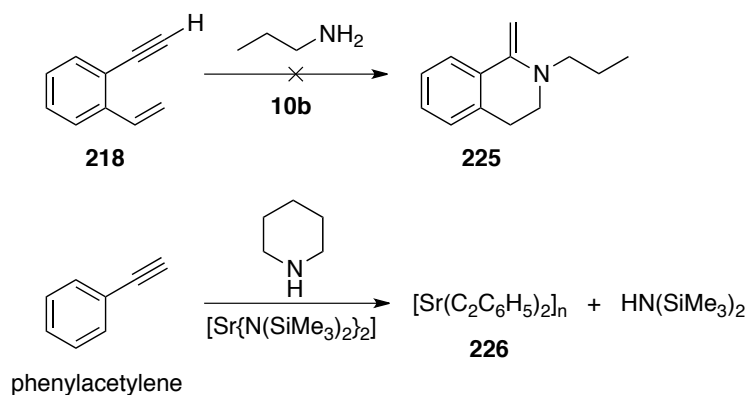
Scheme 60. Attempted Group 2 catalysed hydroamination with substrates not bearing diarylacetylene functionality.



Scheme 61. Lanthanide catalysed intramolecular hydroamination of $-\text{SiMe}_3$ terminated acetylene.¹⁸

In the case of the terminal alkyne, polymerisation products were detectable by ^1H NMR spectroscopy in addition to the immediate formation of an off-white suspension of the suspected $[\text{Sr}(\text{C}\equiv\text{C}\text{Ar})_2]_n$. This did not dissolve further when heated and was highly insoluble when separated from the reaction mixture. Furthermore, the characteristic red/orange solution, consistent with catalyst initiation became decolourised when the terminal alkyne substrate **218** was added.

The alkyne oligomerisation process is considerably more rapid than hydroamination and dominates the catalysis under the reaction conditions outlined in tables 18–20.



Scheme 62. Attempts to achieve hydroamination with terminal acetylenes by strontium complexes.

Previous studies of the hydroamination of phenylacetylene with $[\text{Sr}\{\text{N}(\text{SiMe}_3)_2\}_2]$ have revealed similar results.^{46,158} The acidity of the terminal alkyne versus the amine should be lower ($\text{p}K_{\text{a}}$ of *n*-propylamine = 10.7) and therefore the formation of $[\text{LSr}\{\text{NCH}_2\text{CH}_2\text{CH}_3\}(\text{THF})_n]$ should be favoured. However, due to the insolubility of the strontium alkynyl species the equilibrium appeared to favour the suspected polymerisation process and no activation of the NH-functionality occurred.

With benzylamines, a more consistent pattern was observed with respect to the initial isomer produced in comparison to the alkyl amines in tables 18 and 19. In all cases the first observed product was that of the *E* alkene, corresponding to the *Z* stilbene backbone. Upon further heating with all benzyl amines (Table 20) an increase in the *Z* alkene product was apparent by ^1H NMR spectroscopy, accompanied by a decrease in *E* alkene product. This was most pronounced in the reactions with benzylamine (entry 1), 4-*O*^tBu– (entry 3) and 3,5-dimethoxybenzylamine (entry 5) for which *Z* alkene formation doubled when heated further for the amount of time specified. It is well documented that *Z* stilbene readily isomerises to *E* stilbene under thermal conditions.¹⁵⁹

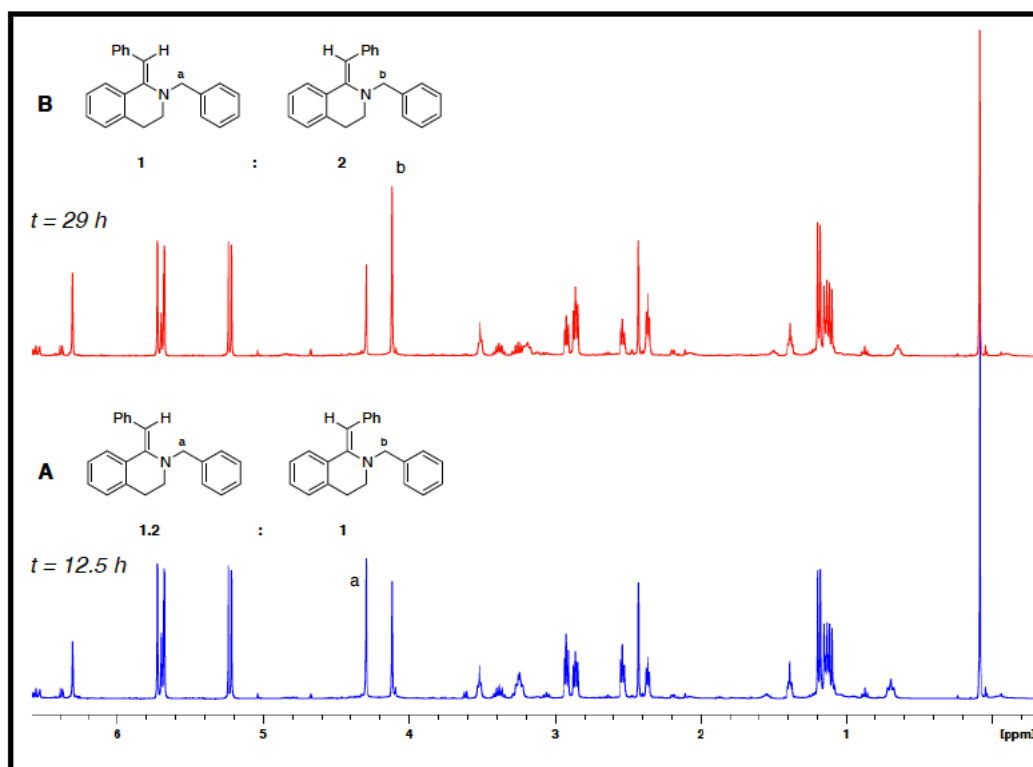


Figure 25. ^1H NMR monitoring of *E:Z* thermal isomerisation mediated by $[(\text{L})\text{SrN}(\text{SiMe}_3)_2(\text{THF})_2]$ **10b** in C_6D_6 at 140°C (Table 20, entry 1). A) $t = 12.5$ h, quantitative conversion to cyclic product, *E:Z* ratio = 1.2:1; B) $t =$ further 16.5 h at 140°C , *E:Z* ratio = 1:2.

In a similar manner to the double hydroamination achieved with divinylbenzene and *n*-propylamine, the inter- and intramolecular steps for the double hydroamination of **194** were found to vary with substrate concentration (Table 21).

Table 21. Effect of concentration of substrate **194** on yield of cyclised enamine product **195** mediated by 10 mol% **10b**, using *n*-propylamine (130°C).^a

Entry	Ratio of substrate 194:PrNH ₂	Concentration of substrate 194/M	Time/h	Ratio of 195:int:PrNH ₂ :sub ^a
1	1:1	0.3	17	41:6:17:36
2	2:1	0.6	14	100:0:0:0
3	10:1	3	2	Polymerisation

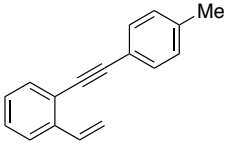
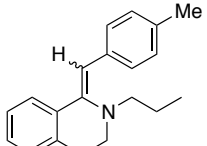
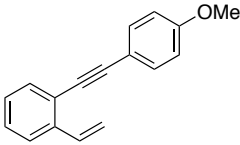
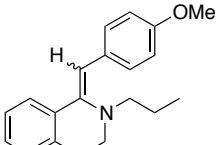
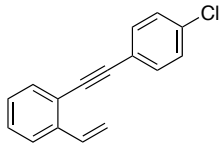
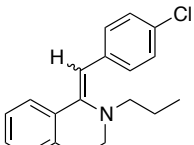
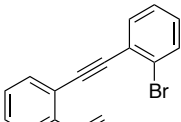
(a) NMR reaction conditions: $[\text{cat}]:[n\text{-propylamine}] = 1:10$, $[\text{PrNH}_2] = 0.3$ M in C_6D_6 at 130°C ; (b) Determined by ^1H NMR spectroscopy at given time t , int = intermolecular hydroamination intermediate, sub = substrate **194**.

Similar to the reaction of divinylbenzene with *n*-propylamine, the subsequential intramolecular cyclization of the intermediate occurred before the intermolecular hydroamination of the styrene moiety was complete.

The results in table 21 show that the cyclohydroamination is favoured considerably when an excess of the substrate **194** is employed, namely in a 2:1 ratio of the amine concentration, which was optimised to be ca. 0.3 M. When a large excess of substrate **194** was added, polymerisation dominated the catalysis. Due to time constraints, detailed kinetic studies were not carried out on these transformations.

The presence of substituents of differing electronic nature on the aromatic ring of the diphenylacetylene functionality led to a marked decrease in cyclic product formation, which is consistent with results obtained previously for alkaline earth metal catalysis.^{5,43} Likewise, the presence of halogen atoms did not increase the activity of the catalytic reaction. The results are outlined in table 22.

Table 22. Effect of substituted diphenylacetylene on cyclisation.^a

Entry	Substrate	Product	Time/h	% Conversion ^b
1	 227	 231	62	47
2	 228	 232	62	30
3	 229	 233	72	24
4	 230	-	24	-

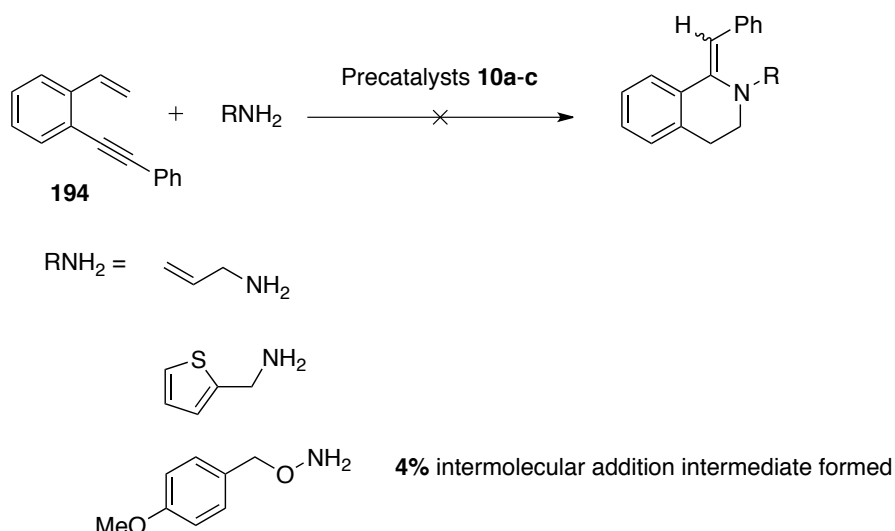
(a) Reaction conditions: [cat]:[amine]:[substrate] = 1:10:20 in *p*-xylene-*d*₁₀ at 130 °C, [amine] = 0.33 M (amine = *n*-propylamine); (b) Determined by ¹H NMR spectroscopy at given time *t*.

Increasing the electron donating ability of the group from methyl to methoxy led to a decreased yield of product, presumably due to the greater repulsion encountered between the nitrogen lone pair and the styrene π electrons during the first addition step.

Polymerisation side reactions were evident during the monitoring of these reactions. This was most pronounced for the halogen substituted aromatic rings whereby the bromine atom in the 2-position led to the formation of a dark green solution when heated (entry 4). A dark brown precipitate was seen to form simultaneous with the appearance of extremely broad alkyl peaks in the ¹H NMR spectrum. Even though the *para*-methyl and methoxy analogues (entries 1 and 2) formed in reasonable amounts, oligomerisation of the styrene unit prevented the products from being isolated in reduced form in quantifiable yields, i.e. as the 1-

benzyltetrahydroisoquinoline analogues. The presence of the chlorine atom led to reduced activity (entry 3), presumably due to deactivation of the catalyst, a problem that has previously been encountered in the hydroamination of *para*-chlorostyrene with benzylamine.⁴⁶

Catalysts **10a–c** were unable to catalyse the addition of allylamine, 2-thiophenemethylamine and O-(4-methoxybenzyl)hydroxylamine to substrate **194**. When allylamine was studied, significant polymerisation of the amine occurred. In all cases, addition of the primary amine to complexes **10a–c** resulted in decolourisation of the complex in solution and no colour indication of catalyst formation was detected.

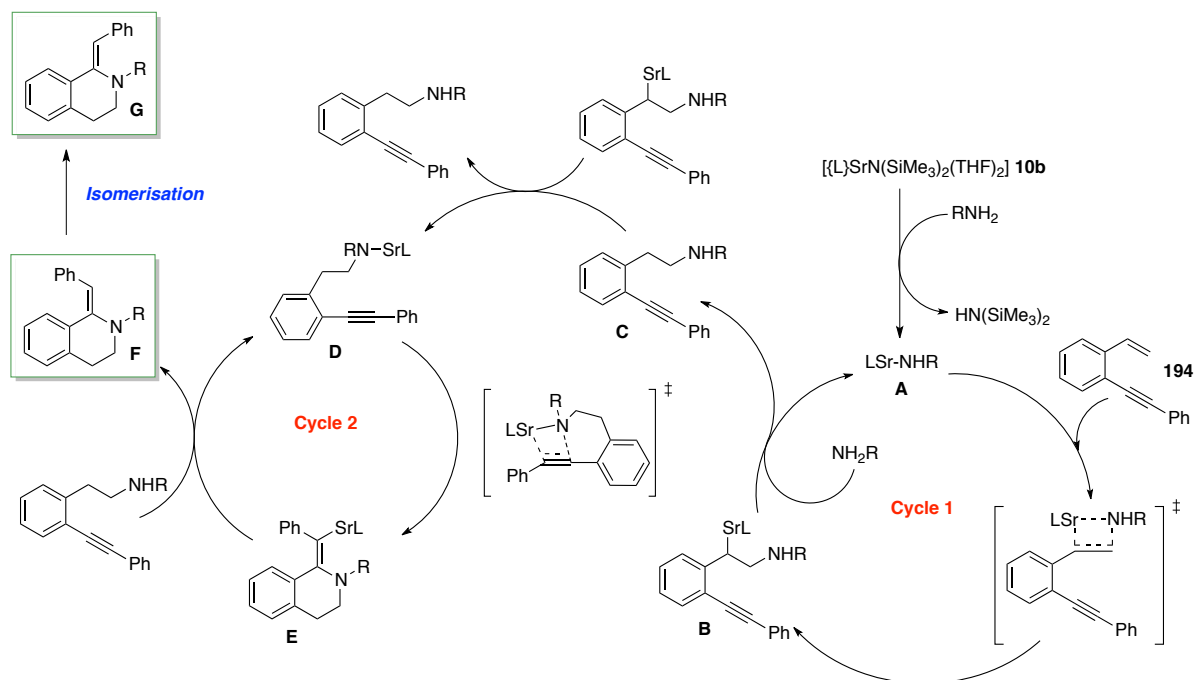


Scheme 63. Attempted hydroamination with allylamine, 2-thiophenemethylamine and O-(4-methoxybenzyl)hydroxylamine.

No intermolecular addition products were detected with allylamine and thiophenemethylamine. However, when analysing the addition of O-(4-methoxybenzyl)hydroxylamine, only 4% of the intermolecular addition product was observed which did not cyclise and the yield could not be improved further.

Taking all of these observations and results into consideration, a proposed mechanism for the ene-yne cyclisations is illustrated in Scheme 64. The initial chemoselective and aryl-directed 2,1-addition of the amine to the alkene component

of the ene-yne substrate and the subsequent predominance of the *E*-alkene isomer of the THIQ product lead us to suggest the provisional mechanism illustrated in scheme 64. The observation that production of the arylethylamine intermediate **C** takes place prior to cyclization indicates that intramolecular addition of Sr–C to the alkynyl group does not occur prior to protonolysis of species **B**. As the concentration of **B** increases, amine **C** will compete with the primary amine substrate to effect protonolysis and provide the necessary strontium amide species **D**. Intramolecular cyclization of **D** will then occur to form the vinyl strontium intermediate **E** which, through protonolysis by **C** or residual amine substrate, releases the *Z* stilbene THIQ product **F**. This *Z*-stilbene in turn may isomerize to its *E*-isomer **G** under the thermal conditions of the catalysis.



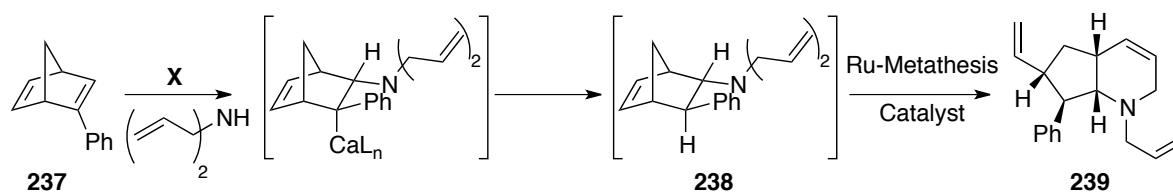
Scheme 64. Proposed mechanism for group 2 catalysed ene-yne cyclisations.

2.2.2 Attempted Hydroaminations

2.2.2.1 Attempted intermolecular hydroamination of strained alkenes

Due to the remarkable success of lanthanide catalysed tandem C–N and C–C bond-forming reactions to effect the construction of pyrrolizidine, indolizidine and many other heteroatom-containing frameworks,^{118,18,119} these processes raised the interesting question of whether multiple C–N and C–C bond formation could be coupled in sequence to assemble, by analogy with the lanthanide catalytic systems similar heteroatom-containing skeletons in a single catalytic cycle.

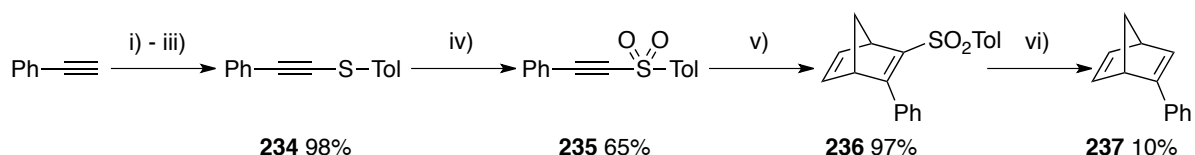
The first of these to be tested was phenyl norbornadiene **237**. It was visualised that norbornadiene **237** would undergo a regioselective calcium-catalysed hydroamination reaction with diallylamine and with *endo*-addition to provide the calcium alkyl species (Scheme 65). Subsequent *endo*-protonation would regenerate the catalyst and provide amine **238**. This product would further be subjected to a ring opening and ring closing metathesis to provide heterocycle **239**. Such alkene reorganisation reactions, coupled with diene hydroamination have very considerable value in organic synthesis.



Scheme 65. Tandem diene hydroamination ring opening/ring closing metathesis envisaged to occur with group 2 precatalysts.

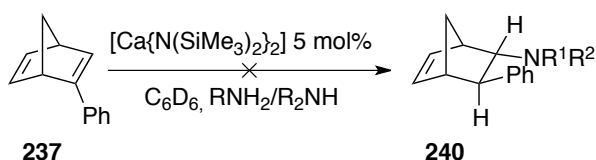
The norbornadiene substrate **237** was synthesised by employing a Diels Alder reaction between **235** and cyclopentadiene as the key step. Following this, a reductive desulfonylation using Sml_2 or Na/Hg was carried out to produce **237**. The

Diels Alder precursor **235** was synthesised from commercially available phenyl acetylene, which was lithiated and reacted with *p*-tolyl disulphide to give alkynyl sulphide **234**. Oxidation using *m*-CPBA produced the alkynyl sulfone in 65% yield. Removal of the aryl sulfone group proved difficult as over reduction of the norbornadiene ring system commonly occurred when Na/Hg was employed. The by-product resulting from this was inseparable from phenyl norbornadiene **237** by column chromatography and also by distillation. Sml_2 solved this problem and cleanly afforded substrate **237**. This alternative step suffered from a severely diminished yield of 10% versus 45% obtained for the Na/Hg reduction. Product **237** was also highly volatile.



Scheme 66. Synthesis of phenyl norbornadiene **237**. i) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$, 30 min; ii) *p*-Tolyl disulphide, THF, $-78\text{ }^{\circ}\text{C}$ – RT, 1.5 h; iii) 4-Nitrobenzyl bromide, THF, $-40\text{ }^{\circ}\text{C}$ – RT, 12 h; iv) *m*-CPBA, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$ – RT, 1 h; v) cyclopentadiene, C_6H_6 , reflux, 48 h; vi) Sml_2 , THF, DMPU, MeOH, RT, 30 min.

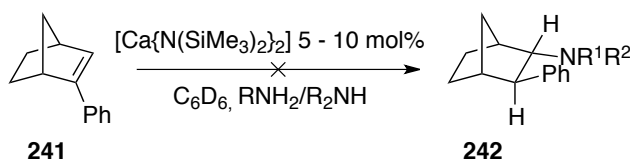
Phenyl norbornadiene **237** was found to rapidly polymerise upon standing at room temperature due to the highly reactive nature of the diene.^{160,161} Because of this, the substrate was kept below $0\text{ }^{\circ}\text{C}$ and introduced to a reaction mixture consisting of 5 mol% $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ and 1 equivalent of amine (Scheme 67).



Scheme 67. Attempted hydroamination of phenyl norbornadiene **240** with primary and secondary amines.

After standing for several hours at room temperature followed by heating, the ^1H NMR did not change and no catalysis took place. Previous attempts to catalytically add primary and secondary amines across substituted styrenes such as β -methylstyrene and 1,2-dihydronaphthalene have been met with limited success, mainly due to ^{steric} impediments calculated to be encountered during the insertive transition state.⁴⁶ Furthermore, when allylamine or diallylamine were examined as amine substrates in Scheme 67, rapid polymerisation of the amines took place and these were deemed unsuitable for further study. Due to the high competing polymerisation reactivity of **237**, the intermolecular hydroamination was not successful.

A strained vinyl arene such as 2-phenyl-2-norbornene was also tested as a suitable substrate for catalytic hydroamination with *n*-propylamine, and pyrrolidine. Likewise, ^1H NMR monitoring did not expose any addition product incorporating these amines using 5–10 mol% of $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2]$ and heating from 80–130 °C (Scheme 68).



Scheme 68. Attempted hydroamination of 2-phenyl-2-norbornene **241**.

2.2.2 Conclusion

Hydroamination of divinylarenes provides a concise synthesis of *N*-alkyl-1-methyltetrahydroisoquinoline structures via coupled intermolecular hydroamination/subsequent intramolecular hydroamination sequences.

Extending the substrate functionality to an activated ene-yne presents a broad reaction scope including alkyl and benzylamines, mediated by the heteroleptic alkaline earth metal complexes supported by the imino anilide ligand $[\{L\}AeN(SiMe_3)_2(THF)_n]$ **10a–c**. These complexes both chemo- and regioselectively catalysed the tandem C–N bond formation providing the corresponding exocyclic enamine products which were further reduced with sodium borohydride to the more stable *N*-substituted-1-benzyltetrahydroisoquinolines. Preliminary data suggest a rate limiting alkyne insertion into the pendant Sr–N bond (involving a highly organised and sterically sensitive transition state) followed by rapid protonolysis to yield the cyclic enamine. The reaction also proceeds with electron rich substituents on the non-styrenyl aromatic ring of the substrate but with reduced activity. Likewise, halogen atoms promote oligomerisation side reactions.

Attempts to achieve intermolecular hydroamination and sequential tandem bicyclisation of trivinylbenzene to construct new C–C bond-forming processes have met with limited success, mainly due to the preferential polymerisation of trivinylbenzene under the reaction conditions. Likewise, due to the competing polymerisation of phenylnorbornadiene **237**, intermolecular hydroamination could not be achieved.

Nonetheless, the methodology described in this chapter provides the first group 2 catalysed tandem C–N bond forming reactions and also an efficient route to access tetrahydroisoquinoline skeletons. The development of these catalytic processes has been supported by the discovery of new fundamental reactions in group 2 and trivalent lanthanide chemistry and by the identification of factors that control these reactions.

2.2.3 Future Work

Coupled intermolecular hydroamination and intramolecular cyclisations mediated by heteroleptic heavier alkaline earth complexes have been efficiently incorporated into catalytic cycles. Such transformations can be readily integrated into novel and regioselective catalytic reactions. One possible application is the assembly of pyrrolizidine, indolizidine and other *N*-containing heterocycles through a series of tandem C–N/C–C bond-forming steps. Such catalytic reactions have previously been attempted with group 2 β -diketiminate complexes but have resulted in isomerisation side reactions.¹²¹ The studies presented in this chapter suggest that the nature of the metal and the supporting ligand may have a dramatic effect upon the relative ease of such reaction steps. Therefore, it remains possible that the bicyclisation product **193** may be formed under different reaction conditions and hence, access to multiple ring systems in a single operation remains promising for future development of the catalytic potential of heteroleptic heavier alkaline earth metal complexes.

3.0 Experimental

3.1 General Experimental Procedures

3.1.1 Analytical Methods

Nuclear magnetic resonance (NMR) spectroscopy

All spectra were obtained at +25 °C unless otherwise stated. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 400 (400 MHz for ^1H and 100 MHz for ^{13}C). Kinetic studies were carried out in cooperation with the NMR service staff of Imperial College London and measured by Peter Haycock. Chemical shifts are stated in *parts per million* (ppm) and referenced to the residual solvent peak (CDCl_3 : ^1H : δ = 7.26 ppm, ^{13}C δ = 77.16 ppm; C_6D_6 : ^1H : δ = 7.15 ppm, ^{13}C : δ = 128.06 ppm) or to tetrakis(trimethylsilyl)silane (^1H : δ = 0.258 ppm (C_6D_6)). Coupling constants (J) are quoted in Hertz (Hz). The following abbreviations are used for the multiplicity of the signals: s = singlet, d = doublet, t = triplet, m = multiplet, bt = broad triplet, bm = broad multiplet, bs = broad singlet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, ttt = triplet of triplets, q = quartet, quin = quintet, sext = sextet, sep = septet, non = nonet.

Mass Spectrometry (MS)

The EI- and ESI-MS spectra were measured with a Micromass Platform II spectrometer (low resolution) and a Micromass Autospec Q spectrometer (low and high resolution) in methanol or ether. The measurements were conducted by the Mass Spectrometry Service of Imperial College London by Jonathan Barton and Lisa Haigh.

Thin Layer and Column Chromatography

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) and then by a potassium permanganate, vanillin, PMA or ninhydrin staining for permanent visualisation. Column chromatography was performed on Merck silica gel 60, particle size 20-63 μm . All chromatography eluents were BDH GPR grade and used without further purification.

Infrared (IR) Spectroscopy

IR spectra were recorded on Unicam and Mattson FTIR spectrometers. Samples were recorded neat with the highest absorptions reported in wavenumbers (cm^{-1}).

3.1.2 General Experimental Methods

Inert Atmosphere Techniques

Experimental work described in this report involved the use and isolation of air-sensitive and hygroscopic magnesium, calcium, strontium and barium complexes. All synthetic work involving these complexes was carried out under a dry inert gas atmosphere (Ar) using a vacuum line (10^{-2} Torr) and glovebox (< 5 ppm of O_2). Generally, standard inert-atmosphere Schlenk techniques were employed for reactions with heavier alkaline earth catalysts and compounds in oven-dried Schlenk glassware which was dried at $180\text{ }^{\circ}\text{C}$ for at least 12 hours prior to evacuation and being filled with dry argon between each evacuation. Solid reagents were pre-weighed in a glovebox under a dry argon atmosphere and added directly to the Schlenk tube in the glovebox.

Catalytic NMR Experiments

The relevant amounts of dry substrates, precatalyst and NMR solvent were directly added to a Young's tap NMR tube under inert atmosphere. All liquids were measured with Eppendorf pipettes. The NMR tube was then sealed and a homogenous solution was obtained by repeatedly turning the tube upside down. After full or maximum conversion of the substrate was reached, the mixture was exposed to air, diluted with Et₂O and filtered through Celite. The evaporated solution yielded a crude oil, which was purified by column chromatography or used immediately for further analysis and reaction.

Sonagashira Cross-Coupling Reactions

PdCl₂(PPh₃)₂ (0.05 equiv) was added to a solution of the terminal acetylene (1.29 equiv) and the aryl iodide (1 equiv) in triethylamine (0.5 M) at 0 °C and allowed to stir for 5 minutes. CuI (0.1 equiv) was then added and the solution was warmed to room temperature and stirred for 12 h, or until deemed complete by TLC analysis. The mixture was filtered through a pad of celite and washed multiple times with diethyl ether. The organic filtrate was successively washed with water and sat. aq. NaCl solution, dried over MgSO₄ and concentrated. The residue was then purified by column chromatography.

3.1.3 Solvents and Reagents

All glassware, celite and molecular sieves were oven dried for 24 hours at 150 °C prior to use.

Solvents

Solvents were purchased from BDH laboratory supplies or the Aldrich Chemical Company. Solvents for flash chromatography were reagent or GPR grade and were used as received. Reaction solvents were distilled as specified: THF and Et₂O were

distilled from sodium benzophenone ketyl. Hexane and toluene were distilled from sodium under an argon atmosphere. CH_2Cl_2 , MeOH, pyridine and Et_3N were distilled from calcium hydride under a nitrogen atmosphere. If not specified otherwise all reagents were purchased from Aldrich Chemical Company. NMR solvents for catalytic reactions were of spectroscopic grade and were purchased from Cambridge Isotope Laboratories. D_6 -benzene, d_8 -toluene and p -xylene- d_{10} were dried through vacuum-transfer from potassium (preheated to 75 °C for 12 hours) and further dried over 4 Å molecular sieves prior to use if employed for analysis or catalytic reactions. All liquid substrates were distilled and degassed by freeze-pump-thaw methods and stored in the glovebox over 4 Å molecular sieves for at least 24 h prior to use.

Substrates for Catalysis

4-Pentyn-1-ol (**72**), 5-hexyn-1-ol (**80**) and 5-(trimethylsilyl)-4-pentyn-1-ol (**86**) were purchased from Sigma Aldrich and used as received. All liquids for the hydroalkoxylation reactions were first distilled under inert atmosphere or reduced pressure then followed by freeze-pump-thaw methods and directly transferred to the glovebox. The alkynyl alcohol substrates were then dried over 4 Å molecular sieves for at least 12 hours. Solid substrates were dried for several hours *in vacuo* or sublimed. Substrates **78**,¹⁶² **108**,¹⁶³ **111**,¹⁶⁴ **118**,¹⁶⁵ **120**¹⁶⁶ and **124**¹¹² were synthesised according to literature procedures and all NMR spectra matched that reported.

For the hydroamination catalysis all liquid amines were purchased from Sigma Aldrich. After distillation from CaH_2 under inert atmosphere, the amines were then degassed by freeze-pump-thaw methods three times to eliminate oxygen and transferred to the glovebox. Divinylbenzene (**181**),¹⁶⁷ trivinylbenzene (**190**)¹⁶⁸ and phenylnorbornadiene (**237**)¹⁶⁰ were synthesised according to literature procedures. Substrates **181**, **190** and **237** were purified via column chromatography (Et_2O /pent) and then subjected to freeze-pump-thaw methods before being transferred to the glovebox. 2-Phenyl-2-norbornene (**241**) was purchased from Sigma Aldrich, distilled from CaH_2 and degassed before being subjected to catalysis.

Inorganic Reagents

Ferrocene and (tetrakis(trimethylsilyl))silane (TMSS) were purchased from Sigma Aldrich Chemical Company and used as received. MgI_2 , CaI_2 , SrI_2 and BaI_2 were purchased from Sigma Aldrich Chemical Company and used as received. Solid potassium hexamethyldisilazane was purchased from Sigma Aldrich Chemical Company and used directly as received in the glovebox. 2.5 M $n\text{BuLi}$ in hexanes and $[\text{Ph}_3\text{P}]_3\text{PdCl}_2$ were purchased from Acros Organics. LiAlH_4 , NaBH_4 and $(n\text{Bu})_2\text{Mg}$ (1.0 M in heptanes) were purchased from Aldrich Chemical Company. CuI was purchased from Alfa Aesar. All were used directly as received.

Ligand Precursors

The β -diketiminate ligand precursor $[(\text{Dipp})\text{NC}(\text{Me})\text{CHC}(\text{Me})\text{NH}(\text{Dipp})]^{169}$ (Dipp = 2,6-di-*iso*-propylphenyl) and the imino anilide ligand $[(\text{Dipp})\text{NCHArNH}(\text{Dipp})]^{170}$ were synthesised using literature procedures.

Organometallic and Organo-group 2 complexes

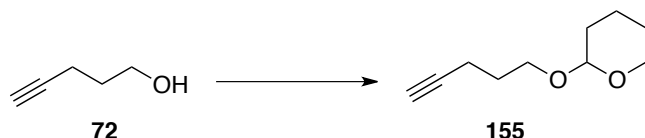
The homoleptic group 2 amides $[\text{M}\{\text{N}(\text{SiMe}_3)_2\}_2]$ ($\text{M} = \text{Ca}, \text{Sr}, \text{Ba}$),¹⁷¹ $[\text{M}\{\text{N}(\text{SiMe}_3)_2\}_2(\text{THF})_2]$ ($\text{M} = \text{Ca}, \text{Sr}, \text{Ba}$)¹⁷² and the calcium alkyl complex $[\text{Ca}\{\text{CH}(\text{SiMe}_3)_2\}_2(\text{THF})_2]^{173}$ were synthesised using literature procedures.

The heteroleptic complexes of the type $[(\text{L})\text{Ae}\{\text{X}\}(\text{THF})_n]$ ($\text{L} = [(\text{Dipp})\text{NC}(\text{Me})\text{CHC}(\text{Me})\text{N}(\text{Dipp})]$, $\text{X} = \text{Me}$, $\text{Ae} = \text{Mg}$, $n = 0$ (**2a**); $\text{X} = \text{N}(\text{SiMe}_3)_2$, $\text{Ae} = \text{Ca}$, $n = 1$ (**2b**)³¹ and ($\text{L} = [(\text{Dipp})\text{NCHArN}(\text{Dipp})]$, $\text{X} = \text{N}(\text{SiMe}_3)_2$, $\text{Ae} = \text{Ca}$, $n = 1$ (**10a**), Sr , $n = 2$ (**10b**), Ba , $n = 2$ (**10c**)³² were synthesised using literature procedures.

