KINGSTON
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APPROACHES TOWARDS

A

STEREOSELECTIVE NICHOLAS

REACTION

Julien Millet

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Abstract

This programme of work has focused on developing ways of inducing stereoselectivity into the Nicholas reaction towards the synthesis of natural products.

The first chapter of the thesis reviews the developments of the Nicholas reaction since its discovery in 1972 as well as other applications of cobalt clusters. The following chapter describes chirality and various approaches towards asymmetric synthesis.

Chapter 3 details our investigations as well as the results that we achieved in the two areas we explored.

The first part of the project attempted to determine which oxazolidinone derivative would provide optimum levels of selectivity in 1, 4-conjugate addition reactions, and then investigate such derivatives in the Nicholas reaction. It was found that oxazolidinones bearing a phenyl group at the C4 position induced much higher levels of stereoselectivity than those with benzyl or methyl groups at the C4 position. Although 4-phenyl-2-oxazolidinone provided optimum levels of diastereoselectivity in the asymmetric conjugate addition reaction of pentenyl organometallic reagents, it proved less efficient when applied sequencially in an intermolecular Nicholas reaction. In contrast, 4-methyl-2-oxazolidinone provided poor selectivity in an asymmetric conjugate addition reaction; however it was the auxiliary of choice for the corresponding Nicholas reaction providing optimum levels of diastereoselectivity.

In the second part of our project, we focused on studying the intramolecular Nicholas reaction carried out upon optically active propargyl alcohols derived from citronellal. These were prepared from two different approaches. In the first approach, racemic propargyl alcohols were prepared *via* a Grignard reaction, then oxidised to the

corresponding ketone before being reduced to the optically pure alcohol *via* a stereoselective reduction using alpine borane®.

In the second approach, optically active propargyl alcohols were prepared *via* zinc catalysed asymmetric alkynylation reactions. After complexation of these propargyl alcohols to cobalt octacarbonyl, the addition of a Lewis acid led to the intramolecular Nicholas cyclisation reaction providing tri-substituted six membered rings in 55% yield. The results show that the reactions carried out on opposite diastereoisomers or racemic mixture provided the same mixture of diastereoisomers of the cyclised products.

The final chapter describes all the experimental procedures that were carried out as well as the characterisation of every compound presented in this document.

Acknowledgements

Firstly, I would like to thank my supervisor, Dr Liz Tyrrell, for giving me the opportunity to work as a research assistant in the final year of my undergraduate studies. This is where I understood what I wanted to do for the next few years of my life, and Liz gave me the opportunity to carry it out. I am not sure I could have gone through all the ups and downs that I encountered during this period without the help, support and guidance of a great supervisor.

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Finally, last but not least, I am grateful to all my family, Laure, and my friends, back in France, who have supported me during the eight years that I spent in Kingston.

Abbreviations

atm	atmosphere
9-BBN	9-borabicyclo[3.3.1]nonane
$BF_3 \cdot OEt_2$	boron trifluoride diethyl etherate
Boc_2O	ditert-butyldicarbonate
n-BuLi	butyllithium
Bu_2BOTf	dibutylboron triflate
CAN	ceric ammonium nitrate
$CuBr \cdot Me_2S$	copper bromide dimethyl sulphide complex
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de values	diastereoisomeric excess
DIPEA	N,N'-diisopropylethylamine
dr values	diastereoisomeric ratio
DMAP	4-dimethylaminopyridine
eq.	equivalents
EtOH	ethanol
Et_2AlCl	diethylaluminium chloride
$Fe(NO_3)_3$	ferric nitrate
GC-MS	gas chromatography with mass spectroscopy
H_2O_2	hydrogen peroxide
$HF \cdot SbF_5$	fluoroantimonic acid
$HBF_4 \cdot Et_2O$	tetrafluoroboric acid diethyl etherate
HMDS	1,1,1,3,3,3-hexamethyldisilazane
^1H NMR	Proton nuclear magnetic resonance

^{13}C NMR	carbon nuclear magnetic resonance
NOEDS	nuclear Overhauser effect difference spectra
NOE	nuclear Overhauser effect
HRMS	high resolution mass spectroscopy
IR	infrared
$(iPr)_2NEt$	*N,N*-diisopropylethyl amine
KOH	potassium hydroxide
K_2CO_3	potassium carbonate
LDA	lithium diisopropylamide
MeOH	methanol
Me_2AlCl	dimethylaluminium chloride
mmol	millimoles
MTPACl	methoxy-trifluoro-methylphenylacetyl chloride
$NaBH_4$	sodium tetrafluoroborate
$NaHCO_3$	sodium bicarbonate
NEt_3	triethylamine
NME	*N*-methylephedrine
THF	tetrahydrofuran
PCC	pyridinium chlorochromate
Ph_3CCl	triphenylcarbenium chloride
ppm	parts per million
PTSA	*para*-toluenesulfonic acid
RAMP	(R)-aminopyrrolidine
SAMP	(S)-aminopyrrolidine
$SOCl_2$	thionyl chloride

TEA	triethylamine
$TiCl_4$	titanium tetrachloride
TLC	thin layer chromatography
TBDMSCl	*ter*-butyldimethylsilyl chloride
TMSCl	chlorotrimethylsilane
$Zn(OTf)_2$	zinc triflate

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1.0 Introduction

This research programme has focused on developing methodologies to induce stereocontrol into the Nicholas reaction.[1] In order to reach that goal several strategies were used. Primarily, the use of chiral auxiliaries was investigated. The second approach has focused on using a starting material from the chiral pool and the use of asymmetric reagents to prepare enantiomerically pure compounds that would undergo an intramolecular Nicholas Reaction.

1.1 The Nicholas reaction

The main characteristic of the Nicholas reaction is the complexation of cobalt octacarbonyl to an alkyne in order to stabilise the carbocationic charge generated at the propargylic position prior to a reaction with a nucleophile.

1.1.1 Dicobalt octacarbonyl complex

Although hardly any metallic cobalt was used until the twentieth century, its ores have been used for thousands of years to confer a blue colour to glass and pottery. Cobalt belongs to the transition metal category in the periodic table, and although widely distributed, stands thirtieth in the order of abundance. Because it possesses an odd number of valence electrons cobalt can only satisfy the 18-electron rule in its carbonyl complexes if metal-metal bonds are present.

A characteristic feature of *d*-group transition metal atoms is their ability to form complexes with a variety of neutral molecules. The vacant π orbitals of ligands such as carbon monoxide can accept electrons from filled metal orbitals

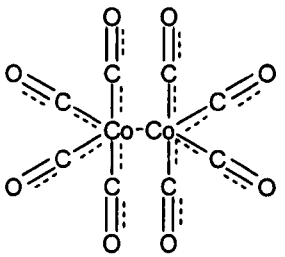
to form a type of π bonding that supplements the σ bonding from lone-pair donation.[2]

The 18-electron rule, as applied to binuclear metal carbonyls, states that the electrons in metal-metal bonds should be divided evenly between the two metals. Terminal carbon monoxide groups are considered to donate two electrons while the bridging carbonyl groups contribute one electron to each metal atom.

The 18-electron rule for dicobalt octacarbonyl

Cobalt	9 valence electrons
Terminal CO groups	2 × 3 = 6 electrons
Bridge CO groups	1 × 2 = 2 electrons
Co-Co bond	1 electron
Total	18 electrons

In order to determine the correct structure of dicobalt octacarbonyl, extensive spectral studies were undertaken in the 1950's. Investigations using infrared technology showed that dicobalt octacarbonyl contains two types of carbonyl groups, bridge and terminal.[3] Several proposed structures emerged from this work before being reduced to only two possible structures, the first in which all of the carbonyl groups were terminal (1), and another in which two of the carbonyl groups were bridging (2).



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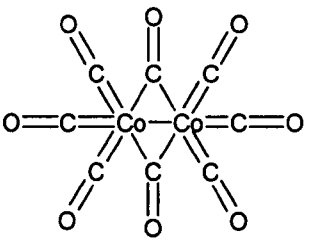


2

Figure 1.

The infra-red spectrum (IR) of dicobalt octacarbonyl shows the presence of three carbon monoxide type carbonyl bands at 2070, 2043 and 2025 cm^{-1} as well as a ketone like carbonyl at 1858 cm^{-1}. There was also the possibility that two or more molecular forms were responsible for the two sets of bands. In order to either confirm or reject that hypothesis, the spectrum of the vapour state and of solutions of different concentrations were investigated. No change in the relative intensities of the bands in both cases confirmed the structure containing two bridge carbonyl groups and six terminal carbonyl groups as the only possible one.[4]

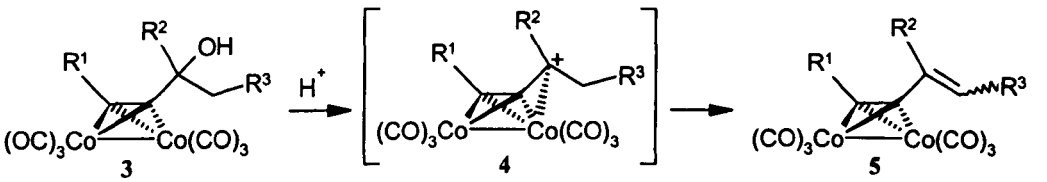
Dicobalt octacarbonyl loses two molecules of carbon monoxide when it complexes with an alkyne, this enabled chemists to use it as a protecting group for carbon-carbon triple bonds. Upon complexation, dicobalt hexacarbonyl bridges the carbon-carbon triple bond, forming four bonds involving the π electrons from the triple bond.

At the time, IR spectra of a wide range of acetylene compounds complexed to cobalt hexacarbonyl were studied. These showed that the carbon monoxide type carbonyls were still present, whereas both bands accounting for the carbon-carbon triple bond and the bridge carbonyls were absent.[5] This observation suggested that the two bridge carbonyl groups were lost in the

complexation with the carbon-carbon triple bond. It was also noticed that in the case of terminal acetylenes being complexed to dicobalt octacarbonyl, the band corresponding to the triple bond also disappeared, leading to the conclusion that there is no carbon-carbon triple bond in acetylenic dicobalt hexacarbonyl complexes, or that more sp^2 characteristics are present upon complexation.[6]

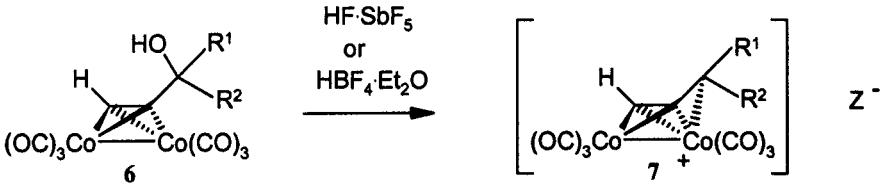
1.1.2 The Nicholas reaction

Kenneth M. Nicholas first reported the stabilisation effects of the cobalt complex in 1971 while investigating the use of the dicobalt octacarbonyl as a protecting group for triple bonds.[7] He then went on to report the ready acid-catalysed dehydration of complexed propargyl alcohols (3) into 1,3-enyne derivatives (5) (Scheme 1).[8]



Scheme 1.

Although isolation of the cation proved elusive, dissolution of either 3 or 5 in *d*-fluoroacetic acid produced the cation (4), observable by ^1H NMR. These results lead Nicholas and Pettit to the conclusion that the likely intermediates, propargylium dicobalt hexacarbonyl cations, possessed considerable stability. Later in the studies stable salts of such cations (7) were isolated as dark red solids upon protonation of propargyl alcohol complexes (6) with excess of $HF{\cdot}SbF_5$ or $HBF_4{\cdot}Et_2O$ at -45 °C (Scheme 2). The rationale behind these experiments was to determine the structural characterisation of these cations.[9]



Scheme 2.

The IR spectra of the studied salts indicated a significant charge delocalisation onto the dicobalt hexacarbonyl moiety. The carbonyl group absorptions for the complexed propargyl alcohol typically appear at 2025, 2050 and 2090 cm^{-1}, whereas these values shift to 2085, 2150 and 2130 cm^{-1} for the propargyl carbocation. These increases are consistent with greater C-O bonding as is expected from a decreased $d(Co) \rightarrow \pi^*$ (CO) donation from the *d* orbital electrons in cobalt towards the π^* orbitals of the carbon monoxide groups in the electron deficient cations.

In the same manner, ^1H NMR resonances of alkyl groups α- to the cationic centre experience small deshielding effects as well as the ^{13}C NMR resonances of the co-ordinated C≡C-C system.[10] These observations all confirmed the idea of a significant charge dispersal in the alkynyl-($Co_2(CO)_6$) system that results from an interaction of the electron deficient propargylic carbon with both cobalt tricarbonyl units.

Since these early investigations towards a full characterisation and a better understanding of such propargyl carbocations, the interest in their properties and applications has kept on growing. Schreiber[11] proposed a structure for dicobalt hexacarbonyl propargyl complexes which features a bending of the propargylic carbon towards one of the cobalt atoms with two distinct fluxional processes. A lower energy fluxional process was observed respectively with cations (8) and (9) and (10) and (11) which resulted in the interconversion of

diastereotopic groups only (Figure 2). The enantiomerisation between (8) and (9) results from the antarafacial migration of the alkylidene ligand from one cobalt tricarbonyl unit to the other. The higher energy fluxional process interconverts the *syn* and *anti* isomers and can occur in two different processes, either by a 180° rotation of the alkylidene ligand or a 120° rotation with suprafacial migration. The proposal resulted from variable temperature NMR spectroscopic analysis.

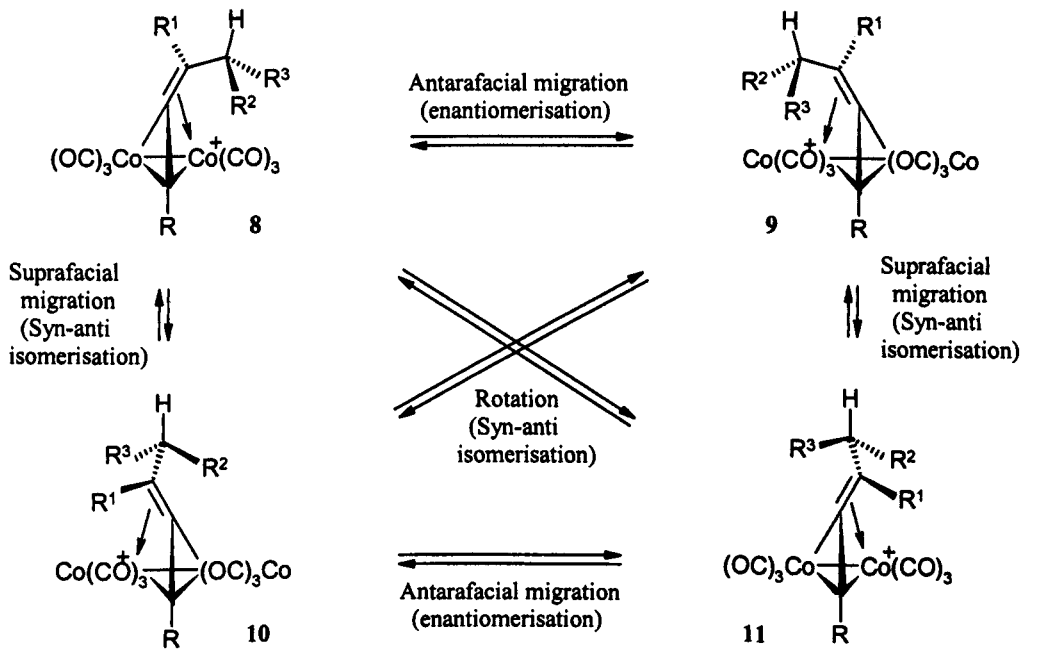
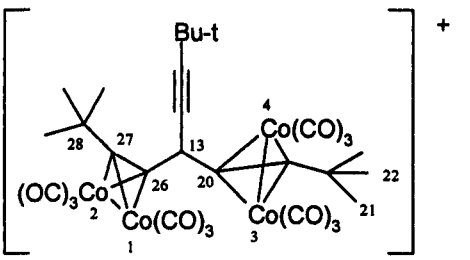


Figure 2.

Schreiber suggested that the dynamic behaviour of these stabilised organo-cobalt cations has a relevance to the stereochemistry of the propargylic substitution reaction. If the Lewis acid mediated alkylation reaction occurs with a static cobalt cation then the stereochemistry would be retained. However the fluxional properties of the cations have a direct effect on the nucleophilic attack. The antarafacial migration and rotation processes show the

opposite enantiopic face to the nucleophile and the suprafacial migration preserves exposure of the kinetically formed enantioface of the ethylidene ligand. This means that the stereospecificity of the nucleophilic attack depends on the relative rates of alkylation and enantiomerisation.

Confirmation of Schreiber's assertions came when the Melikyan group were able to isolate a crystalline sample of propargyl dicobalt hexacarbonyl complex (12) and performed X-ray crystallographic structural analysis (Figure 3).[12] The analysis showed distinct differences in each of the sets of the two C_{α}^{+}-Co distances for the to $Co_2(CO)_6$ units, substantial dihedral angles about the C_{α}-CC-$C_{\alpha'}$ bonds and a nearly perfect sp^2 hybridised, trigonal planar orientation at the propargylic carbon.



12

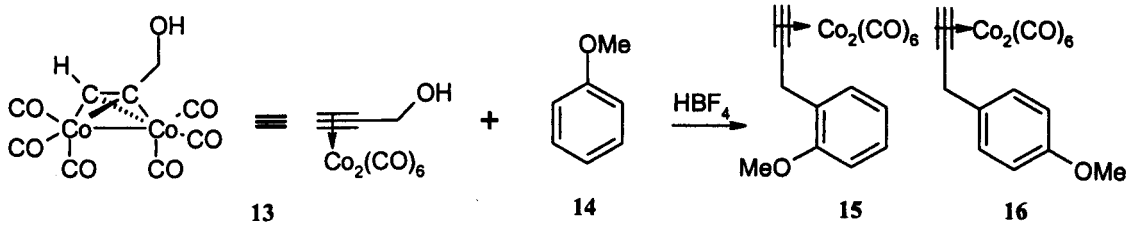
C(13)-C(26)-C(27)-C(28) = 55°
C(13)-C(20)-C(21)-C(22) = 43°
C(13)-Co(1) = 3.07 Å
C(13)-Co(2) = 2.81 Å
C(13)-Co(3) = 3.27 Å
C(13)-Co(4) = 2.89 Å

Figure 3. Crystal structure of a cobalt stabilised propargyl cation.

While much attention had been concentrated on characterising and understanding these propargyl dicobalt hexacarbonyl intermediates, interest also turned towards their reaction with a wide variety of nucleophiles.

1.1.2.1 Aromatic nucleophiles

As reported by Nicholas, the reaction of propargyl dicobalt hexacarbonyl carbocations with electron-rich aromatic compounds, such as anisole (14) (Scheme 3), phenol or N,N-dimethylaniline, proceeds in good to excellent yield at room temperature and below.

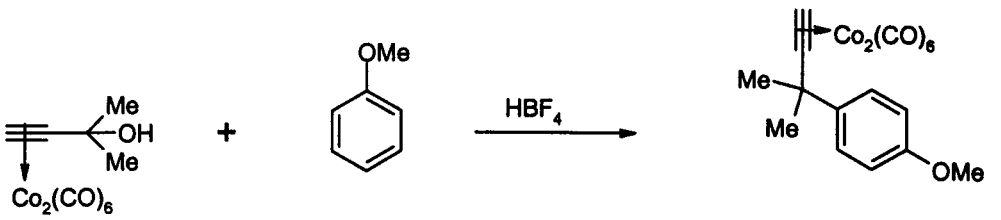


13 14 15 16

36 : 41

Scheme 3.

The presence of the methoxy group, an electron donating group, directs the reaction on the *ortho/para* positions. Hence the reaction of anisole (14) with dicobalt hexacarbonyl propargyl alcohol (13) yields a mixture of the ortho and para products (15) and (16). This can be avoided by using a bulkier propargyl alcohol such as 2-methyl-3-butyn-2-ol (17) (Scheme 4) in the reaction that only yields the *para* substituted compound (18).[13]

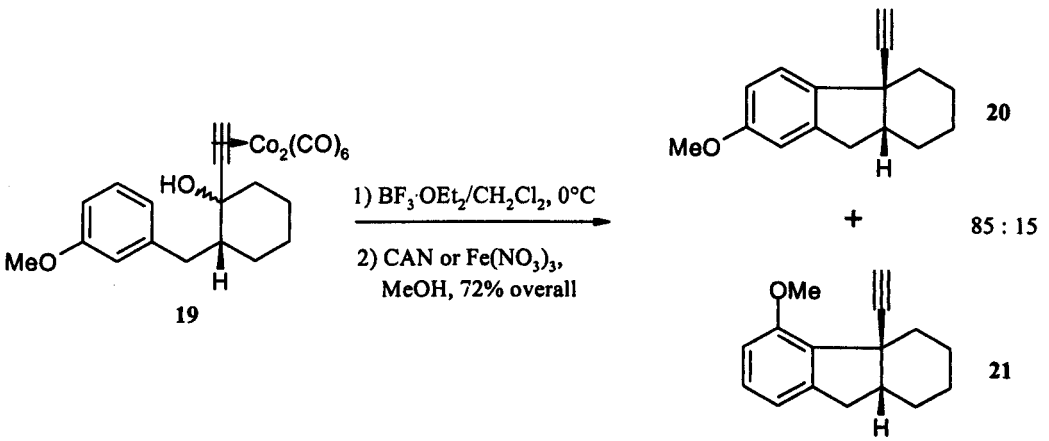


17 14 18

Scheme 4.

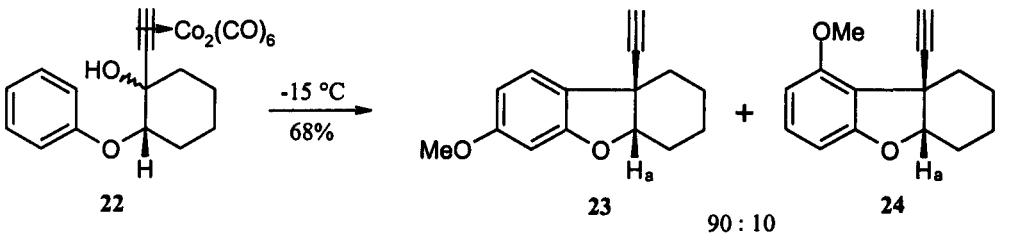
Many other aromatic compounds have been used as nucleophiles in the Nicholas reaction. Grove *et al.* decided to utilise such compounds to determine whether the Friedel-Crafts cyclisation of diastereomeric alcohols would be a

stereospecific or stereoconvergent process. Following Schreiber's proposal on the fluxional properties of propargyl dicobalt hexacarbonyl cations, Grove predicted that the intramolecular cyclisation of compound (19) would yield the *cis* isomers of (20) and (21) provided that the ring closure was slower than the migratory processes (Scheme 5).[14]



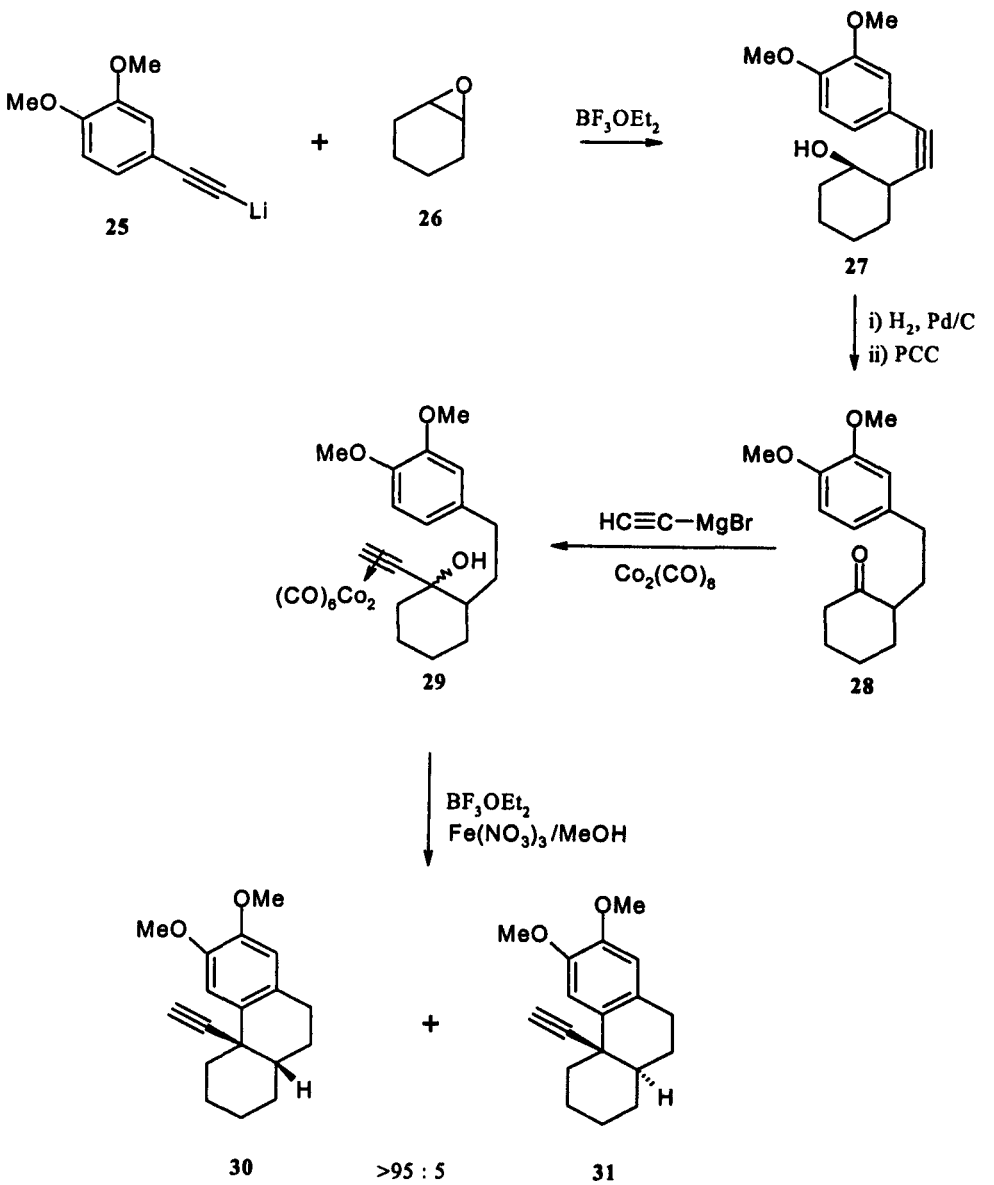
Scheme 5.

At that stage it was not possible to identify whether the *cis* or *trans* isomer had been formed; nevertheless ^{1}H NMR analysis clearly showed that a single stereoisomer had been formed. The same reaction without the methoxy group or with the methoxy group in the *para* position only provided a less substituted enyne. A further reaction allowed confirmation of the expected *cis* configuration of the cyclised product. The reaction was carried out with an oxygen-linked substrate (22), which cyclised under the same conditions as (19) to yield a mixture of (23) and (24) (Scheme 6). The *cis* stereochemistry was confirmed using NOEDS NMR studies after conversion of the triple bond to an ethyl group. Mutual enhancement between H_a and the protons of the ethyl group supported the conclusion.



Scheme 6.

Using this approach, Grove *et al.* developed a methodology using the dicobalt hexacarbonyl-(alkyne) moiety as a stereocontrol element in intramolecular Friedel-Crafts alkylations towards morphinan-based compounds (Scheme 7).[15]

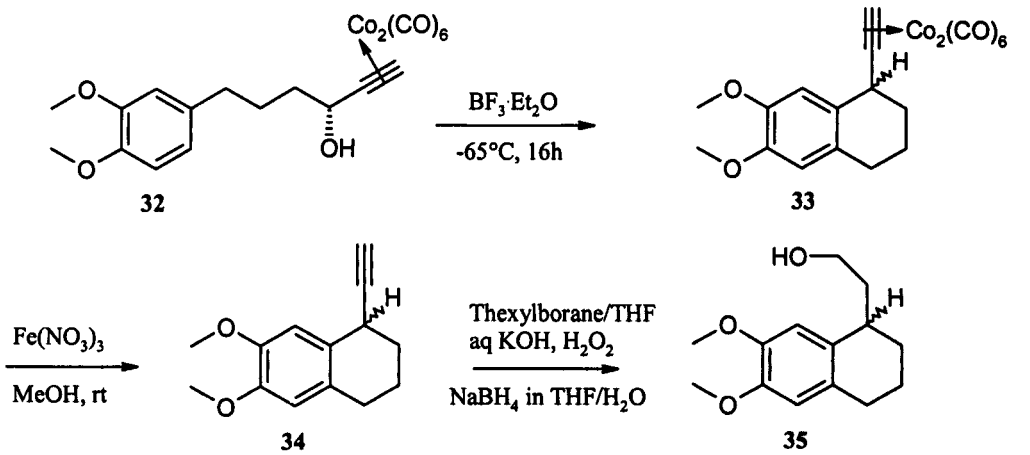


Scheme 7.

The lithium anion (25) was generated from the corresponding alkyne with butyllithium, then treated with $BF_3 \cdot OEt_2$ at -78 °C and reacted with cyclohexane oxide (26) to give the alkynol (27). Hydrogenation of the triple bond followed by oxidation with PCC yielded compound (28) which in turn was reacted with ethynylmagnesium bromide and dicobalt octacarbonyl to give the complex (29). The complex was then cyclised upon addition of $BF_3 \cdot OEt_2$ at -78°C and decomplexed *in situ*. The reaction yielded a mixture of compounds (30) and (31). The same strategy was repeated with a proton in place of the methoxy group situated *para* to the alkyne chain. When carried out at -78 °C the ratio of products in the mixture was similar but the reaction gave a slightly lower yield than with the two methoxy groups. This reaction was also carried out at 0°C, affording a 10 : 1 mixture with a 54 % yield. Proton NMR and X-ray analysis confirmed the presence of a major regio- and stereo-isomer with the *cis* stereochemistry at the ring juncture. Finally, carrying out the reaction using the same conditions, but cobalt-free, gave no cyclised product. Thus, proving the presence of the cobalt hexacarbonyl moiety essential for these Friedel-Crafts reactions to proceed in good yield.

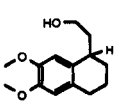
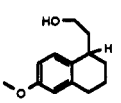
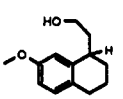
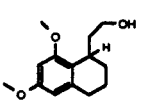
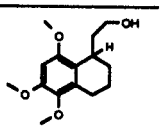
Other approaches were developed towards enantiospecific Nicholas reactions. Muehldorf *et al.*[16] constructed a series of aromatic compounds designed to study the possibility of enantiospecific cyclisation reactions under the Nicholas reaction conditions. The idea was to investigate the possibility that compounds such as (32) might retain their chirality after undergoing an intramolecular Nicholas cyclisation reaction. The cyclised product (34) proved unstable, and was therefore converted to the hydroxyl derivative (35), via a hydroboration-

oxidation reaction, which was shown to retain the enantiomeric purity initially present in the alkyne (Scheme 8).



Scheme 8.

Among the various solvents tested for these reactions, dichloromethane gave the best results. The most appropriate Lewis acid was boron trifluoride diethyl etherate. As mentioned above, several compounds were synthesised with 1, 2 or 3 methoxy groups on the benzene ring. The reactions were also carried out at different temperatures. The results are listed in Table 1.

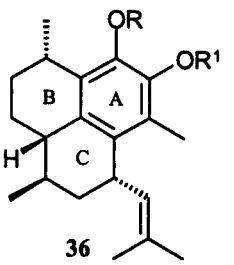
Products					
Rxn temp.	-65°C	-55°C	-25°C	-40°C	-30°C
Corr. ee	97%	71%	0%	88%	23%
Yield*	72%	68%	73%	72%	53%

*Yields are overall from complexation to hydroboration-oxidation included

Table 1.

The effect of the size of the ring, formed by the intramolecular Nicholas reaction, on the enantiomeric excess was also studied and the best results were obtained when a 6-membered ring was formed.

Kocienski and co-workers have used a similar ring closure methodology in their approach to the synthesis of pseudopterosin G aglycone (36) (Figure 4).

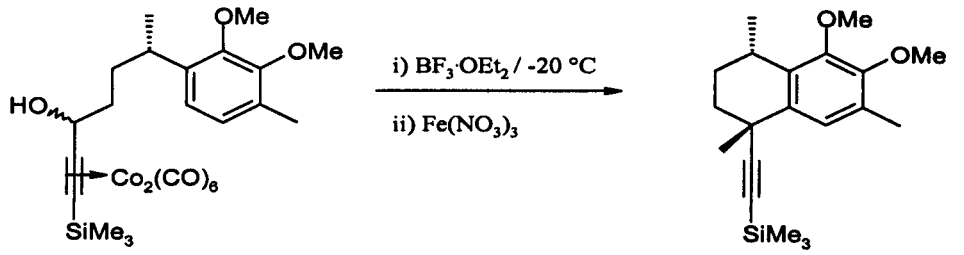


36

R: 2-Methyltetrahydropyran-3,4,5-triol, Me, H.
R^1: Me, H.
$R = R_1 = CH_2$

Figure 4.

The pseudopterosin family is a group of 12 compounds which only differ in their stereochemistry and the substituents on the aromatic ring. In this synthesis, the intramolecular Nicholas cyclisation reaction was used for the formation of the second ring (B). The precursor to complex (37) was prepared in four steps before complexation with dicobalt octacarbonyl. The cyclisation step was carried out at -20°C, using boron trifluoride diethyl etherate with a recorded yield of 65% after decomplexation using ferric nitrate. The cyclised product (38) was obtained with a diastereoisomeric ratio of 95:5. The *dr* value was determined by NMR spectroscopy but confirmation of the stereochemistry could only be ascertained in the later stages of the full synthesis of (36) where $R = R^1 = Me$ (Scheme 9). The desired compound (36) was recrystallised from methanol, allowing an X-ray analysis to be undertaken from which the stereochemistry was confirmed.[17]

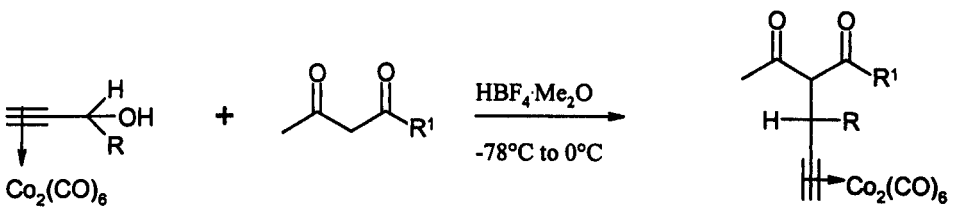


37 38

Scheme 9.

1.1.2.2. β-Dicarbonyl nucleophiles

Nicholas was first to report the facile alkylation of β-dicarbonyl compounds (40) with dicobalt hexacarbonyl complexed propargyl alcohols (39). All reactions were reported to achieve good to excellent yields, with no side products generated (Scheme 10).[18]



39 40 41 (a-f)

Scheme 10.

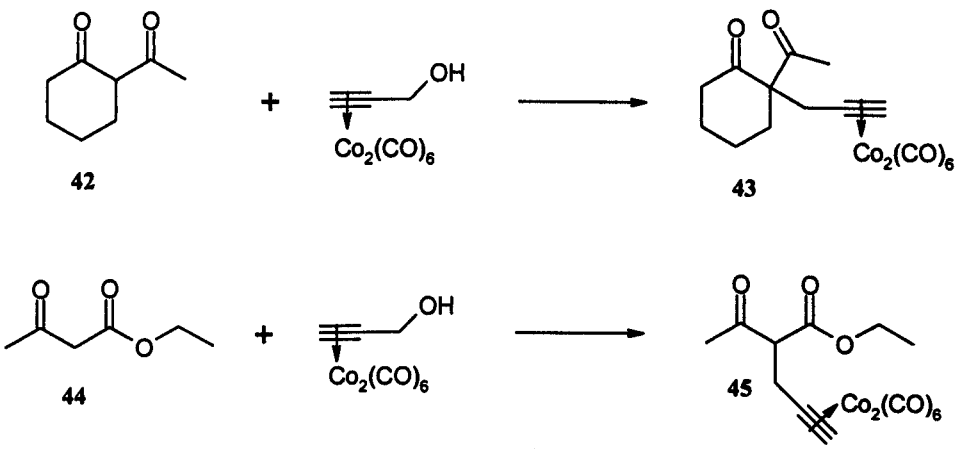
A series of compounds was generated from this methodology with different R and R^1 groups. The results obtained are listed in Table 2.

Reaction	R	R^1	Yield of (41)	
1	H	CH_3	a	95%
2	CH_3	CH_3	b	65%
3	Ph	CH_3	c	91%
4	H	Ph	d	90%
5	CH_3	Ph	e	65%
6	Ph	Ph	f	95%

Table 2.

Only four of these intermolecular Nicholas reactions (5 and 6) generated a new asymmetric centre. The ratios of diastereoisomers formed were deduced by examining the corresponding ^1H NMR spectra and gave 65:35 and 80:20 for reactions (5) and (6) respectively. However, when the synthesis of (41f) was repeated at -78°C, instead of 0°C, and quenched with solid $NaHCO_3$, the ratio of diastereoisomers increased to 93:7.

The alkylation of 2-acetylcyclohexanone (42) and the β-ketoester ethylacetoacetate (44) were also reported by Nicholas and Hodes (Scheme 11). Although these reactions both provided compounds, (43) and (45), with newly generated stereogenic centres, the levels of stereoselectivity were not reported at that point.

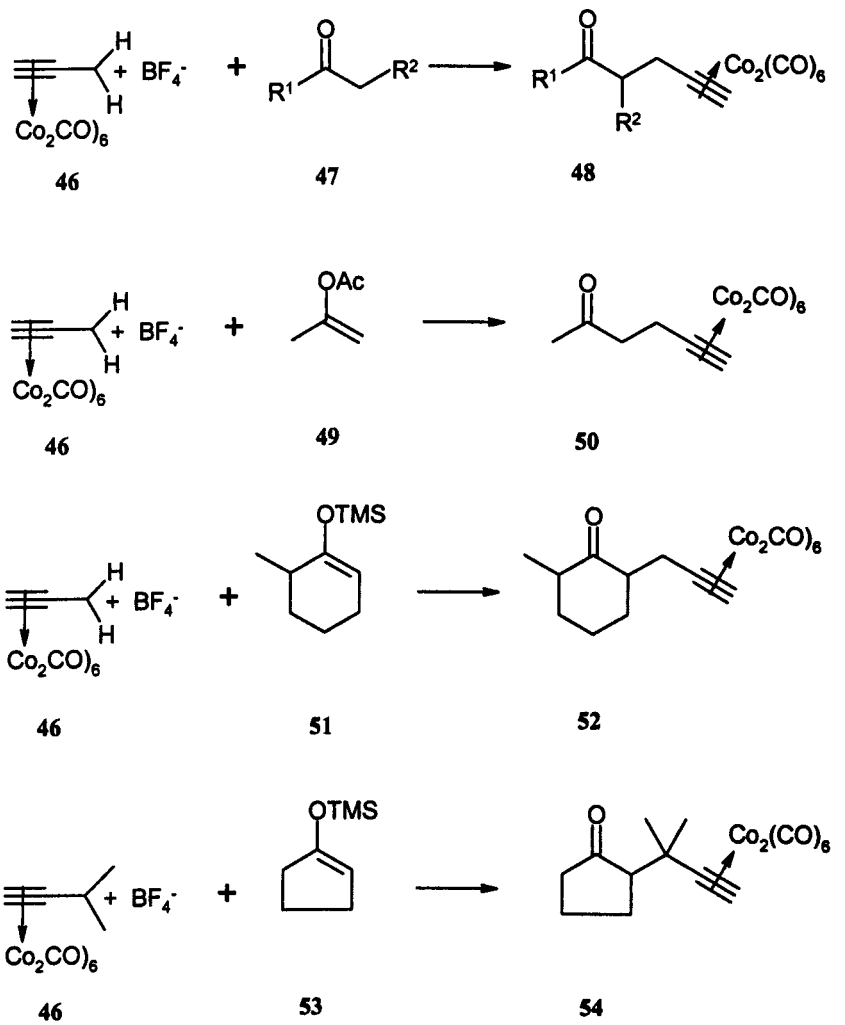


Scheme 11.

1.1.2.3 Ketone and enol derivatives as nucleophiles

Following the reports of the facile alkylation of aromatic and β-dicarbonyl nucleophiles, attention turned towards ketone nucleophiles. Nicholas reported the discovery of a reaction between cobalt complexed propargylic cation salts and acetone while testing the later as an NMR solvent.[1]

The reactions were carried out at or below 0 °C by dissolution of complex (46) in an excess of the dry ketone (47). The reaction, which proceeds *via* the enol tautomer, produces *mono* α-alkylated products (48) in good to excellent yields and with very good regioselectivity with asymmetric ketones. The degree of selectivity being extremely high, above 95 %, is consistent with a mechanism that involves attack by the complex at the more substituted α-carbon. The fact that the Nicholas reaction using ketones as nucleophiles proceeds *via* the enol tautomer, led to new investigative studies of such reactions carried out with carbonyl enol derivatives such as enol acetate (49) and trimethylsilyl enolethers (51) and (53), (Scheme 12).[19]



Scheme 12.

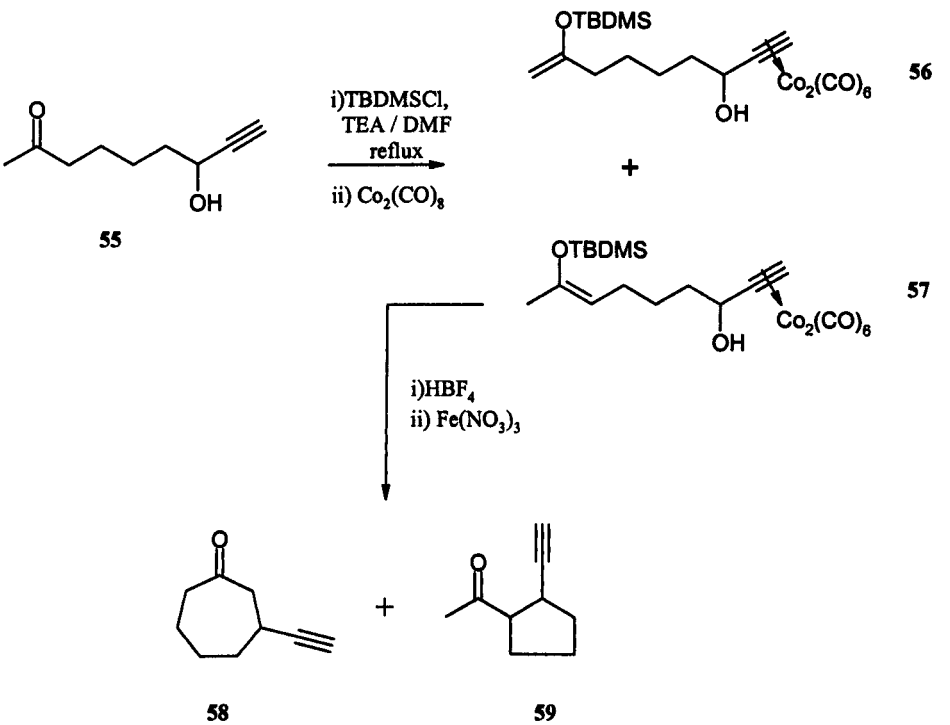
All these reactions were carried out at 0°C and produced the desired compounds in the range of 60 to 100% yield. Further investigation by Schreiber *et al.* shed more light on the stereochemistry of these alkylation reactions of silylenol derivatives. By creating a series of compounds with different size substituents at the propargylic carbon it was possible to ascertain that bulkier groups provide higher stereoselectivity where the *syn* diastereoisomer predominated.[20]

It is to be noted that Nicholas also conducted an investigation on the stereoselective coupling of alkynyl acetal cobalt complexes with enol silanes.[21] The investigation was also conducted on a series of compounds where the influence of the reaction parameters on stereoselectivity were studied. The alkylation involving cyclised enol silane gave much better results when conducted at 0°C whereas open chain silyl enol ethers alkylated in much better ratios at -78°C.

Nicholas reactions using silyl enol ethers as nucleophiles have also been used in an intramolecular approach towards the synthesis of medium sized rings bearing an asymmetric centre. The aim in this programme of research was to generate linear molecules consisting of a terminal propargyl alcohol at one end separated by 5, 6, 7, and 8 carbons from the silyl enol ether functional group at the other end. The carbon-carbon triple bond could then be complexed to dicobalt hexacarbonyl before inducing the cyclisation step upon addition of a Lewis acid.[22]

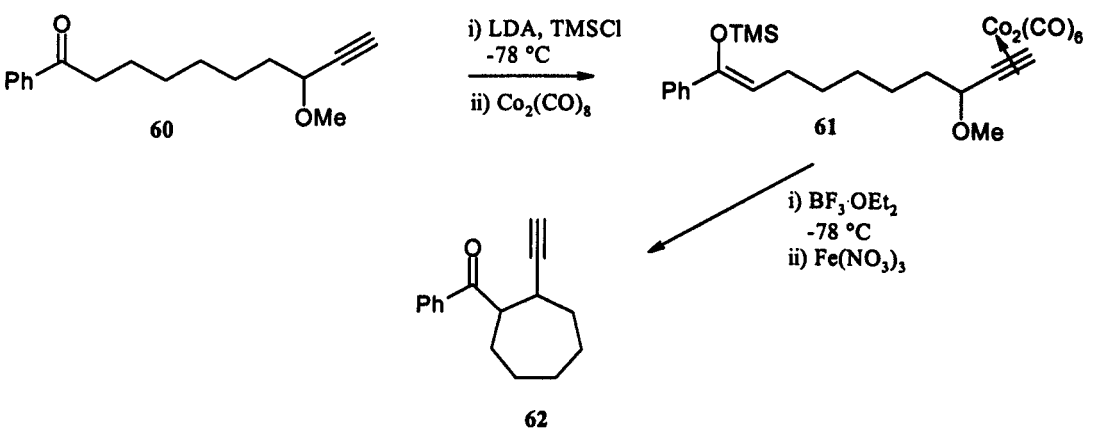
In a first approach the formation of silyl enol ether from the propargyl alcohol (55) yielded mixtures of the kinetic and thermodynamic enolates (56) and (57). These, after treatment with dicobalt octacarbonyl and HBF_4 gave a mixture of

different size ring compounds (58) and 59) with a ratio of 2.3:1 (Scheme 13). Analysis showed that the major product (58) was derived from the less stable kinetic enolate.



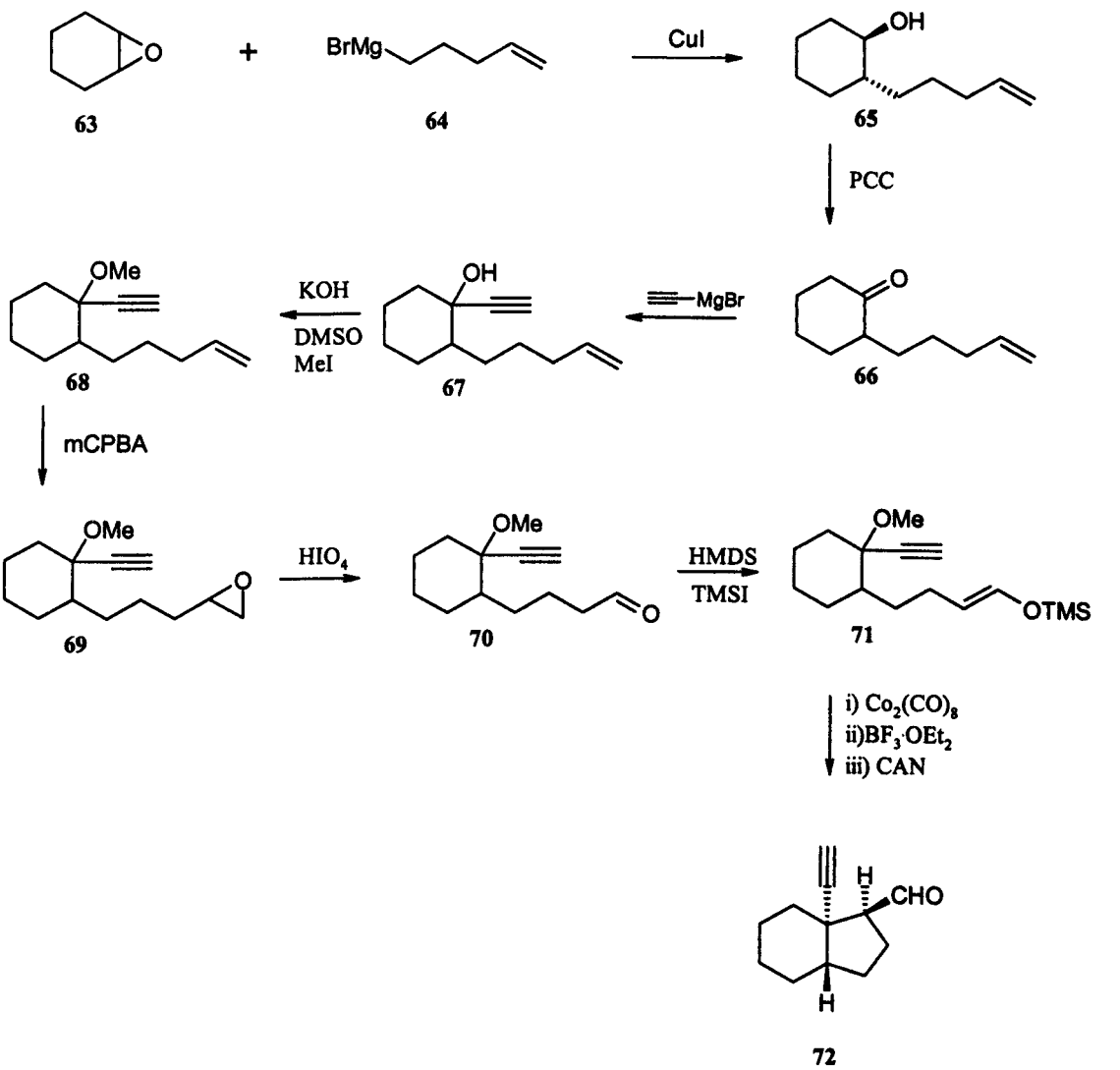
Scheme 13.

In a second approach, the aim was to generate a single silyl enolether (61) from compound (60) that would lead to a single cyclised product (62) (Scheme 13). Compound (62) was obtained in a 40 % yield over the last three steps (Scheme 14).



Scheme 14.

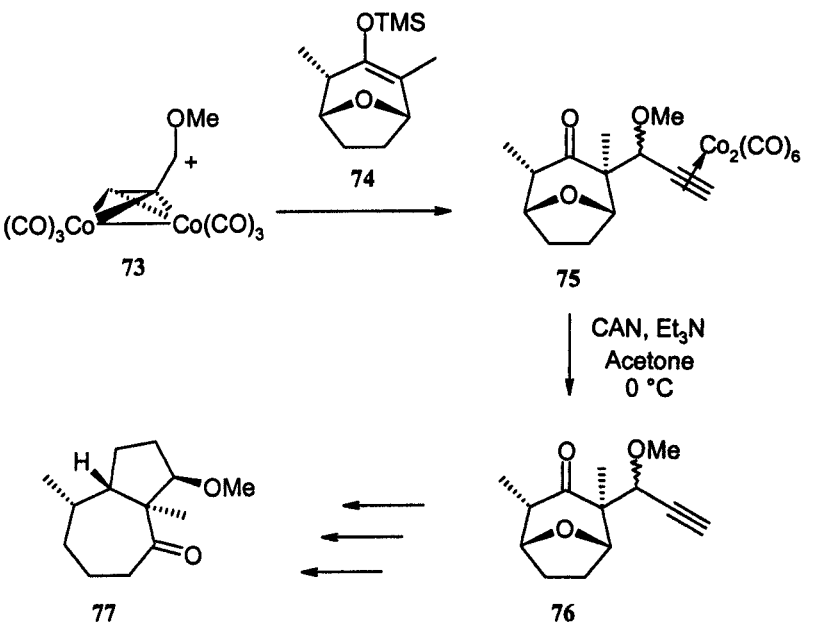
Tyrrell *et al.* extended these studies to the development of an intramolecular Nicholas reaction for the synthesis of fused ring systems.[23] The precursor to the cyclised product was prepared in several steps. First, the copper catalysed ring opening of cyclohexene oxide (63) in the presence of the 5-(1-pentenyl)magnesium bromide (64) gave the alcohol (65). Oxidation to the corresponding ketone (66) and subsequent treatment with ethynylmagnesium bromide produced a diastereoisomeric mixture of the propargyl alcohol (67) (Scheme 15).



Scheme 15.

The propargyl alcohol was then methylated to the propargyl ether (68) and epoxidised to give compound (69). Oxidative cleavage of the epoxide produced the aldehyde (70) which was then converted to the silyl enol ether (71). Compound (71) could now be complexed with dicobalt octacarbonyl and undergo cyclisation upon treatment of the complex with boron trifluoride diethyl etherate. Decomplexation using an excess of CAN yielded the desired cyclised compound (72). Proton NMR confirmed the presence of a single diastereoisomer, but the instability of the compound precluded all attempts to determine the full stereochemistry of the compound. However, it was possible to assign the stereochemistry at the ring junction using carbon NMR analysis. In *cis*-fused rings, the chemical shift of the carbon atom at the ring junction are typically found at δ 39 ppm whereas the *trans*-fused rings give a signal at δ 47 ppm. In the case of compound (72) a signal was observed at δ 45.9 ppm which corresponds to a *trans*-fused ring system.

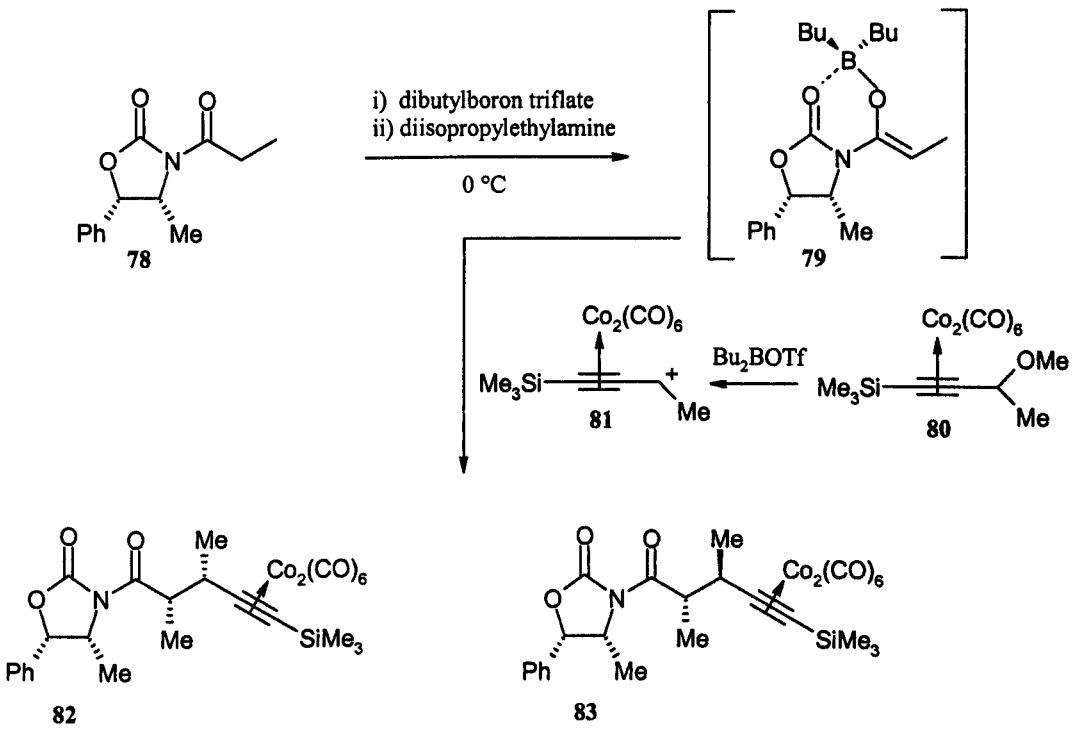
Montana *et al.* have used an intermolecular Nicholas reaction in their enantioselective synthesis of a *trans*-fused bicyclo[5.3.0] decane ring (77). The nucleophilic attack of silyl enol ether (74) upon the *in situ* generated stabilised carbocation (73) gave compound (75) in 85% yield. The cobalt complex was demetallated using an excess of cerric ammonium nitrate (CAN) to give compound (76) which was later converted into the five-membered ring in compound (77). The *trans*-fused bicyclo[5.3.0] decane ring (77) was obtained from (76) in a further seven step synthesis (Scheme 16). The bulkiness of the organocobalt cluster, favoured the attack of (74) on the stabilised cation via the *exo* face of the silyl enol ether (74), thus forming only two diastereoisomers of (77) in a 1:1 ratio.[24,25]



Scheme 16.

Boron enolates are another class of enol derivative that were found to react with propargyldicobalt hexacarbonyl complexes. Schreiber[11] showed that boron enolates derived from Evans' chiral oxazolidinones react with stabilised organocobalt carbocations to afford chiral products in good yield. The oxazolidinone derivative (78) was treated with two equivalents of dibutylboron triflate and one equivalent of diisopropylethylamine to generate the boron enolate (79) at 0 °C. Addition of the cobalt complex (80) at -78 °C, generated the stabilised cation (81) which then reacted with the boron enolate. The reaction afforded a 12:1 mixture of *syn / anti* diastereoisomers (82) and (83) from the racemic complex (80) (Scheme 17).

This result was consistent with Schreiber's postulate concerning the fluxional properties of stabilised organocobalt carbocations which rapidly interconvert at a rate that is faster than the alkylation reaction.



Scheme 17.

Jacobi *et al.* have also used Evans' chiral auxiliary derived enolate with a range of selected organocobalt cations. Some of the results of the investigation are listed in (Table 3) and (Table 4).

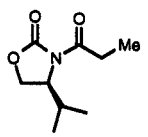
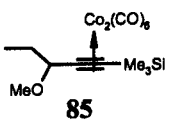
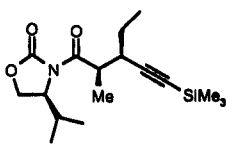
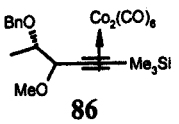
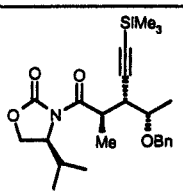
Chiral Auxiliary	Cobalt complex	Product	Yield	*syn / anti* ratio
 84	 85	 87	94 %	> 98 : 2
	 86	 88	93 %	> 98 : 2

Table 3.

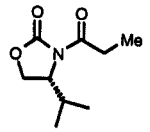
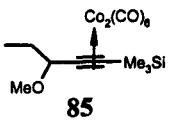
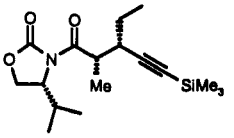
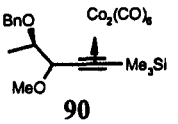
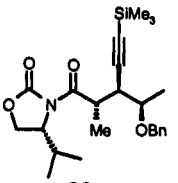
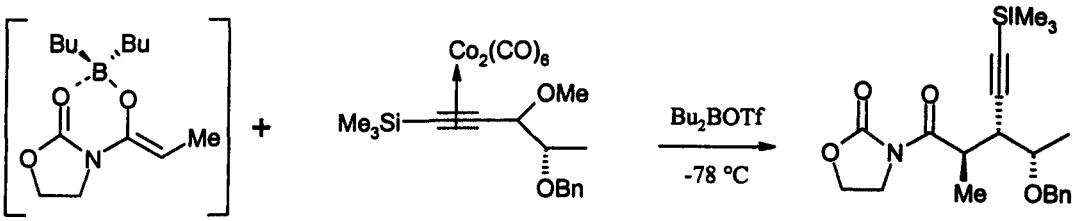
Chiral Auxiliary	Cobalt complex	Product	Yield	*syn / anti* ratio
 **89**	 **85**	 **91**	80 %	> 98 : 2
	 **90**	 **92**	78 %	> 98 : 2

Table 4.

