Approaches to quaternary carbon centres using organoboron chemistry

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Declaration

The work described herein is a presentation of the results of research carried out by the candidate, except where other author's results are duly acknowledged.

This work has not been submitted previously, nor is it being concurrently submitted, either in part or in full, to any other university in candidature for a degree.

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Prof. K. Smith   D. Heulyn Jones

(Supervisor)

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Date

Acknowledgements

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Lastly, I wish to thank my family and close friends for their love and support, and for helping me to unwind after a bad day in the lab. Diolch yn fawr iawn i chi gyd.

Abstract

The main focus of the work contained within this thesis was to explore the possible use of novel organoboron chemistry in generating quaternary carbon centres, with the ultimate aim of developing new routes for the asymmetric synthesis of chiral quaternary carbon centres.

Chapter 1 contains a general introduction to the literature of organoboron chemistry, focusing particularly on organoboron reactions that contain 1, 2 - boron to carbon migrations.

Chapters 2 and 3 contain attempts at generating tertiary alkyl groups bonded to boron in an asymmetric fashion. Chapter 2 specifically deals with attempts at designing a chiral version of the dichloromethyl methyl ether (DCME) reaction, giving disappointing results most probably due to the instability of the chiral analogue of DCME.

Chapter 3 focuses on attempts at designing a chiral version of the cyanidation reaction. Although the generation of tertiary alkyl groups next to boron was shown to be possible when using imidoyl chlorides as the acylating reagent for relatively unhindered trialkylboranes, alkene side-products predominated when using hindered trialkylboranes – which meant that the reaction was unlikely to become an efficient method for the asymmetric generation of tertiary alkyl groups bonded to boron.

Chapter 4 contains a detailed investigation into the migration of tertiary alkyl groups in the reaction between tertiary-alkyl boronic esters and (bromomethyl)lithium. As well as gaining a better understanding of the factors at work in this potentially highly important reaction, the reaction was applied to a number of highly hindered boronic esters.

Chapter 5 deals with attempts at tertiary alkyl group migration using 3-chloro-1-lithiopropyne, which were in general disappointing due to the apparent instability of the intermediate 'ate' complex.

Chapter 6 contains novel work on the migration of alkyl groups using the previously unreported 1-lithio-3-chloropropene organolithium reagent. The reaction was successfully applied to the migration of several alkyl groups (including tertiary), giving the corresponding 3-alkylprop-1-en-3-ols in good to excellent yields.

Abbreviations

APCI	Atmospheric Pressure Chemical Ionisation
app	apparent
aq	aqueous
Ar	unspecified aryl substituent
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
b.p.	boiling point
br	broad
Bu	butyl
Ch	cyclohexyl
Cp	cyclopentyl
d	doublet
DCM	dichloromethane
DCME	dichloromethyl methyl ether
DCTB	dicyclohexylthexylborane
dd	doubled doublet
ddd	doubled doubled doublet
decomp	decomposition
DEPT	Distortionless Enhancement by Polarization Transfer
DIB	(diisobutyl)-3-yl (*i.e.* 2,4,4-trimethylpent-3-yl)
DMF	*N*,*N*–dimethylformamide
DMSO	dimethyl sulfoxide
dt	doubled triplet
ee	enantiomeric excess
EI$^+$	electron impact
eq.	equivalent(s)
ES	electrospray
E.S.	experimental section
Et	ethyl
EWG	electron withdrawing group
g	gram(s)
GC	gas chromatography
h	hour(s)
HCA	hexachloroacetone
HPLC	High Performance/Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HV	High Vacuum
Hz	Hertz
IPA	isopropanol
iPr	isopropyl
IR	infra red
J	coupling constant (in Hz)
L	litre
LDA	lithium diisopropylamide

LiDBB	lithium-4,4-di-*tert*-butylbiphenyl radical anion
LiN	lithium naphthalene radical anion
lit.	literature
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
LR	low resolution
m	multiplet
Me	methyl
mg	milligram(s)
min	minute(s)
mL	millilitre(s)
mm	millimeter(s)
mmol	millimole(s)
m.p.	melting point
MS	mass spectrometry
n-BuLi	normal butyllithium
NMR	Nuclear Magnetic Resonance
pent	pentet
Ph	phenyl
ppm	parts per million
q	quartet
quat C	quaternary carbon
R	undefined group
rt	room temperature
sec	secondary
sept	septet
sex	sextet
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
tert	tertiary
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFEF	trifluoroethyl formate
Thexyl	2,3-dimethyl-2-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TPPO	triphenylphosphine oxide
UV	ultraviolet
VT	variable temperature

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Chapter 1: Literature review of general organoboron chemistry

1.1 Preparation of organoboranes - hydroboration

Since the original observation of the facile hydroboration of alkenes using diborane in ethereal solvents in 1956,[1] the chemistry of organoboranes has exploded into a rich and invaluable area within both organic and inorganic chemistry. The easy access to organoboranes *via* the hydroboration reaction made it possible to explore the chemistry of the organoboranes themselves, which turned out to be both vast and highly useful with regard to new methodology.[2,3]

The hydroboration reaction was first observed as a side-reaction when adding anhydrous aluminium chloride in an attempt to enhance the reductive capabilities of sodium borohydride.[1,4] Switching the Lewis acid to boron trifluoride made it possible to prepare solutions of organoboranes in diglyme. Borane·THF complex solutions were prepared in a similar fashion from diborane and THF, a reagent which is still used frequently to this day. Recently however, borane dimethyl sulfide complex is often the hydroborating reagent of choice as it can be bought at a much higher concentration, is much more stable than borane·THF complex, while it retains the former's reactivity.[5,6,7]

The hydroboration reaction itself is a concerted cis addition of the boron – hydrogen bond across a double or triple carbon – carbon bond *via* a four membered transition state. The concerted nature of the reaction explains the stereoselectivity observed in the reaction – for example during the hydroboration of 1-methylcyclohexene to form only one possible stereoisomer (Scheme 1.1).[8]

Scheme 1.1 Hydroboration of 1-methylcyclohexene *via* a cyclic 4-membered transition state
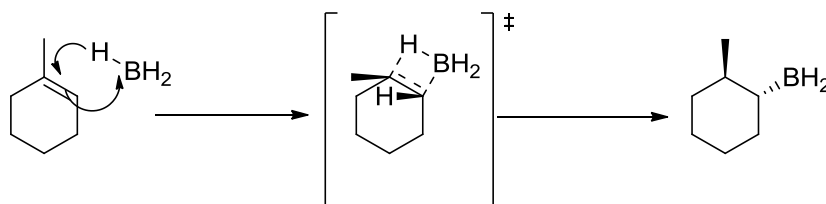
For unhindered alkenes, all three boron – hydrogen bonds are utilised, resulting in a trialkylborane. However, certain sterically hindered alkenes are slower to hydroborate, and through careful control of the reaction conditions the reaction can be made to stop at the mono (thexylborane (**1.3**)[9], DIB borane ((diisobutyl)-3-ylborane)[10] or dihydroboration stage (dicyclohexylborane (**1.1**)[9], disiamylborane (**1.2**)[9], 9-BBN (9-borabicyclo[3.3.1]nonane[11,12])) (Scheme 1.2). This effect has been used to generate 'mixed' trialkylboranes by using alkenes of different steric hindrance.[2]

Scheme 1.2 Examples of mono/dihydroboration of representative hindered alkenes
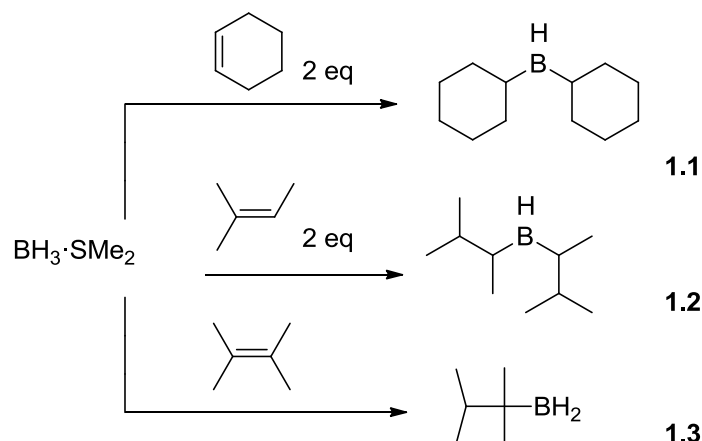
A vital aspect of the hydroboration reaction is that it is usually quite regioselective, with the boron atom being placed on the less hindered/less substituted side of the double/ triple bond, giving so called 'anti –Markovnikov' products. Hydroboration of simple primary alkenes places around 94% of the boron on the terminal position.[13] The first hydroboration is the least regioselective, with the selectivity increasing for the second and third hydroborations due to the increase in hindrance around the boron atom. This feature was taken advantage of, by using disiamylborane to increase the regioselectivity of the hydroboration reaction in the cases where using borane alone gave unsatisfactory regioselectivities (allyl chloride (**1.5**)[14], styrene (**1.6**)[15]). Another dialkylborane (9-BBN[11]) gave a similar increase in regioselectivity with the added benefit of being an easy to handle, relatively air stable solid (Table 1.1).
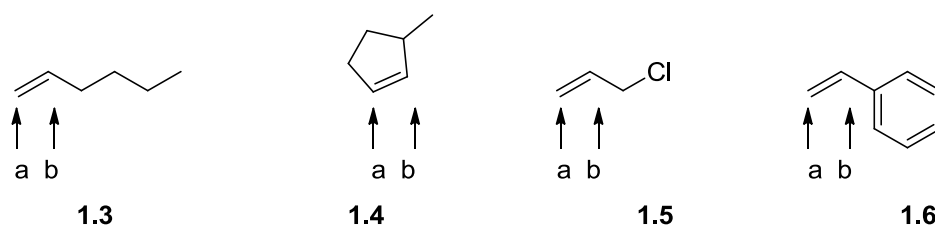
Table 1.1 Improvement in regioselectivity of the hydroboration reaction through use of hindered hydroborating reagents

	1.3		1.4	
	a	b	a	b
BH$_3$·THF	94	6	55	45
Sia$_2$BH (**1.2**)	99	1	60	40
9-BBN[a]	99.9	0.1	78	22
	1.5		1.6	
	a	b	a	b
BH$_3$·THF	60	40	81	19
Sia$_2$BH (**1.2**)	95	5	98	2
9-BBN	98.5	1.5	98.5	1.5

[a] 9-borabicyclo[3.3.1]nonane.

The hydroboration of alkynes, in general, is inherently a less clean reaction.[16,17] For terminal alkynes, a certain amount of dihydroboration product is seen, where the initial alkenylborane undergoes a further hydroboration. The hydroboration of internal alkynes proceeds to give predominantly the trialkenylborane, although the regioselectivity of the hydroboration is relatively low.

For the cases when a monoalkylborane or dialkylborane is the preferred product and the alkene is not sufficiently sterically hindered to stop after the first hydroboration step with a borane complex; mono and dihydroborating reagents possessing replaceable groups have been developed. Among dihydroborating reagents, both monochloroborane etherate[18] and monobromoborane dimethyl sulfide complex[19] undergo hydroboration with alkenes/alkynes to give the corresponding dialkyl/dialkenylhaloboranes.

Monohydroborating reagents developed include dibromoborane dimethyl sulfide complex[20,21], dichloroborane etherate[22], catecholborane[23,24] and pinacolborane.[25]

Dichloroborane ethereate suffers some practical difficulties of being unstable, and also of requiring stoichiometric quantities of boron trichloride in order to make the desired monoalkyldichloroborane product (simple hydroboration using dichloroborane etherate alone is a slow process, giving a mixture of mono and dialkyl hydroboration products) (Scheme 1.3a).

Dibromoborane dimethyl sulfide complex[20,21] is surprisingly a more efficient hydroborating reagent (due to the fact that dibromoborane forms a weaker complex with dimethyl sulfide relative to dichloroborane), with heating in dichloromethane for a few hours usually being sufficient for the hydroboration of both alkenes and alkynes. The hydroboration of alkynes using dibromoborane dimethyl sulfide complex is particularly useful as it overcomes the difficulties aforementioned when using borane·THF. The addition of water to the alkyl/alkenyldibromoborane products gives easy access to a large variety of boronic acids, which are particularly useful given the importance of the Suzuki cross-coupling reaction (Scheme 1.3b).[26]

Catecholborane,[23,24] easily prepared from catechol and borane·THF/borane dimethyl sulfide complex is an alternative to dibromoborane dimethyl sulfide complex. Both alkenes and alkynes can be hydroborated, although some heating is required (especially for alkenes). The alkyl/alkenylcatecholborane products are easily hydrolysed to give the corresponding boronic acids (Scheme 1.3c).

Scheme 1.3 Representative monohydroborating reagents
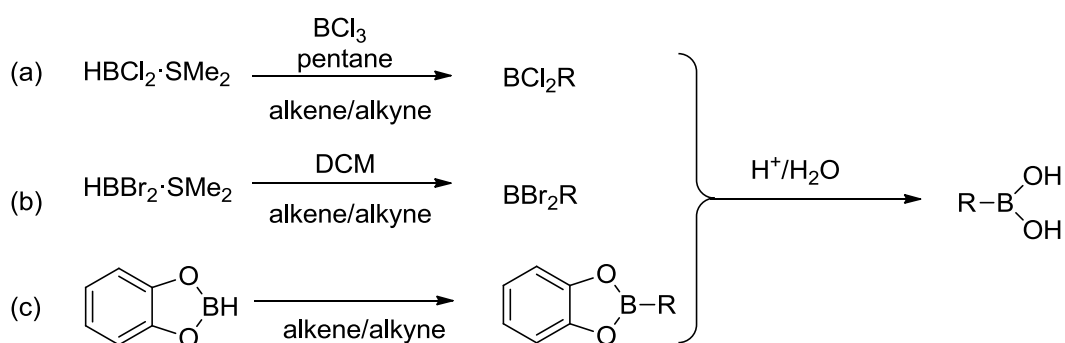
Pinacolborane[25] and other dialkoxyboranes are less reactive than most of the previously mentioned hydroborating reagents, requiring elevated temperatures to achieve hydroboration - although several catalysts (including dicyclohexylborane[27]) have been used to overcome

this. These hydroborating reagents give access to synthetically useful alkylboronic esters, without the need to use the alternative hydroboration/hydrolysis/reaction with a diol sequence.

The hydroboration reaction can even be performed asymmetrically by using optically active hydroborating reagents, such as diisopinocampheylborane[28,29] (of which both optically active forms are readily available).

1.2 Preparation of organoboranes – transmetallation

Hydroboration is not the only method of generating organoboranes; transmetallation is also a powerful method of preparing these useful compounds. Transmetallation is especially important for the preparation of certain organoboranes that cannot be prepared through means of hydroboration *e.g. tert*-butyl, Ph, Me, alkynyl boranes.

In the transmetallation method, an organometallic reagent is added to the boron compound, replacing one of the groups bonded to boron. It has been shown that using alkoxy groups on the boron compound has the advantage of being able to control the addition of the organometallic reagent (*i.e.* ensure that only one addition is made, and not unwanted multiple additions). Typically, a Grignard or organolithium reagent is added to a boron compound possessing an alkoxy group, forming the initial 'ate' complex. The final product is not usually obtained however, without addition of something to help dissociate the alkoxy group (usually an acid or Lewis acid) (*e.g.* Scheme 1.4).[30,31,32]

Scheme 1.4 Typical transmetallation sequences, providing access to new organoboranes

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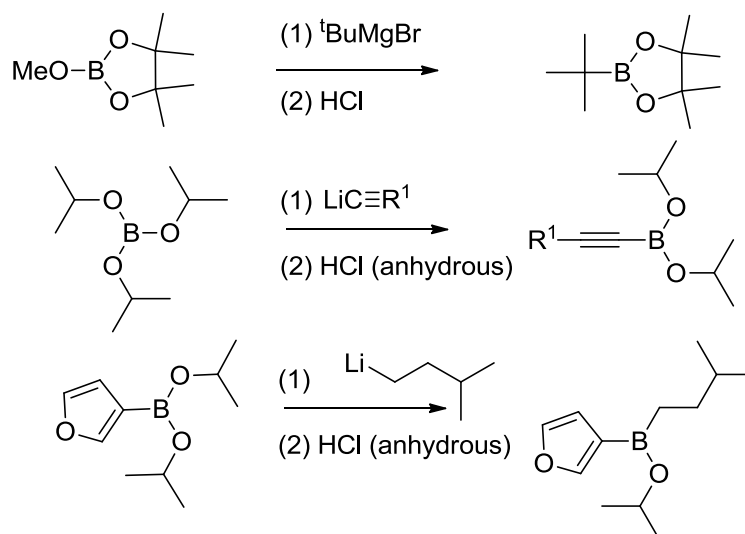
1.3 General reactions of organoboranes

Undoubtedly the most well-known reaction of organoboranes is the oxidation reaction, where oxygen takes the place of boron with retention of configuration to give the corresponding alcohol.[33] It is one of the most important reactions in an organic chemist's toolkit, and the transformation of an alkene to the 'anti –Markovnikov' alcohol is complementary to the oxymercuration-reduction reaction.[34]

The reaction is usually carried out using alkaline hydrogen peroxide, with yields being quantitative in almost all cases. Alkylboranes are transformed to the corresponding alcohols, while the oxidation of alkenylboranes gives either ketones or aldehydes depending on whether the original starting material was an internal or terminal alkyne respectively (Scheme 1.5).[35,36]

Scheme 1.5 Different outcomes of the oxidation reaction, dependant on the starting organoborane

$$BR^1_3 \xrightarrow{\text{NaOH, } H_2O_2} 3\ R^1OH$$
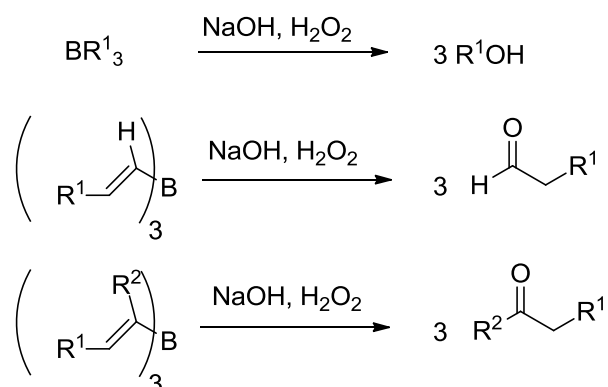
The hydroboration-oxidation reaction can be performed asymmetrically, by using a chiral hydroborating reagent such as mono/diisocampheylborane[37,38] to give enantiomerically enriched alcohols. The reaction is also used as a final step for most other organoborane reaction sequences, as it is a clean way of releasing the final product from the boron atom.

The oxidation of organoboranes is not the only reaction in which the boron atom can be replaced by another functional group with retention of configuration. Through the reaction of a trialkylborane with hydroxylamine-*O*-sulfonic acid, the boron atom can be replaced by a nitrogen atom to give an amine as the final product (Scheme 1.6a).[39,40] One drawback is that the reaction only uses two of the three available alkyl groups on the trialkylborane. Methyl groups seem to be non-migratatory in nature for this particular reaction, and so by using $RBMe_2$ the wastage of valuable alkyl groups can be avoided.

Scheme 1.6 Synthesis of primary and secondary amines
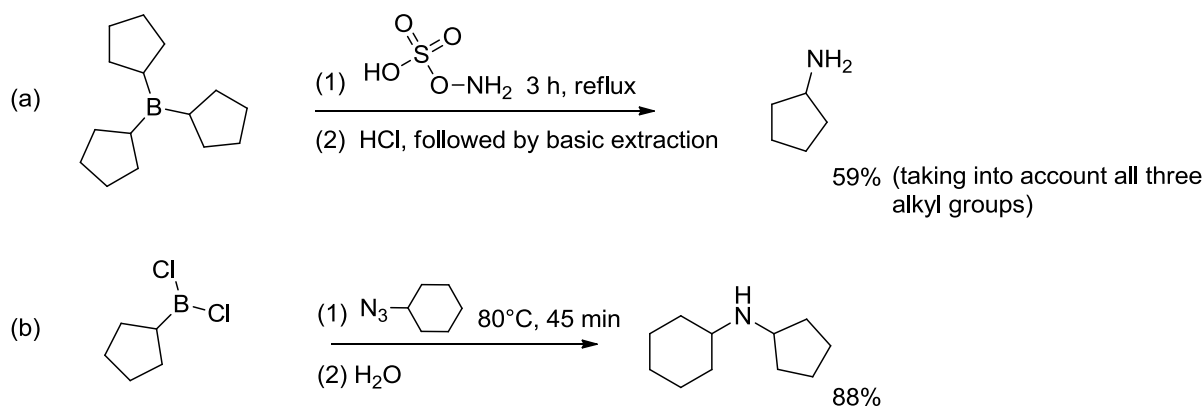
Secondary amines are accessible by the reaction of trialkylboranes,[41] dialkylchloroboranes[42] or alkyldichloroboranes[43] with organic azides, with the reaction proceeding with retention of configuration (Scheme 1.6b). Although less well explored as a synthetic route, trialkylamines

can also be synthesised as long as a free radical inhibitor is added to the reaction mixture[44], e.g. the reaction of tri-*n*-butylborane with chlorodimethylamine gives *n*-butyldimethylamine.

The boron atom can also be replaced (although with inversion), by a halogen. Organoboranes react with bromine/iodine in the presence of an alkali to give the corresponding halo-compound.[45,46] The reaction has a similar drawback to the amination reaction, in that only two of the three alkyl groups are sometimes utilised. However, by using nonreactive/'blocking groups' on the trialkylborane (such as disiamyl/9-BBN[47]), wastage of alkyl groups can be avoided.

Alkenyl boronic acids also react with halogens in a useful fashion, with the reaction with iodine/NaOH giving the *trans* iodoalkene[48] (retention of configuration), while reaction with bromine/NaOH gives the *cis* bromoalkene[49] (Scheme 1.7).

Scheme 1.7 Reaction of boronic acids with bromine/iodine
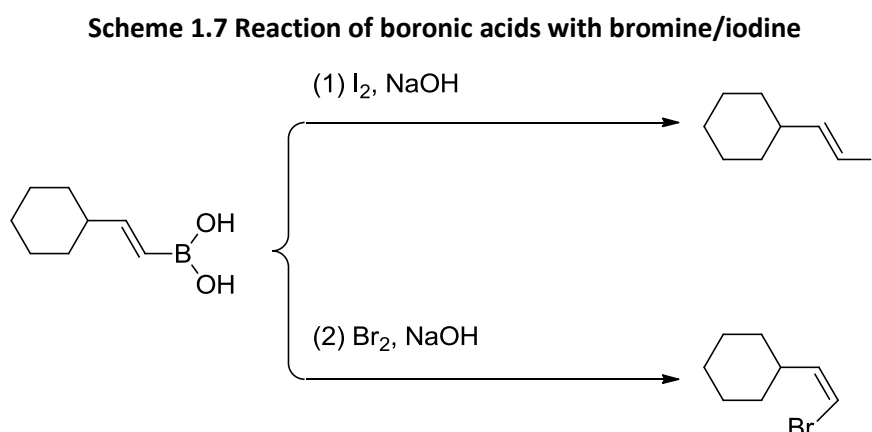
Although organoboranes are relatively unreactive towards water, they undergo a protonolysis reaction with carboxylic acids that proceeds with retention of configuration. Alkylboranes require relatively harsh conditions[50] (refluxing in propionic acid for a few hours), while alkenyl, alkynyl and allenic boranes are much more prone to protonolysis, reaction with acetic acid for few minutes at 0 °C usually being sufficient.[51,52] The hydroboration-protonolysis sequence therefore, is an alternative to the hydrogenation of an alkene (Scheme 1.8).[2,52]

Scheme 1.8 Protonolysis of alkyl and allenicboranes

(1) BH$_3$, diglyme 1 h, rt

(2) propionic acid, reflux 2 h

88%

(1) acetic acid 1 h, rt

77%
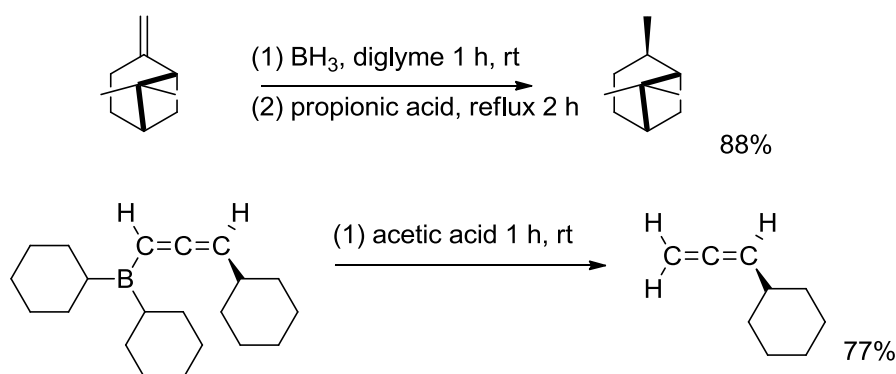
Allyl,[53] allenic[54] and propargylic organoboranes[55] have unique reactivity among organoboranes, undergoing a facile insertion reaction with aldehydes, ketones and imines.[56] The reaction seems to proceed through a 6-membered transition state (Scheme 1.9). For a triallylborane, the third insertion is a slow process[53] and so it is preferable to use allyldialkylboranes, with the alkyl groups being non-participating in nature (*e.g.* 9-BBN-allylboranes[57]).

Scheme 1.9 Mechanism of allylborane insertion reactions

insertion
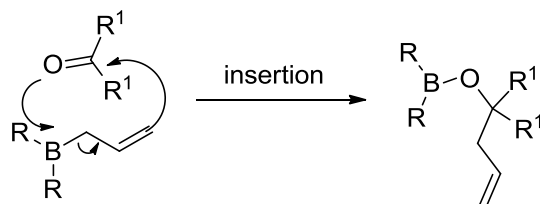
1.4 Carbon-carbon bond forming reactions involving organoboranes

1.41 Suzuki –Miyaura cross coupling reaction

One of the most important types of reactions in organic chemistry is the formation of new carbon-carbon bonds. Organoboron chemistry is full of such reactions. Perhaps the most famous of these reactions is the Suzuki-Miyaura cross coupling reaction.[26] Strictly speaking, it is the palladium catalyst that brings the two carbon chains together to form a new carbon-carbon bond in the reductive elimination step of the catalytic cycle. Even so, the organoboron reagent is an essential feature of this important reaction (Scheme 1.10). Boronic acids, boronic acid esters and organotrifluoroborate salts can all take part in the reaction with the last being particularly attractive due to their comparative stability.

Scheme 1.10 Catalytic cycle of a typical Suzuki-Miyaura cross coupling reaction
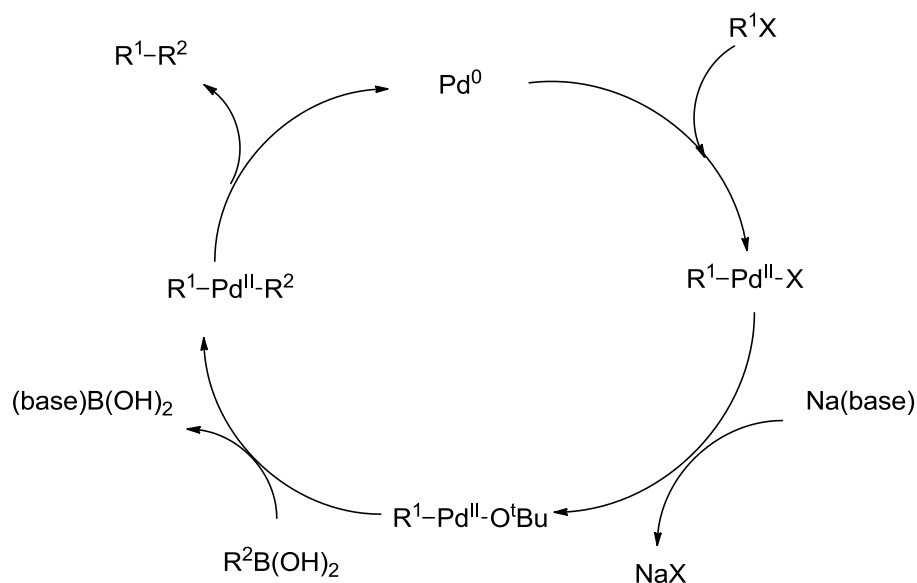
1.42 Addition of alkyl carbanions/carbanion equivalents to boron

Organoboron compounds themselves can bring two or more alkyl groups together to form new carbon-carbon bonds. Many of these reactions follow a general mechanism, whereby a carbanion/carbanion equivalent containing one or more possible leaving groups adds to the electrophilic boron atom of an organoboron compound forming a tetracoordinate 'ate' complex (Scheme 1.11). To relieve the negative charge, one of the alkyl groups attached to boron undergoes a 1,2-migration to the carbon of the carbanion, with loss of a leaving group.

Scheme 1.11 Typical mechanism for a 1,2-alkyl group migration of organoboron compounds
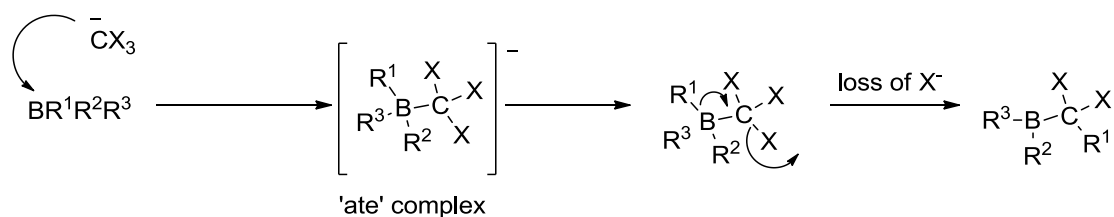
One of the first and best known of these reactions is the carbonylation reaction. Carbon monoxide acts as the role of the carbanion equivalent, forming an 'ate' complex with the trialkylborane. Depending on the reaction conditions, the reaction can be halted at one migration to give an aldehyde, left to migrate twice to give a ketone or be forced to migrate thrice to give a tertiary alcohol as the product (Scheme 1.12).

At a temperature of around a 100 – 125 °C, many trialkylboranes adsorb 1 mole of carbon monoxide, and upon alkaline hydrogen peroxide oxidation affords the corresponding tertiary alcohols in excellent yields.[58,59]

If the reaction is carried out in the presence of water, the reaction is halted after the second migration (by transforming the intermediate **1.7** after two migrations to a boraglycol (**1.8**)), and this intermediate can either be oxidised in the usual manner to give the corresponding ketone or hydrolysed with an alkali to give the secondary alcohol.[60] The use of thexylborane ensures there is no wastage of alkyl groups,[61] and also gives the opportunity to make 'mixed' ketones.