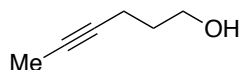
3.2 Alkynyl Alcohol Hydroalkoxylation/Cyclisation

3.2.1 Preparation of Substrates

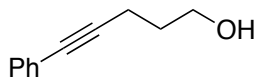
Synthesis of 2-(4-pentyn-1-yloxy)tetrahydro-2*H*-pyran **155**



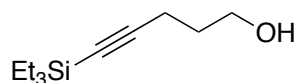
X was prepared via a modified literature procedure.¹⁷⁴ 3,4-Dihydro-2*H*-pyran (3.24 ml, 35.7 mmol) was added dropwise to a solution of 4-pentyn-1-ol (2.77 ml, 29.8 mmol) in dichloromethane (45 ml) at room temperature. Pyridinium *p*-toluene sulfonate (0.1 g, 0.4 mmol) was then added and the reaction mixture stirred at room temperature for 3 hours. After the reaction was complete by TLC analysis, saturated sodium bicarbonate was added and the layers separated. The organic layer was removed and washed with brine (20 ml). The aqueous layers were then combined and washed with 2 × 20 ml of dichloromethane. The organic extracts were combined, dried over MgSO₄, filtered and concentrated to afford a pale yellow oil which was purified by column chromatography (10% EtOAc:hex) to afford a colourless oil (4.50 g, 90%). **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 4.59 (t, 2H, *J* = 2.8 Hz, OCHO), 3.79-3.85 (m, 2H, OCHOCH_aH_b, CH_aH_bOCHO), 3.44-3.51 (m, 2H, OCHOCH_aH_b, CH_aH_bOCHO), 2.28-2.32 (m, 2H, HC≡CCH₂), 1.94 (t, 1H, *J* = 2.6 Hz, HC≡CCH₂), 1.78-1.84 (quint, 2H, *J* = 6.8 Hz, HC≡CCH₂CH₂CH₂), 1.71 (tt, 1H, *J* = 3.1, 12.9, 21.9 Hz, OCHCH_aH_b), 1.50-1.62 (m, 5H, OCHCH_aH_bCH₂CH₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 98.81 (OCHO), 84.00 (HC≡C), 68.44 (HC≡C), 65.78 (CH_aH_bOCHO), 62.21 (CH_aH_bOCHOCH_aH_b), 30.66 (OCHCH_aH_b), 28.69 (HC≡CCH₂CH₂CH₂), 25.47 (OCHCH_aH_bCH₂CH₂), 19.51 (OCHCH_aH_bCH₂CH₂), 15.34 (HC≡CCH₂). The NMR data was in agreement with the literature reported data.¹⁷⁴

Synthesis of hex-4-yn-1-ol **84**

The alcohol was readily prepared from the tetrahydropyranyl ether of 4-pentyn-1-ol **155** and iodomethane¹⁷⁴: A hexane solution of *n*-butyllithium (20 mL of a 2.5 M solution, 150 mmol) was added dropwise under an argon atmosphere at $-78\text{ }^{\circ}\text{C}$ to a solution of 2-(4-pentyn-1-yloxy)tetrahydro-2*H*-pyran **155** (17.2 g, 42 mmol) in 50 mL of dry THF. After 10 min, 3.5 mL (55 mmol) of iodomethane was added dropwise at $-78\text{ }^{\circ}\text{C}$ to the solution of the alkynyl lithium intermediate. The reaction mixture was maintained at $-78\text{ }^{\circ}\text{C}$ for 1 h, and, after warming to room temperature, the THF was removed by mild rotary evaporation (or distillation at atmospheric pressure). The crude product was dissolved in 50 mL of ether and washed with brine (25 mL), and the aqueous phase was back-extracted with ether (15 mL). The combined organic phases were concentrated and the residue was dissolved in 100 mL of methanol. *p*-Toluenesulfonic acid (2 g) was added and the resulting solution was heated at reflux for 3 h. The solvent was removed and the residue dissolved in 50 mL of ether and the solution was then extracted with 15 mL of aqueous 10% sodium carbonate solution. The organic solution was dried over MgSO_4 . The ether was removed by distillation and the residue was distilled through a short path Kugelrohr to give 7.80 g (94%) of hex-4-yn-1-ol. **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 3.74 (t, 2H, $J = 6.1\text{ Hz}$, CH_2OH), 3.39 (s, 1H, OH), 2.23-2.27 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 1.78 (s, 3H, CH_3), 1.73 (t, 2H, $J = 6.5\text{ Hz}$, $\text{CH}_2\text{C}\equiv\text{C}$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 78.47, 76.15, 61.91, 31.35, 15.32, 3.40. The NMR data was in agreement with the literature reported data.¹⁷⁵

Synthesis of 5-phenyl-4-pentyn-1-ol **91**

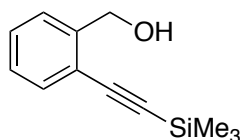
91 was synthesised from iodobenzene and 4-pentyn-1-ol according to the general procedure for Sonagashira cross-coupling reactions. The product was purified by column chromatography (20% EtOAc:hex) to yield the desired alcohol (4.92 g, 82%). **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 7.43 (m, *H*_{Ar}, 2H), 7.30-7.31 (m, *H*_{Ar}, 3H), 3.85 (t, 2H, CH₂OH), 2.58 (t, 2H, *J* = 6.9 Hz, C≡C-CH₂), 1.90 (quint, 2H, *J* = 6.55 Hz, CH₂CH₂CH₂OH). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 131.56 (*C*_{Ar}), 128.24 (*C*_{Ar}), 127.70 (*C*_{Ar}), 123.72 (*C*_{Ar}), 89.33 (Ph-C≡C), 81.16 (Ph-C≡C), 61.84 (CH₂OH), 31.99 16.01. The NMR data was in agreement with the literature reported data.¹⁷⁶

5-(triethylsilyl)pent-4-yn-1-ol **89**

2.5 M *n*-BuLi in hexanes (17.6 ml, 44 mmol) was added at -78 °C to a solution of 4-pentyn-1-ol (1.86 ml, 20 mmol) in THF (20 ml) and stirred at -78 °C for 1 h. Triethylsilyl chloride (10.0 ml, 59.5 mmol) was added dropwise to the reaction mixture and was stirred at -78 °C for a further hour, warmed to room temperature and stirred overnight. 2M HCl (100 ml) was added and the reaction mixture was stirred for 48 h or until deemed complete by TLC analysis. The mixture was extracted with Et₂O (2 × 100 ml) and the combined organic layers were washed with water (2 × 100 ml). The organic phase was dried over MgSO₄, concentrated and the resulting residue was purified by column chromatography (20% EtOAc:hex) to afford **89** as a colourless oil (3.09 g, 78%). **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 3.77 (q, 2H, *J* = 5.8 Hz, CH₂OH), 2.37 (t, 2H, *J* = 6.8 Hz, C≡C-CH₂), 1.78 (quin, 2H, *J* = 6.6 Hz, CH₂CH₂CH₂OH), 1.64 (t, 1H, *J* = 5.6 Hz, OH), 0.97 (t, 9H, *J* = 7.8 Hz, SiCH₂CH₃), 0.58 (q, 6H, *J* = 7.8 Hz, SiCH₂CH₃). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 101.72 (Et₃Si-C≡C), 82.52 (Et₃Si-C≡C), 61.98 (CH₂OH), 31.31 (CH₂CH₂CH₂), 16.60

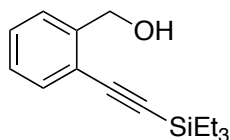
($\text{C}\equiv\text{CCH}_2$), 7.44 (SiCH_2CH_3), 4.48 (SiCH_2CH_3). The NMR data was in agreement with the literature reported data.¹⁷⁷

Synthesis of (2-((trimethylsilyl)ethynyl)phenyl)methanol **99**



99 was synthesised from 2-iodobenzyl alcohol and (trimethylsilyl)acetylene according to the general procedure for Sonagashira cross-coupling reactions. The product was purified by column chromatography (20% EtOAc:hex) to yield the desired alkynyl alcohol as a colourless oil (3.63 g, 83%). **¹H NMR** (400 MHz, CDCl_3) δ /ppm: 7.50 (d, 1H, $J = 7.6$ Hz, H_{Ar}), 7.44 (d, 1H, $J = 7.3$ Hz, H_{Ar}), 7.36 (t, 1H, $J = 6.3$ Hz, H_{Ar}), 7.26 (t, 1H, $J = 8.7$ Hz, H_{Ar}), 4.83 (d, 2H, $J = 6.6$ Hz, CH_2OH), 2.32 (t, 1H, OH), 0.29 (s, 9H, $\text{Si}(\text{CH}_3)_3$). **¹³C NMR** (101 MHz, CDCl_3) δ /ppm: 143.16 (C_{q}), 132.43 (C_{Ar}), 128.96 (C_{Ar}), 127.36 (C_{Ar}), 127.19 (C_{Ar}), 121.16 (C_{q}), 102.60 ($\text{Ar}-\text{C}\equiv\text{C}-\text{SiMe}_3$), 99.60 ($\text{Ar}-\text{C}\equiv\text{C}-\text{SiMe}_3$), 64.07 (CH_2OH), 0.22 ($\text{Si}(\text{CH}_3)_3$). **MS** (EI) m/z : calc. for $\text{C}_{12}\text{H}_{16}\text{OSi}$: 204.0970; found 204.0967. The NMR data was in agreement with the literature reported data.¹⁷⁸

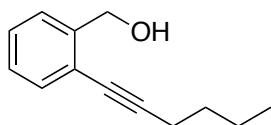
(2-((triethylsilyl)ethynyl)phenyl)methanol **102**



102 was synthesised from 2-iodobenzyl alcohol and (triethylsilyl)acetylene according to the general procedure for Sonagashira cross-coupling reactions. The product was purified by column chromatography (25% EtOAc:hex, $R_f = 0.45$) to yield the desired alcohol as a colourless oil (4.47 g, 76%). **¹H NMR** (400 MHz, CDCl_3) δ /ppm: 7.29-7.52 (m, 4H, H_{Ar}), 4.86 (d, 2H, $J = 6.62$ Hz, CH_2OH), 2.33 (t, 1H, $J = 6.5$ Hz, OH), 1.09 (t, 9H, $J = 7.9$ Hz, SiCH_2CH_3), 0.74 (q, 6H, $J = 7.7$ Hz, SiCH_2CH_3).

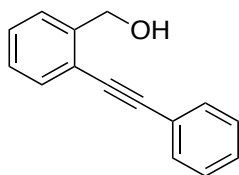
^{13}C NMR (101 MHz, CDCl_3) δ/ppm : 143.14 (C_q), 132.16 (C_{Ar}), 128.87 (C_{Ar}), 127.33 (C_{Ar}), 127.13 (C_{Ar}), 121.33 (C_q), 103.75 ($\text{Ar-C}\equiv\text{C-SiEt}_3$), 97.14 ($\text{Ar-C}\equiv\text{C-SiEt}_3$), 64.13 (CH_2OH), 7.54 (SiCH_2CH_3), 4.42 (SiCH_2CH_3).

(2-(hex-1-ynyl)phenyl)methanol **104**



104 was synthesised from 2-iodobenzyl alcohol and 1-hexyne according to the general procedure for Sonagashira cross-coupling reactions. The product was purified by column chromatography (20% EtOAc:hex) to yield the desired alcohol (3.50 g, 78%). **^1H NMR** (400 MHz, CDCl_3) δ/ppm : 7.38-7.42 (m, 2H, H_{Ar}), 7.20-7.30 (m, 2H, H_{Ar}), 4.79 (d, 2H, $J = 6.5$ Hz, CH_2OH), 2.46 (t, 2H, $J = 6.8$ Hz, $\text{C}\equiv\text{C-CH}_2$), 2.17 (t, 1H, $J = 6.8$ Hz, OH), 1.58-1.65 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.45-1.54 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.96 (t, 3H, $J = 7.4$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$). **^{13}C NMR** (101 MHz, CDCl_3) δ/ppm : 143.39 (C_q), 132.22 (C_{Ar}), 127.93 (C_{Ar}), 127.39 (C_{Ar}), 127.24 (C_{Ar}), 122.23 (C_q), 95.50 ($\text{C}\equiv\text{C}$), 78.11 ($\text{C}\equiv\text{C}$), 64.29 (CH_2OH), 30.83 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 22.04 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 19.21 ($\text{Ar-C}\equiv\text{C-CH}_2$), 13.60 (CH_3). The NMR data was in agreement with the literature reported data.^{179,178}

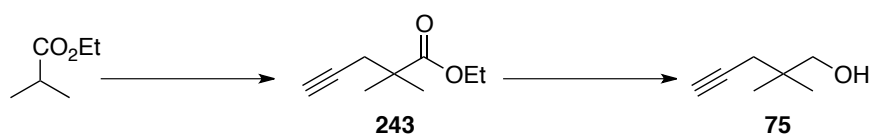
(2-(phenylethynyl)phenyl)methanol **106**



106 was synthesised from 2-iodobenzyl alcohol and phenylacetylene according to the general procedure for Sonagashira cross-coupling reactions. The product was purified by column chromatography (20% EtOAc:hex) to yield the desired alcohol (4.47 g, 90%). **106** could be further purified by recrystallisation from CH_2Cl_2 /hexane

to give white flakes (mp 64–66 °C; lit. mp 65–66 °C)¹⁸⁰. **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 7.51–7.58 (m, 4H, *H*_{Ar}), 7.29–7.41 (m, 5H, *H*_{Ar}), 4.95 (d, 2H, *J* = 6.4 Hz, CH₂OH), 2.17 (t, 1H, *J* = 6.5 Hz, OH). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 142.56 (*C*_q), 132.21 (*C*_{Ar}), 131.58 (*C*_{Ar}), 128.77 (*C*_{Ar}), 128.59 (*C*_{Ar}), 128.47 (*C*_{Ar}), 127.52 (*C*_{Ar}), 127.29 (*C*_{Ar}), 122.93 (*C*_q), 121.33 (*C*_q), 94.22 (C≡C), 86.74 (C≡C), 64.07 (CH₂OH). The NMR data was in agreement with the literature reported data.¹⁸⁰

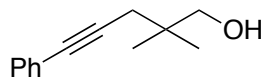
Synthesis of 2,2-dimethylpent-4-yn-1-ol **75**



75 was readily prepared from ethyl isobutyrate according to the literature procedure.¹⁸¹ Reduction of **243** → **75** was achieved via a modified procedure.

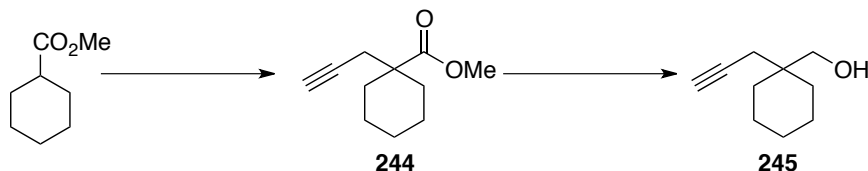
A slurry of lithium aluminium hydride (0.45 g, 11.8 mmol) in dry diethyl ether (30 ml) was cooled to 0 °C. 2,2-dimethyl-pent-4-ynoic acid ethyl ester **243** (1.14 g, 7.4 mmol) was added dropwise over 30 min and stirred at 0 °C for a further hour. The reaction was quenched by the dropwise addition of sat. NH₄Cl (30 ml) (extremely vigorous) and the resulting insoluble precipitate dissolved in 2M HCl. The grey emulsion was transferred to a separating funnel and extracted with diethyl ether (3 × 30 ml). The organic extracts were combined, washed with NaHCO₃ (30 ml), brine (30 ml), dried over MgSO₄, filtered and concentrated under reduced pressure to yield alcohol **75**. Purification by column chromatography (30% EtOAc:hex) yielded **75** as a colourless oil (0.75 g, 90%). **¹H NMR** (400 MHz, CDCl₃): δ/ppm = 3.42 (d, 2H, *J* = 6.0 Hz, CH₂OH), 2.16 (d, 2H, *J* = 2.6 Hz, HC≡C-CH₂), 1.99 (t, 1H, *J* = 2.8 Hz, HC≡C), 1.72 (t, 1H, *J* = 6.0 Hz, OH), 0.97 (s, 6H, C(CH₃)₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 81.13 (HC≡C), 70.80 (CH₂OH), 70.18 (HC≡C), 35.43 (C(CH₃)₂), 26.87 (CH₂C≡CH), 23.70 (C(CH₃)₂). The NMR data was in agreement with the literature reported data.¹⁸¹

Synthesis of 2,2-dimethyl-5-phenylpent-4-yn-1-ol **94**



94 was synthesised from iodobenzene and 2,2-dimethylpent-4-yn-1-ol **75** according to the general procedure for Sonagashira cross-coupling reactions. The product was purified by column chromatography (20 % EtOAc:hex) to yield the desired alcohol as a colourless oil (4.04 g, 77%). **¹H NMR** (400 MHz, *d*₆-benzene) δ /ppm: 7.42-7.44 (m, 2H, *H*_{Ar}), 6.97-6.99 (m, 3H, *H*_{Ar}), 3.21 (s, 2H, CH₂OH), 2.27 (s, 2H, Ph-C $\equiv$ CCH₂), 1.14 (s, 1H, OH), 0.92 (s, 6H, CH₃). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 131.55 (*C*_{Ar}), 128.22 (*C*_{Ar}), 127.65 (*C*_{Ar}), 123.83 (*C*_q), 87.71 (Ph-C $\equiv$ C), 82.58 (Ph-C $\equiv$ C), 71.12 (CH₂OH), 36.00 (C(CH₃)₂), 29.2 (Ph-C $\equiv$ C-CH₂), 23.91 (C(CH₃)₂). The NMR data was in agreement with the literature reported data.¹⁸²

Synthesis of (1-(prop-2-ynyl)cyclohexyl)methanol **245**

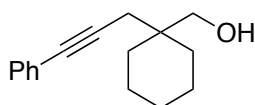


Synthesis of **245** was achieved according to the literature procedure.¹⁸³

Reduction of **244** $\rightarrow$ **245** was achieved via a modified procedure. A slurry of lithium aluminium hydride (0.46 g, 12.2 mmol) in dry diethyl ether (30 ml) was cooled to 0 °C. **244** (2.91 g, 16.2 mmol) was added dropwise over 30 min and stirred at 0 °C for a further hour. The reaction was quenched by the dropwise addition of sat. NH₄Cl (30 ml) (extremely vigorous) and the resulting insoluble precipitate dissolved in 2M HCl. The grey emulsion was transferred to a separating funnel and extracted with diethyl ether (3 $\times$ 30 ml). The organic extracts were combined, washed with NaHCO₃ (30 ml), brine (30 ml), dried over MgSO₄, filtered and concentrated under reduced pressure to yield alcohol **245**. Purification by column chromatography (20% EtOAc:hex) yielded **245** as a colourless oil (1.49 g, 80%). **¹H NMR** (400 MHz,

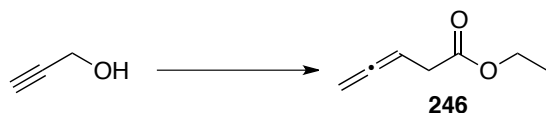
CDCl₃) δ /ppm: 3.55 (s, 2H, CH₂OH), 2.26 (d, 2H, J = 2.6 Hz, CH₂C $\equiv$ CH), 2.00 (t, 1H, J = 2.8 Hz, CH₂C $\equiv$ CH), 1.38-1.46 (m, 10H, (CH₂)₅). ¹³C NMR (101 MHz, CDCl₃) δ /ppm: 82.01 (HC $\equiv$ CCH₂), 70.43 (CH₂OH), 68.61 (HC $\equiv$ CCH₂), 37.62 (C(CH₂)₅), 31.87 (cyclohexyl ring; CH₂(CH₂)₃CH₂), 26.15 (cyclohexyl ring; (CH₂)₂CH₂(CH₂)₂), 25.12 (CH₂C $\equiv$ CH), 21.52 (cyclohexyl ring; CH₂CH₂CH₂CH₂CH₂). The NMR data was in agreement with the literature reported data.¹⁸⁴

2,2-Cyclohexyl-5-phenylpent-4-yn-1-ol **96**



96 was synthesised from iodobenzene and **245** according to the general procedure for Sonagashira cross-coupling reactions. The product was purified by column chromatography (20 % EtOAc:pent; R_f = 0.5) to yield the desired alcohol as a colourless oil (3.89 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ /ppm: 7.37-7.40 (m, 2H, H_{Ar}), 7.25-7.27 (m, 3H, H_{Ar}), 3.6 (s, 2H, CH₂OH), 2.46 (s, 2H, C $\equiv$ CCH₂), 1.65 (s, 1H, OH), 1.43-1.50 (m, 10H, (CH₂)₅). ¹³C NMR (101 MHz, CDCl₃) δ /ppm: 131.58 (C_{Ar}), 128.23 (C_{Ar}), 127.65 (C_{Ar}), 123.83 (C_q), 87.57 (C $\equiv$ C), 82.86 (C $\equiv$ C), 68.85 (CH₂OH), 38.22 (C(CH₂)₅), 32.06 (cyclohexyl ring; CH₂(CH₂)₃CH₂), 26.23 (cyclohexyl ring; (CH₂)₂CH₂(CH₂)₂), 26.17 (CH₂-C $\equiv$ C), 21.63 (cyclohexyl ring; CH₂CH₂CH₂CH₂CH₂).

Synthesis of ethyl penta-3,4-dienoate **246**



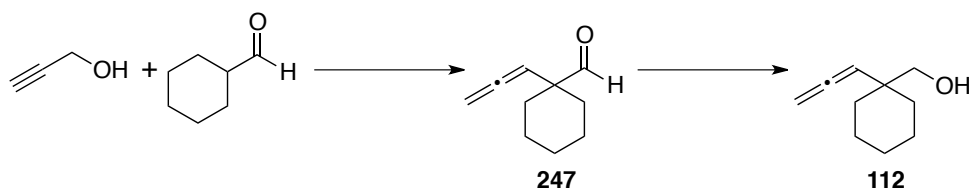
The allene was prepared via a modified literature procedure.¹⁸⁵ A mixture of propargyl alcohol (6.93 ml, 119 mmol) and triethyl orthoacetate (74.2 ml, 405 mmol) was heated to 100 °C with stirring in a two-neck flask fitted with a still head. Propionic acid (1.51 ml, 20.2 mmol) was added and the reaction mixture heated to 160 °C, allowing the steady distillation of ethanol out of the reaction flask. When the

distillation had ceased (approx. 3 h), propionic acid (1.07 ml, 14.3 mmol) was added and the mixture stirred for a further 3 hours at 160 °C. The reaction was cooled to room temperature and 1M HCl (15 ml) was added. The resulting mixture was extracted with Et₂O (3 × 25 ml) and the combined organic extracts washed with saturated NaHCO₃ (15 ml) then brine (15 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude liquid was purified by distillation (65–71 °C, 20 mmHg; lit. b.p. 65–70 °C, 20 mmHg) to afford the corresponding ester as a colourless oil (8.90 g, 59%). ¹H NMR (400 MHz, CDCl₃) δ/ppm: 5.22 (m, 1H, CH₂=C=CH), 4.73 (m, 2H, CH₂=C=CH), 4.12 (qua, 2H, *J* = 7.1 Hz, CO₂CH₂CH₃), 3.00 (m, 2H, CH₂CO₂Et), 1.23 (t, 3H, *J* = 7.1 Hz, COCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) δ/ppm: 209.3 (C=C=C), 171.4 (C=O), 83.5 (HC=C=CH₂), 75.7 (HC=C=CH₂), 60.8 (COCH₂CH₃), 34.2 (CH₂CO₂Et), 14.2 (COCH₂CH₃). The NMR data was in agreement with the literature reported data.

Synthesis of 3,4-pentadien-1-ol **110**



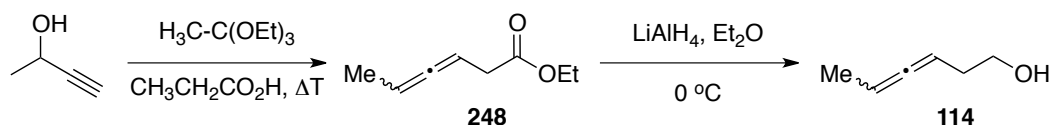
3,4-Penta-dien-1-ol was prepared via the reduction of the corresponding ethyl ester **246** by LiAlH₄ according to the literature procedure.¹⁸⁵ Purification by column chromatography (30% Et₂O:pent) gave **110** as a colourless oil (5.47 g, 68%). ¹H NMR (400 MHz, CDCl₃): δ/ppm = 5.10 (q, 1H, *J* = 6.7 Hz, H₂C=C=CH), 4.68-4.72 (m, 2H, H₂C=C=CH), 3.68 (q, 2H, *J* = 6.1 Hz, CH₂OH), 2.22-2.27 (m, 2H, CH₂CH₂CH₂OH), 1.94 (t, 1H, *J* = 5.8 Hz, OH). ¹³C NMR (101 MHz, CDCl₃) δ/ppm: 208.63 (C=C=C), 86.47 (H₂C=C=CH), 75.18 (H₂C=C=C), 61.90 (CH₂OH), 31.60 (HCCH₂CH₂OH). The NMR data was in agreement with the literature reported data.¹⁸⁵

Synthesis of 2,2-cyclohexylpenta-4,4-dien-1-ol **112**

2,2-Cyclohexylpenta-4,4-dien-1-ol was prepared from cyclohexanecarboxaldehyde according to a reported procedure.¹⁸⁶ A mixture of propargyl alcohol (3.06 ml, 52.6 mmol), cyclohexanecarboxaldehyde (6.38 ml, 52.6 mmol) and *para*-toluenesulfonic acid (88 mg) in toluene (88 ml) was heated at reflux with azeotropic removal of water using a Dean-Stark apparatus. After 24 h the reaction was cooled and concentrated *in vacuo*. The crude oil was dissolved in EtOH (100 ml), cooled to 0 °C and sodium borohydride added portionwise (2 g, 52.6 mmol). The reaction mixture was warmed to room temperature and stirred for 6 h. Acetone was added and the solvents removed *in vacuo*. EtOAc (50 ml) was added and water (50 ml) and the layers separated. The aqueous phase was extracted with EtOAc (3 × 30 ml). The organic layers were combined, washed with brine (50 ml), dried over MgSO₄, filtered and concentrated. The crude mixture was purified by column chromatography (20% EtOAc:hex) to afford **112** as a pale yellow oil (1.52 g, 19%).

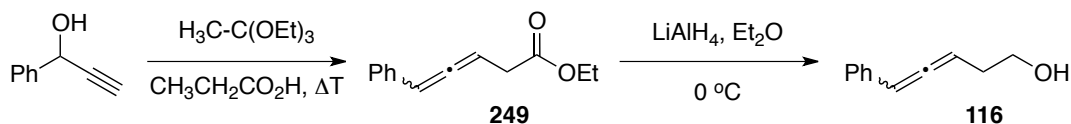
¹H NMR (400 MHz, CDCl₃) δ/ppm: 4.95 (t, 1H, *J* = 6.7 Hz, H₂C=C=CH), 4.78 (d, 2H, *J* = 6.7 Hz, H₂C=C=CH), 3.37 (d, 2H, *J* = 6.3 Hz, CH₂OH), 1.27-1.58 (m, 11H, (CH₂)₅, OH). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 208.3 (C=C=C), 95.5 (H₂C=C=CH), 76.5 (CH₂=C=CH), 71.4 (CH₂OH), 40.6 (C(CH₂)₅), 32.8 (cyclohexyl ring; CH₂(CH₂)₂CH₂), 26.3 (cyclohexyl ring; (CH₂)₂CH₂(CH₂)₂), 22.0 (cyclohexyl ring; CH₂CH₂CH₂CH₂CH₂). The NMR data was in agreement with previously reported data.¹⁸⁶

Synthesis of hexa-3,4-dien-1-ol **114**



Hexa-3,4-dien-1-ol **114** was synthesised according to the literature procedure.¹⁸⁷ Purification by column chromatography gave **114** as a colourless oil (0.42 g, 64% (from LiAlH₄ reduction)). ¹H NMR (400 MHz, CDCl₃) δ/ppm: 4.94-5.00 (m, 2H, CH₃HC=C=CHCH₂), 3.44 (t, 2H, *J* = 5.9 Hz, CH₂OH), 2.03-2.09 (m, 2H, HCCCH₂CH₂OH), 1.56 (brs, 1H, OH), 1.47-1.50 (m, 3H, CH₃HC=C=CH). ¹³C NMR (101 MHz, CDCl₃) δ/ppm: 205.63 (C=C=C), 87.06 (CH₃HC=C=C), 85.73 (CH₃HC=C=C), 61.88 (CH₂OH), 32.52 (CHCH₂CH₂OH), 14.29 (CH₃). The NMR data was in agreement with the literature reported data.

Synthesis of 5-phenylpenta-3,4-dien-1-ol **116**



5-Phenylpenta-3,4-dien-1-ol was prepared via an adapted method.¹⁸⁷ An oven dried three-neck flask was charged with 1-phenyl-2-propyn-1-ol (8.74 ml, 71.9 mmol), triethyl orthoacetate (44.8 ml, 244.4 mmol) and propionic acid (0.91 ml, 12.2 mmol) and fitted with a Dean-Stark trap. The reaction mixture was heated to 150 °C for 2.5 h at which point additional propionic acid (0.64 ml, 8.63 mmol) was added and the reaction mixture stirred for a further 2.5 h. The reaction mixture was cooled to room temperature and all volatiles carefully removed *in vacuo*. The allenic ester **249** was purified by a short flash chromatography (20% Et₂O:pent) and used directly in the next step.

A slurry of lithium aluminium hydride (0.64 g, 16.93 mmol) in dry THF (40 ml) was cooled to 0 °C. **249** (1.71 g, 8.46 mmol) was added dropwise and stirred at 0 °C for

a further hour. The reaction was quenched by the dropwise addition of sat. NH_4Cl (20 ml) (extremely vigorous) and the resulting insoluble precipitate dissolved in 2M HCl . The grey emulsion was transferred to a separating funnel and extracted with diethyl ether (3×40 ml). The organic extracts were combined, washed with NaHCO_3 (30 ml), brine (30 ml), dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by column chromatography (30% Et_2O :pent) yielded homoallenic alcohol **116** as a colourless oil (0.96 g, 71%).

^1H NMR (400 MHz, CDCl_3) δ /ppm: 6.18-6.21 (m, 1H, $\text{PhHC}=\text{C}=\text{CH}$), 5.59 (q, 1H, $J = 6.6$ Hz, $\text{PhHC}=\text{C}=\text{CH}$), 3.79 (t, 2H, $J = 6.2$ Hz, CH_2OH), 2.30-2.43 (m, 2H, $\text{HCCH}_2\text{CH}_2\text{OH}$), 1.54 (bs, 1H, OH). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 205.73 ($\text{C}=\text{C}=\text{C}$), 134.43 (C_q), 128.69 (C_Ar), 126.98 (C_Ar), 126.67 (C_Ar), 95.17 ($\text{PhHC}=\text{C}=\text{CH}$), 91.52 ($\text{PhHC}=\text{C}=\text{CH}$), 62.00 (CH_2OH), 32.09 ($\text{HCCH}_2\text{CH}_2\text{OH}$). The NMR data was in agreement with the literature reported data.¹⁸⁸

Synthesis of 2-methylenetetrahydrofuran **73**



Tetrahydrofurfuryl bromide (1.03 ml, 9.09 mmol) was added to a cold solution of anhydrous potassium hydroxide (1.04 g, 18.1 mmol) in diethylene glycol (5 ml) under argon. The mixture was fitted with a distillation apparatus and warmed to 115 °C; distillation commenced and the temperature was raised to 155 °C. The distillate was collected over potassium carbonate, and separated into two layers. The organic layer was then filtered through a cotton plug and redistilled through a Vigreux column to give a colourless oil (0.34 g, 45%); bp 101–102 °C. The exocyclic enol ether must be used immediately when formed and decomposes under inert atmosphere within a few hours. **^1H NMR** (400 MHz, CDCl_3): δ /ppm = 4.51 (s, 1H, $\text{OC}=\text{CH}_{\text{trans}}\text{H}_{\text{cis}}$), 3.89 (s, 1H, $\text{OC}=\text{CH}_{\text{trans}}\text{H}_{\text{cis}}$), 3.63 (t, 2H $J = 6.6$ Hz, OCH_2), 2.09 (t, 2H, $J = 7.3$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.33 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 163.16 ($\text{H}_2\text{C}=\text{C}$), 79.03 ($\text{H}_2\text{C}=\text{C}$), 70.27 (OCH_2),

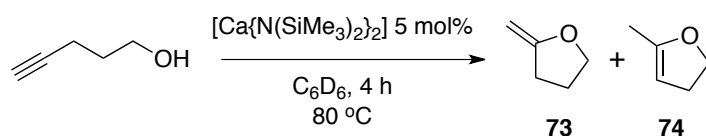
29.10 (OCH₂CH₂CH₂), 25.07 (OCH₂CH₂CH₂). The NMR data was in agreement with the literature reported data.⁹⁹

3.2.2 Catalytic Hydroalkoxylation Reactions

General procedure for the catalytic intramolecular hydroalkoxylation of alkynyl alcohols:

In a glovebox, a freshly prepared solution of the corresponding heavier alkaline earth bis(amide) (**75a–c**) in *d*₆-benzene (100 g/L, 0.075 mmol) was added to a Young's tap NMR tube filled with the alkynyl alcohol (0.15 mmol) and *d*₆-benzene (*V*_{Total} = 500.0 μL) to yield a colourless solution. The tube was sealed and shaken to mix the two components. The tube was removed from the glovebox and placed in a pre-heated oil bath (60–120 °C) for 0.3–72 h. After full/maximum conversion was observed by ¹H NMR spectroscopy, the yield was determined by using the released HN(SiMe₃)₂ or added Si(SiMe₃)₄ or ferrocene as an internal integration standard and ¹³C and 2D NMR spectra were recorded. The reaction was then diluted with Et₂O, filtered over Celite and the solvent carefully removed under reduced pressure to yield a colourless oil which was submitted for high resolution mass spectrometry.

Synthesis of 2-methylenetetrahydrofuran **73**

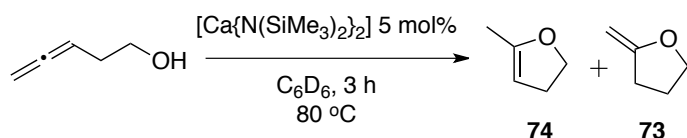


According to the general procedure for catalytic NMR experiments **73** was quantitatively formed after 4 h at 80 °C.

Characterisation for **73**: ¹H NMR (400 MHz, *d*₆-benzene) δ/ppm: 4.47–4.58 (m, 1H, C=CH_{trans}H_{cis}), 3.85–3.98 (m, 1H, C=CH_{trans}H_{cis}), 3.64 (t, 2H, *J* = 6.6 Hz, OCH₂CH₂CH₂), 2.10 (tt, 2H, *J* = 1.6 Hz, *J* = 7.7 Hz, OCH₂CH₂CH₂), 1.32 (quint, 2H, *J* = 7.1 Hz, OCH₂CH₂CH₂). ¹³C NMR (101 MHz, *d*₆-benzene) δ/ppm: 163.3

($C=CH_{trans}H_{cis}$), 79.1 ($C=CH_{trans}H_{cis}$), 70.4 ($OCH_2CH_2CH_2$), 29.2 ($OCH_2CH_2CH_2$), 25.2 ($OCH_2CH_2CH_2$). **MS** (EI) m/z : 85 (M^+), 84 (M).

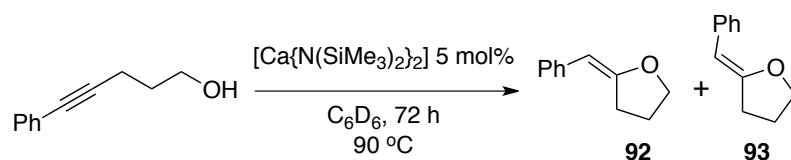
Synthesis of 5-methyl-2,3-dihydrofuran **74** and 2-methylenetetrahydrofuran **73**



According to the general procedure for catalytic NMR experiments quantitative conversion was achieved after 4 h, 90 °C.

Characterisation for **74**: **^1H NMR** (400 MHz, d_6 -benzene) δ /ppm: 4.37–4.46 (m, 1H, $\text{CH}_3\text{C}=\text{CH}$), 4.07 (t, 2H, $J = 9.3$ Hz, OCH_2CH_2), 2.23–2.35 (m, 2H, OCH_2CH_2), 1.60–1.74 (m, 3H, $\text{CH}_3\text{C}=\text{CH}$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 155.5 ($\text{CH}_3\text{C}=\text{CH}$), 94.3 ($\text{CH}_3\text{C}=\text{CH}$), 69.9 (OCH_2CH_2), 30.5 (OCH_2CH_2), 13.5 ($\text{CH}_3\text{C}=\text{CH}$). **MS** (EI) m/z : 85 (M^+), 84 (M).

Synthesis of (*E*)/(*Z*)-2-benzylidenetetrahydrofuran **92** and **93**

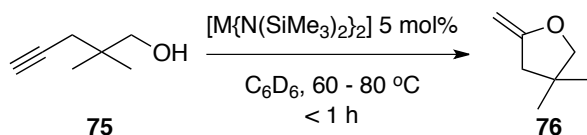


92 was prepared according to the general procedure for catalytic NMR experiments.