The most interesting result of Jacobi's work with these boron enolates happened when the same reaction was carried out with an enolate (93) derived from a non chiral oxazolidinone.[26] The nucleophiles attacked the dicobalt hexacarbonyl propargyl complex (86) affording compound (94) in 93 % yield with an *syn / anti* ratio exceeding 98 : 2 (Scheme 18).



93 **86** **94**

Scheme 18.

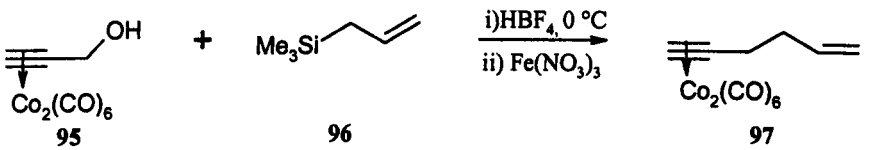
The boron enolate (93) was generated using the procedure developed by Schreiber. The structure of compound (94) was confirmed by performing X-ray analysis, after cleavage of the chiral auxiliary by hydrolysis to the corresponding carboxylic acid. This result showed how the chirality of the

cation alone can contribute to controlling the stereoselectivity of the Nicholas reaction.[27]

1.1.2.4 Allylsilanes as nucleophiles

After the investigations into the reaction of stabilised organocobalt cations with aromatic, β-dicarbonyl, ketone, and enol derived nucleophiles, a final class of π- nucleophiles was to be investigated: allylsilanes. Nicholas reported a highly selective route to 1,5-eneyne compounds which are useful intermediates in the synthesis of acyclic isoterpenoids.[28]

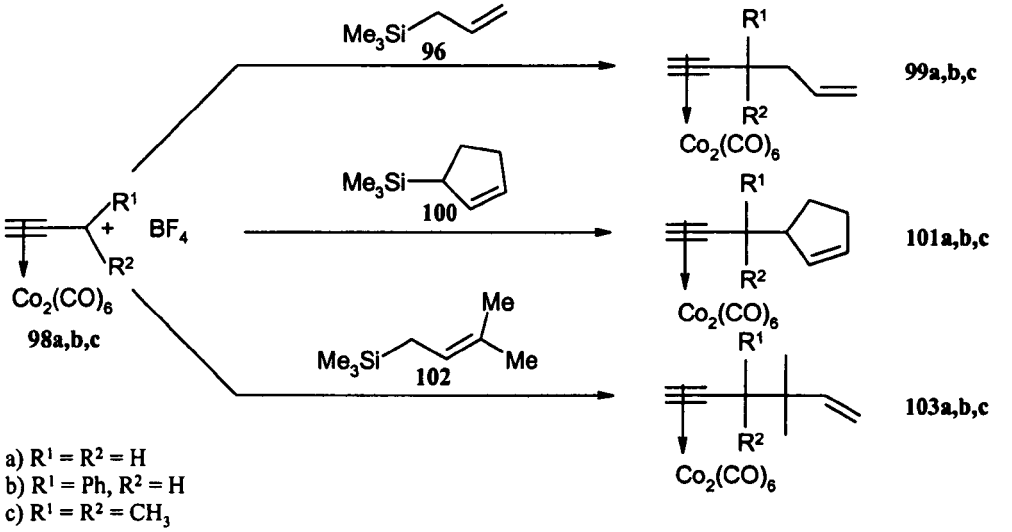
Allyltrimethyl silane (96) rapidly reacts at, 0 °C, with the carbocation generated from the propargyl alcohol complex (95) to yield the 1,5-enyne compound (97) (Scheme 19).



95 96 97

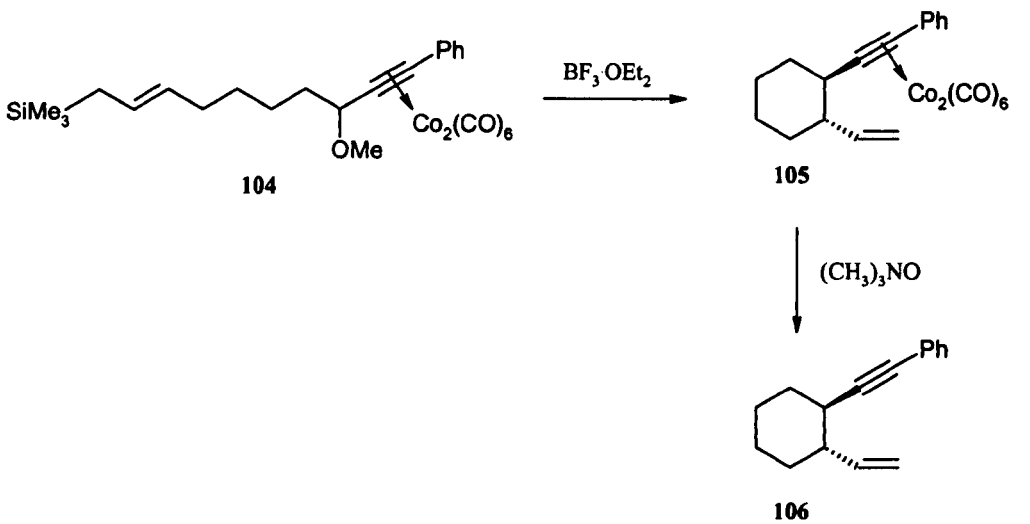
Scheme 19.

The flexibility of this reaction allows the production of a wide variety of substituted 1, 5-enynes (Scheme 20). All reactions proceed in good yields (70-97 %).



Scheme 20.

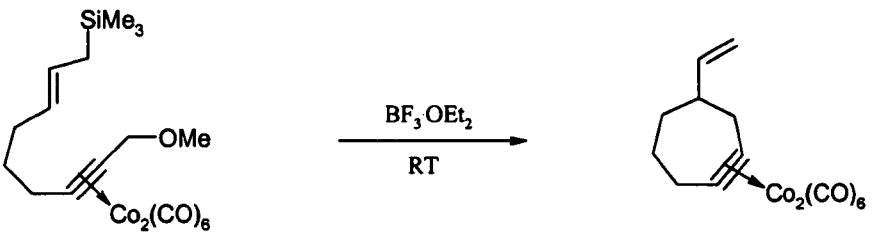
From these results, Schreiber[20] developed a strategy to form six-, seven-, and eight membered rings through an exocyclic internal alkylation. Treatment of allylic silanes such as (104) with boron trifluoride diethyl etherate in DCM at -78°C affords the disubstituted six-membered ring complex (105). Decomplexation is achieved upon addition of trimethylamine *N*-oxide to yield the more stable six-membered ring (106) rather than the less favoured eight-membered ring (Scheme 21).



Scheme 21.

The ring (106) is formed with complete stereocontrol and affords the *trans* configuration only.

Along the same lines, an endocyclic internal alkylation provided intraannular cobalt complexes of cycloalkynes. Treatment of allyl silane complex (107) with $BF_3{\cdot}OEt_2$ in DCM at room temperature afforded the seven membered cycloalkyne complex (108) in 55% yield (Scheme 22).

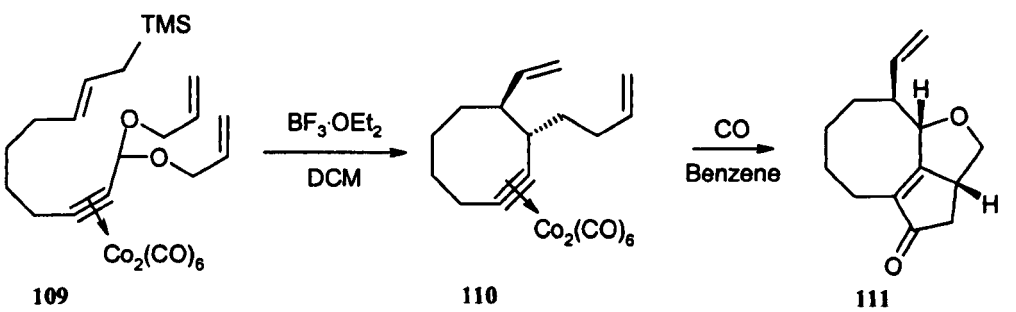


107 108

Scheme 22.

When Schreiber combined this approach with a Pauson-Khand (*cf*: chapter 1.1.3.) cyclisation reaction polycyclic compounds were generated.

Formation of the eight-membered cycloalkyne complex (110) was achieved using the same protocol involving the allyloxy acetal complex (109). Sequential treatment of compound (110) with 1 atm of carbon monoxide in benzene at 60 °C provided the single tricyclic compound (111) in 85% yield (Scheme 23).



109 110 111

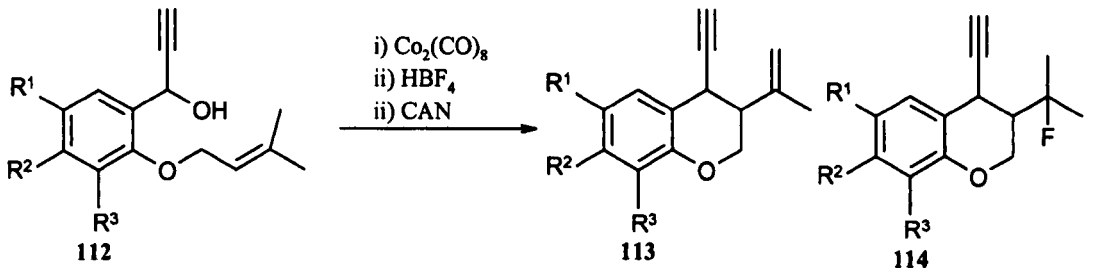
Scheme 23.

The stereochemistry of compound (111) was determined by ^{1}H NMR NOE experiments and comparison of these results with a compound of very similar structure. In later work, Schreiber et al. used the tandem Nicholas and Pauson-Khand reactions towards the synthesis of (+)-Epoxydictymene, a diterpene containing a *trans*-fused 5-5 ring system.[29]

1.1.2.5 Alkenes as nucleophiles

In previous sections, the carbon nucleophiles discussed were all activated by aromaticity, carbonyl groups or silicon. However, the use of non-activated carbon nucleophiles such as alkenes have also been studied and found to enter into efficient coupling with dicobalt hexacarbonyl complexes.

In these studies compounds such as (112) were found to undergo an intramolecular cyclisation reaction after treatment with dicobalt octacarbonyl, activation from a Lewis acid, and decomplexation in a one pot procedure (Scheme 24).[30]



a) $R^1 = R^2 = R^3 = H$
b) $R^1 = NO_2$, $R^2 = R^3 = H$
c) $R^1 = R^3 = Cl$, $R^2 = H$

Scheme 24.

When carried out with compound (112a) the reaction gave a 1:1 mixture of benzopyrans (113a) and (114a) in 35% yield.

The stereochemistry of the methine protons in compounds (113a) and (114a) was determined by ^{1}H NMR and shown to be *trans* from the magnitude of the coupling constants.

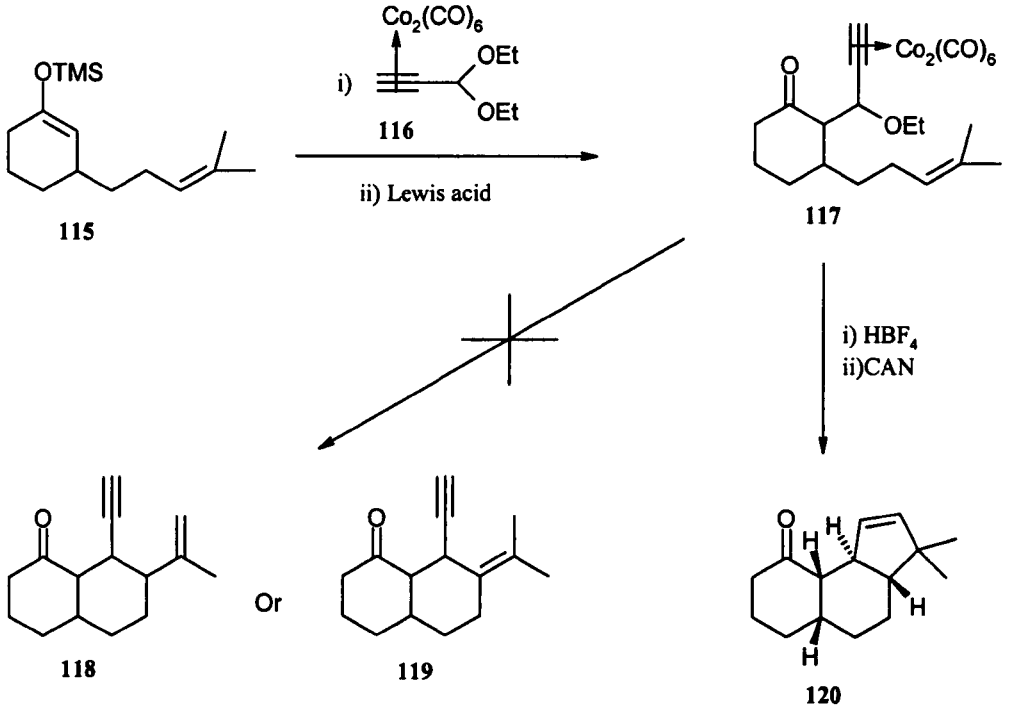
Compounds (112b) and (112c) only produced the fluoro-compounds (114b) and (114c).

From the early results of this investigation, a series of similar compounds with different substituents on the benzene ring was prepared using the one pot procedure described above.[31] The results are listed in (Table 5).

R^1	R^2	R^3	Yield of (113) (%)
Cl	H	Cl	59
H	H	OMe	66
NO_2	H	H	66
Br	H	Br	62
H	OMe	H	63
Cl	H	H	70
OMe	H	H	64
I	H	I	71
Br	H	H	66

Table 5.

The method was then extended and developed into a tandem intermolecular Nicholas reaction followed by an intramolecular Nicholas cyclisation reaction as a means to afford decalones such as (118) or (119), (Scheme 25).[32]



Scheme 25.

The silyl enol ether (115) reacted with 3,3-diethoxy-1-propyne dicobalt hexacarbonyl complex (116) to give the complexed compound (117) which then underwent an intramolecular cyclisation upon activation of the stabilised carbocation. After decomplexation, the reaction yielded a single product. In contrast to previous studies, however, spectroscopic analysis of the isolated product excluded the possibility of the reaction having formed either compound (118) or (119). Extensive NMR studies along with HRMS analysis led to the conclusion that the tricyclic compound (120) had been synthesised. The presence of a signal consistent with geminal dimethyl groups at δ 0.66 and δ 0.85 ppm on the ^{1}H NMR spectra, along with the presence of signals accounting for two =CH carbon atoms as well as four methine carbon atoms on the ^{13}C NMR spectra confirmed the structure of compound (120).

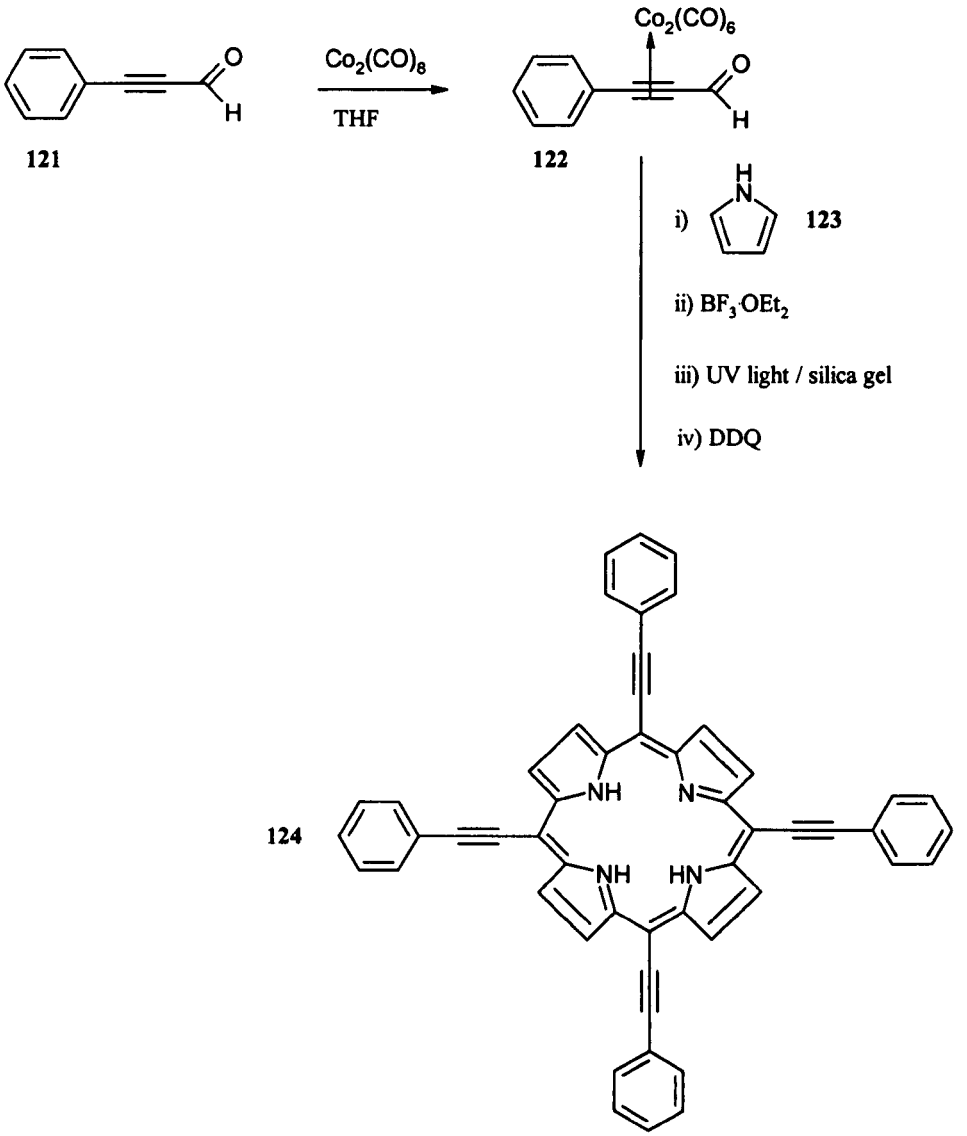
1.1.3 Other applications of cobalt clusters

In addition to their role in the Nicholas reaction, cobalt clusters have additional applications. Dicobalt octacarbonyl was first used as a protecting group for carbon-carbon triple bonds. It is also used for the Pauson-Khand reaction. More recently, there have been reports of the use of hexacarbonyl dicobalt complexes as anticancer agents.

1.1.3.1 Dicobalt octacarbonyl as a protecting group

The primary use of dicobalt octacarbonyl by organic chemists has always been as a protecting group. In recent years Milgrom *et al.* have reported the use of the cobalt complex as a protecting group for carbon-carbon triple bonds in the synthesis of tetraethynylporphyrins. In a first attempt to synthesise a series of compounds such as these, Milgrom followed a reported method involving pyrrole, phenylpropargyl aldehyde, and dibutylboron triflate. These experiments afforded the desired compounds in low yields and with an unsymmetrical by-product.[33, 34]

Using the protection of the alkyne approach, a ten-fold increase in yield was observed. The ethynyl group of the aldehyde precursor (121) was protected using dicobalt octacarbonyl. From that point the same method as in his first attempt was used. The protected aldehyde (122) was reacted with pyrrole (123) under Lindsey conditions [35] using $BF_3 \cdot OEt_2$. After oxidation with DDQ, TLC analysis showed the presence of a new compound. Exposure to UV light turned the brown spot of the complexed product into a green spot which was identified as the desired structure (124) (Scheme 26).

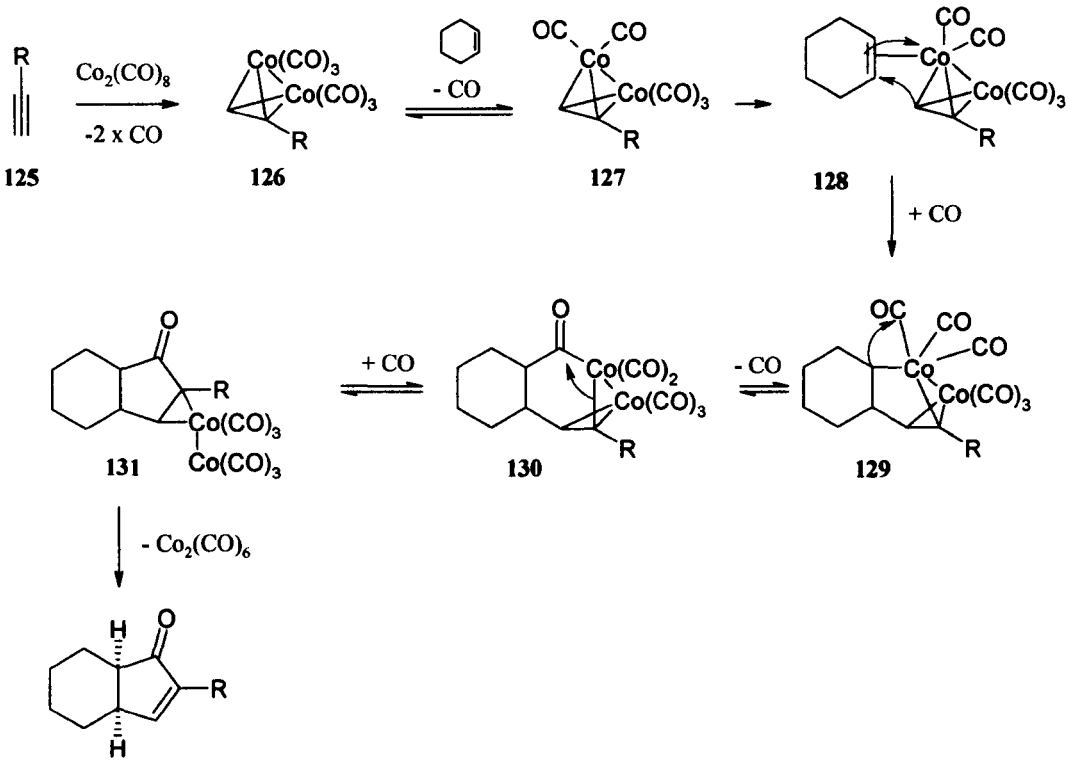


Scheme 26.

Using this methodology a series of compounds with different substituents at the *meta-* and *para-* positions on the benzene ring was constructed. By protecting the ethynyl groups, there was not only a ten-fold increase in yields over the previous procedure, but it also increased the solubility of certain compounds allowing them to be synthesised.[36]

1.1.3.2 Pauson-Khand reaction

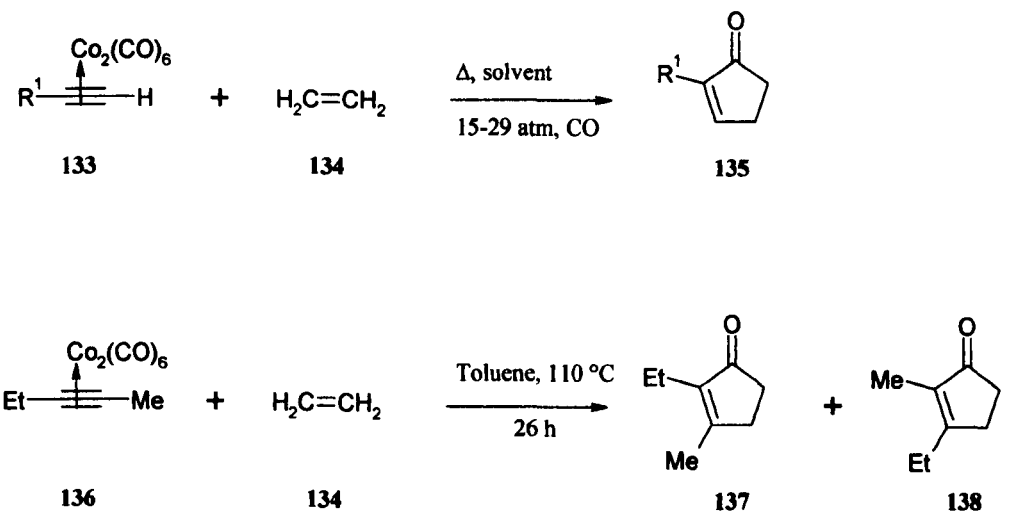
The Pauson-Khand reaction is a formal [2+2+1] cycloaddition reaction involving an alkyne, an activated alkene and carbon monoxide, mediated by a dicobalt hexacarbonyl complex to yield cyclopentenones.[37] Since its discovery in 1973, catalytic methodologies as well as asymmetric syntheses have been reported.[38] The mechanism is thought to involve two distinct stages, namely the formation of the dicobalt hexacarbonyl alkyne complex followed by the subsequent decomplexation in the presence of an alkene. It is assumed that the complexation of the alkene to one cobalt atom occurs *via* a dissociative mechanism as shown in (128), which involves the initial loss of carbon monoxide in (126) to give (127). The process leading from (125) to (127) is thought to be reversible. Subsequently, irreversible insertion of the complexed face of the alkyne π bond into one of the formal cobalt-carbon bonds of the alkyne complex (126) occurs in the step that probably is both rate- and product-determining. This is followed by addition of CO to the coordinatively unsaturated double bond (128). The metallocycle that forms may proceed to the product by a standard sequence of steps, beginning with the migratory insertion of cobalt bound CO which gives (130), addition of a ligand, and reductive elimination of the cobalt tricarbonyl moiety. The structure obtained is simply the dicobalt hexacarbonyl complex of the final enone (131). Loss of the $Co_2(CO)_6$ fragment, either before or after attachment of the additional ligand, completes the process and yields the final product (132) (Scheme 27).[39]



125 126 127 128 131 130 129 132

Scheme 27.

The reaction can occur in both inter- and intra-molecular fashions. In the intermolecular version the reaction of a monosubstituted alkyne such as (133) with ethylene (134) affords the C-2 substituted compound (135) exclusively.[40] On the other hand, disubstituted alkynes such as (136) are less selective giving mixtures of cyclopentenone (137) and (138) (Scheme 28).[41]

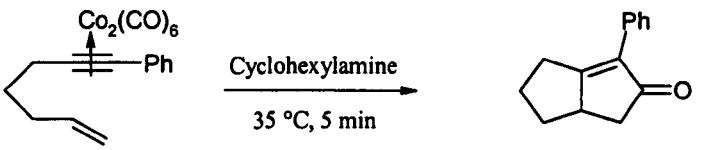


133 134 135 136 134 137 138

Scheme 28.

The versatility of the Pauson-Khand reaction allows a wide variety of compounds to be synthesised. This results from the fact that all the substituents, both in the alkyne and the alkene can be changed from alkyls, phenyls, allylsilanes or cyclic groups.

The intramolecular variation of the Pauson-Khand reaction has also been the centre of much interest, particularly for the formation of fused bicyclic ring systems. The enyne compound (139) yields the bicyclic enone (140) in 99 % yield, when heated at 35 °C for five minutes (Scheme 29).[42]



139 140

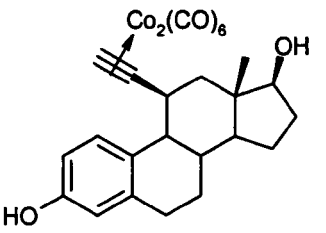
Scheme 29.

The intramolecular Pauson-Khand reaction is as versatile as its intermolecular variation, yielding a wide variety of bicyclic enones, depending on the starting material.

1.1.3.3 Dicobalt hexacarbonyl complexes as anticancer agents

In recent years, it has been demonstrated that dicobalt hexacarbonyl propargyl complexes represent a novel class of antitumor drugs.[43] Their cytotoxic potency depends on the structure of the used acetylene ligand. These complexes were initially designed as labelling agents. In an approach for the treatment of hormone dependent tumors, metal complexes of estradiol derivatives were synthesised. Out of this series of compounds the 11β-ethynylestradiol dicobalt

hexacarbonyl complex (141) (Figure 5) was used to monitor the binding of steroids to the estrogen receptor.[44]

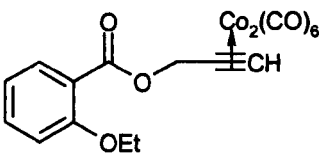


141

Figure 5.

These studies have shown that the addition of an unsaturated, bulky and lipophilic organometallic moiety in position 11β permits strong binding with the estrogen receptor. It was also shown that compound (141) can act as a strong estrogenic hormone, devoid of pronounced cytotoxicity.[45]

These early results led to the development of new strategies for the design of anticancer drugs. Complexes based upon alkynyl derivatives of salicylates such as (142) (Figure 6) have been shown to be more potent in some cancers than the current benchmark drug cisplatin.



142

Figure 6.

These studies have shown that the potency of the drug depends on the structure of the used acetylene ligand. Out of the series of compounds synthesised, (142)

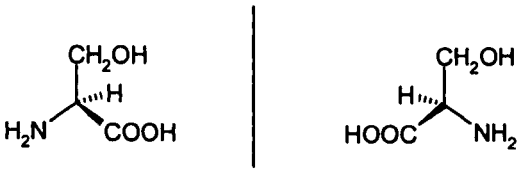
was shown to possess the highest antitumor activity in lung adenocarcinoma and mammary carcinoma cell lines.[46]

2.0 Asymmetric synthesis

Asymmetric synthesis is probably one of the few fields in science that has been the centre of so much attention in the last fifty years. This directly results from the fact that chirality is a characteristic of natural products and biologically active molecules. Asymmetric synthesis cannot be discussed without defining chirality.

2.1 Chirality

Chirality is a term that characterises objects which cannot be superimposed upon their mirror image. In terms of chemistry, chirality is applied to the three-dimensional structure of molecules in which two molecules that are mirror images of each other and cannot be superimposed upon one another are called enantiomers. Chiral molecules are also said to have a chiral centre which in one range of compounds, is an atom whose substituents are all different atoms or groups of atoms. An amino acid such as serine has two enantiomers (143) and (144) which are mirror images of each other (Figure 7).



143 mirror plane 144

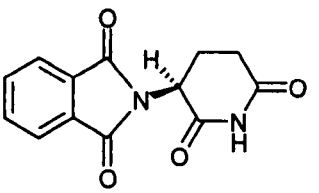
Figure 7.

In an achiral environment, these two enantiomers have identical chemical and physical properties, such as melting point, solubility, IR and NMR spectra. There is one property which always differs between one enantiomer and the

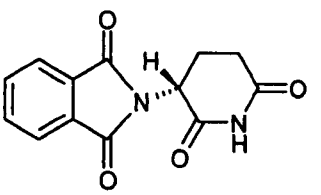
other and that is their optical activity. The optical activity refers to the way that chiral molecules rotate the plane of plane-polarised light, the two enantiomers rotating it in opposite directions. Optical activity provides the basis for the nomenclature of enantiomers as well as a mean of determination of enantiomeric purity.

When a molecule contains more than one chiral centre, the stereoisomers can either be enantiomers or diastereoisomers, if they are not mirror images of each other. If n is the number of stereogenic centres, there can be 2^n stereoisomers. The most prevalent stereogenic centres in organic chemistry are carbon atoms, which have four different groups bound to them. While enantiomers have similar physical and chemical properties, those of diastereoisomers are often different.

As well as their interaction with plane-polarised light, enantiomers also react differently with other chiral molecules such as receptors. The controversial drug thalidomide (145/146), sold in the 1950s and 60s as a sleeping aid and as an antiemetic to combat morning sickness is a good example of the differences between enantiomers (Figure 8). While the (+)-enantiomer (145) produces the desired sedative effect, the (-)-enantiomer (146) was proved to cause foetal deformities.[47]



145



146

Figure 8.

When such problems are encountered it is important to be able to deliver the right enantiomer of the drug to patients. Preparing a single enantiomer rather than a mixture is a close definition of the term "asymmetric synthesis".

The same kind of problems can be encountered when the molecule contains more than one chiral centre. Aspartame is an artificial sweetener derived from the chiral pool and is a good example here, as only the stereoisomer (147) is sweet while the enantiomer (148) and diastereoisomers (149-150) have a bitter taste (Figure 9). As a consequence a manufacturer will be looking at ways of synthesising the single desired diastereoisomer rather than trying to isolate it by purification. There are two reasons for this.

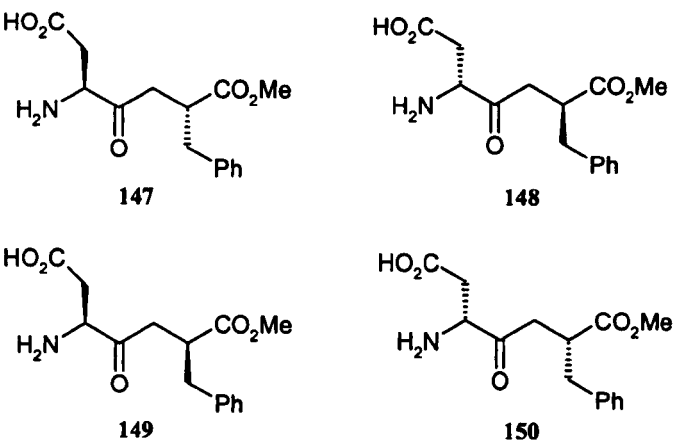
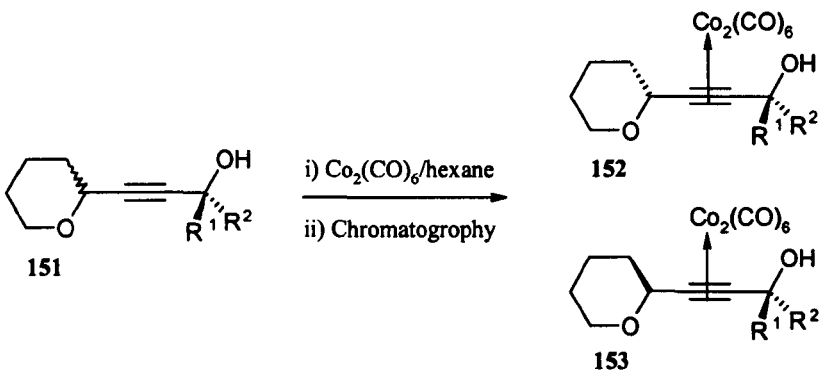


Figure 9.

First, if it is sometimes possible to separate the desired enantiomer from the other one, the task becomes much more difficult when more than two stereoisomers are generated. Secondly, even if the unwanted compounds are proven to be biologically inert they still represent a waste of starting material. This leads to the conclusion that in terms of time and money savings, an asymmetric synthesis method is often preferable.

2.2. Strategies towards asymmetric synthesis

Even though it is always preferable to generate enantiomerically or diastereoisomerically pure compounds, a few words can be said about resolution, especially if it involves the use of cobalt clusters. Mioskowski[47] reported that converting an inseparable mixture of diastereoisomeric propargyl alcohols (151) into their corresponding dicobalt hexacarbonyl complexes (152) and (153) allowed not only to discriminate between them but also to separate them by chromatography (Scheme 30).



Scheme 30.

When a new stereogenic centre is created from a previously achiral molecule, using achiral reagents, usually a racemic mixture is obtained. This is due to the transition states, leading to the two enantiomers being of equal energy (Figure 10). However, the use of a chiral auxiliary, chiral reagent or catalyst might result in transition states of different energy, which would lead to the formation of the product with the lower-energy transition state (Figure 11).[48,49]

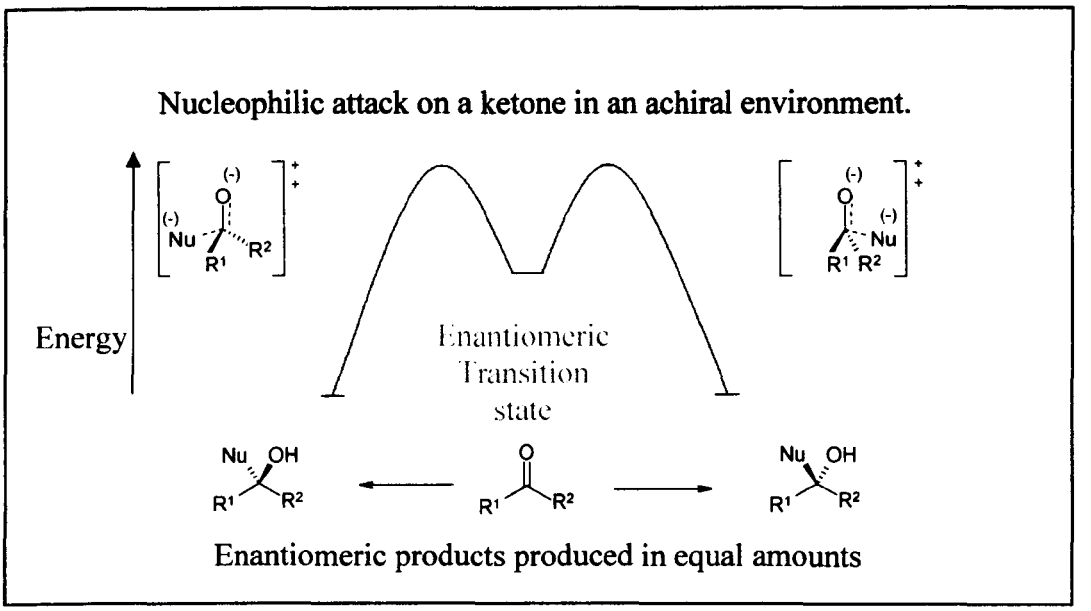


Figure 10.

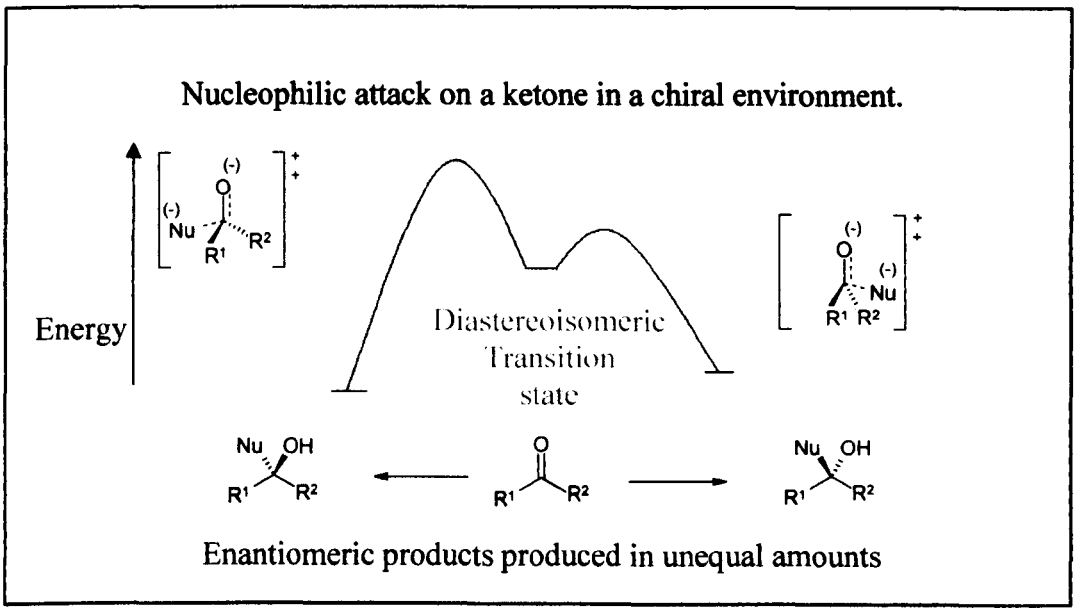


Figure 11.

Both figures reproduced from J. Clayden, N. Greeves, S. Warren, P. Wothers, Organic Chemistry, Oxford University Press, 2001, 1225.

There are several ways to achieve asymmetric synthesis such as the use of chiral auxiliary technologies, often derived from the chiral pool, or the use of chiral reagents and catalysts. These different approaches have all been used in the course of our project and the latter two will be discussed in section 3.2.

2.3 Chiral auxiliaries

The use of a chiral auxiliary in a chemical reaction is, in many regards, very similar to that of a protecting group. The enantiomerically pure compound must be attached to the starting material, it must be stable to the reaction conditions, and it must be removed at the end of the reaction. However, unlike a protecting group, the chiral auxiliary has an active role in the reaction. It must provide the vehicle for asymmetric induction. Of the auxiliaries developed to date, those that rely upon asymmetric functionalisation of attached enolate fragments have found the most widespread use.[50]

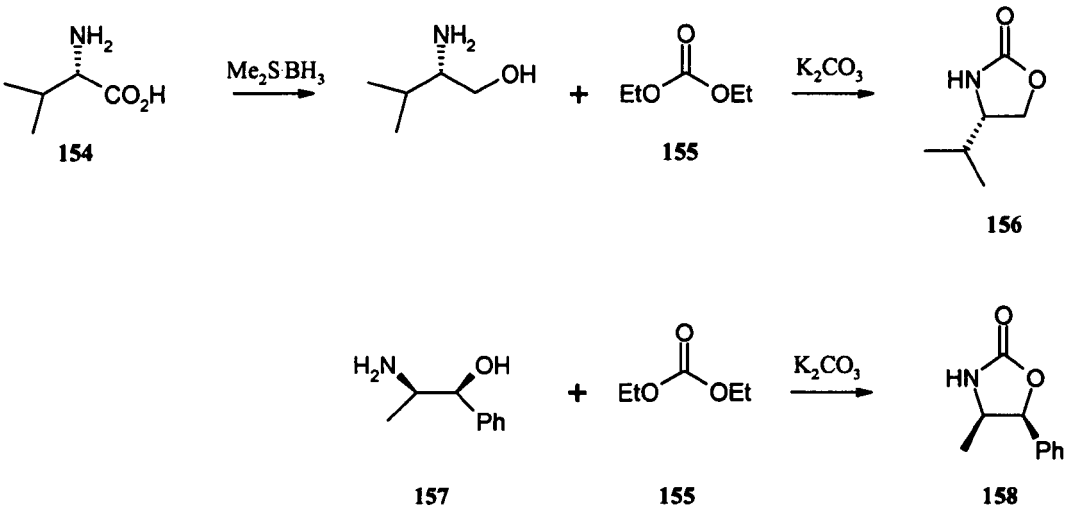
2.3.1 Synthesis of chiral auxiliaries

The most commonly known auxiliaries belong to the family of chiral oxazolidinones, also known as Evans' chiral auxiliaries. These are readily synthesised from amino acids or amino alcohols, depending on the substituent required on the oxazolidinone ring. The oxazolidinone (156) is obtained from (S)-valine (154) and carbonic acid diethyl ester (155) while the auxiliary (158) can be prepared from norephedrine (157) (Scheme 31).[51,52]

The various routes to oxazolidinones have been extensively reviewed.[53]

However, a few examples are going to be detailed here. From their interest in this field, as well as the recognition of the importance of chiral auxiliaries in

asymmetric synthesis, Davies *et al.* have developed series of new chiral auxiliaries, namely the "Quats" (164) and "Superquats"(169).



154 155 156

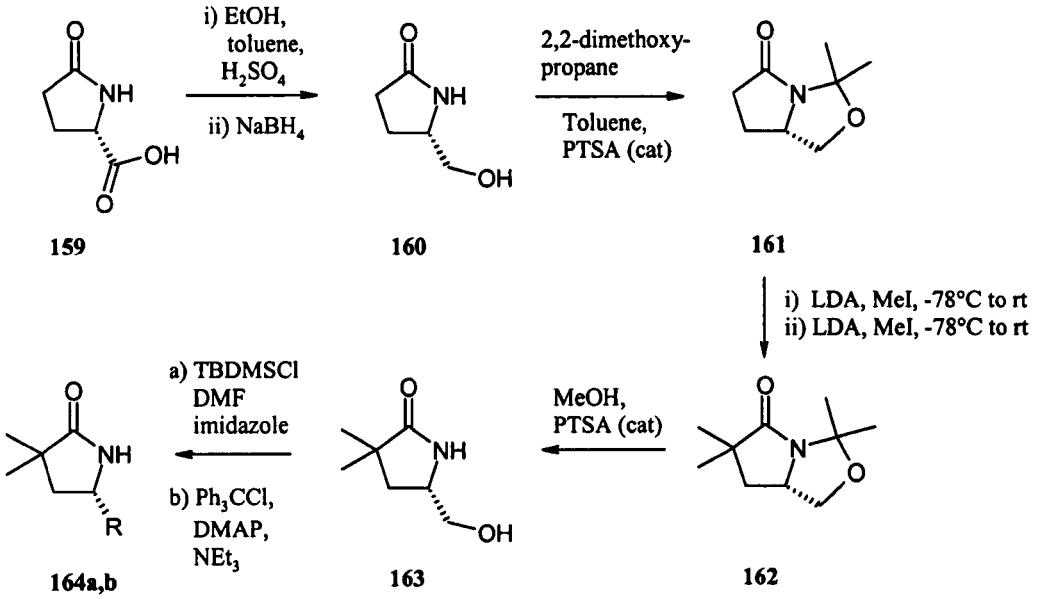
157 155 158

Scheme 31.

The synthesis and applications of "Quat" auxiliaries were first reported by Davies.[54,55]

The synthesis of "Quats" began from L-pyroglutamic acid (159), which was converted into (S)-(+)-5-hydroxy-methyl-2-pyrrolidinone (160) *via* a two step procedure of Levy and Silverman[56] in 68% yield. In order to introduce the geminal dimethyl groups adjacent to the carbonyl, the hydroxymethyl and lactam functionality was protected using an excess of 2,2-dimethoxypropane and a catalytic quantity of *para*-toluene sulfonic acid. The oxazolidine product (161) was then quaternised adjacent to the carbonyl group using a one-pot procedure involving two consecutive treatments with LDA and methyl iodide at – 78 °C followed by a warming of the reaction mixture to 0 °C. The aqueous work-up was followed by a recrystallisation to yield compound (162). Deprotection of the hydroxyl methyl group was achieved in boiling methanol with a catalytic amount of *para*-toluenesulfonic acid to afford compound (163).

Subsequent treatment of the latter with *ter*-butyldimethylsilyl chloride in the presence of imidazole in DMF gave the target molecule (164) in good yield (Scheme 32).



a) R = CH_2OTBS
b) R = CH_2OCPh_3

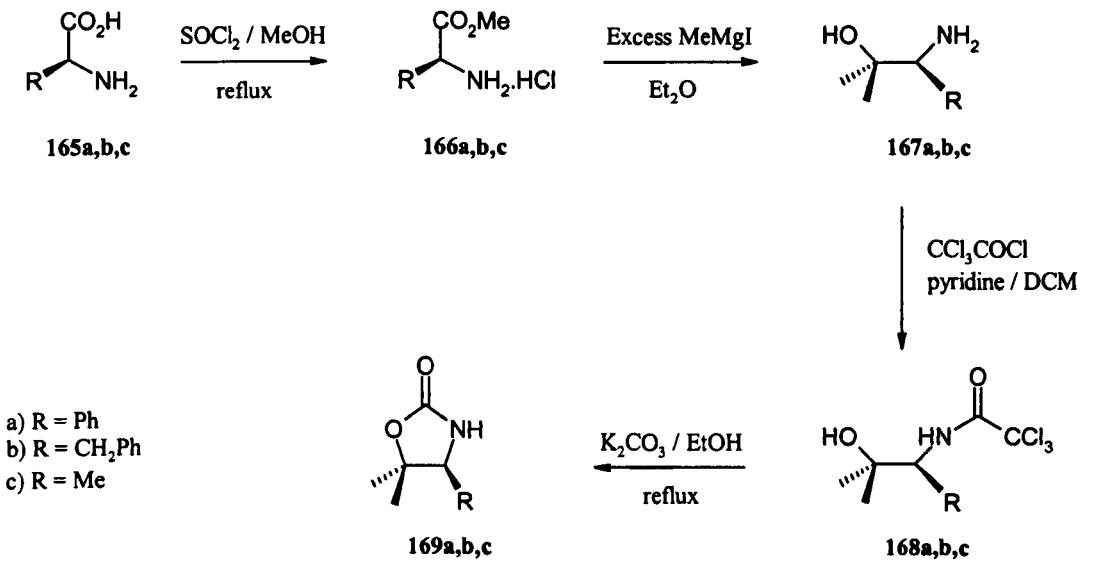
Scheme 32.

Transformation of the alcohol (163) into the corresponding tosylate also led to various derivatives of compound (164), where the R group can be a methyl, ethyl, and bromomethyl.

Davies' rationale behind the "Quat" auxiliaries was that the *gem*-dimethyl groups would protect the ring carbonyl from nucleophilic attack and hence promote the desired exocyclic cleavage against the endocyclic cleavage upon removal of the elaborated *N*-acyl fragment.[57]

The idea behind the synthesis of "Superquat" auxiliaries was very similar. On the one hand, the carbonyl would still be protected, and on the other hand the *gem*-dimethyl groups were expected to control the conformation of the

substituents at the carbon 3, thus enhancing the face-stereoselective shielding of acyl fragments. The series of "Superquat" derivatives were all prepared in the same manner. The amino acids (165a,b,c) were esterified using thionyl chloride and methanol to give compounds (166a,b,c) in quantitative yields. Subsequent treatment with an excess of methyl magnesium iodide yielded compounds (167a,b,c). The ring closure was obtained from treatment of compounds (167a,b,c) with trichloroacetyl chloride to give (168a,b,c) before a reflux in the presence of potassium carbonate afforded the desired auxiliaries (169) (Scheme 33).[58]



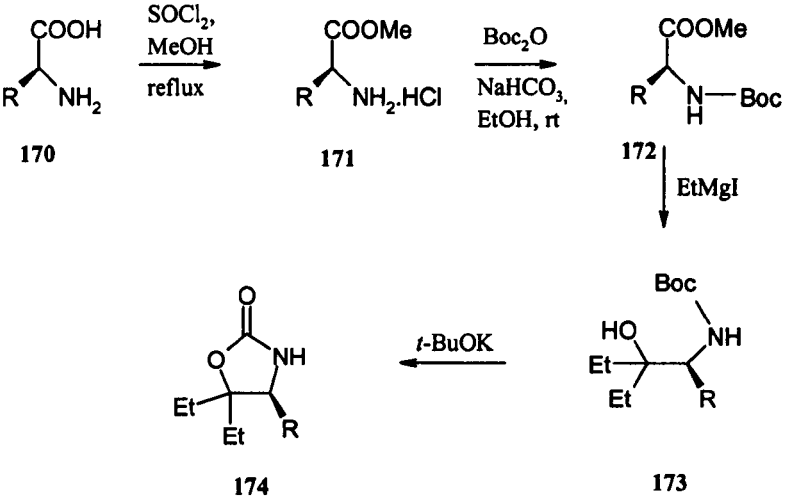
165a,b,c **166a,b,c** **167a,b,c**

168a,b,c **169a,b,c**

Scheme 33.

In the synthesis towards substituted chiral oxazolidinone, it is always possible to choose the stereochemistry of the product, depending on which enantiomer of the starting material is used. In more recent times, a similar approach towards the synthesis of a series of "Superquats" has been used. In these new auxiliaries, the geminal-methyl groups have been replaced by geminal-ethyl groups.[59]

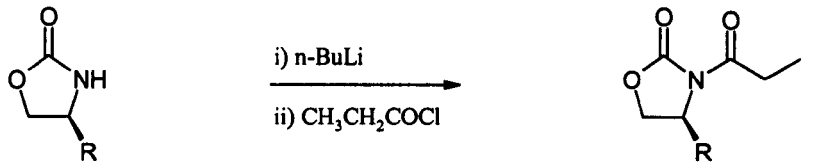
This approach also involves a four step synthesis, where the amino acid (170) was esterified with methanol to afford compound (171) before being reacted with Boc_2O to give the *t*-butoxycarbonylaminoaryl-acetic acid methyl ester (172). Subsequent coupling with ethylmagnesium iodide yielded compound (173), which was then cyclised in the presence of potassium *t*-butoxide to provide the final product (174) (Scheme 34).



Scheme 34.

2.3.2 Applications of chiral auxiliaries

Auxiliaries such as oxazolidin-2-ones, "Quats", and "Superquats", have been used in a variety of highly diastereoselective reactions. The majority of reactions are performed on *N*-acyloxazolidinone derivatives in the presence of a metal atom. *N*-acyloxazolidinones are readily accessible from the reaction of n-butyllithium with the auxiliary, followed by the addition of acid chlorides.[60] Deprotonation of the oxazolidinone (175) with n-BuLi in THF followed by reaction with propionyl chloride yields the *N*-acyl-oxazolidinone (176) Scheme 35).



175 176

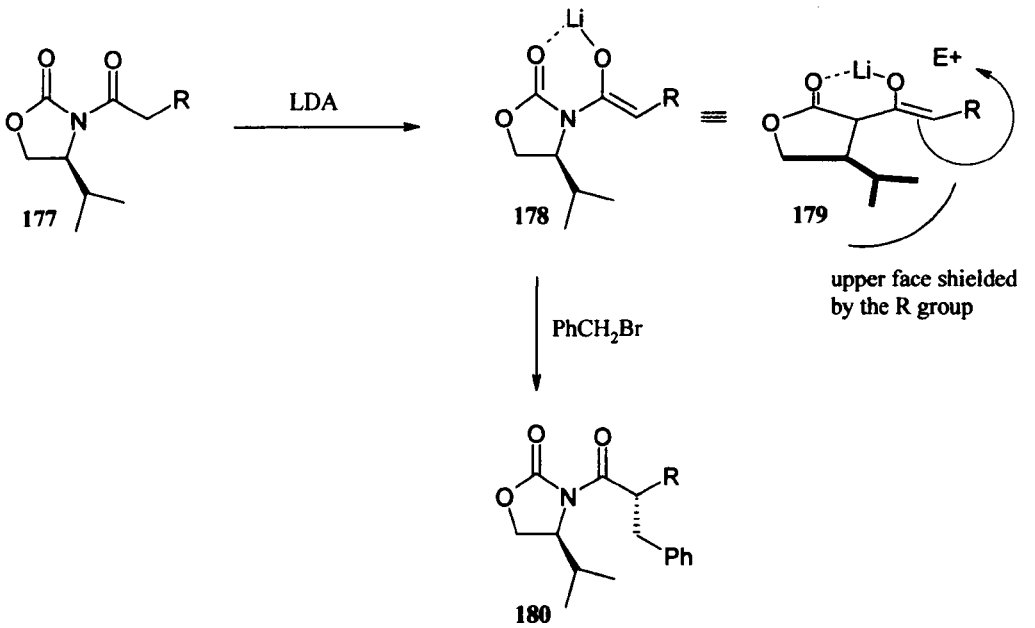
Scheme 35.

The *N*-acyl derivatives can undergo a wide variety of reactions including alkylation, amination, hydroxylation, aldol additions, and Diels-Alder cycloadditions. Only a few examples of these reactions will be discussed here as the subject has already been extensively reviewed.[53]

2.3.2.1 The alkylation reaction

One of the most common reactions carried out upon *N*-acyl oxazolidinones is the alkylation reaction. Treatment of an oxazolidinone derivative (177) with LDA at low temperature produces the enolate (178). The coordination of the lithium ion to both oxygen atoms makes the whole structure rigid, fixing the R group in a favourable position to facilitate the attack to one face of the enolate (179). The product (180) was obtained with a ratio of diastereoisomers superior too 99:1 (Scheme 36).

In the course of these early investigations in this field, Evans reported that the *N*-acyl oxazolidinone specifically formed the Z-metal enolates. The assignment of the (Z)-enolates geometry was not rigorously established, but was consistent with the interpretation of the results obtained in which the enolisation stereoselectivity for this reaction must have been above 100:1.[61]



Scheme 36.

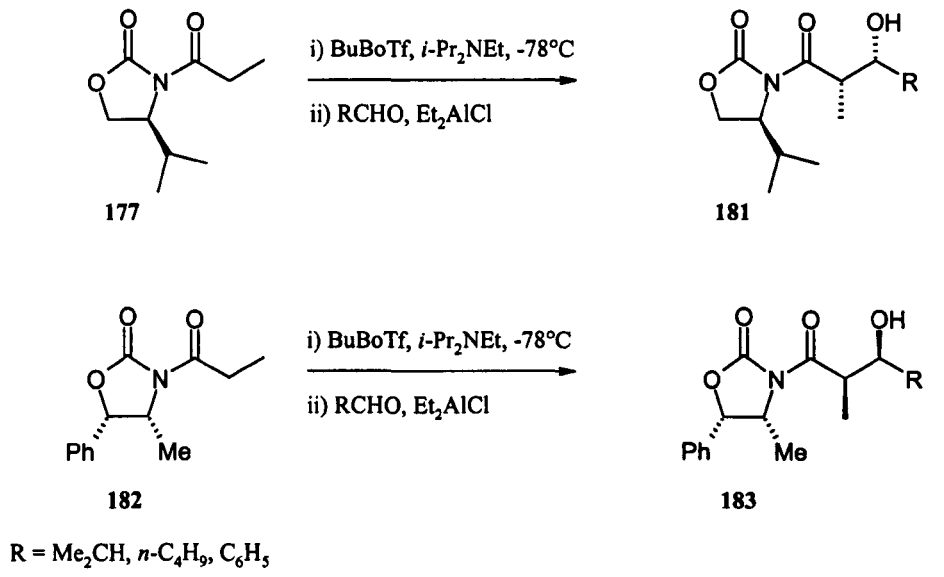
In the series of experiments carried out by Evans, several electrophiles and R groups were tested. In all the reactions, the sense of asymmetric induction was interpreted by assuming that the diastereofacial selectivity was dictated by the C_4-substituent on the oxazolidinone ring.

2.3.2.2 The aldol reaction

Using the same *N*-acyl oxazolidinone (177) where R = Me, Evans also developed a method to carry out stereoregulated aldol condensation reactions (Scheme 37).[62] Once again, a series of compounds was generated from two different N-acyl chiral auxiliaries (177) and (182) with three different aldehydes. The oxazolidinone derivative (177) showed more consistent results for the *erythro* selection than the products from the other auxiliary (Table 6).

N-acyl-oxazolidinone	aldehyde	*erythro* selection	Yield
177	Me_2CHCHO	497 : 1	78
177	*n*-C_4H_9CHO	141 : 1	75
177	C_6H_5CHO	500 : 1	88
182	Me_2CHCHO	1 : 500	91
182	*n*-C_4H_9CHO	1 : 500	95
182	C_6H_5CHO	1 : 500	89

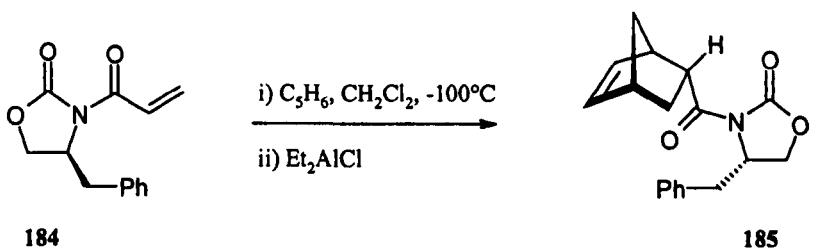
Table 6.



Scheme 37.

