Catalytic and Tandem-Catalytic Routes to Small Molecules

Nicolas D Spiccia
BScAdv(Hons) Monash University, MRACI

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Declaration

To the best of the author's knowledge, this thesis contains no material which has been accepted for the award of any other degree or diploma in any university and contains no material previously published or written by another person except where due reference is made.

Nicolas Daniel Spiccia
School of Chemistry
Monash University, Clayton Campus
Melbourne, Australia
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Abstract

A valuable PA-11 precursor, methyl 11-aminoundecanoate hydrochloride, was synthesised from methyl undec-9-enoate. This ester, obtained from renewable canola oil, was transformed in a three step, multi-catalytic sequence involving cross-metathesis, palladium-catalysed benzylic amine addition and concomitant hydrogenation/hydrogenolysis in 58% overall yield without the use of column chromatography. The corresponding unsaturated PA-11 precursor, methyl 11-aminoundec-9-enoate hydrochloride, was synthesised in a similar sequence of cross-metathesis, palladium-catalysed benzylamine addition and hydrolysis in 53% overall yield.

Methods for the Brønsted masking of the amino group during metathesis reactions were also developed, and highlighted the importance of solvent and counterion selection. A collection of unsaturated diamine salts of various lengths, all useful for the production of copolymer polyamides, was synthesised in high yield. The corresponding saturated diamine salts were also synthesised in excellent yield by employing an addition assisted-tandem hydrogenation *via* the residual ruthenium emanating from the metathesis step. Similarly, cross-metathesis and tandem cross-metathesis/hydrogenation reactions of alkenyl ammonium salts with acrylates gave unsaturated and saturated amino carboxylate salts useful for homopolymer polyamides in excellent conversion.

In closing, this new methodology was utilised to complete a formal synthesis of the biologically active alkaloid perhydrohistrionicotoxin. This new synthesis employs a cross-metathesis of an alkenyl ammonium salt as a key step and generates an advanced literature intermediate in a five step convergent synthesis with a total yield of 30%.

Abbreviations

^{13}C	Carbon 13
^{1}H	Proton
Ac	Acetate
ACN	Acetonitrile
Bn	Benzyl
Boc	*tert*-Butyl carbamate
BSA	Benzene sulphonate
Bu	Butyl
Bz	Benzoyl
CM	Cross-metathesis
Conc.	Concentrated
Cy	Cyclohexyl
dba	dibenzylacetone
DCM	Dichloromethane
Eq.	Molar equivalents
ESI	Electrospray ionisation
Et	Ethyl
EtOAc	Ethyl acetate
Fer	Ferrocenyl
Fmoc	9-Fluorenylmethyloxycarbonyl
GC	Gas chromatography
GI	Grubbs catalyst first generation
GII	Grubbs catalyst second generation
HGI	Hoveyda-Grubbs catalyst first generation
HGII	Hoveyda-Grubbs catalyst second generation
HMPA	Hexamethylphosphorylamide
HRMS	High resolution mass spectrometry
Hz	Hertz
^{i}Bu	*iso*-Butyl

^{i}Pr	*iso*-Propyl
lit.	Literature
LRMS	Low resolution mass spectrometry
m.p.	Melting point
Me	Methyl
Mes	2,4,6-Trimethylbenzene
MHz	Megahertz
mins	Minutes
MsOH	Methane sulphonic acid
n.m.r.	Nuclear magnetic resonance
*n*BuLi	*n*-Butyl lithium
PA	Polyamide
PMB	*para*-Methoxybenzyl
Pr	Propyl
psi	Pounds per square inch
Pth	Phthaloyl
*p*TsOH	*p*-Toluene sulphonic acid
Py	Pyridine
Quant.	Quantitative yield
RCM	Ring closing metathesis
ROMP	Ring opening metathesis polymerisation
RT	Room temperature
SiO_2	Silica 60
^{t}Bu	*tert*-Butyl
TFA	Trifluoroacetic acid
TfOH	Trifluoromethane sulphonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosyl
UV	Ultra violet
X4	Hexanes

δ	Chemical shift
Δ	Heat (to reflux)
υ_{max}	Infrared spectra

General Introduction

1.1 Catalysis

A more modern and environmentally conscious society has steered chemists into investigating greener and more sustainable chemical transformations.[1-3] This has led to an explosion of research into transition metal catalysed reactions, which in turn has provided a plethora of atom-efficient organic transformations suitable for small through to industrial scale synthesis. With such interests at hand, the new and quickly expanding field of tandem catalysis has provided greener routes to highly-functionalised organic molecules (Figure 1).[4-10]

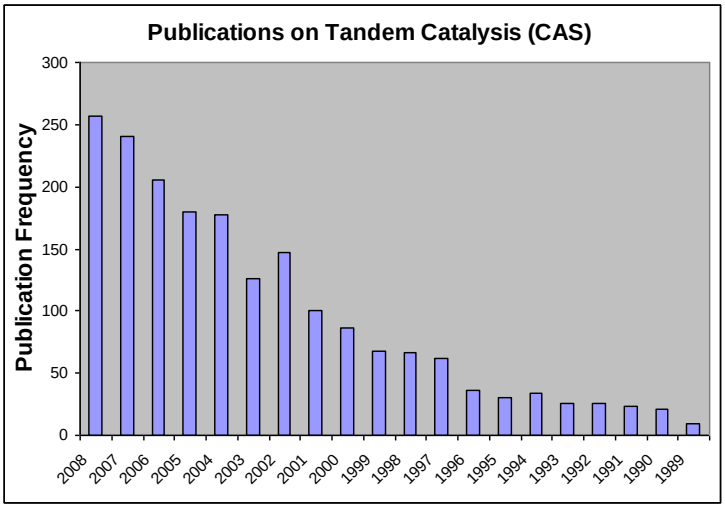

Figure 1: Publications containing the concept of tandem catalysis.

1.2 Tandem catalysis

Tandem catalysis involves two or more "one-pot" catalytic events that result in multiple chemical transformations where a major benefit is a reduction in isolation and purification steps. A taxonomy proposed by Fogg *et al.*,[4] highlights the main classes of tandem catalysis. Orthogonal tandem catalysis involves two or more mechanistically

distinct catalysts being present at the onset of the reaction. These two catalysts do not interact with each other and the product from one catalytic cycle is the substrate for the next catalytic cycle (Figure 2).

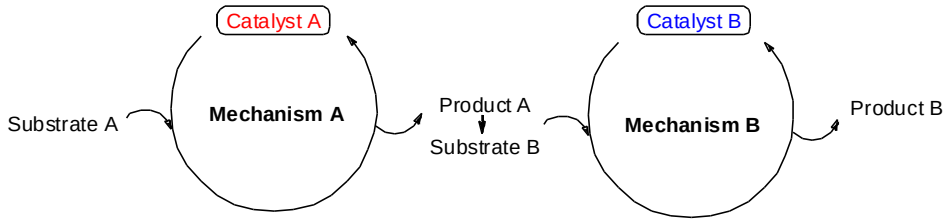

Figure 2: Orthogonal catalysis cycle.[4]

An elegant example of this type of tandem catalysis involves the orthogonal use of Hoveyda-Grubbs second generation catalyst (**HGII**) and PtO_2 in a high yielding, tandem cross metathesis/hydrogenation sequence for the synthesis of saturated silyl-substituted carbonyl compounds (Figure 3).[11]

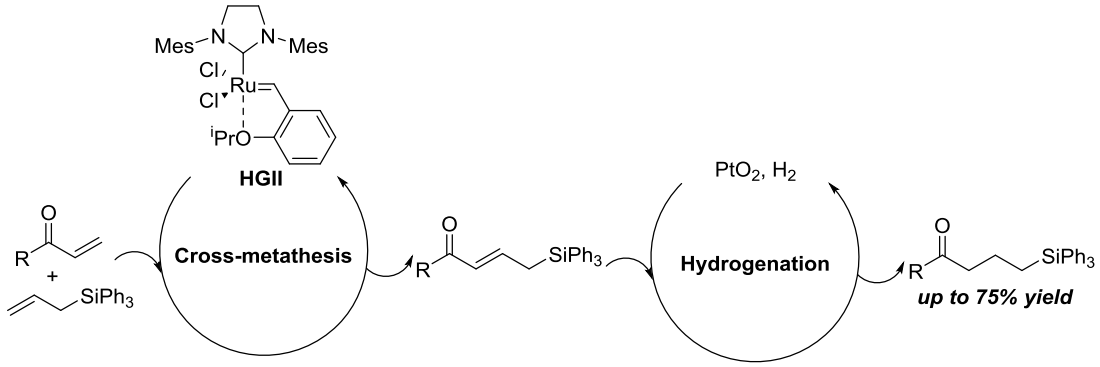

Figure 3: Orthogonal tandem cross metathesis/hydrogenation sequence.

Auto-tandem catalysis involves a singular pre-catalyst that performs two mechanistically distinct, but compatible, catalytic cycles on a substrate. Similar to orthogonal tandem catalysis, the product from the first catalytic cycle is the substrate for the second catalytic cycle (Figure 4).

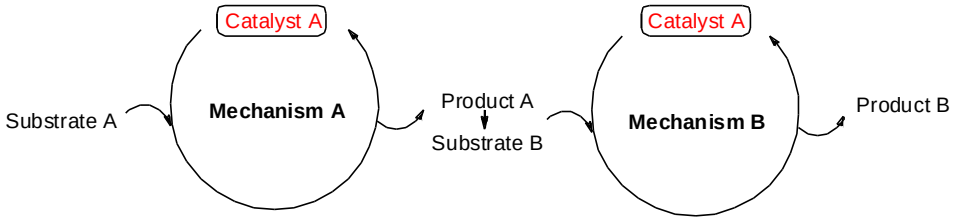

Figure 4: Auto-tandem catalysis.[4]

An illustrative example of auto-tandem catalysis by Meyers *et al.*[12] involves an intermolecular Pd-catalysed oxidative C-N bond formation followed by a intramolecular Pd-catalysed C-C bond formation *via* C-H activation of the electron-deficient quinoline (Figure 5).

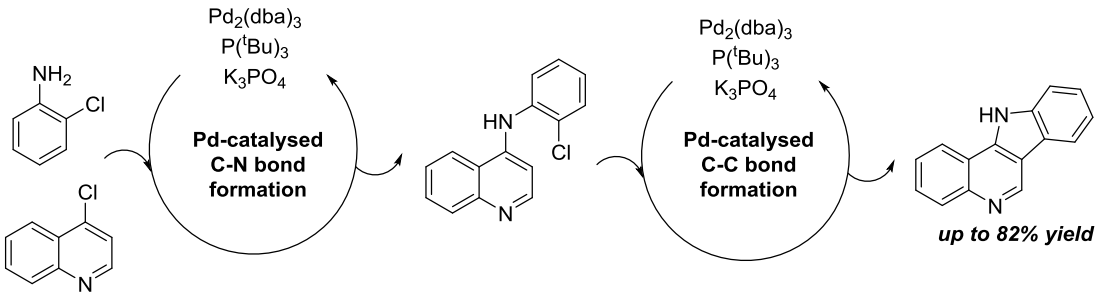

Figure 5: Auto-tandem Pd-catalysed C-N and C-C bond formation.

Assisted tandem catalysis involves a single pre-catalyst which is transformed into a secondary catalyst (with a different mechanism) by the addition of activating reagents. Once again, the product from the first catalytic cycle is the substrate for the second (Figure 6).

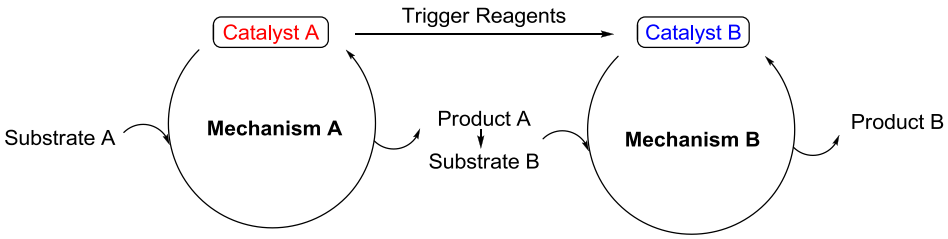

Figure 6: Assisted tandem catalysis.[4]

Snapper and co-workers[13] have employed a tandem ruthenium alkylidene catalysed ring closure followed by a ruthenium hydride catalysed double bond isomerisation sequence for the synthesis of substituted cyclic enol ethers (Figure 7). This was achieved by altering the composition of the inert gas atmosphere from nitrogen to a 95:5 mix of nitrogen and hydrogen gas respectively, which favours the formation of the ruthenium hydride species.

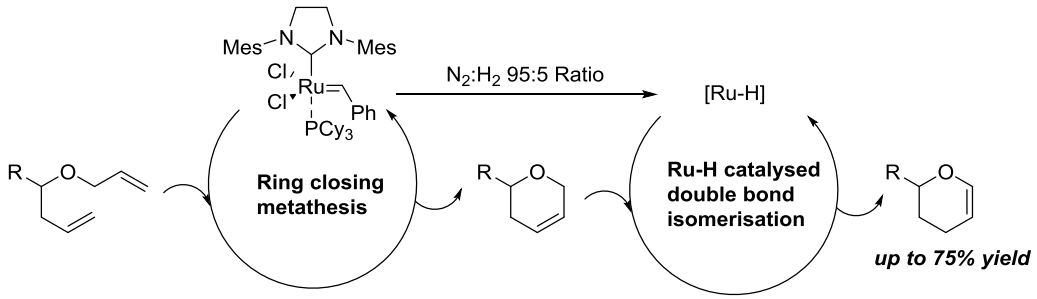

Figure 7: Assisted tandem Ru-catalysed RCM and subsequent Ru-H catalysed double bond isomerisation.

1.3 Tandem metathesis/hydrogenation

One of the more commonly employed tandem catalytic reactions involving olefin metathesis chemistry is the tandem metathesis/hydrogenation reaction. With the exception of orthogonal tandem metathesis/hydrogenation reactions such as those developed by Cossy *et al* (Figure 3),[11, 14] most of these involve the use of the residual ruthenium from Grubbs' catalysts after olefin metathesis as the secondary catalyst for hydrogenation.[15-22] This is advantageous as it doesn't require the use of additional precious metal catalysts to perform the hydrogenation. An illustrative example of assisted tandem metathesis/hydrogenation was published by Fürstner *et al* in 2003 (Figure 8).[21] This involved the ring closing metathesis of 2,6-di(hex-5-enyl)pyridine using a ruthenium-indenylidene catalyst followed by tandem hydrogenation of the ring closed product by the addition of high pressure hydrogen.

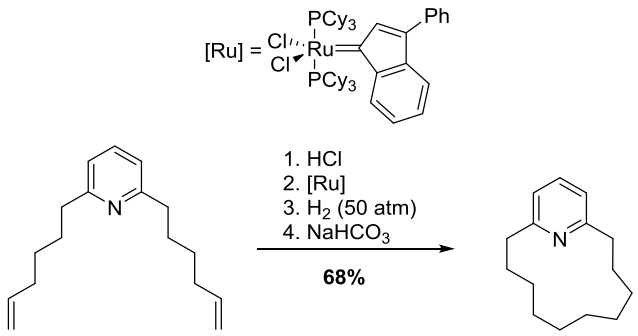

Figure 8: Assisted tandem ring closing metathesis/hydrogenation[21]

1.4 Research goals

Research in this project will focus on the use of catalysis for the synthesis of small organic molecules, with particular emphasis on molecules containing the amino group. The research aims were to develop efficient catalytic and tandem catalytic methodologies, with the intention of performing new organic transformations that extend the reach of organic chemistry. Such methodologies were then to be applied to the synthesis of complex biologically active molecules. More specifically, this research aimed to develop a new catalytic approach to the preparation of the biologically active alkaloid perhydrohistrionicotoxin. Throughout this thesis, the use of ruthenium alkylidene cross-metathesis will be emphasised and its propensity for incorporation into tandem catalytic sequences will also be highlighted.

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Nylons from renewables

2.1 Introduction

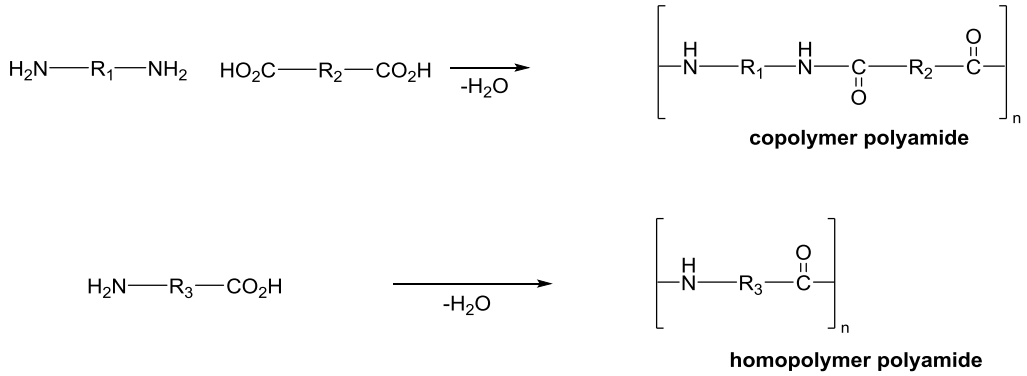
2.1.1 Polyamides

Since Wallace Carothers' inception in the 1930's at DuPont®, the multi-billion dollar polyamide industry has supplied the world with synthetic polymers used in the production of resins and fibres (Figure 1).[1, 2]

Figure 1: Nylon fibres[3] and resin beads.[4]

Polyamides are typically categorised by the monomers from which they are synthesised.[5] These are distributed between two end member types: Aramids, which are polyamides that are derived from aromatic monomers (e.g. Kevlar® and Nomex®), and nylons, which are those that are derived from aliphatic monomers (Stanyl® and Rilsan®).[6, 7] There are two mechanisms for polymerisation of these monomers: copolymerisation and homopolymerisation. Copolymer polyamides are synthesised by the condensation step-growth polymerisation of diamines with dicarboxylic acids, e.g. Kevlar®, Nomex® and Stanyl® PA-4,6 (Table 1, Entry 1).[7] Homopolymer polyamides are synthesised by the condensation step-growth polymerisation of amino acids or their derivatives, e.g PA-6 and Rilsan® PA-11 (Table 1, Entry 4).[8]

Table 1: Types of polyamides.



Entry	Name(s)	Type	R_1	R_2	R_3
1	PA-4,6 (Stanyl®)	Nylon	4	4	-
2	PA-6	Nylon	-	-	5
3	PA-6,6	Nylon	6	4	-
4	PA-11 (Rilsan®)	Nylon	-	-	10
5	Kevlar®	Aramid	*p*-Ph	*p*-Ph	-
6	Nomex®	Aramid	*m*-Ph	*m*-Ph	-

Different combinations of monomers can be used together to give a plethora of unique polyamides with diverse and tuneable properties suitable for a variety of applications such as clothing, electronics and automotive parts (Figure 2).[1]

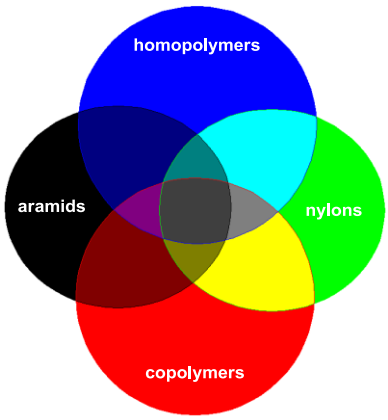
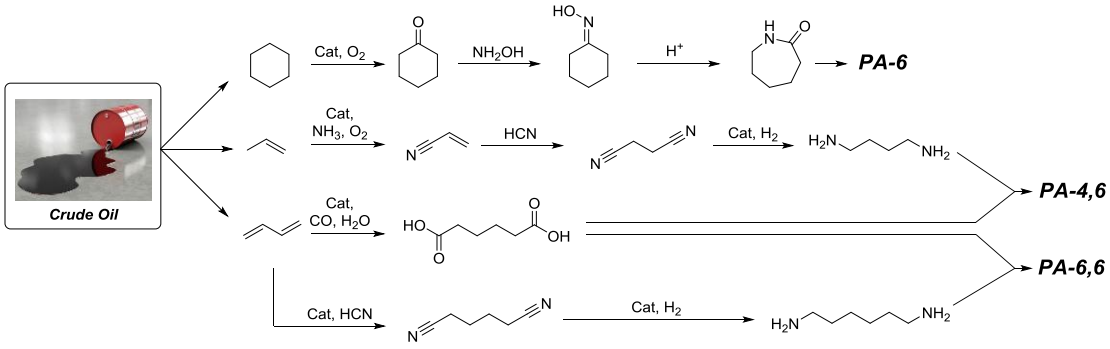


Figure 2: Combinations of polyamides.

Currently, most polyamide monomers are derived from petrochemical feedstocks such as cyclohexane (PA-6), propene (PA-4,6) and butadiene (PA-4,6 and PA-6,6) (Scheme 1) or occasionally from natural oils such as castor oil (PA-11) (Scheme 2).[2, 5, 8, 9] The

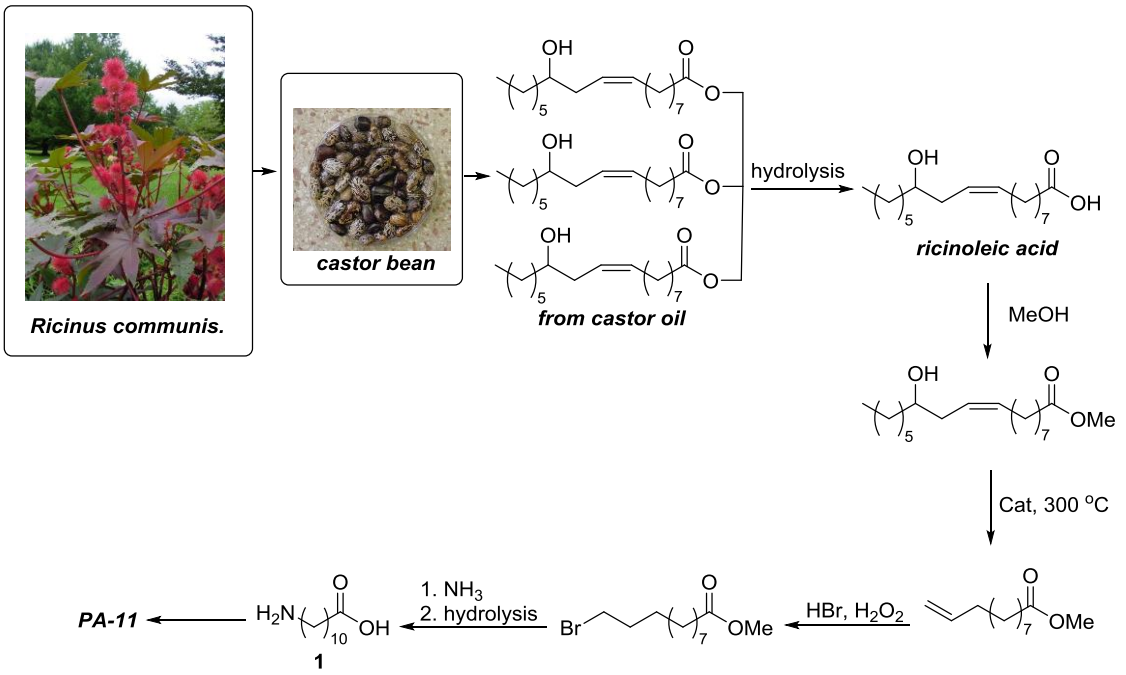
chemistry utilised in synthesising these monomers, although cost effective, is somewhat unfashionable by modern standards. They generally rely on the use of many undesirable chemicals such as hydrogen cyanide, acrylonitrile, carbon monoxide and high pressurised hydrogen which pose serious risk to the manufacturers and the surrounding environment (Scheme 1).[5, 7, 8, 10]



Scheme 1: Industrial synthesis of various polyamide monomers.

2.1.2 Fine chemicals from renewable oils

The production of fine chemicals from renewable natural oils has attracted much interest recently from an environmentally conscious society.[1, 11-15] Natural oils, such as canola, peanut and soybean are rich in triglycerides and are currently used as chemical feedstocks for a variety of applications, such as detergents, surface coatings and biofuels.[2, 3] Arkema's Rilsan®, which is more commonly known as PA-11, is produced by the condensation homopolymerisation of the amino acid monomer 11-aminoundecanoic acid **1**. Rilsan® has useful chemical properties which include high chemical resistance, low density and low moisture absorption, making it suitable for applications within the automotive, fuel and electronics industries.[4, 5] The PA-11 monomer 1 is produced using a five step sequence from castor oil, which is extracted from seeds (also known as castor beans) harvested from the crop *Ricinus communis* (Scheme 2).[6]



Scheme 2: Industrial synthesis of PA-11.

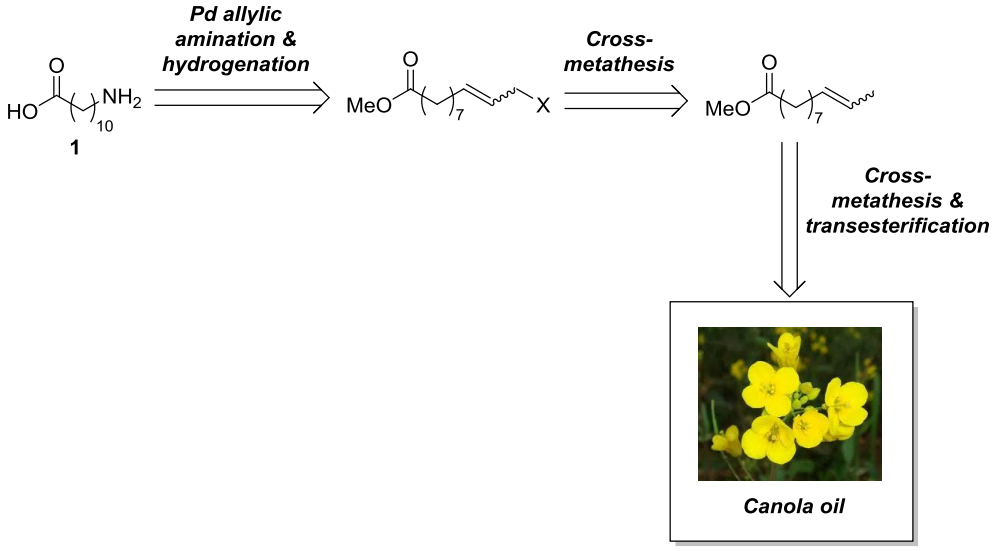
Castor oil is a minor component (~0.15%) of the international seed oil trade and is currently produced in a 0.83 million tonne scale per year.[16] Due to variability in seed ripening within the crop, harvesting is performed manually several times each season and defoliants often need to be employed on denuded plants. During harvesting and processing of the seed, extreme caution must be exercised due to potential exposure to the ricin toxin which can be lethal *via* injection, inhalation and ingestion.[17, 18] Therefore the price of castor oil is strongly influenced by fluctuation in production and speculation, and is almost twice that of palm, soya and canola oils.[9]

2.1.3 Towards 11-aminoundecanoic acid 1

Due to the complications associated with the production of castor oil, it was proposed that the PA-11 monomer could instead be synthesised from an alternative renewable feedstock, canola oil. Canola oil is an edible oil extracted from rapeseed, which is grown on a 60 million tonne scale per year,[16] and is rich in the mono-unsaturated C18 fatty acid oleic acid. Cleavage of oleic acid obtained from natural oils *via* metathesis chemistry has recently been reported using a range of olefinic cross partners such as

acrylonitrile[19] allyl chloride[20] and ethylene.[21] The establishment of biorefineries utilizing triglyceride/ethylene feedstocks has illustrated the commercial viability of these processes.[22] It has been reported that much greater catalyst efficiency can be achieved in this transformation through the use of 2-butene in the cross metathesis reaction,[12] where the highest turnovers (TON up to 470,000) result from oils containing predominantly oleic acid.[13]

In this chapter an exploration of a novel methodology to convert canola oil into the PA-11 monomer, 11-aminoundecanoic acid **1**, and derivatives by a sequence involving Ru-catalysed cross metathesis, palladium-catalysed amination and hydrogenation will be investigated (Scheme 3).

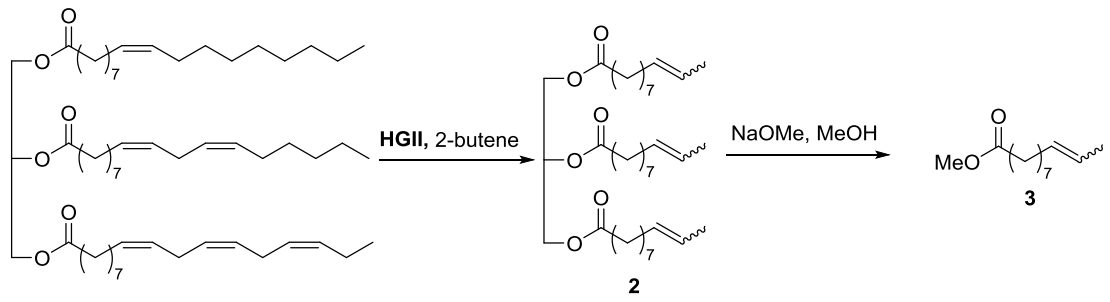


Scheme 3: Retrosynthesis of 1.

2.2 Results and Discussion

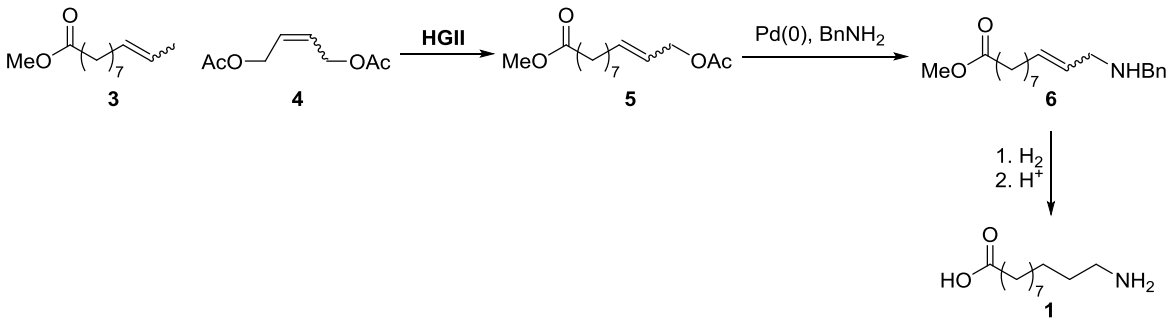
2.2.1 Background research

The proposed approach for the synthesis of PA-11 monomer **1** extends research developed in our group by Patel *et al.*.[12, 13] This involved cross-metathesis of natural oils containing high levels of C9-unsaturated fatty acids (e.g. canola and sunflower oil) with 2-butene, followed by transesterification of the resultant triglyceride **2** to give methyl undec-9-enoate **3** (Scheme 4). Methyl undec-9-enoate **3** was thought to be a useful starting precursor for the synthesis of PA-11 monomer **1** as it contains both an appropriate number of carbons, and the required terminal carboxylate functionality.



Scheme 4: Synthesis of methyl undec-9-enoate 3.[12, 13]

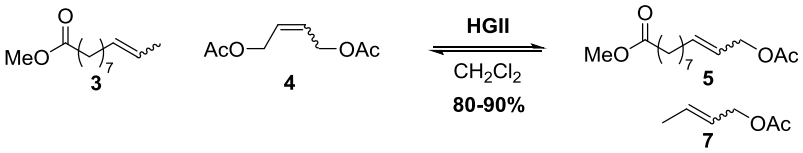
It was envisaged that a second cross-metathesis reaction of **3** with 1,4-diacetoxy-but-2-ene **4** would give allylic acetate **5** which could then be reacted with benzylamine using a palladium(0) catalysed allylic addition developed by Trost *et al.*.[23] This would give the amino ester **6**, which after hydrogenation and hydrolysis would give the PA-11 monomer **1** (Scheme 5)**.**



Scheme 5: Proposed synthesis for 1.

2.2.2 Synthesis of allylic acetate 5

Cross metathesis of methyl undec-9-enoate **3** with 10 molar equivalents of *cis*-1,4-diacetoxy-but-2-ene **4** using 1 mol% Hoveyda-Grubbs second generation catalyst gave allylic acetate **5** in excellent yield (90%) after column chromatography (Scheme 6).

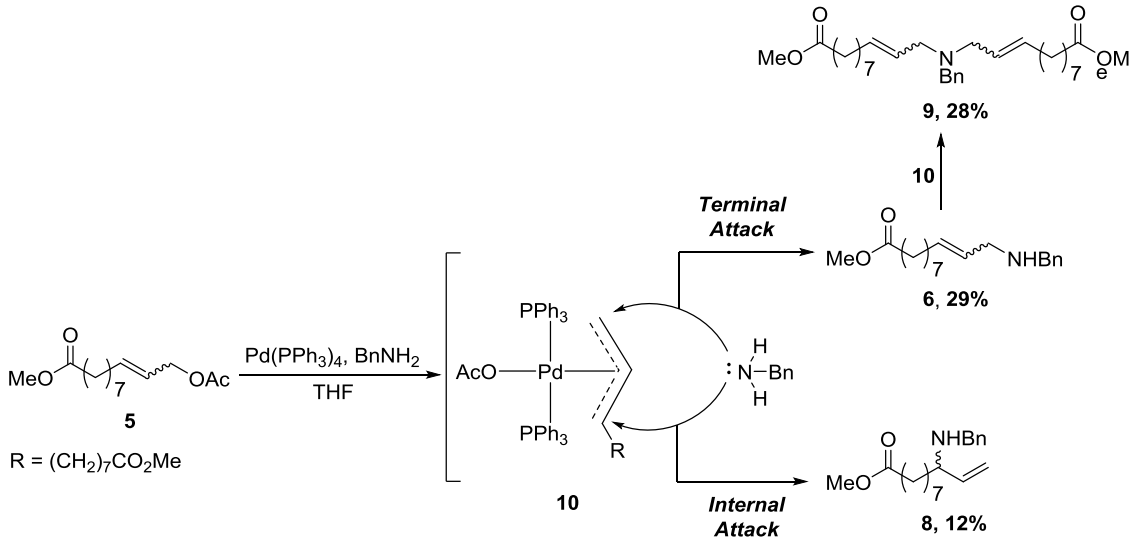


Scheme 6: Cross-metathesis of 3 & 4.

The major by-product, (*E,Z*)-2-butenylacetate **7**, which forms *via* reaction of the propenyl fragment of methyl undec-9-enoate **3** with 1,4-diacetoxyl-but-2-ene **4**, was readily removed by co-distillation with excess **4**. This leaves behind a residue which after simple filtration through silica (to remove expended **HGII** catalyst) gave pure allylic acetate **5** in good yield (80%) (Scheme 6). The recovered distillate of (*E,Z*)-2-butenylacetate **7** and 1,4-diacetoxy-2-butene **4**, now a 70:30 mixture of *E*- and *Z*-isomers, could be reused in further cross metathesis reactions with **3** without loss of yield.

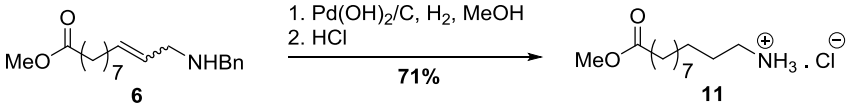
2.2.3 Synthesis of amino ester 6

The allylic acetate **5** was then reacted with benzylamine under palladium(0)-tetrakis(triphenylphosphine) catalysis using conditions described by Trost and Keinan (Scheme 7).[23]



Scheme 7: Palladium catalysed benzylamine addition to 5.

The target amino ester **6** was isolated in poor yield (29%) due to the formation of the isomeric branched amine **8** (12% yield) and the linear double addition product **9** (28% yield) (Scheme 7). The branched amine by-product **8** arises from the nucleophilic attack of π-allylpalladium intermediate **10** by benzylamine at the internal carbon. The linear double addition by-product arises from the nucleophilic attack of **10** by amino ester **6** at the terminal carbon (Scheme 7). Slow gradient chromatography was needed to isolate pure product **6**. One-pot hydrogenation and hydrogenolysis of **6** over Pearlman's catalyst then gave the saturated primary amino ester salt **11** in 71% yield after acidification (Scheme 8).



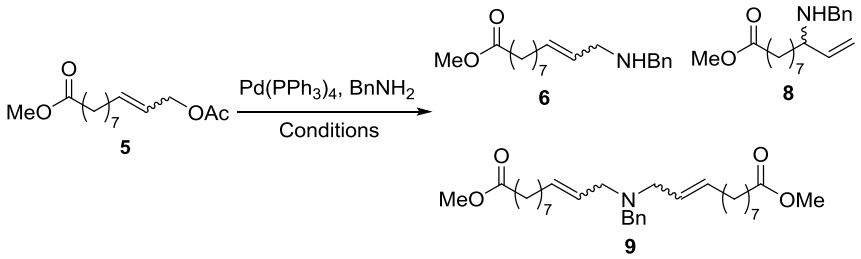
Scheme 8: Hydrogenolysis of 6.

2.2.4 Optimisation of conditions

The sub-optimal yields of the desired amino ester **6** warranted further investigation of the experimental conditions involving the reaction of benzylamine and allylic acetate **5.**

It was envisaged that the production of the double addition product **9** could be reduced with a change in molar ratio of benzylamine to allylic acetate **5** (Table 2).

Table 2: Optimisation of palladium-catalysed benzylamine addition to 5



Entry	Solvent	Conditions	Equivalents $BnNH_2$	Conversion to 6, 8 & 9 (%)	6 (%)[a]	8 (%)[a]	9 (%)[a]
1	THF	Δ, 3 hrs	0.5	100	35	12	53
2	THF	Δ, 1 hr[b]	0.5	100	-	<5	>95
3	THF	Δ, 3 hrs	1	100	48	12	40
4	THF	Δ, 3 hrs	2	100	57	11	32
5	THF	Δ, 3 hrs	4	100	71	10	19
6	THF	Δ, 3 hrs	10	100	78	12	10
7	THF	Δ, 3 hrs[c]	20	100	79	13	8
8	Dioxane	Δ, 1 hr	10	100	74	18	8
9	THF	0 °C to rt, 24 hrs	10	0	-	-	-

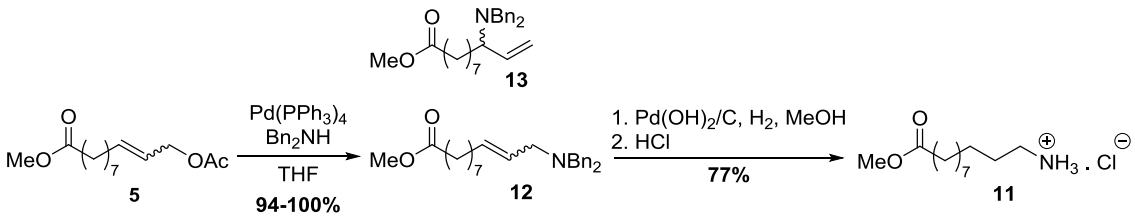
[a] %conversion estimated by ^{1}H n.m.r. spectroscopy. [b] Slow addition of benzylamine over 10 mins to **5** and $Pd(PPh_3)_4$ in THF at reflux. [c] Slow addition of **5** to benzylamine and $Pd(PPh_3)_4$ in dioxane at reflux.

As expected, with a lower molar ratio of benzylamine to allylic acetate **5** (Entry 1), the amount of the double addition product **9** increased to 53%. The proportion of **9** could be further increased to >95% by slow addition of benzylamine to a refluxing solution of allylic acetate **5** and $Pd(PPh_3)_4$ (Entry 2). In this case, the disubstituted product **9** was isolated in 90% yield after chromatography to provide a potentially useful monomer for the synthesis of branched polyamides. The proportion of double addition product **9** was decreased when a higher molar ratio of benzylamine to allylic acetate **5** was employed, thus providing improved yields of the target amine **6** (Entries 3-7). It was observed that the proportion of branched product **8** produced was not appreciably affected by the molar ratio of benzylamine. The reaction temperature and solvent were also briefly investigated in an attempt to reduce the formation of the by-products **8** and **9**. Slow addition of **5** to an excess of benzylamine at higher temperature failed to improve the selectivity for amino ester **6** (Entry 8). Reaction of **5** with a large excess of benzylamine at low temperature was unsuccessful (Entry 9).

2.2.5 Dibenzylamine approach

Although successful in synthesising the PA-11 precursor amino ester **11**, the approach was deemed not viable due to the need for either large amounts of benzylamine and/or column chromatographic purification (Table 2).

Thus, in order to eliminate the formation of the disubstituted product **9** and potentially reduce the amount of branched by-product **8**, dibenzylamine was used in the Pd-catalysed amination reaction with allylic acetate **5** (Scheme 9). It was proposed that, since dibenzylamine is a secondary amine, it cannot participate in two addition reactions, thus eliminating the disubstituted by-product. Synergistically, the extra steric bulk from the second benzyl group may promote nucleophilic addition to the least sterically hindered carbon in the palladium π-allyl complex **10**, hence reducing the proportion of the undesired branched by-product.

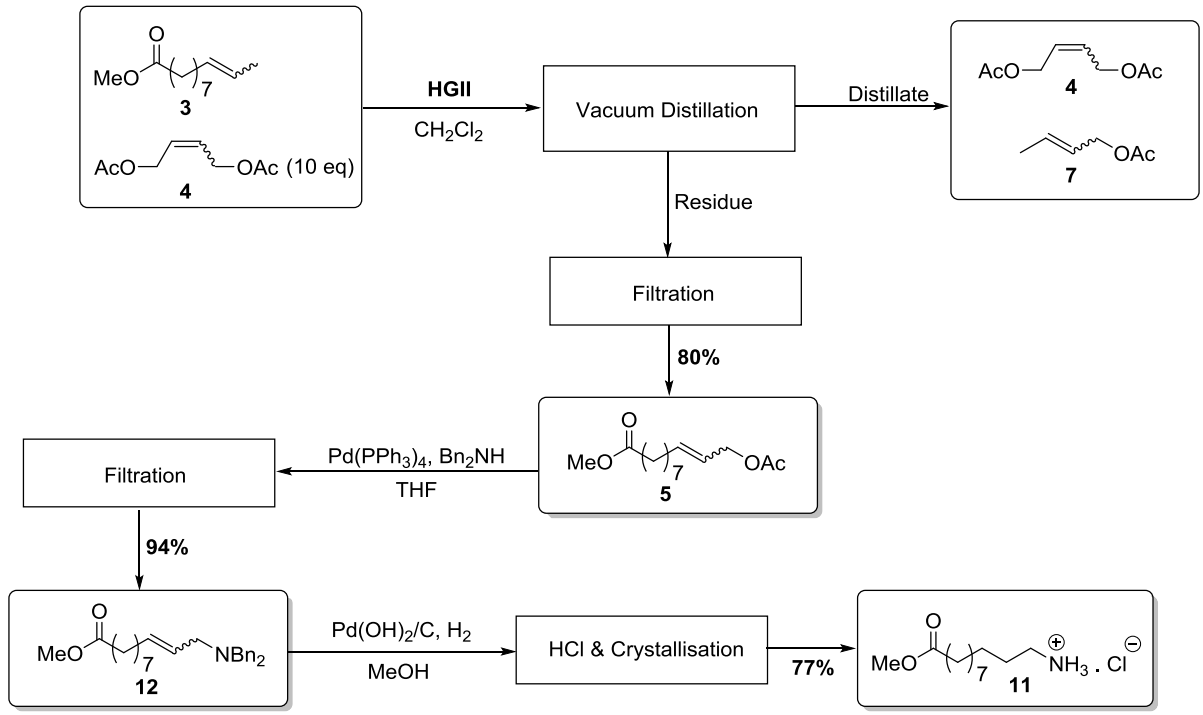


Scheme 9: Synthesis of amino ester salt 11.

Encouragingly, the Pd-catalysed addition of only one molar equivalent of dibenzylamine to allylic acetate **5** generated the desired linear amino ester **12** in quantitative yield after purification with column chromatography, or in a comparable yield (94%) after purification by filtration through a short pad of silica (Scheme 9). High selectivity for the linear adduct **12** over the branched ester **13** was also observed (>95% for **12**). Subsequent hydrogenation and hydrogenolysis of **12** over Pearlman's catalyst gave the saturated primary amino ester salt **11** in 77% yield after acidification.

To highlight the industrial applicability of this process, the three catalytic reactions transforming **3** → **11**, namely cross-metathesis, amination and

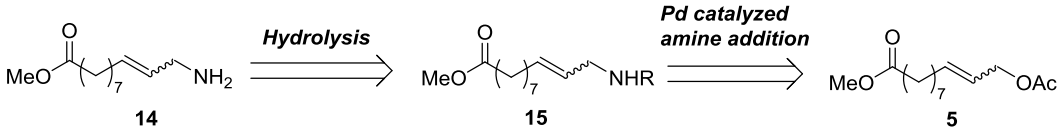
hydrogenation/hydrogenolysis, provide the PA-11 precursor **11** in 69% overall yield or 58% without the use of column chromatography (Scheme 10).



Scheme 10: Process summary for synthesis of 11.

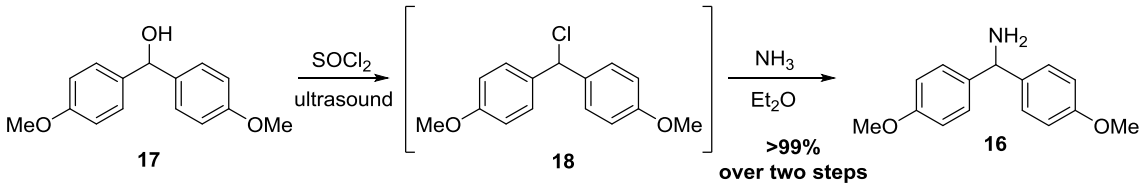
2.2.6 Synthesis of an unsaturated nylon monomer

Having developed methodologies for the synthesis of the PA-11 precursor methyl 11-aminoundecanoate **11**, our attention was focused on the synthesis of the related unsaturated relative methyl 11-aminoundec-9-enoate **14.** This monomer could be used for the production of unsaturated nylons where the remaining chain unsaturation could be exploited to generate crosslinked networks and polymers possessing lower melt crystallization temperatures.[24, 25] The proposed synthesis of the unsaturated PA-11 precursor **14** is divergent from the same allylic acetate intermediate **5** used for the synthesis of the saturated PA-11 precursor **11** (Scheme 11).



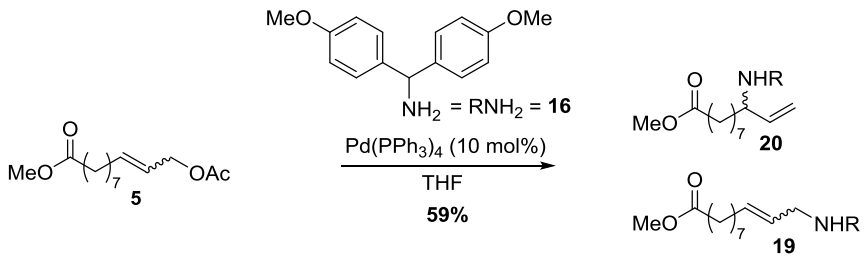
Scheme 11: Retrosynthesis for 14.

The route to amino ester **14** specifically involves the Pd(0) catalysed addition of an amine bearing an acid labile R-group to **5** to generate amino ester **15**. An acid hydrolysable R-group is required as typical hydrogenolysis conditions for debenzylation result in concomitant hydrogenation of alkene moieties.[26] This transformation was used to our advantage in the synthesis of the saturated PA-11 precursor **11**. Thus, the amine bis-(4-methoxybenzyl)methylamine **16** was chosen as it is compatible with palladium catalysed allylic addition chemistry and is easily hydrolysed with acid *via* an assisted cleavage promoted by the electron donating methoxyl groups on the aromatic rings.[23] This amine **16** was synthesised in two steps from the commercially available bis-(4-methoxybenzyl)methanol **17**. Sonication of **17** in excess thionyl chloride gave the crude chloride **18** which was telescopically reacted with excess gaseous ammonia in CH_2Cl_2 to give bis-(4-methoxybenzyl)methylamine **16** in quantitative yield (Scheme 12).



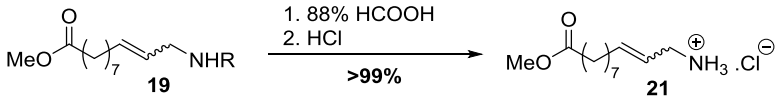
Scheme 12: Synthesis of 16.

The allylic acetate **5** was then subjected to the Pd-catalysed addition reaction using bis-(4-methoxybenzyl)methylamine **16** as the nucleophilic amine (Scheme 13)**.** The allylic aminoester **19** was generated in a 4:1 ratio to the branched isomer **20** as estimated by ^1H n.m.r. spectroscopy. This necessitated the use of column chromatography for purification where the allylic aminoester **19** was isolated in a moderate 59% yield.



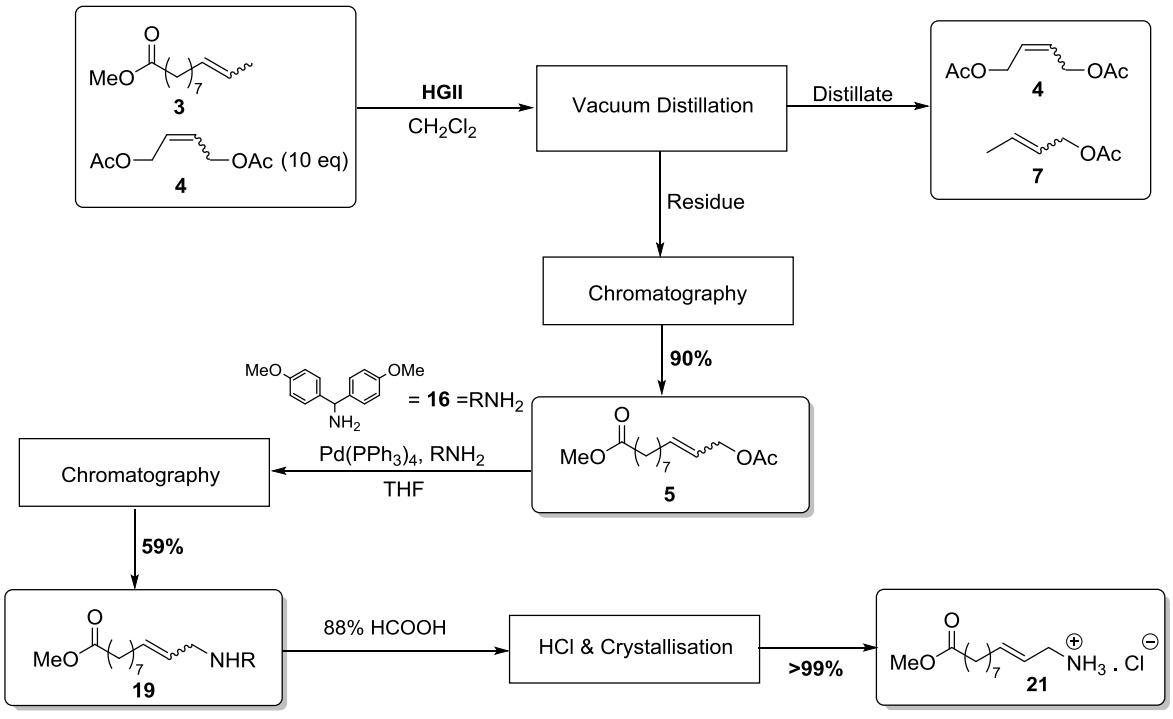
Scheme 13: Palladium-catalysed addition of 16 to 5.

Interestingly, the disubstituted product was not observed for this reaction and this was thought to be due to steric crowding around the amine group on the allylic aminoester **19**, which would slow the second addition into the π-allylpalladium intermediate. Hydrolysis of the benzhydryl group on **19** with 88% formic acid gave the unsaturated PA-11 precursor, which was isolated as the hydrochloride salt **21** in quantitative yield (Scheme 14).



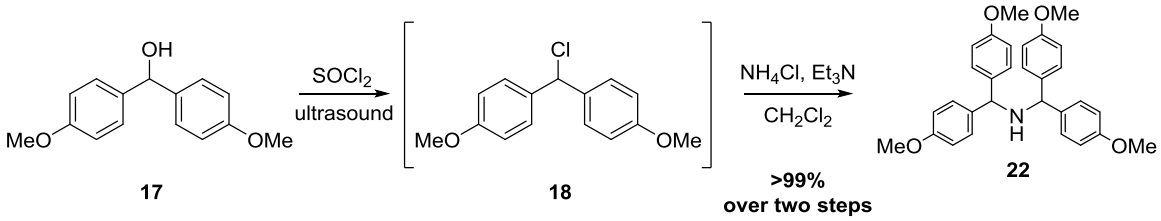
Scheme 14: Hydrolysis of 19.

The unsaturated PA-11 precursor methyl 11-aminoundec-9-enoate **21** was synthesised in three steps from methyl undec-9-enoate in 53% overall yield but required the use of column chromatography (Scheme 15).



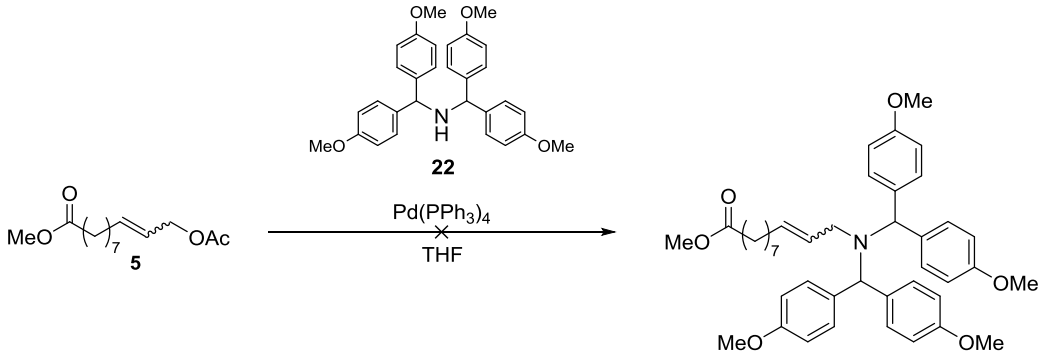
Scheme 15: Process summary for the synthesis of 21.

To increase the product selectivity for the linear allylic aminoester **19** during the Pd-catalysed addition reaction and eliminate the need for column chromatography, it was proposed that di(bis-(4-methoxybenzyl)methyl)amine **22** could be used analogously to dibenzylamine for the synthesis of the saturated PA-11 precursor (Scheme 9). This novel compound was synthesised from bis(4-methoxybenzyl)methanol **17** by sonication in excess thionyl chloride to give bis(4-methoxybenzyl)methyl)chloride **18** (Scheme 16).



Scheme 16: Synthesis of amine 22.

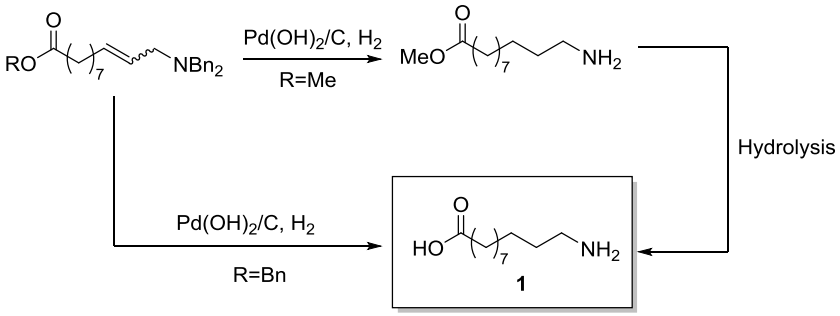
The chloride **18** was then telescopically reacted with half an equivalent of ammonium chloride. Dropwise addition of triethylamine to the mixture led to the slow release of ammonia to promote the double alkylation reaction. This method successfully gave di(bis-(4-methoxybenzyl)methyl)amine **22** in quantitative yield (Scheme 16). However, all attempts to use **22** in the palladium(0) catalysed allylic amine addition were unsuccessful, presumably due to reduced nucleophilicity as a result of increased steric bulk around the amine (Scheme 17).



Scheme 17: Attempted palladium-catalysed addition of 22 to 5.

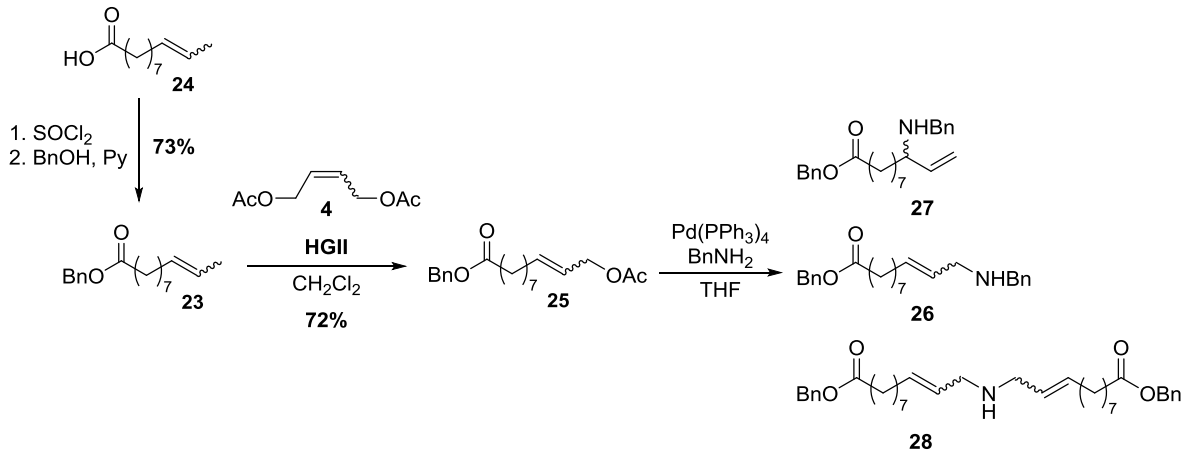
2.2.7 Towards 11-aminoundecanoic acid 1

To access the free amino acid monomer **1** required for condensation homopolymerization, the previously synthesised amino ester **11** would require an additional ester hydrolysis step. It was thought that this extra step could be avoided by using a benzyl ester, which could be removed during the palladium hydroxide on carbon catalysed hydrogenation/hydrogenolysis step (Scheme 18).



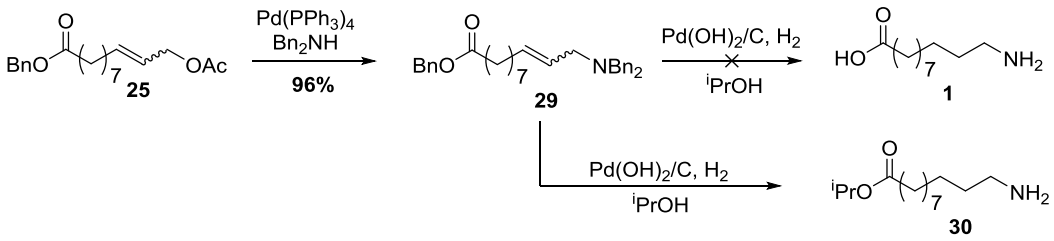
Scheme 18: A new route to 1.

Reaction of benzyl undec-9-enoate **23** (from the benzyl esterification of undec-9-enoic acid **24** in 73% yield) with 1,4-diacetoxyl-but-2-ene **4** in the presence of Hoveyda-Grubbs second generation catalyst (**HGII**) gave the desired benzylic acetate **25** in good yield (72%, Scheme 19).



Scheme 19: Synthesis of 26.

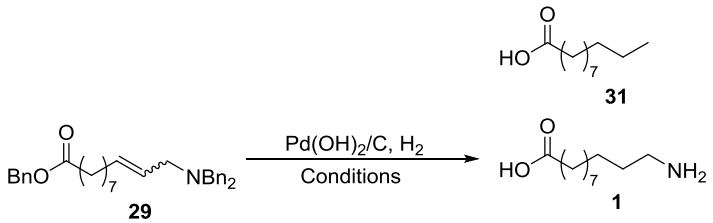
Palladium catalysed allylic addition using benzylamine to benzylic acetate **25** gave the expected mixture of amino esters **26-28** in a 15:1:9 ratio respectively, as estimated by ^{1}H n.m.r. spectroscopy. This addition ratio was analogous to that observed for the corresponding methyl ester reported in Section 2.2.4. Attention was thus diverted to the use of dibenzylamine to increase the selectivity for the linear product (Scheme 20).



Scheme 20: Palladium-catalysed dibenzylamine addition and hydrogenolysis.

As expected, the palladium catalysed allylic amine addition with one equivalent of dibenzylamine gave the linear amino ester **29** in excellent isolated yield (96%). Hydrogenation/hydrogenolysis was performed on **29** using Pearlman's catalyst in isopropanol in an attempt to generate the free amino acid **1**. Disappointingly, the major isolated product was the isopropyl amino ester **30**. This was presumably due to concomitant transesterification of **29** into the isopropyl ester, preventing the ester hydrogenolysis and hence formation of the desired free acid **1**. To combat this unwanted side reaction, further investigation into the reaction conditions was performed (Table 3).

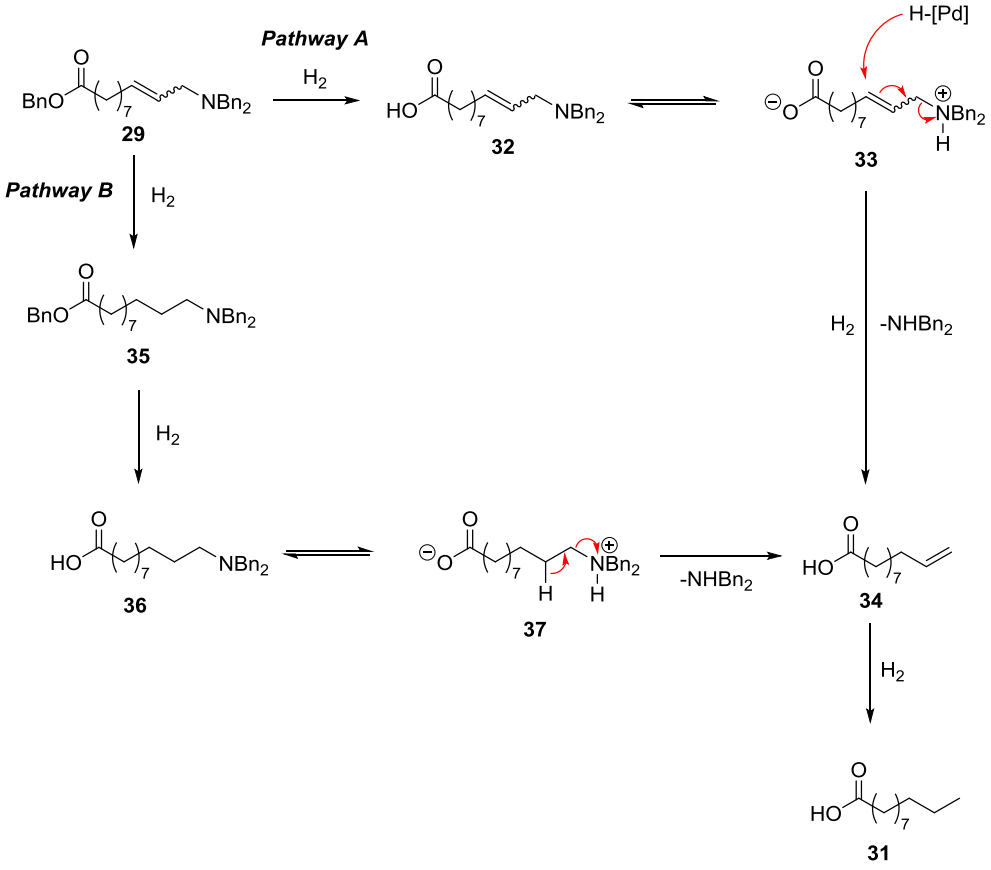
Table 3: Optimisation of hydrogenolysis conditions.



Entry	Solvent	Conditions	1	31
1	THF	90psi, 60 °C	22%	78%[a]
2	MeOH:H_2O (4:1)	90psi, 60 °C	34%	66%[a]
3	^{i}PrOH:H_2O (4:1)	90psi, 60 °C	43%	57%[a]

[a] Estimated by ^{1}H n.m.r. spectroscopy.

A simple solution to avoid the unwanted transesterification was to perform the hydrogenation/hydrogenolysis reaction in a non-alcoholic solvent (e.g. tetrahydrofuran or toluene). Tetrahydrofuran was chosen as it is reported to be a suitable solvent for the hydrogenolysis of benzylic amines using Pearlman's catalyst.[26] Using tetrahydrofuran as the reaction solvent avoided the unwanted transesterification, however the major product of the reaction was not the desired PA-11 monomer **1** but undecanoic acid **31** (Table 3, Entry 1). The dibenzylamine elimination was not observed in appreciable amounts when performing the hydrogenation on the corresponding methyl ester **12** and therefore must be promoted by the presence of a free acid group. It was proposed that the undecanoic acid **31** could be generated by two possible pathways which are both facilitated by the presence of a free acid group (Scheme 21).



Scheme 21: Mechanism for hydrogenolysis of 29.

Pathway **A** firstly involves the hydrogenolysis of the *O*-benzyl ester of **29** to give the amino acid **32**. Intramolecular proton transfer to form zwitterion **33** would enhance

SN2' hydride promoted elimination of dibenzylamine to give alkenyl acid **34**. Palladium catalysed hydrogenation of this acid then leads to undecanoic acid **31**. Alternatively, pathway **B** firstly involves the hydrogenation of the alkene to give **35** followed by hydrogenolysis of the resultant *O*-benzyl ester to give amino acid **36.** Intramolecular proton transfer then generates zwitterion **37** ready for E2 elimination and transformation into the unsaturated acid **34.** Hydrogenation then leads to the observed undecanoic acid **31**. This by-product **31** was not detected when isopropanol was employed as the solvent, thus it was concluded that the rate of dibenzylamine elimination was much greater in tetrahydrofuran. The choice was made to use the protic solvent methanol, but diluted to a 4:1 mixture with water to slow unwanted transesterification (Table 3, Entry 2). This was successful in demoting the unwanted transesterification but only gave the desired PA-11 monomer **1** in a poor 34% isolated yield, where a significant amount of deaminated product **31** was still detected by ^{1}H n.m.r spectroscopy. By switching to an isopropanol water mixture (4:1), the yield of the PA-11 monomer was improved to 42% but a significant amount of the deaminated byproduct **31** was still detected by ^{1}H n.m.r. spectroscopy (Table 3, Entry 3).

2.2.8 Conclusion

Using a mild, multi-catalytic sequence, the PA-11 precursor, methyl 11-aminoundecanoate **11**, was prepared in a three step sequence from renewable, canola oil-derived methyl 11-undecanoate **1** in 69% yield or 58% yield without the use of column chromatography. The corresponding unsaturated amino ester, methyl 11-aminoundec-9-enoate **21** was synthesised in 53% overall yield *via* an analogous sequence, but required the use of column chromatography. These methods provides a viable alternative to the current synthesis, without the economic fluctuations and harvesting hazards associated with using castor oil as a feedstock.

2.3 Experimental

2.3.1 General Experimental

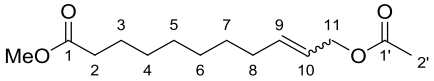
Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), EtOAc (EtOAc), diethyl ether (Et_2O), hexane (C_6H_{14}), methanol (MeOH), dimethylsulfoxide (DMSO) and toluene (PhMe) were used as supplied by Merck. Benzene (C_6H_6) was supplied by Sigma-Aldrich®. Deuterated solvents ($CDCl_3$) were used as supplied by Merck. Anhydrous Et_2O and THF were stored over sodium (Na) wire then distilled from Na benzophenone prior to use. Anhydrous CH_2Cl_2 was dried over $CaCl_2$ and distilled from CaH_2 prior to use. Anhydrous PhMe and C_6H_6 were stored over Na wire and distilled prior to use. All solvents and reagents used in metal-catalysed reactions were degassed with nitrogen prior to use.

(1,3-Dimesitylimidazolidin-2-ylidene)(2-isopropoxybenzylidene)ruthenium(II) dichloride (2nd generation Hoveyda-Grubbs catalyst **HGII**), was used as supplied by Sigma-Aldrich®. Tetrakis(triphenylphosphine)palladium(0) (palladium tetrakis) was used as supplied by Strem Chemicals. *cis*-1,4-Diacetoxy-but-2-ene **4** (95%) was purchased from Sigma-Aldrich® and was deoxygenated by the freeze-pump-thaw method prior to use. Methyl undec-9-enoate **3** was prepared using a method described by Patel *et al.*.[13,14] All other chemicals were purchased from Sigma-Aldrich® and used without further purification unless stated otherwise. Melting points (m.p.) were measured on a Stuart Scientific SMP 3 melting point apparatus. The ^1H and ^{13}C nuclear magnetic resonance (n.m.r.) spectra were recorded using a Brüker DPX 200 MHz spectrometer (200 MHz for ^1H, 50 MHz for ^{13}C), Brüker DPX 300 MHz spectrometer (300 MHz for ^1H, 75 MHz for ^{13}C) or a Brüker DRX 400 MHz spectrometer (400 MHz for ^1H n.m.r., 100 MHz for ^{13}C n.m.r.), as solutions in deuterated solvents as specified. Chemical shifts (δ) are measured in parts per million (ppm) and are reported to the residual solvent peak. Multiplicities are denoted as singlet (s), doublet (d), triplet (t), multiplet (m) or prefixed broad (b) or as a combination where necessary. The ^{13}C n.m.r. spectra were recorded using a JMOD pulse sequence or proton decoupled pulse sequence unless stated otherwise. Each resonance is assigned according to the following

convention: chemical shift (multiplicity, observed coupling constants (*J* = Hz), integration, and proton assignment). Low-resolution electrospray ionisation (LR-ESI) mass spectra were recorded on a Micromass Platform II API QMS-quadrupole electrospray mass spectrometer as specified. $[M]^+$ denotes the molecular ion. High-resolution electrospray (HR-MS) were recorded on a Brüker BioApex 47e Fourier Transform mass spectrometer and were recorded as specified. Analytical thin layer chromatography was performed on plastic plates with 0.25mm of silica gel (PolyGram SIL G/UV_{254}). Flash chromatography was performed using Merck silica gel 60, 0.040-0.062 mm (230-400 mesh). Visualisation of the molecules was achieved under 254 nm of ultraviolet radiation or through the use of chemical stains including vanillin, ninhydrin, permanganate and iodine. Infrared spectra (IR) were recorded on a Perkin-Elmer Spectrum RX1 Fourier Transform infrared spectrometer as either a neat liquid film between sodium chloride plates (neat), or in solid state as potassium bromide (KBr) discs. IR absorbance (ν_{max}) are reported in wave numbers (cm^{-1}) with the relative intensities expressed as: strong (s), medium (m), weak (w) or prefixed broad (b).

2.3.2 Experimental procedures

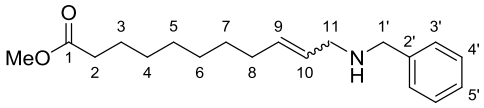
Synthesis of (E/Z)-methyl 11-acetoxyundec-9-enoate 5



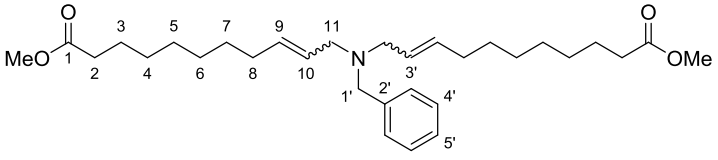
A Schlenk tube was loaded with methyl undec-9-enoate **1** (1.00 g, 5.04 mmol), 1,4-diacetoxybut-2-ene **4** (8.04 mL, 50.4 mmol), **HGII** catalyst (32 mg, 50 µmol) and CH_2Cl_2 (3 mL). The reaction mixture was stirred under an inert atmosphere at room temperature for 4 hours and then terminated by addition of ethyl vinyl ether (2 drops). The solvent was then removed *in vacuo* and the crude residue was purified by column chromatography (SiO_2; EtOAc: hexane, 1:5). The desired product **5** was isolated as a colourless oil (1.17 g, 90%).

A second reaction, performed under identical conditions, was purified using flash distillation (0.3 mmHg, 90-100 °C). The resultant residue was then filtered through a short pad of silica (EtOAc: hexane, 1:5) to obtain **5** as a colourless oil (1.02 g, 80%) in a mixture of the geometric isomers (*Z*:*E*, 1:5) . Spectral data were consistent with those reported in the literature.[18] υ_{max} (neat): 2930s, 2856s, 1750s, 1437s, cm^{-1}. ^{1}H n.m.r. (400 MHz, $CDCl_3$), (*E*)-isomer: δ 5.79-5.70 (m, 1H, H10), 5.66-5.47 (m, 1H, H9), 4.50 (dd, *J* = 6.4, 0.8 Hz, 1H, H11, 3.65 (s, 3H, OMe), 2.29 (t, *J* = 7.6 Hz, 2H, H2), 2.09-2.00 (m, 2H, H8), 2.04 (s, 3H, $COCH_3$), 1.64-1.56 (p, *J* = 7.2 Hz, 2H, H3), 1.41-1.24 (m, 8H, H4-H7). ^{1}H n.m.r. (400 MHz, $CDCl_3$), (*Z*)-isomer: δ 5.79-5.70 (m, 1H, H10), 5.66-5.47 (m, 1H, H9), 4.60 (d, *J* = 6.8 Hz, 1H, H11, 3.65 (s, 3H, OMe), 2.29 (t, *J* = 7.6 Hz, 2H, H2), 2.09-2.00 (m, 2H, H8), 2.04 (s, 3H, COMe), 1.64-1.56 (p, *J* = 7.2 Hz, 2H, H3), 1.41-1.24 (m, 8H, H4-H7). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 174.5 & 171.1 (C1 & C1′), 136.8 (C10), 124.0 (C9), 65.5 (C11), 51.7 (OMe), 34.0, 32.3, 29.3, 29.3, 29.2, 29.0, 25.1, 21.3 ($COCH_3$). LR-MS (ESI+, MeOH): *m/z* 279.2 $(M+Na)^+$. $C_{14}H_{24}O_4Na^+$ requires 279.2.

Synthesis of (E/Z)-methyl 11-(benzylamino)undec-9-enoate 6

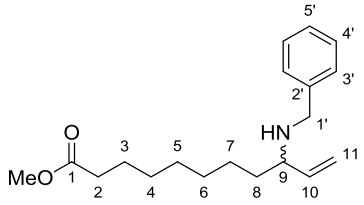


The reaction was performed using a procedure described by Trost and Keinan.[23] Benzylamine (175 µL, 1.56 mmol) was added to a stirred solution of (E/Z)-methyl 11-acetoxyundec-9-enoate **5** (205 mg, 0.80 mmol) and tetrakis(triphenylphosphine)palladium(0) (92 mg, 80 µmol) in THF (3.0 mL). The reaction was heated at reflux for 3 hours before being cooled and concentrated in vacuo. The resulting oil was purified by column chromatography (SiO2; EtOAc: hexane: triethylamine, 1:7:0.4), to give the disubstituted tertiary amine **9** as a colourless oil (57 mg, 28%).



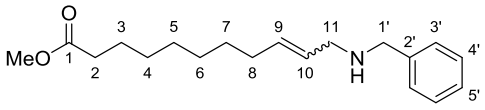
υ_{max} (neat):2927s, 2855s, 1738s, 1455s, 1436s, 1362m, 1263s, 1197s, 1172s, 971m cm^{-1}. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.34-7.18 (m, 5H, H3′-H5′), 5.63-5.41 (m, 4H, H9 & H10), 3.65 (s, 6H, 2×OCH_3), 3.54 (s, 2H, H1′), 3.00 (d, *J* = 5.7 Hz, 4H, H11), 2.29 (t, *J* = 7.5 Hz, 4H, H2), 2.07-1.95 (m, 4H, H8), 1.61 (p, *J* = 6.9 Hz, 4H, H3), 1.44-1.19 (m, 16H, H4-H7). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 174.4 (C1), 139.9, 134.2, 129.1, 128.2, 127.3, 126.8, 57.4, 55.6, 51.1, 34.2, 32.5, 29.4, 29.2, 29.2, 29.1, 25.1. HR-MS (ESI, +ve, MeOH): *m/z* 500.3736 $(M+H)^+$. $C_{31}H_{50}NO_4^+$ requires 500.3734.

Further elution (SiO_2; EtOAc: hexane; 1:3) gave the branched regioisomer **8** as a colourless oil (29 mg, 12%).



υ_{max} (neat):, 2928s, 2854s, 1739s, 1452s, 1260m, 1197m, 1170m, 1106m, 1027m cm^{-1}. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.34-7.20 (m, 5H, H3′-H5′), 5.67–5.56 (m, 1H, H10), 5.16–5.07 (m, 2H, H11), 3.82 (d, *J* = 13.2 Hz, 1H, H1′), 3.66 (s, 3H, OCH_3), 3.64 (d, *J* = 13.2 Hz, 1H, H1′), 3.00 (q, *J* = 7.8 Hz, 1H, H9), 2.29 (t, *J* = 7.5 Hz, 2H, H2), 1.59 (p, *J* = 7.3 Hz, 2H, H3), 1.55-1.19 (m, 10H, H4-H8,) NH not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (C1), 141.5, 140.9, 128.5, 128.3, 126.9, 116.1 (C11), 61.4, 51.6, 51.4, 35.8, 34.2, 29.6, 29.3, 29.2, 25.9, 25.1. HRMS (ESI+, MeOH): *m/z* 304.2277 $(M+H)^+$. $C_{19}H_{30}NO_2^+$ requires 304.2271.

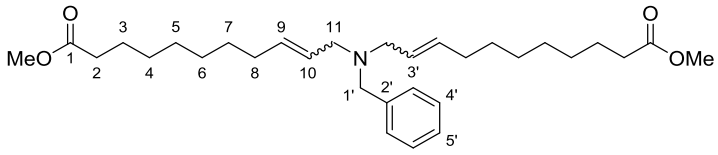
Further elution (SiO_2; EtOAc, 100%) gave the amino ester **6** as a colourless oil (70 mg, 29%).