Characterisation for **92** and **93**: **^1H NMR** (400 MHz, d_6 -benzene) δ /ppm: 7.56–7.58 (m, H_{Ar}), 7.25–7.33 (m, H_{Ar}), 7.11–7.13 (m, H_{Ar}), 6.35 (s, 1H, $\text{Ph}-\text{CH}=\text{C}$, **92**), 5.35 (s, 1H, $\text{Ph}-\text{CH}=\text{C}$, **93**), 3.85 (t, 2H, $J = 6.7$ Hz, OCH_2CH_2 , **93**), 3.73 (t, 2H, $J = 6.8$ Hz, OCH_2CH_2 , **92**), 2.54 (t, 2H, $J = 6.8$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2$, **93**), 2.37–2.39 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$, **92**), 1.84 (quint, 2H, $J = 6.6$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2$, **93**), 1.44 (quint, 2H, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2$, **92**). **^{13}C NMR** (101 MHz, d_6 -benzene) δ /ppm: 159.7 ($\text{Ph}-\text{CH}=\text{C}$, **92**), 157.4 ($\text{Ph}-\text{CH}=\text{C}$, **93**), 138.6 (C_q), 137.9 (C_q), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 127.4 (C_{Ar}), 127.2 (C_{Ar}), 124.9 (C_{Ar}), 124.7 (C_{Ar}), 99.6 ($\text{Ph}-\text{CH}=\text{C}$, **92**), 97.8 ($\text{Ph}-\text{CH}=\text{C}$, **93**).

CH=C, **93**), 71.8 (OCH₂CH₂CH₂, **93**), 69.1 (OCH₂CH₂CH₂, **92**), 31.0 (OCH₂CH₂CH₂, **93**), 28.4 (OCH₂CH₂CH₂, **92**), 25.1 (OCH₂CH₂CH₂, **92**), 24.1 (OCH₂CH₂CH₂, **93**). **HRMS** (ESI) *m/z*: calc. for C₁₂H₁₃O: 161.0966; found 161.0960.

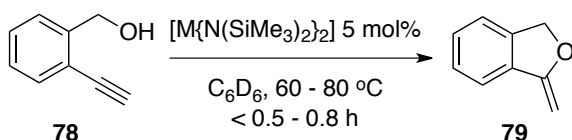
Synthesis of 4,4-dimethyl-2-methylenetetrahydrofuran **76**



76 was prepared according to the general procedure for catalytic NMR experiments.

¹H NMR (400 MHz, *d*₆-benzene) δ/ppm: 4.54 (s, 1H, C=CH_{cis/trans}), 3.92 (s, 1H, C=CH_{cis/trans}), 3.44 (s, 2H, OCH₂), 1.99 (s, 2H, OCH₂C(CH₃)₂CH₂), 0.74 (s, 6H, C(CH₃)₂). **¹³C NMR** (101 MHz, *d*₆-benzene) δ/ppm: 163.3 (OC=CH₂), 81.3 (OCH₂), 80.1 (OC=CH₂), 43.9 (OCH₂C(CH₃)₂CH₂), 37.7 (C(CH₃)₂), 24.5 (C(CH₃)₂). **MS** (EI) *m/z*: 113 (MH⁺).

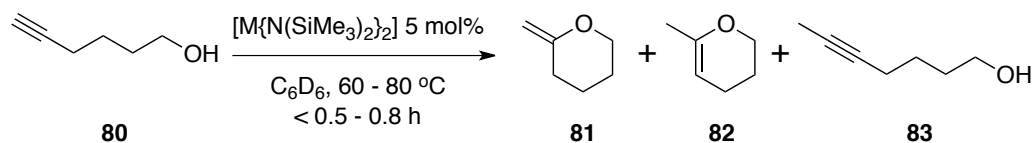
Synthesis of 1-methylene-1,3-dihydroisobenzofuran **79**



79 was prepared according to the general procedure for catalytic NMR experiments.

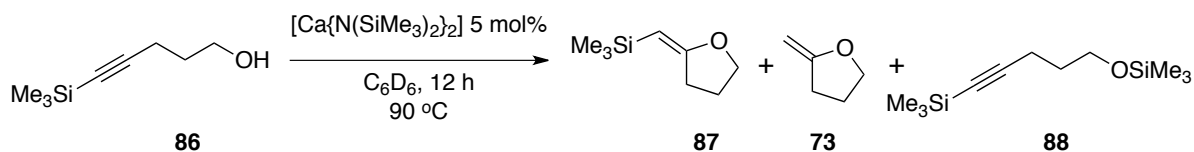
¹H NMR (400 MHz, *d*₆-benzene) δ/ppm: 7.16-7.24 (m, 1H, *H*_{Ar}), 6.90-7.00 (m, 2H, *H*_{Ar}), 6.62-6.70 (m, 1H, *H*_{Ar}), 4.80 (s, 2H, CH₂O), 4.72 (s, 1H, C=CH_{cis}), 4.55 (s, 1H, C=CH_{trans}). **¹³C NMR** (101 MHz, *d*₆-benzene) δ/ppm: 162.5 (OC=CH₂), 140.6 (*C*_q), 134.2 (*C*_q), 128.8 (*C*_q), 128.8 (*C*_{Ar}), 127.9 (*C*_{Ar}), 121.3 (*C*_{Ar}), 120.8 (*C*_{Ar}), 78.2 (CH₂O), 73.5 (OC=CH₂). **HRMS** (ESI) *m/z*: calc. for C₉H₈O: 132.0575; found 132.0574.

Synthesis of 2-methylenetetrahydro-2*H*-pyran **81**



81 was prepared according to the general procedure for catalytic NMR experiments. Characterisation of **81**: 1H NMR (400 MHz, d_6 -benzene) δ /ppm: 4.51 (s, 1H, $C=CH_2$), 4.03 (s, 1H, $C=CH_2$), 3.60 (t, 2H, $J = 5.4$ Hz, OCH_2CH_3), 1.98 (t, 2H, $J = 6.3$ Hz, $H_2C=CCH_2$), 1.22-1.38 (m, 4H, OCH_2CH_2 , $H_2C=CCH_2CH_2$). ^{13}C NMR (101 MHz, d_6 -benzene) δ /ppm: 160.6 ($C=CH_2$), 91.2 ($C=CH_2$), 69.2 (OCH_2), 29.6 ($H_2C=CCH_2$), 25.4 ($H_2C=CCH_2CH_2$), 23.4 (OCH_2CH_2).

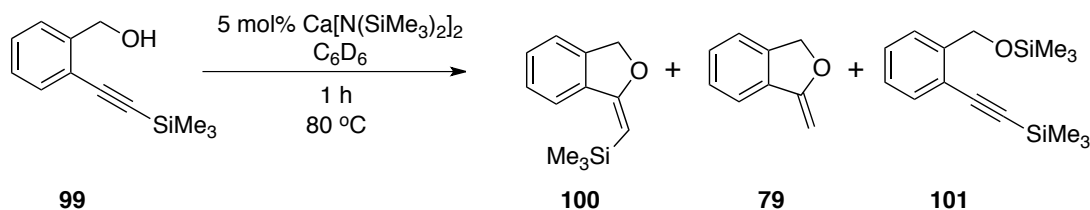
Synthesis of trimethyl(5-(trimethylsilyl)pent-4-ynyloxy)silane **88**



87, **73** and **88** were prepared according to the general procedure for catalytic NMR experiments.

Characterisation for **88**: 1H NMR (400 MHz, d_6 -benzene) δ /ppm: 3.65 (t, 2H, $J = 6.0$ Hz, CH_2OSiMe_3), 2.35 (t, 2H, $J = 7.0$ Hz, $Me_3SiC\equiv CCH_2$), 1.69-1.75 (m, 2H, $C\equiv C-CH_2CH_2CH_2OSiMe_3$), 0.32 (s, 9H, $CH_2OSi(CH_3)_3$), 0.19 (s, 9H, $(CH_3)_3Si-C\equiv C$). ^{13}C NMR (101 MHz, $CDCl_3$) δ /ppm: 107.28 ($Me_3Si-C\equiv C$), 84.50 ($Me_3Si-C\equiv C-CH_2$), 60.59 (CH_2OSiMe_3), 31.50 ($CH_2CH_2CH_2OSiMe_3$), 16.30 ($C\equiv C-CH_2$), 0.07 ($OSi(CH_3)_3$), -0.72 ($(CH_3)_3Si-C\equiv C$). **MS** (CI) m/z : 229 (MH^+) **88**, 157 (MH^+) **87**, 85 (MH^+) **73**.

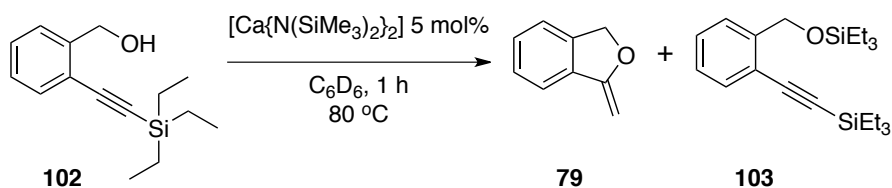
Synthesis of (*E*)-(isobenzofuran-1(3*H*)-ylidenemethyl)trimethylsilane **100**



100, **79** and **101** were prepared according to the general procedure for catalytic NMR experiments.

Characterisation for **100**: $^1\text{H NMR}$ (400 MHz, d_6 -benzene) δ /ppm: 7.77-7.80 (m, 1H, H_{Ar}), 7.55-7.58 (m, 1H, H_{Ar}), 7.32-7.34 (m, 1H, H_{Ar}), 7.07-7.10 (m, 1H, H_{Ar}), 5.18 (s, 2H, CH_2O), 5.11 (s, 1H, $\text{C}=\text{CHSiMe}_3$), 0.37 (s, 9H, $\text{Si}(\text{CH}_3)_3$). $^{13}\text{C NMR}$ (101 MHz, d_6 -benzene) δ /ppm: 143.70 ($\text{C}=\text{CHSiMe}_3$), 140.369 (C_q), 132.47 (C_q), 132.00 (C_{Ar}), 128.62 (C_{Ar}), 126.67 (C_{Ar}), 120.57 (C_{Ar}), 62.86 ($\text{C}=\text{CHSiMe}_3$), 62.76 (CH_2O), -0.18 ($\text{Si}(\text{CH}_3)_3$). **MS** (EI) m/z : 277 (MH^+) **101**, 276 (M) **101**, 205 (MH^+) **100**, 204 (M) **100**, 133 (MH^+) **79**.

Synthesis of triethyl(2-((triethylsilyl)ethynyl)benzyloxy)silane **103**

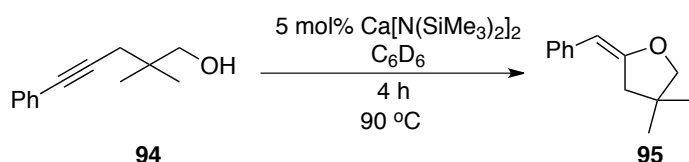


79 and **103** were prepared according to the general procedure for catalytic NMR experiments.

$^1\text{H NMR}$ (400 MHz, d_6 -benzene) δ /ppm: 7.89-7.95 (d, 1H, $J = 7.7$ Hz, H_{Ar} , **103**), 7.57-7.59 (m, 1H, H_{Ar} , **103**), 7.33-7.35 (m, 1H, H_{Ar} , **103**), 7.24-7.28 (m, 2H, H_{Ar} , **79**), 7.07-7.10 (m, 1H, H_{Ar} , **103**), 7.00-7.04 (m, 1H, H_{Ar} , **79**), 6.78-6.81 (m, 1H, H_{Ar} , **79**), 5.27 (s, 2H, $\text{CH}_2\text{OSiEt}_3$, **103**), 4.93 (s, 2H, CH_2O , **79**), 4.85 (s, 1H, $\text{C}=\text{CH}_{\text{cis}}$, **79**), 4.68 (s, 1H, $\text{C}=\text{CH}_{\text{trans}}$, **79**), 1.25 (t, 9H, $J = 7.8$ Hz, $\text{OSiCH}_2\text{CH}_3$, **103**), 1.14 (t, 9H, $J = 8.0$ Hz, $\text{C}\equiv\text{C}-\text{SiCH}_2\text{CH}_3$, **103**), 0.76-0.85 (m, 12H, SiCH_2CH_3 , **103**). $^{13}\text{C NMR}$ (101

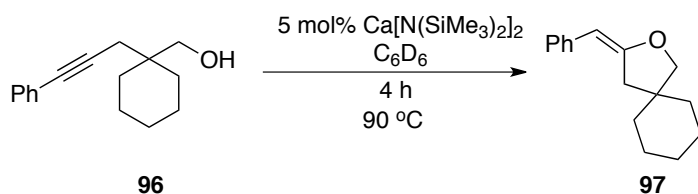
MHz, *d*₆-benzene) δ /ppm: 162.27 (OC=CH₂, **79**), 144.0 (C_q, **103**), 140.36 (C_q, **79**), 134.01 (C_q, **79**), 132.03 (C_{Ar}, **103**), 127.71 (C_{Ar}, **103**), 128.81 (C_{Ar}, **79**), 128.60 (C_{Ar}, **79**), 126.51 (C_{Ar}, **79**), 125.88 (C_{Ar}, **103**), 121.10 (C_{Ar}, **79**), 120.55 (C_{Ar}, **103**), 120.23 (C_q, **103**), 104.35 (Ar-C $\equiv$ C, **103**) 96.74 (C $\equiv$ C-SiEt₃, **103**), 77.94 (C=CH₂, **79**), 73.27 (CH₂OSiEt₃, **103**), 63.23 (CH₂O, **79**) 7.62 (OSi(CH₂CH₃)₃, **103**), 6.85 (C $\equiv$ C-Si(CH₂CH₃)₃, **103**), 4.69 (OSi(CH₂CH₃)₃, C $\equiv$ C-Si(CH₂CH₃)₃, **103**). **MS** (Cl) *m/z*: 360 (MH⁺) **103**, 133 (MH⁺) **79**, 132 (M) **79**.

Synthesis of (*E*)-2-benzylidene-4,4-dimethyltetrahydrofuran **95**



95 was prepared according to the general procedure for catalytic NMR experiments. **¹H NMR** (400 MHz, *d*₆-benzene) δ/ppm: 7.28-7.34 (m, 4H, H_{Ar}), 7.13-7.17 (m, 1H, H_{Ar}), 6.37 (s, 1H, CH=C), 3.54 (s, 2H, OCH₂), 2.38 (s, 2H, OCH₂C(CH₃)₂CH₂), 0.83 (s, 6H, C(CH₃)₂). **¹³C NMR** (101 MHz, *d*₆-benzene) δ/ppm: 159.55 (OC=CH), 138.30 (C_q), 128.39 (C_{Ar}), 127.24 (C_{Ar}), 124.57 (C_{Ar}), 100.39 (PhCH=C), 80.01 (OCH₂), 43.32 (OCH₂C(CH₃)₂CH₂), 38.13 (C(CH₃)₂), 24.72 (C(CH₃)₂). **MS** (EI) *m/z*: 189 (MH⁺), 188 (M).

Synthesis of (*E*)-2-benzylidene-4,4-cyclohexyltetrahydrofuran **97**

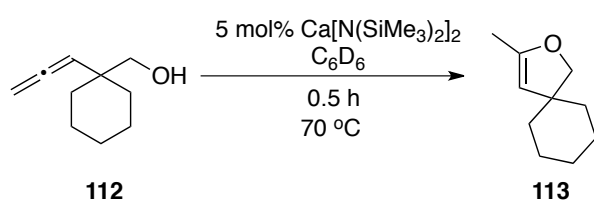


97 was prepared according to the general procedure for catalytic NMR experiments.

¹H NMR (400 MHz, *d*₆-benzene) δ/ppm: 7.20-7.21 (m, 4H, *H*_{Ar}), 7.01-7.03 (m, 1H, *H*_{Ar}), 6.25 (t, 1H, *J* = 2.1 Hz, CH=C), 3.57 (s, 2H, OCH₂), 2.39 (d, 2H, *J* = 2.0 Hz,

OCH₂C(CH₂)₅CH₂), 1.10 (m, 10H, (CH₂)₅). **¹³C NMR** (101 MHz, *d*₆-benzene) δ/ppm: 159.23 (OC=CHPh), 138.39 (C_q), 128.43 (C_{Ar}), 127.24 (C_{Ar}), 124.53 (C_{Ar}), 100.31 (PhCH=C), 78.27 (OCH₂), 42.41 (OCH₂C(CH₂)₅CH₂), 40.99 (OCH₂C(CH₂)₅CH₂), 34.33 (cyclohexyl ring; CH₂(CH₂)₃CH₂), 25.84 (cyclohexyl ring; (CH₂)₂CH₂(CH₂)₂), 23.30 (cyclohexyl ring; CH₂CH₂CH₂CH₂CH₂). **MS** (EI) *m/z*: 229 (MH⁺), 228 (M).

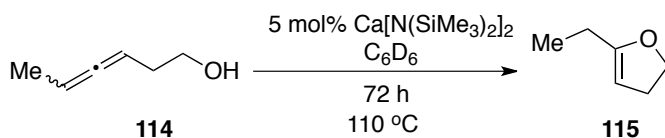
Synthesis of 3,3-cyclohexyl-5-methyl-2,3-dihydrofuran **113**



113 was prepared according to the general procedure for catalytic NMR experiments.

¹H NMR (400 MHz, *d*₆-benzene) δ/ppm: 4.55 (s, 1H, C=CH), 3.96 (s, 2H, OCH₂), 1.69 (s, 3H, H₃CC=C), 1.14-1.42 (m, 10H, (CH₂)₅). **¹³C NMR** (101 MHz, *d*₆-benzene) δ/ppm: 153.98 (OC=CH), 104.47 (OC=CH), 80.89 (OCH₂), 47.75 (OCH₂C(CH₂)₅CH), 25.83 (cyclohexyl ring; CH₂(CH₂)₃CH₂), 23.42 (cyclohexyl ring; (CH₂)₂CH₂(CH₂)₂), 23.33 (cyclohexyl ring; CH₂CH₂CH₂CH₂CH₂) 13.67 (CH₃C=C). **MS** (CI) *m/z*: 153 (MH⁺), 152 (M).

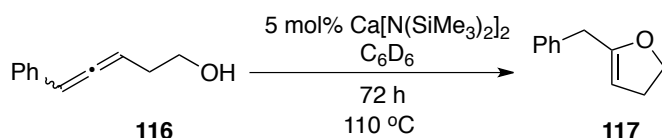
Synthesis of 5-ethyl-2,3-dihydrofuran **115**



115 was prepared according to the general procedure for catalytic NMR experiments.

^1H NMR (400 MHz, d_6 -benzene) δ /ppm: 5.12-5.16 (m, 1H, C=CH), 3.72 (t, 2H, J = 6.8 Hz, OCH_2), 2.25-2.31 (m, 2H, OCH_2CH_2), 1.51-1.54 (m, 2H, $\text{CH}_3\text{CH}_2\text{C}=\text{C}$), 0.88 (t, 3H, J = 7.3 Hz, $\text{CH}_3\text{CH}_2\text{C}=\text{C}$).

Synthesis of 5-benzyl-2,3-dihydrofuran **117**



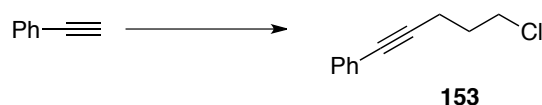
117 was prepared according to the general procedure for catalytic NMR experiments.

^1H NMR (400 MHz, d_6 -benzene) δ /ppm: 7.19-7.21 (m, H_{Ar}), 7.04-7.09 (m, H_{Ar}), 4.41-4.43 (m, 1H, C=CH), 3.61 (t, 2H, J = 6.8 Hz, OCH_2), 2.64 (dq, 2H, J = 1.8, 9.4, 18.6 Hz, PhCH_2), 1.21-1.27 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}$).

3.3 Attempted Cascade Reactions of Dialkynyl Alcohols

3.3.1 Preparation of Dialkynyl Alcohol Substrates

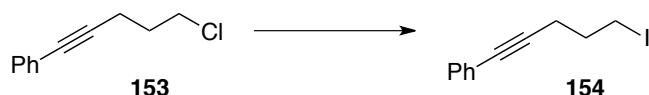
Synthesis of 1-phenyl-5-chloro-1-pentyne **153**



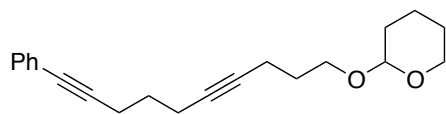
To a round-bottom flask were added phenylacetylene (4.92 ml, 44.8 mmol) and dry THF (50 ml) and cooled to $-78\text{ }^\circ\text{C}$. A 2.5 M solution of $n\text{-BuLi}$ in hexanes (25 ml, 54 mmol) was added dropwise over 30 min. The resulting bright yellow solution was stirred at this temperature for a further 20 min and 1-bromo-3-chloropropane (6.20 ml, 62.7 mmol) added at $-78\text{ }^\circ\text{C}$. The resulting mixture was then warmed to room temperature and heated to $80\text{ }^\circ\text{C}$ (reflux) for 16 hours. The solution was then cooled to $0\text{ }^\circ\text{C}$ and NH_4Cl (sat) added. The solution was extracted with Et_2O (20 ml x 3),

washed with brine (20 ml), dried over MgSO_4 , filtered and concentrated to yield a pale yellow oil. The crude mixture was then purified by column chromatography (100% pentane) to afford a colourless oil (4.81 g, 60%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 7.38-7.41 (m, 2H, H_{Ar}), 7.28-7.30 (m, 3H, H_{Ar}), 3.72 (t, 2H, $J = 6.4$ Hz, CH_2Cl), 2.61 (t, 2H, $J = 6.8$ Hz, $\text{C}\equiv\text{CCH}_2$), 2.06 (q, 2H, $J = 6.7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 131.06 (C_{ar}), 128.26 (C_{ar}), 127.81 (C_{ar}), 123.59 (C_{ar}), 88.09 (Ph- $\text{C}\equiv\text{C}$), 81.54 (Ph- $\text{C}\equiv\text{C}$), 43.77 (CH_2Cl), 31.49 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$), 16.89 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$). The NMR data was in agreement with the literature reported data.¹⁸⁹

Synthesis of 1-phenyl-5-iodo-1-pentyne **154**



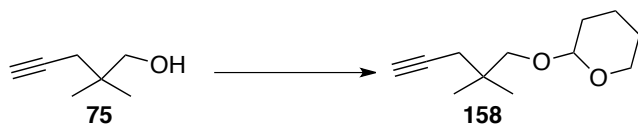
To a round-bottom flask were added 1-phenyl-5-chloro-1-pentyne (4.21 g, 23.6 mmol), sodium iodide (5.30 g, 35.4 mmol) and acetone (80 ml) and the solution was heated to 65 °C (reflux). After 20 hours, the mixture was cooled to room temperature, was added water and extracted with ethyl acetate (20 ml x 3). The organic extracts were combined, washed with brine (30 ml), dried over Na_2SO_4 , filtered and concentrated to yield a yellow oil. Filtration through a pad of silica gel using hexane as an eluent afforded 1-phenyl-5-iodo-1-pentyne (4.46 g, 70%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 7.46-7.48 (m, 2H, H_{Ar}), 7.34-7.36 (m, 3H, H_{Ar}), 3.40 (t, 2H, $J = 6.7$ Hz, CH_2I), 2.61 (t, 2H, $J = 6.7$ Hz, $\text{C}\equiv\text{CCH}_2$), 2.13 (quint, 2H, $J = 6.7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 131.66 (C_{ar}), 128.34 (C_{ar}), 127.87 (C_{ar}), 123.66 (C_{ar}), 87.93 (Ph- $\text{C}\equiv\text{C}$), 81.81 (Ph- $\text{C}\equiv\text{C}$), 32.26 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$), 20.58 ($\text{C}\equiv\text{CCH}_2$), 5.59 (CH_2I). The NMR data was in agreement with the literature reported data.¹⁹⁰

Synthesis of 2-(10-phenyldeca-4,9-diynyloxy)tetrahydro-2H-pyran **156**

Protected alcohol **155** (0.41 g, 2.42 mmol) was dissolved in dry THF (6 ml) and cooled to $-78\text{ }^{\circ}\text{C}$. A 2.5 M solution of *n*-BuLi in hexanes (1.35 ml, 2.90 mmol) was added dropwise over 10 minutes and stirred for an additional 10 minutes at $-78\text{ }^{\circ}\text{C}$. 1-Phenyl-5-iodo-1-pentyne **154** (0.85 g, 3.15 mmol) was added dropwise at $-78\text{ }^{\circ}\text{C}$ and the resulting light brown mixture warmed to room temperature and heated to $80\text{ }^{\circ}\text{C}$ (reflux) for 16 hours. The solution was then cooled to $0\text{ }^{\circ}\text{C}$ and NH_4Cl (sat) added. The solution was extracted with Et_2O (3 x 10 ml), washed with brine (10 ml), dried over MgSO_4 , filtered and concentrated to yield a light brown oil. Purification by column chromatography provided **156** (10% EtOAc:hex; $R_f = 0.27$) as a colourless oil (0.66 g, 88%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 4.63 (t, 1H, $J = 2.8\text{ Hz}$, OCHO), 3.83-3.90 (m, 2H, $\text{OCHOCH}_a\text{H}_b$, $\text{CH}_a\text{H}_b\text{OCHO}$), 3.48-3.55 (m, 2H, $\text{OCHOCH}_a\text{H}_b$, $\text{CH}_a\text{H}_b\text{OCHO}$), 2.55 (t, 2H, $J = 7.0\text{ Hz}$, $\text{Ph-C}\equiv\text{CCH}_2$), 2.29-2.37 (m, 4H, $\text{Ph-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2\text{-C}\equiv\text{C-CH}_2\text{CH}_2$), 1.77-1.84 (m, 4H, $\text{Ph-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 1.53-1.74 (m, 6H, $\text{CH}_2\text{OCHCH}_2\text{CH}_2\text{CH}_2$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 131.57 (C_{ar}), 128.20 (C_{ar}), 127.58 (C_{ar}), 123.89 (C_{ar}), 98.79 (OCHO), 89.41 ($\text{Ph-C}\equiv\text{C}$), 81.03 ($\text{Ph-C}\equiv\text{C}$), 80.26 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 79.24 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 66.06 ($\text{CH}_a\text{H}_b\text{OCHO}$), 62.19 ($\text{OCHOCH}_a\text{H}_b$), 30.71 ($\text{CH}_2(\text{THP})$), 29.24 ($\text{CH}_2\text{C}\equiv\text{CCH}_2$), 28.29 ($\text{CH}_2(\text{THP})$), 25.50 ($\text{CH}_2(\text{THP})$), 19.54 ($\text{CH}_2\text{C}\equiv\text{CCH}_2$), 18.58 ($\text{Ph-C}\equiv\text{C-CH}_2$), 18.06 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2$), 15.66 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2$).

Synthesis of 10-phenyldeca-4,9-diyne-1-ol **127**

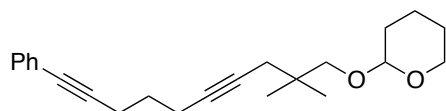
To a round-bottom flask were added **156** (0.48 g, 1.54 mmol), methanol (10 ml) and pyridinium-*p*-toluene sulfonate (0.039 g, 0.15 mmol). The resulting solution was then heated to reflux for 2 hours. TLC analysis determined completion of the reaction. The reaction mixture was then cooled to room temperature and the methanol removed under reduced pressure. The resulting pale yellow oil was dissolved in dichloromethane (10 ml) and sat. NaHCO_3 added (10 ml). The organic phase was separated and washed with brine (10 ml), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting alcohol was purified by column chromatography (30% EtOAc:hex; $R_f = 0.24$) to yield **127** as a colourless oil (0.28 g, 80%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 7.42-7.44 (m, 2H, H_{Ar}), 7.30-7.34 (m, 3H, H_{Ar}), 3.78 (qua, 2H, $J = 6.0$ Hz, CH_2OH), 2.55 (t, 2H, $J = 7.1$ Hz, $\text{Ph-C}\equiv\text{C-CH}_2$), 2.30-2.39 (m, 4H, $\text{Ph-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CCH}_2$), 1.74-1.85 (m, 4H, $\text{CH}_2\text{CH}_2\text{C}\equiv\text{CCH}_2\text{CH}_2$), 1.64 (t, 1H, $J = 5.4$ Hz, OH). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 131.58 (C_{ar}), 128.22 (C_{ar}), 127.62 (C_{ar}), 123.85 (C_{ar}), 89.31 ($\text{Ph-C}\equiv\text{C}$), 81.11 ($\text{Ph-C}\equiv\text{C}$), 80.11 ($\text{Ph-C}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}$), 79.92 ($\text{Ph-C}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}$), 62.01 (CH_2OH), 31.59 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 28.21 ($\text{Ph-C}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2$), 18.60 ($\text{Ph-C}\equiv\text{CCH}_2$), 18.03 ($\text{Ph-C}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}$), 15.42 ($\text{Ph-C}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CCH}_2$). **HRMS** (ES) m/z : calc. for $\text{C}_{16}\text{H}_{18}\text{O}$: 227.1436, found 227.1447.

Synthesis of 2-(2,2-dimethylpent-4-ynyloxy)tetrahydro-2H-pyran **158**

To a solution of alcohol **75** (0.75 g, 6.69 mmol) in dichloromethane (10 ml) was added pyridinium-*p*-toluene sulfonate (0.084 g, 0.33 mmol). The resulting solution

was stirred at room temperature for 4 hours. TLC analysis determined completion of the reaction. NaHCO_3 (sat) was added to the solution and the organic layer separated. The organic layer was then washed with brine, dried over MgSO_4 , filtered and concentrated to give a pale yellow oil. This was purified by column chromatography (10 % EtOAc:hex) to give protected alcohol **158** as a colourless oil (1.07 g, 82%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ /ppm: 4.58 (t, 1H, $J = 3.3$ Hz, CH_2OCH), 3.82-3.87 (m, 1H, $\text{CH}_2\text{OCHOCH}_a\text{H}_b$), 5.52 (d, 1H, $J = 9.2$ Hz, $\text{CH}_a\text{H}_b\text{OCHOCH}_2$), 3.48-3.51 (m, 1H, $\text{CH}_2\text{OCHOCH}_a\text{H}_b$), 3.09 (d, 1H, $J = 9.2$ Hz, $\text{CH}_a\text{H}_b\text{OCHOCH}_2$), 2.18-2.20 (m, 2H, $\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}\equiv\text{C-H}$), 1.96 (t, 1H, $J = 2.6$ Hz, $\text{H-C}\equiv\text{C}$), 1.49-1.83 (m, 6H, $\text{CH}_2\text{OCHCH}_2\text{CH}_2\text{CH}_2$), 1.01 (s, 3H, $\text{C}(\text{CH}_3)_2$), 0.99 (s, 3H, $\text{C}(\text{CH}_3)_2$). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ /ppm: 99.92 (CH_2OCHO), 82.42 ($\text{H-C}\equiv\text{C}$), 75.03 ($\text{CH}_a\text{H}_b\text{O}$), 69.75 ($\text{H-C}\equiv\text{C}$), 61.81 ($\text{CH}_2\text{OCHOCH}_2$), 34.62 ($\text{C}(\text{CH}_3)_2$), 30.57 ($\text{CH}_2(\text{THP})$), 28.60 ($\text{H-C}\equiv\text{C-CH}_2$), 25.54 ($\text{CH}_2(\text{THP})$), 24.22 ($\text{C}(\text{CH}_3)_2$), 24.09 ($\text{C}(\text{CH}_3)_2$), 19.28 ($\text{CH}_2(\text{THP})$).

Synthesis of 2-(2,2-dimethyl-10-phenyldeca-4,9-diynyloxy)tetrahydro-2H-pyran **250**



Protected alcohol **158** (0.90 g, 4.59 mmol) was dissolved in dry THF (10 ml) and cooled to -78 °C. A 2.5 M solution of $n\text{-BuLi}$ in hexanes (2.60 ml, 5.51 mmol) was added dropwise over 15 min at -78 °C and stirred for an additional 15 min at this temperature. 1-Phenyl-5-iodo-1-pentyne **154** (1.74 g, 6.43 mmol) was added dropwise over 10 min and the solution warmed to room temperature then heated at 80 °C (reflux) for 16 h. The solution was cooled to 0 °C and NH_4Cl (sat) added (10 ml). The solution was extracted with Et_2O (3×20 ml) and the organic extracts combined, washed with NaHCO_3 (20 ml) and brine (20 ml). Drying over MgSO_4 followed by filtration and concentration under reduced pressure afforded a yellow oil. Purification via column chromatography (10 % EtOAc:hex; $R_f = 0.4$) gave **250** as a colourless oil (1.06 g, 70%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ /ppm: 7.41-7.43 (m, 2H, H_{Ar}), 7.29-7.32 (m, 3H, H_{Ar}), 4.62 (t, 1H, $J = 3.2$ Hz, OCHO), 3.87-3.92 (m, 1H,

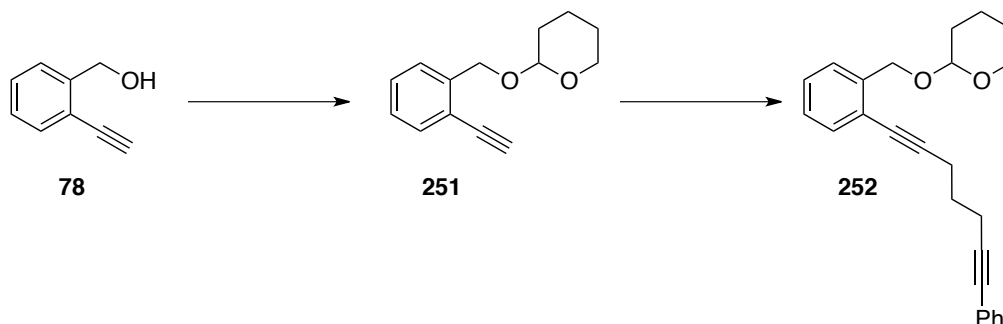
OCHOCH_aH_b), 3.51-3.57 (m, 2H, CH_aH_bOCHO, OCHOCH_aH_b), 3.12 (d, 1H, *J* = 9.2 Hz, CH_aH_bOCHO), 2.56 (t, 2H, *J* = 7.1 Hz, Ph-C≡C-CH₂), 2.35-2.40 (ttt, 2H, *J* = 2.4, 7.0, 13.8 Hz, Ph-C≡C-CH₂CH₂CH₂), 2.18-2.20 (m, 2H, Ph-C≡C-CH₂CH₂CH₂-C≡C-CH₂), 1.82 (quint, 2H, *J* = 6.9 Hz, Ph-C≡C-CH₂CH₂CH₂), 1.53-1.75 (m, 6H, CH₂(THP)). ¹³C NMR (101 MHz, CDCl₃) δ/ppm: 131.57 (C_{Ar}), 128.20 (C_{Ar}), 127.58 (C_{Ar}), 123.90 (C_q), 98.94 (OCHO), 89.41 (Ph-C≡C), 81.03 (Ph-C≡C), 80.68 (CH₂-C≡C-CH₂), 78.67 (CH₂-C≡C-CH₂), 75.21 (CH₂OCHO), 61.76 (OCHOCH₂), 34.86 (C(CH₃)₂), 30.61 (CH₂(THP)), 29.03 (CH₂C(CH₃)₂CH₂O), 28.37 (Ph-C≡C-CH₂CH₂CH₂), 25.58 (CH₂(THP)), 24.33 (CH₃), 24.26 (CH₃), 19.32 (CH₂(THP)), 18.60 (Ph-C≡C-CH₂), 18.09 (Ph-C≡C-CH₂CH₂CH₂).