2.3.2.3 The Diels-Alder reaction

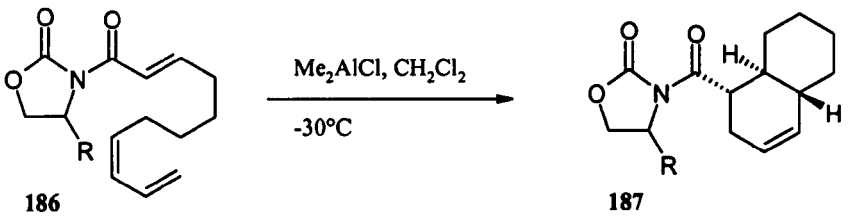
Evans later turned his attention to the formation of two new carbon-carbon bonds in an entirely regio-, and diastereoselective Diels-Alder cycloaddition reaction. Such reactions can be carried out with α,β-unsaturated *N*-acyl-oxazolidinones such as (184) which behave as good dienophiles in the Diels-Alder process. A single cycloadduct (185) was obtained in a few seconds from treatment of (184) with an excess of cyclopentadiene and diethylaluminium chloride at -100 °C (Scheme 38).[63]



Scheme 38.

The intramolecular variant also showed excellent diastereoselectivity.[63]

Treatment of a dilute DCM solution of compound (186) with dimethylaluminium chloride at -30 °C for 5 hours provided the cyclised compound (187) (Scheme 39).



186 187

Scheme 39.

Three chiral auxiliaries were tested for that experiment. The results are presented in (Table 7).

R group	Endo / exo ratio
iso-propyl	92 / 8
benzyl	97 / 3
cyclohexane	6 / 94

Table 7.

2.3.2.4 The 1,4-conjugate addition reaction

The last example developed here is another major topic in carbon-carbon bond formation. Asymmetric 1,4-conjugate addition reactions to α,β-unsaturated *N*-acyl oxazolidinones were first reported in 1987 by Pourcelot.[64]

It was while investigating 1,4-conjugate additions as a whole that Pourcelot *et al.* had the idea of testing different derivatives from two chiral auxiliaries to assess their effect towards the induction of stereoselectivity. [65]

The two chiral auxiliaries used in this investigation were 4-methyl-5-phenyl-2-oxazolidinone and 1,4-dimethyl-5-phenyl-2-imidazolidone given as the lithium derivatives (188) and (193). The *N*-acyl derivatives (189), (190), (194), and

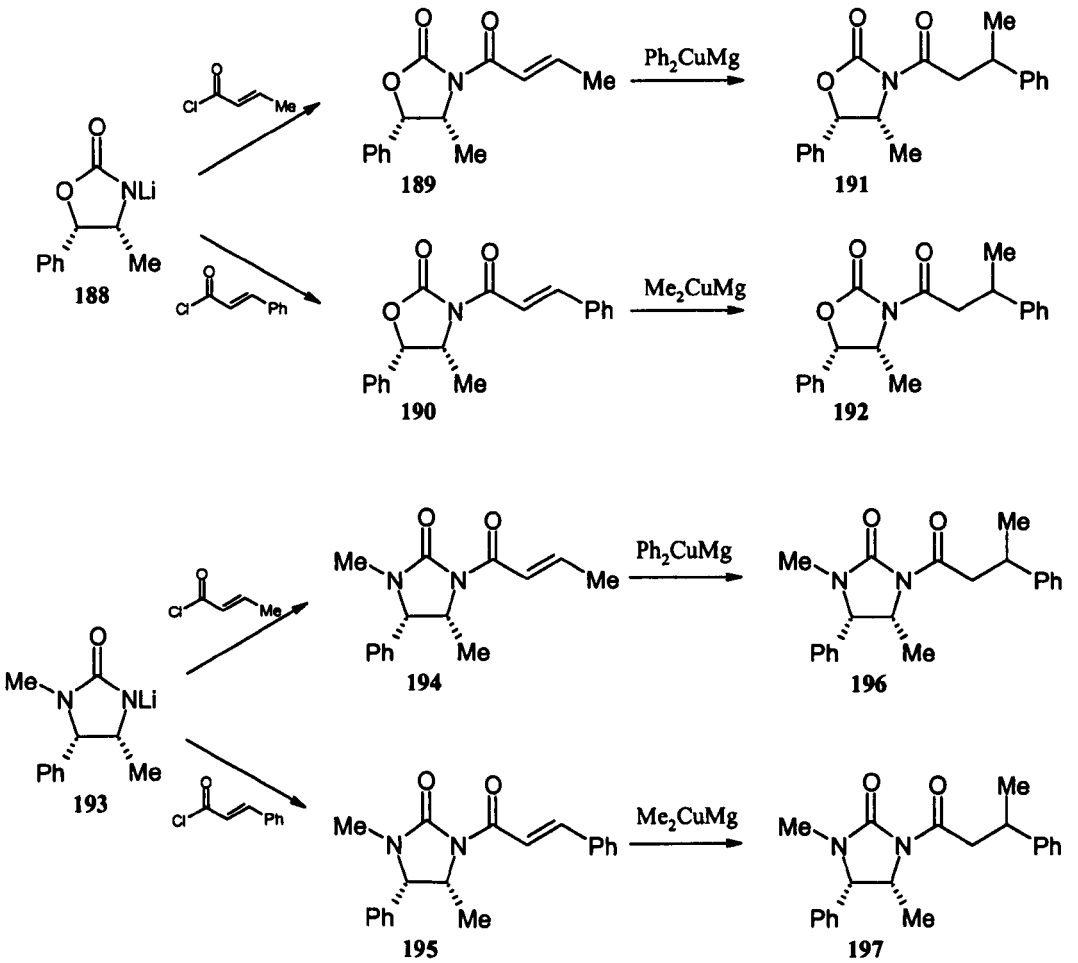
(195) were obtained from the *N*-lithiated derivatives and the corresponding acyl chlorides. The reaction with the organocuprate was carried out at -50 °C, in a mixture of diethyl ether and THF (Scheme 40). The products of the conjugate addition reactions (191), (192), (196), and (197) were then treated with potassium carbonate in methanol to yield the corresponding esters. The esters were then converted to the corresponding optically active carboxylic acids in order to determine the enantiomeric excess *via* optical rotation analysis (Table 8).

Acid obtained from	Configuration	ee (%)
191	S(+)	75
192	S(+)	60
196	S(+)	97
197	R(-)	82

Table 8.

The most surprising result in this study was the fact that the *N*-acyl oxazolidinones (189) and (190) led to the same major diastereoisomer. While unable to explain this result Pourcelot *et al.* referred to a piece of work published by Corey[66] where a proposal for the mechanism of copper-mediated conjugate addition reactions was presented. From this study, Corey concluded that the conjugate addition reaction of organocuprates with enones proceeds *via* reversible d,π^*-complex and copper (III) β-adduct formation. Pourcelot explained the better selectivity obtained with the imidazolidone (193) by a further complexation between the arene and the metal induced by the phenyl group close to the imide.

Even though compounds (191)/(192) and (196)/(197), in Scheme 40, are the same they have been labelled with different numbers due to the differences in their synthesis.



Scheme 40.

Melnyk *et al.* then carried the investigation forward by undertaking a series of conjugate addition reactions to a variety of *N*-acyl derivatives of the imidazolidinone (193).[67] Different kinds of organocuprates and organolithium were used in the course of their study. They reported good to excellent *de* values, which were determined by ^{1}H NMR spectroscopy. Their results led them to a proposal for the mechanism of the conjugate addition reaction. The R^2 group always approaches from the *si* face, and if R^1 and R^2 interchange the

configuration of the product is reversed (Figure 12). Corey's work is referred to again by stating that the copper-(carbon-carbon double bond) complexation is one of the major factors that contributes to a good stereoselective induction.

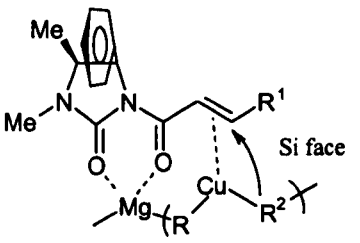
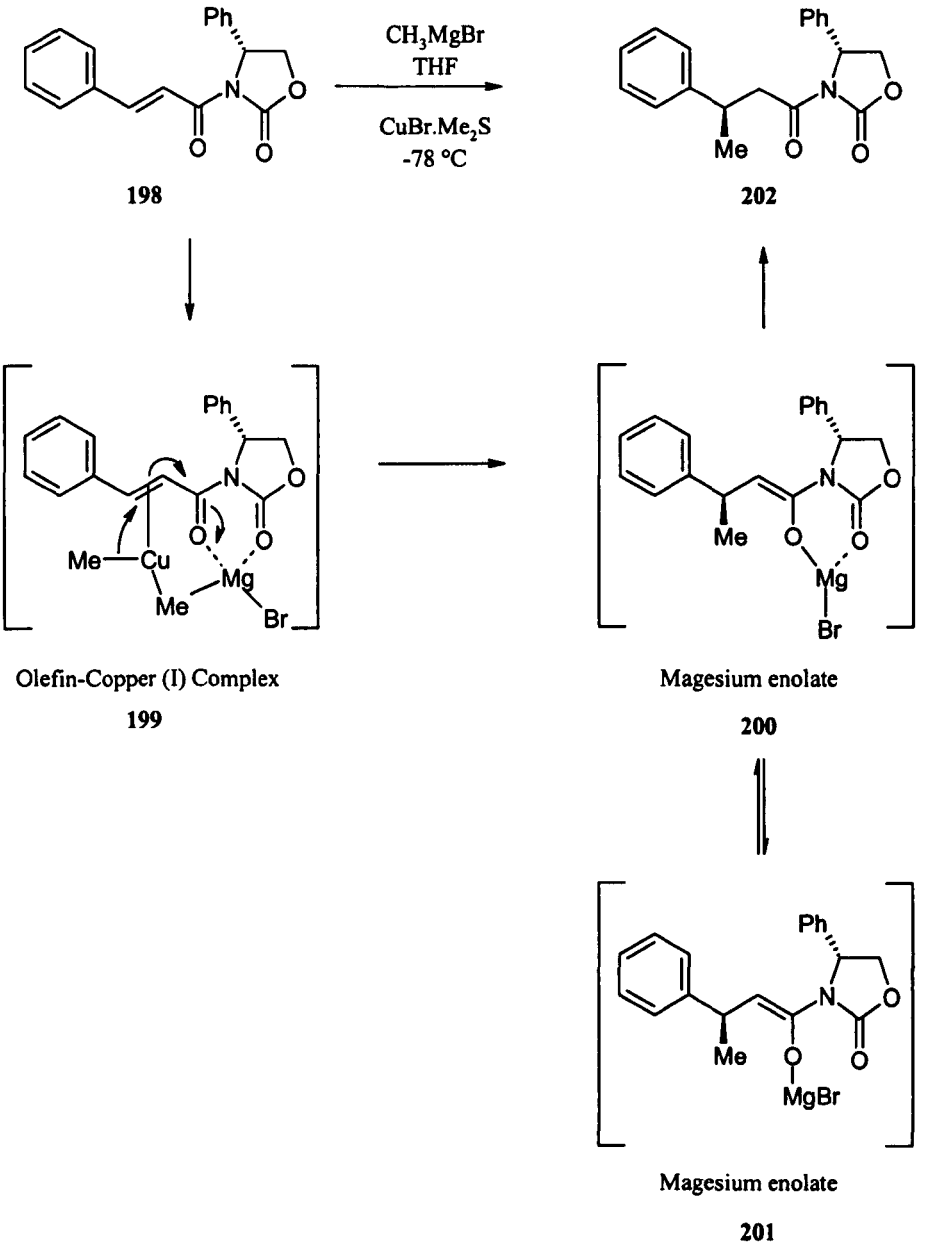


Figure 12.

The mechanism for the 1,4-conjugate addition reactions proposed by Corey was later confirmed by an investigation conducted by Hruby *et al.* where different intermediates of conjugate addition reactions with *N*-acyl oxazolidinone were observed by ^{1}H and ^{13}C NMR spectroscopy in the temperature range from 213 to 318 K.[68] In the course of the study some important chemical shifts and coupling constants corresponding to the intermediates (199-201) were observed (Scheme 41). From this investigation, Hruby concluded that the organocuprate, at 213 K, does not add the methyl group to the oxazolidinone derivative, but forms a rather stable π-complex which is characterised by a bond between the copper(I) moiety and the π-system of the double bond and an interaction of the magnesium with the carbonyl oxygen atom in the intermediate (199). When the temperature rises above 253 K, the enolate is formed. Despite the difficulties in determining the exact structure of the two enolate conformers (200) and (201) from the NMR studies, Hruby based his hypothesis on previously reported results.[69] The Michael type addition should therefore produce a magnesium enolate that contains a magnesium-oxygen bond and a magnesium-oxygen chelate such as



198 202

Olefin-Copper (I) Complex 199

Magesium enolate 200

Magesium enolate 201

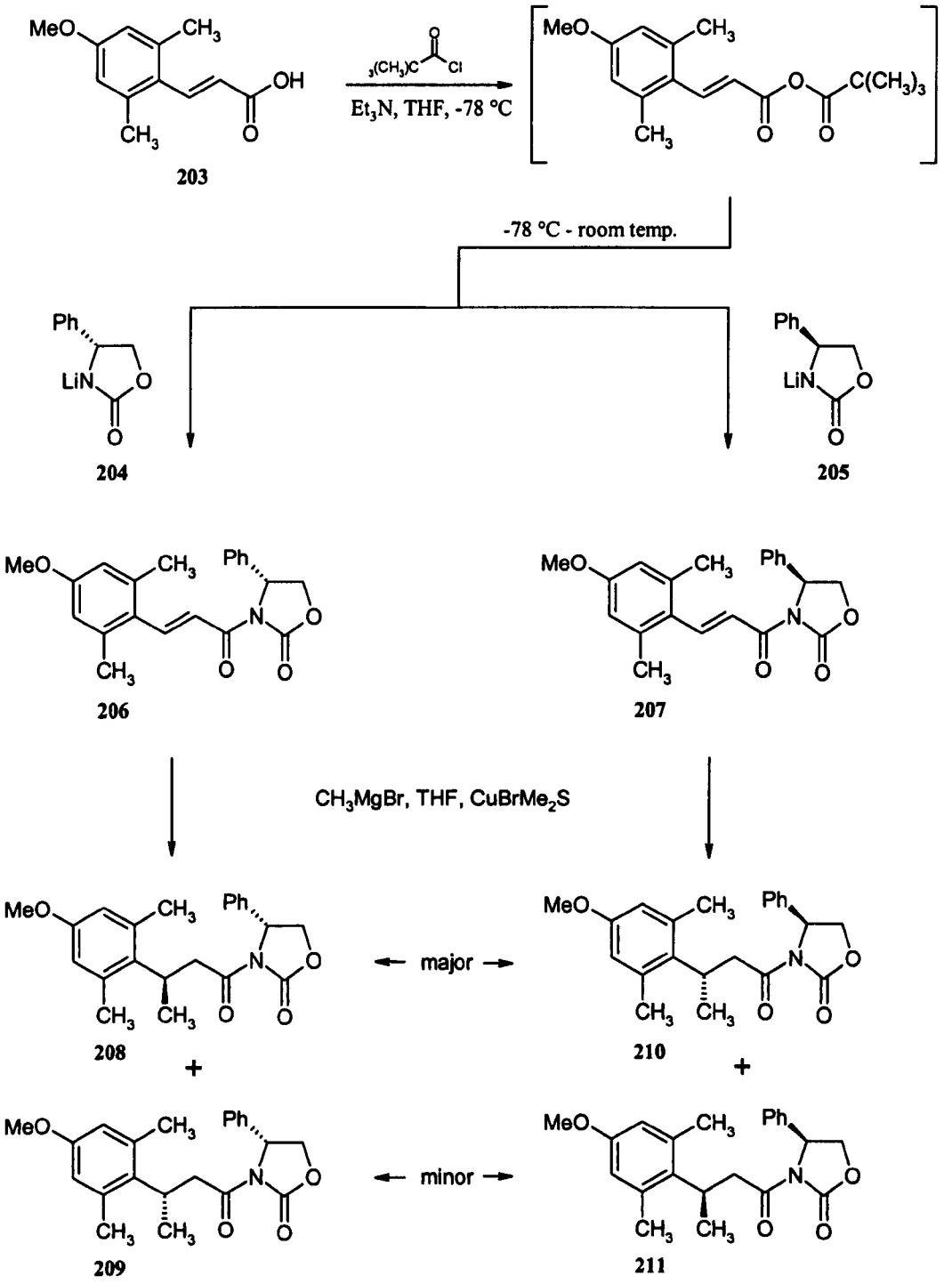
in the intermediate (200). At higher temperatures, the magnesium-oxygen coordination is dissociated and provides the thermodynamically stable intermediate (201).

Scheme 41.

From these studies, Hruby *et al.* used the 1,4-conjugate addition reaction of organocuprates to *N*-acyl oxazolidinone to synthesise a variety of amino acids.

In a first series of results the synthesis of all four isomers of 2',6'-dimethyl-β-methyltyrosine (212/213) and (216/218) using two different approaches was reported.[70]

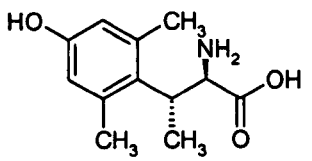
In the first approach, (2E)-3-[(4'-methoxy-2',6'-dimethylphenyl]-2-propenoic acid (203) was coupled to the optically pure 4-phenyl-2-oxazolidinones (204) and (205), to yield compounds (206) and (207), (Scheme 42).



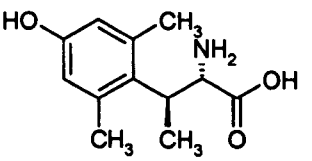
Scheme 42.

The key step was a 1,4-conjugate addition reaction of (206) and (207) with the organocuprate prepared from methylmagnesium bromide. Each yielded a major isomer (208) and (210) and a minor isomer (209) and (211) respectively. The recorded ratios were 9 : 1 for the isomers (208) and (209), and 95 : 5 for

(210) and (211). In both cases the major isomers (208) and (210) were isolated by gravity chromatography. Successive bromination at the carbon α- to the carbonyl group and displacement of the bromides with nucleophilic azide *via* an S_N2 mechanism, followed by the removal of the chiral auxiliary yielded the corresponding azido acids. Finally, these were reduced to the corresponding amine by standard catalytic hydrogenation, before the reversal of the O-methoxy protecting group back to the alcohol function to yield the two isomers of the tyrosine derivatives (212) and (213), (Figure 13).



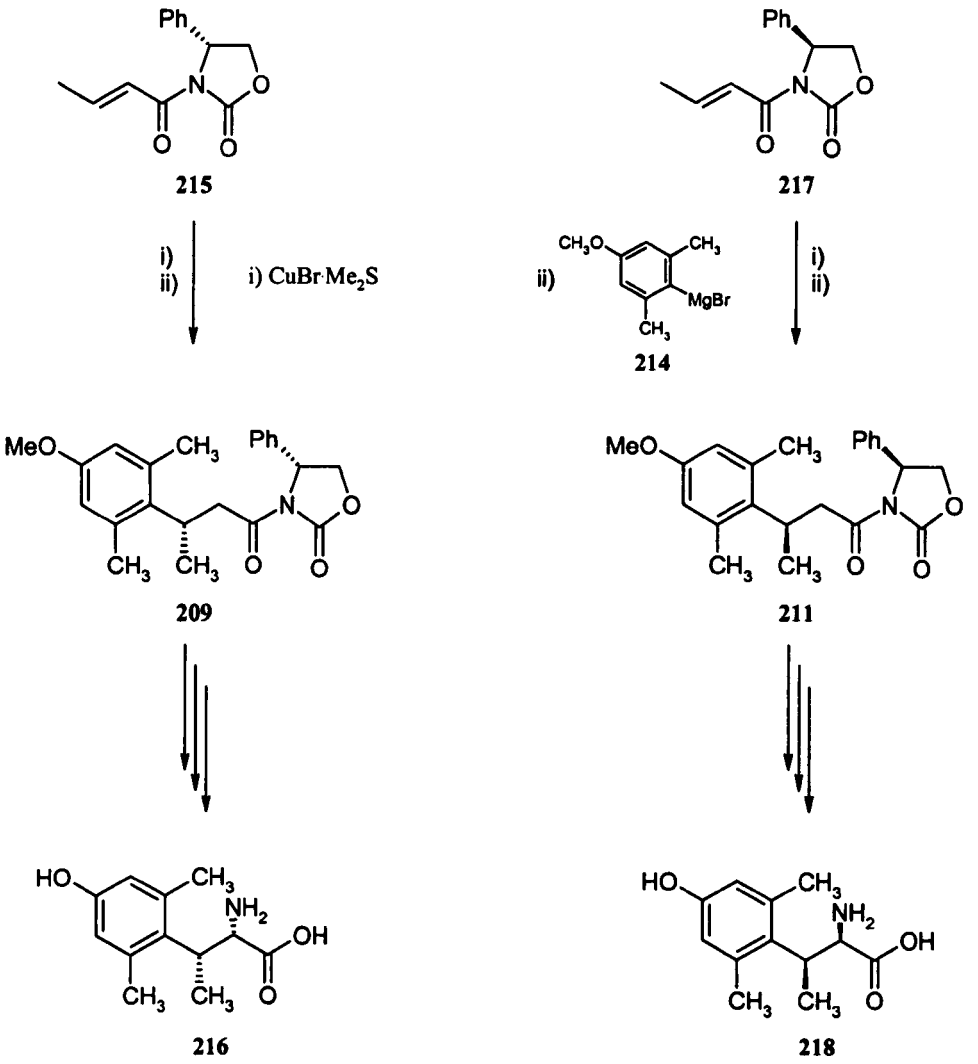
212



213

Figure 13.

In a second approach, Hruby started the synthesis from the *N*-acyl derivatives (215) and (217) of the oxazolidinones (204) and (205) prepared from crotonyl chloride. Once again, the key step in this synthesis towards the last two isomers of 2',6'-dimethyl-β-methyltyrosine was a 1,4-conjugate addition reaction involving the derivatives (215) and (217) with the organocuprate prepared from the Grignard reagent (214). This time the conjugate addition yielded compounds (209) and (211), as the major isomers produced. It is to be noted that the presence of compounds (208) and (210) could not be detected by ^1H NMR spectroscopy. The same sequence of reactions as in the first approach was then used to obtain the two isomers (216) and (218), (Scheme 43).



Scheme 43.

Using the same approach, Hruby also reported the synthesis of all four isomers of isopropylphenylalanine (219). The very bulky isopropyl group constrains the torsional rotations of the molecule to a small range of torsional angles.[71,72] This methodology was also used to synthesise the four optically pure isomers of β-methyl-3-(2'-naphthyl)alanine (220), (Figure 14).[73]

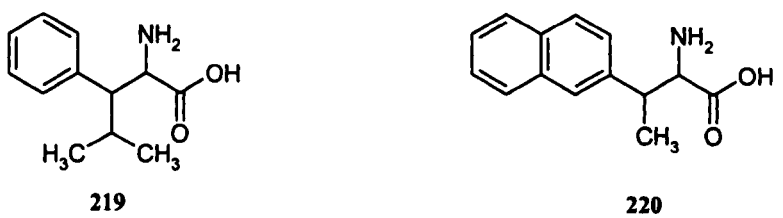
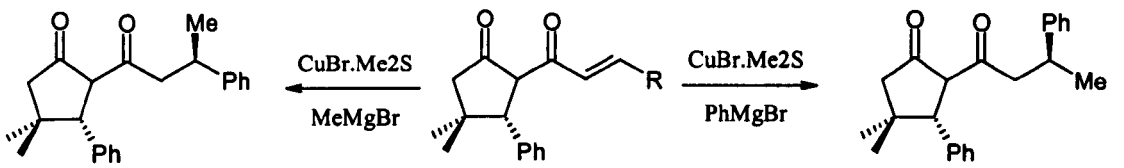


Figure 14.

With these extensive investigations towards the synthesis of various amino acids, Hruby has shown that Evans type auxiliaries are powerful tools for the induction of stereocontrol in 1,4-conjugate addition reactions.

Davies *et al.* also reported excellent diastereoselectivity for conjugate addition carried out with *N*-acyl derivatives of Superquat (221) and (223).[58]

The reactions proceeded in good yield and gave *de* values >99% after recrystallisation of the products (222) and (224), (Scheme 44).

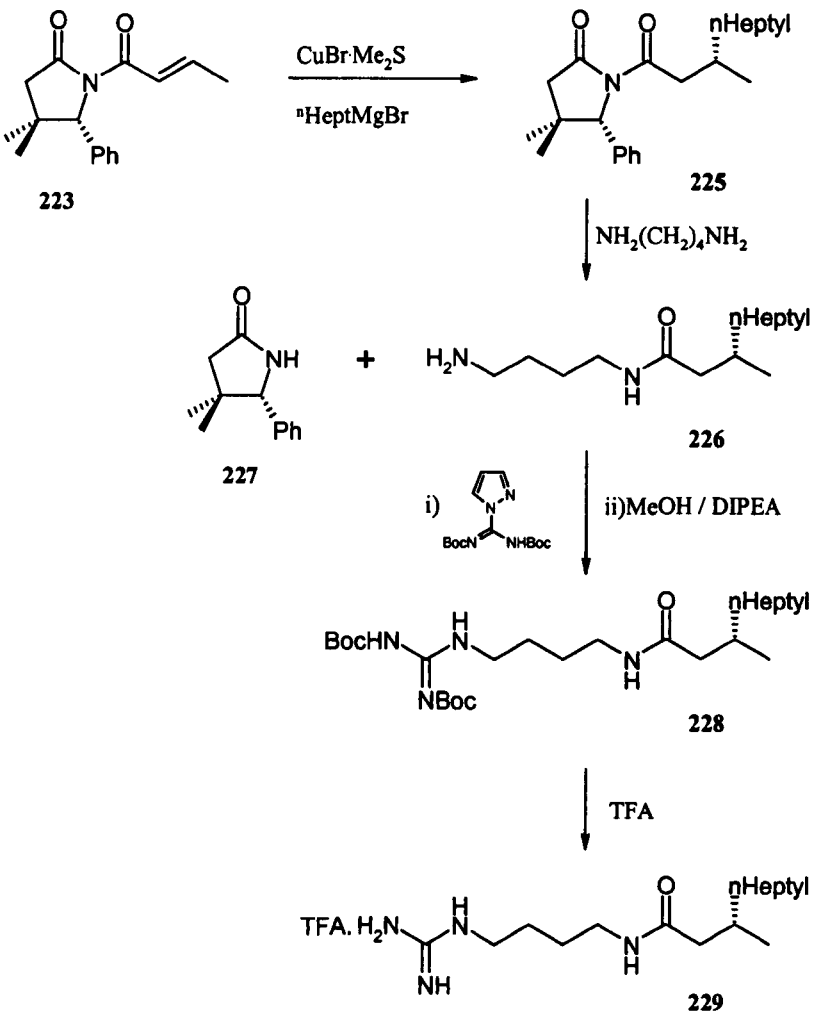


224 221, R = Ph 223 R = Me 222

Scheme 44.

These early results led Davies to use this methodology towards the asymmetric synthesis of Aplysillamide B, a new guanidine alkaloid isolated from a marine sponge by Kobayashi *et al.*[74].

The key step in the synthesis was the 1,4-conjugate addition reaction between the *N*-acyl derivative (223) and the organocuprate generate from *N*-heptylmagnesium bromide, which afforded the compound (225). Consecutive cleavage of the chiral auxiliary with 1,4-diaminobutane gave the amino amide (226) in 91 % yield and the chiral auxiliary (227). The guanidylation step gave the bis-Boc protected natural product (228). Finally, the Boc deprotection reaction was achieved by adding trifluoroacetic acid and afforded Apylsillamide B (229), (Scheme 45).


CuBr·Me2S
nHeptMgBr
Ph
223
nHeptyl
225
NH2(CH2)4NH2
NH
227
H2N
226
i)
BocN
NHBoc
ii)MeOH / DIPEA
BocHN
NBoc
228
TFA
TFA. H2N
NH
229

Scheme 45.

3.0 Results and Discussion

This chapter is divided into three sections which reflect the way our project has evolved with time. Each set of results have raised questions or doubts which in turn led to conclusions which guided our decisions regarding future experiments.

Section 3.1 looks at a chiral auxiliary approach towards the asymmetric synthesis of polycyclic compounds involving the following steps: an asymmetric 1,4-conjugate addition reaction where an alkenyl group is installed, followed by an intermolecular Nicholas reaction to introduce the propargyl alcohol complex which is necessary to perform a sequential intramolecular Nicholas reaction.

Section 3.2 discusses two different approaches that involve a series of propargyl alcohols, derived from citronellal, which undergo an intramolecular Nicholas cyclisation reaction. The first approach involves the oxidation of a racemic propargyl alcohol to the corresponding ketone which then undergoes an asymmetric reduction to yield a pure isomer of the propargyl alcohol. In the second approach the diastereoisomerically pure propargyl alcohols are generated by a stereoselective zinc catalysed alkynylation reaction.

The last section of this chapter presents the conclusions of our work and looks at future work that could be undertaken in this field.

3.1 The chiral auxiliary approach

The initial aims of this project were to extend upon work that had previously been carried out at Kingston University. Previous studies presented the development of a series of novel tandem cyclisation reactions that proved to be successful methodologies towards the synthesis of bicyclic and tricyclic ring systems, as reported in chapter 1 (p. 28).[32]

Our rationale was to take this series of results forward by trying to improve the stereoselectivity at the key stages i.e. the inter- and intramolecular Nicholas reactions. Although our main aim was to concentrate on the development of new methodologies towards optimising the selectivity of the Nicholas reactions, we did not ignore the fact that the project could lead us to the synthesis of highly fused polycyclic rings such as compound (230), (Figure15).

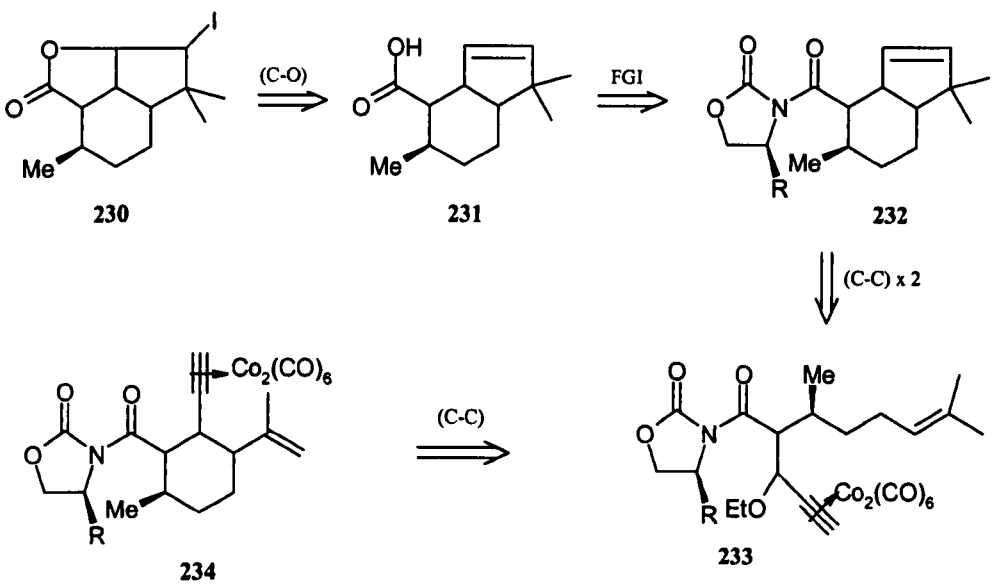


Figure 15.

The compound (231) should easily be obtained from its precursor (232) by cleavage of the chiral auxiliary. The bicyclic compound (232) was expected to form from a one-pot procedure involving the activation of compound (233)

with a Lewis acid, followed by the *in situ* decomplexation of the hexacarbonyl complex. At this stage, it is also possible for the intramolecular Nicholas reaction to yield the monocyclic compound (234). The cobalt complex (233) can be obtained by intermolecular Nicholas reaction upon compound (235) which results from a 1,4-conjugate addition reaction to the *N*-acyl oxazolidinone (236), (Figure 16).

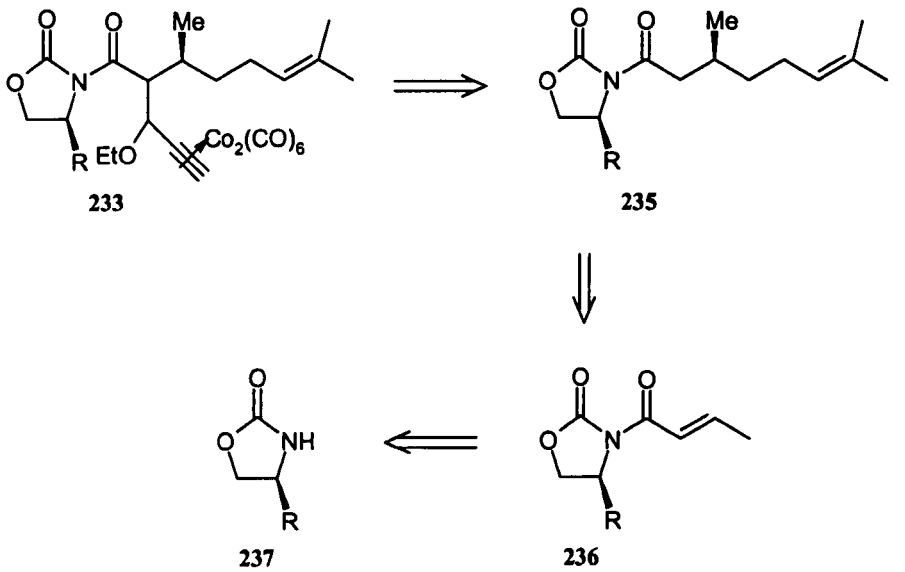


Figure 16.

Although we considered this synthesis a strong possibility, our initial aim was always to concentrate on the development of new methodologies to carry out the Nicholas reactions. Reports have been made in the literature regarding the *syn-anti* diastereoselectivity in the generation of two new chiral centres when the propargyl cation reacts with silyl enol ethers as nucleophiles.[21]

However, there are fewer reports of studies regarding the induction of enantioselectivity in these reactions.[75] Our approach therefore consisted of the three following steps:

i) An asymmetric conjugate addition reaction to a chiral *N*-enoyl derivative.

ii) An intermolecular Nicholas Reaction

iii) An intramolecular Nicholas Reaction

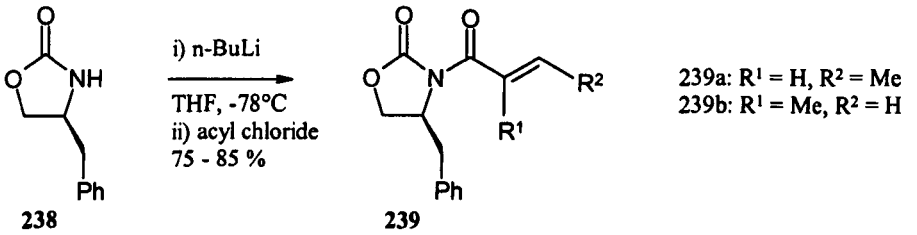
3.1.1 N-acylation and conjugate additions.

In the first part of this project, our main aim was to identify the chiral auxiliary which would provide the best stereoselectivity in the conjugate addition reactions.

It was also decided to carry out these reactions with two different *N*-acyl oxazolidinone derivatives in order to assess the effect of the distance between the chiral auxiliary and the generated chiral centre upon the stereoselectivity of the reaction. This part of our research was based on the good results reported by Hruby *et al.* where asymmetric 1,4-conjugate addition reactions were performed with chiral α,β-unsaturated *N*-acyl-4-phenyl-2-oxazolidinones.[76]

Although some of the oxazolidinone derivatives would be the same, the organometallic reagents used by Hruby for the Michael-type additions were much simpler than the ones planned in our synthesis.

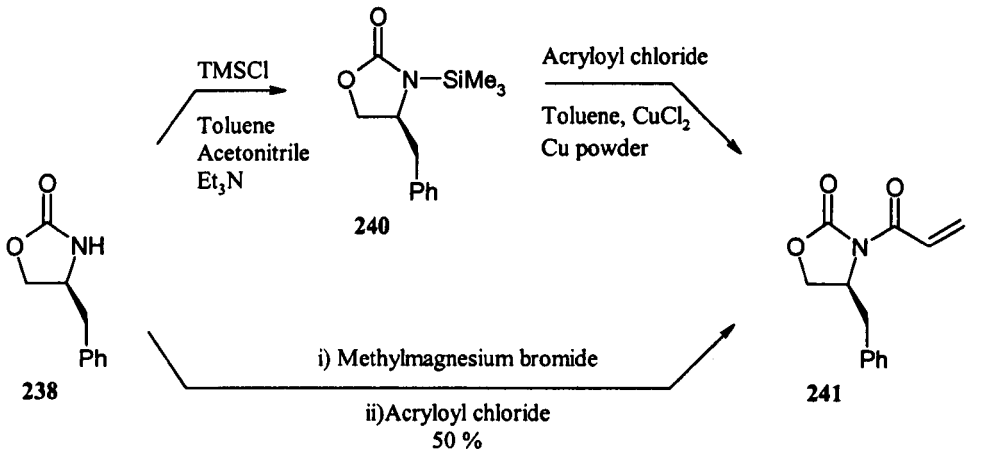
In order to familiarise ourselves with the experimental procedures reported by Hruby *et al.*, we started our project by working with one of the most common of Evans chiral auxiliaries (238). The first key step in the use of a chiral oxazolidinone in synthesis is the functionalisation of the nitrogen atom of the heterocycle. *N*-acyl oxazolidinones are easily obtained by treating auxiliaries such as (238) with n-BuLi, followed by the addition of an acid chloride. This reaction was carried out with crotonyl chloride to afford compound (239a) and methacryloyl chloride to afford compound (239b) affording yields between 75 and 85% (Scheme 46).



238 239

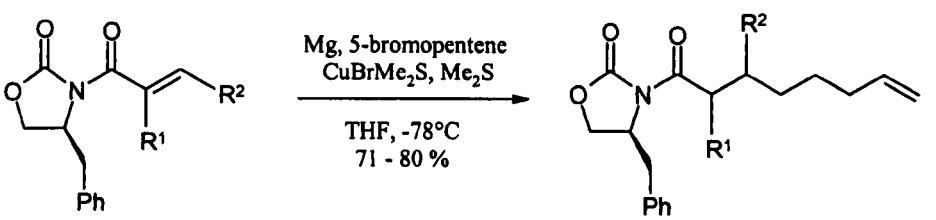
Scheme 46.

However, this method emphasised the limitations when trying to perform the addition with acryloyl chloride to afford the derivative (241). Indeed the latter tends to homopolymerise when used in the presence of n-BuLi. Several procedures for the acylation of chiral oxazolidinones have been proposed[77,78], out of which two, one by Kocienski[79] and the other by Evans[63], were considered. The first one involves a two-step procedure in which the oxazolidinone (238) is converted to the *N*-trimethylsilyl derivative (240) before being heated under reflux for 59 hrs with acryloyl chloride (Scheme 47). The time scale and poor subsequent yield of this reaction helped in our decision to employ the much easier and faster procedure proposed by Evans *et al.* For this reaction, the oxazolidinone is treated with methylmagnesium bromide at -20°C prior to the addition of acryloyl chloride to afford (241) in approximately 50 % yield (Scheme 47).



Scheme 47.

The three *N*-acyl oxazolidinone derivatives were then used for the 1,4-conjugate addition reactions using analogous experimental conditions. The Grignard reagent was initially prepared in dry THF from 5-bromopentene and magnesium turnings. The organocopper reagent was obtained by transfering the Grignard reagent to a suspension of copper bromide-dimethyl sulfide complex in THF and DMS. The resulting mixture was cooled to -78 °C, and the *N*-acyl oxazolidinone derivative, dissolved in dry THF, was added dropwise. After work up, purification by flash chromatography afforded the desired compounds (242), (243), and (244), (Scheme 48).



239a: R^1 = H, R^2 = Me
239b: R^1 = Me, R^2 = H
241 : R^1 = H, R^2 = H

242: R^1 = H, R^2 = Me
243: R^1 = Me, R^2 = H
244: R^1 = H, R^2 = H

Scheme 48.

Details of the reactions results are listed below, (Table 9).

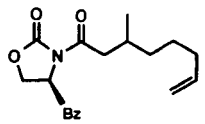
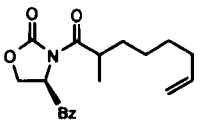
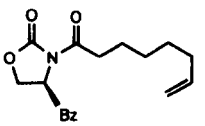
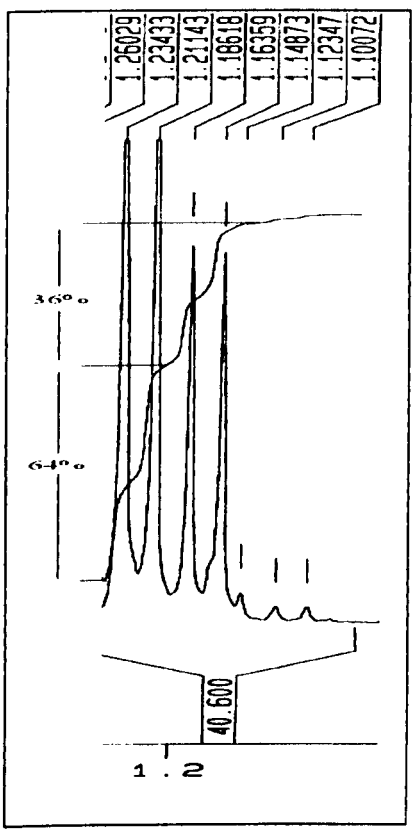
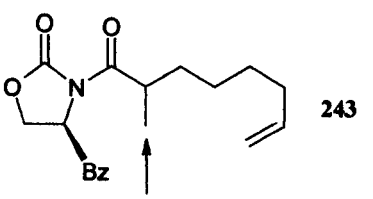
Product	Yield	Diastereoisomeric Ratio	*de* value
 **242**	71%	64 / 36	28%
 **243**	80%	64 / 36	28%
 **244**	74%	N/A	N/A

Table 9.

The diastereoisomeric excess (*de)* values were obtained from the corresponding ^{1}H NMR spectra by measurement of the integrals of the doublets arising from the methyl group (Figure 17).

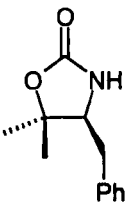




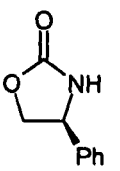
Methyl group expanded on the ^{1}H NMR

Figure 17: Expansion of the ^{1}H NMR spectra from compound 243.

The data in (Table 9) suggest that the chiral auxiliary (238) provided minimal levels of selectivity. This may be rationalised in terms of the rotation of the benzyl group, which must only offer partial facial selectivity. Compound (244), having its only stereogenic centre on the auxiliary, should give us a good idea of the selectivity of the Nicholas reaction. From the results obtained we should also be able to assess the effect of the chiral auxiliary on the later step. However, as Evans auxiliary (238) provided low levels of selectivity during the conjugate addition reaction, we regarded its use in a subsequent intermolecular Nicholas reaction with caution, and therefore decided to evaluate other chiral auxiliaries in order to identify a candidate that would provide higher levels of stereoselectivity during the conjugate addition reactions. At that point we set our sights on two relatively different chiral auxiliaries (245) and (246), (Figure 18).



245 = Xc_1

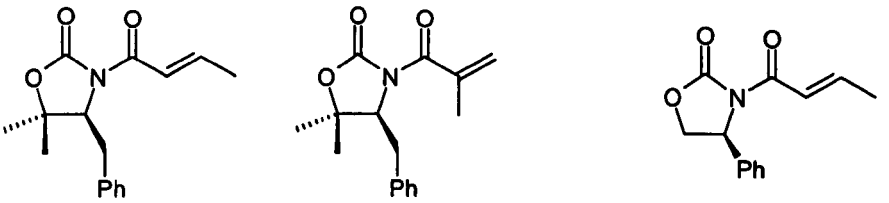


246 = Xc_2

Figure 18.

The gem-dimethyl groups at the C5 position on auxiliary (245) might impede the mobility of the adjacent benzyl group and hence improve the *de* value for conjugate addition reactions. We also anticipated that the phenyl group in (246) would be less flexible than the corresponding benzyl group in (238), which should therefore improve the selectivity during the reaction.

The oxazolidinone (245) was transformed to both *N*-acyl oxazolidinone (247) and (248) whereas (246) was only derivatised to the *N*-acyl oxazolidinone (249) in good to excellent yields (Figure 19).



247 248 249

Figure 19.

From these three compounds, a series of conjugate addition reactions was conducted, and the products obtained are presented in (Table 10).

We should note that we were able to correlate some of these results to previous reports in the literature. Davies reported excellent *de* values for conjugate additions carried out with enoyl derivatives of 4-phenyl-5,5-dimethyl-oxazolidinone. Although the synthesis and use of auxiliaries such as (238) and (245) were reported, these were not used in asymmetric conjugate addition reactions by Davies.[57,58] Hruby reported that a phenyl group at the C4 position on the oxazolidinone induces much greater levels of stereoselectivity than a benzyl group.[80] Other results reported by Williams *et al.* can be correlated to our findings.[81,82] Williams carried out a series of comparative conjugate addition reactions with both 4- benzyl and 4-phenyl *N*-enoyloxazolidinones, and their results show that conjugate addition carried out to the derivative (249) gave consistently better *de* values than those carried out with the derivative (239a). There also was a surprising result where the conjugate addition with the allyl organocuprate reagent gave *de* values > 97 %. This is consistent with our finding that the conjugate addition with the allyl organocuprate gave much

better results than the other reactions carried out with the same auxiliary derivative.

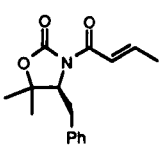
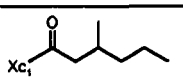
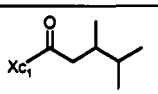
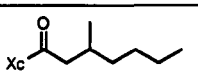
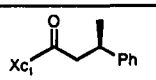
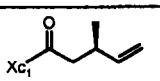
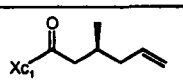
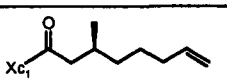
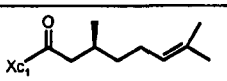
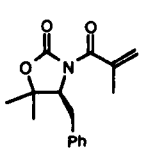
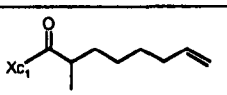
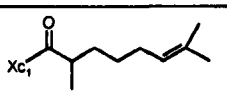
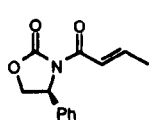
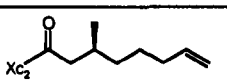
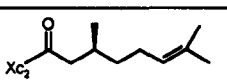
Precursor	Product	Product Number	Yield	*de* Values
		(250)	63 %	26 %
		(251)	60 %	undetermined
		(252)	62 %	26 %
		(253)	59 %	undetermined
		(254)	73 %	40 %
		(255)	68 %	72.8 %
		(256)	71 %	54 %
		(257)	78 %	42 %
		(258)	64 %	12 %
		(259)	83 %	14 %
		(260)	95 %	98 %
		(261)	83 %	80 %

Table 10.

In most of the examples, the *de* values were obtained from the measurement of the integration of the signals attributed to the methyl group emerging from the side chain. This is shown for the methyl group signal of compound (260), which, as anticipated, provided significantly improved levels of diastereoselectivity, (Figure 20).

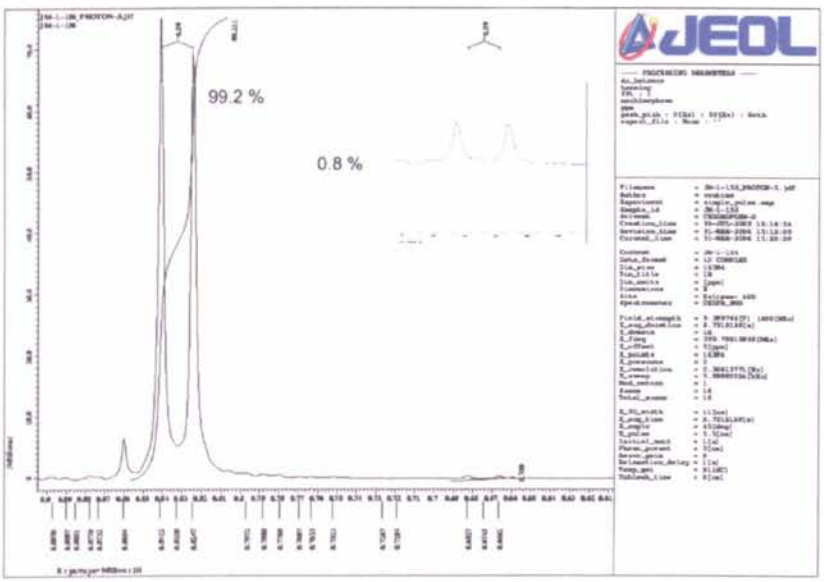


Figure 20.

For compounds (258) and (259) the *de* values were obtained by GC-MS analysis, as for these examples, the ^{1}H NMR data did not allow us to determine these values unambiguously. It is interesting to note that out of the whole series of compounds, only these two examples separated in the GC-MS column.

The relative stereochemistry at the chiral centre was confirmed by GC-MS analysis. Compound (261) was also prepared from (R)-citronellic acid, by conversion to the acyl chloride followed by the reaction with (S)-4-phenyl-2-oxazolidinone. The picture below shows the GC spectra of both the (R)-citronellic acid derivative and the product of the conjugate addition. It shows that the (S)-isomer was the major product of the conjugate addition which confirmed what we expected from Hruby's model, (Figure 21).

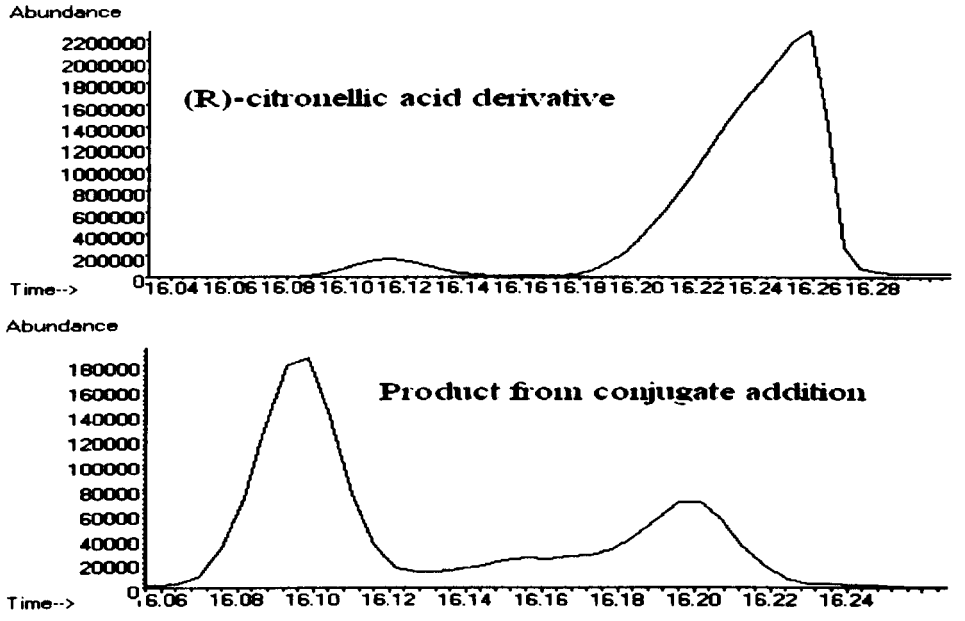


Figure 21.

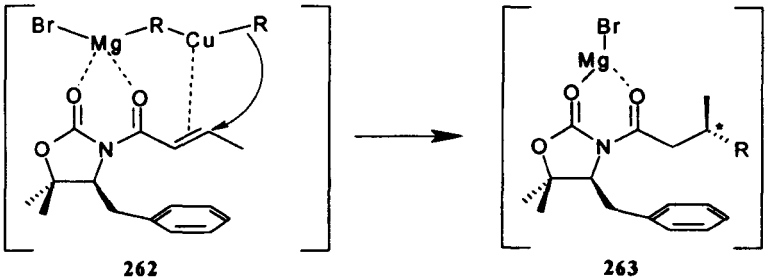
3.1.2. Conclusion to the conjugate addition

The results obtained from this series of conjugate addition reactions allowed us to come to a number of conclusions regarding each chiral auxiliary, as well as the presence of double bonds on the organocuprate adducts. From this study, we concluded that the chiral auxiliary we should use in our project was the oxazolidinone with the phenyl group at the C4 position, as this provided optimum levels of diastereoselectivity.

The extended work carried out with the Superquat type auxiliary gave us more information. First, the results obtained for compounds (256) and (257) compared to those of (258) and (259) led us to conclude that the *N*-acyl derivatives obtained from methacryloyl chloride provided much lower levels of diastereoselectivity, compared to the crotonyl derivatives.

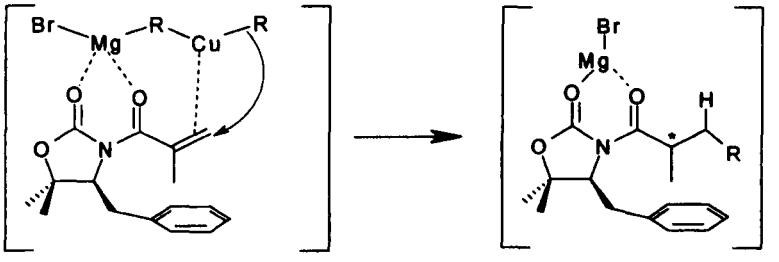
The first observation that we made was that the conjugate addition reactions carried out with the crotonyl derivatives of the Superquat auxiliary provided much higher levels of stereoselectivity than those carried out with the

methacryloyl derivative. This might result from the fact the terminal double bond could be less shielded in (264) than it is in (262). But the fact that the new chiral centre in (264) is not generated at the reaction centre might be a more plausible explanation for the loss of stereoselectivity, (Figure 22).



262 263

Olefin-Copper Complex and Magnesium Enolate fron the Crotonyl chloride derivative



264 265

Olefin-Copper Complex and Magnesium Enolate fron the Methacryloyl chloride derivative

Figure 22.

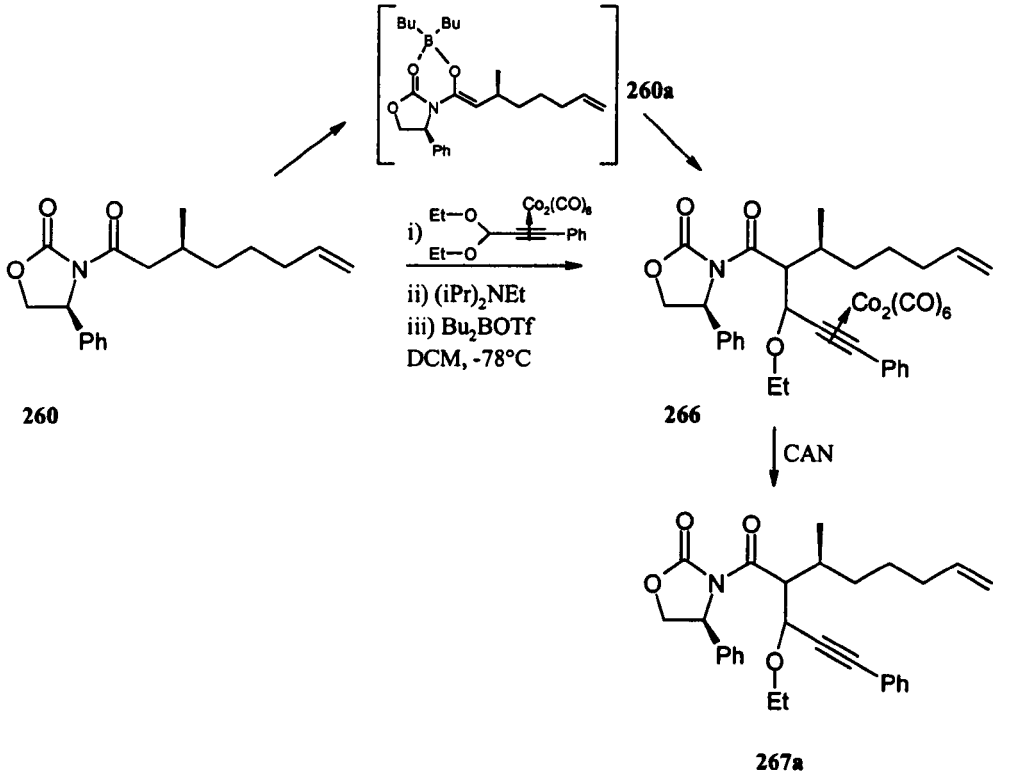
The series of compounds prepared from the *N*-acyl oxazolidinone (247) led us to several conclusions. It was noticeable that the presence of a double bond on the organocopper reagent leads to an improvement in the *de* values. Even though we were only able to determine two *de* values out of the three compounds with aliphatic chains, the results concurred and showed that conjugate additions with aliphatic organocopper reagents provide lower levels of stereoselectivity than those where a double bond is present. The effect seemed to be enhanced when the double bond was closer to the reaction centre, with the allyl and vinyl derivatives giving the highest *de* values. However, the

presence of the terminal *gem*-dimethyl seemed to reduce the levels of the *de* values, in (257) and (261).

Finally, the fact that the chiral auxiliary with the phenyl group at the C4 position on the oxazolidinone ring provided better selectivity than the two auxiliaries bearing a benzyl group at that same C4 position can also be explained. Although the phenyl ring on (249) rotates, it is always in the same position with respect to the reaction centre whereas the addition of a methylene group between the oxazolidinone and the aryl ring permits the phenyl group to rotate away from the reaction centre. The presence of the *gem*-dimethyl group at C5 position of Superquat may moderate in part the rotation, explaining the enhanced *de* obtained compared to those with the Evans auxiliary. Having reached these conclusions from the conjugate addition reactions undertaken, it was decided to carry on to the next step of our synthesis: the intermolecular Nicholas reaction. We decided to use the compound (260), bearing the chiral auxiliary with the phenyl group at the C4 position, which gave the best stereoselectivity for the conjugate addition reactions.

3.1.3 Intermolecular Nicholas reaction

For this part of our project we decided to follow a procedure reported by Schreiber while investigating the fluxional properties of dicobalt hexacarbonyl propargyl complexes.[11] Schreiber reported an alkylation reaction of an oxazolidinone based boron enolate with cobalt complexes of propargylic ethers (Scheme 51), and we applied his methodology to our intermolecular Nicholas reaction. The boron enolate (260a) was generated by deprotonation using diisopropylethyl amine and addition of dibutylboron triflate (Scheme 49).



Scheme 49.

The dicobalt hexacarbonyl complex was prepared by treatment of phenylpropargyl aldehyde diethyl acetal with dicobalt octacarbonyl complex in DCM. The reaction was monitored by the evolution of carbon monoxide, and filtration over silica gel with DCM as a solvent afforded the complex in 100 % yield. Our first attempt at the intermolecular Nicholas reaction produced the desired crude compound in a low yielding reaction, which upon purification afforded the complex (266) in 11 % yield plus decomposition products. The decomplexation reaction was performed at 0°C using an excess of CAN to give the decomplexed compound (267a) in 80 % yield. Analysis of (267a) by ^{1}H NMR was used to confirm the structure of the compound. Analysis of the ^{1}H NMR of the product proved very interesting. For instance, (Figure 23) reveals part of the ^{1}H NMR spectra attributed to the O-CH_aH_b-CH_3 moiety. It consists of a series of multiplets at δ 3.2 ppm, 3.4 pmm, 3.5 ppm, and 3.6 ppm. We assigned the more intense signals at δ 3.4 ppm and 3.6 ppm to the protons H_a

and H_b on the major isomer giving rise to two doublets of quartets. The signals arise from *gem* coupling between H_a and H_b with each of them coupled to the CH_3. We have attributed the other two multiplets at δ 3.5 ppm and 3.2 ppm to a diastereoisomer. Measurement of the integrals suggests a 3 : 1 ratio, giving a de value of 40 %, (Figure 23).