υ_{max} (neat): 2929s, 2855s, 1720s, 1670m, 1437s, 1371s, 1247s, 911s cm^{-1}. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.37–7.21 (m, 5H, H3′-H5′), 5.64–5.48 (m, 2H, H9 & H10), 3.77 (s, 2H, H1′), 3.66 (s, 3H, OMe), 3.21 (d, *J* = 5.2 Hz, 2H, H11), 2.29 (t, *J* = 7.5 Hz, 2H,

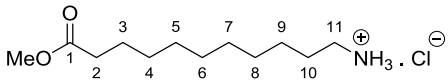
H2), 1.61 (p, *J* = 7.2 Hz, 2H, H3), 1.43–1.21 (m, 10H, H4-H8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (C1), 140.5, 133.1, 128.5, 128.3, 128.3, 127.0, 53.4, 51.6, 51.3, 34.2, 32.5, 29.4, 29.4, 29.2, 29.1, 25.1. HRMS (ESI+, MeOH): *m/z* 304.2273 $(M+H)^+$. $C_{19}H_{30}NO_2^+$ requires 304.2271.

Synthesis of (E/Z)-dimethyl 11,11'-(benzylamino)bis(undec-9-enoate) 9



Benzylamine (23 µL, 0.21 mmol) in THF (1.0 mL) was added dropwise over a period of 10 minutes to a solution of (*E/Z*)-methyl 11-acetoxyundec-9-enoate **5** (105 mg, 0.41 mmol) and tetrakis(triphenylphosphine)palladium(0) (47 mg, 41 µmol) in THF (2.0 mL) at reflux. The reaction was heated at reflux for a further hour before being cooled and concentrated *in vacuo*. A ^{1}H n.m.r. spectrum of the crude residue revealed a mixture of the desired disubstituted product **9** and the branched product **8** in a 95:5 ratio. The resulting oil was purified by column chromatography (SiO_2; EtOAc: hexane: triethylamine, 1:5:0.3) to give the title compound **9** as a colourless oil (92 mg, 90%). Spectral data for **8** and **9** were consistent with those previously reported.

Synthesis of methyl 11-aminoundecanoate hydrochloride salt 11

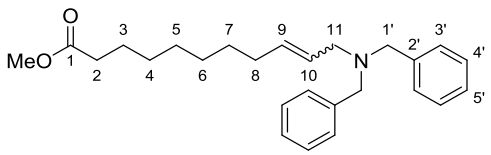


A Fischer-Porter tube was loaded with methyl 11-(benzylamino)undec-9-enoate **6** (170 mg, 0.33 mmol), palladium hydroxide on carbon 20% w/w (17 mg) and methanol (2 mL). The headspace of the vessel was purged with argon over three cycles, charged with hydrogen (60 psi) and heated at 60 °C for 18 hours. The hydrogen was then vented from the vessel and the reaction mixture was filtered through a short plug of diatomaceous earth and concentrated *in vacuo*. The residue was treated with EtOAc saturated with HCl gas (5 mL) to generate the hydrochloride salt. The salt was

precipitated from the reaction mixture by addition of CH_2Cl_2:hexane (1:5) and collected by centrifugation to give the title compound **11** as a hygroscopic, off-white solid (99 mg, 71%).

Alternatively, a Fischer-Porter tube was loaded with methyl 11-(dibenzylamino)undec-9-enoate **12** (100 mg, 0.25 mmol), palladium hydroxide on carbon 20% w/w (20 mg) and methanol (3 mL). The headspace of the vessel was purged with argon over three cycles, charged with hydrogen (90 psi) and heated at 60 °C for 18 hours. The hydrogen was then vented from the vessel and the reaction mixture was filtered through filter paper and concentrated *in vacuo*. The reside was treated with diethyl ether saturated with HCl gas (2 mL) to generate the hydrochloride salt. The salt was precipitated from the reaction mixture by addition of CH_2Cl_2:hexane (1:5) and collected by centrifugation to give the title compound **11** as a hygroscopic off-white solid (49 mg, 77%), m.p. 146.0-148.9 °C. υ_{max} (neat): 3415m, 2922s, 2851m,, 1735s, 1617m, 1569m, 1517m, 1468m, 1437m, 1137m cm^{-1}. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 8.26 (bs, 3H, NH_3^+), 3.66 (s, 3H, Me), 2.97 (t, *J* = 7.6 Hz, 2H, H11), 2.30 (t, *J* = 7.6Hz, 2H, H2), 1.76 (p, *J* = 7.5 Hz, 2H, H10), 1.61 (p, *J* = 7.2 Hz, 2H, H3), 1.44-1.23 (m, 12H, H4-H9). ^{13}C n.m.r. (100 MHz, $CDCl_3$): 174.4 (C1), 51.6 (OCH_3), 40.1 (C11), 34.3, 29.4, 29.4, 29.3, 29.3, 29.1, 27.8, 26.6, 25.1. HRMS (ESI+, MeOH): *m/z* 216.1960 $(M\text{-}HCl+H)^+$. $C_{12}H_{24}NO_2^+$ requires 216.1958.

Synthesis of (E/Z)-methyl 11-(dibenzylamino)undec-9-enoate 12



Method A:

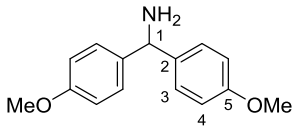
Dibenzylamine (83 µL, 0.43 mmol) was added to a stirred solution of (*E/Z*)-methyl 11-acetoxyundec-9-enoate **5** (110 mg, 0.43 mmol) and tetrakis(triphenylphosphine)palladium(0) (50 mg, 43 µmol) in THF (2.2 mL). The reaction was heated at reflux for 1 hour before being cooled and concentrated *in vacuo*.

^{1}H n.m.r. analysis of the crude residue revealed a mixture of the required product **12** and the branched regioisomer **13** in a 95:5 ratio. Attempted purification of the resulting oil by column chromatography (SiO_2; EtOAc: hexane, 1:3) again supplied the titled compound **12** contaminated with 5% **13** as a light yellow oil (171 mg).

Method B:

Dibenzylamine (280 µL, 1.45 mmol) was added to a stirred solution of (*E/Z*)-methyl 11-acetoxyundec-9-enoate **5** (370 mg, 1.45 mmol) and tetrakis(triphenylphosphine)palladium(0) (167 mg, 145 µmol) in THF (3.0 mL). The reaction was heated at reflux for 1 hour, cooled to room temperature, diluted with hexane (6.0 mL) and filtered through a short pad of silica using a hexane eluent. The filtrate was concentrated *in vacuo* to give the title compound **12** together with 5% **13** as a light yellow oil (569 mg, 94%). υ_{max} (neat): 2929m, 1741s, 1454m, 1439m, 1365m, 1201m, 1175m, 974m, 914m cm^{-1}. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.0 Hz, 4H, H3′), 7.32 (t, *J* = 7.2 Hz, 4H, H4′), 7.26-7.20 (m, 2H, H5′), 5.64-5.44 (m, 2H, H9 & H10), 3.67 (s, 3H, OCH_3), 3.57 (s, 4H, H1′), 3.01 (d, *J* = 5.8 Hz, 2H, H11), 2.29 (t, *J* = 7.6 Hz, 2H, H2), 2.09-1.97 (m, 2H, H8), 1.61 (p, *J* = 6.8 Hz, 2H, H3), 1.42-1.22 (m, 8H, H4-H7). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 174.6 (C1), 134.4, 134.4, 129.3, 128.4, 127.3, 126.9, 57.5, 55.7, 51.7, 34.3, 32.7, 29.5, 29.3, 29.3, 29.2, 25.2. HRMS (ESI+, MeOH): *m/z* 394.2738 $(M+H)^+$. $C_{26}H_{36}NO_2^+$ requires 394.2741.

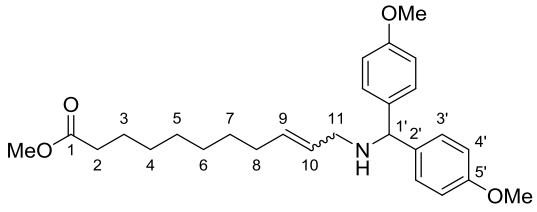
Synthesis of bis(4-methoxyphenyl)methylamine 16



Thionyl chloride (6.8 mL, 93 mmol) was added dropwise to a solution of bis(4-methoxyphenyl)methanol **17** (2.6 g, 9.3 mmol) in dry CH_2Cl_2 (15 mL) under nitrogen. The reaction mixture wassonicated for two hours at room temperature and then concentrated *in vacuo*. Excess thionyl chloride was removed by repeated addition of CH_2Cl_2 (3×20 mL), followed by solvent evaporation. The crude residue was dissolved

in diethyl ether (40 mL) and anhydrous ammonia was bubbled through the solution for 30 mins. The gas source was removed and the solution was stirred at room temperature for a further 16 hours. The reaction mixture was then diluted with saturated $NaHCO_3$ (40 mL) and the phases were separated. The aqueous layer was further extracted with EtOAc (3×40 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the titled compound **16** as a viscous oil (2.3 g, quant.) which was used in subsequent reactions without further purification. Spectral data were consistent with those reported in the literature.[27] ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 7.23–7.12 (m, 4H, H4), 6.80–6.73 (m, 4H, H3), 5.06 (s, 1H, H1), 3.71 (s, 6H, OMe), 1.68 (bs, 2H, NH_2).

Synthesis of (E/Z)-methyl 11-((bis(4-methoxyphenyl)methyl)amino)-undec-9-enoate 19

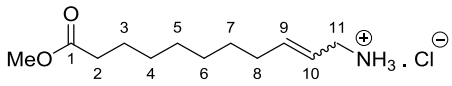


4,4'-Dimethoxybenzhydrylamine (378 mg, 1.56 mmol) was added to a stirred solution of (*E/Z*)-methyl 11-acetoxyundec-9-enoate **5** (0.20 g, 0.78 mmol) and tetrakis(triphenylphosphine)palladium(0) (70 mg, 63 µmol) in THF (2.2 mL). The reaction mixture was stirred at room temperature for 16 hours before being concentrated *in vacuo*. ^{1}H n.m.r. analysis of the crude residue revealed a mixture of the desired product **19** and branched regioisomer **20** in a 80:20 ratio.* The crude product was purified by column chromatography (SiO_2; EtOAc: hexane: MeOH/NH_3 1:8:0.1) to give the titled compound **19** as a pale yellow oil (201 mg, 59%). υ_{max} (neat): 2997s, 2930s, 2845s, 1734s, 1673m, 1609s, 1584m, 1509s, 1463s, 1441s, 1301s, 1174s cm^{-1}. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.8 Hz, 4H, H4′), 6.83 (d, *J* = 8.8 Hz, 4H, H3′), 5.58-5.46 (m, 2H, H9 & H10), 4.77 (s, 1H, H1′), 3.77 (s, 6H, 2×ArOMe), 3.66 (s, 3H, OMe),

*Determined from ratios of diagnostic olefinic peaks. ^{1}H n.m.r. **20** (300 MHz, $CDCl_3$): δ 5.14 (m, 2H, $=CH_2$).

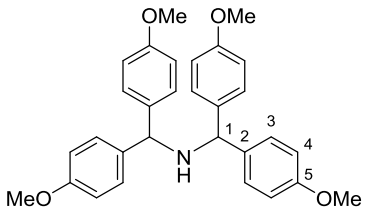
3.11 (d, *J* = 24.0 Hz, 2H, H11), 2.30 (t, *J* = 7.6 Hz, 2H, H2), 2.02-1.97 (m, 2H, H8), 1.64-1.57 & 1.39-1.23 (m, 10H, H3-H7). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 174.5 (C1), 158.7, 136.8, 132.9, 128.6, 128.5, 114.0, 65.4 (C1′), 55.4 (2×ArOMe), 51.6 (OMe), 50.0 (C11), 34.3, 32.6, 29.4, 29.3, 29.3, 29.2, 25.1 (C3-C7). HRMS (ESI+, MeOH): *m/z* 440.2796 $(M+H)^+$. $C_{27}H_{38}NO_4^+$ requires 440.2795. $C_{27}H_{37}NO_4$ requires C, 73.8; H, 8.5; N 3.2%; found C, 73.0; H, 8.5; N, 3.1%.

Synthesis of (E/Z)-methyl 11-aminoundec-9-enoate hydrochloride salt 21



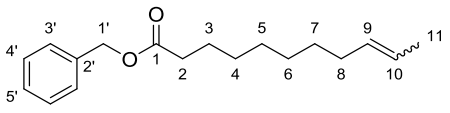
Methyl 11-((bis(4-methoxyphenyl)methyl)amino)undec-9-enoate **19** (75 mg, 0.17 mmol) was dissolved in 88% formic acid (2 mL) and heated at 80 °C for 1 hour. The reaction mixture was then concentrated *in vacuo* and basified with a saturated Na_2CO_3 solution (20 mL). The mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was further extracted with Et_2O (3×20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was treated with EtOAc saturated with HCl gas (5 mL), precipitated (CH_2Cl_2: hexane 1:10) and collected by centrifugation to give a mixture of geometric isomers of the title compound **21** as a hygroscopic, off-white solid (42 mg, 99%), m.p. 76.5-78.8 °C. υ_{max} (neat): 3349m, 2921s, 2851s, 1734s, 1464m, 1378m, 1258m, 1214w, 1173m, 1129w, 968m cm^{-1}. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 8.33 (bs, 3H, NH_3^+), 5.89 (dt, *J* = 14.8 Hz, 6.8Hz, 1H, H10), 5.68-5.52 (m, 1H, H9), 3.66 (s, 3H, OMe), 3.55 (bs, 2H, H11), 2.30 (t, *J* = 7.6 Hz, 2H, H2), 2.12-2.00 (m, 2H, H8), 1.61 (p, *J* = 6.8 Hz, 2H, H3), 1.43-1.21 (m, 8H, H4-H7). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ.174.5 (C1), 139.7 (C9), 120.7 (C10), 51.6 (OMe), 41.8 (C11), 34.2, 32.4, 29.2, 29.2, 29.1, 28.8, 25.1. HRMS (ESI+, MeOH): *m/z* 214.1798 $(M-HCl+H)^+$. $C_{12}H_{24}NO_2^+$ requires 214.1802.

Synthesis of di(bis(4-methoxyphenyl))methylamine 22



Thionyl chloride (2.3 mL, 31 mmol) was added dropwise to a solution of bis(4-methoxyphenyl)methanol **17** (0.67 g, 3.1 mmol) in dry CH_2Cl_2 (15 mL) under nitrogen. The reaction mixture was sonicated for 2 hours at room temperature and then concentrated *in vacuo*. The crude residue was dissolved in CH_2Cl_2 (10 mL) and ammonium chloride was added (83 mg, 1.6 mmol) followed by dropwise addition of a solution containing triethylamine (1.1 mL, 7.8 mmol) and CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 16 hours, then diluted with a saturated $NaHCO_3$ solution (20 mL). The phases were separated and the aqueous layer was further extracted with CH_2Cl_2 (3×10 mL). The combined organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2; EtOAc: hexane, 1:5) to give the title compound **22** as a yellow oil (694 mg, quant.). ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 7.22–7.10 (m, 8H, H4), 6.86–6.67 (m, 8H, H3), 4.54 (s, 2H, H1), 3.70 (s, 12H, OMe). ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 158.7 (C5), 136.6 (C2), 128.7 (C3), 113.90 (C4), 62.4 (OMe), 55.4 (C1). HRMS (ESI+, MeOH), fragmented ion: *m/z* 227.1058 $(M-[C_{15}H_{17}NO_2^-])^+$. $C_{15}H_{15}O_2^+$ requires 227.1067.

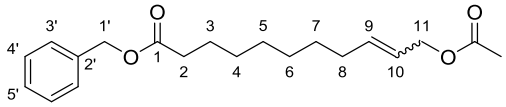
Synthesis of (E/Z)-Benzyl undec-9-enoate 23



Thionyl chloride (8.96 mL, 123 mmol) was added dropwise to a stirred solution of undec-9-enoic acid **24** (1.13 g, 6.1 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen. The reaction mixture was then sonicated for 2 hours at room temperature before concentration *in vacuo*. The residual thionyl chloride was removed by azeotropic

distillation with toluene (2×10 mL) to give the acid chloride as a light yellow oil υ_{max} (neat): 2938s, 2866s, 1800s, 1458m, 1404m, 1374m, 965m, 723m, 679w. The crude product was dissolved in CH_2Cl_2 (15mL), cooled to 0 °C and pyridine (550 µL, 6.8 mmol) was added, followed by dropwise addition of benzyl alcohol (704 µL, 6.8 mmol). The reaction mixture was stirred at room temperature for 16 hours, then diluted with water (15 mL). The phases were separated and the aqueous layer was further extracted with CH_2Cl_2 (3×20 mL). The combined organic extract was washed with 1 M HCl (3×20 mL), saturated $NaHCO_3$ (3×20mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; EtOAc: hexane: 1:4) to give (*E/Z*)-benzyl undec-9-enoate **23** as light yellow oil (1.23 g, 73%). ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 7.41-7.29 (m, 5H, H3′-H5′), 5.47-5.37 (m, 2H, H9 & H10), 5.13 (s, 2H, H1′), 2.36 (t, *J* = 7.5 Hz, 2H, H2), 2.17-1.89 (m, 2H, H8), 1.80-1.51 (m, 3H, H11), 1.49-1.25 (m, 10H, H3-H7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7 (C1), 136.3, 131.7, 130.9, 128.6, 128.3, 128.2 124.7, 123.8, 66.1 (C1′), 34.4, 32.6, 29.6, 29.6, 29.2, 29.2, 29.2, 29.2, 29.1, 26.9, 25.1, 18.0 (C11). HRMS (ESI+, MeOH): *m/z* 297.1822 $(M+Na)^+$. $C_{18}H_{26}O_2Na^+$ requires 297.1825.

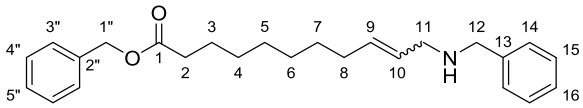
Synthesis of (E/Z)-benzyl 11-acetoxyundec-9-enoate 25



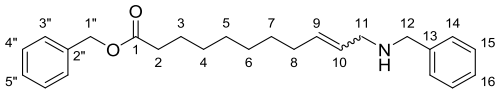
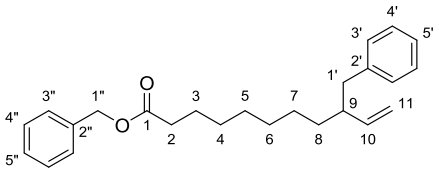
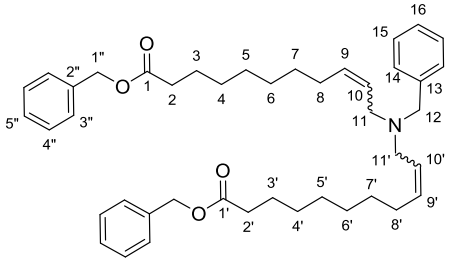
A Schlenk tube was loaded with benzyl undec-9-enoate **23** (400 mg, 1.46 mmol), 1,4-diacetoxybut-2-ene **4** (2.33 mL, 14.6 mmol), **HGII** catalyst (9.0 mg, 15 µmol) and CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 16 hr. The metathesis reaction was exposed to oxygen and flash distillation (0.3 mmHg, 90-100 °C) was employed to recover excess 1,4-diacetoxybut-2-ene **4**. The resulting residue was purified by flash chromatography (EtOAc: hexane; 1:15) to obtain the title compound **25**, in a mixture of geometric isomers (*Z*:*E*, 1:4), as a colourless oil (351 mg, 72%). Spectral data were consistent with those reported in the literature.[14] ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 7.50–7.17 (m, 5H, H3′-H5′), 5.85–5.44 (m, 2H, H9 & H10), 5.11 (s, 2H, H1′), 4.61 (d, *J* = 6.6 Hz, 2H, H11 (*Z*-isomer)), 4.50 (d, *J* =

6.4 Hz, 2H, H11 (*E*-isomer)), 2.34 (t, *J* = 7.5 Hz, 2H, H2), 2.15–1.97 (m, 2H, H8), 2.04 (s, 3H, CO*C*H$_3$), 1.64 (p, *J* = 7.1 Hz, 2H, H3), 1.47–1.12 (m, 8H, H4-H7). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 173.6 & 170.8 (C1, *C*OCH$_3$), 136.5, 135.4, 128.6, 128.2, 123.9, 66.1, 65.3, 34.3, 32.2, 29.1, 29.0, 28.8, 25.0, 21.0 (CO*C*H$_3$). HRMS (ESI+, MeOH): *m/z* 355.1877 $(M+Na)^+$. $C_{20}H_{28}O_4Na^+$ requires 255.1880.

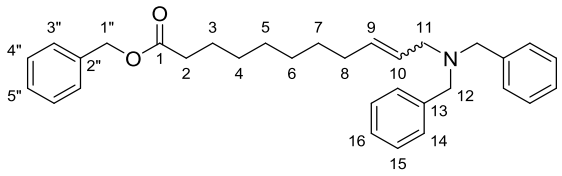
Attempted synthesis of (E/Z)-benzyl 11-(benzylamino)undec-9-enoate 26



Benzylamine (95 µL, 0.87 mmol) was added to a stirred solution of (*E/Z*)-benzyl 11-acetoxyundec-9-enoate **25** (0.15 g, 0.44 mmol) and tetrakis (triphenylphosphine)palladium(0) (50 mg, 43 µmol) in THF (5 mL). The reaction was heated at reflux for 16 hours, before being cooled to room temperature and concentrated *in vacuo*. ^{1}H n.m.r. analysis of the residue revealed a mixture of **26**, **27** & **28** in a 20:1:10 ratio.

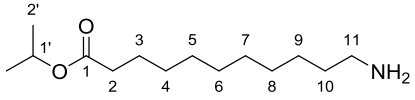
Compound	Diagnostic proton resonance(s)
(*E/Z*)-Benzyl 11-(benzylamino)undec-9-enoate **26** 	^{1}H n.m.r. (400MHz, $CDCl_3$): δ 3.80 (s, 2H, H12), 3.23 (d, *J* = 5.7 Hz, 2H, H11).
(*E/Z*)-Benzyl 11-(benzylamino)undec-9-enoate **27** 	^{1}H n.m.r. (400MHz, $CDCl_3$): δ 4.98-4.91 (m, 2H, H11).
(*E/Z*)-Dibenzyl 11,11'-(benzylamino)bis(undec-9-enoate) **28** 	^{1}H n.m.r. (400MHz, $CDCl_3$): δ 3.55 (s, 2H, H12), 3.23 (d, *J* = 5.7 Hz, 2H, H11).

Synthesis of (E/Z)-benzyl 11-(dibenzylamino)undec-9-enoate 29



Dibenzylamine (82 µL, 0.43 mmol) was added to a stirred solution of (*E/Z*)-benzyl 11-acetoxyundec-9-enoate **25** (140 mg, 0.42 mmol) and tetrakis (triphenylphosphine)-palladium(0) (50 mg, 43 µmol) in THF (5 mL). The reaction mixture was heated at reflux for 1 hour before being cooled and concentrated *in vacuo*. ^{1}H n.m.r. analysis of the crude residue revealed a mixture of **29** and branched regioisomer in a 97:3 ratio. The resulting residue was purified by flash chromatography (SiO_2; EtOAc: hexane; 1:7) to afford the desired product **29** as a light yellow oil (189 mg, 96%). ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.32-7.10 (m, 15H, H3″-H5″ & H15-H15), 5.54–5.37 (m, 2H, H9 & H10), 5.04-5.01 (m, 2H, H1″), 3.47 (s, 4H, H12), 2.91 (d, *J* = 5.7 Hz, 2H, H11), 2.30-2.22 (m, 2H, H2), 2.02-1.88 (m, 2H, H8), 1.63-1.48 (m, 2H, H3), 1.33-1.14 (m, 8H, H4-H7). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 172.6 (C1), 138.8, 135.1, 133.1, 127.8, 127.5, 127.1, 127.1, 126.1, 125.7, 65.1 (C1”), 56.6 (C12), 54.5 (C11), 33.3, 31.4, 28.2, 28.0, 27.9, 27.7, 23.9, 23.8. HRMS (ESI+, MeOH): *m/z* 470.3053 $(M+H)^+$. $C_{32}H_{40}NO_2^+$ requires 470.3054.

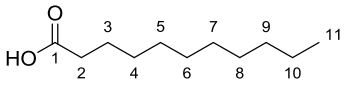
Synthesis of isopropyl 11-aminoundecanoate 30



A Fischer-Porter tube was loaded with (*E/Z*)-benzyl 11-(dibenzylamino)undec-9-enoate **29** (0.10 mg, 0.21 mmol), palladium hydroxide on carbon 20% w/w (20 mg) and isopropanol (2 mL). The headspace of the vessel was purged with argon over three cycles, charged with hydrogen (90 psi) and heated at 60 °C for 18 hours. The hydrogen was then vented from the vessel and the reaction mixture was filtered through a short plug of diatomaceous earth and concentrated *in vacuo*. The product was precipitated

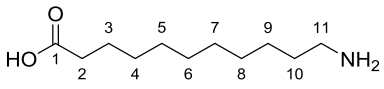
with acetone and collected by filtration to give the title compound **30** as a colourless semi-solid (28 mg, 65%). ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 8.00 (bs, 2H, NH_2), 3.16 (p, *J* = 6.3 Hz, 1H, H1′), 2.84-2.66 (m, 2H, H11), 2.16 (t, *J* = 6.3 Hz, 2H, H2), 1.76-1.62 (m, 2H, H10), 1.62-1.48 (m, 2H, H3), 1.32 (d, *J* = 6.5 Hz, 6H, H2′), 1.34-1.18 (m, 12H, H4-H9).

Synthesis of undecanoic acid 31



A Fischer-Porter tube was charged with (*E/Z*)-benzyl 11-(dibenzylamino)undec-9-enoate **29** (31 mg, 0.21 mmol), palladium hydroxide on carbon 20% w/w (6 mg) and tetrahydrofuran (1 mL). The headspace of the vessel was purged with argon over three cycles, charged with hydrogen (90 psi) and heated at 60 °C for 18 hours. The hydrogen was then vented from the vessel and the reaction mixture was filtered through a short plug of diatomaceous earth and concentrated *in vacuo* to give a light yellow oil (36 mg). Analysis of the crude mixture by ^{1}H n.m.r. showed a mixture of the titled compound **31** and 11-aminoundecanoic acid **1** in a 9:1 ratio. Spectral data were consistent with those reported by Sigma-Aldrich®.[28] ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 6.40 (bs, 1H, OH), 2.32 (t, *J* = 7.4 Hz, 2H, H2), 1.75–1.50 (m, 2H, H3), 1.43–1.10 (m, 14H, H4-H10), 0.88 (t, *J* = 6.6 Hz, 3H, H11).

Synthesis of 11-aminoundecanoic acid 1



General procedure

A Fischer-Porter tube was loaded with (*E/Z*)-benzyl 11-(dibenzylamino)undec-9-enoate **29**, palladium hydroxide on carbon 20% w/w and solvent. The headspace of the vessel was purged with argon over three cycles, charged with hydrogen (90 psi) and heated at 60 °C for 18 hours. The hydrogen was then vented from the vessel and the reaction

mixture was filtered through a short plug of diatomaceous earth and concentrated *in vacuo.* The residue was then precipitated with acetone, filtered and washed with acetone (3×10mL) to give 11-aminoundecanoic acid **1** as a white solid.

Reaction	Solvent	Substrate	Catalyst	1
1	THF	40 mg,	8 mg (20% w/w)	9mg, 22%[a]
2	MeOH:H_2O (4:1)	130 mg,	26 mg (20% w/w)	16 mg, 34%
3	^{i}PrOH:H_2O (4:1)	141 mg,	28 mg (20% w/w)	26 mg, 43%

[a]Conversion to **1** estimated by ^{1}H n.m.r. spectroscopy.

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Chapter 3

Metathesis routes to polyamide monomers

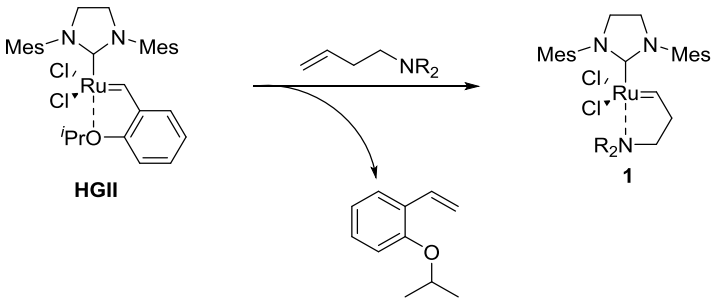
3.1 Introduction

3.1.1 Amines

Large scale synthesis of amines arguably started with the Haber-Bosch process which generated ammonia using osmium, iron and later ruthenium-based heterogeneous catalysts.[1, 2] The ammonia produced was initially used as a feedstock for nitrates for explosives and fertilizers, but later applied to the synthesis of amines which are now a common place feedstock in the fine chemical industry for the production of dyes, fuel additives, agrochemicals, pharmaceuticals and polymers (in particular polyamides).[3]

3.1.2 Amines and olefin metathesis

The hard Lewis-basicity of amines confers high affinity for high oxidation state transition metals. This reactivity towards metals can be detrimental in the context of organometallic catalysis as coordination of amines to the active metal centre can affect the mechanism of the catalytic cycle and outcome of the reaction. It is well documented in the literature that the amino functional group is troublesome in ruthenium catalysed olefin metathesis reactions and this issue was reviewed by Compain in 2007.[4, 5] Presumably, the inhibition of metathesis occurs *via* competitive coordination to the ruthenium centre, blocking the olefinic substrates from interaction with the site of catalysis.[4] Furthermore, the use of alkenyl amines as metathesis substrates can be particularly troublesome due to the simultaneous co-ordination of the olefinic and amino functional groups to form a κ(C,N) chelate complex **1** (Scheme 1).



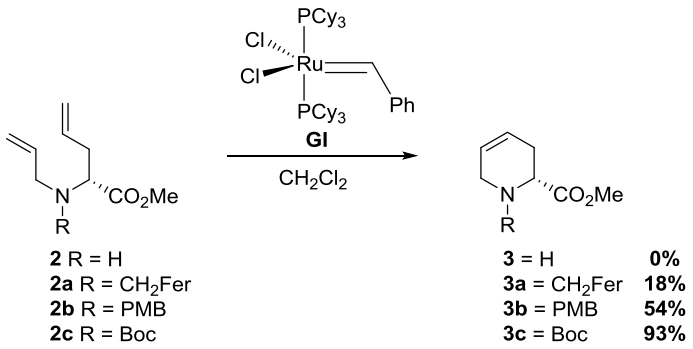
Scheme 1: κ(C,N) chelate complex.

This is exemplified by the use of ruthenium κ(C,N) chelating alkylidene ligands as latent olefin metathesis catalysts.[6, 7] These catalysts are typically inactive, or have low reactivity under standard metathesis conditions, and require extreme conditions, such as elevated temperatures, to activate the pre-catalyst. It should be noted that the Schrock type Mo-alkylidene olefin metathesis catalysts tend to be more tolerant of amine functional groups, but due to their heightened air and moisture sensitivity their use was not further considered in this research study.[4]

3.1.3 Protecting group strategies for amines

The issue of deleterious coordination of amines to the ruthenium catalyst may be resolved by careful choice of catalyst and reaction conditions[8-11] or the use of protecting groups.[4, 12, 13] A successful protecting group strategy is achieved by reducing the nucleophilicity of the amino functional group so it resists coordination to the ruthenium catalyst. This is performed by either increasing the steric crowding around the amino group or *via* changing the electronics of the amino group to reduce its nucleophilicity.[8-10] The more commonly used amine protecting groups for olefin metathesis reactions include amides, carbamates and sulphonamides.[4, 14]

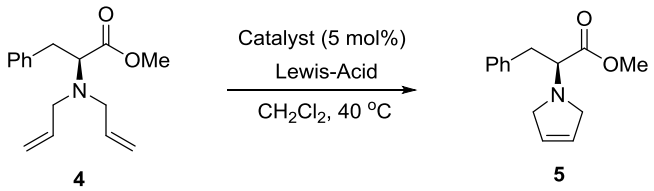
In 1997 Rutjes *et al.* reported that the ring closing metathesis of amino diene **2** using first generation Grubbs catalyst to give dehydropiperidine **3** was largely influenced by the functional group (R) attached to the nitrogen (Scheme 2).[15]



Scheme 2: Ring closing metathesis of 2.

The unsubstituted amine **2** being the least sterically hindered of the amino dienes failed to give any conversion to ring closed product **3**. Protection of the amine **2** as the bulkier methylene-ferrocenyl **2a** and *p*-methoxybenzyl **2b** derivatives improved conversion to the piperidines **3a** and **3b**, and these were isolated in 18% and 54% yield respectively. The best yield was achieved *via* protection of the nitrogen as the Boc carbamate **2c** which gave the piperidine **3c** in excellent yield (93%). The increased yield for **3c** is attributed to the increased steric bulk and electron withdrawing properties of the adjacent carbonyl group of Boc group, which synergistically decreases the nucleophilicity of the nitrogen and prevents deleterious coordination to the catalyst. Similar results to these have been reported extensively in the literature for the ring closing metathesis of amine containing amines.[12, 13] Although the use of protecting groups is effective, these groups are often difficult to remove and require extra synthetic steps, which detracts from the efficiency of the synthetic strategy.[16] It is also reported that protecting groups can promote olefin isomerisation[17, 18] and retard metathesis through unproductive catalytic cycles promoted by chelation.[19, 20] A different strategy involves the use of Lewis- or Brønsted-acids as additives in olefin metathesis reactions to mask the lone pair of electrons on the amino group (Table 1).[11]

Table 1: Ring closing metathesis of 4.



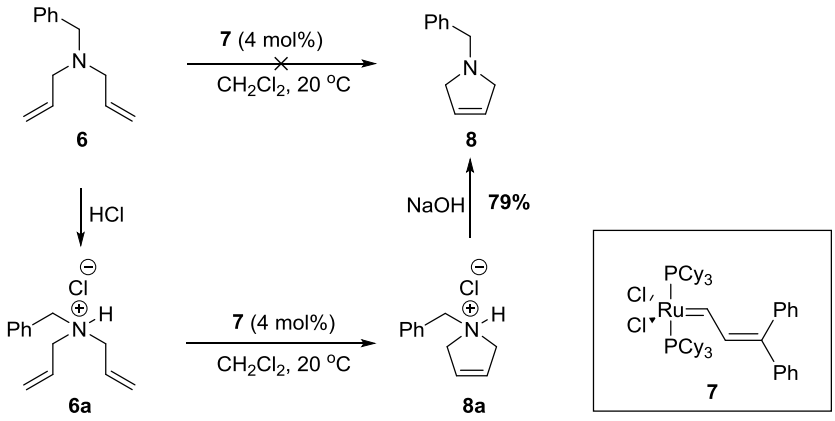
4 **5**

Entry	Catalyst	Lewis-Acid	Amount (mol%)	Time	Yield (%)
1	**GI**	-	-	48 hrs	0
2	**GII**	-	-	48 hrs	24
3	**HGII**	-	-	48 hrs	11
4	**GII**	LiI	100	36 hrs	0
5	**GII**	$AlCl_3$	100	2 hrs	0
6	**GII**	$La(OTf)_3$	100	2 hrs	0
7	**GII**	$Ti(O^iPr)_4$	100	2 hrs	91
8	**GII**	$Ti(O^iPr)_4$	20	2 hrs	93

In 2005, Yang *et al.* reported on the ring closing metathesis of phenylalanine derived tertiary diallylamine **4** using a variety of olefin metathesis catalysts and conditions (Table 1).[11] They discovered that using standard metathesis conditions with three different catalysts (**GI**, **GII**, **HGII**) provided only poor yields (<25%) of ring closing metathesis derived pyrrolidine **5** (Entries 1-3). This was attributed to the nucleophilicity (or basicity) of the amino group in **4**. They postulated that the addition of Lewis acids to the reaction mixture could prevent the deleterious coordination to the ruthenium centre *via* competitive coordination of the amino nitrogen to the Lewis acid. This Lewis acid approach had previously proved useful for assisting in the ring closing metathesis of alkenyl esters, which can be difficult substrates due to analogous κ(C,O) chelate formation.[21, 22] They discovered that addition of one molar equivalent of the Lewis acid $Ti(O^iPr)_4$ gave the desired pyrrolidine **5** in excellent yield (91%, Entry 7). Furthermore the $Ti(O^iPr)_4$ was found to be effective in masking the amino group with only 20 mol% equivalents to give the pyrrolidine **5** in comparable yield (Entry 8). This technique was then used to synthesise a range of pyrrolidines with varying chemical functionality.[11]

3.1.4 Brønsted-acid masking of amines

Brønsted-acids have also be used for the masking of amines in ruthenium catalysed ring closing metathesis reactions by direct protonation of the amino group to form an ammonium salt; this renders the amino group non-nucleophilic as the lone pair of electrons has accepted a proton, giving the nitrogen a formal positive charge. This was exemplified in 1993 by Grubbs *et al.* who reported on the ring closing metathesis of tertiary amino diene **6** with ruthenium alkylidiene catalyst **7** (Scheme 3).[23]

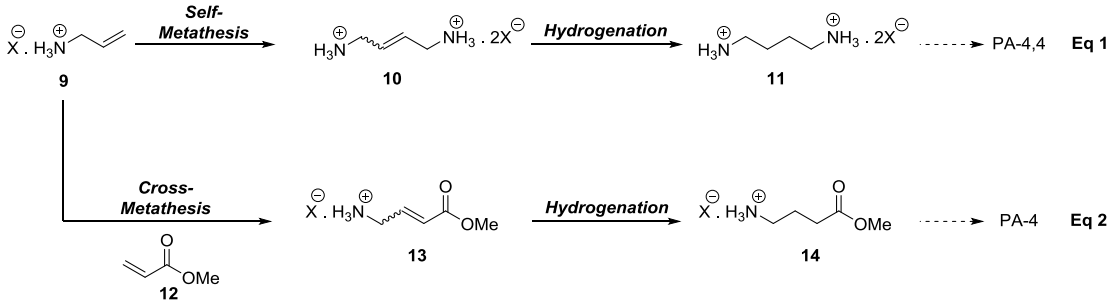


Scheme 3: Ring closing metathesis of 6.

As expected, the unprotected ring closing metathesis of **6** failed to convert to the pyrrolidine **8.** Masking of the coordinating amino group with a Brønsted-acid (HCl) gave the ammonium chloride salt **6a** which allowed for facile ring closure to pyrrolidinium salt **8a**. Basic workup afforded the pyrrolidine **8** in good yield (79%). This ammonium salt protection approach has been used several times in the literature for the ruthenium alkylidene ring closing metathesis of amine containing substrates but at the onset of this project had not been applied to cross-metathesis reactions. The advantage of this protecting group approach is the relative cheapness of the Brønsted acids when compared to covalent protecting groups or Lewis-acid additives. These salts can be formed quickly by an acid-base exchange and can be synthesised *in situ* without need for isolation or purification of the 'salt protected' intermediate. The deprotection step could also be incorporated into a simple basic aqueous workup to liberate the free amine into the organic layer.

3.1.5 Research Proposal

In this chapter, the Brønsted-acid salt protection of alkenyl amines will be applied to ruthenium-alkylidene catalysed self- and cross-metathesis reactions, where the literature has previously focused on using this method for ring closing metathesis reactions. This may aid in developing a general strategy for the protection of primary, secondary and tertiary amines during ruthenium catalysed metathesis reactions. More specifically this protecting group strategy will firstly be applied to the synthesis of polyamide monomers; these targets serve as simple amine containing model compounds suitable for evaluation and optimisation of the strategy. It was envisaged that α,ω-diamines (for copolymer polyamides) and ω-amino acids (for homopolymer polyamides) could be synthesised *via* ruthenium alkylidene catalysed cross-metathesis reactions followed by hydrogenation (Scheme 4).



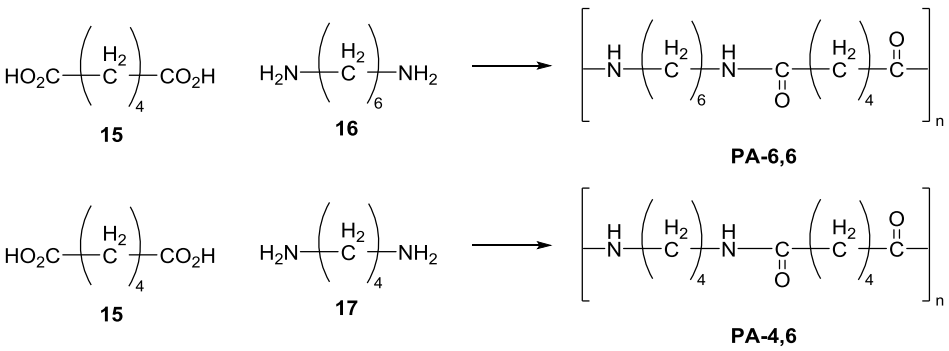
Scheme 4: Proposed synthetic pathways for 11 & 14.

For example, the self-metathesis (or homodimerisation) of 'salt protected' allylamine **9** generates unsaturated diamine **10**, which after hydrogenation would give **11,** a monomer used in the production of copolymer PA-4,4 or DSM Stanyl® (Scheme 4, Equation 1). Alternatively, the cross-metathesis of **9** with methyl acrylate **12** generates ω-amino acid **13**, which after hydrogenation would give amino acid **14**, a monomer used in the production of homopolymer polyamide PA-4 (Scheme 4, Equation 2). This approach would improve the efficiency of the previously described synthesis of PA-11 monomer 11-aminoundecanoic acid, reported in Chapter 2, due to a shortened number of synthetic steps.

3.2 Results and discussion

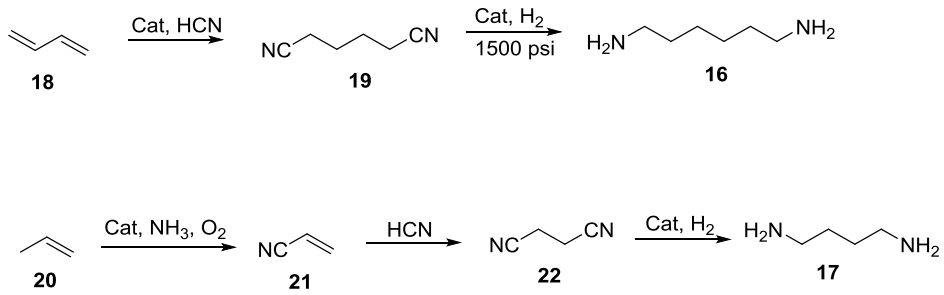
3.2.1 Synthesis of diamines

Diamines are important monomers used in the production of nylon-based plastics and fibres. Approximately 1.3 million tonnes of the diamine hexamethylenediamine is synthesised annually, most of which is used for the polyamide industry.[24] One of the most common nylons, PA-6,6, is produced on a 2 million tonne scale annually[25] by the condensation copolymerisation of adipic acid **15** with hexamethylenediamine **16** (Scheme 5).[26]



Scheme 5: Copolymer polyamides: PA-6,6 & PA-4,6.

Another common nylon, PA-4,6 or DSM Stanyl®, is produced by the condensation polymerisation of adipic acid **15** with 1,4-diaminobutane **17** (also known as putrescine). The PA-6,6 monomer, hexamethylenediamine **16**, is currently synthesised industrially in a two-step sequence involving the hydrocyanation of butadiene **18** to give adiponitrile **19**, followed by high pressure hydrogenation (up to 650 bar) (Scheme 6).[27]



Scheme 6: Industrial synthesis of 16 & 17.

The PA-4,6 monomer, 1,4-diaminobutane **17**, is currently synthesised by DSM in a three step sequence involving the amino oxidation of propene **20** to give acrylonitrile **21**, followed by conjugate addition of cyanide to give succinonitrile **22**. High pressure hydrogenation then gives 1,4-diaminobutane **17.** It was proposed that each of these monomers could be efficiently synthesised by the self-metathesis of alkenyl amines salts followed by catalytic hydrogenation (Scheme 4, Equation 1). Such an approach would eliminate the need for toxic chemicals such as hydrogen cyanide and acrylonitrile, and remove the ultra-high pressure hydrogenation.

3.2.2 Qualitative evaluation of synthetic strategy

Before attempting any cross-metathesis reactions with salt protected alkenyl amines a simple qualitative test was developed in order to establish the feasibility of this approach (Figure 1). It was quickly discovered that the addition of a "free" alkenyl amine such as allylamine **9** (~50 mg) to Hoveyda-Grubbs second generation catalyst in CH_2Cl_2 (1 mg/mL) at room temperature resulted in a colour change from light green (Figure 1, Vial A) to a red-orange over a few minutes (Figure 1, Vial C).

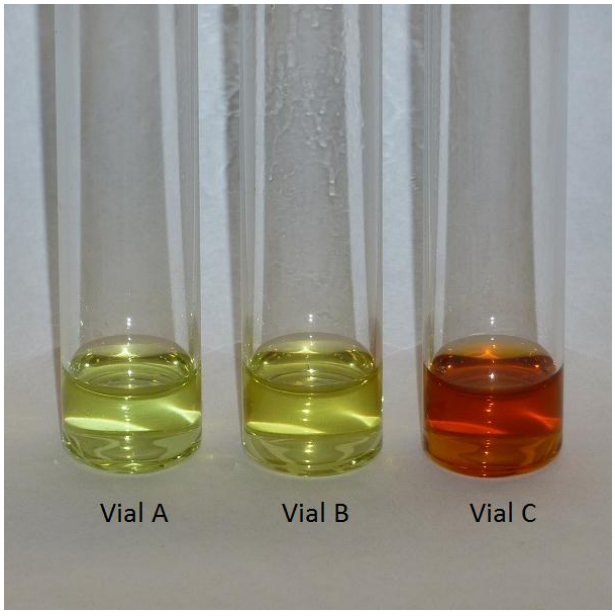
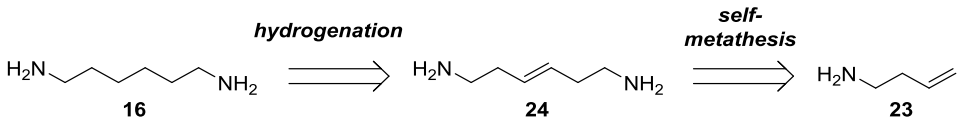


Figure 1: Qualitative assessment of catalyst stability.

Interestingly, the addition of Brønsted-acid protected allylammonium tosylate **9a** (~50 mg) to a solution of Hoveyda-Grubbs second generation catalyst (**HGII**) in CH_2Cl_2 (1 mg/mL) did not give an appreciable colour change over a 20 minute period (Figure 1, Vial B). This colourmetric test suggested that Brønsted-acid protection of allylamine could provide suitable amine protection and slow unwanted deleterious interaction with the catalyst. It also indicated that the weakly acidic allylammonium tosylate **9a** does not quickly decompose the catalyst in solution. These two positive conclusions catalysed further investigation of this strategy.

3.2.3 Self-metathesis of 3-butenylammonium salts

Retrosynthetically, it was proposed that the self-metathesis of suitably protected butenylamine **23** would very quickly generate the carbon scaffold for hexamethylenediamine **16**. Catalytic hydrogenation of the unsaturated diamine **24** intermediate would then give hexamethylenediamine **16** (Scheme 7).[28]



Scheme 7: Retrosynthesis of 16

As expected, the self-metathesis of free 3-butenylamine **23** did not show any conversion to unsaturated diamine **24** using 5 mol% Hoveyda-Grubbs second generation catalyst in refluxing CH_2Cl_2 (Table 2, Entry 1). It was proposed that the metathesis of butenylamine **23** might be achieved by reaction in toluene saturated with dry hydrogen chloride. Fortuitously, this gave the desired unsaturated diamine salt **24a**, albeit with poor conversion (38%). The poor conversion was attributed to catalyst instability in the presence of excess hydrogen chloride and poor solubility of the 3-butenylammonium chloride **23a** salt in toluene (Entry 2).

Table 2: Self-metathesis of 23

23a-d **24a-d**

Entry	X	Solvent	Conditions	Yield (%)
1	free amine	CH_2Cl_2	Δ, 24 hrs	0
2	Cl (**23a**)	HCl/toluene	80 °C, 24 hrs	38 (**24a**)
3	OTf (**23b**)	CH_2Cl_2	Δ, 24 hrs	8 (**24b**)
4	OTf (**23b**)	CH_2Cl_2	Δ, 24 hrs	78 (**24b**)
5	BF_4 (**23c**)	CH_2Cl_2	Δ, 24 hrs	91[a] (**24c**)
6	OTs (**23d**)	CH_2Cl_2	Δ, 24 hrs	90 (**24d**)
7	OTs (**23d**)	CH_2Cl_2	μwave, 100 °C, 100 W, 2 hrs	95 (**24d**)

[a] Conversion (%) based on ^{1}H n.m.r. spectroscopy.

In attempt to solubilise the 3-butenylammonium chloride salt for the metathesis reaction, an *in situ* counterion exchange with AgOTf was performed to give 3-butenylammonium triflate **23b**. Unfortunately, analysis of the crude reaction mixture following metathesis showed poor conversion (8%) to the unsaturated diamine salt **24b** (Entry 3). The poor conversion was attributed to deleterious coordination of the alkene to the liberated AgCl generated in the counterion exchange. It is feasible to suggest that such an interaction could slow interaction of the alkene with the metathesis catalyst. Thus it was deemed necessary to remove the AgCl by-product *via* filtration prior to metathesis. The triflate, tetrafluoroborate and tosylate of the 3-butenylammonium salt were also synthesised using the salt-elimination method, removing the AgCl by-product by filtration. These salts exhibited moderate to good solubility in CH_2Cl_2 with heating. Gratifyingly, a large increase in yield (78%) was observed for the self-metathesis of **23b** to give the unsaturated diamine **24b** (Entry 4), illustrating the need for filtration of the AgCl by-product. Notably, the now doubly charged unsaturated diamine salt **24b** precipitated from the reaction mixture and was isolated in high purity by a simple filtration and wash with cold CH_2Cl_2. Similarly, the self-metathesis of 3-butenylammonium tetrafluoroborate salt **23c** gave the unsaturated diamine **24c** in excellent conversion (91%), but decomposed upon filtration (Entry 5). Fortunately, the corresponding tosylate salt **23d** (derived from **23a**) gave the diamine **24d** in excellent

yield (90%), which was isolated by precipitation from CH_2Cl_2. (Entry 6). Rapid synthesis of the unsaturated diamine tosylate salt **24d** could be performed by heating with microwave energy. This gave **24d** in an excellent isolated yield (95%) after two hours of microwave irradiation (Entry 7).

3.2.4 Isomerisation and precipitation

Interestingly, mass spectroscopy of the isolated products **24b-d** showed no evidence of olefin isomerisation. **HGII**-promoted self-metathesis of carbamate (Fmoc or Boc) protected 3-butenylamine, however, is accompanied by olefin isomerisation and only poor conversion (<30%) to the protected diamine product is achieved.[29] This highlights a further advantage of Brønsted-acid masking of the amino group, where conventional amide/carbamate protection groups result in deleterious coordination of the carbonyl group to the ruthenium catalyst, causing retardation of metathesis (Figure 2).[19, 20]

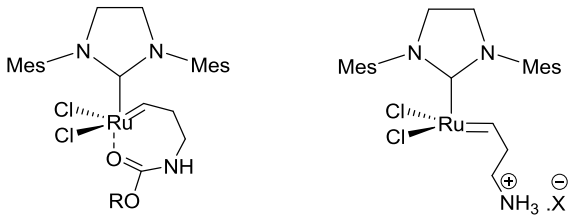
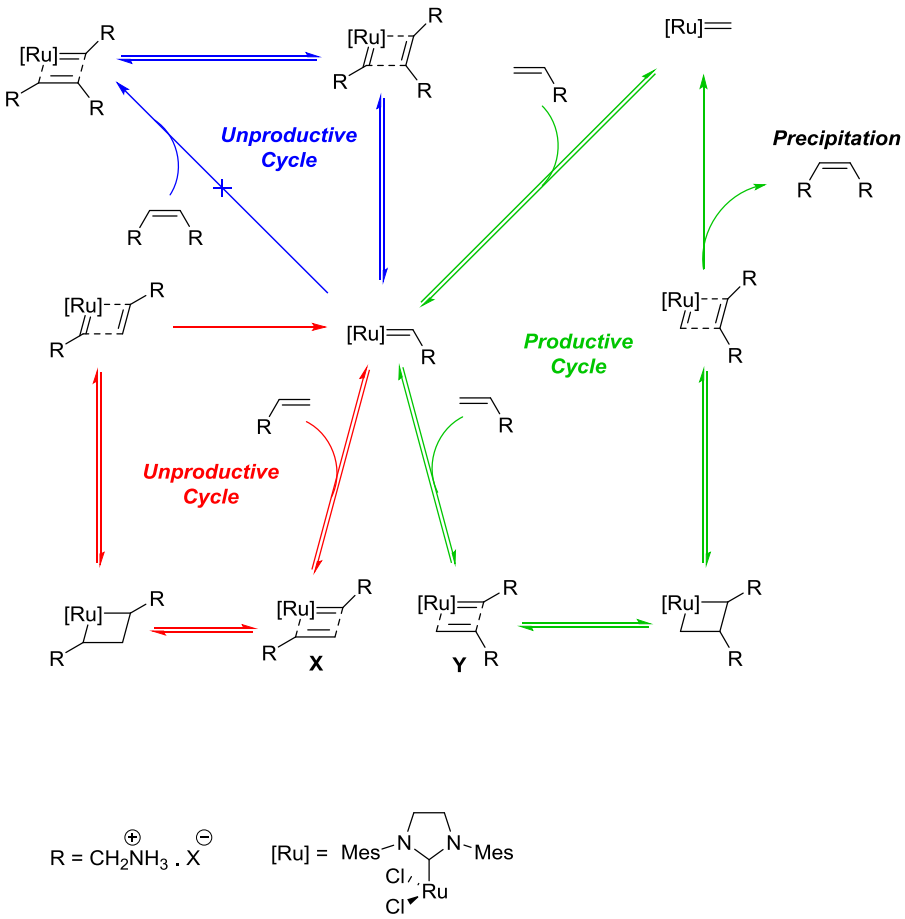


Figure 2: Deleterious coordination of carbonyl group.

It was hypothesised that the high conversion obtained with the new strategy was facilitated by the concomitant precipitation of the unsaturated diammonium salts **24b-d** from the solution, which based on La Chatelier' s principle would drive the equilibrium of the reaction to completion (Scheme 8, Green Cycle).

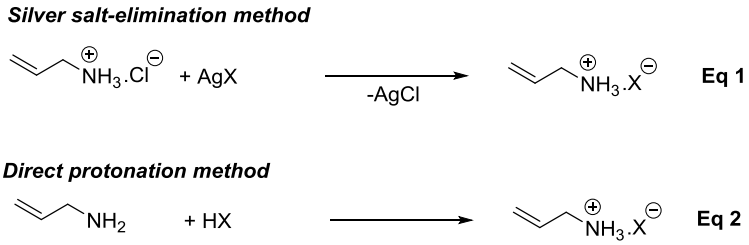


Scheme 8: Self-metathesis cycle.

The lack of isomerisation in the products is also attributed to the precipitation of **24b-d**. This prevents reaction of the products with any isomerisation catalyst formed as a result of catalyst decomposition in solution. Also, as products **24b-d** have precipitated from solution, re-entry into the catalytic cycle is suppressed. This eliminates one of the unproductive metathesis cycle, which would normally result in wasted turn overs and potentially increase decomposition of the catalyst (Blue Cycle). The other unproductive catalytic cycle involves the formation of a 1,3-metallocyclobutane **X** instead of a 1,2-metallocyclobutane **Y** required for product formation (Red Cycle). To increase the formation of **Y** over **X** it is reported that a steric reversal strategy can be employed, however will not be subjected to investigation in this thesis.[30]

3.2.5 Synthesis of Brønsted acid protected alkenyl amines

The silver salt-elimination method for the preparation of Brønsted acid protected alkenyl amines for metathesis reaction was effective, but very atom uneconomical. This warranted investigation into the direct protonation of the alkenyl amines with Brønsted acids (Scheme 9).



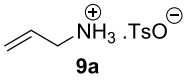
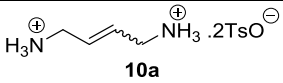
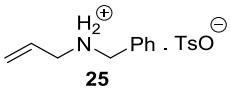
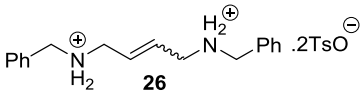
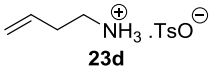
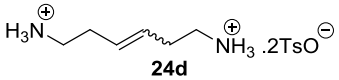
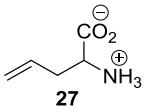
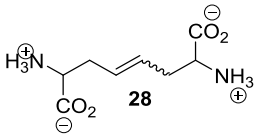
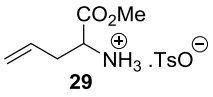
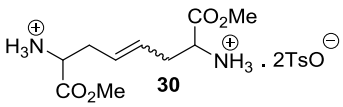
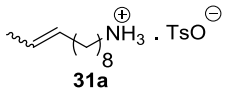
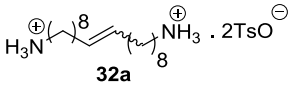
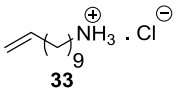
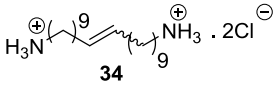
Scheme 9: Examples for synthesis of alkenyl amine salts.

This was performed by addition of one molar equivalent of Brønsted acid to alkenyl amine in DCM or Et_2O at 0 °C followed by concentration *in vacuo*. This provided clean and, in most cases, crystalline starting materials in quantitative yield. Salts prepared in this way perform as per the silver salt elimination method and can be directly used in olefin metathesis reactions.

3.2.6 Scope of self-metathesis reactions

A range of alkenylammonium tosylate salts were synthesised *via* addition of tosic acid to the conjugate alkenyl amines. These salts were used for evaluation of the scope for the Brønsted-acid masking of amines during metathesis (Table 3). The tosylate anion was initially chosen as the derived ammonium salts showed good solubility in CH_2Cl_2, the tosic acid (*cf* HCl, HBF_4, TfOH) was easy to handle and dispense, and most importantly, good conversion had previously been obtained during the self-metathesis of 3-butenylammonium tosylate **23d** (Table 2, Entries 6 and 7).

Table 3: Scope of self-metathesis reaction.

Entry	Substrate	Product	Conventional Yield (%)	Microwave Yield (%)
1	 **9a**	 **10a**	40	74
2	 **25**	 **26**	23	46
3	 **23d**	 **24d**	90	95
4	 **27**	 **28**	0	0
5	 **29**	 **30**	92, 94[a]	90
6	 **31a**	 **32a**	92[b]	88[b]
7	 **33**	 **34**	81	82

[a] Salt formation performed by Brønsted acid addition *in situ*. [b] Olefin isomerisation products observed by ESI-MS.

The ammonium tosylate salt of allylamine **9a** was subjected to self-metathesis using 5 mol% **HGII**. The desired diammonium salt **10a** was isolated in a modest 40% yield, which was further improved to 74% by employing microwave heating (Table 3, Entry 1). This was a significant result as it was reported that the self-metathesis of *N*-acyl protected allylamine did not yield the desired dimeric product; instead, an inseparable mixture of isomerised starting material and product was obtained.[17, 31] It can be seen that this diammonium salt **10a** is structurally related to the PA-4,6 monomer 1,4-diaminobutane **17**. Interestingly, the self-metathesis of salt protected *N*-benzylallylamine **25** gave the diammonium product **26** in only a poor 23% yield, or 46% yield aided by the use of microwave irradiation (Entry 2). The lower yield was attributed to the presence of a bulkier secondary amine adjacent to the reacting olefin. This is justified by reports that the steric environment of an olefin can have a profound effect on its reactivity in cross-metathesis reactions.[30, 32, 33] The self-metathesis of tosylate salt of 3-butenylamine **23d** (generated from the addition of *p*-toluene sulphonic acid to 3-butenylamine) gave the corresponding diammonium salt **24d** in 90% and 95%

for conventional and microwave methods respectively (Entry 3). It was proposed that the zwitterionic amino acid **27** may have sufficient protonation to mask the amino group during metathesis. Unfortunately, the insolubility of **27** in CH_2Cl_2 prevented it from participating in the self-metathesis reaction and thus self-metathesis product **28** was not detected (Entry 4). Methyl esterification of **27** followed by treatment with *p*-toluene sulphonic acid gave an isolatable solid ammonium salt **29**, which showed good solubility in CH_2Cl_2. This compound was subjected to self-metathesis and gratifyingly, the desired 1,6-diammonium salt **30** was isolated in excellent yields of 92% and 90% for the conventional and microwave methods respectively (Entry 5)**.** Alternatively, the salt formation can be performed *in situ* by addition of *p*-toluene sulphonic acid to the free amino ester, which under the standard conditions gave **30** in a comparable yield (94%). The self-metathesis of the long chained undec-9-enylamine tosylate salt **31a** also gave excellent yields of dimeric products **32a** (Entry 6, 92% and 88%). However, alkyl chain elongation and truncation was detected by mass spectrometry *via* the presence of molecular ions with atomic masses separated by 14 a.m.u (Figure 3).

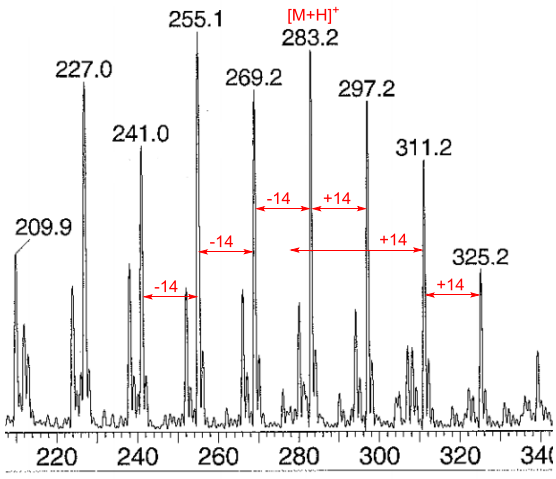


Figure 3: Low resolution ESI+ mass spectrometry showing isomerisation of 31a/32a during metathesis.

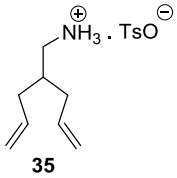
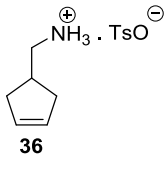
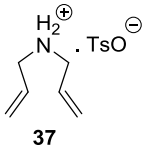
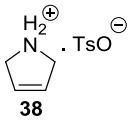
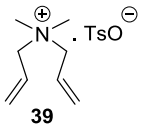
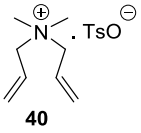
This was attributed to concomitant olefin isomerisation of the products followed by re-entry of these non-symmetrical olefins into the metathesis cycle. As there was no observed precipitation of **32a** during the course of the reaction, it would imply that the

product **32a** was still in contact with the Ru-alkylidene catalyst (and its decomposition products) becoming susceptible to further metathesis processing and isomerisation respectively. Conversely, the small chain, tosylate salt-protected alkenyl amines (Entries 1-5) precipitate on formation and show no evidence of olefin isomerisation. This supports the hypothesis that precipitation of the diammonium salt products during the self-metathesis reaction is essential for eliminating olefin isomerisation in the products. In concordance with this hypothesis, the chloride salt of undecenyl amine **33** was subjected to self-metathesis, and surprisingly the product precipitated out of solution to give the desired diammonium salt **34** without any detected chain elongation or truncation in good yields of 81% and 82% for the conventional and microwave reactions respectively (Entry 7).

3.2.7 Ring closing metathesis

Although the focus of this research was directed towards the synthesis of polyamide monomers, a few ring closing metathesis examples were included to show the broader applicability of the approach (Table 4).

Table 4: Ring closing metathesis of amine salts

Entry	Substrate	Product	Conventional Conversion (%)[a]	Microwave Conversion (%)[a]
1	 **35**	 **36**	>95	>9
2	 **37**	 **38**	>95	>95
3	 **39**	 **40**	9	>95

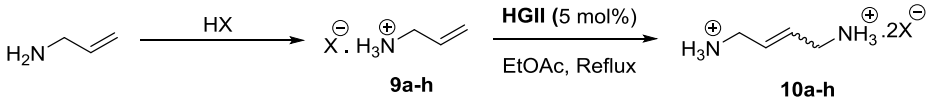
[a] Conversion determined by ^{1}H n.m.r. spectroscopy in d_4-MeOH.

Ring closing metathesis of primary ammonium tosylate salt **35** gave the cyclopentene salt **36** in excellent conversion, but unlike the self-metathesis diammonium salt products did not precipitate during the course of the reaction (Entry 1). Similarly the ring closing metathesis of secondary amine **37** gave the pyrrolidine **38** in excellent conversion (Entry 2). Interestingly, the hindered quaternary ammonium salt **39** gave poor conversion to the desired pyrrolidine **40** using the standard conditions, but excellent conversion by utilising microwave irradiation. This is significant as the Grubbs' group attempted the ring closing metathesis of chloride salt of **39** and were unsuccessful.[31]

3.2.8 Optimisation of allylamine self-metathesis

The self-metathesis of 3-butenylammonium salts **23b-d** generally gave good yields regardless of the counterion and did not require much optimisation. However, the tosylate salt of allylamine **9a** gave the dimeric product in a less than ideal 40% yield using conventional heating techniques. Optimisation of this reaction was thus warranted as the product is useful for the synthesis of the industrially-relevant PA-4,6 monomer, 1,4-diaminobutane **17**. Synthesis of the allylammonium salts was performed by direct addition of Brønsted-acids to allylamine. This generated a library of compounds **9a-h** that were trialled in self-metathesis reactions. It was quickly determined that the most suitable solvent for the self-metathesis reaction was ethyl acetate based on the solubilities of allylammonium salts **9a-h**. As a test of this newly chosen solvent, the self-metathesis of allylammonium tosylate **9a** using 5 mol% Hoveyda-Grubbs second generation catalyst was performed in refluxing ethyl acetate. This gave the desired diammonium product **10a** in modest isolated yield (35%) (Table 5, Entry 1), which was comparable to the 40% yield obtained for the self-metathesis of **9a** in refluxing CH_2Cl_2 (Table 3, Entry 1).

Table 5: Optimisation of allylammonium salt self-metathesis.



Entry	X	Conversion (%)[a]	Yield (%)
1	TsO (**9a**)	40	35 (**10a**)
2	Cl (**9b**)	<5	0 (**10b**)
3	HSO_4 (**9c**)	13	0 (**10c**)
4	MsO (**9d**)	10	0 (**10d**)
5	BSA (**9e**)	23	23 (**10e**)
6	TFA (**9f**)	<5	0 (**10f**)
7	TfO (**9g**)	>95	91 (**10g**)
8	BF_4 (**9h**)	>95	>95 (**10h**)

[a] Conversion determined by ^{1}H n.m.r. spectroscopy in d_4-MeOH.

Initially, the counterions chloride **9b**, hydrogen sulphate **9c** and mesylate **9d** were chosen as their conjugate acids are inexpensive, making them more industrially viable. Unfortunately, these ammonium salts performed poorly in the self-metathesis reaction and only trace amounts of products were detected by ^{1}H n.m.r. spectroscopy (Table 5, Entries 2-4). This was mainly attributed to their insolubility in ethyl acetate, which prevented them from interacting with the catalyst. The benzene sulphonate counterion **9e** performed similarly to the *p*-toluene sulphonate counterion **9a** in the self-metathesis reaction, achieving a poor 23% isolated yield of the desired diammonium product **10e** (Entry 5). The trifluoroacetate counterion **9f** also performed poorly in self-metathesis with only trace amounts of **10f** detected by ^{1}H n.m.r. spectroscopy (Entry 6). Surprisingly, the triflate counterion **9g** gave excellent conversion to the desired diammonium product **10g** (>95%), which could be isolated in good yield (91%) by precipitation (Entry 7). Similarly, the tetrafluoroborate counterion **9h** also provided excellent conversion, giving the desired diammonium product **10h** in quantitative yield by precipitation (Entry 8).

It was hypothesised that the relative acidity of the parent acids may show correlation with conversion to the self-metathesis products (e.g. the stronger the parent acid, the better the conversion). Simply, this relates to the strength of the Brønsted acid (e.g. pKa value) and hence the degree of protonation of allylamine in solution, and thus reflects the Brønsted acid's ability to mask the amino group during metathesis. Unfortunately, the pKa of the parent acid alone in water could not predict the conversion to the self-

metathesis products (Table 6). For example, the allylammonium trifluoroacetate salt **9f** performed poorly in self-metathesis, which has a parent acid pKa in water of -0.23 (Entry 2). Conversely, the allylammonium tetrafluoroborate salt **9h**, which has a similar pKa of -0.4 in water, performed extremely well in the self-metathesis transformation (Entry 7).

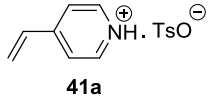
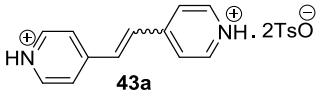
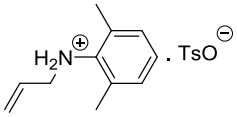
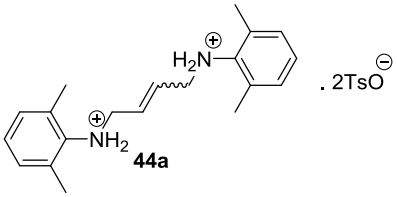
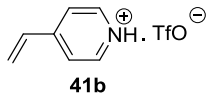
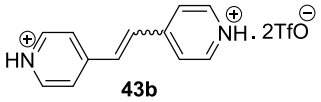
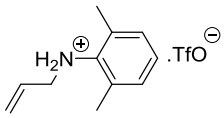
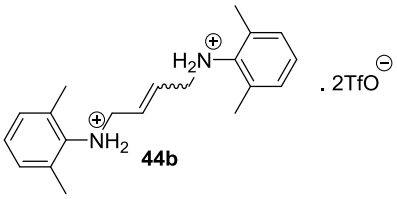
Table 6: Comparisons of self-metathesis conversions and pKa values of parent acids.

Entry	X =	pKa (H_2O)[34]	pKa (ACN)[35]	Solubility[a]	Conversion (%)[b]
1	Cl (**9b**)	-8.0	8.9	Low	<5
2	TFA (**9f**)	-0.25	12.7	High	<5
3	MsO (**9d**)	-2.6	10.0	Low	10
4	HSO_4 (**9c**)	-3.0	7.2	Low	13
5	BSA (**9e**)	-2.8	-	Med	22
6	TsO (**9a**)	-2.8	8.0	Med	40
7	BF_4 (**9h**)	-0.4	1.8[c]	High	>95
8	TfO (**9g**)	-14	2.6	High	>95

[a] Qualitatively assessed by attempting to dissolved a small amount of salt (~50 mg) in 1 mL of ethyl acetate. [b] Conversion determined by ^{1}H n.m.r. spectroscopy in d_4-MeOH. [c] Calculated pKa in ACN as determined by Kutt *et al*.[36]

However, when the pKa values of the parent acid determined in acetonitrile are matched against the conversion they show stronger correlation with conversion to the self-metathesis product (Table 6). This is rationalised in terms of polarity index (PI) of solvent, whereby acetonitrile (PI = 5.8) is a better representative for the ethyl acetate (PI = 4.4) used in the reaction than water (PI = 9). The solubility of the starting ammonium salts must also be acknowledged, as an insoluble starting material will be reluctant to participate in self-metathesis reactions (Table 6). Generally the alkenylammonium salts bearing tetrafluoroborate and triflate counter ions were the most soluble in ethyl acetate; the remaining salts displayed only partial or poor solubility at room temperature. Thus, suitable Brønsted acids for the masking of the amino group during metathesis possess a pKa in acetonitrile below 6 and the conjugate alkenylammonium salt also exhibits good solubility in ethyl acetate. This was exemplified by performing self-metathesis on the ammonium salts of 4-vinylpyridine **41** and *N*-allyl-2,6-dimethyl aniline **42** (Table 7).

Table 7: Self-metathesis of aromatic salts.

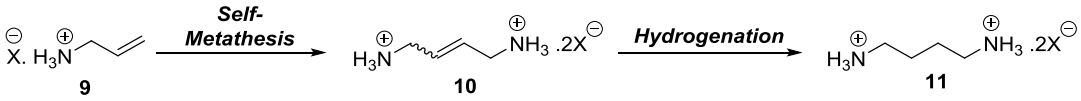
Entry	Substrate	Product	Yield (%)
1	 **41a**	 **43a**	0
2	 **42a**	 **44a**	0
3	 **41b**	 **43b**	93
4	 **42b**	 **44b**	>95

The tosylate salts of these aromatic alkenyl amines (**41a** & **42a**) performed poorly in self-metathesis as they were extremely insoluble in CH_2Cl_2 (Entries 1 and 2). However, when the triflate counterions (**41b** & **42b**) were used, the salts were soluble in ethyl acetate and thus excellent conversion to the desired self-metathesis products (**43b** & **44b)** was obtained (Entries 3 and 4). [*] Although these test substrates are less useful for the synthesis of PA monomers, they emphasise the need for judicious choice of counterion for each substrate.

3.2.9 Tandem approach to saturated diamines

Having optimised the conditions for the self-metathesis of allylammonium salts **10a-h**, it was thought that the PA-4,6 monomer, 1,4-diaminobutane **17**, could be accessed by a simple hydrogenation of the double bond after the metathesis reaction (Scheme 10).

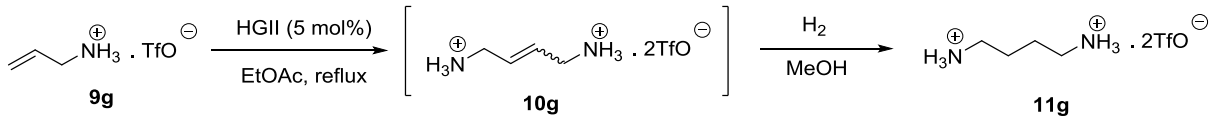
[*] The self-metathesis of 2-vinylpyridine triflate **45** was also attempted, but no conversion to the desired self-metathesis product was detected by ^{1}H n.m.r. spectroscopy.



Scheme 10: Tandem self-metathesis/hydrogenation

Typically this hydrogenation reaction would be performed by addition of an extra catalyst such as palladium on charcoal, but a much more atom economical method would involve the use of the residual ruthenium from the self-metathesis reaction to perform the hydrogenation.[37-39] Until recently,[40-45] only a few examples of using tandem metathesis/hydrogenation with Hoveyda-Grubbs second generation catalyst (**HGII**) had been reported.[46] Some research groups had previously reported that tandem hydrogenation was unsuccessful when using **HGII** as the precatalyst.[47] We decided to challenge this claim and to investigate the development of a tandem metathesis/hydrogenation procedure using **HGII** for the synthesis of saturated diamines. Tandem metathesis/hydrogenation reactions are typically performed by the addition of hydrogen and activating agents to the metathesis reaction mixture.[37] Due to the precipitation of the diammonium salts from the reaction mixture during self-metathesis, it was thought to be important to add or exchange the solvent with methanol post-metathesis in order to solubilise the products for the tandem hydrogenation and also assist in the hydrogenation, which are usually accelerated in a protic solvent (Table 8).

Table 8: Optimisation of hydrogenation conditions.



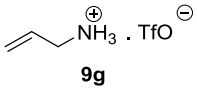
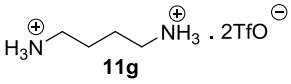
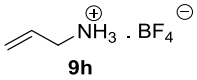
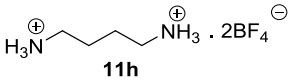
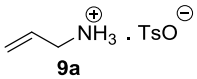
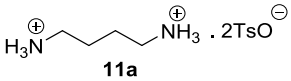
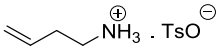
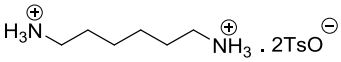
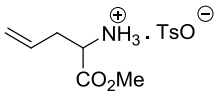
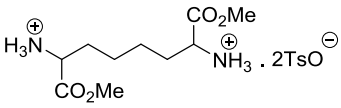
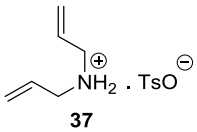
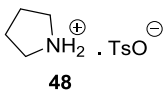
Hydrogenation Conditions	Conversion (%)[c]
H_2 Balloon[a]	0
0 psi[b]	66
15 psi[b]	90
30 psi[b]	100
60 psi[b]	100

[a] Reaction performed in a round bottom flask with attached balloon filled with hydrogen. [b] Reaction performed in a Fischer-Porter tube evacuated and filled with hydrogen to given pressure. [c] Conversion estimated by ^{1}H n.m.r. spectroscopy from depreciation of diagnostic olefinic resonance.

Allylammonium triflate **9g** was firstly chosen as the test substrate for the investigation into tandem metathesis/hydrogenation reactions as saturated product **11g** is a useful

monomer for the production of PA-4,6 (Table 8). Metathesis was performed with the standard conditions of 5 mol% Hoveyda-Grubbs second generation catalyst refluxed in ethyl acetate followed by solvent exchange with methanol and addition of hydrogen. Using a simple balloon atmosphere of hydrogen failed to give conversion to the desired saturated product **11g**, where only **10g** was detected by ^{1}H n.m.r. spectroscopy (Entry 1). By switching to a Fischer-Porter tube and charging the vessel to atmospheric pressure of hydrogen (0 psi) the saturated product **11g** was detected in an encouraging 66% conversion (Entry 2). This was further increased to an excellent 90% conversion by employing a positive pressure of 15 psi (Entry 3). Quantitative conversion to the saturated product **11g** was obtained using pressures of hydrogen above 30 psi (Entries 4 and 5). With the tandem hydrogenation conditions of 60 psi of hydrogen in methanol, the scope of this reaction was evaluated (Table 9).

Table 9: Scope of self-metathesis/hydrogenation.

Entry	Substrate	Product	Yield (%)
1	 **9g**	 **11g**	90
2	 **9h**	 **11h**	>95
3	 **9a**	 **11a**	57
4	 **23d**	 **46d**	>95
5	 **29**	 **47**	63
6	 **37**	 **48**	>95[a]

[a] Conversion determined by ^{1}H n.m.r. spectroscopy in d_4-MeOH.

The self-metathesis of allylammonium triflate **9g** followed by tandem hydrogenation gave the desired diammonium salt **11g** in an excellent 90% isolated yield after precipitation (Entry 1). Other allylammonim salts, the tetrafluoroborate **9g** and tosylate **9a** salts of allylamine, were also investigated and gave quantitative and 57% isolated

yield for **11h** and **11a** respectively (Entries 2 & 3). The tandem self-metathesis/hydrogenation of homologous 3-butenylammonium tosylate **23d** gave the desired diammonium salt **46d** in excellent isolated yield (>95%) (Entry 4). This compound is the protonated salt of hexamethylenediamine **16** which serves as a useful monomer for the production of the widely used PA-6,6. Tandem self-metathesis/hydrogenation of allylglycine tosylate salt **29** gave the 1,6-diester substituted salt **47** in moderate yield (63%). The tandem ring closing metathesis/hydrogenation of diallylammonium tosylate **37** gave pyrrolidine **48** in quantitative conversion. In summary, a general method has been developed for the synthesis of both saturated and unsaturated diamines using a tandem self-metathesis/hydrogenation sequence with Brønsted-acid protected alkenyl amines (Figure 4).