Synthesis of 2,2-dimethyl-10-phenyldeca-4,9-diynyl-1-ol **131**



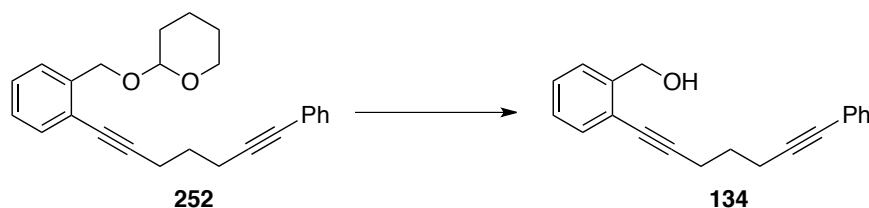
Deprotection of **250** was achieved following the same procedure as that for the preparation of **127**. Alcohol **131** was obtained from flash chromatography (30% EtOAc:hex; *R_f* = 0.36) as a colourless oil (0.75 g, 94%). ¹H NMR (400 MHz, CDCl₃) δ/ppm: 7.41-7.44 (m, 2H, *H_{Ar}*), 7.29-7.32 (m, 3H, *H_{Ar}*), 3.47 (d, 2H, *J* = 4.7 Hz, CH₂OH), 2.56 (t, 2H, *J* = 7.0 Hz, Ph-C≡C-CH₂), 2.37-2.40 (m, 2H, CH₂CH₂C≡CCH₂C(CH₃)₂), 2.16 (t, 2H, *J* = 2.4 Hz, CH₂C≡CCH₂C(CH₃)₂), 1.83 (q, 2H, *J* = 5.6 Hz, Ph-C≡C-CH₂CH₂CH₂), 1.64 (bt, 1H, OH), 1.00 (s, 6H, C(CH₃)₂). ¹³C NMR (101 MHz, CDCl₃) δ/ppm: 131.58 (C_{ar}), 128.20 (C_{ar}), 127.61 (C_{ar}), 123.86 (C_{ar}), 89.27 (Ph-C≡C), 81.28 (Ph-C≡C), 81.12 (C(CH₃)₂CH₂C≡C), 78.32 (C(CH₃)₂CH₂C≡C), 71.24 (CH₂OH), 35.62 (C≡C-CH₂C(CH₃)₂), 28.85 (C(CH₃)₂CH₂C≡C), 28.26 (Ph-C≡C-CH₂CH₂CH₂), 23.88 (C≡C-CH₂C(CH₃)₂), 18.63 (Ph-C≡C-CH₂), 18.06 CH₂C≡CCH₂C(CH₃)₂). HRMS (ES) *m/z*: calc. for C₁₈H₂₂O: 255.1749, found 255.1749.

Synthesis of 2-(2-(7-phenylhepta-1,6-diynyl)benzyloxy)tetrahydro-2H-pyran **252**



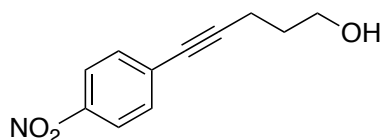
Protection of benzyl alcohol **78** was performed according to the procedure for **155**. Purification by column chromatography (10% EtOAc:hex; R_f = 0.34) afforded a colourless oil (0.76 g, 92%). **251** was used immediately without further analysis. Compound **251** was alkylated with 1-phenyl-5-iodo-1-pentyne **154** using the same procedure adapted for the synthesis of **156**. Purification by column chromatography (10% EtOAc:hex; R_f = 0.29) afforded **252** as a colourless oil (0.75 g, 60%). **¹H NMR** (400 MHz, CDCl_3) δ /ppm: 7.43-7.52 (m, 4H, H_{Ar}), 7.24-7.34 (m, 4H, H_{Ar}), 4.96 (d, 1H, J = 12.9 Hz, $\text{CH}_a\text{H}_b\text{O}$), 4.81 (t, 1H, J = 3.5 Hz, OCHO), 4.75 (d, 1H, J = 12.9 Hz, $\text{CH}_a\text{H}_b\text{O}$), 3.96-4.01 (m, 1H, $\text{Ar-C}\equiv\text{C-CH}_a\text{H}_b$), 3.57-3.62 (m, 1H, $\text{Ar-C}\equiv\text{C-CH}_a\text{H}_b$), 2.63-2.69 (m, 4H, $\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{C-Ph}$), 1.56-1.99 (bm, 8H, $\text{ArCH}_2\text{OCHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$). **¹³C NMR** (101 MHz, CDCl_3) δ /ppm: 140.12 (C_q), 132.08 (C_{ar}), 131.59 (C_{ar}), 128.22 (C_{ar}), 127.82 (C_{ar}), 127.65 (C_{ar}), 127.41 (C_{ar}), 127.06 (C_{ar}), 123.84 (C_q), 122.37 (C_q), 98.42 (OCHO), 93.81 ($\text{Ph-C}\equiv\text{C}$), 93.81 ($\text{Ph-C}\equiv\text{C}$), 89.15 ($\text{Ar-C}\equiv\text{C}$), 81.27 ($\text{Ar-C}\equiv\text{C}$), 67.41 ($\text{CH}_a\text{H}_b\text{OCHO}$), 62.12 ($\text{Ar-C}\equiv\text{C-CH}_a\text{H}_b\text{CH}_2$), 30.62 ($\text{CH}_2(\text{THP})$), 28.00 ($\text{CH}_2(\text{THP})$), 25.53 ($\text{CH}_2(\text{THP})$), 19.41 ($\text{CH}_2(\text{THP})$), 18.87 ($\text{Ph-C}\equiv\text{C-CH}_2\text{CH}_2$), 18.68 ($\text{Ph-C}\equiv\text{C-CH}_2\text{CH}_2$).

Synthesis of (2-(7-phenylhepta-1,6-diynyl)phenyl)methanol **134**



Compound **252** was deprotected according to the procedure for the synthesis of **127**. **134** was purified by column chromatography (30% EtOAc:hex; R_f = 0.35) to give **134** as a colourless oil (0.53 g, 93%). **¹H NMR** (400 MHz, CDCl₃) δ /ppm: 7.43-7.46 (m, 4H, H_{ar}), 7.28-7.35 (m, 5H, H_{ar}), 4.85 (s, 2H, CH₂O), 2.63-2.70 (m, 4H, Ar-C $\equiv$ C-CH₂CH₂CH₂), 2.19 (bs, 1H, OH), 1.96 (q, 2H, J = 7.0 Hz, Ar-C $\equiv$ C-CH₂CH₂CH₂). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 142.43 (C_q), 132.30 (C_{ar}), 131.30 (C_{ar}), 128.25 (C_{ar}), 128.13 (C_{ar}), 127.72 (C_{ar}), 127.42 (C_{ar}), 127.25 (C_{ar}), 123.74 (C_{ar}), 121.95 (C_q), 94.23 (Ar-C $\equiv$ C), 88.91 (Ph-C $\equiv$ C), 81.45 (Ar-C $\equiv$ C), 78.83 (Ph-C $\equiv$ C), 64.19 (CH₂OH), 27.85 (CH₂CH₂CH₂), 18.79 (CH₂CH₂CH₂), 18.70 (CH₂CH₂CH₂). **HRMS** (ES) m/z : calc. for C₂₀H₁₈O: 275.1436, found 275.1445.

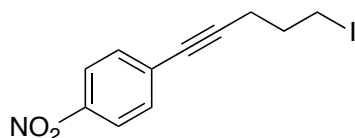
Synthesis of 5-(4-nitrophenyl)pent-4-yn-1-ol **159**



1-Iodo-4-nitrobenzene (9.11 g, 36.6 mmol) was added to a solution of 4-pentyn-1-ol (2.27 ml, 24.4 mmol) in excess triethylamine (50 ml) at room temperature. The resulting colourless solution was cooled to 0 °C and bis(triphenylphosphine)palladium(II) chloride (0.28 g, 0.24 mmol) was added followed by copper(I) iodide (0.09 g, 0.49 mmol). The resulting yellow suspension was warmed to room temperature and stirred for 12 hours. The solution was then filtered through celite with diethyl ether washings and extracted three times with water (50 ml) and brine (50 ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and concentrated to yield a yellow oil, which was purified by column chromatography (30% EtOAc: hex; R_f = 0.12) to give a colourless oil (4.11 g, 82%). **¹H NMR** (400 MHz, CDCl₃) δ /ppm: 8.05 (d, 2H, J = 8.3 Hz, H_{Ar}), 7.41 (d, 2H, J = 8.9 Hz, H_{Ar}), 3.71 (quart, 2H, J = 5.9 Hz, CH₂OH), 2.48 (t, 2H, J = 7.1 Hz, Ar-C $\equiv$ CCH₂), 1.77 (q, 2H, J = 7.0 Hz, C $\equiv$ CCH₂CH₂CH₂), 1.38 (t, 1H, J = 7 Hz, OH). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 146.69 (C_q), 132.29 (C_{ar}), 130.87 (C_{ar}), 123.53 (C_{ar}), 95.62 (Ar-C $\equiv$ C), 79.69 (Ar-C $\equiv$ C), 61.55 (CH₂OH), 31.10

(CH₂CH₂CH₂OH), 16.11 (Ar-C≡C-CH₂). The NMR data was in agreement with the literature reported data.¹⁶⁵

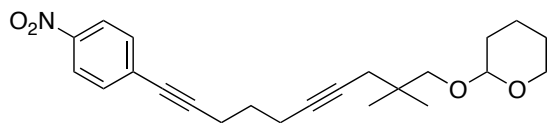
Synthesis of 1-(5-iodopent-1-ynyl)-4-nitrobenzene **162**



1-(5-Iodopent-1-ynyl)-4-nitrobenzene was prepared via the mesylate of alcohol **159**. To a solution of **159** (4.09 g, 19.95 mmol) in THF (70 mL) at 0 °C was added triethylamine (3.03 mL, 21.7 mmol) followed by MsCl (1.55 mL, 20.0 mmol). After 1 h at 0 °C, the solution was filtered through Celite with ether washings and then concentrated to afford a pale yellow solid (5.75 g, quant.). **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 8.06 (d, 2H, *J* = 8.8 Hz, *H*_{Ar}), 7.74 (d, 2H, *J* = 8.8 Hz, *H*_{Ar}), 4.29 (t, 2H, *J* = 6.0 Hz, CH₂O), 2.94 (s, 3H, OSO₂CH₃), 2.53 (t, 2H, *J* = 6.8 Hz, C≡C-CH₂), 1.99 (q, 2H, *J* = 6.5 Hz, C≡C-CH₂CH₂CH₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 146.66 (C_q), 132.37 (C_{ar}), 130.39 (C_{ar}), 123.58 (C_{ar}), 93.60 (Ar-C≡C), 80.46 (Ar-C≡C), 68.15 (CH₂O), 37.48 (OSO₂CH₃), 27.91 (CH₂CH₂CH₂), 15.93 (C≡C-CH₂).

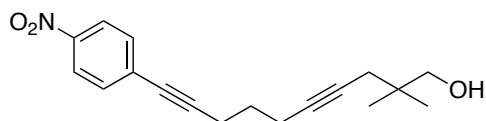
The mesylate (5.75 g, 20.3 mmol) was dissolved in dry acetone (90 mL), and NaI (12.0g, 80.0 mmol) was added. The solution was heated at reflux for 2 h, cooled, and filtered through Celite with acetone washings. The product was purified by column chromatography (10% EtOAc in hexanes; *R*_f = 0.46) to yield 5.50 g (76%) of 1-(5-iodopent-1-ynyl)-4-nitrobenzene **162** as a pale yellow oil. **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 8.06 (d, 2H, *J* = 8.8 Hz, *H*_{Ar}), 7.42 (d, 2H, *J* = 8.8 Hz, *H*_{Ar}), 3.42 (t, 2H, *J* = 6.8 Hz, CH₂I), 2.51 (t, 2H, *J* = 6.8 Hz, C≡C-CH₂), 2.00 (q, 2H, *J* = 6.78 Hz, CH₂CH₂CH₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 146.81 (C_q), 123.35 (C_{ar}), 130.59 (C_q), 123.55 (C_q), 93.94 (Ar-C≡C), 80.28 (Ar-C≡C), 31.37 (CH₂CH₂CH₂), 20.63 (C≡C-CH₂), 4.92 (CH₂I).

Synthesis of 2-(2,2-dimethyl-10-(4-nitrophenyl)deca-4,9-diynyloxy)tetrahydro-2H-pyran **165**



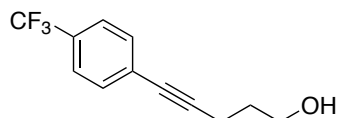
Under an argon atmosphere a solution of 2-(4-pentyn-1-yloxy)tetrahydro-2H-pyran **158** (1.75 g, 8.93 mmol) in dry THF (30 ml) was cooled to -78 °C and *n*-BuLi (2.5 M in hexanes 4.29 ml, 10.7 mmol) was added. The resulting mixture was stirred for 15 min at -78 °C and then a solution of **162** (3.66 g, 11.6 mmol) in dry THF (10 ml) added slowly. The resulting bright red solution was warmed to room temperature and heated under reflux at 80 °C for 48 h. The dark brown reaction mixture was cooled to room temperature and sat. NH₄Cl added (25 ml). The aqueous layer was separated and extracted with diethyl ether (3 x 30 ml). The combined organic extracts were washed with brine (30 ml), dried over anhydrous MgSO₄, filtered and concentrated to yield a viscous brown oil which was purified by column chromatography (5% EtOAc:pent; *R_f* = 0.27) to produce a light orange oil (1.26 g, 37%). **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 8.05 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 7.41 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 4.48 (t, 1H, *J* = 3.3 Hz, OCHO), 3.72-3.75 (m, 1H, OCHOCH_aH_b), 3.42 (d, 1H, *J* = 9.1 Hz, C(CH₃)₂CH_aH_bOCHO), 3.37-3.39 (m, 1H, OCHOCH_aH_b), 2.97 (d, 1H, *J* = 9.2 Hz, C(CH₃)₂CH_aH_bOCHO), 2.46 (t, 2H, *J* = 7.1 Hz, Ar-C≡C-CH₂), 2.21-2.26 (m, 2H, Ar-C≡C-CH₂CH₂CH₂), 2.05 (bs, 2H, CH₂C≡CCH₂C(CH₃)₂), 1.69 (t, 2H, *J* = 7.0 Hz, Ar-CH₂CH₂CH₂), 1.40-1.51 (m, 6H, OCHCH₂CH₂CH₂CH₂O), 0.94 (s, 3H, C(CH₃)₂), 0.89 (s, 3H, C(CH₃)₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 146.66 (C_q), 130.30 (C_{Ar}), 131.00 (C_{Ar}), 123.51 (C_{Ar}), 98.91 (OCHO), 95.70 (Ar-C≡C), 80.28 (Ar-C≡C), 79.71 (CH₂C≡CCH₂C(CH₃)₂), 79.01 (CH₂C≡CCH₂C(CH₃)₂), 75.18 (C(CH₃)₂CH₂OCHO), 61.74 (CH₂OCHOCH₂), 34.86 (C(CH₃)₂), 30.59 (C(THP)), 29.02 (C≡C-CH₂C(CH₃)₂), 27.96 (Ar-CH₂CH₂CH₂), 25.75 (C(THP)), 24.32 (C(CH₃)₂), 19.28 (C(THP)), 18.69 (Ar-C≡C-CH₂), 18.10 (Ar-C≡C-CH₂CH₂CH₂).

Synthesis of 2,2-dimethyl-10-(4-nitrophenyl)deca-4,9-diyne-1-ol **138**



To a round-bottom flask were added **165** (1.13 g, 2.97 mmol), methanol (15 ml) and pyridinium-*p*-toluene sulfonate (0.075 g, 0.100 mmol). The resulting solution was then heated to reflux for 3-5 hours. TLC analysis determined completion of the reaction. The reaction mixture was then cooled to room temperature and the methanol removed under reduced pressure. The resulting pale yellow oil was dissolved in dichloromethane (15 ml) and sat. NaHCO₃ added (15 ml). The organic phase was separated and washed with brine (15 ml), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The resulting crude alcohol was purified by column chromatography (30% EtOAc:hex; *R_f* = 0.44) to yield a colourless oil (0.74 g, 84%). **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 8.15 (d, 2H, *J* = 8.8 Hz, *H_{Ar}*), 7.52 (d, 2H, *J* = 8.8 Hz, *H_{Ar}*), 3.42 (s, 2H, CH₂OH), 2.57 (t, 2H, *J* = 7.1 Hz, Ar-C≡C-CH₂), 2.33-2.37 (tt, 2H, *J* = 2.5, 4.6 Hz, Ar-C≡C-CH₂CH₂CH₂), 2.13 (t, 2H, *J* = 2.4 Hz, Ar-C≡C-CH₂CH₂CH₂-C≡C-CH₂), 1.81 (q, 2H, *J* = 7.0 Hz, Ar-C≡C-CH₂CH₂CH₂), 1.65 (bs, 1H, OH), 0.96 (s, 6H, C(CH₃)₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 146.67 (C_q), 132.30 (C_{ar}), 130.94 (C_{ar}), 132.51 (C_{ar}), 95.53 (Ar-C≡C), 80.87 (Ar-C≡C), 79.77 (C≡CCH₂C(CH₃)₂), 78.64 (C≡CCH₂C(CH₃)₂), 71.21 (CH₂OH), 35.61 (C(CH₃)₂), 28.82 (CH₂C≡CCH₂C(CH₃)₂), 27.86 (Ar-C≡C-CH₂CH₂CH₂), 23.86 (C(CH₃)₂), 18.71 (Ar-C≡C-CH₂), 18.07 (Ar-CH₂CH₂CH₂C≡C-CH₂).

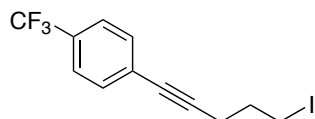
Synthesis of 5-(4-(trifluoromethyl)phenyl)pent-4-yn-1-ol **160**



Under an argon atmosphere, 4-iodobenzotrifluoride (5.00 g, 18.4 mmol) was added to a solution of 4-pentyn-1-ol (1.32 ml, 14.1 mmol) in excess triethylamine (40 ml) at

room temperature. The resulting colourless solution was cooled to 0 °C and bis(triphenylphosphine)palladium(II) chloride (0.163 g, 0.141 mmol) was added followed by copper(I) iodide (0.054 g, 0.283 mmol). The resulting yellow suspension was warmed to room temperature and stirred for 12 hours. The solution was then filtered through celite with diethyl ether washings and extracted three times with water (50 ml) and brine (50 ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and concentrated to yield a yellow oil which was purified by column chromatography (30% EtOAc:pent) to give a colourless oil (2.41 g, 80%). **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 7.54 (d, 2H, *J* = 8.3 Hz, *H*_{Ar}), 7.48 (d, 2H, *J* = 8.3 Hz, *H*_{Ar}), 3.82 (qua, 2H, *J* = 6.0 Hz, CH₂OH), 2.56 (t, 2H, *J* = 7.0 Hz, Ar-C≡C-CH₂CH₂CH₂), 1.87 (q, 2H, *J* = 6.6 Hz, Ar-C≡C-CH₂CH₂CH₂OH), 1.55 (s, 1H, *J* = 5.3 Hz, OH). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 131.79 (*C*_{ar}), 129.60 (*C*_q), 129.27 (*C*_q), 127.61 (CF₃), 125.14 (*C*_{ar}), 92.19 (Ar-C≡C), 79.99 (Ar-C≡C), 61.66 (CH₂OH), 31.21 (Ar-C≡C-CH₂CH₂CH₂OH), 15.98 (Ar-C≡C-CH₂CH₂CH₂OH). The NMR data was in agreement with the literature reported data.

Synthesis of 1-(5-iodopent-1-ynyl)-4-(trifluoromethyl)benzene **163**



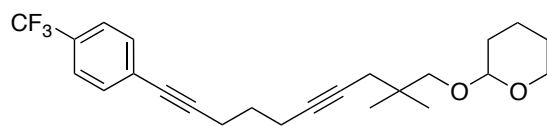
Alcohol **160** was mesylated using the same procedure for the preparation of **162** to afford a pale yellow solid (3.12 g, quant.) which was used for the next step without further purification. **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 7.55 (d, 2H, *J* = 8.3 Hz, *H*_{ar}), 7.49 (d, 2H, *J* = 8.3 Hz, *H*_{ar}), 4.41 (t, 2H, *J* = 6.1 Hz, CH₂OSO₂CH₃), 3.04 (s, 3H, CH₂OSO₂CH₃), 2.61 (t, 2H, *J* = 6.9 Hz, Ar-C≡C-CH₂), 2.06 (q, 2H, *J* = 6.4 Hz, Ar-C≡C-CH₂CH₂CH₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 131.84 (CF₃), 129.86 (*C*_q), 129.53 (*C*_q), 127.21 (*C*_{ar}), 125.29 (*C*_{ar}), 125.22 (*C*_{ar}), 122.59 (*C*_{ar}), 90.35 (Ar-C≡C), 80.80 (Ar-C≡C), 68.31 (CH₂OSO₂CH₃), 37.40 (SO₂CH₃), 27.99 (Ar-C≡C-CH₂CH₂CH₂), 15.77 (Ar-C≡C-CH₂CH₂CH₂).

Conversion of the mesylate to the corresponding iodide was achieved using the same procedure for the preparation of **162**. Purification by distillation gave **163** as a

pale yellow oil (2.84 g, 84%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ /ppm: 7.55 (d, 2H, $J = 8.4$ Hz, H_{ar}), 7.49 (d, 2H, $J = 8.3$ Hz, H_{ar}), 3.36 (t, 2H, $J = 6.7$ Hz, CH_2I), 2.58 (t, 2H, $J = 6.8$ Hz, $\text{Ar-C}\equiv\text{C-CH}_2$), 2.10 (q, 2H, $J = 6.8$ Hz, $\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2\text{I}$). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ /ppm: 131.85 (C_{ar}), 129.74 (C_{q}), 129.41 (C_{q}), 127.41 (CF_3), 125.20 (C_{ar}), 90.63 ($\text{Ar-C}\equiv\text{C}$), 80.58 ($\text{Ar-C}\equiv\text{C}$), 31.91 ($\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2\text{I}$), 20.50 ($\text{Ar-C}\equiv\text{C-CH}_2$), 5.14 (CH_2I).

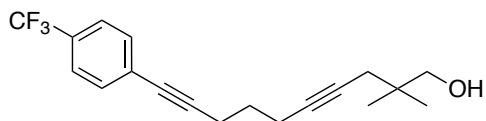
Synthesis of

2-(10-(4-(trifluoromethyl)phenyl)deca-4,9-diynyloxy)tetrahydro-2H-pyran **166**



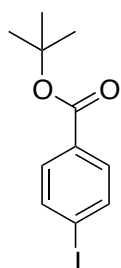
Under an argon atmosphere a solution of 2-(4-pentyn-1-yloxy)tetrahydro-2H-pyran **158** (1.27 g, 6.46 mmol) in dry THF (25 ml) was cooled to -78 °C and $n\text{-BuLi}$ (2.5 M in hexanes 3.10 ml, 7.78 mmol) was added. The resulting mixture was stirred for 15 min at -78 °C and then a solution of **163** (2.84 g, 8.4 mmol) in dry THF (6 ml) was added slowly. The resulting bright blue solution was warmed to room temperature and heated under reflux at 80 °C for 48 h. The dark brown reaction mixture was cooled to room temperature and sat. NH_4Cl added (15 ml). The aqueous layer was separated and extracted with diethyl ether (3 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried over anhydrous MgSO_4 , filtered and concentrated to yield a viscous brown oil which was purified by column chromatography (5% EtOAc:pent; $R_f = 0.38$) to produce a colourless oil (1.35 g, 52%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ /ppm: 4.58 (t, 1H, 3.3 Hz, OCHO), 3.83-3.89 (m, 1H, $\text{OCHOCH}_a\text{H}_b$), 3.47-3.54 (d, m, 1H, 1H, $\text{C}(\text{CH}_3)_2\text{CH}_a\text{H}_b\text{OCHO}$, $\text{OCHOCH}_a\text{H}_b$), 3.10 (d, 1H, $J = 9.1$ Hz, $\text{C}(\text{CH}_3)_2\text{CH}_a\text{H}_b\text{OCHO}$), 2.55 (t, 2H, $J = 7.1$ Hz, $\text{Ar-C}\equiv\text{C-CH}_2$), 2.32-2.36 (m, 2H, $\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2$), 2.16 (bs, 2H, $\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_a\text{H}_b\text{OCHO}$), 1.81 (q, 2H, $J = 4.7$ Hz, $\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2$), 1.49-1.76 (m, 6H, $\text{CH}_a\text{H}_b\text{OCHCH}_2\text{CH}_2\text{CH}_2\text{CH}_a\text{H}_b\text{O}$), 0.99 (s, 3H, $\text{C}(\text{CH}_3)_2$), 0.98 (s, 3H, $\text{C}(\text{CH}_3)_2$).

Synthesis of 10-(4-(trifluoromethyl)phenyl)deca-4,9-diyn-1-ol **139**



Tetrahydropyranyl ether **166** was cleaved using the same procedure for compound **138**. Purification by column chromatography (20% EtOAc:pent; R_f = 0.47) afforded 10-(4-(trifluoromethyl)phenyl)deca-4,9-diyn-1-ol as a colourless oil (0.94g, 88%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 7.54 (d, 2H, J = 8.3 Hz, H_{ar}), 7.49 (d, 2H, J = 8.3 Hz, H_{ar}), 3.43 (d, 2H, J = 5.6 Hz, CH_2OH), 2.54 (2H, t, J = 7.1 Hz, $\text{Ar-C}\equiv\text{C-CH}_2$), 2.33-2.37 (m, 2H, $\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2$), 2.13 (t, 2H, J = 2.3 Hz, $\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$), 1.80 (q, 2H, J = 7.0 Hz, $\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2$), 1.63 (t, 1H, J = 6.1 Hz, OH), 0.97 (s, 6H, $\text{C}(\text{CH}_3)_2$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 131.81 (C_{ar}), 129.54 (C_{q}), 129.20 (C_{q}), 127.71 (CF_3), 125.15 (C_{ar}), 92.13 ($\text{Ar-C}\equiv\text{C}$), 81.04 ($\text{Ar-C}\equiv\text{C}$), 80.02 ($\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2\text{-C}\equiv\text{C}$), 78.49 ($\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2\text{-C}\equiv\text{C}$), 71.23 (CH_2OH), 35.62 ($\text{C}(\text{CH}_3)_2$), 28.83 ($\text{CH}_2\text{C}(\text{CH}_3)_2$), 28.02 ($\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2$), 23.87 ($\text{C}(\text{CH}_3)_2$), 18.61 ($\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2$), 18.06 ($\text{Ar-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2$).

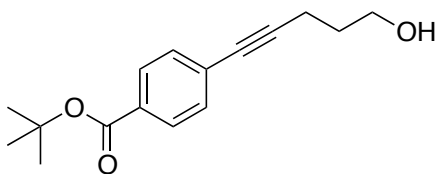
Synthesis of *tert*-butyl 4-iodobenzoate **253**



4-Iodobenzoic acid (7.29 g, 29.4 mmol) in DMF (20 ml) was treated with carbonyl-1,1-diimidazole (7.15 g, 44.1 mmol) at room temperature. The reaction mixture was heated to 45 °C and stirred for 3 h. *tert*-Butan-1-ol (8.43 ml, 88.2 mmol) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene was then added at room temperature. The resulting pale yellow suspension was stirred at room temperature for 12 h. Diethyl ether (20 ml) was added to the reaction mixture and the aqueous layer extracted

twice more with ether washings (2 x 20 ml). The organic extracts were combined and washed with 1M HCl (20 ml), sat. K_2CO_3 (20 ml) and brine (20 ml). The organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to yield a yellow oil which was purified by column chromatography (1:1 EtOAc:hex) to give *tert*-butyl 4-iodobenzoate as a colourless oil (7.92 g, 87%). 1H NMR (400 MHz, $CDCl_3$) δ /ppm: 7.77 (d, 2H, J = 8.6 Hz, H_{ar}), 7.96 (d, 2H, J = 8.6 Hz, H_{ar}), 1.58 (s, 9H, $CO_2OC(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ /ppm: 165.24 ($C=O$), 137.51 (C_{ar}), 131.51 (C_q), 130.96 (C_{ar}), 100.04 (C_q), 81.49 ($C(CH_3)_3$), 28.16 ($C(CH_3)_3$). The NMR data was in agreement with the literature reported data.¹⁹¹

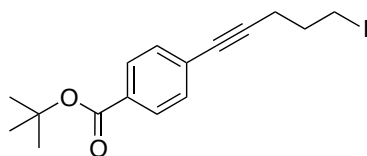
Synthesis of *tert*-butyl 4-(5-hydroxypent-1-ynyl)benzoate **161**



Under an Ar atmosphere, *tert*-butyl 4-iodobenzoate **253** (7.92 g, 26.1 mmol) was added to a solution of 4-pentyn-1-ol (1.86 ml, 20.0 mmol) in excess triethylamine (65 ml) at room temperature. The resulting colourless solution was cooled to 0 °C and bis(triphenylphosphine)palladium(II) chloride (0.232 g, 0.200 mmol) was added followed by copper(I) iodide (0.0763 g, 0.40 mmol). The resulting yellow suspension was warmed to room temperature and stirred for 12 hours. The solution was then filtered through celite with diethyl ether washings and washed three times with water (80 ml) and brine (80 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to yield a yellow oil which was purified by column chromatography (20% EtOAc:pent; R_f = 0.23) to give a colourless oil (3.04 g, 90%). 1H NMR (400 MHz, $CDCl_3$) δ /ppm: 7.90 (d, 2H, J = 8.3 Hz, H_{ar}), 7.41 (d, 2H, J = 8.4 Hz, H_{ar}), 3.82 (t, 2H, J = 6.2 Hz, CH_2OH), 2.56 (t, 2H, J = 7.0 Hz, $Ar-C\equiv C-CH_2$), 1.87 (q, 2H, J = 6.7 Hz, $Ar-C\equiv C-CH_2CH_2CH_2OH$), 1.66 (bs, 1H, OH), 1.58 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ /ppm: 165.33 ($C=O$), 131.24 (C_{ar}), 130.91 (C_q), 129.27 (C_{ar}), 127.96 (C_q), 92.39 ($C(CH_3)_3$), 81.22 ($Ar-C\equiv C$), 80.71

(Ar-C≡C), 61.71 (CH₂OH), 31.26 (Ar-C≡C-CH₂CH₂CH₂OH), 28.19 (C(CH₃)₃), 16.08 (Ar-C≡C-CH₂).

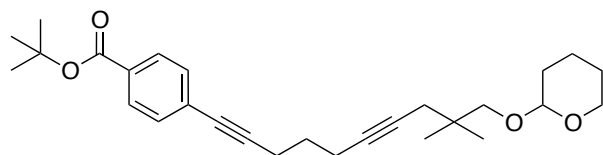
Synthesis of *tert*-butyl 4-(5-iodopent-1-ynyl)benzoate **164**



Alcohol **161** was mesylated following the same procedure as for compound **159** to afford a pale yellow solid, which was used in the next step without any further purification. **¹H NMR** (400 MHz, C₆D₆): δ/ppm: 7.91 (d, 2H, *J* = 8.3, *H*_{ar}), 7.42 (d, 2H, *J* = 8.3 Hz, *H*_{ar}), 4.41 (t, 2H, *J* = 6.1 Hz, CH₂OSO₂CH₃), 3.04 (s, 3H, OSO₂CH₃), 2.61 (t, 2H, *J* = 6.9 Hz, Ar-C≡C-CH₂), 2.06 (q, 2H, *J* = 6.4 Hz, Ar-C≡C-CH₂CH₂CH₂OH), 1.59 (s, 9H, C(CH₃)₃). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 165.22 (C=O), 131.35 (C_{ar}), 131.20 (C_q), 129.33 (C_{ar}), 127.53 (C_q), 90.49 (C(CH₃)₃), 81.54 (Ar-C≡C), 81.28 (Ar-C≡C), 68.39 (CH₂OSO₂CH₃), 37.38 (OSO₂CH₃), 28.18 (Ar-C≡C-CH₂CH₂CH₂), 28.02 (C(CH₃)₃), 15.84 (Ar-C≡C-CH₂).

Conversion of the mesylated alcohol to the iodide **164** was achieved following the same procedure for the preparation for **162**. Purification by column chromatography (1:1 EtOAc:hex; *R*_f = 0.72) gave **164** as a pale yellow oil (3.91 g, 82%). **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 7.91 (d, 2H, *J* = 8.35 Hz, *H*_{ar}), 7.43 (d, 2H, *J* = 8.31 Hz, *H*_{ar}), 3.36 (t, 2H, *J* = 6.8 Hz, CH₂I), 2.58 (t, 2H, Ar-C≡C-CH₂), 2.12 (q, 2H, *J* = 14.2 Hz, Ar-C≡C-CH₂CH₂CH₂I), 1.59 (s, 9H, C(CH₃)₃). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 165.27 (C=O), 131.36 (C_{ar}), 131.05 (C_q), 129.29 (C_{ar}), 127.76 (C_q), 90.80 (C(CH₃)₃), 81.30 (Ar-C≡C), 81.23 (Ar-C≡C), 31.99 (Ar-C≡C-CH₂CH₂CH₂I), 28.19 (C(CH₃)₃), 20.58 (Ar-C≡C-CH₂), 5.26 (CH₂I).

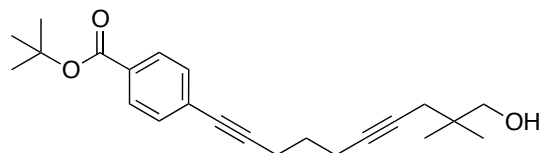
Synthesis of *tert*-butyl 4-(9,9-dimethyl-10-(tetrahydro-2H-pyran-2-yloxy)deca-1,6-diynyl)benzoate **167**



Under an argon atmosphere a solution of 2-(4-pentyn-1-yloxy)tetrahydro-2H-pyran (1.72 g, 8.75 mmol) in dry THF (40 ml) was cooled to -78 °C and *n*-BuLi (2.3 M in hexanes 4.60 ml, 10.5 mmol) was added. The resulting mixture was stirred for 15 min at -78 °C and then a solution of **28** (4.21 g, 11.4 mmol) in dry THF (10 ml) was added slowly. The resulting bright orange solution was warmed to room temperature and heated under reflux at 80 °C for 48 h under N₂. The dark brown reaction mixture was cooled to room temperature and sat. NH₄Cl (20 ml) was added. The aqueous layer was separated and extracted with diethyl ether (3 x 30 ml). The combined organic extracts were washed with brine (30 ml), dried over anhydrous MgSO₄, filtered and concentrated to yield a viscous brown oil which was purified by column chromatography (5% EtOAc: pent; R_f = 0.20) to produce a pale yellow oil (1.90 g, 49%). **¹H NMR** (400 MHz, CDCl₃) δ/ppm = 7.90 (d, 2H, *J* = 8.3 Hz, *H*_{ar}), 7.42 (d, 2H, *J* = 8.3 Hz, *H*_{ar}), 4.58 (t, 1H, *J* = 3.2 Hz, OCHO), 3.83-3.89 (m, 2H, OCHOCH_aH_b), 3.42-3.54 (d, m, 1H, 1H, C(CH₃)₂CH_aH_bOCHO, OCHOCH_aH_b), 3.10 (d, 1H, *J* = 9.2 Hz, C(CH₃)₂CH_aH_bOCHO), 2.55 (t, 2H, *J* = 7.1 Hz, Ar-C≡C-CH₂), 2.32-2.36 (m, 2H, Ar-C≡C-CH₂CH₂CH₂), 2.14 (bs, 2H, CH₂C(CH₃)₂CH_aH_bOCHO), 1.79 (q, 2H, *J* = 7.1 Hz, Ar-C≡C-CH₂CH₂CH₂), 1.39-1.74 (m, s, 15H, OCHCH₂CH₂CH₂CH_aH_bO, C(CH₃)₃), 0.99 (s, 3H, C(CH₃)₂), 0.97 (s, 3H, C(CH₃)₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 165.32 (C=O), 131.46 (C_{Ar}), 131.32 (C_{ar}), 130.82 (C_q), 129.37 (C_{ar}), 129.23 (C_{ar}), 128.14 (C_q), 98.93 (OCHO), 92.48 (C(CH₃)₃), 81.16 (Ar-C≡C), 80.66 (Ar-C≡C), 80.51 (Ar-C≡C-CH₂CH₂CH₂C≡C), 78.82 (Ar-C≡C-CH₂CH₂CH₂C≡C), 75.20 (C(CH₃)₂CH_aH_bOCHO), 61.76 (C(CH₃)₂CH_aH_bOCHOCH_aH_b), 34.86 (C(CH₃)₂), 30.76 (C(THP)), 30.60 (CH₂C(CH₃)₂CH_aH_bO), 29.02 (Ar-C≡C-CH₂CH₂CH₂), 28.19 (C(CH₃)₃), 25.57

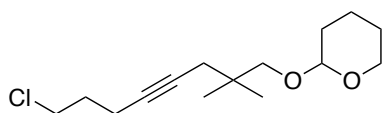
(C(THP)), 24.32 (C(CH₃)₂), 19.30 (C(THP)), 18.68 (Ar-C≡C-CH₂), 18.11 (Ar-C≡C-CH₂CH₂CH₂).