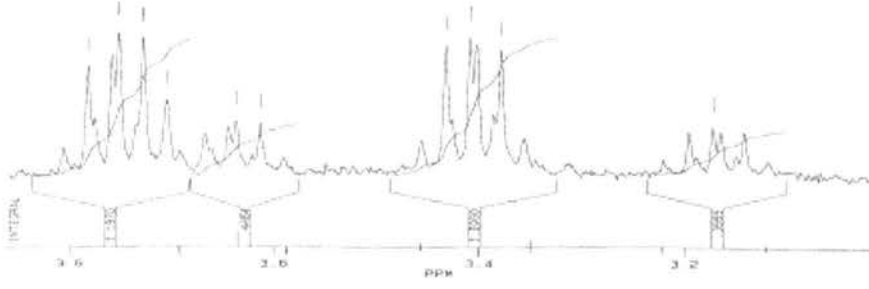
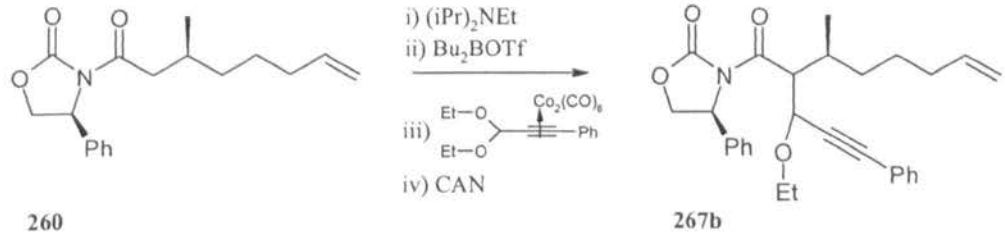


Figure 23.

In our attempts to improve the yield of the reaction we generated the boron enolate prior to its addition to the cobalt complex. Compound (260) was treated with 1.1 equivalent of Hunig's base and 2.2 equivalent of dibutyl boron triflate, the excess acting as the activating agent to form the carbocation. It was also decided to carry out the decomplexation reaction *in situ* as one-pot procedures have been shown to efficiently improve the yield of the reaction (Scheme 50).[32]



260 **267b**

Scheme 50.

The yield for (267b) was only improved slightly (15%), however, interestingly the ^{1}H NMR analysis suggested an improvement in stereoselectivity, as no duplicated signals could be observed this time.

Molecular modelling of the boron enolate derived from compound (260), (Quantum CAChe) suggested that a combination of the phenyl group, at the C4 position on the oxazolidinone ring, the butyl groups, attached to the boron atom, and the methyl group, alpha to the reactions centre, all contribute to steric hindrance (Figure 24).

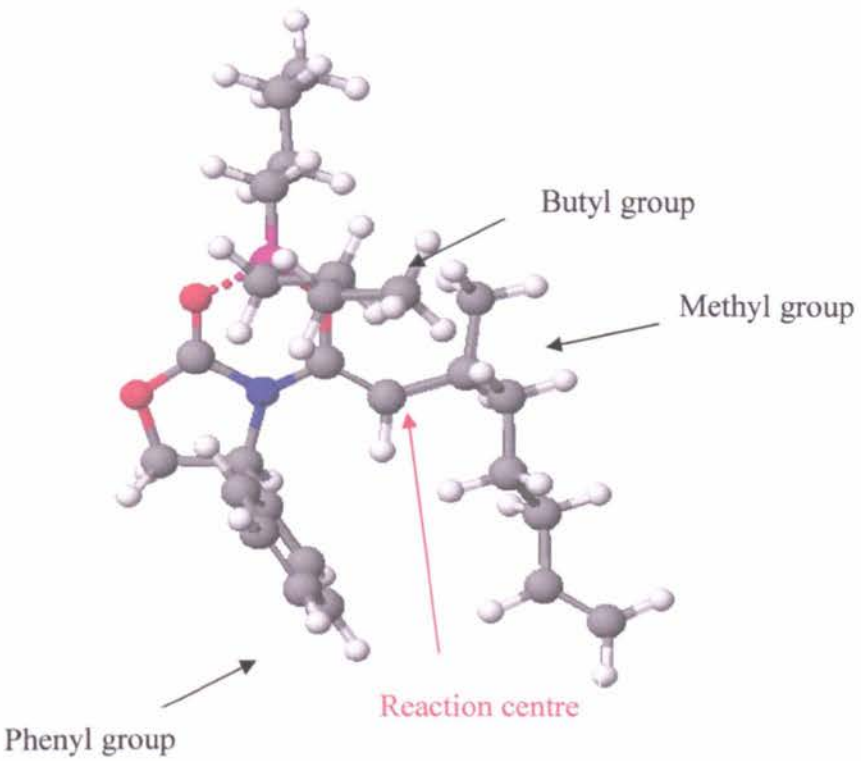
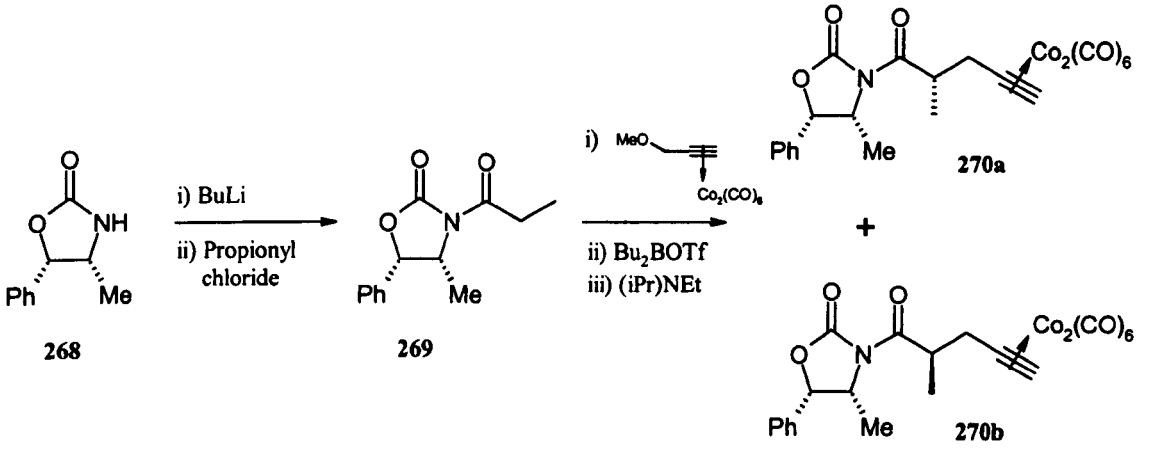


Figure 24.

This fact may explain the low yield in this reaction, with steric hindrance preventing the enolate from approaching the stabilised cobalt cation in combination with substrate degradation.

Having thought of reasons to explain our poor yield, we were still encouraged by the fact that the reaction did give the targeted compound and seemed to

show some stereoselectivity. As a result, we focused upon attempting the intermolecular Nicholas alkylation reaction using a less hindered reaction centre. In order to investigate the alkylation reaction further, and in the process scrutinise our hypothesis regarding the steric hindrance, we decided to carry out a series of alkylation reactions using an alternative chiral auxiliary bearing a methyl group at the C4 position and a phenyl group at the C5 position on the oxazolidinone ring (268). At that stage we thought it was important to reproduce the exact reaction conditions carried out and reported by Schreiber, i.e. a simpler model than the one proposed (Scheme 51).[11]



Scheme 51.

The *N*-propionyl-4-methyl-5-phenyl-2-oxazolidinone (269) was obtained in 95 % yield. The intermolecular Nicholas reaction, performed upon (269), provided the complexes (270a,b) as red crystals in 70 % yield. The ratio of diastereoisomers (270a) and (270b), which was found to be 15 : 1, was determined by measurement of the integrals of the ^{1}H NMR signal attributed to the methine group α- to the carbonyl group, (Figure 25).

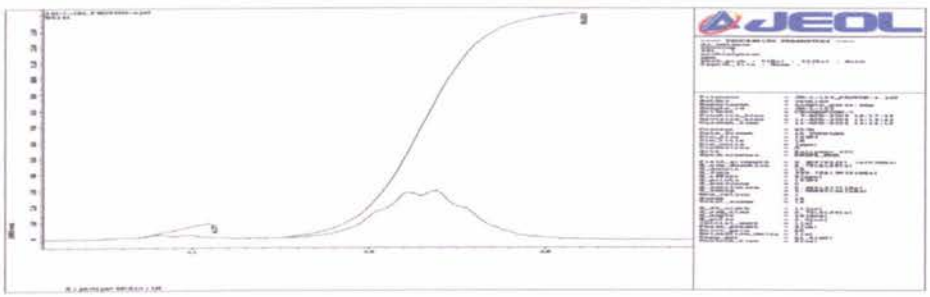


Figure 25.

Schreiber reported the (S)-diastereoisomer (270a) to be the major product of the alkylation reaction, following the suggestion made by Evans concerning the *Z*-enolate geometry. The diastereofacial selection is dictated by the C4-substitutent on the oxazolidinone ring (Figure 26).

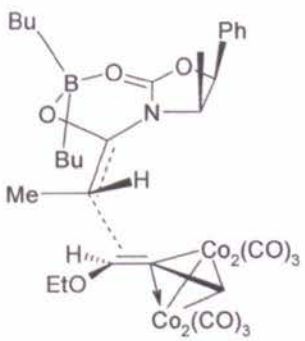
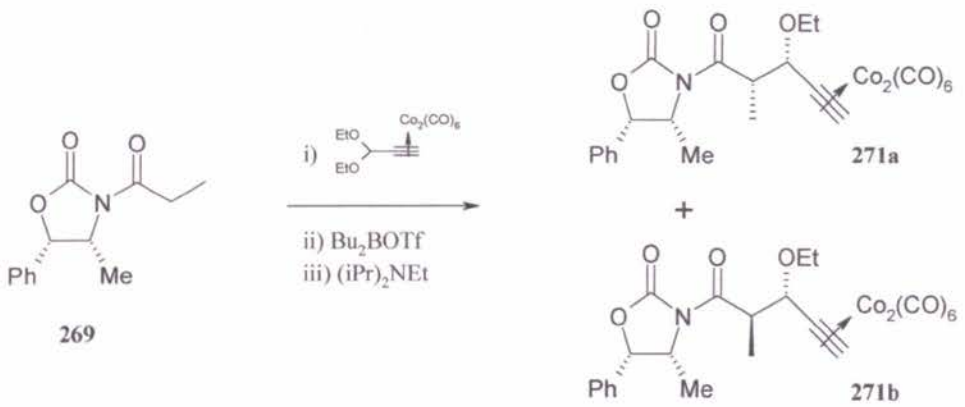


Figure 26: Z-enolate intermediate for the intermolecular Nicholas reaction

Even though our yield and *de* value were lower than the ones reported by Schreiber, these results were considered as a good step forward. In our plan of action, the next step was to verify that a bulkier propargyl dicobalt hexacarbonyl complex would react in the same manner with the same oxazolidinone derivative (Scheme 52).



Scheme 52.

The reaction yielded approximately a 60 % yield of the desired product as a mixture of diastereoisomers (271a) and (271b) in a 15 : 1 ratio. The ratio was determined by integration of the proton signal attributed to the O-CH_2 group (Figure 27).

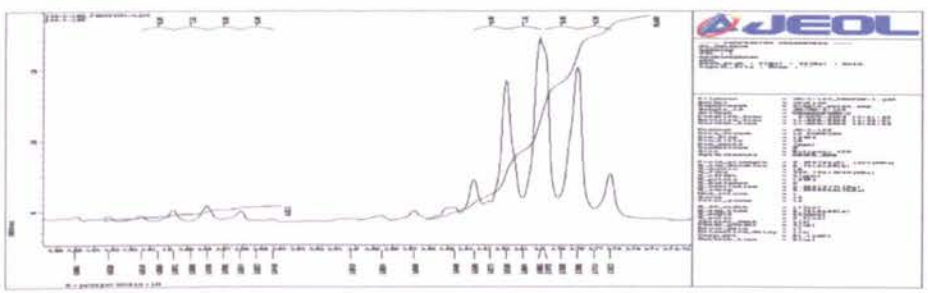
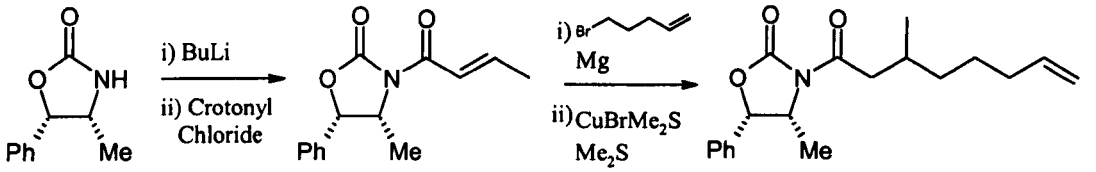


Figure 27.

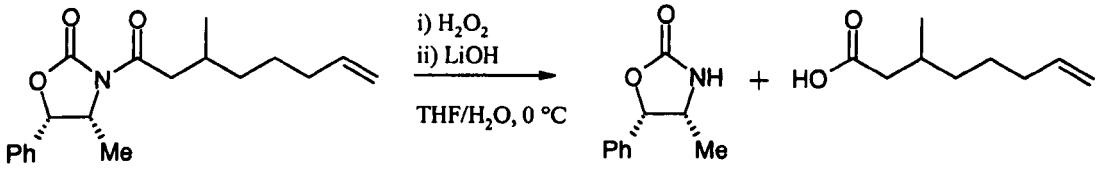
These results led us to believe that our hypothesis regarding the steric hindrance generated by a phenyl group at the C4 position on the oxazolidinone ring (249) was correct. To prove it we had to carry out the same reaction as the one represented in (Scheme 50) with the alternative chiral auxiliary (268). The *N*-acylation and conjugate addition reactions were carried out as before (Scheme 53).



268 272 273

Scheme 53.

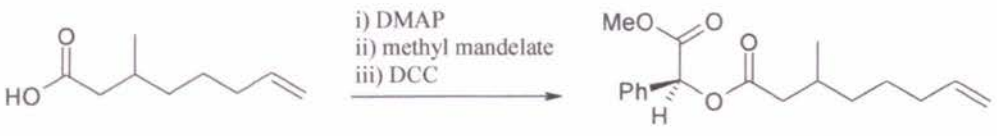
Compound (272) was obtained in 96 % yield, and compound (273) in 80 % yield. Both ^{1}H NMR and GC-MS analysis suggested that (273) was formed with high levels of diastereoselectivity as no duplicated signals or separation of signals could be observed. The importance of determining the *de* for (273) prior to the intermolecular Nicholas reaction led us to a different approach to probe the *de* value. Cleaving the side chain from the chiral auxiliary generated the corresponding carboxylic acid from which we were able to form a Mosher ester and use this to determine the *de* value.[83,84] The method for the cleavage of the chiral auxiliary to yield the corresponding carboxylic acid was reported by Evans (Scheme 54).[63]



273 268 274

Scheme 54

The carboxylic acid (274) was obtained in 61 % yield, and was then reacted with methyl mandelate, under non-racemising conditions, to form the corresponding Mosher ester (275), (Scheme 55).



274 275

Scheme 55

The ester was formed in 80 % yield, and allowed the determination of the *de* value by integration of the signal from the methyl group β to the carbonyl group on the side chain (Figure 28).

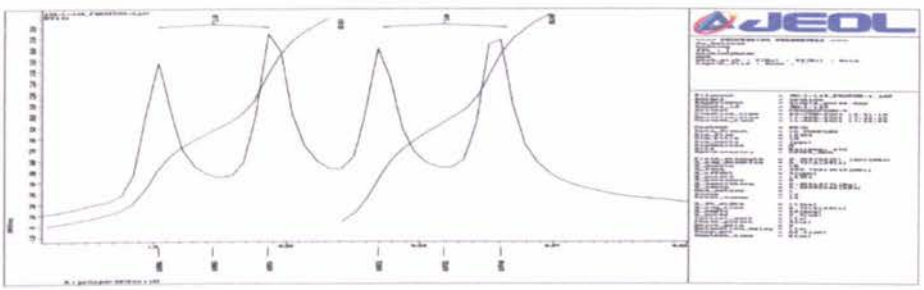
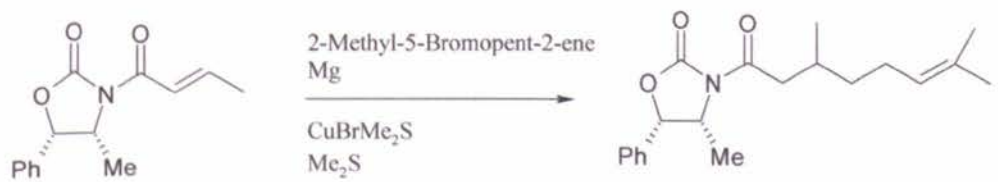


Figure 28.

As the figure above shows, the chiral auxiliary did not induce any stereoselectivity into the conjugate addition reaction. This reinforced the idea that the C4 substituent has a major role to play in the diastereofacial selectivity of the reaction. For comparison purposes with the other chiral auxiliaries used, we also synthesised the 2-methyl-5-bromo-pent-2-ene derivative (276) (Scheme 56).

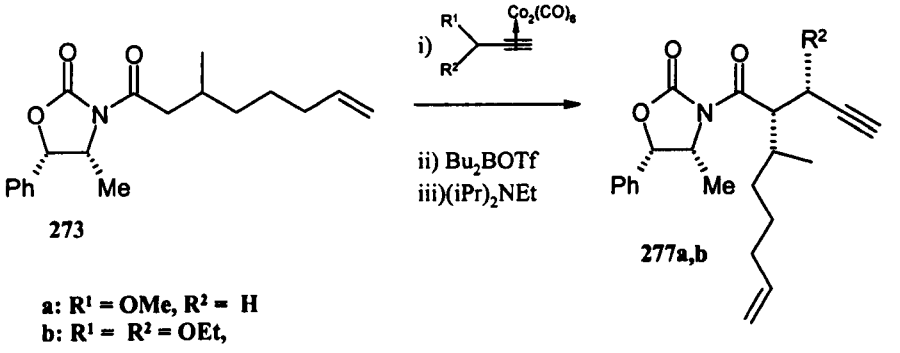


272 276

Scheme 56.

The GC-MS spectra showed comparative results, with a diastereoisomeric ratio of 50 : 50.

This led us to conclude that the methyl group is too small to have an impact on the face selection of the conjugate addition, compared to benzyl and phenyl groups at the C4 position. However, we were still interested in carrying out intermolecular Nicholas alkylation reactions to compounds bearing that chiral auxiliary. Compound (273) was reacted with two different propargyl dicobalt hexacarbonyl complexes (Scheme 57).



Scheme 57.

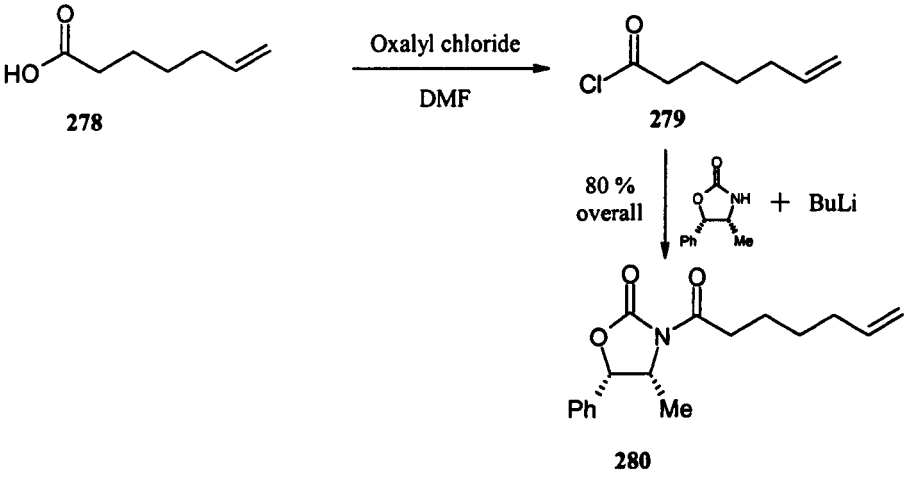
The results for these reactions are tabulated below (Table 11).

Product	Yield	Ratio	*de* value
277a	70 %	60 : 40	20 %
277b	90 %	60 : 40	20 %

Table 11.

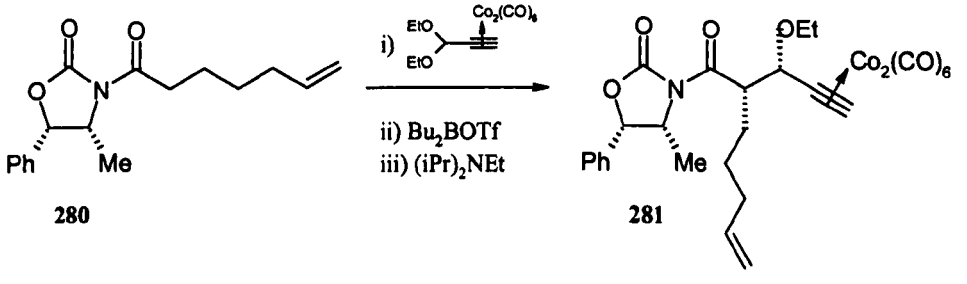
This series of experiments suggested that steric hindrance played a major role in the low yield for the intermolecular Nicholas reaction when the reaction was carried out with compound (260). Despite (273) existing as a 50 : 50 mixture at the β-methyl group a diastereoselective reaction appears to have taken place to afford a modest *de* of 20 %. It suggests that in order for this to occur one face of the stabilised cation must be exposed preferentially to the other to afford an

enriched mixture of diastereoisomers. However, we could not, at this point, elaborate any conclusive discussion about the stereoselectivity of the intermolecular Nicholas alkylation reaction. The results above seem to show that there is some selectivity. In order to gain a better understanding with regards to the stereoselectivity of this reaction, we focused upon a simpler model system. To do so, 6-heptenoic acid (278) was transformed to the corresponding acyl chloride (279), and reacted with the chiral auxiliary to yield the derivative (280), (Scheme 58).



Scheme 58.

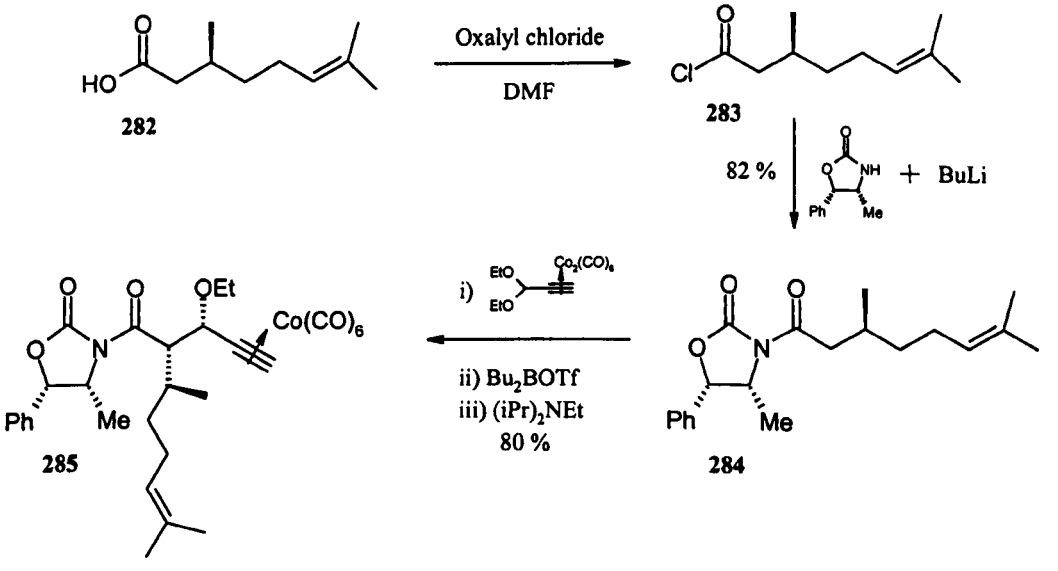
Compound (280) was then reacted with hexacarbonyl[diethyl acetal propiolaldehyde]dicobalt to afford the alkylated derivative (281) in 77% yield, (Scheme 59).



Scheme 59.

The ratio, 86 : 14, giving a *de* value of 72 % was determined in the same manner as for compounds (271a) and (271b), by integration of a prochiral proton signal attributed to the CH_2 at the acetal group. These results were later confirmed by GC-MS analysis of the decomplexed product. Analysis of the ^1H NMR spectrum for (281) showed that the propargylic methine hydrogen atom resonated at δ 4.28 ppm, for the minor diastereoisomer, and δ 4.30 ppm for the major isomer. The signals were doublet of doublets with coupling constants *J* 8.5 Hz and 1.8 Hz for the major isomer. The upfield signal for the minor isomer was found to have coupling constants *J* 9.5 Hz and 2.2 Hz. On the basis of the coupling constant data, as well as the rationale presented by Schreiber to explain the preference for *syn* selectivity with a chiral imide boron enolate, we tentatively assigned the major diastereoisomer as the *syn* product (281).

The same series of reactions were carried out with an adduct derived from (S)-citronellic acid (282). Conversion to the corresponding acyl chloride (283), and reaction with the chiral auxiliary in presence of butyl lithium gave compound (284), in 82 % yield. This was then used in the alkylation reaction to afford the desired product (285), in 80 % yield (Scheme 60).



Scheme 60

All reactions produced good yields (>80 %), and the ratio was determined following the same technique as previously stated. The ratio was found to be 90 : 10, giving a *de* value of 80 % as the picture below demonstrates, showing the resonance attributed to the O-CH_2-CH_3 group (Figure 29).

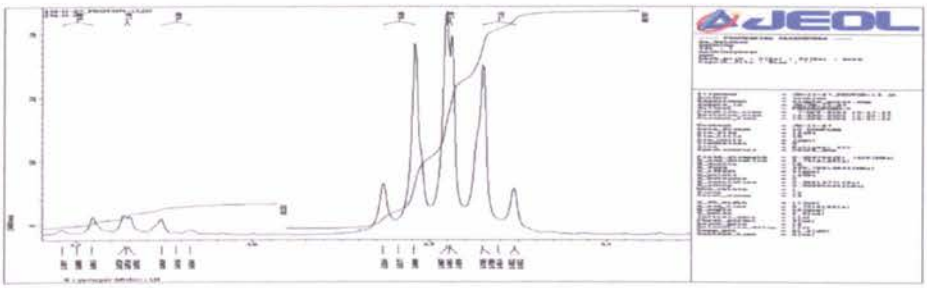


Figure 29.

Further analysis of the ^{1}H NMR spectrum of the complex (285) showed that the methine hydrogen atom α to the carbonyl group occurred as two sets of double doublets, with the major isomer centred at δ 4.45 ppm, *J* 10.2 Hz and 4.4 Hz, and the minor isomer upfield at δ 4.39 ppm, *J* 9.8 Hz and 4.7 Hz. From the Hruby model, the *syn* isomer was expected to be the major one, so one could assign the coupling constants as demonstrated in (Figure 30).

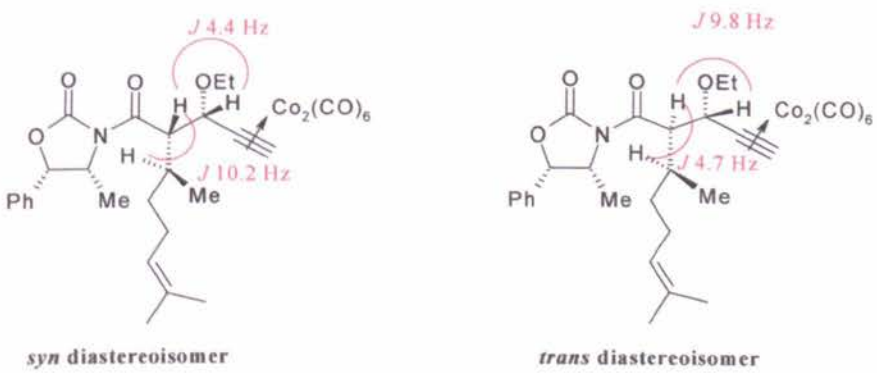


Figure 30.

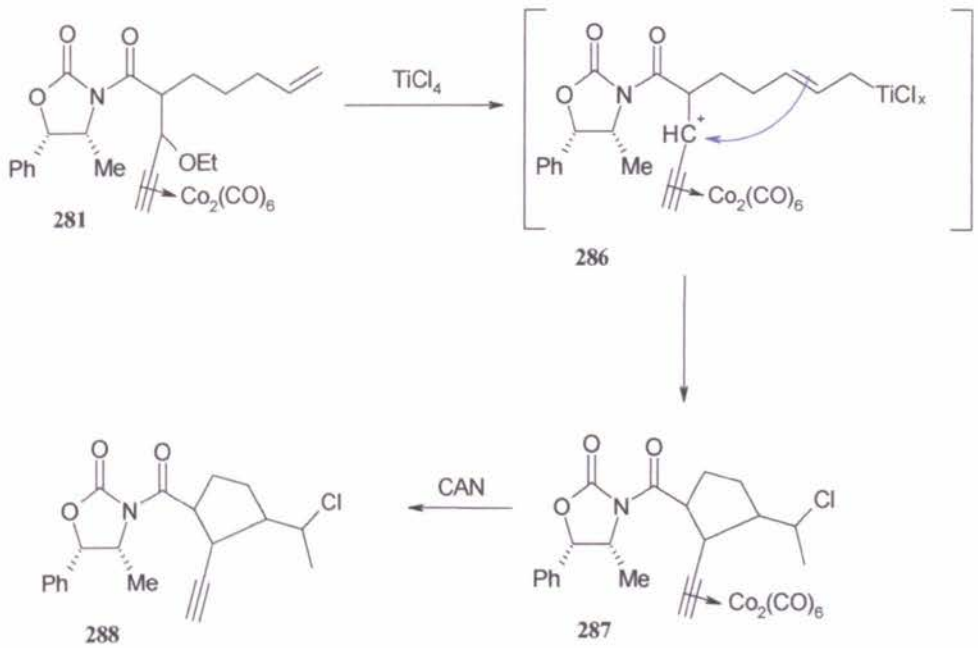
With regards to the propargylic hydrogen atom this appears as a doublet only, reflecting the double bond character of the complex, at a chemical shift δ 4.75

ppm. We have assumed that in the absence of a second doublet, representative of the minor isomer that the two resonances are overlapping, with a coupling constant of *J* 10.2 Hz for the doublet. On the face of it, we were tempted to speculate that a reversal in the stereochemistry of the major diastereoisomers from *syn* to *anti* had taken place in this reaction based upon the magnitude of the coupling constant. However, the preference for the formation of the *syn* isomer has been very well documented and verified.[68] Due to the *syn/anti* ambiguity as a result of these coupling constants i.e. 10.2 Hz and 9.8 Hz coupled with a lack of suitable sample for X-ray analysis we are keeping an open mind.

3.1.4 Intramolecular Nicholas reaction.

After establishing that alkylation reactions between *N*-enoyl derivatives (273), (280), (284), and several propargyl cobalt complexes occurs with good levels of stereoselectivity, the investigation of the tandem intramolecular cyclisation step was our next aim. This required investigating a suitable Lewis acid. Previous studies undertaken at Kingston University had shown that Lewis acids such as $TiCl_4$, HBF_4, $BF_3{\cdot}Et_2O$, or Bu_2BOTf, could be successfully used in such intramolecular cyclisation work.[31,32] Of these four Lewis acids, only $TiCl_4$ proved suitable. The reactions were conducted with a range of dicobalt hexacarbonyl oxazolidinone derivatives such as (281), with recorded yields not exceeding 60 %. Optimum yields were obtained when the reaction was carried out at -10 °C, and lower yields were afforded at lower temperatures, such as -78 °C. The products obtained turned out to be very difficult to characterise. Analysis by ^1H NMR spectroscopy of the complexed products provided poorly resolved spectra, and the ^{13}C NMR spectra turned out to show even less,

sometimes only noise. It was assumed that this might be caused by cobalt impurities in the products, interfering with the magnetic field of the instrument. Decomplexed products provided much better ^{1}H NMR spectra, and showed that the reaction had taken place by the loss of the O-CH_2-CH_3 group, as well as the loss of the olefinic protons in compound (285). We attempted the reaction with compound (281). The NMR spectrum showed the loss of the O-CH_2-CH_3 group, and also showed a new peak at δ 4 ppm. This resonance is characteristic of a proton attached to a carbon bearing an halogen atom. This outcome was consistent with results on intramolecular Nicholas reactions previously carried out at Kingston University.[85] Tyrrell *et al.* reported a mechanism for intramolecular Nicholas reactions carried out with adducts bearing a terminal carbon-carbon double bond. The mechanism involved proposed a titanium assisted double bond migration to the more stable disubstituted alkene (286). Further reaction with the Lewis acid generates the cation which then reacts with the double bond. The presence of the peak at δ 4 ppm led us to believe that this was what had happened with (281). In the presence of the titanium Lewis acid the double bond migration and formation of the stabilised cation occur to form (286). An intramolecular Nicholas cyclisation reaction occurs, yielding compound (287). Decomplexation using an excess of CAN leads to compound (288), (Scheme 61).



Scheme 61.

Another clear signal on the NMR spectra, a doublet at δ 1.5 ppm, *J* 6.6 Hz, corresponding to the signal of a methyl group next to a chlorine atom, confirmed that our theory was the correct one.

Spectroscopic analysis of the crude decomplexed compound showed the presence of several products for the reaction. This could be observed by inspection of the signal corresponding to the terminal alkyne proton. The expansion of this signal, (Figure 31), shows the presence of a number of products with a major compound.

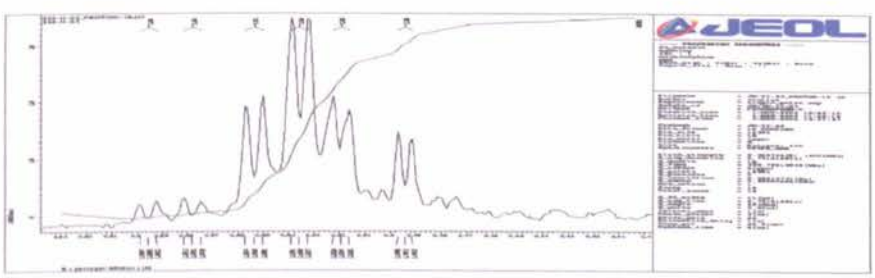


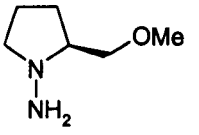
Figure 31.

When the reaction was carried out with the citronellic acid derived cobalt complex (285), the same loss of stereoselectivity was observed. The presence of several isomers of the cyclised product rendered characterisation very difficult, and hence not such a useful synthetic procedure. In hindsight it may have been appropriate to hydrolyse the chiral auxiliary prior to the Nicholas reaction. It is evident from the results that the chiral auxiliary offered no control over the intramolecular Nicholas reaction, and perhaps the use of a chelator may have provided an enhancement in this reaction. As a result, we decided to focus our attention upon alternative synthesis. Despite proving very efficient in terms of stereoselectivity towards the intermolecular Nicholas reaction *via* a boron enolate, the presence of a chiral auxiliary on the cyclisation precursor seemed to complicate the reaction on different levels. The first point was that all yields and selectivity for the cyclisation reaction were quite low, and the changes applied to the reaction conditions, such as the temperature of the reaction, only improved the yields slightly. Secondly, characterisation was very difficult, due to the presence of several unresolvable diastereoisomers. This lack of stereoselectivity led us to believe that the remoteness of the chiral auxiliary failed to exert its influence on the cyclisation process. As a result, we decided to explore another route using a completely different chiral auxiliary technology, with the auxiliaries SAMP and RAMP, (S)- and (R)-1-amino-2-methoxymethyl-pyrrolidine,.

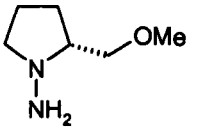
3.1.5 The SAMP/RAMP approach.

In this approach we decided to investigate the use of (S)-1-amino-2-methoxymethylpyrrolidine (SAMP, 289) as chiral auxiliary technology (Figure 32). The motivation behind this was an attempt to place the auxiliary closer to

the reaction centre, and therefore improve the influence of the auxiliary on the tandem Nicholas reactions.



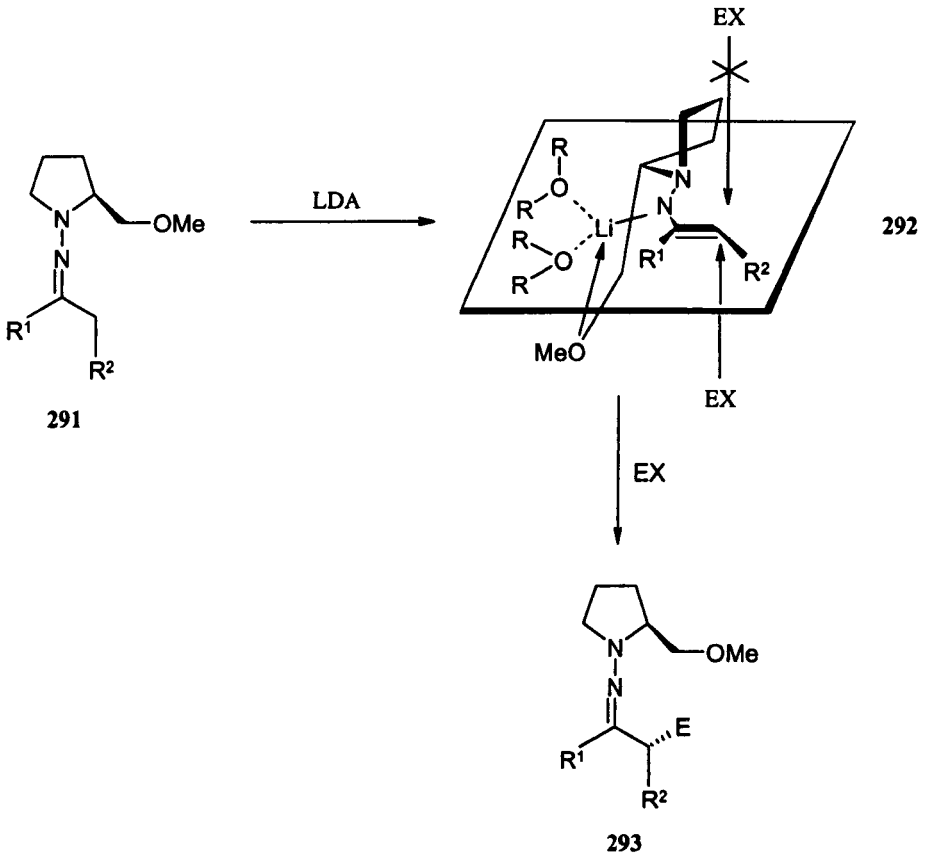
SAMP (289)



RAMP (290)

Figure 32.

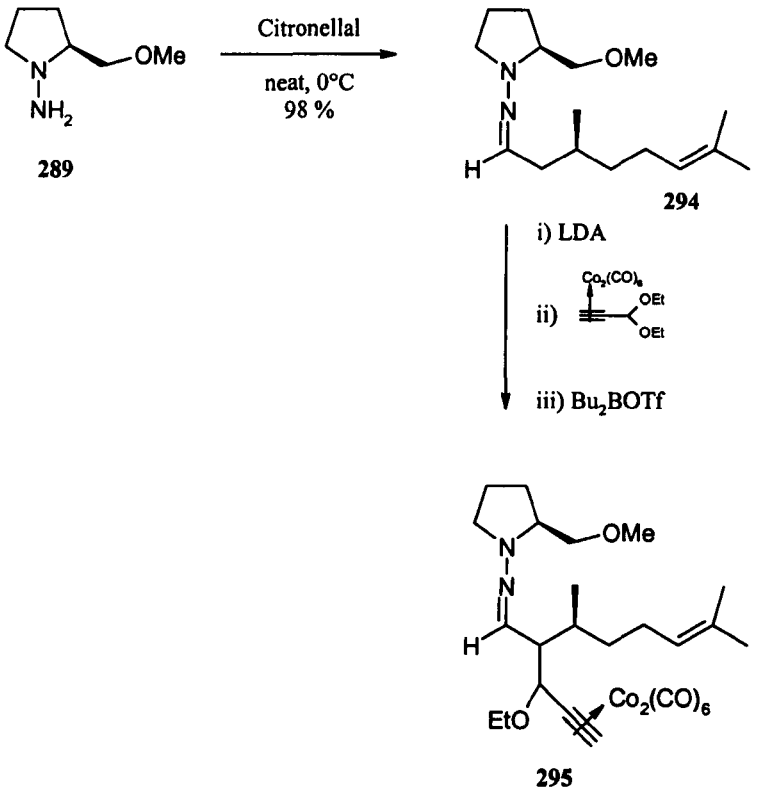
The wide range of asymmetric reactions which can be undertaken with either SAMP or its opposite enantiomer RAMP (290) has been widely reviewed.[86] These include alkylation, aldol, conjugate addition, rearrangement, and Diels-Alder reactions. The principle is the same as for any other chiral auxiliary. The first step is to functionalise the auxiliary, and then undertake the asymmetric reaction. The SAMP-hydrazone (291) may be deprotonated, with LDA, to form an azaenolate (292) that can then react with an electrophile (EX) yielding a diastereoisomerically enriched hydrazone (293), (Scheme 62).



Scheme 62.

Studies undertaken by Enders *et al.* in order to determine the exact structure of the azaenolate led to the conclusion that the azaenolate (292) shows an *E*-conformation at the carbon-carbon bond, and a *Z* conformation at the carbon-nitrogen bond, (Scheme 62).[87,88,89]

Our plan of action was to functionalise the SAMP auxiliary (289) with the aldehyde citronellal to form the corresponding SAMP-hydrazone (294). Formation of the azaenolate and reaction with the carbocation derived from the propiolaldehyde diethyl acetal dicobalt hexacarbonyl complex should yield the desired product (295), (Scheme 63).



Scheme 63.

The synthesis of the SAMP-hydrazone (294) was carried out following the methodology reported by Enders, consisting of dropwise addition of (S)-(-)-citronellal to neat SAMP (289) at 0°C.[87] This provided the desired SAMP-hydrazone in quantitative yield after 2 hrs. For the alkylation reaction with the cobalt complex, we followed the procedure used with the oxazolidinone derived compounds. The *in situ* generation of the azaenolate, in the presence of the cobalt complex, was followed by the addition of a Lewis acid to form the carbocation. The reaction was monitored by TLC analysis, and did not seem to proceed. After two hours, and no sign of a new spot on the TLC plate, the cold bath was removed and the temperature left to rise slowly. No noticeable change was observed. As we thought that the low temperature might be a problem in this reaction, we also carried it out at 0°C, but to no avail. We also tried to follow a similar procedure to the one applied for the synthesis of compound

(267b) in (Scheme 50). The azaenolate was prepared in one flask, and the stable cation in another before being transferred to the azaenolate flask *via* canula. Unfortunately, the reaction did not proceed, and we were not able to investigate the reasons for the non-advancement of this reaction. These results, combined to those obtained while investigating the intramolecular Nicholas cyclisation reaction, led us to turn our attention to an alternative approach.

3.2 Chiral Pool and chiral reagents approach

3.2.1 Introduction

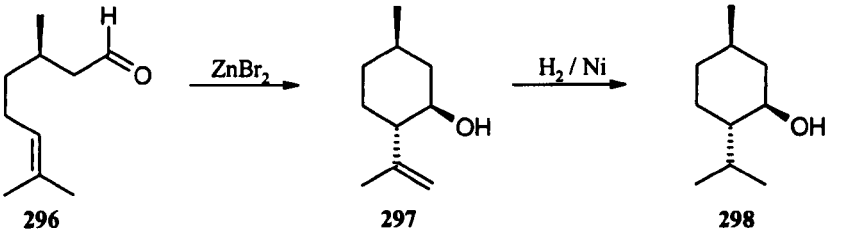
In this section the discussion will follow two different approaches involving a series of optically active propargyl alcohols, derived from citronellal, which then undergo an intramolecular Nicholas cyclisation reaction. In the first approach, oxidation of the racemic propargyl alcohol to the corresponding ketone was followed by an asymmetric reduction to yield an optically pure propargyl alcohol. In the second approach the diastereoisomerically pure propargyl alcohols are generated by a stereoselective zinc catalysed alkynylation reaction.

This final stage of the project was designed to investigate an intramolecular Nicholas reaction. Using a simpler enantiomerically pure precursor for the intramolecular Nicholas cyclisation reaction, should allow us to investigate the stereoselective outcome of the reaction.

3.2.2 Citronellal, a useful natural product

In both of the approaches discussed in this section, citronellal acts as the substrate. Citronellal is a monoterpenoid, and is the main component in the mixture of terpenoid compounds that give citronella oil its distinctive lemon scent. It is widely used in the cosmetic industry in products such as soap and perfumes, and for ambiance products such as candles and oils. It is also used in synthetic chemistry.

Isopulegol (297), a monoterpenic alcohol also widely used in the flavour and perfume industries, and an intermediate to the synthesis of menthol (298) can be obtained from citronellal (296), (Scheme 64).



296 297 298

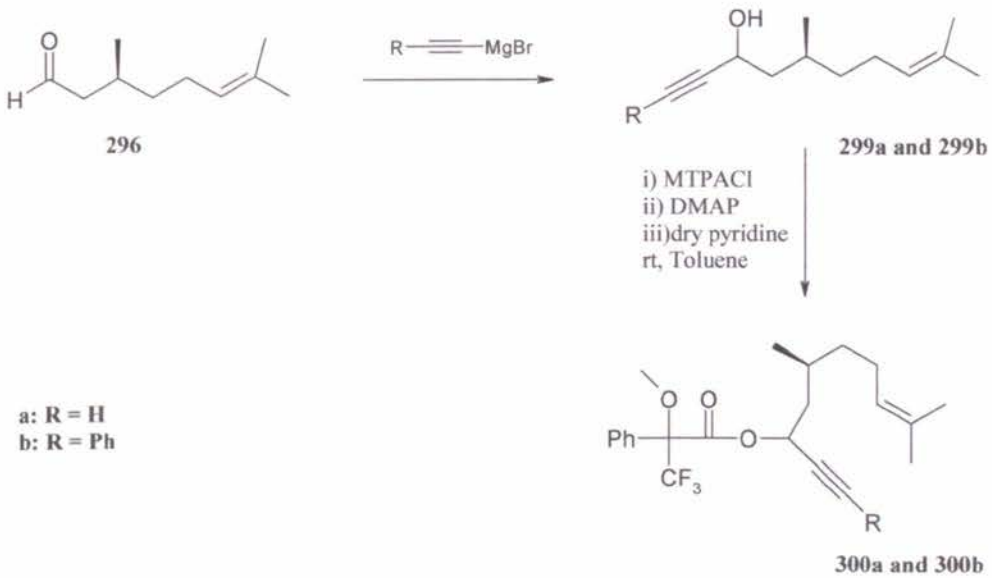
Scheme 64.

In this approach developed by the Japanese chemical company, Takagaso, (R)-citronellal is converted to isopulegol through a Lewis acid catalysed carbonyl ene reaction. The methyl group at the C3 position in citronellal favours an equatorial position in the chair arrangement of the transition state, directing the formation of the two new chiral centres, affording the isopulegol with a stereoselectivity of 94%. Hydrogenation of the isopulegol intermediate affords the L-menthol isomer.[90] In recent years, there have been several new developments towards the synthesis of isopulegol from citronellal. Chuah *et al.* have tested a series of zirconium catalysts, and reported cyclisation reactions of citronellal to isopulegol with excellent yields and selectivity. The catalysts

were shown to have a strong Lewis acid site and a weak Brønsted acid site. The reported mechanism for the reaction includes the binding of the citronellal molecule to a zirconium Lewis acid site via the aldehyde's oxygen and the π-electrons of the double bond to obtain the desired configuration for the cyclisation. This is followed by protonation of the aldehyde via the Brønsted acid site that initiates the cyclisation.[91] Other reports using different catalysts have been made but show either lower yield or lower selectivity.[92,93] The use of solid catalysts under solvent free conditions have also been reported for this reaction with good selectivity and excellent yields, showing that green chemistry has a viable future.[94]

3.2.3 The oxidation-reduction approach

Our rationale for this part of our project was to prepare an enantiomerically pure compound with which we could study the stereoselectivity of an intramolecular Nicholas reaction. The first step involved the synthesis of a propargyl alcohol (299ab) by reacting (S)-citronellal (296) with an alkynylmagnesium bromide Grignard reagent. As we may have anticipated, the level of diastereoselectivity in this reaction was minimal with a *de* value of 10 %. This was shown through conversion to the corresponding MTPA-Cl Mosher esters (300a) and (300b), (Scheme 65).[109, 110]



Scheme 65.

^{1}H NMR studies showed duplicated signals for the C3 methyl group, with a ratio of 55 : 45 as the picture below demonstrates, (Figure 33).

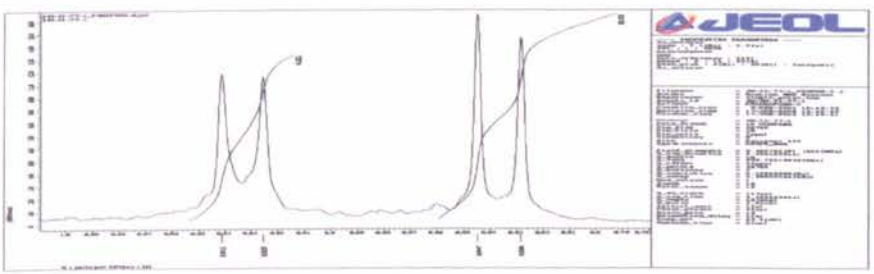


Figure 33.

The lack of diastereoselectivity in this Grignard reaction led to the adoption of a two step procedure in order to obtain optically pure isomers of the propargyl alcohols. The two step reactions included an oxidation of the secondary propargyl alcohol to the corresponding ketone, followed by an asymmetric reduction back to the alcohol, to yield the desired pure isomers. A literature survey showed various possibilities to perform the oxidation of secondary alcohols to their corresponding ketones. Corey and Suggs reported that pyridinium chlorochromate is a useful reagent for such conversions.[95] Dess and Martin reported periodinane is known to be a good oxidising agent for

secondary alcohols.[96] Both these procedures were considered, however, Jones reagent, chromium oxide in aqueous sulphuric acid provided the best conversion rates.[97] The easy preparation of the reagent, the simple work-up for the reaction, and similar work previously reported led us to choose this procedure.[98] The oxidation of alcohols with chromic acid follows a two step mechanism.[99] The first step involves the formation of a chromate ester of the alcohol (299) which donates an electron pair to the chromium atom as an oxygen atom accepts a proton, forming the intermediate 1. The intermediate 2 results from a transfer of protons, where one oxygen atom loses a proton while another accepts one (Figure 34).

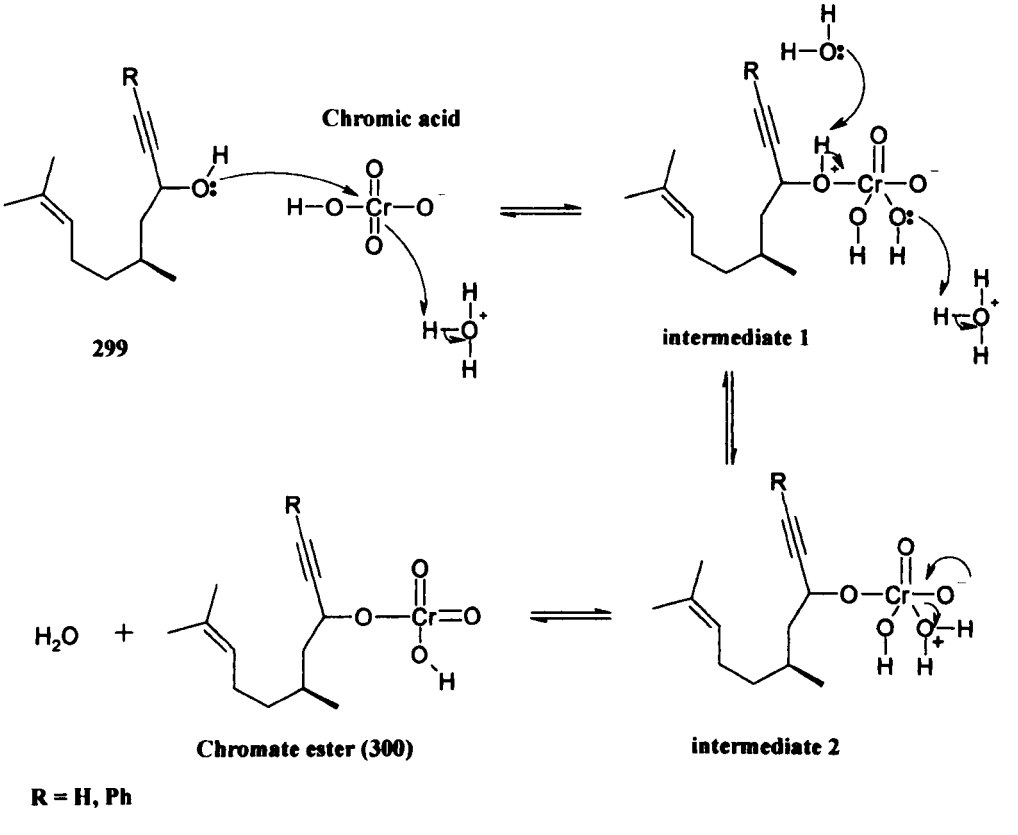


Figure 34. Chromate oxidation: step I

The chromate ester is then generated as a chromium-oxygen double bond forms and a molecule of water departs. In the second step of the oxidation, the

chromium atom departs with a pair of electrons from the alcohol, leading to the formation of the ketone (302a,b), (Figure 35).

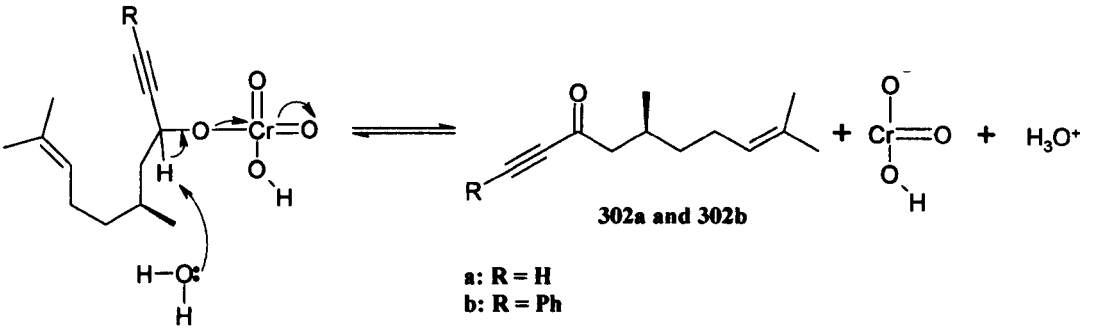
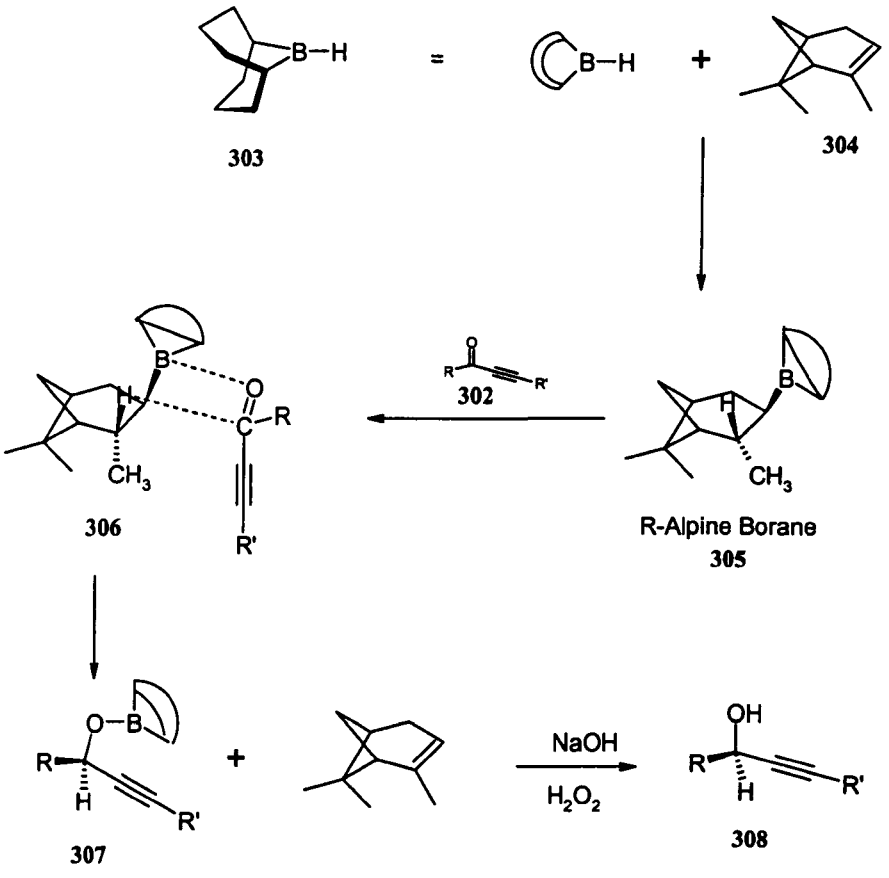


Figure 35. Chromate oxidation: step II

All of the oxidation reactions carried out provided the desired products in over 80% yield. However, the two most important steps of our synthesis still had to be carried out. The next step was the stereoselective conversion of the ketone back to the corresponding alcohol. Reports of successful asymmetric reductions of propargyl ketones to their corresponding alcohol using alpine borane led us to explore that route. Midland *et al.* reported a series of such asymmetric reduction reactions to various propargyl ketones, affording the alcohols in good yields and enantiomeric excesses.[100,102] Alpine borane is easily prepared from α-pinene and 9-BBN (303). As a general observation reagents prepared from (+)-α-pinene (304) provide the (R)-propargyl alcohols and those prepared from (-)-α-pinene the (S)-propargyl alcohols (308). This may be explained by the mechanism of the reaction (Scheme 66).

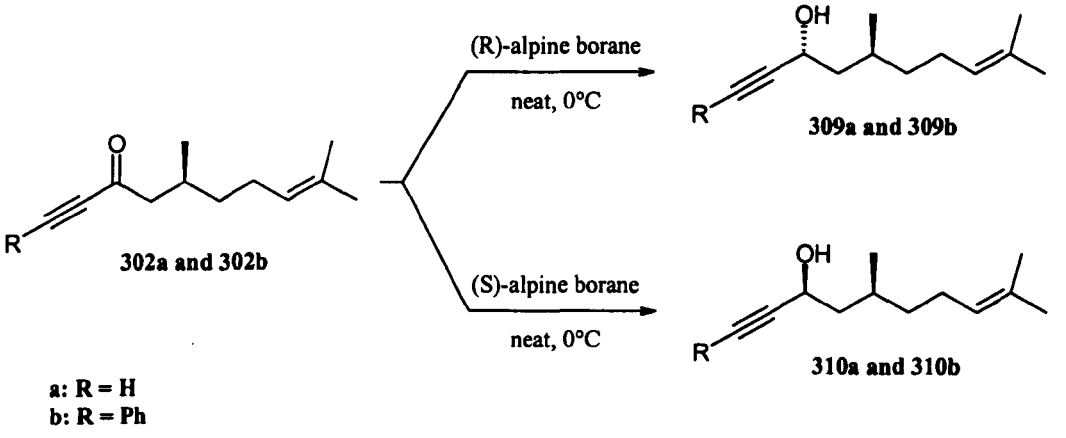


Scheme 66.