To get the single migration product, an active hydride reagent must be present.[62] Oxidation of the intermediate gives an aldehyde, while alkali hydrolysis gives a primary alcohol. 9-BBN can be utilised as a non-migrating blocking group, ensuring no wastage of alkyl groups.[63]

Scheme 1.12 Mechanism of the carbonylation reaction
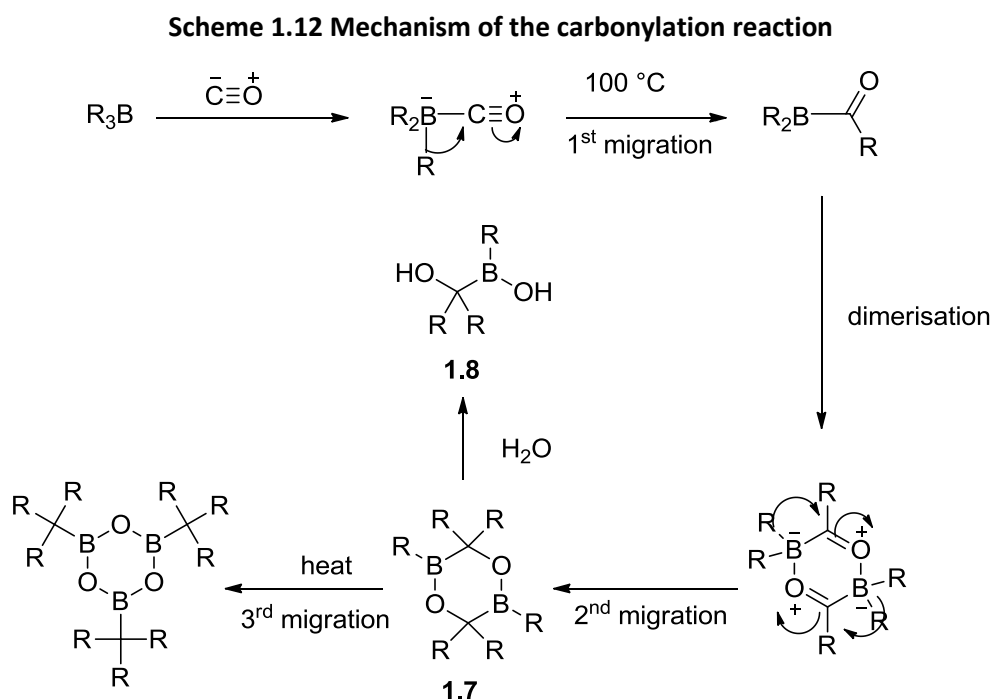
Carbonylation has two sister reactions – the cyanidation reaction[64] and the DCME reaction.[65] The cyanidation reaction involves the addition of a cyanide anion to a trialkylborane, giving the expected 'ate' complex.[64, 66] An electrophilic reagent (such as trifluoroacetic anhydride (TFAA), benzoyl chloride, acetyl chloride and imidoyl chlorides) must be added to induce migrations, and in the case of TFAA the amount added and the reaction conditions determine

whether two or three migrations take place (Scheme 1.13). Although the synthesis of very hindered tertiary alcohols using this methodology suffers from some disadvantages,[66] the mild conditions make it an attractive method of preparing ketones. As with the carbonylation reaction, the thexyl group can be used as a non-migrating blocking group.[67]

Scheme 1.13 Mechanism of the cyanidation reaction of a trialkylborane
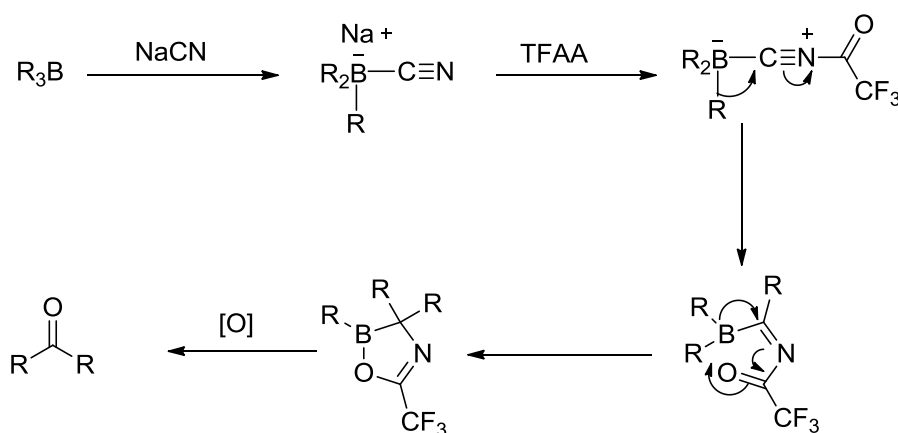
Trialkylboranes have been shown to react with a variety of haloforms in the presence of a hindered base such as LiOC(Et)$_3$, giving the corresponding tertiary alcohol as the product.[65] Although chlordifluoromethane initially gave the most promising results with tri-*n*-butylborane, problems with the oxidation of more hindered examples[68] meant that dichloromethyl methyl ether (DCME) became the reagent of choice for this transformation (DCME reaction).[69,70] The DCME reagent is deprotonated with a hindered base, and the anion formed adds to a trialkylborane to give the 'ate' complex. Three migrations then occur under very mild conditions (typically 15 min at 0 °C), with the two chlorides and methoxide acting as leaving groups to give, after oxidation, the tertiary alcohol (Scheme 1.14a). Due to the mild conditions of the reaction, this is usually the reaction of choice for the synthesis of tertiary alcohols using organoboranes – working even for highly hindered trialkylboranes[70] (e.g thexylcyclohexylcyclopentylborane).

The DCME reaction can be manipulated to give the doubly migrated ketone as a product, as long as a dialkylalkoxyborane[71] or dialkylchloroborane[72] is employed. The reaction can be carried out asymmetrically by using optically pure alkyldialkoxyboron compounds (boronic esters), reacting them with lithium acetylides or alkyllithiums and then carrying out the DCME reaction on the diorganylalkoxy intermediate (Scheme 1.14b).[73, 74] Lithium *tert-*

butoxide has been shown to be the base of choice for two and one migrations in the DCME reaction (Scheme 1.14b, c), as it gives comparable results with LiOC(Et)$_3$, while being easier to separate from the product due to *tert*-butanol's greater water solubility.

A single migration to give a carboxylic acid product has also been achieved for the DCME reaction by using *B*-alkyl-9oxa-10-borabicyclo[3.3.2]decanes (Scheme 1.14c).[7] The resistance of the *B*-alkyl-9oxa-10-borabicyclo[3.3.2]decanes to undergo a second migration to give the ketone product has been attributed to the large energy barrier needed for further ring expansion.

Scheme 1.14 Various versions of the DCME reaction
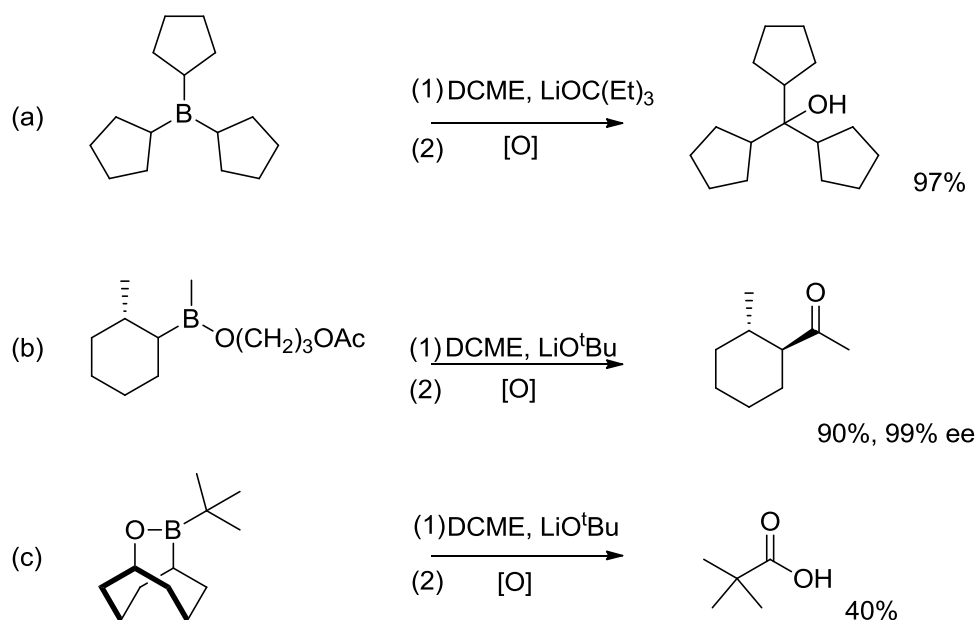
Tris(phenylthio)methyllithium is an alternative reagent to DCME, giving two spontaneous migrations and with mercury(II) chloride promoting a third migration to give ketones and tertiary alcohols respectively.[76] The reaction is somewhat unusual in that it seems that tertiary alkyl groups migrate in preference to primary alkyl groups for at least one of the first two migrations, thus opening up a route to otherwise difficult to synthesise ketones (Scheme 1.15). Although the reaction is sometimes tolerant of very hindered trialkylboranes (tricyclohexylborane gives a yield of 83% of tertiary alcohol), it is a little erratic with regard to hindrance around the boron (bis-(2-methylcyclohexyl)-*n*-hexylborane failing to react whatsoever).

13

Scheme 1.15 Unusual migration characteristics using tris(phenylthio)methyllithium
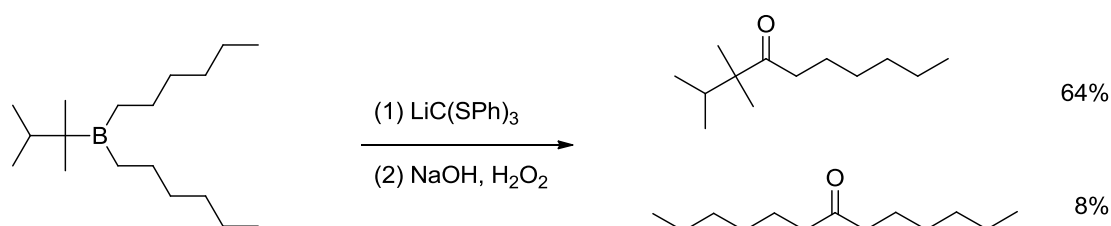
Yet another alternative is the less well-explored reaction of dialkylchloroboranes with lithium aldimines.[77] The reaction is slightly different to those aforementioned, as one of the alkyl groups is derived from the carbanion itself. The addition of the anion, followed by thioglycolic acid and alkaline hydrogen peroxide oxidation gives the ketone arising from a single migration. However, addition of sodium hydroxide and heating induces a second migration to give the corresponding tertiary alcohol. Trialkylboranes also react with lithium aldimines, and undergo two migrations to give the corresponding tertiary alcohol without the need to add sodium hydroxide.

Trialkylboranes react with 1-lithio-1,3-benzodithioles, to give either secondary or tertiary alcohols in good yield (the addition of HgCl$_2$ is necessary to induce the second migration).[78,79] The reaction is similar to that of lithium aldimines, in that one of the alkyl groups incorporated in the end product is derived from the carbanion equivalent. The use of thexyl as a blocking group to avoid wastage of alkyl groups is only partially successful in this case (Scheme 1.16a). In fact, when using methyl fluorosulfonate to induce the second migration, the thexyl group migrates in preference to an *n*-octyl group (Scheme 1.16b).

Scheme 1.16 Reaction of trialkylboranes with 1-lithio-1,3-benzodithioles
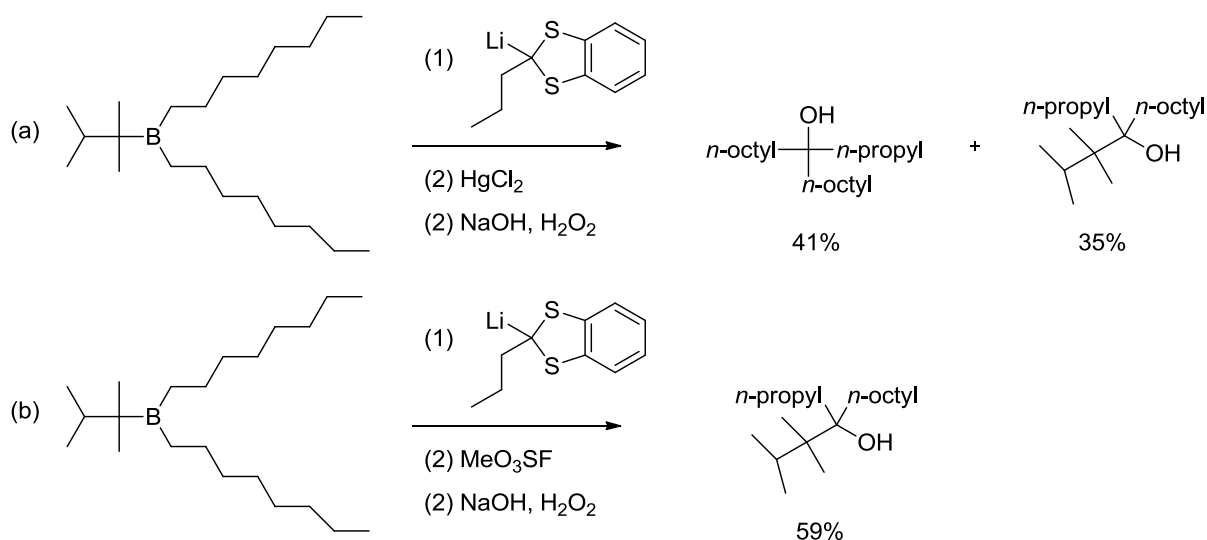
The Matteson reaction uses dichloromethyllithium as the anion, and this possesses two leaving groups. The anion reacts with trialkylboranes to give the expected secondary alcohols, although the reaction is very sensitive to the steric bulk of the alkyl groups - hindered secondary alcohols are not accessible *via* this method (Scheme 1.17a).[80] The anion also reacts with dialkylborinic esters in the same way to give secondary alcohols as the products, with hindered secondary alcohols being synthesised in good yields (Scheme 1.17b).[80]

Scheme 1.17 Reaction of trialkylboranes and dialkylborinic esters with dichloromethyllithium
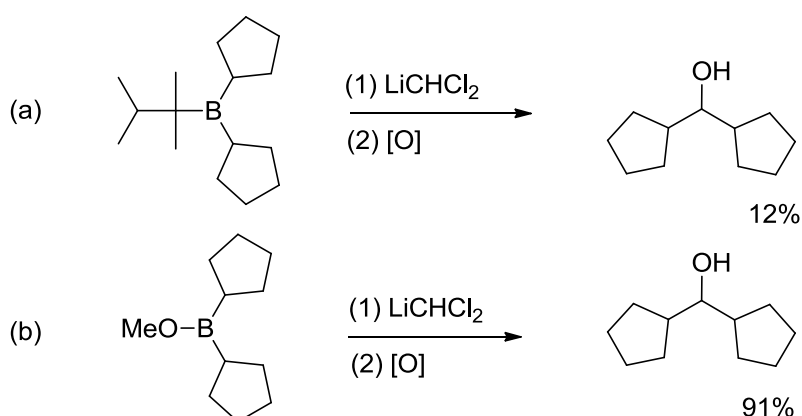
Dialkoxyalkylboranes also react with the dichloromethyl lithium anion to give α-chloroalkyldialkoxyboranes which can either be isolated,[81] reduced by potassium triisopropoxyhydroborate to replace the chlorine atom with a hydrogen atom,[82] or reacted with a Grignard/organolithium reagent to induce a further alkyl group migration with

inversion - with the oxidation of the intermediate giving a secondary alcohol (Scheme 1.18).[83] The displacement reaction using a Grignard/organolithium reagent can be carried out asymmetrically using chiral diols such as pinanediol and zinc chloride to give the chiral organoborane intermediate with ees of up to 99%.[84]

Scheme 1.18 Reaction of dichloromethyllithium with dialkoxyalkylborane, with subsequent reactions of the intermediate formed
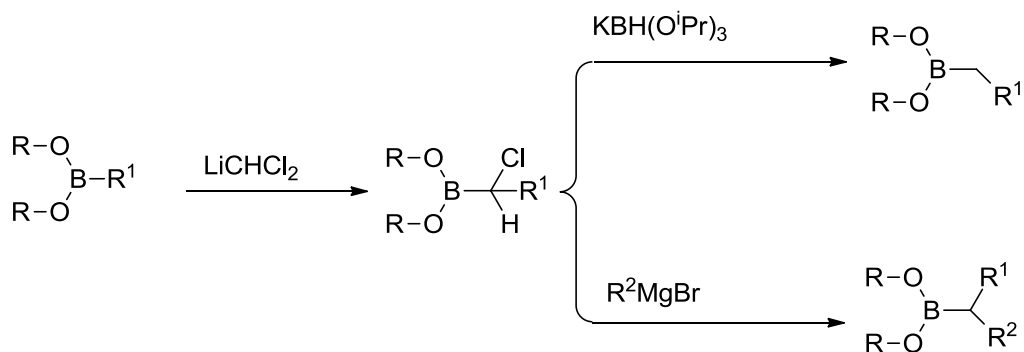
In a similar reaction, trichloromethyllithium reacts with alkyldithioboronic esters.[85] Three migrations occur, with both the alkyl group and the sulfur groups migrating to give either a carboxylic acid (on oxidative work-up), or 2-alkyl-1,3-dithiolanes (on alkaline hydrolysis) (Scheme 1.19). Yields were good, especially so for hindered alkyl groups, and the two sulfur groups meant that no wastage of alkyl groups occurred. The 2-alkyl-1,3-dithiolanes could be quantitatively dethioacetalized by treatment with red HgO and trifluoroborane diethyl etherate to give the corresponding aldehydes.

Scheme 1.19 Reaction of trichloromethyllithium with alkyldithioboronic esters
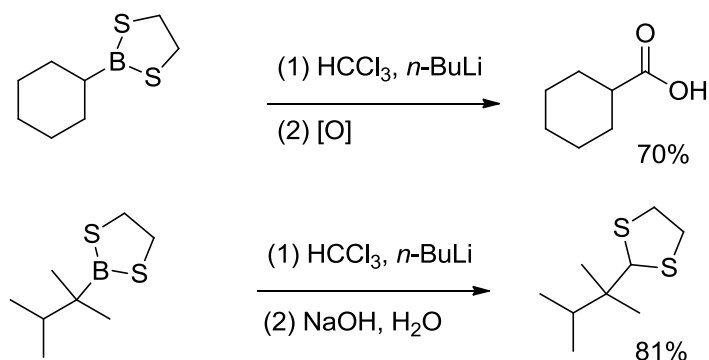
Carbanions bearing a single leaving group also react with organoboranes in a similar way, giving rise to a single alkyl group migration. Matteson showed that boronic esters react with

in-situ prepared chloromethyllithium (*n*-BuLi/chloroiodomethane) to give the homologated boronic esters (Scheme 1.20a).[86]

Further study of this reaction showed that boronic esters also react with chloromethyllithium (bromochloromethane/*n*-BuLi) or with dichloromethyllithium (dichloromethane/LDA) followed by reduction of the intermediate with potassium triisopropoxyhydroborate to give the homologated boronic esters in excellent yields for primary and secondary alkyl groups (Scheme 1.20b).[87] The yields for tertiary-alkylboronic esters were substantially lower (thexylboronic esters giving around 40% yield for both methods mentioned above).

Boronic esters react with *in-situ* prepared bromomethyllithium (dibromomethane/*n*-BuLi) in much the same way to give homologated boronic esters, which upon oxidation give the corresponding primary alcohol (Scheme 1.20c).[88] A more detailed study on this reaction showed that iodo, bromo and chloromethyllithium react with a variety of boronic esters, and that the use of bromomethyllithium gives a slight increase in yield for hindered alkyl groups compared to chloro and iodomethyllithium.[89]

Scheme 1.20 Various methods for the one carbon homologation of boronic esters

(a) BrClCH$_2$, *n*-BuLi → 90%

(b) (1) CH$_2$Cl$_2$, LDA / (2) KIPBH → 89%

(c) (1) CH$_2$Br$_2$, *n*-BuLi / (2) [O] → 66%
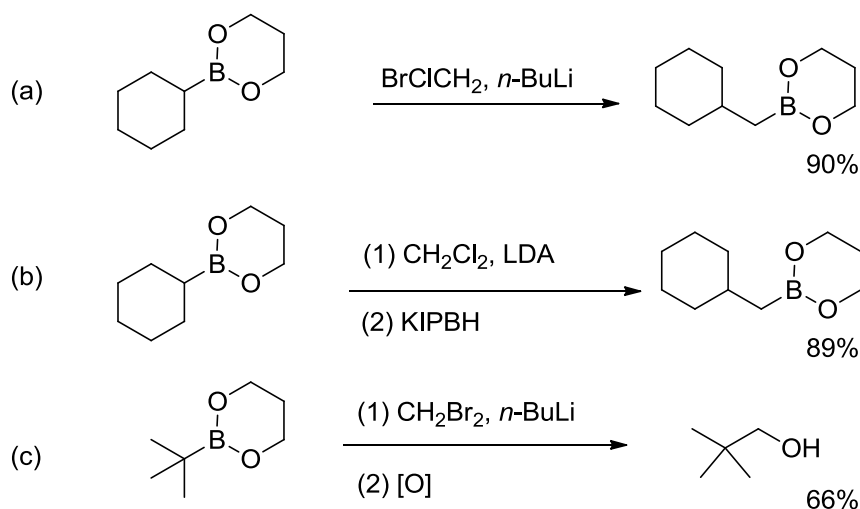
Another approach to this type of reaction is to have a bromine α to the boron of a boronic ester starting material, with a Grignard/organolithium reagent then added to induce alkyl group migration (Scheme 1.21).[90] Primary, secondary and alkenyl organometallic reagents migrate effectively to give the product boronic esters in excellent yields. However, the

addition of tertiary alkyl organometallic reagents to the α-bromo boronic esters led to significantly reduced yields.

Scheme 1.21 Reaction of α-bromoalkyl boronic esters with organometallic reagents
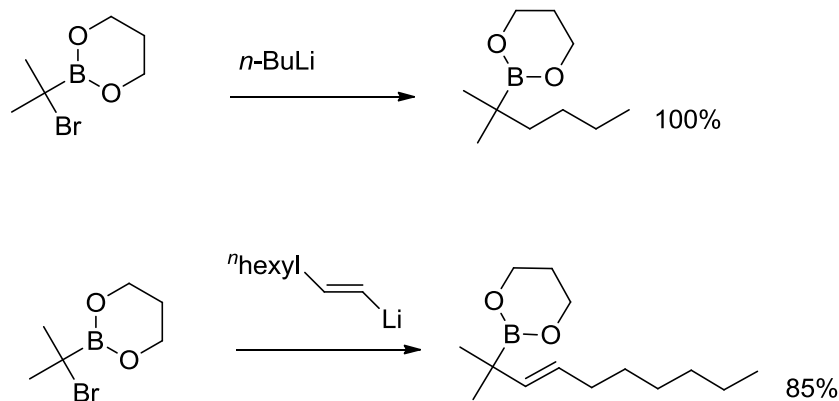
More recently, it has been shown that optically pure carbamates (derived from optically pure secondary alcohols) with an acidic proton can be deprotonated with *s*-Buli, and the anion formed adds to either trialkylboranes or alkylboronic esters.[91] The resulting 'ate' complex then rearranges, giving either the *tert*-alkyldialkylborane or *tert*-alkylboronic ester. Oxidation of these organoborane intermediates gave the corresponding chiral tertiary alcohols in high yields and excellent ees. Unexpectedly, the use of alkylboronic esters meant the reaction proceeded with retention of configuration, while the use of trialkylboranes proceeded with inversion – thus both enantiomers of the chiral tertiary group on boron could be made from one optically pure carbamate (Scheme 1.22). One drawback of this reaction however, is the need for an acidic proton in the carbamate starting material in order to produce the carbanion.

Scheme 1.22 Reaction of lithiated carbamates with trialkylboranes/alkylboronic esters
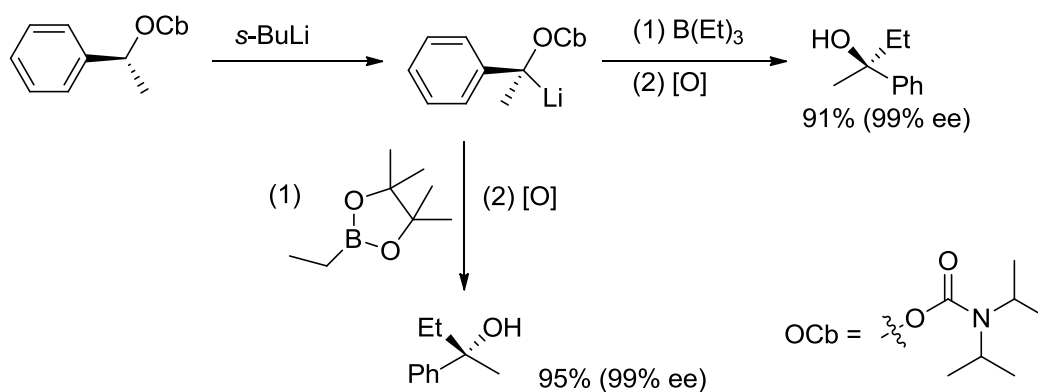
1.43 Addition of alkenyl carbanions/carbanion equivalents to boron

Alkenyl and alkynyl carbanions possessing leaving groups can also react with organoboranes in a similar manner to the alkyl carbanions discussed in the above section.

Both isopropenyllithium[92] and vinylmagnesium bromide[93] react with trialkylboranes, with the addition of iodine resulting in an alkyl group migration to give the substituted alkene as the product (Scheme 1.23). The use of 9-BBN alkylboranes circumvents the problem of alkyl group wastage.[92]

Scheme 1.23 Reaction of isopropenyllithium with trialkylboranes and iodine
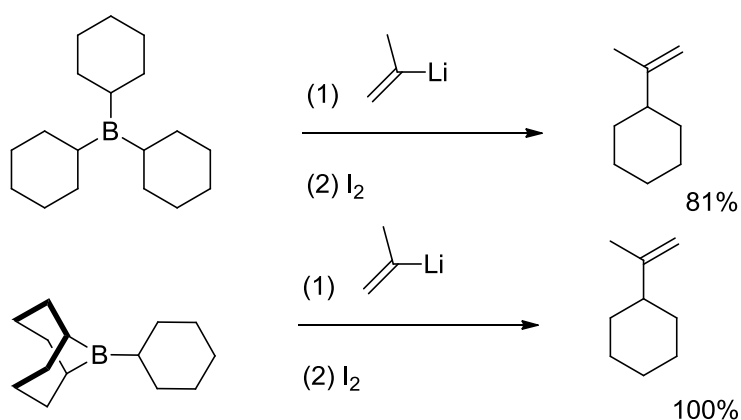
The alkenyllithium compounds can be prepared *in situ* from the iodoalkene and *n*-BuLi, and then the trialkylborane added to form the 'ate' complex, with the addition of iodine facilitating the migration itself. The reaction is general, with a range of trialkylboranes and starting iodoalkenes giving good to excellent yields of the corresponding alkenes.[94]

Alkenyllithium reagents also add to alkylboronic esters, with the addition of iodine inducing the expected migration (Scheme 1.24).[95]

Scheme 1.24. Reaction of alkenyllithium compounds with alkylboronic esters and iodine
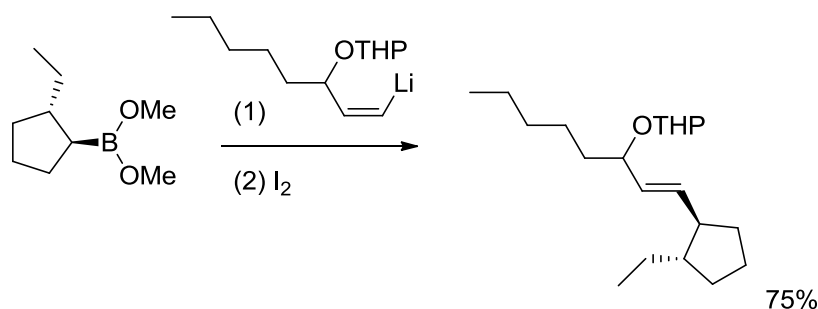
Another method for alkenyl group transfer from boron to carbon is by the Zweifel olefin synthesis, although in this case the alkenyl group is not added as an alkenyl carbanion. In the *cis* Zweifel olefin synthesis, an alkyne is hydroborated with a dialkylborane to give a dialkylalkenylborane.[96] Sodium hydroxide is added to form the 'ate' complex, and iodine to induce the migration of one of the alkyl groups to give the *cis* alkene product (Scheme 1.25a). Unfortunately, the wastage of one of the alkyl groups cannot be overcome by the use of thexylalkylboranes.[97]

The Zweifel *trans* olefin synthesis involves a slight modification, in which a bromo/iodoalkyne is hydroborated with a dialkylborane.[98] Addition of sodium methoxide forms the 'ate' complex, with one of the alkyl groups migrating and displacing the halide leaving group to give the corresponding *trans* alkenylalkylalkoxyboron compound, which upon protonolysis releases the *trans* alkene (Scheme 1.25b). In this case, the use of the thexyl group as a blocking group is successful.[99]

Scheme 1.25 *Cis* and *trans* Zweifel olefin syntheses
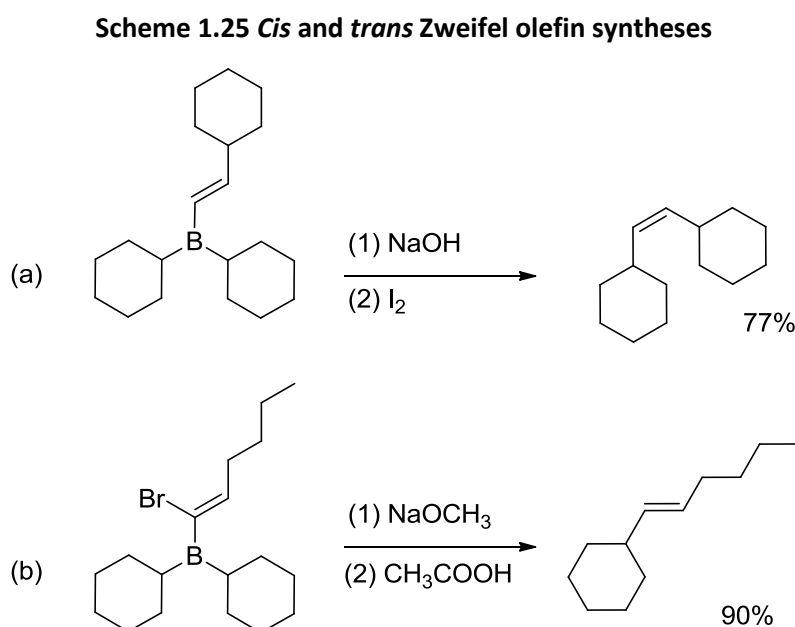
1.44 Addition of alkynyl carbanions/carbanion equivalents to boron

Trialkylboranes react with alkynyllithium reagents in a similar manner as mentioned above for alkenyllithium reagents, although the addition of iodine to such 'ate' complexes gives an alkyne as the product (Scheme 1.26).[100,101] Attempts at limiting the wastage of alkyl groups

through the use of blocking groups (such as 9-BBN, and dicyclohexyl), and dialkylalkoxyboranes has given mixed results.[102]

Scheme 1.26 Reaction of alkynyl lithium reagents with trialkylborane

95%
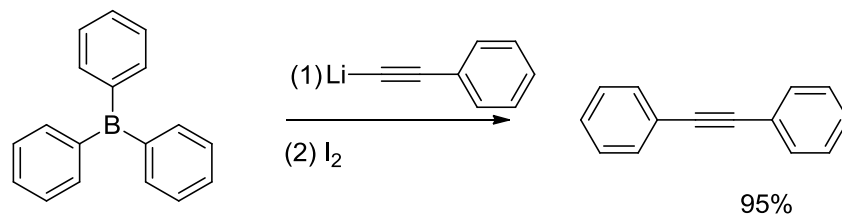
Trialkylboranes also react with lithiated propargyl chloride, which upon migration give the corresponding allenic boranes (Scheme 1.27a).[52] These allenic boranes have been shown to be versatile intermediates. The allenic boranes themselves are prone to undergoing a rearrangement reaction to place the more hindered alkyl group further away from boron (Scheme 1.27b). Both the initial allenic borane and its rearranged analogue can undergo a number of reactions (protonolysis to give the free allene[52], or reaction with aldehydes or ketones[54]) (Scheme 1.27b).