Synthesis of *tert*-butyl 4-(10-hydroxy-9,9-dimethyldeca-1,6-diynyl)benzoate **142**



Deprotection of **167** afforded alcohol **142** following the same procedure used for the deprotection of compound **165**. Purification by column chromatography (30% EtOAc:hex; *R_f* = 0.26) afforded *tert*-butyl 4-(10-hydroxy-9,9-dimethyldeca-1,6-diynyl)benzoate as a colourless oil (0.24 g, 71%). **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 7.90 (d, 2H, *J* = 8.1 Hz, *H_{Ar}*), 7.42 (d, 2H, *J* = 8.3 Hz, *H_{Ar}*), 3.42 (bs, 2H, CH₂OH), 2.54 (t, 2H, *J* = 7.0 Hz, Ar-C≡C-CH₂), 2.35 (t, 2H, *J* = 6.9 Hz, Ar-C≡C-CH₂CH₂CH₂), 2.13 (bs, 2H, CH₂C(CH₃)₂CH₂OH), 1.80 (q, 2H, *J* = 7.0 Hz, Ar-C≡C-CH₂CH₂CH₂), 1.62 (bs, 1H, OH), 1.58 (C(CH₃)₃), 0.96 (C(CH₃)₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 165.33 (C=O), 131.47 (C_{ar}), 131.34 (C_{ar}), 130.86 (C_q), 129.38 (C_{ar}), 129.25 (C_{ar}), 128.08 (C_q), 92.33 (C(CH₃)₃), 81.18 (Ar-C≡C), 81.11 (Ar-C≡C), 80.73 (Ar-C≡C-CH₂CH₂CH₂-C≡C), 78.46 (Ar-C≡C-CH₂CH₂CH₂-C≡C), 71.22 (CH₂OH), 35.62 (C(CH₃)₂CH₂OH), 28.83 (C≡C-CH₂C(CH₃)₂CH₂OH), 28.19 (C(CH₃)₃), 28.07 (Ar-C≡C-CH₂CH₂CH₂), 23.88 (CH₂C(CH₃)₂CH₂OH), 18.70 (Ar-C≡C-CH₂CH₂CH₂), 18.08 (Ar-C≡C-CH₂CH₂CH₂).

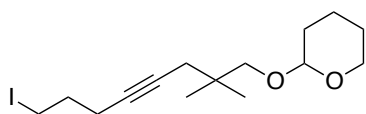
Synthesis of 2-(8-chloro-2,2-dimethyloct-4-ynyloxy)tetrahydro-2*H*-pyran **168**



To a round-bottom flask were added 2-(4-pentyn-1-yloxy)tetrahydro-2*H*-pyran **158** (1.50 g, 7.65 mmol) and dry THF (26 ml) and cooled to -78 °C. A 2.5 M solution of *n*-BuLi in hexanes (3.67 ml, 9.18 mmol) was added dropwise over 30 min. The

resulting bright yellow solution was stirred at this temperature for a further 20 min and 1-bromo-3-chloropropane (1.06 ml, 10.7 mmol) added at -78 °C. The resulting mixture was then warmed to room temperature and heated to 80 °C (reflux) for 16 hours. The solution was then cooled to 0 °C and NH₄Cl (sat) added. The solution was extracted with Et₂O (3 × 20 ml), washed with brine (20 ml), dried over MgSO₄, filtered and concentrated to yield a pale yellow oil. The crude mixture was then purified by column chromatography (5% EtOAc:pent; R_f = 0.32) to afford a colourless oil (1.43 g, 69%). **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 4.57 (t, 1H, *J* = 3.2 Hz, OCHO), 3.82-3.87 (m, 1H, OCHOCH_aH_bTHP), 3.66 (t, 2H, *J* = 6.4 Hz, CH₂Cl), 3.52 (d, 1H, *J* = 9.2 Hz, C(CH₃)₂CH_aH_bOCHO), 3.48-3.52 (m, 1H, OCHOCH_aH_bTHP), 3.08 (d, 1H, *J* = 9.2 Hz, C(CH₃)₂CH_aH_bOCHO), 2.33-2.37 (m, 2H, CH₂C≡CCH₂C(CH₃)₂), 2.14 (bs, 2H, CH₂C≡CCH₂C(CH₃)₂), 1.93 (q, 2H, *J* = 6.5 Hz, Cl-CH₂CH₂CH₂), 1.49-1.69 (m, 6H, OCHCH₂CH₂CH₂CH_aH_bO), 0.98 (s, 3H, C(CH₃)₂), 0.96 (s, 3H, C(CH₃)₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 98.92 (OCHO), 79.64 (Cl-CH₂CH₂CH₂C≡C), 79.06 (Cl-CH₂CH₂CH₂C≡C), 75.16 (C(CH₃)₂CH_aH_bOCHO), 61.76 (OCHOCH_aH_b), 43.82 (CH₂Cl), 34.82 (C(CH₃)₂), 31.83 (Cl-CH₂CH₂CH₂), 30.59 (C(THP)), 28.97 (C≡C-CH₂C(CH₃)₂), 25.56 (C(THP)), 24.30 (C(CH₃)₂), 19.30 (C(THP)), 16.24 (Cl-CH₂CH₂CH₂).

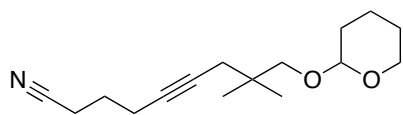
Synthesis of 2-(8-iodo-2,2-dimethyloct-4-ynyloxy)tetrahydro-2*H*-pyran **169**



Compound **168** (1.43 g, 5.25 mmol) was dissolved in dry acetone (20 mL), and NaI (3.93g, 26.2 mmol) was added. The solution was heated at reflux for 20 h, cooled, and filtered through Celite with acetone washings. The product was purified by column chromatography (5% EtOAc:pent; R_f = 0.23) to yield 1.62 g (85%) of 2-(8-iodo-2,2-dimethyloct-4-ynyloxy)tetrahydro-2*H*-pyran as a pale yellow oil. **¹H NMR** (400 MHz, CDCl₃) δ/ppm: 4.58 (t, 1H, *J* = 3.3 Hz, OCHO), 3.82-3.88 (m, 1H, OCHOCH_aH_b), 3.49-3.52 (d, m, 1H, 1H, CH_aH_bOCHO, OCHOCH_aH_b), 3.31 (t, 2H, *J* = 6.8 Hz, CH₂I), 3.08 (d, 1H, *J* = 9.2 Hz, CH_aH_bOCHO), 2.28-2.33 (m, 2H, I-

CH₂CH₂CH₂), 2.10-2.13 (m, 2H, I-CH₂CH₂CH₂-C≡C-CH₂), 1.95 (q, 2H, *J* = 6.6 Hz, I-CH₂CH₂CH₂), 1.49-1.71 (m, 6H, OCHCH₂CH₂CH₂CH₂CH_aH_bO), 0.98 (s, 3H, C(CH₃)₂), 0.96 (s, 3H, C(CH₃)₂). ¹³C NMR (101 MHz, CDCl₃) δ/ppm: 98.94 (OCHO), 79.35 (I-CH₂CH₂CH₂-C≡C), 79.27 (I-CH₂CH₂CH₂-C≡C), 75.17 (CH_aH_bOCHO), 61.80 (CH_aH_bOCHOCH_aH_b), 34.83 (C(CH₃)₂), 32.52 (I-CH₂CH₂CH₂), 30.60 (C(THP)), 28.98 (I-CH₂CH₂CH₂-C≡C-CH₂), 25.56 (C(THP)), 24.32 (C(CH₃)₂), 19.83 (I-CH₂CH₂CH₂), 19.31 (C(THP)), 5.76 (I-CH₂).

Synthesis of 8,8-dimethyl-9-(tetrahydro-2*H*-pyran-2-yloxy)non-5-ynenitrile **170**



Conversion of the alkyl iodide **169** to the nitrile functionality was performed by a modified literature procedure.¹⁹² Alkyl iodide **169** (1.62 g, 4.45 mmol) was dissolved in DMSO (20 ml) and sodium cyanide (0.26 g, 5.34 mmol) added at room temperature. The resulting reaction mixture was heated to 70 °C and stirred at this temperature for 3 h. The reaction mixture was cooled to room temperature and a 1:1 sat. NaHCO₃:H₂O (15 ml) added. The organic layer was separated by addition of ethyl acetate (20 ml) and washed twice with water (2 x 15 ml) followed by brine (15 ml). The organic extract was dried over anhydrous MgSO₄, filtered and concentrated to give a pale yellow oil which was purified by column chromatography (15% EtOAc:pent; *R_f* = 0.39) to produce a colourless oil (0.90 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ/ppm: 4.56 (t, 2H, *J* = 3.3 Hz, OCHO), 3.81-3.87 (m, 1H, OCHOCH_aH_b), 3.47-3.52 (d, m, 1H, 1H, C(CH₃)₂CH_aH_bOCHO, OCHOCH_aH_b), 3.06 (d, 1H, *J* = 9.2 Hz, C(CH₃)₂CH_aH_bOCHO), 2.48 (t, 2H, *J* = 7.3 Hz, CH₂CN), 2.32-2.37 (m, 2H, CN-CH₂CH₂CH₂-C≡C), 2.14 (t, 2H, *J* = 2.4 Hz, CH₂CH₂CH₂-C≡C-CH₂), 1.83 (q, 2H, *J* = 6.9 Hz, CN-CH₂CH₂CH₂), 1.49-1.72 (m, 6H, OCHCH₂CH₂CH₂CH_aH_bO), 0.97 (s, 3H, C(CH₃)₂), 0.96 (s, 3H, C(CH₃)₂). ¹³C NMR (101 MHz, CDCl₃) δ/ppm: 119.93 (N≡C), 98.96 (OCHO), 80.12 (CN-CH₂CH₂CH₂-C≡C), 78.75 (CN-CH₂CH₂CH₂-C≡C), 75.16 (C(CH₃)₂CH_aH_bOCHO), 61.84 (OCHOCH_aH_bTHP), 34.79 (C(CH₃)₂), 30.59 (C(THP)), 28.93 (C≡C-CH₂C(CH₃)₂),

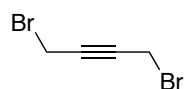
25.54 (C(THP)), 25.03 (CN-CH₂CH₂CH₂), 24.28 (C(CH₃)₂), 19.32 (C(THP)), 17.96 (CN-CH₂CH₂CH₂), 16.10 (CN-CH₂CH₂CH₂).

Synthesis of 9-hydroxy-8,8-dimethylnon-5-ynenitrile **146**



Deprotection of **170** was carried out using the same procedure as for **138**. Purification by column chromatography (20% EtOAc:pent; R_f = 0.24) afforded 9-hydroxy-8,8-dimethylnon-5-ynenitrile as a colourless oil (0.45 g, 92%). **¹H NMR** (400 MHz, CDCl₃) δ /ppm: 3.39 (bs, 2H, CH₂OH), 2.48 (t, 2H, J = 7.1 Hz, CH₂CN), 2.33-2.37 (m, 2H, CN-CH₂CH₂CH₂), 2.12 (t, 2H, J = 2.4 Hz, CN-CH₂CH₂CH₂C $\equiv$ C-CH₂), 1.84 (q, 2H, J = 6.9 Hz, CNCH₂CH₂CH₂), 1.63 (bs, 1H, OH), 0.95 (s, 6H, C(CH₃)₂). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 119.32 (N $\equiv$ C), 79.83 (CN-CH₂CH₂CH₂-C $\equiv$ C), 79.20 (CN-CH₂CH₂CH₂-C $\equiv$ C), 70.95 (CH₂OH), 35.58 (C(CH₃)₂), 28.62 (C $\equiv$ C-CH₂C(CH₃)₂), 24.88 (CN-CH₂CH₂CH₂), 23.82 (C(CH₃)₂), 17.98 (CN-CH₂CH₂CH₂), 16.18 (CN-CH₂CH₂CH₂).

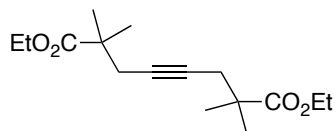
Synthesis of 1,4-dibromobut-2-yne **171**¹⁹³



Phosphorus tribromide (6.78 mL, 72.1 mmol) was slowly added to a solution of 2-butyne-1,4-diol (7.76 g, 90.1 mmol) and pyridine (1.29 mL) in Et₂O (116 mL) at 0 °C. The solution was stirred at this temperature for 30 min, then refluxed for 4 h. After cooling down, water was added (80 ml) and the aqueous layer was separated and extracted with Et₂O (2 x 40 ml). The combined organic extracts were washed with saturated NaHCO₃ (100 ml) and brine (100 ml) then dried over anhydrous MgSO₄, filtered and concentrated to yield a light brown oil. Fractional distillation (40 °C/5 $\times$ 10⁻² torr) yielded 1,4-dibromobut-2-yne as a colourless oil (17.2 g, 92%). **¹H NMR** (400 MHz, CDCl₃) δ /ppm: 3.95 (s, 4H, BrCH₂-C $\equiv$ C-CH₂Br). **¹³C NMR** (101 MHz,

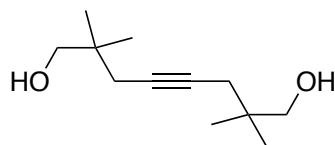
CDCl_3) δ/ppm : 81.61 ($\text{BrCH}_2\text{-C}\equiv\text{C-CH}_2\text{Br}$), 13.91 ($\text{BrCH}_2\text{-C}\equiv\text{C-CH}_2\text{Br}$). The NMR data was in agreement with the literature reported data.¹⁹³

Synthesis of diethyl 2,2,7,7-tetramethyloct-4-ynedioate **172**



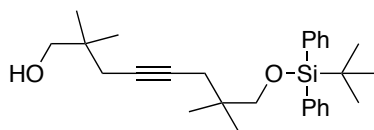
Diester **172** was synthesized via a modified literature procedure.¹⁹⁴ Lithium diisopropylamide (149 mmol) was formed by the addition of 2.5 M *n*-BuLi in hexanes (60 ml 149 mmol) to a stirred solution of diisopropylamine (21 ml, 149 mmol) in dry THF (186 ml) at 0 °C under argon and stirred at this temperature for a further 30 min. After cooling to -78 °C, diethylisobutyrate (20 ml, 149 mmol) was added slowly keeping the temperature below -78 °C and the mixture was then stirred at 0 °C for 1 hour. The mixture was recooled to -78 °C and a solution of compound **171** (10.3 g, 49.6 mmol) in dry THF (10 ml) was added dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction was then quenched with saturated ammonium chloride (80 ml) and the organic phase was separated. The aqueous layer was extracted with diethyl ether (3 × 100 ml). The combined organic extracts were washed with brine (100 ml), dried over anhydrous MgSO_4 , filtered and concentrated to yield a pale yellow oil. The crude product was purified by column chromatography (5% EtOAc:pent) to yield a colourless oil (11.9 g, 85%). **¹H NMR** (400 MHz, CDCl_3) δ/ppm : 4.13 (q, 4H, $J = 7.1$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.39 (s, 4H, $\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 1.26 (s, 12H, $\text{C}(\text{CH}_3)_2$), 1.22 (t, 6H, $J = 5.8$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$). **¹³C NMR** (101 MHz, CDCl_3) δ/ppm : 176.87 (C=O), 78.87 ($\text{C}(\text{CH}_3)_2\text{CH}_2\text{-C}\equiv\text{C-CH}_2\text{C}(\text{CH}_3)_2$), 60.57 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 42.26 ($\text{C}(\text{CH}_3)_2$), 29.99 ($\text{CH}_2\text{C}\equiv\text{C}$), 24.51, ($\text{CO}_2\text{CH}_2\text{CH}_3$), 14.17 ($\text{C}(\text{CH}_3)_2$).

Synthesis of 2,2,7,7-tetramethyloct-4-yne-1,8-diol **173**



A solution of **172** (7.19 g, 25.5 mmol) in dry ether (10 ml) was added to a stirred solution of LiAlH_4 (1.90 g, 51 mmol) in dry ether (90 ml) at 0 °C and stirred for an additional hour at 0 °C. The mixture was then carefully quenched with sat. NH_4Cl until no further evolution of hydrogen was observed, followed by addition of 2 M HCl to dissolve the precipitated salts. The phases were separated and the aqueous layer was extracted with ether (3 × 100 ml). The organic layers were combined, washed with sat. NaHCO_3 (100 ml), brine (100 ml), dried over anhydrous MgSO_4 , filtered and concentrated to give a colourless oil. The residue was purified by column chromatography (1:1 EtOAc:hex; $R_f = 0.22$) to yield a colourless oil (4.19 g, 83%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 3.40 (s, 4H, 2 $\text{C}(\text{CH}_3)\text{CH}_2\text{OH}$), 2.13 (s, 4H, $\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 1.98 (2 OH), 0.95 (s, 12H, 2 $\text{C}(\text{CH}_3)_2$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 79.67 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 71.10 (CH_2OH), 35.69 ($\text{C}(\text{CH}_3)_2$), 28.83 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 23.94 ($\text{C}(\text{CH}_3)_2$).

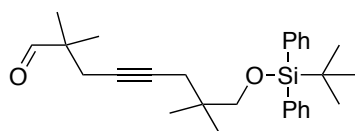
Synthesis of 8-(*tert*-butyldiphenylsilyloxy)-2,2,7,7-tetramethyloct-4-yn-1-ol **174**



Mono-protection of diol **173** was achieved according to the literature procedure.¹⁹⁵ To a suspension of 60% NaH (0.91 g, 22.6 mmol) in dry THF (17 ml) was added dropwise a solution of diol **173** (4.46 g, 22.5 mmol) in dry THF (7 ml) at room temperature. After stirring for 45 min, *tert*-butyl(chloro)diphenylsilane (5.89 ml, 22.6 mmol) was added dropwise to this solution. The reaction was stirred for 30 min and then diluted with 70 ml Et_2O . The organic phase was washed twice with water (40 ml) followed by brine (40 ml), dried over anhydrous MgSO_4 , filtered and

concentrated *in vacuo*. Purification by column chromatography (20% EtOAc:pent; $R_f = 0.47$) afforded **174** as a colourless oil (4.12 g, 42%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 3.43 (d, 2H, $J = 6.1$ Hz, CH_2OH), 3.30 (s, 2H, CH_2OTBS), 2.10-2.13 (dt, 4H, $J = 2.3, 10.8$ Hz, $\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 1.58 (t, 1H, $J = 7.2$ Hz, OH), 0.97 (s, 6H, $\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$), 0.91 (s, 6H, $\text{C}(\text{CH}_3)_2\text{CH}_2\text{OTBS}$), 0.89 (s, 9H, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.02 (s, 6H, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 135.71 (C_{Ar}), 133.80 (C_{q}), 129.54 (C_{Ar}), 127.60 (C_{Ar}), 80.13 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 79.04 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 71.33 (CH_2OH), 71.25 (CH_2OTBDPS), 36.33 ($\text{C}(\text{CH}_3)_2$), 35.67 ($\text{C}(\text{CH}_3)_2$), 28.90 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 28.80 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 26.86 ($\text{OSiPh}_2\text{C}(\text{CH}_3)_3$), 23.99 ($\text{HOCH}_2\text{C}(\text{CH}_3)_2$), 23.90 ($\text{C}(\text{CH}_3)_2\text{CH}_2\text{OTBDPS}$), 19.43 ($\text{OSiPh}_2\text{C}(\text{CH}_3)_3$).

Synthesis of 8-(*tert*-butyldimethylsilyloxy)-2,2,7,7-tetramethyloct-4-ynal **175**

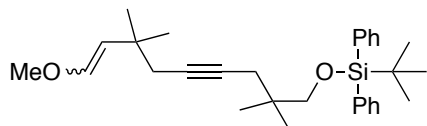


To a 22 ml CH_2Cl_2 solution of oxalylchloride (0.96 ml, 11.3 mmol) at -78°C was added a 10 ml CH_2Cl_2 solution of DMSO (1.54 ml, 21.7 mmol). The reaction mixture was stirred for 15 min. Alcohol **174** (4.12 g, 9.43 mmol) in CH_2Cl_2 (15 ml) was slowly added dropwise. After stirring for 30 min at -78°C , triethylamine (6.57 ml, 47.2 mmol) was added at once. The reaction mixture was maintained at -78°C for an additional 20 minutes, then warmed to rt. After dilution with 30 ml CH_2Cl_2 , the organic phase was washed with sat. NH_4Cl (2 x 30 ml), water (2 x 30 ml) and brine (30 ml). The organic phase was dried over anhydrous MgSO_4 , filtered and concentrated to yield a colourless oil which was used for the next step without any further purification (3.83 g, 93%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 9.55 (s, 1H, CHO), 3.28 (s, 2H, CH_2OTBS), 2.32 (t, 2H, $J = 2.4$ Hz, $\text{CHOC}(\text{CH}_3)_2\text{CH}_2$), 2.08 (t, 2H, $J = 2.4$ Hz, $\text{OTBSCH}_2\text{C}(\text{CH}_3)_2\text{CH}_2$), 1.14 (s, 6H, $\text{CHOC}(\text{CH}_3)_2$), 0.89 (s, 6H, $\text{C}(\text{CH}_3)_2\text{CH}_2\text{OTBS}$), 0.88 (s, 9H, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.02 (s, 6H, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 205.19 (CHO), 81.20 ($\text{CHOC}(\text{CH}_3)_2\text{CH}_2\text{C}\equiv\text{C}$), 76.70 ($\text{CHOC}(\text{CH}_3)_2\text{CH}_2\text{C}\equiv\text{C}$), 70.60 (CH_2OTBS), 45.72

(CHOC(CH₃)₂), 35.91 (C(CH₃)₂CH₂OTBS), 28.45 (OSi(CH₃)₂C(CH₃)₃), 27.32 (C≡C-CH₂C(CH₃)₂CH₂OTBS), 25.88 (CHOC(CH₃)₂CH₂), 23.75 (C(CH₃)₂CH₂OTBS), 21.27 (OSi(CH₃)₂C(CH₃)₃), 18.28 (CHOC(CH₃)₂), -5.52 (OSi(CH₃)₂C(CH₃)₃).

Synthesis of

tert-butyl(9-methoxy-2,2,7,7-tetramethylnon-8-en-4-ynyloxy)dimethylsilane **176**

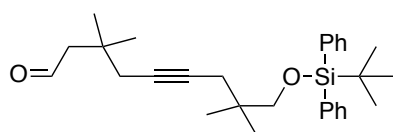


Compound **176** was synthesised via a modified literature procedure method.¹⁹⁶

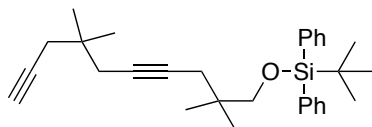
To a stirred suspension of powdered KHMDS (2.11 g, 10.6 mmol) in dry THF (20 ml) was added (methoxymethyl)triphenylphosphonium chloride (3.62 g, 10.6 mmol) in dry THF (15 ml) at 0 °C. The bright orange solution was allowed to warm to rt for 1 h and the resultant deep red solution recooled to -78 °C. Aldehyde **175** (3.83 g, 8.81 mmol) in dry THF (10 ml) was then added dropwise. The reaction mixture was stirred at -78 °C for 1 h and allowed to warm to room temperature and stirred overnight. The resultant product was quenched with water (30 ml). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 x 30 ml). The combined organic extracts were washed with water (30 ml) and brine (30 ml), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude product mixture was purified by column chromatography (2% Et₂O:pent R_f = 0.47, 0.38) to yield a mixture of *E*:*Z* isomers (2.70 g, 67%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ/ppm: 6.29 (d, 1H, *J* = 12.9 Hz, CH=CHOMe, *E*), 5.73 (d, 1H, *J* = 6.9 Hz, CH=CHOMe, *Z*), 4.87 (d, 1H, CH=CHOMe *J* = 12.9 Hz, *E*), 4.27 (d, 1H, *J* = 6.9 Hz, CH=CHOMe, *Z*), 3.54 (s, 2H, CH₂OTBS, *E*), 3.49 (s, 2H, CH₂OTBS, *Z*), 3.31 (d, 3H, *J* = 1.8 Hz, OCH₃), 2.08-2.13 (m, 4H, CH₂-C≡C-CH₂), 1.56 (s, 3H, OCH₃, *Z*), 1.08 (s, 6H, OMeHC=CHC(CH₃)₂), 0.91 (s, 6H, C(CH₃)₂CH₂OTBS), 0.88 (s, 9H, OSi(CH₃)₂C(CH₃)₃), 0.022 (s, 6H, OSi(CH₃)₂C(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ/ppm: 145.53 (CH=CHOMe, *E*), 145.44 (CH=CHOMe, *Z*), 114.57 (CH=CHOMe, *Z*), 112.67 (CH=CHOMe, *E*), 80.01 (OMeHC=CHC(CH₃)₂CH₂-C≡C), 79.89 (OMeHC=CHC(CH₃)₂CH₂-C≡C), 70.65

(CH=CHOCH₃, *E*), 59.65 (CH₂OTBS, *E*), 55.81 (CH₂OTBS, *Z*), 35.97 (OMeHC=CHC(CH₃)₂CH₂), 34.78 (OMeHC=CHC(CH₃)₂, 32.82 (C(CH₃)₂CH₂OTBS), 28.61 (CH₂-C≡C-CH₂C(CH₃)₂CH₂OTBS), 27.72 (OMeHC=CHC(CH₃)₂), 25.87 (OSi(CH₃)₂C(CH₃)₃), 23.73 C(CH₃)₂CH₂OTBS), 18.28 (OSi(CH₃)₂C(CH₃)₃), -5.52 (OSi(CH₃)₂C(CH₃)₃).

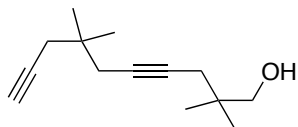
Synthesis of 9-(*tert*-butyldimethylsilyloxy)-3,3,8,8-tetramethylnon-5-ynal **177**



Hydrolysis of methoxy enol ether **176** was achieved by acid hydrolysis. 2N HCl (11 ml) was added to a solution of **176** (2.70 g, 5.86 mmol) in dioxane (50 ml). The mixture was stirred at rt for 3 h and diluted with diethyl ether (60 ml). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 x 60 ml). The combined organic extracts were washed with water (50 ml) followed by brine (50 ml), dried over anhydrous MgSO₄, filtered and concentrated to yield aldehyde **177** as a colourless oil (2.81 g, quant). ¹H NMR (400 MHz, CDCl₃) δ/ppm: 9.85 (t, 1H, *J* = 2.9 Hz, CHO), 3.30 (s, 2H, CH₂OTBS), 2.40 (d, 2H, *J* = 2.8 Hz, CH₂CHO), 2.20 (t, 2H, *J* = 2.3 Hz, CHOCH₂C(CH₃)₂CH₂), 2.11 (t, 2H, *J* = 2.3 Hz, CH₂C(CH₃)₂CH₂OTBS), 1.11 (s, 6H, CHOCH₂C(CH₃)₂), 0.91 (s, 6H, C(CH₃)₂CH₂OTBS), 0.88 (s, 9H, OSi(CH₃)₂C(CH₃)₃), 0.022 (s, 6H, OSi(CH₃)₂C(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ/ppm: 230.02 (CHO), 81.09 (CHOCH₂C(CH₃)₂CH₂C≡C), 78.25 (CHOCH₂C(CH₃)₂CH₂C≡C), 70.64 (CH₂OTBS), 53.97 (CHOCH₂), 35.96 (CHOCH₂C(CH₃)₂), 33.97 (C(CH₃)₂CH₂OTBS), 32.79 (CHOCH₂C(CH₃)₂CH₂), 28.52 (OSi(CH₃)₂C(CH₃)₃), 27.38 (CH₂-C≡C-CH₂C(CH₃)₂CH₂OTBS), 25.88 (CHOCH₂C(CH₃)₂), 23.81 (OSi(CH₃)₂C(CH₃)₃), 18.30 (C(CH₃)₂CH₂OTBS), -5.51 (OSi(CH₃)₂C(CH₃)₃).

Synthesis of *tert*-butyldiphenyl(2,2,7,7-tetramethyldeca-4,9-diynyloxy)silane **179**


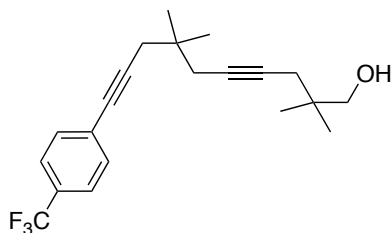
K_2CO_3 (1.91 g, 13.8 mmol) was added to a solution of aldehyde **177** (2.78 g, 6.22 mmol) in MeOH (75 mL) at 0 °C. Following this, diethyl 1-diazo-2-oxopropylphosphonate **178** (1.91 g, 13.8 mmol) in MeOH (19 mL) was added dropwise to the mixture, which was stirred for a further three h at 0 °C. The reaction was then warmed to room temperature and stirred for 48 h. The reaction was then diluted with Et_2O (100 mL) and washed with sat. NaHCO_3 (120 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 120 mL). The combined organic layers were washed with brine (120 mL), dried (MgSO_4) and concentrated *in vacuo*. The crude material was purified by column chromatography (3% EtOAc:pent; R_f = 0.46) to give **179** as a colourless oil (2.46 g, 89%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 7.69-7.71 (m, 4H, H_{Ar}), 7.39-7.47 (m, 6H, H_{Ar}), 3.43 (s, 2H, $\text{CH}_2\text{OSiC}(\text{CH}_3)_3\text{Ph}_2$), 2.25-2.26 (m, 2H, $\text{H-C}\equiv\text{C-CH}_2$), 2.19-2.20 (m, 4H, $\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 2.02 (t, 1H, J = 2.6 Hz, $\text{H-C}\equiv\text{C}$), 1.09 (s, 9H, $\text{Si-C}(\text{CH}_3)_3$), 1.06 (s, 6H, $\text{C}(\text{CH}_3)_2$), 1.01 (s, 6H, $\text{C}(\text{CH}_3)_2$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 135.70 (C_{Ar}), 133.82 (C_{q}), 129.53 (C_{Ar}), 127.60 (C_{Ar}), 82.27 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 80.11 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 78.96 ($\text{H-C}\equiv\text{C}$), 71.36 (CH_2O), 70.06 ($\text{H-C}\equiv\text{C}$), 36.35 ($\text{C}(\text{CH}_3)_2$), 33.95 ($\text{C}(\text{CH}_3)_2$), 31.49 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 30.92 ($\text{CH}_2\text{-C}\equiv\text{C-CH}_2$), 28.79 ($\text{H-C}\equiv\text{C-CH}_2$), 26.87 ($\text{Si-C}(\text{CH}_3)_3$), 26.33 ($\text{C}(\text{CH}_3)_2$), 23.97 ($\text{C}(\text{CH}_3)_2$), 19.44 ($\text{Si-C}(\text{CH}_3)_3$).

 Synthesis of 2,2,7,7-tetramethyldeca-4,9-diyn-1-ol **180**


To silyl ether **179** (2.40 g, 5.40 mmol) in THF (57 mL) was added TBAF (10.8 mL, 10.8 mmol) at 0 °C. The reaction mixture was warmed to room temperature and

stirred for 12 h. Sat. NH_4Cl (30 ml) was added followed by EtOAc (60 ml). The organic layer was separated and the aqueous layer extracted with EtOAc (3×50 ml). The organic extracts were combined and washed with brine (60 ml), dried over MgSO_4 , filtered and concentrated to give an orange oil. Purification by column chromatography (20% EtOAc:pent; $R_f = 0.27$) gave **180** as a colourless oil (0.79 g, 71%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 3.45 (d, 2H, $J = 5.8$ Hz CH_2OH), 2.20-2.22 (m, 4H, $(\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2)$), 2.17-2.18 (m, 2H, $\text{H}-\text{C}\equiv\text{C}-\text{CH}_2$), 2.03 (t, 1H, $J = 2.7$ Hz, $\text{H}-\text{C}\equiv\text{C}-\text{CH}_2$), 1.64 (t, 1H, $J = 4.2$ Hz, OH), 1.08 (s, 6H, $\text{C}(\text{CH}_3)_2$), 1.00 (s, 6H, $\text{C}(\text{CH}_3)_2$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 82.14 ($\text{H}-\text{C}\equiv\text{C}$), 79.63 ($\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$), 79.56 ($\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$), 71.27 (CH_2OH), 70.13 ($\text{H}-\text{C}\equiv\text{C}$), 35.71 ($\text{C}(\text{CH}_3)_2$), 33.96 ($\text{C}(\text{CH}_3)_2$), 31.39 ($\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$), 30.97 ($\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$), 28.86 ($\text{H}-\text{C}\equiv\text{C}-\text{CH}_2$), 26.37 ($\text{C}(\text{CH}_3)_2$), 23.90 ($\text{C}(\text{CH}_3)_2$).

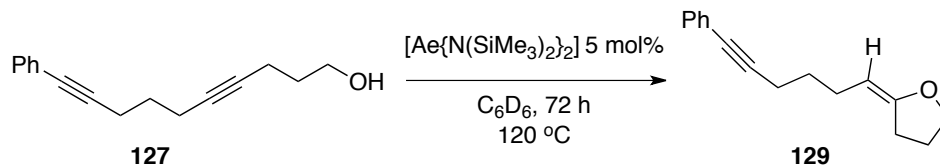
Synthesis of 2,2,7,7-tetramethyl-10-(4-(trifluoromethyl)phenyl)deca-4,9-diyne-1-ol **149**



Dialkynyl alcohol **149** was prepared from **180** and 4-iodobenzotrifluoride according to the standard procedure for Sonagashira cross-coupling reactions. Purification by column chromatography (20% EtOAc:pent; $R_f = 0.38$) gave **149** as a colourless oil (0.78 g, 95%). **^1H NMR** (400 MHz, CDCl_3) δ /ppm: 7.51-7.58 (m, 4H, H_{Ar}), 3.46 (d, 2H, $J = 5.9$ Hz, CH_2OH), 2.45 (s, 2H, $\text{Ar}-\text{C}\equiv\text{C}-\text{CH}_2$), 2.27 (t, 2H, $J = 2.3$ Hz, $\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$), 2.19 (t, 2H, $J = 2.3$ Hz, $\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$), 1.62-1.64 (m, 1H, OH), 1.14 (s, 6H, $\text{C}(\text{CH}_3)_2$), 1.01 (s, 6H, $\text{C}(\text{CH}_3)_2$). **^{13}C NMR** (101 MHz, CDCl_3) δ /ppm: 131.81 (C_{Ar}), 129.51 (C_{q}), 129.19 (C_{q}), 127.79 (CF_3), 125.15 (C_{Ar}), 90.87 ($\text{Ar}-\text{C}\equiv\text{C}$), 81.44 ($\text{Ar}-\text{C}\equiv\text{C}$), 79.80 ($\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$), 79.53 ($\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$), 71.27 (CH_2OH), 35.74 ($\text{C}(\text{CH}_3)_2$), 34.55 ($\text{C}(\text{CH}_3)_2$), 31.99 ($\text{Ar}-\text{C}\equiv\text{C}-\text{CH}_2$), 31.64 ($\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$), 28.87 ($\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2$), 26.58 ($\text{C}(\text{CH}_3)_2$), 23.91 ($\text{C}(\text{CH}_3)_2$).