Midland *et al.* suggested that the hydride transfer occurs from a boat-like transition state (306) where the acetylene occupies an axial position delivering the proton to the opposite side of the R group. The stereoselectivity of the reaction results from the fact that the transition state for the minor compound is not favoured, due to the diaxial interaction of the pinanyl methyl group and the R group of the ketone. Midland concluded that the stereoselectivity of the reagent is based solely on steric grounds.[100,101]

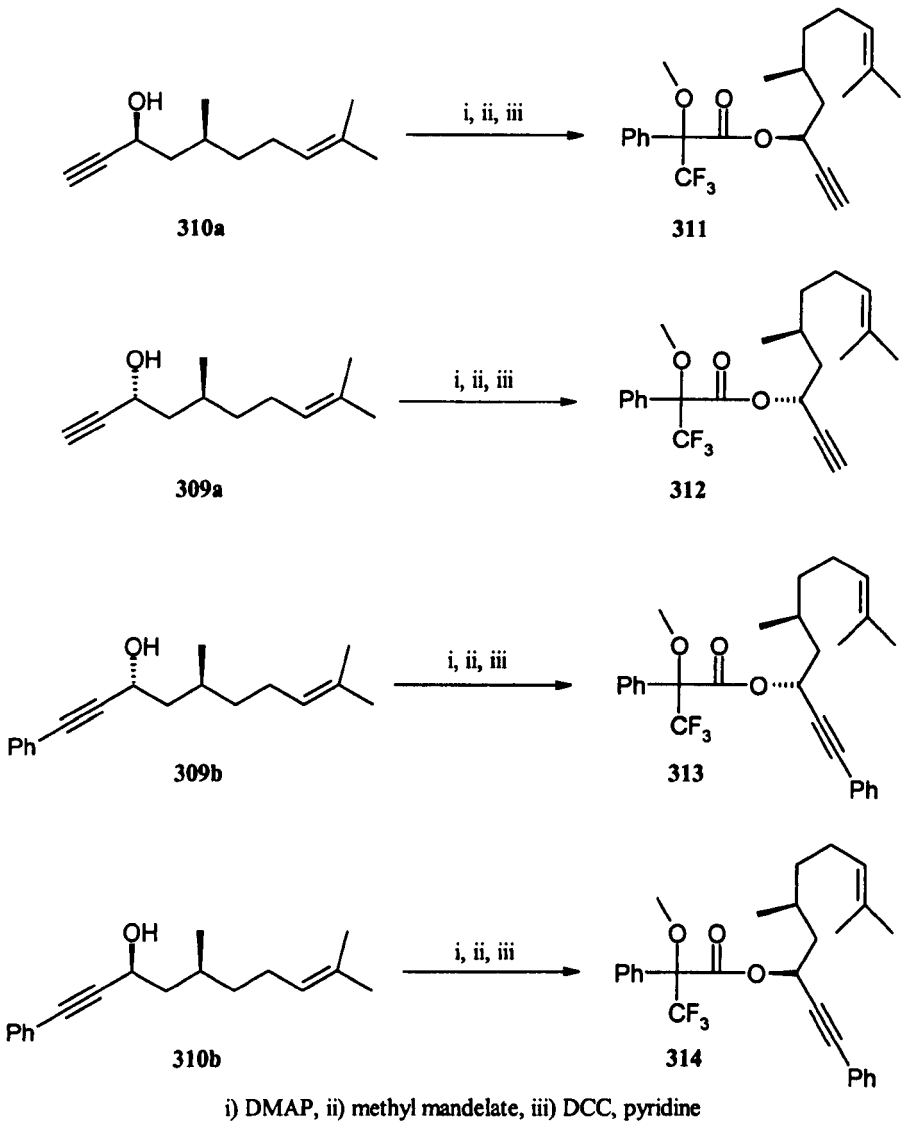
Having shown that alpine borane is a good reagent for asymmetric reduction of aldehydes and propargyl ketones, Midland also reported that the reaction with aldehydes was much faster than with ketones, suggesting that the differences in the kinetics of the reactions might be due to steric and/or electronic influence of

the substituent on the acetylene. Having synthesised the propargyl ketones (302a) and (302b), our next step was the asymmetric reduction of these two compounds. We decided to carry out the reduction with both (R)-alpine borane and (S)-alpine borane, (Scheme 67). The alpine borane reagents were freshly prepared by heating to reflux either α-pinene with 9-BBN.



Scheme 67.

The reactions were extremely slow, and were left reacting for up to three or four days, giving yields of up to 60 %. Additionally, the reactions were technically difficult to undertake. Due to the absence of solvent, the viscosity of both ketones and alpine borane, as well as the air sensitivity of the reducing agent led to difficult experimental conditions. However, ^{1}H NMR analysis of compounds (309a,b) and (310a,b) showed excellent levels of diastereoselectivity, exceeding 98 % *de* in some cases. Analysis of the ^{1}H NMR spectra of the corresponding Mosher esters confirmed the high stereoselectivity of the reactions, giving slightly lower values than those directly measured via NMR spectroscopy. This can only be explained by the purity of the MTPACl (98%) used for the formation of the Mosher ester, (Scheme 68).



i) DMAP, ii) methyl mandelate, iii) DCC, pyridine

Scheme 68.

The results are tabulated below (Table 12).

Compounds	Yield	*de* values from compounds	Corresponding Mosher ester	de values from Mosher esters
309a	45 %	98.1 %	312	97.6 %
309b	59 %	96.6 %	313	91.4 %
3109a	30 %	98.4 %	311	93.0 %
3019b	32 %	93.7 %	314	91 %

Table 12.

Figure 36 below shows the expansions in the ^1H NMR signals of the methyl groups derived from the Mosher ester for the three esters prepared from phenyl propargyl alcohols. (A) is derived from a Mosher ester prepared from the racemic alcohol (299b). (B) is from the Mosher ester prepared from the alcohol (310b) prepared with (S)-alpine borane, and (C) from compound (309b) reduced with (R)-alpine borane (Figure 36).

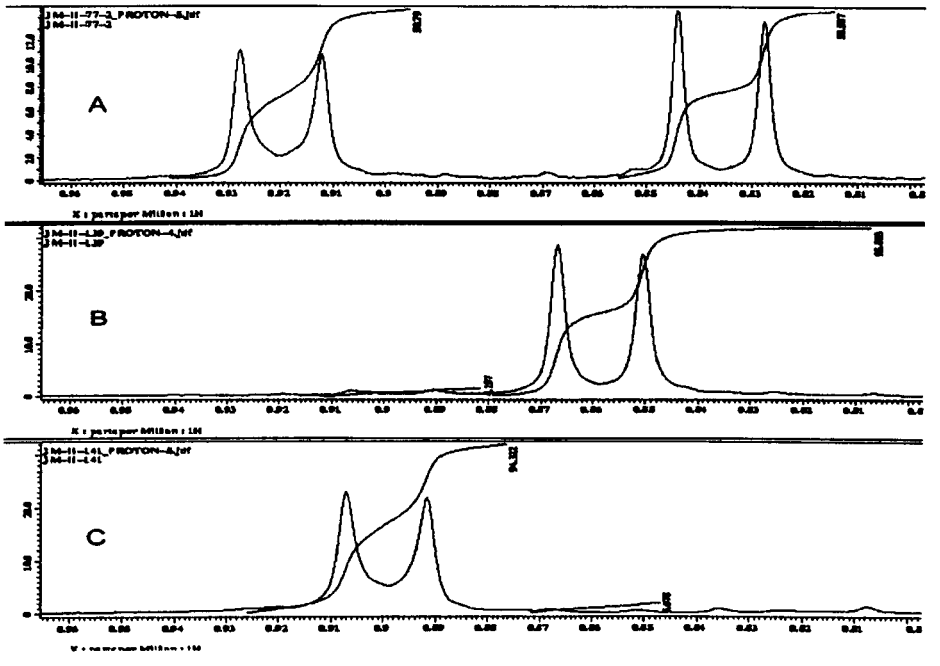


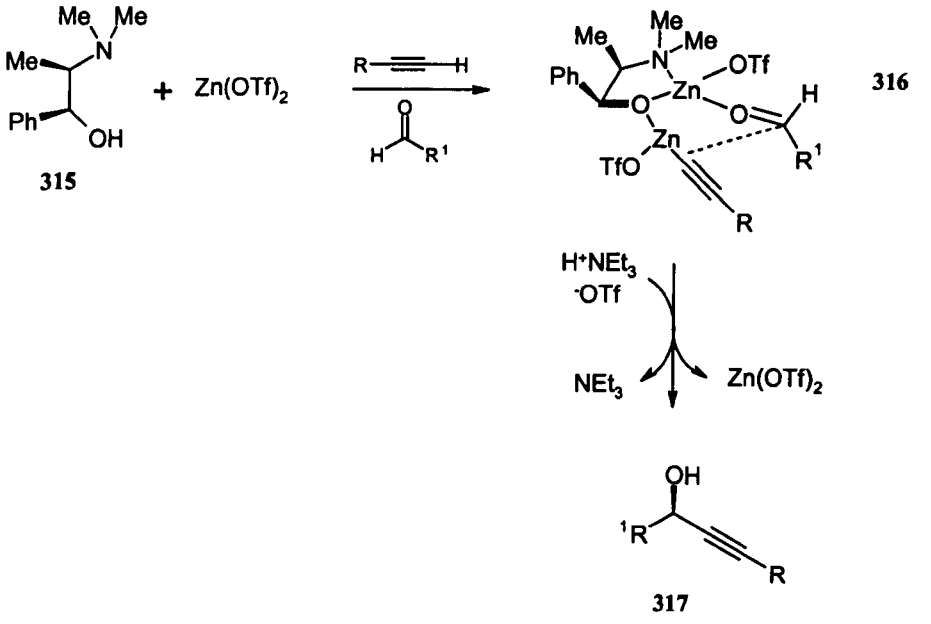
Figure 36.

This two step approach to synthesise optically pure propargyl alcohol precursors for an intramolecular Nicholas reaction gave very promising results. The alcohols were obtained with very high levels of stereoselectivity. However, this route also showed a few disadvantages. Even though the Jones oxidation step worked very well, the asymmetric reduction step was quite slow, technically difficult to carry out, and did not produce as high yields as we would have hoped. This led us to study an alternative route where the optically

pure propargyl alcohols can be directly prepared through a zinc catalysed enantioselective alkynylation of an aldehyde.

3.2.4 The stereoselective zinc-catalysed alkynylation approach

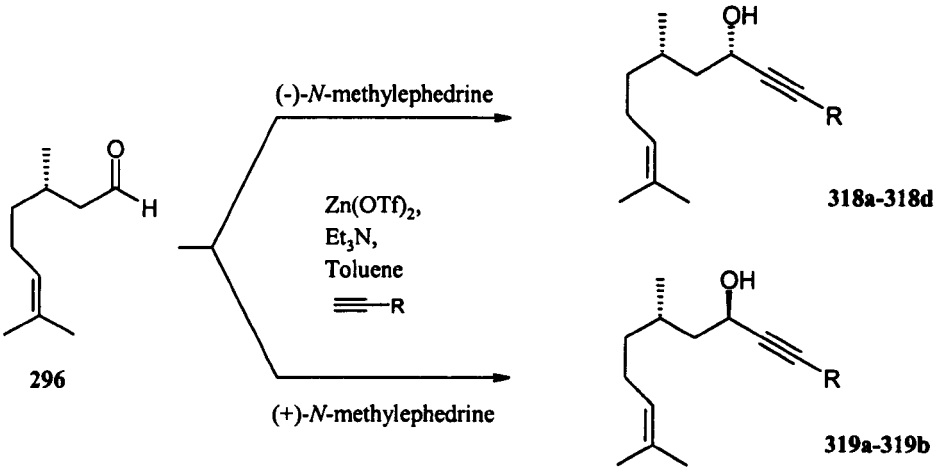
In recent years, Carreira *et al.* have reported a methodology for a facile enantioselective synthesis of propargyl alcohols by direct addition of terminal alkynes to aldehydes.[103,104,105] It is interesting to read the arguments put forward by Carreira to explain the advantages of such a reaction and justify his choice of investigating this field of asymmetric synthesis as our chain of thought was very similar. The simultaneous formation of a new C-C bond and a stereogenic centre is a much more efficient approach than a procedure where the C-C bond and the new chiral centre are formed separately.[106] In their preliminary studies, Carreira *et al.* observed that terminal acetylenes undergo addition to aldehydes in the presence of zinc triflate and an amine base. Further investigations showed that optically active adducts could be obtained when the addition reaction was carried out in the presence of optically active amino alcohols ligands such as (+)-*N*-methylephedrine (315). The reaction is thought to involve a zinc-alkyne, and a zinc-aldehyde-ligand complex (316), (Scheme 69).



Scheme 69.

In this reaction, the choice of the ligand has been correlated to the stereochemical outcome of the reaction. Thus, additions using (-)-NME afford adducts exclusively with an (S)-configuration (318a-318d) whereas (+)-NME affords the corresponding adducts with an (R)-configuration (319a-319b).[107] This outcome results directly from the orientation of the bulky phenyl group on the ephedrine, suggesting that the addition to the aldehydes will occur to one face of the intermediate complex (316). This, in accordance with the fact that the aldehyde will only be positioned with the R^1 group facing away from the complex due to the steric interactions with the triflate group, provides the stereoselective outcome for this reaction.[108]

Another advantage of this reaction was the fact that several different alkynes were readily available, allowing us to conduct a series of experiments with different kinds of functional groups on the terminal alkynes. We decided to conduct some of the reactions with both (+)- and (-)-NME, (Scheme 70).



Scheme 70.

It should be noted that these experiments were carried out at the very end of our studies, when time became an issue. This did not allow us to undertake these reactions more than once, which prevented us from the opportunity to optimise the results. The good yields, and good to excellent levels of diastereoselectivity comforted us in this choice.

The results of the series of alkynylations are summarised below (Table 13).

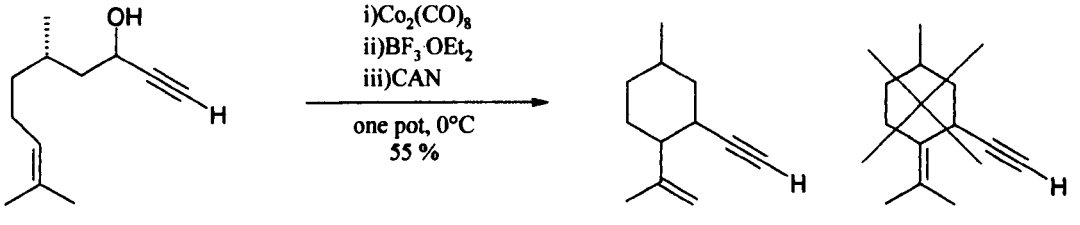
Compound	Alkyne	Ligand	% Yield	% *de*
318a	Ph—	(-)-NME	66	85
318b	H_3C—	(-)-NME	65	86
318c	TMS—	(-)-NME	64	98
318d	CH_3O—	(-)-NME	70	84
319a	Ph—	(+)-NME	65	92
319b	H_3C—	(+)-NME	64	91

Table 13.

Having synthesised a range of propargyl alcohols with good yields and diastereoselectivity, we still had to investigate an intramolecular Nicholas reaction.

3.2.5 Intramolecular Nicholas reaction

Having encountered major difficulties in our approach towards the intramolecular Nicholas reaction with our precursors bearing a chiral auxiliary, we were hoping that our new strategy would provide more positive and analysable results. In order to get the best possible results, we opted to carry out the complexation, cyclisation, and decomplexation steps in a one pot procedure. As we have seen before, this tends to provide better yields for the reactions. We decided to use boron trifluoride diethyletherate, rather than titanium chloride or tetrafluoroboric acid as the reaction seemed to proceed in a smoother fashion. TLC analysis of reaction mixtures from our attempts with $TiCl_4$ and HBF_4 were quite messy in contrast with the clearer ones obtained with $BF_3{\cdot}OEt_2$. Our first attempt at the intramolecular Nicholas cyclisation reaction was carried out on the diastereomeric propargyl alcohol (299a) (Scheme 71).



299a 320 321

Scheme 71.

The reaction proceeded in 78 % yield and produced compound (320) alone rather than a mixture containing (321). Indeed, from the results of previous cyclisation reactions carried out with substrates bearing the *gem*-dimethyl group at the double bond, we could have expected to obtain a mixture of compounds (320) and (321).[31,32] However ^{1}H NMR analysis denied the presence of compound (321). The spectrum shows a signal at δ 4.80 ppm accounting for the two protons at the carbon-carbon double bond. The signal at δ 1.7 ppm accounted for the vinyl CH_3 group. If there was a mixture of compounds (320) and (321) we would expect the signal at δ 4.80 ppm to account for less than two protons. GC-MS analysis confirmed that the reaction yielded a mixture of diastereoisomers, with the major one accounting for 70 % of the mixture, (Figure 37).

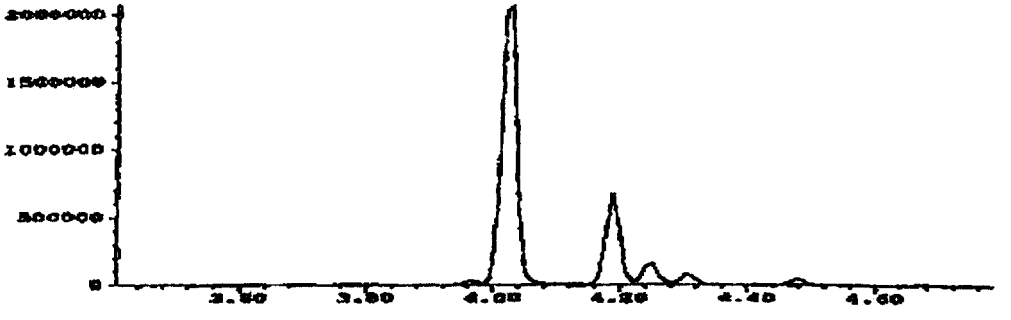
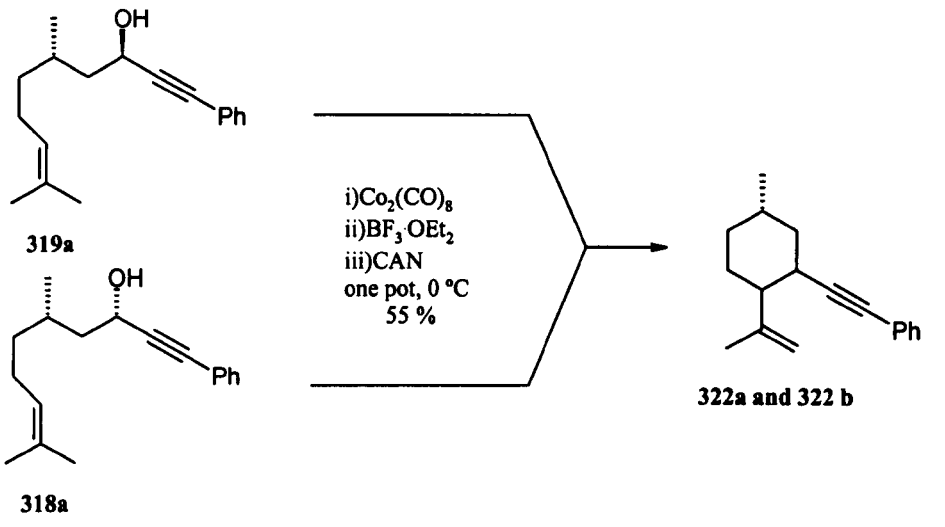


Figure 37.

The ^{13}C NMR analysis also confirmed our hypothesis as only two signals from CH_3 group carbons were present on the spectrum, as well as only one alkene quaternary carbon at δ 148 ppm.

These encouraging results led us to conduct several cyclisation reactions upon optically active precursors. The first two intramolecular Nicholas cyclisation

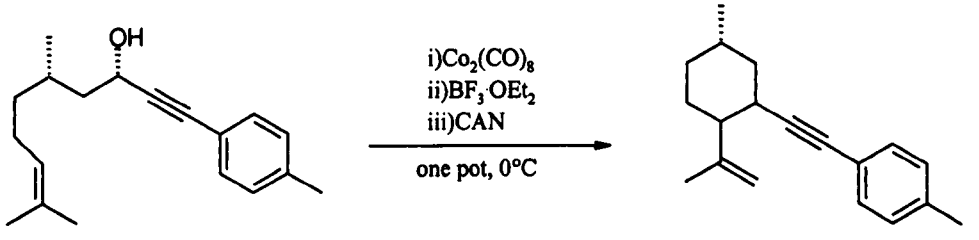
reactions were carried out with the two opposite diastereoisomers (319a) and (318a), as depicted below (Scheme 72).



Scheme 72.

Both reactions yielded the cyclised products (322a) and (322b) in good yield, i.e. 60 % over the three steps. NMR analysis and GC-MS analysis showed that the reactions both produced the same two major products with the exact same retention times. However, the GC-MS analysis showed that the ratios of products were different from one reaction to the other. The ^{1}H NMR spectrum was rather more difficult to use in respect to the calculation of the ratios between the two compounds generated as most signals were situated between δ 2.5 and 1.0 ppm, rendering this area of the spectrum fairly crowded. However, we were quite confident that the cyclisation reaction only yielded the product (322a/b) and not the corresponding compound with a *gem*-dimethyl at the double bond. This was deduced from the integrals for the peaks assigned to the $=CH_2$ and CH_3 groups. Out of the two cyclisation reactions, GC-MS analysis showed that the compound (319a) provided the best selectivity, with a ratio of 79 : 21, compared to 61 : 39 ratio for the product obtained from (318a). This

difference in ratios observed for the two products, obtained from two precursors where only the orientation of the OH group differed, led us to think that this might control the stereoselectivity of the reaction. However, this hypothesis did not stand after we decided to compare these two GC-MS spectra with the one obtained from the cyclised product derived from a racemic propargyl alcohol precursor. Apart from the slight differences in terms of ratio, they were very similar, showing two major products and traces of other diastereoisomers of the cyclised compound. This result suggested that any selectivity observed during the Nicholas reaction may not have much to do with the orientation of the -OH group, i.e. a rear attack from the nucleophile as the -OH group leaves is not a realistic mechanism. At this point it seemed that the compound (318a) did not afford as good a ratio as compound (319a) as a consequence of differences in the procedure rather than the selectivity of the reaction. It is possible that slight differences between the procedures, in term of time of the reaction or temperature, might have affected the reaction in such a way. One more cyclisation was performed, using the substrate (318b), (Scheme 73).



318b 323

Scheme 73.

The results obtained with this reaction helped us confirm our hypothesis. The GC-MS analysis showed that two major cyclised products were formed, in a ratio of 78 : 22, which is nearly identical to the ratio of products obtained from the cyclisation reaction carried out with the propargyl alcohol (319a). The major difference between these two compounds, aside from the difference of the functional groups attached to the alkyne, was the orientation of the OH group. In the case of (319a), the OH group was *anti* in respect to the methyl group, whereas in compound (318b) the OH group and methyl group were *syn*. This confirmed that the orientation of the OH group is of no influence to the stereoselectivity of this reaction. What was perhaps more surprising was that we observed the same product ratio, in terms of selectivity, from the intramolecular Nicholas reaction with diastereoisomeric propargyl alcohols (Scheme 72) as we did with the optically pure propargyl alcohols (318a/b) and (319a). Our interpretation of these data is that all of these cyclisation reactions are propagated *via* an analogous cobalt stabilised carbocation. According to the Schreiber hypothesis one face of the cation either cyclises at a faster rate than the other or remains exposed to the nucleophile for longer than the other fluxional state, therefore affording a form of resolution. Schreiber has shown that antarafacial migration occurs at lower temperatures than the suprafacial migration, and that while both processes accomplish the same task, antarafacial migration should be the lower energy process. This fact combined to the outcome of our cyclisation reactions led us to believe that only antarafacial migration occurred, (Figure 38).

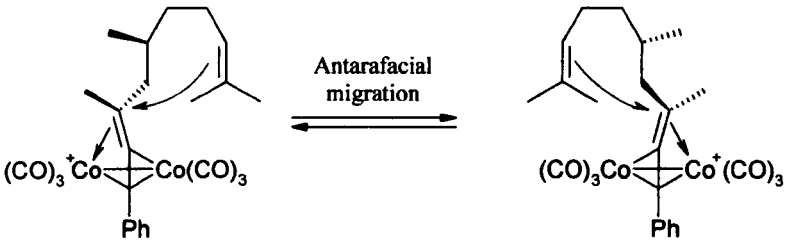
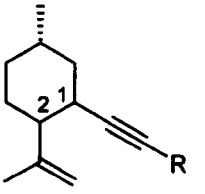


Figure 38.

Correlation of the ^{13}C NMR resonance data for the methine carbon atoms C1 and C2, (Table 14), provides an opportunity to tentatively speculate on the stereochemistry of the ring substituents.

Compound	C1 ppm	C2 ppm
320	33.23	50.88
322a/b	34.79	51.21
323	34.22	51.21
2-methyl-cyclohexanol	C1'	C2'
cis	71.1	35.8
trans	76.6	39.7



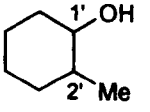


Table 14.

A correlation has been determined for the chemical shifts for 2-methyl cyclohexanol (Table 14).[111] Thus although we are unable to confirm the relative stereochemical relationship of the substituents on the major diastereoisomers what we can assert with some confidence is that they all have the same relationship either *cis* or *trans*. If we observed any stereochemical scrambling with the cycloadducts the continuity in the chemical shift data i.e. for C1 would show inconsistency. This would arise due to the 5 ppm chemical shift

difference between diastereoisomers that can be observed with 2-methyl cyclohexanol.

If we assume that the cyclised product will occupy a chair conformation, which molecular modelling confirms as the lowest energy conformation, then we can identify a possible conformation in which the C-C bonds created during the cyclisation reaction occupy the *trans* position as the two substituents adopt a diequatorial conformation (Figure 39).

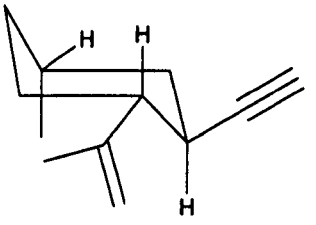


Figure 39.

3.3 Conclusion and future work

The results of this programme of research have led us to several conclusions in the various areas which we have investigated. The extensive investigations that we carried out on the 1,4-conjugate addition reaction, using a range of different chiral auxiliaries have shown that the C4 substituent of oxazolidinones plays a major role in the stereoselectivity of the reaction. The best results were obtained with the chiral auxiliary (246), which has a phenyl group at the C4 position. This auxiliary was the most suited for this kind of reaction, where the reaction centre is β- to the carbonyl group, as its shielding of one face of the magnesium enolate proved to be more effective than any other substituent that we have tried at this position. However, the size of this phenyl group appears to be a major disadvantage when the intramolecular Nicholas reaction is carried

out α- to the carbonyl group. This conclusion arose from our investigation of the intermolecular Nicholas alkylation reaction, where the reaction did not proceed well at all with the phenyl group at the C4 position. However, when the phenyl group was replaced by a methyl group, the reaction did proceed in good yields and high levels of stereoselectivity. We did encounter problems when trying to perform an intramolecular Nicholas cyclisation reaction with the precursors bearing a chiral auxiliary, which led us to investigate a different approach towards a stereoselective intramolecular Nicholas cyclisation reaction. From this, we studied two different ways of preparing optically active propargyl alcohols. Both approaches afforded high levels of stereoselectivity. However, while the zinc alkynylation approach afforded much better yields, the oxidation/reduction approach offered better levels of selectivity. In the final part of our project we investigated an intramolecular Nicholas cyclisation reaction with the optically active propargyl alcohols. The results we obtained led us to the conclusion that this type of Nicholas reaction involves a diastereoisomeric kinetic resolution, as opposite stereoisomers of the propargyl alcohols led to the formation of the same two major diastereoisomers of the cyclised products.

In conclusion, we feel that we have contributed to these fields of chemistry, by investigating known areas in a way that has not previously been reported in the literature.

Future work in these areas could include:

1) Cleaving the chiral auxiliary bearing the phenyl group at the C4 position after the conjugate addition and replacing it with the 4-methyl-5-phenyl-oxazolidin-2-one prior to the intermolecular Nicholas reaction.

2) Cleaving the chiral auxiliary to the corresponding carboxylic acid prior to the intramolecular Nicholas reaction to afford a new type of tri-substituted cyclohexanoic acid such as compound (324), (Figure 40).

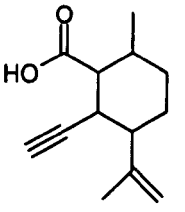
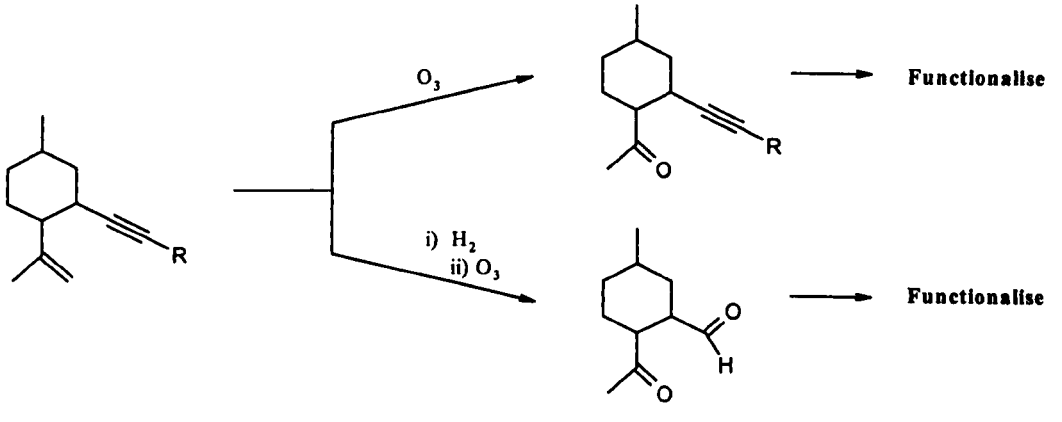


Figure 40. **324**

3) Investigate further the intramolecular Nicholas reaction with propargyl alcohols, especially the effect of temperature on the stereoselective outcome of the reaction.

4) Optimise the methods for Midland's stereoselective reduction and Carreira's zinc catalysed alkynylation reaction.

5) Synthesis of a crystalline derivative of the trisubstituted cyclohexane compounds (Scheme 74):



Scheme 74.

4.0 Experimental

General procedures

Starting materials were used as provided by Sigma-Aldrich unless otherwise stated. Organic extractions were performed using unpurified solvents and the organic extracts were dried over anhydrous magnesium sulfate and concentrated using a Bucchi rotary evaporator. Thin layer chromatography, TLC, was carried out on silica gel with aluminum backed plates with fluorescent indicator UV_{254}. TLC plates were visualized using either shortwave UV radiation, heating after immersion in potassium permanganate solution, or heating after immersion in a solution of phosphomolybdic acid in 0.2% aqueous sodium hydroxide. Flash chromatography separation was conducted over silica gel with air compression using unpurified solvents.

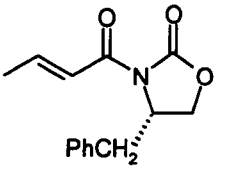
Instrumentation

High resolution mass spectrometry (HRMS) was carried out at the EPSRC unit in Swansea using a Finnigan MAT900XL-Qtrap VG autospec. Elemental analysis, CHN, was performed and reported by the London School of Pharmacy using a Carlo-Erba EA 1108. GC-MS analysis was carried out using an Agilent Technologies GC 6890N network GC system fitted with a 30m×0.250mm×0.25μm HP-5MSI column, with the data presented on the Agilent Chem. Station software. 300MHz NMR was conducted using a Bruker AC-300 Fourier Transform Nuclear Magnetic Resonnance spectrometer. 400MHz NMR was collected using a Jeol Eclipse^{+} 400 spectrometer with 64-slot autosample changer. Jeol Delta Software Ver 4.3.4 was used for data analysis.

Infrared analyses were performed on either a Perkin-Elmer 1004 FT-IR or a Perkin-Elmer Spectrum One FT-IR. Sampling techniques: KBr disk, NaCl plates, nujol mull, neat film, evaporated drop of sample in suitable solvent. Optical activity measurements were conducted using an AA-10 polarimeter.

General procedure for *N*-acylation of oxazolidinone (*GP1*)

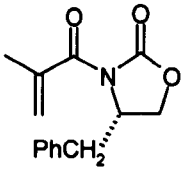
Synthesis of (S)-4-benzyl-*N*-but-2-enoyl-2-oxazolidinone (239a)



To a stirred solution of (4S)-benzyl-2-oxazolidinone (2.00 g, 11.0 mmol, 1.0 eq) in dry THF (40 cm^3) at -78°C under nitrogen, was added n-BuLi (1.6M in hexanes, 7.0 cm^3, 11 mmol, 1.0 eq). When the addition was complete the solution went from colourless to orange. The resulting solution was left to stir for 20min, and freshly distilled crotonyl chloride (1.15 cm^3, 12 mmol, 1.1 eq) was added. The mixture was left to sir at -78 °C for 30 min and at 0 °C for two hours. The reaction was then quenched with a saturated solution of ammonium chloride (40 cm^3). The resulting suspension was allowed to reach room temperature and the solvent was evaporated and replaced by ethyl acetate. The organic layer was then extracted and consecutively washed with saturated solutions of sodium bicarbonate and brine (2×20 cm^3). Finally the organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. Purification by flash chromatography on silica gel (7:3 hexane/ EtOAc) gave the desired compound (239a) as a colourless crystalline solid (1.90 g, 75%), $[\alpha]_D$ = +78 (c = 1.01, $CHCl_3$); mp 77-79 °C; R_f 0.45; ν_{max}(KBr)/cm^{-1} 2990, 1785, 1687, 1638, 1340, 1200, 713; δ_H(300 MHz, $CDCl_3$) 7.40-7.15 (7H, m, Ar*H*, -C*H*=C*H*-), 4.77-4.69 (1H, m, -N-C*H*), 4.25-4.10 (2H, m, -O-CH_2), 3.35-3.30 (1H, dd, J_1 = 3.2 Hz, J_2 = 13.4 Hz, PhCH_a), 2.75-2.83 (1H, dd, J_1 = 9.5 Hz, J_2 = 13.3 Hz PhCH_b), 2.0 (3H, d, J = 5.1 Hz, CH_3); δ_C(75 MHz, $CDCl_3$) 189.0, 164.5, 147.1, 135.4, 129.5,

128.9, 127.3, 121.8, 66.1, 55.3, 37.8, 18.6; Calc. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71; Found: C, 68.52; H, 6.35; N, 5.65. m/z: Calc: 246.1130, Found: 246.1130.

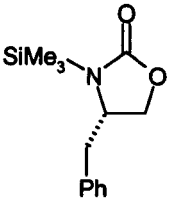
Synthesis of (S)-4-benzyl-*N*-(2-methyl-acryloyl)-2-oxazolidinone (239b)



Compound (239b) was prepared according to *GP1*, using the following quantities of (4S)-benzyl-2-oxazolidinone (2.00 g, 11.29 mmol, 1.0 eq), n-Butyllithium (4.0 cm^3 of a 2.7M sol., 11.29 mmol, 1.0 eq), and freshly distilled metacryloyl chloride (1.2 cm^3, 12.42 mmol, 1.1 eq). Purification by flash chromatography yielded the colourless crystalline product, (2.14 g, 80%), Mp 88.8–91.2 °C; $[\alpha]_D$ +77.1 (c = 0.99, $CHCl_3$) ; ν_{max}(KBr)/cm^{-1} 2924, 1789, 1683, 1354, 1219; δ_H(300 MHz, $CDCl_3$) 7.37-7.16, (5H, m, Ar*H*), 5.46-5.45, (1H, s, =C*H*), 5.42, (1H, s, =C*H*), 4.78-4.64, (1H, m, NC*H*), 4.28-4.23, (1H, dd, J_1 = 8.97 Hz, J_2 = 8.1 Hz, OC*H*,), 4.19-4.16, (1H, dd, J_1 = 4.76 Hz, J_2 = 8.97 Hz, OC*H*,), 3.36-3.32 (1H, dd, J_1 = 3.30 Hz, J_2 = 13.46 Hz, PhCH_a,), 2.86-2.81 (1H , dd J_1 = 9.15 Hz, J_2 = 13.46 Hz, , PhCH_b,), 2.05 (3H, s, CH_3); δ_C(75 MHz, $CDCl_3$) 189.0,139.5, 134.5 129.5, 128.9, 127.4, 120.8, 66.5, 55.3, 37.5, 19.1; *m/z* calc 246.1130, found 246.1130.

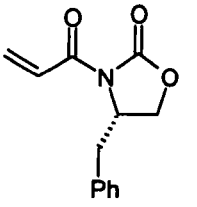
Procedure for the trimethylsilyl derivative of chiral auxiliaries

Synthesis of (S)-4-benzyl-*N*-trimethylsilanyl-oxazolidin-2-one (240)



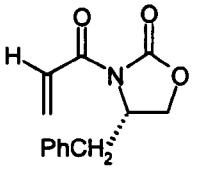
To a stirred solution of (S)-4-benzyl-2-oxazolidinone (2.05 g, 11.5 mmol, 1 eq), in dry toluene (30 mL) containing acetonitrile (7 mL) was added chlorotrimethylsilane (7 mL, 55 mmol, 5 eq). The mixture was then cooled to 0 °C and triethylamine (1.9 mL, 13 mmol, 1.1 eq) in toluene was added slowly. A white precipitate immediately formed upon addition. After the addition was complete, the resulting mixture was stirred at r.t. for 1h. The resulting suspension was then filtered. The filtrate was washed with toluene (20 mL), and the combined toluene portions evaporated under vacuum, yielding the colourless crystalline product (1.6 g, 56 %); mp 50.9-52.7 °C; $[\alpha]_D$ -51.1 (c = 1.9, $CHCl_3$); ν_{max} (film)/cm^{-1} 3028, 2958, 2923, 1738, 1387, 1252, 1214, 1137, 846, 783, 739, 700; δ_H(300 MHz, $CDCl_3$) 7.20-6.96 (5H, m, Ar*H*), 3.91-3.89 (2H, d, J = 4.5 Hz, Ph-CH_2-), 3.77-3.69 (1H, m, -N-C*H*-), 2.82-2.77 (1H, dd, J_1 = 3.8 Hz, J_2 = 13.5 Hz, -O-CH_aH$_b$), 2.57-2.49 (1H, dd, J_1 = 10. Hz, J_2 = 13.5 Hz, -O-CH$_a$$H_b$), 0.20 (9H, s, Si-C$H_3$); δ_C(75 MHz, $CDCl_3$) 161.3, 136.1, 129.2, 128.9, 127.1, 68.0, 57.6, 41.7, -0.7.

Synthesis of (S)-4-benzyl-*N*-propenoyl-oxazolidin-2-one (241) from the TMS precursor



To a solution of (S)-4-benzyl-3-(trimethylsilyl)oxazolidin-2-one (1.0 g, 4.0 mmol, 1 eq) in toluene was added propenoyl chloride (1.8 mL, 22.2 mmol, 5.5 eq), $CuCl_2$ (0.76 g, 5.65 mmol, 1.4 eq), and Cu powder (18 mg, 0.28 mmol, 0.07 eq). The mixture was then heated at reflux for 2 days, cooled, filtered and concentrated under vacuum. Purification by flash chromatography afforded the title product (241) as colourless needles (0.40 g, 45 %); mp 71-73 °C, ; $[\alpha]_D$ +83.5 (c = 0.5, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3029, 2920, 1778, 1687, 1619, 1497, 1390, 1353, 1316, 1213, 1114, 985, 744, 703; δ_H(300 MHz, $CDCl_3$) 7.70-7.61 (1H, dd, J_1 = 10.4 Hz, J_2 = 16.9 Hz, C*H*=CH_2), 7.51-7.34 (5H ,m, Ar*H*), 6.78-6.72 (1H, dd, J_1 = 1.8 Hz, J_2 = 16.9 Hz, CH=CH_a), 6.10-6.06 (1H, dd, J_1 = 1.8 Hz, J_2 = 10.5 Hz, CH=CH_a), 4.92-4.84 (1H ,m, NC*H*), 4.41-4.27, (2H, m, OCH_2), 3.52-3.47 (1H, dd, J_1 = 3.27 Hz, J_2 = 13.3 Hz, PhCH_a), 2.99-2.91, (1H, dd, J_1 = 9.6 Hz, J_2 = 13.4 Hz, PhCH_b); δ_C(75 MHz, $CDCl_3$) 188.0, 164.8, 153.5, 135.2, 131.9, 129.4, 128.9, 127.4, 66.2, 55.3, 37.8.

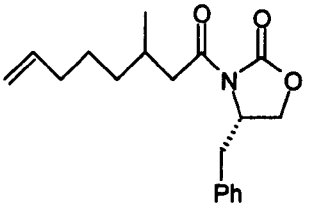
Synthesis of (S)-*N*-acryloyl-4-benzyl-2-oxazolidinone (241)



To a solution of (4S)-benzyl-2-oxazolidinone (1.00 g, 5.64 mmol, 1.0 eq) in dry THF (20 cm^3) at 0 °C was added methyl magnesium bromide (4 cm^3 of a 1.4M sol., 5.64 mmol, 1.0 eq). After 10 min the solution was cooled to -78 °C (CO_2 / acetone) and acryloyl chloride (0.46 cm^3, 5.64 mmol, 1.0 eq) was added. The reaction mixture was then maintained at 0 °C for 20 minutes, before being quenched by the addition of a saturated solution of aqueous ammonium chloride (15 mL). The solvent was evoporated *in vacuo* and the reaction mixture extracted with diethyl ether (3×30 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to yield a pale yellow oil. Purification by flash chromatography yielded the title product (241) as colourless crystals (0.62 g, 48%); m.p. 73.5-74.5 °C; $[\alpha]_D$ +84.4 (c = 0.7, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2910, 1779, 1686, 1353, 1212; δ_H(300 MHz, $CDCl_3$) 7.70-7.61 (1H, dd, J_1 = 10.4 Hz, J_2 = 16.9 Hz, C*H*=CH_2), 7.51-7.34 (5H ,m, Ar*H*), 6.78-6.72 (1H, dd, J_1 = 1.8 Hz, J_2 = 16.9 Hz, CH=CH_a), 6.10-6.06 (1H, dd, J_1 = 1.8 Hz, J_2 = 10.5 Hz, CH=CH_a), 4.92-4.84 (1H ,m, NC*H*), 4.41-4.27, (2H, m, OCH_2), 3.52-3.47 (1H, dd, J_1 = 3.27 Hz, J_2 = 13.3 Hz, PhCH_a), 2.99-2.91, (1H, dd, J_1 = 9.6 Hz, J_2 = 13.4 Hz, PhCH_b); δ_C(75 MHz, $CDCl_3$) 188.0, 164.8, 153.5, 135.2, 131.9, 129.4, 128.9, 127.4, 66.2, 55.3, 37.8; *m/z* calc: 232.0973, found: 232.0972.

General procedure for 1,4-conjugate addition (*GP2*)

Synthesis of (S)-4-benzyl-*N*-(3-(S)-methyl-oct-7-enoyl)-2-oxazolidinone (242)

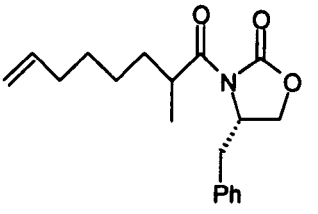


A solution of 5-bromo-1-pentene (1.50 mL, 12.2 mmol, 3.0 eq) was added dropwise to a suspension of magnesium turnings (0.32 g, 12.6 mmol, 3.1 eq) in dry THF. The mixture was stirred for an hour at room temperature, and then cooled to - 40°C. At this stage, a solution of CuBr-$(Me)_2S$ complex (1.25 g, 6.1 mmol, 3.0 eq) in dry THF (10mL) and dimethyl sulfide (5mL) was added over a period of 30 minutes.

The resulting organocopper solution was left to stir until the cold bath temperature reached -15°C, and N-but-2-enoyl-4-benzyl-2-oxazolidinone (239a) (1.0 g, 4.1 mmol, 1.0 eq) in dry THF was added via a cannula. The cold bath was removed and the reaction mixture was left to stir for two hours until it reached room temperature. The reaction was quenched with saturated aqueous ammonium chloride and the organic solvent was evaporated and replaced by ethyl acetate. The organic layer was washed in sequence by a 10% aqueous solution of ammonia (30mL), water (30mL) and brine (30mL), and dried over magnesium sulfate. The solvent was evaporated off. Purification by flash chromatography (7:3 hexane / EtOAc) yielded (242) as a colourless oil (0.95g, 74%); R_f 0.5; $[\alpha]_D$ +78 (c = 0.99, $CHCL_3$); ν_{max}(thin film)/cm^{-1} 2929, 1783, 1698, 1454, 1386, 1351, 1210, 1098, 911; δ_H(300 MHz, $CDCl_3$) 7.33-7.20 (5H,

m, Ar*H*), 5.86-5.74 (1H m, CH_2=C*H*), 5.04-4.91 (2H, t, CH_2=CH), 4.72-4.64 (1H, m, N-C*H*-), 4.25-4.08 (2H, m, -O-CH_2 -), 3.40-3.23 (1H, dd, J_1 = 3.3 Hz, J_2 = 13.3 Hz, -CH_2 -Ph), 3.02-2.67 (3H, m, CH_2 –Ph and O=C-CH_2), 2.07-1.92 (3H, m), 1.51-1.13 (4H, m,), 0.93-0.89 (3H, t); δ_C(75 MHz, $CDCl_3$) 189.0, 172.8, 153.4, 138.9, 135.5, 1294, 128.9, 1273, 114.4, 66.1, 55.2, 42.5, 37.9, 36.3, 36.2, 33.9, 29.5, 26.3, 19.7. m/z: calc: 333.2173, found: 333.2170.

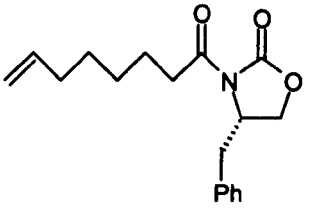
Synthesis of (S)-4-benzyl-*N*-(2-methyl-oct-7-enoyl)-2-oxazolidinone (243)



Compound (243) was prepared according to *GP2*, using the following quantities of magnesium turnings (0.17 g, 7.0 mmol, 3.1 eq), 5-bromo-pent-2-ene (0.8 mL, 6.75 mmol, 3.0 eq), $CuBrMe_2S$ complex (0.69 g, 3.4 mmol, 1.5 eq), and 4-benzyl-N-(2-methyl-acryloyl)-2-oxazolidinone (0.55 g, 2.25 mmol, 1.0 eq). Purification by flash chromatography (7:3 hexane / EtOAc) yielded a colourless oil (0.57g, 80%); R_f 0.53 and 0.48. The two diastereoisomers were separated by column chromatography (9:1 hexane / ethyl acetate with 1% Et_3N). $[\alpha]_D$ +70.7 (c = 1.24, $CHCl_3$) for the first diastereoisomer and $[\alpha]_D$ +28.1 (c = 2.16, $CHCl_3$) for the second. ν_{max}(thin film)/cm^{-1} 2931, 1782, 1698, 1640, 1454, 1386, 1349, 1237, 1210, 1098, 912; δ_H(300 MHz, $CDCl_3$) 7.32-7.12, (5H, m, Ar*H*), 5.78-5.65, (1H, m, C*H*=CH_2), 5.02-4.95, (1H, dq, J_{bc} = 2 Hz, J_{ac} = 17 Hz, CH=CH_2 trans), 4.95-4.89, (1H , d quintet, J_{ac} = 10.2 Hz, , CH=CH_2 cis), 4.70-4.64, (1H, m, $PhCH_2$C*H*), 4.19-4.16, (1H, dd, J_1 = 0.55 Hz, J_2 = 9.15 Hz, O-CH_2), 4.15-

4.12, (1H, dd, J_1 = 3.5 Hz, J_2 = 9.15 Hz, O-C*H*$_2$), 3.77-3.68, (1H, m, CH_3C*H*), 3.30-3.23, (1H, dd, J_1 = 3.3 Hz, J_2 = 13.3 Hz, Ph-C*H*$_2$), 2.74-2.68, (1H, dd, J_1 = 9.8 Hz, J_2 = 13.3, Ph-C*H*$_2$), 2.07-2.02, (2H, m, =CHC*H*$_2$), 1.81-1.74, (1H, m, CH3CHC*H*$_2$), 1.48-1.31, (5H, m, H aliph), 1.17-1.15, (3H, d, J = 6.7 Hz, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 189.0, 177.2, 153.0, 138.8, 135.3, 129.4, 128.9, 127.3, 114.4, 96.5, 66.0, 55.3, 37.9, 37.7, 33.6, 33.2, 28.8, 26.7, 17.3. m/z: $[M=H]^+$ calc: 316.1907, found: 316.1910

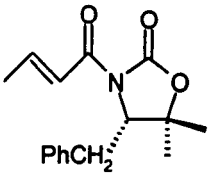
Synthesis of (S)-4-benzyl-*N*-oct-7-enoyl-2-oxazolidinone (244)



Compound (244) was prepared according to *GP2*, using the following quantities of magnesium turnings (0.17 g, 7.0 mmol, 3.1 eq), 5-bromo-pent-2-ene (0.8 mL, 6.7 mmol, 3.0 eq), $CuBrM_2S$ (0.69 g, 3.4 mmol, 1.5 eq) and 4-benzyl-N-acryloyl-2-oxazolidinone (0.49 g, 2.1 mmol, 1.0 eq). Purification by column chromatography yielded a colourless oil (0.36g, 75%). $[\alpha]_D$ +45.3 (c = 1, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2928, 1782, 1700, 1454, 1388, 1351, 1211, 912. δ_H(300 MHz, $CDCl_3$) 7.30-7.10, (5H, m, Ar*H*), 5.79-5.65, (1H, m, C*H*=CH_2), 4.95-4.84, (2H, m, CH=C*H*$_2$), 4.64-4.54, (1H, m, C*H*-CH_2Ph), 4.15-4.0, (2H, m, -O-C*H*$_2$)), 3.22-3.17, (1H, dd, J_1 = 3.3 Hz, J_2 = 13.3 Hz, C*H*$_2$-Ph), 2.89-2.80, (2H, m, -COC*H*$_2$), 2.72-2.64, (1H, dd, J_1 = 9.5 Hz, J_2 = 13.3 Hz, C*H*$_2$-Ph), 2.02-1.95, (2H, m, C*H*$_2$-CH=CH_2), 1.66-1.56, (2H, m, -$COCH_2$C*H*$_2$), 1.40-1.25, (4H, m, CH_2 × 2); δ_C(75 MHz, $CDCl_3$) 189.0, 173.3, 153.5, 138.8, 135.3, 129.4, 128.9, 127.3,

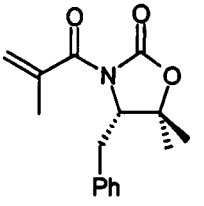
114.4, 66.2, 55.1, 37.8, 35.5, 33.6, 28.6, 28.5, 24.1; m/z $[M=H]^+$ calc: 302.1751, found: 302.1752

Synthesis of (S)-4-benzyl-5, 5-dimethyl-*N*-but-2-enoyl-2-oxazolidinone (247)



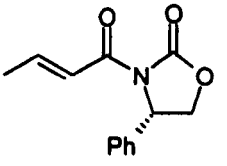
Compound (247) was prepared according to *GP1*, using the following quantities of (4S)-benzyl-5,5-dimethyl-2-oxazolidinone (1.23 g, 6.00 mmol, 1.0 eq), n-Butyllithium (2.4 mL of a 2.5M sol., 6.00 mmol, 1.0 eq), and freshly distilled crotonyl chloride (0.65 mL, 6.60 mmol, 1.1 eq). Purification by flash chromatography yielded the title product as colourless needles (1.12g, 68%). $[\alpha]_D$ -40.74 (c = 0.27, $CHCl_3$), ν_{max}(KBr)/cm^{-1} 2976, 1774, 1683, 1636, 1355, 1277,1235; δ_H(300 MHz, $CDCl_3$) 7.31-7.20 (5H, m, Ar*H*), 7.17-7.12 (1H, q, J = 6.8 Hz, CH_3CH=), 7.12-7.10 (1H, d, J = 6.8 Hz, CH_3CH=C*H*), 4.56-4.52 (1H, dd, J_1 = 3.5 Hz, J_2 = 9.9 Hz, NC*H*), 3.23-3.19 (1H, dd, J_1 = 3.48 Hz, J_2 = 14.3 Hz, PhCH_a), 2.90-2.84 (1H, dd, J_1 = 9.7 Hz, J_2 = 14.4 Hz, PhCH_b), 1.96-1.94 (3H, dd, J_1 = 1.5 Hz, J_2 = 6.7 Hz, =CHCH_3), 1.36 (3H, s, CH_3), 1.34 (3H, s, CH_3); δ_C(75 MHz, $CDCl_3$) 189.0, 152.5, 146.6, 137.1, 129.0, 128.7, 126.7, 122.2, 97.1, 63.7, 35.2, 28.5, 22.3, 18.5; *m/z* calc: 274.1438, found: 274.1437.

Synthesis of 4-benzyl-5,5-dimethyl-*N*-(2-methyl-acryloyl)-2-oxazolidinone (248)



Compound (248) was prepared according to *GP1*, using the following quantities of (4S)-benzyl-5, 5-dimethyl-2-oxazolidinone (1.23 g, 6.00 mmol, 1.0 eq), n-Butyllithium (2.4 mL of a 2.5M sol., 6.00 mmol, 1.0 eq), and freshly distilled methacryloyl chloride (0.65 mL, 6.60 mmol, 1.1 eq). Purification by flash chromatography (8:2 hexane / EtOAc) yielded the title product as colourless crystals (1.39 g, 85%), R_f 0.3; ν_{max}(KBr)/cm^{-1} 2981, 1781, 1686, 1354, 1277,1211, 1100; δ_H(300 MHz, $CDCl_3$) 7.30-7.14 (5H, m, Ar*H*), 5.37 (2H, s, =CH_2), 4.45-4.41 (1H, dd, *J* 4.4 and 9.6, NC*H*), 3.30-3.21 (1H, dd, J_1 = 4.3 Hz, J_2 = 14.1 Hz, PhCH_a), 2.78-2.70 (1H, dd, J_1 = 9.6 Hz, J_2 = 14.1 Hz, PhCH_b), 1.89 (3H, s, =CCH_3), 1.36 (3H, s, CH_3), 1.19 (3H, s, CH_3); δ_C(75 MHz, $CDCl_3$) 189.0, 171.5, 152.2, 140.0, 136.4, 129.1, 128.7, 126.9, 121.2, 96.9, 82.4, 63.9, 34.6, 28.2, 22.4, 19.0; m/z calc: 274.1443, found: 274.1444.

Synthesis of (S)-4-phenyl-N-but-2-enoyl-2-oxazolidinone (249)

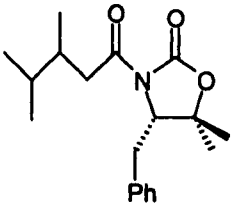


Compound (249) was prepared according to *GP1*, using the following quantities of (S)-4-phenyl-2-oxazolidinone (1.96 g, 12.0 mmol, 1.0 eq), n-butyllithium

(4.50 mL of a 2.7M sol., 12.0 mmol, 1.0 eq), and freshly distilled crotonyl chloride (1.3 mL, 13.2 mmol, 1.1 eq). Purification by flash chromatography (8:2 hexane / EtOAc) yielded the title product as colourless needles (1.99 g , 72%), m.p. 74.8-75.5 °C; $[\alpha]_D$ 108 (c = 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2976, 2917, 1777, 1686, 1636, 1394, 1330, 1230, 1072, 964, 715; δ_H(400 MHz, $CDCl_3$) 7.39–7.27 (6H, m, Ar*H*, =C*H*), 7.13–7.03 (1H, dq, J_1 = 7.3 Hz, J_2 = 15.2 Hz, =C*H*CH_3), 5.48-5.45 (1H, dd, J_1 = 3.8 Hz, J_2 = 8.7 Hz, O-CH_2), 4.70-4.66 (1H, t, C*H*-Ph) , 4.27-4.24 (1H, dd, , J_1 = 3.8 Hz, J_2 = 8.7 Hz, O-CH_2), 1.92-1.91 (3H, d, J = 6.9Hz, =CCH_3); δ_C(100 MHz, $CDCl_3$) 164.7, 153.8, 147.4, 139.2, 129.3, 128.7, 126.0, 121.8, 70.0, 57.8, 18.6; m/*z* calc: 232.0973, found: 232.0971.

General procedure for the parallel synthesis (*GP3*).

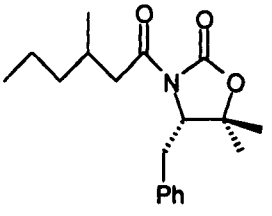
Synthesis of 4-(S)-benzyl-*N*-(3,4-dimethyl-pentanoyl)-5,5-dimethyl-2-oxazolidinone (251)



To a suspension of $CuBrMe_2S$ (0.23 g, 1.1 mmol, 1.5 eq) in dry THF (20mL) and dimethyl sulfide (1mL) at –40°C, was added a solution of isopropyl magnesium bromide (1.1 mL of a 2M sol., 2.2 mmol, 3.0 eq). The reaction mixture was left to stir until the temperature reached –15°C, at which point 4-benzyl-5, 5-dimethyl-N-but-2-enoyl-2-oxazolidinone (0.20 g, 0.73 mmol, 1.0 eq) was added. The cold bath was removed and the reaction mixture was left to stir for two hours

until it reached room temperature. The reaction was quenched with saturated aqueous ammonium chloride and the organic solvent was evaporated and replaced by ethyl acetate. The organic layer was washed in sequence by a 10% aqueous solution of ammonia (15mL), water (15mL) and brine (15mL), and dried over magnesium sulfate. The solvent was evaporated off. Purification by flash chromatography yielded the title product (251) as a colourless oil (0.19g, 83%). ν_{max}(thin film)/cm^{-1} 2960, 2874, 1778, 1697, 1604, 1455, 1355, 1276, 1097, 910; δ_H(300 MHz, $CDCl_3$) 7.29-7.12 (5H, m, Ar*H*), 4.47-4.42 (1H, dd, J_1 = 3.7 Hz, J_2 = 9.7 Hz, N-C*H*-), 3.09-3.04 (1H, dd, J_1 = 3.7Hz, J_2 = 14.4 Hz, CH_2-Ph), 2.90-2.84 (1H, dd, J_1 = 4.9 Hz, J_2 = 15.9 Hz, O=C-CH_2), 2.83-2.77 (1H, dd, J_1 = 9.7 Hz, J_2 = 14.4 Hz, CH_2-Ph), 2.69-2.62 (1H, dd, J_1 = 9.1 Hz, J_2 = 15.7 Hz, O=C-CH_2), 1.93-1.83 (1H, m, CH_2-C*H*), 1.58-1.48 (1H, m, CH_3-C*H*-CH_3), 1.29 (3H, s, O-C(CH_3)$_2$), 1.27 (3H, s, O-C(CH_3)$_2$), 0.83-0.81 (3H, d, J = 6.8 Hz, CH_3), 0.80-0.78 (3H, d, J = 6.9 Hz). δ_C(75 MHz, $CDCl_3$) 173.5, 152.6, 137.0, 129.0, 128.6, 126.7, 81.9, 63.5, 40.0, 35.3, 35.2, 32.1, 28.5, 22.3, 19.9, 18.1, 15.5 .