Scheme 1.27 Reaction of lithiated propargyl chloride with trialkylboranes, and subsequent reactions of the intermediate allenic boranes

(a)

75%

(b)
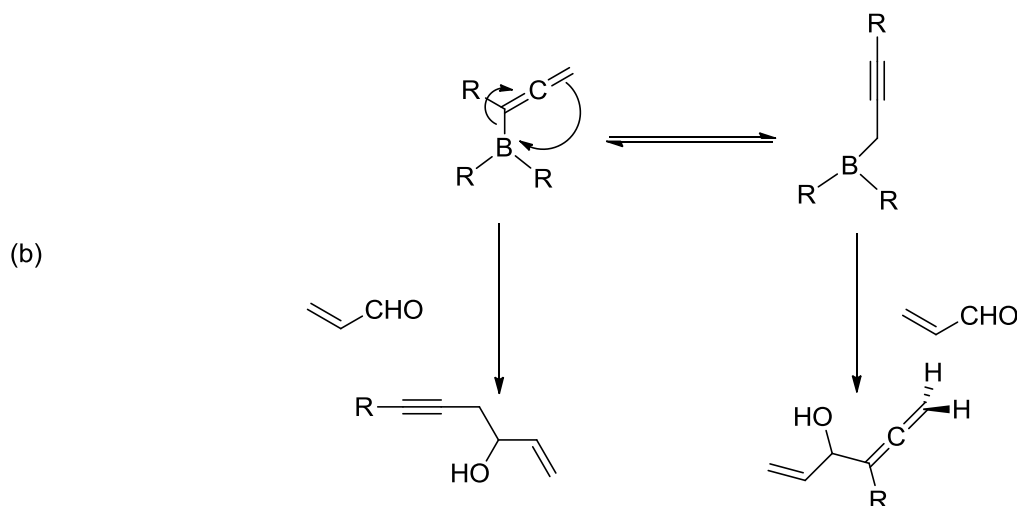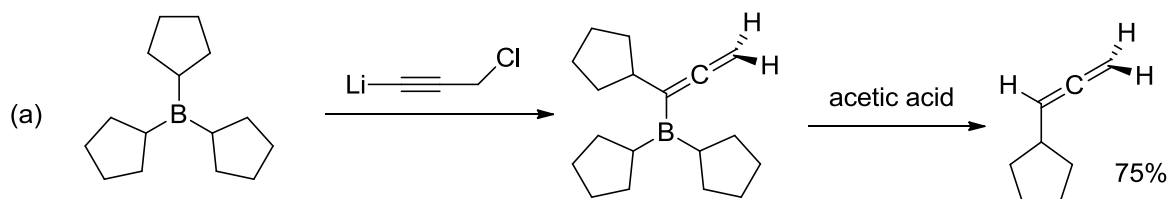
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Chapter 2: Attempts at designing a chiral version of the DCME reaction

2.1 Aims and introduction

The overall goal of the research undertaken in this thesis is to explore the possible use of organoboron chemistry in generating quaternary carbon centres, with the ultimate aim of developing new routes for the asymmetric synthesis of chiral quaternary carbon centres. The research can be divided into two distinct parts – developing a route for the asymmetric synthesis of tertiary groups bonded to boron, and secondly investigating an efficient method for the migration of tertiary groups from boron to carbon.

One efficient way of generating tertiary alkyl groups bonded to boron is by using the DCME reaction mentioned in the first chapter review.[1,2,3] The DCME reaction brings together three (possibly different) alkyl groups to generate a tertiary alkyl group, which in principle can be a chiral tertiary alkyl group bonded to boron. We envisaged that replacement of the methoxy group in the starting material α,α-dichloromethyl methyl ether (DCME) by a chiral alkoxy group would allow the reaction to be carried out asymmetrically in the event that three different alkyl groups were present in the starting trialkylborane (Scheme 2.1).

Scheme 2.1 Envisaged pathway for an asymmetric version of the DCME reaction
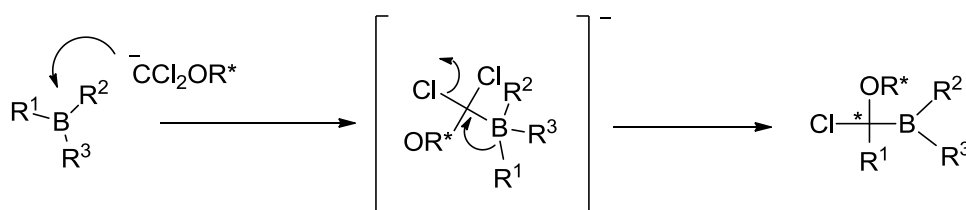
The DCME reaction involves three boron-carbon migrations, with presumably chloride anion being the first of three leaving groups. In that event, if a mixed trialkylborane is used, then the first migration will be the step that generates a chiral centre next to boron. A chiral alkoxy group in the DCME starting material *should* influence this critical first migration, making the process for making one enantiomer more favoured than the other. The subsequent two boron-carbon migrations should occur with control of the configuration at the migrating terminus, thus giving a diastereotopically enriched chiral tertiary alkyl group bonded to boron.

The result of such a reaction could be checked by oxidising the tertiary group next to boron to give the corresponding tertiary alcohol, and then measuring its ee either by reaction with Mosher's acid chloride or more conveniently by HPLC analysis using a chiral column. If good enough stereoselectivity is realised, then the boron compound obtained following completion of the DCME reaction could be taken to the final step (Scheme 2.2). Migration of the enantiomerically enriched tertiary alkyl group (e.g. through the bromomethyllithium homologation mentioned in the Chapter 1 review) would yield the desired chiral quaternary carbon centre.

Scheme 2.2 Intended route for the generation of chiral quaternary carbon centres using novel organoboron chemistry
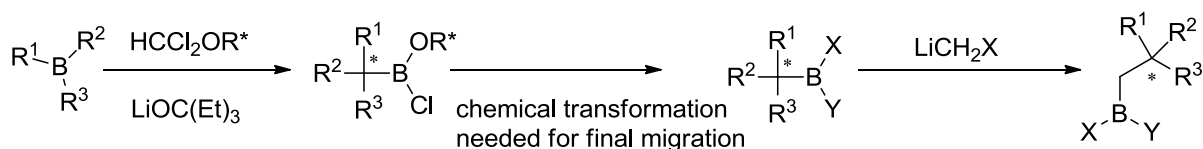
2.2 Results and discussion

2.21 DCME test reactions

The deprotonation of α,α-dichloromethyl methyl ether in the DCME reaction is traditionally accomplished by the addition of lithium triethylcarboxide (**2.1**) (prepared by the addition of *n*-BuLi to 3-ethyl-3-pentanol). The base's sterically hindered nature dissuades it from adding directly to the trialkylborane (which is also present in the reaction mixture) in preference to deprotonating DCME itself (Scheme 2.3).

Scheme 2.3 Role of lithium triethylcarboxide (2.1) in the DCME reaction
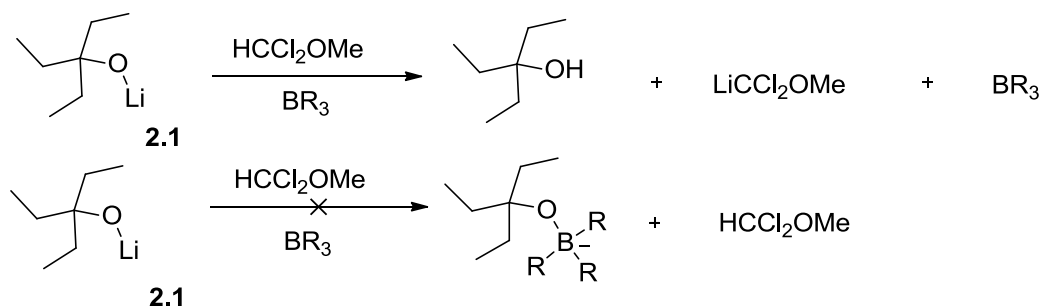
One disadvantage of using lithium triethylcarboxide (**2.1**) as the base in the reaction is that the protonated base (3-ethyl-3-pentanol) has to be separated from the desired product following work-up (which is often non-trivial as the products from the DCME-oxidation

reaction are also tertiary alcohols). Therefore, it was decided to complete a few test reactions to check both that all was well with the reagents/procedures and to search for an alternative hindered base that might be easier to separate from the reaction products.

Two trialkylboranes were chosen for the small study – tricyclopentylborane and tri-*n*-octylborane, along with three hindered bases – lithium tetramethylpiperidide (LiTMP), lithium *tert*-butoxide and the regular base lithium triethylcarboxide (**2.1**). Tricyclopentylborane and tri-*n*-octylborane were prepared by literature procedures[4,5] by the reaction of the corresponding alkenes with borane·THF, while the bases were prepared by the addition of *n*-BuLi to TMP and 3-ethyl-3-pentanol (in the case of lithium *tert*-butoxide a solution in dry THF was purchased). The reaction of the trialkylboranes with DCME/hindered base, followed by oxidation gave the corresponding tertiary alcohols, which were purified by column chromatography on neutral alumina (Scheme 2.4). The products of these reactions are known,[6,7] but their structures were confirmed by full characterisation (E.S. 2.32a, 2.32b). Once a pure sample of the product was obtained, so that its GC response factor with respect to a hydrocarbon standard (tetradecane) could be determined, the reaction was followed by GC analysis thereafter.

Scheme 2.4 Synthesis and reaction of tricyclopentylborane under DCME conditions to give tricyclopentylmethanol (2.2)

$$BH_3 \cdot THF \xrightarrow[\text{3 h, rt}]{\text{(3 eq)}} \quad B \xrightarrow[\substack{\text{(2) NaOH, } H_2O_2 \\ \text{3 h, 50 °C}}]{\substack{\text{(1) DCME, LiOC(Et)}_3 \\ \text{30 min, 0 °C}}} \quad OH$$

2.2 72%[a]
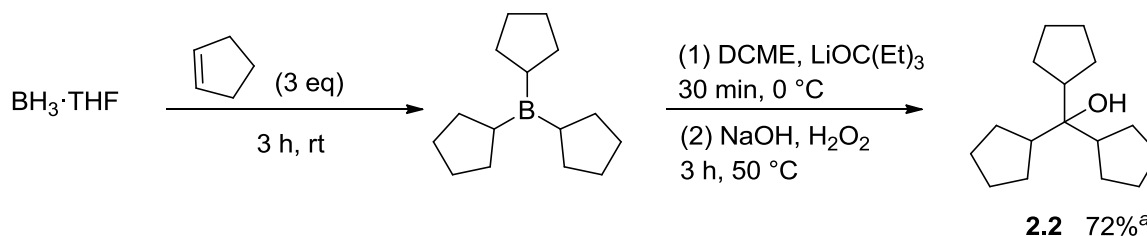
[a] GC yield relative to internal standard.

Lithium triethylcarboxide (**2.1**) performed well in the DCME reaction of both tricyclopentylborane and tri-*n*-octylborane, although the yields were lower than those for the same/closely related examples in the literature (97% by GC for tricyclopentylborane and 94% by GC for tri-*n*-butylborane[2]) (Table 2.1). It is probable that a portion of the lowering in yield compared to the literature is due to the fact that these reactions were completed on a 5 mmol scale, while those reported in the literature were completed on a 50 mmol scale. It is also possible that a lowering in the concentration of the borane.THF complex or *n*-BuLi used could account for some of this lowering in yield.

LiTMP gave lower yields for both trialkylboranes relative to lithium triethylcarboxide, although the base could be separated from the product without the need for column chromatography by acidification of the aqueous phase during extraction. The use of two equivalents of LiTMP and DCME did improve matters for tri-*n*-octylborane, and so this stoichiometry was used for the subsequent reactions presented in Table 1. This increase in yield when a larger amount of LiTMP/DCME is used could be due to a number of factors - *e.g.* the concentration of *n*-BuLi was lower than estimated or that the base is used up in a process other than its role in the DCME reaction.

Lithium *tert*-butoxide gave slightly lower yields relative to lithium triethylcarboxide (even though two equivalents of both base and DCME were used), which is consistent with reactions reported in the literature.[2]

The importance of having a sterically hindered base was demonstrated by carrying out a reaction where lithium triethylcarboxide was added to tri-*n*-octylborane, followed by DCME. The yield of tri-*n*-octylmethanol (**2.3**) for this reaction dropped to 35% (as compared to 72%), indicating that even the highly hindered base triethylcarboxide (**2.1**) will complex to trialkylboranes with detrimental results to the DCME reaction.

Table 2.1 DCME reaction of tricyclopentylborane and tri-*n*-octylborane with various hindered bases

Product	Base/DCME[a] equivalents used	LiTMP[b]	Li^{t}BuO	LiOC(Et)$_3$
tri-*n*-octylmethanol (**2.3**)	1.0	30% (isolated)	-	72% by GC
	2.0	66% (isolated)	59% by GC	-
tricyclopentylmethanol (**2.2**)	1.0	-	-	72% by GC
	2.0	48% by GC	57% by GC	-

^{a} α,α-Dichloromethyl methyl ether. ^{b} Lithium tetramethylpiperidide.

Two final reactions were carried out in an attempt to generate the DCME anion *ex-situ* before the addition of the trialkylborane. If successful, this would negate the need to use such sterically hindered bases and perhaps make LiTMP or some other lithium amide the base of choice. However, both attempts (one at 0 ºC, and one at -78 ºC) failed to give any product

whatsoever, highlighting the unstable nature of the anion of DCME. The decision was therefore taken to use lithium triethylcarboxide (**2.1**) in all further DCME reactions.

2.22 Synthesis of a model chiral tertiary alcohol

To ascertain whether any future chiral DCME reactions work, a suitable model tertiary alcohol would need to be prepared from a mixed trialkylborane. Such mixed trialkylboranes are most easily synthesised by controlled sequential hydroborations of three different alkenes of decreasing steric bulk.

The controlled, sequential hydroboration of 2,3-dimethyl-2-butene, cyclopentene and 1-octene, followed by reaction with DCME/triethylcarboxide (100% excess) and finally ethylene glycol followed by oxidation, gave the novel racemic tertiary alcohol cyclopentyl(*n*-octyl)(thexyl)methanol (**2.4**) in 57% GC yield. Compound **2.4** was fully characterised, with the data in accordance with the proposed structure (E.S. 2.32c)

The yield was a little lower than that reported for a closely-related example in the literature - (cyclopentyl)(*n*-pentyl)(thexyl)methanol (75% by GC).[3] This result confirmed that the sequential hydroboration had been successful; however the lack of aromaticity in the compound would make it a difficult compound to be observed by the HPLC UV detector. For this reason, the reaction was repeated, except 4-methoxystyrene was used in place of 1-octene to give the novel racemic tertiary alcohol cyclopentyl(2-(4-methoxyphenyl)ethyl)(thexyl)methanol (**2.5**) in 55% GC yield (Scheme 2.5). Compound **2.5** was fully characterised, with the data in accordance with the proposed structure (E.S. 2.32d).

Scheme 2.5 Synthesis of cyclopentyl(2-(4-methoxyphenyl)ethyl)(thexyl)methanol (2.5) by the DCME reaction
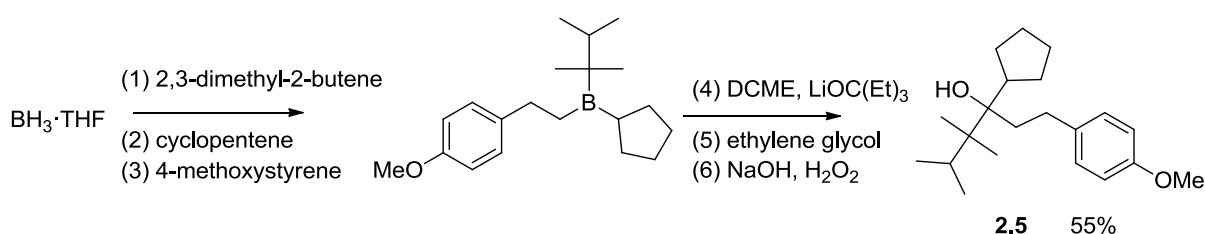
Following purification by column chromatography on neutral alumina, the UV of **2.5** was taken and showed λ_{max} = 228 nm. A sample of the compound was then taken to find suitable conditions for the separation of the enantiomers by chiral HPLC analysis. After trialling a

few different chiral columns, the enantiomers were separated using a Chiralcel® OD column, using 0.5% isopropanol in hexane as the eluent (Figure 2.1), and so now the stage was set to measure the ee of the product for a chiral DCME reaction using the mixed trialkylborane shown above.

Figure 2.1 Separation of racemic cyclopentyl(2-(4-methoxyphenyl)ethyl)(thexyl)methanol (2.5) on a chiral OD column
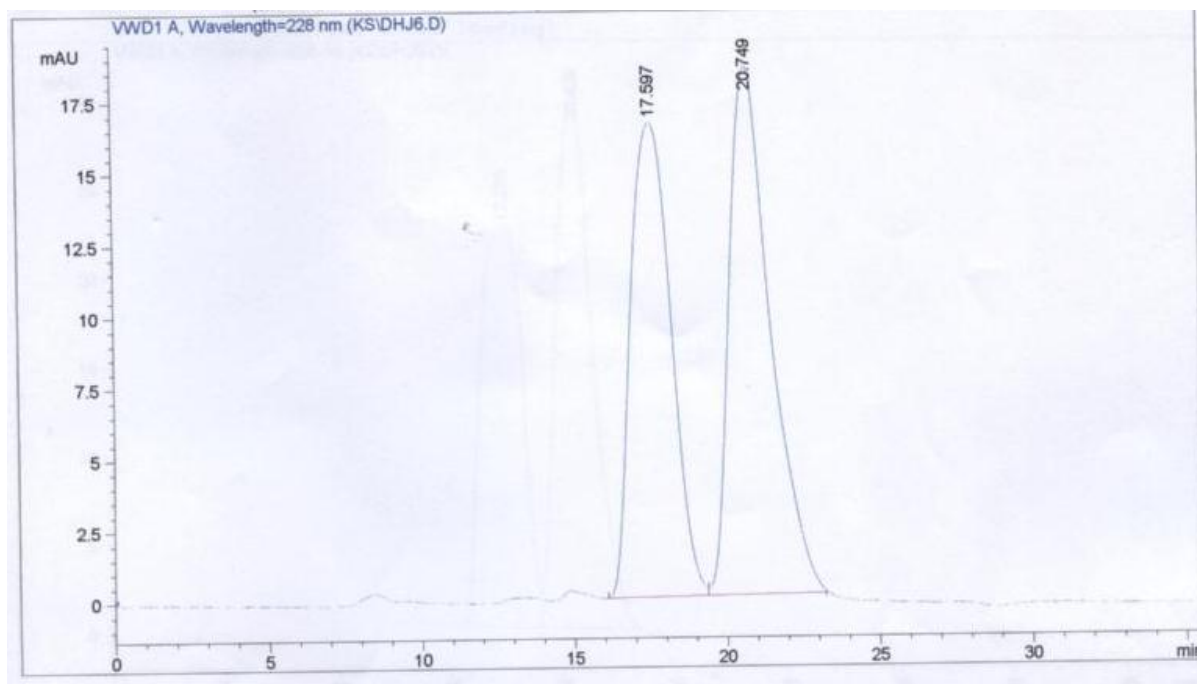
2.23 Synthesis of dichloromethyl menthyl ether using PCl₅ and POCl₃

There are very few methods present in the literature for the synthesis of dichloroalkoxymethanes. The most attractive method was developed by H. Gross *et al.* and involves chlorination of the appropriate formate with phosphorus pentachloride, as used for the synthesis of DCME.[8,9,10] We therefore set about synthesising a chiral formate from the starting alcohol.

Menthol was chosen as the first alcohol to study, as it is both relatively cheap and available in both enantiomers. D. R. Hill *et al.* developed an excellent formylating reagent (2,2,2-trifluoroethyl formate, **2.6**) in 2002, which they used to formylate a number of alcohols (including menthol) in excellent yields.[11] This reagent was therefore used for our synthesis of 1-menthyl formate (**2.7**).

2,2,2-Trifluoroethyl formate (**2.6**) was prepared by heating 2,2,2-trifluoroethanol and formic acid overnight. The product was purified by fractional distillation to give 2,2,2-trifluoroethyl formate (**2.6**) in 82% yield, with the characterisation data being consistent with those reported (Scheme 2.6a, E.S. 2.31a).[11] The purified 2,2,2-trifluoroethyl formate (**2.6**) was then used to formylate (-)-menthol by the reported procedure, and gave (-)-menthyl formate (**2.7**) in 96% yield without need for purification other than concentration under reduced pressure (Scheme 2.6b). The structure of the formate was confirmed by its spectral properties, which matched those of the reported compound[11] (E.S. 2.31b). The optical purity was confirmed by measuring the optical rotation, α_D=-82 ° (lit.[10] α_D=-75.5 °).

Scheme 2.6 Synthesis of 2,2,2-trifluoroethyl formate (2.6), and (-)-menthyl formate (2.7)
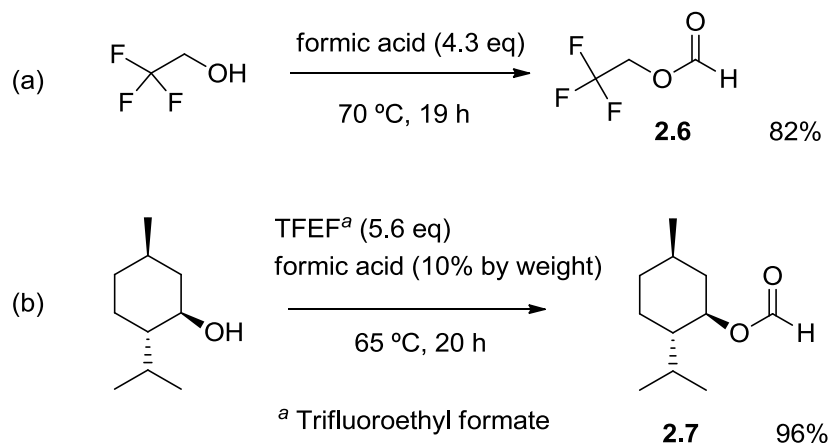
(-)-Menthyl formate (**2.7**) was then subjected to the conditions that H. Gross *et al.* used for the synthesis of DCME from methyl formate (addition of the formate to phosphorus pentachloride/phosphorus oxychloride, and stirring for 2 h).[8,9] In all cases, a small sample was taken for NMR analysis once the reaction was completed. Initial reactions showed a mixture of some of the starting material (-)-menthyl formate, a very small amount of what appeared to be the desired product (with the distinctive $OCCl_2H$ proton present at 7.14 ppm in the ^{1}H NMR spectrum, and a signal also seen in the ^{13}C NMR spectrum at 98.3 ppm-which is similar to the position of this CH for DCME itself[13]), and an unknown compound as the major component.

When the reaction was left for a longer time and at a higher temperature (45 °C for 6 hours), the unknown compound was formed almost exclusively (as seen in the ^{1}H spectrum of the crude product).

By using this ^{1}H NMR spectrum and comparing it to the reported spectra of neomenthyl chloride[14] and menthyl chloride,[15] we came to the conclusion that the compound was menthyl chloride (**2.8**, Scheme 2.7, both the chemical shift and coupling constants of the methyl groups in the ^{1}H NMR spectrum, along with the chemical shift of one of the methyl groups in the ^{13}C NMR spectrum were indicators, E.S. 2.31e). The ^{1}H NMR spectrum from the reaction product showed two doublets at 0.69 and 0.84 ppm with coupling constants of 6.8 Hz and 6.4 Hz respectively, which were consistent with the reported values for menthyl chloride (0.70 and 0.86, 6.8 Hz and 6.3 Hz), and not with neomenthyl chloride (three doublets at 0.88, 0.91 and 0.93 all with coupling constants of 6.6 Hz). Furthermore, the least downshielded methyl group in the ^{13}C NMR spectrum of the reaction product was at 15.1 ppm (consistent with 15.1 ppm for menthyl chloride, and not 20.1 ppm for neomenthyl chloride. Indeed, menthyl chloride has previously been synthesised by the reaction of (-)-menthol and phosphorus pentachloride/ferric chloride. The optical rotation was consistent specifically with (-)-menthyl chloride, and showed $\alpha_{D=}$-30.0 ° (lit.[15] $\alpha_{D=}$ -44.0 °).

Scheme 2.7 Reaction of (-)-Menthyl formate (2.7) with PCl$_5$, POCl$_3$

2.7	**2.7**	**2.8**	**2.9**
	minor	major	trace
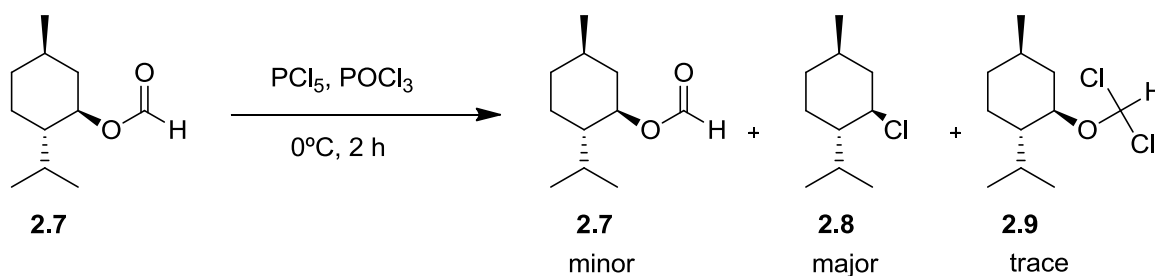
The reaction was repeated, but the reaction mixture was stirred for 6 hours at 0 °C in an attempt to allow all the (-)-menthyl formate (**2.7**) to be fully consumed while not promoting the production of the side-product menthyl chloride (**2.8**). Following completion of this reaction, an NMR sample was taken from the crude product under nitrogen, which showed an 85:15 mixture of dichloromethyl menthyl ether (**2.9**) and menthyl chloride (**2.8**, determined by comparing the relative integrations of the downfield OCCl$_2$H signal at 7.14 ppm with the downfield CH signal at 3.74 ppm for the desired product and menthyl chloride, respectively), along with trace amounts of the starting formate **2.7**. The bubbling of the NMR solution (even when under nitrogen) suggested that the product was very unstable in the presence of the phosphorus compounds left at the end of the reaction.

Several different methods were attempted to try to separate the desired product **2.9** from the phosphorus compounds (POCl$_3$ and residual PCl$_5$) left at the end of the reaction. Flash chromatography of the reaction mixture resulted in decomposition to give menthyl chloride (**2.8**). Washing the crude reaction mixture with ice-cold sodium bicarbonate resulted in violent decomposition to give menthyl chloride (**2.8**). All attempts at distillation of the product from the crude reaction mixture also resulted in this decomposition. The only procedure that gave some success was first to evaporate the POCl$_3$ at room temperature under reduced pressure, and then to dissolve the product in dry hexane. The hexane solution was then filtered to remove most of the residual PCl$_5$ (all under nitrogen) and the filtrate concentrated to give relatively pure product **2.8**. Even by this method, some decomposition always occurred.

To see if the α,α-dichloromethyl menthyl ether (**2.9**) behaved as wanted in the DCME reaction, a sample was prepared as pure as possible from the above procedure and was then added to a solution of tricyclopentylborane. Lithium triethylcarboxide (**2.1**) was added, and the reaction mixture was oxidised with hydrogen peroxide and sodium hydroxide. GC analysis of the crude reaction mixture showed the presence of tricyclopentylmethanol (**2.2**) in low yield (Scheme 2.8) (Table 2.2). The reaction was also repeated using tri-*n*-octylborane as the trialkylborane in case the low yield was as a result of the increased steric bulk of the α,α-dichloromethyl menthyl ether anion (which might be an obstacle when forming the 'ate' complex with a hindered trialkylborane such as tricyclopentylborane).

Scheme 2.8 Reaction of various trialkylboranes with dichloromethyl menthyl ether (2.9)/LiOC(Et)₃ (2.1)
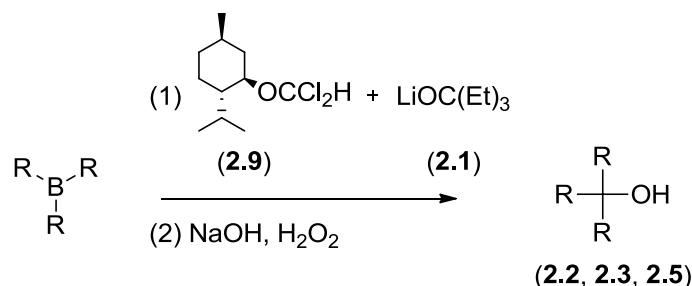
Table 2.2 Attempted reactions of various trialkylboranes with dichloromethyl menthyl ether/LiOC(Et)₃ according to Scheme 2.8

Trialkylborane used	DCME analogue (**2.9**)/LiOC(Et)₃ equivalents used	Yield (%)^a
tricyclopentylborane	1.0	4 (**2.2**)
tri-*n*-octylborane	1.2	5 (**2.3**)
tri-*n*-octylborane	2.0	3 (**2.3**)
cyclopentyl(2-(4-methoxyphenyl)ethyl)thexylborane	2.0	0 (**2.5**)

^{a}Determined by GC analysis with an internal standard (tetradecane).