3.3.2 Attempted Cascade Reactions

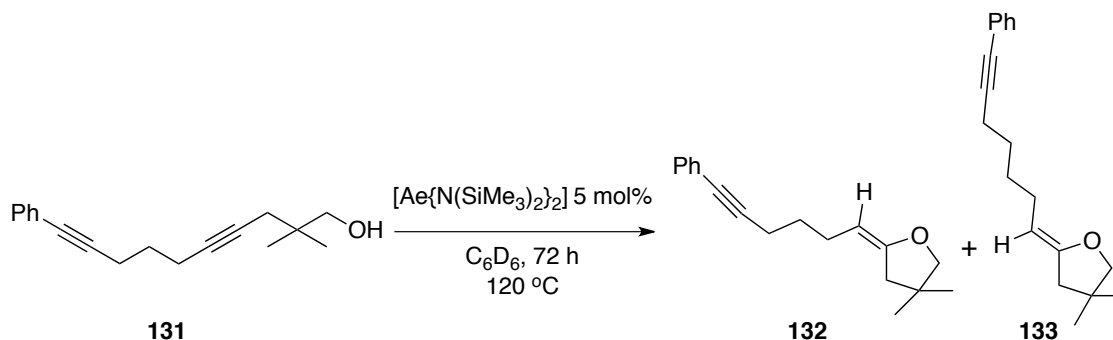
Synthesis of (*E*)-2-(6-phenylhex-5-ynylidene)tetrahydrofuran **129**



129 was synthesised according to the standard procedure for catalytic hydroalkoxylation reactions.

^1H NMR (400 MHz, C_6D_6) δ /ppm: 7.47-7.49 (m, H_{ar}), 7.00-7.03 (m, H_{ar}), 4.87-4.92 (tt, 1H, $J = 7.8, 15.6$ Hz, $\text{C}=\text{CH}$), 3.64 (t, 2H, $J = 6.7$ Hz, OCH_2), 2.29 (t, 2H, $J = 7.0$ Hz, $\text{Ph-C}\equiv\text{C-CH}_2$), 2.10-2.15 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 2.04-2.08 (m, 2H, $\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2$), 1.55 (q, 2H, $J = 7.0$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.37 (q, 2H, $J = 7.0$ Hz, $\text{Ph-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2$). **^{13}C NMR** (101 MHz, C_6D_6) δ /ppm: 156.95 (C_{ar} , q), 131.56 (C_{ar}), 128.15 (C_{ar}), 124.58 (C_{ar}), 94.03 ($\text{C}=\text{CH}$), 90.53 ($\text{Ph-C}\equiv\text{C}$), 81.50 ($\text{Ph-C}\equiv\text{C}$), 69.04 (OCH_2), 25.62 ($\text{OCH}_2\text{CH}_2\text{CH}_2$), 24.59 ($\text{OCH}_2\text{CH}_2\text{CH}_2$), 18.54 ($\text{Ph-C}\equiv\text{C-CH}_2\text{CH}_2\text{CH}_2$), 17.95 ($\text{Ph-C}\equiv\text{C-CH}_2$), 15.29 ($\text{C}=\text{CHCH}_2$). **HRMS** (ES) m/z : calc. for $\text{C}_{16}\text{H}_{19}\text{O}$: 227.1447; found 227.1436.

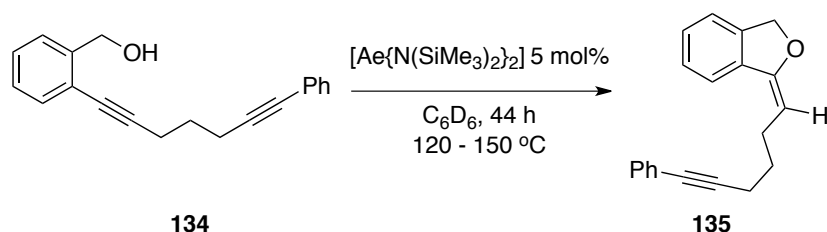
Synthesis of (*E*)-4,4-dimethyl-2-(6-phenylhex-5-ynylidene)tetrahydrofuran **132**



132 was synthesised according to the standard procedure catalytic hydroalkoxylation reactions.

Characterisation for **132**: $^1\text{H NMR}$ (400 MHz, d_6 -benzene) δ /ppm: 7.47-7.49 (m, 2H, H_{Ar}), 6.95-7.02 (m, 3H, H_{Ar}), 4.88-4.92 (tt, 1H, $J = 2.1$ Hz, 10.0 Hz, $\text{C}=\text{CH}$), 3.43 (s, 2H, OCH_2), 2.31 (t, 2H, $J = 7.0$ Hz, $\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2$), 2.05-2.10 (m, 4H, $\text{CH}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2$), 1.55 (q, 2H, $J = 7.0$ Hz, $\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CPh}$), 0.79 (s, 6H, $\text{C}(\text{CH}_3)_2$). $^{13}\text{C NMR}$ (101 MHz, d_6 -benzene) δ /ppm: 157.20 ($\text{OC}=\text{CH}$), 131.54 (C_{ar}), 128.18 (C_{ar}), 124.58 (C_{ar}), 95.08 ($\text{OC}=\text{CH}$), 90.58 ($\text{Ph}-\text{C}\equiv\text{C}$), 81.15 ($\text{Ph}-\text{C}\equiv\text{C}$), 80.18 (OCH_2), 40.79 ($\text{OC}=\text{CHCH}_2$), 37.42 ($\text{OCH}_2\text{C}(\text{CH}_3)_2$), 29.61 ($\text{Ph}-\text{C}\equiv\text{C}-\text{CH}_2\text{CH}_2\text{CH}_2$), 226.63 ($\text{CH}_2\text{C}=\text{CHCH}_2$), 24.66 ($\text{C}(\text{CH}_3)_2$), 18.46 ($\text{Ph}-\text{C}\equiv\text{C}-\text{CH}_2$). **HRMS** (EI) m/z : calc. for $\text{C}_{18}\text{H}_{22}\text{O}$: 254.1670; found 254.1671.

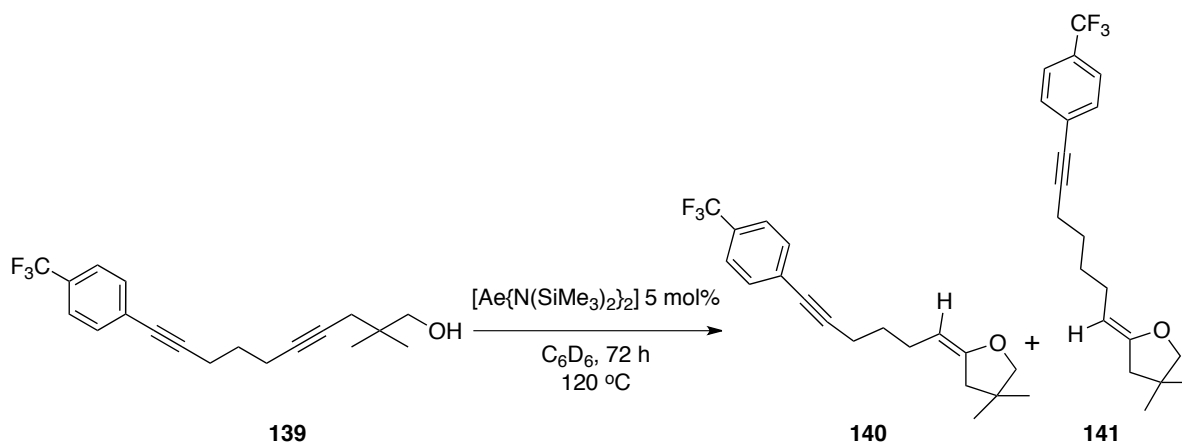
Synthesis of (*E*)-1-(6-phenylhex-5-ynylidene)-1,3-dihydroisobenzofuran **135**



135 was synthesised according to the standard procedure catalytic hydroalkoxylation reactions.

$^1\text{H NMR}$ (400 MHz, C_6D_6) δ /ppm: 7.52 (d, 2H, H_{ar}), 7.46-7.48 (m, 2H, H_{ar}), 7.26-7.27 (m, 2H, H_{ar}), 6.49-6.96 (m, 3H, H_{ar}), 6.71 (d, 2H, H_{ar}), 5.32 (t, 1H, $J = 8.2$ Hz, $\text{C}=\text{CH}$), 4.84 (s, 2H, CH_2O), 2.49-2.55 (m, 2H, $\text{C}=\text{CHCH}_2$), 1.72-1.76 (m, 2H, $\text{Ph}-\text{C}\equiv\text{C}-\text{CH}_2$), 1.53-1.55 (m, 2H, $\text{C}=\text{CHCH}_2\text{CH}_2\text{CH}_2$). **HRMS** (EI) m/z : calc. for $\text{C}_{18}\text{H}_{22}\text{O}$: 254.1670; found 254.1671.

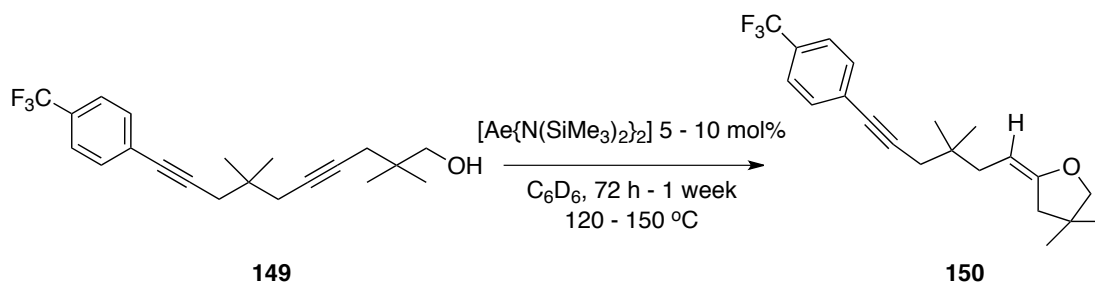
Synthesis of

(E)-4,4-dimethyl-2-(6-(4-(trifluoromethyl)phenyl)hex-5-ynylidene)tetrahydrofuran **140**

140 was synthesised according to the standard procedure catalytic hydroalkoxylation reactions.

¹H NMR (400 MHz, C₆D₆) δ/ppm: 7.37 (d, 2H, *J* = 8.2 Hz, *H*_{ar}, *Z*), 7.22 (d, 2H, *J* = 8.5 Hz, *H*_{ar}, *E*), 7.19 (d, 2H, *J* = 8.6 Hz, *H*_{ar}, *E*), 7.08 (d, 2H, *J* = 8.2 Hz, *H*_{ar}, *Z*), 4.88-4.92 (tt, 1H, *J* = 8.0, 16.0 Hz, OC=CH, *E*), 4.19 (t, 1H, *J* = 7.3 Hz, OC=CH, *Z*), 3.45 (s, 2H, OCH₂, *Z*), 3.43 (s, 2H, OCH₂, *E*), 2.44 (q, 2H, *J* = 7.3 Hz, OC=CHCH₂, *E*), 2.36 (t, 2H, *J* = 6.9 Hz, Ar-C≡C-CH₂, *Z*), 2.27 (t, 2H, *J* = 7.0 Hz, Ar-C≡C-CH₂, *E*), 2.03-2.05 (m, 2H, OC=CHCH₂, *Z*), 2.01-2.03 (bs, 2H, OCH₂C(CH₃)₂CH₂, *Z*), 1.98 (bs, 2H, OCH₂C(CH₃)₂CH₂, *E*), 1.71 (quint, 2H, *J* = 7.2 Hz, Ar-C≡C-CH₂CH₂CH₂, *E*), 1.53 (q, 2H, *J* = 7.2 Hz, Ar-C≡C-CH₂CH₂CH₂, *Z*) 0.79 (s, 6H, OCH₂C(CH₃)₂, *E*), 0.76 (s, 6H, OCH₂C(CH₃)₂, *Z*). **¹³C NMR** (101 MHz, C₆D₆) δ/ppm: 157.27 (OC=CH, *E*), 131.73 (*C*_{Ar}), 129.26 (*C*_q), 125.34 (CF₃), 125.00 (*C*_{Ar}), 123.00 (*C*_q), 94.90 (OC=CH, *E*), 93.73 (OC=CH, *Z*), 93.67 (Ar-C≡C, *Z*), 92.45 (Ar-C≡C, *E*), 82.89 (Ar-C≡C, *E*), 81.22 (Ar-C≡C, *Z*), 79.18 (OCH₂, *E*), 78.84 (OCH₂, *Z*) 43.63 (OCH₂C(CH₃)₂CH₂, *E*), 40.82 (OC=CHCH₂, *E*), 35.34 (OCH₂C(CH₃)₂, *E*), 28.64 (Ar-C≡C-CH₂, *E*), 24.64 (Ar-C≡C-CH₂CH₂CH₂, *E*), 24.35 (OCH₂C(CH₃)₂, *E*). **HRMS** (ES) *m/z*: calc. for C₁₉H₂₂F₃O: 323.1615; found 323.1623.

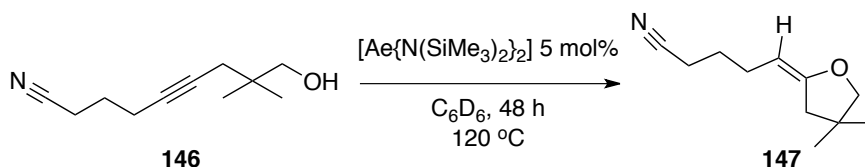
Synthesis of (*E*)-2-(3,3-dimethyl-6-(4-(trifluoromethyl)phenyl)hex-5-ynylidene)-4,4-dimethyltetrahydrofuran **150**



150 was synthesised according to the standard procedure catalytic hydroalkoxylation reactions.

^1H NMR (400 MHz, d_6 -benzene) δ /ppm: 7.30-7.44 (m, H_{Ar}), 7.10-7.13 (m, H_{Ar}), 4.95 (tt, 1H, $J = 1.9, 8.2, 16.5$ Hz, $\text{HC}=\text{C}$), 3.47 (s, 2H, OCH_2), 2.23 (s, 2H, $\text{Ar}-\text{C}\equiv\text{C}-\text{CH}_2$), 2.12-2.13 (m, 2H, $\text{CH}_2\text{C}=\text{C}$), 1.98-2.00 (m, 2H, $\text{CH}_2\text{C}=\text{C}$), 1.02 (s, 6H, $\text{C}(\text{CH}_3)_2$), 0.87 (s, 6H, $\text{C}(\text{CH}_3)_2$). **^{13}C NMR** (101 MHz, d_6 -benzene) δ /ppm: 158.01 ($\text{OC}=\text{CH}$), 131.62 (C_{Ar}), 129.00 (C_{q}), 126.58 (CF_3), 125.67 (C_{Ar}), 123.00 (C_{q}), 92.15 ($\text{HC}=\text{C}$), 91.86 ($\text{C}\equiv\text{C}$), 81.33 ($\text{C}\equiv\text{C}$), 79.96 (OCH_2), 31.61 ($\text{Ar}-\text{C}\equiv\text{C}-\text{CH}_2$), 28.51 ($\text{CH}_2\text{C}=\text{C}$), 36.31 ($\text{C}(\text{CH}_3)_2$), 36.00 ($\text{C}(\text{CH}_3)_2$), 39.61 ($\text{CH}_2\text{C}=\text{C}$), 26.40 ($\text{C}(\text{CH}_3)_2$), 24.58 ($\text{C}(\text{CH}_3)_2$). **HRMS** (ES) m/z : calc. for $\text{C}_{21}\text{H}_{26}\text{F}_3\text{O}$: 351.1934; found 351.1936.

Synthesis of (*E*)-5-(4,4-dimethyldihydrofuran-2(3*H*)-ylidene)pentanenitrile **147**



147 was synthesised according to the standard procedure catalytic hydroalkoxylation reactions.

^1H NMR (400 MHz, C_6D_6): δ /ppm: 4.47 (tt, 1H, $J = 2.1, 7.8, 15.6$ Hz, $\text{HC}=\text{C}$), 3.59 (s, 2H, OCH_2), 2.23 (m, 2H, CH_2CN), 2.20-2.21 (m, 2H, $\text{OCH}_2\text{C}(\text{CH}_3)_2\text{CH}_2$), 1.96-2.00 (m, 2H, $\text{OC}=\text{CHCH}_2$), 1.59 (quint, 2H, $J = 7.0$ Hz, $\text{CNCH}_2\text{CH}_2\text{CH}_2$), 1.01 (s, 6H, $\text{C}(\text{CH}_3)_2$). **^{13}C NMR** (101 MHz, d_6 -benzene) δ /ppm: 158.35 ($\text{OC}=\text{CH}$), 120.19

(C≡N), 93.99 (HC=C), 80.06 (OCH₂), 41.21 (OCH₂C(CH₃)₂CH₂), 38.30 (C(CH₃)₂), 26.48 (OC=CHCH₂), 24.02 (C(CH₃)₂), 26.34 (NCCH₂CH₂CH₂), 16.33 (CH₂CN). **MS** (CI) *m/z*: 197 (MNH₄⁺), 180 (MH⁺).

3.4 Heavier Alkaline Earth Catalysed Polyunsaturated Arene Hydroamination

Catalytic NMR Experiments

The divinylbenzene (**181**), trivinylbenzene (**190**) and 1-(phenylethynyl)-2-vinylbenzene (**194**) dry substrates (0.40 mmol), catalyst (5–10 mol%), amine (0.20 mmol) and d_6 -benzene (600 μ l) were directly added to a Young's tap NMR tube under inert atmosphere in a glovebox. All liquids were measured with Eppendorf pipettes. The NMR tube was then sealed and a homogenous solution was obtained by repeatedly turning the tube upside down. The tube was then removed from the glovebox and brought to the indicated temperature (90–150 °C) and the proceeding catalytic reaction monitored by ^1H NMR and referenced using $\text{Si}(\text{SiMe}_3)_4$ or quantitatively generated $\text{HN}(\text{SiMe}_3)_2$ as the internal standard. After a quantifiable conversion of the amine was reached, the mixture was exposed to air, diluted with Et_2O and filtered through celite with Et_2O washings. The evaporated solution yielded an orange/yellow oil, which was either purified directly by column chromatography or immediately subjected to reductive or oxidative conditions without further purification to form the corresponding 1-benzyl-*N*-alkyl-tetrahydroisoquinolines or the benzolactam.

Reduction of Enamines

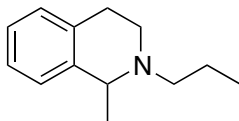
To a solution of the enamine in dry methanol (3 ml) was added NaBH_4 (0.4 mmol) in one portion at room temperature under argon. The solution was stirred for 1 hour at room temperature. The solvent was then removed under vacuum and water (5 ml) was added to the residue. The solution was extracted with Et_2O (3 x 10 ml) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (Et_2O :hexane) to isolate the product.

Preparative-Scale Catalytic Inter/Intramolecular Hydroamination Reactions

In a glovebox, $[\{L^1\}AeN(SiMe_3)_2(THF)_n]$ precatalyst **10a–b** (0.1 mmol), amine (1.0 mmol), divinylbenzene (**181**) or 1-(phenylethynyl)-2-vinylbenzene (**194**) (2 mmol) and C_6D_6 (2.0 ml) were loaded into a round-bottomed flask equipped with a magnetic stir bar and a J. Young valve. The valve was then closed and the solution stirred for 30 h at 130 °C. MeOH (5.0 ml) was added to the reaction mixture and the immediately precipitated polymer and catalyst were filtered through a pad of Al_2O_3 with MeOH washings (3 x 3.0 ml). The solvent was then removed under vacuum.

For subsequent reduction, the residue was then dissolved in dry MeOH (15 ml) and $NaBH_4$ (2.0 mmol) was added portionwise at room temperature under an argon atmosphere. The reaction mixture was then stirred at room temperature for 1 hour and the solvent was removed under vacuum. Water (10 ml) was added and the mixture extracted with Et_2O (3 x 20 ml), then the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography on silica gel (Et_2O :hexane) afforded the pure 1-benzyl-2-alkyl-tetrahydroisoquinolines.

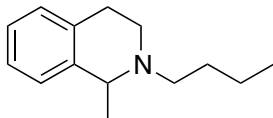
Synthesis of 1-methyl-2-propyl-1,2,3,4-tetrahydroisoquinoline **182**



According to the general procedure for catalytic NMR experiments **182** was formed from divinylbenzene after 48 h, 120 °C (78%).

¹H NMR (400 MHz, CDCl₃) δ/ppm = 7.08-7.15 (m, 4H, *H*_{Ar}), 3.90 (q, 1H, *J* = 6.7 Hz, *HCCH*₃), 3.07-3.13 (m, 1H, *NCHHCHH*), 2.90-2.94 (m, 1H, *NCHHCHH*), 2.74-2.83 (m, 2H, *NCHHCHH*), 2.54-2.59 (m, 2H, *NCH₂CH₂CH₃*), 1.60 (m, 2H, *NCH₂CH₂CH₃*), 1.36 (d, 3H, *J* = 6.8 Hz, *HCCCH₃*), 0.95 (t, 2H, *J* = 7.3 Hz, *NCH₂CH₂CH₃*). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 142.06 (*C_q*), 140.23 (*C_q*), 129.72 (*C_{Ar}*), 128.84 (*C_{Ar}*), 127.39 (*C_{Ar}*), 125.81 (*C_{Ar}*), 56.47 (*CHCH₃*), 55.93 (*NCH₂CH₂CH₃*), 43.99 (*NCHHCHH*), 26.85 (*NCHHCHH*), 20.39 (*NCH₂CH₂CH₃*), 19.85 (*CHCH₃*), 12.00 (*NCH₂CH₂CH₃*). **HRMS** (ESI) *m/z*: calc. for C₁₃H₂₀N: 190.1596; found 190.1603.

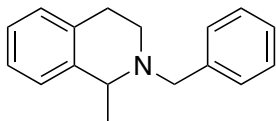
Synthesis of 2-butyl-1-methyl-1,2,3,4-tetrahydroisoquinoline **183**



According to the general procedure for catalytic NMR experiments **183** was formed from divinylbenzene after 32 h, 120 °C (59%).

¹H NMR (400 MHz, CDCl₃) δ/ppm = 7.07-7.13 (m, 4H, *H*_{Ar}), 3.90 (q, 1H, *J* = 6.7 Hz, *CHCH₃*), 3.05-3.11 (m, 1H, *NCHHCH₂*), 2.89-2.97 (m, 3H, *NCH₂CH₂CH₂CH₃*, *NCHHCHH*), 2.73-2.81 (m, 2H, *NCHHCHH*), 2.56-2.62 (m, 2H, *NCH₂CH₂CH₂CH₃*), 1.50-1.59 (m, 2H, *NCH₂CH₂CH₂CH₃*), 1.35 (d, 3H, *J* = 6.8 Hz, *CHCH₃*), 0.95 (t, 3H, *J* = 8.0 Hz, *NCH₂CH₂CH₂CH₃*). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 142.27, (*C_q*), 140.49 (*C_q*), 128.80 (*C_{Ar}*), 127.39 (*C_{Ar}*), 126.14 (*C_{Ar}*), 125.72 (*C_{Ar}*), 56.41 (*HCCCH₃*), 53.74 (*NCH₂CH₂CH₂CH₃*), 44.03 (*NCHHCHH*), 36.61 (*NCH₂CH₂CH₂CH₃*), 29.94 (*NCH₂CH₂CH₂CH₃*), 27.33 (*NCHHCHH*), 20.78 (*CHCH₃*), 14.10 (*NCH₂CH₂CH₂CH₃*).

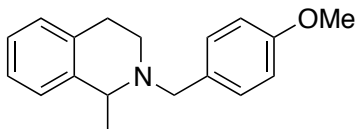
Synthesis of 2-benzyl-1-methyl-1,2,3,4-tetrahydroisoquinoline **184**



According to the general procedure for catalytic NMR experiments **184** was formed from divinylbenzene after 44 h, 140 °C (46%).

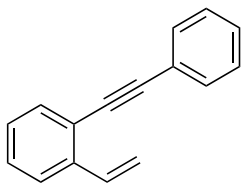
¹H NMR (400 MHz, CDCl₃) δ/ppm = 7.05-7.14 (m, 4H, *H*_{Ar}), 7.27-7.30 (m, 1H, *H*_{Ar}), 7.32-7.40 (m, 4H, *H*_{Ar}), 3.90 (q, 1H, *J* = 6.7 Hz, CHCH₃), 3.68-3.84 (m, 2H, CH₂Ph), 3.04-3.10 (m, 1H, NCHHCH₂), 2.87-2.95 (m, 1H, NCH₂CHH), 2.66-2.74 (m, 2H, NCHHCHH), 1.39 (d, 3H, *J* = 6.7 Hz, CHCH₃). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 130.88 (*C*_q), 129.05 (*C*_q), 128.87 (*C*_{Ar}), 128.74 (*C*_{Ar}), 128.22 (*C*_{Ar}), 127.44 (*C*_{Ar}), 126.86 (*C*_{Ar}), 126.71 (*C*_{Ar}), 125.77 (*C*_{Ar}), 125.62 (*C*_{Ar}), 125.51 (*C*_{Ar}), 122.76 (*C*_q), 58.19 (NCH₂Ph), 56.26 (HCCH₃), 43.81 (NCH₂CH₂), 27.45 (NCH₂CH₂), 19.71 (CHCH₃).

Synthesis of 2-(4-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline **187**



According to the general procedure for catalytic NMR experiments **187** was formed from divinylbenzene after 68 h, 150 °C (24%).

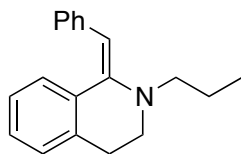
¹H NMR (400 MHz, CDCl₃) δ/ppm = 7.29-7.30 (m, 2H, *H*_{Ar}), 7.04-7.13 (m, 4H, *H*_{Ar}), 6.85-6.87 (m, 2H, *H*_{Ar}), 3.90 (q, 1H, *J* = 6.6 Hz, HCCH₃), 3.81 (s, 3H, OCH₃), 3.63-3.80 (m, 2H, NCH₂Ar), 3.02-3.08 (m, 1H, NCHHCH₂), 2.86-2.93 (m, 1H, NCH₂CHH), 2.65-2.72 (m, 2H, NCHHCHH), 1.38 (d, 3H, *J* = 6.7 Hz, HCCH₃). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 158.58 (*C*_q), 140.43 (*C*_q), 134.33 (*C*_q), 133.63 (*C*_q), 131.48 (*C*_{Ar}), 129.87 (*C*_{Ar}), 128.86 (*C*_{Ar}), 127.45 (*C*_{Ar}), 126.56 (*C*_{Ar}), 125.75 (*C*_{Ar}), 125.59 (*C*_{Ar}), 113.58 (*C*_{Ar}), 57.48 (NCH₂Ar), 56.03 (HCCH₃), 55.25 (OCH₃), 43.60 (NCH₂CH₂), 27.38 (NCH₂CH₂), 19.66 (HCCH₃).

Synthesis of 1-(phenylethynyl)-2-vinylbenzene **194**

Substrate **194** was synthesised following Sonagashira conditions.

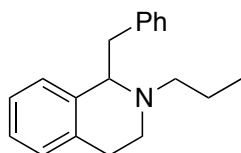
Phenylacetylene (1.65 ml, 15 mmol) was added to a suspension of 1-bromo-2-vinylbenzene (1.29 ml, 10 mmol) in NEt₃ (40 ml) at room temperature. To this solution at 0 °C was added PdCl₂(PPh₃)₂ (281 mg, 0.4 mmol) and the resulting yellow suspension stirred at 0 °C for 5 min. CuI (152 mg, 0.8 mmol) was then added and the reaction mixture warmed to room temperature and then heated under reflux for 12 h until the starting material was no longer visible by TLC analysis. The mixture was cooled to room temperature and filtered through celite with ether washings. Saturated NH₄Cl (40 ml) was added to the filtrate and the organic layer separated. The organic phase was washed with H₂O (3 x 40 ml) and brine (3 x 40 ml), and dried (MgSO₄). The solvent was then evaporated under vacuum and the resulting residue purified by column chromatography (silica gel, 100% pentane) to afford 1-(phenylethynyl)-2-vinylbenzene as a colourless oil (1.79 g, 88%; *R*_f = 0.42).

¹H NMR (400 MHz, CDCl₃) δ/ppm = 7.63 (dd, 1H, *J* = 1.2, 7.7 Hz, HC=CH₂), 7.54-7.59 (m, 3H, *H*_{Ar}), 7.25-7.41 (m, 6H, *H*_{Ar}), 5.88 (dd, 1H, *J* = 0.9, 17.7 Hz, HC=CH_{cis}*H*_{trans}), 5.41 (dd, 1H, *J* = 0.9, 11.1 Hz, HC=CH_{cis}*H*_{trans}). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 138.99 (*C*_q), 134.96 (*C*_{Ar}), 132.51 (*C*_{Ar}), 131.55 (*C*_{Ar}), 128.44 (*C*_{Ar}), 128.37 (2 × *C*_{Ar}), 127.50 (*C*_{Ar}), 124.67 (HC=CH₂), 123.33 (*C*_q), 121.94 (*C*_q), 115.60 (HC=CH₂), 93.97 (Ar-C≡C-Ph), 87.73 (Ar-C≡C-Ph). **HRMS** (EI) *m/z*: calc. for C₁₆H₁₂: 204.0939; found 204.0940.

Synthesis of (*E*)-1-benzylidene-2-propyl-1,2,3,4-tetrahydroisoquinoline **195**

According to the general procedure for catalytic NMR experiments the *E* isomer was quantitatively formed after 19 h, 110 °C.

¹H NMR (400 MHz, C₆D₆) δ /ppm = 7.71-7.73 (m, 1H, *H*_{Ar}), 7.28-7.30 (m, 2H, *H*_{Ar}), 7.07-7.11 (m, 3H, *H*_{Ar}), 6.93-6.95 (m, 2H, *H*_{Ar}), 6.68-6.73 (m, 1H, *H*_{Ar}), 5.65 (s, 1H, C=CHPh), 3.05 (t, 2H, *J* = 7.3 Hz, NCH₂CH₂CH₃), 2.83 (t, 2H, *J* = 5.7 Hz, CH₂CH₂N), 2.48 (t, 2H, *J* = 5.7 Hz, CH₂CH₂N), 1.52 (sext, 2H, *J* = 7.5 Hz, NCH₂CH₂CH₃), 0.74 (t, 3H, *J* = 7.4 Hz, NCH₂CH₂CH₃). **HRMS** (ESI) *m/z*: calc. for C₁₉H₂₂N: 264.1752; found 264.1759.

Synthesis of 1-benzyl-2-propyl-1,2,3,4-tetrahydroisoquinoline **254**

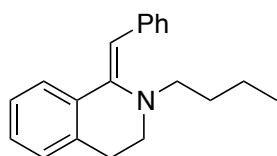
254 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:pentane, 1:1) afforded pure amine **254** in 64% yield, *R*_f = 0.30.

Yield for preparative scale = 68%.

¹H NMR (400 MHz, CDCl₃) δ /ppm = 7.27-7.30 (m, 2H, *H*_{Ar}), 7.22-7.24 (m, 1H, *H*_{Ar}), 7.04-7.20 (m, 5H, *H*_{Ar}), 6.77 (d, 1H, *J* = 7.9 Hz, *H*_{Ar}), 3.91 (t, 1H, *J* = 6.4 Hz, HCCH₂Ph), 3.32 (ddd, 1H, *J* = 2.9, 8.6, 13.6 Hz, NCH_aH_bCH₂), 3.13 (dd, 1H, *J* = 7.0, 13.6 Hz, HCCH_aH_bPh), 2.95-3.00 (m, 1H, NCH₂CH_aH_b), 2.85-2.92 (m, 2H, NCH_aH_bCH₂, HCCH_aH_bPh), 2.58-2.61 (m, 1H, NCH₂CH_aH_b), 2.56 (t, 2H, *J* = 6.7 Hz, NCH₂CH₂CH₃), 1.45 (sext, 2H, *J* = 6.2 Hz, NCH₂CH₂CH₃), 0.81 (t, 3H, *J* = 7.3 Hz, NCH₂CH₂CH₃). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 140.39 (*C*_q), 138.25 (*C*_q),

134.75 (C_q), 129.72 (C_{Ar}), 128.83 (C_{Ar}), 128.26 (C_{Ar}), 127.91 (C_{Ar}), 125.95 (C_{Ar}), 125.80 (C_{Ar}), 125.19 (C_{Ar}), 63.17 ($HCCH_2Ph$), 55.87 ($NCH_2CH_2CH_3$), 43.76 (NCH_2CH_2), 42.04 ($HCCH_2Ph$), 25.04 (NCH_2CH_2), 21.16 ($NCH_2CH_2CH_3$), 11.75 ($NCH_2CH_2CH_3$). **HRMS** (ESI) m/z : calc. for $C_{19}H_{24}N$: 266.1909; found 266.1907. **IR** (cm^{-1}): 3061, 2917, 2849, 1710, 1637, 1601.

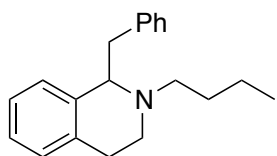
Synthesis of (Z)-1-benzylidene-2-butyl-1,2,3,4-tetrahydroisoquinoline **200**



According to the general procedure for catalytic NMR experiments the *Z* isomer was quantitatively formed after 22 h, 140 °C.

1H NMR (400 MHz, C_6D_6) δ/ppm = 7.72-7.74 (m, 1H, H_{Ar}), 7.28-7.30 (m, 2H, H_{Ar}), 7.05-7.11 (m, 3H, H_{Ar}), 6.93-6.95 (m, 2H, H_{Ar}), 6.68-6.73 (m, 1H, H_{Ar}), 6.18 (s, 1H, $C=CHPh$), 2.95 (t, 2H, J = 7.8 Hz, $NCH_2CH_2CH_2CH_3$), 2.88 (t, 2H, J = 5.6 Hz, NCH_2CH_2), 2.50 (t, 2H, J = 5.0 Hz, NCH_2CH_2), 1.49 (quin, 2H, J = 7.5 Hz, $NCH_2CH_2CH_2CH_3$), 0.92 (sext, 2H, J = 7.4 Hz, $NCH_2CH_2CH_2CH_3$), 0.64 (t, 3H, J = 7.3 Hz, $NCH_2CH_2CH_2CH_3$). **HRMS** (ESI) m/z : calc. for $C_{20}H_{24}N$: 278.1909; found 278.1910.

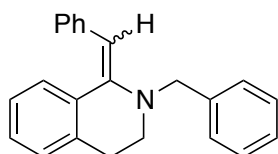
Synthesis of 1-benzyl-2-butyl-1,2,3,4-tetrahydroisoquinoline **255**



255 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et_2O :hexane, 1:4) afforded pure amine **255** in 64% yield, R_f = 0.13.

^1H NMR (400 MHz, CDCl_3) δ/ppm = 7.28-7.30 (m, 2H, H_{Ar}), 7.20-7.24 (m, 1H, H_{Ar}), 7.09-7.18 (m, 4H, H_{Ar}), 7.03-7.70 (m, 1H, H_{Ar}), 6.77 (d, 1H, $J = 7.6$ Hz, H_{Ar}), 3.91 (t, 1H, $J = 6.6$ Hz, HCCH_2Ph), 3.28-3.34 (m, 1H, $\text{NCH}_a\text{H}_b\text{CH}_2\text{CH}_2\text{CH}_3$), 3.11-3.16 (dd, 1H, $J = 7.1, 13.6$ Hz, $\text{HCCH}_a\text{H}_b\text{Ph}$), 2.85-3.00 (m, 3H, $\text{NCH}_a\text{H}_b\text{CH}_2$, $\text{NCH}_a\text{H}_b\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{HCCH}_a\text{H}_b\text{Ph}$), 2.56-2.63 (m, 3H, $\text{NCH}_a\text{H}_b\text{CH}_2$), 1.41 (quin, 2H, $J = 8.0$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.25 (sext, 2H, $J = 7.3$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.86 (t, 3H, $J = 7.3$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$). **^{13}C NMR** (101 MHz, CDCl_3) δ/ppm : 140.35 (C_q), 138.18 (C_q), 134.68 (C_q), 129.88 (C_{Ar}), 128.80 (C_{Ar}), 128.24 (C_{Ar}), 127.89 (C_{Ar}), 125.93 (C_{Ar}), 125.78 (C_{Ar}), 125.16 (C_{Ar}), 63.18 (HCCH_2Ph), 53.53 (NCH_2CH_2), 43.67 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 41.99 (HCCH_2Ph), 30.13 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 24.97 (NCH_2CH_2), 20.42 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 14.03 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$). **HRMS** (ESI) m/z : calc. for $\text{C}_{20}\text{H}_{26}\text{N}$: 280.2060; found 280.2056. **IR** (cm^{-1}): 3025, 2955, 2926, 2859, 1738, 1655.