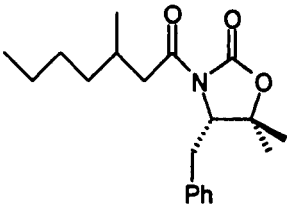
Synthesis of 4-(S)-benzyl-5,5-dimethyl-*N*-(3-methyl-hexanoyl)-2-oxazolidinone (250)



Compound (250) was prepared according to *GP3*, using the following quantities of $CuBrMe_2S$ (0.23 g, 1.1 mmol, 1.5 eq), propylmagnesium chloride (1.1 mL of a 2M sol., 2.2 mmol, 3.0 eq), and 4-benzyl-5, 5-dimethyl-N-but-2-enoyl-2-

oxazolidinone (0.20 g, 0.73 mmol, 1.0 eq). Purification by flash chromatography yielded a colourless oil (15g, 65%); ν_{max}(thin film)/cm^{-1} 2958, 2931, 2872, 1778, 1697, 1605, 1495, 1455, 1354, 1276, 1237, 1093; δ_H(300 MHz, $CDCl_3$) 7.28-7.10 (5H, m, Ar*H*), 4.47-4.43 (1H, dd, J_1 = 3.8 Hz, J_2 = 9.7 Hz, N-C*H*-), 3.09-3.05 (dd, 1H, J_1 = 3.8 Hz, J_2 = 14.4 Hz, CH_2-Ph), 2.86-2.75 (2H, m, O=C-CH_2), 2.70-2.64 (1H, dd, J_1 = 8.24 Hz, J_2 = 15.8 Hz, CH_2-Ph), 2.01-1.89 (1H, m, C*H*-CH_3), 1.32-1.08 (10H, m, CH_3 ×2, CH_2 × 2), 0.87-0.80 (6H, m, CH_3 × 2); δ_C(75 MHz, $CDCl_3$) 173.0, 152.6, 136.9, 129.0, 128.6, 126.7, 81.9, 63.4, 42.5, 39.0, 35.9, 29.5, 28.5, 22.2, 20.0, 19.6, 14.1; m/z $[M+H]^+$ calc: 318.2064 found: 318.2062.

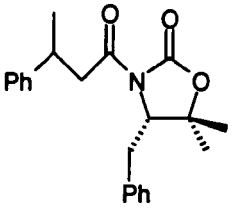
Synthesis of 4-(S)-benzyl-5,5-dimethyl-*N*-(3-methyl-heptanoyl)-oxazolidin-2-one (252)



Compound (252) was prepared according to *GP3*, using the following quantities of $CuBrMe_2S$ (0.23 g, 1.1 mmol, 1.5 eq), butylmagnesium chloride (1.1 mL of a 2M sol., 2.2 mmol, 3.0 eq), and 4-benzyl-5, 5-dimethyl-N-but-2-enoyl-2-oxazolidinone (0.20 g, 0.73 mmol, 1.0 eq). Purification by flash chromatography yielded a colourless oil (0.18 g, 75 %). ν_{max}(thin film)/cm^{-1} 2931, 2872, 1777 , 1697, 1605, 1497, 1455, 1355, 1276, 1093, 964, 733, 700; δ_H(300 MHz, $CDCl_3$) 7.25-7.13 (5H, m, Ar*H*), 4.47-4.44 (1H, dd, J_1 = 3.8 Hz, J_2 = 9.5 Hz, N-C*H*-), 3.09-3.04 (1H, dd, J_1 = 3.8 Hz, J_2 = 14.5 Hz, CH_2-Ph), 2.86-2.78 (2H, m, O=C-CH_2), 2.70-2.64 (1H, dd, J_1 = 8.0 Hz, J_2 = 15.9 Hz, CH_2-Ph), 2.01-1.70 (1H, m,

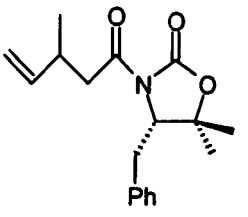
C*H*-CH_3), 1.29 (3H, s, O-C(C*H*$_3$)$_2$), 1.28 (3H, s, O-C(C*H*$_3$)$_2$), 1.25-1.15 (6H, m, C*H*$_2$ × 2), 0.86-0.80 (6H, m, C*H*$_3$ × 2); δ_C(75 MHz, $CDCl_3$) 177.0, 152.5, 136.9, 129.0, 128.6, 126.7, 82.0, 63.3, 42.3, 36.3, 35.2, 29.6, 29.4, 29.0, 28.3, 23.7, 22.0, 19.6, 14.1.

Synthesis of 4-(S)-benzyl-5,5-dimethyl-*N*-(3-phenyl-butyryl)-2-oxazolidinone (253)



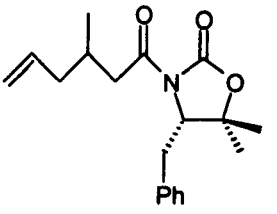
Compound (253) was prepared according to *GP3*, using the following quantities of $CuBrMe_2S$ (0.23 g, 1.1 mmol, 1.5 eq), phenyl magnesium bromide (2.2 mL of a 1M sol., 2.2 mmol, 3.0 eq), and 4-benzyl-5, 5-dimethyl-N-but-2-enoyl-2-oxazolidinone (0.20 g, 0.73 mmol, 1.0 eq). Purification by flash chromatography yielded a colourless oil (0.17 g, 68 %); ν_{max}(thin film)/cm^{-1} 3061, 3028, 2930, 2873, 1778, 1698, 1603, 1495, 1454, 1356, 1276, 1097, 910; δ_H(300 MHz, $CDCl_3$) 7.24-7.09 (10H, m, Ar*H*), 4.40-4.36 (1H, dd, J_1 = 3.5 Hz, J_2 = 9.8 Hz, N-C*H*), 3.42-3.24 (2H, m, C*H*$_2$), 3.09-2.99 (1H, m, CH_3-C*H*), 2.91-2.87 (1H, dd, J_1 = 3.4 Hz, J_2 = 14.3 Hz, C*H*$_2$-Ph), 2.63-2.56 (1H, dd, J_1 = 9.7 Hz, J_2 = 14.4 Hz, C*H*$_2$-Ph), 1.30-1.20 (9H, m, CH_3 × 3); δ_C(75 MHz, $CDCl_3$) 172.5, 152.5, 145.8, 137.2, 128.9, 128.6, 128.4, 126.9, 126.7, 126.3, 82.0, 63.4, 43.2, 36.2, 34.9, 28.5, 22.2 .

Synthesis of 4-(S)-benzyl-5,5-dimethyl-*N*-(3-methyl-pent-4-enoyl)-2-oxazolidinone (254)



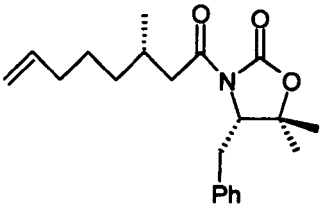
Compound (254) was prepared according to *GP3*, using the following quantities of $CuBrMe_2S$ (0.23 g, 1.1 mmol, 1.5 eq), vinyl magnesium bromide (2.2 mL of a 1M sol., 2.2 mmol, 3 eq), and 4-benzyl-5, 5-dimethyl-N-but-2-enoyl-2-oxazolidinone (0.20 g, 0.73 mmol, 1.0 eq). Purification by flash chromatography yielded a colourless oil (0.16 g, 73 %); ν_{max}(thin film)/cm^{-1} 2973, 1777, 1698, 1604, 1455, 1356, 1277, 1236, 1183, 1098; δ_H(300 MHz, $CDCl_3$) 7.29-7.09 (5H, m, Ar*H*), 5.77-5.67 (1H, m, CH_2=C*H*), 4.98-4.84 (2H, m, CH_2=CH), 4.45-4.40 (1H, dd, J_1 = 3.7 Hz, J_2 = 9.9 Hz, N-C*H*), 3.09-3.05 (1H, dd, J_1 = 3.8 Hz, J_2 = 14.4 Hz, CH_2-Ph), 2.86-2.80 (1H, dd, J_1 = 6.8 Hz, J_2 = 15.5 Hz, O=C=CH_2), 2.81-2.75 (1H, dd, J_1 = 9.7 Hz, J_2 = 14.5 Hz, CH_2-Ph), 2.71-2.65 (1H, dd, , J_1 = 7.1 Hz, J_2 = 15.2 Hz, O=C=CH_2), 1.28 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.01-0.99 (3H, d, J = 6.8 Hz, CH_3); δ_C(75 MHz, $CDCl_3$) 172.2, 142.5, 129.0, 128.6, 126.7, 113.3, 63.5, 41.9, 35.3, 34.2, 28.5, 27.4, 22.2; m/z $[M+H]^+$ 302.1751 found: 302.1751.

Synthesis of 4-(S)-benzyl-5,5-dimethyl-*N*-(3-methyl-hex-5-enoyl)-2-oxazolidinone (255)



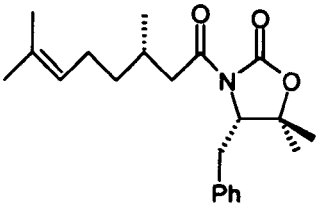
Compound (255) was prepared according to *GP3*, using the following quantities of $CuBrMe_2S$ (0.23 g, 1.1 mmol, 1.5eq), allyl magnesium bromide (2.2 mL of a 1M sol., 2.2 mmol, 3.0 eq), and 4-benzyl-5, 5-dimethyl-N-but-2-enoyl-2-oxazolidinone (0.20 g, 0.73 mmol, 1.0 eq). Purification by flash chromatography yielded a colourless oil (0.17 g, 77 %); $[\alpha]_D$= -31.1 (c = 0.48, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2973, 2930, 1778, 1698, 1640, 1455, 1355, 1276, 1235, 1182, 1097, 910; δ_H(300 MHz, $CDCl_3$) 7.25-7.08 (5H, m,Ar*H*), 5.76-5.65 (1H. m, CH_2=C*H*), 4.98-4.93 (2H, m, CH=CH_2), 4.46-4.43 (1H, dd, J_1 = 3.8 Hz, J_2 = 9.5 Hz, N-C*H*-), 3.09-3.04 (1H, dd, J_1 = 3.8 Hz, J_2 = 14.5 Hz, CH_2- Ph), 2.89-2.84 (1H, dd, J_1 = 5.6 Hz, J_2 = 16.3Hz, O=C-CH_2), 2.82-2.76 (1H, dd, J_1 = 9.5 Hz, J_2 = 14.4 Hz, CH_2- Ph), 2.71-2.65 (1H, dd, J_1 = 7.6 Hz, J_2 = 16.1 Hz, O=C-CH_2), 2.10-1.83 (3H, m, CH_3-C*H*-CH_2-), 1.29 (3H, s, CH_3), 1.27 (3H, s, CH_3), 0.88-0.87 (3H, d, *J* = 6.5 Hz, CH_3); δ_C(75 MHz, $CDCl_3$) 173.0, 152.6, 136.5, 129.0, 128.6, 126.7, 116.5, 82.0, 63.4, 41.8, 41.0, 35.3, 29.5, 28.5, 22.2, 19.5.

Synthesis of (S)-4-benzyl-5,5-dimethyl-*N*-(3-(S)-methyl-oct-7-enoyl)-2-oxazolidinone (256)



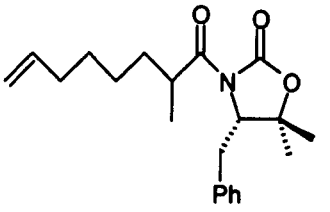
Compound (256) was prepared according to *GP2*, using the following quantities of magnesium turnings (0.37 g, 15.1 mmol, 3.1 eq), 5-bromo-pent-2-ene (1.70 mL, 14.6 mmol, 3.0 eq), $CuBrM_2S$ (1.50 g, 7.3 mmol, 1.5 eq) and 4-benzyl-N-acryloyl-2-oxazolidinone (1.33 g, 4.9 mmol, 1.0 eq). Purification by column chromatography yielded a colourless oil (1.15g, 71%). ν_{max}(film)/cm^{-1} 2930, 1778, 1697, 1640, 1455, 1355, 1276, 1234, 1160, 910; δ_H(300 MHz, $CDCl_3$) 7.27-7.13, (5H,m, Ar*H*)), 5.79-5.65, (1H, m, C*H*=CH_2), 4.96-4.80, (2H, m, CH=C*H*$_2$), 4.47-4.42, (1H, dd, J_1= 3.8 Hz, J2 = 9.5 Hz), 3.09-2.98, (1H, dd, J1 = 3.8 Hz, J2 = 14.3 Hz, -CH_2-Ph), 2.87-2.76, (2H, m, $CH_2CH=CH_2$), 2.71-2.62, (1H, dd, J1 = 8.0 Hz, J2 = 15.9 Hz, CH_2-Ph), 1.99-1.95, (3H m, CH_2-CH-CH_3), 1.29 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.40-1.15, (4H, m, CH_2 × 2), 0.87-0.85, (3H, d, J = 6.6 Hz, CH_3); δ_C(75 MHz, CDCl3) 173.0, 153.2, 138.8, 136.9, 129.0, 128.6, 126.7, 114.4, 81.9, 63.4, 42.5, 36.2, 35.4, 33.8, 29.6, 28.5, 26.2, 22.3, 19.6; m/z $[M=H]^+$ calc: 344.2220, found: 344.2220.

Synthesis of (S)-4-benzyl-*N*-((3S)-3,7-dimethyl-oct-6-enoyl)-5,5-dimethyl-2-oxazolidinone (257)



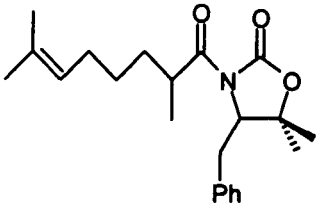
Compound (257) was prepared according to *GP2*, using the following quantities of magnesium turnings (0.10 g, 3.9 mmol, 3.1 equiv.), 5-bromo-pent-2-ene (0.5 mL, 3.7 mmol, 3.0 eq), $CuBrM_2S$ (0.39 g, 1.9 mmol, 1.5 eq) and 4-benzyl-N-acryloyl-2-oxazolidinone (0.34 g, 1.24 mmol, 1.0 eq). Purification by column chromatography yielded a colourless oil (0.44g, 78%); $[\alpha]_D$= -7.2 (c = 0.41, $CHCl_3$); ν_{max}(film)/cm^{-1} 2963, 2925, 2854, 1778, 1698, 1455, 1354, 1276, 1100; δ_H(300 MHz, $CDCl_3$) 7.25-7.13 (5H, m, Ar*H*), 5.04-4.99 (1H, m, C*H*=C$(CH_3)_2$), 4.47-4.42 (1H, dd, J_1 = 3.8 Hz, J_2 = 9.6 Hz, N-C*H*-CH_2), 3.10-3.04 (1H, dd, J_1 = 3.8 Hz, J_2 = 14.3 Hz, CH_2-Ph), 2.84-2.76 (2H, dd, J_1 = 9.4 Hz, J_2 = 14.6 Hz, CH_2-Ph), 2.75-2.67 (1H, dd, J_1 = 7.9 Hz, J_2 = 15.9 Hz, O=C-CH_2), 1.99-1.87 (3H m,CH_3-C*H*, =CH-CH_2), 1.60 (3H, s, =C(CH_3)$_2$), 1.52 (3H, s, =C(CH_3)$_2$), 1.29 (3H, s, O-C(CH_3)$_2$), 1.27 (3H, s, O-C(CH_3)$_2$), 0.90-0.85 (3H, d, CH-CH_3); δ_C(75 MHz, $CDCl_3$) 189.0, 173.0, 137.0, 131.4, 129.0, 128.6, 126.7, 124.3, 82.0, 63.5, 42.5, 36.8, 35.4, 29.5, 28.5, 25.7, 25.4, 22.3, 19.5, 17.6; m/z $[M]^+$ calc: 357.2298, found: 357.2300.

Synthesis of (S)-4-benzyl-5,5-dimethyl-*N*-(2-methyl-oct-7-enoyl)-2-oxazolidinone (258)



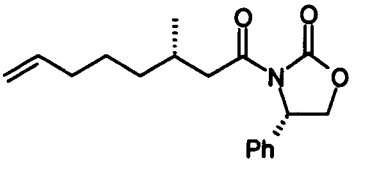
Compound (258) was prepared according to *GP2*, using the following quantities of magnesium turnings (0.14 g, 5.7 mmol, 3.1 eq), 5-bromo-pent-2-ene (0.0.65 mL, 5.5 mmol, 3.0 eq), $CuBrM_2S$ (0.56 g, 2.75 mmol, 1.5equiv.) and 4-benzyl-5, 5-dimethyl-N-(2-methyl-acryloyl)-2-oxazolidinone (0.5 g, 1.8 mmol, 1.0 eq). Purification by column chromatography yielded a colourless oil (0.38, 64 %). $[\alpha]_D$= -17.9 (c = 0.67, $CHCl_3$; ν_{max}(thin film)/cm^{-1} 2976, 2932, 2856, 1774, 1697, 1497, 1353, 1237, 1098, 991; δ_C(300 MHz, $CDCl_3$) 7.30-7.09 (5H, m, Ar*H*), 5.78-5.63 (1H, m, CH_2=C*H*-), 4.99-4.82, 2H, m, =C*H*$_2$), 4.47-4.37 (1H, m, N-C*H*), 3.69-3.62 (1H, m, C*H*$_2$-Ph), 3.08-2.92 (1H, m, CH-CH_3), 2.86-2.76 (1H, m, C*H*$_2$-Ph), 2.02-1.95 (2H, m, =CHC*H*$_2$-), 1.37-0.98 (15H, m, CH_3 × 3, CH_2 × 3); δ_C(75 MHz, $CDCl_3$) 177.4, 152.2, 138.7, 136.9, 129.0, 128.5, 126.5, 114.3, 81.8, 63.5, 37.5, 35.3, 33.5, 33.3, 28.7, 28.3, 26.6, 26.3, 22.2, 17.3, 16.7; m/z: $[M=H]^+$ calc: 344.2220, found: 344.2222.

Synthesis of (S)-4-benzyl-*N*-(2,7-dimethyl-oct-6-enoyl)-5,5-dimethyl-2-oxazolidinone (259)



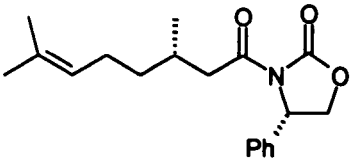
Compound (259) was prepared according to *GP2*, using the following quantities of magnesium turnings (0.14 g, 5.6 mmol, 3.1 eq), 2-methyl-5-bromo-pent-2-ene (0.74 mL, 5.5 mmol, 3.0 eq), $CuBrM_2S$ (0.56 g, 2.75 mmol, 1.5 eq) and 4-benzyl-5, 5-dimethyl-N-(2-methyl-acryloyl)-2-oxazolidinone (0.5 g, 1.8 mmol, 1.0 eq). Purification by column chromatography yielded a colourless oil (0.52 g, 83 %); $[\alpha]_D$= -23 (c = 0.65, $CHCl_3$); ν_{max}(film)/cm^{-1} 2932, 2857, 1777, 1698, 1640, 1353, 1238, 1098, 732, 700; δ_H(300 MHz, $CDCl_3$) 7.25-7.13 (5H, m, Ar*H*), 5.08-4.97 (1H, m, C*H*=C(CH_3)$_2$), 4.47-4.37 (1H, m, N-C*H*-), 3.07-2.93 (1H, m, CH_2-Ph), 2.85-2.76 (1H, m, CH_2-Ph), 2.28-2.21 (2H, m, =CHCH_2) 1.94-1.82 (2H, m, =CHCH_2CH_2), 1.63-1.51 (6H, m, =C(CH_3)$_2$, 1.30-1.22 (8H, m, C(CH_3)$_2$, CH_2), 1.09-1.03 (3H, dd, J_1 = 6.8 Hz, J_2 = 7.8 Hz, CHCH_3); δ_C(75 MHz, $CDCl_3$) 177.4, 152.2, 138.7, 136.9, 129.0, 128.5, 126.5, 114.3, 81.8, 63.5, 37.5, 35.3, 33.5, 33.3, 28.7, 28.3, 26.6, 26.3, 22.2, 17.3, 16.7; m/z $[M+H]^+$ calc: 358.2377, found: 358.2380.

Synthesis of (S)-4-phenyl-*N*-(3-(S)-methyl-oct-7-enoyl)-2-oxazolidinone (260)



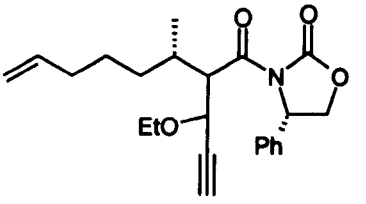
Compound (260) was prepared according to *GP2*, using the following quantities of magnesium turnings (0.32 g, 13.0 mmol, 3.1 eq), 5-bromo-pent-2-ene (1.55 mL, 13.0 mmol, 3.0 eq), $CuBrMe_2S$ complex (1.34 g, 6.5 mmol, 1.5 eq), and 3-But-2-enoyl-4-phenyl-2-oxazolidinone (1.0 g, 4.3 mmol, 1.0 eq). Purification by flash chromatography (7:3 hexane / EtOAc) yielded a colourless oil (1.24 g, 95 %); R_f 0.6; ; $[\alpha]_D$= -33.0 (c = 0.42, $CHCl_3$); ν_{max}(film)/cm^{-1} 2926, 1781, 1702, 1456, 1383, 1321, 1200, 910, 761, 707, 684; δ_H(300 MHz, $CDCl_3$) 7.43-7.56 (5H, m, Ar*H*), 5.85-5.71 (1H, m, CH_2-C*H*-), 5.45-5.40 (1H, dd, J_1 = 3.7 Hz, J_2 = 8.7 Hz, O-CH_2), 5.05-4.89 (2H, m, CH=CH_2), 4.70-4.64 (1H, t, J = 8.8 Hz, -C*H*-Ph), 4.27-4.23 (1H, dd, J_1 = 3.7 Hz, J_2 = 8.9 Hz, O-CH_2), 3.02-2.95 (1H, dd, J_1 = 5.3 Hz, J_2 = 16 Hz, O=C-CH_2), 2.71-2.63 (1H, dd, J_1 = 8.5 Hz, J_2 = 16 Hz, O=C-CH_2), 2.07-1.95 (3H, m, CH_3-C*H*-CH_2-), 1.46-1.07 (4H, m, =CH-CH_2-CH_2), 0.84-0.82 (3H, d, J = 6.6 Hz, CH_3); δ_C(75 MHz, $CDCl_3$) 172.0, 153.5, 139.1, 138.6, 128.9, 128.4, 125.7, 114.2, 69.6, 57.3, 42.3, 36.1, 33.6, 29.3, 25.9, 19.3; m/z $[M+H]^+$ calc: 302.1756, found: 302.1755.

Synthesis of 4-(S)-phenyl-*N*-(3-(S)-3,7-dimethyl-oct-6-enoyl)-2-oxazolidinone (261)



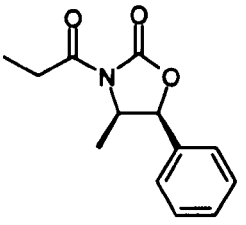
Compound (261) was prepared according to *GP2*, using the following quantities of magnesium turnings (0.17 g, 6.7 mmol, 3.1 eq), 2-methyl-5-bromopent-2-ene (0.9 mL, 6.7 mmol, 3.0 eq), $CuBrMe_2S$ complex (0.67 g, 3.24 mmol, 1.5 eq), and 3-but-2-enoyl-4-phenyl-2-oxazolidinone (0.5 g, 2.1 mmol, 1.0 eq). Purification by flash chromatography (7:3 hexane / EtOAc) yielded a colourless oil (0.60 g, 88 %); R_f 0.53; $[\alpha]_D$= -25.8 (c = 0.46, $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 7.41-7.24 (5H, m, Ar*H*), 5.44-5.40 (1H, dd, J_1 = 3.7 Hz, J_2 = 8.8 Hz, O-CH_2), 5.06-5.01 (1H, m, $(CH_3)_2$C=C*H*), 4.69-4.63 (1H, t, *J* = 8.8 Hz, Ph-C*H*-), 4.27-4.22 (1H, dd, J_1 = 3.7 Hz, J_2 = 8.8 Hz, O-CH_2), 3.01-2.94 (1H, dd, , J_1 = 5.2 Hz, J_2 = 16 Hz, O=C-CH_2), 2.74-2.66 (1H, dd, , J_1 = 8.5 Hz, J_2 = 16 Hz, O=C-CH_2), 2.09-1.90 (3H, m, CH_3-C*H*-CH_2-), 1.65 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.38-1.08 (2H, m, =CH-CH_2-), .84-0.82 (3H, d, *J* = 6.6 Hz, CH_3); δ_C(75 MHz, $CDCl_3$) 172.3, 153.7, 139.2, 131.4, 129.1, 128.9, 125.9, 124.3, 69.8, 57.6, 42.4, 36.8, 29.3, 25.7, 25.4, 19.5, 17.6; m/z$[M+NH_4]^+$ calc: 333.2173, found: 333.2170.

Synthesis of 4-(S)-phenyl-*N*-[2-(1-ethoxy-prop-2-ynyl)-3-methyl-oct-7-enoyl]-oxazolidin-2-one (267b)



Compound (266) was prepared according to *GP5*, using the following quantities of 3-(3-methyl-oct-7-enoyl)-4-phenyl-2-oxazolidinone (260), (0.12 g, 0.4 mmol, 1.0 eq), propiolaldehyde diethyl acetal cobalt complex (0.21 g, 0.44 mmol, 1.1 eq), diisopropylethylamine (0.08 mL, 0.44 mmol, 1.1 eq) and dibutyl boron triflate (0.9 mL, 0.9 mmol, 2.22 eq). However, the decomplexation was carried out *in situ* to better the yield using an excess of CAN (2.20g, 4 mmol, 10 eq). Purification by flash chromatography yielded the title product as a yellow oil (0.04 g, 15 %); ν_{max} (neat)/cm^{-1} 2963, 2931, 2360, 2334, 1780, 1704,1643, 1456, 1382, 1320, 1197, 1102, 756, 698; δ_H (400 MHz, $CDCl_3$) 7.28-7.04 (5H, m, Ar*H*), 5.78-5.67 (1H, m, CH_2=C*H*-), 5.45-5.36 (1H, dd, J_1 = 3.7 Hz, J_2 = 8.7 Hz, -O-C*H*$_2$-), 4.95-4.86 (2H, m, CH=C*H*$_2$), 4.60-4.45 (3H, m, Ph-C*H*-, O=C-C*H*-C*H*-O-), 4.11-4.07 (1H, dd, J_1 = 3.3 Hz, J_2 = 8.7 Hz, -O-C*H*$_2$-), 3.78-3.70 (1H, m, -O-C*H*$_2$-CH_3), 3.43-3.38 (1H, m, -O-C*H*$_2$-CH_3), 2.10-1.86 (2H, m, CH_2=CH-C*H*$_2$-), 1.48-1.20 (4H, m, -C*H*$_2$-C*H*$_2$-), 1.17-1.12 (3H, t, O-CH_2-C*H*$_3$), 0.94-0.92 (3H, d, J = 6.8 Hz, CH-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 172.0, 153.5, 139.1, 138.6, 129.35, 129.0, 128.7, 128.5, 127.3, 126.7, 126.2, 114.2, 84.6, 75.5, 69.6, 64.8, 60.1, 57.3, 53.7, 36.0, 33.6, 29.4, 25.9, 17.2, 14.9.

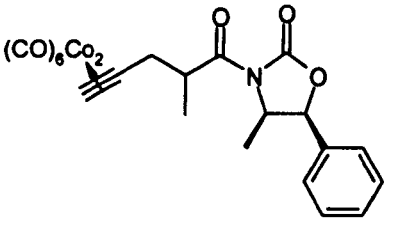
Synthesis of (4R, 5S)-4-methyl-5-phenyl-*N*-propionyl-oxazolidin-2-one (269)



Compound (269) was prepared according to *GP1*, using the following quantities of (4R, 5S)-(+)-4-Methyl-5-phenyl-2-oxazolidinone (1.5 g, 8.47 mmol, 1.0 eq), n-BuLi (2.5M in hexanes, 3.4 cm^3, 11.0 mmol, 1.0 eq) and propionyl chloride (0.82 mL, 9.32 mmol, 1.1 eq). Purification by flash chromatography (7:3 Hexane / ethyl acetate) yielded the product as colourless crystals (1.88 g, 95 %); R_f 0.5; mp 96-98 °C; $[\alpha]_D$ +48.8, (c = 2.5, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2981, 2939, 1780, 1694, 1644, 1450, 1371, 1243, 1070, 972, 768, 702; δ_H(400 MHz, $CDCl_3$) 7.42-7.27 (5H, m, Ar*H*), 5.66-5.64 (1H, d, *J* = 7.3 Hz, Ph-C*H*-), 4.78-4.72 (1H, m, N-C*H*-), 3.04-2.86 (2H, m, CH_3-CH_2-), 1.19-1.15 (3H, t, *J* = 7.3 Hz, CH_2-CH_3), 0.89-0.87 (3H, d, *J* = 6.6 Hz, N-CH-CH_3); δ_C(100 MHz, $CDCl_3$) 173.8, 153.1, 133.3, 128.7, 128.6, 125.6, 78.9, 54.7, 29.2, 14.5, 8.2; m/z $[M+NH_4]^+$ calc: 251.1390, found: 251.1390.

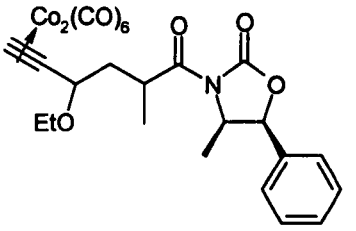
General Procedure for the intermolecular Nicholas reaction (*GP5*)

Synthesis of (4R,5S)-4-methyl-3-(2-methyl-pent-4-ynoyl)-5-phenyl-oxazolidin-2-one cobalt complex (270)



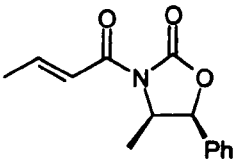
(4R, 5S)-4-Methyl-5-phenyl-3-propionyl-oxazolidin-2-one (0.5 g, 2.14 mmol, 1.0 eq) and methyl propargyl ether dicobalt hexacarbonyl complex (0.84 g, 2.35 mmol, 1.1 eq) were added to a dry round-bottomed flask which was evacuated and purged with nitrogen several times. Dry DCM (15mL) was added and the solution was cooled to −78 °C (CO_2/acetone). Diisopropylethylamine (0.45 mL, 2.61 mmol, 1.2 eq) and dibutylboron triflate (4.75 mL of a 1.0M sol., 4.75 mmol, 2.22 eq) were added in sequence via a syringe. The cold bath was removed, and after one hour the solvent was evaporated off. The crude product was purified by flash chromatography to yield a dark red oil (0.54 g, 4 5%); $[\alpha]_D$ +47.6 (c = 0.042, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.41-7.29 (5H, m, Ar*H*), 5.69-5.67 (1H, d, *J* = 5.9 Hz, Ph-C*H*-), 4.79-4.76 (1H, m, CH_3-C*H*-N), 3.97-3.96 (1H, m, CH_3-C*H*-CH_2-), 3.51-3.46 (1H, dd, J_1 = 7.3 Hz, J_2 = 15.0 Hz, CH_aH$_b$-C≡C-), 2.92-2.87 (1H, dd, J_1 = 4.7 Hz, J_2 = 15.0 Hz, CH$_a$*H*$_b$-C≡C-), 1.35-1.34 (3H, d, *J* = 6.2 Hz, CH-C*H*$_3$), 0.94-0.93 (3H, d, *J* = 5.1 Hz, N-CH-C*H*$_3$); δ_C(100 MHz, $CDCl_3$) 199.5, 175.2, 152.5, 133.2, 128.8, 125.6, 93.3, 78.9, 73.7, 55.0, 40.1, 37.7, 18.0, 14.6; m/z $[M\text{-}CO]^+$ calc 528.9613, found 528.9620.

Synthesis of (4R,5S)-3-(4-ethoxy-2-methyl-hex-5-ynoyl)-4-methyl-5-phenyl-oxazolidin-2-one dicobalt hexacarbonyl complex (271)



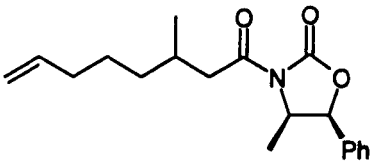
Compound (271) was prepared according to *GP5*, using the following quantities of (4R, 5S)-4-methyl-5-phenyl-3-propionyl-oxazolidin-2-one (0.5 g, 2.14 mmol, 1.0 eq), propiolaldehyde diethyl acetal cobalt complex (0.90 g, 2.35 mmol, 1.1 eq), diisopropylethylamine (0.45 mL, 2.31 mmol, 1.2 eq) and dibutyl boron triflate (4.75 mL, 4.75 mmol, 2.22 eq). Purification by flash chromatography yielded the title product as a dark red oil (0.76 g, 59 %); ν_{max} (neat)/cm^{-1} 2965, 2930, 2355, 2093, 2056, 2030, 1783, 1339, 1192, 1118, 733; δ_H (400 MHz, $CDCl_3$) 7.41-7.27 (5H, m, Ar*H*), 6.05 (1H, s, C≡C*H*), 5.65-5.62 (1H, dd, J_1 = 4.7 Hz, J_2 = 7.3 Hz, Ph-C*H*-), 4.83-4.69 (1H, m, CH_3-C*H*-N), 4.57-4.55 (1H, d, J = 9.8 Hz, C≡C-C*H*-), 4.24-4.17 (1H, m, CH_3-C*H*-), 3.83-3.76 (1H, m, O-CH_aH_b-CH_3), 3.57-3.50 (1H, m, O-CH_aH_b-CH_3),1.26-1.24 (3H, d, J = 6.9 Hz, N-CH-CH_3), 1.17-1.14 (3H, t, CH_2-CH_3), 0.88-0.86 (3H, d, CH-CH_3); δ_C (100 MHz, $CDCl_3$) 173.7, 153.1, 152.5, 133.4, 128.7, 125.6, 82.3, 78.9, 72.5, 66.7, 54.6, 44.7, 29.2, 14.8, 14.4, 8.2.

Synthesis of (4R,5S)-*N*-but-2-enoyl-4-methyl-5-phenyl-2-oxazolidinone (272)



Compound (272) was prepared according to *GP1*, using the following quantities of (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (3.00 g, 17.0 mmol, 1.0 eq), n-Butyllithium (6.8 mL of a 2.5M sol., 17.0 mmol, 1.0 eq), and freshly distilled crotonyl chloride (1.8 mL, 19.00 mmol, 1.1 eq). Purification by flash chromatography (8:2 hexane / EtOAc) yielded the title product as colourless needles (3.43 g, 96%). m.p. 59.2-60.1 °C; $[\alpha]_D$ + 33.3 (c = 0.18, $CHCl_3$); R_f 0.35; ν_{max}(thin film)/cm^{-1} 2982, 1779, 1686, 1637, 1350, 1198, 972, 701; δ_H(300 MHz, $CDCl_3$) 7.44–7.27 (6H, m, Ar*H*), 7.2–7.12 (1H, m), 5.66 (1H, d, *J* = 7.32), 4.83-4.76,(1H, m, CH=C*H*CH_3), 1.97-1.95 (3H, dd, J_1 = 1.1 Hz, J_2 = 6.6 Hz, =CHC*H*$_3$), 0.92-0.90 (3H, d, *J* = 6.6 Hz, NCHC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 164.7, 153.0, 146.7, 133.3, 128.6, 125.6, 121.9, 78.9, 54.8, 18.4, 14.5; m/z calc: 246.1125, found: 246.1124.

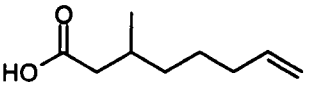
Synthesis of (R)-4-methyl–5-(S)-phenyl-*N*-(3-methyl-oct-7-enoyl)-2-oxazolidinone (273)



Compound (273) was prepared according to *GP2*, using the following quantities of 5-bromo-1-pentene (4.37 mL, 36.90 mmol, 3.0 eq), magnesium turnings (0.93 g, 38.10 mmol, 3.1 eq), CuBr-(Me_2)S complex (3.78 g, 18.40 mmol, 3.0 eq), dimethyl sulfide (5mL) and (4R,5S)-4-methyl-5-phenyl-2-*N*-But-2-enoyl-oxazolidinone (272) (3.0 g, 12.30 mmol, 1.0 eq). Purification by flash chromatography yielded a colourless oil (0.93 g, 78 %); $[\alpha]_D$= +10.7 (c = 0.44, $CHCl_3$); ν_{max}(film)/cm^{-1} 2931, 1782, 1699, 1456, 1347, 1219, 1198; δ_H(300 MHz, $CDCl_3$) 7.43-7.27 (5H, m, Ar*H*), 5.85-5.75 (1H, m, CH_2-C*H*-), 5.66-5.64 (1H, d, J = 7.3 Hz, Ph-C*H*-), 5.02-4.97 (1H, dd, J_{bc} = 1.5 Hz, J_{ac} = 17.2 Hz, CH=CH_2 trans), 4.94-4.91 (1H, dd, J_{bc} = 2 Hz, J_{ab} = 10.2 Hz, CH=CH_2 cis), 4.79-4.73 (1H, m, N-C*H*-CH_3), 3.01-2.96 (1H, dd, J_1 = 5.5 Hz, J_2 = 16.1 Hz, O=C-CH_2), 2.91-2.80 (2H, m, CH_2-C*H*-CH_3), 2.74-2.67 (1H, dd, J_1 = 8.4 Hz, J_2 = 8.4 Hz, O=C-CH_2), 2.14-1.96 (3H, m, CH_3-C*H*-CH_2), 1.51-1.49 (4H, m, =CH-CH_2-CH_2), 0.97-0.94 (3H, dd, J_1 = 5.9 Hz, J_2 = 6.6 Hz, N-CH-CH_3), 0.89-0.87 (3H, dd, J_1 = 1.3 Hz, J_2 = 7.2 Hz, CH_3); δ_C(75 MHz, $CDCl_3$) 173.1, 153.2, 138.8, 128.7, 125.6, 114.4, 78.8, 54.7, 42.5, 36.3, 33.8, 29.5, 26.2, 19.6, 14.5; m/z $[M+NH_4]^+$ calc: 333.2173, found: 333.2169.

Procedure for the cleavage of the chiral auxiliary

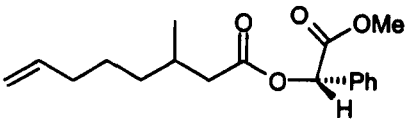
Synthesis of 3-(S)-methyl-oct-7-enoic acid (274)



A solution of compound (273), (1.0g, 3.17 mmol, 1 eq) in THF and water (10 mL) was stirred at 0 °C under N_2, and was treated with H_2O_2 (2.9 mL, 25.4 mmol, 8 eq) followed by LiOH (0.15 g, 6.34 mmol, 2 eq). The reaction mixture was left to stir at room temperature overnight, cooled to 0 °C and treated with a solution of sodium sulfite (3.55g, 28.2 mmol, 8.9 eq) in water (10 mL) followed by 20 mL of 0.5 M $NaHCO_3$. The THF was then evaporated before the reaction mixture was extracted with DCM (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the oxazolidinone as colourless crystals (0.49 g). The aqueous layer was reacidified to a pH below pH 1 with 4M HCl and extracted with EtOAc (3 × 50 mL). The ethyl acetate layers were combined, dried and filter, and finally concentrated under vacuum to yield the desired carboxylic acid (274), (0.31 g, 61 %); ν_{max}(film)/cm^{-1} 3465, 2980, 2940, 2850, 1710, 1445, 1415, 1303, 1231, 943, 825, 735; δ_H(300 MHz, $CDCl_3$) 5.83-5.73 (1H, m, H_2C=C*H*-), 5.01-4.96 (1H, doublet of quartet, J_{ab} = 3.6 Hz, J_{ac} = 17.0 Hz, -CH=CH_aH$_b$, Ha trans), 4.95-4.91 (1H, doublet of quintet, J = 10.2 Hz, -CH=CH$_a$$H_b$, Hb cis), 2.37-2.31 (1H, dd, J_1 = 5.8 Hz, J_2 = 15.0 Hz, O=C-CH_aH$_b$), 2.17-2.11 (1H, dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz, O=C-CH$_a$$H_b$), 2.06-2.00 (2H, m, =CH-CH_2-), 1.98-1.91 (1H, m, -C*H*-CH$_3$), 1.48-1.17 (4H, m, -CH_2-CH_2-), 0.97-0.95 (3H, d, J = 6.6 Hz, -CH_3); δ_C(75 MHz, $CDCl_3$) 180.0, 138.7, 114.4, 41.5, 36.0, 33.7, 29.9, 26.1, 19.6.

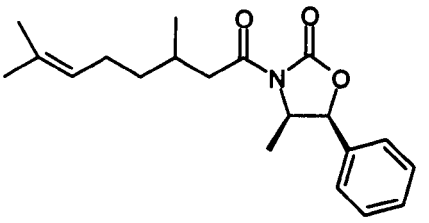
Procedure for Mosher ester synthesis from carboxylic acids

Synthesis of 3-methyl-oct-7-enoic acid methoxycarbonyl-phenyl-methyl ester (275).



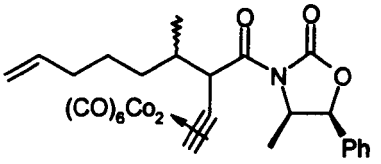
To a stirred solution of 3-methyl-oct-7-enoic acid (274), (0.100g, 0.64 mmol, 1 eq), in DCM at -10 °C under an atmosphere of nitrogen was added 4-dimethylaminopyridine (3 mg), followed by methyl (S)-mandelate (0.106, 0.64 mmol, 1 eq), and 1,3-dicyclohexylcarbodiimide (0.132 g, 0.64 mmol, 1 eq). After 30 minutes, TLC analysis showed the presence of a new compound. The reaction mixture was filtered, and the solvent evaporated. Purification by flash chromatography gave the desired ester as an oil (0.15 g, 79 %); ν_{max}(neat)/cm^{-1} 3068, 3034, 2930, 2856, 1741, 1672, 1639, 1497, 1456, 1436, 1215, 1169, 1045, 912, 734, 696; δ_H(300 MHz, $CDCl_3$) 7.47-7.34 (5H, m, Ar*H*), 5.92 (1H, s, -O-C*H*-Ph), 5.83-5.73 (1H, m, CH_2=C*H*-), 5.01-4.95 (1H, doublet of quartet, J_{ab} = 3.3 Hz, j_{ac} = 17.2 Hz, CH_c=CH_aH$_b$, H_a trans), 4.94-4.91 (1H, doublet of quintet, J = 10.2 Hz, CH_c=CH_aH$_b$, H_b cis), 3.70 (3H, s, -O-CH_3), 2.50-2.39 (1H, dd × 2, J_1 = 5.8 Hz, J_2 = 15.0 Hz, O=C-CH_aH$_b$-), 2.32-2.21 (1H, dd × 2, J_1 = 8.0 Hz, J_2 = 15.0 Hz, O=C-CH$_a$H$_b$-), 2.08-1.96 (3H, m, CH_3-C*H*-, =CH-CH_2-), 1.49-1.19 (4H, m, -CH_2-CH_2-), 0.99-0.98 (1.5 H, d, J = 6.5 Hz, CH-CH_3), 0.99-0.97 (1.5H, d, J = 6.9 Hz, CH-CH_3); δ_C(75 MHz, $CDCl_3$) 172.3, 169.2, 138.6, 133.7, 129.0, 128.6, 127.5, 114.3, 74.1, 52.4, 41.2, 35.9, 33.7, 30.1, 26.0, 19.5.

Synthesis of (4R,5S)-*N*-(3,7-dimethyl-oct-6-enoyl)-4-methyl-5-phenyl-oxazolidin-2-one (276)



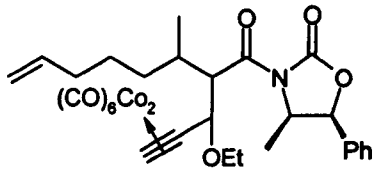
Compound (276) was prepared according to *GP2*, using the following quantities of 2-methyl-5-bromopent-2-ene (1.6 mL, 12.1 mmol, 3.0 eq), magnesium turnings (0.32 g, 13.0 mmol, 3.1 eq), CuBr-(Me_2)S complex (1.26 g, 6.12 mmol, 1.5 eq), dimethyl sulfide (8mL) and N-but-2-enoyl-4-methyl-5-phenyl-2-oxazolidinone (272) (1.0 g, 4.0 mmol, 1.0 eq). Purification by flash chromatography yielded a colourless oil (1.20 g, 89 %); $[\alpha]_D$= +13.4 (c = 0.39, $CHCl_3$); ν_{max}(film)/cm^{-1} 2931, 1782, 1699, 1456, 1347, 1219, 1198; 733, 700 δ_H(300 MHz, $CDCl_3$) 7.42-7.28 (5H, m, Ar*H*), 5.65-5.64 (1H, d, *J* = 7.3 Hz, Ph-C*H*-), 5.13-5.05 (1H, m, =C-C*H*-), 4.82-4.73 (1H, m, N-C*H*-), 300-2.70 92h, m, O=C-CH_2-), 2.11-1.94 (3H, m, CH_3-C*H*-CH_2-), 1.67 (3H, s, =C(CH_3)$_2$), 1.59 (3H, s, =C(CH_3)$_2$), 1.45-1.37 (1H, m, =CH-CH_2-), 1.32-1.19 (1H, m, =CH-CH_2-), 0.98-0.97 (3H, d, *J* = 6.2 Hz, N-CH-CH_3), 0.89-0.87 (3H, d, *J* = 6.6 Hz, CH-CH_3); δ_C(75 MHz, $CDCl_3$) 173.2, 154.0, 138.7, 128.7, 125.6, 114.4, 78.8, 54.6, 42.4, 36.3, 33.8, 29.5, 26.2, 19.7, 14.5; m/z [M+H]+ calc: 330.2064, found: 330.2068.

Synthesis of (4R,5S)-*N*-(2-ethynyl-3-methyl-oct-7-enoyl)-4-methyl-5-phenyl-oxazolidin-2-one cobalt complex (277a)



Compound (277a) was prepared according to *GP5*, using the following quantities of *N*-(3-methyl-oct-7-enoyl)-4-(R)-methyl–5-(S)-phenyl-2-oxazolidinone (273), (0.40 g, 1.36 mmol, 1.0 eq), propiolaldehyde diethyl acetal cobalt complex (0.53 g, 1.49 mmol, 1.1 eq), diisopropylethylamine (0.30 mL, 1.62 mmol, 1.2 eq) and dibutyl boron triflate (3.0 mL, 3.0 mmol, 2.22 eq). Purification by flash chromatography yielded the title product as a dark red oil (0.60 g, 70 %); ν_{max} (neat)/cm^{-1} 2963, 2929, 2350, 2094, 2057, 2032, 1783, 1695, 1339, 1192, 1118, 733; δ_H (400 MHz, $CDCl_3$) 7.43-7.28 (5H, m, Ar*H*), 5.85 (1H, s, C≡C*H*), 5.83-5.74 (1H, m, CH_2=C*H*-), 5.65-5.64 (1H, d, *J* = 7.3 Hz, Ph-C*H*-), 5.03-498 (1H, dq, J_{ab} = 17.2 Hz, CH_a=CH_bH$_c$, H_b trans), 4.96-4.93 (1H, dq, J_{ac} = 10.2 Hz, CH_a=CH$_b$$H_c$, H_c cis), 4.08-3.99 (1H, m, O=C-C*H*-), 3.53-3.46 (1H, m, HC≡C*H*-), 2.12-1.89 (3H, m, CH_3-C*H*-, =CH-CH_2-), 1.57-1.24 (4H, m, -CH_2- CH_2-), 0.96-0.94 (3H, d, J = 6.6 Hz, N-CH-CH_3), 0.90-0.88 (3H, d, *J* = 6.9 Hz, CH-CH_3); δ_C (100 MHz, $CDCl_3$) 174.1, 138.5, 133.3, 128.7, 125.6, 114.6, 78.8, 73.5, 55.3, 49.9, 35.3, 34.6, 33.7, 31.0, 26.5, 15.1, 14.3.

Synthesis of 4-(R)-methyl-5-(S)-phenyl-*N*-[2-(1-ethoxy-prop-2-ynyl)-3-methyl-oct-7-enoyl]-2-oxazolidinone cobalt complex (277b)

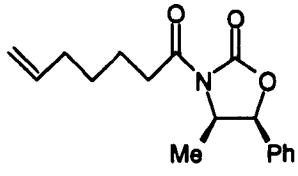


Compound (277b) was prepared according to *GP5*, using the following quantities of N- (3-methyl-oct-7-enoyl)- 4-methyl –5-phenyl-2-oxazolidinone (0.63 g, 2.01 mmol, 1.0 eq), propiolaldehyde diethyl acetal dicobalt hexacarbonyl complex (1.00 g, 2.41 mmol, 1.2 eq), diisopropylethylamine (0.43 mL, 2.45 mmol, 1.2 eq) and dibutylboron triflate (4.46 mL of a 1.0M sol., 4.46 mmol, 2.22 eq). The crude product was purified by flash chromatography to yield a mixture of diastereoisomers that could not be separated. The NMR analysis showed a double signal for the alkyne proton which allowed the ratio of the diastereoisomers (60 – 40) to be calculated from the integrals. The product came out as a dark red oil (0.89g, 65%); ν_{max} (neat)/cm^{-1} 2965, 2929, 2358, 2095, 2054, 2028, 1783, 1693, 1339, 1192, 1118; δ_H (400 MHz, $CDCl_3$) 7.37-7.24 (5H, m, Ar*H*), 5.799-5.797 (0.3H, d, J = 0.73 Hz, C≡C*H*), 5.931-5.930 (0.7H, d, J = 0.73 Hz, C≡C*H*), 5.81-5.65 (1H, m, CH_2=C*H*-), 5.54-5.50 (1H, d, J = 7.3 Hz, Ph-C*H*-), 5.00-4.94 (1H, dq, J_{bc} = 1.6 Hz, J_{ac} = 17.1 Hz, CH=CH_2 trans), 4.92-4.88 (1H, d quintet, J_{ab} = 10.0 Hz, CH=CH_2 cis), 4.79-4.72 (1H, m, N-C*H*-), 4.70-4.64 (1H, dd, J_1 = 0.5 Hz, J_2 = 10.9 Hz, O=C-C*H*-), 4.42-4.38 (1H, dd, J_1 = 4.2 Hz, J_2 = 10.4 Hz), 3.78-3.70 (1H, m, O-CH_2-CH_3), 3.46-3.38 (1H, m, O-CH_2-CH_3), 2.05-1.98 (1H, m, CH_3-C*H*-CH_2-), 1.96-1.78 (2H, m, CH_3-CH-CH_2-), 1.64-1.11 (4H, m, -CH_2- CH_2-), 1.04-1.02 (1.1H, d, J = 6.9 Hz, N-CH-CH_3), 1.02-0.98 (3H,

t, J = 6.9 Hz, CH_2-CH_3), 0.93-0.91 (1.9H, d, J = 6.9 Hz, N-CH-CH_3), 0.87-0.85 (3H, d, J = 6.6 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 199.6, 172.9, 152.5, 138.6, 133.3, 128.7, 125.6, 114.7, 78.3, 72.4, 66.9, 55.1, 53.7, 52.6, 33.9, 32.7, 30.4, 27.3, 26.5, 16.9, 14.8, 14.1. Accurate mass spectrometry was obtained from a small sample of the purified decomplexed compound, m/z $[M+NH^4]^+$ calc 415.2591, found 451.2591.

General procedure for *N*-acylation from carboxylic acids (*GP4*).

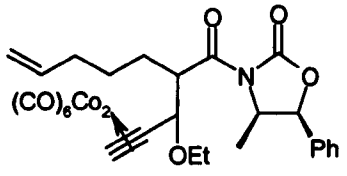
Synthesis of 4-(R)-methyl-5-(S)-phenyl-*N*-hept-6-enoyl-oxazolidin-2-one (280)



In this procedure, 6-heptenoyl chloride was prepared by treating 6-heptenoic acid (0.85 mL, 6.21 mmol, 1.1 eq) with oxalyl choride (0.98 mL, 11.3 mmol, 2 eq) and a drop of DMF in DCM at room temperature under nitrogen atmosphere. When TLC analysis showed that all the starting material had reacted, the solvent was evaporated and the reaction mixture redissolved in DCM and evaporated again. In a second flask, (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (1.0g, 5.65 mmol, 1 eq) was treated with BuLi (2.25 mL, 5.65 mmol, 1 eq) at – 78 °C, before the freshly prepared heptenoyl choride was added dropwise. Purification by flash chromatography afforded the title product as colourless crystals (1.65 g, 80 %); mp 70.7 -72.6 °C, ν_{max}(film)/cm^{-1} 2931, 1782, 1699, 1456, 1347, 1219, 1198; 915, 733, 700; δ_H(300 MHz, $CDCl_3$) 7.43-7.27 (5H, m, Ar*H*), 5.85-5.75 (1H, m, CH_2=C*H*-), 5.66-5.64 (1H, d, J = 7.32 Hz, Ph-C*H*-), 5.04-4.98 (1H, d quartet, J_{bc}

= 1.5 Hz, J_{ac} = 17.2 Hz, CH=CH_2 trans), 4.97-4.93 (1H, d quintet, J_{bc} = 1.1 Hz, J_{ab} = 10.2 Hz, CH=CH_2 cis), 4.78-4.72 (1H, quintet, N-CH-CH_3), 3.02-2.86 (2H, m, O=C-CH_2), 2.12-2.06 (2H, m, =CH-CH_2-), 1.75-1.62 (2H, m, O=C-CH_2), 1.51-1.43 (2H, m, -CH_2-CH_2-CH_2-), 0.89-0.87 (3H, d, J = 6.59 Hz, CH_3) δ_C(75 MHz, $CDCl_3$) 171.0, 151.1, 136.5, 131.4, 126.8, 123.7, 112.8, 76.9, 52.8, 33.6, 33.4, 31.5, 26.4, 21.8, 12.6; m/z calc: 288.1594, found: 288.1591.

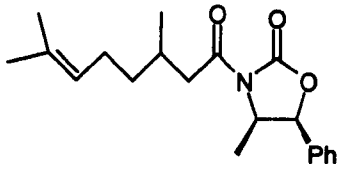
Synthesis of 4-(R)-methyl-5-(S)-phenyl-*N*-[2-(1-ethoxy-prop-2-ynyl)-hept-6-enoyl]- oxazolidin-2-one dicobalt hexacarbonyl complex (281)



Compound (281) was prepared according to *GP5*, using the following quantities of 3-hept-6-enoyl-4-methyl-5-phenyl-oxazolidin-2-one (280), (0.75 g, 2.61 mmol, 1.0 eq), propiolaldehyde diethyl acetal cobalt complex (1.62 g, 3.92 mmol, 1.1 eq), diisopropylethylamine (0.75 mL, 4.18 mmol, 1.2 eq) and dibutyl boron triflate (6.0 mL, 6.0 mmol, 2.22 eq). Purification by flash chromatography yielded the title product as a dark red oil (1.28 g, 77 %); ν_{max} (neat)/cm^{-1} 2977, 2933, 2341, 2095, 2054, 2029, 1785, 1695, 1456, 1397, 1339, 1192, 1119, 975, 766, 699; δ_H (400 MHz, $CDCl_3$) 7.43-7.30 (5H, m, ArH), 6.04 (1H, s, C≡CH), 5.83-5.71 (1H, m, CH_2=CH-), 5.63-5.61 (1H, d, J = 7.3 Hz, Ph-CH-), 5.03-4.95 (2H, m, CH=CH_2), 4.86-4.78 (1H, m, N-CH-), 4.52-4.50 (1H, d, J = 9.5 Hz, O=C-CH-), 4.36-4.30 (1H, td, J_1 = 3.3 Hz, J_2 = 10.2 Hz, CH-O-CH_2-), 3.81-3.74 (1H, m, -O-CH_2), 3.52-3.47 (1H, m, -O-CH_2), 2.08-2.03 (2H, m, =CH-CH_2),

1.85-1.66 (2H, m, CH-C*H*$_2$-), 1.49-1.30 (CH_2- C*H*$_2$- CH_2-), 1.08-1.05 (3H, t, CH_2-C*H*$_3$), 0.93-0.92 (3H, d, J = 6.6 Hz, CH-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 198.1, 176.5, 151.1, 136.7, 132.1, 127.4, 124.3, 113.5, 76.9, 71.3, 65.2, 53.6, 48.5, 43.5, 38.2, 32.3, 27.8, 24.6, 13.4, 12.8. Accurate mass spectroscopy was obtained from a small sample of the purified decomplexed compound, m/z $[M+H]^+$ calc 370.2013, found 370.2014.

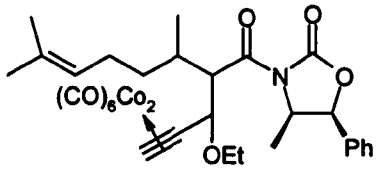
Synthesis of *N*-(3,7-dimethyl-oct-6-enoyl)-4-(R)-methyl-5-(S)-phenyl-oxazolidin-2-one (284)



Compound (284) was prepared according to *GP5*, using the following quantities of (S)-(-)-citronellic acid (1.0mL, 5.42 mmol, 1.5 eq), oxalyl chloride (0.78 mL, 9.02 mmol, 2.5 eq), 1 drop of DMF, (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (0.64 g, 3.61 mmol, 1 eq), and BuLi (1.5 mL, 3.61 mmol, 1 eq). Purification by flash chromatography yielded the title product as an oil (1.18 g, 82 %), ν_{max}(film)/cm^{-1} 2933, 1781, 1699, 1455, 1347, 1221, 1197; 915, 733, 700; δ_H(300 MHz, $CDCl_3$) 7.43-7.27 (5H, m, Ar*H*), 5.65-5.63 (1H, d, J = 7.3 Hz, Ph-C*H*-), 5.11-5.07 (1H, m, =C*H*-), 4.80-4.73 (1H, m, N-C*H*-), 2.87-2.85 (2H, d, J = 6.9 Hz, O=C-C*H*$_2$-), 2.11-1.92 (3H, m, CH_3-C*H*-C*H*$_2$-), 1.67 (3H, s, =C(C*H*$_3$)$_2$), 1.59 (3H, s, =C(C*H*$_3$)$_2$), 1.46-1.35 (1H, m, =C-C*H*$_2$-), 1.29-1.19 35 (1H, m, =C-C*H*$_2$-), 0.99-0.97 (3H, d, J = 6.6 Hz, N-CH-C*H*$_3$), 0.89-0.87 (CH-C*H*$_3$); δ_C(75

MHz, $CDCl_3$) 172.5, 153.0, 133.3, 128.7, 125.6, 124.3, 78.8, 54.7, 42.5, 36.8, 29.4, 25.7, 25.4, 19.5, 17.6, 14.5; m/z calc: 330.2064, found: 330.2068.