The similar result with tri-*n*-octylborane suggested that steric bulk of the DCME analogue was not necessarily the problem, and it was suspected that perhaps the impurities (menthyl chloride (**2.8**), and perhaps residual phosphorus compounds) present in the dichloromethyl menthyl ether (**2.9**) were the real reasons for the large drop in yield compared to the literature DCME reaction. Another possibility is that lithium triethylcarboxide (**2.1**) promotes the decomposition of α,α-dichloromethyl menthyl ether (**2.9**) instead of deprotonating the acidic OCCl₂H proton. The reaction was repeated using cyclopentyl(2-(4-methoxyphenyl)ethyl)thexylborane as only a few mgs of product would be enough to discover whether any enantioselectivity had been achieved by using the already set-up chiral HPLC parameters. However, none whatsoever of the expected *tert*-alcohol product **2.5** could be seen in the GC traces of the crude reaction mixture. A search was therefore conducted for a better way of preparing α,α-dichloromethyl menthyl ether (**2.9**).

2.24 Synthesis of dichloromethyl menthyl ether using DCME and ZnCl₂

In 1968, H. Gross *et al.* published an alternative route to such dichloroalkoxy compounds, which involved addition of DCME and anhydrous zinc chloride to the starting formate (Scheme 2.9).[16]

Scheme 2.9 Synthesis of a dichloroalkoxy compound using DCME/ZnCl₂

(-)-Menthyl formate (**2.7**) was subjected to these conditions, however analysis of the crude product by NMR showed only starting material **2.7** and menthyl chloride (**2.8**, Scheme 2.10). Several attempts using less-harsh reaction conditions were attempted, in case the observed menthyl chloride (**2.8**) was as a result of the decomposition of initially formed dichloromethyl menthyl ether (**2.9**). However, only **2.8** and starting material were observed in all cases (Table 2.3). Leaving the reaction mixture to stir overnight at room temperature resulted in the clean formation of **2.8**. A similar reaction has been reported between (-)-menthol, zinc chloride and HCl.[17] Due to these results, our attention turned to other chlorinating reagents.

Scheme 2.10 Generation of menthyl chloride (2.8) using DCME/ZnCl₂
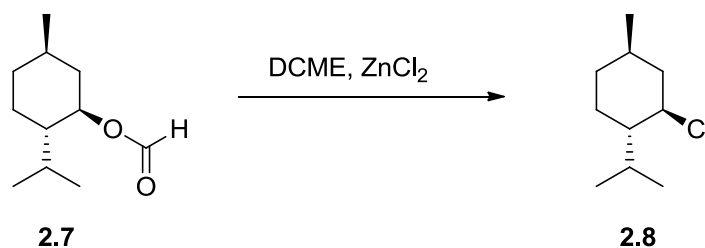
Table 2.3 Generation of menthyl chloride (2.8) using DCME/ZnCl₂ according to Scheme 2.10

Reaction time (h)	Temperature	**2.7** (%)[a]	**2.8** (%)[a]
1.0	77 °C	21	79
1.0	rt	62	38
3.0	rt	47	53
12.0	rt	3	97

[a] Proportions determined by relative ¹H NMR integration of the two compounds in the crude product.

2.25 Synthesis of dichloromethyl menthyl ether using miscellaneous chlorinating reagents

Dichloromethyl phenyl ethers have been prepared in Photo-Reimer-Tiemann reactions using UV light, although in very small quantities – which seemed impractical for medium-scale synthesis.[18] A few other chlorinating methods for the preparation of dichloroalkoxy compounds have been published within a patent for the synthesis of DCME and dichloromethyl ethyl ether.[19] Therefore, a few of these chlorinating reagents were screened to see if any would prove to be effective in our case (Scheme 2.11) (Table 4).

Scheme 2.11 Synthesis of dichloromethyl menthyl ether 2.9 using various chlorinating reagents
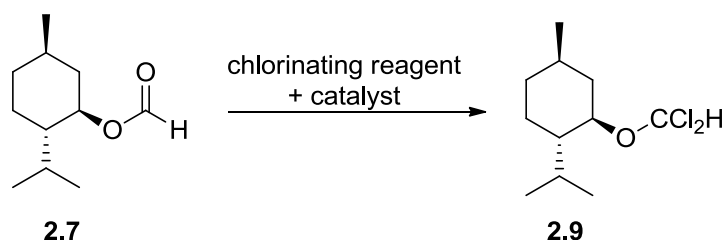
Table 2.4 Screening of chlorinating reagents for the synthesis of dichloromethyl menthyl ether (2.9) according to Scheme 2.11

Chlorinating reagents/catalyst	Reaction time (h)	Yield **2.9** (%)[a]
triphosgene/DMF[b]	20.0	trace
phosphorus oxychloride/DMF	20.0	9%
thionyl chloride/DMF	12.0	19%
thionyl chloride/TPPO[c]	20.0	trace

[a] Proportions determined by relative ^{1}H NMR integration of the product and starting material in the crude product. [b] *N, N*-dimethylformamide. [c] Triphenylphospine oxide.

Of the reagents screened, heated triphosgene (which releases phosgene) and thionyl chloride/triphenylphosphine oxide gave poor results. This is particularly surprising for the former reagent, as phosgene/DMF was the mixture of choice in the patent.[19] Thionyl chloride/DMF was promising, especially as the gaseous by-products from thionyl chloride are easy to remove, and the product can also be separated easily from the DMF salt at the end of the reaction by extracting with hexane.

Since thionyl chloride/DMF gave the best results, this system was investigated more thoroughly and several reactions were conducted under a variety of conditions (Table 2.5). By looking at the ^{1}H NMR spectrum of the crude products, initial experiments with thionyl chloride indicated that no reaction had occurred whatsoever without the DMF catalyst (even when heated to 80 °C for 24 hours). The desired product was produced at a slow rate at moderate temperatures. Attempts at speeding-up the reaction by the addition of more catalyst or employing higher temperatures resulted in the production of the unwanted by-product menthyl chloride (**2.8**, possibly by the decomposition of the desired product).

Table 2.5 Small-scale (100 mg) optimisation reactions of thionyl chloride/DMF chlorination of (-)-menthyl formate (2.7)

Reaction time (h)	Catalyst	Temperature	Starting material **2.7** (%)[b]	Product **2.9**[a] (%)[b]	Side-product **2.8**[d] (%)[b]
3.0	-	rt	100	0	0
24.0	-	80 ℃	100	0	0
3.0	DMF[c]	rt	100	0	0
3.0	DMF	80 ℃	45	17	38
6.0	DMF	80 ℃	25	0	75
12.0	DMF	58 ℃	56	19	25
30.0	DMF	58 ℃	48	27	25
20.0	DMF	70 ℃	23	10	66

[a] Dichloromethyl menthyl ether. [b] Proportions determined by relative ^{1}H NMR integration of the products and starting material in the crude product. [c] *N*, *N*-dimethylformamide. [d] Menthyl chloride.

At a larger scale, the reaction proceeded at an even slower rate – heating at 75 °C for a week giving only 35% of the desired product **2.9**. Attempts at isolating the product **2.9** from this mixture using different solvents resulted in decomposition to give menthyl chloride (**2.8**). In view of the difficulty in obtaining dichloromethyl menthyl ether (**2.9**), it was decided to attempt preparation of a simpler analogue.

2.26 Synthesis and stability evaluation of dichloromethyl cyclohexyl ether (**2.10**)

It was evident that making and purifying dichloromethyl menthyl ether (**2.9**) was not a trivial process, and so we wanted to check whether the instability of the compound was due to the

specific properties of **2.9** or just a general feature of such compounds. To this end, cyclohexyl formate (**2.11**) was produced in 97% isolated yield from cyclohexanol using trifluoroethylformate (**2.6**, TFEF)/formic acid (Scheme 2.11), in the same way as was used to produce (-)-menthyl formate (**2.7**, Scheme 2.6). There was no need for purification other than evaporation of the volatiles. Compound **2.11** was fully characterised, with the data in accordance with the literature values (E.S. 2.33a).[20]

Scheme 2.11 Synthesis of cyclohexyl formate (2.11)
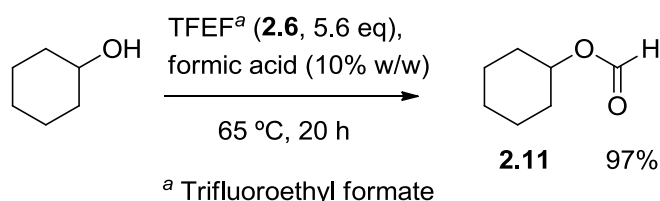
Cyclohexyl formate (**2.11**) was then reacted with phosphorus pentachloride/phosphorus oxychloride for 4 hours at room temperature, and the reaction was worked up in the same manner as for the dichloromethyl menthyl ether (**2.9**). A sample was taken under nitrogen for NMR analysis, which showed the presence of chlorocyclohexane (**2.12**)[13] and the starting formate **2.11** in a 77:28 ratio, respectively (by integrating the CHCl and CHO proton signals at 3.90 and 7.95 ppm in the ^{1}H NMR spectrum). The ^{13}C NMR spectrum also pointed towards a mixture of chlorocyclohexane (**2.12**) and the starting formate **2.11**. Both spectra had no indication of the desired dichloromethyl cyclohexyl ether. With this in mind, we decided to turn our attention to the DCME's sister reaction – the cyanidation reaction[21] and the results are reported in the following chapter.

2.3 Experimental Section

The following details are relevant to all the experimental sections contained within this thesis.

Unless otherwise stated, commercially available reagents were used without further purification and all reactions were followed and monitored by TLC, ^{1}H NMR, ^{13}C NMR and mass spectrometry as appropriate. The strengths of the borane dimethyl sulfide complex and borane·THF complex used were periodically tested using an analytical gas burette to measure the hydrogen liberated on hydrolysis. The strengths of *n*-BuLi/*tert*-BuLi solutions were periodically tested using the Gilman double-titration technique (using benzyl chloride and phenolphthalein).[22] All solvents needed for air-sensitive reactions were distilled using known procedures.[5] Thionyl chloride was freshly distilled prior to its use.

TLC refers to analytical thin layer chromatography analysis, using aluminium plates coated with pressed Merck Kieselgel 60 GF$_{254}$. Product spots were viewed either by the quenching of UV fluorescence, or by staining with a solution of 2% aqueous potassium permanganate. Column chromatography was performed using chromatography grade silica gel 60A (35-70 micron). Under reduced pressure refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump.

Melting points were recorded using a Gallenkamp melting point apparatus and are uncorrected.

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 660 plus FTIR instrument using polished NaCl plates. The samples were prepared neat when the compound was a liquid/oil, or either as a thin film deposited with chloroform or a nujol mull when the compound was a solid. All absorptions are quoted in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded using an Avance Bruker DPX 400 instrument (400 MHz), an Avance Bruker DPX 500 instrument (500 MHz) or an Avance Bruker DPX 250 (250 MHz) instrument. ^{11}B NMR spectra were recorded using a Jeol JNM-ECP 300 instrument (300 MHz). UV/vis spectra were recorded using a Jasco V570 UV/Vis/NIR spectrophotometer.

HPLC separation was performed using a HPLC Agilent Technologies 1200 series/Hewlett Packard series 1100 instrument fitted with a Chiralcel® OD column. GC experiments were performed using a Shimadzu GC-2014 gas chromatograph fitted with a ZB-5 column (30.0 M, 0.32 mm inner diameter and 1.00 μm film thickness). The carrier gas used was He, using

the split injection mode and a pressure of 69.3 kPa. Separation of the components was performed by heating from 70 °C to 260 °C at 6 °C/min, with an end hold time of 4 min.

Low and high resolution mass spectrometric data were determined using a Waters GCT Premier E1 instrument using electron impact ionization (EI). Optical rotations were determined using an Opticalactivity AA-10R instrument.

X-ray crystal structure data were recorded using a Nonius Kappa CCD diffractometer using graphite-monochromated Mo-Ka, (l= 0.710 73 Å) radiation at 150 K. Structures were determined in SHELXS-97 and refined using SHELXL-97. Structures were visualized using Mercury 2.3 (Build RC4) and ORTEP-3 V2.02

2.31 Synthesis of dichloromethyl menthyl ether

2.31a Synthesis of 2,2,2-trifluoroethyl formate (2.6).
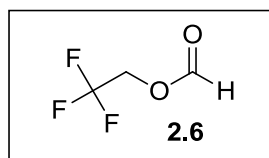
An oven dried, two-necked, 100 mL flask equipped with a septum, magnetic stirrer and reflux condenser was assembled while hot and flushed with N_2 for 10 min. 2,2,2-Trifluoroethanol (16.67 g, 186.6 mmol) and 95% formic acid (30.28 mL, 802.5 mmol) were added, and the mixture brought to gentle reflux, which was maintained for 19 h. The resulting solution was fractionally distilled, and the fraction boiling at 62 °C (lit. b.p. 60 °C[11]) collected to give 2,2,2-trifluoroethyl formate[11] (**2.6**) as a colourless liquid (18.62 g, 82% yield); b.p. 62°C; δ^1H (400 MHz; CDCl$_3$): 8.00 (1H, s, O=CH), 4.45 (2H, q, J = 8.3 Hz, CH$_2$O); $\delta^{13}C$ (125 MHz; CDCl$_3$): 158.9 (quat C, C=O), 122.5 (quat C, q, J = 278 Hz, CF$_3$), 59.5 (CH$_2$, q, J = 38 Hz, *C*H$_2$CF$_3$); $\delta^{19}F\{^1H\}$ (280 MHz; CDCl$_3$): -74.0 (s); LR EI-MS m/z (%): *neither the molecular ion nor any characteristic fragments were seen*; v_{max} (neat/cm^{-1}): 2979, 1735 (C=O), 1454, 1410, 1284, 1150, 979.

2.31b Synthesis of 1-menthyl formate (2.7).
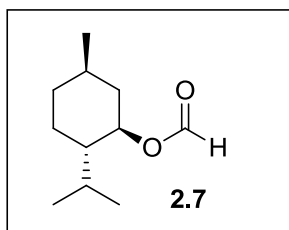
An oven dried 100 mL flask equipped with a septum capped reflux condenser and magnetic stirrer bar was assembled while still hot. (-)-Menthol (2.5 g, 16 mmol), 2,2,2-trifluoroethyl formate (11.06 g, 79.9 mmol) and formic acid (95%, 1.25 g) were added, the apparatus flushed with N_2 for 10 min, and the mixture heated at 65 °C for 20 h. The resulting solution was extracted with diethyl ether, washed several times with brine and distilled water, and dried over anhydrous magnesium sulfate. After filtration, the volatiles were evaporated under reduced pressure to give pure (-)-1-menthyl formate[11] (**2.7**) as a light yellow liquid (2.81 g, 96% yield), δ^1H (400 MHz; CDCl$_3$): 8.00 (1H, s, O=CH), 4.75 (1H, app dt, J = 10.9 Hz, 4.4 Hz, CHO), 1.91 – 1.99 (1H, m, CH), 1.77 – 1.87 (1H, m, CH), 0.95 – 1.70 (7H, m, CH$_2$ and CH), 0.85 (6H, m, CH$_3$), 0.70 (3H, d, J = 7.0, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 159.3 (CH, O=CH), 72.5 (CH, Cl$_2$CHO), 45.2 (CHO), 39.3 (CH$_2$), 32.6 (CH$_2$), 29.8 (CH), 24.2 (CH), 21.6 (CH$_2$), 20.4 (CH$_3$), 19.2 (CH$_3$), 14.5 (CH$_3$); $[\alpha]_D$ -82 ° (lit. -75.5 °)[11]; LR EI-MS m/z (%): *molecular ion not seen*, 138 (M$^+$- CHO, 80%), 123 (83), 109 (19), 95 (100), 81 (92), 67 (60), 55 (13); $v$max (neat/cm^{-1}): 3426, 2924, 2727, 2352, 1717 (C=O), 1456, 1388, 1372, 1240, 1181, 1096, 1038, 1008.

2.31c Synthesis of dichloromethyl menthyl ether (2.9, PCl$_5$ method).
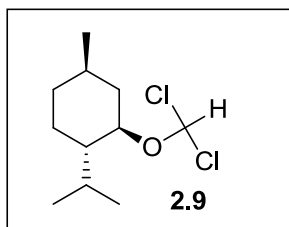
An oven dried piece of glassware consisting of 2×100 mL round bottomed flasks joined together by a sintered glass tube (with one flask equipped with a magnetic stirrer bar and septum – capped stopcock, and the other with a septum) was assembled while hot and flushed with N_2 for 10 min. The flask was then transferred to a N_2 glove-bag, where phosphorus

pentachloride (1.5 g, 7.2 mmol) was added to the flask quickly before replacing the septum and introducing phosphorus oxychloride (2.0 mL, excess). The flask was taken out of the glove-bag and immersed in an ice bath, and 1-menthyl formate (1.0 g, 5.4 mmol) was added drop-wise with vigorous stirring of the reaction mixture. The reaction mixture was stirred at 0 °C for a further 6 h. Excess phosphorus oxychloride was removed under reduced pressure *via* the stopcock. Dry hexane (25 mL) was introduced, and the solution was filtered through the sinter into the second flask. The hexane solution was transferred *via* cannula to a 50 mL flask already under N_2, and the hexane evaporated under a N_2 stream to give the crude product dichloromethyl menthyl ether (**2.9**)* as a very air-sensitive oil (80% conversion determined by integration of the ^{1}H NMR under N_2 atmosphere); δ^1H (400 MHz; CDCl$_3$): 7.10 (1H, s, CHCl$_2$), 3.70 (1H, app dt, CHO), 0.65 – 2.30 (18H, m, CH, CH$_2$, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 98.3 (CH, *C*HCl$_2$), 81.8 (CH, *C*HOCCl$_2$H), 48.0 (CH), 40.9 (CH$_2$), 34.5 (CH$_2$), 33.3 (CH), 27.4 (CH), 23.1 (CH$_2$), 22.2 (CH$_3$), 20.9 (CH$_3$), 16.8 (CH$_3$); unable to get further data due to the compound's instability.

*This crude product may be transferred drop-wise via cannula to a solution of (tri-*n*-octyl)borane and used in the DCME reaction to give tri-*n*-octylmethanol (5% yield), or to a solution of tricyclopentylborane to give tricyclopentylmethanol (4% yield). When the crude product was transferred to a solution of thexylcyclopentyl(4-methoxyphenylethyl)borane, no tertiary alcohol was observed in the GC trace or in the NMR spectrum of the crude mixture following work-up.

2.31d Synthesis of dichloromethyl menthyl ether (2.9, SOCl$_2$/DMF method). 1-Menthyl formate (1.0 g, 5.4 mmol) was added to an oven dried 25 mL round bottomed flask containing a magnetic stirrer bar. The flask was quickly connected to a septum–capped reflux condenser, and the apparatus was flushed with N_2 for 10 min. After cooling to 0 °C, freshly distilled thionyl chloride (1.18 mL, 16.2 mmol) was added drop-wise with stirring. Anhydrous DMF (0.05 mL) was added drop-wise, the reaction mixture was heated to 75 °C and was left to stir for a week. Excess thionyl chloride was removed at 40 °C under a fast stream of N_2, and dry hexane (10 mL) added and the solution stirred for 5 min. The supernatant hexane layer was transferred via cannula to a 25 mL flask already under N_2, and the hexane evaporated under N_2 to give a mixture of dichloromethyl menthyl ether and 1-menthyl formate (around 35% conversion as determined by ^{1}H NMR under N_2).

The method for phosphorus oxychloride was identical to that shown above, but with phosphorus oxychloride replacing thionyl chloride. For the triphosgene method, the triphosgene was weighed and added to the flask first, followed by the drop-wise addition of the formate by syringe.

2.31e Attempted Synthesis of dichloromethyl menthyl ether (DCME/ anhydrous zinc chloride method).

2.8
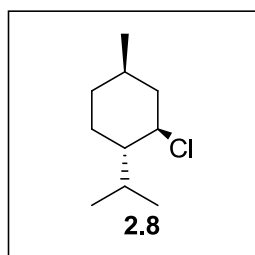
1-Menthyl formate (100 mg, 0.54 mmol) was added to an oven dried 25 mL flask equipped with a stopcock and was flushed with N_2. DCME (0.62 g, 5.4 mmol) was added drop-wise with stirring, and anhydrous zinc chloride solution in diethyl ether (1.0 M, 2 − 3 drops) was added. The stopcock was closed, and the solution left to stir for 24 h at rt. Excess DCME was evaporated under N_2, and the mixture extracted with dry hexane as in procedure 2.31d to give menthyl chloride[2] (**2.8**) almost exclusively; δ^1H (400 MHz; CDCl$_3$): 3.60 (1H, app t, $J = 4.2$ Hz, CH), 0.70 − 2.30 (18H, m, CH, CH$_2$ and CH$_3$); $\delta^{13}C$ (125 MHz; CDCl$_3$): 63.9 (CH), 50.4 (CH), 46.8 (CH$_2$), 34.3 (CH$_2$), 33.5 (CH), 28.0 (CH), 24.3 (CH$_2$), 22.3 (CH$_3$), 21.9 (CH$_3$), 15.1 (CH$_3$); LR EI-MS m/z (%): *molecular ion not seen*, 138 (M$^+$-HCl, 28%), 123 (30), 95 (80), 84 (100), 81 (79), 67 (38); v_{max} (neat/cm^{-1}): 2955, 2871, 1727 (impurity), 1456, 1387, 1370; [α]$_D$ -30 ° (lit. -44 °)[2].

2.32 DCME test reactions

2.32a Typical procedure for the DCME reaction with tri-*n*-octylborane.
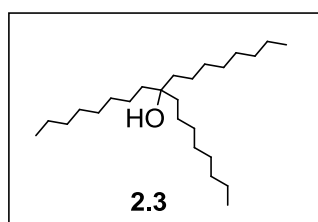
2.3

An oven dried 100 mL round bottomed flask equipped with a stirrer bar and septum was flushed with N_2 for 10 min. Once immersed in an ice bath, borane·THF complex (1.0 M, 5.0 mL, 5.0 mmol) was added, followed by the drop-wise addition of 1-octene (2.35 mL, 15.0 mmol). Once the addition was complete, the reaction mixture was left to stir for 90 min at 0°C. Dichloromethyl methyl ether (0.50 mL, 5.5 mmol) was added drop-wise, and a freshly prepared solution of lithium triethylcarboxide in THF (see below this procedure) prepared in tandem with the hydroboration step was introduced drop-wise *via* a cannula over a 20 min period. Once the addition was complete, the ice bath was removed and the mixture left to stir for a further 1 h. The flask was then immersed in an ice bath, and a solution of sodium hydroxide (1.20 g in 5 mL of distilled water) added carefully drop-wise. Once the initial reaction subsided, a solution of hydrogen peroxide in water (30% by weight, 4.0 mL) and ethanol (5 mL) were added. The mixture was heated to 45-50 °C for a further 1 h, with additional ethanol added as needed to dissolve any boron salts that precipitated. The aqueous layer was salted out with potassium carbonate, and the organic phase kept along with several diethyl ether washings of the aqueous salt. The organic phase was then washed with brine and distilled water, and dried over anhydrous magnesium sulfate, filtered and the solvents evaporated under reduced pressure to give a mixture containing tri-*n*-octylmethanol (72% by GC analysis using an internal standard) and triethylmethanol which was purified by column chromatography on neutral aluminium oxide (hexane, followed by 1:1 diethyl ether: hexane) to give tri-*n*-octylmethanol[7] (**2.3**) as a colourless oil (1.22 g , 66%); δ^1H (400 MHz; CDCl$_3$): 5.75 (1H, s, OH), 1.20 – 1.40 (42H, m, CH$_2$), 0.80 (9H, t, *J* = 6.0, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 74.4 (quat C, COH), 39.8 (CH$_2$), 32.8 (CH$_2$), 31.8 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 23.9 (CH$_2$), 23.1 (CH$_2$), 14.2 (CH$_3$); LR EI-MS m/z (%): *molecular ion not seen*, 350 (M$^+$-OH, 62%), 255 (100), 237 (41), 154 (94), 139 (100), 126 (53), 111 (96), 97 (100), 69 (98); v_{max} (neat/cm^{-1}): 3390 (OH), 2924, 2853, 1716, 1467, 1378, 1301, 1256, 1139, 1072; Rf = 0.57 in 1:1 diethyl ether: hexane..

Synthesis of lithium triethylcarboxide (2.1). An oven dried 50 mL flask equipped with a septum and magnetic stirrer was assembled while still hot and flushed with N_2 for 10 min. 3-Ethyl-3-pentanol (1.42 mL, 10 mmol) and dry THF (10.0 mL) were added, the mixture cooled to 0 °C and a solution of *n*-butyllithium in hexanes (2.0 M, 5.0 mL, 10 mmol) was added drop-wise. The mixture was left to stir for 90 min to give a clear solution of lithium triethylcarboxide (**2.1**) in THF.

Synthesis of lithium 2,2,6,6-tetramethylpiperidide. An oven dried 50 mL flask equipped with a septum and magnetic stirrer was assembled while still hot and flushed with N_2 for 10 min. 2,2,6,6-Tetramethylpiperidine (1.69 mL, 10 mmol) and dry THF (7.5 mL) were added, the solution cooled to -78 °C a solution of *n*-butyllithium in hexanes (2.0 M, 5.0 mL, 10 mmol) was added drop-wise. The mixture was left to stir for 90 min to give a clear solution of lithium 2,2,6,6-tetramethylpiperidide in THF.

2.32b Typical procedure for reaction of DCME with tricyclopentylborane.
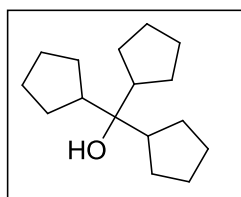
Procedure 2.32a was repeated using cyclopentene (1.33 mL, 15 mmol; hydroboration step left for 3 h at rt) to give a mixture of tricyclopentylmethanol (72% yield by GC analysis using an internal standard) and triethylmethanol. The mixture was purified by column chromatography on neutral aluminium oxide (hexane, followed by 1:1 ether: hexane) to give tricyclopentylmethanol[6] (**2.2**) as a colourless oil (0.86 g, 73%), δ^1H (400 MHz; CDCl$_3$): 4.15 (1H, br s, OH), 2.10 (3H, m, CH), 0.85 – 1.70 (24H, m, CH$_2$); δ^{13}C (125 MHz; CDCl$_3$): 61.8 (quat C, COH), 48.9 (CH), 29.7 (CH$_2$), 26.0 (CH$_2$); LR EI-MS m/z (%): *molecular ion not seen*, 218 (M$^+$- OH, 5%), 149 (100), 107 (27), 81 (82), 67 (73); v_{max} (neat/cm^{-1}): 3522 (OH), 2954, 2342, 1728, 1451, 1379, 1274, 1168, 1074, 1019; Rf = 0.50 in 1:1 diethyl ether: hexane.

2.32c Synthesis of thexylcyclopentyl-*n*-octylmethanol (2.4).
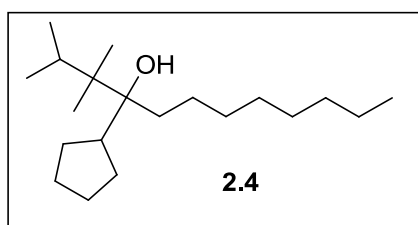
An oven dried 100 mL round bottomed flask equipped with a magnetic stirrer bar and septum was flushed with N_2 for 10 min. Borane·THF complex solution (1.0M, 5.0 mL, 5.0 mmol) was added drop-wise and the flask was cooled to -10 °C using an ice salt bath. 2,3-Dimethyl-2-butene (0.63 g, 7.5 mmol) was added drop-wise with stirring, and the solution left to stir for

a further 90 min before being cooled to between -30 and -20 °C using a calcium chloride hexahydrate – ice bath. Cyclopentene (0.34 g, 5.0 mmol) was added slowly with stirring, and the reaction mixture was left to stir for 90 min. 1-Octene (0.56 g, 5.0 mmol) was added drop-wise and the solution left to warm to rt and stirred for an additional 1 h. Dichloromethyl methyl ether (0.50 mL, 5.5 mmol) was added drop-wise, and a solution of lithium triethylcarboxide in THF (see procedure 2.32a) prepared in tandem with the hydroboration steps introduced drop-wise *via* a cannula with stirring over a 20 min period. Once the addition was complete, the ice bath was removed and the mixture left to stir for a further 1 h. Anhydrous ethylene glycol (0.90 mL, 16 mmol) was added and the solution was left to stir for 1 h at rt. The mixture was then oxidised and worked–up as in procedure 2.32a to give the crude product (57% yield by GC analysis using an internal standard), which was purified by column chromatography on neutral aluminium oxide (hexane, followed by 1:1 diethyl ether: hexane), to give fairly pure racemic thexylcyclopentyl-*n*-octylmethanol (**2.4**) as a colourless viscous oil (0.14 g, 9%); δ^1H (400 MHz; CDCl$_3$): OH not observed, 0.70 – 2.20 (39H, m, CH, CH$_2$, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 80.5 (quat C, COH), 48.9 (CH), 45.6 (CH$_3$), 33.4 (CH), 32.6, 31.5, 30.8, 30.1, 29.8, 29.7, 28.0, 26.2, 26.0, 23.1, 21.9 (CH$_3$), 20.8 (CH$_2$), 20.6 (CH$_3$), 14.9 (CH$_3$); HR EI-MS m/z: *molecular ion not seen*; calculated for C$_{20}$H$_{38}$ 278.2974, found 278.2971 (M$^+$- OH, 5%); ν_{max} (neat/cm^{-1}): 3300 (br, OH), 2925; Rf = 0.65 in 1:1 diethyl ether: hexane.