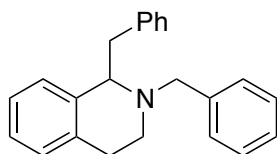
Synthesis of 2-benzyl-1-benzylidene-1,2,3,4-tetrahydroisoquinoline **210**



According to the general procedure for catalytic NMR experiments a quantitative mixture of *E/Z* isomers was formed in a ratio of 0.5:1 after 17.25 h, 140 °C.

^1H NMR (400 MHz, C_6D_6) δ/ppm = 7.65-7.72 (m, 3H, H_{Ar} , *E* and *Z*), 7.18-7.22 (3H, m, H_{Ar} , *E* and *Z*), 7.02-7.15 (m, 15H, H_{Ar} , *E* and *Z*), 6.30 (s, 1H, $\text{C}=\text{CHPh}$, *Z*), 5.67 (s, 0.5H, $\text{C}=\text{CHPh}$, *E*), 4.29 (s, 1H, NCH_2Ph , *E*), 4.11 (s, 2H, NCH_2Ph , *Z*), 2.91 (t, 1H, $J = 5.7$ Hz, NCH_2CH_2 , *E*), 2.85 (t, 2H, $J = 5.6$ Hz, NCH_2CH_2 , *Z*), 2.53 (t, 1H, $J = 5.7$ Hz, NCH_2CH_2 , *E*), 2.54 (t, 2H, $J = 5.6$ Hz, NCH_2CH_2 , *Z*). **HRMS** (ESI) m/z : calc. for $\text{C}_{23}\text{H}_{22}\text{N}$: 312.1752; found 312.1751.

Synthesis of 1,2-dibenzyl-1,2,3,4-tetrahydroisoquinoline **256**

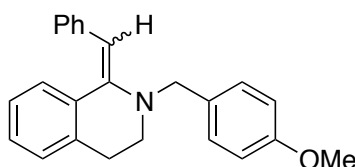


256 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:pentane, 1:20) afforded pure amine **256** in 71% yield, $R_f = 0.16$.

Yield for preparative scale reaction = 73 %.

¹H NMR (400 MHz, CDCl₃) δ /ppm = 7.18-7.28 (m, 6H, H_{Ar}), 7.08-7.15 (m, 7H, H_{Ar}), 6.83 (d, 1H, $J = 7.5$ Hz, H_{Ar}), 3.88 (dd, 1H, $J = 5.7, 8.0$ Hz, $HCCH_2Ph$), 3.78 (d, 1H, $J = 13.7$ Hz, NCH_aH_bPh), 3.73 (d, 1H, $J = 13.7$ Hz, NCH_aH_bPh), 3.37 (ddd, 1H, $J = 4.8, 10.7, 15.7$ Hz, $NCH_aH_bCH_2$), 3.12 (dd, 1H, $J = 8.2, 13.8$ Hz, $HCCH_aH_bPh$), 2.94-3.03 (m, 1H, $NCH_aH_bCH_2$), 2.83-2.91 (m, 2H, $HCCH_aH_bPh$, $NCH_2CH_aH_b$), 2.57 (ddd, 1H, $J = 2.2, 4.9, 16.8$ Hz, $NCH_2CH_aH_b$). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 140.16 (C_q), 139.46 (C_q), 138.11 (C_q), 134.58 (C_q), 129.72 (C_{Ar}), 128.97 (C_{Ar}), 128.62 (C_{Ar}), 128.27 (C_{Ar}), 128.05 (C_{Ar}), 127.91 (C_{Ar}), 126.67 (C_{Ar}), 126.05 (C_{Ar}), 125.82 (C_{Ar}), 125.46 (C_{Ar}), 62.67 ($HCCH_2Ph$), 57.92 (NCH_2Ph), 42.99 (CH_2CH_2N), 42.46 ($HCCH_2Ph$), 24.46 (CH_2CH_2N). **HRMS** (ESI) m/z : calc. for C₂₃H₂₄N: 314.1909; found 314.1926. **IR** (cm⁻¹): 3061, 3027, 2925, 2852, 1648, 1600.

Synthesis of 1-benzylidene-2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **211**

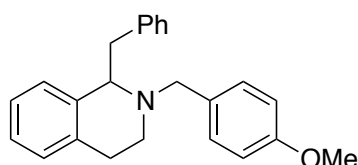


According to the general procedure for catalytic NMR experiments a quantitative mixture of *E/Z* isomers was formed in a ratio of 0.9:1 after 15 h, 140 °C.

¹H NMR (400 MHz, C₆D₆) δ /ppm = 7.67-7.74 (m, 3.8H, H_{Ar} , *E* and *Z*), 7.18-7.27 (m, 5.7H, H_{Ar} , *E* and *Z*), 7.01-7.12 (m, 11.6H, H_{Ar} , *E* and *Z*), 6.85-6.87 (m, 1.8H, H_{Ar} , *E*),

6.65-6.67 (m, 2H, H_{Ar} , *Z*), 6.32 (s, 1H, $C=CHPh$, *Z*), 5.76 (s, 0.87H, $C=CHPh$, *E*), 4.29 (s, 1.8H, NCH_2Ar , *E*), 4.11 (s, 2H, NCH_2Ar , *Z*), 3.33 (s, 2.6H, OCH_3 , *E*), 3.26 (s, 3H, OCH_3 , *Z*), 2.96 (t, 1.8H, $J = 5.7$ Hz, NCH_2CH_2 , *E*), 2.90 (t, 2H, $J = 5.5$ Hz, NCH_2CH_2 , *Z*), 2.55 (t, 1.8H, $J = 5.7$ Hz, NCH_2CH_2 , *E*), 2.39 (t, 2H, $J = 5.5$ Hz, NCH_2CH_2 , *Z*). **HRMS** (ESI) m/z : calc. for $C_{24}H_{24}NO$: 342.1858; found 342.1864.

Synthesis of 1-benzyl-2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **257**

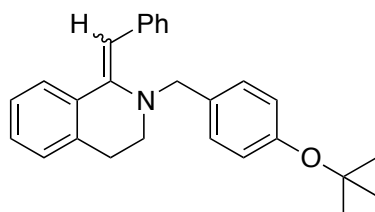


257 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et_2O :pentane, 1.5:10) afforded pure amine **257** in 68% yield, $R_f = 0.28$.

Yield for preparative scale reaction = 72 %.

1H NMR (400 MHz, $CDCl_3$) δ /ppm = 7.26-7.29 (m, 3H, H_{Ar}), 7.08-7.23 (m, 5H, H_{Ar}), 7.02-7.04 (m, 2H, H_{Ar}), 6.85-6.87 (m, 1H, H_{Ar}), 6.75-6.77 (m, 2H, H_{Ar}), 3.89 (t, 1H, $J = 6.9$ Hz, $HCCH_2Ph$), 3.81 (s, 3H, OCH_3), 3.65-3.74 (m, 2H, NCH_2Ar), 3.32-3.39 (m, 1H, $CH_2CH_aH_bN$), 3.11-3.17 (m, 1H, $HCCH_aH_bPh$), 2.96-3.04 (m, 1H, $CH_2CH_aH_bN$), 2.85-2.92 (m, 2H, $CH_aH_bCH_2N$, $HCCH_aH_bPh$), 2.54-2.59 (m, 1H, $CH_aH_bCH_2N$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ /ppm: 158.44 (C_q), 140.23 (C_q), 138.16 (C_q), 134.63 (C_q), 131.48 (C_q), 129.73 ($2 \times C_{Ar}$), 128.97 (C_{Ar}), 128.28 (C_{Ar}), 127.90 (C_{Ar}), 126.03 (C_{Ar}), 125.81 (C_{Ar}), 125.45 (C_{Ar}), 113.44 (C_{Ar}), 62.40 ($HCCH_2Ph$), 57.23 (NCH_2Ph), 55.24 (OCH_3), 42.88 (CH_2CH_2N), 42.41 ($HCCH_2Ph$), 24.44 (CH_2CH_2N). **HRMS** (ESI) m/z : calc. for $C_{24}H_{26}NO$: 344.2014; found 344.2025. **IR** (cm^{-1}): 3061, 3026, 2929, 2835, 1649, 1603.

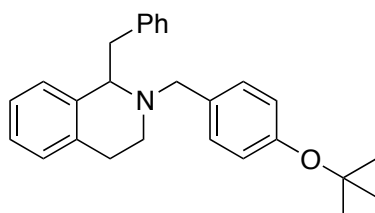
Synthesis of 1-benzylidene-2-(4-*tert*-butoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **212**



According to the general procedure for catalytic NMR experiments a 55% mixture of *E/Z* isomers was formed in a ratio of 0.5:1 after 15 h, 140 °C.

¹H NMR (400 MHz, C₆D₆) δ /ppm = 7.65-7.68 (m, 3H, *H*_{Ar}, *E* and *Z*), 7.19-7.24 (m, 4.5H, *H*_{Ar}, *E* and *Z*), 7.04-7.12 (m, 9H, *H*_{Ar}, *E* and *Z*), 6.81-6.84 (m, 3H, *H*_{Ar}, *E* and *Z*), 6.29 (s, 1H, *HC=C*, *Z*), 5.68 (s, 0.5H, *HC=C*, *E*), 4.30 (s, 1H, *CH*₂Ar, *E*), 4.08 (s, 2H, *CH*₂Ar, *Z*), 3.05 (t, 2H, *J* = 5.6 Hz, *NCH*₂*CH*₂, *E*), 2.89 (t, 2H, *J* = 5.5 Hz, *NCH*₂*CH*₂, *Z*), 2.55 (t, 2H, *J* = 5.6 Hz, *NCH*₂*CH*₂, *E*), 2.38 (t, 2H, *J* = 5.5 Hz, *NCH*₂*CH*₂, *Z*), 1.19 (s, 4.5H, *OC(CH*₃*)*₃, *E*), 1.17 (s, 9H, *OC(CH*₃*)*₃, *Z*). **HRMS** (ESI) *m/z*: calc. for C₂₇H₃₀NO: 384.2327; found 384.2332.

Synthesis of 1-benzyl-2-(4-*tert*-butoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **258**

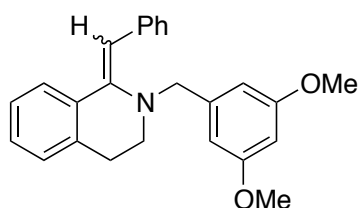


258 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:pentane, 1:3) afforded pure amine **258** in 69% yield, *R*_f = 0.51.

¹H NMR (400 MHz, CDCl₃) δ /ppm = 7.24-7.29 (m, 3H, *H*_{Ar}), 7.09-7.18 (m, 5H, *H*_{Ar}), 7.01 (d, 2H, *J* = 8.0 Hz, *H*_{Ar}), 6.84-6.86 (m, 2H, *H*_{Ar}), 3.90 (dd, 1H, *J* = 6.0, 7.7 Hz, *HCCH*₂Ph), 3.76 (d, 1H, *J* = 13.1 Hz, *NCH*_a*H*_bAr), 3.70 (d, 1H, *J* = 13.1 Hz, *NCH*_a*H*_bAr), 3.40 (ddd, 1H, *J* = 4.8, 10.8, 15.7 Hz, *NCH*_a*H*_b*CH*₂), 3.15 (dd, 1H, *J* =

8.2, 13.8 Hz, $\text{HCCH}_a\text{H}_b\text{Ph}$), 2.97-3.07 (m, 1H, $\text{NCH}_2\text{CH}_a\text{H}_b$), 2.87-2.94 (m, 2H, $\text{NCH}_a\text{H}_b\text{CH}_2$, $\text{HCCH}_a\text{H}_b\text{Ph}$), 2.60 (dd, 1H, $J = 2.6, 16.8$ Hz, $\text{NCH}_2\text{CH}_a\text{H}_b$), 1.37 (s, 9H, $\text{OC}(\text{CH}_3)_3$). **^{13}C NMR** (101 MHz, CDCl_3) δ/ppm : 154.12 (C_q), 140.16 (C_q), 138.03 (C_q), 134.51 (C_q), 134.09 (C_q), 129.71 (C_{Ar}), 129.15 (C_{Ar}), 128.99 (C_{Ar}), 128.33 (C_{Ar}), 127.93 (C_{Ar}), 126.10 (C_{Ar}), 125.83 (C_{Ar}), 125.48 (C_{Ar}), 123.81 (C_{Ar}), 78.17 ($\text{OC}(\text{CH}_3)_3$), 62.32 (HCCH_2Ph), 57.36 (NCH_2Ar), 43.12 (NCH_2CH_2), 42.44 (HCCH_2Ph), 28.90 ($\text{OC}(\text{CH}_3)_3$), 24.42 (NCH_2CH_2). **HRMS** (ESI) m/z : calc. for $\text{C}_{27}\text{H}_{32}\text{NO}$: 386.2484; found 386.2478. **IR** (cm^{-1}): 3025, 2974, 2925, 2852, 1603, 1505.

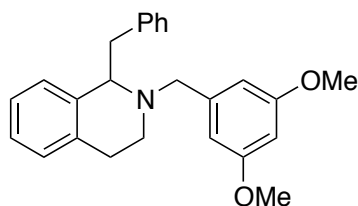
Synthesis of 1-benzylidene-2-(3,5-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **214**



According to the general procedure for catalytic NMR experiments a 78% mixture of *E/Z* isomers was formed in a ratio of 0.8:1 after 15 h, 140 °C.

^1H NMR (400 MHz, C_6D_6) δ/ppm = 7.39-7.70 (m, 3.6H, H_{Ar} , *E* and *Z*), 7.19-7.28 (m, 5.4H, H_{Ar} , *E* and *Z*), 7.06-7.11 (m, 7.2H, H_{Ar} , *E* and *Z*), 6.57 (s, 1.6H, H_{Ar} , *E*), 6.43 (s, 2H, H_{Ar} , *Z*), 6.41 (s, 0.8H, H_{Ar} , *E*), 6.36 (s, 1H, H_{Ar} , *Z*), 6.29 (s, 1H, $\text{C}=\text{CH}$, *Z*), 5.74 (s, 0.8H, $\text{C}=\text{CH}$, *E*), 4.35 (s, 1.6H, NCH_2Ar , *E*), 4.11 (s, 2H, NCH_2Ar , *Z*), 3.41 (s, 4.8H, OCH_3 , *E*), 3.35 (s, 6H, OCH_3 , *Z*), 3.04 (t, 1.6H, $J = 5.6$ Hz, NCH_2CH_2 , *E*), 2.96 (t, 2H, $J = 5.6$ Hz, NCH_2CH_2 , *Z*), 2.63 (t, 1.6H, $J = 5.6$ Hz, NCH_2CH_2 , *E*), 2.47 (t, 2H, $J = 5.6$ Hz, NCH_2CH_2 , *Z*). **HRMS** (ESI) m/z : calc. for $\text{C}_{25}\text{H}_{26}\text{NO}_2$: 372.1964; found 372.1979.

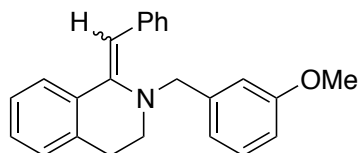
Synthesis of 1-benzyl-2-(3,5-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **259**



259 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:pentane, 1:3) afforded pure amine **259** in 56% yield, $R_f = 0.33$.

¹H NMR (400 MHz, CDCl₃) δ /ppm = 7.25-7.28 (m, 2H, H_{Ar}), 7.12-7.23 (m, 6H, H_{Ar}), 6.90 (d, 1H, $J = 7.4$ Hz, H_{Ar}), 6.39 (d, 2H, $J = 2.2$ Hz, H_{Ar}), 6.35 (t, 1H, $J = 2.2$ Hz, H_{Ar}), 3.96 (dd, 1H, $J = 5.8, 8.0$ Hz, $HCCH_2Ph$), 3.73 (s, 6H, $2 \times OCH_3$), 3.66-3.71 (m, 2H, NCH_2Ar), 3.33 (ddd, 1H, $J = 4.9, 10.5, 15.5$ Hz, $NCH_aH_bCH_2$), 3.16 (dd, 1H, $J = 8.2, 13.9$ Hz, $HCCH_aH_bPh$), 2.92-3.03 (m, 2H, $NCH_2CH_aH_b$, $HCCH_aH_bPh$), 2.85 (ddd, 1H, $J = 2.6, 6.1, 13.2$ Hz, $NCH_aH_bCH_2$), 2.56 (ddd, 1H, $J = 2.8, 4.7, 16.8$ Hz, $NCH_2CH_aH_b$). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 160.62 ($2 \times C_q$), 142.20 (C_q), 140.18 (C_q), 138.17 (C_q), 134.61 (C_q), 129.65 (C_{Ar}), 128.99 (C_{Ar}), 128.18 (C_{Ar}), 127.89 (C_{Ar}), 126.08 (C_{Ar}), 125.83 (C_{Ar}), 125.50 (C_{Ar}), 106.32 (C_{Ar}), 99.22 (C_{Ar}), 63.02 ($HCCH_2Ph$), 58.18 (NCH_2Ar), 55.28 (OCH_3), 42.60 (NCH_2CH_2), 42.48 ($HCCH_2Ph$), 24.41 (NCH_2CH_2). **HRMS** (ESI) m/z : calc. for C₂₅H₂₈NO₂: 374.2120; found 374.2138. **IR** (cm⁻¹): 3024, 3000, 2934, 2836, 1701, 1595.

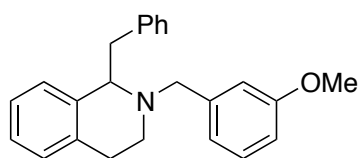
Synthesis of (Z)-1-benzylidene-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **215**



According to the general procedure for catalytic NMR experiments an 83% mixture of *E/Z* isomers was formed in a ratio of 1:0.67 after 12.5 h, 140 °C.

¹H NMR (400 MHz, C₆D₆) δ /ppm = 7.64-7.70 (m, 3.2H, *H*_{Ar}, *E* and *Z*), 7.17-7.25 (m, 5H, *H*_{Ar}, *E* and *Z*), 7.02-7.11 (m, 8.5H, *H*_{Ar}, *E* and *Z*), 6.64-6.73 (m, 5H, *H*_{Ar}, *E* and *Z*), 6.31 (s, 0.67H, HC=C, *Z*), 5.74 (s, 1H, HC=C, *E*), 4.31 (s, 2H, NCH₂Ar, *E*), 4.13 (s, 1.30H, NCH₂Ar, *Z*), 3.33 (s, 3H, OCH₃, *E*), 3.28 (s, 2H, OCH₃, *Z*), 2.95 (t, 2H, *J* = 5.7 Hz, NCH₂CH₂, *E*), 2.89 (t, 1.34H, *J* = 5.6 Hz, NCH₂CH₂, *Z*), 2.55 (t, 2H, *J* = 5.7 Hz, NCH₂CH₂, *E*), 2.40 (t, 1.34H, *J* = 5.6 Hz, NCH₂CH₂, *Z*). **HRMS** (ESI) *m/z*: calc. for C₂₄H₂₄NO: 342.1858; found 342.1859.

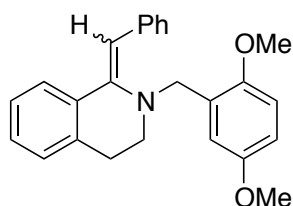
Synthesis of 1-benzyl-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **260**



260 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:hexane, 1:10) afforded pure amine **260** in 62% yield, *R*_f = 0.10.

¹H NMR (400 MHz, CDCl₃) δ /ppm = 7.22-7.29 (m, 3H, *H*_{Ar}), 7.11-7.18 (m, 6H, *H*_{Ar}), 6.89 (d, 1H, *J* = 7.5 Hz, *H*_{Ar}), 6.73-6.79 (m, 3H, *H*_{Ar}), 3.93 (dd, 1H, *J* = 6.0, 8.0 Hz, HCCH₂Ph), 3.70-3.79 (m, 2H, NCH₂Ar), 3.75 (s, 3H, OCH₃), 3.36 (ddd, 1H, *J* = 4.8, 10.7, 15.6 Hz, NCH_aH_bCH₂), 3.16 (dd, 1H, *J* = 8.2, 13.9 Hz, HCCH_aH_bPh), 2.84-3.04 (m, 3H, NCH₂CH_aH_b, NCH_aH_bCH₂, HCCH_aH_bPh), 2.57 (ddd, 1H, *J* = 2.9, 4.9, 17.1 Hz, NCH₂CH_aH_b). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 159.59 (*C*_q), 141.26 (*C*_q), 140.18 (*C*_q), 138.15 (*C*_q), 134.62 (*C*_q), 129.70 (*C*_{Ar}), 128.99 (*C*_{Ar}), 128.57 (*C*_{Ar}), 127.92 (2 × *C*_{Ar}), 126.08 (*C*_{Ar}), 125.84 (*C*_{Ar}), 125.50 (*C*_{Ar}), 120.99 (*C*_{Ar}), 113.64 (*C*_{Ar}), 112.77 (*C*_{Ar}), 62.87 (HCCH₂Ph), 57.97 (NCH₂Ar), 55.15 (OCH₃), 42.79 (NCH₂CH₂), 42.48 (HCCH₂Ph), 24.44 (NCH₂CH₂). **HRMS** (ESI) *m/z*: calc. for C₂₄H₂₆NO: 344.2014; found 344.1997. **IR** (cm⁻¹): 3022, 2933, 2834, 2851, 1608, 1584.

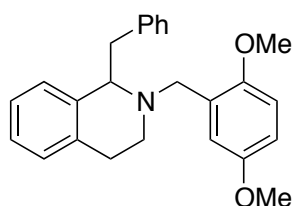
Synthesis of 1-benzylidene-2-(2,5-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **216**



According to the general procedure for catalytic NMR experiments an 80% mixture of *E/Z* isomers was formed in a ratio of 1:1 after 15 h, 140 °C.

¹H NMR (400 MHz, C₆D₆) δ /ppm = 7.65-7.70 (m, 4H, *H*_{Ar}, *E* and *Z*), 7.13-7.20 (m, 6H, *H*_{Ar}, *E* and *Z*), 7.01-7.10 (m, 8H, *H*_{Ar}, *E* and *Z*), 6.96 (s, 1H, *H*_{Ar}, *E*), 6.94 (s, 1H, *H*_{Ar}, *Z*), 6.66-6.71 (m, 2H, *H*_{Ar}, *E* and *Z*), 6.54-6.56 (m, 1H, *H*_{Ar}, *E*), 6.38-6.40 (m, 1H, *H*_{Ar}, *Z*), 6.28 (s, 1H, HC=C, *Z*), 5.74 (s, 1H, HC=C, *E*), 4.66 (s, 2H, NCH₂Ar, *E*), 4.41 (s, 2H, NCH₂Ar, *Z*), 3.40 (s, 3H, OCH₃, *E*), 3.37 (s, 6H, OCH₃, *E* and *Z*), 3.15 (s, 3H, OCH₃, *Z*), 2.98-3.02 (m, 4H, NCH₂CH₂, *E* and *Z*), 2.55 (t, 2H, *J* = 5.9 Hz, NCH₂CH₂, *E*), 2.44 (t, 2H, *J* = 5.9 Hz, NCH₂CH₂, *Z*). **HRMS** (ESI) *m/z*: calc. for C₂₅H₂₆NO₂: 372.1964; found 372.1970.

Synthesis of 1-benzyl-2-(2,5-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **261**

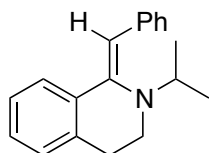


261 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:hexane, 1:5) afforded pure amine **261** in 56% yield, *R*_f = 0.12.

¹H NMR (400 MHz, CDCl₃) δ /ppm = 7.18-7.26 (m, 3H, *H*_{Ar}), 7.06-7.16 (m, 5H, *H*_{Ar}), 6.93 (d, 1H, *J* = 2.7 Hz, *H*_{Ar}), 6.84 (d, 1H, *J* = 7.5 Hz, *H*_{Ar}), 6.73-6.80 (m, 2H, *H*_{Ar}), 4.02 (t, 1H, *J* = 6.4 Hz, HCCH₂Ph), 3.88 (d, 1H, *J* = 15.0 Hz, NCH_aH_bAr), 3.74 (d, 1H, *J* = 15.0 Hz, NCH_aH_bAr), 3.73 (s, 3H, OCH₃), 3.71 (s, 3H, OCH₃), 3.31 (ddd, 1H,

$J = 5.0, 10.1, 14.8$ Hz, $\text{NCH}_a\text{H}_b\text{CH}_2$), 3.21 (dd, 1H, $J = 7.4, 13.9$ Hz, $\text{HCCH}_a\text{H}_b\text{Ph}$), 2.94-3.04 (m, 2H, $\text{NCH}_2\text{CH}_a\text{H}_b$, $\text{HCCH}_a\text{H}_b\text{Ph}$), 2.83 (ddd, 1H, $J = 3.7, 5.5, 12.9$ Hz, $\text{NCH}_a\text{H}_b\text{CH}_2$), 2.57 (dt, 1H, $J = 4.3, 16.8$ Hz, $\text{NCH}_2\text{CH}_a\text{H}_b$). **^{13}C NMR** (101 MHz, CDCl_3) δ/ppm : 153.73 (C_q), 151.88 (C_q), 140.18 (C_q), 138.41 (C_q), 134.89 (C_q), 129.74 (C_{Ar}), 129.08 (C_q), 128.89 (C_{Ar}), 128.10 (C_{Ar}), 127.86 (C_{Ar}), 125.93 (C_{Ar}), 125.75 (C_{Ar}), 125.26 (C_{Ar}), 115.25 (C_{Ar}), 112.47 (C_{Ar}), 111.49 (C_{Ar}), 63.60 (HCCH_2Ph), 56.06 (OCH_3), 55.73 (OCH_3), 51.60 (NCH_2Ar), 43.24 (NCH_2CH_2), 42.34 (HCCH_2Ph), 25.18 (NCH_2CH_2). **HRMS** (ESI) m/z : calc. for $\text{C}_{25}\text{H}_{28}\text{NO}_2$: 374.2120; found 374.2104. **IR** (cm^{-1}): 3003, 2955, 2915, 2835, 1738, 1602, 1499.

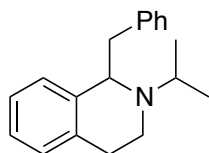
Synthesis of (Z)-1-benzylidene-2-isopropyl-1,2,3,4-tetrahydroisoquinoline **201**



According to the general procedure for catalytic NMR experiments the Z isomer was formed in 64% yield after 32 h, 140 °C.

^1H NMR (400 MHz, C_6D_6) δ/ppm = 7.71 (d, 2H, $J = 7.7$ Hz, H_{Ar}), 7.25-7.28 (m, 3H, H_{Ar}), 7.17-7.20 (m, 4H, H_{Ar}), 6.18 (s, 1H, $\text{HC}=\text{C}$), 3.84 (sep, 1H, $J = 6.9$ Hz, $\text{NCH}(\text{CH}_3)_2$), 2.84 (t, 2H, $J = 5.8$ Hz, NCH_2CH_2), 2.50 (t, 2H, $J = 5.8$ Hz, NCH_2CH_2), 0.85 (d, 6H, $J = 6.6$ Hz, $\text{NCH}(\text{CH}_3)_2$). **HRMS** (ESI) m/z : calc. for $\text{C}_{19}\text{H}_{22}\text{N}$: 264.1752; found 264.1760.

Synthesis of 1-benzyl-2-isopropyl-1,2,3,4-tetrahydroisoquinoline **262**

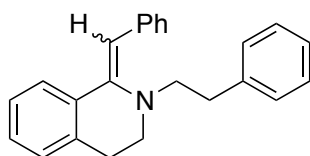


262 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et_2O :hexane, 1:5) afforded pure amine **262** in 51% yield, $R_f = 0.15$.

Yield for preparative scale reaction = 54%.

¹H NMR (400 MHz, CDCl₃) δ/ppm = 7.18-7.34 (m, 3H, *H*_{Ar}), 7.03-7.10 (m, 5H, *H*_{Ar}), 6.75 (d, 1H, *J* = 7.3 Hz, *H*_{Ar}), 4.08 (t, 1H, *J* = 6.2 Hz, HCCH₂Ph), 3.16-3.22 (m, 1H, NCH_aH_bCH₂), 3.04 (dd, 1H, *J* = 6.0, 13.0 Hz, HCCH_aH_bPh), 2.92-3.01 (m, 2H, NCH(CH₃)₂, NCH_aH_bCH₂), 2.87 (dd, 1H, *J* = 6.5, 13.5 Hz, HCCH_aH_bPh), 2.74-2.81 (m, 1H, NCH₂CH_aH_b), 2.53 (dt, 1H, *J* = 5.5, 16.0 Hz, NCH₂CH_aH_b), 1.08 (d, 3H, *J* = 5.7 Hz, CH₃), 1.06 (d, 3H, *J* = 5.7 Hz, CH₃). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 139.99 (*C*_q), 138.83 (*C*_q), 136.20 (*C*_q), 130.03 (*C*_{Ar}), 128.32 (*C*_{Ar}), 127.93 (*C*_{Ar}), 127.66 (*C*_{Ar}), 125.77 (*C*_{Ar}), 125.75 (*C*_{Ar}), 125.16 (*C*_{Ar}), 60.76 (HCCH₂Ph), 50.68 (NCH(CH₃)₂), 43.77 (HCCH₂Ph), 40.78 (NCH₂CH₂), 27.40 (NCH₂CH₂), 21.39 (NCHCH₃CH₃), 19.38 (NCHCH₃CH₃). **HRMS** (ESI) *m/z*: calc. for C₁₉H₂₄N: 266.1903; found 266.1897. **IR** (cm⁻¹): 3025, 2963, 2926, 1602, 1493, 1452.

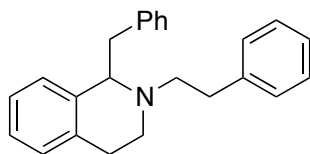
Synthesis of 1-benzylidene-2-phenethyl-1,2,3,4-tetrahydroisoquinoline **202**



According to the general procedure for catalytic NMR experiments a quantitative mixture of *E/Z* isomers was formed in a ratio of 0.4:1 after 15 h, 130 °C.

¹H NMR (400 MHz, C₆D₆) δ/ppm = 7.60-7.63 (m, 2.8H, *H*_{Ar}, *E* and *Z*), 7.18-7.27 (m, 7H, *H*_{Ar}, *E* and *Z*), 7.04-7.07 (m, 10H, *H*_{Ar}, *E* and *Z*), 6.22 (s, 1H, HC=C, *Z*), 5.74 (s, 0.4H, HC=C, *E*), 3.38-3.41 (m, 0.8H, NCH₂CH₂Ph, *E*), 3.20 (t, 2H, *J* = 8.2 Hz, NCH₂CH₂Ph, *Z*), 2.90 (t, 2H, *J* = 5.5 Hz, NCH₂CH₂, *Z*), 2.80 (t, 0.8H, *J* = 7.3 Hz, NCH₂CH₂Ph, *E*), 2.71 (t, 0.8H, *J* = 5.7 Hz, NCH₂CH₂, *E*), 2.62 (t, 2H, *J* = 8.2 Hz, NCH₂CH₂Ph, *Z*), 2.47 (t, 2H, *J* = 5.5 Hz, NCH₂CH₂, *Z*), 2.40 (t, 0.8H, *J* = 5.7 Hz, NCH₂CH₂, *E*). **HRMS** (ESI) *m/z*: calc. for C₂₄H₂₄N: 326.1909; found 326.1915.

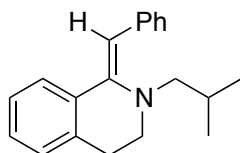
Synthesis of 1-benzyl-2-phenethyl-1,2,3,4-tetrahydroisoquinoline **263**



263 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:hexane, 1:5) afforded pure amine **263** in 57% yield, $R_f = 0.15$.

¹H NMR (400 MHz, CDCl₃) δ /ppm = 7.19-7.31 (m, 6H, H_{Ar}), 7.06-7.17 (m, 7H, H_{Ar}), 6.81 (d, 1H, $J = 7.5$ Hz, H_{Ar}), 4.01 (t, 1H, $J = 6.6$ Hz, $HCCH_2Ph$), 3.33-3.41 (m, 1H, $NCH_aH_bCH_2$), 3.13 (dd, 1H, $J = 7.0, 13.5$ Hz, $HCCH_aH_bPh$), 2.84-2.99 (m, 5H, $NCH_2CH_aH_b$, $NCH_aH_bCH_2$, $HCCH_aH_bPh$, NCH_2CH_2Ph), 2.71-2.75 (m, 2H, NCH_2CH_2Ph), 2.60 (dd, 1H, $J = 3.7, 14.1$ Hz, $NCH_2CH_aH_b$). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 140.55 (C_q), 140.14 (C_q), 138.00 (C_q), 134.62 (C_q), 129.70 (C_{Ar}), 128.82 (C_{Ar}), 128.74 (C_{Ar}), 128.23 ($2 \times C_{Ar}$), 127.98 (C_{Ar}), 126.04 (C_{Ar}), 125.88 (C_{Ar}), 125.85 (C_{Ar}), 125.29 (C_{Ar}), 63.29 ($HCCH_2Ph$), 56.02 (NCH_2CH_2Ph), 43.97 (NCH_2CH_2), 42.17 ($HCCH_2Ph$), 34.76 (NCH_2CH_2Ph), 25.17 (NCH_2CH_2). **HRMS** (ESI) m/z : calc. for C₂₄H₂₆N: 328.2065; found 328.2059. **IR** (cm⁻¹): 3060, 3025, 2923, 2852, 1602, 1494.

Synthesis of 1-benzylidene-2-isobutyl-1,2,3,4-tetrahydroisoquinoline **204**

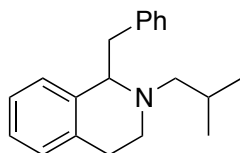


According to the general procedure for catalytic NMR experiments a 64% mixture of *E/Z* isomers was formed in a ratio of 1:0.2 after 15 h, 130 °C. Characterisation for major *E* isomer:

¹H NMR (400 MHz, C₆D₆) δ /ppm = 7.73 (d, 1H, $J = 8.2$ Hz, H_{Ar}), 7.23-7.30 (m, 4H, H_{Ar}), 7.07-7.11 (m, 4H, H_{Ar}), 5.64 (s, 1H, $HC=C$, *E*), 2.94 (d, 2H, $J = 7.3$ Hz,

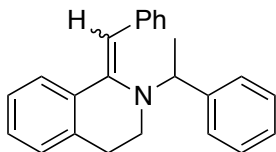
$\text{NCH}_2\text{CH}(\text{CH}_3)_2$, 2.88 (t, 2H, $J = 5.5$ Hz, NCH_2CH_2), 2.50 (t, 2H, $J = 5.5$ Hz, NCH_2CH_2), 2.10 (non, 1H, $J = 6.9$ Hz, $\text{NCH}_2\text{CH}(\text{CH}_3)_2$), 0.79 (d, 6H, $J = 6.8$ Hz, $\text{NCH}_2\text{CH}(\text{CH}_3)_2$). **HRMS** (ESI) m/z : calc. for $\text{C}_{20}\text{H}_{24}\text{N}$: 278.1909; found 278.1922.