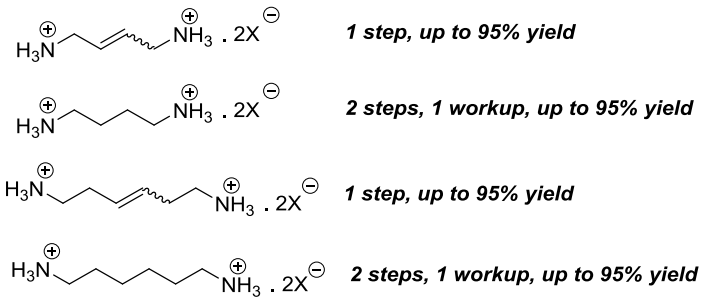


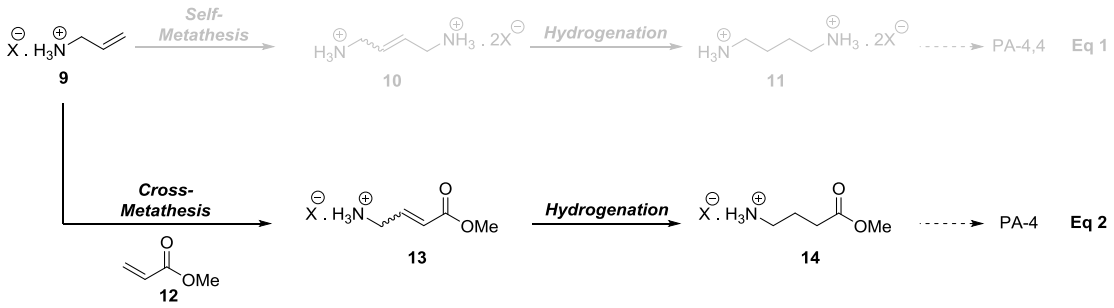
Figure 4: Summary of self-metathesis/hydrogenation reactions

These compounds are useful precursors for the production of nylons such as PA-4,6 and PA-6,6 and the new approach presents viable routes to unsaturated polyamide monomers, which may have interesting new properties.

3.2.10 Cross-metathesis of Brønsted-acid masked amines.

Having developed an efficient method for the self-metathesis of Brønsted-acid masked amines we decided to extend the scope of this strategy to other cross-metathesis reactions. More specifically, the cross-metathesis reaction of Brønsted-acid masked alkenyl amines such as allylamine **9** with methyl acrylate **12** would generate unsaturated

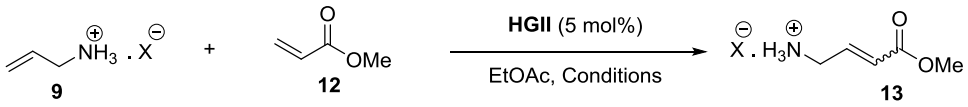
amino esters **13** which could be hydrogenated in tandem to give useful precursors **14** for the synthesis of homopolymer polyamides such as PA-4, PA-6 or PA-11 (Scheme 11).



Scheme 11: Proposed synthesis of 14

This strategy offers an improvement on the methodology developed in Chapter 2 for the synthesis of PA-11 monomers, as it would only require a one pot, two step tandem reaction of cross-metathesis and hydrogenation as opposed to three steps. It would also be considerably more atom economical as it does not require the use of dibenzylamine as an amine source, where two toluene units are liberated from every molecule following hydrogenolysis. This was first attempted with cross-metathesis reactions involving allylammonium salts **9** with methyl acrylate **12** using Hoveyda-Grubbs second generation catalyst (Table 10).

Table 10: Optimisation of cross-metathesis with amine salts.



Entry	X	Equivalents of 12	Conditions	Conversion (%)[a]	(*E*:*Z*)
1	BF_4 (**9h**)	1	Δ, sealed tube	24 (**13h**)	-
2	BF_4 (**9h**)	5	Δ, sealed tube	62 (**13h**)	6:1
3	BF_4 (**9h**)	10	Δ, sealed tube	68 (**13h**)	6:1
4	BF_4 (**9h**)	20	Δ, sealed tube	82 (**13h**)	6:1
5	BF_4 (**9h**)	20	Δ, N_2 bleed	83 (**13h**)	6:1
6	TsO (**9a**)	20	Δ, sealed tube	26 (**13a**)	-
7	TfO (**9g**)	20	Δ, sealed tube	96 (**13g**)	6:1

[a] Conversion estimated by ^{1}H n.m.r. spectroscopy from depreciation of diagnostic olefinic resonance.

The cross-metathesis of allylammonium tetrafluoroborate **9h** with methyl acrylate **12** was first attempted using an equimolar cross-partner ratio at reflux in a sealed tube to

prevent evaporation of the volatile **12**. This gave the unsaturated amino ester cross-metathesis product **13h** in a low 24% conversion as estimated by ^{1}H n.m.r. spectroscopy (Table 10, Entry 1). Using five equivalents of methyl acrylate **12**, the conversion to **13h** was increased to 62% where the ^{1}H n.m.r. spectrum revealed a 6:1 ratio of *E*:*Z* geometric isomers respectively, based on coupling constants of the olefinic proton resonances. The conversion was further increased to 68% then 82% for **13h** using ten and twenty equivalents of methyl acrylate **12** respectively (Entries 3-4). It was thought that a higher conversion to the cross-metathesis product **13** could be obtained by using a nitrogen bleed, which would remove the gaseous ethylene by-product and drive the equilibrium. Unfortunately, this did not substantially improve the conversion to the cross-product **13h** (Entry 5, 83%) when compared to the sealed tube reaction (Entry 4, 82%). The counterion for the allylammonium salts was then examined in order to improve conversion to **13**. As expected, the tosylate salt **9a** gave poor conversion to the cross-metathesis product **13a** using twenty equivalents of methyl acrylate in a sealed tube (Entry 6). Pleasingly, the triflate salt of allylamine **9g** underwent facile cross-metathesis with twenty equivalents of methyl acrylate in a sealed tube to give the desired unsaturated amino ester **13g** in excellent conversion (96%) (Entry 7).

The explanation for the variance in conversion between different counterions is similar to that for the self-metathesis of allylammonium salts. These contributing factors include; starting material solubility, intermediate solubility and acidic strength of the Brønsted acid used to mask the amino group (Figure 5).

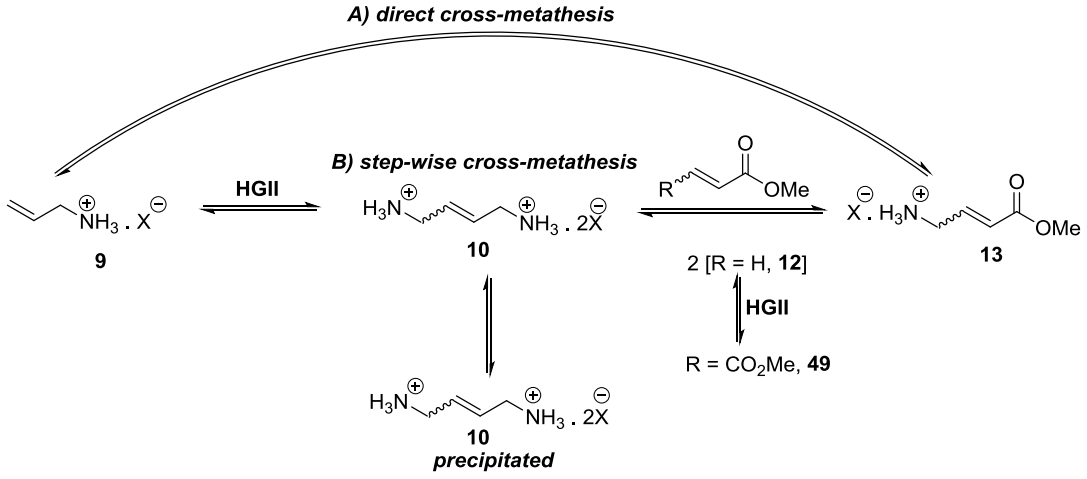


Figure 5: Reaction pathways for cross-metathesis with amine salts.

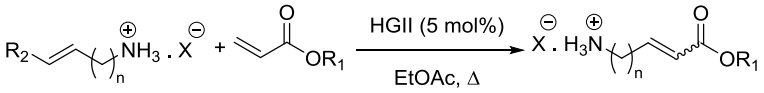
Mechanistically, formation of the amino ester product **13** for the above model system can occur *via* two pathways (Figure 5). The first pathway **A** involves the direct cross-metathesis of methyl acrylate **12** (or **49** from the self-metathesis of **12**) with allylammonium salt **9** to give the unsaturated ammonium ester **13**. The second pathway **B** is a two-step process where self-metathesis of **9** gives dimeric intermediate **10**, which further reacts with **12** (or **49**) to give **13**. It is believed that the pathway **B** is the predominant pathway for such reactions as terminal and electron rich olefins generally react much faster with themselves in a self-metathesis reaction than with the electron poor acrylate olefins of **12** (or **49**).[33] Thus, if pathway **B** is predominant, it is important to consider the solubility of the dimeric intermediate **10** to explain the outcome of the reaction. Simply, if the dimeric self-metathesis intermediate **10** is highly insoluble and precipitates during the reaction, further cross-metathesis reactions cannot occur and thus impact the formation of **13**. This is exemplified by the cross-metathesis of allylammonium tosylate **9a** with methyl acrylate **12** (Table 10, Entry 6) where the low conversion (26%) was attributed to the poor solubility of the dimeric self-metathesis intermediate **10a**, which qualitatively could be seen by a large amount of precipitate at the termination of the reaction. Similarly, a small amount of cloudiness was observed in the reaction mixture for the cross-metathesis of allylammonium tetrafluoroborate **9h** with methyl acrylate **12**, which gave the cross-product **13h** in an improved (83%) but not quantitative conversion (Table 10, Entry 5). Interestingly, the cross-metathesis of allylammonium triflate **9g** with methyl acrylate **12** gave near quantitative conversion to the cross-product **13g** (96%), but initially showed formation of a precipitate which gradually re-dissolved into the reaction mixture to give a homogeneous solution at the terminus of the reaction (Table 10, Entry 7). This would imply that although not completely soluble, the triflate self-metathesis dimer **10g** was sufficiently dissolved to enable further participation in cross-metathesis reactions to give a high conversion to **13g**. Although chain elongation/truncation was not observed for this reaction, it was important to consider that if the dimeric self-metathesis products **10** are very soluble in the reaction solution then this may lead to unwanted catalyst turn overs. High solubility may also result in degradation of the catalyst and chain elongation and truncation *via*

isomerisation of starting materials as seen previously for self-metathesis reactions with longer chained alkenyl amine salts (Table 3, Entry 6).

3.2.11 Scope of cross-metathesis reactions

Having established conditions for the facile cross-metathesis of allylammonium salts **9** with methyl acrylate **12**, the scope of reaction was expanded by using longer carbon chained alkenylammonium salts in order to access different length polyamide monomers, in particular those useful for PA-5, PA-6 and PA-11 (Table 11).

Table 11: Scope of cross-metathesis with amine salts



Entry	n	X	R_1	R_2	Conversion (%)	(*E*:*Z*)
1	2	TfO (**23b**)	Me	H	96 (**50b**)	8:1
2	2	BF_4 (**23c**)	Me	H	97 (**50c**)	7:1
3	2	BF_4 (**23c**)	H	H	95 (**51c**)	9:1
4	3	BF_4 (**52**)	Me	H	97 (**53**)	10:1
5	3	BF_4 (**52**)	H	H	97[a] (70)[b] (**54**)	10:1
6	8	BF_4 (**31b**)	Me	Me	>99[c] (**55b**)	10:1

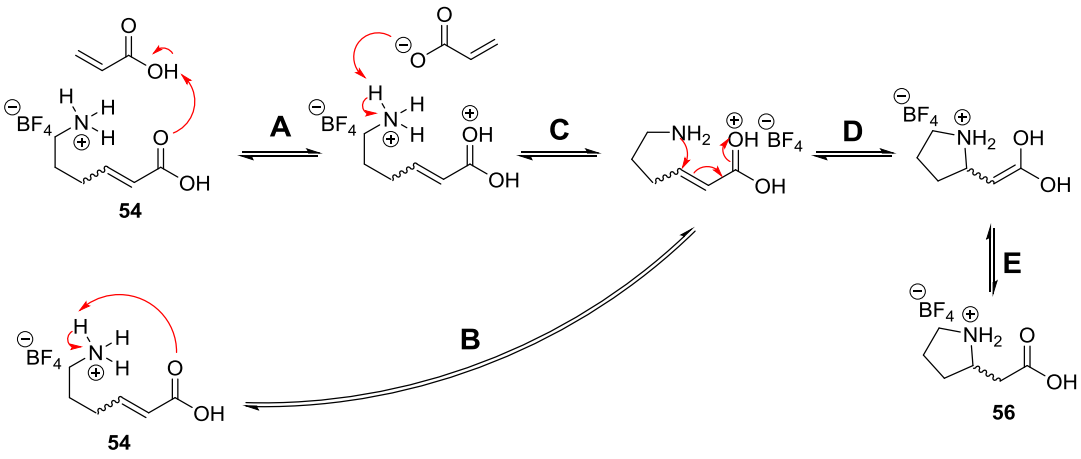
[a] Shortened reaction time to 1 hour. [b] Isolated yield of (*E*)-isomer, product precipitated from EtOAc. [c] Isomerisation detected by LR-MS spectrometry.

3-butenylammonium salts **23** were first evaluated in order to access monomers suitable for the production of unsaturated PA-5. The cross-metathesis of 3-butenylammonium triflate **23b** heated with 5% Hoveyda-Grubbs second generation catalyst in ethyl acetate with ten equivalents of methyl acrylate gave the desired amino ester cross-product **50b** in an excellent 96% conversion with a 8:1 ratio of *E*:*Z* geometric isomers (Entry 1). Similarly, the corresponding tetrafluoroborate salt also gave excellent conversion to the cross-product **50c** (97%) in a similar *E*:*Z* ratio of 7:1 (Entry 2). Interestingly, acrylic acid could also be used as the cross-partner for this reaction instead of methyl acrylate, where the cross-metathesis of butenylammonium tetrafluoroborate **23c** with ten equivalents of acrylic acid gave an excellent 95% conversion to the amino acid cross product **51c** in an *E*:*Z* ratio of 10:1 (Entry 3). This result was significant as it generates free amino acid monomers directly, without the additional step required to hydrolyse

the amino esters before polymerisation. Also, acrylic acid is a much more attractive starting material than methyl acrylate as recently it has been reported that acrylic acid can be obtained from the catalytic dehydration of lactic acid, which can be obtained from the fermentation of renewable biomass, making the process more environmentally friendly.[48] Given the high global production of PA-6, it was deemed necessary to investigate the use of 4-pentenylammonium salts in these cross-metathesis reactions. Gratifyingly, the cross-metathesis of 4-pentenylammonium tetrafluoroborate **52** with methyl acrylate acid gave the amino ester cross-product **53** in excellent conversion (97%, Entry 4). Unexpectedly, when acrylic acid was used as the cross partner under the standard conditions with 4-pentenylammonium tetrafluoroborate **52**, a significant amount (~50%) of decomposition was observed which will be discussed further in Section 3.2.12. This issue however, was quickly resolved by reducing the reaction time from 16 hours to 1 hour reflux in ethyl acetate which gave the desired amino acid salt **54** in excellent conversion (Entry 5). Furthermore it was noticed that a large amount of precipitate formed during the course of the reaction. The reaction mixture was thus cooled and filtered to give a white solid which was identified to be the pure (*E*)-amino acid salt **54** in a good 70% yield. This was a significant result as it is a much more efficient way of removing the starting materials and catalyst than the aqueous extraction process. The longer chained 9-undecenylammonium tetrafluoroborate **31b** was then subjected to cross-metathesis with methyl acrylate under the established conditions (Entry 6). This gave quantitative conversion to the cross-product **55b** determined from analysis of the ^{1}H n.m.r. spectrum with a 10:1 ratio of *E*:*Z* geometric isomers. Unfortunately, low resolution mass spectrometry showed evidence for olefin isomerisation resulting in chain elongation/truncation in the product. This isomerisation is concordant with that reported for the self-metathesis of 9-undecenylammonium tosylate **31a** previously (Entry 6) and could be avoided with careful choice of counterion/solvent, but due to time constraints was not subjected to further investigation.

3.2.12 Decomposition product identification and mechanism

The decomposition product from cross-metathesis of 4-pentenylammonium tetrafluoroborate **52** with acrylic acid (Table 11, Entry 4) was identified by ^{1}H n.m.r. spectroscopy as being the aza-Michael product **56**, which accounts for the relative loss of olefinic protons and the presence of a new methine multiplet from 3.94-3.75 ppm. Mechanistically this reaction must proceed *via* Brønsted-acid catalysis post cross-metathesis, where the first step involves activation of the α,β-unsaturated carbonyl by protonation with acrylic acid **A** (Scheme 12).



Scheme 12: Mechanism for acrylic acid catalysed aza-Michael addition.

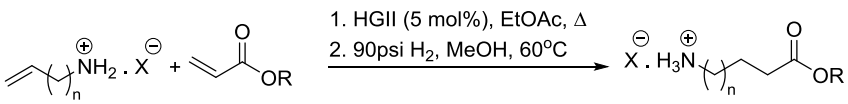
Theoretically this protonation could also occur *via* intramolecular proton transfer from the ammonium group **B**, but this scenario is less probable as acrylic acid is substantially more acidic than the ammonium salt. Also the aza-Michael product was not detected during the cross-metathesis reaction of 4-pentenylammonium tetrafluoroborate **52** with methyl acrylate **12** (Table 11, Entry 4), which also would imply that it is the acrylic acid that facilitates this aza-Michael reaction. Deprotonation of the ammonium group to liberate the free amine is then facilitated by the conjugate base of acrylic acid **C**. This allows for fast aza-Michael addition into the activated α,β-unsaturated carbonyl **D** followed by tautomerisation **E** to give aza-Michael product **56.** Although this side-reaction provides an efficient tandem catalytic way of making complex β-proline

derivatives, it was not the focus of this study and thus it was deemed important to reduce the amount of the aza-Michael by-product **56** formed.

3.2.13 Tandem cross-metathesis/hydrogenation reactions

In order to access saturated amino ester monomers, the tandem cross-metathesis/hydrogenation of alkenylammonium salts with acrylates was investigated similarly to Section 3.2.9. It was anticipated that the minimum conditions required to completely reduce the unsaturated amino ester salts would be harsher than that required for the unsaturated diammonium salts due to the electronic effects from the vicinal carbonyl functionalities. It was discovered that the unsaturated amino ester derived from the cross-metathesis of allylammonium triflate **9g** with methyl acrylate **12** could be hydrogenated to completion using the residual ruthenium residue with only 90 psi of hydrogen at 60 °C in methanol. This generated the C4-saturated amino ester salt **14g**, a suitable precursor for PA-4, in an excellent 98% conversion over the two steps (Table 12, Entry 1).

Table 12: Tandem cross-metathesis/hydrogenation reactions



Entry	n	X	R	Conversion (%)
1	1	TfO (**9g**)	Me	98 (**14g**)
2	2	BF_4 (**23c**)	Me	97 (**57c**)
3	3	BF_4 (**52**)	Me	95 (**58**)
4	3	BF_4 (**52**)	H	95[a, b] (**59**)

[a] Shortened reaction time (1 hr). [b] Transesterification (~10%) to the derivative methyl ester was observed during hydrogenation.

Similarly the tandem cross-metathesis/hydrogenation of 3-butenylammonium tetrafluoroborate **23c** and 4-pentenylammonium tetrafluoroborate **52** with methyl acrylate **12** gave the C5 and C6-saturated amino ester salts (**57c** & **58**) in excellent 97% and 95% conversions respectively (Entries 2 & 3). To access the free amino acid monomer for PA-6 directly, the tandem cross-metathesis/hydrogenation of 4-pentenylammonium tetrafluoroborate **52** with acrylic acid was attempted using a

shortened reaction time during metathesis to prevent aza-Michael addition (Section 3.2.12). This gave the desired C6-saturated amino acid salt **59** in excellent conversion (95%), however the product was contaminated with approximately 10% of the corresponding methyl ester **58** from concomitant transesterification during hydrogenation in the methanol solvent (Entry 4). To summarise, we have successfully expanded the scope of tandem metathesis/hydrogenation for the cross-metathesis of Brønsted protected alkenyl amines with acrylic acid derivatives (Figure 6).

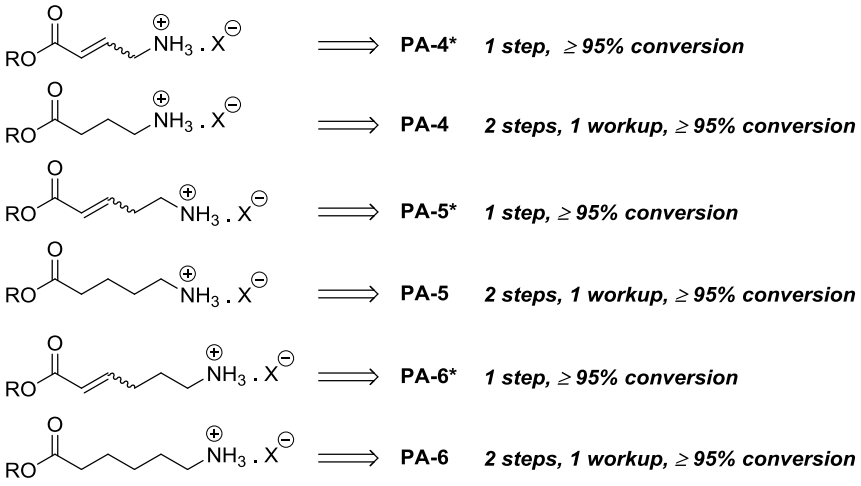


Figure 6: Summary of cross-metathesis/hydrogenation reactions.

This generates both saturated and unsaturated amino ester salts in excellent conversion, which are purified by a simple extraction into water, leaving the remainder of the catalyst and non-ionic starting materials behind. These compounds are suitable monomers for the production of saturated and unsaturated homopolymer polyamides, in particular targeting PA-4, PA-5 and PA-6.

3.2.14 Conclusions and future work

This preliminary study explored the use of Brønsted-acid masking agents for the amino group in an effort to develop efficient conditions for the tandem metathesis/hydrogenation of simple alkenyl amines. Using this method we were successful in achieving metathesis reactions on substrates which were previously

problematic and thus were able to quickly and efficiently access unsaturated and saturated diamines and amino acids, to serve as useful precursors for both homo- and co-polymer polyamides. Further developments should include an expansion in scope for the cross-metathesis of Brønsted-acid masked alkenyl amines by using different olefinic cross-partners such as natural oils. This would provide an alternative, and more expedient synthesis of the longer chained PA-11 monomers, which were synthesised in Chapter 1 using multiple catalysts and more steps. Investigation into the suppression of olefin isomerisation when using longer chained alkenyl amine salts also needs to be investigated as discussed in Section 3.2.11. Investigation into the unexpected aza-Michael reaction would also be interesting as it would allow facile access into β-amino pyrrolidines and piperidines, which are common motifs present in many natural products such as the tricyclic marine[49] or histrionicotoxin[50] family of alkaloids. It would be also interesting to see the effect of having a chiral auxiliary (e.g α-methyl benzyl) on the amino group with the intention of developing an asymmetric tandem cross-metathesis/aza-Michael addition reaction.

3.3 Experimental

3.3.1 General Experimental

Dichloromethane (CH_2Cl_2), EtOAc (EtOAc), diethyl ether (Et_2O), hexane (C_6H_{14}) and methanol (MeOH) were used as supplied by Merck. Deuterated solvents ($CDCl_3$, D_2O, d_4-MeOH, d_6-DMSO and d_6-Acetone) were used as supplied by Merck. Anhydrous CH_2Cl_2 was dried over $CaCl_2$ and distilled from CaH_2 prior to use. All solvents and reagents used in metal-catalysed reactions were degassed with nitrogen prior to use. Anhydrous *p*-toluene sulphonic acid and benzene sulphonic acid were dried under vacuum (1 mmHg) at 100-110 °C for 4h. The following primary amines were synthesised according to literature procedures: 10-undecen-1-amine and 4-penten-1-amine,[51] *N*-benzyl-2-propen-1-amine[52] and 2-allyl-4-penten-1-amine.[53] All solvents and reagents used in metal-catalysed reactions were degassed with nitrogen prior to use. (1,3-Dimesitylimidazolidin-2-ylidene)(2-isopropoxybenzylidene)ruthenium(II) dichloride, Hoveyda-Grubbs 2nd generation catalyst (**HGII**), was used as supplied by Sigma-Aldrich®. All other chemicals were purchased from Sigma-Aldrich® and used without further purification unless stated otherwise. Melting points (m.p.) were measured on a Stuart Scientific SMP 3 melting point apparatus. The ^1H and ^{13}C nuclear magnetic resonance (n.m.r.) spectra were recorded using a Brüker DPX 200 MHz spectrometer (200 MHz for ^1H, 50 MHz for ^{13}C), Brüker DPX 300 MHz spectrometer (300 MHz for ^1H, 75 MHz for ^{13}C) or a Brüker DRX 400 MHz spectrometer (400 MHz for ^1H n.m.r., 100 MHz for ^{13}C n.m.r.), as solutions in deuterated solvents as specified. Chemical shifts (δ) are measured in parts per million (ppm) and are reported to the residual solvent peak. Multiplicities are denoted as singlet (s), doublet (d), triplet (t), multiplet (m) or prefixed broad (b) or as a combination where necessary. The ^{13}C n.m.r. spectra were recorded using a JMOD pulse sequence or proton decoupled pulse sequence unless stated otherwise. Each resonance is assigned according to the following convention: chemical shift (multiplicity, observed coupling constants (J = Hz), integration, and proton assignment). Low-resolution electrospray ionisation (LR-ESI) mass spectra were recorded on a Micromass Platform II API QMS-quadrupole

electrospray mass spectrometer as specified. $[M]^+$ denotes the molecular ion. High-resolution electrospray (HR-MS) were recorded on a Brüker BioApex 47e Fourier Transform mass spectrometer and were recorded as specified.

3.3.2 General procedures for monoamine salt synthesis

Amine salts were synthesised from either direct protonation of the amine or silver salt elimination metathesis. Yields were not measured and assumed to be quantitative in all cases. Brønsted-acid (1 eq) was added to a stirred solution of alkenyl amine (1 eq) in either Et_2O or CH_2Cl_2. After stirring for 10 min the solution was concentrated *in vacuo* to give the amine salt. Alternatively, a silver salt (1 eq) was added to a stirred solution of the alkenylammonium chloride (1 eq) in EtOH. After 10 min, the mixture was filtered to remove AgCl. The filtrate was concentrated *in vacuo* to give the amine salt.

3.3.3 General procedures for the self-metathesis of amine salts

Conventional: The following is an example of a procedure for the conventional metathesis of alkenylammonium salts: An oven dried Schlenk tube (10 mL) was loaded with alkenylammonium salt and degassed solvent. **HGII** catalyst was then added under a high flow of nitrogen and the system was sealed with glass stopper and the reaction mixture was then heated at specified conditions. After the specified period of time, the reaction solvent and volatile species were removed under reduced pressure. The crude product was purified by crystallization from the specified solvent. Conventional self-metathesis experiments are described using the following format: alkenylammonium salt (mg), **HGII** (mg), solvent (mL), reaction temperature (°C), reaction time (hours). **Microwave:** The following is an example of a procedure for the microwave assisted self-metathesis of alkenylammonium salts: Under an inert atmosphere of nitrogen, a quartz microwave vessel was charged with alkenylammonium salt, solvent and **HGII** catalyst. The vessel was sealed and irradiated in a CEM discovery microwave (Benchmate) at 100 ˚C, 100 watts for 2 hours with cooling. The vessel was cooled to

room temperature and the solvent was removed under reduced pressure. The crude product was purified by crystallization from the specified solvent. Microwave assisted self-metathesis experiments were performed on identical scale as conventional experiments stated otherwise. Microwave self-metathesis experiments are described using the following format: alkenylammonium salt (mg), **HGII** (mg), solvent (mL).

3.3.4 General procedure for tandem self-metathesis/hydrogenation of ammonium salts

The following is an example of a procedure for the tandem self-metathesis/hydrogenation of alkenylammonium salts: An oven dried Schlenk tube (10 mL) was loaded with alkenylammonium salt and degassed solvent. **HGII** catalyst was then added under a high flow of nitrogen and the system was sealed with glass stopper and the reaction mixture was then heated at specified conditions. After the specified period of time, the reaction solvent was removed under reduced pressure, re-dissolved in methanol (2 mL) and transferred to a Fischer-Porter pressure tube. The tube was evacuated thrice with hydrogen, charged to a final pressure of 60 psi and left to stir at room temperature for 16 hours. The vessel was then vented to air and the solvent was removed under reduced pressure. The crude product was purified by crystallization from the specified solvent. Conventional tandem self-metathesis/hydrogenation experiments are described using the following format: alkenylammonium salt (mg), **HGII** (mg), metathesis solvent (mL), metathesis reaction temperature (°C), metathesis reaction time (hours).

3.3.5 General procedure for cross-metathesis of unsaturated ammonium salts

The following is an example of a procedure for the conventional cross-metathesis of alkenylammonium salts: An oven dried Schlenk tube (10 mL) was loaded with alkenylammonium salt, olefinic cross partner and degassed EtOAc. **HGII** catalyst was then added under a high flow of nitrogen and the system was sealed with glass stopper

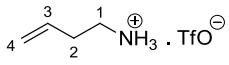
and the reaction mixture was then heated at specified conditions. After the specified period of time, the reaction mixture was then exposed to air and diluted with water (4 mL) and the phases were separated. The organic phase was further extracted with water (3×4 mL), and the combined aqueous extract was washed with EtOAc (4 mL) and concentrated *in vacuo* to give the crude product which was analysed without further purification. Conventional cross-metathesis experiments are described using the following format: alkenylammonium salt (mg), olefinic cross-partner (mg), **HGII** (mg), EtOAc (mL), reaction temperature (°C), reaction time (hours).

3.3.6 General procedure for tandem cross-metathesis/hydrogenation of unsaturated ammonium salts

The following is an example of a procedure for the conventional tandem cross-metathesis/hydrogenation of alkenylammonium salts: An oven dried Schlenk tube (10 mL) was loaded with alkenylammonium salt, olefinic cross partner and degassed EtOAc. **HGII** catalyst was then added under a high flow of nitrogen and the system was sealed with glass stopper and the reaction mixture was then heated at specified conditions. After the specified period of time, the reaction solvent was removed under reduced pressure, re-dissolved in methanol (4 mL) and transferred to a Fischer-Porter pressure tube. The tube was evacuated thrice with hydrogen, charged to a final pressure of 90 psi and left to stir at 60 °C for 16 hours. The vessel was then vented to air and the solvent was removed under reduced pressure. The reaction mixture was then diluted with water (4 mL), EtOAc (4 mL) and the phases were separated. The organic phase was further extracted with water (3×4 mL), and the combined aqueous extract was washed with EtOAc (4 mL) and concentrated *in vacuo* to give the crude product which was analysed without further purification. Conventional tandem cross-metathesis/hydrogenation experiments are described using the following format: alkenylammonium salt (mg), olefinic cross-partner (mg), **HGII** (mg), metathesis reaction temperature (°C), metathesis reaction time (hours).

3.3.7 Reagents and conditions

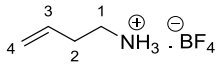
Selected data for 3-butenylammonium triflate 23b



Prepared according to the general procedure described in Section 3.3.2

Colourless solid, m.p. 135-137 °C, ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 5.73-5.67 (m, 1H, H3), 5.25-5.19 (m, 2H, H4), 3.09 (t, 2H, *J* = 7.1 Hz, H1), 2.44 (q, 2H, *J* = 7.1 Hz, H2), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): 134.0 (C3), 119.2 (C4), 39.9 (C1), 32.6 (C2), CF_3 not observed due to relaxation.

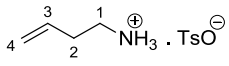
Selected data for 3-butenylammonium tetrafluoroborate 23c



Prepared according to the general procedure described in Section 3.3.2

Colourless solid, m.p. 141-143 °C, 1H n.m.r. (400 MHz, d_6-Acetone): δ 5.91-5.81 (m, 1H, H3), 5.25-5.12 (m, 2H, H4), 3.26 (t, 2H, J = 7.4 Hz, H1), 2.57 (q, 2H, J = 7.4 Hz, H2), NH3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): 134.1 (C3), 119.2 (C4), 40.0 (C1), 32.6 (C2).

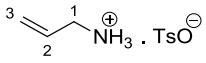
Selected data for 3-butenylammonium tosylate 23d



Prepared according to the general procedure described in Section 3.3.2

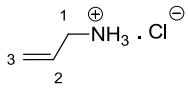
Colourless solid, m.p. 104-106 °C, ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.75 (d, 2H, *J* = 8.1 Hz, ArH), 7.19 (d, 2H, *J* = 8.1 Hz, ArH), 5.61-5.53 (m, 1H, H3), 5.03-4.98 (m, 2H, H4), 2.83 (t, 2H, *J* = 7.6 Hz, H1), 2.36 (s, 3H, $ArCH_3$), 2.28 (q, 2H, *J* = 7.6 Hz, H2). NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, $CDCl_3$): 142.8 (ArC), 141.1 (ArC), 132.8 (C3), 129.3 (ArC), 126.1 (ArC), 118.6 (C4), 39.3 (C1), 31.6 (C2), 21.5 ($ArCH_3$).

Selected data for allylammonium tosylate 9a



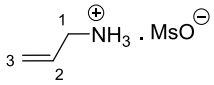
Prepared according to the general procedure described in Section 3.3.2 Colourless solid, m.p. 98-99 °C, ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.85 (bs, 3H, NH_3), 7.73 (d, 2H, *J* = 7.7 Hz, ArH), 7.17 (d, 2H, *J* = 7.7 Hz, ArH), 5.83-5.72 (m, 1H, H2), 5.27-5.16 (m, 2H, H3), 2.36 (s, 3H, $ArCH_3$). ^{13}C n.m.r. (100 MHz, $CDCl_3$): 141.2 (ArC), 141.0 (ArC), 129.7 (C2), 129.2 (ArC), 126.2 (ArC), 121.1 (C3), 42.2 (C1), 21.5 ($ArCH_3$).

Selected data for allylammonium chloride 9b



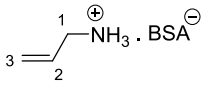
Prepared according to the general procedure described in Section 3.3.2
Pink solid, m.p. 121-123 °C. ^{1}H n.m.r. (400 MHz d_6-DMSO): 8.39 (bs, 3H, NH_3), 5.89 (ddt, *J* = 16.5 Hz, 10.5 Hz, 6.0 Hz, 1H, H2), 5.37 (dq, *J* = 17.3 Hz, 1.5 Hz, 1H, H3), 5.26 (dq, *J* = 10.5 Hz, 1.2 Hz, 1H, H3), 3.40 (dt, *J* = 6.0 Hz, 1.4 Hz, 2H, H1). ^{13}C n.m.r. (100 MHz d_6-DMSO): 131.0 (C2), 119.8 (C3), 40.8 (C1).

Selected data for allylammonium mesylate 9d



Prepared according to the general procedure described in Section 3.3.2
Colourless solid, m.p. 79-82 °C. ^{1}H n.m.r. (400 MHz d_4-MeOH): 5.97 (ddt, *J* = 16.9 Hz, 10.5 Hz, 6.3 Hz, 1H, H2), 5.55–5.29 (m, 2H, H3), 3.57 (d, 2H, H1), 2.70 (s, 3H, CH_3). ^{13}C n.m.r. (100 MHz d_4-MeOH): 131.1 (C2), 121.5 (C3), 42.8 (C1), 39.5 (CH_3).

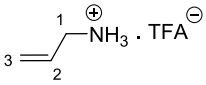
Selected data for allylammonium benzenesulphonate 9e



Prepared according to the general procedure described in Section 3.3.2

Colourless solid, m.p. 99-101 °C. ^{1}H n.m.r. (400 MHz d_4-MeOH): 7.99–7.67 (m, 2H, ArH), 7.62–7.21 (m, 3H, ArH), 5.93 (ddt, J = 16.8 Hz, 10.5 Hz, 6.3 Hz, 1H, H2), 5.58–5.09 (m, 2H, H3), 3.54 (d, J = 6.2 Hz, 1H, H1). ^{13}C n.m.r. (100 MHz d_4-MeOH): 146.2 (ArC), 131.4 (ArC), 130.9 (C2), 129.3 (ArC), 126.8 (ArC), 121.4 (C3), 42.8 (C1).

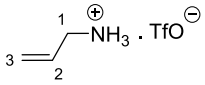
Selected data for allylammonium trifluoroacetate 9f



Prepared according to the general procedure described in Section 3.3.2

Yellow oil. ^{1}H n.m.r. (400 MHz d_4-MeOH): 5.95 (ddt, J = 16.8Hz, 10.4 Hz, 6.3 Hz, 1H, H2), 5.58-5.29 (m. 2H, H3), 3.56 (dt, J = 6.3 Hz, 1.3 Hz, 2H, H1).). ^{13}C n.m.r. (100 MHz d_4-MeOH): 163.1 (q, J = 34.5 Hz, COCF$_3$), 131.0 (C2), 121.5 (C3), 118.2 (q, J = 292.9 Hz, CF$_3$), 42.8 (C1).

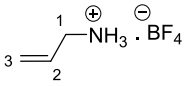
Selected data for allylammonium triflate 9g



Prepared according to the general procedure described in Section 3.3.2

Colourless solid, m.p. 134-136 °C. ^{1}H n.m.r. (400 MHz d_4-MeOH): 5.94 (ddt, J = 16.8 Hz, 10.5 Hz, 6.3 Hz, 1H, H2), 5.52-5.34 (m, 2H, H3), 3.56 (dt, J = 6.3Hz, 1.3 Hz, 2H, H1). ^{13}C n.m.r. (100 MHz d_4-MeOH): 130.8 (C2), 121.8 (q, J = 316 Hz, CF$_3$), 121.8 (C3), 42.9 (C1).

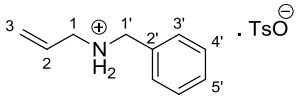
Selected data for allylammonium tetrafluoroborate 9h



Prepared according to the general procedure described in Section 3.3.2

Colourless solid, m.p. 128-129 °C. ^{1}H n.m.r. (400 MHz d_4-MeOH): 5.95 (ddt, J = 16.8 Hz, 10.4 Hz, 6.3 Hz, 1H, H2), 5.49-5.37 (m, 2H, H3), 5.95 (ddt, J = 16.8 Hz, 10.4 Hz, 6.3 Hz, 2H, H1), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz d_4-MeOH): 130.9 (C2), 121.7 (C3), 42.9 (C1).

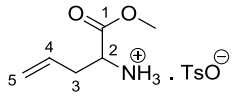
Selected data for N-benzyl-allylammonium tosylate 25



Prepared according to the general procedure described in Section 3.3.2

Colourless solid, m.p. 121-122 °C. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 9.13 (bs, 2H, NH_2), 7.69 (d, 2H, J = 8.4 Hz, ArH), 7.43 (m, 2H, ArH), 7.28 (m, 3H, ArH), 7.18 (d, 2H, J = 8.4 Hz, ArH), 6.00-5.86 (m, 1H, H2), 5.36-5.29 (m, 2H, H3), 4.06 (t, 2H, J = 5.4 Hz, H1'), 3.45 (q, 2H, J = 6.1 Hz, H1), 2.38 (s, 3H, $ArCH_3$). ^{13}C n.m.r. (100 MHz, $CDCl_3$): 141.7 (ArC) , 140.4 (ArC), 130.3, 130.2, 129.2, 129.0, 128.9, 127.9, 125.9, 123.8 (C3), 49.5 (C1'), 48.3 (C1), 21.3 ($ArCH_3$).

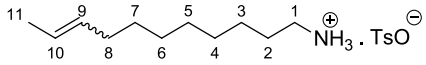
Selected data for 1-methylcarboxy-3-butenylammonium tosylate 29



Prepared according to the general procedure described in Section 3.3.2

Colourless solid, m.p. 110-112 °C. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.75 (d, 2H, J = 8.2 Hz, ArH), 7.15 (d, 2H, J = 8.2 Hz, ArH), 5.68-5.58 (m, 1H, H4), 5.13-5.02 (m, 2H, H5), 4.06 (t, 1H, J = 6.0 Hz, H2), 3.64 (s, 3H, OMe), 2.58 (dt, 2H, J = 6.4 Hz, J = 1.2 Hz, H3), 2.35 (s, 3H, $ArCH_3$), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, $CDCl_3$): 169.4 (CO_2Me), 141.7 (ArC), 140.5 (ArC), 130.4 , 129.0, 126.3, 120.9, 52.8 , 52.7, 34.6 (C3), 21.4 ($ArCH_3$).

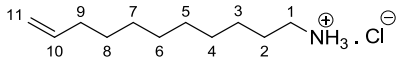
Selected data for 9-undecenylammonium tosylate 31a



Prepared according to the general procedure described in Section 3.3.2

Off white solid, m.p. 72-74 °C. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 7.42 (d, 2H, *J* = 8.1 Hz, ArH), 7.64 (bs, 3H, NH_3), 7.18 (d, 2H, *J* = 7.5 Hz, ArH), 5.48-5.26 (m, 2H, H9 & H10), 2.73 (bs, 2H), 2.36 (s, 3H, $ArCH_3$), 2.11-1.82 (m, 4H), 1.68-1.56 (m, 3H, H11), 1.47 (bs, 2H), 1.34-1.01 (m, 10H). ^{13}C n.m.r. (100 MHz, $CDCl_3$): 141.5 (ArC), 140.9 (ArC), 131.8 (C9), 129.3 (ArC), 126.1 (ArC), 124.8 (C10), 40.2 (C1), 32.8, 29.8, 29.5, 29.4, 29.3, 29.2, 27.6, 26.6, 21.5 ($ArCH_3$), 18.1 (C11).

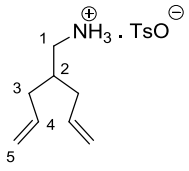
Selected data for 10-undecenylammonium chloride 33



Prepared according to the general procedure described in Section 3.3.2

Colourless semi solid. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 8.30 (bs, 3H, NH_3), 5.84-5.75 (m, 1H, H10), 5.01-4.91 (m, 2H, H11), 2.98 (bs, 2H), 2.03 (m, 2H), 1.77 (m, 2H), 1.42-1.25 (m, 12H). ^{13}C n.m.r. (100 MHz, $CDCl_3$): 139.3 (C10), 114.3 (C11), 34.0 (C1), 32.8, 29.7, 29.6, 29.2, 29.1, 28.0, 26.8, 25.9.

***Selected data for 2-allyl-4-pentenylammonium tosylate* 35**

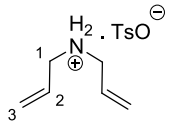


Prepared according to the general procedure described in Section 3.3.2

Colourless semi solid. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.73 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.59 (bs, 3H, NH_3), 7.18 (d, 2H, *J* = 8.0 Hz, Ar-H), 5.64-5.54 (m, 2H, H4), 5.05-4.97 (m, 4H, H5), 2.77 (t, 2H, *J* = 6.0 Hz, NCH_2), 2.33 (s, 3H, $ArCH_3$), 2.03 (m, 4H, CH_2),

1.82 (m, 1H, H2). ^{13}C n.m.r. (100 MHz, $CDCl_3$): 141.1 (ArC), 140.8 (ArC), 135.0 (ArC), 130.7, 129.3, 126.2, 43.0 (C1), 35.6, 35.0, 21.5 ($ArCH_3$).

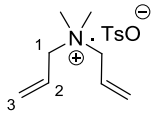
Selected data for diallylammonium tosylate 37



Prepared according to the general procedure described in Section 3.3.2

Colourless ionic liquid. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 8.95 (bs, 2H, NH_2), 7.73 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.19 (d, 2H, *J* = 8.4 Hz, Ar-H), 5.98-5.83 (m, 2H, H2), 5.42-5.36 (m, 4H, H3), 3.59 (q, 4H, *J* 5.6 Hz, H1), 2.38 (s, 3H, $ArCH_3$). ^{13}C n.m.r. (100 MHz, $CDCl_3$): 141.8 (ArC), 140.8 (ArC), 129.1 (ArC), 128.0 (ArC), 126.1 (C2), 124.2 (C3), 48.5 (C1), 21.5 ($ArCH_3$).

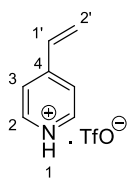
Selected data for N,N',-dimethyl diallylammonium tosylate 39



Prepared according to the general procedure described in Section 3.3.2

Colourless solid, m.p. 45-49 °C. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.77 (d, 2H, *J* = 8.0 Hz, ArH), 7.14 (d, 2H, *J* = 8.0 Hz, ArH), 5.97-5.89 (m, 2H, H2), 5.79-5.67 (m, 4H, H3), 4.16 (d, 4H, *J* = 7.2 Hz, H1), 3.20 (s, 6H, NCH_3), 2.33 (s, 3H, $ArCH_3$). ^{13}C n.m.r. (100 MHz, $CDCl_3$): 143.9 (ArC), 139.2, 129.5, 128.6, 125.8, 124.4 (C3), 65.7 (NCH_3), 49.5 (C1), 21.2 ($ArCH_3$).

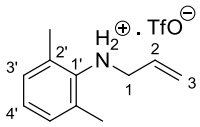
Selected data for 4-vinyl pyridinium triflate 41b



Prepared according to the general procedure described in Section 3.3.2

Colourless solid, m.p. 103-106 °C. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 6.8 Hz, 2H, H2), 8.13 (d, *J* = 6.8 Hz, 2H, H3), 7.02 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H, H1'), 6.52 (d, *J* = 17.6 Hz, 1H, H2'), 5.98 (d, *J* = 10.8 Hz, 1H, H2'), NH not observed due to exchange. ^{13}C n.m.r. (100 MHz, $CDCl_3$) δ 164.2 (C4), 142.7 (C1'), 133.9 (C2), 127.7 (C2'), 125.1 (C3), 121.7 (q, *J* = 317 Hz, CF_3).

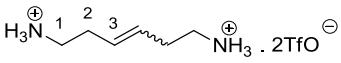
Selected data for N-allyl-2,6-dimethylanilinium triflate 42b



Prepared according to the general procedure described in Section 3.3.2

Colourless semi solid. ^{1}H n.m.r. (300 MHz, $CDCl_3$): 9.21 (bs, 2H, NH_2), 7.32-7.21 (m, 1H, H4'), 7.13 (d, *J* = 7.2Hz, 2H, H3'), 6.06-5.84 (m, 1H, H2), 5.48-5.33 (m, 2H, H3), 4.19-4.03 (m, 2H, H1), 2.47 (s, 6H, $ArCH_3$). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 132.1, 131.2, 130.4, 129.9, 126.3, 126.1, 120.1 (q, *J* = 318Hz, CF_3), 53.7 (C1), 17.7 ($ArCH_3$).

Synthesis of 3-Hexene-1,6-diammonium ditriflate 24b



Prepared according to the general self-metathesis procedures described in Section 3.3.3.

Conventional: 3-butenylammonium triflate (50 mg, 0.23 mmol), **HGII** (7 mg, 11 μmol), CH_2Cl_2 (2 mL), 50 °C, 16 hours. Crystallized from CH_2Cl_2, 36 mg, 78% yield. Light brown solid, m.p. 223 °C (dec). ^{1}H n.m.r. (200 MHz, d_4-MeOH): δ 5.62 (m, 2H, H3), 3.12 (t, *J* 7.2 Hz, 4H, H1), 2.48 (m, 4H, H2), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): 129.9 (C3), 128.8 (*C*F_3), 40.1 (C1), 31.5 (C2). HR-MS (ESI, +ve, MeOH): Calculated m/z 115.1232, Observed m/z 115.1230 $[M\text{-}2TfOH+H]^+$.

Synthesis of 3-Hexene-1,6-diammonium ditetrafluoroborate 24c

Prepared according to the general self-metathesis procedures described in Section 3.3.3. Conventional: 3-butenylammonium tetrafluoroborate (50 mg, 0.31 mmol), **HGII** (10 mg, 16 μmol), CH_2Cl_2 (2 mL), 50 °C, 16 hours. The compound could be precipitated from acetone but decomposed during filtration, 91% conversion, as determined by ^{1}H n.m.r. spectroscopy. Light brown solid. ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 5.63 (m, 2H, C3), 3.01 (t, *J* = 7.2 Hz, 4H, N1), 2.40 (m, 4H, C2), NH_3 not observed due to exchange.

Synthesis of 3-Hexene-1,6-diammonium-ditosylate 24d

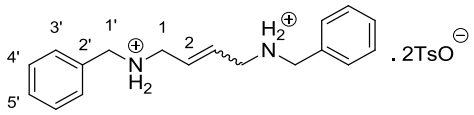
Prepared according to the general self-metathesis procedures described in Section 3.3.3 Conventional: 3-butenylammonium tosylate (219 mg, 0.90 mmol), **HGII** (28 mg, 45 μmol), CH_2Cl_2 (4 mL), 50 °C, 16 hours. Crystallized from CH_2Cl_2, 186 mg, 90% yield. Microwave: 3-butenylammonium tosylate (50 mg, 0.21 mmol), **HGII** (7 mg, 11 μmol), CH_2Cl_2 (2 mL). Crystallized from CH_2Cl_2, 45 mg, 95% yield. Off white solid, m.p. 181-184 °C. ^{1}H n.m.r. (200 MHz, D_2O): δ 7.76 (d, *J* = 8.1 Hz, 4H, ArH), 7.44 (d, *J* = 8.1 Hz, 4H, ArH), 5.68 (m, 2H, H3), 3.12 (t, *J* = 7.2 Hz, 4H, H1), 2.48 (m, 10H, $ArCH_3$ % H2), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): 143.5 (ArC), 141.8 (ArC), 130.1 (C3), 129.9 (ArC), 126.9 (ArC^-), 40.3 (C1), 31.5 (C2), 21.3 ($ArCH_3$). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 115.1230, Observed *m/z* 115.1230 $[M\text{-}2TsOH+H]^+$.

Synthesis of 2-Butene-1,4-diammonium ditosylate 10a

Prepared according to the general self-metathesis procedures described in Section 3.3.3.

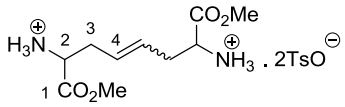
Conventional: Allylammonium tosylate (154 mg, 0.67 mmol), **HGII** (21 mg, 34 μmol), CH_2Cl_2 (2 mL), 50 °C, 16 hours. Crystallized from CH_2Cl_2, 60 mg 40% yield. Microwave: Allylammonium tosylate (50 mg, 0.22 mmol), **HGII** (7 mg, 11 μmol), CH_2Cl_2 (2 mL). Crystallized from CH_2Cl_2, 35 mg, 74 % yield. Off white solid, m.p. 238-242 °C. 1H n.m.r. (300 MHz, D2O): δ 7.77 (d, J = 8.2 Hz, 4H, ArH), 7.45 (d, J = 8.2 Hz, 4H, ArH), 6.06 (m, 2H, H2), 3.74 (m, 4H, H1), 2.47 (m, 6H, ArCH3), NH3 not observed due to exchange. 13C n.m.r. (100 MHz, d_4-MeOH): 143.4 (ArC), 141.9 (ArC), 129.9 (ArC), 129.6 (C2), 126.9 (ArC), 41.6 (C1), 21.3 (ArCH3). HR-MS (ESI, +ve, MeOH): Calculated m/z 87.0917, Observed m/z 87.0919 [M-2TsOH+H]+.

Synthesis of N^1,N^4-Dibenzyl-2-butene-1,4-diammonium ditosylate 26



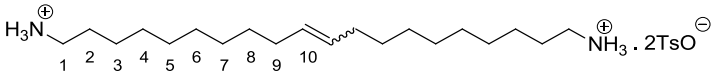
Prepared according to the general self-metathesis procedures described in Section 3.3.3. Conventional: N-Benzyl-allylammonium tosylate (50 mg, 0.16 mmol), **HGII** (5 mg, 8 μmol), CH_2Cl_2 (2 mL), 50 °C, 16 hours. Crystallization did not yield product (23% conversion by ^{1}H n.m.r. spectroscopy). Microwave: Crystallized from acetone, 22 mg, 46% yield. Off white solid, m.p. 190.5-192.5 °C. ^{1}H n.m.r. (400 MHz, d_4-MeOH): 7.69 (d, *J* = 8.0 Hz, 4H, ArH), 7.45 (m, 10H, H3'-C5'), 7.23 (d, *J* = 8.0 Hz, 4H, ArH), 6.12 (m, 2H, H2), 4.20 (s, 4H, H1'), 3.31 (d, *J* 4.4 Hz, 4H, H1), 2.36 (s, 6H, $ArCH_3$), NH_2 not observed due to exchange. ^{13}C n.m.r. (100 MHz d_4-MeOH): 143.5 (ArC), 142.0 (ArC), 132.8 (C2), 131.2 (C3'), 130.9 (ArC), 130.5 (C4'), 130.4 (ArC), 130.1 (C5'), 127.1 (C2), 52.1 (C1'), 49.3 (C1), 21.4 ($ArCH_3$). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 267.1856, Observed *m/z* 267.1854 $[M\text{-}2TsOH+H]^+$.

Synthesis of 1,6-Di(methylcarboxy)-3-hexene-1,6-diammonium ditosylate 30



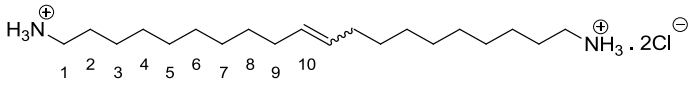
Prepared according to the general self-metathesis procedures described in Section 3.3.3 Conventional: 1-methylcarboxy-3-butenylammonium tosylate (50 mg, 0.17 mmol), **HGII** (5 mg, 8 μmol), CH_2Cl_2 (2 mL), 50 °C, 16 hours. Crystallized from CH_2Cl_2, 48 mg 92% yield. Microwave: Crystallized from CH_2Cl_2, 47 mg, 90 % yield. Light yellow solid, m.p. 214-216 °C. ^{1}H n.m.r. (300 MHz, d_4-MeOH): δ 7.70 (d, J = 8.0 Hz, 4H, ArH), 7.24 (d, J = 8.0 Hz, 4H, ArH), 5.68 (m, 2H, H4), 4.14 (q, J = 6.4 Hz, 2H, H2), 3.83 (s, 6H, OMe), 2.76-2.63 (m, 4H, H3), 2.37 (s, 6H, $ArCH_3$), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): 170.3 (CO_2Me), 143.5 (ArC), 141.8 (ArC), 129.9 (ArC), 128.0 (C4), 126.9 (ArC), 53.7 (OCH_3), 53.5 (C2), 31.5 (C3), 21.3 ($ArCH_3$). HR-MS (ESI, +ve, MeOH): Calculated m/z 231.1339, Observed m/z 231.1338 $[M\text{-}2TsOH+H]^+$.

Synthesis of 10-Icosene-1,20-diammonium ditosylate 32a



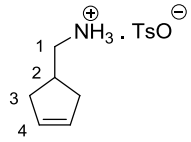
Prepared according to the general self-metathesis procedures described in Section 3.3.3 Undec-9-enylammonium tosylate (52 mg, 0.15 mmol), **HGII** (5 mg, 8 μmol), CH_2Cl_2 (2 mL), 50 °C, 16 hours. Crystallized from acetone, 43 mg, 92% yield, isomerisation observed. Microwave: Crystallized from acetone, 42 mg, 88% yield, isomerisation observed. Off white semi-solid. ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 7.71 (d, J = 8.0 Hz, 4H, ArH), 7.24 (d, J = 8.0 Hz, 4H, ArH), 5.35-5.40 (m, 2H, H10), 2.90 (t, J = 8.0 Hz, 4H, H1), 2.37 (s, 6H, $ArCH_3$), 1.95-2.05 (m, 4H, H9), 1.63 (m, 4H, H8), 1.30 (bs, 24H, 6×CH_2, H2-H7), NH_3 not observed due to exchange. LR-MS (ESI, +ve, MeOH): Showed significant isomerisation, Calculated m/z 311.3, Observed m/z 311.3±14n $[M\text{-}2TsOH+H\pm(CH_2)_n]^+$.

Synthesis of 10-Icosene-1,20-diammonium dichloride 34



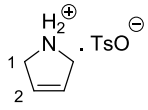
Prepared according to the general self-metathesis procedures described in Section 3.3.3 10-Undecenylammonium chloride (50 mg, 30 mmol), **HGII** (8 mg, 12 μmol), CH_2Cl_2 (2 mL), 50 °C, 16 hours. Crystallized from CH_2Cl_2, 38 mg, 81% yield. Microwave: Crystallized from CH_2Cl_2, 39 mg, 82 % yield. Off white semi-solid. ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 5.39 (s, 2H, H10), 2.91 (t, *J* = 7.6 Hz, 4H, H1), 2.21 (bs, 4H, H9), 1.66 (bs, 4H, H8), 1.49-1.31 (bm, 24H, H2-H7), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): 131.4 (C10), 40.8 (C1), 34.8 (C9), 33.6 (C2), 30.8 (C8), 30.4 (C7), 30.2 (C6), 30.1 (C5), 28.6 (C4), 27.5 (C3). HR-MS (ESI, +ve, MeOH): Calculated m/z 311.3421, Observed m/z 311.3422 $[M\text{-}2HCl+H]^+$.

Synthesis of 1-(3-Cyclopentenyl)methylammonium tosylate 36



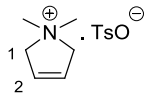
Prepared according to the general self-metathesis procedures described in Section 3.3.3. 2-Allyl pent-4-enylammonium tosylate (21 mg, 7.2 mmol), **HGII** (2 mg, 4 μmol), CH_2Cl_2 (2 mL), 50 °C, 16 hours. Crystallization did not give product (>95% conversion by ^{1}H n.m.r. spectroscopy). Microwave: Crystallization did not give product (>95% conversion by ^{1}H n.m.r. spectroscopy). Brown oil. ^{1}H n.m.r. (400 MHz, $CDCl_3$): 7.73 (d, *J* = 7.6 Hz, 2H, ArH), 7.61, (bs, 3H, NH_3), 7.15 (d, *J* = 7.6 Hz, 2H, ArH), 5.52 (bs, 2H, H4), 2.72 (bs, 2H, H2), 2.45-2.25 (bm, 6H, H2, 0.5×H3 & $ArCH_3$), 2.02-1.75 (bm, 2H, 0.5×H3). ^{13}C n.m.r. (100 MHz, $CDCl_3$): 141.3 (ArC), 140.6 (ArC, 129.0 (C4), 128.9 (ArC), 125.9 (ArC), 44.8 (C1), 36.5 (C3), 35.3 (C2), 21.5 ($ArCH_3$). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 98.0964, Observed *m/z* 98.0958 $[M\text{-}TsOH+H]^+$.

Synthesis of 2,5-Dihydro-1H-pyrrolium tosylate 38



Prepared according to the general self-metathesis procedures described in Section 3.3.3. N,N-Diallylammonium tosylate (130 mg, 0.48 mmol), **HGII** (15 mg, 24 μmol), CH_2Cl_2 (2 mL), 50 °C, 16 hours. Crystallization did not yield product (>95% conversion by ^{1}H n.m.r. spectroscopy). Microwave: Crystallization did not yield product (>95% conversion by ^{1}H n.m.r. spectroscopy). Off white solid, m.p. 115-117 °C. ^{1}H n.m.r. (300 MHz, $CDCl_3$): 7.69 (d, *J* = 7.4 Hz, 2H, ArH), 7.16 (d, *J* = 7.4 Hz, 2H, ArH), 5.75 (bs, 2H, H2), 4.09 (bs, 4H, H1), 2.40 (s, 3H, $ArCH_3$), NH_2 not observed due to exchange. ^{13}C n.m.r. (100 MHz, $CDCl_3$): 141.4 (ArC), 140.9 (ArC), 129.2 (ArC), 126.0 (ArC), 125.1 (C2), 52.4 (C1), 21.3 ($ArCH_3$). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 70.0651, Observed *m/z* 70.0658 $[M\text{-}TsOH+H]^+$.

Synthesis of N,N'-Dimethyl-2,5-dihydro-1H-pyrrolium tosylate 40



Prepared according to the general self-metathesis procedures described in Section 3.3.3. N,N' dimethyl diallylammonium tosylate (50 mg, 0.17 mmol), **HGII** (5 mg, 8 μmol), CH_2Cl_2 (2 mL), 50 °C, 16 hours. Crystallization did not yield product (9% conversion by ^{1}H n.m.r. spectroscopy). Microwave: Crystallization did not yield product (>95% conversion by ^{1}H n.m.r. spectroscopy). ^{1}H n.m.r. (200 MHz, $CDCl_3$): 7.66 (d, *J* = 7.8 Hz, 2H, ArH), 7.10 (d, *J* = 7.8 Hz, 2H, ArH), 5.76 (bs, 2H, H2), 4.31 (bs, 4H, H1), 3.32 (s, 6H, NCH_3), 2.30 (s, 3H, $ArCH_3$). ^{13}C n.m.r. (100 MHz $CDCl_3$): 143.6 (ArC), 139.5 (ArC), 128.7 (ArC), 125.8 (ArC), 124.8 (C2), 72.4 (NCH_3), 53.9 (C1), 21.2 ($ArCH_3$). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 98.0964, Observed *m/z* 98.0969 $[M\text{-}TsOH+H]^+$.

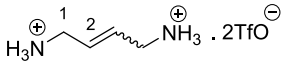
Synthesis of 2-Butene-1,4-diammonium dimesylate 10d

Prepared according to the general self-metathesis procedures described in Section 3.3.3 Conventional: Allylammonium mesylate (25 mg, 0.16 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), 85 °C, 16 hours. Crystallization did not give product (>5 % conversion by ^{1}H n.m.r. spectroscopy). ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 6.02-5.99 (m, 1H, H2), 3.72 (d, J = 5.2 Hz, 2H, H1), NH_3 not observed due to exchange.

Synthesis of 2-Butene-1,4-diammonium dibenzenesulphonate 10e

Prepared according to the general self-metathesis procedures described in Section 3.3.3. Conventional: Allylammonium benzenesulphonate (34 mg, 0.16 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), 85 °C, 16 hours. Crystallized from CH_2Cl_2, 7.5 mg, 25 % yield. Isomeric ratio A:B, 7:1. Off white solid, m.p. 221 °C (dec). ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 7.91-7.75 (m, 2H, ArH), 7.51-7.38 (m, 3H, ArH), 6.05-5.94 (m, 1H, H2, Isomer A), 5.91-5.82 (m, 1H, H2, Isomer B), 3.72 (d, J = 5.5 Hz, 2H, H1, Isomer B), 3.66-3.58 (m, 2H, H1, Isomer A), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): δ 146.3 (ArC), 131.4 (ArC), 129.7 (C2), 129.3 (ArC), 126.9 (ArC), 41.6 (C1). LR-MS (ESI, +ve, MeOH): Calculated *m/z* 87.1, Observed *m/z* 86.5 [M-2$PhSO_3H$+H]$^{+}$.

Synthesis of 2-Butene-1,4-diammonium ditriflate 10g



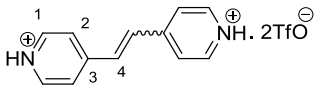
Prepared according to the general self-metathesis procedures described in Section 3.3.3. Conventional: Allylammonium triflate (33 mg, 0.16 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), 85 °C, 16 hours. Crystallized from acetone and diethyl ether (1: 10),

28mg, 91% yield. Light brown solid, m.p. 211 °C (dec). ^{1}H n.m.r. (300 MHz, d_4-MeOH): δ 6.03-5.97 (m, 1H, H2), 3.67-3.61 (m, 2H, H1) , NH_3 not observed due to exchange. ^{13}C n.m.r. (75 MHz, d_4-MeOH): 129.8 (C2), 41.8 (C1), CF_3 not observed due to relaxation. LR-MS (ESI, +ve, MeOH): Calculated *m/z* 237.1, Observed *m/z* 236.9 $[M\text{-}TfOH+H]^+$.

Synthesis of 2-Butene-1,4-diammonium ditetrafluoroborate 10h

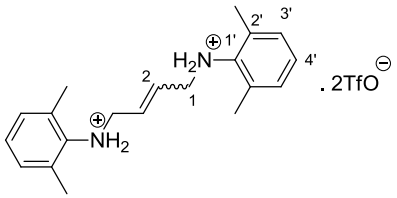
Prepared according to the general self-metathesis procedures described in Section 3.3.3. Conventional: Allylammonium tetrafluoroborate (23 mg, 0.16 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), 85 °C, 16 hours. Crystallized from acetone and diethyl ether (1: 10), 22 mg, >99 % yield Isomeric ratio A:B, 9:1. Light brown solid, m.p. 255 °C (dec). ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 6.07-5.92 (m, 1H, H2 Isomer A), 5.90-5.83 (m, 1H, H2 Isomer B), 3.72 (d, *J* = 5.4 Hz, 2H, H1, Isomer B), 3.66-3.59 (m, 2H, H1, Isomer A), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): δ 129.7 (C2, Isomer A), 128.5 (C2, Isomer B), 41.6 (C1, Isomer A), 37.3 (C1, Isomer B). LR-MS (ESI, +ve, MeOH): Calculated *m/z* 87.1, Observed *m/z* 86.6 $[M\text{-}2HBF_4+H]^+$.

Synthesis of 4,4'-(Ethene-1,2-diyl) bis(pyridin-1-ium) ditriflate 43b



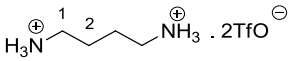
Prepared according to the general self-metathesis procedures described in Section 3.3.3. 4-Vinyl pyridinium triflate (41 mg, 0.16 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), 85 °C, 16 hours. Crystallized from Et_2O, 36 mg, 93% yield. Brown semi-solid,^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 8.73 (d, *J* = 6.4 Hz, 2H, Ar-H), 8.34 (d, *J* = 6.5 Hz, 4H, Ar-H), 7.96 (s, 2H, H4), 7.40 (bs, 2H, NH). ^{13}C n.m.r. (100 MHz, d_4-MeOH): δ 154.2 (C3), 143.4 (C1), 135.6 (C4), 126.5 (C2), 121.8 (d, *J* = 319 Hz, CF_3). LR-MS (ESI, +ve, MeOH): Calculated m/z 183.1, Observed m/z 183.1$[M\text{-}2TfOH+H]^+$.

Synthesis of 4,4'-(But-2-ene-1,4-diyl) bis(3,5-dimethylanilin-1-ium) ditriflate 44b



Prepared according to the general self-metathesis procedures described in Section 3.3.3. N-allyl, 2,6-dimethyl-anilinium triflate (50 mg, 0.16 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), 85 °C, 16 hours. Crystallized from Et_2O, 48 mg, >99% yield. Brown semi-solid. ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 7.38-7.27 (m, 2H, H4'), 7.22 (d, J = 7.6 Hz, 4H, H3'), 6.15-6.03 (m, 2H, H2), 4.09 (d, J = 5.5 Hz, 4H, H1), 2.40 (s, 12H, ArCH_3), NH_2 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): δ 133.1 (C3'), 131.6 (C2), 130.9 (C4'), 130.3 (C2'), 123.4 (C1'), 52.5 (C1), 17.9 (CH_3), CF_3 not observed due to relaxation. LR-MS (ESI, +ve, MeOH): Calculated m/z 295.2, Observed m/z 295.2 $[M\text{-}2TfOH+H]^+$.

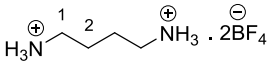
Synthesis of 2-Butane-1,4-diammonium ditriflate 11g



Prepared according to the general tandem self-metathesis/hydrogenation procedure described in Section 3.3.4.

Allylammonium triflate (33 mg, 0.16 mmol), **HGII** (5 mg, 8 μM), EtOAc (4 mL), 85 °C, 16 hours. Crystallized from acetone with diethyl ether (approx 1: 10), 28 mg, 91 % yield. Off-white solid, m.p. 208 °C (dec), 1H n.m.r. (400 MHz, d_4-MeOH): δ 3.03-2.93 (m, 4H, H1), 1.80-1.68 (m, 4H, H2), NH3 not observed due to exchange. 13C n.m.r. (100 MHz, d_4-MeOH): 121.7 (q, J = 317Hz, CF3), 40.1 (C1), 25.6 (C2). LR-MS (ESI, +ve, MeOH): Calculated m/z 239.0, Observed m/z 238.9 [M-TfOH+H]+.

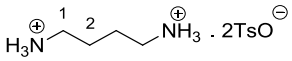
Synthesis of 2-Butane-1,4-diammonium ditetrafluoroborate 11h



Prepared according to the general tandem self-metathesis/hydrogenation procedure described in Section 3.3.4.

Allylammonium tetrafluoroborate (23 mg, 0.16 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), 85 °C, 16 hours. Crystallized from acetone with diethyl ether (approx 1: 10), 25 mg, >99 % yield. Off-white solid, m.p. 199 °C (dec), ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 3.06-2.84 (m, 4H, H1), 1.82-1.64 (m, 4H, H2), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): δ 40.1 (C1), 25.5 (C2). LR-MS (ESI, +ve, MeOH): Calculated *m/z* 89.1, Observed *m/z* 88.6 $[M\text{-}2BF_4+H]^+$.

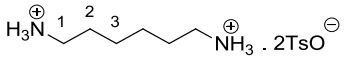
Synthesis of 2-Butane-1,4-diammonium ditosylate 11a



Prepared according to the general tandem self-metathesis/hydrogenation procedure described in Section 3.3.4.

Allylammonium tosylate (106 mg, 0.46 mmol), **HGII** (15 mg, 23 μmol), CH_2Cl_2 (5mL), 85 °C, 16 hours. Crystallized from acetone, 57mg, 57 % yield. Grey solid. ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 7.71 (d, *J* = 8.2 Hz, 4H, ArH), 7.24 (d, *J* = 8.0 Hz, 4H, ArH), 3.09-2.82 (m, 4H, H1), 2.37 (s, 6H, $ArCH_3$), 1.84-1.61 (m, 4H, H2), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 141.8 (ArC), 129.9 (ArC), 126.9 (ArC), 40.1 (C1), 25.6 (C2), 21.3 ($ArCH_3$). LR-MS (ESI, +ve, MeOH): Calculated *m/z* 261.1, Observed *m/z* 260.9 $[M\text{-}TfOH+H]^+$.

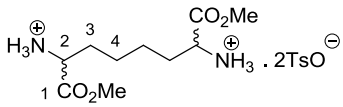
Synthesis of Hexane-1,6-diammonium-ditosylate 46d



Prepared according to the general tandem self-metathesis/hydrogenation procedure described in Section 3.3.4.

3-Butenylammonium tosylate (61 mg, 0.25 mmol), **HGII** (8 mg, 13 μmol), CH_2Cl_2 (5 mL), 85 °C, 16 hours. Crystallized from CH_2Cl_2, 52mg, 90% yield. Off-white solid, m.p. 172 °C. ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 7.71 (d, *J* = 8.1 Hz, 4H, ArH), 7.24 (d, *J* = 8.0 Hz, 4H, ArH), 2.96-2.90 (m, 4H, H1), 2.37 (s, 6H, $ArCH_3$), 1.79-1.61 (m, 4H, H2), 1.52-1.22 (m, 4H, H3), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): δ 143.5 (ArC), 141.8 (ArC), 129.9 (ArC), 126.9 (ArC), 40.6 (C1), 28.3 (C2), 26.8 (C3), 21.3 ($ArCH_3$). LR-MS (ESI, +ve, MeOH): Calculated *m/z* 117.1; Observed *m/z* 116.9 $[M\text{-}2TsOH+H]^+$.

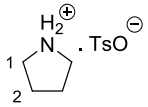
Synthesis of 1,6-Di(methylcarboxy)-hexane-1,6-diammonium ditosylate 47



Prepared according to the general tandem self-metathesis/hydrogenation procedure described in Section 3.3.4.

1-Methylcarboxy-3-butenylammonium tosylate (65 mg, 0.22 mmol), **HGII** (7 mg, 11 μmol), CH_2Cl_2 (5 mL), 85 °C, 16 hours. Crystallized from CH_2Cl_2, 62 mg, 63% yield. ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 7.71 (d, *J* = 8.0 Hz, 4H, ArH), 7.24 (d, *J* = 7.9 Hz, 4H, ArH), 4.15-3.98 (m, 2H, H2), 3.83 (s, 6H, OCH_3), 2.37 (s, 6H, $ArCH_3$), 2.20-1.70 (m, 4H, H3), 1.74-1.15 (m, 4H, H4), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH): δ 170.9 (CO_2Me), 143.5 (ArC), 141.8 (ArC), 129.9 (ArC), 127.0 (ArC), 53.84 & 53.81 (OCH_3 *meso/rac*) 53.6 (C2), 31.13 & 31.10 (C3 *meso/rac*), 25.50 & 25.41 (C4 *meso/rac*), 21.3 ($ArCH_3$). LR-MS (ESI, +ve, MeOH): Calculated m/z 233.2, Observed m/z 232.9 $[M\text{-}2TsOH+H]^+$.

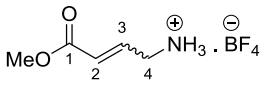
Synthesis of Pyrrolidinum tosylate 48



Prepared according to the general tandem self-metathesis/hydrogenation procedure described in Section 3.3.4.

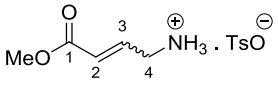
N,N'-Diallylammonium tosylate (63 mg, 0.23 mmol), **HGII** (7 mg, 12 μmol), CH_2Cl_2 (5 mL), 85 °C, 16 hours. Crystallization did not yield product (>95% conversion by ^{1}H n.m.r. spectroscopy). ^{1}H n.m.r. (400 MHz, d_4-MeOH): δ 7.71 (d, *J* = 8.2 Hz, 2H, ArH), 7.24 (d, *J* = 8.0 Hz, 2H, ArH), 3.23 (t, *J* = 6.9 Hz, 4H, H1), 2.36 (s, 3H, $ArCH_3$), 2.06-1.91 (m, 4H, H2), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 141.8 (ArC), 131.0 (ArC), 129.8 (ArC), 127.0 (ArC), 46.7 (C1), 25.0 (C2), 21.3 ($ArCH_3$). LR-MS (ESI, +ve, MeOH): Calculated *m/z* 72.1, Observed *m/z* 71.6 [M-TsOH+H]$^+$.

Synthesis of Methyl 4-ammonium but-2-enoate tetrafluoroborate 13h



Prepared according to the general cross-metathesis procedure described in Section 3.3.5. Allylammonium tetrafluoroborate (23 mg, 0.16 mmol), methyl acrylate 20% v/v in EtOAc (1.6 mL, 3.4 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 82% conversion by ^{1}H n.m.r. spectroscopy, (*E*:*Z)* = 6:1. ^{1}H n.m.r. (400 MHz, d_4-MeOH), (*E*)-Isomer: δ 6.92 (dt, *J* = 15.9 Hz, 6.0 Hz, 1H, H3), 6.17 (dt, *J* = 15.9, 1.7 Hz, 1H, H2), 3.79-3.77 (m, 2H, H4), 3.76 (s, 3H, OCH_3), NH_3 not observed due to exchange. ^{1}H n.m.r. (400 MHz, d_4-MeOH), (*Z*)-Isomer: δ 6.33 (dt, *J* = 11.5 Hz, 6.2 Hz, 1H, H3), 6.12 (dt, *J* = 11.5, 1.9 Hz, 1H, H2), 4.18-4.07 (m, 2H, H4), 3.75 (s, 3H, OCH_3), NH_3 not observed due to exchange.

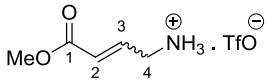
Synthesis of Methyl 4-ammonium but-2-enoate tosylate 13a



Prepared according to the general cross-metathesis procedure described in Section 3.3.5.

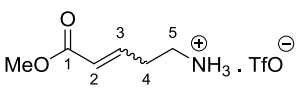
Allylammonium tosylate (37 mg, 0.16 mmol), methyl acrylate 20% v/v in EtOAc (1.6 mL, 3.4 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 26% conversion by ^{1}H n.m.r. spectroscopy, (*E*:*Z)* = 6:1. ^{1}H n.m.r. (400 MHz, d_4-MeOH) δ 7.70 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.23 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.90 (dt, *J* = 15.9 Hz, 5.9 Hz, 1H, H3), 6.15 (dt, *J* = 15.9 Hz, 1.6 Hz, 1H, H2), 3.74 (s, 3H, OCH_3), 3.63-3.46 (m, 2H, H4), 2.73 (s, 3H, $ArCH_3$), NH_3 not observed due to exchange.

Synthesis of Methyl 4-ammonium but-2-enoate triflate 13g



Prepared according to the general cross-metathesis procedure described in Section 3.3.5. Allylammonium triflate (35 mg, 0.17 mmol), methyl acrylate 20% v/v in EtOAc (1.6 mL, 3.4 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 51 mg crude, 96% conversion by ^{1}H n.m.r. spectroscopy, (*E*:*Z)* = 6:1. ^{1}H n.m.r. (400 MHz, d_4-MeOH), (*E*)-Isomer: δ 6.92 (dt, *J* = 15.9 Hz, 5.8 Hz, 1H, H3), 6.24-6.12 (m, 1H, H2), 3.83-3.70 (m, 5H, H4 & OCH_3), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 167.1 (C1), 139.7 (C3), 126.0 (C2), 121.8 (q, *J* = 318 Hz, CF_3), 52.4 (OCH_3), 40.0 (C4). ^{1}H n.m.r. (400 MHz, d_4-MeOH), (*Z*)-Isomer: δ 6.33 (dt, *J* = 12.1 Hz, 6.1 Hz, 1H, H3), 6.20-6.09 (m, 1H, H2), 4.14 (dd, *J* = 6.1 Hz, 1.8 Hz, 2H, H4), 3.83-3.70 (m, 3H, OMe), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 167.3 (C1), 140.2 (C3), 125.1 (C2), 121.8 (q, *J* = 318 Hz, CF_3), 52.2 (OCH_3), 38.7 (C4). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 116.0706, Observed *m/z* 116.0710 $[M\text{-}TfOH+H]^{+}$.