2.32d Synthesis of thexylcyclopentyl(4-methoxyphenylethyl)methanol (2.5).
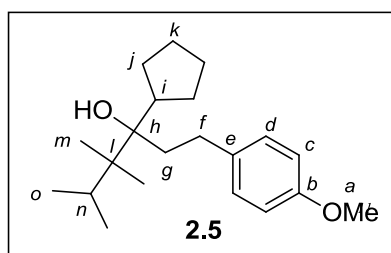
Procedure 2.32c was repeated, except that 4-methoxystyrene replaced 1-octene as the final olefin used for hydroboration to give a mixture of racemic thexylcyclopentyl(4-methoxphenylethyl)methanol (55% by GC analysis using an internal standard) and triethylmethanol. The mixture was purified by column chromatography on neutral aluminium oxide (hexane, followed by 1:2 diethyl ether: hexane) to give pure racemic thexylcyclopentyl(4-methoxphenylethyl)methanol (**2.5**) as a viscous yellow oil/semi-solid (0.29 g, 18%); δ^1H (400 MHz; CDCl$_3$): OH not observed, 7.05 (2H, d, *J* = 8.6 Hz, CH*d*), 6.75

(2H, d, J = 8.6 Hz, CH*c*), 3.70 (3H, s, CH₃*a*), 2.60 (2H, t, J = 8.9 Hz, CH₂*f*), 0.90 – 2.30 (12H, m, CH i, *n*; CH₂ *g, j, k*), 0.80 – 0.85 (12H, m, CH₃ *m, o*); δ¹³C (125 MHz; CDCl₃): 158.1 (quat C, C*b*), 135.8 (quat C, C*e*), 129.5 (CH, CH*d*), 114.3 (CH, CH*c*), 80.7 (quat C, COH), 55.7 (CH₃, OMe*a*), 47.7 (quat C, C*l*), 44.5 (CH, CH*i*), 38.8 (CH₂), 33.7 (CH, CH*n*), 31.8 (CH₂), 25.7 (CH₂), 21.7 (CH₂), 20.7 (CH₃), 20.5 (CH₃); ν_{max} (neat/cm⁻¹): 3584 (OH), 2958, 2871, 2834, 1612, 1584, 1511; UV-vis λ_{max}: 228 nm; HR EI-MS m/z: calculated for C₂₁H₃₄O₂ 318.2559, found 318.2548 (M⁺-OH, 100%); enantiomers separated at 17.6 min and 20.7 min using Chiralcel OD, 0.5% IPA in hexane, 0.7 mL/min, 0.5 μL inection of a 3.125 mg/ mL solution of the compound in isopropanol; Rf = 0.54 in 1:2 diethyl ether: hexane.

2.33 Stability study on dichloromethyl cyclohexyl ether

2.33a Synthesis of cyclohexyl formate (2.11).

2.11
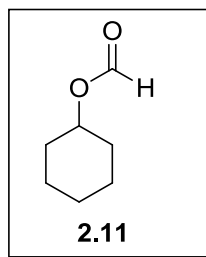
An oven dried 50 mL flask equipped with a stirrer bar and reflux condenser was charged with cyclohexanol (5.0 g, 50 mmol), 2,2,2-trifluoroethylformate (11.96 g, 93 mmol) and formic acid (2.175 g, 47 mmol). The solution was heated to gentle reflux for 20 h. The volatiles were evaporated under reduced pressure to give pure cyclohexyl formate[20] (**2.11**) as a light yellow liquid (6.24 g, 97% yield); δ¹H (400 MHz; CDCl₃): 8.00 (1H, s, O=CH), 4.80 (1H, m, CHO), 1.80 (2H, m), 1.65 (2H, m), 1.15 – 1.90 (6H, m); δ¹³C (125 MHz; CDCl₃): 160.9 (CH, O=CH), 72.7 (CH, *C*HOC=OH), 31.5 (CH₂), 25.2 (CH₂), 23.6 (CH₂); LR EI-MS m/z (%): *molecular ion not seen*, 98 (2%), 86 (70), 84 (90), 82 (100), 67 (100); ν_{max} (neat/cm⁻¹): 2939, 2861, 1725 (C=O), 1451, 1369, 1186, 1010.

2.33b Attempted chlorination of 1-cyclohexylformate. Cyclohexyl formate (1.23 g, 9.6 mmol) was added drop-wise to a suspension of phosphorus pentachloride (2.0 g, 9.6 mmol) in phosphorus oxychloride (5 mL) at 0°C under N₂. The reaction mixture was stirred for an additional 4 h, the excess phosphorus oxychloride removed under reduced pressure, and the ¹H and ¹³C NMR spectra of the crude product taken under N₂. The NMR sample started to bubble once taken from the reaction mixture, indicating decomposition of the product. The

^{1}H/^{13}C NMR spectra confirmed the presence of chlorocyclohexane and the starting formate, with no sign of the desired product (dichloromethyl cyclohexyl ether). No attempts were made to purify the chlorocyclohexane; however signals in both the ^{1}H and ^{13}C NMR spectra were consistent with the literature values.[6]

2.4 References

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Chapter 3: Attempts at designing a chiral version of the cyanidation reaction

3.1 Aims and introduction

Due to the difficulties encountered in synthesising and isolating a chiral dichloromethyl alkyl ether, research interests were switched to the cyanidation reaction.[1,2]

As already discussed in the first chapter review, trifluoroacetic anhydride (TFAA) is usually the acylating reagent of choice for inducing the boron – carbon migrations once the cyanoborate 'ate' complex has been formed in the cyanidation reaction. However, it is hard to imagine how chirality could be incorporated into the trifluoroacetyl group, which would be bonded to the nitrogen of the cyanide. However, other acylating reagents have also been shown to induce the boron-carbon migrations – benzoyl chloride (**3.1**), *N*-phenylbenzimidoyl chloride (**3.2**) and acetyl chloride.[2] Of these other acylating reagents, *N*-phenylbenzimidoyl chloride (**3.2**) was the one in which chirality could be most easily introduced.

Scheme 3.1 Mechanism of *N*-phenylbenzimidoyl chloride (3.2) induced cyanidation reaction
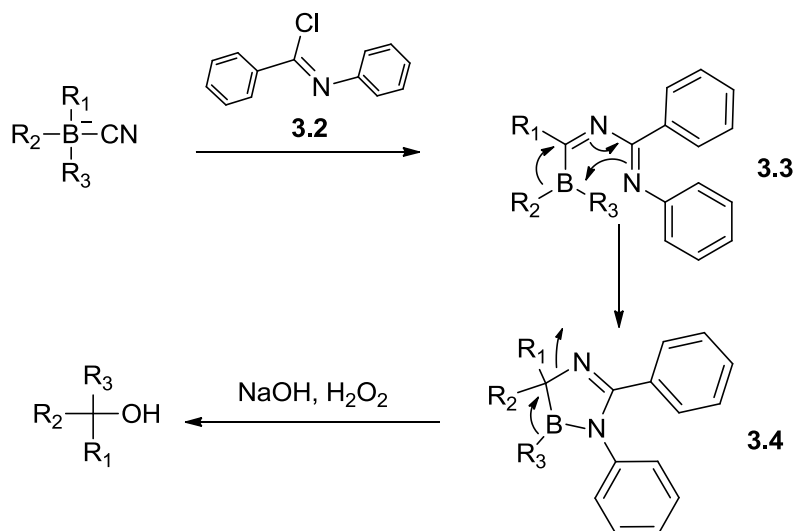
The reaction mechanism for the cyanidation reaction using **3.2** should be similar to that when TFAA or benzoyl chloride (**3.1**) is used as the acylating reagent, i.e. through a cyclic intermediate (Scheme 3.1). In this reaction, unlike the DCME reaction, the important step with regards to generating the stereogenic centre (if a mixed trialkylborane is used) is the second migration. If a chiral substituent is present in place of the phenyl group bonded to nitrogen (Scheme 3.1), then one would expect diastereotopic enrichment of chiral

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intermediate **3.4** to take place. One final migration would have to take place (which has not previously been observed when using **3.2** as the acylating reagent) to give the desired tertiary alkyl group bonded to boron. If this final migration is successful, then the intermediate organoboron compound would contain the desired enantiomerically enriched chiral tertiary alkyl group bonded to boron, which on oxidation would give the corresponding chiral tertiary alcohol. The ee of this alcohol could then be checked by chiral HPLC analysis.

3.2 Results and discussion

3.21 Cyanidation test reactions

It was decided to run a few test reactions to ensure all was well with the reagents/ procedures, and also to obtain a clean sample of di-*n*-octyl ketone (**3.5**) so that we could monitor subsequent reactions by GC analysis.

Tri-*n*-octylborane was prepared according to the literature procedure,[3] and potassium cyanide was added to make the cyanoborate 'ate' complex. Most of the cyanide was seen to dissolve, which confirmed the initial presence of the trialkylborane and formation of the cyanoborate. Benzoyl chloride (**3.1**) was added as the acylating reagent, and the intermediate organoboron compound was oxidised (Scheme 3.2). The crude product was purified by column chromatography followed by recrystallization from cold methanol to give di-*n*-octyl ketone (**3.5**) in 76% isolated yield (comparable to the reported 82% yield for an identical reaction on a 10 mmol scale).[2] The compound was fully characterised, with the data in accordance with the literature values (E.S. 3.32b).[4]

We then set about inducing the third migration using the literature procedure.[2] Potassium cyanotri-*n*-octylborate was prepared as above, excess TFAA (3 eq) was added and the intermediate organoboron compound was oxidised after being left to stir for 3 hours at room temperature. The crude reaction mixture was analysed by GC, and showed a yield of 59% for tri-*n*-octylmethanol (**3.6**, from three migrations), 12% for di-*n*-octyl ketone (**3.5**) and also showed the presence of 1-octanol/2-octanol (Scheme 3.2). In this particular case, it seemed like more time was needed for all the intermediate organoboron compound to undergo the third migration (the reported yield for this reaction on a 10 mmol scale is 82% isolated yield of the tri-*n*-octylmethanol (**3.6**)).[2]

Scheme 3.2 Cyanidation test reactions to prepare di-*n*-octyl ketone (3.5) and tri-*n*-octylmethanol (3.6)
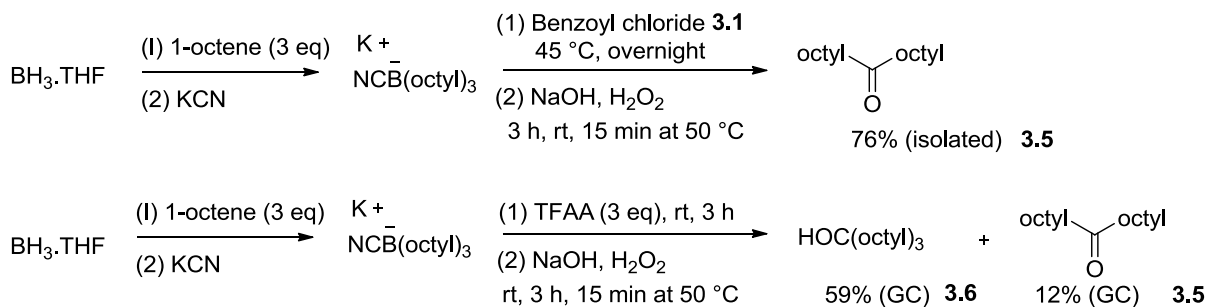
3.22 Synthesis of *N*-phenylbenzimidoyl chloride (3.2)

N-Phenylbenzimidoyl chloride (**3.2**) is commercially available, although relatively expensive. As we would have to make compounds similar to **3.2** in the event of getting the third migration to proceed, we decided to make the compound ourselves to save cost whilst also gaining experience. Aniline (**3.7**) was reacted with benzoyl chloride (**3.1**) in an aqueous alkali solution to give benzanilide (**3.8**, 57% isolated yield), whose characterisation data were the same as those in the literature (E.S. 3.31a).[5] Following recrystallisation and drying, the benzanilide (**3.8**) was refluxed in thionyl chloride for 2 hours according to the literature method,[6] to give the crude product, which was purified by distillation under reduced pressure to give **3.2**, with characterisation data the same as the reported values[6] (87% isolated yield, E.S. 3.31b; literature yield is stated as near-quantitative) (Scheme 3.3).

Scheme 3.3 Synthesis of *N*-phenylbenzimidoyl chloride (3.2)
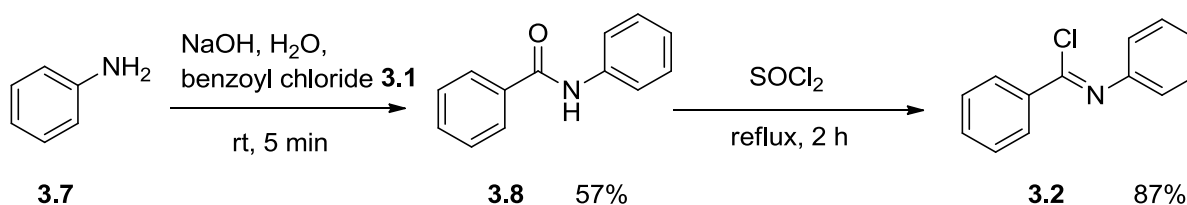
3.23 Attempts at inducing a third migration using 3.2

Before attempting the third migration, a final test reaction was run to test whether **3.2** would react as reported to give the doubly-migrated product. A dry solution of **3.2** in diglyme was added to potassium cyanotri-*n*-octylborate and left to stir at room temperature for 3 hours before being oxidised as usual. GC analysis of the crude reaction mixture showed a yield of 50% for di-*n*-octyl ketone and 10% 1-octanol/2-octanol (based on all three *n*-octyl groups),

proving the first two migrations proceed as planned using **3.2** as the acylating reagent (although in a lower yield than the reported 68% yield of ketone for a 10 mmol scale reaction).[2]

To achieve the third migration, we hoped that adding an excess of TFAA to the intermediate organoboron compound produced after two migrations would acylate the nitrogen β to the boron atom (Scheme 3.4). We hoped this would then facilitate the third migration, which upon oxidation would give the desired tertiary alcohol.

To test this idea, a solution of **3.2** was added to potassium cyanotri-*n*-octylborate as above and left to stir at room temperature overnight. Excess TFAA (10 eq) was then added and the reaction mixture left to stir for 14 hours at room temperature. The reaction mixture was oxidised as usual, and GC analysis of the crude reaction mixture showed a yield of 20% of tri-*n*-octylmethanol (**3.6**) along with some di-*n*-octyl ketone **3.5** (20%) and 1-octanol/2-octanol (14%, based on all three *n*-octyl groups). This result suggests that the TFAA had indeed promoted the third migration (most probably by acylating the nitrogen β to the boron atom). It is worth noting that adding excess TFAA at this point in an asymmetric version of the reaction would not affect the enantioselectivity of the overall reaction, as the subsequent ee would already have been determined after the second migration, assuming the final migration is stereospecific at the migration terminus.

Scheme 3.4 Intended route for third migration using excess TFAA
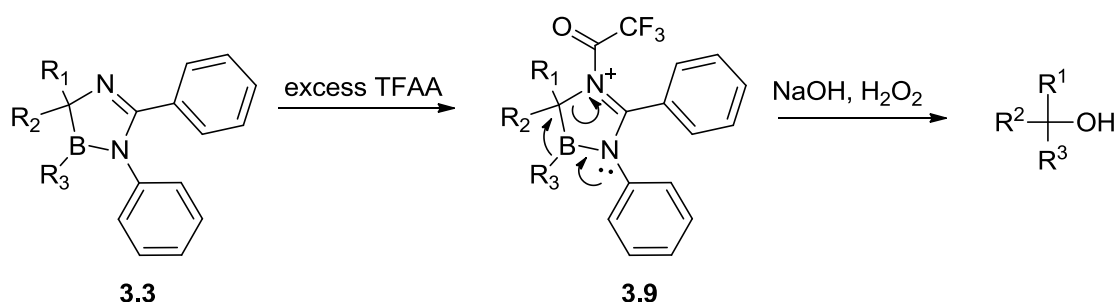
Buoyed by this result, we decided to repeat the experiment but heat the reaction mixture after adding excess TFAA in an attempt to push the third migration to completion. GC analysis of this reaction showed that heating the mixture after the addition of TFAA did indeed increase the amount of tertiary alcohol **3.6** relative to ketone **3.5**; however, a longer time might be needed before the triple-migration tertiary alcohol product is produced selectively (Table 3.1).

Table 3.1 TFAA induced third migration for potassium tri-*n*-octylcyanoborate

Reaction conditions	Yield (%)[a] of 1-octanol /2-octanol	Yield (%) of dioctyl ketone (**3.5**)	Yield (%) of tri-*n*-octylmethanol (**3.6**)
14h, rt, TFAA (10 eq)	14%[b]	20%	20%
14h, 40 °C, TFAA (10 eq)	12%	14%	34%

[a]Yield by GC analysis using internal standard (hexadecane). [b]With respect to 3 alkyl groups.

3.24 Reactions of thexylcyclopentyl(4-methoxyphenylethyl)borane (3.10) with 3.2

Having established that a third boron – carbon migration is possible with the aid of TFAA in the case of tri-*n*-octylborane, we decided to attempt the reaction on the mixed trialkylborane thexylcyclopentyl(2-(4-methoxyphenyl)ethyl)borane (**3.10**). Before attempting the third migration for this mixed trialkylborane though, it was decided to make the ketone arising from two migrations to have a sample of the compound for GC standard purposes.

The mixed trialkylborane **3.10** was prepared by sequential hydroboration as in Chapter 2, and treated with potassium cyanide and a solution of **3.2** in diglyme. The reaction mixture was oxidised, worked-up, and the ^{1}H NMR spectrum of the crude product taken. This showed what appeared to be the presence of the expected cyclopentyl (2-(4-methoxyphenyl)ethyl) ketone (**3.11**) arising from two migrations. The crude product was purified by column chromatography to give pure cyclopentyl(2-(4-methoxyphenyl)ethyl)ketone (**3.11**, 32% isolated yield) (Scheme 3.5). The ketone was fully characterised, with the data in accordance with the proposed structure (the compound has been prepared in the literature, although no characterisation data were reported, E.S. 3.32d).[7]

The yields for this reaction and those contained in Table 3.1 are lower than would be expected for typical cyanidation reactions, and was traced to a bottle of $BH_3.THF$ which had lost a significant amount of its borane content. Borane dimethyl sulfide complex was used for all further reactions. The ketone arising from thexyl group migration was not observed, thus proving that primary/secondary alkyl groups migrate in preference to tertiary alkyl groups when using **3.2** in the cyanidation reaction (as already proven when using TFAA as the

acylating reagent).[2] It is essential that the alkyl groups migrate in an orderly fashion for any asymmetric version of the cyanidation to work.

Scheme 3.5 Synthesis of cyclopentyl (2-(4-methoxyphenyl)ethyl) ketone (3.11)
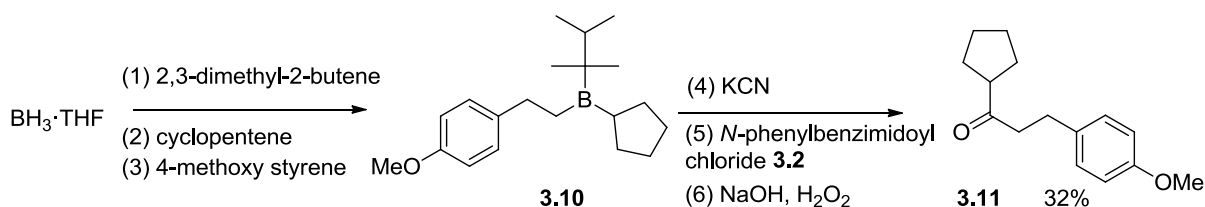
The procedure for the third migration for tri-*n*-octylborane was then applied to trialkylborane **3.10**, except that the reaction mixture was heated for an additional 10 hours at 40 °C after the TFAA was added (in an attempt to ensure that the third migration went to completion). The ^{1}H NMR spectrum of the worked-up crude product was taken, and showed the presence of two compounds, in a 62:38 ratio by relative integrations of the ^{1}H NMR spectrum. The main component was identified as ketone **3.11** by comparing the NMR spectrum to that of the previously purified ketone. The minor component however was harder to identify. It was clear by comparison with an authentic sample prepared as reported in Chapter 2 that the minor component was *not* the desired tertiary alcohol (**2.5**), and contained what appeared to be a signal for an unsaturated CH of an alkene at 5.2 ppm in the ^{1}H NMR spectrum.

Scheme 3.6 Unexpected alkenyl products observed in cyanidation reaction
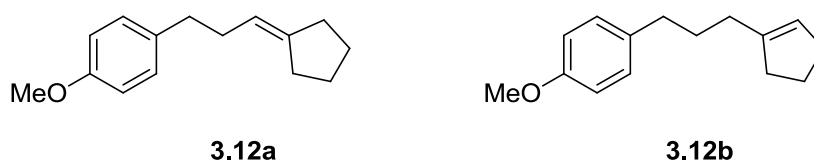
The unknown minor component was purified by column chromatography, and by looking at its NMR spectra the compound was identified as the novel compound 1-(3-cyclopentylidenepropyl)-4-methoxybenzene (**3.12a**, Scheme 3.6, 15% isolated yield) (confirmed by HRMS). The ^{1}H NMR spectrum showed a small amount of the endocyclic alkene (**3.12b**, Scheme 3.6, 12:88 ratio by relative integrations of the olefinic signals). The novel compound was fully characterised, with the data in accordance with the proposed structure (E.S. 3.32b).

Although this result was surprising to us; such internal olefins have previously been reported as minor products in cyanidation reactions with certain bulky trialkylboranes,[2] and also in

DCME reactions involving borinic acid esters,[8] which upon heating give the alkene product almost quantitatively.[9] One possible mechanism for the production of the observed alkene **3.12** involves breaking the carbon-nitrogen bond originally from the cyanide anion, followed by carbocation rearrangement of this intermediate and finally breakage of the boron-carbon bond to release the observed product (Scheme 3.7). The presence of small amounts of the endocyclic alkene **3.12b** seen in the ^{1}H NMR spectrum supports the formation of a carbocation intermediate with a positive charge on the tertiary carbon of the cyclopentyl group.

Scheme 3.7 Possible mechanistic explanation of the production of 1-(3-cyclopentylidenepropyl)-4-methoxybenzene (3.12)

observed alkene
3.12a
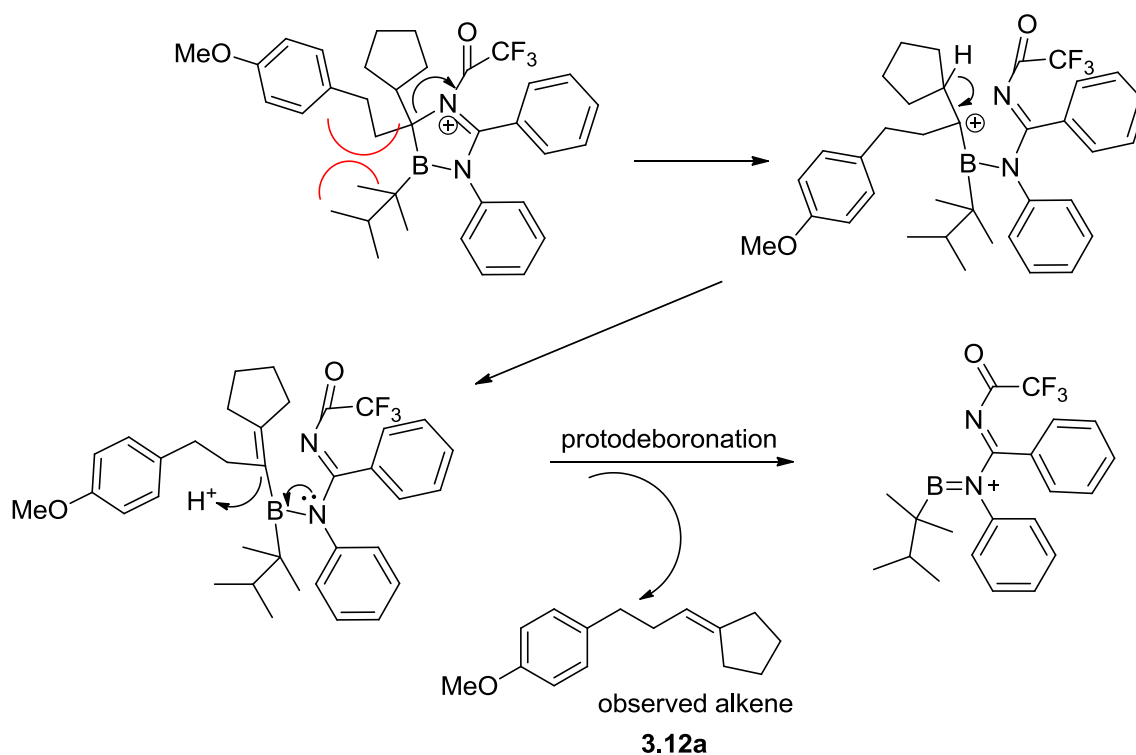
Although this result is in itself interesting, it is not a desired reaction pathway with regard to our aim of generating chiral tertiary alcohols.

It has been shown that heating the intermediate **3.4** (formed after 2 migrations using TFAA as the acylating reagent) in pyridine alone is sufficient to induce a third migration[2] – presumably by forming an 'ate' complex with the organoborane intermediate, where the negative charge can be alleviated by a third migration. Therefore, the intermediate **3.4** formed using trialkylborane **3.10** was prepared as in previous reactions and pyridine (5 mL) added. The reaction mixture was then heated at 80 °C for 24 hours, and the reaction mixture oxidised and

worked-up as usual. The ^{1}H NMR spectrum of the crude product, however, showed only the presence of the ketone **3.11** from two migrations. Heating the intermediate **3.4** in a pyridine-trichloroacetic anhydride solvent mixture also failed to give any tertiary alcohol, only the ketone **3.11** along with some black polymeric material.

3.25 Synthesis of imidoyl chlorides possessing electron-withdrawing groups

We reasoned that having an electron withdrawing group (EWG) attached or conjugated to the C=N carbon atom of the imidoyl chloride would aid the third migration with more hindered trialkylboranes such as trialkylborane **3.10** (Scheme 3.8) by increasing the electron deficiency on the nitrogen atom attached to the migration terminus. To test this hypothesis, we set about producing two such imidoyl chlorides (4-nitro-*N*-phenylbenzimidoyl chloride (**3.13**) and *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (**3.14**).

Scheme 3.8 Electron-withdrawing group to aid third migration
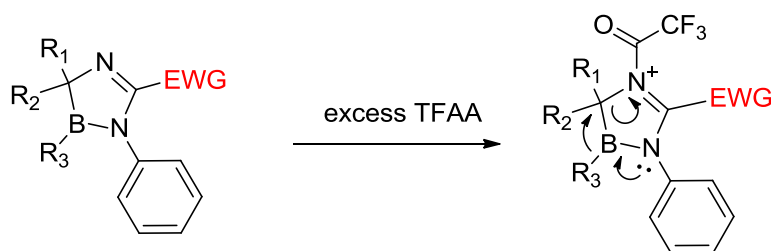
4-Nitro-*N*-phenylbenzimidoyl chloride (**3.13**) was prepared in two steps by the literature method.[10] Firstly, 4-nitro-*N*-phenylbenzamide (**3.15**) was prepared by the slow addition of 4-nitrobenzoyl chloride to a stirred solution of triethylamine and aniline (**3.7**, Scheme 3.9). Following work-up, the product was isolated in 94% yield (compared to the literature yield of 74%), with no purification required. The characterisation data were consistent with those reported in the literature (E.S. 3.36a).[10] Pure 4-nitro-*N*-phenylbenzamide (**3.15**) was then reacted with phosphorus pentachloride by the literature procedure[11] to give the crude imidoyl chloride, which was purified by filtration of a hot diethyl ether solution of the crude product. Evaporation of the diethyl ether gave pure 4-nitro-*N*-phenylbenzimidoyl chloride (**3.13**) in 85% isolated yield, and its characterisation data matched the literature values for this compound (E.S. 3.36b).[11]

Scheme 3.9 Synthesis of 4-nitro-*N*-phenylbenzimidoyl chloride (3.13)
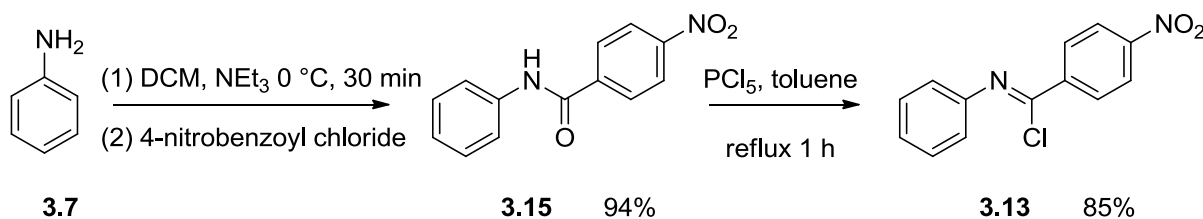
A procedure for the preparation of *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (**3.14**) has been published in the literature as a one-pot reaction of triphenylphosphine, carbon tetrachloride, triethylamine, aniline (**3.7**) and trifluoroacetic acid.[12] However, in order to avoid the use of carbon tetrachloride we envisaged preparing the imidoyl chloride in a similar manner to (**3.2**) – *i.e.* preparing the amide first, and then using a chlorinating reagent to make the corresponding imidoyl chloride.