Synthesis of 1-benzyl-2-isobutyl-1,2,3,4-tetrahydroisoquinoline **264**



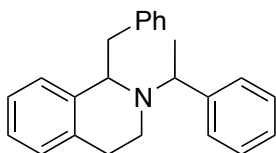
264 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et_2O :hexane, 1:10) afforded pure amine **264** in 52% yield, $R_f = 0.22$.

^1H NMR (400 MHz, CDCl_3) $\delta/\text{ppm} = 7.27\text{--}7.30$ (m, 2H, H_{Ar}), 7.20–7.23 (m, 3H, H_{Ar}), 7.07–7.16 (m, 3H, H_{Ar}), 6.88 (d, 1H, $J = 7.5$ Hz, H_{Ar}), 3.81 (dd, 1H, $J = 6.0, 8.0$ Hz, HCCH_2Ph), 3.36 (ddd, 1H, $J = 4.6, 11.0, 15.6$ Hz, $\text{NCH}_a\text{H}_b\text{CH}_2$), 3.09 (dd, 1H, $J = 7.8, 13.1$ Hz, $\text{HCCH}_a\text{H}_b\text{Ph}$), 2.93–3.01 (m, 1H, $\text{NCH}_2\text{CH}_a\text{H}_b$), 2.82–2.89 (m, 2H, $\text{HCCH}_a\text{H}_b\text{Ph}$, $\text{NCH}_a\text{H}_b\text{CH}_2$), 2.52 (ddd, 1H, $J = 2.1, 4.4, 16.7$ Hz, $\text{NCH}_2\text{CH}_a\text{H}_b$), 2.31 (dd, 2H, $J = 1.1, 6.9$ Hz, $\text{NCH}_2\text{CH}(\text{CH}_3)_2$), 1.61 (non, 1H, $J = 6.9$ Hz, $\text{NCH}_2\text{CH}(\text{CH}_3)_2$), 0.77 (d, 3H, $J = 6.6$ Hz, $\text{NCH}_2\text{CHCH}_3\text{CH}_3$), 0.70 (d, 3H, $J = 6.2$ Hz, $\text{NCH}_2\text{CHCH}_3\text{CH}_3$). **^{13}C NMR** (101 MHz, CDCl_3) δ/ppm : 140.63 (C_q), 138.54 (C_q), 134.93 (C_q), 129.70 (C_{Ar}), 128.92 (C_{Ar}), 128.24 (C_{Ar}), 127.85 (C_{Ar}), 125.90 (C_{Ar}), 125.73 (C_{Ar}), 125.28 (C_{Ar}), 63.91 (HCCH_2Ph), 62.20 ($\text{NCH}_2\text{CH}(\text{CH}_3)_2$), 43.65 (NCH_2CH_2), 42.49 (HCCH_2Ph), 26.53 ($\text{NCH}_2\text{CH}(\text{CH}_3)_2$), 24.40 (NCH_2CH_2), 20.60 ($\text{NCH}_2\text{CHCH}_3\text{CH}_3$), 20.56 ($\text{NCH}_2\text{CHCH}_3\text{CH}_3$). **HRMS** (ESI) m/z : calc. for $\text{C}_{20}\text{H}_{26}\text{N}$: 280.2065; found 280.2084. **IR** (cm^{-1}): 3025, 2950, 2925, 2868, 1602, 1494.

Synthesis of 1-benzylidene-2-(1-phenethyl)-1,2,3,4-tetrahydroisoquinoline **205**

According to the general procedure for catalytic NMR experiments a 20% mixture of *E/Z* isomers was formed in a ratio of 1:2.5 after 13 h, 140 °C.

¹H NMR (400 MHz, C₆D₆) δ /ppm = 7.83 (d, 2H, J = 7.7 Hz, H_{Ar} , *Z*), 7.69 (d, 0.8H, J = 7.6 Hz, H_{Ar} , *E*), 7.18-7.26 (m, 7H, H_{Ar} , *E* and *Z*), 7.01-7.09 (m, 10H, H_{Ar} , *E* and *Z*), 6.41 (s, 1H, $HC=C$, *Z*), 5.83 (s, 0.4H, $HC=C$, *E*), 5.06 (q, 0.4H, J = 7.0 Hz, $HCCH_3$, *E*), 4.67 (q, 1H, J = 6.8 Hz, $HCCH_3$, *Z*), 2.84-2.90 (m, 2.4H, $NCH_aH_bCH_2$, *E*, $NCH_aH_bCH_2$, *Z*), 2.74-2.79 (m, 1H, $NCH_aH_bCH_2$, *E*), 2.38-2.43 (m, 1.4H, $NCH_2CH_aH_b$, *E* and *Z*), 2.24-2.31 (m, 1H, $NCH_2CH_aH_b$, *Z*), 2.06-2.12 (m, 0.8H, $NCH_2CH_aH_b$, *E*), 1.29 (d, 1.4H, J = 6.8 Hz, $HCCCH_3$, *E*), 0.97 (d, 3H, J = 6.6 Hz, $HCCCH_3$, *Z*). **HRMS** (ESI) m/z : calc. for C₂₄H₂₄N: 326.1909; found 326.1916.

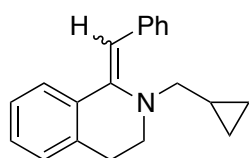
Synthesis of 1-benzyl-2-(1-phenethyl)-1,2,3,4-tetrahydroisoquinoline **265**

265 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:pentane, 1:10) afforded pure amine **265** as the major diastereoisomer in 41% yield, R_f = 0.29.

¹H NMR (400 MHz, CDCl₃) δ /ppm = 7.23-7.25 (m, 3H, H_{Ar}), 7.11-7.17 (m, 5H, H_{Ar}), 6.98-7.05 (m, 5H, H_{Ar}), 6.65 (d, 1H, J = 7.7 Hz, H_{Ar}), 3.84 (t, 1H, J = 7.3 Hz, $HCCH_2Ph$), 3.76 (q, 1H, J = 6.2 Hz, $HCCH_3$), 3.40 (ddd, 1H, J = 4.5, 11.7, 16.8 Hz, $NCH_aH_bCH_2$), 3.26 (dd, 1H, J = 5.7, 14.1 Hz, $NCH_aH_bCH_2$), 3.11 (dd, 1H, J = 7.7, 13.4 Hz, $HCCH_aH_bPh$), 2.95-3.04 (m, 1H, $NCH_2CH_aH_b$), 2.77 (dd, 1H, J = 6.5, 13.9 Hz, $HCCH_aH_bPh$), 2.56 (dd, 1H, J = 3.0, 16.9 Hz, $NCH_2CH_aH_b$), 1.36 (d, 3H, J = 7.0

Hz, HCCH_3). **^{13}C NMR** (101 MHz, CDCl_3) δ/ppm : 146.09 (C_q), 140.01 (C_q), 138.17 (C_q), 134.96 (C_q), 129.87 (C_Ar), 128.86 (C_Ar), 128.55 (C_Ar), 128.09 (C_Ar), 127.84 (C_Ar), 127.34 (C_Ar), 126.43 (C_Ar), 125.93 (C_Ar), 125.74 (C_Ar), 125.26 (C_Ar), 60.87 (HCCH_2Ph), 59.14 (HCCH_3), 42.66 (HCCH_2Ph), 39.43 (NCH_2CH_2), 24.15 (NCH_2CH_2), 21.89 (HCCH_3). **HRMS** (ESI) m/z : calc. for $\text{C}_{24}\text{H}_{26}\text{N}$: 328.2065; found 328.2063. **IR** (cm^{-1}): 3060, 3025, 2970, 2922, 2850, 1737, 1491.

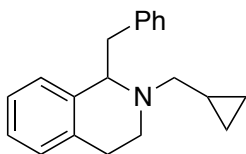
Synthesis of 1-benzylidene-2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinoline **206**



According to the general procedure for catalytic NMR experiments a quantitative mixture of *E/Z* isomers was formed in a ratio of 1:0.4 after 15 h, 130 °C.

^1H NMR (400 MHz, C_6D_6) δ/ppm = 7.70-7.75 (m, 2H, H_Ar , *E*), 7.54-7.57 (m, 0.8H, H_Ar , *Z*), 7.24-7.32 (m, 3H, H_Ar , *E* and *Z*), 7.02-7.20 (m, 7H, H_Ar , *E* and *Z*), 6.24 (s, 0.4H, $\text{HC}=\text{C}$, *Z*), 5.77 (s, 1H, $\text{HC}=\text{C}$, *E*), 3.08 (t, 0.8H, J = 5.8 Hz, NCH_2CH_2 , *Z*), 3.01 (d, 2H, J = 6.3 Hz, $\text{NCH}_2\text{CH}(\text{CH}_\text{a}\text{H}_\text{b})_2$, *E*), 2.94 (t, 2H, J = 5.8 Hz, NCH_2CH_2 , *E*), 2.82 (d, 0.8H, J = 6.8 Hz, $\text{NCH}_2\text{CH}(\text{CH}_\text{a}\text{H}_\text{b})_2$, *Z*), 2.53-2.57 (m, 2.8H, NCH_2CH_2 , *E* and *Z*), 0.96-1.04 (m, 1H, NCH_2CH , *E*), 0.68-0.76 (m, 0.4H, NCH_2CH , *Z*), 0.29-0.33 (m, 2H, $\text{NCH}_2\text{CH}(\text{CH}_\text{a}\text{H}_\text{b})_2$, *E*), 0.14-0.18 (m, 0.8H, $\text{NCH}_2\text{CH}(\text{CH}_\text{a}\text{H}_\text{b})_2$, *Z*), 0.00-0.03 (m, 2H, $\text{NCH}_2\text{CH}(\text{CH}_\text{a}\text{H}_\text{b})_2$, *E*), -0.21--0.17 (m, 0.8H, $\text{NCH}_2\text{CH}(\text{CH}_\text{a}\text{H}_\text{b})_2$, *Z*). **HRMS** (ESI) m/z : calc. for $\text{C}_{20}\text{H}_{22}\text{N}$: 276.1752; found 276.1758.

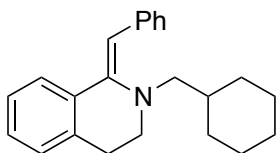
Synthesis of 1-benzyl-2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinoline **266**



266 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:pentane, 1:3) afforded pure amine **266** in 78% yield, $R_f = 0.11$.

¹H NMR (400 MHz, CDCl₃) δ /ppm = 7.26-7.30 (m, 2H, H_{Ar}), 7.08-7.24 (m, 5H, H_{Ar}), 7.04 (t, 1H, $J = 7.6$ Hz, H_{Ar}), 6.74 (d, 1H, $J = 7.6$ Hz, H_{Ar}), 4.13 (t, 1H, $J = 6.3$ Hz, $HCCH_2Ph$), 3.38 (ddd, 1H, $J = 5.4, 10.0, 15.4$ Hz, $NCH_aH_bCH_2$), 3.15 (dd, 1H, $J = 6.9, 13.9$ Hz, $HCCH_aH_bPh$), 3.04 (ddd, 1H, $J = 3.2, 5.6, 12.9$ Hz, $NCH_aH_bCH_2$), 2.86-2.98 (m, 2H, $NCH_2CH_aH_b$, $HCCH_aH_bPh$), 2.56-2.67 (m, 2H, $NCH_aH_bCH(CH_2)_2$, $NCH_2CH_aH_b$), 2.41 (dd, 1H, $J = 6.9, 12.3$ Hz, $NCH_aH_bCH(CH_2)_2$), 0.83-0.88 (m, 1H, $NCH_2CH(CH_2)_2$), 0.45-0.53 (m, 2H, $NCH_2CH(CH_aH_b)_2$), 0.08-0.11 (m, 2H, $NCH_2CH(CH_aH_b)_2$). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 140.28 (C_q), 138.06 (C_q), 134.67 (C_q), 129.72 (C_{Ar}), 128.79 (C_{Ar}), 128.24 (C_{Ar}), 127.91 (C_{Ar}), 125.96 (C_{Ar}), 125.81 (C_{Ar}), 125.19 (C_{Ar}), 62.73 ($HCCH_2Ph$), 58.80 ($NCH_2CH(CH_2)_2$), 43.83 (NCH_2CH_2), 42.17 ($HCCH_2Ph$), 25.02 (NCH_2CH_2), 9.75 ($NCH_2CH(CH_2)_2$), 4.16 ($NCH_2CHCH_2CH_2$), 3.37 ($NCH_2CHCH_2CH_2$). **HRMS** (ESI) m/z : calc. for C₂₀H₂₄N: 278.1909; found 278.1909. **IR** (cm⁻¹): 3061, 3024, 2923, 2853, 1654, 1602.

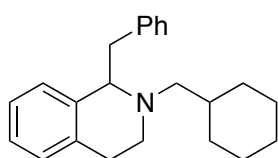
Synthesis of (*Z*)-1-benzylidene-2-(cyclohexylmethyl)-1,2,3,4-tetrahydroisoquinoline **207**



According to the general procedure for catalytic NMR experiments the *Z* isomer was formed in 38% yield after 12.5 h, 140 °C.

^1H NMR (400 MHz, C_6D_6) δ/ppm = 7.75 (d, 1H, J = 7.8 Hz, H_{Ar}), 7.63 (d, 1H, J = 7.1 Hz, H_{Ar}), 7.25-7.31 (m, 7H, H_{Ar}), 6.13 (s, 1H, $\text{HC}=\text{C}$), 3.02 (d, 2H, J = 6.8 Hz, $\text{NCH}_2\text{CH}(\text{CH}_2)_5$), 2.94 (t, 2H, J = 5.8 Hz, NCH_2CH_2), 2.55 (t, 2H, J = 5.6 Hz, NCH_2CH_2), 1.40-1.48 (m, 7H, $\text{NCH}_2\text{CH}(\text{CH}_2)_5$, CH_2 , $4 \times \text{CH}_{\text{eq}}H_{\text{ax}}$), 0.97-1.00 (m, 2H, $2 \times \text{CH}_{\text{eq}}H_{\text{ax}}$), 0.57-0.59 (m, 2H, $2 \times \text{CH}_{\text{eq}}H_{\text{ax}}$). **HRMS** (ESI) m/z : calc. for $\text{C}_{23}\text{H}_{28}\text{N}$: 318.2222; found 318.2229.

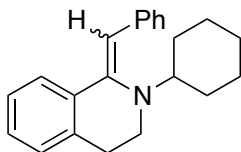
Synthesis of 1-benzyl-2-(cyclohexylmethyl)-1,2,3,4-tetrahydroisoquinoline **267**



267 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et_2O :hexane, 1:5) afforded pure amine **267** in 51% yield, R_f = 0.33.

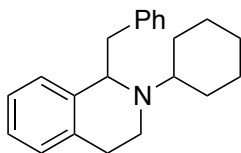
Yield for preparative scale reaction = 58 %.

^1H NMR (400 MHz, CDCl_3) δ/ppm = 7.28-7.30 (m, 2H, H_{Ar}), 7.20-7.24 (m, 3H, H_{Ar}), 7.11-7.17 (m, 3H, H_{Ar}), 6.92 (d, 1H, J = 7.3 Hz, H_{Ar}), 3.82 (dd, 1H, J = 5.7, 8.0 Hz, HCCH_2Ph), 3.36 (ddd, 1H, J = 4.6, 11.8, 16.0 Hz, $\text{NCH}_a\text{H}_b\text{CH}_2$), 3.05-3.13 (m, 1H, $\text{HCCH}_a\text{H}_b\text{Ph}$), 2.93-3.02 (m, 1H, $\text{NCH}_2\text{CH}_a\text{H}_b$), 2.82-2.91 (m, 2H, $\text{HCCH}_a\text{H}_b\text{Ph}$, $\text{NCH}_a\text{H}_b\text{CH}_2$), 2.49-2.54 (m, 1H, $\text{NCH}_2\text{CH}_a\text{H}_b$), 2.29-2.40 (m, 2H, $\text{NCH}_2\text{CH}(\text{CH}_2)_5$), 1.49-1.78 (m, 6H, CH_2 , $4 \times \text{CH}_{\text{eq}}H_{\text{ax}}$), 1.21-1.28 (m, 1H, $\text{NCH}_2\text{CH}(\text{CH}_2)_5$), 1.01-1.15 (m, 2H, $2 \times \text{CH}_{\text{eq}}H_{\text{ax}}$), 0.62-0.80 (m, 2H, $2 \times \text{CH}_{\text{eq}}H_{\text{ax}}$). **^{13}C NMR** (101 MHz, CDCl_3) δ/ppm : 140.70 (C_q), 138.52 (C_q), 134.99 (C_q), 129.67 (C_{Ar}), 128.93 (C_{Ar}), 128.29 (C_{Ar}), 127.85 (C_{Ar}), 125.90 (C_{Ar}), 125.72 (C_{Ar}), 125.32 (C_{Ar}), 63.85 (HCCH_2Ph), 60.83 ($\text{NCH}_2\text{CH}(\text{CH}_2)_5$), 43.95 (NCH_2CH_2), 42.59 (HCCH_2Ph), 36.26 ($\text{NCH}_2\text{CH}(\text{CH}_2)_5$), 31.63 ($\text{NCH}_2\text{CHCH}_2(\text{CH}_2)_4$), 31.50 ($\text{NCH}_2\text{CH}(\text{CH}_2)_4\text{CH}_2$), 26.91 ($\text{NCH}_2\text{CH}(\text{CH}_2)_2\text{CH}_2(\text{CH}_2)_2$), 26.25 ($\text{NCH}_2\text{CHCH}_2\text{CH}_2(\text{CH}_2)_3$), 26.19 ($\text{N}(\text{CH}_2)_3\text{CH}_2\text{CH}_2$), 24.37 (NCH_2CH_2). **HRMS** (ESI) m/z : calc. for $\text{C}_{23}\text{H}_{30}\text{N}$: 320.2373; found 320.2367. **IR** (cm^{-1}): 3060, 3024, 2919, 2849, 1738, 1601, 1493.

Synthesis of 1-benzylidene-2-cyclohexyl-1,2,3,4-tetrahydroisoquinoline **208**

According to the general procedure for catalytic NMR experiments a 25% mixture of *E:Z* isomers was formed in a ratio of 0.4:1 after 15 h, 140 °C. Characterisation for major *Z* isomer:

¹H NMR (400 MHz, C₆D₆) δ /ppm = 7.70 (d, 2H, J = 7.7 Hz, H_{Ar}), 7.23-7.27 (m, 3H, H_{Ar}), 7.17-7.20 (m, 4H, H_{Ar}), 6.19 (s, 1H, $HC=C$), 2.94 (t, 2H, J = 5.9 Hz, NCH_2CH_2), 2.61-2.66 (m, 1H, $NCH(CH_2)_5$), 2.53 (t, 2H, J = 5.9 Hz, NCH_2CH_2), 1.70-1.80 (m, 6H, CH_2 , 4 x $CH_{eq}H_{ax}$), 0.96-1.05 (m, 4H, 4 x $CH_{eq}H_{ax}$). **HRMS** (ESI) m/z : calc. for C₂₂H₂₆N: 304.2065; found 304.2076.

Synthesis of 1-benzyl-2-cyclohexyl-1,2,3,4-tetrahydroisoquinoline **268**

268 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:hexane, 1:5) afforded **268** in 42% yield, R_f = 0.15.

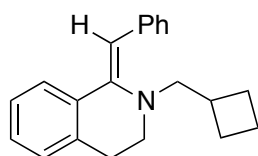
¹H NMR (400 MHz, CDCl₃) δ /ppm = 7.19-7.25 (m, 3H, H_{Ar}), 7.05-7.11 (m, 5H, H_{Ar}), 6.78 (d, 1H, J = 6.9 Hz, H_{Ar}), 4.12 (m, 1H, $HCCH_2Ph$), 3.23 (m, 1H, $NCH_aH_bCH_2$), 2.98-3.07 (m, 2H, $HCCH_aH_bPh$, $NCH_aH_bCH_2$), 2.88 (dd, 1H, J = 5.9, 13.2 Hz, $HCCH_aH_bPh$), 2.74-2.82 (m, 1H, $NCH_2CH_aH_b$), 2.51-2.55 (m, 2H, $NCH(CH_2)_5$, $NCH_2CH_aH_b$), 1.56-1.83 (m, 6H, CH_2 , 4 x $CH_{eq}H_{ax}$), 1.16-1.22 (m, 4H, 4 x $CH_{eq}H_{ax}$). **¹³C NMR** (101 MHz, CDCl₃) δ /ppm: 140.09 (C_q), 139.04 (C_q), 136.15 (C_q), 129.96 (C_{Ar}), 128.40 (C_{Ar}), 127.89 (2 x C_{Ar}), 127.66 (C_{Ar}), 125.73 (C_{Ar}), 125.14 (C_{Ar}), 60.39 ($HCCH_2Ph$), 59.66 ($NCH(CH_2)_5$), 43.99 ($HCCH_2Ph$), 41.06 (NCH_2CH_2), 31.63

(NCH(CH₂)(CH₂)₄), 29.98 (NCH(CH₂)₄CH₂), 27.28 (NCH₂CH₂), 26.22 (NCH(CH₂)₂CH₂(CH₂)₂), 25.90 (NCHCH₂CH₂(CH₂)₃), 25.73 (NCH(CH₂)₃CH₂CH₂).

HRMS (ESI) *m/z*: calc. for C₂₂H₂₈N: 306.2222; found 306.2212.

IR (cm⁻¹): 2929, 2855, 1703, 1641, 1601, 1451.

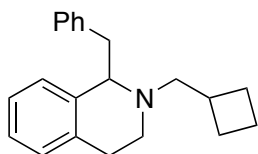
Synthesis of (Z)-1-benzylidene-2-(cyclobutylmethyl)-1,2,3,4-tetrahydroisoquinoline **209**



According to the general procedure for catalytic NMR experiments a 36% mixture of *E:Z* isomers was formed in a ratio of 1:1.2 after 30 h, 140 °C. Characterisation for major *Z* isomer.

¹H NMR (400 MHz, C₆D₆) δ/ppm = 7.66 (d, 2H, *J* = 7.7 Hz, *H*_{Ar}), 7.25-7.29 (m, 3H, *H*_{Ar}), 7.10-7.12 (m, 4H, *H*_{Ar}), 6.19 (s, 1H, HC=C), 3.00 (d, 2H, *J* = 7.3 Hz, NCH₂CH(CH₂)₂CH₂), 2.88 (t, 2H, *J* = 5.5 Hz, NCH₂CH₂), 2.50 (t, 2H, *J* = 5.5 Hz, NCH₂CH₂), 2.31 (sep, 1H, *J* = 7.7 Hz, NCH₂CH(CH₂)₃), 1.94-1.97 (m, 2H, NCH₂CH(CH₂)₂CH₂), 1.55-1.62 (m, 4H, NCH₂CH(CH₂)₂CH₂). **HRMS** (ESI) *m/z*: calc. for C₂₁H₂₄N: 290.1909; found 290.1912.

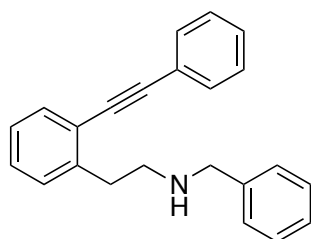
Synthesis of 1-benzyl-2-(cyclobutylmethyl)-1,2,3,4-tetrahydroisoquinoline **269**



269 was synthesised according to the general procedure for reduction of enamines. Purification by column chromatography (silica gel, Et₂O:hexane, 1:5) afforded pure amine **269** in 51% yield, *R*_f = 0.13.

¹H NMR (400 MHz, CDCl₃) δ/ppm = 7.24-7.26 (m, 2H, *H*_{Ar}), 7.21 (d, 1H, *J* = 7.1 Hz, *H*_{Ar}), 7.13-7.17 (m, 2H, *H*_{Ar}), 7.02-7.11 (m, 3H, *H*_{Ar}), 6.78 (d, 1H, *J* = 7.7 Hz, *H*_{Ar}), 3.83 (t, 1H, *J* = 6.1 Hz, *HCCH*₂Ph), 3.30 (ddd, 1H, *J* = 4.5, 10.5, 15.2 Hz, *NCH*_a*H*_bCH₂), 3.07 (dd, 1H, *J* = 7.7, 13.7 Hz, *HCCH*_a*H*_bPh), 2.88-2.97 (m, 1H, *NCH*₂CH_a*H*_b), 2.80-2.86 (m, 2H, *NCH*_a*H*_bCH₂, *HCCH*_a*H*_bPh), 2.59 (d, 2H, *J* = 7.0 Hz, *NCH*₂CH(CH₂)₂CH₂), 2.48-2.53 (m, 1H, *NCH*₂CH_a*H*_b), 2.40 (quin, 1H, *J* = 7.3 Hz, *NCH*₂CH(CH₂)₂CH₂), 1.91-1.99 (m, 1H, *NCH*₂CH(CH_a*H*_b), 1.85-1.90 (m, 1H, *NCH*₂CH(CH_a*H*_b), 1.72-1.83 (m, 2H, *NCH*₂CH(CH₂)₂CH_a*H*_b), 1.56-1.62 (m, 2H, *NCH*₂CH(CH_a*H*_b)₂CH₂). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 140.41 (*C*_q), 138.23 (*C*_q), 134.75 (*C*_q), 129.70 (*C*_{Ar}), 128.82 (*C*_{Ar}), 128.22 (*C*_{Ar}), 127.83 (*C*_{Ar}), 125.91 (*C*_{Ar}), 125.75 (*C*_{Ar}), 125.24 (*C*_{Ar}), 63.19 (*HCCH*₂Ph), 60.14 (*NCH*₂CH(CH₂)₃), 43.83 (*NCH*₂CH₂), 42.38 (*HCCH*₂Ph), 34.49 (*NCH*₂CH(CH₂)₃), 27.12 (2C, *NCH*₂CH(CH₂)₂CH₂), 24.58 (*NCH*₂CH₂), 18.72 (*NCH*₂CHCH₂CH₂CH₂). **HRMS** (ESI) *m/z*: calc. for C₂₁H₂₆N: 292.2065; found 292.2083. **IR** (cm⁻¹): 3024, 2919, 2851, 1738, 1602, 1493.

Synthesis of *N*-benzyl-2-(2-(phenylethynyl)phenyl)ethanamine **270**

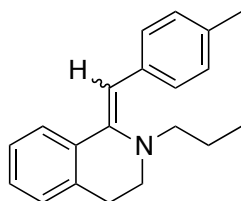


270 was synthesised according to the general procedure catalytic NMR reactions using 5 mol% of precatalyst [*L*¹]*SrN*(SiMe₃)₂(THF)₂ and heating for 12 hours at 90 °C. Purification by column chromatography (silica gel, Et₂O:hexane, 1:5) afforded pure amine **270** in 84% yield, *R*_f = 0.28.

¹H NMR (400 MHz, CDCl₃) δ/ppm = 7.53-7.57 (m, 3H, *H*_{Ar}), 7.38-7.40 (m, 3H, *H*_{Ar}), 7.22-7.32 (m, 8H, *H*_{Ar}), 3.88 (s, 2H, *NCH*₂Ph), 3.12-3.15 (m, 2H, *NCH*₂CH₂Ar), 3.04-3.07 (m, 2H, *NCH*₂CH₂Ar), 1.44 (bs, 1H, *NH*). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 142.09 (*C*_q), 140.47 (*C*_q), 132.37 (*C*_{Ar}), 131.51 (*C*_{Ar}), 129.26 (*C*_{Ar}), 128.48 (*C*_{Ar}), 128.39 (2 × *C*_{Ar}), 128.27 (*C*_{Ar}), 128.06 (*C*_{Ar}), 126.86 (*C*_{Ar}), 126.19 (*C*_{Ar}), 123.43 (*C*_q),

122.93 (C_q), 93.06 ($C\equiv C$), 88.06 ($C\equiv C$), 53.80 (NCH_2Ph), 49.70 (NCH_2CH_2Ar), 35.33 (NCH_2CH_2Ar). **HRMS** (ESI) m/z : calc. for $C_{23}H_{22}N$: 312.1747; found 312.1740. **IR** (cm^{-1}): 3060, 3025, 2923, 2212, 1599, 1493.

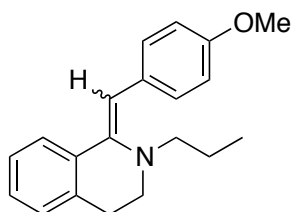
Synthesis of 1-(4-methylbenzylidene)-2-propyl-1,2,3,4-tetrahydroisoquinoline **231**



According to the general procedure for catalytic NMR experiments a 47% mixture of *E:Z* isomers was formed in a ratio of 0.5:1 after 65 h, 140 °C. Characterisation for major *Z* isomer:

1H NMR (400 MHz, d_{10} -xylene) δ/ppm = 7.76-7.84 (m, 2H, H_{Ar}), 7.32-7.34 (m, 1H, H_{Ar}), 7.23-7.28 (m, 5H, H_{Ar}), 6.35 (s, 1H, $HC=C$), 3.11-3.14 (m, 2H, NCH_2CH_2), 3.07-3.09 (m, 2H, $NCH_2CH_2CH_3$), 2.72-2.75 (m, 2H, NCH_2CH_2), 2.41 (s, 3H, CH_3), 1.60 (sext, 2H, J = 7.6 Hz, $NCH_2CH_2CH_3$), 0.81 (t, 2H, J = 7.4 Hz, $NCH_2CH_2CH_3$). **HRMS** (ESI) m/z : calc. for $C_{20}H_{24}N$: 278.1909; found 278.1917.

Synthesis of 1-(4-methoxybenzylidene)-2-propyl-1,2,3,4-tetrahydroisoquinoline **232**

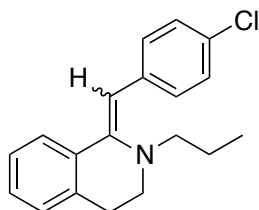


According to the general procedure for catalytic NMR experiments a 30% mixture of *E:Z* isomers was formed in a ratio of 1:2 after 65 h, 140 °C. Characterisation for major *Z* isomer:

1H NMR (400 MHz, d_{10} -xylene) δ/ppm = 7.75-7.77 (m, 2H, H_{Ar}), 7.44-7.45 (m, 1H, H_{Ar}), 7.27-7.29 (m, 3H, H_{Ar}), 6.86-6.87 (m, 2H, H_{Ar}), 6.37 (s, 1H, $HC=C$), 3.63 (s, 3H,

OCH_3), 3.42-3.45 (m, 2H, NCH_2CH_2), 3.32 (t, 2H, $J = 5.8$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 2.77 (t, 2H, $J = 5.8$ Hz, NCH_2CH_2), 1.79 (sext, 2H, $J = 7.4$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 0.83 (t, 3H, $J = 7.6$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_3$). **HRMS** (ESI) m/z : calc. for $\text{C}_{20}\text{H}_{24}\text{NO}$: 294.1858; found 294.1860.

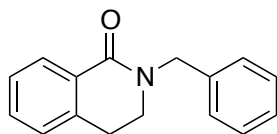
Synthesis of (*Z*)-1-(4-chlorobenzylidene)-2-propyl-1,2,3,4-tetrahydroisoquinoline **233**



According to the general procedure for catalytic NMR experiments a 24% mixture of *E:Z* isomers was formed in a ratio of 0.25:1 after 65 h, 140 °C. Characterisation for major *Z* isomer:

^1H NMR (400 MHz, d_{10} -xylene) δ/ppm = 7.73-7.75 (m, 2H, H_{Ar}), 7.40-7.41 (m, 3H, H_{Ar}), 7.25-7.28 (m, 3H, H_{Ar}), 6.14 (s, 1H, $\text{HC}=\text{C}$), 3.29 (t, 2H, $J = 6.6$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 2.86 (t, 2H, $J = 6.6$ Hz, NCH_2CH_2), 2.61 (t, 2H, $J = 5.8$ Hz, NCH_2CH_2), 1.89 (sext, 2H, $J = 6.8$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 0.78 (t, 2H, $J = 7.3$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_3$). **HRMS** (ESI) m/z : calc. for $\text{C}_{19}\text{H}_{21}\text{NCl}$: 298.1363; found 298.1372.

Synthesis of 2-benzyl-3,4-dihydroisoquinolin-1-(2H)-one **271**



According to the general procedure for preparative scale reactions, 2-benzyl-1-benzylidene-1,2,3,4-tetrahydroisoquinoline **271** was synthesised and subsequently oxidised according to the literature procedure.¹⁹⁷

Tetrabutylammonium iodide (74 mg, 0.2 mmol) was added to a suspension of iodosylbenzene (ISB) (484 mg, 2.2 mmol) in $\text{MeCN}:\text{H}_2\text{O}$ 9:1 (50 ml) and the mixture

was stirred at room temperature for 5 min. To this suspension was added 2-benzyl-1-benzylidene-1,2,3,4-tetrahydroisoquinoline **210** (1 mmol) dissolved in MeCN:H₂O 9:1 (10 ml), and the resultant mixture was stirred at room temperature for an additional 2 h. The solution was then concentrated under reduced pressure and the residue dissolved in CH₂Cl₂ (80 ml), washed with 5 % aq. Na₂S₂O₃ and H₂O, and dried (Na₂SO₄). The solvent was removed under reduced pressure and the crude oil purified by column chromatography (silica gel, Et₂O:pent, 1:5) to afford 2-benzyl-3,4-dihydroisoquinolin-1-(2H)-one as a pale yellow oil (166 mg, 70%, *R_f* = 0.14).

The spectra match that reported for the benzolactam **271**.¹⁹⁸

¹H NMR (400 MHz, CDCl₃) δ/ppm = 7.29-7.45 (m, 8H, *H*_{Ar}), 7.17-7.19 (m, 1H, *H*_{Ar}), 4.82 (s, 2H, NCH₂Ph), 3.51 (t, 2H, *J* = 6.6 Hz, CH₂CH₂N), 2.96 (t, 2H, *J* = 6.6 Hz, CH₂CH₂N). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm: 164.59 (C=O), 138.06 (C_q), 137.47 (C_q), 131.69 (C_{Ar}), 129.41 (C_q), 128.64 (C_{Ar}), 128.48 (C_{Ar}), 128.07 (C_{Ar}), 127.44 (C_{Ar}), 127.07 (C_{Ar}), 126.89 (C_{Ar}), 50.46 (NCH₂Ph), 45.36 (CH₂CH₂N), 28.11 (CH₂CH₂N). **HRMS** (ESI) *m/z*: calc. for C₁₆H₁₆NO: 238.1232; found 238.1238.

Future Directions of Group 2 Catalysis

Heavier alkaline earth metal complexes have proven to be effective homogenous catalysts for a wide range of heterofunctionalisation reactions.¹⁰ These include hydroamination, hydrophosphination, hydrosilylation, hydroboration and hydroalkoxylation¹¹⁷ reactions amongst many more applications. However, control of these reactions and tolerance of additional polar functional groups needs to be addressed if synthetically applied to the construction of important molecules such as natural products. The formation of new C–S bonds is particularly attractive. The hydrothiolation transformation has been achieved with trivalent lanthanide and actinide complexes to make vinyl sulfides.¹⁹⁹

Rare earth metal complexes of Ln^{3+} cations are additionally able to catalyse tandem C–N and C–C bond-forming reactions in the construction of pyrrolizidine, indolizidine, pyrrole and pyrazine skeletons.¹⁸ Group 2 catalysts may not be sufficiently Lewis-acidic to achieve such C–C bond formation. In order to produce a more Lewis-acidic metal centre, design of novel heavier alkaline earth metal complexes with a more naked metal cation supported by monoanionic multi-coordinating ligands is necessary. Discrete cationic complexes of this type have been designed by Sarazin and coworkers and have exhibited increasingly impressive catalytic performances for the ROP of epoxides and cyclic esters.⁷³ This is likely to spark additional interest in the catalytic chemistry of group 2.

To date the application of chiral heavier alkaline earth metal complexes of the type L^*AeX has not been achieved. Previous attempts have included the use of a chiral calcium amide catalyst, based upon the (*S*)-Ph-pybox ligand. Although non-racemic products were produced, extremely low enantioselectivity (< 10% ee) was obtained. The design of chiral bulky monoanionic ligands (L^*) to circumvent the Schlenk-like solution redistribution reactions is fundamental.

4.0 Literature

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