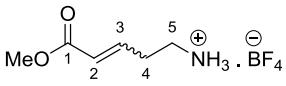
Synthesis of Methyl 5-ammonium pent-2-enoate triflate salt 50b



Prepared according to the general cross-metathesis procedure described in Section 3.3.5.

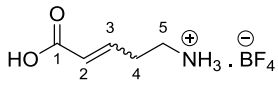
3-Butenylammonium triflate (50 mg, 0.23 mmol), methyl acrylate 20% v/v in EtOAc (1.1 mL, 2.3 mmol), **HGII** (7.0 mg, 12 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 68 mg crude, 96% conversion by ^{1}H n.m.r. spectroscopy, (*E*:*Z)* = 8:1. ^{1}H n.m.r. (400 MHz, d_4-MeOH), (*E*)-Isomer: δ 6.91 (dt, *J* = 15.7 Hz, 7.1 Hz, 1H, H3), 6.02 (dt, *J* = 15.8 Hz, 1.5 Hz, 1H, H2), 3.73 (s, 3H, OMe), 3.16-3.04 (m, 2H, H5), 2.59 (qd, *J* = 7.2 Hz, 1.5 Hz, 2H, H4), NH_3 not observed due to exchange. (*Z*)-Isomer: δ 6.29 (dt, *J* = 11.4 Hz, 7.5 Hz, 1H, H3), 6.02 (m, 1H, H2), 3.73 (s, 3H, OMe), 3.16-3.04 (m, 2H, H5), 2.59 (qd, *J* = 7.2 Hz, 1.5 Hz, 2H, H4), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 167.9 (C1), 144.3 (C3), 125.2 (C2), 52.1 (OMe), 39.2 (C5), 30.9 (C4). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 130.0863, Observed *m/z* 130.0859 $[M\text{-}TfOH+H]^+$.

Synthesis of Methyl 5-ammonium pent-2-enoate tetrafluoroborate salt 50c



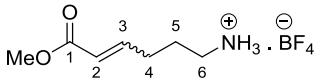
Prepared according to the general cross-metathesis procedure described in Section 3.3.5. 3-Butenylammonium tetrafluoroborate (37 mg, 0.23 mmol), methyl acrylate 20% v/v in EtOAc (1050 μL, 2.3 mmol), **HGII** (7 mg, 12 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 57 mg crude, 97% conversion by ^{1}H n.m.r. spectroscopy, (*E*:*Z)* = 7:1. ^{1}H n.m.r. (400 MHz, d_4-MeOH), (*E*)-Isomer: δ 6.96-6.85 (dt, *J* = 15.7 Hz, 7.1 Hz, 1H, H3), 6.02 (d, *J* = 15.7 Hz, 1H, H2), 3.73 (s, 3H, OCH_3), 3.10 (t, *J* = 7.2 Hz, 2H, H5), 2.59 (q, *J* = 7.0 Hz, 2H, H4), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 168.0 (C1), 144.3 (C3) 125.1 (C2), 52.1 (OCH_3), 39.2 (C5), 30.8 (C4). ^{1}H n.m.r. (400 MHz, d_4-MeOH), (*Z*)-Isomer: δ 6.29 (dt, *J* = 11.4, 7.5 Hz, 1H, H3), 6.19-6.15 (m, 1H, H2), 3.76 (s, 3H, OCH_3), 3.10 (t, *J* = 7.2 Hz, 2H, H5), 2.59 (q, *J* = 7.0 Hz, 2H, H4), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 168.0 (C1), 144.4 (C3), 123.8 (C2), 51.8 (OCH_3), 39.8 (C5), 30.8 (C4). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 130.0863, Observed *m/z* 130.0869 $[M\text{-}HBF_4+H]^+$.

Synthesis of 5-Ammonium pentenoic acid tetrafluoroborate 51c



Prepared according to the general cross-metathesis procedure described in Section 3.3.5. 3-Butenylammonium tetrafluoroborate (37 mg, 0.23 mmol), acrylic acid (158 µL, 2.3 mmol), **HGII** (7 mg, 12 µmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 72 mg crude, 95% conversion by ^{1}H n.m.r. spectroscopy, (*E*:*Z)* = 9:1. ^{1}H n.m.r. (300 MHz, d_4-MeOH), (*E*)-isomer: δ 6.89 (dt, *J* = 15.6, 7.0 Hz, 1H, H3), 5.98 (d, *J* = 15.7 Hz, 1H, H2), 3.09 (t, *J* = 7.3 Hz, 2H, H5), 2.58 (qd, *J* = 7.2, 1.4 Hz, 2H, H4), NH_3 & OH not observed due to exchange. ^{13}C n.m.r. (75 MHz, d_4-MeOH) δ 169.1 (C1), 144.2 (C3), 126.2 (C2), 39.2 (C5), 30.0 (C4). ^{1}H n.m.r. (300 MHz, d_4-MeOH), (*Z*)-isomer: δ 6.26 (dt, *J* = 11.3 Hz, 7.5 Hz, 1H, H3), 6.07-5.89 (m, 1H, H2), 3.03-2.94 (m, 2H, H5), 2.46-2.35 (m, 2H, H4), NH_3 not observed due to exchange. ^{13}C n.m.r. (75 MHz, d_4-MeOH) δ 169.1 (C1), 144.2 (C3), 126.2 (C2), 39.8 (C5), 27.9 (C4). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 116.0706, Observed *m/z* 116.0700 $[M\text{-}HBF_4+H]^+$.

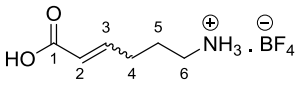
Synthesis of Methyl 6-ammonium hex-2-enoate tetrafluoroborate 53



Prepared according to the general cross-metathesis procedure described in Section 3.3.5. 4-Pentenylammonium tetrafluoroborate (50 mg, 0.29 mmol), methyl acrylate 20% v/v in EtOAc (1.3 µL, 2.9 mmol), **HGII** (9 mg, 14 µmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 76 mg crude, 97% conversion by ^{1}H n.m.r. spectroscopy, (*E*:*Z)* = 10:1. ^{1}H n.m.r. (400 MHz, d_4-MeOH), (*E*)-Isomer: δ 6.95 (dt, *J* = 15.6 Hz, 6.5 Hz, 1H, H3), 5.93 (d, *J* = 15.5 Hz, 1H, H2), 3.71 (s, 3H, OCH_3), 3.03-2.87 (m, 2H, H6), 2.39-2.28 (m , 2H, H4), 1.89-1.76 (m, 2H, H5), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 168.5 (C1), 148.7 (C3), 123.0 (C2), 52.1 (OCH_3), 40.2 (C6), 29.7 (C4), 26.9 (C5). ^{1}H n.m.r. (400 MHz, d_4-MeOH), (*Z*)-Isomer: δ 6.38-6.26 (m, 1H, H3), 5.99-5.85 (m, 1H, H2),

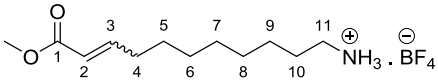
3.74 (s, 3H, OCH_3), 3.03-2.87 (m, 2H, H6), 2.39-2.28 (m, 2H, H4), 1.89-1.76 (m, 2H, H5), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 168.4 (C1), 149.0 (C3), 121.8 (C2), 51.9 (OCH_3), 40.2 (C6), 29.5 (C4), 26.9 (C5). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 144.1019, Observed *m/z* 144.1019 $[M\text{-}HBF_4+H]^+$.

Synthesis of 6-Ammonium hex-2-enoic acid tetrafluoroborate 54



Prepared according to the general cross-metathesis procedure described in Section 3.3.5. 4-pentenylammonium tetrafluoroborate (50 mg, 0.29 mmol), acrylic acid (200 μL, 2.9 mmol), **HGII** (9 mg, 14 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (1 hours). Crude showed 97% conversion by ^1H n.m.r. spectroscopy, (*E*:*Z)* = >10:1. Product (*E*)-isomer crystallized from EtOAc, 44 mg, 70% yield. White solid, m.p. 191 °C. ^1H n.m.r. (400 MHz, d_4-MeOH), (*E*)-Isomer: δ 6.93 (dt, *J* = 15.5 Hz, 6.8 Hz, 1H, H3), 5.89 (d, *J* = 15.6 Hz, 1H, H2), 2.99-2.92 (m, 2H, H6), 2.37-2.29 (m, 2H, H4), 1.82 (p, 7.6 Hz, 2H, H5), NH_3 & OH not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 169.7 (C1), 148.4 (C3), 123.9 (C2), 40.2 (C6), 29.7 (C4), 26.99 (C5). HR-MS (ESI, +ve, MeOH): Calculated *m/z* 130.0863, Observed *m/z* 130.0865 $[M\text{-}HBF_4+H]^+$.

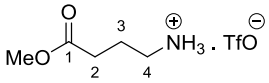
Synthesis of Methyl 11-ammonium undec-2-enoate tetrafluoroborate 55b



Prepared according to the general cross-metathesis procedure described in Section 3.3.5. Undec-9-enylammonium tetrafluoroborate (69 mg, 0.27 mmol), methyl acrylate 20% v/v in EtOAc (1.2 mL, 2.7 mmol), **HGII** (8.0 mg, 13 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 78 mg crude, >99% Conversion by ^1H n.m.r. spectroscopy, (*E*:*Z)* = 10:1. Isomerisation observed by LR-MS. ^1H n.m.r. (400 MHz, d_4-MeOH), (*E*)-Isomer: δ 6.96 (dt, *J* = 15.6, 7.0 Hz, 1H,

H3), 5.84 (dt, *J* = 15.6, 1.6 Hz, 1H, H2), 3.70 (s, 3H, OMe), 2.91 (t, *J* = 7.6 Hz, 2H, H11), 2.28-2.17 (m, 2H, H4), 1.76-1.28 (m, 12H, H5-H10), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 168.9 (C1), 151.3 (C3), 121.8 (C2), 51.9 (OMe), 40.8 (C11), 33.1, 30.1, 30.1, 30.0, 29.1, 28.5, 27.3 (C4-C10). LR-MS (ESI, +ve, MeOH): Showed isomerisation; Calculated *m/z* 214.2, Observed *m/z* 214.3±14n $[M-HBF_4+H\pm(CH_2)_n]^+$.

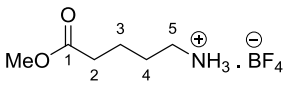
Synthesis of Methyl 4-ammonium butanoate triflate 14g



Prepared according to the general tandem cross-metathesis/hydrogenation procedure described in Section 3.3.6.

Allylammonium triflate (35 mg, 0.17 mmol), methyl acrylate 20% v/v in EtOAc (1.5 mL, 3.4 mmol), **HGII** (5 mg, 8 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 67 mg crude, 98% conversion by 1H n.m.r. spectroscopy. 1H n.m.r. (400 MHz, d_4-MeOH) δ 3.69 (s, 3H, OCH3), 2.99 (t, J = 7.6 Hz, 2H, H4), 2.48 (t, J = 7.2 Hz, 2H, H2), 1.95 (p, J = 7.4 Hz, 2H, H3), NH3 not observed due to exchange. 13C n.m.r. (100 MHz, d_4-MeOH) δ 174.6 (C1), 52.3 (OCH3), 40.1 (C4), 31.4 (C2), 23.7 (C3). HR-MS (ESI, +ve, MeOH): Calculated m/z 118.0863, Observed m/z 118.0864 [M-HBF4+H]+

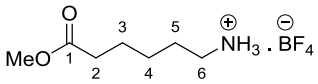
Synthesis of Methyl 5-ammonium pentanoate tetrafluoroborate 57c



Prepared according to the general tandem cross-metathesis/hydrogenation procedure described in Section 3.3.6.

3-Butenylammonium tetrafluoroborate (37 mg, 0.23 mmol), methyl acrylate 20% v/v in EtOAc (1.1 mL, 2.3 mmol), **HGII** (7.0 mg, 12 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 39 mg crude, 97% conversion by ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. (400 MHz, d_4-MeOH) δ 3.67 (s, 3H, OCH_3), 3.03-2.88 (m, 2H, H5), 2.47-2.36 (m, 2H, H2), 1.77-1.62 (m, 4H, H3 & H4), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 175.4 (C1), 52.1 (OCH_3), 40.5 (C5), 34.0 (C2), 27.9 (C3), 22.7 (C4). HR-MS (ESI, +ve, MeOH): *m/z* 132.1019, Observed *m/z* 132.1021 $[M\text{-}HBF_4+H]^+$.

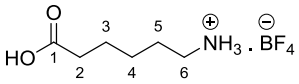
Synthesis of Methyl 6-ammonium hexanoate tetrafluoroborate 58



Prepared according to the general tandem cross-metathesis/hydrogenation procedure described in Section 3.3.6.

4-Pentenylammonium tetrafluoroborate (50 mg, 0.29 mmol), methyl acrylate 20% v/v in EtOAc (1.3 mL, 2.9 mmol), **HGII** (9.0 mg, 14 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (16 hours). Product did not crystallise, 97 mg crude, 95% conversion by ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. (400 MHz, d_4-MeOH) δ 3.66 (s, 3H, OCH_3), 2.93 (t, J = 7.5 Hz, 2H, H6), 2.36 (t, J = 7.3 Hz, 2H, H2), 1.72-1.61 (m, 2H, H3), 1.47-1.36 (m, 4H, H4 & H5), NH_3 not observed due to exchange. ^{13}C n.m.r. (100 MHz, d_4-MeOH) δ 175.8 (C1), 52.1 (OCH_3), 40.7 (C6), 34.4 (C2), 28.2, 26.8, 25.4 (C3, C4 & C5). HR-MS (ESI, +ve, MeOH): *m/z* 146.1176, Observed *m/z* 146.1175 $[M\text{-}HBF_4+H]^+$.

Synthesis of 6-Ammonium hexanoic acid tetrafluoroborate 59



Prepared according to the general tandem cross-metathesis/hydrogenation procedure described in Section 3.3.6.

4-Pentenylammonium tetrafluoroborate (50 mg, 0.29 mmol), acrylic acid (0.20 mL, 2.9 mmol), **HGII** (9.0 mg, 13 μmol), EtOAc (4 mL), reaction temperature (85 °C), reaction time (1 hours). Product did not crystallise, 92 mg crude, 97% conversion to title compound with ~10% methyl ester by ^{1}H n.m.r (see 0). ^{1}H n.m.r. (400 MHz, d_4-MeOH) δ 2.93 (t, *J* = 7.5 Hz, 2H, H6), 2.33 (t, *J* = 7.3 Hz, 2H, H2), 1.76-1.57 (m, 4H, H3 & H5), 1.53-1.32 (m, 2H, H4), NH_3 not observed due to exchange. ^{13}C n.m.r. (75 MHz, d_4-MeOH) δ 40.6 (C6), 34.3 (C2), 28.2 (C3), 26.8 (C5), 25.4 (C4). LR-MS (ESI, +ve, MeOH): Calculated *m/z* 132.1, Observed *m/z* 132.1 $[M\text{-}HBF_4+H]^+$.

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Chapter 4

Synthetic studies towards perhydrohistrionicotoxin

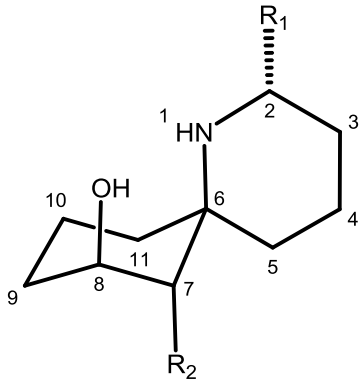
4.1 Introduction

4.1.1 The histrionicotoxins

The histrionicotoxin group of spiro-piperidine alkaloids was first isolated from the skin of the Columbian poison dart frog *Dendrobates histrionicus* by Daly *et al.* in 1971 (Figure 1).[1] The methanolic extracts of four hundred frog skins yielded 53 mg of pure histrionicotoxin-283A.[1] This extract was originally thought to be the first example of acetylenic alkaloids produced by a species in the animal kingdom.[1] Daly later discovered that frogs bred in captivity did not secrete the toxin, and therefore concluded that symbiotic microorganisms or diet were the likely sources of these alkaloids.[2]

Figure 1: Dendrobates histrionicus.[3]

Biological assessments conducted on histrionicotoxin-283A revealed that it is a selective, reversible and non-competitive inhibitor of nicotinic acetylcholine receptors[4] and has weak affinity for sodium and potassium ion channels in brain membranes.[5] Histrionicotoxin-283A and its synthetic relative, perhydrohistrionicotoxin **1**, are also potent local anaesthetics (IC_{50} 17 μM and 0.33 μM respectively).[5] These alkaloids have been shown to block neuromuscular transmission (at 20 μM) in frog muscles and render paralysis.[6] These interesting biological properties make the histrionicotoxin family of alkaloids useful probes for the study of nicotinic acetylcholine receptors in the field of pharmacology and neurophysiology.[7]



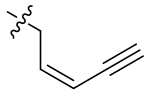
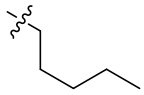
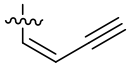
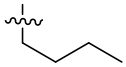
	histrionicotoxin-283A	perhydrohistrionicotoxin **1**
R_1		
R_2		

Figure 2: Representative histrionicotoxin alkaloids.[4]

The structure for histrionicotoxin-283A was solved by x-ray crystallography in 1971 by Daly *et al.* and was shown to be composed of a 1-azaspiro[5.5]undecane core, two unsaturated ene-yne chains at C2 and C7, and a hydroxyl group at C8 (Figure 2).[1] The molecule contains four stereocentres (three contiguous and one isolated), where the hydroxyl substituent and piperidine amine share a *cis* relationship. Interestingly, this arrangement provides an N-O bond distance analogous to that found in the neurotransmitter acetylcholine and this may be responsible for its potent effect at the

[^{3}H] ACh receptor.[8] Being both structurally and biologically interesting, these molecules have become popular synthetic targets for organic chemists, and numerous synthetic approaches to these aza-spirocycles have been published (Figure 3).

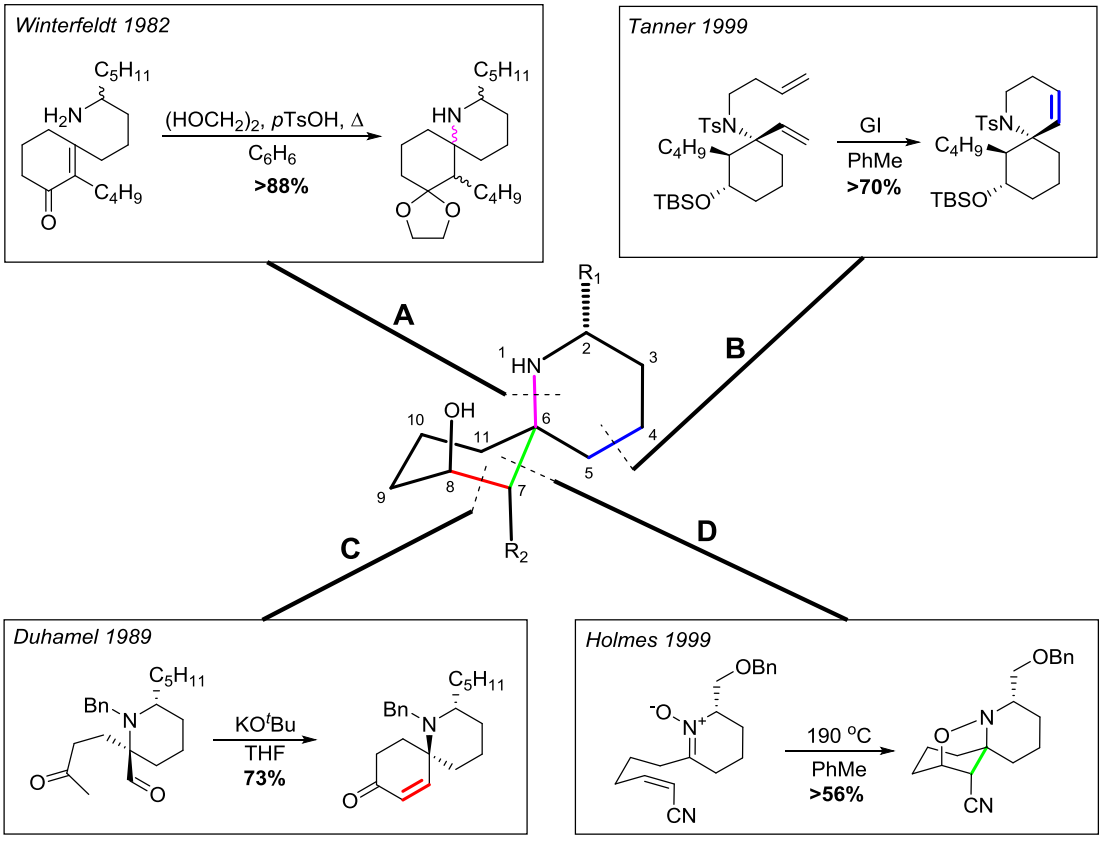


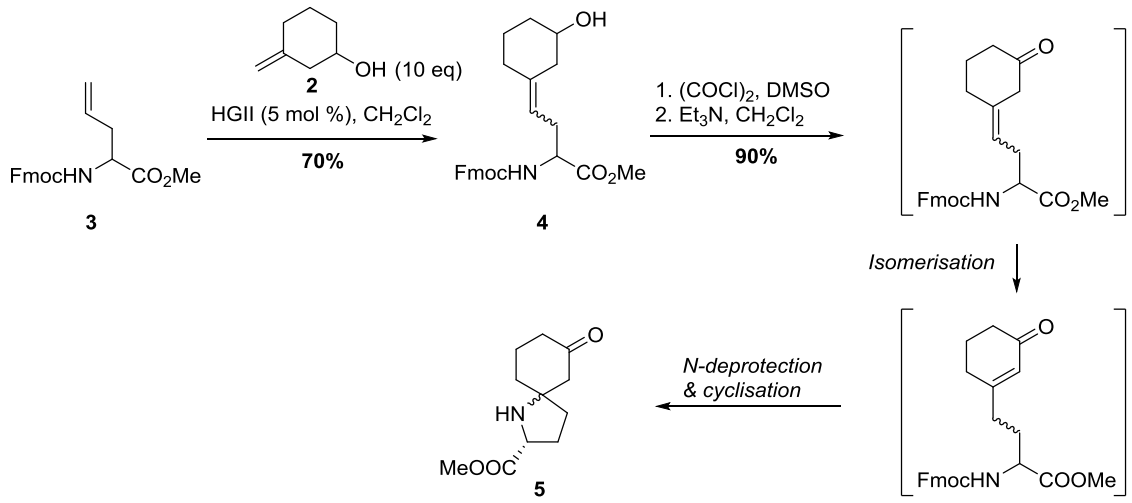
Figure 3: Synthetic approaches to the histrionicotoxin core.[4]

Some notable examples for histrionicotoxin spirocycle formation are included in Figure 3: **A**) The Winterfeldt 1982 synthesis which utilises a high yielding acid catalysed intramolecular aza-Michael cyclisation to form N1-C6;[9] **B**) The Tanner 1999 synthesis which uses a ring closing metathesis reaction to link C4-C5 with first generation Grubbs catalyst in good yield;[10] **C**) The Duhamel 1989 synthesis which uses an intramolecular Claisen condensation to form the spirocycle through C7-C8;[11] and **D**) the Holmes 1999 synthesis which uses a dipolar [3+2] cycloaddition reaction to form the spirocycle *via* bond formation between C6-C7.[12] Although these methods were successful for synthesis of the spirocycle, they have a few drawbacks. For instance, the Winterfeldt aza-Michael cyclisation (strategy **A**) is not stereoselective, and harsh epimerisation

conditions are required in the closing stages of the synthesis to install the correct stereochemistry of the molecule.[9] The Tanner and Duhamel syntheses (strategies **B** and **C**) sequentially install each stereogenic centre before spirocyclisation. Such an approach does not take advantage of the molecule's three contiguous stereocentres and an opportunity to simultaneously install the chirality by thermodynamic substrate control.[4] The Holmes method, although efficient at generating the correct stereochemistry, includes a very lengthy synthesis to the key nitrone (11 steps) and uses a chiral auxiliary to construct this key intermediate.[12]

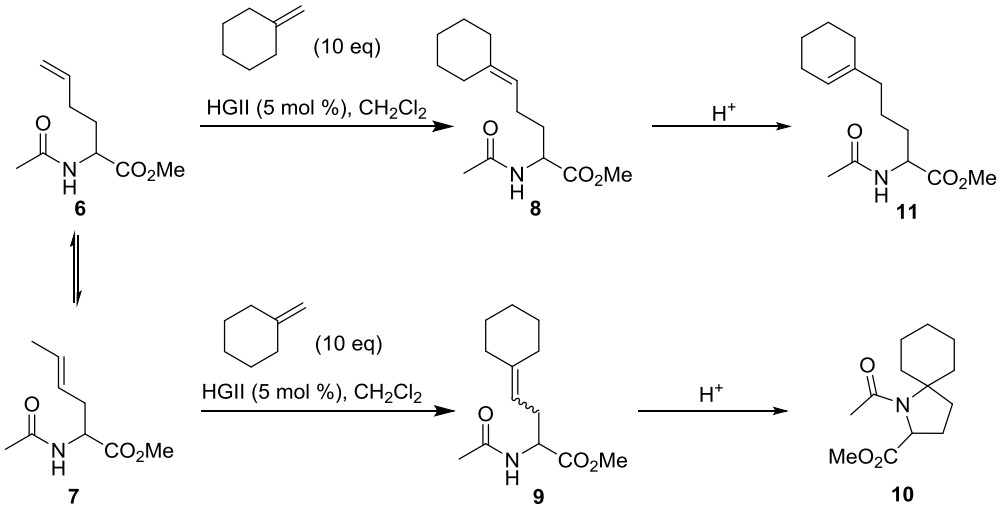
4.1.2 New synthetic approach

Our interest in catalysis prompted us to develop new methodologies for the efficient construction of complex small molecules, with emphasis on the use of olefin metathesis chemistry. Recently we have developed a method for the synthesis of spiro-pyrrolidine alkaloid precursors *via* ruthenium alkylidene catalysed cross metathesis of 3-hydroxymethylenecycloalkanes **2** with 2-allylglycine derivative **3** (Scheme 1). Exposure of the cross product **4** to Swern oxidative conditions was found to cause a concomitant isomerisation and *N*-deprotection before spontaneously cyclising to give spiro-pyrrolidine **5** in excellent yield.[13]



Scheme 1: Synthesis of spiro-pyrrolidines.[13]

We envisaged that the spiro-piperidine core of perhydrohistrionicotoxin **1** could be synthesised using this methodology, with a simple chain homologation of the 2-allylglycine derivatives **3** to 2-homoallylglycines **6** (Scheme 2). Disappointingly however, olefin isomerisation of 2-homoallylglycine derivatives **6** to 2-crotylglycines **7** occurred during metathesis and resulted in the formation of a chromatographically inseparable mixture of intermediates **8** and **9** in a 5 to 1 ratio respectively (Scheme 2). Acid-promoted cyclisation then gave a mixture of spiro-pyrrolidine **10** and endo-isomerised intermediate **11**, and none of the desired spiro-piperidine was detected.[14]



Scheme 2: Concomitant isomerisation during cross metathesis.[14]

The complicating issue of olefin isomerisation prompted us to design a new synthetic approach to facilitate efficient application of this cross metathesis methodology toward the synthesis of spiro-piperidines. It was postulated that the cross metathesis of a suitably protected 2-allylglycine derivative **12** with vinyl cyclohexanes **13** would generate the appropriate chain length intermediates **14** for spiro-piperidine alkaloids **15** (Figure 4).* With only a few examples of metathesis reactions with vinyl cyclohexanes in the literature[15-17] we were prompted to investigate the cross metathesis activity of this olefin family.

* During cross-metathesis, isomerisation of **3** is observed however the resultant internal C2 and C3 olefins do not undergo further cross-metathesis under the reaction conditions employed.

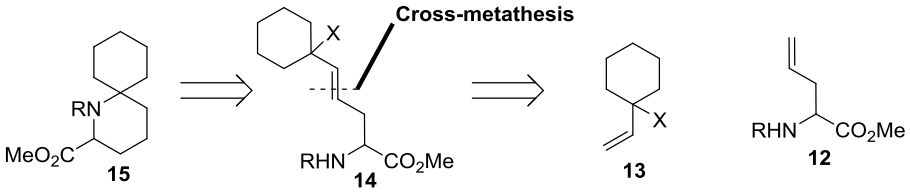
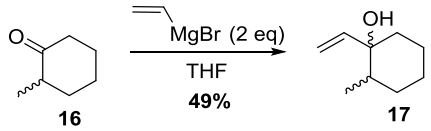


Figure 4: New synthetic approach to spiro-piperidine alkaloids.

4.2 Results and discussion

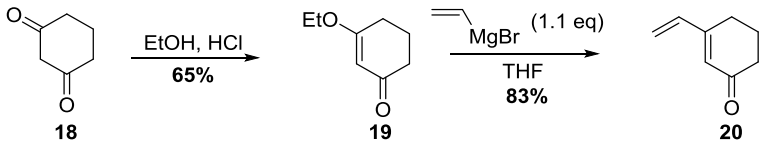
4.2.1 Model studies

In our proposed synthetic approach to the histrionicotoxins, the first question to be addressed was the efficiency of the cross metathesis reaction involving vinyl cyclohexanes. Firstly, 1-vinyl cyclohexanols were explored. These were chosen because of their ease of synthesis from the corresponding cyclohexanones, which can be functionalised with the native perhydrohistrionicotoxin *n*-butyl side chain *via* enolate chemistry. Furthermore, we envisaged that the tertiary alcohol could provide a handle for spirocyclisation *via* activation and elimination. Vinyl magnesium bromide Grignard addition to 2-methyl cyclohexanone **16** gave 2-methyl-1-vinyl-cyclohexanol **17** in a moderate yield of 49% (Scheme 3).



Scheme 3: Synthesis of 2-methyl-1-vinyl cyclohexanol 17.

Secondly, 3-vinyl cyclohexenones were explored. These were chosen because they have oxygenation at the correct position (C8) for the histrionicotoxins and facilitate installation of the *n*-butyl side chain using enolate chemistry. Furthermore, the α,β-unsaturated enone could provide a handle for spirocyclisation by intramolecular aza-ene or aza-Michael addition. Therefore, 1,3-cyclohexadione **18** was converted to the enol-ether **19** in ethanol at low pH on a large scale and in good yield. Subsequent vinyl magnesium bromide addition to the enol-ether **19** gave 3-vinyl-cyclohexenone **20** in high yield[†] (Scheme 4).[18]



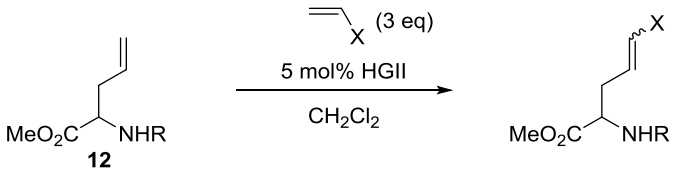
Scheme 4: Synthesis of 3-vinylcyclohexenone 20.

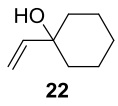
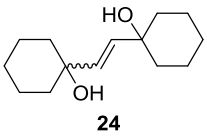
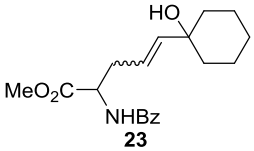
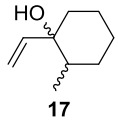
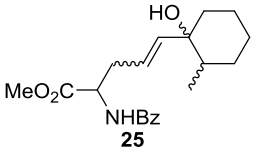
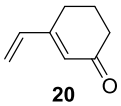
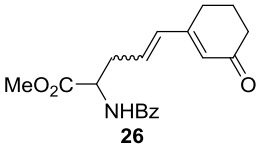
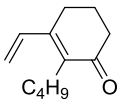
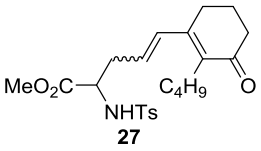
[†] Compound **20** decomposed on standing and was used without purification.

2-Butyl-3-vinylcyclohex-2-enone **21** was synthesised in an analogous manner, and will be discussed later in Section 4.2.4.

These compounds were tested for their activities in cross metathesis reactions under a standard, non-optimised set of conditions: Cross metathesis reactions with 3-vinyl cyclohexenones **20** and **21** were stirred at room temperature to slow olefin degradation. Cross metathesis reactions with 1-vinyl cyclohexanols **17** and **22** were heated at reflux in CH_2Cl_2 (Table 1).

Table 1: Cross metathesis reactions with vinyl cyclohexane derivatives.



CH_2=CHX	Self-metathesis	Cross-metathesis	Yield (%)
 **22**	 **24**	 **23**	63
 **17**	-	 **25**	65
 **20**	-	 **26**	66
 **21**	-	 **27**	59

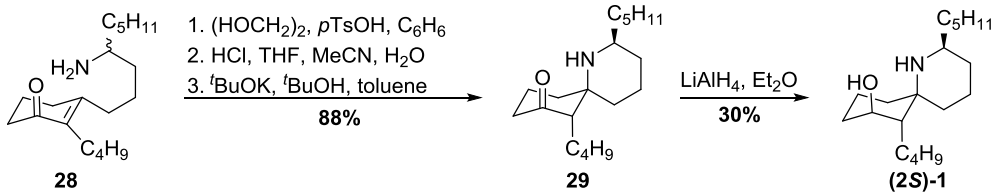
Gratifyingly, the ruthenium alkylidene catalysed cross metathesis of all vinyl cyclohexanes with 2-allylglycine derivatives **12** were productive and gave the expected cross products as a mixture of geometric isomers (Table 1). The isomeric mixture did not require separation because removal of the C4-C5 double bond *via* hydrogenation was planned at a later stage of the synthesis (as discussed in Section 4.2.3). Cross metathesis of 1-vinyl cyclohexanol **22** with the protected allylglycine **12** gave the desired cross-product **23** in 63% yield. This product was accompanied by the diol **24**

which resulted from the self-metathesis of the starting tertiary alcohol **22**. Cross metathesis of 2-methyl-1-vinylcyclohexanol **17** gave the desired cross product **25** in 65% yield. No self-metathesis of the tertiary alcohol **17** was observed which simplified purification of the target molecule **25**.

The absence of the self-metathesis of tertiary alcohol **17** was interesting given that the absence of the 2-methyl group in tertiary alcohol **22** allows for facile self-metathesis to the diol **24**. This difference in reactivity is not without precedent as previous studies in the group have shown that methyl branching of olefins can greatly reduce their activity in cross metathesis reactions.[19] 3-Vinylcyclohexenone **20**, despite its tendency to degrade at room temperature, was successfully crossed with the 2-allylglycine derivative **12** to give the stabilised dienone **26** in 66% yield. Similarly, the substituted 2-butyl-1-vinylcyclohexenone **21** was successfully crossed to give the desired target **27** in a moderate yield of 59%. Interestingly, no self-metathesis of the dienones **20** and **21** was observed and excess, unreacted material could be recovered by column chromatography, indicating that these olefins are stable under the inert conditions employed during the metathesis reaction.

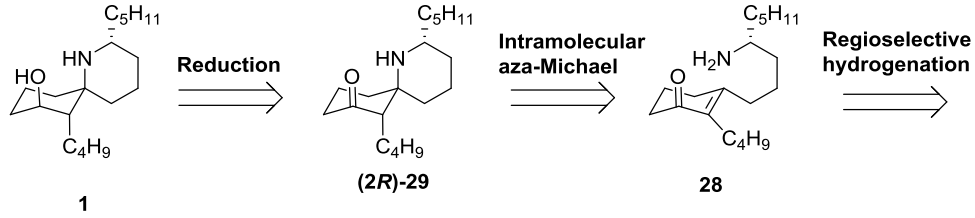
4.2.2 Total synthesis of perhydrohistrionicotoxin

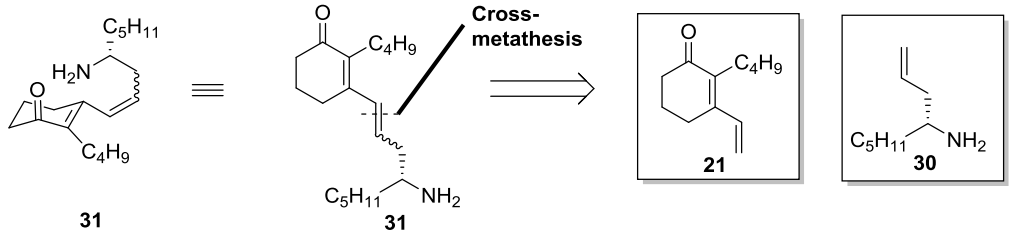
Given that both 1-vinylcyclohexanols **17** and **22** and 3-vinylcyclohexanones **20** and **21** were successful in cross-metathesis reactions with 2-allylglycine derivatives **12** to give intermediates suitable for spiro-piperidine formation, it was proposed that this methodology could be further extended toward the synthesis of the spiro-piperidine alkaloid perhydrohistrionicotoxin **1**.



Scheme 5: Winterfeldt 1982 synthesis of perhydrohistrionicotoxin.[9]

The Winterfeldt synthesis converts the advanced intermediate **28** into (2*S*)-perhydrohistrionicotoxin **1** by acid catalysed acetal formation and spirocyclisation[‡] followed by mild aqueous acid ketal deprotection and epimerisation with base to give spiro-ketone **29** exclusively as a thermodynamically-controlled isomer (Scheme 5).[9] The spiro-ketone is then reduced with lithium aluminium hydride to give (2*S*)-perhydrohistrionicotoxin **1** in low overall yield.





Scheme 6: The retrosynthesis of perhydrohistrionicotoxin 1.

Having the advantageous position of nearly three decades of perhydrohistrionicotoxin literature since Winterfeldt's publication (Scheme 5), we considered an intercepting synthesis *via* enone **28**.[9] Our approach aimed to emphasise the power and efficiency of transition metal catalysed reactions in a convergent total synthesis where the key step would utilise a cross metathesis reaction between the chiral homoallylic amine **30** and the dienone **21** (Scheme 6).[§] This transformation would then give the advanced dienone intermediate **31** which can be transformed into the enantiomerically pure enone **28** by a regioselective hydrogenation of the conjugated γ,δ-alkene. Once the enantiomerically pure Winterfeldt enone **28** is obtained, different strategies could then be employed to

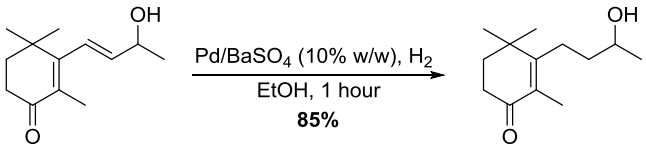
[‡] Acetal formation was deemed necessary to drive the Michael equilibrium in favour of spirocycle formation.

[§] The dienone **21** was chosen as a cross partner for this synthesis, rather than 1-vinyl-2-butyl-cyclohexanol, as it contains an oxo group at C8 for future reduction to the native hydroxyl group.

induce intramolecular aza-Michael cyclisation to the spiro-ketone **(2*R*)-29**, which upon stereoselective reduction would yield perhydrohistrionicotoxin **1**.

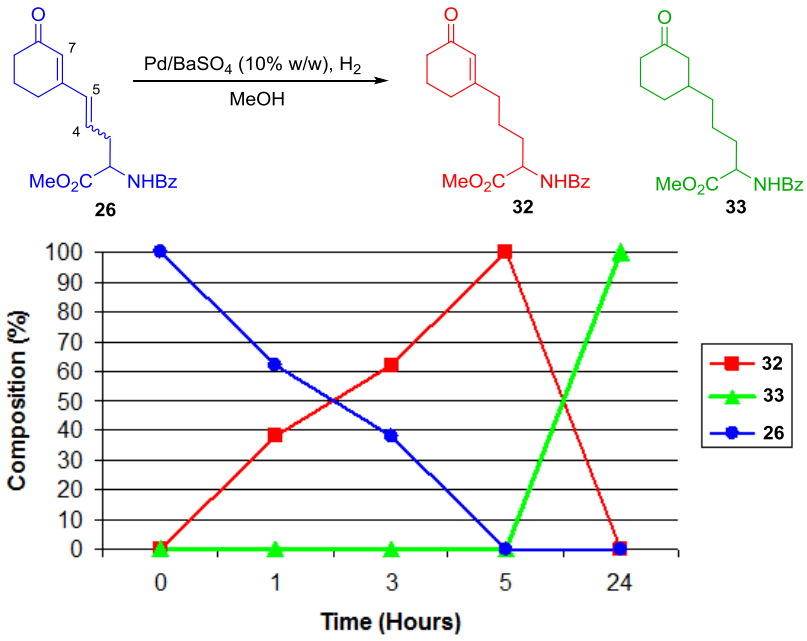
4.2.3 Regioselective hydrogenation study

Upon completion of model cross metathesis reactions with 3-vinylcyclohexanones, it was important to find a method for the regioselective hydrogenation of the conjugated γ,δ-alkene of **31** in presence of the sensitive α,β-unsaturated enone moiety (Scheme 6). Literature precedence for this reaction exists and Kaiser *et al.* regioselectively hydrogenate the conjugated γ,δ-alkene of a cyclic dienone using palladium(0) poisoned with barium sulphate ($Pd/BaSO_4$) (Scheme 7).[20]



Scheme 7: Regioselective hydrogenation of a cyclic dienone.[20]

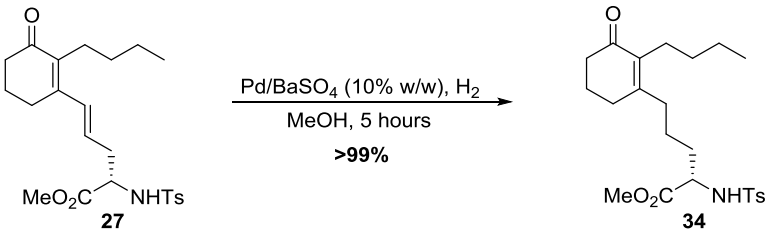
The cross-product dienone **26** was subjected to hydrogenation as a mixture of geometric isomers under an atmosphere of hydrogen gas with 10% $Pd/BaSO_4$. The reaction was followed by ^1H n.m.r. spectroscopy to monitor regioselectivity during the hydrogenation (Scheme 8).



Scheme 8: Regioselective hydrogenation of 26.

Importantly, there was high regioselectivity for the hydrogenation of the conjugated γ,δ-C=C; ^{1}H n.m.r. spectroscopy showed progressive reduction of the olefin proton resonances H4 and H5 relative to the α,β-unsaturated enone proton resonance H7. Semi-hydrogenation to cyclic enone **32** was complete in 5 hours and complete hydrogenation to the saturated cyclic ketone **33** was observed after 24 hours (Scheme 8). Pleasingly, no internal hydrogenation of the α,β-unsaturated enone moiety was observed until all of the conjugated γ,δ-alkene was hydrogenated. The origin of this regioselectivity is believed to relate to relative steric environments, where the conjugated γ,δ-alkene is much less hindered than the α,β-unsaturated enone moiety. The proposed natural product synthesis requires the regioselective hydrogenation of a disubstituted, conjugated γ,δ-alkene over a tetrasubstituted α,β-unsaturated enone moiety (**31,** Scheme 6). The preliminary hydrogenation result described above therefore boded well for our planned regioselective hydrogenation of the intermediate **31**. To test the reproducibility of this method, the hydrogenation of the cross metathesis product **27** was performed (Scheme 9), which is a close structural analogue of the intermediate **31** shown in the previously outlined retrosynthesis (Scheme 6). High regioselectivity was also obtained for this

hydrogenation and after 5 hours quantitative conversion to the target enone **34** was achieved.

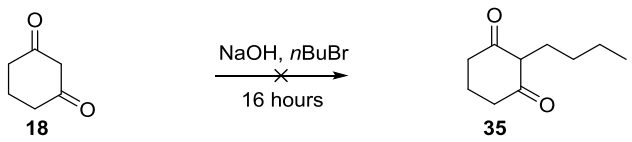


Scheme 9: Regioselective hydrogenation of 27.

4.2.4 Synthesis of 2-butyl-3-vinylcyclohex-2-enone 21

Having completed successful model studies for cross metathesis and regioselective hydrogenation, the required synthesis of 2-butyl-3-vinylcyclohex-2-enone **21** was initiated. It was proposed that this fragment could be synthesised using the same methodology used for the preparation of 3-vinylcyclohexenone **20** (Scheme 4) with an additional alkylation step to add the C7 *n*-butyl side chain.

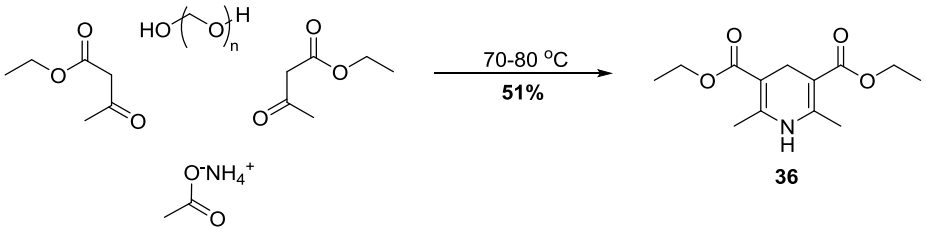
It was envisaged that 2-butyl-3-vinylcyclohex-2-enone **21** could be easily synthesised by treatment of 1,3-cyclohexadione **18** with aqueous sodium hydroxide to generate the corresponding sodium enolate which could be alkylated with *n*-butyl bromide to give 2-butyl-1,3-cyclohexadione **35** as per methodology described by Barrack *et al.*.[21] Unfortunately, this was unsuccessful and only starting material was recovered after reflux for 16 hours (Scheme 10).



Scheme 10: Attempted alkylation of dione 18.

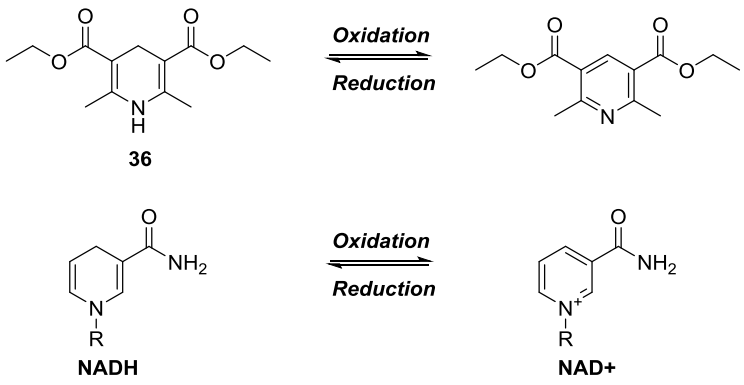
In 2007, Ramachary *et al.* reported that 2-butyl-1,3-cyclohexadione **35** can be readily synthesised by an L-proline-catalysed tandem Knoevenagel condensation/Hantzsch

ester hydrogen transfer reaction.[22] Hantzsch's ester **36** is a commercially available dihydropyridine, albeit at high cost. Fortunately, the dihydropyridine **36** is readily synthesised on a large scale *via* multicomponent condensation of ethylacetoacetate (2 eq), ammonium acetate (1 eq) and paraformaldehyde (1 eq) in moderate yield (Scheme 11).



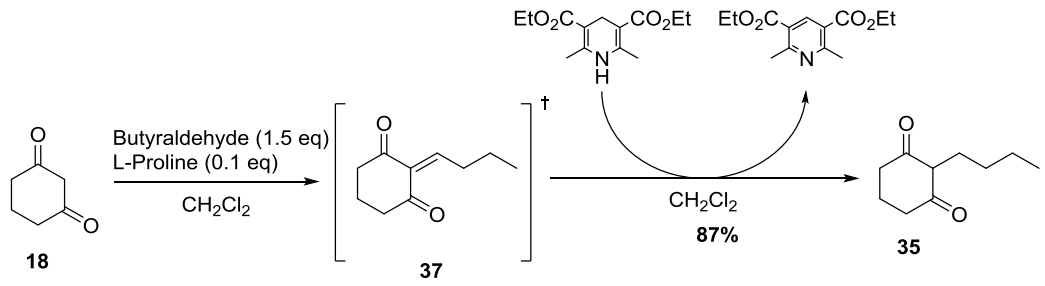
Scheme 11: Multicomponent synthesis of Hantzsch ester 36.

Hantzsch's ester **36** is a bio-inspired hydrogen transfer agent whose mechanism for reduction is reminiscent of the human body's metabolism redox system, $NADH/NAD^+$ (Scheme 12).[23] It is able to reduce various α,β-unsaturated carbonyl compounds to give the corresponding saturated carbonyl compounds at ambient temperature.[22, 23] Therefore it was decided to apply this methodology to achieve alkylation of dione **18**.



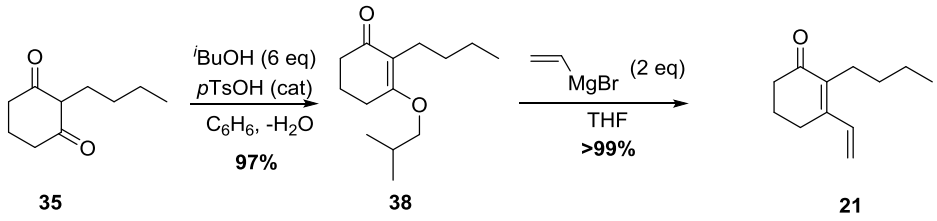
Scheme 12: Analogous redox pairs.[22]

The prepared Hantzsch's ester was used in a L-proline catalysed tandem catalytic reaction, where the unstable Knovenangel condensation product **37**, of butyraldehyde and 1,3-cyclohexadione **18**, was immediately reduced to 2-butyl-1,3-cyclohexadione **35** which was isolated by crystallisation on large scale in high yield (87%, Scheme 13).



Scheme 13: Synthesis of 2-butyl-1,3-cyclohexadione 35.

The diketone **35** was then converted to the enol ether **38** in excellent yield (97%) with *iso*-butanol and *p*-toluene sulphonic acid in a Dean-Stark apparatus (Scheme 14). Vinylic Grignard addition to enol ether **38** required two equivalents of the vinyl magnesium bromide to yield the target 2-butyl-3-vinylcyclohex-2-enone **21** in excellent crude yield with sufficient purity for use in subsequent metathesis reactions. Further purification of this compound was found to result in decomposition. Hence, the crude dienone **21** was used in the following cross metathesis reactions.

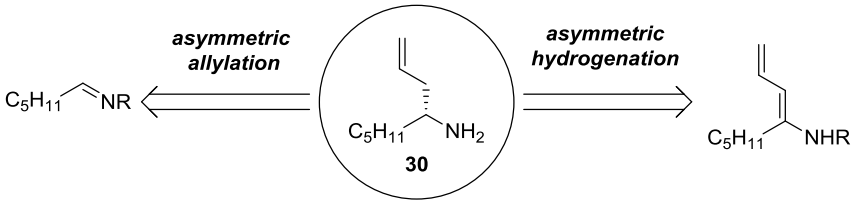


Scheme 14: Synthesis of 2-butyl-3-vinylcyclohex-2-enone 21.

4.2.5 Synthesis of chiral homoallylic amine 30

Having successfully synthesised the dienone **21** fragment for the total synthesis of perhydrohistrionicotoxin **1**, the chiral alkenyl homoallylic amine **30** fragment was the next target. There are numerous methods reported in the literature for the synthesis of chiral homoallylic amines with poor to excellent stereoselectivities.[24-28] A substantial number of these methods however, require a sterically demanding or aromatic functional group attached to the pro-chiral centre to assist in chiral induction. Such

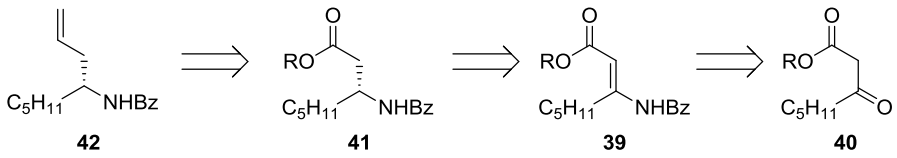
methods are less helpful for the synthesis of chiral homoallylic amine **30** as it only contains a simple pentyl side chain which may make chiral induction challenging. Keeping this concept in mind, the two most appropriate general methods for the direct synthesis of the chiral homoallylic amine **30** were deemed to be asymmetric allylation and asymmetric hydrogenation (Scheme 15).



Scheme 15: Possible routes to 30

4.2.6 Asymmetric hydrogenation route to 30

The first path attempted for the synthesis of chiral homoallylic amine **30** was the asymmetric hydrogenation route because of its functional group tolerance and large degree of tunability in the reaction system by variation of the: catalyst, ligand and reaction conditions to help control both which isomer forms and enantioselectivity.[24, 29, 30]



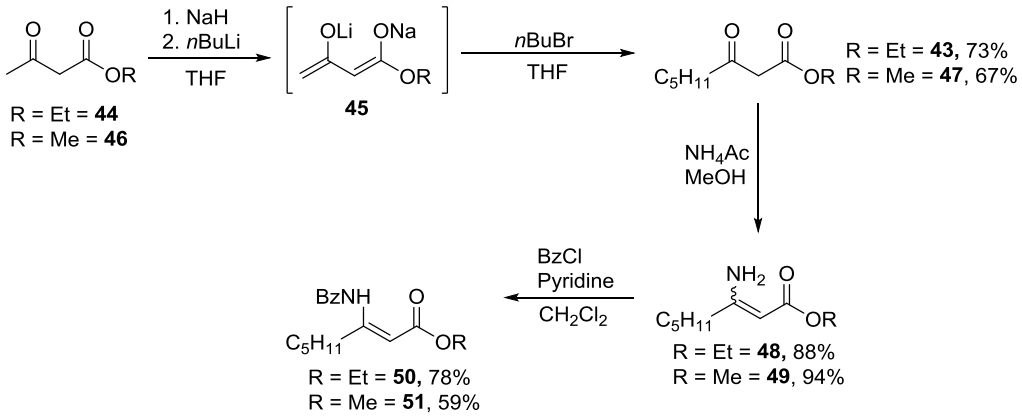
Scheme 16: Retrosynthesis of 42.

The asymmetric hydrogenation of prochiral enamides (similar to **39**) has been described by Burk *et al.*[31] and exploited extensively for the synthesis chiral amine containing products such as α- and β-amino acids (Scheme 16).[30, 32, 33] It was envisaged that this chemistry could be applied to the synthesis of the chiral homoallylic amine **30.** The β-keto ester **40** could be converted to the enamine with ammonium acetate and protected with benzoyl chloride to give enamide **39**. This enamide **39** when subjected to

asymmetric hydrogenation using a Rh(I) based catalyst with chiral phosphine ligands (e.g. DuPHOS or BPE) would give the β^3-amido ester **41.** This ester **41** could be reduced to the aldehyde with DIBAL-H and olefinated with a Wittig reaction to give the benzoyl protected chiral homoallylic amine **42.** As free amines are problematic during metathesis (see Chapter 3), this benzoyl protected version **42** of the homoallylic amine **30** would instead be investigated in the cross-metathesis reaction with **20** to generate the protected advanced intermediate **31** and subsequently transformed into perhydrohistrionicotoxin **1** (Scheme 6).

4.2.7 Synthesis of enamides 50 & 51

Firstly, the β-keto ester **43** was synthesised from ethyl acetoacetate **44** using chemistry developed by Weiler *et al.* (Scheme 17).[34]



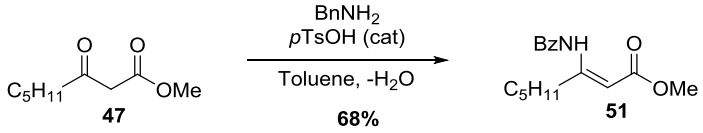
Scheme 17: Synthesis of enamides 50 & 51.

Ethyl acetoacetate **44** was deprotonated with one equivalent of sodium hydride at the more acidic C2 carbon. This anion was then treated with one equivalent of *n*-butyl lithium to give the THF soluble dianion **45** which was then regioselectively alkylated with *n*-butyl bromide at the C4 carbon to give the desired β-keto ester **43** in 73% yield. Similarly, this was performed with methyl acetoacetate **46** to give the corresponding methyl β-keto ester **47** in 67% yield. The β-keto esters **43** and **47** were then condensed with ammonium acetate in methanol to give the enamines **48** and **49** in 88% and 94%

yield respectively as a mixture of geometric isomers (10:1, *Z*:*E*). These enamines were then reacted with benzoyl chloride in the presence of pyridine and chromatographed to isolate the geometrically pure (*Z*)-enamides **50** and **51** in 78% and 59% yield respectively. The corresponding (*E*)-enamides, however, were not isolated as only small amounts of the (*E*)-enamides were observed in the crude mixture. This is thought to be due to an intramolecular hydrogen bond that exists between hydrogen on the enamide nitrogen and the ester carbonyl oxygen which stabilises the structure of the (*Z*)-enamide relative to the (*E*)-enamide (Scheme 18).

Scheme 18: Enamide hydrogen bonding.

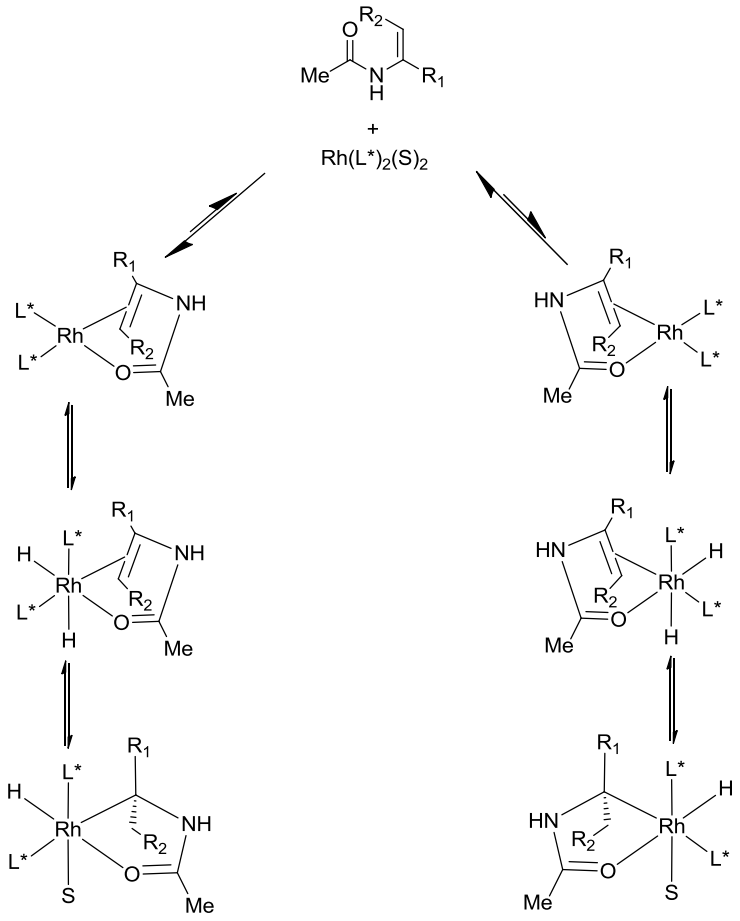
Evidence for this intramolecular hydrogen bond is presented in the proton n.m.r. spectra for the enamide products **50** and **51**, where the amide NH proton in both analogues has moved to a downfield chemical shift of around 12.1 ppm which is typical of a hydrogen bonded system, where normal amide NH protons typically exist between 4-8 ppm. Furthermore, it was discovered that this three step sequence for the synthesis of enamide **51** (Scheme 17) could be shortened by one synthetic step by the direct reaction of benzamide with β-keto ester **47** which gave the (*E*)-enamide **51** in 68% yield after column chromatography (Scheme 19).



Scheme 19: Direct synthesis of enamide 51.

4.2.8 Asymmetric hydrogenation of enamides 50 & 51

It was envisaged that the prochiral enamides **50** and **51** could be hydrogenated under conditions described by Burk *et al*. to give chiral β-amido esters.[31] The mechanism for the asymmetric hydrogenation of prochiral enamides with rhodium(I) complexes with chiral, chelating phosphine ligands was proposed by Halpern[35] and described by Chan *et al.* (Scheme 20).[29]



Scheme 20: Mechanism for Rh-catalysed asymmetric hydrogenation.[29, 35]

Chelation of enamide substrates to the rhodium(I) centre occurs through a five membered ring from the amido oxygen to the alkene moiety (η^2) (Scheme 20). This usually forms one of two distinct diastereomeric complexes in preference based on the chiral ligand choice. Oxidative addition of hydrogen to the complex forms the reactive Rh(III) dihydride complex which then adds hydrogen to the enamide generating a five membered Rh(III) cyclometalate complex. This complex undergoes reductive

elimination with the remaining hydride to recycle Rh(I) and release the hydrogenated enamide. Intuitively, it could be interpreted that the major diastereomeric complex leads to the major isomer product, however this was found to not be the case from experimental results observed by Halpern.[35] It was determined that the minor diastereomeric complex leads to the major isomer hence supporting the notion that hydrogenation of the minor diastereomeric complex is faster.

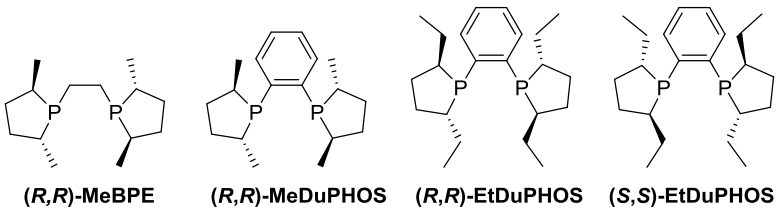
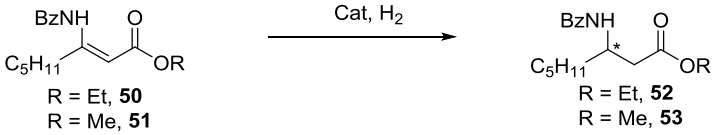


Figure 5: Typical ligands for asymmetric hydrogenation.

To assist in chiral HPLC analysis, the (*Z*)-enamides **50** and **51** were firstly reduced under achiral Pd/C conditions to give the racemic β-amido esters **52** and **53** in 73% and 72% yield respectively (Table 2, Entries 1 & 2). The enamides were then subjected to a number of trial asymmetric hydrogenation conditions using a Rh(I) based catalyst with DuPHOS and BPE phospholane ligands (Figure 5).

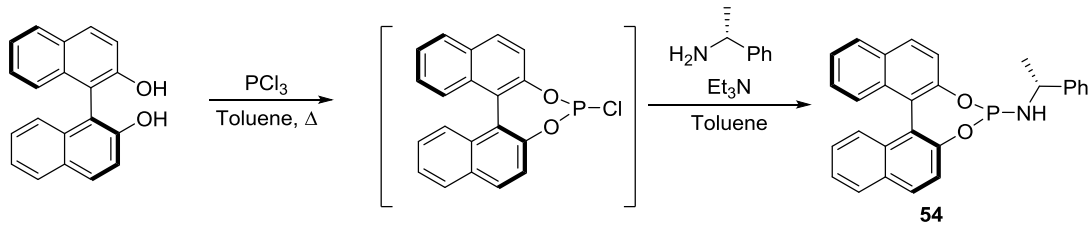
Table 2: Optimisation of hydrogenation conditions.



Entry	Catalyst	R=	Solvent	H_2	Conv (%)	ee (%)	Yield (%)
1	Pd/C	Et	MeOH	75 psi	>99	0	73
2	Pd/C	Me	MeOH	75 psi	>99	0	72
3	Rh(R,R)MeBPE.OTf	Et	MeOH	90 psi	>99	18	-
4	Rh(R,R)MeDuPHOS.OTf	Et	MeOH	90 psi	>99	38	-
5	Rh(R,R)EtDuPHOS.OTf	Et	MeOH	90 psi	>99	50	-
6	Rh(S,S)EtDuPHOS.OTf	Et	MeOH	90 psi	>99	44	-
7	Rh(R,R) EtDuPHOS.OTf	Et	Toluene	90 psi	0	0	-
8	Rh(COD)(**54**)$_2$.OTf	Me	^{i}PrOH	350 psi	>99	97	80

Using the chiral phospholane ligand (*R,R*)-MeBPE for the asymmetric hydrogenation of **50** showed complete conversion to the β-amido ester **52** by chiral HPLC but at a low

enantioselectivity of 18% (Table 2, Entry 3). Switching to the DuPHOS based phospholane ligands increased the enantioselectivity to 38% with (*R*,*R*)-MeDuPHOS (Entry 4) and 50% with the more bulky (*R*,*R*)-EtDuPHOS ligand (Entry 5). As anticipated, the use of the enantiomeric ligand, (*S*,*S*)-EtDuPHOS for the hydrogenation of **50** gave preference for the opposite stereoisomer of **52** (Entry 6). This approach facilitates access to both enantiomers of our required β-amido ester if required. It has been reported that the reaction solvent can affect the enantioselectivities in asymmetric hydrogenation reactions.[36] Unfortunately, when using toluene instead of methanol, no conversion to the desired β-amido ester **52** was observed (Entry 7) under analogous hydrogenation conditions. Having only achieved modest enantioselectivities (≤50%) for the asymmetric hydrogenation of **50** and **51** using chiral phospholane ligands, our attention was directed towards the use of chiral phosphoramidite ligands reported by de Vries *et al.*.[37] These ligands are easily synthesised in a one pot procedure by a reaction of the chiral BINOL ligand with PCl_3 followed by the addition of a chiral, enantiopure amine (Scheme 21).

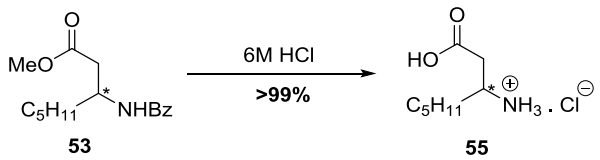


Scheme 21: Phosphoramidite ligand synthesis.

Gratifyingly, the hydrogenation of enamide **51** using phosphoramidite ligand **54** at a low catalyst loading of 0.5 mol% Rh(I)(COD)OTf gave the desired β-amido ester **53** in an excellent enantioselectivity of 97% ee and good isolated yield (80%) (Table 2, Entry 8).

4.2.9 Stereochemical assignment of 53

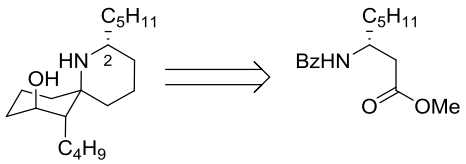
Having successfully synthesised β-amido ester **53** in high enantioselectivity, it was deemed important to assign the stereochemistry of the newly formed chiral centre. A number of methods were considered, however it seemed simpler to derivatise the β-amido ester **53** into the β-amino acid **55** and compare to literature optical rotation data. This was done by acidic hydrolysis in 6M aqueous HCl at reflux to give the β-amino acid **55** as the hydrochloride salt in quantitative yield (Scheme 22).



53 **55**

Scheme 22: Acidic hydrolysis of 53.

The optical rotation for this compound in water (c = 0.8) was determined to be $[\alpha]_D$ = -19.7 which is comparable to that reported for (3*R*)-3-amino octanoic acid hydrochloride $[\alpha]_D$ = -16.6, (c = 1.1, >95% ee).[38] As racemisation is unlikely to occur during the acidic hydrolysis, it can be inferred that we have synthesised the (*R*)-isomer of the β-amido ester **53**. Fortuitously, **(*R*)-53** translates into the correct stereoisomer required for the synthesis of (-)-perhydrohistrionicotoxin **1** (Figure 6).



*(-)-**1*** (*R*)-**53**

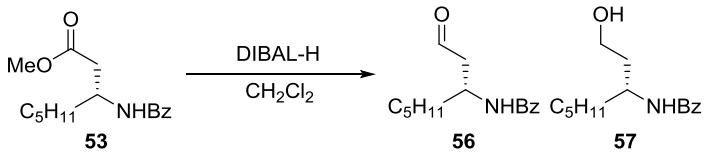
Figure 6: Stereochemical relationship between 53 and (-)-1.

4.2.10 Synthesis of chiral homoallylic amine 42

Transformation of (*R*)-β-amido ester **53** into the target homoallylic amine **42** required reduction of the ester functional group to an aldehyde followed by Wittig methylenation

(Scheme 16). Reduction of **53** with DIBAL-H was found to be capricious and highly dependent on reaction conditions (Table 3).

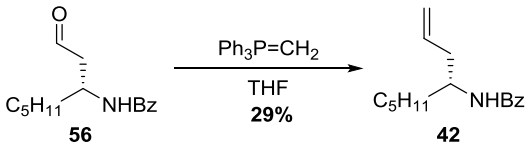
Table 3: DIBAL-H reduction of 53.



		Conversion (%)			
Entry	**DIBAL-H (eq)**	**S.M. (53)**	**Aldehyde (56)**	**Alcohol (57)**	**Yield (56)**
1	1	45	44	11	-
2	2.4	26	74	0	42[a]
3	5	4	17	79	-

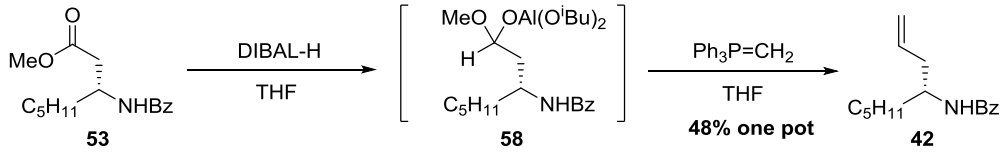
[a]Yield based on ^{1}H n.m.r. spectroscopy of a mixture of **56** and **57** after column chromatography.

Using one equivalent of DIBAL-H gave incomplete conversion to the aldehyde **56**, with a trace amount of the over-reduced alcohol **57** observed by ^{1}H n.m.r. spectroscopy of a small aliquot from the reaction mixture (Entry 1). Using 2.4 equivalents of DIBAL-H gave good conversion to the aldehyde **56** (74%) but starting material **53** still remained (Entry 2). Using five equivalents of DIBAL-H the major product, as expected, was the over reduced alcohol **57** (79% conversion) with only small amounts of aldehyde **56** observed (Entry 3). Although decent conversion to the aldehyde was obtained using 2.4 equivalents of DIBAL-H (74%, Entry 2), full workup gave inconsistent product distributions to those determined from a small aliquot previously. Furthermore, the aldehyde **56** could not be isolated from the alcohol **57** by column chromatography. Therefore the crude mixture was filtered through silica to give an estimated yield of 42% by ^{1}H n.m.r. spectroscopy and the crude product was telescoped into the next reaction. Unfortunately, the Wittig methylenation of aldehyde **56** was also troublesome, presumably due to auto-oxidation of the aldehyde. The target benzoyl protected homoallylic amine **42** was therefore only obtained in poor isolated yield (29%) (Scheme 23).



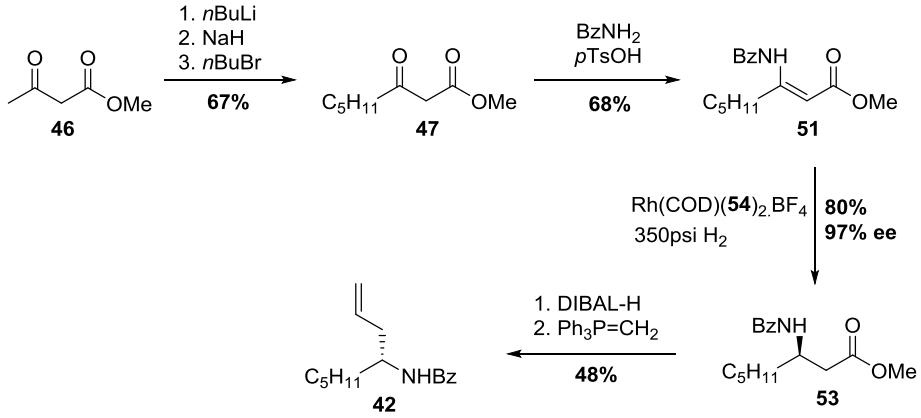
Scheme 23: Wittig olefination of 56.

Although this approach successfully generated the target amine **42**, it was deemed unsatisfactory for expedient and large scale synthesis of the target homoallylic amine. We therefore explored alternative chemistries. It has been reported in the literature that aluminium hydride reduction of esters and subsequent Wittig olefination of the alumino-hemiacetal intermediate **58**, an aldehyde equivalent, can be performed in a one pot procedure without isolation of intermediates (Scheme 24).[39, 40]



Scheme 24: Wittig olefination of alumino-hemiacetal 58.

Using this strategy the required benzoyl protected homoallylic amine **42** was synthesised in 48%. This presented a more synthetically viable strategy when compared to the 12% overall yield for the two pot procedure described above.

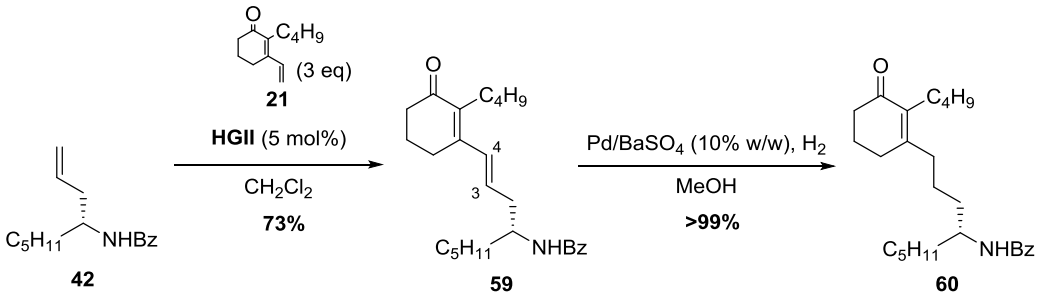


Scheme 25: Summary for synthesis of 42.

In summary, the required benzoyl protected homoallylic amine (*R*)-**42** was synthesised in a 4 step procedure in 17% overall yield and 96% ee from β-keto ester **46** (Scheme 25).

4.2.11 Cross metathesis of 21 and 42

The dienone **21** and homoallylic amide **42** were then reacted in a cross metathesis reaction on a 3 to 1 stoichiometric ratio using 5 mol % Hoveyda-Grubbs second generation catalyst (**HGII**) (Scheme 26).

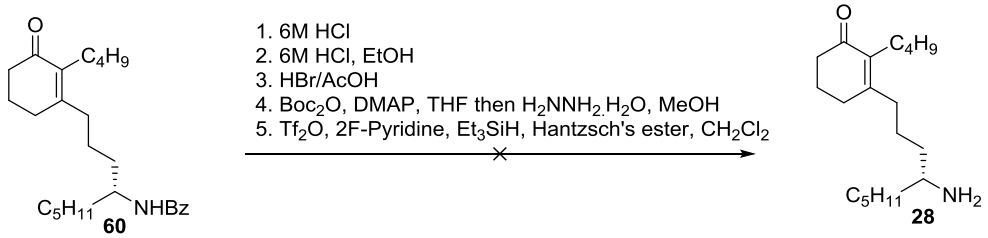


Scheme 26: Synthesis of enone 60.

This gave the advanced intermediate **59** in 73% yield. Interestingly the ^{1}H n.m.r spectrum of **59** showed only one set of olefinic resonances with a coupling constant of 15.7 Hz between H3 and H4. This supports that only the (*E*)-isomer of compound **59** had formed during the metathesis, presumably due to unfavourable steric interactions. Compound **59** was then smoothly hydrogenated with poisoned $Pd/BaSO_4$ catalyst using the previously established conditions to give the enone **60** in excellent yield (>99%).

4.2.12 Attempted de-protection of 60

To intercept the Winterfeldt enone **28**,[9] to complete a formal synthesis of perhydrohistrionicotoxin **1**, a deprotection of the benzoyl group of **60** was needed. This was attempted under a variety of conditions described in Greene *et al.* (Scheme 27).[41]



Scheme 27: Attempted deprotection of 60.

Unfortunately, the benzoyl protecting group could not be removed under any of the above-described conditions, and in most cases only the starting material **60** was recovered. The global reduction of **60** with $LiAlH_4$ was also attempted, but this approach unsurprisingly gave a complex mixture of products whose structures were difficult to elucidate by spectroscopic techniques. Being unable to remove the protecting group was surprising as benzamide cleavage for β-amido ester **53** to the free amino acid **55** had not previously caused trouble (Scheme 22). Upon evaluation of the reaction mechanism of **53** to **55**, and given that compound **60** fails to hydrolyse under identical conditions, would imply that direct hydrolysis is not the prevalent mechanism for the deprotection of **53**. Instead, it was proposed that an assisted cleavage *via* nucleophilic catalysis involving the proximal ester group of **53** is responsible for benzamide cleavage and thus these methods are not suitable for the benzamide cleavage of **60** as no proximal ester moieties are present. This result led us to question the utility of the benzamide protecting group. Although it is required for the asymmetric hydrogenation step, since it provides chelation control during hydride addition, it is not required for the metathesis step providing the nucleophilicity of the nitrogen atom can be reduced.[Ψ] Towards this end, the potential for using a *non-protected* amine equivalent of **42**, in the form of a quaternized salt, was considered. Such an approach would therefore require cross-metathesis between an unprotected homoallylic amine **30** and dienone **21**. Although much more complex, this is chemically analogous to the cross-metathesis reaction between salt masked alkenyl amines and acrylates reported in Chapter 2. Despite being unsuccessful in synthesising **28** *via* the asymmetric hydrogenation route, the failure of this approach provided the opportunity to take the previously reported salt-cross metathesis methodologies and apply them to the total synthesis of perhydrohistrionicotoxin **1**, demonstrating the broad applicability of the approach.

[Ψ] Chelation control *via* carbamate protected amines usually leads to poor conversion and enantioselectivity in asymmetric hydrogenation reactions catalysts by chiral Rh(I) catalysts. Hence replacement of the amide protecting group for a labile carbamate was not a viable option.

4.2.13 Asymmetric allylation route to 30

Although the benzoyl protected homoallylic amine **42** (Scheme 26) could be deprotected to give the free amine **30** for salt cross-metathesis reactions, this approach increases the number of steps in the sequence to five with an expected overall yield of <17%. Hence we decided to explore the asymmetric allylation route with a view to generating the analogous amine substrate in fewer synthetic steps.

Asymmetric allylations usually involve the nucleophilic addition of an allyl group to an electrophilic, pro-chiral carbon centre which is more commonly a part of an aldehyde, ketone or imine.[29] The stereochemical induction can come from the use of a chiral auxiliaries, chiral allyl nucleophile, chiral catalysts or additives.[29] Retrosynthetically, we considered that our desired chiral amine could be easily synthesised by the asymmetric allylation of an imine of 1-hexanal (Scheme 15). A procedure by Sato *et al.* outlines the synthesis of homoallylic amines in high diastereoselectivity (up to 19:1) from titanium-mediated allylation of chiral imines derived from (*R*)-α-methylbenzylamine and an aldehyde.[42] The origin of the diastereoselectivity is attributed to the formation of a six-membered chair transition state between the allyl titanium species and the imine (Figure 7).