2,2,2-Trifluoro-*N*-phenylacetamide (**3.16**) was prepared by a reported literature procedure by heating aniline (**3.7**) and trifluoroacetic acid in xylene (Scheme 3.10).[13] The crude product was purified by column chromatrography to give pure **3.16** (90% isolated yield, compared to the literature yield of 94%),with the data in accordance with the reported values (E.S. 3.35a).[13] Compound **3.16** was then refluxed in thionyl chloride for 3 hours in an attempt to make the imidoyl chloride. Surprisingly, however, only the starting amide was recovered (as seen in the ^{1}H NMR spectrum) showing that no reaction whatsoever had occurred. A similar approach, using the Vilsmeier salt of 2,6-lutidine and oxalyl chloride at 0 °C for 1 hour[14] also gave only starting material (as seen in the ^{1}H NMR spectrum). Due to these results, the decision was taken to use the existing one-pot procedure developed by K. Uneyama *et al.* (Scheme 3.10).[12]

The one-pot procedure was completed, and the crude product purified by distillation under reduced pressure to give pure *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (**3.14**, 29% isolated yield, compared to the literature yield of 73%), whose characterisation matched the reported compound (E.S. 3.35b).[12]

Scheme 3.10 Synthesis of *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (3.14)
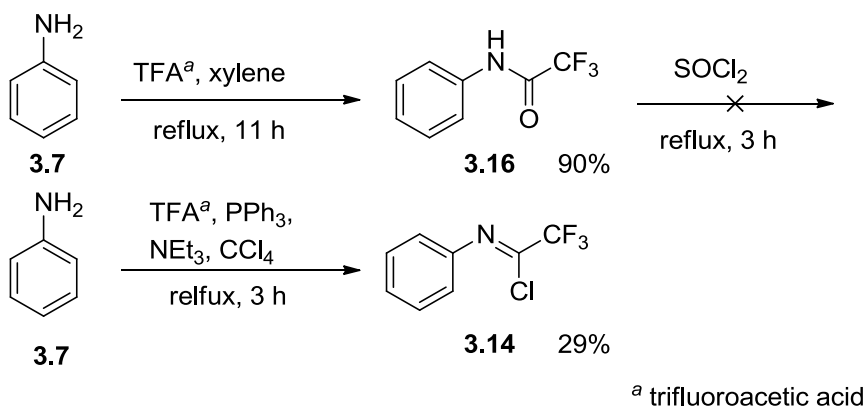
^{a} trifluoroacetic acid

3.26 Test reactions using imidoyl chlorides possessing electron-withdrawing groups

The cyanidation reaction of trialkylborane **3.10** was completed using 4-nitro-*N*-phenylbenzimidoyl chloride (**3.13**), with small aliquots taken from the reaction mixture and worked-up at various points to understand the course of the reaction. The reaction was left overnight at room temperature once the imidoyl chloride **3.13** had been added. A small aliquot after this period confirmed that the first two migrations had occurred as expected by the presence of ketone **3.11** almost exclusively in the ^{1}H NMR spectrum. Excess TFAA (10 eq) was added, and the reaction mixture heated to 40 °C for 14 hours. The reaction mixture was then oxidised and worked up as usual, with the ^{1}H NMR spectrum of the isolated material showing alkene **3.12** as the main component, with a little of ketone **3.11** also being present (in a 78:22 ratio determined by relative integrations of the ^{1}H NMR spectrum of the crude product). This result shows that the inclusion of a nitro group in the benzene ring of the starting imidoyl chloride had speeded up the side-reaction to produce the alkene side-product, and not the third migration product as had been hoped.

The same reaction was then repeated using *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (**3.14**). An aliquot taken after adding the imidoyl chloride and leaving to stir overnight at room temperature showed no presence of the expected ketone or tertiary alcohol by ^{1}H and ^{13}C NMR analysis (only the expected alcohols from the oxidation of the starting trialkylborane). The reaction mixture was then heated to 80 ℃ in an attempt to force the migration to occur, and a small aliquot was once again taken from the reaction mixture and worked-up. ^{1}H and ^{13}C NMR analysis showed only a trace amount of ketone **3.11**. Therefore, the reaction mixture was heated to 150 ℃ for a further 3 hours. However, by this point the reaction mixture had turned a dark colour (possibly because of the decomposition of the

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starting imidoyl chloride), and the ^{1}H and ^{13}C NMR spectra following work-up were the same as the previous aliquot – with the alcohols from oxidation of the starting trialkylborane being the main products, and only a trace amount of the ketone **3.11** arising from two migrations being present.

This result is perhaps not surprising, considering that imidoyl chlorides with electron-withdrawing groups have been shown to be less susceptible to hydrolysis than other imidoyl chlorides.[11] This phenomenon has been explained through reasoning that the imidoyl chloride itself is not the electrophile, but rather the carbocation generated by loss of chloride ion behaves as the electrophile. In the case of *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (**3.14**), it is possible that the electron-withdrawing groups prevent the generation of the reactive carbocation intermediate needed to react with the cyanide of the cyanoborate 'ate' complex.

The introduction of a nitro group into the imidoyl chloride had successfully speeded up the reaction relative to when using (**3.2**); however, the course of the reaction was the same, *i.e.* to produce alkene **3.12** arising from two boron – carbon migrations. As a way around this, we hoped that having two bulky groups at the 2 and 6 positions of the NPh of the starting imidoyl chloride might promote the third migration through alleviating the steric hindrance around the boron atom (Scheme 3.11).

Scheme 3.11 The use of sterically hindered groups in the imidoyl chloride as a way of promoting the third migration
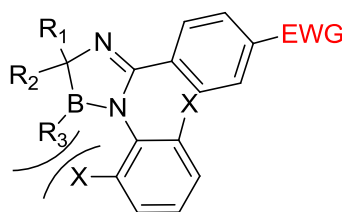
X = sterically hindered group

To this end, we set about producing the corresponding imidoyl chloride from 2,6-diisopropylaniliine. Diisopropylaniline was reacted with triethylamine and 4-nitrobenzoyl chloride as in the synthesis of **3.15** (Scheme 3.9), and the product purified by recrystallization from hot ethanol. The product was fully characterised, and although the melting point was different to the literature value[15] (measured 319 – 320 ºC, literature 303 - 306 ºC), and the ^{1}H data somewhat different to the reported values (literature characterisation is missing the Ar

proton signals for one of the rings), all the data pointed towards pure *N*-(2,6-diisopropylphenyl)-4-nitrobenzamide (**3.17**), which was isolated in 77% yield (Scheme 3.12, E.S. 3.37a).

Scheme 3.12 Synthesis of *N*-(2,6-diisopropylphenyl)-4-nitrobenzimidoyl chloride (3.18)
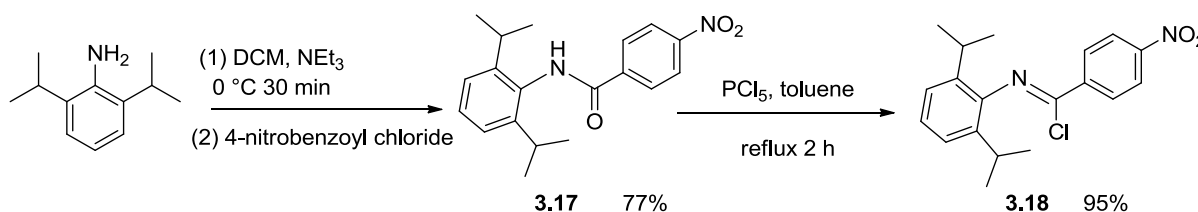
The pure amide **3.17** was reacted with phosphorus pentachloride as in the synthesis of **3.13** (Scheme 3.9), and the product purified to give the novel imidoyl chloride, *N*-(2,6-diisopropylphenyl)-4-nitrobenzimidoyl chloride (**3.18**) in 95% isolated yield (Scheme 3.12). The product was fully characterised, with all the data consistent with the proposed structure of the imidoyl chloride (E.S. 3.37b). HRMS and X-ray analysis were also carried out in order to confirm the structure (Image 3.1). The ^{1}H NMR was particularly interesting, as the signals for the methyl groups of the two isopropyl moieties were not chemically equivalent. The fact that there were two separate doublets at 1.28 and 1.33 ppm suggested that there was hindered rotation around the CH-Me bond of the isopropyl groups.

Image 3.1 X-ray structure of *N*-(2,6-diisopropylphenyl)-4-nitrobenzimidoyl chloride (3.18)
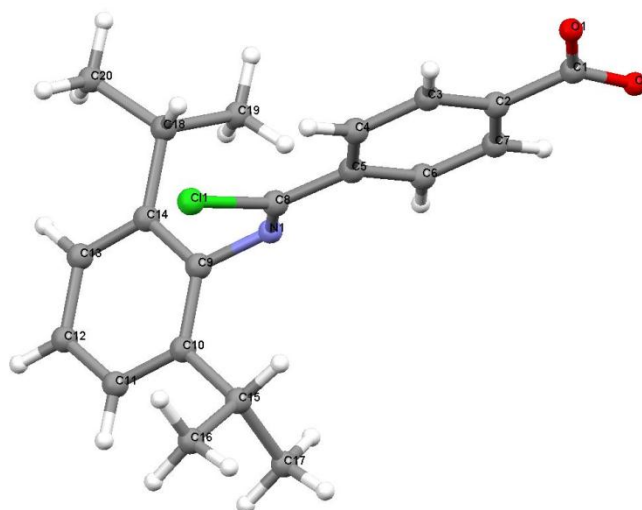
In order to confirm this observation, a small variable-temperature ^{1}H NMR study was conducted. ^{1}H NMR spectra were taken at 30, 35, 40, 45 and 50 ºC (Figure 3.1). The two

doublets became less distinct, finally coalescing at 50 ºC. From this data, $\Delta H^{\ddagger} = 16.9$ kJmol^{-1} and $\Delta S^{\ddagger} = -174.9$ Jmol^{-1} for the rotation around the CH-Me bond of the isopropyl groups, determined using the following formulas: $k_c = \pi(\Delta v)/\sqrt{2}$ at coalescence, followed by plotting $\ln(k/T)$ against $1/T$ to find both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (y $=ab + c$, where a $= - \Delta H^{\ddagger}/R$, and c $= 23.76 + (\Delta S^{\ddagger}/R)$) derived from the Eyring equation.

Figure 3.1 Variable-temperature ^{1}H NMR spectra of the signals arising from the methyl groups of the isopropyl groups in *N*-(2,6-diisopropylphenyl)-4-nitrobenzimidoyl chloride (3.18) at 30, 35, 40, 45 and 50 °C (left to right).
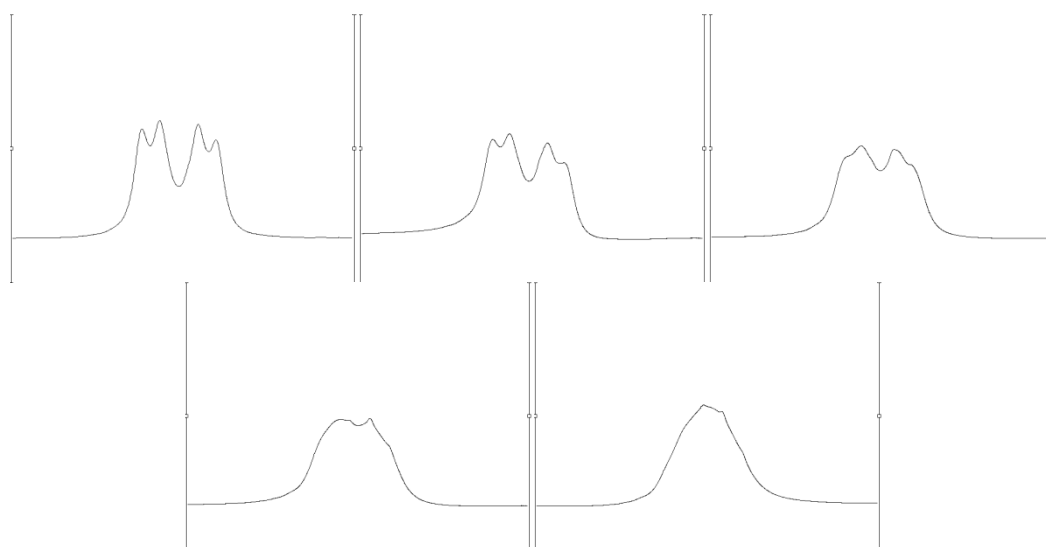
The cyanidation reaction was carried out using trialkylborane **3.10** as in the test reactions for the previously mentioned imidoyl chlorides possessing electron – withdrawing groups. An aliquot was taken after adding **3.18** and leaving to stir at room temperature overnight, and showed the presence of the ketone **3.11** arising from two migrations. Excess TFAA was added and the reaction heated and oxidised as in the previous test reactions. The ^{1}H NMR spectrum of the crude mixture after work-up showed alkene **3.12** as the main component, with a little of the ketone **3.11** (78:22 ratio as determined by relative integration of the two compounds in the ^{1}H NMR spectrum).

Although this result is disappointing with regards to our aim of designing a chiral version of the cyanidation reaction, it is interesting that such a hindered imidoyl chloride **22** can facilitate the cyanidation reaction with such a hindered trialkylborane. In fact, it seems that the addition of the two isopropyl groups in the imidoyl chloride did not affect the reaction in any way relative to 4-nitro-*N*-phenylbenzimidoyl chloride (**3.13**), both giving a 78:22 mixture of alkene **3.12** to ketone **3.11**, respectively.

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3.27 Study of the reaction of 4-nitro-*N*-phenylbenzimidoyl chloride (3.13) with various cyanotrialkylborates

To better understand the factors at work for determining whether the reaction proceeds to give the tertiary alcohol or alkene in the case of 4-nitro-*N*-phenylbenzimidoyl chloride (**3.13**), a small study was conducted using cyanoborates derived from several different trialkylboranes ranging in the steric bulk of their alkyl groups.

The trialkylboranes were prepared by literature procedures,[2,3] and then used in the cyanidation reaction using 4-nitro-*N*-phenylbenzimidoyl chloride (**3.13**), followed by excess TFAA and oxidation.

Tri-*n*-octylborane gave a mixture of tri-*n*-octylmethanol (**3.6**) and di-*n*-octyl ketone (**3.5**). The crude product was purified by column chromatography to give of 49% of **3.6**, and 17% of **3.5** (which translates to a ratio of 74:26, respectively). This result is similar in terms of the ratio of the two products to that observed with *N*-phenylbenzimidoyl chloride (**3.2**), which gave a ratio of 71:29, and so the inclusion of the nitro group seems to have only speeded up the third migration a small amount (if any) for tri-*n*-octylborane.

Scheme 3.13. Cyanidation reaction of tricyclopentylborane
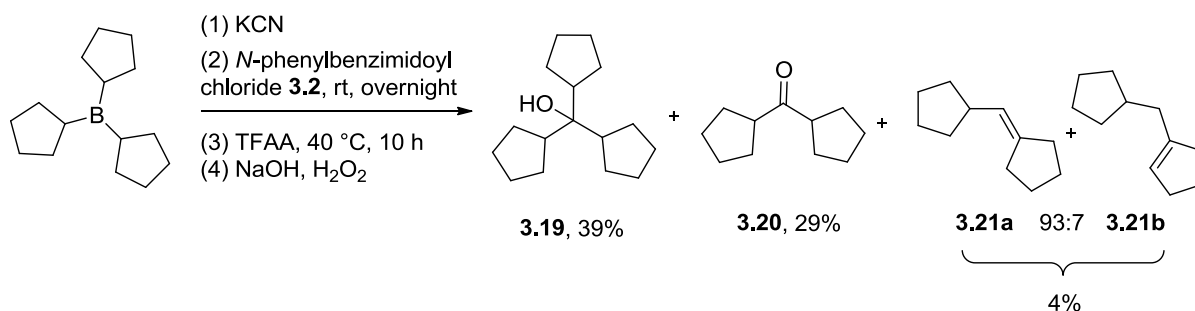
Tricyclopentylborane was subjected to the same conditions, and the products were purified by column chromatography. Tricyclopentylmethanol (Scheme 3.13, **3.19**, 39%) was isolated and had identical ^{1}H and ^{13}C NMR spectra to those of the tricyclopentylmethanol reported in Chapter 2 (E.S. 2.32b), along with dicyclopentyl ketone (Scheme 3.13, **3.20**, 29%) which was fully characterised, with the data in accordance with the literature values (E.S. 3.36g).[2] Along with these two components was isolated a small amount (4% yield) of the alkene product, cyclopentylmethylenecyclopentane (Scheme 3.13, **3.21a**). As in the case of 1-(3-cyclopentylidenepropyl)-4-methoxybenzene (**3.12**), a small amount of the endocyclic alkene (Scheme 3.13, **3.21b,** 7:93 ratio by relative integration with **3.21a** in the ^{1}H NMR spectrum)

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could be seen in the ^{1}H NMR spectrum. Although the molecular ion could not be seen in the LRMS EI data, the ^{1}H and ^{13}C NMR spectra were consistent with the proposed structure (the compound has been reported in the literature, but not fully characterised, E.S. 3.36g).[9]

With tricyclopentylborane, the ratio of tertiary alcohol **3.19** to ketone **3.20** had dropped to 57:43, indicating that the third migration was slower for this more hindered trialkylborane. Also, the small amount of alkene product **3.21** indicates that the reaction pathway to give the alkene product (seen as the dominant pathway when using trialkylborane **3.10**) was beginning to have an influence.

Scheme 3.14. Cyanidation reaction of (di-*n*-octyl)thexylborane
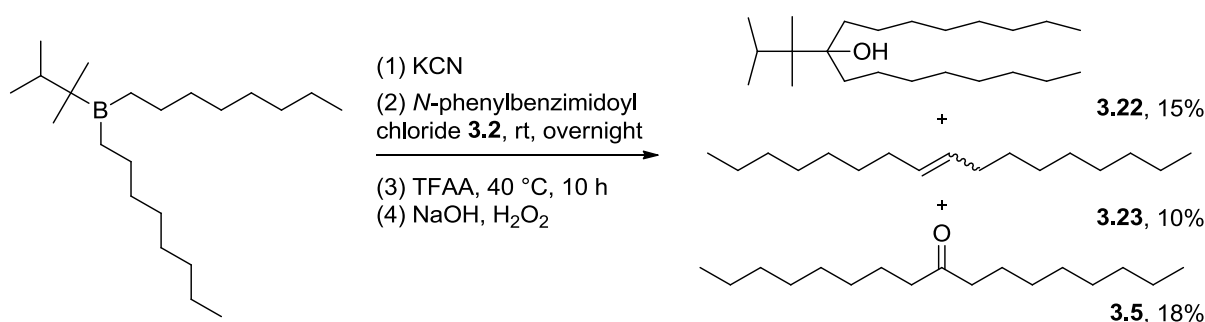
The next trialkylborane used was (di-*n*-octyl)thexylborane, and the crude product was purified by column chromatography to give the tertiary alcohol thexyldi-(*n*-octyl)methanol (**3.22**) in a yield of 15% (Scheme 3.14). The compound was fully characterised, and its spectra matched the reported data (E.S. 3.36h).[2] Di-*n*-octyl ketone (**3.5**) was isolated in a yield of 18% and its spectra matched those of a sample isolated from previous reactions reported in this chapter (Scheme 3.14). Also isolated in a yield of 10% was the alkene heptadec-8-ene (Scheme 3.13, **3.23**, (*Z*)/(*E*) ratio was 88:12 by ^{1}H NMR spectroscopy, consistent with that seen in a similar literature reaction).[9] Alkene **3.23** was fully characterised and its data matched the reported data (E.S. 3.36h).[16]

The overall yield is a little lower (only 43%) than for the other trialkylboranes, which indicates either that the synthesis of the trialkylborane itself was not as successful as in the other cases, or that this trialkylborane is slower to react with the imidoyl chloride. It has been reported that when using excess TFAA in the cyanidation reaction, thexyldi-(*n*-octyl)borane gave a yield of 70% of tertiary alcohol **3.22**, while tricyclopentylborane gave a yield of 86% **3.19**[2] which may suggest that cyanothexyldi-(*n*-octyl)borate reacts a little slower with

acylating reagents than some of the other less hindered cyanotrialkylborates. The three products (tertiary alcohol **3.22**, ketone **3.5** and alkene **3.23**) were all major components of the product mxture, in a ratio of 35: 42: 23, respectively. With the increased steric bulk of this trialkylborane compared to tricyclopentylborane, it seems that the reaction pathway to give alkene was becoming more favoured.

The final trialkylborane in the study was the already mentioned thexylcyclopentyl(2-(4-methoxyphenyl)ethyl)borane (**3.10**), which after purification by column chromatography gave the alkene **3.12** in a yield of 55%, along with the ketone **3.11** in a yield of 5%.

The alkene product had now become the major component with this hindered trialkylborane, with no tertiary alcohol being present whatsoever. The results for all the trialkylboranes surveyed are displayed in Table 3.2, and show the general trend that as the trialkylborane used becomes more and more hindered, so the alkene becomes the major product. However, even quite hindered trialkylboranes (thexyldi-(*n*-octyl)borane) can still give at least some tertiary alcohol from three boron – carbon migrations.

Table 3.2 Reaction of 4-nitro-*N*-phenylbenzimidoyl chloride (**3.13**), followed by TFAA with a range of cyanotrialkylborates

trialkylborane	ketone	olefin	^{t}alcohol
tri-*n*-octylborane	17%^{a} (**3.5**)	0%	49% (**3.6**)
tricyclopentylborane	29% (**3.20**)	4% (**3.21**)	39% (**3.19**)
di-(*n*-octyl)thexylborane	18% (**3.5**)	10% (**3.23**)	15% (**3.22**)
thexylcyclopentyl-(2-(4-methoxyphenyl)ethyl)borane	5% (**3.11**)	55% (**3.12**)	0%

^{a} All yields contained within the table are of isolated purified material.

3.28 Attempts at limiting the production of the alkene side-product

A few different attempts were made to limit or stop completely the production of the unwanted alkene side-product. The cyanidation reaction of **3.10** with imidoyl chloride **3.13**/ TFAA was repeated, except that the reaction mixture was cooled to -78 °C during the addition of the TFAA in case that the unwanted reaction to give the alkene was as a result of an initial rapid reaction when the excess TFAA is added. However, the ^{1}H NMR spectrum of the worked-up crude product showed that the alkene **3.12** was still the major component, along with some of the ketone **3.11** (74:26 ratio by ^{1}H NMR spectroscopy).

Following this result, we reasoned that a more successful method may be to replace the bulky thexyl group after the intial two boron – carbon migrations had occurred. Three possible methods for this would be direct addition of an organolithium reagent to the intermediate organoboron compound, replacement of the thexyl group by a less hindered alkene *via* the organoboron displacement reaction[17] (Scheme 3.15), and displacement of the thexyl group by acetaldehyde[18] followed by the addition of an organolithium reagent (Scheme 3.16).

For the first idea, the initial reaction between trialkylborane **3.10** and 4-nitro-*N*-phenylbenzimidoyl chloride (**3.13**) was completed as before, and the intermediate **3.24** from two boron – carbon migrations was cooled down to -78 °C, *n*-BuLi was added, and the mixture was left to stir at this temperature for one hour, before adding TFAA and oxidising as for previous reactions. The ^{1}H NMR spectrum after work-up showed alkene **3.12** as the main component, with some ketone **3.11** (75:25 ratio by ^{1}H NMR spectroscopy).

Scheme 3.15 Intended displacement of thexyl by 1-octene
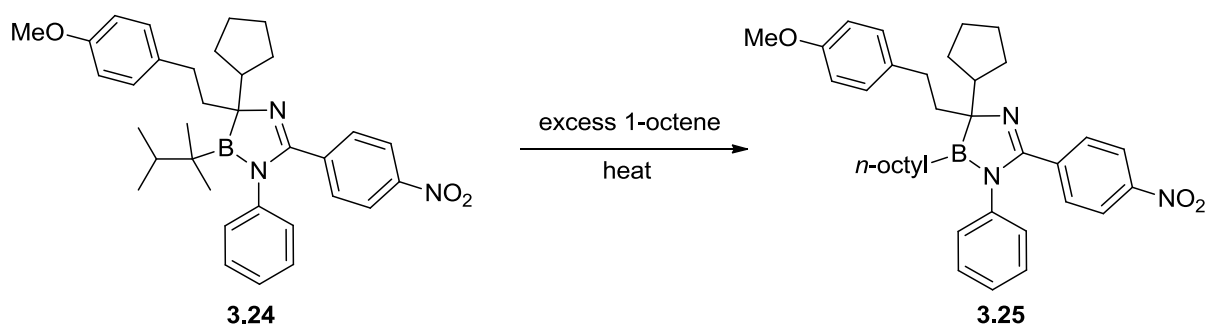
For the second idea, excess 1-octene was added to the intermediate **3.24** resulting from two boron–carbon migrations, and the mixture was heated to 100 °C for 6 hours. Once cooled, TFAA was added and the mixture was oxidised as for previous reactions. The ^{1}H NMR

spectrum after work-up showed the presence of ketone **3.11,** excess 1-octene (in a 79:21 ratio respectively by relative integrations in the ^{1}H NMR spectrum), along with small amounts of unknown species. The absence of 1-octanol suggested that the hydroboration of 1-octene had been unsuccessful; however the lack of alkene **3.12** indicated that the reaction pathway to give the alkene side product had been stopped. However, there was no presence of the tertiary alcohol that would have resulted from a third migration of the *n*-octyl group. This is a puzzling result, and must mean that the excess 1-octene or the heating itself had transformed the intermediate **3.24** after two migrations to a different species that did not give rise to either a tertiary alcohol or an alkene after the addition of TFAA. However, clean displacement of the thexyl group by an *n*-octyl group must not have occurred, as this intermediate would give either cyclopentyl(2-(4-methoxyphenyl)ethyl)*n*-octylmethanol or 1-(3-cyclopentylidenepropyl)-4-methoxybenzene (**3.12**) along with 1-octanol when reacted with excess TFAA and then subsequently being oxidised.

Scheme 3.16 Intended displacement of thexyl by acetaldehyde, followed by reaction with *n*-BuLi

3.24   **3.26**
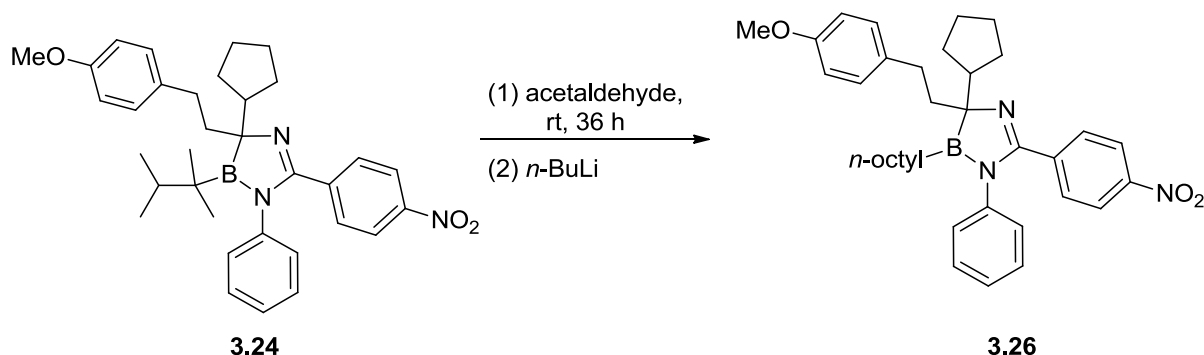
For the final idea, excess acetaldehyde[18] was added to the intermediate **3.24** resulting from two boron – carbon migrations and the mixture was left to stir for 36 hours at room temperature (Scheme 3.16). Excess acetaldehyde was removed under a stream of nitrogen, and the solution cooled to -78 °C for the addition of *n*-BuLi. The reaction mixture was warmed to room temperature and TFAA was added, and the mixture was oxidised as for previous reactions. The ^{1}H NMR spectrum after work-up showed only the ketone **3.11**, with no sign of either alkene **3.12** or tertiary alcohol from *n*-butyl group migration (cyclopentyl(2-(4-methoxyphenyl)ethyl)-*n*-butylmethanol). This suggests that the acetaldehyde was successful in displacing the thexyl group (or at least had transformed intermediate **3.24** in some manner), but that the addition of *n*-BuLi, followed by the migration of the *n*-butyl group was not successful.

3.29 Synthesis of a chiral imidoyl chloride, with the aim of isolating the organoboron intermediate following two migrations

As discussed in section 3.1, the crucial step with regards to enantioselectivity in a chiral version of the cyanidation reaction would be the second boron – carbon migration. Therefore, by isolating the organoboron intermediate **3.4** resulting from two boron – carbon migrations when using a chiral imidoyl chloride it might be possible to ascertain whether any stereoselectivity had been achieved by looking at its ^{1}H NMR spectrum. If any evidence of stereoselectivity was found, then it would warrant further research into the possibility of designing a chiral version of the cyanidation reaction.

(*S*)-α-Methylbenzylamine was chosen as the starting chiral amine, as it is relatively inexpensive, and would result in three groups of different size (phenyl, methyl and hydrogen) in the imidoyl chloride. (*S*)-α-Methylbenzylamine was mixed with aqueous sodium hydroxide, before the drop-wise addition of benzoyl chloride. Following an acidic aqueous work-up, (*S*)-*N*-(1-phenylethyl)benzamide (**3.27**, Scheme 3.17) was isolated in a yield of 64%. The compound was fully characterised, with the data in accordance with the literature values (E.S. 3.34a).[19] The optical purity was checked by measuring the optical rotation of the material, $α_{D=.}$-21.0 ° (lit.[20] $α_{D=}$ -20.1 °).

Scheme 3.17 Synthesis of *N*-(1-(S)-Phenylethyl)benzimidoyl chloride (3.28)
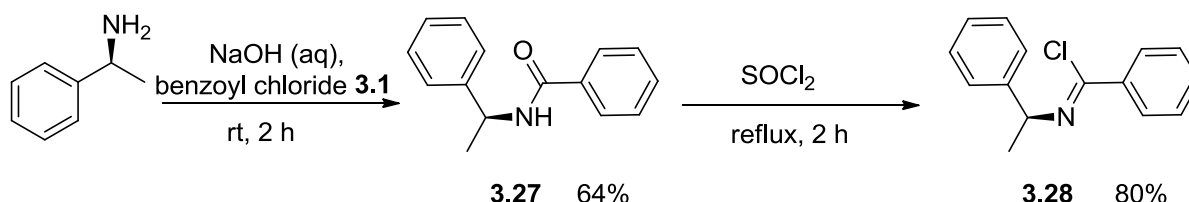
Pure **3.27** was reacted with thionyl chloride according to the literature method (Scheme 3.17)[6] to give *N*-(1-(S)-phenylethyl)benzimidoyl chloride (**3.28**, in an isolated yield of 80%). The compound was fully characterised, with the data in accordance with the literature values[21] except for the IR spectrum (E.S. 3.34b). Present in the IR spectrum was an unexpected peak at 2229 cm^{-1}. We tentatively assign this peak as the cyanide functionality of the minor side-product benzonitrile, which may have been produced by thermal decomposition of imidoyl chloride **3.28** during heating of the reaction mixture ('Von Braun Reaction', Scheme 3.18).[22]

Scheme 3.17 Possible mechanism for the formation of benzonitrile ('Von Braun reaction')

3.28
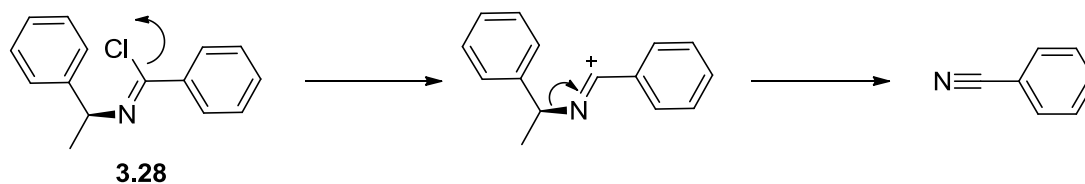
The mixed trialkylborane **3.10** was reacted with potassium cyanide, followed by imidoyl chloride **3.28**. After leaving the reaction mixture to stir overnight at room temperature, an attempt was made to isolate the intermediate resulting from two boron – carbon migrations, using a literature method[2] for a similar organoborane intermediate.[23] The ^{1}H NMR spectrum of the isolated material was highly complicated and although it had the signals at roughly the expected chemical shifts for such a compound it was apparent that there were a number of other compounds present. Many attempts were made to purify the compound; however, the presence of thexanol in the ^{1}H NMR spectra indicated that the compound had begun to oxidise.