Synthesis of 4-(R)-methyl-5-(S)-phenyl-*N*-[2-(1-ethoxy-prop-2-ynyl)-3,7-dimethyl-oct-6-enoyl]- oxazolidin-2-one dicobalt hexacarbonyl complex (285)

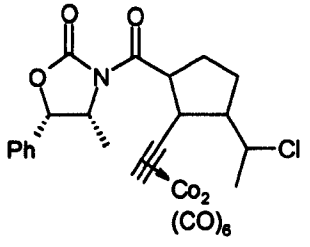


Compound (281) was prepared according to *GP5*, using the following quantities of 3-(3,7-dimethyl-oct-6-enoyl)-4-methyl-5-phenyl-oxazolidin-2-one (284), (0. 50 g, 1.52 mmol, 1.0 eq), propiolaldehyde diethyl acetal cobalt complex (0.69 g, 1.67 mmol, 1.1 eq), diisopropylethylamine (0.45 mL, 2.43 mmol, 1.2 eq) and dibutyl boron triflate (3.50 mL, 3.5 mmol, 2.22 eq). Purification by flash chromatography yielded the title product as a dark red oil (0.84 g, 80 %); ν_{max} (neat)/cm^{-1} 2978, 2934, 2341, 2095, 2055, 2030, 1786, 1695, 1457, 1397, 1340, 1256, 1219, 1193, 1120, 1031, 975, 766, 700; δ_H (400 MHz, $CDCl_3$) 7.43-7.30 (5H, m, Ar*H*), 6.01 (1H, s, C≡C*H*), 5.60-5.58 (1H, d, *J* = 6.9 Hz, Ph-C*H*-), 5.17-5.14 (1H, m, -C*H*=C(CH_3)$_2$), 4.86-4.77 (1H, m, N-C*H*-), 4.75-4.72 (1H, d, J = 10.2 Hz, O=C-CH-), 4.46-4.42 (1H, dd, J_1 = 3.3 Hz, J_2 = 10.2 Hz, C*H*-O-CH_2-), 3.83-3.76 (1H, m, -O-CH_2), 3.52-3.45 (1H, m, -O-CH_2), 2.18-2.09 (2H, m, =CH-CH_2), 1.97-1.86 (2H, m, CH-CH_2-), 1.73 (3H, s, =C(CH_3)$_2$), 1.63 (3H, s, =C(CH_3)$_2$), 1.07-1.04 (3H, t, CH_2-CH_3), 1.00-0.98 (3H, d, *J* = 6.9 Hz, N-CH-CH_3) 0.93-0.91 (3H, d, *J* = 6.6 Hz, CH-CH_3); δ_C (100 MHz, $CDCl_3$ 199.3, 172.8,

133.4, 128.6, 125.6, 124.3, 80.1, 78.4, 66.7, 55.2, 53.6, 46.4, 42.3, 37.3, 33.1, 32.2, 31.1, 23.5, 16.9, 14.7, 13.8.0

Procedure for the Intramolecular Nicholas reaction for the chiral auxiliary approach

Synthesis of 4-(R)-methyl-5-(S)-phenyl-*N*-[3-(1-chloro-ethyl)-2-ethynyl-cyclopentanecarbonyl]-oxazolidin-2-one dicobalt hexacarbonyl complex (287)

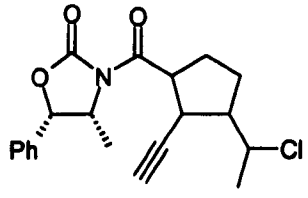


A solution of the cobalt complex (281) (0.8 g, 1.25 mmol, 1 eq) in DCM was stirred at -10 °C under a nitrogen atmosphere. The Lewis acid, $TiCl_4$ (1.4 mL, 12.5 mmol, 10 eq), was added dropwise by syringe. An instantaneous change in colour, from dark red to brown indicated that the reaction seemed to occur very fast. TLC analysis also confirmed a reaction taking place when not showing the starting material after 5 minutes reaction. However it showed the presence of several spots with a lower R_f than the starting material. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (30mL). The organic layer was isolated, dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography, did not allow separation of the new products, but afforded a clean mixture of compounds (0.43 g, 54 %); ν_{max} (neat)/cm^{-1} 2963, 2931, 2360, 2095, 2055, 2029, 1780, 1697, 1613, 1455, 1345,

1196, 1121, 1031, 767, 735, 700; δ_H (400 MHz, $CDCl_3$) the ^1H NMR gave very broad signals which might result from cobalt impurities, however, the ^{13}C NMR gave clearer results. δ_C(100 MHz, $CDCl_3$) 199.9, 199.7, 199.5, 174.6, 152.9, 133.4, 128.8, 125.7, 93.3, 79.0, 70.0, 58.6, 55.1, 41.9, 40.1, 31.2, 25.4, 24.0, 21.0, 14.5.

Procedure for the decomplexation reaction

Synthesis of 4-(R)-methyl-5-(S)-phenyl-*N*-[3-(1-chloro-ethyl)-2-ethynyl-cyclopentanecarbonyl]-oxazolidin-2-one (288)

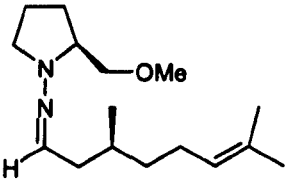


To a solution of the cobalt complex (287) in DCM (0.4 g, 0.62 mmol, 1 eq), at 0 °C, was added a solution of methanolic ceric ammonium nitrate (3.4 g, 6.2 mmol, 10 eq). The reaction was left to stir until no evolution of CO could be observed, and the colour had changed from brown to orange. The reaction mixture was then extracted with diethyl ether (4 × 30 mL). The combined organic layers were washed with brine and distilled water, dried over $MgSO_4$, and concentrated under vacuum. Purification by flash chromatography yielded a mixture a diastereoisomers (0.14 g, 60 %); ν_{max} (neat)/cm^{-1} 2925, 2854, 1780, 1699, 1455, 1345 ,1196, 1120, 1032, 801, 767 ,700; δ_H (400 MHz, $CDCl_3$) 7.43-7.29 (5H, m, Ar*H*), 5.68-5.64 (1H, m, Ph-C*H*-), 4.85-4.73 (1H, m, N-C*H*-CH_3), 4.06-3.98 (1H, m, Cl-C*H*-CH_3), 2.55-2.49 (1H, d × 6, J = 2.2 Hz, -C≡C*H*), 1.75-1.68 (1H, m,

CH_3CHCl-C*H*-), 1.56-1.55 (3H, d, J = 5 Hz, ClHC-CH_3), 1.51-1.49 (1H, dd, J_1 = 6.6 Hz, J_2 = 3.3 Hz, HC≡C-C*H*-), 1.29-1.16 (4H, m, -CH_2-CH_2-), 0.90-0.89 (3H, d, J = 6.6 Hz, N-CH-CH_3).

Procedure for the synthesis of SAMP-hydrazones

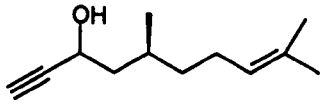
Synthes is of (3,7-dimethyl-oct-6-enylidene)-(2-methoxymethyl-pyrrolidin-1-yl)-amine (294)



To a flask purged with nitrogen, loaded with SAMP (1.7 mL, 12.45 mmol, 1 eq), and cooled to 0 °C, citronellal was added dropwise. After the addition was complete, the cold bath was removed, and the temperature left to rise to rt. After 2h, TLC analysis showed the presence of a single new spot, (Rf = 0.19) with 9 : 1 hexane-ethyl acetate. Purification by flash chromatography afforded the desired SAMP hydrazone (294) in quantitative yield (3.29g, 98 %); ν_{max} 2961, 2923, 1670, 1453, 1377, 1196, 1116, 970, 828; δ_H (400 MHz, $CDCl_3$) 6.65-6.62 (1H, t, J = 5.7 Hz, -N=C*H*-), 5.09-5.04 (1H, m, $(CH_3)_2C$=C*H*-), 3.56-3.51 (1H, m, =N-N-C*H*-), 3.41-3.31 (3H, m, -O-CH_2-, N-CH_2-), 3.34 (3H, s, -O-CH_3), 2.73-2.67 (1H, m, -N-CH_2), 2.23-2.17 (2H, dt, J_1 = 5.7 Hz, J_2 = 14.1 Hz, N=CH-CH_2-), 2.06-1.70 (7H, m, 2×β-CH_2 ring, =CH-CH_2-, CH_3-C*H*-), 1.65 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.42-1.31 (1H, m, CH_3-CH-CH_2-), 1.21-1.12 (1H, m, CH_3-CH-CH_2-), 0.90-0.88 (3H, d, J = 6.7 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 138.7, 131.1, 124.7, 74.8, 63.5, 59.1, 50.6, 40.2, 36.7, 26.5, 25.6, 25.4, 22.1, 19.4, 17.6.

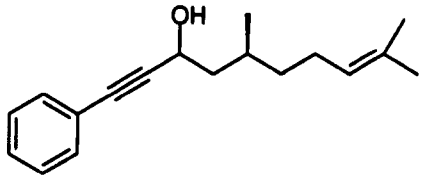
General procedure for the Grignard reaction *(GP6)*

Synthesis of (5S)-5,9-dimethyldec-8-en-1-yn-3-ol (299a)



To a suspension of ethynylmagnesium bromide (44.2 mL of a 0.5 M solution in THF, 22.06 mmol, 2.0 eq) at 0 °C, under a Nitrogen atmosphere, was added citronellal (2.0 mL, 11.03 mmol, 1.0 eq) over a period of half an hour. The reaction mixture was left to stir at 0 °C and then allowed to warm to room temperature. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (50mL). Excess THF was removed *in vacuo*, and the solution extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography yielded the title product as a yellow oil (1.98 g, 100 %); %); δ_H(400 MHz, $CDCl_3$) 5.05-5.00 (1H, m, $(CH_3)_2C{=}CH$-), 4.40-4.36 (1H, m, HO-C*H*), 2.40-2.39 (1H, dd, J_1 = 1.5 Hz, J_2 = 2.2 Hz, C≡C*H*), 2.04-1.84 (2H, m, =CH-CH_2), 1.75-1.64 (3H, m, HO-CH-CH_2, CH_3-C*H*-), 1.61 (3H, s, =C(CH_3)$_2$), 1.53 (3H, s, =C(CH_3)$_2$), 1.32-1.24 (1H, m, CH_3-CH-CH_aH$_b$), 1.17-1.07 (1H, m, CH_3-CH- CH_a*H$_b$*), 0.88-0.85 (3H, d × 2, J = 5.3 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 131.3, 124.5, 85.4, 84.9, 72.9, 72.6, 61.0, 60.5, 45.0, 44.8, 37.0, 29.3, 28.9, 25.7, 25.3, 19.5, 19.1, 17.7; m/z $[M+NH_4]^+$ calc. 198.1852, found 198.1854.

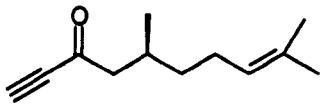
Synthesis of (5S)-5,9-dimethyl-1-phenyldec-8-en-1-yn-3-ol (299b)



Compound (299b) was prepared according to *GP8*, using the following quantites of phenylethynylmagnesium bromide (22.1 mL of a 1.0 M solution in THF, 22.06 mmol, 2.0 eq) and citronellal (2.0 mL, 11.03 mmol, 1.0 eq). Purification by flash chromatography yielded the title product as a yellow oil (2.01 g, 71 %); %); δ_H(400 MHz, $CDCl_3$) 7.44-7.26 (5H, m, Ar*H*), 5.12-5.07 (1H, m, $(CH_3)_2C{=}CH$-), 4.67-4.62 (1H, m, (1H, m, HO-C*H*), 2.07-1.94 (2H, m, (2H, m, =CH-CH_2), 1.88-1.72 (3H, m, (3H, m, HO-CH-CH_2, CH_3-C*H*-), 1.65 (3H, s, =C(CH_3)$_2$), 1.59 (3H, s, =C(CH_3)$_2$), 1.44-1.34 (1H, m, CH_3-CH-CH_aH$_b$), 1.26-1.16 (1H, m, CH_3-CH-CH$_a$*H$_b$*), 0.97-0.94 (3H, d × 2, *J* = 5.3 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 131.6, 131.3, 128.3, 124.5, 122.8, 90.6, 84.7, 61.6, 61.1, 45.2, 45.1, 37.1, 29.4, 29.0, 25.7, 25.3, 19.7, 19.3, 17.7; m/z $[M+NH_4]^+$ calc. 274.2165, found 274.2164.

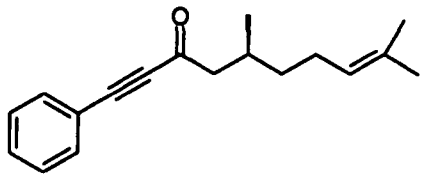
General procedure for the Jones oxidation reaction *(GP7)*

Synthesis of (5S)-5,9-dimethyldec-8-en-1-yn-3-one (302a)



Jones reagent was prepared by dissolving 26.7 g of chromium oxide in 40 mL of water in a 100 mL volumetric flask. Then, 23 mL of concentrated sulfuric acid were added dropwise before the volume was topped up to the 100 mL mark. 5,9-dimethyl-dec-8-en-1-yn-3-ol (0.54 g, 3.0 mmol, 1.0 eq) was dissolved in dry acetone (30 mL) and Jones reagent added from a burette until a persistent orange colour indicated that oxidation was complete. Dilution with distilled water was followed by an extraction using diethyl ether (3 × 20 mL). The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography (9:1 Hexane / EtOAc) yielded the ketone as an orange oil (0.41 g, 77 %); R_f 0.43; %);δ_H(400 MHz, $CDCl_3$) 5.09-5.04 (1H, m, =C*H*-), 3.19 (1H, s, C≡C*H*), 2.59-2.54 (1H, dd, J_1 = 5.7 Hz, J_2 = 15.6 Hz, O=C-CH_aH$_b$), 2.40-2.34 (1H, dd, J_1 = 8.2 Hz, J_2 = 15.5 Hz, O=C-CH$_a$*H$_b$*), 2.18-2.06 (1H, m, CH_3-C*H*), 2.05-1.90 (2H, m, =CH-CH_2), 1.66 (3H, s, =C(CH_3)$_2$), 1.58 (3H, s, =C(CH_3)$_2$), 1.38-1.29 (1H, m, -CH-CH_aH$_b$), 1.26-1.17 (1H, m, -CH-CH$_a$*H$_b$*), 0.94-0.92 (3H, d, J = 5.6 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 187.3, 131.6, 124.0, 81.7, 52.6, 36.6, 29.2, 25.6, 25.3, 19.5, 17.6.

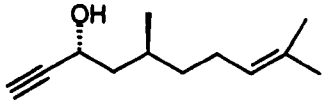
Synthesis of (5S)-5,9-dimethyl-1-phenyldec-8-en-1-yn-3-one (302b)



Compound (302) was prepared according to *GP9*, using the following quantity of 5,9-Dimethyl-1-phenyl-dec-8-en-1-yn-3-ol (1.51 g, 5.9 mmol) and an excess of Jones reagent. Purification by flash chromatography (9:1 Hexane / EtOAc) yielded the desired ketone as an orange oil (1.30 g, 85 %); R_f 0.47; δ_H(400 MHz, $CDCl_3$) 7.57-7.35 (5h, m, Ar*H*), 5.12-5.07 (1H, m, =C*H*-), 2.66-2.61 (1H, dd, J_1 = 5.9 Hz, J_2 = 15.4 Hz, O=C-CH_aH$_b$), 2.47-2.41 (1H, dd, J_1 = 8.2 Hz, J_2 = 15.4 Hz, O=C-CH$_a$$H_b$), 2.26-2.14 (1H, m, CH_3-C*H*), 2.09-1.94 (2H, m, =CH-CH_2), 1.66 (3H, s, =C(CH_3)$_2$), 1.58 (3H, s, =C(CH_3)$_2$),1.44-1.35 (2H, m, =CH-CH_2), 1.31-1.22 (1H, m, -CH-CH$_a$$H_b$), 0.99-0.97 (3H, d, J = 6.6 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 187.9, 132.9, 131.6, 130.6, 128.5, 124.1, 120.0, 90.4, 88.1, 52.8, 36.7, 29.5, 25.6, 25.3, 19.6, 17.6.

General procedure for the stereoselective reduction of ketones to secondary alcohols (*GP8)*

Synthesis of (3R,5S)-5,9-dimethyldec-8-en-1-yn-3-ol (309a)

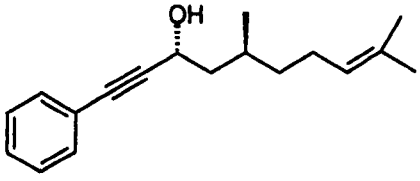


Compound (309a) was synthesised according to *GP10*, using the following quantities of 9-BBN (18.1 mL of a 0.5 M solution in THF, 9.04 mmol, 4.0 eq), (-)-α-pinene (1.50 mL, 9.49 mmol, 4.2 eq), and (5S)-5,9-Dimethyl-dec-8-en-1-yn-

3-one (0.40 g, 2.26 mmol, 1.0 eq). Purification by flash chromatography yielded the secondary alcohol as a colourless oil (0.106 g, 27 %); ν_{max} (neat)/cm^{-1} 3425, 2927, 2956, 2202, 1718, 1666, 1490, 1445, 1381, 1285, 1070, 760, 690; δ_H(400 MHz, $CDCl_3$) 5.10-5.05 (1H, m, =C*H*-), 4.45-4.38 (1H, m, HO-C*H*), 2.45-2.44 (1H, d, *J* = 2.2 Hz, ≡C-*H*), 2.05-1.89 (2H, m, -CH-C*H*$_2$-CH-), 1.81-1.67 (3H, m, =C*H*-C*H*$_2$), 1.66 (3H, s, =C(C*H*$_3$)$_2$), 1.58 (3H, s, =C(C*H*$_3$)$_2$), 1.40-1.31 (1H, m, =CH-C*H*$_2$-), 1.22-1.13 (1H, m, =CH-C*H*$_2$-), 0.91-0.89 (3H, d, *J* = 6.6 Hz, CH-C*H*$_3$); δ_C(100 MHz, $CDCl_3$) 131.3, 124.5, 85.5, 72.7, 60.6, 45.1, 42.0, 37.1, 28.9, 27.2, 25.7, 25.4, 19.3, 17.7; *de* 98.3 %.

The *d.e.* value was determined with the integral of the methyl group represented by the doublet at 0.92 ppm and a much smaller one at 0.76 ppm in the NMR spectrum.

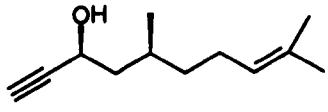
Synthesis of (3R,5S)-5,9-dimethyl-1-phenyldec-8-en-1-yn-3-ol (309b)



Compound (309b) was prepared according to *GP10*, using the following quantities of 9-BBN (7.1 mL of a 0.5 M solution in THF, 3.54 mmol, 2.0 eq), (-)-α-pinene (0.60 mL, 3.89 mmol, 2.2 eq), and 5,9-dimethylphenyldec-8-en-1-yn-3-one (0.45 g, 1.77 mmol, 1.0 eq). Purification by flash chromatography yielded the corresponding alcohol as a yellow oil (0.14g, 31 %); ν_{max} (thin film)/cm^{-1} 3422, 2929, 2958, 2202, 1718, 1665, 1489, 1444, 1379, 1285, 1069, 758, 690; δ_H(400 MHz, $CDCl_3$) 7.42-7.39 (2H, m, Ar*H*), 7.30-7.27 (3H ,m, Ar*H*), 5.11-5.07 (1H, m, C*H*=CH$_2$), 4.67-4.62 (1H, m, HO-C*H*), 2.06-1.92 (2H, m,

CH_2CH=), 1.83-1.81 (2H, dd, J_1 = 1.8 Hz, J_2 = 5.6 Hz, -CHCH_2CH-), 1.80-1.72 (1H, m, CH_3CH-), 1.65 (3H, s, C=CCH_3), 1.58 (3H, s, C=CCH_3), 1.40-1.33 (1H, m, CHCH_2CH_2-), 1.24-1.15 (1H, m, CHCH_2CH_2-), 0.96-0.94 (3H, d, J = 6.4 Hz, CHCH_3); δ_C(100 MHz, $CDCl_3$) 131.8, 131.5, 128.4, 128.3, 124.7, 122.8, 90.3, 85.0, 61.8, 45.2, 37.2, 29.5, 25.8, 25.4, 19.8, 17.8.

Synthesis of (3S,5S)-5,9-dimethyldec-8-en-1-yn-3-ol (310a)

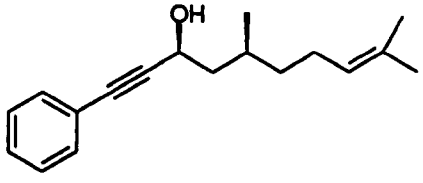


To a round bottom flask fitted with a condenser, and flushed several times with nitrogen, a solution of 9-BBN (20.5 mL of a 0.5 M solution in THF, 10.2 mmol, 1.4 eq) and (+)-α-pinene (1.85 mL, 11.7 mmol, 1.6 eq) were added. The mixture was heated under gentle reflux for two hours and then allowed to cool down to room temperature. The solvent was then evaporated under vacuum and the pressure released with a ballon filled with argon to avoid any contact with air. The flask was then fitted to a high pressure vacuum line overnight to remove all traces of solvent. The ketone, (5S)-5,9-dimethyl-dec-8-en-1-yn-3-one (1.30 g, 7.3 mmol, 1.0 eq), was also dried on the vacuum line before being added to the neat alpine borane at 0 °C. The colour of the mixture was initially yellow and turned to red as the reaction was progressing. The mixture was left to stir at room temperature over two days. The excess of alpine borane was destroyed by adding propionaldehyde (1 mL) before being removed *in vacuo*. Then THF (20 mL) was added, followed by NaOH (6mL of a 3M solution), and hydrogen peroxide (6 mL of a 30% solution). The mixture was stirred for two hours, and then extracted with diethyl ether (20 mL × 3). The organic extracts were then combined, dried

over magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography yielded the pure alcohol as a colourless oil (0.78 g, 59 %); ν_{max} (neat)/cm^{-1} 3425, 2927, 2956, 2202, 1718, 1666, 1490, 1445, 1381, 1285, 1070, 760, 690; δ_H(400 MHz, $CDCl_3$) 5.11-5.04 (1H, m, =C*H*-), 4.46-4.38 (1H, m, HO-C*H*), 2.45-2.44 1H, d, J = 2.2 Hz, ≡C-*H*), 2.05-1.89 (2H, m, -CH-CH_2-CH-), 1.79-1.70 (3H, m, =C*H*-CH_2), 1.66 (3H, s, =C(CH_3)$_2$), 1.58 (3H, s, =C(CH_3)$_2$), 1.37-1.28 (1H, m, =CH-CH_2-), 1.21-1.12 (1H, m, =CH-CH_2-), 0.92-0.91 (3H, d, J = 6.6 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 131.3, 124.5, 85.5, 72.7, 60.6, 45.1, 42.0, 37.1, 28.9, 27.2, 25.7, 25.4, 19.3, 17.7; *de* 98.9 %; m/z $[M]^+$ calc. 180.1514, found 180.1514

The *d.e.* value was determined with the integral of the methyl group represented by the doublet at 0.92 ppm and a much smaller one at 0.76 ppm in the NMR spectrum.

Synthesis of (3S,5S)-5,9-dimethyl-1-phenyldec-8-en-1-yn-3-ol (310b)

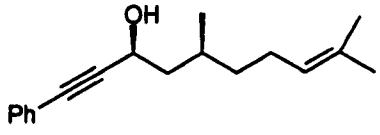


Compound (310b) was prepared according to *GP10*, using the following quantities of 9-BBN (4.60 mL of a 0.5 M solution in THF, 2.30 mmol, 1.6 eq), (+)-α-pinene (0.40 mL, 2.57 mmol, 1.8 eq), and 5,9-dimethyl-1-phenyldec-8-en-1-yn-3-one (0.36 g, 1.43 mmol, 1.0 eq). Purification by flash chromatography yielded the corresponding alcohol as a yellow oil (0.14g, 31 %); ν_{max} (thin film)/cm^{-1} 3422, 2929, 2958, 2202, 1718, 1665, 1489, 1444, 1379, 1285, 1069,

758, 690; δ_H(400 MHz, $CDCl_3$) 7.42-7.38 (2H, m, Ar*H*), 7.31-7.25 (3H ,m, Ar*H*), 5.11-5.07 (1H, m, (1H, m, C*H*=CH_2), 4.67-4.62 (1H, m, HO-C*H*), 2.07-1.92 (2H, m, CH_2CH=), 1.88-1.74 (3H, m, -CH_2CH-CH_3), 1.65 (3H, s, C=CCH_3), 1.59 (3H, s, C=CCH_3), 1.42-1.34 (1H, m, CHCH_2CH_2-), 1.25-1.16 (1H, m, CHCH_2CH_2-), 0.97-0.95 (3H, d, J = 6.6 Hz, CHCH_3); δ_C(100 MHz, $CDCl_3$) 131.8, 131.5, 128.4, 128.3, 124.7, 122.8, 90.3, 85.0, 61.8, 45.2, 37.2, 29.5, 25.8, 25.4, 19.8, 17.8; *de* 96.1 % from NMR.

General procedure for the stereoselective alkynylation *(GP9)*

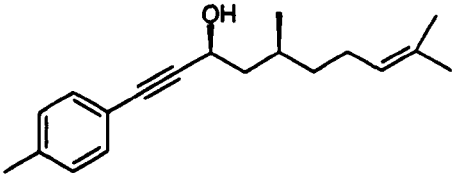
Synthesis of (3S,5S)-5,9-dimethyl-1-phenyldec-8-en-1-yn-3-ol (318a)



A suspension of zinc triflate (3.31 g, 9.10 mmol, 1.1 eq) and (+)-N-methylephedrine (1.78 g, 9.92 mmol, 1.2 eq) in 0.3M triethylamine in dry toluene was left to stir for two hours at 25 °C before phenylacetylene (0.91 mL, 8.27 mmol, 1.0 eq) was added by syringe. After 10 min stirring, citronellal (1.50 mL, 8.27 mmol, 1.0 eq) was added. The reaction was monitored by TLC. Upon completion, the reaction was quenched with a solution of saturated ammonium chloride (30 mL). The reaction mixture was then extracted with diethyl ether (3 × 30mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography using 8:2 hexane / ethyl acetate afforded the secondary alcohol (2.1 g, 66 %) as a colourless oil;

$[\alpha]_D$ +8.3 (c = 0.7, $CHCl_3$,).; ν_{max} (thin film)/cm^{-1} 3422, 2929, 2958, 2202, 1718, 1665, 1489, 1444, 1379, 1285, 1069, 758, 690; δ_H(400 MHz, $CDCl_3$) 7.41-7.37 (2H, m, Ar*H*), 7.30-7.25 (3H ,m, Ar*H*), 5.10-5.05 (1H, m, C*H*=C), 4.69-4.58 (1H, dt, HO-C*H*), 2.06-1.93 (2H, m, CH_2CH=), 1.83-1.89 (2H, d, J = 5.7 Hz, -CHCH_2CH-), 1.79-1.72 (1H, m, CH_3C*H*-), 1.65 (3H, s, C=CCH_3), 1.58 (3H, s, C=CCH_3), 1.40-1.33 (1H, m, CHC$H_2$$CH_2$-), 1.24-1.15 (1H, m, CHC$H_2$$CH_2$-), 0.96-0.94 (3H, d, J = 6.4 Hz, CHCH_3) ,δ_C(100 MHz, $CDCl_3$) 131.7, 131.4, 128.4, 128.3, 124.7, 122.8, 90.7, 84.7, 61.3, 45.3, 37.2, 29.1, 25.8, 25.4, 19.4, 17.8.

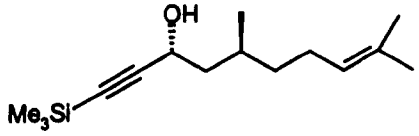
Synthesis of (3S,5S)-5,9-dimethyl-1-p-tolyldec-8-en-1-yn-3-ol (318b)



Compound (318b) was prepared according to *GP7* using the following quantities of zinc triflate (2.20 g, 6.07 mmol, 1.1 eq), (+)-N-methylephedrine (1.19 g, 6.62 mmol, 1.2 eq) in 0.3M triethylamine (22.1 mL, 6.62 mmol, 1.2 eq) in dry toluene, 4-ethynyl-toluene (0.70 mL, 5.52 mmol, 1.0 eq) and citronellal (1.0 mL, 5.52 mmol, 1.0 eq). Purification by column chromatography using 8:2 hexane / ethyl acetate afforded the secondary alcohol (0.85 g, 65 %) as a colourless oil; R_f 0.35; $[\alpha]_D$ -10.4 (c = 0.57, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3406, 2959, 2926, 2199, 1718, 1664, 1606, 1508, 1378, 1289, 1062, 817, 755; δ_H(400 MHz, $CDCl_3$) 7.32-7.30 (2H, d, *J* = 8.0 Hz, o-Ar*H*), 7.12-7.10 (2H, d, *J* = 7.7 Hz, m-Ar*H*), 5.13-5.08

(1H,m, C*H*-CH_2), 4.67-4.63 (1H, dd, J_1 = 5.9 Hz, J_2 = 8.0 Hz, HO-C*H*), 2.34 (3H, s, Ar-CH_3), 2.10-1.94 (2H, m, =CH-CH_2), 1.89-1.86 (2H, dd, J_1 = 5.5 Hz, J_2 = 8.0 Hz, HO-CH-CH_2), 1.83-1.73 (1H, m, CH_3-C*H*), 1.67 (3H, s, =C(CH_3)$_2$), 1.60 (3H, s, =C(CH_3)$_2$), 1.40-1.21 (2H, m, CH_3-CH-CH_2), 0.98-0.96 (3H, d, J = 6.6 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 138.5, 131.7, 129.4, 124.8, 119.7, 89.9, 84.9, 61.4, 45.2, 37.0, 29.1, 26.1, 25.0, 21.3, 19.2, 18.1; m/z calc: $[M+NH_4]^+$ 288.2322, found 288.2320.

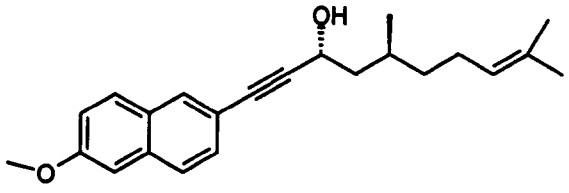
Synthesis of (3R,5S)-5,9-dimethyl-1-trimethylsilanyldec-8-en-1-yn-3-ol (318c)



Compound (318c) was prepared according to *GP7* using the following quantities of zinc triflate (2.03 g, 5.51 mmol, 1.1 eq), (-)-N-methylephedrine (1.09 g, 6.11 mmol, 1.2 eq) in 0.3M triethylamine (20.4 mL, 6.11 mmol, 1.2 eq) in dry toluene, trimethylsilylacetylene (0.72 mL, 5.09 mmol, 1.0 eq) and citronellal (0.92 mL, 5.05 mmol, 1.0 eq). Purification by column chromatography using 8:2 hexane / ethyl acetate afforded the secondary alcohol (0.81 g, 64 %) as a colourless oil; $[\alpha]_D$ +3.6 (c = 0.24, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3423, 2963, 2925, 1733, 1458, 1377, 1290, 1250, 1154, 843, 760; δ_H(400 MHz, $CDCl_3$) 5.08-5.04 (1H, m, =C*H*-), 4.42-4.37 (1H, dd, J_1 = 6.9 Hz, J_2 = 12.6 Hz, HO-C*H*), 2.12-1.86 (4H, m, =CH-CH_2-, -CH-CH_2-CH-), 1.71-1.68 (1H, m, CH_3-C*H*-), 1.66 (3H, s, =C(CH_3)$_2$), 1.58 (3H, s, =C(CH_3)$_2$), 1.25-1.15 (2H, m, -CH-CH_2-CH_2-), 0.93-

0.91 (3H, d, J = 6.9 Hz, -CH-CH_3), 0.15 (9H, s, -Si(CH_3)$_3$); δ_C(100 MHz, $CDCl_3$) 124.6, 120.8, 89.2, 82.9, 61.5, 45.1, 37.0, 29.3, 25.7, 25.3, 19.7, 17.8, -0.07; m/z calc: $[M-H]^+$ 251.1826, found 251.1828.

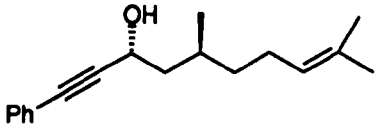
Synthesis of (3R,5S)-1-(6-methoxy-naphthalen-2-yl)-5,9-dimethyldec-8-en-1-yn-3-ol (318d)



Compound (318d) was prepared according to *GP7* using the following quantities of zinc triflate (1.10 g, 3.03 mmol, 1.1 eq), (-)-*N*-methylephedrine (0.59 g, 3.31 mmol, 1.2 eq) in 0.3M triethylamine (11.0 mL, 3.31 mmol, 1.2 eq) in dry toluene, 2-ethynyl-6-methoxynaphthalene (0.50 g, 2.76 mmol, 1.0 eq) and citronellal (0.50 mL, 2.76 mmol, 1.0 eq). Purification by column chromatography using 8:2 hexane / ethyl acetate afforded the secondary alcohol (0.61 g, 70 %) as a colourless oil; R_f 0.3; $[\alpha]_D$ +18.2 (c = 0.27, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3385, 2963, 2926, 1630, 1602, 1498, 1483, 1389, 1245, 1029, 852; δ_H(400 MHz, $CDCl_3$) 7.86 (1H, s, Ar*H*), 7.68-7.64 (2H, m, Ar*H*), 7.44-7.42 (1H, d, J = 8.4 Hz, Ar*H*), 7.16-7.13 (1H, ddd, J_1 = 0.7 Hz, J_2 = 2.5 Hz, J_3 = 8.9 Hz, Ar*H*), 7.099-7.093 (1H, d, J = 2.2 Hz, Ar*H*), 5.13-5.11 (1H, m, $CH_3)_2$C=C*H*-), 4.73-4.69 (1H, m, HO-C*H*), 3.92-3.91 (3H, d, J = 0.7 Hz, O-CH_3), 2.09-1.99 (2H, m, =CH-CH_2-), 1.96-1.95 (1H, d, J = 4.0 Hz, C*H*-CH$_3$), 1.87-1.77 (2H, m, OH-CH-CH_2), 1.68 (3H, s, =C(CH_3)$_2$, 1.61 (3H, s, =C(CH_3)$_2$, 1.48-1.40 (1H, m, CH$_3$-CH-CH_2-), 1.30-1.21 (1H, m, CH$_3$-CH-CH_2-), 0.99-0.98 (3H, d, J = 5.9 Hz,

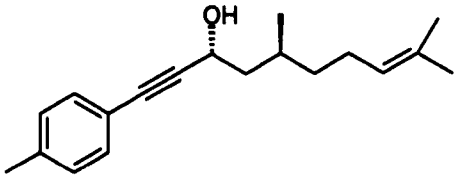
CH-C*H*$_3$); δ_C(100 MHz, $CDCl_3$) 158.4, 134.2, 131.5, 129.4, 129.1, 128.5, 126.9, 124.7, 119.5, 117.6, 105.8, 89.9, 85.6, 61.9, 55.4, 45.3, 37.2, 29.6, 25.8, 25.4, 19.8, 17.8; m/z calc: $[M+NH_4]^+$ 337.2162, found 337.2164.

Synthesis of (3R,5S)-5,9-dimethyl-1-phenyl-dec-8-en-1-yn-3-ol (319a)



Compound (319a) was prepared according to *GP7* using the following quantities of zinc triflate (3.31 g, 9.10 mmol, 1.1 eq), (-)-*N*-methylephedrine (1.78 g, 9.92 mmol, 1.2 eq) in 0.3M triethylamine in dry toluene, phenylacetylene (0.91 mL, 8.27 mmol, 1.0 eq) and citronellal (1.50 mL, 8.27 mmol, 1.0 eq). Purification by column chromatography using 8:2 hexane / ethyl acetate afforded the secondary alcohol (1.35 g, 65 %) as a colourless oil; $[\alpha]_D$ +8.5 (c = 0.46, $CHCl_3$,); ν_{max} (film)/cm^{-1} 3422, 2929, 2958, 2202, 1718, 1665, 1489, 1444, 1379, 1285, 1069, 758, 690; δ_H(400 MHz, $CDCl_3$) 7.42-7.39 (2H, m, Ar*H*), 7.30-7.27 (3H ,m, Ar*H*), 5.11-5.07 (1H, m, C*H*=CH_2), 4.67-4.62 (1H, m, HO-C*H*), 2.06-1.92 (2H, m, CH_2CH=), 1.83-1.72 (2H, dd, J_1 = 1.8 Hz, J_2 = 5.6 Hz, -CHCH_2CH-), 1.80-1.72 (1H, m, CH_3C*H*-), 1.65 (3H, s, C=CCH_3), 1.58 (3H, s, C=CCH_3), 1.40-1.33 (1H, m, CHC$H_2$$CH_2$-), 1.24-1.15 (1H, m, CHC$H_2$$CH_2$-), 0.96-0.94 (3H, d, J = 6.4 Hz, CHCH_3); δ_C(100 MHz, $CDCl_3$) 131.8, 131.5, 128.4, 128.3, 124.7, 122.8, 90.3, 85.0, 61.8, 45.2, 37.2, 29.5, 25.8, 25.4, 19.8, 17.8; *m/z* calc: $[M+NH_4]^+$ 274.2165, found: 274.2165.

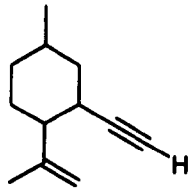
Synthesis of (3R,5S)-5,9-dimethyl-1-p-tolyl-dec-8-en-1-yn-3-ol (319b)



Compound (319b) was prepared according to *GP7* using the following quantities of zinc triflate (2.20 g, 6.07 mmol, 1.1 eq), (-)-*N*-methylephedrine (1.19 g, 6.62 mmol, 1.2 eq) in 0.3M triethylamine (22.1 mL, 6.62 mmol, 1.2 eq) in dry toluene, 4-ethynyl-toluene (0.70 mL, 5.52 mmol, 1.0 eq) and citronellal (1.0 mL, 5.52 mmol, 1.0 eq). Purification by column chromatography using 8:2 hexane / ethyl acetate afforded the secondary alcohol (0.96 g, 64 %) as a colourless oil; $[\alpha]_D$ +3.9 (c = 0.25, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3406, 2959, 2926, 2199, 1718, 1664, 1606, 1508, 1378, 1289, 1062, 817, 755; δ_H(400 MHz, $CDCl_3$) 7.30-7.28 (2H, d, J = 8.0 Hz, o-Ar*H*), 7.10-7.08 (2H, d, J = 7.8 Hz, m-Ar*H*), 5.11-5.08 (1H, m, C*H*=C(CH_3)$_2$), 4.66-4.61 (1H, dd, J_1 = 6.1 Hz, J_2 = 13.5 Hz, HO-C*H*), 2.32 (3H, s, Ar-CH_3), 2.07-1.92 (2H, m, =CH-CH_2), 1.87-1.71 (3H, m, CH_2-CH-CH_3), 1.65 (3H, s, =C(CH_3)$_2$), 1.58 (3H, s, =C(CH_3)$_2$), 1.44-1.35 (1H, m, CH_3-C*H*), 1.25-1.16 (1H, m, CH_3-C*H*), 0.95-0.93 (3H, d, J = 6.2 Hz, -CH-CH_3); δ_C(100MHz, $CDCl_3$) 138.5, 131.6, 131.4, 129.1, 119.7, 89.5, 85.2, 61.6, 45.0, 36.8, 29.4, 25.8, 25.4, 21.5, 19.8, 17.8; m/z calc: $[M+NH_4]^+$ 288.2322, found 288.2324.

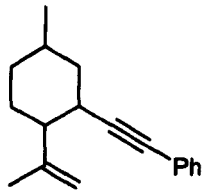
General procedure for the intramolecular cyclisation reaction (*GP10*)

Synthesis of 2-ethynyl-1-isopropenyl-4-methyl-cyclohexane (320)



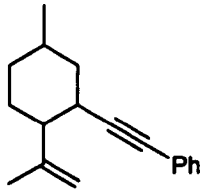
To a solution of the racemic propargyl alcohol (299a), (1.72 g, 9.5 mmol, 1 eq), in DCM at 0 °C under a nitrogen atmosphere, was added dicobalt octacarbonyl (3.42 g, 10 mmol, 1.1 eq). After the evolution of CO was complete, the reaction mixture was cooled to 0 °C, and $BF_3{\cdot}OEt_2$ (1.25 mL, 10mmol, 1.1 eq) was added. After a few minutes, TLC analysis showed the reaction was completed. At this point a saturated solution of ceric ammonium nitrate in methanol was added until the evolution of CO was complete and the colour of the reaction mixture went from brown to orange. Purification by flash chromatography afforded the title compound as an oil (0.85 g, 55 %); ν_{max} (film)/cm^{-1} 2924, 2853, 1715, 1458, 1377, 1113; δ_H(400 MHz, $CDCl_3$) 4.81-4.74 (2H, m, -C=CH_2), 2.30-2.23 (1H, m, -C≡C-C*H*-), 2.01-1.99 (2H, dd, J_1 = 2.2 Hz, J_2 = 7.3 Hz, -CH-CH_2-CH-), 1.96-1.89 (1H, td, J_1 = 3.3 Hz, J_2 = 11.5Hz, =C-C*H*-), 1.70 (3H, s, =C-CH_3), 1.68-1.61 (2H, m, CH_2-CH_2-CH-), 1.52 (1H, d, J = 1.2 Hz, -C≡C-*H*), 1.41-1.33 (1H, m, -C*H*-CH_3), 1.32-1.21 (1H,m, =C-CH-CH_2), 1.01-0.96 (1H, m, =C-CH-CH_2), 0.89-0.88 (3H, d, J = 6.4 Hz, CH-CH_3); δ_C(100MHz, $CDCl_3$) 148.2, 111.0, 8707, 68.5, 50.8, 41.7, 34.6, 33.2, 32.1, 31.9, 22.3, 19.7.

Synthesis of 2-phenylethynyl-1-isopropenyl-4-methyl-cyclohexane (322a).



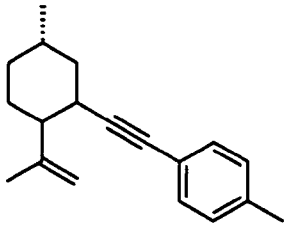
Compound (322a) was synthesised according to *GP 11*, using the following quantities of propargyl alcohol (319a), (1.46 g, 2.7 mmol, 1 eq), $BF_3{\cdot}OEt_2$ (0.36 mL, 2.9 mmol, 1.1 eq), and an excess of methanolic CAN until the evolution of CO was complete. Purification by flash chromatography afforded the title compound as a mixture of diastereoisomers (0.35 g, 55 %);$[\alpha]_D$ -6.59 (c =1.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 3062, 2949, 2925, 2869, 1720, 1490, 1451, 1376, 1277, 1069, 757, 713, 691; δ_H(400 MHz, $CDCl_3$) 7.37-7.32 (2H, m, Ar*H*), 7.27-7.22 (3H, m, Ar*H*), 4.83-4.80 (2H, m, -C=CH_2), 2.50-2.44 (1H, td, J_1 = 3.5 Hz, J_2 = 11.3 Hz, -C≡C-C*H*-), 2.12-2.05 (2H, m, -CH-CH_2-CH-), 2.06-1.99 (1H, td, J_1 = 3.3 Hz, J_2 = 11.5 Hz, =C-C*H*-), 1.76 (3H, s, =C-CH_3), 1.75-1.68 (2H, m, CH_2-CH_2-CH-), 1.49-1.39 (1H, m, CH_3-C*H*-), 1.37-1.30 (1H, td, J_1 = 3.3 Hz, J_2 = 12.7 Hz, -CH-CH_2-CH_2-), 1.05-0.98 (1H, td, J_1 = 3.3 Hz, J_2 = 12.6 Hz, -CH-CH_2-CH_2-), 0.94-0.92 (3H, d, J = 6.6 Hz, CH-CH_3); δ_C(100MHz, $CDCl_3$) 148.3, 131.6, 128.1, 127.4, 124.2, 111.0, 93.3, 81.3, 51.1, 41.8, 34.7, 34.2, 32.2, 31.9, 22.3, 19.9; m/z: $[M]^+$, Calc: 238.1716, Found: 238.1713.

Synthesis of 2-phenylethynyl-1-isopropenyl-4-methyl-cyclohexane (322b).



Compound (322b) was synthesised according to *GP 11*, using the following quantities of propargyl alcohol (319a), (0.60g, 2.34 mmol, 1 eq), dicobalt octacarbonyl (0.96 g, 2.80 mmol, 1.2 eq), $BF_3{\cdot}OEt_2$ (0.35 mL, 2.8 mmol, 1.2 eq), and an excess of methanolic CAN until the evolution of CO was complete. Purification by flash chromatography afforded the title compound as a mixture of diastereoisomers (0.28 g, 51 %);$[\alpha]_D$ -0.45 (c = 0.22; $CHCl_3$), ν_{max} (film)/cm^{-1} 3075, 2924, 2868, 1719, 1490, 1443, 1276, 1069, 888, 756, 712, 691; δ_H(400 MHz, $CDCl_3$) 7.37-7.33 (2H, m, Ar*H*), 7.28-7.22 (3H, m, Ar*H*), 4.84-4.81 (2H, m, -C=CH_2), 2.51-2.44 (1H, td, J_1 = 3.5 Hz, J_2 = 11.6 Hz, -C≡C-C*H*-), 2.13-2.08 (2H, m, -CH-CH_2-CH-), 2.06-2.00 (1H, td, J_1 = 3.5 Hz, J_2 = 11.5 Hz, =C-C*H*-), 1.76 (3H, s, =C-CH_3), 1.75-1.68 (2H, m, CH_2-CH_2-CH-), 1.48-1.39 (1H, m, CH_3-C*H*-), 1.38-1.30 (1H, td, J_1 = 3.5 Hz, J_2 = 12.4 Hz, -CH-CH_2-CH_2-), 1.06-0.98 (1H, td, J_1 = 3.5 Hz, J_2 = 12.6 Hz, -CH-CH_2-CH_2-), 0.94-0.92 (3H, d, J = 6.4 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 148.3, 131.7, 128.1, 127.4, 124.2, 111.0, 93.3, 81.2, 51.2, 41.8, 34.7, 34.2, 32.2, 31.9, 22.3, 19.9; m/z: $[M+H]^+$, Calc: 239.1794, Found: 239.1792.

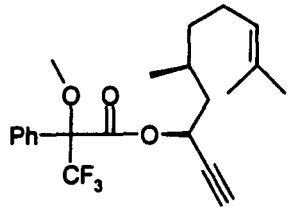
Synthesis of 2-(4-ethynyltoluene)-1-isopropenyl-4-methyl-cyclohexane (323).



Compound (323) was synthesised according to *GP 11*, using the following quantities of propargyl alcohol (319a), (0.89g, 3.29 mmol, 1 eq), dicobalt octacarbonyl (1.35 g, 3.95 mmol, 1.2 eq), $BF_3{\cdot}OEt_2$ (0.48 mL, 3.95 mmol, 1.2 eq), and an excess of methanolic CAN until the evolution of CO was complete. Purification by flash chromatography afforded the title compound as a mixture of diastereoisomers (0.28 g, 51 %);$[\alpha]_D$ + 3.8 (c = 0.79; $CHCl_3$), ν_{max} (film)/cm^{-1} 3027, 2923, 2868, 1718, 1509, 1455, 1376, 1277, 1177, 1106, 816; δ_H(400 MHz, $CDCl_3$) 7.29-7.23 (2H, m, Ar*H*), 7.09-7.04 (2H, m, Ar*H*), 4.84-4.80 (2H, m, -C=C*H*$_2$), 2.49-2.43 (1H, td, J_1 = 3.5 Hz, J_2 = 11.3 Hz, ≡C-C*H*-), 2.31 (3H, s, Ph-C*H*$_3$), 2.12-2.06 (2H, m, -CH-C*H*$_2$-CH-), 2.05-1.99 (1H, td, J_1 = 3.3 Hz, J_2 = 11.9 Hz, CH_2=C-C*H*-), 1.76 (3H, s, =C-C*H*$_3$), 1.75-1.67 (2H, m, CH_2-C*H*$_2$-CH-), 1.49-1.38 (1H, m, CH_3-C*H*<), 1.37-1.30 (1H, td, J_1 = 3.5 Hz, J_2 = 12.9 Hz, -CH-C*H*$_2$-CH_2-), 1.09-1.04 (1H, td, J_1 = 3.5 Hz, J_2 = 12.6 Hz, -CH-C*H*$_2$-CH_2-), 0.94-0.92 (3H, d, J = 6.4 Hz, C*H*$_3$); δ_C(100 MHz, $CDCl_3$) 148.4, 137.3, 131.5, 128.9, 121.1, 110.9, 92.5, 81.3, 51.2, 41.8, 34.8, 34.2, 32.2, 31.9, 22.3, 21.4, 19.9; m/z: $[M]^+$, Calc: 252.1873, Found: 252.1876.

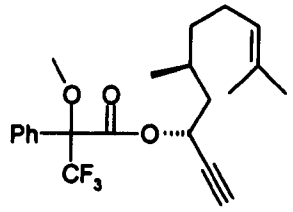
General procedure for the synthesis of Mosher esters (*GP11)*

Synthesis of the MTPA derivative of (3S, 5S)-5,9-dimethyl-dec-8-en-1-yn-3-ol, (311).



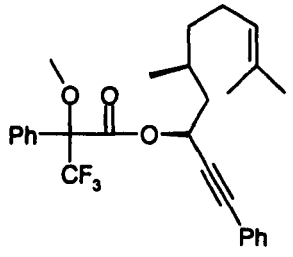
A solution of (3R, 5S)-5,9-dimethyl-dec-8-en-1-yn-3-ol (309a), (0.0273 g, 0.15 mmol, 1.0 eq), S-MTPA-Cl (0.08 mL, 0.45 mmol, 3.0 eq), 4-(dimethylamino)pyridine (0.011 g, 0.091 mmol, 0.6 eq), and dry pyridine (0.03 mL, 0.36 mmol, 2.4 eq) in dry toluene was left to stir at room temperature for one hour. The reaction was quenched by addition of water (1 mL). The product was extracted with EtOAc (4 × 5 mL), washed with 10 % HCl (0.5 mL), and then washed with saturated aqueous $NaHCO_3$ (0.5 mL). The mixture was dried over magnesium sulfate, and concentrated under vacuum to yield the desired ester (0.06 g, 100 %) as an oil; ν_{max} (neat)/cm^{-1} 2954, 1749, 1490, 1451, 1270, 1168, 1122, 1015, 991, 705; δ_H(400 MHz, $CDCl_3$) 7.52-7.29 (5H, m, Ar*H*), 5.54-5.53 (1H, m, =C*H*), 4.96-4.91 (1H, m, ≡C-C*H*-), 3.34 (3H, d, *J* = 1.2 Hz, O-CH_3), 2.47-2.46 (1H, d, *J* = 2.2 Hz, ≡C*H*), 1.87-1.73 (4H, m, ≡C-CH-CH_2, =CH-CH_2), 1.57 (3H, s, =C(CH_3)$_2$), 1.49 (3H, s, =C(CH_3)$_2$), 1.24-1.14 (2H, m, CH_3CH-CH_2), 1.11-1.01 (1H, m, CH_3C*H*-), 0.79-0.77 (3H, d, *J* = 6.6 Hz, CH-CH_3); δ_C(100MHz, $CDCl_3$) 165.7, 131.8, 131.4, 129.6, 126.8, 124.2, 80.2, 74.5, 64.0, 56.1, 55.4, 41.5, 36.8, 28.4, 25.6, 25.1, 18.7, 17.5;

Synthesis of the MTPA-Cl derivative of (3R, 5S)-5,9-dimethyldec-8-en-1-yn-3-ol, (312)



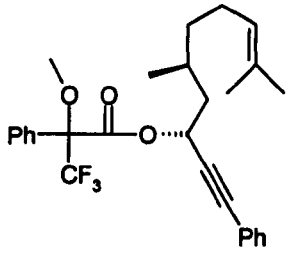
Compound (312) was prepared according to *GP10*, using the following quantites of (3S, 5S)-5,9-dimethyldec-8-en-1-yn-3-ol (0.0115 g, 0.064 mmol, 1.0 eq), S-MTPA-Cl (0.036 mL, 0.19 mmol, 3.0 eq), 4-(dimethylamino)pyridine (0.005 g, 0.004 mmol, 0.6 eq), and dry pyridine (0.012 mL, 0.15 mmol, 2.4 eq). Purification by flash chromatography yielded the desired ester as an oil (0.024 g, 95 %); ν_{max} (neat)/cm^{-1} 2955, 1749, 1489, 1450, 1270, 1168, 1122, 1017, 990, 705; δ_H(400 MHz, $CDCl_3$); 7.53-7.28 (5H, m, Ar*H*), 5.55-5.48 (1H, td, J_1 = 2.0 Hz, J_2 = 7.3 Hz, =C*H*-), 4.99-4.95 (1H, m, ≡C*H*-O-), 3.52 (3H, d, J = 1.1 Hz, O-CH_3), 2.47 (1H, d, J = 2.2 Hz, ≡C*H*), 1.95-1.76 (2H, m, =CH-CH_2), 1.74-1.67 (2H, m, -CH_2-C*H*-CH_3), 1.60 (3H, s, =C(CH_3)$_2$, 1.51 (3H, s, =C(CH_3)$_2$, 1.30-1.14 (2H, m, CH_3CH-CH_2), 1.10-1.01 (1H, m, CH_3-C*H*-), 0.81-0.80 (3H, d, J = 6.4 Hz, -CH-CH_3); δ_C(400MHz, $CDCl_3$); δ_C(100 MHz, $CDCl_3$) 165.5, 133.4, 130.0, 129.6, 128.4, 126.8, 80.2, 74.5, 64.0, 56.1, 55.4, 41.5, 36.9, 28.5, 25.6, 25.2, 18.7, 17.5.

Synthesis of the MTPA-Cl derivative of (3S, 5S)-5,9-dimethyl-1-phenyldec-8-en-1-yn-3-ol, (313)



Compound (313) was prepared according to *GP10*, using the following quantites of (3S, 5S)-5,9-dimethyl-1-phenyldec-8-en-1-yn-3-ol (0.0122 g, 0.047 mmol, 1.0 eq), S-MTPA-Cl (0.027 mL, 0.14 mmol, 3.0 eq), 4-(dimethylamino)pyridine (0.004 g, 0.003 mmol, 0.6 eq), and dry pyridine (0.009 mL, 0.11 mmol, 2.4 eq). Purification by flash chromatography yielded the desired ester as an oil (0.022 g, 81 %); ν_{max} (neat)/cm^{-1} 3040, 2953, 2856, 1750, 1490, 1451, 1269, 1169, 1122, 1017, 991, 758, 718, 692; δ_H(400 MHz, $CDCl_3$); 7.49-7.47 (2H, m, Ar*H*),7.33-7.21 (8H, m, Ar*H*), 5.80-5.76(1H, dd, J_1 = 5 Hz, J_1 = 8.7 Hz, =C*H*-), 5.02-4.98(1H, m, ≡C*H*-O-), 3.51-3.50 (3H, d, J = 0.9 Hz, -O-CH_3), 2.00-1.84 (3H, m, -CH-CH_2-C*H*-CH$_3$), 1.68-1.60 (2H, m, -CH-CH_2-CH$_2$), 1.58 (3H, s, =C(CH_3)$_2$, 1.51 (3H, s, =C(CH_3)$_2$, 1.36-1.27 (1H, m, =CH-CH_2-), 1.21-1.12 (1H, m, =CH-CH_2-), 0.90-0.89 (3H, d, J = 6.0 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 165.9, 132.1, 131.8, 131.7, 129.6, 128.4, 128.3, 128.3, 127.5, 124.3, 86.3, 85.5, 65.5, 55.7, 41.7, 36.9, 29.0, 25.7, 25.3, 19.1, 17.7.

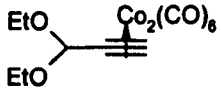
Synthesis of the MTPA-Cl derivative of (3R, 5S)-5,9-dimethyl-1-phenyldec-8-en-1-yn-3-ol, (314)



Compound (314) was prepared according to *GP10*, using the following quantites of (3S, 5S)-5,9-dimethyl-1-phenyldec-8-en-1-yn-3-ol (0.008 g, 0.031 mmol, 1.0 eq), S-MTPA-Cl (0.018 mL, 0.09 mmol, 3.0 eq), 4-(dimethylamino)pyridine (0.003 g, 0.002 mmol, 0.6 eq), and dry pyridine (0.006 mL, 0.07 mmol, 2.4 eq). Purification by flash chromatography yielded the desired ester as an oil (0.012 g, 81 %); ν_{max} (neat)/cm^{-1} 3039, 2954, 2856, 1749, 1491, 1453, 1270, 1169, 1124, 1017, 992, 762, 723, 695; δ_H(400 MHz, $CDCl_3$); 7.55-7.44 (2H, m, Ar*H*), 7.34-7.21 (8H, m, Ar*H*), 5.77-5.73 (1H, dd, J_1 = 5.3 Hz, J_2 = b8.7 Hz, =C*H*-), 5.02-4.98 (1H, m, ≡C*H*-O-), 3.51 93H, d, J = 1.1 Hz, -O-CH_3), 2.01-1.85 (3H, m, -CH-CH_2-C*H*-CH$_3$), 1.68-1.61 ((2H, m, -CH-CH_2-CH$_2$-), 1.59 (3H, s, =C(CH_3)$_2$, 1.51 (3H, s, =C(CH_3)$_2$, 1.36-1.26 (1H, m, =CH-CH_2-), 1.22-1.11 (1H, m, =CH-CH_2-), 0.90-0.89 (3H, d, J = 6.2 Hz, CH-CH_3); δ_C(100 MHz, $CDCl_3$) 165.7, 132.0, 131.7, 131.6, 129.5, 128.8, 128.3, 128.2, 127.4, 124.2, 122.1, 86.2, 85.2, 65.4, 55.5, 41.6, 36.8, 28.9, 25.5, 25.2, 19.0, 17.6; m/z: [M+ NH_4], Calc: 490.2564, Found: 490.2561.

Example of procedure for the complexation reaction of alkynes

Synthesis of hexacarbonyl[propiolaldehyde diethylacetal] dicobalt complex



To a solution of dicobalt octacarbonyl complex (1.0 g, 2.93 mmol, 1 eq) in dry DCM (15 mL) under N_2 atmosphere was added propiolaldehyde diethyl acetal (0.43 mL, 2.93 mmol, 1.0 eq). The reaction mixture was left to stir until the evolution of carbon monoxide ceased. The solvent was removed under vacuum, and the crude product purified by flash chromatography on silica (2:8 EtOAc / hexane) to yield a dark red oil (1.17g, 97%). ν_{max} (neat)/cm^{-1} 2982, 2878, 2097, 2025; δ_H(300 MHz, $CDCl_3$) 6.02 (s, 1H), 5.48 (s, 1H) 3.67 (s, 4H), 1.25 (s, 6H); ; δ_C(75 MHz, $CDCl_3$) 199.55, 101.75, 91.15, 70.84, 62.74, 14.81.

References

1. K. M. Nicholas, *Acc. Chem. Res.*, 1987, **20**, 207.
2. F. A. Cotton, G. Wilkinson and P. L. Gaus, *Basic Inorganic Chemistry*, John Wiley and sons, New York, 2nd ed.
3. J. W. Cable, R. S. Nyholm and R. K. Sheline, *J. Am. Chem. Soc.*, 1954, **76**, 3373.
4. R. A. Friedel, I. Wender, S. L. Shufler and H. W. Sternberg, *J. Am. Chem. Soc.*, 1955, **77**, 3951.
5. H. W. Sternberg, H. Greenfield, R. A. Friedel, J. Wotiz, R. Markby, I. Wender, *J. Am. Chem. Soc.*, 1954, **76**, 1457.
6. H. Greenfield, H. W. Sternberg, R. A. Friedel, J. H. Wotiz, R. Markby and I. Wender, *J. Am. Chem. Soc.*, 1955, **78**, 120.
7. K. M. Nicholas, R. Pettit, *Tetrahedron Lett.*, 1971, **37**, 3475.
8. K. M. Nicholas, R. Pettit, *J. Organomet. Chem.*, 1972, **44**, C21.
9. R. E. Connor, K. M. Nicholas, *J. Organomet. Chem.*, 1977, **125**, C45.
10. S. Padmanabhan, K. M. Nicholas, *J. Organomet. Chem*, 1983, 268, C23.
11. S. L. Schreiber, M. T. Klimas and T. Sammakia, *J. Am. Chem. Soc.*, 1987, **109**, 5749.
12. G. G. Melikyan, S. Bright, T. Monroe, K. I. Hardcaste, J. Ciurash, *Angew. Chem. Int. Ed. Engl.*, 1998, **37**, 161.
13. R. F. Lockwood and K. M. Nicholas, *Tetrahedron Lett*, 1977, **18**, 4163.
14. D. D. Grove, F. Miskevich, C. Smith and J. R. Corte, 1990, *Tetrahedron Lett.*, **31**, 6277.