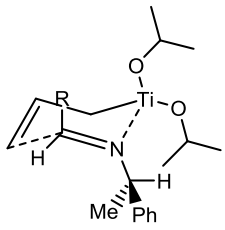
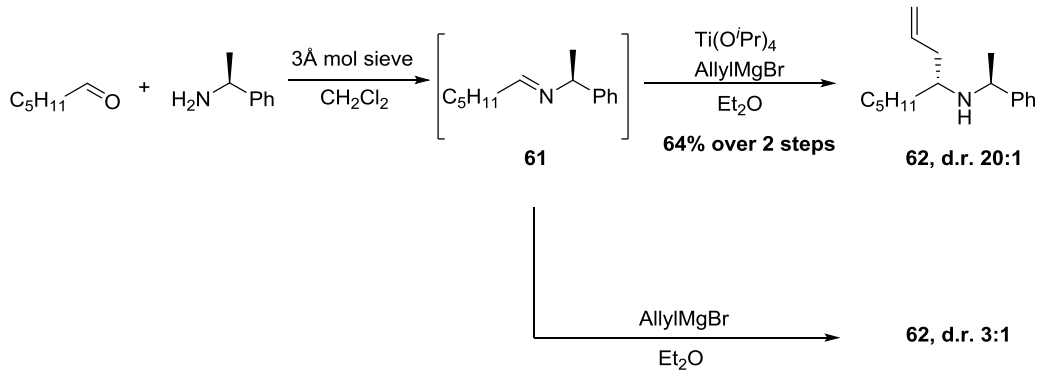


Figure 7: Six-membered transition state.

Hexanal was condensed with (*S*)-α-methylbenzylamine in the presence of 3Å molecular sieves to give the imine **61** which, without isolation, was added slowly to the allyl titanium species generated from the addition of allylmagnesium bromide to titanium(IV) tetraisopropoxide in THF at low temperature (Scheme 28).



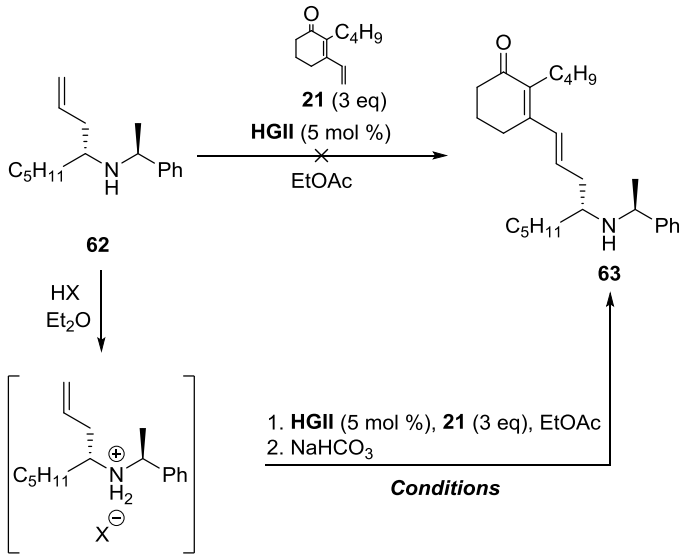
Scheme 28: Allylation of 61.

This approach yielded the desired benzyl homoallylic amine **62** in high diastereoselectivity (20:1 = 90%) and good yield (64%) over two steps (Scheme 28). For comparison, direct addition of the allylic Grignard reagent was also attempted on imine **61**. This gave the benzyl homoallylic amine **62** in a less attractive diastereomeric ratio of 3:1 (Scheme 28). Despite the need for a chiral auxiliary, the diastereoselective allylation path provided an efficient, one step telescopic synthesis of the target chiral unprotected homoallylic amine. This was deemed more attractive than the asymmetric hydrogenation route which required five or more transformations. Based on the proposed mechanism the major diastereomer is likely to be formed as the *syn*-Cram product, which would provide (*R*)-configuration at C2. Several options exist for assigning the stereochemistry of **62** following cyclisation to **1** including ^{1}H n.m.r. spectroscopy and x-ray crystallography. Thus, in the interests of time, stereochemical assignment of **62** was delayed pending successful cross-metathesis and cyclisation.

4.2.14 Cross metathesis reactions with 62

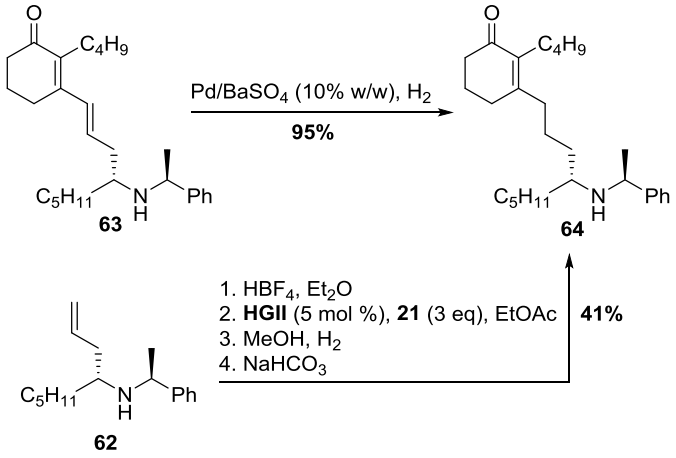
As the benzyl homoallylic amine **62** contains a nucleophilic amine moiety we postulated that its direct use in cross-metathesis reaction would be unsuccessful because of deleterious coordination to the catalyst (as discussed in Chapter 2). Nevertheless the cross-metathesis of the amine **62** with three equivalents of dienone **21** and 5 mol% Hoveyda-Grubbs second generation catalyst (**HGII**) was attempted to examine this hypothesis (Table 4).

Table 4: Synthesis of dienone 63.



Entry	HX	Eq (21)	Conditions	Yield (63)
1	free amine	3	rt, 16 hours	0%
2	TfOH	3	rt, 16 hours	48%
3	HBF_4	3	Δ, 16 hours	45%
4	**HBF_4**	**3**	**Δ, 3 hours**	**63%**
5	HBF_4	1	Δ, 3 hours	49%

As expected the cross-metathesis of free amine **62** with dienone **21** failed to yield the dienone cross product **63** (Table 4, Entry 1). Conversion of the free amino group into its ammonium triflate was achieved by *in situ* protonation with triflic acid. Gratifyingly, subsequent metathesis of the salt with dienone **21** under identical conditions yielded the dienone **63,** exclusively as the (*E*)-isomer, albeit in a modest yield of 48% (Entry 2). This yield for **63** was improved to a respectable 63% using the tetrafluoroborate salt with a shorter reaction time at reflux (Entry 4). Notably, longer reaction time resulted in poorer yield which may imply the instability of the dienone cross-product **63** under the reaction conditions. The cross product was then subjected to the regioselective hydrogenation conditions established previously with $Pd/BaSO_4$ and a balloon of hydrogen to give the enone **64** in excellent isolated yield (Scheme 29).

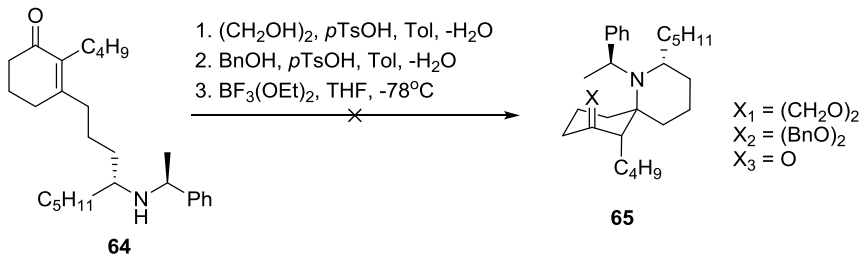


Scheme 29: Synthesis of enone 64.

Conveniently, the tandem cross-metathesis/hydrogenation protocol as developed in Chapter 3 was employed for the synthesis of enone **64**. This gave the enone in **64** in a moderate 41% yield from the homoallylic amine **62** (Scheme 29). Although the tandem protocol shortens the synthetic sequence and only requires the use of one precious metal catalyst, the isolated yield (41%) is less when compared to the two sequential steps (60%). Furthermore, by performing the hydrogenation in tandem, it does not allow for recovery of excess enone **21** which is used in three equivalents for the metathesis step, this detracts from the efficiency of the protocol.

4.2.15 Cyclisation of enone 64

The enone **64** was then subjected to several conditions in attempt to obtain the spirocycle **65** arising from the intramolecular aza-Michael addition of pendant benzylamine into the tetrasubstituted enone (Scheme 30).



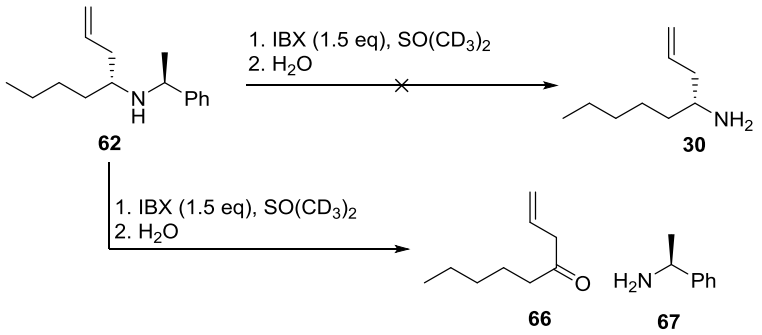
Scheme 30: Attempted cyclisation of 64.

Unfortunately, none of these methods provided any of the spirocyclic product **65** as either the ketone, or masked as the acetal (Scheme 30). This was surprising as Winterfeldt *et al.* described facile cyclisation of the nor-benzylated amine **28** (Scheme 5) *via* method 1 as described in the scheme above (Scheme 30).[9] The failed cyclisation implies that the steric environment around the nucleophilic nitrogen in **64** retards the aza-Michael reaction and hence the equilibrium lies in favour of the uncyclised structure. These difficulties in performing the Michael addition was also reported by Corey *et al.* for an analogous structure, and thus different cyclisation strategies were investigated.[43]

We considered that the issue could be conveniently solved in one of two ways: the first would involve a cleavage of the benzylamine group to liberate the less hindered primary amine which would intercept the Winterfeldt synthesis and thus constitute a formal synthesis of perhydrohistrionicotoxin.[9] The second strategy would utilise chemistry developed by Tanner *et al.* involving the use of iodine mediated cyclization to construct the spirocyclic core of perhydrohistrionicotoxin.[44]

4.2.16 Debenzylation of enone 64

Green describes three main ways to afford debenzylation of benzylic amines.[41] These methods include: hydrogenolytic, oxidative and Von Braun dealkylation, however the latter cannot be used as it only applies to tertiary amines and thus cannot be applied to the debenzylation of **64**. Due to the precious nature of **64**, the homoallylic amine precursor **62** was used as a model for debenzylation of **64** as is contains the same α-methylbenzylamine functional group. Oxidative methods were evaluated first as they were deemed potentially less destructive to the enone moiety in **64** as compared to reductive methods (Scheme 31).

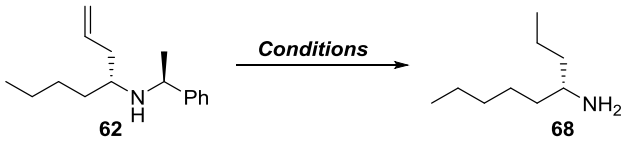


Scheme 31: Oxidative debenzylation of 62.

Homoallylic amine **62** was reacted with a slight excess of 2-iodoxybenzoic acid (IBX) in deuterated DMSO at 45 °C followed by aqueous hydrolysis. The *in situ* analysis of the reaction mixture prior to hydrolysis showed a disappearance of H4 proton, usually located at ~2.50 ppm, and a shift of the H1' proton from 3.85 ppm to 4.66 ppm. Hence, while cleavage was regioselective, the undesired C-N bond was being cleaved resulting in the unsaturated ketone **66** and α-methylbenzylamine **67** rather than the required homoallylic amine **30**.

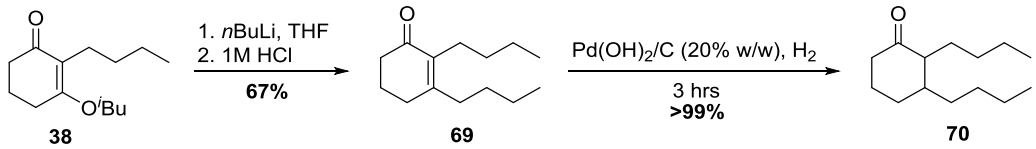
Hydrogenolytic methods were next investigated for the debenzylation of **64**, where again the homoallylic amine **62** was used as a model for such reactions. It was deemed necessary to work out the mildest conditions for the hydrogenolysis of **64** as the enone moiety would be susceptible to hydrogenation under the same conditions. Firstly, transfer hydrogenation conditions were employed using a palladium on charcoal catalyst with five equivalents of ammonium formate as the hydrogen transfer reagent (Table 5, Entry 1). Unfortunately, no conversion to the expected saturated amine **68** was obtained, and only starting material **62** was observed by ^{1}H n.m.r. spectroscopy.

Table 5: Hydrogenolysis of 62.



Entry	Catalyst	H_2	Conditions	Conversion 68 (%)
1	Pd/C	$NH_4^+HCOO^-$	THF:MeOH (1:4), Δ, 16 hours	0
2	$Pd(OH)_2/C$	H_2 balloon	MeOH, rt, 3 hours	~30
3	$Pd(OH)_2/C$	H_2 balloon	MeOH, rt, 16 hours	~80

Pearlman's catalyst ($Pd(OH)_2/C$) is commonly used for the rapid debenzylation of benzyl amines.[41] Using 20 w/w% Pearlman's catalyst under a balloon atmosphere of hydrogen, complete reduction of the alkene together with some debenzylation was observed by ESI+ mass-spectrometry (Entry 2). The reaction was left over-night and increased debenzylation was observed (Entry 3). To establish whether the enone moiety within **64** was stable to these hydrogenation conditions a simple analogue of **64** bearing the reactive enone moiety, 2,3-dibutylcyclohex-2-enone **69**, was synthesised by the addition of *n*BuLi to enol ether **38** followed by acidic hydrolysis (Scheme 32).



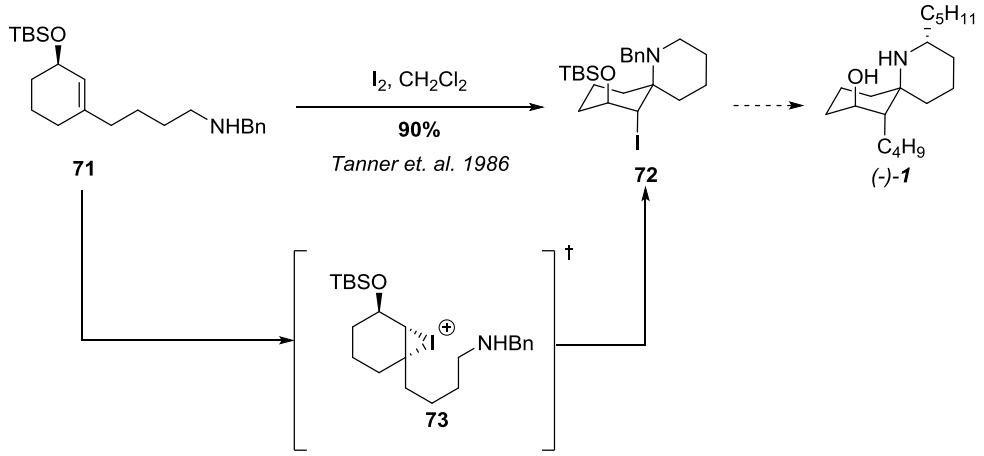
38 **69** **70**

Scheme 32: Hydrogenation of 69.

Unfortunately, under the mildest conditions for the debenzylation of **62**, the enone **69** completely reduced to the saturated ketone **70** after just 3 hours of reaction time. Results from these model studies indicate that the chemoselective debenzylation of **64** would be extremely difficult and thus the interception of the Winterfeld intermediate **28** (Scheme 5) cannot be achieved using this approach.

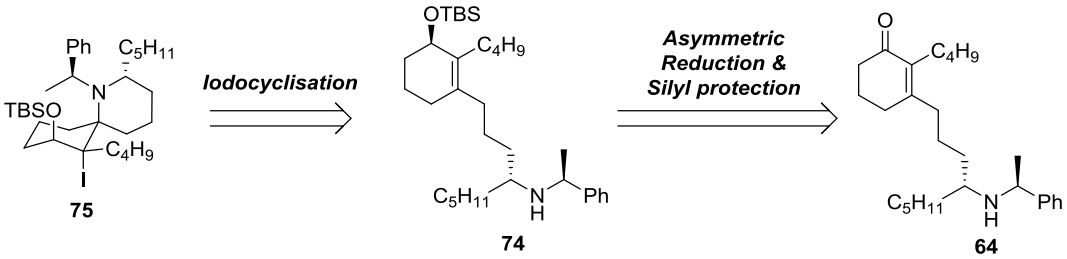
4.2.17 The halocyclisation approach

In 1986, Tanner *et al.* described the iodocyclisation of benzylic amine **71** to give iodo-spirocycle **72** in excellent yield and stereospecificity (Scheme 33).[44]



Scheme 33: Tanner iodocyclisation of 71.

Presumably the stereochemistry in the final product **72** is determined from the sterically favoured *trans*-iodinium intermediate **73**, which is driven by the bulky TBS protecting group.[44] This approach was thought to be useful for our synthesis as a similar silyl ether **74** could be intercepted *via* an asymmetric reduction of enone **64** using asymmetric hydrogenation conditions established by Noyori *et al.* or a chiral borane reduction and subsequent TBS protection of the allylic alcohol (Scheme 34).

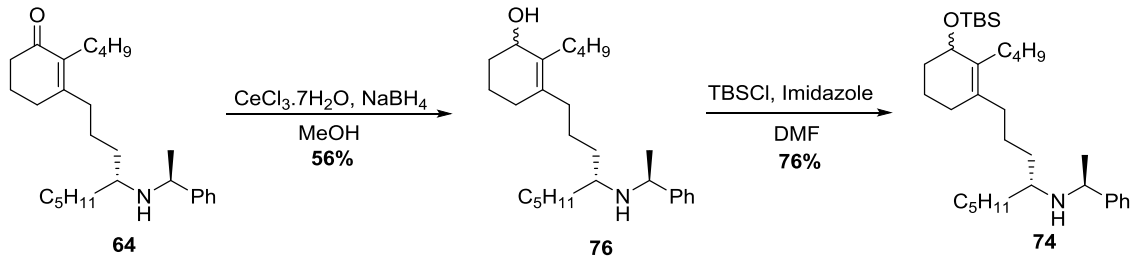


Scheme 34: Retrosynthesis of 75.

Attempted synthesis of this silyl ether **74** was investigated in order to develop conditions for the iodocyclisation leading to the iodo-spirocycle **75**.

4.2.18 Synthesis of silyl ether 74

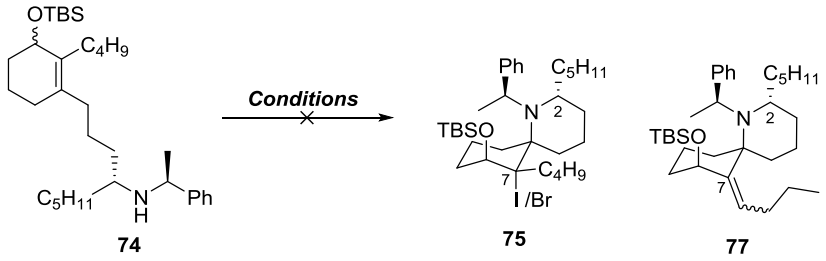
Racemic silyl ether **74** was synthesised in two steps by Luche reduction of **64** which gave allylic alcohol **76** in moderate yield (Scheme 35).



Scheme 35: Synthesis of racemic silyl ether 74.

Protection of the allylic alcohol **76** with TBSCl and imidazole in DMF gave the desired silyl ether **74** in good yield. Silyl ether **74** was then subjected to a number of halo cyclisation conditions to facilitate the formation of the spirocycle **75** (Table 6)**.**

Table 6: Attempted halocyclisation of 74.



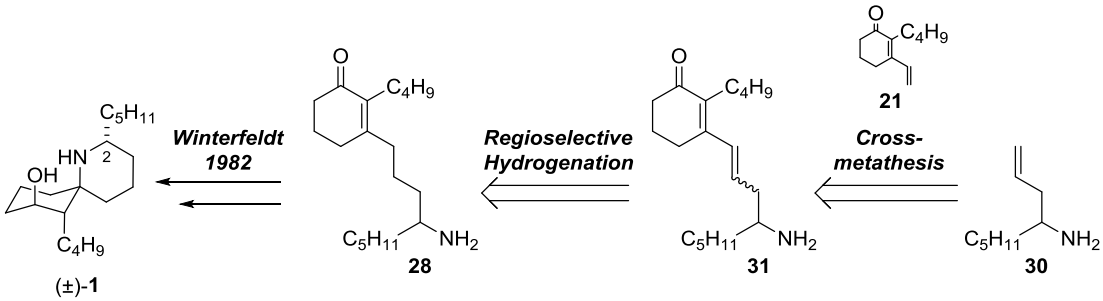
Entry	Halogen	Conditions	75/77 (%)	Observation
1	I_2 (4 eq)	sat. $NaHCO_3$, CH_2Cl_2, 16 hours	0	Complex mixture
2	I_2 (2 eq)	sat. $NaHCO_3$, THF, 1 hours then DBU, 16 hours	0	S.M.
3	I_2 (1.5 eq)	DBU, THF, 16 hours	0	S.M.
4	NBS (2 eq)	K_2CO_3, CH_2Cl_2, 16 hours	0	Complex mixture

Using the biphasic iodocyclisation conditions (CH_2Cl_2 and sat. $NaHCO_3$) established by Tanner *et al*., complete consumption of silyl ether **74** was observed by mass spectroscopy (Entry 1). Disappointingly, none of the desired product **75** was detected, where only a mixture of complex and unidentifiable compounds were observed (Entry 1).[44] This was not surprising as similar iodocyclic compounds to **75** are reported to be highly unstable and decompose rapidly.[45] Thus immediate telescopy of the unstable iodides into Pd-catalysed dehalogenation[45] or base mediated elimination[46] reactions was needed to obtain derivatives that could be isolated and characterised. It was thought that addition of a strong organic base (DBU) to the iodide **75**, would give the dehydrohalogenated exo-cyclic alkene **77**. This alkene would be far more stable and

also more easily detected by ^{1}H n.m.r. spectroscopy due to the presence of a new olefinic methine at approximately 5-6 ppm (Entry 2). The advantage of synthesising exo-cyclic alkene **77** over halide **75** is having the ability to perform asymmetric hydrogenation to install the C7 stereocenter. The iodocyclisation/dehydrohalogenation conditions employed by Sawada *et al.* were used by reacting silyl ether **74** with iodine, sodium bicarbonate in THF followed by rapid workup and addition of DBU (Entry 2).[46] Unfortunately, this only returned starting material. An all-in-one pot procedure of iodocyclisation/dehydrohalogenation was then attempted to afford exo-cyclic alkene **77** by addition of silyl ether **74** to a mixture of iodine and DBU in dry THF over 16 hours (Entry 3). Unfortunately, this too gave none of the desired exo-cyclic alkene **77**. Due to a lack of success with iodine, the bromocyclisation of **74** was attempted using *N*-bromo-succinimide (NBS). This was thought to be a more suitable approach as tertiary alkyl bromides are inherently more stable than tertiary alkyl halides due to a smaller ionic radius. Bromocyclisation with NBS and K_2CO_3 in CH_2Cl_2 showed complete consumption of starting material **74**. However, again, none of the desired product **77** was detected and only mixtures of complex and unidentifiable compounds were observed (Entry 4).

4.2.19 Interception of Winterfeldt enone 28

The previous approaches for the total synthesis of (±)-perhydrohistrionicotoxin involved the synthesis of the N-benzoyl **60** and N-α-methylbenzyl **64** enone intermediates which, disappointingly could not be cyclised or deprotected under a variety of conditions. It was therefore decided to directly intercept the Winterfeldt enone intermediate **28** *via* the direct cross-metathesis of primary homoallylic amine **30** with dienone **21** followed by regioselective hydrogenation (Scheme 36).

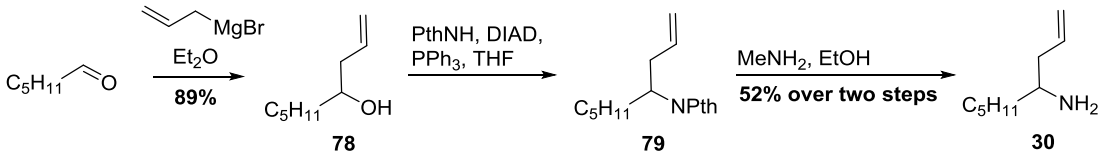


Scheme 36: Retrosynthesis for 28.

Synthesising the enone **28** would then constitute a formal synthesis as transformation of **28** into (±)-perhydrohistrionicotoxin **1** has previously been described by Winterfeldt *et al*. (Scheme 5).[9]

4.2.20 Synthesis of homoallylic amine 30

It was envisaged that the racemic homoallylic amine **30** could be synthesised on large scale in three simple steps from 1-hexanal. Grignard addition of allylmagnesium bromide to hexanal gave the homoallylic alcohol **78** in an excellent 89% yield (Scheme 37).

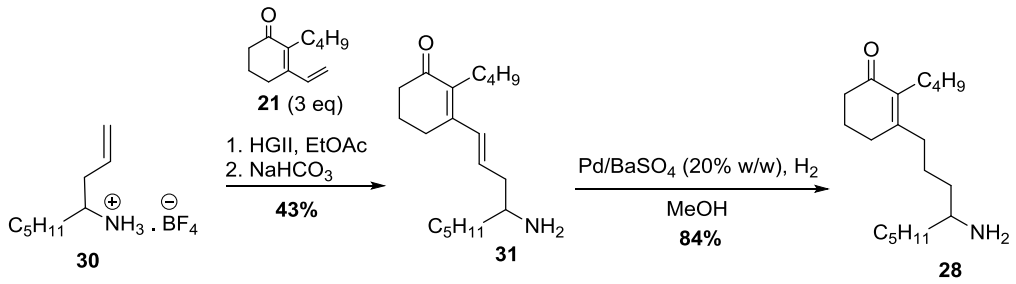


Scheme 37: Synthesis of homoallylic amine 30.

Mitsunobu reaction with homoallylic alcohol **78** using DIAD, triphenylphosphine and phthalimide gave the homoallylic phthalimide **79**, which was directly telescoped into phthalimide cleavage using methylamine in ethanol. This gave racemic homoallylic amine **30** which was isolated by distillation in a respectable 52% yield over the two steps.

4.2.21 Synthesis of Winterfeldt enone 28

The cross-metathesis and regioselective hydrogenation of the homoallylic amine **30** with dienone **21** was then investigated with the intention of intercepting the Winterfeldt enone **28**. The tetrafluoroborate salt of homoallylic amine **30**** was reacted in a cross-metathesis reaction with three equivalents of dienone **21** and 5 mol% Hoveyda-Grubbs second generation catalyst (**HGII**) in ethyl acetate. This gave the extended dienone **31** in moderate yield (43%) after column chromatography (Scheme 38).



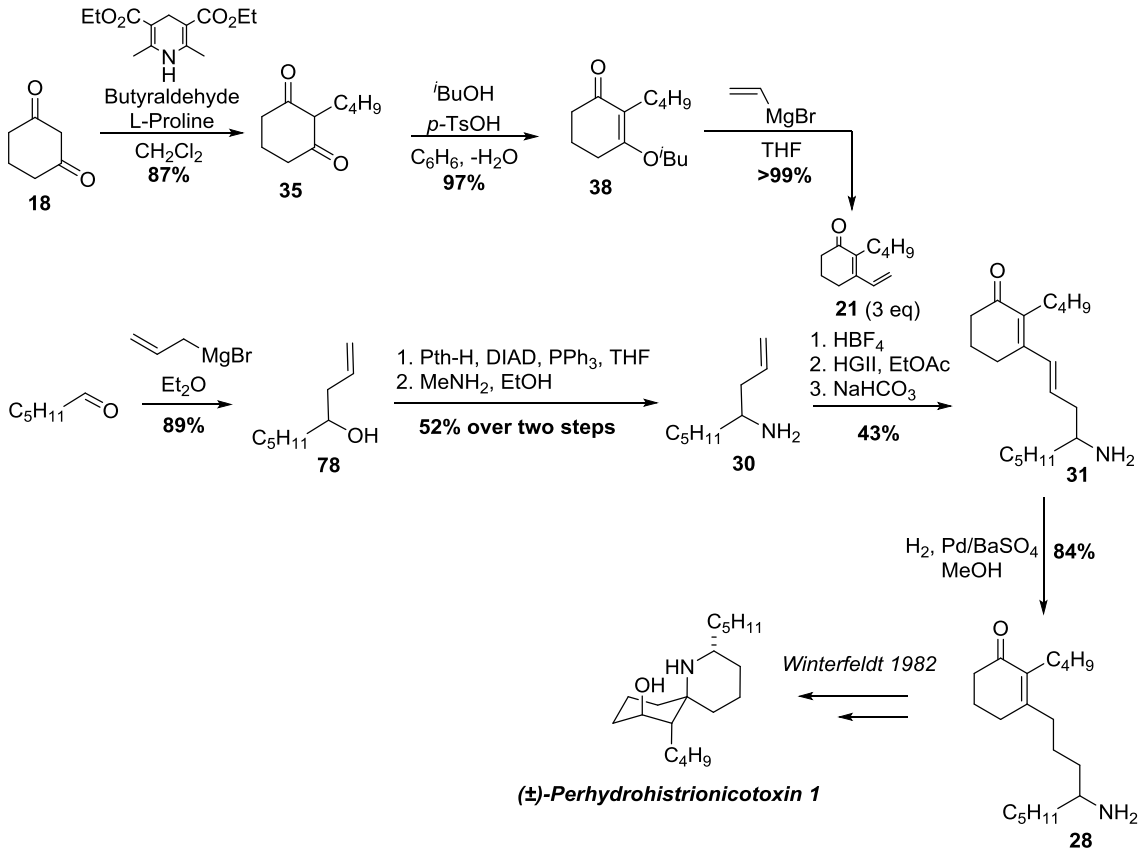
Scheme 38: Synthesis of 28.

The extended dienone **31** was then subjected to the regioselective hydrogenation conditions with $Pd/BaSO_4$ and a balloon of hydrogen to give the Winterfeldt enone **28** in good isolated yield (84%) after column chromatography.

4.2.22 A formal synthesis of *(±)*-perhydrohistrionicotoxin

To summarise, the Winterfeldt enone **28** was synthesised in a convergent seven step synthesis from 1,3-cyclohexadione **18** and 1-hexanal with a longest linear sequence of 5 steps and a total yield of 30% (Scheme 39). Key transformations include a one pot Knoevenagel condensation/transfer hydrogenation mediated by Hantzch's ester, a cross-metathesis reaction of a Brønsted-acid masked primary homoallylic amine and a palladium catalysed regioselective hydrogenation.

** Pre formed by the addition of one molar equivalent of HBF_4 to primary amine **30**.



Scheme 39: A formal synthesis of perhydrohistrionicotoxin 1.

Although longer than the Winterfeldt sequence (3 steps, 21% overall yield)[9, 47], this synthesis illustrates a more complex application of cross-metathesis reactions with alkenyl ammonium salts beyond the scope of the simpler polyamide monomers produced in Chapter 3. This general method involving Brønsted-acid masking of amines during metathesis reactions allows for the efficient synthesis of complex amine containing molecules and challenges the current paradigm which is more focused on covalent protecting group strategies for the amino group.

4.2.23 Conclusions and future work

Although a formal synthesis was achieved for (±)-perhydrohistrionicotoxin **1**, a few additional topics could be investigated in the future to expand this chemistry. Firstly, it would be important to investigate the tandem cross-metathesis/hydrogenation (e.g. Scheme 29) of homoallylic amine **30** with dienone **21** to give the Winterfeldt

intermediate **28** directly without the use of an additional catalyst in a new step, thus shortening the sequence and perhaps obtaining better overall yields. Furthermore it would be interesting to see the effect of having enantiopure homoallylic amine **30** and subjecting the subsequent enantio-enriched Winterfeldt intermediate **28** to cyclisation conditions in an attempt to develop an asymmetric synthesis of-perhydrohistrionicotoxin. It would be interesting to include functionalization sites instead of aliphatic side chains in attempt to access the whole histrionicotoxin family of alkaloids.

4.3 Experimental

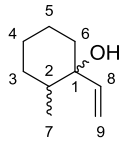
4.3.1 General Experimental

Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), EtOAc (EtOAc), diethyl ether (Et_2O), hexane (C_6H_{14}), methanol (MeOH), dimethylsulfoxide (DMSO) and toluene (PhMe) were used as supplied by Merck. Benzene (C_6H_6) was supplied by Sigma-Aldrich®. Deuterated solvents ($CDCl_3$, d_4-MeOH) were used as supplied by Merck. Anhydrous Et_2O and THF were stored over sodium (Na) wire then distilled from Na benzophenone prior to use. Anhydrous CH_2Cl_2 was dried over $CaCl_2$ and distilled prior to use. Anhydrous PhMe and C_6H_6 were stored over Na wire. All solvents and reagents used in metal-catalysed reactions were degassed with nitrogen prior to use. (1,3-Dimesitylimidazolidin-2-ylidene)(2-isopropoxybenzylidene)ruthenium(II) dichloride, Hoveyda-Grubbs 2nd generation catalyst (**HGII**), was used as supplied by Sigma-Aldrich®. *p*-Toluenesulphonic acid (*p*TsOH) was purified by heating at 110 °C under vacuum for 4 hours prior to use. Analytical thin layer chromatography was performed on plastic plates with 0.25mm of silica gel (PolyGram SIL G/UV_{254}). All other chemicals were purchased from Sigma-Aldrich® and used without further purification unless stated otherwise. Melting points (m.p.) were measured on a Stuart Scientific SMP 3 melting point apparatus. The ^{1}H and ^{13}C nuclear magnetic resonance (n.m.r.) spectra were recorded using a Brüker DPX 200 MHz spectrometer (200 MHz for ^{1}H, 50 MHz for ^{13}C), Brüker DPX 300 MHz spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C) or a Brüker DRX 400 MHz spectrometer (400 MHz for ^{1}H n.m.r., 100 MHz for ^{13}C n.m.r.), as solutions in deuterated solvents as specified. Chemical shifts (δ) are measured in parts per million (ppm) and are reported to the residual solvent peak. Multiplicities are denoted as singlet (s), doublet (d), triplet (t), multiplet (m) or prefixed broad (b) or as a combination where necessary. The ^{13}C n.m.r. spectra were recorded using a JMOD pulse sequence or proton decoupled pulse sequence unless stated otherwise. Each resonance is assigned according to the following convention: chemical shift (multiplicity, observed coupling constants (J = Hz), integration, and proton assignment). Low-resolution electrospray ionisation (LR-ESI) mass spectra were

recorded on a Micromass Platform II API QMS-quadrupole electrospray mass spectrometer as specified. $[M]^+$ denotes the molecular ion. High-resolution electrospray (HR-MS) were recorded on a Brüker BioApex 47e Fourier Transform mass spectrometer and were recorded as specified. Analytical thin layer chromatography was performed on plastic plates with 0.25 mm of silica gel (PolyGram SIL G/UV_{254}). Flash chromatography was performed using Merck silica gel 60, 0.040-0.062mm (230-400 mesh). Visualisation of the molecules was achieved under 254 nm of ultraviolet radiation or through the use of chemical stains including vanillin, ninhydrin, permanganate and iodine. Infrared spectra (IR) were recorded on a Perkin-Elmer Spectrum RX1 Fourier Transform infrared spectrometer as either a neat liquid film between sodium chloride plates (neat), or in solid state as potassium bromide (KBr) discs. IR absorbance (ν_{max}) are reported in wave numbers (cm^{-1}) with the relative intensities expressed as: strong (s), medium (m), weak (w) or prefixed broad (b).

4.3.2 Reagents and conditions

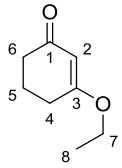
Synthesis of 1-vinyl-2-methylcyclohexanol 17



The synthesis of 2-methyl-1-vinylcyclohexanol **17** was carried out according to a modified procedure described by Albrecht *et al.*.[48] Vinyl magnesium bromide (10.1 mL, 10.1 mmol) was added dropwise over 10 mins to a stirred solution of 2-methylcyclohexanone **16** in dry THF (10 mL) under an atmosphere of nitrogen at 0 °C. The resultant solution was stirred for 24 hours at room temperature, after which the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (20 mL), diluted with Et_2O (50 mL) and the phases were separated. The aqueous phase was further extracted with Et_2O (3×20 mL) and the combined organic extract was dried ($MgSO_4$) and concentrated *in vacuo* to give an oil which was purified by flash chromatography (SiO_2; 1:8; EtOAc:hexane) to give 2-methyl-1-vinylcyclohexanol **17** (344 mg, 49%) as

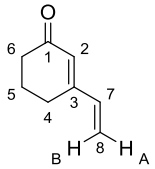
a pale yellow oil. Spectral data were consistent with those reported in the literature.[48] ^{1}H n.m.r. (200 MHz, $CDCl_3$): δ 5.79 (dd, *J* = 17.2 Hz, 10.7 Hz, 1H, H8), 5.05 (m, 2H, H9), 1.66-1.16 (m, 9H, H2-H6), 0.74 (d, *J* = 6.2 Hz, 3H, H7), OH not observed.

Synthesis of 3-ethoxycyclohex-2-enone 19



The synthesis of 3-ethoxycyclohex-2-enone **19** was carried out according to a procedure described by Petersson *et al.*.[18] Conc. HCl (1 mL) was added to a stirred solution of 1,3-cyclohexadione **18** (10.2 g, 90.6 mmol) in absolute ethanol (100 mL) at room temperature. After 72 hours, the solution was diluted with sat. $NaHCO_3$ (10 mL) solution and CH_2Cl_2 (50 mL), and the phases separated. The aqueous phase was further extracted with CH_2Cl_2 (3×100 mL) and the combined organic extract was washed with water (2×100 mL), brine (2×100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude 3-ethoxycyclohex-2-enone **19** (8.2 g, 65%). The crude enol ether **19** was used without purification. Spectral data were consistent with those reported in the literature.[18] ^{1}H n.m.r. (200 MHz, $CDCl_3$): δ 5.32 (s, 1H, H2), 3.88 (q, *J* = 7.0 Hz, 2H, H7), 2.35 (m, 4H, H4 & H6), 1.95 (p, *J* = 6.5 Hz, 2H, H5), 1.34 (t, *J* = 7.0 Hz, 3H, H8).

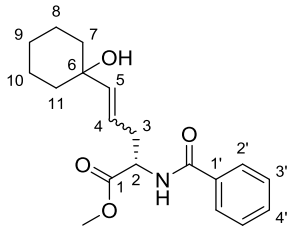
Synthesis of 3-vinylcyclohex-2-enone 20



The synthesis of 3-vinylcyclohex-2-enone **20** was carried out according to a modified procedure described by Petersson *et al.*.[18] Vinyl magnesium bromide (7.56 mL, 7.46 mmol) was added dropwise over 10 mins to a stirred solution of 3-ethoxycyclohex-2-enone **19** in dry THF (20 mL) under an atmosphere of nitrogen at 0 °C. The resulting light orange solution was stirred for 2 hours at room temperature, after which the

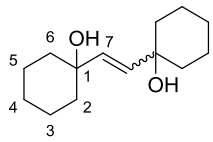
reaction mixture was cooled to 0 °C and quenched with saturated NH_4Cl (20 mL). The mixture was then diluted with Et_2O (50 mL) and the phases separated. The aqueous phase was further extracted with Et_2O (3×20 mL) and the combined organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil which was purified by flash chromatography (SiO_2; CH_2Cl_2) to give 3-vinylcyclohex-2-enone **20** (688 mg, 83%) as a light yellow oil. Spectral data were consistent with those reported in the literature.[18] ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 6.44 (dd, *J* = 17.6Hz, *J* = 10.8 Hz, 1H, H7), 5.89 (s, 1H, H2), 5.64 (d, *J* = 17.6 Hz, 1H, H8B), 5.41 (d, *J* = 10.4 Hz, 1H, H8A), 2.42 (t, *J* = 5.6 Hz, 2H, H6), 2.39-2.33 (m, 2H, H4), 1.99 (p, *J* = 6.4 Hz, 2H, H5). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 200.3 (C1), 156.9 (C3), 137.9 (C2), 128.3 (C7), 120.7 (C8), 37.8 (C6), 24.4 (C4), 22.3 (C5). LR-MS (ESI, +ve, MeOH): *m/z* 122.5 $[M+H]^+$. Calculated $[C_8H_{11}O]^+$ *m/z* 123.0.

Synthesis of (2S)-methyl 2-benzamido-5-(1-hydroxycyclohexyl)pent-4-enoate 23



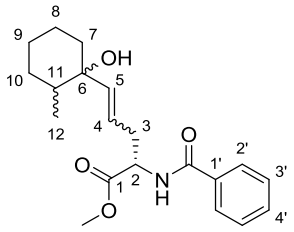
A Schlenk tube (10 mL) was charged with (*S*)-methyl 2-benzamidopent-4-enoate (252 mg, 1.08 mmol), 1-vinylcyclohexanol **22** (0.43 mL, 3.22 mmol) and CH_2Cl_2 (5 mL). **HGII** catalyst (18.2 mg, 54 μmol) was then added under a high flow of nitrogen and the reaction mixture was heated at 45 °C for 48 hours. The mixture was concentrated *in vacuo* and the crude product was then purified *via* flash chromatography (SiO_2; 5:1; CH_2Cl_2:acetone) to give (2*S*)-methyl 2-benzamido-5-(1-hydroxycyclohexyl)pent-4-enoate **23** (225 mg, 63%) as a pale yellow oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.7 Hz, 2H, H2'), 7.54-7.40 (m, 3H, H3' & H4'), 6.67 (d, *J* = 6.9 Hz, 1H, NH), 5.75-5.55 (m, 2H, H4 & H5), 4.89 (m, 1H, H2), 3.77 (s, 3H, OCH_3), 2.78-2.51 (m, 2H, H3), 1.72-1.33 (m, 10H, H7-H11), OH not observed. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 172.6

(CONH), 167.1 (C1), 143.1 (C5), 134.2 (C1'), 132.0 (C4'), 128.8 (C2'), 127.2 (C3'), 121.4 (C4), 71.5 (C6), 52.7 (2C, C2 & OCH_3), 38.2 & 38.1 (2C, C7 & C11), 35.7 (C3), 31.1 , 25.6, 22.3 (C8-C10). LR-MS (ESI, +ve, MeOH): *m/z* 354.1 $[M+Na]^+$. Calculated $[C_{19}H_{25}NO_4Na]^+$ *m/z* 354.4.



Further elution gave 2-di(hydroxycyclohexyl)ethylene **24** as a glassy crystalline solid. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 5.82 (s, 1H, H7'), 1.69-1.32 (m, 10H, H2-H6), OH not observed. LR-MS (ESI, +ve, MeOH): *m/z* 247.0 $[M+Na]^+$. Calculated $[C_{14}H_{24}O_2Na]^+$ *m/z* 247.2.

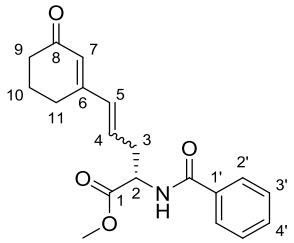
Synthesis of (2S)-methyl 2-benzamido-5-(1-hydroxy-2-methyl-cyclohexyl)pent-4-enoate 25



A Schlenk tube (10 mL) was charged with (*S*)-methyl 2-benzamidopent-4-enoate (116 mg, 0.485 mmol), 2-methyl-1-vinylcyclohexanol **17** (342 mg, 2.43 mmol) and CH_2Cl_2 (5 mL). **HGII** catalyst (16 mg, 24 μmol) was then added under a high flow of nitrogen and the reaction mixture was heated at 45 °C for 24 hours. The mixture was concentrated *in vacuo* and the crude product was then purified *via* flash chromatography (SiO_2; 1:1; EtOAc:hexane) to give (2S)-methyl 2-benzamido-5-(1-hydroxy-2-methylcyclohexyl)pent-4-enoate **25** (109 mg, 65%) as a pale yellow oil. ^{1}H n.m.r. (200 MHz, $CDCl_3$): δ 7.81-7.74 (m, 2H, H2'), 7.51-7.38 (m, 3H, H3' & H4), 6.64 (d, *J* = 6.8 Hz, 1H, NH), 5.45-5.69 (m, 2H, H4 & H5), 4.83 (m, 1H, H2), 3.78 (s, 3H, OCH_3), 2.79-2.52 (m, 2H, H3), 2.29-2.02 (m, 1H, H11), 1.90-1.00 (m, 8H, H7-H10), 0.78-0.68 (dd, *J* = 6.1 Hz, *J* = 3.7, 3H, H12), OH not observed. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 172.6

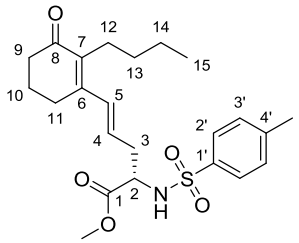
(CONH), 167.0 (C1), 143.4 (C5), 134.1 (C1'), 131.9 (C4'), 128.8 (C2'), 127.2 (C3'), 121.0 (C4), 73.8 (C6), 52.7 (C2 & OCH_3), 39.2 (C11), 39.1 (C7), 35.4 (C3), 30.0 (C10), 26.0 (C9), 21.6 (C8), 15.7 (C12). LR-MS (ESI, +ve, MeOH): *m/z* 368.2 $[M+Na]^+$. Calculated $[C_{20}H_{27}NO_4Na]^+$ *m/z* 368.2.

Synthesis of (2S)-methyl 2-benzamido-5-(3-oxocyclohex-1-enyl) pent-4-enoate 26



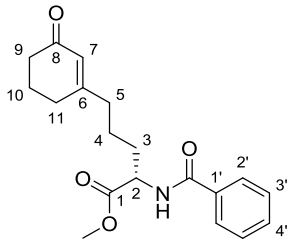
A Schlenk tube (10 mL) was charged with (*S*)-methyl 2-benzamidopent-4-enoate (50 mg, 0.21 mmol), 3-vinylcyclohex-2-enone **20** (82 mg, 0.64 mmol) and CH_2Cl_2 (5 mL). **HGII** catalyst (6.7 mg, 10 μmol) was then added under a high flow of nitrogen and the reaction mixture was stirred at room temperature for 24 hours. The mixture was concentrated *in vacuo* and the crude product was then purified *via* flash chromatography (SiO_2; 1:4 to 1:1; EtOAc:hexane) to give (2*S*)-methyl 2-benzamido-5-(3-oxocyclohex-1-enyl)pent-4-enoate **26** (45 mg, 66%) as a pale yellow oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 7.85-7.73 (m, 2H, H2'), 7.55-7.40 (m, 3H, H3' & H4'), 6.78-6.71 & 6.29-6.13 (m, 3H, H4, H5, H7), 4.99-4.82 (m, 1H, H2), 3.80-3.68 (m, 3H, OCH_3), 2.97-2.65 (m, 2H, H3), 2.57-1.97 (m, 6H, H9-H11), NH not observed. ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 200.4 (C8), 172.2 (CONH), 167.2 (C1), 156.4 & 155.5 (C6), 135.5 & 135.4 (C7), 134.0 (C1'), 132.2 (C4'), 131.6 & 130.7 (C5), 128.9 (C2'), 127.9 (C4), 127.3 (C3'), 52.9 (C2), 52.4 (OCH_3), 37.9 (C9), 36.5 (C3), 25.2 (C11), 22.4 (C10). LR-MS (ESI, +ve, MeOH): *m/z* 328.3 $[M+H]^+$. Calculated $[C_{19}H_{22}NO_4]^+$ *m/z* 328.2.

Synthesis of (2S,4E)-methyl 5-(2-butyl-3-oxocyclohex-1-enyl)-2-(p-tolylsulfonamido)pent-4-enoate 27



A Schlenk tube (10 mL) was charged with (*S*)-methyl 2-(*p*-tolylsulfonamido)pent-4-enoate (185 mg, 0.653 mmol), 2-butyl-3-vinylcyclohex-2-enone **21** (429 mg, 2.40 mmol) and CH_2Cl_2 (5 mL). **HGII** catalyst (20.4 mg, 32.6 μmol) was then added under a high flow of nitrogen and the reaction mixture was stirred at room temperature for 14 hours. The mixture was concentrated *in vacuo* and the crude product was then purified *via* flash chromatography (SiO_2; 1:2; EtOAc:hexane) to give (2*S*,4*E*)-methyl 5-(2-butyl-3-oxocyclohex-1-enyl)-2-(*p*-tolylsulfonamido)pent-4-enoate **27** (168 mg, 59%) as a pale yellow oil. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H, H2'), 7.29 (d, *J* = 8.0Hz, 2H, H3'), 6.59 (d, *J* = 15.6 Hz, H5), 5.97 (dt, *J* = 15.6 Hz, *J* = 7.2 Hz, 1H, H4), 5.40 (d, *J* = 8.8 Hz, 1H, NH), 4.10-4.03 (m, 1H, H2), 3.55 (s, 3H, OCH_3), 2.73-2.54 (m, 2H, H3), 2.32-2.43 (m, 13H, H9, H11-H14, $ArCH_3$), 1.94 (p, *J* = 6.4 Hz, 2H, H10), 0.92-0.82 (m, 3H, H15). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 199.9 (C8), 171.5 (C1), 148.8 (C6), 144.3 (C1'), 137.3 (C4'), 137.1 (C7), 132.6 (C5), 129.9 (C3'), 129.8 (C4), 127.4 (C2'), 55.6 (C2), 52.8 (OCH_3), 38.5 (C9), 37.3 (C3), 32.3 (C13), 26.3 (C11), 24.5 (C10), 23.0 (C14), 22.1 (C12), 21.7 ($ArCH_3$), 14.1 (C15). LR-MS (ESI, +ve, MeOH): *m/z* 456.1 $[M+Na]^+$. Calculated $[C_{23}H_{31}O_5NSNa]^+$ *m/z* 456.2.

Synthesis of (2S)-methyl 2-benzamido-5-(3-oxocyclohex-1-enyl)pentanoate 32



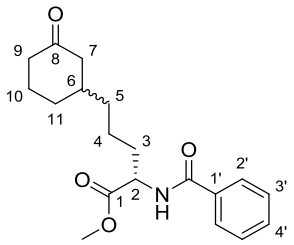
A nitrogen purged round bottom flask was charged with (2*S*)-methyl 2-benzamido-5-(3-oxocyclohex-1-enyl)pent-4-enoate **26** (38 mg, 0.11 mmol), 10% $Pd/BaSO_4$ (5 mg) and dry methanol (10 mL). The headspace of the flask was quickly purged and charged with nitrogen for two cycles using a quick fit stopcock. The flask was then put under a slight vacuum, sealed and a balloon filled with hydrogen gas was attached. The stopcock was opened, the flask then filled will hydrogen and the suspension was then allowed to stir at room temperature. Reaction progress was monitored by ^{1}H n.m.r. spectroscopy by at one, three and five hours before removing the balloon and carefully venting the system.

Time (hours)	26 (%)	32 (%)	33 (%)
0	100	0	0
1	62	38	0
3	36	64	0
5	0	100	0

At the end of the reaction, the mixture was then filtered through a pad of diatomaceous earth and concentrated *in vacuo*. The crude material was then purified by radial chromatography (SiO_2; 1:4 to 1:2; EtOAc:hexane) to give (2*S*)-methyl 2-benzamido-5-(3-oxocyclohex-1-enyl)pentanoate **32** (25 mg, 66%) as a light brown oil. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.6 Hz, 2H, H2'), 7.56-7.50 (m, 1H, H4'), 7.46 (t, *J* = 7.2 Hz, 2H, H3'), 6.69 (bd, *J* = 8.4, 1H, NH), 5.86 (s, 1H, H7), 4.86 (q, *J* = 6.0Hz, 1H, H2), 3.80 (s, 3H, OCH_3), 2.35 (t, *J* = 6.8 Hz, 2H, H9), 2.29-2.23 (m, 2H, H11), 2.07-1.22 (m, 8H, H3-H5 & H10). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 199.7 (C8), 172.9 (C1), 167.0 (CONH), 165.2 (C6), 133.8 (C1'), 131.9 (C4'), 128.6 (C2'), 127.1 (C3'), 126.0 (C7),

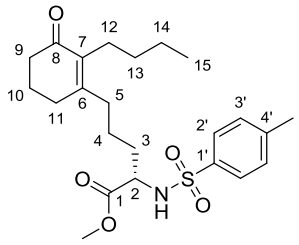
52.7 (C2), 52.2 (OCH_3), 37.3 (C5 & C9), 32.4 (C3), 29.6 (C11), 22.6 (2C, C4 & C10). LR-MS (ESI, +ve, MeOH): *m/z* 330.1 $[M+H]^+$. Calculated $[C_{19}H_{24}NO_4]^+$ *m/z* 330.1.

(2S)-methyl 2-benzamido-5-(3-oxocyclohexyl)pentanoate 33



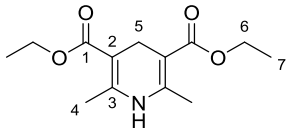
A nitrogen purged round bottom flask was charged with (2*S*)-methyl 2-benzamido-5-(3-oxocyclohex-1-enyl)pent-4-enoate **26** (37.5 mg, 0.114 mmol), 10% $Pd/BaSO_4$ (5 mg) and ethanol (10 mL). The headspace of the flask was quickly purged and charged with nitrogen for two cycles using a quick fit stopcock. The flask was then put under a slight vacuum, sealed and a balloon filled with hydrogen gas was attached. The stop cock was opened, the flask then filled will hydrogen and the solution was then allowed to stir at room temperature for twenty four hours before removing the balloon and carefully venting the system. The mixture was then filtered through a pad of diatomaceous earth and concentrated *in vacuo* to give crude (2*S*)-methyl 2-benzamido-5-(3-oxocyclohexyl)pentanoate **33** (39 mg, 56%) as a clear yellow oil. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 7.83-7.77 (m, 2H, H2' & H6'), 7.55-7.37 (m, 3H, H3'-H5'), 6.78-6.63 (m, 1H, NH), 4.38-4.27 (m, 1H, H2), 3.80-3.75 (m, 3H, OCH_3), 2.43-1.25 (m, 15H, H3-H11). LR-MS (ESI, +ve, MeOH): *m/z* 332.0 $[M+H]^+$. Calculated $[C_{19}H_{26}NO_4]^+$ *m/z* 332.2.

(2S)-methyl 5-(2-butyl-3-oxocyclohex-1-enyl)-2-(p-tolylsulfonamido) pentanoate 34



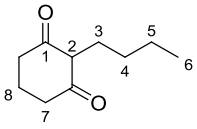
A nitrogen purged round bottom flask was charged with (2*S*,4*E*)-methyl 5-(2-butyl-3-oxocyclohex-1-enyl)-2-(*p*-tolylsulfonamido)pent-4-enoate **27** (45 mg, 0.10 mmol), 10% $Pd/BaSO_4$ (5 mg) and methanol (20 mL). The headspace of the flask was quickly purged and charged with nitrogen for two cycles using a quick fit stopcock. The flask was then put under a slight vacuum, sealed and a balloon filled with hydrogen gas was attached. The stopcock was opened, the flask then filled will hydrogen and the solution was then allowed to stir at room temperature for five hours before removing the balloon and carefully venting the system. The mixture was then filtered through a pad of diatomaceous earth and concentrated *in vacuo* to give (2*S*)-methyl 5-(2-butyl-3-oxocyclohex-1-enyl)-2-(*p*-tolylsulfonamido)pentanoate **34** (51 mg, >99%) as a light yellow oil. ^{1}H n.m.r. (200 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 2H, H2'), 7.29 (d, *J* = 8.0 Hz, 2H, H3'), 5.14 (d, *J* = 9.2 Hz, 1H, NH), 3.98-3.84 (m, 1H, H2), 3.50 (s, 3H, OCH_3), 2.42-2.15 (m, 8H, H3, H9 & H11-H12), 2.41 (s, 3H, $ArCH_3$), 1.90 (p, *J* = 6.6 Hz, 2H, H10), 1.81-1.07 (m, 8H, H4-H5 & H13-H14), 0.89 (t, *J* = 6.6Hz, 3H, H15). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 199.1 (C8), 171.9 (C1), 157.1 (C6), 143.8 (C1'), 136.6 (C4'), 136.2 (C7), 129.7 (C3'), 127.3 (C2'), 55.4 (C2), 52.5 (OCH_3), 38.1 (C9), 33.9 (C13), 33.3 (C3), 31.9 (C11), 30.3 (C5), 24.9 (C12), 23.2 (C14), 22.9 (C10), 22.5 (C4), 21.5 ($ArCH_3$), 14.0 (C15). LR-MS (ESI, +ve, MeOH): *m/z* 436.2 $[M+H]^+$. Calculated $[C_{23}H_{34}NO_5S]^+$ *m/z* 436.2.

Synthesis of Hantzsch's ester 36



The synthesis of Hantzsch's ester **36** was carried out according to a procedure described by Barbe *et al*..[49] A 200 mL beaker was charged with ethyl acetoacetate (6.50 g, 49.9 mmol), ammonium acetate (2.90 g, 37.6 mmol), paraformaldehyde (750 mg, 25.0 mmol) and a large magnetic stir bar. The viscous mixture was then heated to 70 °C and after a few mins the reaction started fizz, and thicken into a bright yellow paste. After 5 mins of heating (where the stir bar ceased to spin) the reaction mixture was cooled, diluted with water (40 mL) and stirred for an additional 10 mins at room temperature. The bright yellow precipitate was collected by vacuum filtration, washed with water (3×50 mL) and recrystallised from boiling ethanol to give Hantzsch's ester **36** (3.20 g, 51%) as bright yellow needles. Spectral data were consistent with those reported in the literature.[49] ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 5.10 (bs, 1H, NH), 4.17 (q, *J* = 7.2 Hz, 4H, H6"), 3.27 (s, 2H, H5), 2.19 (s, 6H, H4), 1.28 (t, *J* = 7.2 Hz, 6H, H7).

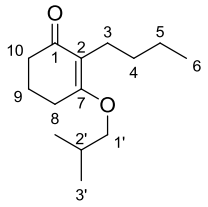
Synthesis of 2-butyl-1,3-cyclohexadione 35



The synthesis of 2-butyl-1,3-cyclohexadione **35** was carried out according to a procedure described by Ramachary *et al.*[22]A solution of 1,3-cyclohexadione **18** (2.07 g, 18.5 mmol) and (*S*)-proline (215 mg, 1.84 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 mins to a stirring suspension of Hantzsch's ester **36** (4.68 g, 18.5 mmol) and 1-butyraldehyde (2.5 mL, 28 mmol) in CH_2Cl_2 (30 mL). The resulting bright yellow solution was allowed to stir at room temperature for 1 hour before concentration *in vacuo* to give bright yellow oil. The crude product was then purified by precipitation (-15 °C; hexane: CH_2Cl_2; 10:1). The precipitate was collected by vacuum filtration, washed with hexane (3×10 mL) and dried *in vacuo* to give 2-butyl-1,3-cyclohexadione

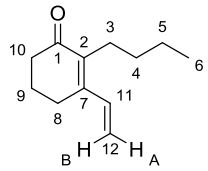
35 (2.70 g, 87%) as a granular white solid Spectral data were consistent with those reported in the literature.[22] ^{1}H n.m.r. (400 MHz, $CDCl_3$ & d_4-MeOH): δ 2.35 (t, *J* = 6.4 Hz, 4H, H7), 2.23-2.17 (m, 2H, H3), 1.89 (p, *J* = 6.8 Hz, 2H, H8), 1.32-1.21 (m, 4H, H4 & H5), 0.89-0.82 (m, 3H, H6), H2 not observed. ^{13}C n.m.r. (75 MHz, $CDCl_3$ & d_4-MeOH): δ 116.5 (C2-enol), 67.8 (C2), 39.9 & 39.1 (C7), 31.1, 29.9, 23.0, 22.9 21.7, 20.9 (C3-C5), 18.4 (C8), 14.2 & 14.0 (C6). LR-MS (ESI, -ve, MeOH): *m/z* 166.7 $[M-H]^-$. Calculated $[C_{10}H_{15}O_2]^-$ *m/z* 167.1.

Synthesis of 2-butyl-3-isobutoxycyclohex-2-enone 38



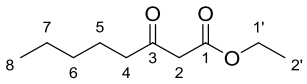
A 10 0 mL round bottom flask was charged with 2-butyl-1,3-cyclohexadione **35** (2.10 g, 12.0 mmol), *iso*-butanol (6.93 mL, 75.0 mmol), benzene (50 mL) and a catalytic amount of *p*-toluene sulphonic acid (200 mg). The flask was then heated to reflux in a Dean-Stark apparatus with water separation for 16 hours. After cooling, the solution was diluted with Et_2O (50 mL), sat. $NaHCO_3$ (20 mL) and the phases were separated. The aqueous phase was further extracted with Et_2O (3×20 mL) and the combined organic extract was washed with water (3×20 mL), dried ($MgSO_4$) and concentrated to give an orange oil. The crude product was purified by bulb-to-bulb distillation (150 °C, 0.2 mbar) to give 2-butyl-3-isobutoxycyclohex-2-enone **38** (2.73 g, 97%) as a clear orange oil. . ^{1}H n.m.r. (200 MHz, $CDCl_3$): δ 3.73 (d, *J* = 6.2 Hz, 2H, H1'), 2.52 (t, *J* = 6.2 Hz, 2H, H10), 2.33-2.21 (m, 4H, H3 & H8), 1.96 (m, 3H, H9 & H2'), 1.34-1.23 (m, 4H, H4 & H5), 0.98 (d, *J* = 6.8 Hz, 6H, H3'), 0.90-0.82 (m, 3H, H6). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 198.4 (C1), 171.6 (C7), 120.0 (C2), 73.9 (C1'), 36.5 (C10), 31.1 (C4), 28.9 (C2'), 25.5 (C8), 22.9 (C5), 21.8 (C9), 21.1 (C3), 19.0 (C3'), 14.1 (C6). LR-MS (ESI, +ve, MeOH): *m/z* 224.9 $[M+H]^+$. Calculated $[C_{14}H_{25}O_2]^+$ *m/z* 225.2.

Synthesis of 2-butyl-3-vinylcyclohex-2-enone 21



The synthesis of 2-butyl-3-vinylcyclohex-2-enone **21** was carried out according to a modified procedure described by Petersson *et al.*.[18] Vinyl magnesium bromide (3.56 mL, 3.56 mmol) was added dropwise over 5 mins to a stirred solution of 2-butyl-3-isobutoxycyclohex-2-enone **38** (398 mg, 1.78 mmol**)** in dry THF (10 mL) under an atmosphere of nitrogen at 0 °C. The resulting light orange solution was stirred at room temperature. After 4 hours, the reaction mixture was cooled to 0 °C and quenched with sat. NH_4Cl (20 mL) solution and diluted with Et_2O (30 mL). The phases were separated, and the aqueous phase was further extracted with Et_2O (3×15 mL). The combined organic extract was washed with water (3×20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude 2-butyl-3-vinylcyclohex-2-enone **21** (485 mg, >99%) as an orange oil. The crude product **21** was used without purification. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 5.84 (dd, *J* = 17.1 Hz, *J* = 10.4 Hz, 1H, H11), 5.26 (dd, *J* = 17.2 Hz, *J* = 1.6 Hz, 1H, H12B), 5.09 (dd, *J* = 10.4 Hz, *J* = 1.6 Hz, H12A), 2.50-1.57 (m, 8H, H3, H8-H10), 1.44-1.22 (m, 4H, H4 & H5), 0.87 (t, *J* = 7.2 Hz, 3H, H6).

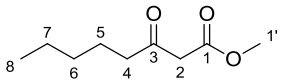
Synthesis of ethyl 3-oxooctanoate 43



Ethyl acetoacetate **44** (1.85 mL, 14.7 mmol) was added dropwise over 5 mins to a stirred solution of sodium hydride (351 mg, 14.7 mmol) in dry THF (15 mL) under an atmosphere of nitrogen at 0 °C. The clear solution was warmed to room temperature for 10 mins before cooling to 0 °C and added *n*-butyl lithium (6.48 mL, 16.1 mmol) dropwise over 5 mins. The resulting red/orange solution was warmed to room temperature for 10 mins before cooling to 0 °C and added *n*-butyl bromide (1.88 mL,

17.6 mmol) in one portion, where the colour dissipated and a precipitate formed. The solution was allowed to stir at 0 °C for 2 hours before warming to room temperature overnight. The reaction mixture was carefully quenched with 1M HCl (10 mL), diluted with Et_2O and the phases were separated. The aqueous phase was further extracted with Et_2O (4×15 mL), dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. The crude product was purified by bulb-to-bulb distillation (110 °C, ~1 mbar) to give ethyl 3-oxooctanoate **43** (1.98 g, 73%) as a clear colourless oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 4.19 (q, *J* = 7.1 Hz, 2H, H1'), 3.42 (bs, 2H, H2), 2.52 (t, *J* = 7.5 Hz, 3H, H4), 1.59 (p, *J* = 7.1 Hz, 2H, H5), 1.42 – 1.16 (m, 4H, H6 & H7), 1.27 (t, *J* = 7.1 Hz, 3H, H2'), 0.88 (t, *J* = 6.6 Hz, 3H, H8).

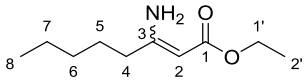
Synthesis of methyl 3-oxooctanoate 47



Methyl acetoacetate **46** (4.23 mL, 39.4 mmol) was added dropwise over 5 mins to a stirred solution of sodium hydride (1.04 g, 43.3 mmol) in dry THF (25 mL) under an atmosphere of nitrogen at 0 °C. The clear solution was warmed to room temperature for 5 mins before cooling to 0 °C and added *n*-butyl lithium (22.8 mL, 43.3 mmol) dropwise over 5 mins. The resulting red/orange solution was warmed to room temperature for 5 mins before cooling to 0 °C and added *n*-butyl bromide (5.06 mL, 47.3 mmol) in one portion, where the colour dissipated and a precipitate formed. The solution was allowed to stir at 0 °C for 30 mins before warming to room temperature. After 30 mins, the reaction mixture was carefully quenched with 1M HCl (20 mL), diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was further extracted with Et_2O (3×20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The crude product was purified by bulb-to-bulb distillation (100 °C, ~1mbar) to give methyl 3-oxooctanoate **47** (4.54 g, 67%) as a clear colourless oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 3.73 (s, 3H, H1'), 3.45 (bs, 2H, H2), 2.51 (t, *J* = 7.2 Hz,

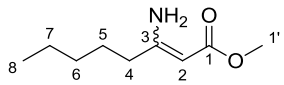
2H, H4), 1.54 (p, *J* = 6.6 Hz, 7.5 Hz, 2H, H5), 1.32 (m, 4H, H6 & H7), 0.89 (t, *J* = 5.7 Hz, 3H, H8). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 202.8 (C3), 167.7 (C1), 52.3 (C1'), 49.0 (C2), 43.0 (C4), 31.3, 23.1, 22.3 (C5-C7), 13.8 (C8). LR-MS (ESI, +ve, MeOH): *m/z* 173.0 $[M+H]^+$. Calculated $[C_9H_{17}O_3]^+$ *m/z* 173.1.

Synthesis of ethyl 3-amino oct-2-enoate 48



Ethyl 3-oxooctanoate **43** (0.98 g, 5.3 mmol) was added to a stirred suspension of ammonium acetate (4.1 g, 53 mmol) in methanol (6 mL). The resulting yellow solution was left to stir at room temperature for 72 hours before concentration *in vacuo*. The reaction mixture was diluted with sat $NaHCO_3$ (30 mL), EtOAc (30 mL) and the phases were separated. The aqueous phase was further extracted with EtOAc (3×30 mL), washed with water (3×30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give ethyl 3-amino oct-2-enoate **48** (856 mg, 88%) as a mixture of indistinguishable geometric isomers (A:B ; 10:90). ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 4.54 (s, 1H, H2), 4.20 (q, *J* = 7.1 Hz, 2H, H1' isomer A), 4.11 (q, *J* = 7.1 Hz, 2H, H1' isomer B), 2.53 (t, *J* = 7.4 Hz, 2H, H4 isomer A), 2.11 (t, *J* = 7.5 Hz, 2H, H4 isomer B), 1.63 – 1.47 (m, 4H, H5 & H6), 1.40 – 1.20 (m, 5H, H7 & H2'), 0.92 – 0.85 (m, 3H, H8). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 170.6 (C1), 164.0 (C3), 83.6 (C2), 58.7 (C1'), 36.6 (C4), 31.4 (C5), 27.7 (C6), 22.5 (C7'), 14.7 (C2'), 14.1 (C8).

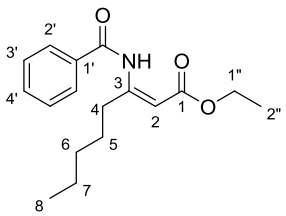
Synthesis of methyl 3-amino oct-2-enoate 49



Methyl 3-oxooctanoate **47** (2.56 g, 14.9 mmol) was added to a stirred suspension of ammonium acetate (11.5 g, 149 mmol) in methanol (40 mL). The resulting yellow solution was left to stir at room temperature for 48 hours before concentration *in vacuo*. The reaction mixture was diluted with water (20 mL), EtOAc (50 mL) and the phases were separated. The aqueous phase was further extracted with EtOAc (3×50 mL),

washed with water (3×25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The crude product was purified by *via* flash chromatography (SiO_2; 1:3; EtOAc:hexane) to give methyl 3-amino oct-2-enoate **49** (2.38 g, 94%) as a mixture of indistinguishable geometric isomers (A:B ; 86:14). ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 4.52 (s, 1H, H2), 3.71 (s, 3H, H1' isomer B), 3.63 (s, 3H, H1' isomer A), 2.50 (t, *J* = 7.5 Hz, 2H, H4 isomer B), 2.10 (t, *J* = 7.5 Hz, 2H, H4 isomer A), 1.61-1.45 (m, 2H, H5), 1.36-1.20 (m, 4H, H6 & H7), 0.87 (t, *J* = 6.9 Hz, 3H), NH_2 not observed. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 170.7 (C1), 164.1 (C4), 82.9 (C2), 50.0 (C1'), 36.4 (C4), 31.1, 27.5, 22.4 (C5-C7), 13.8 (C8). LR-MS (ESI, +ve, MeOH): *m/z* 171.9 $[M+H]^+$. Calculated $[C_9H_{18}NO_2]^+$ *m/z* 172.1.

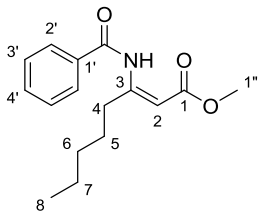
Synthesis of (Z)-ethyl 3-benzamidooct-2-enoate 50



Benzoyl chloride (617 μL, 5.31 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 10 mins to a stirred solution of ethyl 3-amino oct-2-enoate **48** (820 mg, 4.43 mmol) and pyridine (430 μL, 5.31 mmol) in CH_2Cl_2 (15 mL) under an atmosphere of nitrogen at 0 °C. The resulting solution was warmed to room temperature. After 16 hours the reaction mixture was quenched with sat. $NaHCO_3$ (15 mL), diluted with CH_2Cl_2 (30 mL) and the phases were separated. The aqueous phase was further extracted with CH_2Cl_2 (3×30 mL), washed 1M HCl (3×30 mL), sat. $NaHCO_3$ (3×30 mL), water (3×50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude ethyl 3-benzamidooct-2-enoate as a mixture of geometric isomers. The crude product was purified by *via* flash chromatography (SiO_2; 1:8; EtOAc:hexane) to give (*Z*)-methyl 3-benzamidooct-2-enoate **50** (1.0 g, 78%) as a light yellow oil. ^{1}H n.m.r. (200 MHz, $CDCl_3$): δ 12.09 (s, 1H, NH), 7.98 (dt, *J* = 13.9 Hz, *J* = 6.7 Hz, 2H, H2'), 7.76 – 7.36 (m, 4H, H3' & H4'), 5.08 (s, 1H, H2), 4.21 (q, *J* = 7.1 Hz, 2H, H1''), 2.98 – 2.78 (m, 2H, H4), 1.62 (m, 2H, H5), 1.52 – 1.13 (m, 7H, H6, H7 & H2''), 0.96 – 0.84 (m, 3H, H8). ^{13}C n.m.r. (75 MHz,

$CDCl_3$): δ 169.9 (*C*ONH), 165.0 (C1), 159.8 (C3), 134.4, 132.4, 129.0, 127.8, 96.9 (C2), 60.2 (C1"), 34.5, 31.7, 28.3, 22.6, 14.6 (C2"), 14.1 (C8). LR-MS (ESI, +ve, MeOH): *m/z* 290.1 $[M+H]^+$. Calculated $[C_{17}H_{24}NO_3]^+$ *m/z* 290.2.

Synthesis of (Z)-methyl 3-benzamidooct-2-enoate 51

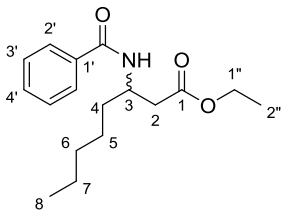


Benzoyl chloride (1.29 mL, 12.3 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 10 mins to a stirred solution of methyl 3-amino oct-2-enoate **49** (2.10 g, 12.3 mmol) and pyridine (1.08 mL, 13.4 mmol) in CH_2Cl_2 (20 mL) under an atmosphere of nitrogen at 0 °C. The resulting solution was warmed to room temperature. After 16 hours the reaction mixture was quenched with sat. $NaHCO_3$ (20 mL), diluted with CH_2Cl_2 and the phases were separated. The aqueous phase was further extracted with CH_2Cl_2 (3×50 mL), washed 1M HCl (3×50 mL), sat. $NaHCO_3$ (3×50 mL), water (3×50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude methyl 3-benzamidooct-2-enoate **51**. The crude product was purified by *via* flash chromatography (SiO_2; 1:7; EtOAc:hexane) to give (*Z*)-methyl 3-benzamidooct-2-enoate **51** (m = 1.98 g, 59%) as a light yellow oil.

Alternatively, a 250 mL round bottom flask was charged with methyl 3-oxooctanoate **47** (2.90 g, 16.8 mmol), benzamide (20.2 g, 167 mmol) and toluene (100 mL) and a catalytic amount of *p*-toluene sulphonic acid (200 mg). The flask was then heated to reflux in a Dean-Stark apparatus with water separation. After 16 hours the mixture was cooled to 0 °C, filtered and concentrated *in vacuo* to give crude methyl 3-benzamidooct-2-enoate **51**. The crude product was purified by *via* flash chromatography (SiO_2; 1:10; EtOAc:hexane) to give (*Z*)-methyl 3-amino oct-2-enoate **51** (3.12 g, 68%) as a light yellow oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): 12.1 (bs, 1H, NH), 8.03-7.96 (m, 2H, H2'), 7.60-7.45 (m, 3H, H3'), 5.09 (s, 1H, H2), 2.91 (d, *J* = 7.8 Hz, 2H, H4), 1.70-1.57 (m,

2H, H5), 1.45-1.28 (m, 4H, H6 & H7), 0.91 (t, *J* = 7.2 Hz, 3H, H8). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 170.1 (CONH), 164.8 (C1), 159.8 (C3), 134.1 (C1'), 132.3 (C4'), 128.8 (C2'), 127.7 (C3'), 96.3 (C2), 51.2 (C1"), 34.3 (C4), 31.5, 28.1, 22.4 (C5-C7), 14.0 (C8). LR-MS (ESI, +ve, MeOH): *m/z* 298.1 $[M+Na]^+$. Calculated $[C_{16}H_{21}NNaO_3]^+$ *m/z* 298.1. ν_{max} (neat): 2955m, 2931m, 1699s, 1671s, 1630s, 1506m, 1488m, 1468m, 1450m, 1436m, 1375s, 1265s, 1247s, 1174s, 1113m cm^{-1}. HPLC (DIACEL CHIRACEL OD 0.46 x 250MM C-048, isocratic elution 98:2; hexane:isopropanol): t_R=6.84mins (100% area).

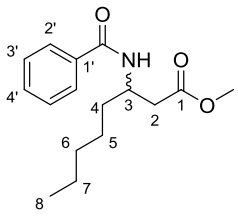
Synthesis of (R/S)-ethyl 3-benzamido octanoate 52



A Fischer-Porter tube was charged with (*Z*)-ethyl 3-benzamidooct-2-enoate **50** (66 mg, 0.23 mmol), palladium on carbon 10% w/w (6.5 mg) and methanol (5 mL). The headspace of the vessel was purged with argon over three cycles, charged with hydrogen (75 psi) and stirred at room temperature for 18 hours. The hydrogen was then vented from the vessel and the reaction mixture was filtered through a short plug of diatomaceous earth and concentrated *in vacuo*. The crude product was purified by *via* flash chromatography (SiO_2; 1:3; EtOAc:hexane) to give (*R*/*S*)-ethyl 3-benzamido octanoate **52** (48 mg, 73%) as a light yellow oil. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.82 – 7.74 (m, 2H, H2'), 7.54 – 7.39 (m, 4H, H3' & H4'), 6.90 (bd, *J* = 9.1 Hz, NH), 4.50 – 4.39 (m, 1H, H3), 4.17 (qd, *J* = 7.1 Hz, *J* = 2.1 Hz, 2H, H1"), 2.64 (qd, *J* = 15.9 Hz, *J* = 4.9 Hz, 2H, H2), 1.74 – 1.50 (m, 2H, H4), 1.48 – 1.23 (m, 6H, H5-H7), 1.27 (t, *J* = 7.2 Hz, 2H, H2"), 0.88 (t, *J* = 7.1 Hz, 2H). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 172.5 (*C*ONH), 170.1 (C1), 134.9, 131.5, 128.7, 127.1 (C1'-C4'), 60.8 (C1"), 46.6 (C3), 38.5 (C2), 34.4 (C4), 31.7 (C5), 26.1 (C6), 22.6 (C7), 14.3 (C2"), 14.1 (C8). LR-MS (ESI, +ve, MeOH): *m/z* 292.1 $[M+H]^+$. Calculated $[C_{17}H_{26}NO_3]^+$ *m/z* 292.2. HPLC (DIACEL

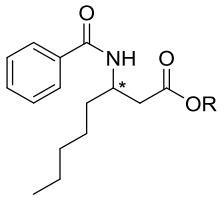
CHIRACEL OD 0.46 x 250MM C-048, isocratic elution 98:2; hexane:isopropanol): t_R=17.72 mins (49.8% area, Isomer A) t_R=20.81 mins (50.2% area, Isomer B).