Due to the difficulties encountered in getting the third migration to proceed cleanly in hindered trialkylboranes, it was decided to switch the research to the equally important second aspect of the overall project (effective migration of a tertiary alkyl group directly bonded to boron).

3.3 Experimental

3.31 Synthesis of *N*-phenylbenzimidoyl chloride (3.2)

3.31a Synthesis of benzanilide (3.8).
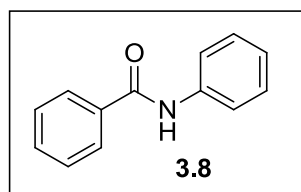
To a dry 500 mL conical flask was added aniline (20 g, 210 mmol), and an aqueous solution of sodium hydroxide (20 g in 50 mL of distilled water). Benzoyl chloride (30 g, 21 mmol) was added drop-wise with vigorous shaking of the flask, whereupon crude benzanilide precipitated as an off - white solid. After completion of addition, the solution was stirred for an additional 5 min, before the crude benzanilide was washed with water (50 mL) and filtered under reduced pressure. The resulting solid was recrystallised from hot ethanol, and dried in a vacuum oven for 2 days to give pure benzanilide (**3.8**, 24.1 g, 57% yield); m.p. 165 °C (lit. 163 °C[24]); δ^1H (400 MHz; CDCl$_3$): 7.05 – 7.85 (10H, m); δ^{13}C (125 MHz; CDCl$_3$): 165.8 (quat C); 138.0 (quat C), 135.0 (quat C), 131.9 (CH), 129.1 (CH), 128.8 (CH), 127.0 (CH), 124.6 (CH), 120.2 (CH); LR CI-MS m/z (%): 198 (M$^+$+1, 100%); v_{max} (thin film/cm^{-1}): 3343 (NH), 2918, 2849, 1705 (C=O), 1655, 1439, 1218, 1135.

3.31b Synthesis of *N*-phenylbenzimidoyl chloride (3.2).
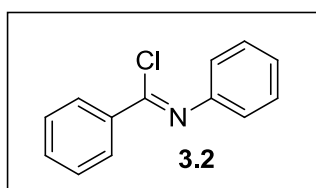
An oven dried 100 mL flask equipped with a magnetic stirrer bar and septum – capped reflux condenser was filled with benzanilide (10.0 g, 51 mmol) and flushed with N$_2$ for 10 min. Freshly distilled thionyl chloride (25 mL, excess) was added drop-wise with stirring, and the solution was heated to reflux for 2 h. Excess thionyl chloride was evaporated at 40 °C under a fast stream of N$_2$ to give a deep yellow solid. The solid was dissolved in hot hexane, filtered while hot and the hexane of the filtrate evaporated to give fairly pure *N*-phenylbenzimidoyl chloride. The *N*-phenylbenzimidoyl chloride was further purified by distillation under reduced pressure (and the condensed solid reheated with a heat gun, allowing it to flow into

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the receiving flask equipped with a stopcock), followed by an immediate stream of N_2 to give very pure *N*-phenylbenzimidoyl chloride as a bright yellow solid (**3.2**, 9.42 g, 87% yield); m.p. 42-43 °C (lit. 38-39 °C[6]); δ^1H (400 MHz; CDCl$_3$): 8.02 – 8.08 (2H, m), 7.20 – 7.40 (5H, m), 7.04 – 7.14 (1H, m), 6.86 – 6.93 (2H, m); δ^{13}C (125 MHz; CDCl$_3$): 146.6 (quat C), 142.2 (quat C), 134.4 (CH), 131.0 (CH), 128.4 (quat C), 127.8 (CH), 127.4 (CH), 124.0 (CH), 119.3 (CH); LR EI-MS m/z (%): 215 (M$^+$, 45%), 180 (100), 136 (18), 105 (100), 93 (83), 84 (88), 77 (100); ν_{max} (thin film/cm^{-1}): 3019, 2918, 2848, 1656, 1600, 1525, 1438, 1215.

3.32 Cyanidation test reactions

3.32a Synthesis of tri-*n*-octylmethanol (3.6) *via* the cyanidation reaction. An oven dried three-necked flask equipped with a magnetic stirrer bar, stopcock, and septum was set up. Dry potassium cyanide (0.342 g, 55 mmol) was ground up prior to use with a pestle and mortar, and transferred into a bent side arm closed at one end, and was fitted to the remaining neck of the flask. The flask was flushed with N_2 for 10 min, and cooled to 0 °C. Borane·THF complex (1.0 M, 5 mL, 5mmol) was added, followed by the drop–wise addition of 1-octene (2.325 mL, 15 mmol). Following completion of addition, the solution was warmed to rt and was left to stir for 1 h. The side arm was rotated to introduce the cyanide, and the mixture was left to stir for an additional hour, whereupon the cyanide dissolved. Trifluoroacetic anhydride (2.05 mL, 15 mmol) was added drop-wise, and the solution was left to stir for 3 h at rt. Excess trifluoroacetic anhydride was evaporated under reduced pressure *via* the stopcock, and the mixture cooled to 0 °C. Sodium hydroxide solution (3 M, 6 mL) was added carefully, followed by hydrogen peroxide (30% by weight, 7 mL). The solution was left to stir for 3 h at rt, and for 15 min at 50 °C to give tri-*n*-octylmethanol (**3.6**, 59% by GC analysis using an internal standard), di-*n*-octylketone (**3.5**, 12% by GC analysis using an internal standard) and 1-/2-octanol (28% yield by GC analysis using an internal standard - based on all three octyl groups).

3.32b Synthesis of di-*n*-octyl ketone (3.5) *via* the cyanidation reaction.

3.5
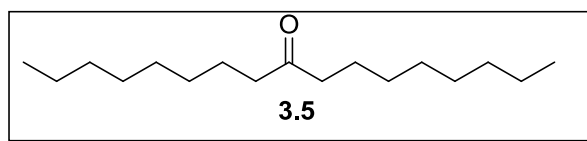
Tri-*n*-octylcyanoborate was prepared as in procedure 3.32a. Benzoyl chloride (**3.1**, 0.7 mL, 6 mmol) was added drop-wise, and the solution was left to stir overnight at rt. The oxidation was carried out as in procedure 3.32a. The product was extracted with diethyl ether, and the combined extracts washed with 1 M HCl, 3 M NaOH, and brine. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the crude product. The product was purified by column chromatography on silica (hexane, followed by 3:1 hexane: ether) to give di-*n*-octyl ketone (**3.5**, 0.96 g, 76% yield), which was further purified by recrystallisation in ice–cold methanol to give very pure product as colourless sheets; m.p 49-50 °C (lit 48-48.5 °C[2]); δ^1H (400 MHz; CDCl$_3$): 2.35 (4H, t, J = 7.4 Hz, CH$_2$C=O), 1.50 (4H, m, CH$_2$), 1.10 – 1.30 (20H, m, CH$_2$), 0.82 (6H, t, J = 6.7 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 211.8 (quat C, C=O), 42.8 (CH$_2$, *CH$_2$*C=O), 31.8 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 23.9 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$); LR CI-MS m/z (%): 296 (M$^+$ +CH$_3$CN, 100 %); v_{max} (thin film/cm^{-1}): 3020, 2940, 1706 (C=O), 1467, 1409, 1377, 1214; Rf = 0.8 in 4:1 hexane: diethyl ether.

3.32d Di-*n*-octyl ketone (**3.5**) was produced in a similar manner by using *N*-phenylbenzimidoyl chloride as the acylating reagent. *N*-Phenylbenzimidoyl chloride (1.295 g in 6 mL of dry diglyme, 1.1 eq) was added drop-wise to a solution of tri-*n*-octylcyanoborate in dry THF (as prepared in procedure 3.32a), and was left to react for 3 h at rt. Oxidation was carried out as in procedure 3.32a. GC analysis of the organic phase using an internal standard showed a 50% yield of di-*n*-octyl ketone (**3.5**) and 1-/2-octanol (10% yield based on all three octyl groups).

3.32d Synthesis of cyclopentyl(4-methoxyphenylethyl)ketone (3.11).

3.11
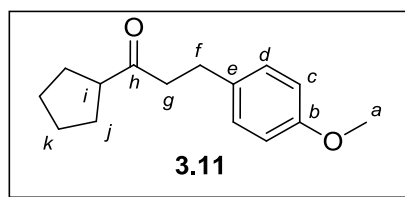
Thexylcyclopentyl(2-(4-methoxyphenyl)ethyl)cyanoborate was prepared according to procedure 2.32d and was treated with *N*-phenylbenzimidoyl chloride (1.295 g in 6 mL of dry diglyme, 1.1 eq) and was left to stir overnight at rt before the mixture was oxidized as in procedure 3.32a. The crude product after work-up was dissolved in hexane and filtered. The filtrate was concentrated under reduced pressure, and the product further purified by column chromatography on silica (*n*-hexane then an increasingly more polar hexane - diethyl ether mixture) to give cyclopentyl(2-(4-methoxyphenyl)ethyl)ketone[7] as a yellow viscous oil (**3.11**, 0.37 g, 32%); δ^1H (400 MHz; CDCl$_3$): 7.00 (2H, d, J = 8.6 Hz, CH*d*), 6.70 (2H, d, J = 8.6 Hz, CH*c*), 3.07 (3H, s, CH$_3$*a*), 2.75 (3H, m, CH$_2$*g*, CH*i*), 2.65 (2H, m, CH$_2$*f*), 1.40 - 1.70 (8H, m, CH$_2$*j, k*); δ^{13}C (125 MHz; CDCl$_3$): 212.4 (quat C, C=O), 158.0 (quat C, quat C*b*), 133.5 (quat C, C*e*), 129.3 (CH, C*d*), 113.9 (CH, C*c*), 55.3 (CH$_3$, OMe*a*), 51.6 (CH, C*i*), 43.6 (CH$_2$, C*g*), 29.0 (CH$_2$, C*f*), 28.8 (CH$_2$, C*j*), 26.0 (CH$_2$, C*k*); LR EI+-MS m/z (%): calculated 232, found 232 (M$^+$, 36%), 163 (54), 121 (100); v_{max} (neat/cm^{-1}): 2954, 2868, 2835, 1708 (C=O), 1612, 1584, 1513, 1451, 1300, 1247, 1178, 1037; Rf = 0.30 in *n*-hexane.

3.33 Cyanidation - third migration using *N*-phenylbenzimidoyl chloride

3.33a General procedure for third migration of *n*-octyl group. Tri-*n*-octylcyanoborate (5 mmol) was prepared as in procedure 3.32a, and *N*-phenylbenzimidoyl chloride (1.295 g in 6 mL of dry diglyme, 1.1 eq) was added drop-wise to the solution of tri-*n*-octylcyanoborate, and the reaction mixture left to stir overnight at rt. Excess trifluoroacetic anhydride (7 mL, 10 eq) was added drop-wise. The reaction time and temperature thereafter is different according to the specific reaction (Table 3.1). Oxidation was achieved in the same manner as the previous cyanidation reactions, and a diluted sample of the crude reaction mixture was analysed by GC.

3.33b General procedure for third migration in thexylcyclopentyl(2-(4-methoxyphenyl)ethyl)cyanoborate.

3.12
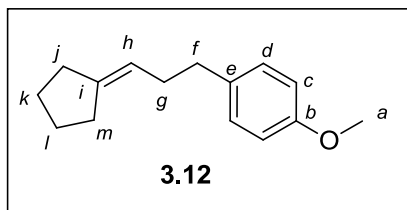
Procedure 3.33a was repeated using a solution of thexylcyclopentyl(2-(4-methoxyphenyl)ethyl)cyanoborate (prepared according to procedure 2.32d), except that the mixture was heated with TFAA at 40 °C for 24 h. The reaction was worked up in the same manner as the other cyanidation reactions to give the crude mixture (0.73 g) consisting of a 62:38 ratio of cyclopentyl(2-(4-methoxyphenyl)ethyl)ketone (**3.11**) to the corresponding olefin from two migrations, 1-(3-cyclopentylidenepropyl)-4-methoxybenzene (**3.12**, by relative integrations in the ^{1}H NMR spectrum). The olefin was purified by column chromatography on silica (*n*-hexane) to give 1-(3-cyclopentylidenepropyl)-4-methoxybenzene as a colourless oil (**3.12**, 0.33 g, 15%); δ^1H(400 MHz; CDCl$_3$): 7.05 (2H, d, *J* = 8.6 Hz, CH*d*), 6.75 (2H, d, *J* = 8.6 Hz, CH*c*), 5.2 (1H, m, CH*h*), 3.7 (3H, s, CH$_3$*a*), 2.5 (2H, t, *J* = 7.3 Hz, CH$_2$*f*), 2.15 (4H, m, CH$_2$*j, m*), 2.05 (2H, m, CH$_2$*g*), 1.50 - 1.60 (4H, m, CH$_2$*k, l*); δ^{13}C (125 MHz; CDCl$_3$): 157.7 (quat C, C*b*), 143.8 (quat C, C*i*), 134.7 (quat C, C*e*), 129.3 (CH, C*d*), 119.2 (CH, C*h*), 113.7 (CH, C*c*), 55.2 (CH$_3$, OMe*a*), 35.1 (CH$_2$), 33.6 (CH$_2$), 31.8 (CH$_2$), 28.6 (CH$_2$), 26.4 (CH$_2$), 26.3 (CH$_2$); HR EI-MS mz: calculated for C$_{15}$H$_{20}$O 216.1514, found 216.1513 (M$^+$, 60%); ν_{max} (neat/cm^{-1}): 3031, 2952, 1755, 1612, 1584, 1512, 1464, 1300, 1245, 1176, 1039; Rf = 0.45 in *n*-hexane.

Heating the intermediate after 2 migrations with pyridine at 80 °C for 24 h gave only **3.11**, and heating the intermediate with trichloroacetic anhydride -pyridine at 100 °C for 24 h gave black polymeric material along with **3.11**. No tertiary alcohol or **3.12** were seen in either experiment.

3.34 Synthesis of a chiral imidoyl chloride - attempt at isolating the cyanidation intermediate

3.34a Synthesis of (*S*)-*N*-(1-phenylethyl)benzamide (3.27).
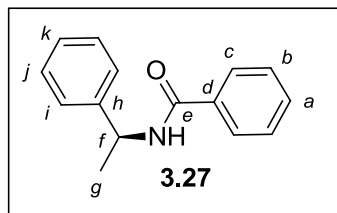
To a dry 100 mL round bottomed flask equipped with a magnetic stirrer bar, was added aqueous NaOH solution (1.6 g in 20 mL, 40 mmol) and (*S*)-α-methylbenzylamine (1.06 mL, 8.25 mmol). The solution was stirred for 10 min at 0 °C, and benzoyl chloride (0.96 mL, 8.25 mmol) was added drop-wise with stirring. The reaction mixture was left to come to rt, and was stirred for a further 2 h. Aqueous HCl solution (2 M) was added drop-wise until the solution was pH 4 - 5, and the product was extracted with diethyl ether and washed with several portions (2 × 30 mL each) of 2 M HCl, brine and water respectively. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give pure (*S*)-*N*-(1-phenylethyl)benzamide (**3.27**, 1.19 g, 64%) as white crystals; m.p 123 – 124 °C (lit 122 – 123 °C[21]); α$_D$ = -21.0 (lit -20.1[20]); δ^{1}H(400 MHz; CDCl$_3$): 7.70 (2H, d, *J* = 7.0 Hz, CH*c*), 7.45 (1H, m, CH*a*), 7.15 - 7.40 (7H, m, CH*b, i, j, k*), 6.25 (1H, b s, NH), 5.25 (1H, app p, *J* = 7.2 Hz, CH*f*), 1.5 (3H, d, *J* = 6.9 Hz, CH$_3$*g*); δ^{13}C (125 MHz; CDCl$_3$): 166.6 (quat C, C=O*e*), 143.2 (quat C, C*h*), 134.6 (quat C, C*d*), 131.5 (CH), 128.8 (CH), 128.6 (CH), 127.5 (CH), 127.0 (CH), 126.3 (CH), 49.2 (CH, C*f*), 21.7 (CH$_3$, C*g*); LR EI+-MS m/z (%): 225 (M$^+$, 57 %), 105 (100), 77 (38); v_{max} (thin film/cm^{-1}): 3442 (NH), 3321, 3064, 3016,1652 (C=O), 1604, 1580, 1515, 1485, 1450, 1216.

3.34b Synthesis of *N*-(1-(*S*)-Phenylethyl)benzimidoyl chloride) (3.28).
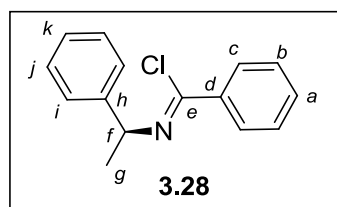
Procedure 3.31b was repeated using (*S*)-*N*-(1-phenylethyl)benzamide (1.0 g, 4.5 mmol) and freshly distilled thionyl chloride (8.0 mL, 110 mmol) to give the crude product. Dry hexane (10 mL) was added, and the mixture stirred for 5 min. The supernatant hexane layer was

transferred to a dry 25 mL flask already under N_2 *via* cannula, and the hexane evaporated under a fast stream of N_2 to give near-pure *N*-(1-(*S*)-Phenylethyl)benzimidoyl chloride[21] (**3.28**, 0.87 g, 80%) as a light yellow oil; δ^1H(400 MHz; CDCl$_3$): 7.45 – 7.50 (3H, m), 7.10 - 7.40 (7H, m), 5.0 (1H, q, *J* = 6.8 Hz, CH*f*), 1.75 (3H, d, *J* = 6.8 Hz, CH$_3$*g*); δ^{13}C (125 MHz; CDCl$_3$): 142.9 (quat C), 132.8 (CH), 132.2 (CH), 129.2 (CH), 128.7 (CH), 128.3 (CH), 126.6 (CH), 119.0 (quat C), 112.4 (quat C), 58.9 (CH, C*f*), 22.7 (CH$_3$, C*g*); LR EI+-MS m/z (%): 244 (M^++1, 8%), 208 (13), 193 (11), 174 (13), 140 (97), 125 (98), 104 (100), 76 (67), 63 (34); ν_{max} (neat/cm^{-1}): 3065, 3033, 2977, 2928, 2867, 2229 (trace benzonitrile), 1599, 1582, 1492, 1455, 1447, 1234, 1027.

This chiral imidoyl chloride was left to react with thexylcyclopentyl(2-(4-methoxyphenyl)ethyl)cyanoborate overnight at rt. The reaction solvents were evaporated under reduced pressure, and dry hexane (25 mL) was added, and the supernatant layer transferred to a dry flask under N_2. The hexane was evaporated under a N_2 stream, and deoxygenated water (5 mL) was added and the solution stirred for 1 h. Excess water was syringed out, and toluene (10 mL) was added. The crude hydrate precipitated as light yellow solid over 2 h, however the NMR spectrum was too complicated as a result of impurities to indicate whether there was any diastereomeric excess. Further attempts to purify the material were unsuccessful, with the mixture slowly oxidising as evident by the appearance of thexanol in the proton NMR spectrum.

3.35 Synthesis and reaction of *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (3.14)

3.35a Synthesis of 2,2,2-trifluoro-*N*-phenylacetamide (3.16).
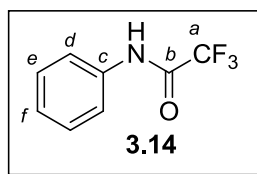
To a 100 mL round bottomed flask equipped with a magnetic stirrer bar were added aniline (6.00 g, 64 mmol), trifluoroacetic acid (14.70 g, 129 mmol, 2 eq) and xylene (50 mL). A reflux condenser was fitted, and the mixture was heated (bath temperature 135 °C) for 11 h. Xylene was evaporated under reduced pressure, and the crude mixture was purified by column chromatography on silica (4:1 hexane: ethyl acetate) to give 2,2,2-trifluoro-*N*-phenylacetamide (**3.16**, 10.90 g, 90%) as peach - white crystals; m.p 89.5-90.5 °C (lit. 90.5 –

91 °C)[13]; δ^1H(400 MHz; CDCl$_3$): 8.25 (1H, b s, NH), 7.45 - 7.50 (2H, d, *J* = 7.7 Hz, CH*d*), 7.25 (2H, app t, *J* = 8.3 Hz, CH*e*), 7.15 (1H, t, *J* = 7.5 Hz, CH*f*); δ^{13}C (125 MHz; CDCl$_3$): 155 (quat C, q, *J* = 31.3 Hz, C=O*b*), 135.1 (quat C, C*c*), 129.3 (CH, C*e*), 126.4 (CH, C*f*), 120.8 (CH, C*d*), 114.6 (quat C, q, *J* = 250 Hz, C*a*); δ^{19}F{^{1}H} (280 MHz; CDCl$_3$): -75.8 (s); LR APCI+-MS m/z (%): 190 (M$^+$+ 1, 30%); ν_{max} (thin film/cm^{-1}): 3422 (NH), 3317, 3154, 3020, 1733 (C=O), 1602, 1549, 1498, 1452, 1286, 1217, 1166; Rf = 0.41 in 4:1 hexane: ethyl acetate.

Attempts at chlorinating the benzamide to make the corresponding imidoyl chloride gave only starting material. Refluxing in thionyl chloride for 3h gave only 2,2,2-trifluoro-*N*-phenylacetamide. Reaction with the Vilsmeier salt of 2,6-lutidine and oxalyl chloride at 0 °C for 1 h also gave only starting material.

3.35b Direct synthesis of *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (3.14).

3.14
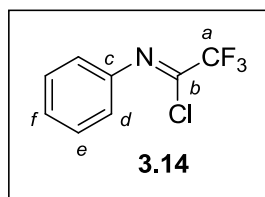
An oven dried three necked 250 mL round bottomed flask was equipped with a magnetic stirrer bar, septum, stopper and septum-capped reflux condenser. Triphenylphosphine (34.5 g, 132 mmol) was added through the side neck, and the apparatus flushed with N$_2$ for 15 min. Triethylamine (7.3 mL, 53 mmol), carbon tetrachloride (21.1 mL, excess) and finally trifluoroacetic acid (3.4 mL, 44 mmol) were added drop-wise at 0 °C. The resulting white solution was stirred for 10 min, and a solution of aniline (4.83 mL, 53 mmol) in carbon tetrachloride (21.1 mL) was added drop-wise with stirring. The mixture was then heated to reflux for 3 h. The volatiles were removed under reduced pressure, and dry hexane (2 × 100 mL) was added. The solution was stirred for 20 min, and the supernatant hexane layer was transferred *via* cannula to an apparatus already under N$_2$ (two 100 mL round bottomed flasks, joined together by a fritted glass tube). This procedure was repeated, and the combined hexane extracts were filtered using positive N$_2$ pressure, and the hexane evaporated under a fast stream of N$_2$ to give the crude product as a yellow oil. The crude product was further purified by distillation under reduced pressure to give *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (**3.14**, 2.67 g, 29%)[12] as a light-yellow oil; δ^1H(400 MHz; CDCl$_3$): 7.4 (2H, app t, *J*

= 7.9 Hz, CH*e*), 7.25 (1H, m, CH*f*), 7.0 (2H, d, *J* = 7.8 Hz, CH*d*); $\delta^{13}C$ (125 MHz; CDCl$_3$): 143.5 (quat C, C*b*), 132.1 (quat C, C*c*), 129.1 (CH, C*e*), 127.4 (CH, C*f*), 120.6 (CH, C*e*), 117 (quat C, q, *J* = 250 Hz, C*a*); $\delta^{19}F\{^1H\}$ (280 MHz; CDCl$_3$): -71.5 (s); LR EI+-MS m/z (%): 207 (M$^+$, 48%), 189 (24), 172 (100), 138 (40), 77 (40); ν_{max} (neat/cm^{-1}): 3071, 3039, 1698, 1597, 1585, 1489, 1287, 1223, 1162.

3.35c Reaction of imidoyl chloride 3.14 with thexylcyclopentyl(2-(4-methoxyphenyl)ethyl) cyanoborate. A solution of *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (6 mmol in 7 mL dry diglyme) was added drop-wise to a solution of thexylcyclopentyl(2-(4-methoxyphenyl)ethyl)cyanoborate in THF (prepared according to procedure 3.33b). The solution was left to stir overnight at rt, an aliquot taken, oxidised and worked-up. There was no evidence of the ketone or tertiary alcohol expected from migrations from boron to carbon in the ^1H and ^{13}C NMR spectra. The reaction mixture was then heated to 80 °C overnight (having been stirring at rt during the aliquot work-up), and again an aliquot taken and oxidised. A trace amount of ketone arising from two migrations was seen in the ^1H NMR spectrum. However, further heating for 3 h at 150 °C did not give more of the ketone. The reaction mixture had turned black at this point, and the *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride had presumably decomposed. The major products at all points in the reaction were the corresponding alcohols from hydroboration -oxidation, as seen in the ^1H NMR spectra taken for each aliquot.

3.36 Synthesis and reaction of 4-nitro-*N*-phenylbenzimidoyl chloride (3.13)

3.36a Synthesis of 4-nitro-*N*-phenylbenzamide (3.15).
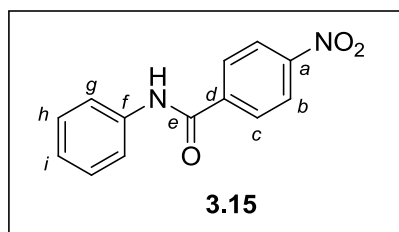
3.15

A 250 mL round bottomed flask equipped with a magnetic stirrer bar and septum was flushed with N$_2$ for 15 min. Aniline (9.86 g, 0.10 mol) and triethylamine (22.16 mL, 0.15 mol) were added, and the solution stirred for 10 min at rt. The solution was cooled to 0°C, and a solution of 4-nitrobenzoyl chloride (19.65 g, 0.10 mol) in dry dichloromethane (100 mL) was added drop-wise *via* a cannula while the reaction mixture was stirred vigorously. On completion of

the addition, the reaction mixture was left to stir at rt for a further 3 h. The reaction mixture was transferred to a separating funnel, and washed several times with water (10×100 mL) and brine (5×10 mL). The solution was dried over magnesium sulfate, filtered, and the dichloromethane evaporated under reduced pressure to give 4-nitro-*N*-phenylbenzamide (**3.15**, 24.09 g, 94%) as a light-yellow solid; m.p 225 – 226 °C (lit. 218 – 219 °C[10]); δ^1H(400 MHz; d$_6$ DMSO): 10.6 (1H, b s, NH), 8.4 (2H, d, J = 8.8 Hz, CH*b*), 8.2 (2H, d, J = 8.8 Hz, CH*c*), 7.8 (2H, d, J = 7.7 Hz, CH*g*), 7.4 (2H, appt, J = 7.7 Hz, CH*h*), 7.1 (1H, t, J = 7.4 Hz, CH*i*); δ^{13}C (125 MHz; d$_6$ DMSO): 164.2 (quat C, C=O*e*), 149.5 (quat C, C*a*), 141.0 (quat C), 139.1 (quat C), 129.6 (CH), 129.0 (CH), 124.5 (CH), 123.9 (CH), 120.9 (CH); LR EI+-MS m/z (%): 242 (M$^+$, 55%), 212 (27), 150 (87), 120 (100), 86 (62); ν_{max} (thin film/cm^{-1}): 3317 (NH), 2925, 1645 (C=O), 1597, 1463, 1377.

3.36b Synthesis of 4-nitro-*N*-phenylbenzimidoyl chloride (3.13).

3.13
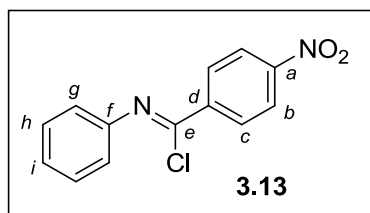
An oven dried two necked 100 mL flask equipped with a magnetic stirrer, septum-capped reflux condenser and septum was flushed with N$_2$ and then transferred to a N$_2$ glovebag. Phosphorus pentachloride (9.7 g, 47 mmol) was added under a N$_2$ atmosphere, and the apparatus taken away from the glovebag. Dry toluene (40 mL) was added, and the mixture stirred for 5 min. 4-Nitro-*N*-phenylbenzamide (11.28 g, 47 mmol) was quickly added to the flask under a fast stream of N$_2$, and the septum replaced by a stopper. The mixture was then heated to reflux for 1 h, where it became homogeneous and gas evolution was observed. Phosphorus oxychloride and toluene were evaporated under reduced pressure. The crude product was purified by quickly dissolving in hot diethyl ether (3×80 mL) and filtering. The diethyl ether washings were collected, and immediately flushed with N$_2$ in a dry stopcock flask. Excess ether was evaporated under a fast stream of N$_2$ overnight, to leave 4-nitro-*N*-phenylbenzimidoyl chloride (**3.13**, 10.41 g, 85%) as bright green-yellow crystals; m.p 123-124 °C (lit. 134- 136 °C[11]); δ^1H(400 MHz; CDCl$_3$): 8.18 - 8.27 (4H, m, CH*b, c*), 7.35 (2H, app t, J = 8.0 Hz, CH*h*), 7.15 (1H, app t, J = 7.4 Hz, CH*i*), 6.95 (2H, d, J = 7.3 Hz, CH*g*); δ^{13}C (125 MHz; CDCl$_3$): 149.8 (quat C), 146.8 (quat C), 141.0 (quat C), 140.9 (quat C), 130.4 (CH), 129.1 (CH), 126.0 (CH), 123.6 (CH), 120.4 (CH); LR EI+-MS m/z (%): 260

(M$^+$, 58%), 225 (100), 1995 (48), 179 (90), 86 (100), 77 (80); ν_{max} (thin film/cm^{-1}): 3104, 2342, 1650, 1603, 1579, 1519.

3.36c Test reaction with thexylcyclopentyl(2-(4-methoxyphenyl)ethyl)cyanoborate. A solution of 4-nitro-*N*-phenylbenzimidoyl chloride (1.46 g, 5.6 mmol) in dry diglyme (7 mL) was added to a solution of thexylcyclopentyl(2-(4-methoxyphenyl)ethyl)cyanoborate (5 mmol, prepared according to procedure 2.32a) in THF (5 mL), and was stirred at rt for 14 h. An aliquot was taken, oxidized and worked-up. The crude ^{1}H NMR spectrum showed cyclopentyl(2-(4-methoxyphenyl)ethyl)ketone almost exclusively. Excess TFAA (10 eq) was added drop-wise to the reaction mixture, and the solution kept at 40 °C for 14 h. The reaction mixture was oxidised and worked-up as in previous cyanidation reactions, and the NMR spectra taken. Analysis of the NMR spectra showed 1-(3-cyclopentylidenepropyl)-4-methoxybenzene (**3.12**) as the major component, with some cyclopentyl 2-(4-methoxyphenyl)ethyl)ketone (**3.11**) (in a 78:22 ratio by relative integration of the ^{1}H NMR spectrum of the crude product).