15. D. D. Grove, J. R. Corte, R. P. Spencer, M. E. Pauly and N. P. Rath, *J. Chem. Soc., Chem. Commun.*, 1994, 49.

16. A. V. Muehldorf, A. Guzman-Perez and A. F. Kluge, *Tetrahedron Lett.*, 1994, **35**, 8758.

17. J-Y. LeBrazidec, P. J. Kociensky, J. D. Connolly and K. Y. Muir, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2475

18. H. D. Hodes and K. M. Nicholas, *Tetrahedron lett.*, 1978, **45**, 4349

19. K. M. Nicholas, M. Mulvaney, M. Bayer, *J. Am Chem. Soc.*, 1980, **102**, 2508.

20. S. L. Schreiber, T. Sammakia and W. E. Crowe, *J. Am. Chem. Soc.*, 1986, **108**, 3128.

21. R. Tester, V. Varghese, A. M. Montana, M. Khan and K. M. Nicholas, *J. Org. Chem.*, 1990, **55**, 186.

22. E. Tyrrell, P. Heshmati, and L. Sarrazin, *Synlett,* 1993, 769.

23. E. Tyrrell, S. Claridge, R. Davis, J. Lebel and J. Berge, *Synlett,*1995, 714.

24. A. M. Montaña, D. Fernández, *Tetrahedron Lett.*, 1999, **40**, 6499.

25. A. M. Montaña, D. Fernández, R. Pagès, A. C. Filippou and G. Kociok-Köhn, *Tetrahedron,* 2000, **56**, 425.

26. P. A. Jacobi and W. Zheng, *Tetrahedron Lett.*, 1993, **34**, 2581.

27. P. A. Jacobi and W. Zheng, *Tetrahedron Lett.*, 1993, **34**, 2585.

28. J. E. O'Boyle and K. M. Nicholas, *Tetrahedron Lett.*,1980, **21**, 1595.

29. Y. F. Jamison, S. Shambayati, W. E. Crowe, and S. L. Schreiber, *J. Am. Chem. Soc.*, 1997, **119**, 4353.

30. J. Berge, S. Claridge, A. Mann, C. Muller and E. Tyrrell, *Tetrahedron Lett.*, 1997, **38**, 685.

31. A. Mann, C. Muller and E. Tyrrell, *J. Chem. Soc.,Perkin Trans. 1*, 1998, 1427.

32. E. Tyrrell and C. Tillett, *Tetrahedron Lett.*, 1998, **39**, 9535.

33. L. R. Milgrom and G. Yahioglu, *Tetrahedron Lett.*, 1995, **36**, 9061.

34. L. R. Milgrom and G. Yahioglu, *Tetrahedron Lett.*, 1996, **37**, 4069.

35. J. S. Lindsey, I. C. Schrieman, H. C. Hsu, P. C. Kearney, and A. M. Marguerattaz, *J. Org. Chem.*, 1987, 52, 827.

36. L. R. Milgrom, R. D. Rees, G. Yahioglu, *Tetrahedron Lett.*, 1997, **38**, 4905.

37. I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, and M. I. Foreman, *J. Chem. Soc.,Perkin Trans. 1*,1973, 997.

38. L. V. R.Bonaga, and M. E. Krafft, *Tetrahedron*, 2004, **60**, 9795;

39. (a) S. T. Ingate, and J. Marco-Contelles, *Org. Prep. Proced. Int.*,1998, 30, 121; (b) J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic chemistry*, Oxford University Press, 2001, 1340.

40. I. U. Khand and P. L. Pauson, *J. Chem. Res. (M)*, 1977, 168.

41. D. C. Billington, P. Bladon, I. M. Helps, P. L. Pauson, W. Thomson, and D. Willison, *J. Chem. Res. (M)*, 1988, 2601.

42. K. M. Brummond and J. L. Kent, *Tetrahedron*, 2000, **56**, 3263.

43. P. Köpf-Maier, *Metal Complexes in Cancer Chemotherapy*, 1993, VCH, Weinheim, B. K. Keppler (Ed.).

44 A. Vessiëres, S, Top, C. Vallant, D. Osella, J.-P. Mornon and G. Jaouen, *Angew. Chem.*, 1992, **104**, 790.

45. D. Osella, G. Cavigiolio, M. Vincenti, A. Vessières, I. Laios, G. Leclercq, E. Napolitano, R. Fiaschi, G. Jaouen, *J. Organomet. Chem.*, 2000, **596**, 242.

46. K. Schmidt, M. Jung, R. Keilitz, B. Schnurr and R. Gust, *Inorganica Chemica Acta*, 2000, **306**, 6.

47. C. Mioskowski, C. Alayrac, J-P. Salaun, F. Durst, *Synlett.*,1992, 73.

48. http://en.wikipedia.org

49. J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry,* Oxford University Press, 2001, 1225.

50. http://www.chem.ox.ac.uk/oc/sgdavies/presearch3.htm

51. J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry,* Oxford University Press, 2001, 1228.

52. D. A. Evans, *Aldrichim. Acta*, 1982, **15**, 23.

53. D.J. Ager, J. Prakash, and D.R. Schaad, Chem. Rev., 1996, **96**, 835.

54. S. G. Davies, G. J. M. Doisneau, J. C. Prodger, and H. J. Sanganee, *Tetrahedron Lett.*, 1994, **35**, 2369.

55. S. G. Davies, G. J. M. Doisneau, J. C. Prodger, and H. J. Sanganee, *Tetrahedron Lett.*, 1994, **35**, 2373.

56. R. B. Silverman, and M. A. Levy, *J. Org. Chem.*, 1980, **45**, 815.

57. S. G. Davies, and H. J. Sanganee, *Tetrahedron: Asymmetry,* 1995, **6**, 671.

58. S. G. Davies, H. J. Sanganee, and P. Szolcsanyi, *Tetrahedron,* 1999, **55**, 3337.

59. J. F. Li, R. Yang, L. Nie, R. Huang, and J. Lin, *J. Pept. Res.*, 2005, **66**, 319.

60. D. A. Evans, J. Bartroli, and T. L Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127.

61. D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737.

62. D. A. Evans, J. Bartroli, and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127.

63. D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238.

64. G. Pourcelot, J. Aubouet, A. Caspar, and P. Cresson, *J. Organomet. Chem.*, 1987, **328**, C43 (French);

65. J. Berlan, Y. Besace, G. Pourcelot, and P. Cresson, *Tetrahedron lett.*, 1986, **42**, 4757, (French).

66. E. J. Corey, and N. W. Boaz, *Tetrahedron Lett.*, 1986, **26**, 6015.

67. O. Melnyk, E. Stephan, G. Pourcelot, and P. Cresson, *Tetrahedron*, 1992, **48**, 841, (French).

68. B-S. Lou, G. Li, F-D. Lung, and V. J. Hruby, *J. Org. Chem.*, 1995, **60**, 5509.

69. a) M. S. Kharasch, O. Reinmuth, *Grignard Reactions of Non-metallic Substances,* Prentice Hall: New York, 1954. b) C. Elschenbroich, A. Salzer, *Organometallics,* 1st ed., VCH Vergagsgesellschaft: Weinheim, New York, 1989, p38.

70. X. Qian, K. C. Russell, L. W. Boteju, V. J. Hruby, Tetrahedron, 1995, **51**, 1033.

71. S. Liao, and V. J. Hruby, *Tetrahedron Lett.*, 1996, **37**, 1563.

72. J. Lin, S. Liao, Y. Han, W. Qiu, and V. J. Hruby, *Tetrahedron Asymmetry*, 1997, **8**, 3213.

73. W. Yuan, and V. J. Hruby, *Tetrahedron Lett.*, 1997, **38**, 3853.

74. K. Honma, M. Tsuda, Y. Mikami, J. Kobayashi, *Tetrahedron Lett.*, 1995, **51**, 3745.

75. A. M. Montaña and M. Cano, *Tetrahedron*, 2002, **58**, 933.

76. E. Nicolás, K. C. Russell, and V. J. Hruby, *J. Org. Chem.*, 1993, **58**, 766.

77. G. B. Villeneuve, and T. H. Chan, *Tetrahedron Lett.*, 1997, **38**, 6489.

78. M. Feroci, A. Inesi, L. Palombi, G. Sotgiu, *J. Org. Chem.*, 2002, **67**, 1719.

79. C. Thom, P. Kocieński, *Synthesis*, 1991, 582-586.

80. E. Nicolás, K. C. Russell, and V. J. Hruby, *J. Org. Chem.*, 1993, **58**, 766.

81. D. R. Williams, W. S. Kissel, and J. J. Li, *Tetrahedron Lett.*, 1998, **39**, 8593.

82. D. R. Williams, W. S. Kissel, J. J. Li, and R. J. Mullins, *Tetrahedron Lett.*, 2002, **43**, 3723

83. J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512

84. E. Tyrrell, M. W. H. Tsang, G. A. Skinner, and J. Fawcett, *Tetrahedron*, 1996, **52**, 9841

85. E. Tyrrell, G. A. Skinner, and T. Bashir, *Synlett.*, 2001, **12**, 1929.

86. A. Job, C. F. Janeck, W. Bettray, R. Peters, and D. Enders, *Tetrahedron*, 2002, **58**, 2253.

87. D. Enders and H. Eichenauer, *Chem. Ber.*, 1979, **112**, 2933.

88. D. Enders, H. Eichenauer, U. Baus, H. Schubert, and K. A. M. Kremer, *Tetrahedron*, 1984, **40**, 1345.

89. D. Enders, A. Zamponi, and G. Raabe, *Synlett*, 1992, **11**, 897.

90. J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic chemistry,* Oxford University Press, 2001, 1237.

91. G. K. Chuah, S. H. Liu, S. Jaenicke, and L. J. Harrison, *J. Catal.*, 2001, **200**, 352.

92. P. Mäki-Arvela, N. Kumar, V. Nieminen, R. Sjöholm, T. Salmi, a D. Y. Murzin, *J. Catal.*, 2004, **225**, 155.

93. K. A. da Silva, P. A. Rbles-Dutenhefner, E. M. B. Sousa, E. F. Kozhevnikova, I. V. Kozhvnikov, E. V. Gusevkaya, *Catal. Commun.*, 2004, **5**, 425.

94. R. G. Jacob, G. Perin, L. N. Loi, C. S. Pinno, and E. J. Leonardão, *Tetrahedron Lett.*, 2003, **44**, 3605.

95. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, **31**, 2647.

96. D. B, Dess and J. C. Martin, *J. Org. Chem..*, 1983, **48**, 4156.

97. K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

98. J. Leder, H. Fujioka, and Y. Kishi, *Tetrahedron Lett.*, 1983, **24**, 1463

99. www.hamline.edu/~rmajerle/Chem3460/pdf/Feb1706.pdf, Alcohols from carbonyl compounds.

100. M. M. Midland, A. Tramontano, A. Kazubski, R. S. Graham, D. J. S. Tsai, and D. B. Cardin, *Tetrahedron*, 1984, **40**, 1371.

101. M. M. Midland and S. A. Zderic, *J. Am. Chem. Soc.*, 1982, **104**, 525.

102. M. M. Midland, D. C. McDowell, R. L. Hatch, A. Tramontano, *J. Am. Chem. Soc.*, 1980, **102**, 867.

103. D. E. Frantz, R. Fässler, and E. M. Carreira, *J. Am. Chem. Soc.*, 2000, **122**, 1806.

104. N. K. Anand and E. M. Carreira, *J. Am. Chem. Soc.*, 2001, **123**, 9687.

105. D. Boyall, D. E. Frantz, and E. M. Carreira, *Org. Lett.*, 2002, **4**, 2605.

106. E. J. Corey and X. M. Chen, *The Logic of Chemical Synthesis*, Wiley, New York, 1989.

107. R. Fässler, *PhD Thesis*, 2003, Swiss Federal Institue of Technology, Zürich.

108. R. Noyori, M. Kitamura, *Agew. Chem. Int. Ed. Engl.*, 1991, **30**, 49.

109. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

110. T. Ema, M. Yoshii, T. Korenaga, and T. Sakai, *Tettrahedron: Asymmetry*, 2002, **13**, 1223.

111. H-O. Kalinowski, S. Berger, S. Braun; *Carbon-13 NMR Spectroscopy*, John Wiley & Sons: New York, 1988, 129.

Publications

Poster:

Asymmetric Alkynylations for a Stereoselective Nicholas Reaction, Elizabeth Tyrrell, Julien Millet and Kibur Hunie-Tesfa, *Asymmetric Synthesis and Biological Methods-Aachen Oct 2005.*

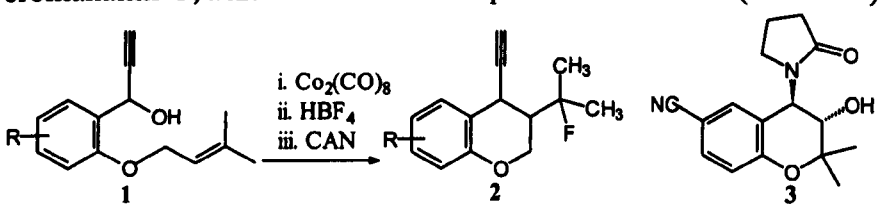
Enantioselective Alkynylation Reactions to Aromatic and Long Chain Aliphatic Aldehydes-The Effects of Aromatic Substituents upon the Enantioslectivity, Elizabeth Tyrrell, Kibur Hunie-Tesfa, Julien Millet and in part Christophe Muller, *Synthesis*, approved for publication, MS Number: P048/06.

The dual role of chiral oxazolidinone for an asymmetric conjugate addition reaction followed by an intramolecular Nicholas reaction, Elizabeth Tyrrell, Julien Millet, Neil Williams and in part Caroline Tillet & Kibur Hunie-Tesfa; In the process of completion.

Abstract: Asymmetric alkynylation reactions to linear alkyl and substituted aromatic aldehydes have been accomplished in good yield and with a range of selectivities. For aromatic aldehydes we observed that the selectivity of the alkynylation reaction appears to depend upon the substituents on the aromatic ring. Thus with electron withdrawing substituents both the yield and enantioselectivities were good to excellent. In contrast to this the presence of electron donating groups provided excellent conversions however these were coupled with poor enantioselectivities.

Key words: Asymmetric alkynylation reaction, aromatic aldehydes, *N*-methylephedrine, organozinc, substituent effects, citronellal.

Background: In a recent paper[1] we revealed a diastereoselective cobalt mediated synthesis of benzopyrans using a novel variation of an intramolecular Nicholas[2] reaction in the key step. Using this chemistry we were able to access a number of functionalised benzopyran derivatives **2** which were then subsequently screened, against cromakalim[3] **3**, a known modulator of potassium channels (Scheme 1).



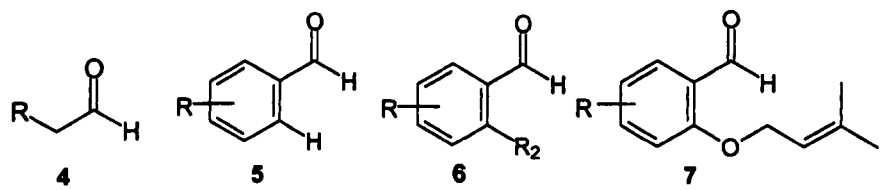
Scheme 1

In our efforts to achieve an enantioselective Nicholas reaction[4] we have focussed upon the synthesis of optically active propargyl alcohols, based upon **1**, for use in benzopyran synthesis. The ability to transfer the stereochemical information, contained within a dicobalt hexacarbonyl complexed chiral propargyl alcohol, into the resulting product still remains a challenge to the synthetic chemist. This limitation has been explained by the fluxional nature of a cobalt-stabilised carbocation that exposes both faces to the incoming nucleophile[5] thus leading to racemisation. One solution to this racemisation process lies in the ability to rapidly quench the cation before delocalisation effects take place. The first example of an enantiospecific Nicholas reaction, a process which provided chiral products from chiral substrates, was disseminated in 1994.[6] In the same year the rapid racemisation of a cobalt-stabilised cation was exploited to afford a stereoselective synthesis of fused ring systems.[7]

Chiral propargyl alcohols may be prepared *via* the asymmetric reduction of ynones[8] or from the asymmetric addition of alkynes to aromatic aldehydes.[9] Although the catalytic enantioselective addition reaction of dialkyl and alkenyl zinc reagents to aldehydes may be carried out efficiently, using a wide range of catalysts, advancements with the corresponding asymmetric alkynylation reaction appears to be far less developed[10]. The major limitations seem to be based upon a combination of factors such as the need to employ stoichiometric amounts of catalyst/ligand, limitations in the availability of appropriate

reagents such as chiral ligands and, in some examples, the production of significant quantities of by-products.[11]

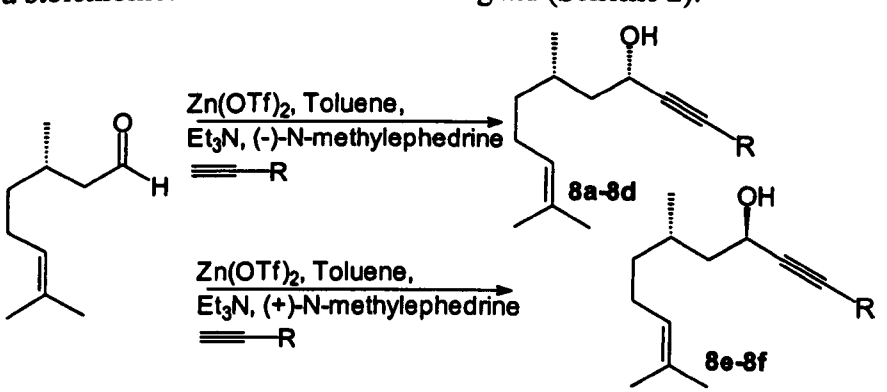
From our inspection of the existing literature, in this interesting area of asymmetric synthesis, we were able to corroborate the inconsistencies in the percentage yields and/or enantioselectivities for asymmetric alkynylation reactions. For instance with aldehydes such as **4** (Fig. 1), R = alkyl, good to excellent yields for the alkynylation reaction have been reported with enantiomeric excess (ee) ranging from good 79%[12] to excellent 99%.[13] With benzaldehyde derivatives, based upon **5**, longer reaction times appear to be the norm affording the corresponding propargyl alcohols in good to excellent yields.[14,15] As a general observation the enantiomeric excesses recorded for benzaldehyde derivatives are significantly lower than the previous examples. These seldom exceed 93%[13c] and typical optimised values appear in the ranges 70-85%. Significantly fewer examples of asymmetric alkynylation reactions to derivatives based upon **6** have been forthcoming. In general the selectivity of alkynylations with substrates such as these provide lower levels of enantioselectivity. Thus when R_2 = Cl, Br or NO_2 yields of 95% and ee's of 89% have been recorded.[14a, 14b] however for R_2 = OMe or Me yields have varied between 70% and ee's 37-69%[12] to 82-90% and ee's 71-74%.[14a, 14b] As far as we have been able to ascertain few if any examples that have focused upon the asymmetric alkynylation reaction of O-substituted derivatives, based upon **7**, have been revealed.



4 **5** **6** **7**

Figure 1

Results and Discussion: As well as attempting the asymmetric synthesis of propargyl alcohols using analogues of **7**, to serve as cyclisation precursors in an intramolecular Nicholas reaction, we also focused upon compounds based upon **8a-8f**. The main advantages with these substrates are that they are readily accessible from citronellal. In addition we have previously shown that the racemic analogues readily undergo intramolecular Nicholas cyclisation reactions.[16] The method of choice for effecting the asymmetric alkynylation reaction was the procedure described by Carreira.[13c] This involves the addition of a zinc acetylide, derived from zinc triflate, to the aldehyde in the presence of a stoichiometric amount of a chiral ligand (Scheme 2).



Scheme 2

up to 98% de

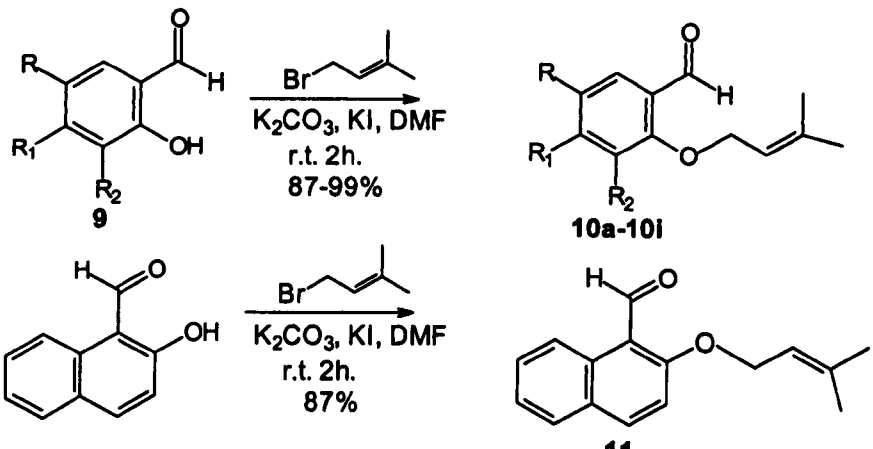
The important stereochemical outcome, resulting from reactions such as these, have been systematically correlated by the Carreira group and shown to be highly dependant upon the choice of chiral ligand. Thus addition reactions using (+)-*N*-methylephedrine affords adducts exclusively with an (R)–configuration whereas (-)-*N*-methylephedrine affords the corresponding adduct with an (S)-configuration. To date no exceptions to this generalisation have been highlighted despite its use with a variety of different aromatic and non-aromatic aldehydes. The results from these propargylation reactions are summarised (Table 1).

Table 1:Optically Active Propargylic Alcohols obtained from (-)-(S)- Citronellal[a]

Entry		Alkyne	Ligand	Yield	% de[b]
1	**8a**	Ph—	(-)-N-Methylephedrine	66	85
2	**8b**	H_3C—	(-)-N-Methylephedrine	65	86
3	**8c**	TMS—	(-)-N-Methylephedrine	58	98
4	**8d**	CH_3O—	(-)-N-Methylephedrine	70	84
5	**8e**	Ph—	(+)-N-Methylephedrine	65	92
6	**8f**	H_3C—	(+)-N-Methylephedrine	55	91

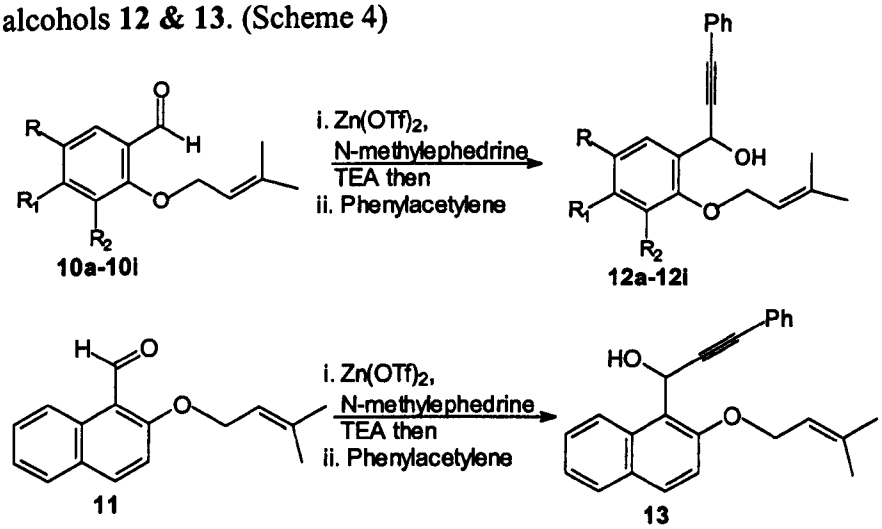
Notes: [a] Alkynylation of (-)-(S)- Citronellal, in the absence of a chiral ligand, gave a 45:55 ratio of diastereoisomers. [b]The de values were calculated using GC-MS as well as from a measurement of the integrals obtained from the corresponding ^{1}H NMR spectrum of the reaction mixture.The results obtained from these NMR studies corroborated well with data obtained from the Mosher ester[17] of the corresponding diastereomeric mixture.

In comparison to the corresponding racemic alkynylation reaction (2 hours, 95-98%) the picture that emerges from these data are that the use of an alkynylzinc reagent, in the presence of a chiral ligand, tends to favour longer reaction times, typically about 30 hours, coupled with a reduction in yield. However, good to excellent levels of diastereoselectivity are observed regardless of the nature of the alkyne. With regard to the stereochemistry of the resulting propargyl alcohols we have tentatively assigned the configuration on the basis of the literature precedent. Thus for the propargyl alcohols, entries 1-4 (Table 1), we have assigned an (S)-stereochemistry and entries 5 & 6 as (R).



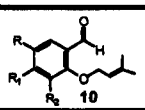
Scheme 3

A range of additional aldehydes, **10a-i** & **11**, based upon **7**, were obtained very efficiently *via* an *O*-alkylation of the corresponding salicylaldehyde derivative **9** or naphthyl derivative (Scheme 3).
With these aldehydes in hand we were able to investigate the corresponding asymmetric addition reactions to afford propargyl alcohols **12** & **13**. (Scheme 4)



Scheme 4

From our interpretation of the literature coupled with our experiences with the asymmetric alkynylation reaction using citronellal we anticipated that the C-2 alkoxy moiety would have an impact upon the reaction in terms of the overall efficiency of the transformation (%age yields) the duration and most importantly the enantioselectivity of the reaction. Using experimental conditions that had previously been optimised for the alkynylation of benzaldehyde derivatives, such as **5**, we observed low conversion rates and modest enantioselectivities (entry 1, Table 2). We found however that a considerable improvement in the yield could be achieved by using a three-fold excess of phenylacetylene although no enhancement in the selectivity was observed (entry 2, Table 2).

Table 2: Optically active propargylic alcohols derived from **10** using phenylacetylene in the presence of ligand *N*-methylephedrine 

Entry	Aldehyde	Time (days)		Yield	% ee[a]	$[\alpha]_D^{20}$
1	**10a** R = R_1 = R_2 = H	3[b]	**12a**	25	45	+0.7
2	**10a** R = R_1 = R_2 = H	7[c]	**12a**	89	45	+0.7
3	**10b** R=OMe, R_1=R_2=H	7	**12b**	99	43	+ 0.3
4	**10c** R=H, R_1=OMe, R_2=H	7	**12c**	63	23	+ 0.8
5	**10d** R=R_1=H, R_2=OMe	7	**12d**	91	56	-1.7
6	**10e** R=NO_2, R_1=R_2= H	7	**12e**	92	78	+18.1
7	**10f** R=Br, R_1=R_2=H	7	**12f**	82	84	-0.8
8	**10g** R=Cl, R_1=R_2=H	7	**12g**	96	75	-2.2
9	**10h** R=Br,R_1=H, R_2=Br	7	**12h**	85	91	-26.3
10	**10i** R= Cl, R_1=H, R_2=Cl	7	**12i**	99 [d]	90	+14.3
11	**11**	7	**13**	55 (71)[d]	25 (24)[d]	+8.0

Notes: a The ee values were determined by HPLC with Chiracel-OD-H column and, for initial trials,confirmed by NMR studies of the Mosher ester.[17]
b Initially we used the following quantities:Zn(OTf)2 1.1 eq. phenylacetylene(1.5 eq).
c Optimised yields were obtained with 3 eq. of phenylacetylene.
d Data obtained using (-)-*N*-methylephedrine

Interestingly the analogous racemic propargylation reaction with phenylethynylmagnesium bromide provided the corresponding propargyl alcohol in high yield (<95%) in about 2 hours.

Predictably long reaction times were indeed necessary in order to obtain the corresponding chiral propargyl alcohols however the efficiency of the reaction in terms of the yield and the levels of enantioselectivity varied considerably (compare entries 3 and 5 with entry 4, Table 2). The picture that emerges from these data are that the formation of a chiral complex, involving a zinc alkyne, a zinc-aldehyde complex and the chiral ligand, leads to a considerable increase in the time required for efficient conversion to the chiral propargyl alcohol compared to the corresponding racemic synthesis. Despite the fact that the percentage yields for the alkynylations are good to excellent (55-99% yields) the same is not true for the corresponding enantioselectivities and here significant differences manifest themselves. Thus the presence of electron donating groups on the aromatic ring appear to reduce the enantioselectivity to the level observed for **10a** (entries 3 & 5,Table 2) however when the methoxy group is positioned *para* to the carbonyl i.e. R_1 = OMe, the ee is halved to 23% (entry 4, Table 2). In contrast to this observation when R is electron withdrawing NO_2, Cl or Br, (entries 6 to 8, Table 2) there is an accompanying enhancement in the ees which are enhanced even further when both R and R_2 are halogens (entries 9 & 10, Table 2). For alkynylations with naphthyl derivatives, entry 11, the enantioselectivity is comparable to that observed with a *p*-methoxy group, (entry 4).

Apart from our own observation suggesting a link between the enantioselectivity of alkynylation reactions and the electron rich/poor nature of substituents in the aromatic ring the only other report of relevance that we could find was revealed by Kang.[15b] In their asymmetric addition of phenylacetylene to benzaldehyde derivatives, using an oxazolidine promoter, they reported the following optimised enantioselectivities: the 3-nitro-(99%), 3-bromo (90%) compared to 3-tolyl (87%) and 3-methoxy derivative (86%) respectively. As the overall enantioselectivities were excellent the significance of the small reduction in the ees associated with a substituent effect was probably missed and as a result not commented upon.

In summary this paper describes a series of asymmetric alkynylation reactions to provide a range of enantio-enriched propargylic alcohols for use in attempted asymmetric Nicholas cyclisation reactions.[18]

As a general observation most alkynylation reactions have been attempted with relatively simple aliphatic aldehydes or benzaldehyde derivatives. Our contribution to this area is in the use of more complex, linear alkyl aldehydes as well as substituted aromatic derivatives. We have now established that with use of an excess of the alkyne the desired propargylic alcohols are accessable in good to excellent yield. In addition we have observed that the enantioselectivity that accompanies these addition reactions is very dependent upon the electronic nature of the aromatic ring with electron withdrawing groups providing optimal levels of selectivity. The paradox however is that

although high yielding the alkynylation reaction itself remains a lengthy process.

General methods:[19]

Melting point determinations were recorded using a Stuart Scientific SMP3 digital melting point apparatus tube apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer and were calibrated using a standard polystyrene film. The spectra were recorded either as thin films for liquids, between sodium chloride discs or for solids as a Nujol mull. All infrared data are quoted in wave numbers (cm^{-1}). Proton nuclear magnetic resonance spectra (^1H NMR) were recorded at 400 MHz using a JEOL Eclipse 400 MHz spectrometer. Peak positions are quoted using the δ scale relative to tetramethylsilane ($\delta = 0$) as an internal standard. Carbon-13 NMR spectra (^{13}C NMR) were recorded at 100 MHz on a JEOL Eclipse 400 MHz spectrometer using deuterochloroform as an internal standard. Low resolution mass spectra were recorded on a VG TRIO-2 mass spectrometer under electron impact conditions at an ionising potential of 70 eV and/or with a Hewlett Packard GC-MS HP5890 (GC) with capillary column and HP 5971 (MS). Accurate mass analyses were performed and reported on a VG-ZAB-E under EI conditions by the EPSRC National Mass Spectrometry Service Centre (Swansea) using the EI Peak Match on M+ method. Enantiomeric excesses were measured by HPLC method (Chiralcel-OD-H column) using Waters 996 photodiode array diode detector.

Typical procedure for the asymmetric addition of alkynes to (S)-(-)-Citronellal:

(3S, 5S)-5, 9-Dimethyl-1-phenyl-dec-8-en-1-yn-3-ol (8a)

A suspension of zinc triflate (2.2g, 6.05 mmol) and (-)-*N*-methylephedrine (1.19g, 6.62 mmol) in 0.3M triethylamine in dry toluene was stirred for 2 hours at 25°C. After 2 hours phenylacetylene (0.56g, 0.61 ml, 5.52 mmol) was delivered to the suspension *via* syringe followed by (S)-(-)-citronellal (0.85g, 5.52 mmol). The progress of the reaction was monitored by thin layer chromatography. Upon completion , *circa* 30 hours, the reaction mixture was quenched by the addition of a saturated solution of ammonium chloride (30 ml). The mixture was extracted with diethyl ether (3 x 30 ml) and the combined organic layers were dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. Purification by column chromatography on silica using hexane:ethyl acetate (8:2) gave the title compound as a colourless oil 0.99g, 66%. The diastereoisomeric excess (de) was determined and corroborated by GC-MS, measurement of the integrations of the corresponding ^1H NMR spectrum of the crude reaction mixture and the ^1H NMR spectrum of the corresponding Mosher ester.[17]

$[\alpha]_D^{20}$ + 8.3 (c = 0.4, $CHCl_3$)

V_{max}/cm^{-1} 3422, 2929, 2202, 1664, 1489, 1444, 1379, 1285, 1069 & 758.

^{1}H NMR ($CDCl_3$; 400 MHz): δ = 7.42-7.39 (2 H, m, Ar*H*), 7.30-7.27 (3H, m, Ar*H*), 5.11.-5.07 (1H, m, CH=C$(CH_3)_2$, 4.67-4.62 (1H, m, HO-C*H*), 2.06-1.92 (2H, m, CH_2 CH=), 1.83-1.82 (2H, dd, *J* 1.8, 5.6 Hz, CHCH_2CH-), 1.80-1.72 (1H,m, CH_3C*H*-), 1.65 (3H, s, C=CCH_3), 1.58 (3H, s, C=CCH_3), 1.4-1.33 (1H, m, CHCH_2CH_2-), 1.24-1.15 (1H, m, CHCH_2CH_2-), 0.96-0.94 (3H, d, *J* 6.4 Hz, CHCH_3).

^{13}C NMR ($CDCl_3$; 100 MHz): δ = 131.8, 131.5, 128.4, 128.3, 124.7, 122.8, 90.3, 85.0, 61.8, 45.2, 37.2, 29.5, 25.8, 19.8, 17.8.

MS calcd for $C_{18}H_{24}O$: 274.2165 $(M+NH_4)^+$ found 274.2165.

Mosher ester derivative of (3S, 5S)-5, 9-Dimethyl-1-phenyl-dec-8-en-1-yn-3-ol (8a)

To a toluene solution of (3S, 5S)-5, 9-dimethyl-1-phenyl-dec-8-en-1-yn-3-ol (8a) (0.0346 g, 0.13 mmol), was sequentially added (S)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (75 μl, 0.40 mmol), 4-dimethylaminopyridine (0.01g, 0.08 mmol) and dry pyridine (27 μl, 0.33 mmol).The mixture was left to stir at an ambient temperature for about 1 hour whereupon water was added (1 ml) in order to quench the reaction. The mixture was extracted with ethyl acetate (4 x 5 ml), washed with dilute hydrochloric acid (0.5 ml, 10% solution) followed by a wash with a saturated solution of aqueous sodium bicarbonate (0.5 ml). The mixture was dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to afford the desired Mosher ester (0.06g, 98%) as a clear oil.

V_{max}/cm^{-1} 2953.8, 1749, 1490.9, 1451.8, 1269.9, 1168.9, 1122.4, 1015.5, 991.8 & 705.4.

^{1}H NMR ($CDCl_3$; 400 MHz): δ = 7.49-7.48 (2 H, d, *J* 6.9 Hz, Ar*H*), 7.35-7.22 (8H, m, Ar*H*), 5.77.-5.73 (1H, dd, *J* 5.1,8.7 Hz, O-C*H*), 4. 98 (1H, tt, J 1.2, 7.1 Hz, C*H*=C$(CH_3)_2$), 3.51-3.50 (3H, d, *J* 0.9Hz, OCH_3), 2.00-1.85 (3H, m, CH_2 CH=, CH_3C*H*), 1.68-1.60 (2H, m, CH_3CHCH_2), 1.58 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.36-1.27 (1H, m, CH_3CH_2CH), 1.20-1.12 (1H, m, CH_2C*H*CH), 0.90-0.89 (3H, d, *J* 6.0 Hz, CHCH_3).

^{13}C NMR ($CDCl_3$; 100 MHz): δ = 165.9, 132.2, 131.8, 131.7, 131.6, 128.6, 128.4, 127.5, 124.3, 122.1, 86.2, 85.5, 65.5, 55.7, 41.7, 36.9, 29.0, 25.8, 25.3, 19.1, 17.7.

MS calcd for $C_{28}H_{31}F_3O_3$: 490.2564 $(M+NH_4)^+$ found 490.2561

(3S, 5S)-5, 9-Dimethyl-1-*p*-tolyl-dec-8-en-1-yn-3-ol (8b)

The typical procedure for **8a** was followed

$[\alpha]_D^{20}$ – 10.4 (*c* = 0.6, $CHCl_3$)

V_{max}/cm^{-1} 3406, 2959, 2926, 2199, 1718, 1664, 1606, 1508, 1378, 1289, 1062, 817 & 755.

^{1}H NMR ($CDCl_3$; 400 MHz): δ = 7.30-7.28 (2 H, d, *J* 8 Hz, Ar*H*), 7.10-7.08 (2H, d, *J* 7.8 Hz, Ar*H*), 5.11.-5.08 (1H, m, C*H*=C$(CH_3)_2$), 4.66-4.61 (1H, dd, *J* 6.1,13.5 Hz, HO-C*H*), 2.32 (3H, s, ArCH_3), 2.07-1.92 (2H, m, =CHCH_2), 1.87-1.71 (3H, m, CH_2C*H*CH_3), 1.65 (3H, s, C=CCH_3), 1.58 (3H, s, C=CCH_3), 1.44-1.35 (1H, m, CH_3C*H*), 1.25-1.16(1H, m, CH_3C*H*), 0.95-0.93 (3H, d, *J* 6.2 Hz, CHCH_3).

^{13}C NMR ($CDCl_3$; 100 MHz): δ = 138.5, 131.6, 131.4, 129.1, 124.6, 119.7, 89.5, 85.2, 61.6, 45.0, 36.8, 29.4, 25.8, 25.4, 21.5, 19.8, 17.8.
MS calcd for $C_{19}H_{26}O$: 288.2322 $(M+NH_4)^+$ found 288.2324.

(3S, 5S)-5, 9-Dimethyl-1-trimethylsilanyl-dec-8-en-1-yn-3-ol (8c)
The typical procedure for **8a** was followed
$[\alpha]_D^{20}$ + 3.6 (*c* = 0.3, $CHCl_3$)
V_{max}/cm^{-1} 3423, 2963, 2925, 1733, 1448, 1377, 1290, 1250, 1154, 843 & 760.
^1H NMR ($CDCl_3$; 400 MHz): δ = 5.09.-5.05 (1H, m, C*H*=C$(CH_3)_2$), 4.65-4.60 (1H, dd, *J* 6.0,13.5 Hz, HO-C*H*), 2.07-1.92 (2H, m, =CHCH_2), 1.87-1.70 (3H, m, CH_2C*H*CH_3), 1.64 (3H, s, C=CCH_3), 1.58 (3H, s, C=CCH_3), 1.40-1.32 (1H, m, CH_3C*H*), 1.25-1.16(1H, m, CH_3C*H*), 0.95-0.92 (3H, d, *J* 6.1 Hz, CHCH_3), 0.15 (3H, s, Si$(CH_3)_3$)
^{13}C NMR ($CDCl_3$; 100 MHz): δ = 124.0, 119.3, 92.3, 89.5, 60.9, 44.9, 36.8, 29.6, 25.3, 21.4, 19.8, 17.6, -0.04
MS calcd for $C_{15}H_{28}SiO$: 251.1826 $(M-H)^+$ found 251.1828

(3S, 5S)-1-(6-Methoxynaphthalen-2-yl)-5,9-Dimethyldec-8-en-1-yn-3-ol (8d)
The typical procedure for **8a** was followed
$[\alpha]_D^{20}$ +18.2 (*c* = 0.3, $CHCl_3$)
V_{max}/cm^{-1} 3385, 2963, 2926, 1630, 1602, 1498, 1483, 1389, 1245, 1029, 852.
^1H NMR ($CDCl_3$; 400 MHz): δ = 7.86 (1H, s ArH), 7.68-7.64 (2H, m, ArH), 7.44.-7.42 (1H, d, *J* 8.4 Hz, Ar*H*), 7.16-7.13 (1 H, ddd, *J* 0.7, 2.5, 8.9 Hz, Ar*H*), 7.099-7.093 (1H, d, *J* 2.2 Hz, Ar*H*), 5.13.-5.11 (1H, m, C*H*=C$(CH_3)_2$), 4.73-4.69 (1H, m, HO-C*H*), 3.92-3.91 (3H, d, *J* 0.7 Hz, O-CH_3), 2.09-1.99 (2H, m, =CHCH_2),1.96-1.95 (1H, d, *J* 4.0 Hz, C*H*-CH_3) 1.87-1.77 (2H, m, HO-CHCH_2), 1.68 (3H, s, C=CCH_3), 1.61 (3H, s, C=CCH_3), 1.48-1.40 (1H, m, CH_3C*H*), 1.30-1.21(1H, m, CH_3C*H*), 0.99-0.98 (3H, d, *J* 5.9 Hz, CHCH_3).
^{13}C NMR ($CDCl_3$; 100 MHz): δ = 158.4, 134.2, 131.5, 129.4, 129.1, 124.6, 128.6, 126.9, 124.7, 119.5, 117.6, 105.8, 89.9, 85.6, 61.9, 55.4, 45.3, 37.2, 29.6, 25.8, 25.4, 19.8, 17.8.
MS calcd for $C_{23}H_{28}O_2$: 337.2162 $(M+H)^+$ found 337.2164.

Typical procedure for the *O*-alkylation of salicylaldehyde derivatives:
Synthesis of 2-[(3-methylbut-2-en-1-yl)oxy]benzaldehyde 10a
To a solution of salicylaldehyde (1.0g, 8.18 mmol) and 4-bromo-2-methyl-2-butene (1.1 g, 8.99 mmol) in dry DMF (25 cm^3) was added finely ground anhydrous potassium carbonate (3.72g, 27 mmol) and potassium iodide (0.12g, 0.68 mmol). The reaction mixture was left to stir at room temperature under a nitrogen atmosphere for about 2.5 hours whereupon analysis of the reaction mixture by thin layer chromatography (TLC) showed the presence of a new compound (R_f: 0.48, 1:3 diethyl ether: light petroleum). The reaction mixture was

poured in to water and partitioned in diethyl ether. The aqueous phase was extracted with diethyl ether (6 x 15 cm^3). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated in *vacuo* to afford the desired product as a yellow oil (1.10g, 84%).

V_{max} cm^{-1}(neat) 3034, 1686, 1598 & 1286.

^1H NMR ($CDCl_3$; 400 MHz) δ 10.46 (1H, d, *J* 0.7Hz, *H*-C=O); 7.78 (1H, dd, *J* 1.8, 7.9Hz, Ar-*H*); 7.50 -7.45 (1H, m, Ar-*H*); 6.97-6.93 (2H, m, Ar-*H*); 5.48-5.43 (1H, m, C=C-*H*); 4.59 (2H, d, *J* 6.8 Hz, H_2C-O); 1.76 (3H, s, CH_3); 1.71 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$;100 MHz) δ 189.63, 161.12, 138.40, 135.63, 127.94, 124.82, 120.27, 118.80, 112.73, 65.20, 25.53, 18.04.

MS Calcd. for $C_{12}H_{14}O_2$: 191.1067 $[M+H]^+$ found 191.1066.

Typical procedure for the asymmetric addition of phenylacetylene to aldehyde 10a:

Synthesis of (1*R*)-(+)-1-{2-[(3-methylbut-2-en-1-yl)oxy]phenyl}-3-phenylprop-2-yn-1-ol (12a)

A 100 ml flask was charged with $Zn(OTf)_2$ 2.1010g, 5.78 mmol, 1.1 eq) and (1S, 2R)-(+)-N-methylephedrine (1.1311g, 6.31 mmol, 1.2 eq) and purged with nitrogen for 15 minutes whereupon anhydrous toluene (242mL) and triethylamine (1.76 mL, 1.2770g, 12.62 mmol, 2.4 eq) were added *via* syringe. The resulting mixture was left to stir for 2 hours before phenylacetylene (1.73 mL, 1.6117g, 15.78 mmol, 3 eq) was added by syringe in one portion. After 15 min of stirring, 2-[(3-methylbut-2-en-1-yl)oxy]benzaldehyde (1.0g, 5.26 mmol, 1 eq) was added in one portion. The progress of the reaction was monitored by TLC analysis where product started to form after 24 hours and optimal results were obtained after 7 days.

The reaction was quenched by the addition of an aqueous saturated solution of ammonium chloride (31 mL). The reaction mixture was extracted with diethyl ether (100 mL). The layers were separated and the aqueous layer was further extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed sequentially with a saturated ammonium chloride solution (100 mL) followed by saturated brine (100 mL). The organic layers were isolated and dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude product. Purification by column chromatography on silica gel using 3:2 chloroform: light petroleum gave the pure chiral alcohol as a clear yellow oil (0.74g 89%). The enantiomeric excess was determined by HPLC analysis and found to be 45% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm) Retention time: t_{major} 12.39 min. and t_{minor} 14.81 min.

$[\alpha]_D^{20}$ + 0.7 (*c* = 10.3, $CHCl_3$)

V_{max}/cm^{-1} 3529, 3425, 3067, 3035, 2929, 2202, 1664, 1489, 1444, 1379, 1285, 1069 & 758.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.62 (1H, dd, *J* 1.7 and 7.5 Hz, Ar-*H*); 7.50-7.46 (2H, m, Ar-*H*); 7.33-7.29 (4H, m, Ar-*H*); 7.00 (1H, dt, *J* 1.1 and 7.5 Hz, Ar-*H*); 6.95 (1H, dd, *J* 0.7 and 8.2, Ar-*H*); 5.91 (1H, d,

J 6.4, OH-C-*H*); 5.55-5.50 (1H, m, *H*-C=C); 4.63 (2H, d, *J* 6.8, O-C*H*$_2$); 3.31(1H, d, *J* 6.4, O*H*); 1.79 (3H, s, C*H*$_3$); 1.75 (3H, s, C*H*$_3$).
^{13}C NMR ($CDCl_3$,100 MHz): δ 156.35, 138.57, 131.86, 129.69, 129.22, 128.43, 128.31, 128.17, 122.94, 120.93, 119.51, 112.25, 88.48, 86.13, 65.41, 62.25 , 25.88, 18.38.
MS Calcd: for $C_{20}H_{20}O_2$: 291.1380 $[M-H]^+$ found 291.1376;
UV (^{i}PrOH) λ_{max} 243 nm; Abs: 1.33.

(1*R*)-(+)-1-{2-[(3-methylbut-2-en-1-yl)oxy]-5-nitrophenyl}-3-phenylprop-2-yn-1-ol (12e)
The typical procedure for **12a** was followed and was isolated as yellow oil (92%). The enantiomeric excess was determined by HPLC analysis and found to be 78% (Chiralcel OD-H, 15% ^{i}PrOH in hexane, 254 nm) Retention time: t_{major} 12.13 min. and t_{minor} 66.87 min.
$[\alpha]_D^{20}$ +18.1 (c = 3.1, $CHCl_3$).
V_{max}/cm^{-1} 3420, 3082, 2975, 2202, 1674, 1592, 1514, 1490,1384, 1268, 1086 & 974.
^{1}H NMR ($CDCl_3$; 400 MHz) δ 8.58 (1H, d, *J* 2.9 Hz, Ar-*H*); 8.24 (1H, dd, *J* 2.9 and 9.2 Hz, Ar-*H*); 7.51-7.44 (2H, m, Ar-*H*); 7.35-7.30 (3H, m, Ar-*H*); 6.99 (1H, d, *J* 9.2 Hz, Ar-*H*); 5.94 (1H, d, *J* 6.0 Hz, *H*-CPh); 5.52-5.47 (1H, m, C=C-*H*); 4.73 (2H, d, *J* 6.6 Hz, CH_2); 2.94 (1H, d, *J* 6.0 Hz, O*H*); 1.81 (3H, s, C*H*$_3$); 1.76 (3H, s, C*H*$_3$).
^{13}C NMR ($CDCl_3$,100 MHz,) δ 161.05, 141.34, 140.10 , 131.91, 130.28, 128.85, 128.43, 125.88, 124.02, 122.26, 118.20, 111.75, 87.18, 86.84, 65.32, 60.83, 25.89, 18.47.
MS Calcd: for $C_{20}H_{19}NO_4$:355.1652 $[M+NH_4]^+$ found: 355.1652

(1*R*)-(-)-1-{3,5-dibromo-2-[(3-methylbut-2-en-1-yl)oxy]phenyl}-3-phenylprop-2-yn-1-ol (12h)
The typical procedure for **12a** was followed and was isolated as white solid (85%). The enantiomeric excess was determined by HPLC analysis and found to be 91% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm) Retention time: t_{major} 6.54 min. and t_{minor} 12.11 min.
m.p.94.8-95.4°C
$[\alpha]_D^{20}$ -26.3 (c= 9.4, $CHCl_3$).
V_{max}/cm^{-1} 3408, 3068, 2972, 2226, 1672, 1490, 1444, 1380, 1308, 1218, 1144, 1034, 942, 864, 756 & 690.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (1H, dd, *J* 0.4 and 2.4 Hz, Ar-*H*); 7.69 (1H, d, *J* 2.4 Hz, Ar-*H*); 7.47-7.43 (2H, m, Ar-*H*); 7.37-7.30 (3H, m, Ar-*H*); 5.92 (1H, d, *J* 5.9 Hz, *H*-CPh); 5.66-5.61 (1H, m, C=C-*H*); 4.70-4.61 (2H, m, C*H*$_2$); 2.89 (1H, d, *J* 5.9 Hz, O*H*); 1.81 (3H, d, *J* 1.0 Hz, C*H*$_3$); 1.73 (3H, d, *J* 1.0 Hz, C*H*$_3$).
^{13}C NMR ($CDCl_3$, 100 MHz,) δ 152.97, 140.46, 138.06, 135.99, 131.82 (x 2), 130.60, 128.94, 128.46 (x 2), 122.04, 119.25, 118.53, 117.55, 87.92, 87.12, 71.19, 60.88, 25.98, 18.35 .
MS Calcd: for $C_{20}H_{18}Br_2O_2$: 466.0012 $[M+NH_4]^+$ Found: 466.0013

(1*R*)-(+)-1-{2-[(3-methylbut-2-en-1-yl)oxy]-1-naphthyl}-3-phenylprop-2-yn-1-ol (13)

The typical procedure for **12a** was followed and was isolated as yellow oil (55%). The enantiomeric excess was determined by HPLC analysis and found to be 25% (Chiralcel OD-H, 5% ^{i}PrOH in hexane, 254 **nm**) Retention time: t_{major} 29.23 min. and t_{minor} 32.43 min.

$[\alpha]_D^{20}$ 8.0 (c= 0.5, $CHCl_3$)

V_{max}/cm^{-1} 3422, 3056, 2972, 2920, 2226, 1672, 1624, 1596, 1510, 1464, 1440, 1378, 1236,1072, 1014, 956, 808, 756 & 692.

^{1}H NMR (400 MHz, $CDCl_3$,) δ 8.46-8.44 (1H, d, *J* 8.6 Hz, Ar-*H*); 7.84-7.54 (2H, dd, *J* 2.9 & 8.6 Hz, Ar-*H*); 7.57-7.54 (1H, t, *J* 7.5Hz Ar-*H*); 7.41-7.39 (3H, m, Ar-*H*); 7.31-7.24 (4H, m, Ar-*H*); 6.66 (1H, s, *H*-CPh); 5.62-5.58 (1H, m, C=C-*H*); 4.80-4.72 (2H, m, CH_2); 3.92 (1H, s (broad), O*H*); 1.80 (3H, s, CH_3); 1.77 (3H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.07, 138.86, 131.44, 130.42, 129.78, 128.72, 128.72, 128.29, 128.27, 126.97, 124.05, 123.77, 123.19, 122.58, 119.70, 115.52, 90.26, 85.01, 67.14, 58.64, 25.95, 18.44.

MS Calcd: for $C_{24}H_{22}O_2$: 365.1512 $[M+Na]^+$, Found: 365.1512

(1*R*)-(+)-1-{2-[(3-methylbut-2-en-1-yl)oxy]-5-methoxyphenyl}-3-phenylprop-2-yn-1-ol (12b)

The typical procedure for **12a** was followed and was isolated as yellow crystalline solid (99%). The enantiomeric excess was determined by HPLC analysis and found to be 43% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm) Retention time: t_{major} 12.73 min. and t_{minor} 16.54 min.

m.p. 42.8-43.2°C (from IMS)

$[\alpha]_D^{20}$ +0.3 (c = 7.2, $CHCl_3$).

(1*R*)-(+)-1-{2-[(3-methylbut-2-en-1-yl)oxy]-4-methoxyphenyl}-3-phenylprop-2-yn-1-ol (12c)

The typical procedure for **12a** was followed and was isolated as a yellow oil (23%). The enantiomeric excess was determined by HPLC analysis and found to be 23% (Chiralcel OD-H, 5% ^{i}PrOH in hexane, 254 nm) Retention time: t_{major} 13.18 min. and t_{minor} 20.28 min.

$[\alpha]_D^{20}$ +0.8° (c = 3.5, $CHCl_3$).

(1*R*)-(-)-1-{2-[(3-methylbut-2-en-1-yl)oxy]-3-methoxyphenyl}-3-phenylprop-2-yn-1-ol (12d)

The typical procedure for **12a** was followed and was isolated as a yellow crystalline solid (91%). The enantiomeric excess was determined by HPLC analysis and found to be 56% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm) Retention time: t_{major} 12.69 min. and t_{minor} 18.40 min.

m.p. 66.6-67.8°C

$[\alpha]_D^{20}$ -1.7 (c= 3.0, $CHCl_3$).

(1*R*)-(-)-1-{2-[(3-methylbut-2-en-1-yl)oxy]-5-bromophenyl}-3-phenylprop-2-yn-1-ol (12f)

The typical procedure for **12a** was followed and was isolated as a

yellow oil (82%). The enantiomeric excess was determined by HPLC analysis and found to be 84% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm) Retention time: t_{major} 9.0 min. and t_{minor} 14.16 min.
$[\alpha]_D^{20}$ -0.8^0 (c= 3.5, $CHCl_3$).

(1*R*)-(-)-1-{2-[(3-methylbut-2-en-1-yl)oxy]-5-chlorophenyl}-3-phenylprop-2-yn-1-ol (12g)

The typical procedure for **12a** was followed and was isolated as a yellow oil (96%). The enantiomeric excess was determined by HPLC analysis and found to be 75% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm) Retention time: t_{major} 9.11 min. and t_{minor} 14.29 min.
$[\alpha]_D^{20}$ -2.2 (c= 6.9, $CHCl_3$).

(1*S*)-(+)-1-{2-[(3-methylbut-2-en-1-yl)oxy]-3,5-dichlorophenyl}-3-phenylprop-2-yn-1-ol (12i)

The typical procedure for **12a** was followed and was isolated as a waxy solid (99%). The enantiomeric excess was determined by HPLC analysis and found to be 90% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm) Retention time: t_{major} 11.38 min. and t_{minor} 6.35 min.
m.p. 86.6-87.3°C (from IMS)
$[\alpha]_D^{20}$ +14.3 (c= 1.4, $CHCl_3$).

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References

(1) Mann, A.; Muller, C.; Tyrrell, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1427.
(2) Nicholas, K.M. *Acc. Chem. Res.*,**1987**, 20, 207.
(3) Reviewed: Roxburgh, C.J.; *Synthesis*, **1996**, 3, 307.
(4) Tyrrell, E.; Millet, J.; Tesfa, K.H.. Asymmetric Synthesis with Chemical and Biological Methods, Aachen, **2005**, p226.
(5) Schreiber, S.L.; Klimas, M.T.; Sammakia, T. *J. Am. Chem. Soc.*, **1987**, 20, 207.
(6) Muehldorf, A.V.; Guzman-Perez, A.; Kluge, A.F. *Tetrahedron Lett.*, **1994**,35, 8755.
(7) Grove, D.D.; Corte, J.R.; Spencer, R.P.; Pauly, M.E.; Rath, N.P. *J. Chem. Soc., Chem. Commun.*, **1994**, 49.
(8) Using asymmetric hydroboration techniques: Corey, E.J.; Helal, C. J. *Tetrahedron Lett.*, **1995**,36, 9153. Parker, K.A.; Ledeboer, M.W. *J. Org. Chem.* **1996**, 61, 3214. Using transition metal catalysed hydrogenation see Matsumura,K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.*, **1997**, 119, 8738.
(9) Lu, G.; Li, Y-M.; Li, X-S.; Chan, A.S.C. *Coordination Chemistry Reviews*, **2005**, 249, 1736.
(10) Katritzky, A.R.; Meth-Cohn, O.; Rees, C.W. *Comprehensive Organic Functional Group Transformations*, Elsevier Sciences Ltd, **2005**, 1, 1.21

(11) Pu, L.; Yu, H-B. *Chem. Rev.*, **2001**, 101, 757.
(12) Watts, C.C.; Thoniyot, P.; Hirayama, L.C.; Romano, T.; Singaram,B. *Tetrahedron: Asymmetry*, **2005**, 16, 1829.
(13) (a) Frantz, D.E.; Fassler, R.; Carreira, E.M. *J. Am. Chem. Soc.*, **2000**, 122, 1806. (b) Anand, N. K.; Carreira, E.M. *J. Am. Chem. Soc.*, **2001**, 123, 9687. (c). Boyall, D.; Frantz, D.E.; Carreira, E.M. *Organic Letters*, **2002**, 4, 2605.
(14) (a) Lu, G.; Li, X.; Zhou, Z.; Chan, W.L. Chan, A.S.C. *Tetrahedron: Asymmetry*, **2001**, 12, 2147. (b) Li, Z.; Upahhyay, V.; DeCamp, A.E.; DiMichele, L.; Reider, P.J. *Synthesis*, **1999**, 1453.
(15) (a) Pizzuti, M.G.; Superchi, S. *Tetrahedron: Asymmetry*, **2005**, 16, 2263. (b) Kang, Y-f.; Wang, R.; Liu, L.; Da, C-s.; Yan, W-j.; Xu, Z-q. *Tetrahedron Lett.*, **2005**, 46, 863.
(16) Tyrrell, E.; Tillett, C. *Tetrahedron Lett.*, **1998**, 39, 9535.
(17) Dale, J.A.; Dull, D.; Mosher, H.S. *J. Org. Chem.*, **1969**, 34, 2543. Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.*, **1973**, 95, 512.
(18) The results from these studies will be disseminated at a later date (although see ref: 4).
(19) All compounds provided satisfactory spectral data that were consistent with the assigned structures. For succinctness we have limited the experimental section to a representative example of salicylaldehyde derivatives e.g. non-substituted, mono- and di-substituted and naphthyl derivatives. Optical rotation data and HPLC retention times are included for all relevant examples.