Synthesis of (R/S)-methyl 3-benzamido octanoate 53



A Fischer-Porter tube was charged with (*Z*)-methyl 3-benzamidooct-2-enoate **51** (535 mg, 1.93 mmol), palladium on carbon 10% w/w (54 mg) and methanol (15 mL). The headspace of the vessel was purged with argon over three cycles, charged with hydrogen (75 psi) and stirred at room temperature for 18 hours. The hydrogen was then vented from the vessel and the reaction mixture was filtered through a short plug of diatomaceous earth and concentrated *in vacuo*. The crude product was purified by *via* crystallisation (1:10; CH_2Cl_2:hexane) to give (*R*/*S*)-methyl 3-benzamido octanoate **53** (390 mg, 73%) as an off white solid. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.82 – 7.73 (m , 2H, H2'), 7.54 – 7.37 (m, 4H, H3' & H4'), 6.88 (bd, *J* = 8.7 Hz, NH), 4.54 – 4.32 (m, 1H, H3), 3.71 (s, 3H, OMe), 2.66 (qd, *J* = 16.0 Hz, 4.9 Hz, 2H, H2), 1.74 – 1.48 (m, 2H, H4), 1.48 – 1.17 (m, 6H, H5-H7), 0.87 (t, *J* = 7.0 Hz, 3H, H8). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 172.9 (*C*ONH), 166.9 (C1), 134.8, 131.5, 128.7, 127.1 (C1'-C4'), 51.9 (OMe), 46.5 (C3), 38.2 (C2), 34.3 (C4), 31.7 (C5), 26.1 (C6), 22.6 (C7), 14.11 (C8). LR-MS (ESI, +ve, MeOH): *m/z* 278.1 $[M+H]^+$. Calculated $[C_{16}H_{24}NO_3]^+$ *m/z* 278.2. ν_{max} (neat): 3306m, 2957m, 2924m, 2855m, 1737s, 1636s, 1535s cm^{-1}. HPLC (DIACEL CHIRACEL OD 0.46 x 250MM C-048, isocratic elution 98:2; hexane:isopropanol): t_R=21.98 mins (48.8% area, Isomer A) t_R=26.88 mins (51.2% area, Isomer B).

General procedure for asymmetric reduction of enamides 50 & 51



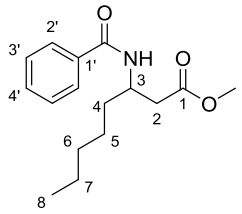
In a nitrogen filled dry box, a Fischer-Porter tube was charged with degassed substrate (~0.8 mmol), asymmetric hydrogenation catalyst (~5 mg, spatula tip), solvent (10 mL), sealed and removed from the dry box. The headspace of the vessel was purged with argon over three cycles, charged with hydrogen and stirred at room temperature for 18 hours. The hydrogen was then vented from the vessel and the reaction mixture was concentrated *in vacuo*. A small sample of the crude product was purified by preparative thin layer chromatography (SiO_2; 1:1:0.1; EtOAc:hexane:methanol) for chiral HPLC analysis. HPLC (DIACEL CHIRACEL OD 0.46 x 250MM C-048, isocratic elution 98:2; hexane:isopropanol).

R =	Catalyst	Solv	H_2	Conv	tR (mins) Isomer A	%Area Isomer A	tR (mins) Isomer B	%Area Isomer B
Me	Pd/C	MeOH	75psi	>99%	21.98	48.8%	26.88	51.2%
Et	Pd/C	MeOH	75psi	>99%	17.72	49.8%	20.81	50.2%
Et	Rh(R,R)MeBPE.OTf	MeOH	90psi	>99%	18.08	58.6%	21.50	41.4%
Et	Rh(R,R)MeDuPHOS.OTf	MeOH	90psi	>99%	18.31	30.6%	21.80	69.4%
Et	Rh(R,R)EtDuPHOS.OTf	MeOH	90psi	>99%	17.29	25.2%	20.36	74.8%
Et	Rh(S,S)EtDuPHOS.OTf	MeOH	90psi	>99%	19.17	71.5%	22.84	28.5%
Et	Rh(R,R) EtDuPHOS.OTf	Toluene	90psi	0%	-	-	-	-
Me	Rh(COD)(**54**)$_2$.OTf	^{i}PrOH/CH_2Cl_2	350psi	>99%	23.24	1.5%	27.80	98.5%

Synthesis of Rh(COD)(54)OTf

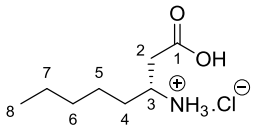
In a nitrogen filled dry box, a small volumetric flask (2 mL) was charged with **54** (36 mg, 83 μmol), Rh(COD)OTf (18 mg, 41 μmol) and filled to the 2mL line with dichloromethane. This provided an approximate 21 μM solution of Rh(COD)(**54**)OTf in dichloromethane which was used without isolation.

Synthesis of (+)-methyl 3-benzamido octanoate (+)-53



In a nitrogen filled dry box, a Fischer-Porter tube was charged with degassed (*Z*)-methyl 3-benzamidooct-2-enoate **51** (1.7 g, 6.0 mmol), isopropanol (10 mL) and a solution of Rh(COD)(**54**)OTf (1.4 mL, 30 μmol). The vessel sealed, removed from the dry box and the headspace of the vessel was purged with argon over three cycles, charged with hydrogen (350 psi) and stirred at room temperature for 16 hours. The hydrogen was then vented from the vessel and the reaction mixture was concentrated *in vacuo*. The crude material was then purified by gradient flash chromatography (SiO_2; 1:6 to 1:1; EtOAc:hexane) to give (+)-methyl 3-benzamido octanoate (+)-**53** (1.34 g, 80%) as colourless oil. Spectra for (+)-methyl 3-benzamido octanoate were consistent with previously recorded data. $[\alpha]^{20}$ =+42.2° (c=0.88, CH_2Cl_2). HPLC (DIACEL CHIRACEL OD 0.46 x 250MM C-048, isocratic elution 98:2; hexane:isopropanol): t_R=23.24 mins (1.5% area, Isomer A) t_R=27.80 mins (98.5% area, Isomer B).

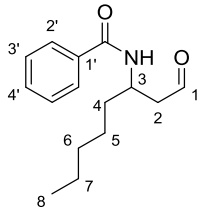
Synthesis of (R)-3-amino octanoic acid hydrochloride 55



(+)-Methyl 3-benzamido octanoate (+)-**53** (54 mg, 0.19 mmol, 97% ee) was added to a 25 mL round bottom flask which containing 6M HCl (10 mL). The mixture was heated at reflux for 16 hours before being cooled, diluted with dichloromethane (10 mL) and the phases separated. The aqueous phase was further washed with dichloromethane (3×10 mL) and then concentrated *in vacuo* to give (*R*)-3-amino octanoic acid hydrochloride **55** (38 mg, >99%) as a light yellow coloured oil. Spectral data were consistent with that reported in the literature.[38] ^{1}H n.m.r. (200 MHz, D_2O): δ 3.79 – 3.61 (m, 1H, H3), 2.83 (qd, *J* = 17.6 Hz, *J* = 6.4 Hz, 2H, H2), 1.88 – 1.66 (m, 2H, H4), 1.60

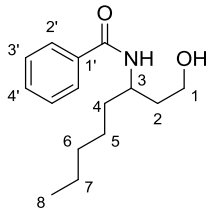
– 1.24 (m, 6H, H5-H7), 0.95 (t, *J* = 6.6 Hz, 3H, H8). $[\alpha]^{20}$ =-19.7° (c=0.80, H_2O). Literature optical $[\alpha]^{20}$ =-16.6° (c=1.1, H_2O).[38]

Selected data for 3-benzamido octanal 56



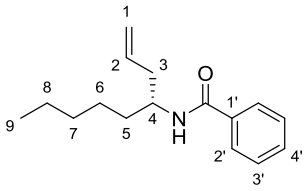
^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 9.80 (s, 1H, H1), 7.80 – 7.68 (m, 2H, H2'), 7.54 – 7.36 (m, 3H, H3' 7 H4'), 6.55 (s, 1H, NH), 4.59 – 4.42 (m, 1H, H3), 2.84 – 2.70 (m , 2H, H2), 1.77 – 1.56 (m, 2H, H4), 1.48 – 1.19 (m, 6H, H5-H7), 0.86 (t, *J* = 7.0 Hz, 3H, H8). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 201.6 (C1), 167.3 (*C*ONH), 134.5, 131.7, 128.7, 127.0 (C1'-C4'), 48.4 (C3), 46.0 (C2), 34.7 (C4) , 31.6 (C5), 26.1 (C6), 22.6 (C7), 14.1 (C8). LR-MS (ESI, +ve, MeOH): *m/z* 248.2 $[M+H]^+$. Calculated $[C_{15}H_{24}NO_2]^+$ *m/z* 248.2.

Selected data for 3-benzamido octanol 57



^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.1 Hz, 2H, H2'), 7.51 (t, *J* = 7.3 Hz, 1H, H4'), 7.43 (t, *J* = 7.4 Hz, 2H, H3'), 6.20 (d, *J* = 8.6 Hz, 1H, NH), 4.34 – 4.20 (m, 1H, H3), 3.83 (bs, 1H, OH), 3.72 – 3.54 (m, 2H, H1), 2.05 – 1.86 (m, 2H, H2), 1.72 – 1.51 (m, 2H, H4), 1.51 – 1.35 (m, 2H, H5), 1.35 – 1.21 (m, 4H, H6 & H7), 0.88 (t, *J* = 6.9 Hz, 3H, H8). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 168.7 (*C*ONH), 134.2, 131.8, 128.8, 127.1 (C2'-C4'), 58.8 (C1), 47.1 (C3), 38.6 (C2), 35.6 (C4), 31.7 (C5), 26.2 (C6), 22.7 (C7), 14.1 (C8). LR-MS (ESI, +ve, MeOH): *m/z* 250.2 $[M+H]^+$. Calculated $[C_{15}H_{24}NO_2]^+$ *m/z* 250.2.

Synthesis of (R)-4-benzamido non-1-ene 42

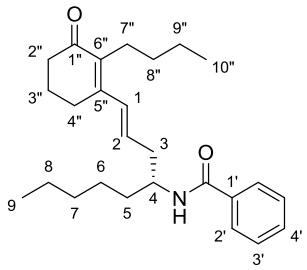


n-Butyl lithium (1.41 mL, 2.56 mmol) was added dropwise over five mins to a stirred solution of methyltriphenylphosphonium bromide (953 mg, 2.67 mmol) in dry THF (15 mL) at 0 °C under an atmosphere of nitrogen. After the addition was completed the bright yellow solution was stirred at 0 °C for 20 mins before being warmed to room temperature and stirred for a further five mins. The mixture was then cooled (0 °C) and (*R*)-3-benzamido octanal **56** (550 mg, 66% w/w, 1.48 mmol) was added dropwise as a solution in THF (5 mL). After the addition was completed, the reaction mixture was allowed to stir to room temperature over 16 hours. The mixture was then quenched with the addition of sat. ammonium chloride solution (10 mL), diluted with diethyl ether (30 mL) and the phases were separated. The aqueous layer was further extracted with diethyl ether (3×30 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by flash chromatography (SiO_2; 1:5; EtOAc:hexane) to give (*R*)-4-benzamido non-1-ene **42** (107 mg, 29%) as a clear oil.

Alternatively, diisobutyl aluminium hydride (2.5 mL, 3.24 mmol) was added dropwise over 10 mins to a Schlenk flask containing a stirred solution of methyl 3-benzamido octanoate **53** (900 mg, 3.24 mmol) in dry THF (20 mL) at -78 °C under an atmosphere of nitrogen. After the addition was completed the mixture was stirred for 1 hour at -78 °C. Meanwhile, a solution of methylenetriphenylphosphorane (15 mL, 4.87 mmol) in tetrahydrofuran was prepared in a second Schlenk flask by dropwise addition of *n*-butyl lithium (4.43 mL, 4.87 mmol) to methyltriphenylphosphonium bromide (1.74 g, 4.87 mmol) in dry THF (15 mL) at 0 °C under an atmosphere of nitrogen. After the addition was completed the bright yellow solution was stirred at 0 °C for 20 mins before being

warmed to room temperature and stirred for a further five mins. This ylid mixture was again cooled to 0 °C and was transferred dropwise by nylon cannula to the Schlenk flask containing the methyl (*R*)-3-benzamido octanoate **53** and DIBAL-H at -78 °C. The combined mixture was stirred to room temperature overnight before being quenched with 1M HCl (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography (SiO_2; 1:3; EtOAc:hexane) to give (*R*)-4-benzamido non-1-ene **42** (384 mg, 48%) as a clear oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 7.78 – 7.70 (m, 2H, H2), 7.53 – 7.38 (m, 3H, H3 & H4), 5.99 – 5.74 (m, 2H, H2 & NH), 5.19 – 5.03 (m, 2H, H1), 4.29 – 4.13 (m, 1H, H4), 2.49 – 2.21 (m, 2H, H5), 1.75 –1.21 (m, 6H, H6-H8), 0.98 – 0.78 (m, 3H, H9). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 167.3 (*C*ONH), 135.5, 134.7, 131.6, 128.9, 127.1(C2 & C1'-C4'), 118.3 (C1), 49.4 (C4), 39.5 (C3), 34.8 (C5), 32.1 (C6), 26.0 (C7), 22.9 (C8), 14.3 (C9). LR-MS (ESI, +ve, MeOH): *m/z* 246.2 $[M+H]^+$. Calculated $[C_{15}H_{24}NO_2]^+$ *m/z* 246.2.

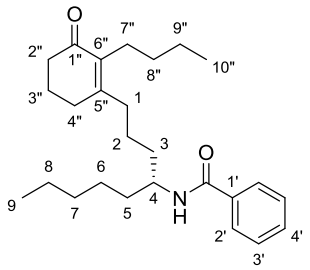
Synthesis of dienone 59



A Schlenk tube (10 mL) was charged with 4-benzamido non-1-ene **42** (200 mg, 0.82 mmol), crude 2-butyl-3-vinylcyclohex-2-enone **21** (436mg, 2.45 mmol, crude from 0) and CH_2Cl_2 (5 mL). **HGII** catalyst (26 mg, 41 μmol) was then added under a high flow of nitrogen and the reaction mixture was heated at reflux for 16 hours. The reaction mixture then was cooled, exposed to oxygen and concentrated *in vacuo*. The crude product was then purified by gradient flash chromatography (SiO_2; 1:7 to 1:2; EtOAc:hexane) to give dienone **59** (236 mg, 73%) as a light yellow oil. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.74 – 7.67 (m, 2H, H2'), 7.55 – 7.47 (m, 1H, H4'), 7.47 – 7.38 (m, 2H, H3'), 6.61 (d, *J* = 15.7 Hz, 1H, H1), 6.16 (dt, *J* = 15.6 Hz, 7.5 Hz, 1H, H2), 5.84 (d, *J* = 8.8 Hz, 1H, NH), 4.29 (dq, *J* = 8.4, *J* = 5.6 Hz, 1H, H4), 2.63 – 2.32 (m, 8H, H3,

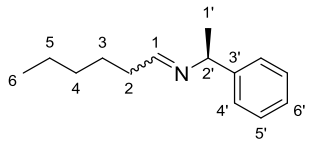
H2", H4" & H7"), 1.93 (p, *J* = 6.8 Hz, 2H, H3"), 1.73 – 1.16 (m, 12H, H5-H8, H8" & H9"), 0.95 – 0.79 (m, 6H, H9 & H10"). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 199.8 (C1"), 167.4 (*C*ONH), 149.1 (C5"), 136.4, 135.02 (C6" & C1'), 133.4 (C2'), 131.6, 131.2 (C3' & C4'), 128.8 (C1), 126.9 (C2), 49.6 (C4), 39.8, 38.2, 34.9, 32.3, 31.8, 26.4, 25.9, 24.4, 23.0, 22.7, 22.2 (C5-C8, C2"-C4" & C7"-C9"), 14.2, 14.1 (C9 & C10"). LR-MS (ESI, +ve, MeOH): *m/z* 418.2 $[M+Na]^+$. Calculated $[C_{15}H_{24}NO_2]^+$ *m/z* 418.3.

Synthesis of enone 60



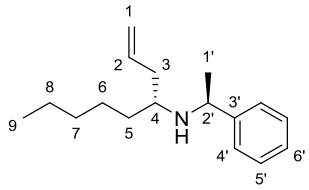
A nitrogen purged round bottom flask was charged with dienone **59** (32 mg, 80 μmol), 10% $Pd/BaSO_4$ (3 mg) and methanol (5 mL). The headspace of the flask was quickly purged and charged with nitrogen for two cycles using a quick fit stopcock. The flask was then put under a slight vacuum, sealed and a balloon filled with hydrogen gas was attached. The stopcock was opened, the flask then filled will hydrogen and the solution was then allowed to stir at room temperature for five hours before removing the balloon and carefully venting the system. The mixture was then filtered through a pad of diatomaceous earth and concentrated *in vacuo* to give enone **60** (35 mg, >99%) as yellow semi-solid. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.80 – 7.70 (m, 2H, H2'), 7.55 – 7.39 (m, 3H, H3' & H4'), 5.80 (d, *J* = 9.1 Hz, 1H, NH), 4.25 – 4.08 (m, 1H, H4), 2.40 – 2.17 (m, 8H, H1, H2", H4" & H7"), 1.88 (dt, 6.2 Hz, 2H, H3), 1.71 – 1.17 (m, 16H, H2, H3, H5-H8, H8" & H9"), 0.94 – 0.80 (m, 6H, H9 & H10"). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 199.3 (C1"), 167.3 (*C*ONH), 158.3 (C5"), 136.1, 135.1 (C6" & C1'), 131.5 (C2'), 128.8 (C3'), 126.9 (C4'), 49.6 (C4), 38.3, 35.9, 35.6, 34.9, 32.1, 31.9, 30.7, 25.8, 25.1, 24.6, 23.1 (C1-C3, C5-C7, C2"-C4", C7" & C8"), 22.7 (2C, C8 & C9"), 14.15 (2C, C9 & C10").

Synthesis of imine 61



(*S*)-α-Methyl benzylamine (3.2 g, 26 mmol) was added to a suspension of anhydrous sodium sulfate (20 g) and 1-hexanal (3.2 mL, 26 mmol) in CH_2Cl_2 (30 mL) at room temperature. The mixture was stirred at room temperature for 2 hours, filtered, and concentrated *in vacuo* to give the crude imine **61** which was used without further purification. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.74 (t, *J* = 5.1 Hz, 1H, H1), 7.41 – 7.27 (m, 5H, H4'-H6'), 4.28 (q, *J* = 6.7 Hz, 1H, H2'), 2.31 – 2.18 (m, 2H, H2), 1.58 – 1.47 (m, 2H, H3), 1.49 (d, *J* = 6.7 Hz, 3H, H1'), 1.45 – 1.23 (m, 4H, H4 & H5), 0.99 – 0.82 (m, 3H, CH_3).

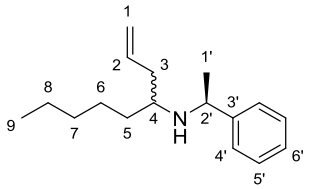
Synthesis of (-)-homoallylic amine 62



Allylmagnesium bromide (0.7M in Et_2O, 56 mL, 39 mmol) was added dropwise to a solution of titanium(iv) isopropoxide (11.5 mL, 39 mmol) in dry Et_2O (20 mL) over 20 mins, carefully maintaining the temperature between -50 °C and -60 °C using an ethanol/dry-ice bath. After the addition was completed the mixture was stirred for a further 60 mins at temperature. Imine **61** (approx 26 mmol) in dry Et_2O (15 mL) was then added dropwise to this solution over 5 mins at -50 °C. The cooling bath was then removed and the mixture was allowed to stir for 16 hours. The reaction was then cooled to 0 °C and quenched by slow addition of saturated NH_4Cl (30 mL). The phases were separated and the aqueous phase was further extracted with Et_2O (5×30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by flash chromatography (SiO_2; 1:10; EtOAc:hexane) to give chiral homoallylic amine **62** (4.10

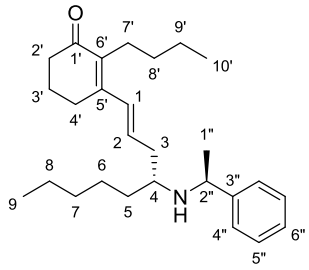
g, 64%, d.r. 20:1) as a light yellow oil. ^{1}H n.m.r. (400 MHz, $CDCl_3$), Major diastereomer: δ 7.45 – 7.10 (m, 5H, H4'-H6'), 5.84 – 5.71 (m, 1H, H2), 5.12 – 4.98 (m, 2H, H1), 3.93 – 3.82 (m, 1H, H2'), 2.45 – 2.35 (m, 1H, H4), 2.22 – 2.11 (m, 2H, H3), 1.52 – 1.07 (m, 8H, H5-H8), 1.31 (d, *J* = 6.6 Hz, 3H, H1'), 0.84 (t, *J* = 7.2 Hz, 3H, H9). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 146.4 (C3'), 135.7 (C2), 128.5 (C4'), 126.9 (C5'), 126.7 (C6), 117.1 (C1), 55.2, 53.9 (C2' & C4), 37.9 (C3), 34.9, 32.1, 25.7, 25.1 (C5-C8), 22.8 (C1'), 14.2 (C9). ^{1}H n.m.r. (400 MHz, $CDCl_3$), Minor diastereomer: δ 7.45 – 7.10 (m, 5H, H4'-H6'), 5.70 – 5.56 (m, 1H, H2), 5.12 – 4.98 (m, 2H, H1), 3.93 – 3.82 (m, 1H, H2'), 2.45 – 2.35 (m, 1H, H4), 2.05 – 1.94 (m, 2H, H3), 1.48 – 1.08 (m, 8H, H5-H8), 1.33 (d, *J* = 6.6 Hz, 3H, H1'), 0.88 (t, *J* = 7.1 Hz, 3H, H9). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 146.4 (C3'), 136.4 (C2), 128.5 (C4'), 126.9 (C5'), 126.7 (C6'), 117.2 (C1), 55.1, 53.6 (C4 & C2'), 39.3 (C3), 33.7, 32.3, 25.2, 24.8 (C5-C8), 22.8 (C1'), 14.2 (C9). LR-MS (ESI, +ve, MeOH): *m/z* 246.4 $[M+H]^+$. Calculated $[C_{17}H_{28}N]^+$ *m/z* 246.2. $[\alpha]^{20}$ =-35.1° (c=1.36, $CHCl_3$).

Synthesis of racemic homoallylic amine 62



Allylmagnesium bromide (1.3M in Et_2O, 1.77 mL, 2.30 mmol) was added dropwise to a solution of imine **61** (360 mg, 1.77 mmol) in dry Et_2O (10 mL) over five mins at 0 °C. The cooling bath was then removed and the mixture was allowed to warm to room temperature over an hour before being quenched by slow addition of saturated NH_4Cl (10 mL). The phases were separated and the aqueous phase was further extracted with Et_2O (3×10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give homoallylic amine **62** (140 mg, 32%, d.r. 3:1) as a light yellow oil. Spectral data was consistent with that reported for **62** previously.

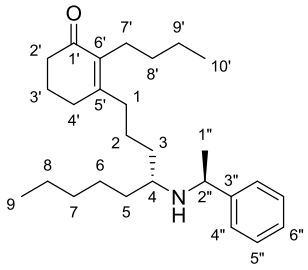
Synthesis of extended dienone 63



A Schlenk tube was charged with homoallylic amine tetrafluoroborate salt **62** (1.71 mmol[††]), 2-butyl-3-vinylcyclohex-2-enone **21** (930 mg, 5.22 mmol) and degassed EtOAc (5 mL). **HGII** catalyst (54 mg, 86 μmol) was added under a high flow of nitrogen and the tube was sealed and heated at reflux for 2 hours. The reaction mixture was then cooled and diluted with sat. $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer was further extracted with EtOAc (3×10 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was then purified by gradient flash chromatography (SiO_2; 1:99 to 1:4; EtOAc:hexane) to give dienone **63** (423 mg, 63%) as a light yellow oil. ^{1}H n.m.r. (400 MHz, $CDCl_3$), (*E*)-Isomer δ 7.37 – 7.20 (m, 5H, H4”-H6”), 6.59 (d, *J* = 15.7 Hz, 1H, H1), 6.12 (dt, *J* = 15.7 Hz, *J* = 7.6 Hz, 1H, H2), 3.92 (q, *J* = 6.6 Hz, 1H, H2”), 2.52 – 2.25 (m, 9H, H3, H4, H2’, H4’ & H7’), 1.95 (p, *J* = 6.3 Hz, 2H, H3’), 1.48 – 1.08 (m, 12H, H5-H8, H8’ & H9’), 1.33 (d, *J* = 6.6 Hz, 3H, H1”), 0.90 (t, *J* = 7.0 Hz, 3H, H10’), 0.84 (t, *J* = 7.2 Hz, 3H, H9). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 199.8 (C1’), 149.6 (C5’), 145.9 (C3”), 135.9 (C6’), 134.8, 130.7 128.5, 127.1, 126.8 (C1, C2, C4”-C6”), 55.2, 54.2 (C4 & C2”), 38.2, 37.9, 35.0 (C3, C4’ & C7’), 32.3, 32.0, 26.4, 25.7, 25.0, 24.4, 23.0, 22.7, 22.2 (C5-C8, C2’, C3’, C8’, C9’ & C1”), 14.2, 14.1 (C9 & C10’). LR-MS (ESI, +ve, MeOH): *m/z* 396.3 $[M+H]^+$. Calculated $[C_{27}H_{42}NO]^+$ *m/z* 396.3

[††] Tetrafluoroborate salt was prepared by addition of amine **62** (420 mg, 1.71 mmol) to 40% HBF_4 (275 μL. 1.71 mmol) in Et_2O(10 mL) and stirred at room temperature for 30 mins before concentration *in vacuo*. Salt was used without further purification.

Synthesis of enone 64



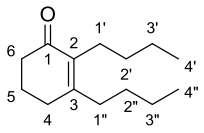
A nitrogen purged round bottom flask was charged with dienone **63** (390 mg, 0.99 mmol), 10% Pd/$BaSO_4$ (78 mg) and methanol (5 mL). The headspace of the flask was quickly purged and charged with nitrogen for two cycles using a quick fit stopcock. The flask was then put under a slight vacuum, sealed and a balloon filled with hydrogen gas was attached. The stopcock was opened, the flask then filled will hydrogen and the solution was then allowed to stir at room temperature for five hours before removing the balloon and carefully venting the system. The mixture was then filtered through a pad of diatomaceous earth and concentrated *in vacuo.* The crude product was then purified by flash chromatography (SiO_2; 1:5; EtOAc:hexane) to give enone **64** (372 mg, 95%) as a light yellow oil. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.31 – 7.09 (m, 5H, H4”-H6”), 3.77 (q, *J* = 6.6 Hz, 1H, H2”), 2.36 – 2.09 (m, 9H, H1, H4, H2’, H4’ & H7’), 1.89 – 1.78 (m, 2H, H3’), 1.49 – 1.01 (m, 16H, H2, H3, H5-H8, H8’ & H9’), 1.26 (d, *J* = 6.6 Hz, 3H, H1”), 0.83 (t, *J* = 7.0 Hz, 3H, H10’), 0.78 (t, *J* = 7.2 Hz, 3H, H9’). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 199.4 (C1’), 158.9 (C5’), 146.2 (C3”), 135.9 (C6’), 128.5 (C4”), 127.0 (C6”), 126.8 (C5”) , 55.1, 53.9 (C4 & C2”), 38.3, 35.3, 34.7, 33.8, 32.1, 32.1, 30.7, 25.6, 25.1, 24.9, 23.8, 23.1, 22.8, 22.7 (C1-C3, C5-C8, C2’-C4’, C7’-C9’ & C1”) 14.1 (2C, C9 & C10’). LR-MS (ESI, +ve, MeOH): *m/z* 398.2 $[M+H]^+$. Calculated $[C_{27}H_{44}NO]^+$ *m/z* 398.3.

Alternatively: a Schlenk tube was charged with homoallylic amine tetrafluoroborate salt **62** (1.0 mmol[‡‡]), 2-butyl-3-vinylcyclohex-2-enone **21** (534 mmol, 3.0 mmol) and dry degassed EtOAc (5 mL). **HGII** catalyst (31 mg, 49 μmol) was added in one portion

[‡‡] Tetrafluoroborate salt was prepared by addition of amine **62** (245 mg, 1 mmol) to 40% HBF4 (150 μL. 1.71 mmol) in Et_2O (5 mL) and stirred at room temperature for 30 mins before concentration *in vacuo*. Salt was used without further purification.

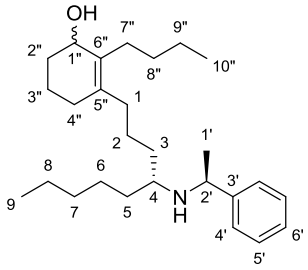
under a high flow of nitrogen and the tube was sealed and heated at reflux. After 2 hours the reaction mixture was cooled, exposed to oxygen and concentrated *in vacuo*. The crude product was then dissolved in methanol (5 mL) and transferred into a Fischer-Porter tube. The headspace of the tube was purged with argon over three cycles, charged with hydrogen (90 psi) and stirred at 60 °C for 18 hours. The hydrogen was then vented from the vessel and the reaction mixture was cooled and concentrated *in vacuo*. The crude product was then purified by flash chromatography (SiO_2; 1:3; EtOAc:hexane) to give enone **64** (163 mg, 41%) as a light yellow oil. Spectral data was consistent with that reported previously for **64** previously.

Synthesis of 2,3-dibutyl cyclohex-2-enone 69



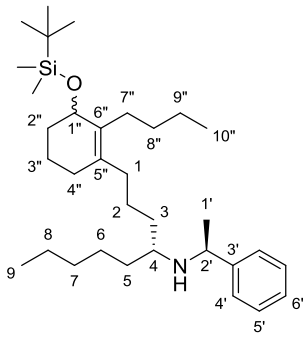
n-butyl lithium (1.4M, hexanes, 2.03 mL, 2.85 mmol) was added dropwise over 5 mins to a stirred solution of 2-butyl-3-isobutoxycyclohex-2-enone **38** (280 mg, 1.24 mmol) in dry THF (7 mL) under an atmosphere of nitrogen at 0 °C. The resulting solution was stirred at room temperature. After 2 hours, the reaction mixture was cooled to 0 °C and quenched with sat. NH_4Cl (10 mL) solution and diluted with Et_2O (10 mL). The phases were separated, and the aqueous phase was further extracted with Et_2O (3×10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2; 1:4; EtOAc:hexane) to give 2,3-dibutyl cyclohex-2-enone **69** (190 mg, 67%) as a light yellow oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 2.35 – 2.08 (m, 8H, H4, H6 H1', H2"), 1.85 (p, *J* = 6.5 Hz, 2H, H5), 1.51 – 1.07 (m, 8H, H2', H3', H2" & H3"), 0.99 – 0.72 (m, 6H, H4' & H4"). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 199.4 (C1), 159.3 (C3), 135.6 (C2), 38.1, 34.7, 31.97, 30.7, 30.2, 24.9, 23.0, 22.6 (C4-C6, C1'-C3' & C1"-C3"), 14.0, 14.0 (C4' & C4").

Synthesis of allylic alcohol 76



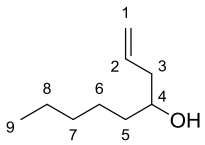
$NaBH_4$ (10 mg, 0.26 mmol) was added in one portion to a solution of enone **64** (100 mg, 0.25 mmol) and $CeCl_3.7H_2O$ (94 mg, 0.25 mmol) in MeOH (2 mL) at room temperature. The mixture was stirred at room temperature for 1 hour before diluting with H_2O (10 ml), EtOAc (10 mL) and the phases were separated. The aqueous layer was further extracted with EtOAc (3×10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by gradient flash chromatography (SiO_2; 0:100 to 1:4; EtOAc:hexane) to give the allylic alcohol **76** (56 mg, 56%) as a light yellow oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 7.37 – 7.19 (m, 5H, H3'-H6'), 4.12 – 4.00 (m, 1H, H1"), 3.87 (q, *J* = 6.6 Hz, 1H, H2'), 2.39 – 1.08 (m, 27H, H1-H8, H2"-H4", H7"-H9"), 1.35 (d, *J* = 6.6 Hz, 3H, H1') , 0.91 (t, *J* = 7.0 Hz, 3H, H10'), 0.84 (t, *J* = 7.1 Hz, 3H, H9). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 145.9 (C3'), 135.7, 132.9, 128.5, 127.0, 126.8 (C4'-C6', C5" & C6"), 67.4 (C1"), 55.2, 54.1 (C4 & C2'), 34.5, 33.5, 32.4, 32.1, 31.9, 29.9, 29.7, 25.6, 24.7, 24.2, 24.1, 23.3, 22.8, 18.13 (C1-C3, C5-C8, C1', C2"-C4", C7"-C9"), 14.2, 14.2 (C9 & C10"). Compound did not ionise using ESI+ LR-MS.

Synthesis of silyl ether 74



TBSCl (142 mg, 0.94 mmol) was added in one portion to a solution of allylic alcohol **76** (250 mg, 0.63 mmol) and imizadole (128 mg, 1.88 mmol) in DMF (5 mL). The mixture was stirred for 16 hours at room temperature before being diluted with water (15 mL), EtOAc (15 mL) and the phases were separated. The aqueous layer was further extracted with EtOAc (3×15 mL) and the combined organic extracts were washes with water (3×15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2; 1:5; EtOAc:hexane) to give the silyl ether **74** (244 mg, 76%) as a colourless oil. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.34 – 7.19 (m, 5H, H4'-H6'), 4.11 (t, *J* = 4.4 Hz, 1H, H1"), 3.85 (q, *J* = 6.6 Hz, 1H, H2'), 2.39 – 2.22 (m, 1H, H4), 2.12 – 1.80 (m, 6H, H1, H4" & H7"), 1.81 – 1.04 (m, 20H, H2, H3, H5-H8, H2", H3", H8" & H9"), 1.33 (d, *J* = 6.6 Hz, 3H, H1'), 0.93 – 0.88 (m, 3H, H9), 0.90 (d, *J* = 1.1 Hz, 9H, Si^{t}Bu), 0.84 (t, *J* = 7.2 Hz, 3H, H10"), 0.08 (d, *J* = 2.2 Hz, 6H, $SiMe_2$). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 146.5 (C3'), 134.2, & 134.1 (C6"), 133.7 & 133.6 (C5"), 128.5 (C4'), 126.9 (C6'), 126.8 (C5'), 68.5 & 68.5 (C1"), 55.2 & 55.1 (C4), 54.1 (C2'), 34.8, 33.8, 33.7, 33.3, 32.1, 31.9, 29.8, 29.4 , 26.1 ($SiC(CH_3)_3$), 25.8, 25.6, 25.6, 25.0, 24.1, 24.0, 23.4, 22.8, 18.9, 18.9, 18.3, 14.3 (C9), 14.2 (C10"), -3.4 ($SiC(CH_3)_3$), -4.0 (SiMe), -4.5 (SiMe). LR-MS (ESI, +ve, MeOH): *m/z* 514.3 $[M+H]^+$. Calculated $[C_{33}H_{60}NOSi]^+$ *m/z* 514.4.

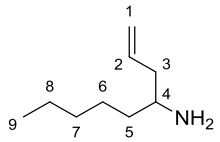
Synthesis of non-1-en-4-ol 78



Allylmagnesium bromide (0.9M in Et_2O, 25.0 mL, 22.5 mmol) was added dropwise to a solution of hexanal (2.5 mL, 2.0 mmol) in dry Et_2O (15 mL) over five mins at 0 °C under an atmosphere of nitrogen. The cooling bath was then removed and the mixture was allowed to warm to room temperature over 16 hours. The mixture was quenched by slow addition of saturated NH_4Cl (30 mL) and the phases were then separated. The aqueous phase was further extracted with Et_2O (3×50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was then purified by bulb to bulb distillation

(~120 °C, 20 mbar) to give non-1-en-4-ol **78** (2.53 g, 89%) as a colourless oil. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 5.91 – 5.74 (m, 1H, H2), 5.19 – 5.07 (m, 2H, H1), 3.69 – 3.58 (m, 1H, H4), 2.37 – 2.06 (m, 2H, H3), 1.51 – 1.37 (m, 4H, H5 & H6), 1.39 – 1.18 (m, 4H, H7 & H8), 0.89 (t, *J* = 6.9 Hz, 3H, H9). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 135.1 (C2), 118.1 (C1), 70.9 (C4), 42.1 (C3), 36.9 , 32.0, 25.5, 22.8 (C5-C8), 14.2 (C9). LR-MS (ESI, +ve, MeOH): *m/z* 142.3 $[M]^+$. Calculated $[C_9H_{18}N]^+$ *m/z* 142.1.

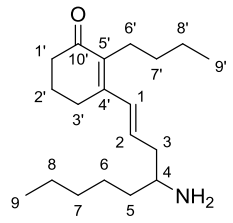
Synthesis of non-1-enyl-4-amine 30



Diisopropyl azodicarboxylate (1.96 mL, 9.97 mmol) was added dropwise over five mins to a flame dried Schlenk flask containing non-1-en-4-ol **78** (1.18 g, 8.38 mmol), triphenylphosphine (2.60 g 9.97 mmol), phthalimide (1.5 g, 10 mmol) and dry THF (15 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature overnight before being concentrated *in vacuo*. The mixture was diluted with Et_2O (50 mL), cooled (0 °C), filtered and concentrated *in vacuo* to give the crude phthalimide **79**. ^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 7.83 – 7.77 (m, 2H, Ar-H), 7.73 – 7.66 (m, 2H, Ar-H), 5.78 – 5.60 (m, 1H, =CH), 5.06 – 4.89 (m, 2H, $=CH_2$), 4.34 – 4.22 (m, 1H, CH), 2.87 – 2.43 (m, 2H, CH_2), 2.17 –1.65 (m, 2H, CH_2), 1.40 – 1.14 (m, 6H, 3×CH_2), 0.83 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 168.9 (*C*=O), 135.0, 133.9, 132.0, 123.2, 117.8 (=*C*H_2), 51.9 (*C*HN), 37.2, 32.2, 31.6, 26.5, 22.6, 14.1 (CH_3). Aqueous methylamine (6 mL, 40% w/w) was added to a solution of the crude phthalimide in ethanol (10 mL) and the mixture was heated in a sealed tube at 70 °C for 16 hours. The mixture was then carefully concentrated *in vacuo* and acidified with 3M HCl (100 mL), diluted with CH_2Cl_2 (50 mL) and the phases were separated. The aqueous phase was further washed with CH_2Cl (2×50 mL) then slowly basified to pH 9 by addition of 6M NaOH. The aqueous layer was then extracted with diethyl ether (3×50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a light yellow oil. The crude product was then purified by bulb to bulb distillation (100

°C, 30 mbar) to give non-1-enyl-4-amine **30** (610 mg, 52%) as a colourless oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 5.84 – 5.59 (m, 1H, H1), 5.12 – 4.94 (m, 2H, H2), 2.80 – 2.58 (m, 1H, H4), 2.28 – 1.79 (m, 2H, H3), 1.38 – 1.10 (m, 8H, H5-H8), 0.81 (dt, *J* = 6.7, *J* = 3.1 Hz, 3H, H9). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 136.0 (C2), 117.2 (C1), 50.6 (C4), 42.6 (C3), 37.6, 32.0, 25.9, 22.6 (C5-C8), 14.0 (C9). LR-MS (ESI, +ve, MeOH): *m/z* 142.3 $[M+H]^+$. Calculated $[C_9H_{20}N]^+$ *m/z* 142.2

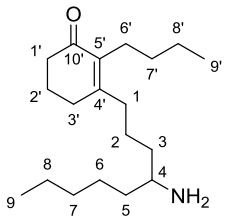
Synthesis of dienone 31



A Schlenk tube was charged with non-1-enyl-4-ammonium tetrafluoroborate **30** (154 mg, 0.67 mmol[§§]), 2-butyl-3-vinylcyclohex-2-enone **21** (360 mg, 2.00 mmol) and degassed EtOAc (4 mL). **HGII** catalyst (21 mg, 34 μmol) was added under a high flow of nitrogen and the tube was sealed and heated at reflux for 2 hours. The reaction mixture was cooled and diluted with sat. $NaHCO_3$ (5 mL). The phases were separated and the aqueous layer was further extracted with EtOAc (3×10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was then purified by flash chromatography (SiO_2; 100:5:1; CH_2Cl_2:MeOH:Et_3N) to give dienone **31** (85 mg, 43%) as a light yellow oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 6.62 (d, *J* = 15.6 Hz, 1H, H1), 6.20 – 6.05 (dt, *J* = 15.6 Hz, *J* =7.7 Hz, 1H, H2), 2.93 – 2.79 (m, 1H, H4), 2.54 – 2.08 (m, 8H, H3, H1', H3', H6'), 1.93 (p, *J* = 6.3 Hz, 2H, H2'), 1.53 – 0.98 (m, 12H, H5-H8 & H7'-H8'), 0.86 (t, *J* = 6.6 Hz, 6H, H9 & H9'). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 199.7 (C10'), 149.3, 136.1, 134.4, 131.03 (C1, C2, C4' & C5'), 51.2 (C4), 42.0 (C3), 38.2, 37.4, 32.3, 32.0, 26.4, 25.9, 24.4, 23.0, 22.7, 22.2 (C5-C8, C1'-C3' & C6'-C8'), 14.1 (C9), 14.1 (C9'). HR-MS (ESI, +ve, MeOH): *m/z* 292.2639 $[M+H]^+$. Calculated $[C_{19}H_{34}NO]^+$ *m/z* 292.2635.

[§§] Tetrafluoroborate salt was prepared by addition of amine **30** (458 mg, 3.35 mmol) to 40% HBF4 (510 μL. 3.35 mmol) in Et_2O(10 mL) and stirred at room temperature for 30 mins before concentration *in vacuo*. Salt was used without further purification.

Synthesis of enone 28



A nitrogen purged round bottom flask was charged with dienone **31** (72 mg, 0.25 mmol), 20% $Pd/BaSO_4$ (14 mg) and methanol (2 mL). The headspace of the flask was quickly purged and charged with nitrogen for two cycles using a quick fit stopcock. The flask was then put under a slight vacuum, sealed and a balloon filled with hydrogen gas was attached. The stopcock was opened, the flask then filled will hydrogen and the solution was allowed to stir at room temperature for five hours before removing the balloon and carefully venting the system. The mixture was then filtered through a pad of diatomaceous earth and concentrated *in vacuo.* The crude product was purified by flash chromatography (SiO_2; 10:1; CH_2Cl_2:MeOH) to give enone **28** (61 mg, 89%) as a light yellow oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 2.99 – 2.76 (m, 1H, H4), 2.44 – 2.09 (m, 8H, H1, H1', H3' & H6'), 1.90 (p, *J* = 6.2 Hz, 2H, H2'), 1.75 – 1.09 (m, 16H, H2, H3, H5-H8 & H7'-H8'), 0.87 (t, *J* = 6.7 Hz, 6H, H9 & H9'). ^{13}C n.m.r. (75 MHz, $CDCl_3$): δ 199.2 (C10'), 158.0 (C4'), 136.1 (C5'), 51.7 (C4), 38.2, 34.8, 32.1, 31.9, 30.6, 25.5, 25.1, 24.3, 23.1, 22.7, 22.7 (C1-C3, C5-C8, C1'-C3' & C6'-C8'), 14.1 14.1 (C9 & C9'). LR-MS (ESI, +ve, MeOH): *m/z* 294.3 $[M+H]^+$. Calculated $[C_{19}H_{36}NO]^+$ *m/z* 294.3.

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Appendices

List of publications

C. P. Woodward, N. D. Spiccia, W. R. Jackson and A. J. Robinson, *Chem. Comm.*, 2011, **47**, 779-781.

A. S. R. Chesman, M. Yang, N. D. Spiccia, G. B. Deacon, S. R. Batten and A. Mudring, *Chem. Eur. J.*, 2012, **18**, 9580-9589.

N. D. Spiccia, E. Border, J. Illesinghe, W. R. Jackson and A. J. Robinson, *Synthesis*, 2013, **45**, 1683-1688.

Z. J. Wang, N. D. Spiccia, W. R. Jackson and A. J. Robinson, *J. Pept. Sci.*, 2013, **8**, 470-476.

Z. J. Wang, N. D. Spiccia, C. Gartshore, J. Illesinghe, W. R. Jackson and A. J. Robinson, *Synthesis*, 2013, Advance Article, DOI: 10.1055/s-0033-1338527.

Z. J. Wang, N. D. Spiccia, W. R. Jackson and A. J. Robinson, PCT International Application *"Amino acid analogues and methods for their synthesis"*, PCT/AU2013/000747 (filed July 8, 2013).

N. D. Spiccia, C. P. Woodward, W. R. Jackson and A. J. Robinson, PCT International Application "*Processes for producing amine compounds*", PCT/AU2013/000745 (filed July 8, 2013).

A simple amine protection strategy for olefin metathesis reactions†

Clint Peter Woodward, Nicolas Daniel Spiccia, William Roy Jackson and Andrea Jane Robinson*

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Acyclic diamines are valuable feedstocks for polyamide synthesis. Ruthenium-alkylidene catalysed cross metathesis of amino alkenes is problematic and acyl derivatisation can result in less efficient syntheses, poor catalyst turnover and isomerisation. Temporary amine masking *via* stable and soluble ammonium salts delivers cyclic and acyclic aminoalkenes in high yield and purity.

Advances in homogeneous catalysts have led to their widespread use in organic synthesis.[1] The recent rise in popularity of olefin metathesis can be directly attributed to the commercial availability of the catalysts **1–3**, the ease in which they can be handled, and the broad variety of olefins and functional groups that these catalysts accommodate (Fig. 1).[2] These catalyst systems however, are susceptible to poisoning by substrates containing moieties that act as strong donor ligands. Amines, for example, can result in inhibition of the catalytic cycle by competitively binding to the ruthenium metal centre.[3] This phenomenon may be avoided by masking the problematic functional group with a protecting group, reducing the donating capabilities of the relevant heteroatom. Unfortunately, protection can lead to competing olefin isomerization[4] and unproductive catalytic cycles due to deleterious protecting group chelation.[5] Hence, finding alternate methods to mask strong donors such as amines remains a challenge and an important endeavour.

Towards this end, *in situ* deactivation of the amino group, *via* Brønsted[6] or Lewis acid addition,[7] has been used to affect ring closing metathesis (RCM) of dienes containing secondary and tertiary amines. Our investigations, however, sought to enable cross metathesis (CM) of unprotected amine-containing substrates, with a particular emphasis on primary amines as they have previously proven to be particularly difficult metathesis substrates.[8] Our attempts to homodimerise salt-masked

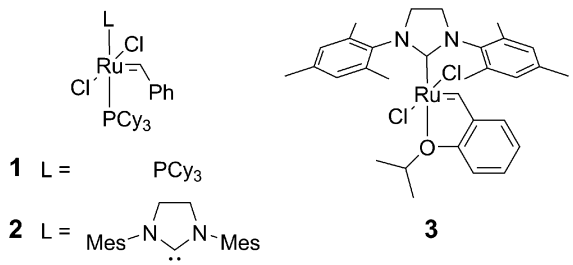
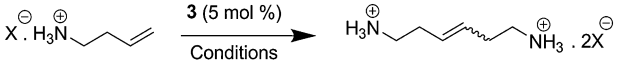


Fig. 1 Olefin metathesis catalysts.

School of Chemistry, Wellington Road, Clayton 3800, Victoria, Australia. [redacted]3

† Electronic supplementary information (ESI) available: Spectral data for compounds **4a–m** and **5a–m**. See DOI: 10.1039/c0cc03716h

Table 1 CM of 3-butenyl ammonium salts



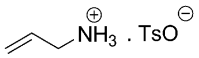
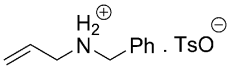
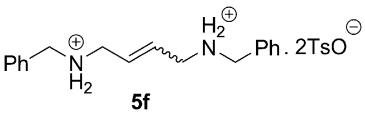
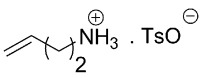
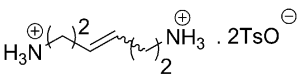
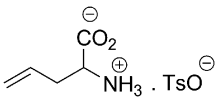
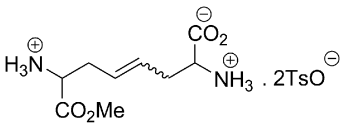
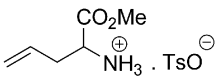
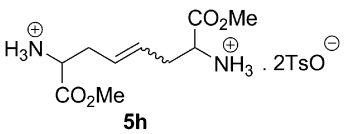
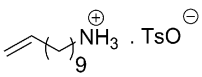
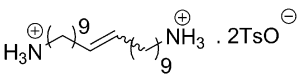
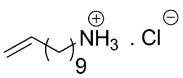
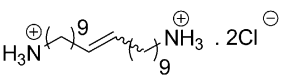
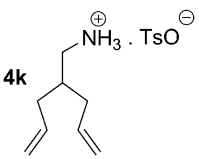
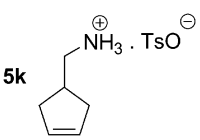
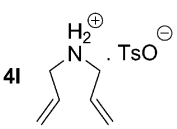
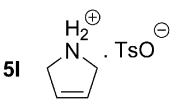
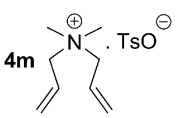
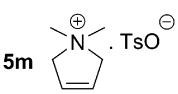
4a-d **5a-d**

Entry	Counterion X	Conditions	Product	Yield
1	Free amine	CH_2Cl_2, Δ	—	0[a]
2	**4a**, Cl	80 °C in HCl satd toluene	**5a**	38[a]
3	**4b**, OTf[b]	CH_2Cl_2, Δ	**5b**	8[a]
4	**4b**, OTf[c]	CH_2Cl_2, Δ	**5b**	83[d]
5	**4c**, BF_4[c]	CH_2Cl_2, Δ	**5c**	91[a]
6	**4d**, OTs[c]	CH_2Cl_2, Δ	**5d**	92[d], 95[d,e]

Conditions: catalyst = **3**, substrate concentration = ~0.1 mol L^{-1}, 24 h, under N_2. [a] % Conversion determined by ^1H NMR spectroscopy in D_2O. [b] Salt metathesis preformed *in situ* with AgOTf. [c] Preformed ammonium salt. [d] Isolated yield. [e] Microwave heating used, 2 h, 100 °C, 100 W.

amines in organic media therefore began by investigating 3-butenyl ammonium salts **4a–d** (Table 1). While cross metathesis of unadultered 3-butenylamine was unsuccessful (entry 1, 0%), metathesis of **4a** in HCl-saturated toluene gave reasonable conversion (38%) to the target homodimer **5a** (Table 1, entry 2). The observed incomplete reaction was attributed to poor substrate solubility in toluene. We therefore sought to rectify this problem by solubilising the ammonium chloride salt of 3-butenylamine *in situ* by the addition of AgOTf. The resultant triflate salt **4b** was immediately treated with Hoveyda Grubbs' catalyst (**3**, 5 mol%). Unfortunately, only poor conversion to the desired product **5b** was obtained (Table 1, entry 3, 8%). The low cross metathesis conversion was attributed to the deleterious coordination of the AgCl by-product to the butenyl olefin resulting in a non-reactive olefinic substrate. In light of this result it was deemed important to preform the ammonium salts and completely remove the AgCl prior to olefin cross metathesis (entries 4–6). The ammonium salts **4b–d**, prepared by a standard silver chloride salt elimination reaction, were subjected to cross metathesis to generate their respective homodimers **5b–d** (entries 4–6). Solubility tests revealed that the tosylate adduct **4d** readily dissolved in dichloromethane at room temperature, whereas the triflate **4b** and tetrafluoroborate **4c** salts displayed only partial solubility at ambient temperature but became soluble upon heating. The results of the cross metathesis of the AgCl-free olefinic ammonium salts **4b–d** are displayed in Table 1 (entries 4–6) and show high conversions (83–95%) for all three salts. The tosylate analogue marginally out performed the other two salts screened. The homodimer products **5b–d** were readily separated from the reaction mixture by selective precipitation. Conveniently, the crude products were simply

Table 2 CM and RCM of olefinic ammonium salts (**4e–m**)

Entry	Substrate	Product[e]	Yield[a] Conv.	Yield[a] MW
1	 **4e**	 **5e**	40	74
2	 **4f**	 **5f**	23[c]	46
3	 **4d**	 **5d**	92	95
4	 **4g**	 **5g**	0	0
5	 **4h**	 **5h**	92	90
6			94[b]	—
7	 **4i**	 **5i**	92[d]	88[d]
8	 **4j**	 **5j**	81	82
9	 **4k**	 **5k**	>95[c]	>95[c]
10	 **4l**	 **5l**	>95[c]	>95[c]
11	 **4m**	 **5m**	9[c]	>95[c]

Conventional conditions: catalyst = **3**, substrate concentration = ~0.1 mol L^{-1}, catalyst loading 5 mol%, 24 h, 40 °C, under N_2. Microwave conditions: substrate concentration = ~0.1 mol L^{-1}, 2 h, 100 °C 100 W, under N_2. [a] Isolated yield. [b] Salt formation performed *in situ*. [c] Conversion determined by ^{1}H NMR spectroscopy in d_4-MeOH. [d] Olefin isomerisation products observed by ESI-MS. [e] Stereochemical assessment of acyclic products was examined by NMR spectroscopy and GC analysis of derivative diacetates.

washed with solvent to remove catalyst and ruthenium residues. Homodimerisation of the tosylate adduct **4d** could be further improved to >95% by the use of microwave heating. Importantly, no olefin isomerisation was observed in any of these reactions. This was a significant result as exposure of carbamate protected 3-butenylamine (Fmoc or Boc) to ruthenium-alkylidene catalyst **2** results in significant isomerisation of the starting amine and poor conversion (<30%) to the

target homodimer. Given the success of this approach in providing a temporary and expedient mask of amines during CM we decided to extend this methodology to additional amine-containing substrates (Table 2). To remove the likelihood of AgCl contamination we applied an alternative method to preparing the starting olefinic ammonium salts by direct proton exchange of an olefinic amine with anhydrous *p*-toluenesulfonic acid. The tosylate salts **4d–m** were found to possess excellent solubility in dichloromethane and their low hygroscopic nature facilitated easy handling.

The silver-free olefinic ammonium salts were subjected to both the conventional and microwave reaction conditions used for **4d**, with the results shown in Table 2. In most cases pure target homodimer **5** was obtained by precipitation from solution using cold dichloromethane, acetone or hexane, and washing the filtered product with the same solvent. The tosylate salt of propenylamine **4e** underwent smooth homodimerisation under microwave conditions (entry 1). Notably, Miller *et al.* showed that homodimerisation of *N*-acyl derivatives of propenylamine are unsuccessful: in all cases, a complex mixture of isomerised starting material/product resulted and the target homodimer could not be isolated.[9] Gratifyingly, the *N*-benzyl derivative of propenylamine **4f**, a secondary amine, also underwent cross metathesis without isomerization (entry 2), although the use of microwave heating was required to achieve a respectable yield.

The tosylate salt of butenylamine underwent near quantitative homodimerisation without isomerization (entry 3). Poor solubility of the zwitteric allylglycine **4g** in DCM prevented homodimerisation (entry 4), however the tosylate salt of the methyl ester derivative **4h** underwent smooth cross metathesis to generate the target dimer **5h** as a mixture of geometric isomers and in excellent yield (entry 5). Conveniently, we also found that the tosylate salts of these substrates could be generated *in situ* prior to addition of the metathesis catalyst by direct proton exchange without affecting yield. This is exemplified by homodimerisation of **4h** in 94% yield under conventional heating conditions (entry 6).

An interesting relationship between alkyl chain length of the ammonium salts and the yield of homodimer was also observed (entries 7 and 8). Short chain homodimers, such as those derived from **4d** and **4e**, 3-butenyl and allylamine, respectively, immediately precipitate from solution reducing the chance of concomitant isomerization. As the alkyl chain length is increased however, to undecenylamine for example, the dimerised product can remain soluble for an extended period of time potentiating the chance for secondary reaction (Table 2, entry 7). The mass spectrum of the bis-tosylate product **5i** showed molecular ion peaks separated by m/z 14 a.m.u. suggesting that isomerization processes were operating. By switching the counterion from tosylate **4i** to chloride **4j** however, the solubility of the dichloride homodimer product **5j** was decreased to promote early precipitation and eliminate undesired olefin isomerisation (Table 2, entry 8). Hence, the point at which the dimerisation product precipitates can be tuned *via* modification of the counterion, making product purification straightforward. Significantly, this feature also appears to minimise, and in some cases prevent, *trans–cis* isomerisation of the acyclic homodimers.

Lastly, to show the general applicability of the approach, we examined three ring closing metathesis reactions involving primary, secondary and quaternary amines (entries 9–11). Under conventional and microwave heating conditions, the tosylate salts of **4k** and **4l** underwent near quantitative (>95%) conversion to the expected aminocyclopentene analogues (entries 9 and 10). Quaternary amine **4m**, however, resisted RCM when heated at reflux in DCM in the presence of Hoveyda Grubbs' catalyst **3**. This result is consistent with a report by Grubbs and Hong where only low RCM conversion (<5%) of the analogous chloride salt derivative was observed using a specialised water soluble metathesis catalyst.[9] Significantly, under microwave irradiation, the amine salt **4m** underwent smooth RCM to provide the target pyrrolidine analogue in excellent yield (>95%, entry 11).

In conclusion, we have developed a method to directly and temporarily mask primary amines as stable and soluble ammonium salt derivatives to enable olefin metathesis to proceed in good to excellent yields without olefin isomerization. The bis-ammonium tosylate products **5e–l** can be readily used in subsequent chemical transformations by 'deprotecting' the ammonium salt pair with a base, such as triethylamine or potassium carbonate. This approach therefore provides an efficient strategy for the metathesis of substrates containing amine functionality. It is also applicable to the synthesis of a broad range of diamines and could therefore find widespread use in polyamide and pharmaceutical production.

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Lanthanoid-Based Ionic Liquids Incorporating the Dicyanonitrosomethanide Anion

Anthony S. R. Chesman,[a, b, c] Mei Yang,[b] Nicolas D. Spiccia,[a] Glen B. Deacon,*[a] Stuart R. Batten,*[a] and Anja-Verena Mudring*[b]

Abstract: A series of low-melting-point salts with hexakisdicyanonitrosomethanidolanthanoidate anions has been synthesised and characterised: $(C_2mim)_3[Ln(dcnm)_6]$ (**1Ln**; **1Ln** = **1La**, **1Ce**, **1Pr**, **1Nd**), $(C_2C_1mim)_3[Pr(dcnm)_6]$ (**2Pr**), $(C_4C_1pyr)_3[Ce(dcnm)_6]$ (**3Ce**), $(N_{1114})_3[Ln(dcnm)_6]$ (**4Ln**; **4Ln** = **4La**, **4Ce**, **4Pr**, **4Nd**, **4Sm**, **4Gd**), and $(N_{1112OH})_3[Ce(dcnm)_6]$ (**5Ce**) (C_2mim = 1-ethyl-3-methylimidazolium, C_2C_1mim = 1-ethyl-2,3-dimethylimidazolium, C_4C_1py = *N*-butyl-4-methylpyridinium, N_{1114} = butyltrimethylammonium, N_{1112OH} = 2-(hydroxyethyl)trimethylammonium = choline). X-ray crystallography was used to determine the structures of complexes **1La**, **2Pr**, and **5Ce**, all of which contain $[Ln(dcnm)_6]^{3-}$ ions. Complexes **1Ln** and **2Pr** were all ionic liquids (ILs), with complex **3Ce** melting at 38.1 °C, the lowest melting point of any known complex containing the $[Ln(dcnm)_6]^{3-}$ trianion. The ammonium-based cations proved to be less suitable for forming ILs, with complexes **4Sm** and **4Gd** being the only salts with the N_{1114} cation to have melting points below 100 °C. The choline-containing complex **5Ce** did not melt up to 160 °C, with the increase in melting point possibly being due to extensive hydrogen bonding, which could be inferred from the crystal structure of the complex.

Keywords: dicyanonitrosomethanide · ionic liquids · lanthanides · thermal properties · X-ray diffraction

Introduction

The novel property combinations possible in ionic liquids (ILs), such as negligible vapour pressures, wide electrochemical windows, and good thermal stabilities, have resulted in an exponential growth in the field as researchers find applications for these unique media in areas such as catalysis,[1] green chemistry,[2] industrial chemical synthesis,[3] and many more. Of particular interest is the incorporation of a metal into an IL, with the aim of imparting a property of the metal atom to the bulk material, such as magnetism or luminescence.[4] This is exemplified by $(C_nmim)[FeCl_4]$ (C_nmim = 1-alkyl-3-methylimidazolium; n = 2, 4), an IL that responds strongly to a magnetic field due to the presence of the paramagnetic iron centre, and by the highly luminescent $(C_nmim)[MnX_4]$ (n = 2–4, 6; X = Cl, Br).[5]

The unique luminescent and magnetic properties of lanthanoids make them ideal candidates for inclusion into ILs,[6] although there are considerable synthetic hurdles that have hitherto limited the quantity of lanthanoids that may be dissolved in ILs.[7,8] Lanthanoid salts often appear to have poor solubility in ILs as the generally only weakly Lewis acidic cations and Lewis basic anions of the IL have difficulty in solvating the ions, and high viscosities may further kinetically hamper the dissolution process.[8] One synthetic strategy for obtaining lanthanoid-containing ILs is to react a lanthanoid salt with an ionic liquid having the same anion. The bis(trifluoromethanesulfonyl)amide (Tf_2N) anion is one of the most prominent IL anions. After it was shown to coordinate to divalent ytterbium in $(C_3C_1pyr)[Yb(Tf_2N)_4]$ (C_3C_1pyr = *N*-propyl-*N*-methylpyrrolidinium),[9] the Eu^{III}-based ionic liquids $(C_3mim)/(C_4mim)[Eu(Tf_2N)_4]$ (C_3mim = 1-propyl-3-methylimidazolium; C_4mim = 1-butyl-3-methylimidazolium), which exhibit bright-red luminescence, were developed.[10] Since then, other lanthanoid-based ionic liquids were synthesized following this simple synthetic approach.[11] It was shown that in some cases even hydrous starting materials can be employed and reactions can be performed under ambient conditions.[12] However, this may lead to the incorporation of water as a neutral co-ligand, as found in a series of ILs with the formula $(C_4mim)_{x-3}[Ln-$

[a] Dr. A. S. R. Chesman, N. D. Spiccia, Prof. Dr. Dr. G. B. Deacon, Prof. Dr. S. R. Batten
School of Chemistry
Monash University
Clayton, Victoria 3800 (Australia)
[redacted]
Homepage: http://www.chem.monash.edu.au/staff/sbatten/index.html

[b] Dr. A. S. R. Chesman, M. Yang, Prof. Dr. A.-V. Mudring
Anorganische Chemie I – Festkörperchemie und Materialien
Ruhr Universität Bochum
44780 Bochum (Germany)
[redacted]
Homepage: http://www.anjamudring.de

[c] Dr. A. S. R. Chesman
CSIRO Materials Science and Engineering
Bayview Ave, Clayton, Victoria 3169 (Australia)

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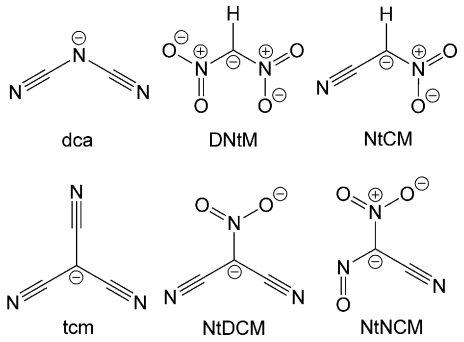
$(NCS)_x(H_2O)_y]$ ($x=6$–8; $y=0$–2; Ln = Y, La–Yb).[13] The related dysprosium-based ionic liquids $(C_6mim)_{5-x}[Dy(SCN)_{8-x}(H_2O)_x]$ ($x=0$–2; C_6mim = 1-hexyl-3-methylimidazolium) were shown to be luminescent and also exhibited a stronger response to a magnetic field than previously investigated transition metal-based ILs.[14]

The polynitrile anions dicyanamide (dca) and tricyanomethanide (tcm) have been incorporated into numerous ILs,[15,16] and the products obtained have already found applications in solar cells and organic chemistry.[17,18] A number of their characteristics make these anions ideal for ILs, namely their low point symmetry and high charge delocalization.[19] These properties are shared by novel nitro-/nitroso-functionalized methanides,[20] with several of them beginning to find application in IL synthesis,[21] and these anions have the potential to form energetic ILs (Scheme 1).[22]



Scheme 1. Nitrile-/nitroso-/nitro-containing molecules that have acted as anions in ionic liquids; DNtM = dinitromethanide, NtCM = cyanonitromethanide, NtDCM = dicyanonitromethanide, NtNCM = cyanonitronitrosomethanide.

Despite being first synthesised nearly 80 years ago,[23] to the best of our knowledge the anion dicyanonitrosomethanide (dcnm) (Figure 1a) has only recently been incorporated into ILs,[24] and has yet to receive the same attention in the literature as related methanides that have proven to be conducive to forming room-temperature ionic liquids (RTILs).

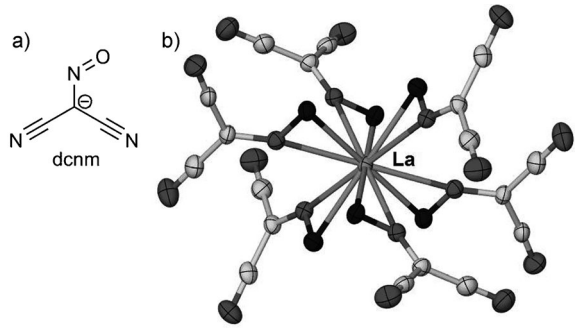


Figure 1. a) The dicyanonitrosomethanide (dcnm) anion. b) The $[La(dcnm)_6]^{3-}$ anion from the crystal structure of $(N_{2222})_3[La(dcnm)_6]$ (N_{2222} = tetraethylammonium),[26a] with ellipsoids shown at 50% probability.

The dcnm anion has been shown to coordinate to lanthanoids through its nitroso group,[25] and in the absence of sterically hindering co-ligands the 12-coordinate homoleptic trianions $[Ln(dcnm)_6]^{3-}$ (Ln = La–Gd) are formed (Figure 1b).[26]

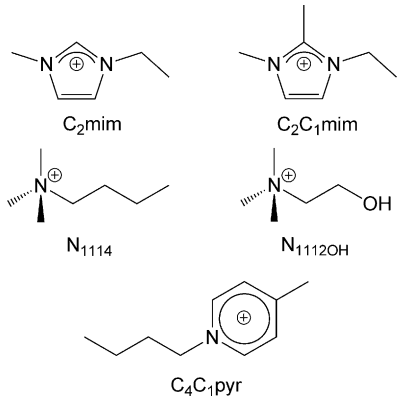
The trianions $[Ln(dcnm)_6]^{3-}$ may be synthesised in high yield, and the previously reported low melting points of their tetraethylammonium salts suggested that an IL may be synthesised when such an anion is coupled with a judiciously selected countercation. Recently, we reported the synthesis of the first series of lanthanoid-based ILs to contain the dicyanonitrosomethanide ligand, $(N_{4444})_3[Ln(dcnm)_6]$ (Ln = La, Ce, Pr, Nd), which displayed polymorph-dependent melting points, as proven by a novel in situ synchrotron-based X-ray powder diffraction technique.[27] Herein, we report an extension of the family of ionic liquids with the $[Ln(dcnm)_6]^{3-}$ anion and a variety of cations, and examine the crystal structures of the complexes and their thermal behaviour.

Results and Discussion

Synthesis: The syntheses of complexes of the type $(cat)_3[Ln(dcnm)_6]$ (cat = cation) proceed via a metathesis reaction between the silver salt of dicyanonitrosomethanide, the respective lanthanoid chloride hydrate, and a halide salt of the desired counter cation in an alcoholic solution (Eq. (1)). This results in the formation of an insoluble precipitate of silver halide, which is removed from the reaction solution by filtration, leaving the target complex in solution. This is then isolated by either simply cooling the reaction solution to −50 °C, or by cooling in conjunction with reducing the volume of the solution under vacuum, resulting in rapid crystallization of the product, followed by washing with cold ethanol and diethyl ether and drying under high vacuum. Extending the duration of crystallization increased the resultant yield, although 18 h proved to be suitable for most samples, and generally after one month no additional material was observed to deposit from solution, nor was any improvement of the crystal quality achieved.

$$6Ag(dcnm) + 3(cat)X + LnCl_3 \cdot x\,H_2O \rightarrow (cat)_3[Ln(dcnm)_6] + 3AgX\downarrow + 3AgCl\downarrow + xH_2O \quad (1)$$

The aforementioned method yielded a range of ILs with imidazolium-, pyridinium-, and ammonium-based counter cations (Scheme 2). 1-Ethyl-3-methylimidazolium (C_2mim) and 1-ethyl-2,3-dimethylimidazolium (C_2C_1mim) were used in the synthesis of $(C_2mim)_3[Ln(dcnm)_6]$ (**1Ln**; **1Ln** = **1La**, **1Ce**, **1Pr**, **1Nd**) and $(C_2C_1mim)_3[Pr(dcnm)_6]$ (**2Pr**), respectively. The C_2mim cation has proven to be suitable for the formation of ILs as the positive ionic charge is delocalized over the N-C-N moiety of the imidazolium ring, but the cation also contains an acidic proton in the 2-position,[28] which may participate in intermolecular hydrogen bonding.[29] The C_2C_1mim cation has the same delocalized ionic



Scheme 2. The cations combined with the $[Ln(dcnm)_6]^{3-}$ anion in this work.

charge, but the possibility of detrimental intermolecular interactions due to the presence of an acidic proton is circumvented by the presence of a methyl group in this position.

The incorporation of a pyridinium-based cation into an ionic system is highly conducive to the formation of an IL as the positive charge is delocalized over the ring. As such a cation bears no protons of appreciable acidity, additional interactions such as hydrogen bonding are suppressed, and hence compounds with the lowest melting points are expected to be formed. The use of 1-butyl-4-methylpyridinium (C_4C_1py) readily gave $(C_4C_1py)_3[Ce(dcnm)_6]$ (**3Ce**), although washing with cold ethanol and diethyl ether led to rapid dissolution of some of the product, resulting in a lower yield of 33%.

The cations butyltrimethylammonium (N_{1114}) and choline (N_{1112OH}) were used in the formation of $(N_{1114})_3[Ln(dcnm)_6]$ (**4Ln**; **4Ln**=**4La**, **4Ce**, **4Pr**, **4Nd**, **4Sm**, **4Gd**) and $(N_{1112OH})_3[Ce(dcnm)_6]$ (**5Ce**), respectively. The butyltrimethylammonium cation, like the C_4C_1py cation, has no protons that are likely to be involved in hydrogen bonding, but because of less charge delocalization somewhat higher melting points are expected. The use of ammonium cations proved beneficial for the formation of $[Ln(dcnm)_6]^{3-}$ complexes containing the heavier lanthanoids samarium and gadolinium, which were not accessible under similar reaction conditions when imidazolium cations were used. The properties of ammonium-based cations such as N_{1114} make them not as suitable for incorporation into ILs as imidazolium- and pyridinium-based cations, possibly because their positive ionic charge is not delocalized to the same extent. The presence of the alcohol functionality on the choline cation results in cation–anion hydrogen bonding, and the increased intermolecular interactions lead to higher melting points.

Attempts to synthesise complexes containing lanthanoids heavier than gadolinium proved problematic, presumably due to the smaller radii of these lanthanoids inhibiting the formation of 12-coordinate complexes. This difficulty was encountered in previous attempts to synthesise $[Ln(dcnm)_6]^{3-}$ complexes with the smaller tetramethylammonium and tetraethylammonium cations.[26]

X-ray crystal structures: Light-yellow, needle-shaped crystals of **1La** of X-ray quality were obtained by recrystallising the product from an ethanol/acetone solution, which was stored at −50 °C for three weeks. The complex **1La** crystallized in the space group $P\bar{3}c1$, with the asymmetric unit containing one-sixth of the $[La(dcnm)_6]^{3-}$ anion, the lanthanoid atom of which resides on a threefold inversion axis, and one-half of the C_2mim cation (Figure 2a). The methyl and ethyl groups of the C_2mim cation are disordered over two positions related by a two-fold rotation axis and occupy the same position with both groups attached to the crystallographically unique nitrogen atom of the imidazolium ring. As observed previously for $[Ln(dcnm)_6]^{3-}$, the six dcnm ligands form an octahedral-like environment around the central lanthanum atom, and are arranged in a mutually perpendicular fashion (Figure 2).

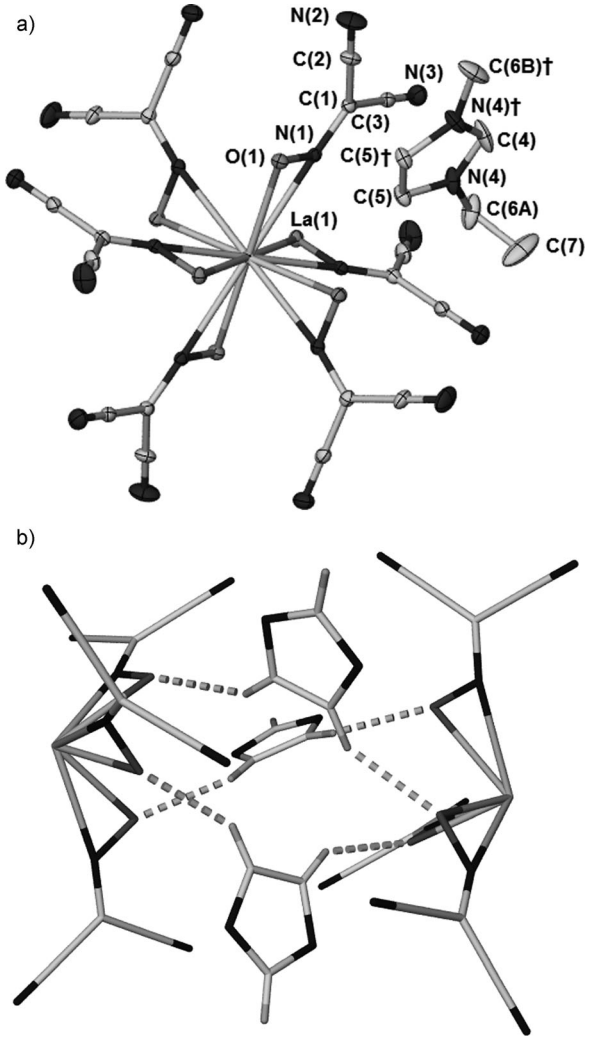


Figure 2. a) A $[La(dcnm)_6]^{3-}$ anion and a C_2mim cation from the crystal structure of **1La**. Ellipsoids shown at 30% probability; hydrogen atoms and symmetry-generated disorder of the C_2mim cation have been omitted for clarity. Symmetry elements used: †=$y, x, {}^1/_2-z$; ‡=$-x+y, -x, z$; §=$y, -x+y, -z$. b) Hydrogen bonding between the C_2mim cation and the $[La(dcnm)_6]^{3-}$ trianion; alkyl groups of the cations and some dcnm ligands of the anions have been omitted for clarity.

The dcnm ligands coordinate in an unusual η^2(N, O) mode, which may be deemed to be asymmetric as there is a significant difference between the La–O and La–N bond lengths (0.072(4) Å, see Table S1 in the Supporting Information), in contrast to a more symmetric η^2(N, O) coordination, in which the difference between the La–O and La–N interatomic distances may be as small as 0.019(5) Å.[26a] The degree of asymmetry in the bonding mode is usually affected by steric crowding due to the presence of a co-ligand or inter- and intramolecular hydrogen bonding, as observed in the related $[Ln(ccnm)_6]^{3-}$ anions (ccnm = carbamoylcyanonitrosomethanide).[26b]

In systems containing an imidazolium-based cation, the hydrogen atom in the 2-position normally participates in hydrogen bonding due to its weakly acidic nature, but in this instance it would appear that the other two C–H groups of the imidazolium ring interact with the anion. The oxygen atom of the nitroso group acts as a hydrogen-bond acceptor, although the hydrogen bond is certainly rather long (Table S1 in the Supporting Information). Due to the hydrogen bonding, the C_2mim cations bridge between $[La(dcnm)_6]^{3-}$ trianions (Figure 2b). The acidic proton in the 2-position of the C_2mim cation is directed towards the nitrile group of a dcnm ligand of an adjacent complex. However, the long C···N interatomic distance of 3.262(5) Å precludes this from being viewed as a classical hydrogen bond (Table S1 in the Supporting Information).

The complexes pack in layers parallel to the *ab* plane, with the cations occupying the space in between, in a similar fashion to the arrangement observed in the crystal structures of $(Me_4N)_3[Ln(dcnm)_6]$ (Ln = La, Ce, Nd, Sm),[26b] although in the present instance no disordered solvent is observed in the lattice (Figure 3).

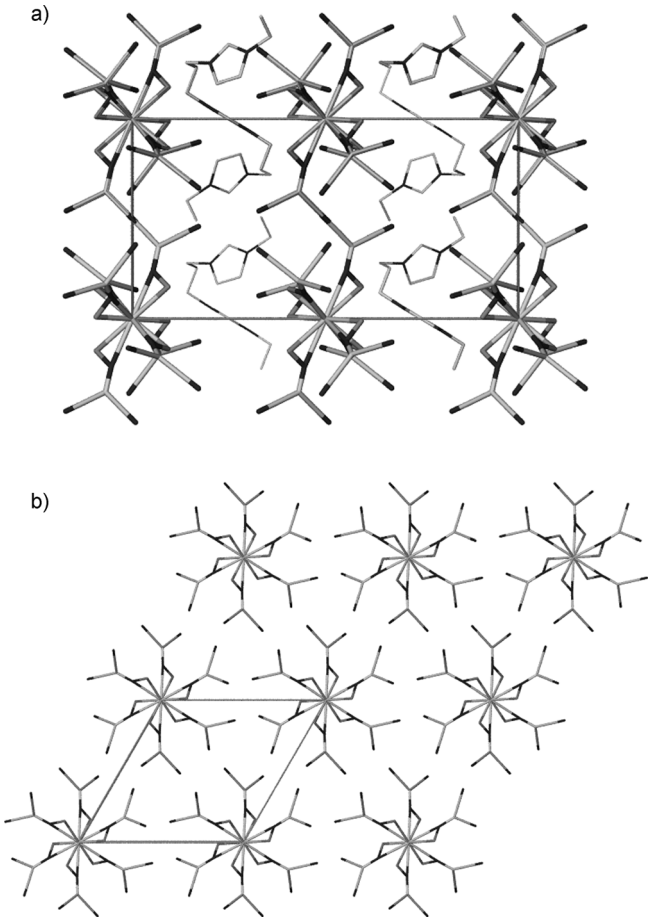


Figure 3. a) The crystal packing of **1La** as viewed down the *a*-axis. b) Layers of $[La(dcnm)_6]^{3-}$ running parallel to the *ab*-plane in the structure of $(C_2mim)_3[La(dcnm)_6]$ (**1La**).

Yellow, block-shaped crystals of **2Pr** of X-ray quality were obtained by crystallising the product from a dilute solution stored at −50 °C. The complex **2Pr** crystallises in the space group $Pa\bar{3}$, with the asymmetric unit containing one crystallographically unique C_2C_1mim cation and one-third of the $[Pr(dcnm)_6]^{3-}$ anion, with the praseodymium atom residing on a threefold inversion axis (Figure 4a).

In comparison with **1La**, the coordinating dcnm ligands show a greater degree of symmetry in the bonding mode, with differences between the Pr–O and Pr–N bond lengths of only 0.033(6) and 0.047(6) Å (Table S2 in the Supporting Information). This may be due to less extensive hydrogen bonding between the C_2C_1mim cation and $[Pr(dcnm)_6]^{3-}$. As observed in the crystal structure of **1La**, the two C–H groups of the imidazolium ring are directed towards the oxygen atoms of the nitroso groups of two dcnm ligands, but the interatomic distances are too long for a hydrogen-bonding interaction (Figure 4b and Table S2 in the Supporting Information). Despite this, the cation may still influence the coordination by the dcnm ligands, which may have to slightly alter their position relative to the lanthanoid centre to allow for the proximity of the cation. The complexes pack in a cubic array (Figure 4c).

X-ray quality crystals of **5Ce** were obtained by recrystallising the product from a concentrated solution in ethanol stored at −18 °C over a period of one week. Upon reheating the solution to room temperature, the crystals rapidly dissolved. Complex **5Ce** crystallises in the rhombohedral space group $R\bar{3}$, with the asymmetric unit containing one unique choline cation and separate sixths of two crystallographically unique $[Ce(dcnm)_6]^{3-}$ trianions, the respective lanthanoid atoms of which reside on threefold inversion axes.

The crystal structure of **5Ce** is the first instance of two crystallographically unique $[Ln(dcnm)_6]^{3-}$ complexes being observed in one structure, which is most likely due to the crystal packing, with the choline cation leading to two geometrically distinct lanthanoid complexes. In the complex containing Ce(1), the dcnm ligands show moderately symmetric η^2(N, O) bonding ($\Delta = 0.026(6)$ Å), while in the other complex they exhibit more asymmetric η^2(N, O) coordination ($\Delta = 0.045(8)$ Å) (Table S3 in the Supporting Information). The first complex (containing Ce(1)) displays a geometry comparable to those of all previously observed $[Ln(dcnm)_6]^{3-}$ anions, in which the dcnm ligands adopt a pseudo-octahedral geometry around the central cerium atom and are oriented mutually perpendicularly. No signifi-

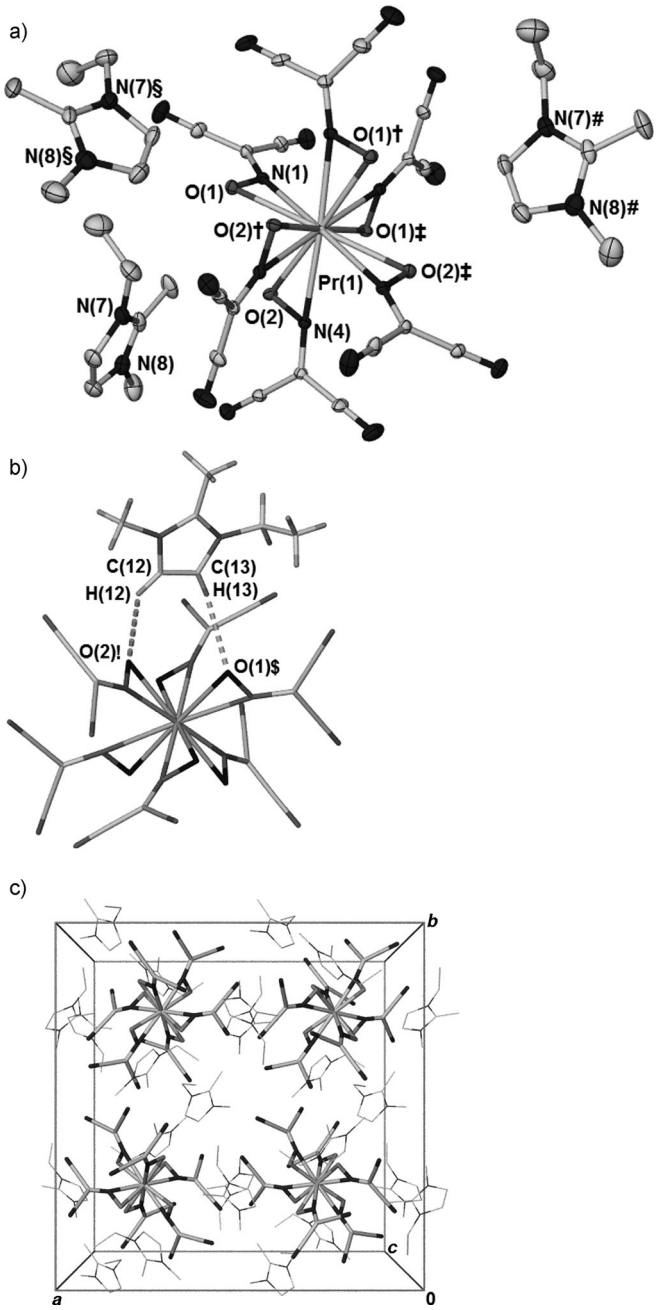


Figure 4. a) The $[Pr(dcnm)_6]^{3-}$ anion and surrounding C_2C_1mim cations from the crystal structure of **2Pr**. Ellipsoids shown at 30% probability; hydrogen atoms have been omitted for clarity. b) The C-H bonds of the C_2C_1mim cation directed toward the $[Pr(dcnm)_6]^{3-}$ trianion. c) The packing of the complexes and cations in the crystal structure of **2Pr**. Symmetry elements used: $\dagger = {}^1/_2+y, {}^1/_2-z, 1-x$; $\ddagger = 1-z, x-{}^1/_2, {}^1/_2-y$; $\S = {}^1/_2+z, x, {}^1/_2-y$; $\# = {}^1/_2+x, y, {}^1/_2-z$; $! = {}^1/_2-z, x-{}^1/_2, y$; $\$ = y, {}^1/_2-z, x-{}^1/_2$.

cant variations are expected for this complex as the choline cations in the lattice are orientated with their methyl groups directed towards the complex, suggesting that no significant geometric intermolecular interactions are present (Figure 5a).

In contrast, the second complex (containing Ce(2)) is "sandwiched" between six choline cations (three cations on

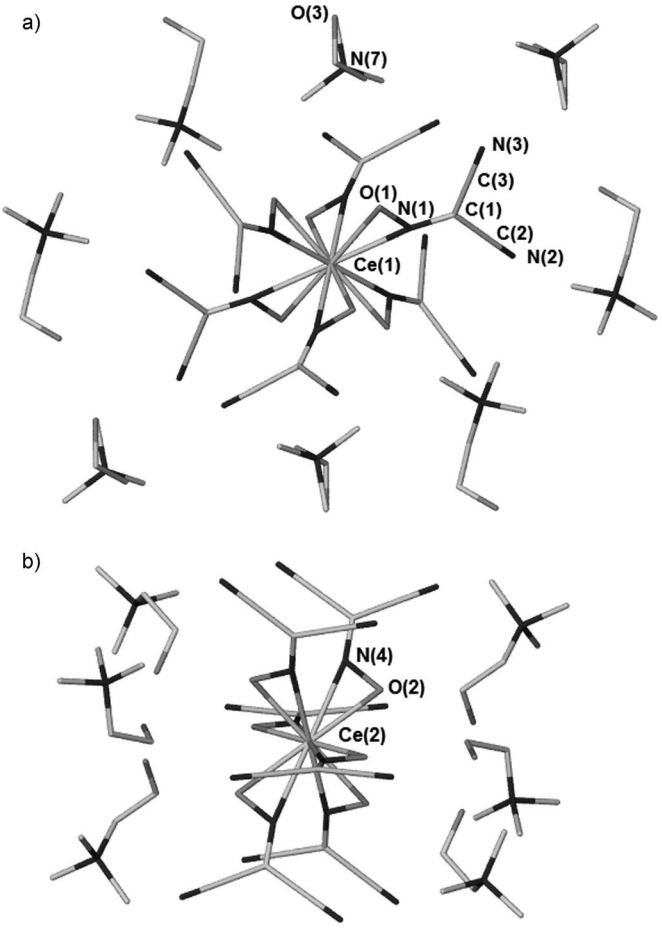


Figure 5. a) The orientation of choline cations around the $[Ce(dcnm)_6]^{3-}$ anion in the crystal structure of **5Ce**, with the methyl groups of choline directed towards the complex. b) The "sandwiched" $[Ce(dcnm)_6]^{3-}$ anion with three choline cations positioned on either side. Hydrogen atoms have been omitted for clarity.

either side), with their hydroxyethyl groups directed to a position over the centre of the complex. The interatomic distances between the oxygen atoms (2.56(3) Å) of a group of three choline cations suggest possible hydrogen bonding, although large atomic displacement parameters, due to either thermal motion or disorder that could not be modeled, prohibit unequivocal determination of the positions of the hydrogen atoms. Although the nitroso group of the neighbouring $[Ce(dcnm)_6]^{3-}$ complex (Ce(2)) may act as a hydrogen-bond acceptor, the distance of 3.28(2) Å between the oxygen atom of this nitroso group and the oxygen atom of a choline cation suggests that there is no hydrogen bonding between them. The degree of distortion of the second complex from a pseudo-octahedral geometry is difficult to quantify, as the ligands retain a fairly symmetrical bonding mode ($\Delta = 0.045(8)$ Å). The distortion can most easily be discerned by considering the angles and torsion angles between neighbouring ligands. In previously studied complexes of $[Ln(dcnm)_6]^{3-}$, the N-Ln-N angles between adjacent nitroso groups have been found to lie in the ranges 74–76° and 103–107°. In the present complex, the angles fall well outside of

these ranges at 65.72(7)° and 114.28(7)°. Furthermore, the torsion angle between a nitroso group coordinating to the lanthanoid and the oxygen atom of the nitroso group of an adjacent ligand should be close to 90°; a similar measurement on the second complex gave a typical value of 130.9(3)°. This is a result of the ligands twisting away relative to each other to allow for the proximity of the six choline cations "sandwiching" the complex.

Thermal analysis: Measurements of the thermal properties of complexes **1Ln** indicated that they all have melting points below 100 °C and can therefore be classified as ILs. The melting points and enthalpies of the phase transitions are given in Table 1. The onset of melting of complex **1La** was observed at 57.7 °C. The complex recrystallised upon cooling in the temperature range −9.4 to 6.4 °C, but the transition was only partially complete, with the remainder of the sample recrystallising over the same temperature range following reheating (Figure 6a). Complex **1Ce** commenced melting at 43.4 °C but did not recrystallise upon cooling, with the sample undergoing a liquid to glass transition at −30.6 °C (Figure S2 in the Supporting Information). Upon heating, complex **1Pr** commenced melting at 64.7 °C, and only formed a supercooled glass at −43.4 °C upon cooling, but then underwent recrystallisation in two distinct transition steps in the temperature ranges −6.0 to 12.3 °C and 15.6 to 25.6 °C (Figure 6b).

Table 1. Thermal behaviour of complexes containing the $[Ln(dcnm)_6]^{3-}$ trianion.[a]

Sample	Cycle	Heating Transition	T [°C]	ΔH [kJ mol^{-1}]	Cooling Transition	T [°C]	ΔH [kJ mol^{-1}]
1La	1	S→L	57.7	72.92	L→S (P)	6.4	−20.56
	2	L→S (P)	−7.4	−38.08			
	2	S→L	59.2	71.15			
1Ce	1	S→L	43.4	60.79	L→G	−30.6	
	2	G→L	−31.9				
1Pr	1	S→L	64.7	83.01	L→G	−43.4	
	2	G→L	−47.4				
	2	L→S (P)	−6.0	−34.16			
	2	L→S (P)	15.6	−25.23			
	2	S→L	62.4	83.24			
1Nd	1	S→L	60.9	74.89	L→S	23.1	−38.95
	2		13.9	0.82			
	2	S→L	40.1	37.82	L→S	20.3	−39.24
2Pr	1	S→L	62.9	60.79	L→G	−32.0	
	2	G→L	−33.5				
	2	L→S	5.1	−41.81			
	2	S→L	61.4	63.83			
3Ce	1	S→L	38.1	44.16	L→G	−28.7	
	2	G→L	−29.8				
4La	2	S→L	109.1	68.67	L→S	105.2	−68.2
4Ce	2	S→L	106.3	55.63	L→S	93.8	−46.72
4Pr	2	S→L	104.8	69.72	L→S	96.9	−65.54
4Nd	2	S→L	102.5	74.28	L→S	90.6	−71.71
4Sm	2	S→L	83.7	47.31	L→S	75.4	−50.33
4Gd	2	S→L	74.8	45.02	L→S	55.8	−44.68
5	1	no transition observed					

[a] T, onset temperature of transition; ΔH, enthalpy of transition; S→L, solid to liquid transition; L→S, liquid to solid transition; G→L, glass to liquid transition; L→G, liquid to glass transition; (P) denotes partial transition.

Complex **1Nd** displayed interesting thermal behaviour. While complexes **1La** and **1Pr** commenced melting at the same temperature after recrystallisation, complex **1Nd** melted at a discernibly lower temperature after the sample had been recrystallised (Figure 6c). The complex began to melt at 60.9 °C, commenced recrystallisation at 23.1 °C upon cooling, and then during reheating commenced melting at 40.1 °C. Furthermore, the enthalpy of fusion was determined to be approximately 37 kJ mol^{-1} higher in the first heating cycle than in the subsequent cycles. This may have been due to the complex recrystallising as a second, less thermodynamically stable polymorph, thereby lowering the melting point. While unusual, this behaviour has also been observed in the related series of complexes $(N_{4444})_3[Ln(dcnm)_6]$. In situ synchrotron-based X-ray powder diffraction analysis revealed recrystallisation of the complexes as a second polymorph upon cooling.[27]

DSC measurements of complex **2Pr** showed the sample to melt at 62.9 °C, and that the molten sample formed a supercooled glass at −32.0 °C upon cooling. Upon heating, the sample underwent a glass to liquid transition, with the onset of recrystallisation occurring at 5.1 °C (Figure S5 in the Supporting Information). Complex **3Ce** was found to melt at 38.1 °C, the lowest melting point of all the complexes containing the $[Ln(dcnm)_6]^{3-}$ trianion. The melt did not recrystallise upon cooling and formed a supercooled glass at −28.7 °C (Figure S6 in the Supporting Information).

Complexes **4Ln** showed a decrease in melting point across the series, from **4La** melting at 109.1 °C to **4Gd** melting at 74.8 °C (Figures S7–S13 in the Supporting Information). The distinct downward two-step trend within this series (Figure S14) is similar to the thermal behavior observed for complexes $(C_4mim)_4[Ln(NCS)_7(H_2O)]$, for which the melting points of the lanthanum, praseodymium, and neodymium examples decrease across the series, and the complexes containing the heavier lanthanoids are RTILs.[13] While it may appear counterintuitive that a heavier metal centre can give a lower melting point, it may in fact be due to the lanthanoid contraction causing a reduction in the size of $[Ln(dcnm)_6]^{3-}$ trianion. Unfortunately, difficulties were encountered in attempting to formalise a nonlinear relationship between the physical properties of the ILs and their melting points, resolution of which is beyond the scope of this study. The observed relationship is discussed in greater detail in the Supporting Information and illustrated in Figure S14.

DSC measurements on complex **5Ce** showed that it did not melt up to 160 °C. This result may have been due to hydrogen-bonding interactions between the choline countercations, as observed in the crystal structure of **5Ce**, and high-

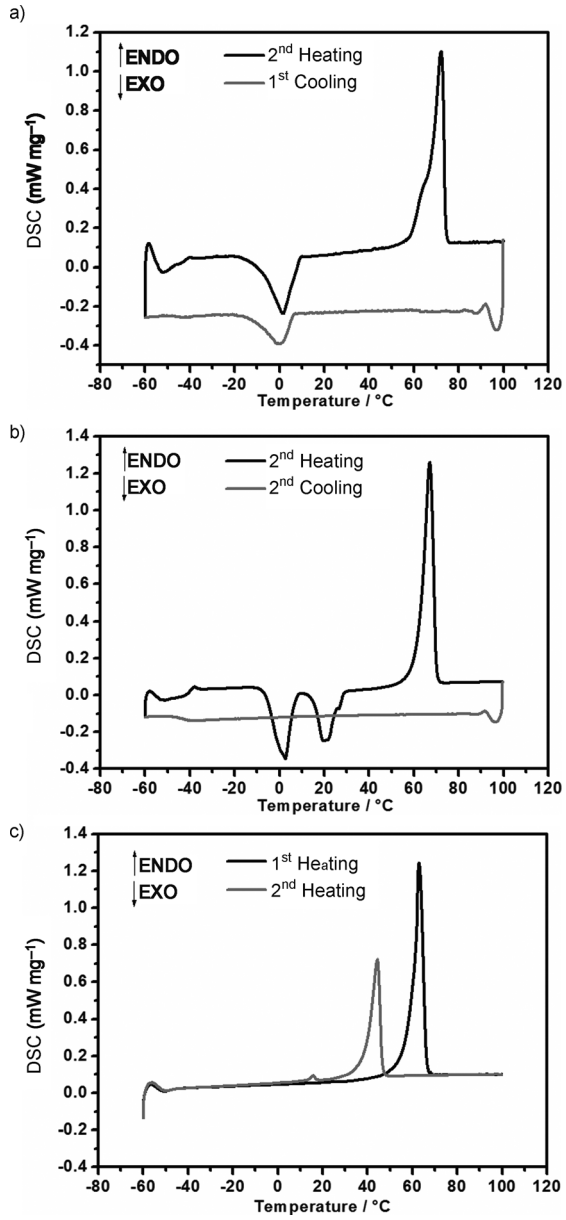


Figure 6. DSC thermograms for a) $(C_2mim)_3[La(dcnm)_6]$ (**1La**), b) $(C_2mim)_3[Pr(dcnm)_6]$ (**1Pr**), and c) $(C_2mim)_3[Nd(dcnm)_6]$ (**1Nd**).

lights the necessity of using countercations with minimal interactions in the synthesis of ILs. The thermal properties of complexes **4Ln** and **5Ce** show that smaller ammonium countercations are not suitable for forming ILs with the $[Ln(dcnm)_6]^{3-}$ trianion, whereas complexes $(N_{4444})_3[Ln(dcnm)_6]$ (Ln = La–Nd) could all be classified as ILs.[27]

Conclusion

A simple metathesis reaction has been shown to be a viable means of synthesising a range of complexes containing the $[Ln(dcnm)_6]^{3-}$ trianion. Complexes $(C_2mim)_3[Ln(dcnm)_6]$ (**1Ln** = **1La**, **1Ce**, **1Pr**, **1Nd**) and $(C_2C_1mim)_3[Pr(dcnm)_6]$ (**2Pr**) were all shown by DSC measurements to be ILs. $(C_4C_1py)_3[Ce(dcnm)_6]$ (**3Ce**) melts at 38.1 °C, the lowest melting point of the complexes characterised in this study. The use of ammonium-based counter cations gave complexes with higher melting points than those containing the imidazolium and pyridinium counter cations. While $(N_{1114})_3[Ln(dcnm)_6]$ (**4Ln** = **4Sm**, **4Gd**) are ILs, the analogues containing lighter lanthanoids melt above 100 °C. The complex $(N_{1112OH})_3[Ce(dcnm)_6]$ (**5Ce**) was not observed to melt below 160 °C, with the elevated melting point most likely being due to the presence of stronger intermolecular interactions in the form of hydrogen bonding, the existence of which may be inferred from the crystal structure. The future aims of this project are to synthesise the dysprosium analogue of the $[Ln(dcnm)_{(6-x)}]^{(x-3)}$ anion in order to create magnetically responsive ILs, and to couple the $[Ln(dcnm)_6]^{3-}$ anion with other cations to form RTILs.[27]

Experimental Section

General: All materials and solvents were purchased from standard commercial sources and were used without further purification. No protective atmosphere was required. Ag(dcnm) was prepared by a literature method.[23] Vibrational spectroscopy was carried out on an Alpha-P ATR spectrometer (Bruker, Karlsruhe, Germany) in attenuated total reflection configuration with a diamond crystal as an internal reflection element. The solid IL was directly pressed onto the crystal. Differential scanning calorimetry (DSC) was performed with a computer-controlled Phoenix DSC 204 F1 thermal analyser (Netzsch, Selb, Germany) with argon as the protecting gas. The samples were placed in aluminium pans, which were cold-sealed under argon. Experimental data are displayed in such a way that exothermic peaks occur at negative heat flow and endothermic peaks at positive heat flow. DSC runs involved heating and subsequent cooling at 5 °C min^{-1}. Temperatures correspond to the onset of the respective thermal processes. Melting points and thermal behaviours are given in Table 1. Elemental analyses were performed on a Vario EL elemental analyzer (Elementar Analysensysteme GmbH, Hanau, Germany). N.B.: The dcnm anion in $[Ln(dcnm)_6]^{3-}$ has been observed to undergo nucleophilic addition of water to form the carbamoylcyanonitrosomethanide anion when stored under ambient conditions for one year.[26b,30] Therefore, if $[Ln(dcnm)_6]^{3-}$-containing complexes are to be stored for a long period, it is recommended that an inert atmosphere is used.

Synthesis of $(C_2mim)_3[Ln(dcnm)_6]$ (1Ln; 1Ln = 1La, 1Ce, 1Pr, 1Nd): Ag(dcnm) (500 mg, 2.476 mmol) was added to a solution of $(C_2mim)Cl$ (182 mg, 1.238 mmol) and $LnCl_3{\cdot}xH_2O$ ($La/CeCl_3{\cdot}7H_2O$ = 153 mg, $PrCl_3{\cdot}6H_2O$ = 0.147 mg, $NdCl_3{\cdot}6H_2O$ = 148 mg, 0.411 mmol) in ethanol (10 mL). The solution was protected from light and stirred for 1 h, whereupon AgCl was precipitated. The reaction mixture was then filtered through filter paper to remove the precipitate, which was further washed with additional ethanol (5 mL). The filtrate was stored at −50 °C for one week, yielding light-yellow needle-shaped crystals of **1La**, ruby-red crystals of **1Ce**, or yellow needle-shaped crystals of **1Pr**. Light-mauve needle-shaped crystals of **1Nd** formed after two weeks. The crystals were filtered from the reaction solutions, immediately washed with cold ethanol and diethyl ether, and placed under high vacuum for 3 h. **1La**: Yield: 258 mg, 61 %; IR (ATR): $\tilde{\nu}$ = 3157 (w), 3116 (m), 2229 (m), 1621 (vw), 1569 (w), 1463 (vw), 1450 (vw), 1412 (s), 1336 (w), 1301 (vw), 1256 (m), 1191 (s), 1169 (vs), 1023 (vw), 953 (vw), 840 (m), 808 (vw), 760 (m), 704 (vw), 682 (vw), 648 (m), 621 (m), 592 (m), 563 (s), 475 (vw), 406 cm^{-1} (m); elemental analysis calcd (%) for $C_{36}H_{33}LaN_{24}O_6$ (1036.71): C 41.71, H 3.21, N 32.43; found: C 41.76, H 3.29, N 32.33. X-ray quality single crystals of **1La** were obtained by dissolving 100 mg of the product in 10:1 ethanol/acetone (5 mL) and storing the solution at −50 °C for three

weeks. **1Ce**: Yield: 310 mg, 73%. IR (ATR): $\tilde{\nu}$=3156 (w), 3116 (m), 2229 (m), 1622 (vw), 1568 (w), 1463 (vw), 1413 (s), 1336 (vw), 1301 (vw), 1256 (m), 1194 (s), 1170 (vs), 1023 (vw), 954 (vw), 841 (m), 809 (w), 761 (m), 703 (w), 682 (vw), 648 (m), 621 (m), 593 (m), 564 (s), 487 (w), 407 cm^{-1} (m); elemental analysis calcd (%) for $C_{36}H_{33}CeN_{24}O_6$ (1037.92): C 41.66, H 3.20, N 32.39; found: C 41.50, H 3.52, N 32.62. **1Pr**: Yield: 276 mg, 65%; IR (ATR): $\tilde{\nu}$=3157 (w), 3116 (m), 2229 (m), 1622 (vw), 1569 (w), 1463 (vw), 1412 (s), 1336 (vw), 1301 (vw), 1256 (m), 1194 (s), 1170 (vs), 1023 (vw), 953 (vw), 840 (m), 809 (w), 761 (m), 704 (vw), 684 (vw), 648 (m), 621 (m), 593 (m), 564 (s), 476 (vw), 406 cm^{-1} (m); elemental analysis calcd (%) for $C_{36}H_{33}N_{24}O_6Pr$ (1038.71): C 41.63, H 3.20, N 32.36; found: C 41.68, H 3.14, N 32.60. **1Nd**: Yield: 292 mg, 68%; IR (ATR): $\tilde{\nu}$=3156 (w), 3115 (m), 2229 (m), 1620 (vw), 1568 (w), 1463 (vw), 1450 (vw), 1411 (s), 1336 (vw), 1301 (vw), 1256 (m), 1193 (s), 1169 (vs), 954 (vw), 841 (m), 809 (vw), 761 (m), 703 (vw), 685 (vw), 648 (m), 621 (m), 593 (m), 564 (s), 476 (vw), 405 cm^{-1} (m); elemental analysis calcd (%) for $C_{36}H_{33}N_{24}NdO_6$ (1042.05): C 41.49, H 3.19, N 32.26; found: C 41.31, H 3.12, N 32.62.

Synthesis of $(C_2C_1mim)_3[Pr(dcnm)_6]$ (2Pr): Ag(dcnm) (500 mg, 2.476 mmol) was added to a solution of $(C_2C_1mim)Cl$ (200 mg, 1.238 mmol) and $PrCl_3{\cdot}6H_2O$ (147 mg, 0.411 mmol) in ethanol (10 mL). The solution was protected from light and stirred for 1 h, whereupon AgCl was precipitated. The reaction mixture was then filtered through filter paper to remove the precipitate, which was further washed with additional ethanol (5 mL). The filtrate was stored at −50 °C for 18 h yielding lime-green needles of **2Pr**. The crystals were filtered from the reaction solution, immediately washed with cold ethanol and diethyl ether, and dried under high vacuum for 3 h. Yield: 241 mg, 54%; IR (ATR): $\tilde{\nu}$=3144 (w), 2225 (m), 1588 (w), 1536 (w), 1452 (w), 1403 (s), 1264 (m), 1240 (vw), 1202 (vs), 1134 (m), 1088 (vw), 954 (vw), 743 (m), 727 (vw), 712 (vw), 666 (m), 593 (m), 566 (m), 481 (w), 414 cm^{-1} (m); elemental analysis calcd (%) for $C_{39}H_{39}N_{24}O_6Pr$ (1080.79): C 43.34, H 3.64, N 31.10; found: C 43.06, H 3.75, N 30.87. X-ray quality crystals of **2Pr** were grown from a dilute solution at −50 °C over a period of one month.

Synthesis of $(C_4C_1py)_3[Ce(dcnm)_6]$ (3Ce): Ag(dcnm) (2 g, 9.904 mmol) was added to a solution of $(C_4C_1py)Br$ (1.136 g, 4.936 mmol) and $CeCl_3{\cdot}7H_2O$ (612 mg, 1.643 mmol) in ethanol (40 mL). The solution was protected from light and stirred for 1 h, whereupon AgBr/AgCl was precipitated. The reaction mixture was filtered through silica, which was further washed with a sufficient amount of ethanol to remove the orange product that had adhered to it. The combined filtrate and washings were then concentrated under vacuum until the product began to precipitate. The concentrated solution was then stored at −50 °C for 18 h so that further product separated. The deep-red precipitate was collected by filtration, immediately washed with cold ethanol and diethyl ether, and dried under high vacuum for 3 h. Yield: 631 mg, 33%; IR (ATR): $\tilde{\nu}$=3063 (vw), 2951 (w), 2937 (vw), 2877 (w), 2223 (s), 1631 (m), 1577 (vw), 1512 (w), 1472 (w), 1412 (s), 1313 (vw), 1258 (m), 1190 (vs), 1041 (w), 961 (vw), 821 (m), 756 (w), 726 (vw), 705 (w), 683 (vw), 594 (m), 566 (s), 537 (m), 491 (w), 472 (w), 409 cm^{-1} (m); elemental analysis calcd (%) for $C_{48}H_{48}CeN_{21}O_6$ (1155.15): C 49.91, H 4.19, N 25.46; found: C 49.70, H 3.93, N 25.62.

Synthesis of $(N_{1114})_3[Ln(dcnm)_6]$ (4Ln; 4Ln=4La, 4Ce, 4Pr, 4Nd, 4Sm, 4Gd): Ag(dcnm) (500 mg, 2.476 mmol) was added to a solution of $(N_{1114})Br$ (347 mg, 1.769 mmol) and $LnCl_3{\cdot}xH_2O$ ($La/CeCl_3{\cdot}7H_2O$= 153 mg, $PrCl_3{\cdot}6H_2O$=0.147 mg, $NdCl_3{\cdot}6H_2O$=148 mg, $SmCl_3{\cdot}6H_2O$= 148 mg, 0.411 mmol) in a mixture of methanol (3 mL) and ethanol (7 mL), except for the reaction with $SmCl_3{\cdot}6H_2O$, for which only ethanol (10 mL) was used. The solution was protected from light and stirred for 1 h, whereupon AgBr/AgCl was precipitated. The solution was filtered through filter paper to remove the precipitate. In the synthesis of **4Sm**, the precipitate was washed with ethanol (5 mL). The filtrate was stored at −50 °C for 18 h, yielding yellow blocks of **4La** and **4Sm**, ruby-red blocks of **4Ce**, lime-green blocks of **4Pr**, or brownish-purple blocks of **4Nd**. The crystals were collected by filtration, immediately washed with cold ethanol and diethyl ether, and dried under high vacuum for 3 h. X-ray quality single crystals of **4Pr** were formed by diffusion of diethyl ether into a concentrated solution of the product in ethanol. **4La**: Yield: 139 mg, 32%; IR (ATR): $\tilde{\nu}$=3650 (vw), 2967 (w), 2938 (vw), 2879 (w), 2227 (s), 1488 (m), 1474 (m), 1414 (s), 1262 (m), 1200 (vs), 1098 (vw), 1060 (vw), 1027 (vw), 970 (m), 931 (w), 895 (m), 807 (vw), 738 (w), 682 (vw), 592 (s), 564 (s), 478 (vw), 413 cm^{-1} (m); elemental analysis calcd (%) for $C_{39}H_{54}LaN_{21}O_6$ (1051.89): C 44.53, H 5.17, N 27.96; found: C 44.45, H 5.26, N 28.17. **4Ce**: Yield: 220 mg, 51%; IR (ATR): $\tilde{\nu}$=3656 (vw), 2968 (w), 2939 (vw), 2879 (w), 2228 (s), 1488 (m), 1474 (m), 1413 (s), 1263 (m), 1200 (vs), 1098 (vw), 1060 (vw), 1028 (vw), 970 (m), 931 (w), 895 (m), 804 (vw), 738 (w), 682 (vw), 593 (s), 564 (s), 478 (vw), 414 cm^{-1} (m); elemental analysis calcd (%) for $C_{39}H_{54}CeN_{21}O_6$ (1053.10): C 44.48, H 5.17, N 27.93; found: C 43.99, H 5.38, N 27.93; **4Pr**: Yield: 193 mg, 45%; IR (ATR): $\tilde{\nu}$=3631 (vw), 2967 (w), 2938 (vw), 2879 (w), 2227 (s), 1488 (m), 1474 (m), 1411 (s), 1262 (m), 1201 (vs), 1098 (vw), 1060 (vw), 1027 (vw), 969 (m), 930 (w), 895 (m), 806 (vw), 738 (w), 682 (vw), 592 (s), 564 (s), 478 (vw), 414 cm^{-1} (m); elemental analysis calcd (%) for $C_{39}H_{54}N_{21}O_6Pr$ (1053.89): C 44.45, H 5.16, N 27.91; found: C 44.19, H 4.90, N 28.25. **4Nd**: Yield: 175 mg, 40%; IR (ATR): $\tilde{\nu}$=3650 (vw), 2968 (w), 2938 (vw), 2879 (vw), 2227 (s), 1488 (m), 1474 (m), 1412 (s), 1263 (m), 1201 (vs), 1098 (vw), 1028 (vw), 969 (m), 931 (w), 895 (m), 809 (vw), 738 (w), 683 (vw), 593 (s), 565 (s), 478 (vw), 413 cm^{-1} (m); elemental analysis calcd (%) for $C_{39}H_{54}N_{21}NdO_6$ (1057.23): C 44.31, H 5.15, N 27.82; found: C 44.22, H 5.10, N 28.26. **4Sm**: Yield: 194 mg, 44%; IR (ATR): $\tilde{\nu}$=3654 (vw), 2967 (w), 2939 (vw), 2879 (w), 2227 (m), 1488 (m), 1474 (m), 1411 (s), 1263 (m), 1201 (vs), 1098 (vw), 1059 (vw), 1027 (vw), 969 (m), 931 (w), 895 (m), 808 (vw), 738 (w), 684 (w), 593 (m), 565 (m), 478 (vw), 414 cm^{-1} (m); elemental analysis calcd (%) for $C_{39}H_{54}N_{21}O_6Sm$ (1063.34): C 44.01, H 5.12, N 27.66; found: C 44.02, H 5.17, N 27.99. **4Gd**: Yield: 65 mg, 15%; IR (ATR): $\tilde{\nu}$=3042 (vw), 2987 (w), 2938 (vw), 2879 (w), 2227 (m), 1488 (m), 1475 (m), 1412 (s), 1262 (m), 1196 (vs), 1061 (vw), 1027 (vw), 970 (m), 930 (w), 896 (m), 738 (w), 687 (vw), 593 (m), 566 (s), 479 (vw), 416 cm^{-1} (m); elemental analysis calcd (%) for $C_{39}H_{54}GdN_{21}O_6$ (1070.23): C 43.77, H 5.09, N 27.48; found: C 43.53, H 5.86, N 27.51.

Synthesis of $(N_{1112OH})_3[Ce(dcnm)_6]$ (5Ce): Ag(dcnm) (500 mg, 2.476 mmol) was added to a solution of choline chloride (172 mg, 1.232 mmol) and $CeCl_3{\cdot}7H_2O$ (153 mg, 0.411 mmol) in ethanol (10 mL). The reaction mixture was protected from light and stirred for 1 h, whereupon methanol (3 mL) was added. The diluted mixture was stirred for a further 10 min, filtered through filter paper to remove the precipitated AgCl, and the orange filtrate was placed in a freezer at −50 °C for 42 h. Thereafter, a red crystalline product had separated, which was collected by filtration and immediately washed with cold ethanol. Yield: 112 mg, 27%; IR (ATR): $\tilde{\nu}$=3471 (w, br), 2229 (m), 1473 (w), 1413 (s), 1343 (vw), 1261 (m), 1197 (vs), 1136 (vw), 1083 (m), 1002 (w), 952 (m), 866 (w), 682 (vw), 595 (w), 566 (m), 482 (vw), 406 cm^{-1} (w); elemental analysis calcd (%) for $C_{33}H_{42}CeN_{21}O_9$ (1016.94): C 38.98, H 4.16, N 28.92; found: C 38.70, H 4.80, N 29.37. X-ray quality crystals of **5Ce** were obtained by recrystallising the product from a concentrated solution in ethanol, which was stored at −18 °C for one week.

Crystallography: Crystals were mounted on fine glass fibres using viscous hydrocarbon oil. Data were collected on Bruker Apex II CCD (**1La**, **2Pr**) or Nonius Kappa CCD (**5Ce**) diffractometers employing graphite-monochromated $Mo_{K\alpha}$ radiation (λ=0.71073 Å). Data collection temperatures were maintained at 123 K for **1La** and **2Pr** or 173 K for **5Ce** using open-flow N_2 cryostreams. For data collection on the Nonius Kappa CCD diffractometer, integration was carried out with the program DENZO-SMN and data were corrected for Lorentz polarisation effects and for absorption using the program SCALEPACK.[31] Data collected on the Bruker X8 Apex II were integrated with the program SAINT and corrected for Lorentz polarisation effects and for absorption using the Apex II program suite.[32] All data sets were treated for the effects of absorption. Solutions were obtained by direct methods using SHELXS-97[33] followed by successive refinements by full-matrix least-squares against F^2 using SHELXL-97.[33] The program X-Seed was used as a graphical SHELX interface.[34] Hydrogen atoms were placed in idealised positions and refined using a riding model on the atom to which they were attached.

Crystal data for 1La: $C_{36}H_{33}LaN_{24}O_6$, $M=1036.77$, light-yellow needle, $0.40\times0.20\times0.20$ mm^3, trigonal, space group $P\bar{3}c1$ (no. 165), $a=b=11.6647(2)$ Å, $c=19.4428(5)$ Å, $V=2291.06(8)$ Å^3, $Z=2$, $\rho_{calcd}=1.503$ g cm^{-3}, $F_{000}=1044$, $2\theta_{max}=55.0°$, 25316 reflections collected, 1768 unique ($R_{int}=0.0315$). Final $GooF=1.275$, $R1=0.0331$, $wR2=0.0692$, R indices based on 1713 reflections with $I>2\sigma(I)$ (refinement on F^2), 109 parameters, 0 restraints. Lp and absorption corrections applied, $\mu=1.004$ mm^{-1}.

Crystal data for 2Pr: $C_{39}H_{39}N_{24}O_6Pr$, $M=1080.85$, yellow shard, $0.30\times0.30\times0.15$ mm^3, cubic, space group $Pa\bar{3}$ (no. 205), $a=21.9847(2)$ Å, $V=10625.80(17)$ Å^3, $Z=8$, $\rho_{calcd}=1.351$ g cm^{-3}, $F_{000}=4384$, $2\theta_{max}=55.0°$, 19652 reflections collected, 4051 unique ($R_{int}=0.0347$). Final $GooF=1.227$, $R1=0.0542$, $wR2=0.1233$, R indices based on 3741 reflections with $I>2\sigma(I)$ (refinement on F^2), 214 parameters, 0 restraints. Lp and absorption corrections applied, $\mu=0.982$ mm^{-1}.

Crystal data for 5Ce: $C_{33}H_{42}CeN_{21}O_9$, $M=1017.00$, red block, $0.25\times0.20\times0.20$ mm^3, trigonal, space group $R\bar{3}$ (no. 148), $a=b=17.512(3)$ Å, $c=26.490(5)$ Å, $V=7035(2)$ Å^3, $Z=6$, $\rho_{calcd}=1.440$ g cm^{-3}, $F_{000}=3102$, $2\theta_{max}=55.0°$, 11701 reflections collected, 3610 unique ($R_{int}=0.1932$). Final $GooF=1.059$, $R1=0.0579$, $wR2=0.1507$, R indices based on 2583 reflections with $I>2\sigma(I)$ (refinement on F^2), 198 parameters, 0 restraints. Lp and absorption corrections applied, $\mu=1.041$ mm^{-1}. Large ADPs of C11 and O3 are attributable to disorder that could not be satisfactorily modelled; the hydrogen atom attached to O3 could not be located from the Fourier difference map or modelled with a riding model.

CCDC-841377, CCDC-841378 and CCDC-841379 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Preparation of a Nylon-11 Precursor from Renewable Canola Oil

Nicolas Daniel Spiccia, Emily Border, Jayamini Illesinghe, William Roy Jackson, Andrea Jane Robinson*

School of Chemistry, Monash University, Clayton 3800, Australia

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Dedicated to Professor David Cole-Hamilton on the occasion of his retirement and for his outstanding contribution to transition-metal catalysis

Abstract: We report a multi-catalytic sequence to a valuable nylon-11 precursor, methyl 11-aminoundecanoate, which is prepared by a ruthenium-catalysed cross-metathesis and a highly regioselective palladium-catalysed amination–hydrogenation reaction, from canola oil, a renewable, natural vegetable oil feedstock.

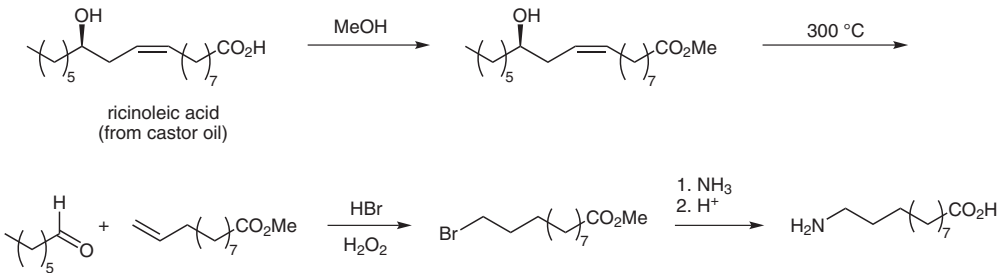
Key words: metathesis, hydrogenation, amination, catalysis, polymers, nylon-11, canola, renewable

There is considerable interest in the production of fine chemicals from renewable natural oils and fats.[1] Triglycerides can be obtained in plentiful supply from both natural and genetically modified crops and have long been used to prepare a range of detergents, surface coatings and biofuels.[2–4] Nylon-11, or Arkema Rilsan®, is synthesised by the condensation polymerisation of the amino acid monomer 11-aminoundecanoic acid. Physical properties of this polyamide include high chemical resistance, low density, and low moisture absorption, making it suitable for applications within the automotive, fuel and electronics industries.[5–7]

Currently, the 11-aminoundecanoic acid monomer is produced by a four-step sequence from ricinoleic acid, which in turn is obtained from castor oil through the harvesting of *Ricinus communis* L., a crop that is now cultivated in all temperate countries around the world (Scheme 1).[8]

Inedible castor oil is produced on a 0.83 million tonne scale per year and comprises approximately 0.15% of the international seed oil trade.[8] Manual harvesting is performed several times each season due to seed ripening variability within the crop, and mechanical harvesting must be performed on denuded plants, requiring the application of defoliants. Extreme caution must also be exercised during harvesting and processing due to potential exposure to ricin toxin which can be lethal via injection, inhalation and ingestion.[9] The price of castor oil is therefore strongly influenced by fluctuation in production and speculation, and is almost twice that of canola, soya and palm oils.[10]

This paper describes our efforts to synthesise the nylon-11 monomer from an alternative renewable feedstock, namely canola oil. Canola oil is derived from rapeseed, which is grown in a 60 million tonne scale per annum,[8] and possesses a high proportion of the mono-unsaturated C18 fatty acid oleic acid. Over many years, numerous attempts have been made to selectively cleave carbon–carbon double bonds present in unsaturated fatty acids. Early work demonstrated the high yielding reaction of natural unsaturated esters with ethylene in the presence of heterogeneous catalysts.[11] Recently, cleavage of unsaturated fatty acids via metathesis chemistry by using acrylonitrile,[12] ethylene[13] and allyl chloride has been reported.[14] The commercial viability of this approach is illustrated by the recent establishment of biorefineries utilising this technology and triglyceride feedstock.[15] We have also reported that much greater catalyst efficiency can be achieved through the use of but-2-ene in the cross-metathesis reaction,[16] with the highest turnovers resulting from oils containing predominantly oleic acid.[17] The resulting unsaturated esters can then be selectively functionalised at the terminal carbon atom via a palladium-catalysed isomerisation–methoxycarbonylation sequence[18] by using catalysts developed by Tooze et al.[19] and exploited by the Cole-Hamilton group.[20] This process provides a highly efficient route to diacid monomers suitable for the produc-



Scheme 1

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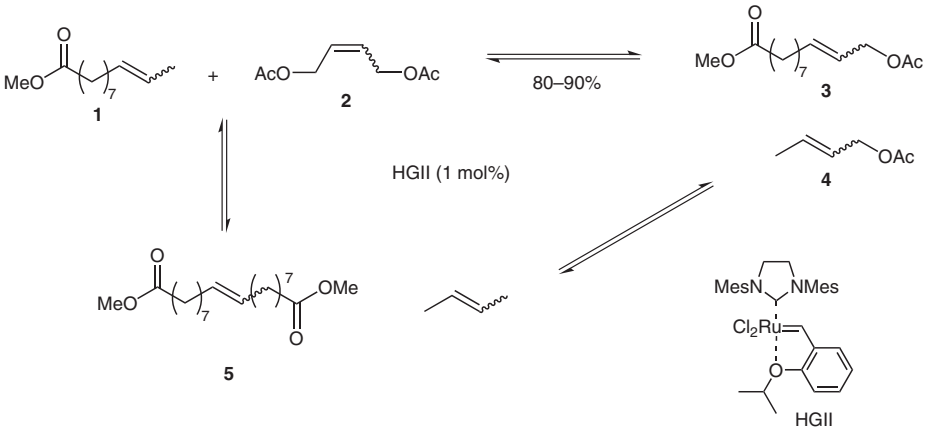
tion of commercial polyamides. In this paper, we disclose methodology to selectively functionalise the same unsaturated esters via a sequence of ruthenium-catalysed cross-metathesis and palladium-catalysed amination and hydrogenation. The method is exemplified by the preparation of methyl 11-aminoundecanoate.

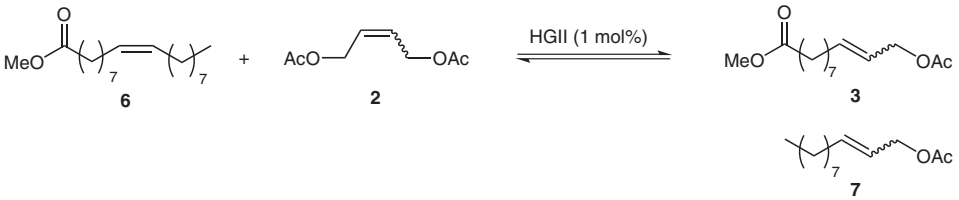
(*E*/*Z*)-Methyl undec-9-enoate (**1**) was prepared in two steps from canola oil, as previously described by our research group, as an 80:20 equilibrium mixture of *E*- and *Z*-isomers.[16,17] Cross-metathesis of **1** with a ten molar excess of 1,4-diacetoxybut-2-ene (**2**) by using the Hoveyda–Grubbs second-generation catalyst (HGII; 1 mol%) gave an equilibrium mixture of methyl (*E*)- and (*Z*)-11-acetoxyundec-9-enoate (**3**), which was isolated in 90% yield after column chromatography. Alternatively, the major byproduct (*E*,*Z*)-but-2-enyl acetate (**4**), generated from the reaction of **2** with but-2-ene (arising from homodimerisation of **1** to **5** or the reaction of **1** with **2** directly) was readily removed by co-distillation with excess **2**, leaving behind the high-boiling undecenoate diester **3** in 80% yield (Scheme 2). The recovered distillate of (*E*,*Z*)-but-2-enyl acetate (**4**) and 1,4-diacetoxybut-2-ene (**2**), now a 70:30 mixture of *E*- and *Z*- isomers, could be reused in further cross-metathesis reactions with **1** to generate **3** without loss of yield. The stereochemistry of the double bond is not important as the two isomers are in equilibrium.

Significantly, the formation of methyl (*E*,*Z*)-11-acetoxyundec-9-enoate (**3**) via an analogous route has recently been reported by the reaction of methyl oleate (**6**) with 1,4-diacetoxybut-2-ene (**2**) by using the Hoveyda–Grubbs second-generation catalyst (HGII; 1 mol%) (Scheme 3).[21] We chose to react 1,4-diacetoxybut-2-ene (**2**) with methyl undec-9-enoate (**1**) instead of methyl oleate (**6**), as the desired unsaturated diester **3** can only be separated from the unsaturated monoester **7** by column chromatography. Removal of the lower boiling point ester **4** by distillation provides a more viable commercial proposition. Although this synthesis involves two metathesis reactions, the turnover numbers for the first reaction involving methyl oleate (**6**) and but-2-ene is very high (i.e., effective TONs of up to 470,000).[17] A similar approach has been reported recently by Meier et al. involving a ruthenium-catalysed cross-metathesis of 1,4-diacetoxybut-2-ene (**2**) with methyl undec-10-enoate.[22]

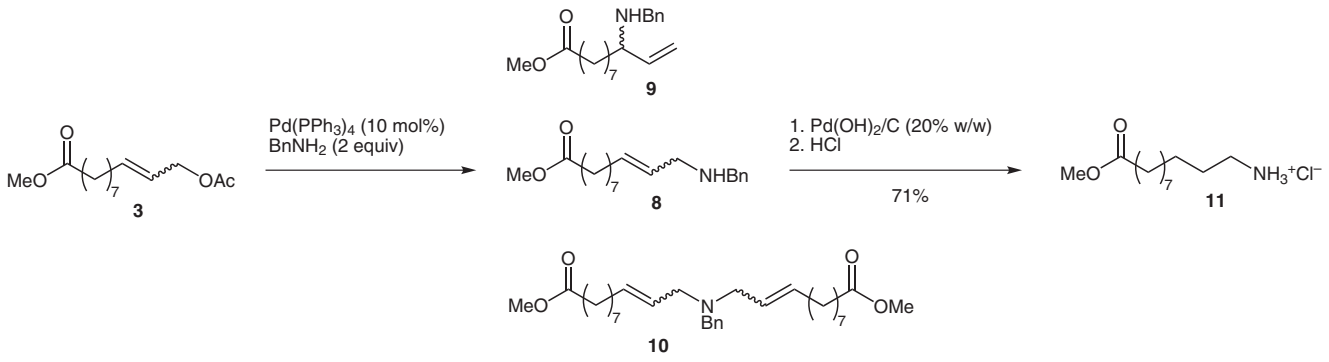
The undecenoate diester **3** was next reacted with benzylamine by using the palladium(0)-catalysed conditions described by Trost et al. (Scheme 4).[23] The target unsaturated amino ester **8** was isolated in poor yield (29%) due to the concomitant formation of the isomeric branched amine **9** (12% yield) and double addition product **10** (28% yield). This necessitated the use of slow gradient chromatography to isolate pure product **8**. One-pot hydrogenation and hydrogenolysis of **8** over Pearlman's catalyst then gave the saturated primary amino ester salt **11** in 71% yield after acidification (Scheme 4).



Scheme 2



Scheme 3



Scheme 4

The sub-optimal yields of the desired amino ester **8** warranted further investigation of the experimental conditions involving the reaction of benzylamine and allylic acetate **3** (Table 1). A series of reactions under reflux all gave complete conversion of the allylic acetate **3** to the amine mixture (**8**–**10**), but no reaction was observed at 0 °C.

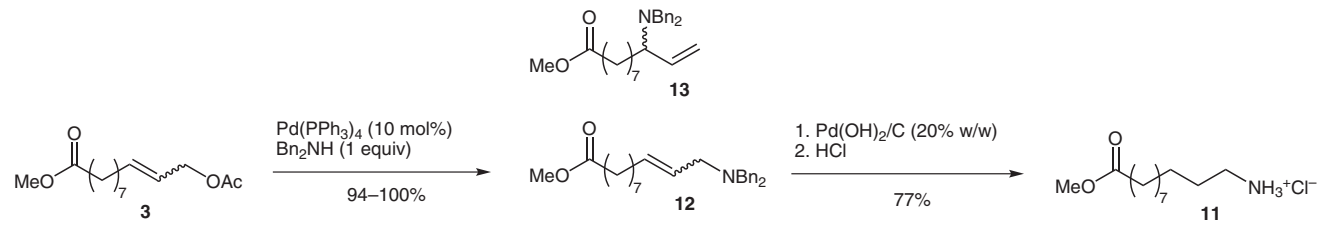
Table 1

Entry	Solvent	Conditions[a]	$BnNH_2$ (equiv)	Yield (%)[b]		
				8	**9**	**10**
1	THF	heat, 3 h	0.5	35	12	53
2	THF	heat, 1 h[c]	0.5	–	5	95
3	THF	heat, 3 h	1	48	12	40
4	THF	heat, 3 h	2	57	11	32
5	THF	heat, 3 h	4	71	10	19
6	THF	heat, 3 h	10	78	12	10
7	THF	heat, 3 h[d]	20	79	13	8
8	dioxane	heat, 1 h	10	74	18	8
9	THF	0 °C to r.t., 24 h	10	–	–	–

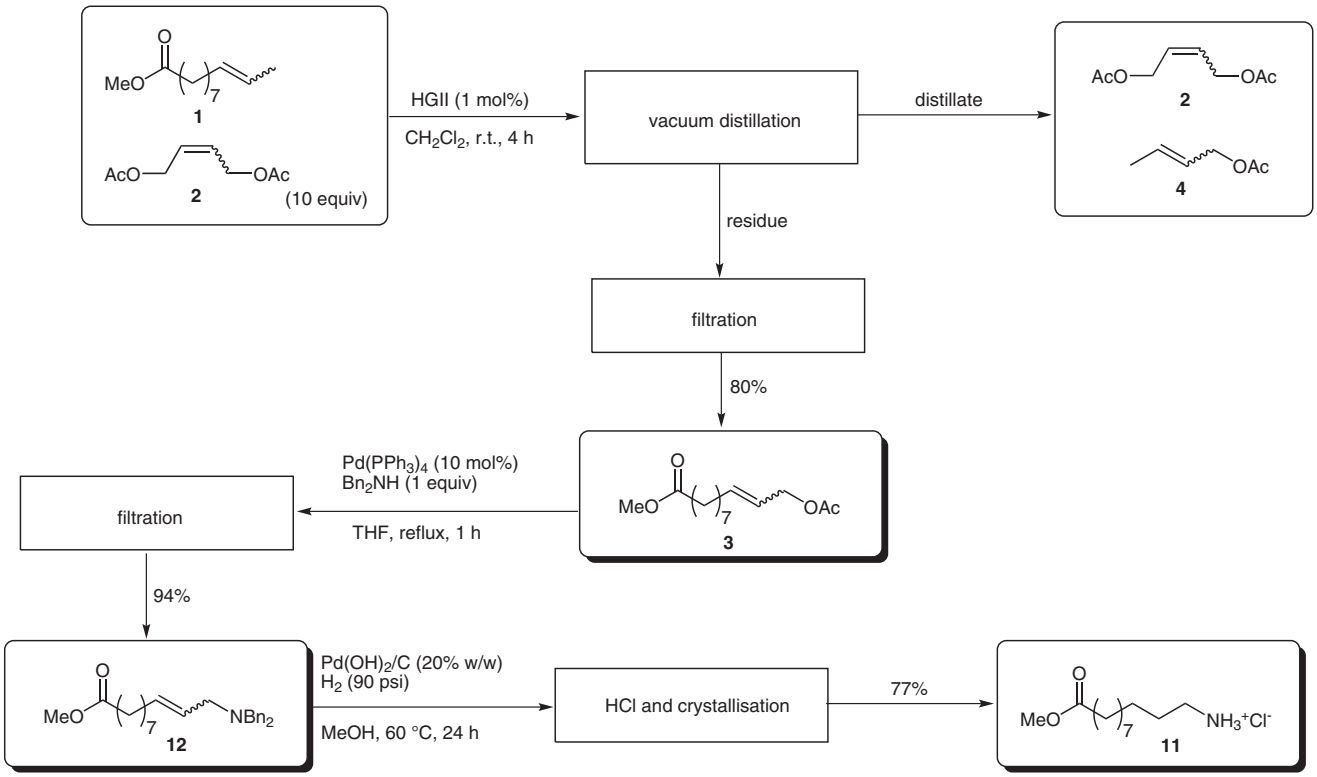
[a] Reagents and conditions: reaction concentration 0.3 M, $Pd(PPh_3)_4$ (10 mol%).
[b] Percent conversion estimated by ^1H NMR spectroscopy.
[c] Slow addition of $BnNH_2$ over 10 min to **3** and $Pd(PPh_3)_4$, THF, reflux.
[d] Slow addition of **3** to $BnNH_2$ and $Pd(PPh_3)_4$, dioxane, reflux.

It was envisaged that the production of the double addition product **10** could be manipulated by a change in molar ratio of benzylamine to allylic acetate **3**. As expected, with a lower molar ratio of benzylamine (Table 1, entry 1), the amount of the double addition product **10** increased to 53%. The proportion of **10** could be further increased to 95% by slow addition of benzylamine to a refluxing solution of allylic acetate **3** and $Pd(PPh_3)_4$ (entry 2). In this case, **10** was isolated in 90% yield after chromatography to provide a potentially useful monomer for the synthesis of dendritic polyamides. Conversely, the generation of double addition product **10** steadily decreased with additional equivalents of benzylamine (entries 3–7) to provide improved yields of the target amine **8**. It was noted, however, that formation of the branched product **9** was not appreciably affected by the molar ratio of benzylamine. To reduce the formation of the double addition product **10**, and further improve the product selectivity for **8** over **9**, reaction temperature and solvent were also investigated. Slow addition of **3** to an excess of benzylamine at higher temperature failed to improve the yield of amino ester **8** (entry 8). Reaction of **3** with a large excess of benzylamine at low temperature was unsuccessful (entry 9).

In order to negate the formation of **10**, and potentially improve the linear to branched ratio resulting from palladium-catalysed amination, the use of dibenzylamine was investigated (Scheme 5). Gratifyingly, palladium-catalysed addition of one molar equivalent of dibenzylamine to **3** generated the desired amino ester **12** in quantitative yield (100%) after purification by column chromatography, or in a comparable yield (94%) after purification by filtration through a short pad of silica. Importantly, high selectivity for the linear adduct **12** over the branched ester



Scheme 5



Scheme 6

13 was also observed (>95% for **12**). Subsequent hydrogenation and hydrogenolysis of **12** over Pearlman's catalyst gave the saturated primary amino ester salt **11** in 77% yield after acidification (Scheme 5). Attempts were made to utilize the palladium(0) (10 mol%) from the aminolysis reaction to affect hydrogenation. While successful, the transformation to **11** could not be achieved selectively: concomitant hydrogenolysis of the terminal amine and partial debenzylation complicated this transformation.

To highlight the industrial applicability of this process, the three catalytic reactions transforming **1** to **11**, namely cross-metathesis, amination and hydrogenation–hydrogenolysis, were performed in sequence without the use of flash chromatography (Scheme 6). This gave the pure saturated amino ester salt **11** in 58% isolated yield over three steps.

By using a mild, multi-catalytic sequence, the nylon-11 precursor methyl 11-aminoundecanoate hydrochloride (**11**) was prepared in a three-step sequence from renewable, canola oil derived methyl undec-9-enoate (**1**) in 69% yield or 58% yield without the use of column chromatography. This provides a viable alternative to the current synthesis, without the economic fluctuations and harvesting hazards associated when using castor oil as a feedstock.

Anhydrous THF and 1,4-dioxane were stored over Na wire, then distilled from sodium benzophenone prior to use. CH_2Cl_2 was dried over CaH_2 and distilled prior to use. (1,3-Dimesitylimidazolidin-2-ylidene)(2-isopropoxybenzylidene)ruthenium(II) dichloride, the Hoveyda–Grubbs second-generation catalyst (HGII), was used as supplied by Sigma-Aldrich. [$Pd(PPh_3)_4$] was used as supplied by Strem Chemicals. All solvents and reagents used in metal-catalysed reactions were degassed with N_2 prior to use. *cis*-1,4-Diacetoxybut-2-ene (95%) was purchased from Sigma-Aldrich and was deoxygenated prior to use. Methyl (*E*/*Z*)-undec-9-enoate (**1**; *E*/*Z*, 4:1) was prepared by a method described by Patel et al.[16,17] All other chemicals were purchased from Sigma-Aldrich and used without further purification unless stated otherwise. Melting points were measured on a Stuart Scientific SMP 3 melting point apparatus. The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 MHz spectrometer (300 MHz for ^1H, 75 MHz for ^{13}C) or a Bruker DRX 400 MHz spectrometer (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR); samples were prepared as solutions in deuterated solvents as specified. The ^{13}C NMR spectra were recorded by using a JMOD pulse sequence or proton decoupled pulse sequence.

Methyl (*E*/*Z*)-11-Acetoxyundec-9-enoate (3)

A Schlenk tube was loaded with **1** (1.00 g, 5.04 mmol), **2** (8.04 mL, 50.4 mmol), HGII (32 mg, 50 μmol) and CH_2Cl_2 (3 mL). The reaction mixture was stirred under an inert atmosphere at r.t. for 4 h. The metathesis reaction was terminated by exposure to O_2 and the addition of ethyl vinyl ether (2 drops). The reaction mixture was then concentrated in vacuo and purified by column chromatography (silica gel, EtOAc–hexane, 1:5); this gave product **3**.

Yield: 1.17 g (90%); colourless oil.

A second reaction was performed under identical conditions and the product was purified by flash distillation (0.3 mmHg, 90–100 °C). The distillation residue was then filtered through a short pad of silica gel (EtOAc–hexane, 1:5); this gave a mixture of the geometric isomers of **3**.

Yield: 1.02 g (80%); *Z*/*E* (1:5); colourless oil.

Spectral data were consistent with those reported in the literature.[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79–5.70 (m, 1 H, =CH), 5.66–5.47 (m, 1 H, =CH), 4.60 [d, *J* = 6.8 Hz, OCH_2 (*Z*-isomer)], 4.50 [dd, *J* = 6.4, 0.8 Hz, OCH_2 (*E*-isomer)], 3.65 (s, 3 H, OCH_3), 2.29 (t, *J* = 7.6 Hz, 2 H, CH_2), 2.09–2.00 (m, 2 H, CH_2), 2.04 (s, 3 H, $COCH_3$), 1.64–1.56 (quin, *J* = 7.2 Hz, 2 H, CH_2), 1.41–1.24 (m, 8 H, 4 × CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 171.1 (2 × C=O), 136.8 (=CH), 124.0 (=CH), 65.5 (OCH_2), 51.7 (OCH_3), 34.0, 32.3, 29.3, 29.3, 29.2, 29.0, 25.1, 21.3 ($COCH_3$).

IR (neat): 2930 (s), 2856 (s), 1750 (s), 1437 (s) cm^{-1}.

MS (ES^+, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{24}O_4Na^+$: 279.2; found: 279.2.

Methyl (*E*/*Z*)-11-(Benzylamino)undec-9-enoate (8), Methyl (*E*/*Z*)-9-(Benzylamino)undec-9-enoate (9), and Dimethyl (*E*/*Z*)-11,11′-(Benzylamino)bis(undec-9-enoate) (10)

The reaction was performed using a procedure described by Trost and Keinan.[23] $BnNH_2$ (175 μL, 1.56 mmol) was added to a solution of allylic acetate **3** (205 mg, 0.80 mmol) and [$Pd(PPh_3)_4$] (92 mg, 80 μmol) in THF (3.0 mL). The mixture was heated under reflux for 3 h before being cooled and concentrated in vacuo. The resulting oil was purified by column chromatography (silica gel, EtOAc–hexane–Et_3N, 1:7:0.4); this gave firstly the disubstituted product **10**. Further elution (EtOAc–hexane, 1:3) gave the branched regioisomer **9**. Further elution (EtOAc) gave the amino ester **8**.

[The reactions of entries 1, 3–9 (Table 1) were performed in an analogous fashion. The product ratio was determined by ^{1}H NMR spectroscopic analysis of crude reaction aliquots.]

Diester 10

Yield: 57 mg (28%); colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.18 (m, 5 H, 5 × PhH), 5.63–5.41 (m, 4 H, 4 × =CH), 3.65 (s, 6 H, 2 × OCH_3), 3.54 (s, 2 H, CH_2Ph), 3.00 (d, *J* = 5.7 Hz, 4 H, 2 × NCH_2), 2.29 (t, *J* = 7.5 Hz, 4 H, 2 × CH_2), 2.07–1.95 (m, 4 H, 2 × CH_2), 1.61 (quin, *J* = 6.9 Hz, 4 H, 2 × CH_2), 1.44–1.19 (m, 16 H, 8 × CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4 (C=O), 139.9, 134.2, 129.1, 128.2, 127.3, 126.8, 57.4, 55.6, 51.1, 34.2, 32.5, 29.4, 29.2, 29.2, 29.1, 25.1.

IR (neat): 2927 (s), 2855 (s), 1738 (s), 1455 (s), 1436 (s), 1362 (m), 1263 (s), 1197 (s), 1172 (s), 971 (m) cm^{-1}.

HRMS (ES^+, MeOH): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{50}NO_4^+$: 500.3734; found: 500.3736.

Branched Regioisomer 9

Yield: 29 mg (12%); colourless oil.

IR (neat): 2928 (s), 2854 (s), 1739 (s), 1452 (s), 1260 (m), 1197 (m), 1170 (m), 1106 (m), 1027 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H, 5 × PhH), 5.67 – 5.56 (m, 1 H, =CH), 5.16–5.07 (m, 2 H, $=CH_2$), 3.82 (d, *J* = 13.2 Hz, 1 H, CHPh), 3.66 (s, 3 H, OCH_3), 3.64 (d, *J* = 13.2 Hz, 1 H, CHPh), 3.00 (q, *J* = 7.8 Hz, 1 H, CHN), 2.29 (t, *J* = 7.5 Hz, 2 H, CH_2), 1.59 (quin, *J* = 7.3 Hz, 2 H, CH_2), 1.55–1.19 (m, 10 H, 5 × CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4 (C=O), 141.5, 140.9, 128.5, 128.3, 126.9, 116.1 ($=CH_2$), 61.4, 51.6, 51.4, 35.8, 34.2, 29.6, 29.3, 29.2, 25.9, 25.1.

HRMS (ES^+, MeOH): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{30}NO_2^+$: 304.2271; found: 304.2277.

Amino Ester 8

Yield: 70 mg (29%); colourless oil.

IR (neat): 2929 (s), 2855 (s), 1720 (s), 1670 (m), 1437 (s), 1371 (s), 1247 (s), 911 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 5 H, 5 × PhH), 5.64–5.48 (m, 2 H, 2 × =CH), 3.77 (s, 2 H, NCH_2), 3.66 (s, 3 H, OCH_3), 3.21 (d, *J* = 5.2 Hz, 2 H, NCH_2), 2.29 (t, *J* = 7.5 Hz, 2 H, CH_2), 1.61 (quin, *J* = 7.2 Hz, 2 H, CH_2), 1.43–1.21 (m, 10 H, 5 × CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4 (C=O), 140.5, 133.1, 128.5, 128.3, 128.3, 127.0, 53.4, 51.6, 51.3, 34.2, 32.5, 29.4, 29.4, 29.2, 29.1, 25.1.

HRMS (ES^+, MeOH): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{30}NO_2^+$: 304.2271; found: 304.2273.

Dimethyl (*E*/*Z*)-11,11′-(Benzylamino)bis(undec-9-enoate) (10)

$BnNH_2$ (23 μL, 0.21 mmol) in THF (1.0 mL) was added dropwise over 10 min to a refluxing solution of allylic acetate **3** (105 mg, 0.41 mmol) and [$Pd(PPh_3)_4$] (47 mg, 41 μmol) in THF (2.0 mL). The reaction was heated at reflux for 1 h before being cooled and concentrated in vacuo. A ^{1}H NMR spectrum of the product revealed a 5:95 ratio of the branched regioisomer **9** to the disubstituted product **10** respectively: No evidence for the formation of **8** was observed. The resulting oil was purified by column chromatography (silica gel, EtOAc–hexane–Et_3N, 1:5:0.3); this gave **10**.

Yield: 92 mg (90%); colourless oil.

Spectra for **9** and **10** were consistent with the previously recorded data.

Methyl 11-Aminoundecanoate Hydrochloride (11)

A Fischer-Porter tube was charged with **8** (170 mg, 0.33 mmol), $Pd(OH)_2$/C (20 wt%; 17 mg) and MeOH (2 mL). The headspace of the vessel was purged with argon over three cycles, charged with H_2 (60 psi) and heated at 60 °C for 18 h. The H_2 was then vented from the vessel and the reaction mixture was filtered through a short plug of diatomaceous earth and concentrated in vacuo. The product was treated with EtOAc saturated with HCl gas (5 mL) to generate the hydrochloride salt **11**. The salt was precipitated from the reaction mixture by dilution (CH_2Cl_2– hexane, 1:5) and collected by centrifugation; this gave **11**.

Yield: 99 mg (71%); off-white, hygroscopic solid.

Alternatively, a Fischer-Porter tube was charged with **12** (100 mg, 0.25 mmol), $Pd(OH)_2$/C (20 wt%; 20 mg) and MeOH (3 mL). The headspace of the vessel was purged with argon over three cycles, charged with H_2 (90 psi) and heated at 60 °C for 18 h. The H_2 was then vented from the vessel and the reaction mixture was filtered through filter paper and concentrated in vacuo. The product was treated with Et_2O saturated with HCl gas (2 mL) to generate the hydrochloride salt. The salt was precipitated from the reaction mixture by addition of (CH_2Cl_2–hexane, 1:5) and collected by centrifugation; this gave **11**.

Yield: 49 mg (77%); off-white, hygroscopic solid; mp 146.0–148.9 °C.

IR (neat): 3415 (m), 2922 (s), 2851 (m), 1735 (s), 1617 (m), 1569 (m), 1517 (m), 1468 (m), 1437 (m), 1137 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (br s, 3 H, NH_3^+), 3.66 (s, 3 H, OCH_3), 2.97 (t, *J* = 7.6 Hz, 2 H, NCH_2), 2.30 (t, *J* = 7.6 Hz, 2 H, CH_2), 1.76 (quin, *J* = 7.5 Hz, 2 H, CH_2), 1.61 (quin, *J* = 7.2 Hz, 2 H, CH_2), 1.44–1.23 (m, 12 H, 6 × CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4 (C=O), 51.6 (OCH_3), 40.1 (NCH_2), 34.3, 29.4, 29.4, 29.3, 29.3, 29.1, 27.8, 26.6, 25.1.

HRMS (ES^+, MeOH): *m*/*z* [M]$^+$ calcd for $C_{12}H_{24}NO_2^+$: 216.1958; found: 216.1960.

Methyl (*E*/*Z*)-11-(Dibenzylamino)undec-9-enoate (12)

Bn_2NH (83 μL, 0.43 mmol) was added to a solution of **3** (110 mg, 0.43 mmol) and [$Pd(PPh_3)_4$] (50 mg, 43 μmol) in THF (2.2 mL). The mixture was heated under reflux for 1 h before being cooled. A

^{1}H NMR spectrum of the product revealed a 95:5 ratio of **12** to the branched regioisomer **13** by comparison of diagnostic proton resonances in **12** and **13**. The resulting oil was purified by column chromatography (silica gel, EtOAc–hexane, 1:3); this gave **12** with 5% **13** as a light yellow oil (171 mg).

Alternatively, Bn_2NH (280 μL, 1.45 mmol) was added to a solution of **3** (370 mg, 1.45 mmol) and [$Pd(PPh_3)_4$] (167 mg, 145 μmol) in THF (3.0 mL). The reaction mixture was heated at reflux for 1 h before being cooled and diluted with hexane (6.0 mL) and filtered through a short pad of silica with hexane and concentrated in vacuo; this gave **12** together with 5% **13**.

Yield: 569 mg (94%); light yellow oil.

IR (neat): 2929 (m), 1741 (s), 1454 (m), 1439 (m), 1365 (m), 1201 (m), 1175 (m), 974 (m), 914 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 7.0 Hz, 4 H, 4 × PhH), 7.32 (t, *J* = 7.2 Hz, 4 H, 4 × PhH), 7.26–7.20 (m, 2 H, 2 × PhH), 5.64–5.44 (m, 2 H, 2 × =CH), 3.67 (s, 3 H, OCH_3), 3.57 (s, 4 H, 2 × CH_2Ph), 3.01 (d, *J* = 5.8 Hz, 2 H, NCH_2), 2.29 (t, *J* = 7.6 Hz, 2 H, CH_2), 2.09–1.97 (m, 2 H, CH_2), 1.61 (quin, *J* = 6.8 Hz, 2 H, CH_2), 1.42–1.22 (m, 8 H, 4 × CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6 (C=O), 134.4, 134.4, 129.3, 128.4, 127.3, 126.9, 57.5, 55.7, 51.7, 34.3, 32.7, 29.5, 29.3, 29.3, 29.2, 25.2.

HRMS (ES^+, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{36}NO_2^+$: 394.2741; found: 394.2738.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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Tandem Ru-alkylidene-catalysed cross metathesis/hydrogenation: synthesis of lipophilic amino acids

Zhen J. Wang, Nicolas D. Spiccia, W. Roy Jackson and Andrea J. Robinson*

Highly efficient synthesis of lipidic amino acids can be achieved via Ru-alkylidene-catalysed cross metathesis of long chain alkenes with commercially available allylglycine. The resultant unsaturated analogues can be then optionally hydrogenated under mild reaction conditions by using the spent metathesis catalyst. Copyright © 2013 European Peptide Society and John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: lipophilic amino acids; tandem catalysis; cross metathesis; hydrogenation

Introduction

α-Amino acids with extended alkyl sidechains are commonly called lipidic amino acids (LAAs, **1**). Sequence incorporation of these non-coded residues can be used to enhance the absorption and passage of peptides through otherwise impenetrable biological membranes [1]. Hence, there is considerable interest in utilising these amino acids to solve present-day peptide drug delivery, formulation, vaccination and *in vivo* stability challenges [2]. Current research in this area is hampered, however, by the high commercial cost and limited availability of LAAs.

Racemic syntheses of LAAs have been described, which require subsequent diastereomeric resolution to isolate chiral material. Towards this end, reaction of readily accessible α-bromoalkanoic acids with ammonium hydroxide yields racemic material in 60–70% yield [3]. Alternatively, base-induced reaction of dialkyl acetomalonate with alkyl halides leads to incorporation of the lipophilic sidechain after hydrolysis and partial decarboxylation [4]. Subsequent enzymatic resolution of derivatised *N*-chloroacetylated LAA racemates by acylase I then affords enantiomerically pure material, but this method is unsuitable for longer chain members of the class ($n > 9$) because of poor substrate tolerance [3].

Chemical resolution has also been employed to generate optically pure sources of LAAs via the generation of diastereomeric 2-hydroxypinan-3-one derivatives of LAA methyl esters (Scheme 1) [5]. The requirement for chromatography to separate the resultant Schiff base isomers, however, is not trivial and also unsuitable for large-scale synthesis. An asymmetric synthesis of LAAs ($n = 11$, 13 and 15) has also been reported using a diastereoselective alkylation of the Schiff base of 2-hydroxypinan-3-one and *tert*-butyl glycinate (Scheme 1) [6]. Although the observed diastereoselectivity is excellent (>90% de), the alkylation yields are low and require the more expensive (+)-isomer of the α-pinene derivative to access L-configured LAAs. Furthermore, the six-step synthesis also retains an undesirable chromatographic purification before delivering Fmoc-protected LAAs **2** suitable for use in solid-phase peptide synthesis.

Additionally, Gibson and co-workers have investigated a cross-metathesis (CM) approach to racemic, unsaturated LAAs via the reaction of allylglycine and homoallylglycine derivatives with 1-hexene and 1-octene in the presence of first-generation Grubbs catalyst [$(Cy_3P)_2Cl_2RuCHPh$] [7]. Isolation of the desired cross products, however, was complicated by the accompanying self-metathesis products (and starting material), resulting in the need for chromatographic purification and low mass recovery (<50% yield).

In this paper, we report an analogous catalysis-driven strategy for the synthesis of known and novel, unsaturated and saturated, chiral LAAs by using a later-generation Ru-benzylidene catalyst. The target saturated LAA analogues are generated via a highly efficient tandem sequence of Ru-catalysed olefin metathesis and hydrogenation. Significantly, this two-step process utilises commercially available starting materials, a single Ru-alkylidene pre-catalyst and mild experimental conditions, and does not require protecting group manipulation or chromatographic purification.

Materials and Methods

General Experimental

Melting points (mps) were determined using a Reichert hot-stage melting point apparatus and were uncorrected.

Infrared spectra (IR) were recorded on a Perkin–Elmer 1600 series Fourier Transform infrared spectrophotometer as thin films of liquid (neat) between sodium chloride plates. IR absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}) with the relative intensities expressed as s (strong), m (medium), w (weak) or prefixed b (broad).

Proton nuclear magnetic resonance (^1H nmr) spectra were recorded on a Bruker DRX400 spectrometer operating at 400 MHz, as solutions in deuterated solvents as specified. Each resonance was assigned according to the following convention: chemical shift (rotamers), multiplicity, number of protons, observed coupling

* *Correspondence to: Andrea J. Robinson, School of Chemistry, Wellington Road, Clayton 3800, Victoria, Australia.* [redacted]

School of Chemistry, Monash University, Wellington Road, Melbourne, 3800, Victoria, Australia

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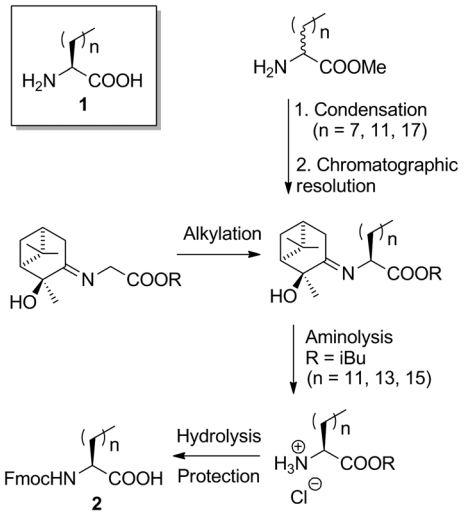

Scheme 1. Existing preparation of LAAs **1**.

constants (*J* in Hz) and proton assignment. Chemical shifts (δ), measured in parts per million (ppm), are reported relative to the residual proton peak in the solvent used as specified. Multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), multiplet (m) or prefixed broad (b), or a combination where necessary.

Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Bruker DRX400 spectrometer operating at 100 MHz, as solutions in deuterated solvents as specified. Chemical shifts (δ), measured in parts per million (ppm), are reported relative to the residual proton peak in the deuterated solvent (as specified).

Low-resolution electrospray ionisation (ESI) mass spectra were recorded on a Micromass Platform Electrospray mass spectrometer (quadrupole mass spectrometry–quadrupole mass electrometry) as solutions in specified solvents. Spectra were recorded in positive and negative modes (ESI^+ and ESI^-) as specified. High-resolution electrospray mass spectra (HRMS) were recorded on a Bruker BioApex 47e Fourier Transform mass spectrometer (4.7 T magnet) fitted with an analytical electrospray source. The mass spectrometer was calibrated with an internal standard solution of sodium iodide in methanol (MeOH).

Analytical normal-phase high-performance liquid chromatography was performed on an Agilent 1200 series instrument equipped with photodiode array detection (controlled by ChemStation software) and an automated injector (100-μl loop volume). Analytical separations were performed on a Nucleosil 100-5 OH (4.6 × 250 mm, 5 μm) analytical column at flow rates of 1.0 ml min^{-1}. The solvent system used for compounds **21a** and **22–28** was buffer A: isopropanol; buffer B: hexane. Isocratic flow of 1% isopropanol (buffer A) and 99% hexane (buffer B) was employed throughout this study.

Reverse-phase high-performance liquid chromatography (RP-HPLC) was performed on a Vydac C18 analytical column (4.6 × 250 mm, 5 μm) at a flow rate of 1.5 ml min^{-1}. Peptide **29** was purified using buffer A: 0.1% aqueous TFA; buffer B: 0.1% TFA in MeCN.

Dichloromethane (DCM) was supplied by Merck Australia (Kilsyth, VIC, Australia) and distilled over CaH_2 prior to use. Acetic acid (AcOH), diethyl ether, ethyl acetate (EtOAc), hexane and MeOH were used as supplied by Merck. (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(*o*-isopropoxyphenylmethylene)ruthenium [Hoveyda–Grubbs catalyst (HGII)], *cis*-2-butene (99%), 1-butene, 1-pentene, 1-hexene, 1-heptene, 1-octene, 1-nonene, 1-decene and (*S*)-2-(Fmoc-amino)-4-pentenoic acid were used as supplied by Sigma Aldrich (Castle Hill, NSW, Australia). High-purity (<10 ppm oxygen) argon and hydrogen were supplied by BOC Australia (North Ryde, NSW, Australia) gases, and additional purification was achieved by passage of the gases through water, oxygen and hydrocarbon traps.

General Procedure for the Synthesis of Lipophilic *N*-Fmoc Amino Acids

In a dry box under N_2 atmosphere, a Schlenk vessel equipped with a magnetic stir bar was charged with *N*-Fmoc allylglycine **3a** (100 mg, 0.296 mmol), degassed DCM (6.0 ml), terminal alkene (1.48 mmol, 5 eq.) and HGII (9.29 mg, 5 mol%). The vessel was sealed, removed from the dry box and attached to a vacuum manifold. The vessel was placed under a flow of nitrogen and the stopper replaced with a Suba seal pierced with a 26-gauge needle to allow a constant flow of nitrogen over the top of the reaction. The reaction was stirred at room temperature overnight, allowing all of the DCM to evaporate. The residue was washed with hexane (2 × 10 ml) and collected via filtration or centrifugation. The residue was then redissolved in MeOH (10 ml) and transferred to a Fischer–Porter tube. The vessel was charged with H_2 (60 psi), sealed and stirred at room temperature overnight. The reaction mixture was then concentrated *in vacuo*, and the residual brown solid was purified via column chromatography to obtain pure lipodated *N*-Fmoc amino acid. Alternatively, the residual brown solid was taken up in a small quantity of diethyl ether. Dimeric amino acid by-products, resulting from homodimerisation, and catalyst decomposition products were insoluble and removed via filtration. The filtrate was concentrated *in vacuo* to give an off-white solid of sufficient purity to use directly in SPPS.

Compound Characterisation

Spectral data for compounds 21a–29 are available in the Supporting Information Section.

*Compound **21a***

Cis-2-butene was used as a propene equivalent. The titled compound was obtained as a colourless solid (105 mg, 93%), mp 129–130 °C. ν_{max} (neat): 3484s, 1699s, 1674s, 1559m, 1476m, 1449m, 1390m, 1323m, 1267m, 1165m, 1088w, 1048w, 934w, 859w, 888w, 754w, 739w. ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.96–0.85 (m, 3H, H6), 1.44–1.23 (m, 4H, H4 & H5), 1.97–1.65 (m, 2H, H3), 4.23 (t, J = 6.4 Hz, 1H, H2), 4.47–4.36 (m, 2H, CH_2), 4.49 (bs, 1H, H9′), 5.27 (bd, J = 7.2 Hz, 1H, NH), 7.31 (t, J = 6.8 Hz, 2H, H2′ & H7′), 7.40 (t, J = 7.2Hz, 2H, H3′ & H6′), 7.63–7.52 (m, 2H, H1′ & H8′), 7.76 (d, J 7.2H, 2H, H4′ & H5′), OH not observed. ^{13}C nmr (100 MHz, $CDCl_3$): δ 14.0 (C6), 32.2, 27.5, 22.4, 54.0, 47.4, 67.3, 127.9, 127.3, 125.3, 125.0, 120.2, 141.5, 143.9 & 144.1 (C8′a & C9′a), 156.3 (OCONH), 177.4 (C1). LR-MS: **21a** t_R = 5.21 min (>98% pure), (ESI^+, MeOH): *m/z* 376.1 $(M+Na)^+$, $C_{21}H_{23}NNaO_4^+$ requires 376.15.

*Compound **21b***

The titled compound was obtained as a colourless oil (111 mg, 78%). ν_{max} (neat): 3366s, 2960s, 2874s, 1699s, 1653s, 1507s, 1457s, 1394s, 1368s, 1249s, 1164s, 1107m, 1049m, 1021m, 851w, 799w, 738w. Mixture of rotamers observed (A : B = 1 : 2), ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.90 (t, J = 6.0 Hz, 3H, H6), 1.29–1.41 (m, 4H, H4

& H5), 1.44 (s, 9H, H2″), 1.58–1.94 (m, 2H, H3), 4.12 (m, 1H, H2, rotamer A), 4.30 (m, 1H, H2 rotamer B), 5.01 (bs, 1H, NH rotamer B), 6.21 (bs, 1H, NH rotamer A), 8.30 (bs, 1H, OH). ^{13}C nmr (100 MHz, $CDCl_3$): δ 13.9 (C6), 22.4 (C5), 27.5 (C4), 28.5 (C2″), 33.3 (C3), 53.6 (C2), 80.3 (C1″), 155.8 (C1′), 177.8 (C1). HRMS (ESI^-, MeOH): *m/z* 230.1394 $(M-H)^-$, $C_{11}H_{20}NO_4^-$ requires 230.1398.

Compound ***22***

The titled compound was obtained as a colourless solid (93.5 mg, 86%), mp 111–112 °C. ν_{max} (neat): 3376m, 2920s, 2853s, 1751s, 1734s, 1671s, 1560s, 1457s, 1377m, 1268m, 1181m, 1167m, 1124m, 1044w, 739m, 734m. ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.89 (3H, t, J = 6.4 Hz, H7), 1.26–1.38 (6H, m, H4–6), 1.66–1.94 (2H, m, H3), 4.23 (1H, t, J = 6.8 Hz, H2), 4.38–4.45 (1H, m, CH), 4.42 (2H, d, J = 6.8 Hz, CH_2), 5.26 (1H, d, J = 7.6 Hz, NH), 7.31 (t, J = 7.4 Hz, 2H, H2′ & H7′), 7.40 (t, J = 7.4 Hz, 2H, H3′ & H6′), 7.58–7.61 (m, 2H, H1′ & H8′), 7.76 (d, J = 7.4 Hz, 2H, H4′ & H5′), OH not observed. ^{13}C nmr (100 MHz, $CDCl_3$): δ 14.1 (C7), 22.5, 25.0, 31.4, 32.4, 47.3, 54.0, 67.2, 120.1, 125.2, 127.2, 127.9, 141.5, 143.8 & 144.0 (C8′a & C9′a), 156.2 (OCONH), 177.4 (C1). LC-MS: **22** t_R = 5.55 min (>98% pure), (ESI^+, MeOH): *m/z* 390.1$(M+Na)^+$, $C_{22}H_{25}NO_4Na$ requires 390.17.

Compound ***23***

The titled compound was obtained as a colourless solid (73.4 mg, 65%), mp 123–124 °C. ν_{max} (neat): 3374m, 2923s, 2856s, 1754s, 1739m, 1675s, 1558s, 1456s, 1377m, 1266m, 1165m, 1125m, 1088w, 1046w, 741m, 734m cm^{-1}. ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 6.8 Hz, H8), 1.29–1.43 (8H, m, H4–7), 1.66–1.94 (2H, m, H3), 4.23 (1H, t, J = 6.8 Hz, H2), 4.38–4.45 (1H, m, CH), 4.42 (2H, d, J = 6.8 Hz, CH_2), 5.26 (1H, d, J = 8.0 Hz, NH), 7.31 (t, J = 7.4 Hz, 2H, H2′ & H7′), 7.40 (t, J = 7.4 Hz, 2H, H3′ & H6′), 7.58–7.61 (m, 2H, H1′ & H8′), 7.76 (d, J = 7.4 Hz, 2H, H4′ & H5′), OH not observed. ^{13}C nmr (100 MHz, $CDCl_3$): δ 14.2 (C8), 22.7, 25.3, 28.9, 31.7, 32.5, 47.3, 54.0, 67.2, 120.1, 125.2, 127.2, 127.9, 141.5, 143.9 & 144.0 (C8′a & C9′a), 156.2 (OCONH), 177.4 (C1). LC-MS: **23** t_R = 5.23 min (>98% pure), (ESI^+, MeOH): *m/z* 404.1 $(M+Na)^+$, $C_{23}H_{27}NO_4Na$ requires 404.18.

Compound ***24***

The titled compound was obtained as a colourless solid (94.8 mg, 81%), mp 112–114 °C. ν_{max} (neat): 3323bm, 2928s, 2856s, 1716s, 1635m, 1519s, 1450s, 1418m, 1338m, 1264m, 1115w, 1078m, 1050m, 758m, 739s. ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 6.8 Hz, H9), 1.26–1.42 (10H, m, H4–8), 1.64–1.94 (2H, m, H3), 4.22 (1H, t, J = 6.8 Hz, H2), 4.38–4.45 (1H, m, CH), 4.41 (2H, d, J = 7.2 Hz, CH_2), 5.26 (1H, d, J = 8.0 Hz, NH), 7.30 (t, J = 7.4 Hz, 2H, H2′ & H7′), 7.39 (t, J = 7.4 Hz, 2H, H3′ & H6′), 7.57–7.60 (m, 2H, H1′ & H8′), 7.75 (d, J = 7.4 Hz, 2H, H4′ & H5′), OH not observed. ^{13}C nmr (100 MHz, $CDCl_3$): δ 14.2 (C9), 22.7, 25.4, 29.2, 29.3, 31.9, 32.5, 47.3, 54.0, 67.2, 120.1, 125.2, 127.2, 127.9, 141.5, 143.9 & 144.0 (C8′a & C9′a), 156.3 (OCONH), 177.2 (C1). LC-MS: **24** t_R = 5.49 min (>98% pure), (ESI^+, MeOH): *m/z* 418.1 $(M+Na)^+$, $C_{24}H_{29}NO_4Na$ requires 418.20.

Compound ***25***

The titled compound was obtained as a colourless solid (88.5 mg, 73%), mp 65–67 °C. ν_{max} (neat): 3431bm, 3065m, 2925s, 2854s, 1718s, 1696s, 1539m, 1517m, 1450s, 1419w, 1340m, 1248m, 1115w, 1052m, 758m, 738s. ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 6.8 Hz, H10), 1.26–1.37 (12H, m, H4–9), 1.64–1.93 (2H, m, H3), 4.22 (1H, t, J = 6.8 Hz, H2), 4.37–4.48 (1H, m, CH), 4.41 (2H, d, J = 6.8 Hz, CH_2), 5.30 (1H, d, J = 8.4 Hz, NH), 7.30 (t, J = 7.4 Hz, 2H, H2′ & H7′), 7.39 (t, J = 7.4 Hz, 2H, H3′ & H6′), 7.57–7.60 (m, 2H, H1′ & H8′), 7.75 (d, J = 7.4 Hz, 2H, H4′ & H5′), OH not observed. ^{13}C nmr (100 MHz, $CDCl_3$): δ 14.2 (C10), 22.8, 25.4, 29.31, 29.35, 29.5, 32.0, 32.5, 47.3, 54.0, 67.2, 120.1, 125.2, 127.2, 127.9, 141.5, 143.9 & 144.0 (C8′a & C9′a), 156.3 (OCONH), 177.5 (C1). LC-MS: **25** t_R = 5.48 min (>98% pure), (ESI^+, MeOH): *m/z* 432.1 $(M+Na)^+$, $C_{25}H_{31}NO_4Na$ requires 432.22.

Compound ***26***

The titled compound was obtained as a colourless solid (95.3 mg, 76%), mp 96–98 °C. ν_{max} (neat): 3417bm, 2926s, 2854s, 1717s, 1647s, 1559m, 1517m, 1450m, 1419w, 1339m, 1247m, 1105w, 1051w, 758m, 738m. ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 6.8 Hz, H11), 1.26–1.32 (14H, m, H4–10), 1.61–1.91 (2H, m, H3), 4.23 (1H, t, J = 6.8 Hz, H2), 4.40–4.47 (3H, m, CH & CH_2), 5.25 (1H, d, J = 8.0 Hz, NH), 7.31 (t, J = 7.4 Hz, 2H, H2′ & H7′), 7.40 (t, J = 7.4 Hz, 2H, H3′ & H6′), 7.59–7.60 (m, 2H, H1′ & H8′), 7.76 (d, J = 7.4 Hz, 2H, H4′ & H5′), OH not observed. ^{13}C nmr (100 MHz, $CDCl_3$): δ 14.2 (C12), 22.8, 25.4, 29.3, 29.4, 29.5, 29.6, 32.0, 32.5, 47.3, 53.9, 67.2, 120.1, 125.2, 127.2, 127.9, 141.5, 143.9 & 144.0 (C8′a & C9′a), 156.2 (OCONH), 177.4 (C1). LC-MS: **26** t_R = 5.47 min (>98% pure), (ESI^+, MeOH): *m/z* 446.1 $(M+Na)^+$, $C_{26}H_{33}NO_4Na$ requires 446.23.

The reaction was also performed on larger scale, following the general procedure previously described. *N*-Fmoc allylglycine (1.00 g, 2.96 mmol), degassed DCM (30 ml), 1-octene (2.32 ml, 14.8 mmol, 5 eq.) and HGII (46.5 mg, 2.5 mol%) were used. After purification, the titled compound was obtained (0.89 g, 71%). Spectroscopic data were consistent with previously described data for **26**.

Compound ***27***

The titled compound was obtained as a colourless solid (103.6 mg, 80%), mp 61–62 °C. ν_{max} (neat): 3334bm, 2924s, 2853s, 1715s, 1635m, 1521m, 1465m, 1450s, 1419m, 1339m, 1247m, 1117w, 1079m, 1052m, 758m, 738m. ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 6.8 Hz, H12), 1.26–1.37 (16H, m, H4–11), 1.64–1.93 (2H, m, H3), 4.22 (1H, t, J = 6.8 Hz, H2), 4.37–4.48 (1H, m, CH), 4.41 (2H, d, J = 6.8 Hz, CH_2), 5.31 (1H, d, J = 8.0 Hz, NH), 7.30 (t, J = 7.4 Hz, 2H, H2′ & H7′), 7.39 (t, J = 7.4 Hz, 2H, H3′ & H6′), 7.57–7.60 (m, 2H, H1′ & H8′), 7.75 (d, J = 7.4 Hz, 2H, H4′ & H5′), OH not observed. ^{13}C nmr (100 MHz, $CDCl_3$): δ 14.2 (C12), 22.8, 25.4, 29.3, 29.46, 29.54, 29.71, 29.72, 32.0, 32.5, 47.3, 54.1, 67.2, 120.1, 125.2, 127.2, 127.9, 141.5, 143.8 & 144.0 (C8′a & C9′a), 156.3 (OCONH), 177.6 (C1). LC-MS: **27** t_R = 5.45 min (>98% pure), (ESI^+, MeOH): *m/z* 460.2 $(M+Na)^+$, $C_{27}H_{35}NO_4Na$ requires 460.25.

Compound ***28***

The title compound was obtained as a colourless solid (100.2 mg, 75%), mp 95–96 °C. ν_{max} (neat): 3339m, 3065m, 2925s, 2852s, 1718s, 1696s, 1539m, 1517m, 1465m, 1450m, 1419w, 1340m, 1247m, 1079w, 1052w, 758m, 739 s. ^{1}H nmr (400 MHz, $CDCl_3$): δ 0.89 (3H, t, J = 6.8 Hz, H13), 1.26–1.37 (18H, m, H4–12), 1.62–1.93 (2H, m, H3), 4.22 (1H, t, J = 6.8 Hz, H2), 4.38–4.48 (1H, m, CH), 4.41 (2H, d, J = 6.8 Hz, CH_2), 5.30 (1H, d, J = 8.0 Hz, NH), 7.30 (t, J = 7.4 Hz, 2H, H2′ & H7′), 7.39 (t, J = 7.4 Hz, 2H, H3′ & H6′), 7.58–7.61 (m, 2H, H1′ & H8′), 7.76 (d, J = 7.4 Hz, 2H, H4′ & H5′), OH not observed. ^{13}C nmr (100 MHz, $CDCl_3$): δ 14.2 (C13), 22.8, 25.4, 29.3, 29.49, 29.54, 29.71, 29.75, 29.76, 32.1, 32.5, 47.3, 54.0, 67.2, 120.1, 125.2, 127.2, 127.9, 141.5, 143.8 & 144.0 (C8′a & C9′a), 156.3 (OCONH),

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177.6 (C1). LC-MS: **28** $t_R = 5.44$ min (>98% pure), (ESI^+, MeOH): *m/z* 474.1 $(M + Na)^+$, $C_{28}H_{37}NO_4Na$ requires 474.26.

Compound ***29***

Manual SPPS was carried out using fritted plastic syringes, allowing filtration of solution without the loss of resin. The tap-fitted syringes were attached to a vacuum tank, and all washings were removed *in vacuo*. This involved soaking the resin in the required solvent for a reported period of time followed by evacuation to allow the removal of excess reagents before subsequent coupling reactions.

In a fritted syringe, the Fmoc-Rink amide resin (250 mg, 0.10 mmol, loading 0.4 mmol g^{-1}) was swollen with DCM (5 ml; 3 × 1 min, 1 × 60 min) and DMF (5 ml; 3 × 1 min, 1 × 30 min). Prior to the first coupling, the resin was subjected to Fmoc deprotection in the presence of 20% v/v piperidine in DMF (5 ml; 1 × 1 min, 2 × 10 min) and further washed with DMF (5 ml, 5 × 1 min) to ensure traces of excess reagent, and by-products had been removed. Amino acid pre-activation was achieved by the addition of NMM (6 eq) to a solution of the designated protected amino acid, Fmoc-L-Xaa-OH (3 eq) and HATU (3 eq) in DMF (3 ml). The mixture was sonicated for ~1 min and the resulting solution then added to the resin-tethered amino acid and shaken gently for 2 h. At the end of this reaction duration, the peptidyl resin was washed with DMF (7 ml, 3 × 1 min) to ensure excess reagents were removed. Kaiser tests were performed to monitor coupling success, and any incomplete coupling reactions were repeated with extended reaction times. Once a negative test for the presence of free amines was achieved, the resin-tethered peptide was deprotected with 20% v/v piperidine in DMF (5 ml; 1 × 1 min, 2 × 10 min) and further washed with DMF (5 ml, 5 × 1 min) to remove traces of base prior to subsequent amino acid couplings. The aforementioned procedure was repeated until the desired sequence was constructed. After sequence completion, the Fmoc-deprotected and resin-bound peptide was transferred into a fritted syringe and washed with DMF (5 ml, 3 × 1 min), DCM (5 ml, 3 × 1 min), MeOH (5 ml, 3 × 1 min), DCM (5 ml, 3 × 1 min) and MeOH (5 ml, 3 × 1 min) and then left to dry *in vacuo* for 1 h. The resin-tethered peptide was subjected to TFA-mediated cleavage for RP-HPLC and mass spectral analysis. This supported the formation of the desired peptide **29**. Mass spectrum (ESI^+, MeCN : H_2O : HCOOH): *m/z* 597.3 $[M + H]^+$, $C_{27}H_{49}N_8O_7$ requires 597.37. RP-HPLC (Agilent: Vydac C18 analytical column, 15 → 45% buffer B over 30 min): $t_R = 16.3$ min, purity > 95%.

Compound ***12a***

^{1}H nmr (400 MHz, $CDCl_3$): δ 1.66 (d, $J = 6.2$ Hz, 3H, H6), 2.39–2.63 (m, 2H, H3), 4.08–4.27 (m, 1H, H2), 4.36–4.55 (m, 3H, CH_2 & H9′), 5.26–5.37 (m, 2H, H4 & NH), 5.52–5.62 (m, 1H, H5), 7.31 (t, $J = 7.3$ Hz, 2H, H2′ & H7′), 7.40 (t, $J = 7.4$ Hz, 2H, H3′ & H6′) 7.54–7.64 (m, 2H, H1′ & H8′), 7.77 (d, $J = 7.4$ Hz, 2H, H4′ & H5′), 8.81 (bs, 1H, OH). LR-MS: (ESI^+, MeOH): *m/z* $(M + Na)^+$ 374.1, $C_{21}H_{21}NO_4Na$ requires 374.14.

Compound ***12b***

^{1}H nmr (400 MHz, $CDCl_3$): δ 1.44 (s, 9H, H2″), 1.67 (d, $J = 6.2$ Hz, 3H, H6), 2.34–2.59 (m, 2H, H3), 4.02–4.45 (m, 1H, H2), 4.99 (bs, 1H, NH), 5.26–5.73 (m, 2H, H4 & H5), OH not observed. LR-MS: (ESI^+, MeOH): *m/z* 252.1 $(M + Na)^+$, $C_{11}H_{19}NNaO_4^+$ requires 252.12.

Compound ***13***

^{1}H nmr (400 MHz, $CDCl_3$): δ 0.98 (3H, t, $J = 6.8$ Hz, H7), 2.02–2.10 (2H, m, H6), 2.40–2.65 (2H, m, H3), 4.13–4.23 (1H, m, H2), 4.40–4.55 (3H, m, CH & CH_2), 5.17 (1H, d, $J = 7.6$ Hz, NH), 5.26–5.35 (1H, m, H5), 5.55–5.65 (1H, m, H4), 7.29 (t, $J = 7.4$ Hz, 2H, H2′ & H7′), 7.40 (t, $J = 7.4$ Hz, 2H, H3′ & H6′), 7.58–7.61 (m, 2H, H1′ & H8′), 7.76 (d, $J = 7.4$ Hz, 2H, H4′ & H5′), OH not observed. LRMS: (ESI^+, MeOH): *m/z* 388.1 $(M + Na)^+$, $C_{22}H_{23}NO_4Na$ requires 388.15.

Compound ***14***

^{1}H nmr (400 MHz, $CDCl_3$): δ 0.98 (3H, t, $J = 6.8$ Hz, H8), 1.70–1.74 (2H, m, H7), 2.02–2.10 (2H, m, H6), 2.40–2.65 (2H, m, H3), 4.13–4.23 (1H, m, H2), 4.40–4.55 (3H, m, CH & CH_2), 5.17 (1H, d, $J = 7.6$ Hz, NH), 5.26–5.35 (1H, m, H5), 5.55–5.65 (1H, m, H4), 7.29 (t, $J = 7.4$ Hz, 2H, H2′ & H7′), 7.40 (t, $J = 7.4$ Hz, 2H, H3′ & H6′), 7.58–7.61 (m, 2H, H1′ & H8′), 7.76 (d, $J = 7.4$ Hz, 2H, H4′ & H5′), OH not observed. LR-MS: (ESI^+, MeOH): *m/z* 401.9 $(M + Na)^+$, $C_{23}H_{25}NO_4Na$ requires 402.17.

Compound ***15***

^{1}H n.m.r. (400 MHz, $CDCl_3$): δ 0.90 (3H, t, $J = 6.8$ Hz, H9), 1.33–1.38 (4H, m, H7 & 8), 1.99–2.06 (2H, m, H6), 2.42–2.56 (2H, m, H3), 4.14–4.24 (1H, m, H2), 4.41–4.56 (3H, m, CH & CH_2), 5.29–5.35 (2H, m, H5 & NH), 5.57–5.62 (1H, m, H4), 7.29 (t, $J = 7.4$ Hz, 2H, H2′ & H7′), 7.40 (t, $J = 7.4$ Hz, 2H, H3′ & H6′), 7.58–7.61 (m, 2H, H1′ & H8′), 7.76 (d, $J = 7.4$ Hz, 2H, H4′ & H5′), 10.22 (1H, br s, OH). LRMS: (ESI^+, MeOH): *m/z* 416.1 $(M + Na)^+$, $C_{24}H_{27}NO_4Na$ requires 416.18.

Compound ***16***

^{1}H nmr (400 MHz, $CDCl_3$): δ 0.88 (3H, t, $J = 6.8$ Hz, H10), 1.23–1.38 (6H, m, H7–9), 1.96–2.06 (2H, m, H6), 2.46–2.61 (2H, m, H3), 4.16–4.26 (1H, m, H2), 4.34–4.54 (3H, m, CH & CH_2), 5.29–5.34 (2H, m, H5 & NH), 5.56–5.64 (1H, m, H4), 7.29 (t, $J = 7.4$ Hz, 2H, H2′ & H7′), 7.40 (t, $J = 7.4$ Hz, 2H, H3′ & H6′), 7.58–7.61 (m, 2H, H1′ & H8′), 7.76 (d, $J = 7.4$ Hz, 2H, H4′ & H5′), 9.65 (1H, br s, OH). LRMS: (ESI^+, MeOH): *m/z* 430.1 $(M + Na)^+$, $C_{25}H_{29}NO_4Na$ requires 430.20.

Compound ***17***

^{1}H nmr (400 MHz, $CDCl_3$): δ 0.90 (3H, t, $J = 6.8$ Hz, H11), 1.27–1.38 (8H, m, H7–10), 1.96–2.06 (2H, m, H6), 2.48–2.61 (2H, m, H3), 4.19–4.24 (1H, m, H2), 4.41–4.48 (3H, m, CH & CH_2), 5.29–5.39 (2H, m, H5 & NH), 5.58–5.61 (1H, m, H4), 7.29 (t, $J = 7.4$ Hz, 2H, H2′ & H7′), 7.40 (t, $J = 7.4$ Hz, 2H, H3′ & H6′), 7.58–7.61 (m, 2H, H1′ & H8′), 7.76 (d, $J = 7.4$ Hz, 2H, H4′ & H5′), 9.82 (1H, br s, OH). LRMS: (ESI^+, MeOH): *m/z* 444.1 $(M + Na)^+$, $C_{26}H_{31}NO_4Na$ requires 444.21.

Compound ***18***

^{1}H nmr (400 MHz, $CDCl_3$): δ 0.90 (3H, t, $J = 6.8$ Hz, H12), 1.27–1.38 (10H, m, H7–11), 1.96–2.06 (2H, m, H6), 2.44–2.61 (2H, m, H3), 4.19–4.24 (1H, m, H2), 4.41–4.48 (3H, m, CH & CH_2), 5.27–5.39 (2H, m, H5 & NH), 5.58–5.62 (1H, m, H4), 7.29 (t, $J = 7.4$ Hz, 2H, H2′ & H7′), 7.40 (t, $J = 7.4$ Hz, 2H, H3′ & H6′), 7.58–7.61 (m, 2H, H1′ & H8′), 7.76 (d, $J = 7.4$ Hz, 2H, H4′ & H5′), 9.98 (1H, br s, OH). (ESI^+, MeOH): *m/z* 458.1 $(M + Na)^+$, $C_{27}H_{33}NO_4Na$ requires 458.23.

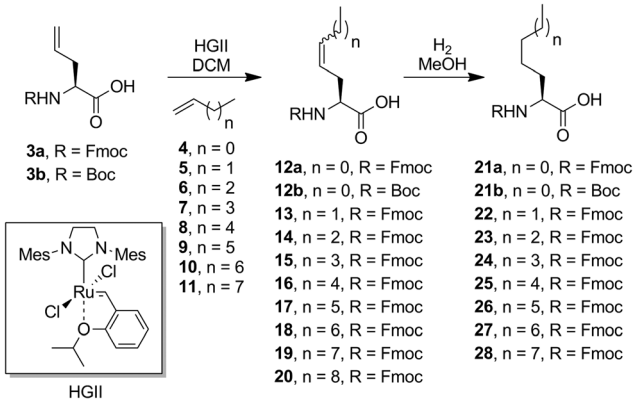
Compound ***19***

^{1}H nmr (400 MHz, $CDCl_3$): δ 0.90 (3H, t, $J = 6.8$ Hz, H13), 1.26–1.38 (12H, m, H7–12), 1.96–2.08 (2H, m, H6), 2.48–2.61 (2H, m, H3), 4.19–4.24 (1H, m, H2), 4.38–4.48 (3H, m, CH & CH_2), 5.30–5.39 (2H, m, H5 & NH), 5.55–5.62 (1H, m, H4), 7.29 (t, $J = 7.4$ Hz, 2H, H2′ & H7′), 7.40 (t, $J = 7.4$ Hz, 2H, H3′ & H6′), 7.58–7.61

(m, 2H, H1′ & H8′), 7.76 (d, $J = 7.4$ Hz, 2H, H4′ & H5′), 10.16 (1H, br s, OH). (ESI$^+$, MeOH): *m/z* 472.0 $(M + Na)^+$, $C_{28}H_{35}NO_4Na$ requires 472.25.

Results and Discussion

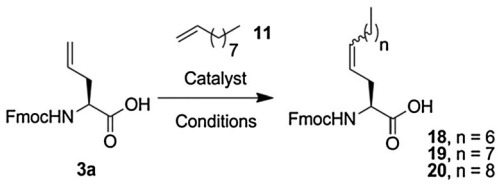
Herein, we report a generic Ru-alkylidene-catalysed tandem CM/hydrogenation route to lipoamino acids (Scheme 2). This process utilises commercially available *N*-Fmoc and *N*-Boc derivatives of allylglycine, **3a** and **3b** respectively, and the derived LAAs can be directly incorporated into peptide sequences without chromatography. The carboxylic acid functionality in **3** is also well tolerated by Ru-based metathesis catalysts, which eliminates unnecessary functional group protection and deprotection steps from the reaction process. It is also worthwhile noting that previous work by our group has found that the stereogenic centre adjacent to the carbonyl functionality is not epimerised under mild Ru-alkylidene-catalysed metathesis reactions [8].



Scheme 2. Cross-metathesis route to optically pure LAAs.

Cross metathesis of commercially available *N*-protected-allylglycines **3a** and **3b** with terminal alkenes **4–11** was sensitive towards reaction conditions. Optimisation of the CM reaction was performed using *N*-Fmoc-protected allylglycine **3a** and 1-decene **11**. Whilst giving excellent conversions, reactions performed in DCM or EtOAc heated at reflux yielded not only the desired cross product **19** but also side-chain extended and truncated homologues **18** and **20** (Table 1). These analogues are difficult to detect in nmr spectra but clearly apparent in mass spectra of reaction mixtures. Formation of these by-products suggested that concomitant olefin isomerisation and secondary metathesis processes were occurring, marring an otherwise efficient process. Olefin isomerisation induced by Ru-alkylidene metathesis catalysts is well documented in the literature [9]. To develop an efficient synthesis of LAAs, we needed to eliminate the formation of the undesired homologues to prevent the need for downstream purification. Towards this end, various reaction conditions, solvents and additives were screened with the aim of minimising and/or eliminating this deleterious side reaction. Gratifyingly, reactions run at ambient temperature yielded only the target cross product **19**; however, this result came at the expense of conversion (Table 1, Entry 3). Altering the stoichiometry, addition of molecular sieves and performing the reaction in EtOAc, while maintaining the reaction at room temperature, all failed to produce any considerable increase in conversion (Table 1, Entries 4–9). When the reaction was performed with a continuous flow of nitrogen through the head space, however, a significant increase in conversion was observed (Table 1,

Table 1. Optimisation of the CM reaction.



Entry	Catalyst (5 mol%)	Molar equivalence (eq, **11**)	Condition	**19** (%)[a]	By-products **18** + **20**
1	HGII	5	DCM, Δ	93	Yes
2	HGII	5	EtOAc, Δ	90	Yes
3	HGII	5	DCM, r.t.	66	No
4	GII	5	EtOAc, r.t.	52	No
5	HGII	5	EtOAc, r.t.	62	Trace
6	HGII	5	DCM, r.t.	52[b]	No
7	HGII	1	DCM, r.t.	32	No
8	HGII	2	DCM, r.t.	65	No
9	HGII	10	DCM, r.t.	70	No
10	HGII	5	DCM, r.t.	87[c]	No

[a]Conversion determined by ^{1}H nmr spectroscopy.
[b]Molecular sieves added to the reaction.
[c]Reaction performed with an N_2 bleed.
r.t., room temperature.

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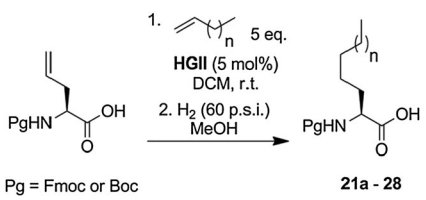
Entry 10). It was reasoned that the continuous nitrogen flow facilitated efficient removal of ethylene, an expected by-product generated during the CM, and concentrated the reagents during the course of the reaction to drive the equilibrium towards the target product **19** [10].

With the optimised CM conditions in hand, synthesis of the *N*-protected-alkylglycine series ($n = 0 \rightarrow 7$) commenced. Cross metathesis of allylglycine derivatives **3a** and **3b** with 1-alkenes **4–11** gave, in excellent conversion, the alkene intermediates **12–19** as mixtures of *E*-isomers and *Z*-isomers. Metathesis conversion was monitored by ^{1}H nmr spectroscopy and found to be complete over 16 h. Without workup, the mixture was subjected to hydrogenation. The use of recycled Ru-alkylidene catalyst as a hydrogenation catalyst has been documented in literature; however, most examples employ the phosphine-based Grubbs and second-generation Grubbs catalysts as opposed to the phosphine-free HGII [11]. Furthermore, the experimental conditions used in many of these examples, which employ high pressure/temperature [12] and/or strong bases [13], are clearly unsuitable for amino acid and peptide substrates. The tandem metathesis/hydrogenation via a single catalyst under mild experimental conditions therefore appeared to be essential for accessing chiral LAAs **21–28**. Hence, after completion of the CM reaction, MeOH was added to the residue material, and the solutions were transferred to a Fischer–Porter tube. The tandem Ru-catalysed hydrogenation was then performed at 60 psi H_2 pressure and ambient temperature to afford the saturated LAA products **21–28** in excellent yield (Table 2). Furthermore, the highly efficient, two-step, tandem CM/hydrogenation process could also be easily scaled. Compound **26** was synthesised on gram scale with yields comparable to small-scale reactions.

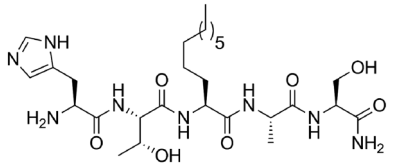
Although it has been reported that the exposure of the bis-cyclohexylphosphine Ru-alkylidene catalyst [14] to hydrogen affords the hydride complex $RuHCl(H_2)(PCy_3)_2$ [15], a known hydrogenation catalyst, the nature of the Ru complex responsible for hydrogenation in the described system is unclear. Remarkably, the Ru residue following metathesis can perform the required hydrogenation reaction under mild hydrogen pressure, low temperature and without the addition of a strong base. The residue can also be left in air for several days and still generates an active hydrogenation catalyst on exposure to a hydrogen atmosphere. Investigations on the nature of the hydrogenation catalyst are currently underway.

Table 2. Tandem CM/hydrogenation yields.



Entry	*n*	Protecting group	Product	Tandem yield (%)
1	0	Fmoc	**21a**	93[a]
2	0	Boc	**21b**	78
3	1	Fmoc	**22**	86
4	2	Fmoc	**23**	65
5	3	Fmoc	**24**	81
6	4	Fmoc	**25**	73
7	5	Fmoc	**26**	76
8	6	Fmoc	**27**	80
9	7	Fmoc	**28**	75

[a]Non-terminal *cis*-2-butene was used as a 1-propene equivalent in this reaction.



29

Figure 1. Facile incorporation of readily prepared *N*-Fmoc LAAs into a peptide sequence via SPPS.

Facile isolation and purification of the saturated *N*-Fmoc amino acids **21–28** were achieved via selective precipitation. Although column chromatography could be used to obtain final products with higher purity, we were able to demonstrate that the material obtained from the selective precipitation work-up is of sufficient purity to be directly used in solid phase peptide synthesis (SPPS). Despite the lipophilic character of the C9 side chain in **26**, the incorporation of the *N*-Fmoc-protected residue **26** into a pentapeptide sequence was straightforward (Figure 1). LC-MS analysis of the material obtained after cleavage from the resin showed one major peak in the chromatogram, which corresponded in mass to peptide **29**, the target sequence.

In summary, a generic, facile and highly practical, two-step synthesis of valuable and chiral lipophilic amino acids has been developed. The products can be incorporated into a peptide sequence without further purification. Greater accessibility to these chiral, non-proteinaceous amino acids will initiate further interest in their use in peptidomimetic research.

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A Concise Cross-Metathesis Route to Enantiopure 1-Azaspirocycles

Zhen James Wang, Nicolas Daniel Spiccia, Christopher James Gartshore, Jayamini Illesinghe, William Roy Jackson, Andrea Jane Robinson*

School of Chemistry, Monash University, Clayton 3800, Australia
[redacted]

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We dedicate this manuscript to Adrian Blackman (University of Tasmania) and wish him well in his retirement.

Abstract: A concise synthesis of spiropyrrolidines and spiropiperidines has been developed. The approach employs a ruthenium–alkylidene-catalysed cross-metathesis reaction of enantiopure N-protected allylglycine with methylenecycloalkanes. The resultant alkene intermediates can then undergo a tandem acid-catalysed cyclisation to form spiropyrrolidines. Ring expansion of the spiropyrrolidine system, via an aziridinium intermediate, grants access to the homologous spiropiperidine ring system with excellent stereoretention.

Key words: spiro compounds, metathesis, ring expansion, catalysis, piperidines, pyrrolidines

The 1-azaspirocyclic ring system **1** (Figure 1) can be found in a number of bioactive natural product families.[1] Lepadiformine (**2**),[2] cephalotaxine (**3**)[3] and cylindricine A (**4**)[4] all share a common spirocyclic pyrrolidine core (n = 1), and fasicularin (**5**),[2e,5] halichlorine (**6**),[6] histrionicotoxin (**7**)[7] and cylindricine B (**8**)[8] possess a homologous spirocyclic piperidine centre (n = 2). Many different strategies have been developed to construct the azaspirocyclic motif within these alkaloids and these include the use of Diels–Alder cycloaddition,[9] semipinacol rearrangement[10] and acid-catalysed diene–iminium cyclisation.[11] Nitrone–alkene cycloaddition of acyclic diene intermediates, generated via olefin cross-metathesis (CM),[12] has also been used to generate the spiropiperidine core of histrionicotoxin (**7**).[13] To the best of our knowledge, with the exception of this single communication, the use of CM chemistry to efficiently construct 1-azaspirocyclic structures **1** has not yet been explored. Herein, we report the development of a generic, catalysis-driven approach to 1-azaspiranes exploiting an alkene CM reaction and subsequent Brønsted acid induced cyclisation (Scheme 1). Advantages of this strategy include high functional group tolerance, modular design and telescopic processing to form the target spirocyclic pyrrolidine architecture. In addition, a commercially available α-amino acid is used to provide requisite alkaloid stereochemistry and ring expansion into chiral spirocyclic piperidines.

Our synthetic approach is based on previous work which employed a catalytic two-step synthesis of 5,5-dimethylproline derivatives via the CM of allylglycine derivatives with isobutylene.[14] In this study, we extended this strategy to the CM of the *N*-benzoylallylglycine **9** with the methylenecycloalkanes **10**–**12** to rapidly generate alkene intermediates **13**–**15** for subsequent cationic cyclisation.[15] Unfortunately, this ruthenium–alkylidene-catalysed transformation was initially found to be capricious and optimum conditions were therefore firstly developed for the CM of **9** with methylenecyclohexane (**11**) (Table 1). Under conventional heating in a Fischer–Porter tube, the reaction suffered from poor conversion despite a long reaction time (Table 1, entry 1). When conventional heating was replaced by microwave (MW) irradiation, an enhancement in conversion was achieved in a shorter reaction time (Table 1, entry 2).

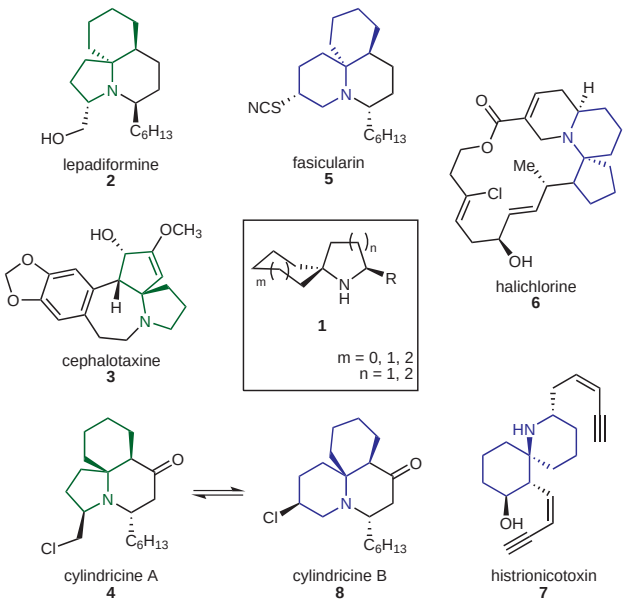
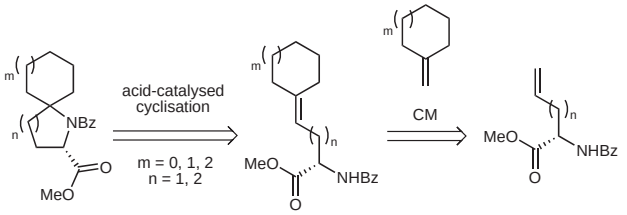


Figure 1 Marine alkaloids bearing the 1-azaspirocyclic core



Scheme 1 Tandem CM/acid-catalysed cyclisation route to 1-azaspirocycles

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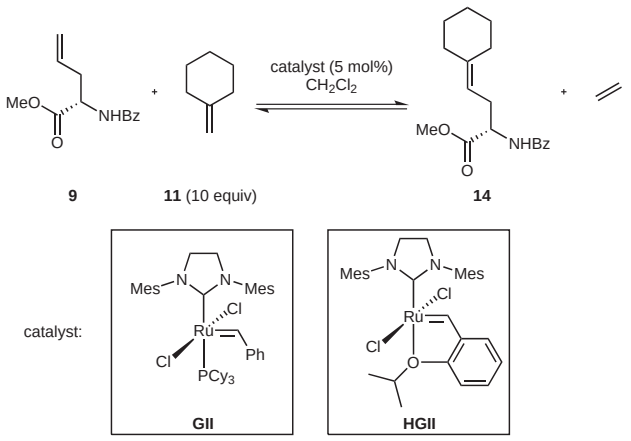
Table 1 Optimisation of the CM Reaction between **9** and **11**



Entry	Catalyst	Conditions	Conversion[a] (%)
1	**GII**	heat, 48 h	40
2	**GII**	MW (100 W), 100 °C, 2 h	60
3	**HGII**	MW (100 W), 100 °C, 2 h	76
4	**HGII**	MW (100 W), 100 °C, 4 h	79
5	**HGII**	MW (100 W), 100 °C, 4 h[b]	96

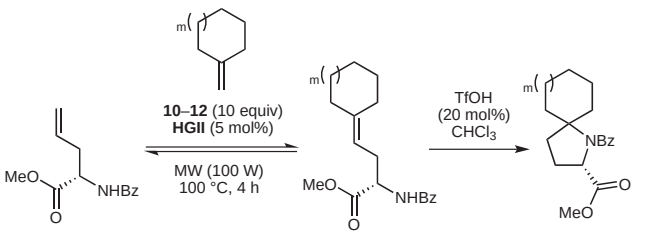
[a] Determined by ^{1}H NMR spectroscopy.
[b] Volatiles purged after 2 h.

Further improvement in conversion was achieved when second-generation Grubbs catalyst (**GII**) was replaced with second-generation Hoveyda–Grubbs catalyst (**HGII**) (Table 1, entries 3 and 4). Optimal CM conditions were obtained when the reaction was microwave-irradiated (100 W) at 100 °C for four hours with a purge of the volatile ethylene byproduct after two hours (Table 1, entry 5). Attempts were made to lower the equivalents of alkene **11**, however this resulted in reduced conversion into **14** in all cases; the given stoichiometry (10 equiv) was deemed necessary to achieve quantitative conversion into **14**. Nevertheless, excess, unreacted **11** could be readily recovered by distillation and recycled in subsequent reactions.

With the optimised reaction conditions in hand, CM of **9** with homologous methylenecycloalkanes **10** and **12** were explored. Gratifyingly, the corresponding alkenes **13** and **15** were also obtained in good to excellent yields from **10** and **12**, respectively (Table 2).

It should be noted that access to trisubstituted alkenes bearing pendent amide functionality (general structure of **13**–**15**) via traditional olefination chemistry has been reported. In comparison, these other methods[16] require a higher number of synthetic steps and/or do not yield an enantiopure product. More specifically, access to the general trisubstituted alkenyl amide structure has been achieved via Wittig olefination of cyclohexanone followed by functional group interconversion,[16a,b] nucleophilic substitution of prefunctionalised alkenyl

Table 2 Preparation of Enantiopure 1-Azaspirocycles **16**–**18**



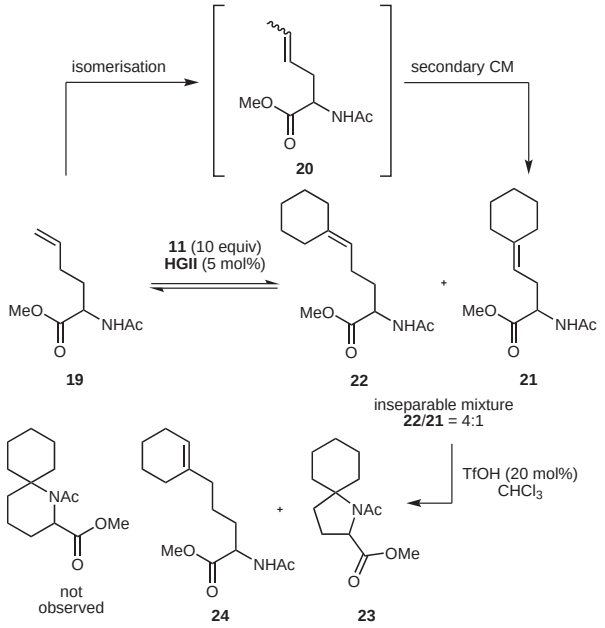
Entry	Cross partner[a]	Yield (%) of **13**–**15**	Yield[b] (%) of **16**–**18**
1	**10** (m = 0)	**13**, 95	**16**, 85 (87)
2	**11** (m = 1)	**14**, 96	**17**, 79 (80)
3	**12** (m = 2)	**15**, 79	**18**, 80 (67)

[a] Volatiles purged at 2 h.
[b] Yield in parentheses obtained via the telescopic method.

halides,[16c,d] quenching of a zirconocene complex with ketenes,[16e] and aldol condensation[16f] or nickel(0)-catalysed addition of isocyanates to vinylcyclohexane.[16g] We believe that CM represents a facile and synthetically viable approach to trisubstituted alkenes such as **13**–**15**.

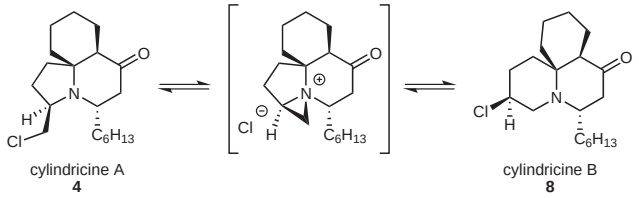
Next, the key acid-catalysed cationic cyclisation was investigated. Trifluoromethanesulfonic acid induced (20 mol%) cyclisation of olefin intermediates **13**–**15** gave the corresponding spiropyrrolidines **16**–**18** in 85%, 79% and 80% yield, respectively. Chiral HPLC analysis showed no loss of enantiopurity over the two catalytic steps. Furthermore, comparable yields were obtained when telescopic processing was employed to generate the target spiropyrrolidines **16**–**18** (Table 2, yields in parentheses). This conveniently eliminates the need for intermediate isolation and purification.

Unfortunately, extension of this chemistry towards the construction of homologous spiropiperidines was unsuccessful. Cross-metathesis of the N-protected homoallylglycine **19** with methylenecyclohexane (**11**) under the previously optimised reaction conditions led to partial isomerisation of **19** to the crotylglycine derivative **20** which upon sequential CM reaction with **11** gave the truncated alkene byproduct **21** (Scheme 2). This byproduct was chromatographically inseparable from the desired cross product **22**. Additives such as benzoquinone and acetic acid have been used previously to suppress such isomerisation;[17] however, the addition of benzoquinone to these CM reactions merely suppressed the overall yields without eliminating the isomerisation process. In addition, attempts to cyclise the mixture of **21** and **22** only resulted in the spiropyrrolidine analogue **23** (generated from **21**) and endo-isomerised alkene **24** (generated from **22**). Our attempts to prepare spiropiperidine compounds via acid-catalysed cyclisation were unsuccessful, as per the observations made by Haskins and Knight.[15]



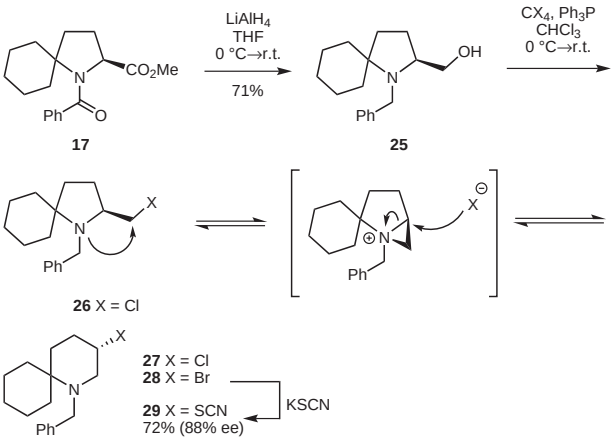
Scheme 2 Attempted preparation of spiropiperidines

Fortunately, nature provides the key to a viable synthesis of the elusive spiropiperidine framework. Interconversion between the spirocyclic marine alkaloids cylindricine A and B is postulated to involve a stereospecific ring expansion of the pyrrolidine via an aziridinium intermediate (Scheme 3).[4a–c,18] Hence, we postulated that access to spiropyrrolidine and spiropiperidine systems could be realised through a common and readily prepared CM-generated precursor.



Scheme 3 Interconversion between cylindricine A and B

Towards this end, the previously prepared spiropyrrolidine **17** was globally reduced with lithium aluminum hydride to give amino alcohol **25** in good yield (Scheme 4). Interestingly, when **25** was subjected to Appel conditions using carbon tetrachloride, a 1:1 mixture of regioisomers **26** and **27** (X = Cl) was obtained. The equilibrium that exists between chlorides **26** and **27** mirrors that found in the cylindricine family, notably cylindricine A and B. In contrast, when carbon tetrabromide was used in the Appel reaction, only the spiropiperidine analogue **28** was observed. Due to its instability on silica gel during chromatography, isolation of **28** proved to be difficult; however, it was conveniently converted in situ into the thiocyanate analogue **29** (Scheme 4), a motif found in the ascidian alkaloids cylindricine J and fasicularin (**5**). Chiral



Scheme 4 Ring expansion of a spiropyrrolidine to access spiropiperidines

HPLC analysis of the thiocyanate analogue **29** showed high retention of enantiomeric excess.

In conclusion, a facile and generic route to enantiopure spiropyrrolidine and spiropiperidine frameworks has been achieved through a common trisubstituted alkene. Ruthenium-catalysed CM of commercially available allylglycine and methylenecycloalkanes followed by acid-catalysed cyclisation facilitates expedient access to synthetically useful, chiral spiropyrrolidine analogues. These spiropyrrolidines can then be ring expanded to generate spiropiperidine analogues. In order to complete the synthesis of tricyclic marine alkaloids (Figure 1) via this strategy, the methylenecycloalkane CM partner needs to bear reactive functionality in the α-position. We have recently described chemistry for the cross-metathesis of this olefin subtype[19] which should provide facile entry into 1-azaspirocyclic alkaloid natural products in the future.

Melting points were determined using a Reichert hot-stage melting point apparatus. IR spectra were recorded on a Perkin-Elmer 1600 series Fourier transform infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX300 spectrometer (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR) or a Bruker DRX400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR). Low-resolution electrospray ionisation (ESI) mass spectra were recorded on a Micromass Platform Electrospray mass spectrometer (quadrupole mass electrometry) as solutions in the specified solvents. High-resolution electrospray mass spectra (HRMS) were recorded on a Bruker BioApex 47e Fourier transform mass spectrometer (4.7 tesla magnet). Optical rotations $[\alpha]_D^{25}$ were measured on a Perkin-Elmer model 141 polarimeter. Gas chromatograms were recorded on an Agilent 6850 GC system equipped with an SGE capillary column HP1-(PN190912-413) (30 m × 0.32 mm × 0.25 μm). The capillary column was operated with standard parameters, which involved holding the system at a constant 80 °C for 1 min, a ramp of 10 °C/min until 280 °C was reached, and a second hold period at this temperature for 9 min. Chiral GC was performed on a [50CP2/XE60.SVALSAPEA] column (50 cm × 0.25 mm), using helium as the carrier gas (5 mL/min). Chiral HPLC was performed on an Agilent 1200 LC binary system with an Agilent variable UV–vis detector. Analysis was performed on a Daicel Chiralcel OD column using a flow rate of 1.0 mL/min at 254 nm with a solvent mixture of *i*-PrOH–hexane (1:9). Microwave reactions were carried out using a CEM Discover® system fitted with a benchmate

option. CH_2Cl_2 was supplied by Merck and distilled over CaH_2 prior to use. $CHCl_3$, EtOAc, hexane and MeOH were used as supplied by Merck. Et_2O and THF were stored over Na wire and distilled prior to use. [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(*o*-isopropoxyphenylmethylene)ruthenium (**HGII**) and benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (**GII**) were used as supplied by Aldrich.

(*S*)-Methyl 2-Benzamidopent-4-enoate (9)

(*S*)-2-Benzamidopent-4-enoic acid (1.00 g, 4.57 mmol) was dissolved in a solution of methanolic HCl (50 mL, pH 2). After being stirred at r.t. for 18 h, the reaction mixture was diluted with H_2O (10 mL) and sat. aq $NaHCO_3$ (10 mL), and the MeOH was removed under reduced pressure. The aqueous phase was then extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extract was washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **9** as a colourless solid; yield: 1.05 g (99%); mp 44–47 °C.

Chiral GC (run isothermally at 200 °C for 40 min): t_R = 16.8 min (>99% ee).

$[\alpha]_D^{25}$ +50.7 (*c* 1.09, $CHCl_3$).

IR (KBr): 3325 (br, w), 3062 (w), 2955 (w), 2360 (w), 1743 (s), 1644 (s), 1603 (w), 1580 (w), 1538 (m), 1489 (m), 1438 (w), 1360 (w), 1268 (w), 1225 (w), 1159 (w), 1075 (w), 1028 (w), 925 (m), 802 (w), 714 (w), 668 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 2 H), 7.52–7.39 (m, 3 H), 6.71 (br d, *J* = 6.5 Hz, 1 H), 5.81–5.67 (m, 1 H), 5.18–5.12 (m, 2 H), 4.91–4.85 (m, 1 H), 3.76 (s, 3 H), 2.74–2.56 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 167.3, 134.1, 132.7, 131.9, 128.7, 127.3, 119.2, 52.5, 52.3, 36.6.

MS (ESI^+, MeOH): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{15}NNaO_3$: 256.1; found: 256.2.

Conventional Cross-Metathesis; General Procedure

In a nitrogen-filled drybox, a Fischer–Porter tube was loaded with substrate (50 mg), deoxygenated solvent, reacting olefin and catalyst (5 mol%). The system was sealed, removed from the drybox, immersed in a water bath and heated at a specified temperature for a specified period of time. The reaction mixture was then exposed to air and the solvent was removed under reduced pressure. Metathesis experiments are described using the following format: substrate (mg), catalyst (mg), reacting olefin (10 equiv), solvent (mL), reaction temperature (°C), reaction time (h). Reaction conversion into the desired cross product was determined by ^1H NMR spectroscopy. The crude product was purified by column chromatography. Chromatographic purification conditions and isolated yields (%) are listed where applicable.

Microwave Cross-Metathesis; General Procedure

In a nitrogen-filled drybox, a microwave reactor vessel was loaded with substrate (50–100 mg), deoxygenated solvent, reacting olefin and catalyst (5 mol%). The system was sealed, removed from the drybox, and microwave-irradiated and stirred at 100 °C. After 2–4 h, the reaction mixture was cooled to r.t. and exposed to air. The solvent was then removed under reduced pressure. Metathesis experiments are described using the following format: substrate (mg), catalyst (mg), reacting olefin (10 equiv), solvent (mL), reaction temperature (°C), microwave power (W), reaction time (h). Reaction conversion into the desired cross product was determined by ^1H NMR analysis. The crude product was purified by column chromatography. Chromatographic purification conditions and isolated yields (%) are listed where applicable.

(*S*)-Methyl 2-Benzamido-4-cyclopentylidenebutanoate (13)

(*S*)-Methyl 2-benzamidopent-4-enoate (**9**) was subjected to the microwave cross-metathesis procedure with methylenecyclopentane (**10**) under the following conditions: (*S*)-**9** (50 mg, 0.22 mmol), **HGII** (6.27 mg, 5 mol%), **10** (227 μL, 2.15 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 4 h (evacuate and purge with argon at time = 2 h). Purification by silica gel column chromatography (hexane–EtOAc, 3:1) gave (*S*)-**13** as a colourless crystalline solid; yield: 58.7 mg (95%); mp 74.0–76.2 °C.

Chiral GC (run isothermally at 200 °C for 40 min): t_R = 24.9 min (>99% ee).

IR (KBr): 3323 (s), 2944 (s), 1744 (s), 1641 (s), 1580 (w), 1533 (s), 1487 (s), 1435 (m), 1354 (w), 1277 (w), 1221 (m), 1200 (m), 1097 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.75 (m, 2 H), 7.52–7.39 (m, 3 H), 6.70 (br d, *J* = 7.5 Hz, 1 H), 5.23–5.16 (m, 1 H), 4.83 (dt, *J* = 7.5, 5.5 Hz, 1 H), 3.76 (s, 3 H), 2.67–2.54 (m, 2 H), 2.28–2.12 (m, 4 H), 1.64–1.55 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 167.0, 148.6, 134.3, 131.8, 128.8, 127.1, 113.1, 52.5(3), 52.5(0), 33.9, 32.6, 29.1, 26.3(7), 26.3(6).

HRMS (ESI^+, MeOH): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{21}NNaO_3$: 310.1414; found: 310.1399.

(*S*)-Methyl 2-Benzamido-4-cyclohexylidenebutanoate (14)

Table 1, Entry 1

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecyclohexane (**11**) was carried out according to the conventional cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **GII** (9.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 50 °C, 48 h. ^1H NMR analysis showed 40% conversion into compound **14**.

Table 1, Entry 2

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecyclohexane (**11**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **GII** (9.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 2 h. ^1H NMR analysis showed 60% conversion into compound **14**.

Table 1, Entry 3

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecyclohexane (**11**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 2 h. ^1H NMR analysis showed 76% conversion into compound **14**.

Table 1, Entry 4

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecyclohexane (**11**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 4 h. ^1H NMR analysis showed 79% conversion into compound **14**.

Table 1, Entry 5

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecyclohexane (**11**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 4 h (evacuate and purge with argon at time = 2 h). ^1H NMR analysis showed 99% conversion into compound **14**. The crude product was purified via silica gel column chromatography (hexane–EtOAc, 1:4) to give (*S*)-**14** as a colourless solid; yield: 60.5 mg (96%); mp 72.6–73.5 °C.

IR (KBr): 3344 (br, s), 3060 (w), 3026 (w), 2926 (s), 2852 (s), 1751 (s), 1641 (s), 1527 (s), 1489 (m), 1432 (m), 1218 (m), 1175 (m), 1101 (w), 818 (w), 721 (w), 693 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.68 (m, 2 H), 7.48–7.32 (m, 3 H), 6.62 (br d, *J* = 5.5 Hz, 1 H), 4.95 (t, *J* = 7.5 Hz, 1 H), 4.77 (dt, *J* = 7.5, 5.5 Hz, 1 H), 3.71 (s, 3 H), 2.75–2.43 (m, 2 H), 2.05–1.95 (m, 4 H), 1.50–1.25 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 167.2, 145.1, 134.3, 131.9, 128.8, 127.3, 114.2, 52.8, 52.6, 37.5, 30.0, 29.0, 28.9, 28.1, 26.9.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}NO_3$: 302.1756; found: 302.1751.

(*S*)-Methyl 2-Benzamido-4-cycloheptylidenebutanoate (15)

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecycloheptane (**12**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), **12** (236 mg, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 4 h (evacuate and purge with argon at time = 2 h). Purification by silica gel column chromatography (hexane–EtOAc, 4:1) gave (*S*)-**15** as a colourless solid; yield: 53.3 mg (79%); mp 71.8–72.4 °C.

IR (KBr): 3317 (m), 2921 (s), 2850 (m), 1743 (m), 1643 (m), 1603 (w), 1580 (w), 1532 (m), 1489 (w), 1439 (w), 1213 (w), 695 (w), 632 (w), 579 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 2 H), 7.51–7.46 (m, 1 H), 7.43–7.39 (m, 2 H), 6.71 (br d, *J* = 7.5 Hz, 1 H), 5.08 (t, *J* = 7.5 Hz, 1 H), 4.84 (dt, *J* = 7.5, 5.5 Hz, 1 H), 3.76 (s, 3 H), 2.73–2.51 (m, 2 H), 2.23–2.18 (m, 4 H), 1.53–1.45 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 167.0, 146.2, 134.1, 131.7, 128.7, 127.1, 117.8, 52.4(9), 52.4(7), 38.0, 30.5, 30.1, 29.8, 29.3, 29.1, 27.0.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{25}NNaO_3$: 338.1727; found: 338.1728.

1-Azaspirocycles 16–18 by the Telescopic Method; General Procedure

A microwave vessel was charged with (*S*)-methyl 2-benzamidopent-4-enoate (**9**; 50 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), methylenecycloalkane **10**, **11** or **12** (2.14 mmol, 10 equiv) and CH_2Cl_2 (2.0 mL). The reaction vessel was sealed and microwave-irradiated (100 W) whilst being stirred at 100 °C for 4 h (evacuate and purge with argon at time = 2 h). Then, the reaction mixture was cooled to r.t. and the solvent was removed in vacuo to afford the crude cross product as a brown oil. To the crude reaction mixture was then added a solution of TfOH (3.8 μL, 0.04 mmol) in $CHCl_3$ (4.0 mL). The system was sealed and microwave-irradiated (40 W) whilst being stirred at 50 °C. After 60 min, the reaction mixture was cooled to r.t. and quenched with sat. aq $NaHCO_3$ (10 mL). The phases were then separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil. Purification via column chromatography yielded the desired spirocyclic product **16**–**18**.

(*S*)-Methyl 1-Benzoyl-1-azaspiro[4.4]nonane-2-carboxylate (16)

In a microwave vessel under argon atmosphere, TfOH (7.4 μL, 0.083 mmol) was added to a stirred solution of (*S*)-methyl 2-benzamido-4-cyclopentylidenebutanoate (**13**; 120 mg, 0.42 mmol) in $CHCl_3$ (5.0 mL). The system was sealed and microwave-irradiated (40 W) whilst being stirred at 50 °C for 30 min. The reaction mixture was then cooled to r.t. and quenched with sat. aq $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil. Purification via silica gel column chromatography (hexane–EtOAc, 4:1) gave **16** as a colourless oil; yield: 102 mg (85%).

Yield from telescopic method: 87%.

Chiral GC: t_R = 19.8 min (>99% ee).

$[\alpha]_D^{25}$ –101.2 (*c* 1.00, $CHCl_3$).

IR (neat): 2944 (s), 2867 (s), 1744 (s), 1644 (s), 1577 (w), 1444 (m), 1394 (s), 1272 (m), 1200 (s), 1177 (s), 1106 (w), 1017 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 7.34–7.31 (m, 3 H), 7.30–7.27 (m, 2 H), 4.34 (dd, *J* = 8.0, 2.0 Hz, 1 H), 3.53 (s, 3 H), 2.79–2.57 (m, 2 H), 2.21–2.11 (m, 1 H), 2.03–1.88 (m, 5 H), 1.63–1.46 (m, 4 H).

^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 172.6, 169.7, 138.6, 128.8, 128.0, 126.1, 73.0, 63.0, 51.6, 40.7, 36.6, 36.4, 28.3, 25.0(7), 25.0(6).

The ^{1}H and ^{13}C NMR spectra were recorded at elevated temperatures, due to the presence of rotamers.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{21}NNaO_3$: 310.1414; found: 310.1409.

(*S*)-Methyl 1-Benzoyl-1-azaspiro[4.5]decane-2-carboxylate (17)

In a microwave vessel under argon atmosphere, TfOH (2.9 μL, 0.033 mmol) was added to a stirred solution of (*S*)-methyl 2-benzamido-4-cyclohexylidenebutanoate (**14**; 50 mg, 0.17 mmol) in $CHCl_3$ (5.0 mL). The system was sealed and microwave-irradiated (40 W) whilst being stirred at 50 °C for 1 h. The reaction mixture was then cooled to r.t. and quenched with sat. aq $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil. Purification via silica gel column chromatography (hexane–EtOAc, 4:1) gave **17** as a colourless solid; yield: 40.5 mg (79%); mp 116–118 °C.

Yield from telescopic method: 80%.

IR (KBr): 2935 (s), 2857 (s), 1741 (s), 1715 (w), 1642 (s), 1396 (s), 1364 (s), 1235 (w), 1212 (s), 1103 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 7.32–7.30 (m, 3 H), 7.25–7.23 (m, 2 H), 4.33 (m, 1 H), 3.54 (s, 3 H), 2.95–2.65 (m, 2 H), 2.16–2.06 (m, 2 H), 1.94–1.86 (m, 2 H), 1.81–1.74 (m, 3 H), 1.61–1.56 (m, 1 H), 1.45–1.27 (m, 4 H).

^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 172.7, 170.3, 139.0, 128.6, 127.7, 125.9, 67.9, 63.1, 51.6, 34.5, 34.3, 32.7, 27.4, 25.0, 24.5, 24.0.

The ^{1}H and ^{13}C NMR spectra were recorded at elevated temperatures, due to the presence of rotamers.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}NO_3$: 302.1756; found: 302.1752.

(*S*)-Methyl 1-Benzoyl-1-azaspiro[4.6]undecane-2-carboxylate (18)

In a microwave vessel under argon atmosphere, TfOH (2.8 μL, 0.032 mmol) was added to a stirred solution of (*S*)-methyl 2-benzamido-4-cycloheptylidenebutanoate (**15**; 50 mg, 0.16 mmol) in $CHCl_3$ (5.0 mL). The system was sealed and microwave-irradiated (40 W) whilst being stirred at 50 °C for 1 h. The reaction mixture was then cooled to r.t. and quenched with sat. aq $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil. Purification via silica gel column chromatography (hexane–EtOAc, 4:1) gave **18** as a colourless oil; yield: 40 mg (80%).

Yield from telescopic method: 67%.

IR (neat): 2920 (m), 2857 (m), 1748 (s), 1639 (s), 1447 (m), 1391 (s), 1356 (m), 1195 (m), 1173 (s), 1028 (m) cm^{-1}.

^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 100 °C): δ = 7.34–7.33 (m, 3 H), 7.28–7.26 (m, 2 H), 4.35 (dd, *J* = 8.0, 3.0 Hz, 1 H), 3.54 (s, 3 H), 2.83–2.61 (m, 2 H), 2.23–2.14 (m, 1 H), 2.03–1.99 (m, 2 H), 1.96–1.80 (m, 4 H), 1.75–1.52 (m, 5 H), 1.47–1.40 (m, 2 H).

^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 172.7, 169.9, 139.0, 128.6, 127.9, 126.0, 70.9, 63.0, 51.5, 37.9, 37.7, 37.1, 28.5, 28.2, 27.3, 24.2, 23.6.

The ^{1}H and ^{13}C NMR spectra were recorded at elevated temperatures, due to the presence of rotamers.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{26}NO_3$: 316.1907; found: 316.1912.

(±)-Methyl 2-Acetamidohex-5-enoate (19)

(±)-2-Acetamidohex-5-enoic acid (2.00 g, 11.7 mmol) was added to a stirred solution of methanolic HCl (50 mL, pH 2). After being stirred at r.t. for 18 h, the reaction mixture was diluted with sat. aq $NaHCO_3$ (50 mL), and the MeOH was removed under reduced pressure. The aqueous phase was then extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extract was washed with H_2O (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **19** as a colourless solid; yield: 2.16 g (99%); mp 57.0–58.5 °C.

IR (KBr): 3362 (br, s), 3080 (m), 2979 (s), 2929 (m), 1740 (s), 1663 (s), 1506 (s), 1466 (m), 1450 (m), 1390 (w), 1370 (w), 1313 (m), 1270 (m), 1202 (m), 1143 (m), 1097 (m), 1079 (m), 1032 (w), 915 (m), 858 (m), 813 (w), 785 (w), 759 (w), 684 (w), 640 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.07 (br s, 1 H), 5.81–5.72 (m, 1 H), 5.06–4.96 (m, 2 H), 4.66–4.58 (m, 1 H), 3.73 (s, 3 H), 2.09–2.06 (m, 2 H), 1.99 (s, 3 H), 2.01–1.73 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 170.1, 136.9, 115.6, 53.4, 51.8, 31.5, 29.5, 22.3.

MS (ESI$^+$, MeOH): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{15}NNaO_3$: 208.1; found: 208.0.

Attempted Synthesis of Methyl 2-Acetamido-5-cyclohexylidenepentanoate (22)

The cross-metathesis of (±)-methyl 2-acetamidohex-5-enoate (**19**) and methylenecyclohexane (**11**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (±)-**19** (38.9 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 4 h (evacuate and purge with argon at time = 2 h). The reaction mixture was concentrated in vacuo and gave a chromatographically inseparable mixture of alkenes **21** and **22** in ca. 1:4 ratio. Further attempts to isolate compound **22** were unsuccessful.

Attempted Synthesis of Methyl 1-Acetyl-1-azaspiro[5.5]undecane-2-carboxylate

In a microwave vessel under argon atmosphere, TfOH (2.9 μL, 0.033 mmol) was added to a stirred solution of a mixture of alkenes **21** and **22** (1:4) in $CHCl_3$ (5.0 mL). The system was sealed and microwave-irradiated (40 W) whilst being stirred at 50 °C for 1 h. The reaction mixture was then cooled to r.t. and quenched with sat. aq $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Analysis of the residue by ^{1}H NMR spectroscopy showed a mixture of compounds **23** and **24**.

[(*S*)-1-Benzyl-1-azaspiro[4.5]decan-2-yl]methanol (25)

Freshly distilled THF (3.0 mL) was added to $LiAlH_4$ (65.0 mg, 1.71 mmol) under an inert atmosphere. The resultant grey suspension was cooled to 0 °C before a solution of (*S*)-methyl 1-benzoyl-1-azaspiro[4.5]decane-2-carboxylate (**17**; 172 mg, 0.571 mmol) in THF (2.0 mL) was added dropwise via syringe. The reaction mixture was stirred for a further 16 h at r.t. Upon complete conversion of the starting material **17**, the reaction mixture was quenched by sequential addition of H_2O (0.4 mL), 20% NaOH solution (0.4 mL) and H_2O (0.8 mL). Vigorous gas formation was observed and further stirring resulted in a white suspension. The reaction mixture was dried ($MgSO_4$), filtered and concentrated in vacuo to give a clear oil. Purification by silica gel flash chromatography (EtOAc–hexane, 1:3) gave **25** as a colourless oil; yield: 105 mg (71%).

IR (neat): 3441 (br, s), 3085 (m), 3062 (m), 3028 (s), 2921 (s), 1603 (w), 1493 (s), 1453 (s), 1394 (m), 1356 (m), 1322 (m), 1255 (m), 1209 (m), 1184 (m), 1132 (m), 1078 (m), 1029 (m), 963 (w), 942 (w), 904 (m), 880 (w), 847 (w), 825 (w), 737 (m), 700 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.11 (m, 5 H), 4.02 (d, *J* = 14.5 Hz, 1 H), 3.22 (d, *J* = 14.5 Hz, 1 H), 3.02 (dd, *J* = 11.0, 1.5 Hz, 1 H), 2.94–2.90 (m, 1 H), 2.83 (dd, *J* = 11.0, 3.0 Hz, 1 H), 2.00 (br s, 1 H), 1.94–0.98 (m, 14 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 128.5, 127.8, 126.9, 66.0, 65.5, 63.5, 52.2, 38.6, 33.8, 28.3, 26.5, 26.2, 24.8, 24.1.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{26}NO$: 260.2009; found: 260.2012.

(*S*)-1-Benzyl-2-(chloromethyl)-1-azaspiro[4.5]decane (26) and (*S*)-1-Benzyl-3-chloro-1-azaspiro[5.5]undecane (27)

Carbon tetrachloride (48.0 μL, 0.49 mmol) was added to a stirred solution of [(*S*)-1-benzyl-1-azaspiro[4.5]decan-2-yl]methanol (**25**; 115 mg, 0.44 mmol) in $CHCl_3$ (4.0 mL). The reaction mixture was cooled to 0 °C before a solution of Ph_3P (128 mg, 0.49 mmol) in $CHCl_3$ (2 mL) was added dropwise via syringe. The reaction mixture was stirred at r.t. for 72 h and then concentrated in vacuo to give a yellow oil. Purification by silica gel flash chromatography (EtOAc–hexane, 1:10) gave compound **26**, and the isomeric piperidine isomer **27**, as an inseparable 1:1 mixture; yield: 79 mg (64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (compound **26**) = 7.38–7.19 (m, 5 H), 4.11 (d, *J* = 15.0 Hz, 1 H), 3.45 (d, *J* = 15.0 Hz, 1 H), 3.18–3.10 (m, 1 H), 2.96 (dd, *J* = 12.0, 3.0 Hz, 1 H), 2.87 (dd, *J* = 12.0, 1.0 Hz, 1 H), 2.09–1.28 (m, 14 H); δ (compound **27**) = 7.38–7.19 (m, 5 H), 4.03–3.93 (m, 1 H), 3.96 (d, *J* = 15 Hz, 1 H), 3.43 (d, *J* = 15.0 Hz, 1 H), 2.85–2.81 (m, 1 H), 2.73 (dd, *J* = 12.0, 9.0 Hz, 1 H), 2.09–1.28 (m, 14 H).

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{25}{}^{35}ClN$: 278.1676; found: 278.1669; *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{25}{}^{37}ClN$: 280.1646; found: 280.1641.

(*R*)-1-Benzyl-1-azaspiro[5.5]undecan-3-yl Thiocyanate (29)

Carbon tetrabromide (194 mg, 0.586 mmol) was added to a stirred solution of [(*S*)-1-benzyl-1-azaspiro[4.5]decan-2-yl]methanol (**25**; 75.9 mg, 0.293 mmol) in $CHCl_3$ (2.0 mL). The reaction mixture was cooled to 0 °C before a solution of Ph_3P (84.5 mg, 0.322 mmol) in $CHCl_3$ (2.0 mL) was added dropwise via syringe. The reaction mixture was stirred at r.t. for 24 h and then concentrated in vacuo to give a yellow oil. The residue, containing crude bromide **28**, was dissolved in acetone (5.0 mL) and potassium thiocyanate (287 mg, 2.93 mmol) was added. The reaction mixture was stirred for a further 12 h and then concentrated in vacuo to give a white solid. Purification by silica gel flash chromatography (EtOAc–hexane, 1:10) gave **29** as an off-white solid; yield: 63.0 mg (72%); mp 89.4–90.2 °C.

Chiral HPLC: t_R = 11.0 min (minor enantiomer) and 13.0 min (major enantiomer), 88% ee.

$[\alpha]_D^{25}$ –49.2 (*c* 1.00, CH_2Cl_2).

IR (KBr): 3021 (w), 2929 (s), 2853 (s), 2150 (s), 1493 (w), 1455 (s), 1447 (s), 1419 (w), 1368 (w), 1316 (w), 1224 (m), 1208 (m), 1194 (m), 1127 (m), 1074 (m), 1009 (w), 888 (w), 754 (m), 728 (s), 698 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.15 (m, 5 H), 4.00 (d, *J* = 14.0 Hz, 1 H), 3.26 (d, *J* = 14.0 Hz, 1 H), 3.24–3.19 (m, 1 H), 2.56 (dd, *J* = 12.5, 2.0 Hz, 1 H), 2.43 (dd, *J* = 12.5, 5.0 Hz, 1 H), 2.11–0.92 (m, 14 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 128.4, 128.3, 127.1, 114.2, 66.4, 63.2, 52.2, 41.7, 38.1, 33.1, 28.8, 27.9, 26.1, 24.8, 24.1.

HRMS (ESI$^+$, MeOH): *m/z* $[M + H]^+$ calcd for $C_{18}H_{25}N_2S$: 301.1733; found: 301.1735.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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