3.36d Synthesis of 1-(3-cyclopentylidenepropyl)-4-methoxybenzene. Procedure 3.36c was repeated, but an aliquot was not taken prior to the addition of TFAA. The components of the crude mixture were separated by column chromatography on silica (hexane) to give 1-(3-cyclopentylidenepropyl)-4-methoxybenzene (**3.12**, 0.59 g, 55% yield) and cyclopentyl 2-(4-methoxyphenyl)ethyl)ketone (**3.11**, 0.058 g, 5% yield).

3.36e Test reaction for reactivity of 4-nitro-*N*-phenylbenzimidoyl chloride. A solution of 4-nitro-*N*-phenylbenzimidoyl chloride (1.46 g, 5.6 mmol) in diglyme (5 mL) was added drop-wise to a solution of tri-*n*-octylcyanoborate (5 mmol, prepared according to procedure 3.32a) in THF (5 mL). The reaction was left to stir for 3 h at rt, and the mixture oxidised and worked-up as before. The components were separated by column chromatography on neutral alumina (hexane, followed by 3:1 hexane: diethyl ether) to give di-*n*-octylketone (**3.5**, 0.64 g, 50% yield), and 1-/2-octanol (0.86 g, 44% yield based on three octyl groups).

3.36f Reaction of tri-*n*-octylcyanoborate with 4-nitro-*N*-phenylbenzimidoyl chloride, followed by TFAA. A solution of 4-nitro-*N*-phenylbenzimidoyl chloride (1.46 g, 5.6 mmol) in diglyme (5 mL) was added drop-wise to a solution of tri-*n*-octylcyanoborate (5 mmol, procedure 3.32a) in THF (5 mL). The mixture was left to stir overnight at rt, and excess

TFAA (7 mL) was added drop-wise. The reaction mixture was heated to 40 °C for 14 h, the excess TFAA evaporated under reduced pressure and the mixture oxidised and worked-up as in procedure 3.32a. The crude product was purified by column chromatography on neutral alumina (hexane, followed by 3:1 hexane: diethyl ether) to give di-*n*-octylketone (**3.5**, 0.22 g, 17% yield) and tri-*n*-octylmethanol (**3.6**, 0.90 g, 49% yield).

3.36g Reaction of tricyclopentylcyanoborate with 4-nitro-*N*-phenylbenzimidoyl chloride, followed by TFAA.
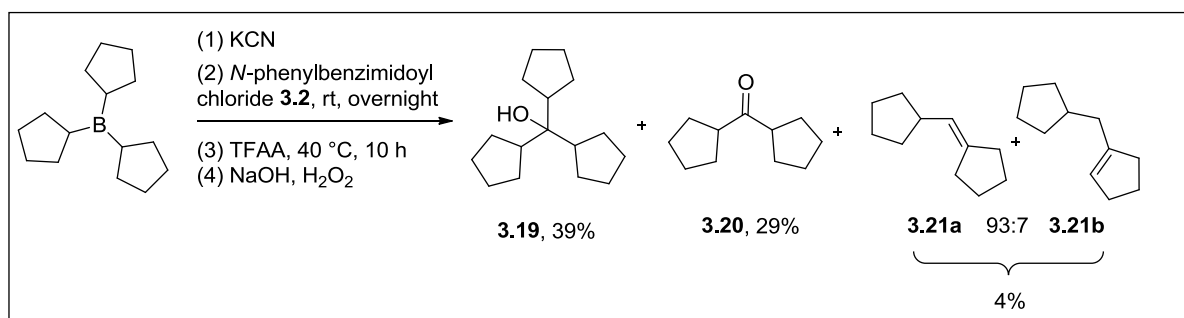
Procedure 3.36f was repeated, except that tricyclopentylcyanoborate (5 mmol) was the cyanoborate used. Separation of the components first by using column chromatography on neutral alumina (4:1 hexane: diethyl ether), followed by preparative chromatography to separate the two least polar components gave cyclopentylmethylenecyclopentane[9] (**3.21**, 0.031 g, 4%) as a colourless oil; δ^1H(400 MHz; CDCl$_3$): 5.10 (1H, m, alkenyl CH), 2.45 (1H, m, CH), 2.10 - 2.20 (4H, m), 1.70 (2H, m), 1.40 - 1.60 (8H, m), 1.15 (2H, m); δ^{13}C (125 MHz; CDCl$_3$): 147.1 (quat C, alkenyl C), 125.6 (CH, alkenyl C), 40.8 (CH, Cp CH), 33.6 (CH$_2$), 33.4 (CH$_2$), 31.2 (CH$_2$), 30.9 (CH$_2$), 28.6 (CH$_2$), 26.5 (CH$_2$), 26.4 (CH$_2$), 25.3 (CH$_2$); Rf = 0.76 in 3:1 hexane: diethyl ether, dicyclopentyl ketone (**3.20**, 0.249 g, 29%)[2] as a colourless oil; δ^1H(400 MHz; CDCl$_3$): 2.90 (2H, m), 1.40 - 1.80 (16H, m, CH$_2$); δ^{13}C (125 MHz; CDCl$_3$): 216.0 (quat C, C=O), 50.7 (CH), 26.1 (CH$_2$), 25.2 (CH$_2$); LR EI+-MS m/z (%): 166 (M$^+$, 24%), 97 (98), 69 (100); v_{max} (neat/cm^{-1}): 2952, 2868, 1705 (C=O), 1451, 1368, 1303, 1116, 915; Rf = 0.70 in 3:1 hexane: diethyl ether, and tricyclopentylmethanol (**3.19**, 0.41 g, 39%) as a light yellow oil; Rf = 0.48 in 3:1 hexane: diethyl ether.

3.36h Reaction of di-*n*-octylthexylcyanoborate with 4-nitro-*N*-phenylbenzimidoyl chloride, followed by TFAA.
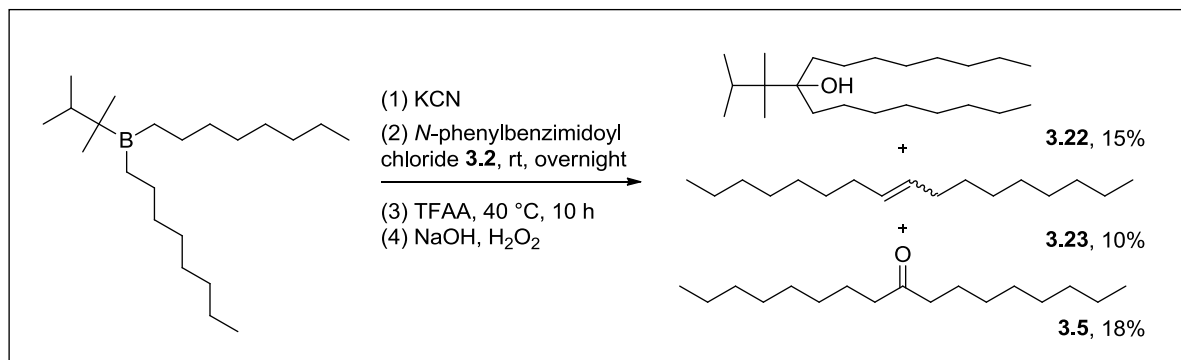
Hydroboration was achieved by the drop-wise addition of 2,3-dimethyl-2-butene (0.63 g, 7.5 mmol) to neat borane dimethyl sulfide (0.5 mL 10 M, 5 mmol) at 0 °C, and then the reaction mixture was left to stir for 2 h. Dry THF (5 mL) was added, followed by the drop-wise addition of 1-octene (1.57 mL, 10 mmol). The reaction mixture was left to stir for 2 h at 0 °C, dry finely ground potassium cyanide (0.342 g) was added *via* the bent side-arm, and the mixture was stirred for 90 min at rt. A solution of 4-nitro-*N*-phenylbenzimidoyl chloride (1.46 g, 5.6 mmol) in diglyme (5 mL) was added drop-wise, and the solution left to stir at rt overnight. Excess TFAA (7 mL) was added drop-wise, and the mixture heated to 40 °C for 14 h. The reaction mixture was oxidised and worked-up in the same manner as previous cyanidation reactions. The components of the crude product were separated by column chromatography on neutral alumina (hexane, followed by increasingly polar diethyl ether-hexane eluents) to give heptadec-8-ene[16] as a mixture of isomers (*Z*)/(*E*): 88:12 by relative integrations in the ^{1}H NMR spectrum, colourless oil (**3.23**, 0.12 g, 10%); δ^1H (400 MHz; CDCl$_3$): 5.25 – 5.35 (2H, m, alkenyl CH), 1.90 – 2.00 (4H, m), 1.10 – 1.30 (22H, m), 0.80 (6H, t, *J* = 7 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 130.3 (CH, alkenyl CH), 32.3 (CH$_2$), 30.6 (CH$_2$), 30.2 (CH$_2$), 30.1 (CH$_2$), 28.5 (CH$_2$), 23.1 (CH$_2$), 14.5 (CH$_3$); LR EI+-MS m/z (%): 238 (M$^+$, 45%), 119 (100), 111 (21), 97 (44), 84 (100), 71 (100), 57 (100); v_{max} (neat/cm^{-1}): 3004, 2956, 2925, 2854, 1718, 1467; Rf = 0.91 in 4:1 hexane: ethyl acetate, di-*n*-octylketone (**3.5**, 0.23 g, 18% yield) and di-*n*-octylthexylmethanol[2] (**3.22**, 0.26 g, 15%) as a yellow oil; δ^1H (400 MHz; CDCl$_3$): 1.80 (1H, m, CH), 1.50 (4H, m), 1.10 – 1.30 (24H, m), 0.85 (6H, d, *J* = 6.8 Hz, CH$_3$), 0.80 (6H, t, *J* = 6.7 Hz, CH$_3$), 0.75 (6H s, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 79.6 (quat C, COH), 43.7 (quat C), 36.4 (CH$_2$), 32.8 (CH), 31.9 (CH$_2$), 30.8 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 25.0 (CH$_2$), 22.7 (CH$_2$), 20.3 (CH$_3$), 20.1 (CH$_3$), 14.0 (CH$_3$); HR EI+-MS

m/z (%): calculated for $C_{23}H_{47}$ 323.3678, found 323.3663 (M^+ - H_2O, 28%); ν_{max} (neat/cm^{-1}): 3533, 2924, 2854, 1716; Rf = 0.63 in 4:1 hexane: ethyl acetate.

3.36i Low Temperature addition of TFAA. Procedure 3.36d was repeated, but the addition of TFAA was carried out at -78 °C in an attempt to stop the production of the alkene **3.12**. ^{1}H NMR analysis of the crude product showed a 74:26 ratio of alkene **3.12** to ketone **3.11**.

3.36j Attempt at displacing the thexyl group by an octyl group following first two migrations, followed by subsequent migration of octyl group by TFAA. Procedure 3.36d was repeated, however before addition of the TFAA, 1-octene (2.35 mL, 15 mmol) was added, and the reaction mixture was heated to 100 °C for 6 h. TFAA was added as before, and the procedure was identical thereafter. ^{1}H NMR analysis of the crude product showed the presence of excess 1-octene and the ketone **3.11** (in a 79:21 ratio respectively by relative integrations in the ^{1}H NMR spectrum), but no trace of alkene **3.12** or 1-octanol was present.

3.36k Direct lithiation of intermediate after two migrations. Procedure 3.36d was repeated, and following reaction with the imidoyl chloride, the reaction mixture was cooled to -78 °C. A solution of *n*-BuLi in hexanes (1.45 M, 3.45 mL, 5.0 mmol) was added drop-wise with vigorous stirring. The reaction was left to stir at low temperature for 1 hour. The addition of TFAA and subsequent steps were carried out as in experiment 3.6d. ^{1}H analysis of the crude mixture showed a 75:25 ratio of alkene **3.12** to ketone **3.11** by relative integrations in the ^{1}H NMR spectrum.

3.36l Displacement of thexyl group by acetaldehyde, followed by addition of *n*-BuLi and subsequent migration with TFAA. Procedure 3.36d was repeated until the reaction with the imidoyl chloride was complete. Acetaldehyde (0.56 mL, 10 mmol) was added drop-wise by syringe, and the solution left to stir at rt for 36 h. Excess acetaldehyde was removed under a fast stream of N_2, and a solution of *n*-BuLi in hexanes (1.45 M, 3.45 mL, 5.0 mmol) was added drop-wise with vigorous stirring at -78 °C. The addition of TFAA and subsequent steps were carried out as in procedure 3.36d. Analysis of the crude mixture by ^{1}H NMR spectroscopy showed only the ketone **3.11**, with no presence of alkene **3.12**.
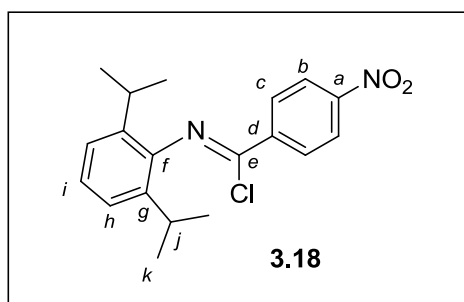
3.37 Synthesis and reaction of *N*-(2,6-diisopropylphenyl)-4-nitrobenzimidoyl chloride (3.18)

3.37a Synthesis of *N*-(2,6-diisopropylphenyl)-4-nitrobenzamide (3.17).
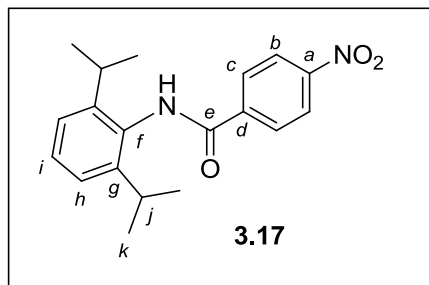
Procedure 3.36a was repeated on a 57 mmol scale, except that 2,6-diisopropylaniline replaced aniline, and the crude product was washed an additional two times with aqueous acid during the work up. The crude product was recrystallised from hot ethanol to give *N*-(2,6-diisopropylphenyl)-4-nitrobenzamide (**3.17**, 6.80 g, 77%) as light yellow crystals; m.p 319-320 °C (lit. 303-306 °C^{15}); δ^{1}H (250 MHz; CDCl$_3$): 8.15 (2H, d, *J* = 7.7 Hz, CH*b*), 7.95 (2H, d, *J* = 8.8 Hz, CH*h*), 7.65 (1H, b s, NH), 7.35 (1H, m, CH*i*), 7.15 (2H, d, *J* = 7.5 Hz, CH*c*), 3.00 (2H, sept, *J* = 6.9 Hz, CH*j*), 1.10 (12H, d, *J* = 6.9 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 165.2 (quat C, C=O*e*), 149.7 (quat C), 146.5 (quat C), 140.5 (quat C), 132.6 (quat C), 129.4 (CH), 128.4 (CH), 124.2 (CH), 123.5 (CH), 28.6 (CH), 23.9 (CH$_3$), 23.7 (CH$_3$); LR EI+-MS m/z (%): 326 (M$^+$, 75%), 296 (97), 283 (73), 253 (86), 176 (95), 120 (98), 92 (74), 84 (100), 71 (52), 65 (34); *v*$_{max}$ (thin film/cm^{-1}): 2966, 1677 (C=O), 1602, 1528, 1477, 1348.

3.37b Synthesis of *N*-(2,6-diisopropylphenyl)-4-nitrobenzimidoyl chloride (3.18).

Procedure 3.37b was repeated using phosphorus pentachloride (4.42 g, 21 mmol), dry toluene (30 mL) and *N*-(2,6-diisopropylphenyl)-4-nitrobenzamide (6.90 g, 21 mmol), except the reflux was left for 2 h, to give *N*-(2,6-diisopropylphenyl)-4-nitrobenzimidoyl chloride (3.18, 6.93 g, 95%) as bright yellow prisms; m.p 144-146 °C; δ^{1}H (400 MHz; CDCl$_3$): 8.25 (2 H, d,

J = 8.4 Hz), 8.17 (2 H, d, *J* = 8.4 Hz), 7.05–7.12 (2 H, m), 6.97–7.04 (1 H, m), 2.66 (2 H, app. sept, *J* = 6.9 Hz), 1.11 (6 H, d, *J* = 6.6 Hz), 1.05 (6 H, d, *J* = 6.6 Hz) – the two 6 H doublets coalesced at 50 °C to give a singlet due to hindered rotation of the CH - Me bond, VT- ^{1}H NMR (using MestreNova software) showed that for this rotation: $\Delta H^{\ddagger}$ = + 16.9 kJmol^{-1} and $\Delta S^{\ddagger}$ = - 174.9 J mol^{-1}; δ^{13}C (125 MHz; CDCl$_3$): 149.9 (quat C), 143.4 (quat C), 141.8 (quat C), 140.1 (quat C), 136.3 (CH), 130.3 (CH), 125.5 (CH), 123.7 (CH), 123.3 (CH), 28.8 (CH), 23.3 (CH$_3$), 22.8 (CH$_3$); HR EI$^+$-MS m/z: calculated for C$_{19}$H$_{21}$N$_2$O$_2$^{35}Cl 344.1292, found 344.1301; v_{max} (thin film/cm^{-1}): 3017, 2966, 2929, 2871, 1662, 1605, 1529, 1349, 1216, 1168, 1461; Crystallography data (diglyme): Triclinic, space group: P1, *a* = 8.2988(4) Å, *b* = 10.4667(3) Å, *c* = 10.9665(3) Å, α = 75.568(2), β = 85.411(2), γ = 74.145(2), 887.335 Å^3, *Z* =2, *R$_1$* = 6.16.

3.37c Reaction of *N*-(2,6-diisopropylphenyl)-4-nitrobenzimidoyl chloride. Procedure 3.36d was repeated, except that *N*-(2,6-diisopropylphenyl)-4-nitrobenzimidoyl chloride replaced 4-nitro-*N*-phenylbenzimidoyl chloride. Analysis of the crude mixture by ^{1}H NMR spectroscopy showed mostly alkene **3.12**, with some of ketone **3.11** (78:22 ratio by relative integrations in the crude ^{1}H NMR spectrum).

3.4 References

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Chapter 4: Generation of quaternary carbon centres by homologation of tertiary alkylboronic esters

4.1 Aims and introduction

As mentioned in Chapter 1, boronic esters can be homologated by the addition of (bromomethyl)lithium to the starting boronic esters at low temperatures, followed by warming to room temperature to effect migration of the alkyl group with bromide acting as a leaving group. If the alkyl group in the starting boronic ester is a tertiary alkyl group, then the migration of the tertiary alkyl group would generate a quaternary carbon (Scheme 4.1).

Scheme 4.1 Homologation of a tertiary alkylboronic ester using (bromomethyl)lithium

R^1 = tertiary alkyl group, R^2 = alkyl group
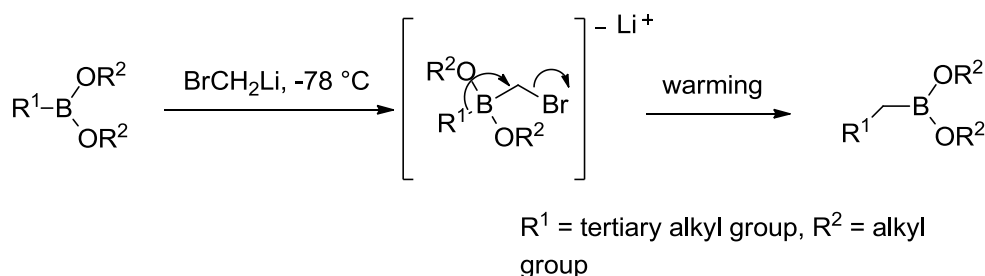
D. S. Matteson and T. J. Michnick first demonstrated that the highly unstable (bromomethyl)lithium could be efficiently trapped by either aldehydes/ketones or boronic esters.[1] Even though it has been shown that (bromomethyl)lithium decomposes at temperatures above -130 °C without the presence of LiBr,[2] excellent yields of the homologated boronic esters were achieved by the drop-wise addition of *n*-BuLi to phenyl- and isopropylboronic esters in the presence of dibromomethane at a temperature of -78 °C (Scheme 4.2).

Scheme 4.2 First examples of the homologation of boronic esters using (bromomethyl)lithium
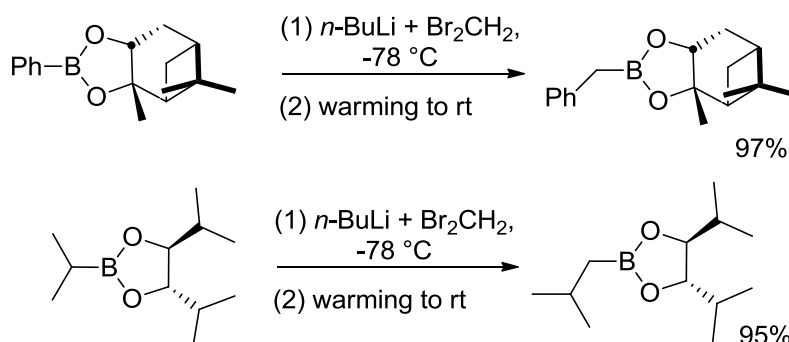
In 1992, R. H. Wallace and K. K. Zong used this method for the homologation of a primary alkylboronic ester.[3] However, it was not until 1994 that a more detailed piece of work was published by H. C Brown *et al.* on this promising organoboron reaction.[4] The migration of several different alkyl groups was explored (Table 4.1), with all giving excellent yields of the corresponding alcohols from homologation of the starting boronic esters except for the migration of a tertiary butyl group. This result is of special importance to our research interests, as the migration of a tertiary group would generate our target quaternary carbon centre. Three carbenoid reagents were explored ((bromomethyl)lithium, (chloromethyl)lithium and (iodomethyl)lithium), with the first of these giving the best result for the migration of the tertiary butyl group.

Table 4.1 Homologation and subsequent oxidation of various boronic esters using (halomethyl)lithium reagents

$$R^1-B\underset{O}{\overset{O}{\Big\langle}} \quad \xrightarrow[\substack{(2)\text{ warming to rt}\\(3)\text{ NaOH, H}_2\text{O}_2}]{\substack{(1)\ n\text{-BuLi + CH}_2\text{XY,}\\-78\ ^\circ\text{C}}} \quad R^1 \diagup OH$$
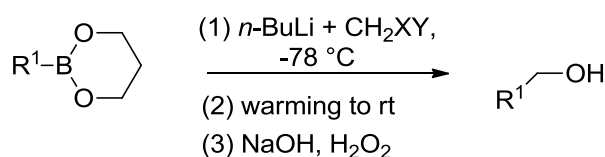
R^1	Yield (%)[a]		
	Cl	Br	I
n-Bu	96	89	68
sec-Bu	92	87	63
tert-Bu	41	66	51
Ph	92	92	82

[a] Yields based on GC analysis of the homologated alcohols.

A certain amount of the lowering in yield for tertiary butyl migration in the case of (chloromethyl)lithium was apportioned to an unwanted oxygen-migration side-reaction (around 20% seen in the ^{11}B NMR spectrum prior to oxidation). Several different *n*-butyl- and phenylboronic esters derived from different diols were also explored, and showed that the boronic esters derived from 1,3-propanediol gave the highest yields of homologated product.

More recently, V. K. Aggarwal *et al.* used the reaction as a way of generating chiral quaternary carbon centres from the chiral tertiary boronic esters prepared from chiral secondary alcohols.[5] In agreement with previous work,[4] (chloromethyl)lithium gave lower yields due to some oxygen-migration and switching to (bromomethyl)lithium overcame this problem. However, the yields were still low in some of the pinacol-derived boronic esters containing more hindered tertiary alkyl groups. Switching to a less hindered diol (2,2-dimethyl-1,3-propanediol instead of pinacol) did raise the yield somewhat (Table 4.2).

Table 4.2 Homologation of various tertiary boronic esters using (bromomethyl)lithium
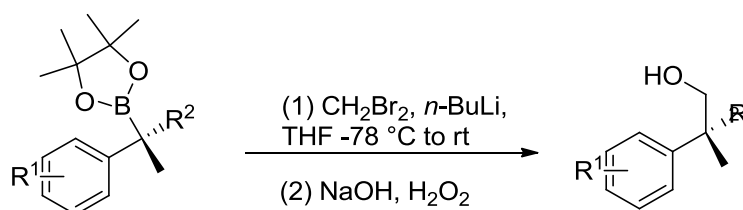
R^1	R^2	Yield (%)[a]
4-Cl	Et	88
H	iPr	37[b]
H	iPr	30
4-MeO	Ph	41

[a] Isolated yields. [b] Boronic ester derived from 2,2-methyl-1,3-propanediol used.

In our attempts to generate chiral quaternary carbon centres, we decided to look at this homologation reaction in more detail with regard to the migration of tertiary alkyl groups, in the hope of gaining a better understanding of why there is at present a lowering of yield compared to the migration of primary and secondary alkyl groups and of developing a better experimental procedure.

4.2 Results and discussion

4.21 Synthesis and reactions of selected thexylboronic esters

Initially, we chose to study a range of thexylboronic esters due to their ease of preparation and also because the thexyl alkyl group is a quite sterically demanding tertiary alkyl group and so would serve as a good test of the homologation reaction. A previous student in the group had achieved encouraging results with dimethoxythexylborane (**4.1**), although the results were not always reproducible.[6] We reasoned this might be due to the compound's instability towards both oxidation and hydrolysis, and so a range of cyclic thexylboronic esters were produced in the hope that this would aid the problem of instability.

The thexylboronic esters were produced in two steps, first by the monohydroboration of 2,3-dimethyl-2-butene with $BH_3 \cdot SMe_2$,[7] and then by reaction with the appropriate diol (Scheme 4.3). Following completion of reaction, the dimethyl sulfide was removed under a stream of nitrogen to give the thexylboronic esters.

Scheme 4.3 Synthesis of a range of thexylboronic esters
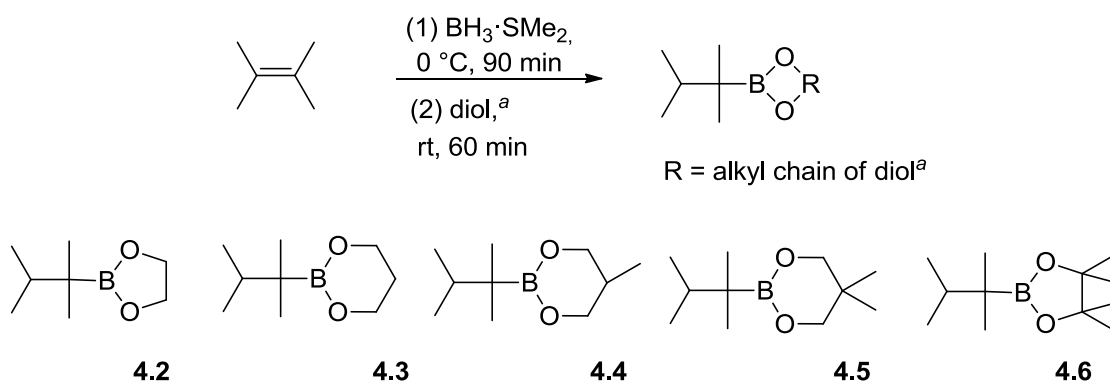
[a] diols (left to right) = ethylene glycol, 1,3-propanediol, 2-methyl-1,3-propanediol, 2,2-dimethyl-1,3-propanediol and pinacol.

The boronic esters were fully characterised, with the data in accordance to those reported in the literature (boronic esters **4.4** and **4.5** were novel, but all the data were in agreement with the proposed structures, E.S. 4.31).[8] The thexylboronic esters were essentially pure (by $^1H/^{13}C/^{11}B$ NMR spectroscopy) with no need for further purification (boronic ester **4.4** had some small impurities present, with the ^1H and ^{13}C NMR spectra both showing the presence of another thexyl group).

The procedure for producing the thexylboronic esters having been established, they were freshly prepared without isolation for all subsequent homologation reactions (due to their instability over an extended period of time). Each boronic ester was surveyed for the homologation/oxidation reaction using *in-situ* prepared (bromomethyl)lithium (from 1.2 eq of dibromomethane and 1.1 eq of *n*-BuLi) (Table 4.3).

The extent of oxidised homologated product was measured by careful integration of the thexanol (**4.8**) and thexylmethanol (**4.7**) signals present in the ^{1}H NMR spectrum of the crude product following an aqueous work-up. Great care was taken during the evaporation of solvent following the aqueous work-up to ensure that the result was not affected by preferential evaporation of thexanol relative to thexylmethanol (generally the reaction mixture was evaporated to 120 - 140% of the weight for the theoretical yield).

Table 4.3 Homologation of various thexylboronic esters by *in situ* prepared (bromomethyl)lithium
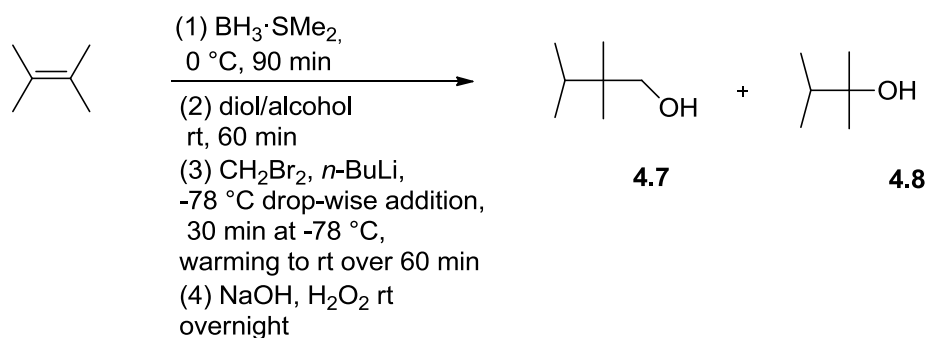
Thexylboronic ester[a]	Yield (%)[b]	
	thexylmethanol (**4.7**)	thexanol (**4.8**)
4.1[c]	78	22
4.2	80 (75)[d]	20
4.3	79	21
4.4	64	36
4.5	70	30
4.6	35	65

The less hindered thexylboronic esters (**4.1 – 4.3**) performed well in the homologation/oxidation reaction, with boronic ester **4.2** giving the best result. The more hindered boronic esters (especially **4.6**) gave lower yields of **4.7**. A likely explanation for this trend is that the highly reactive (bromomethyl)lithium is less-effectively captured in boronic esters **4.4 – 4.6** due to the greater steric hindrance around the boron atom.

Even in the case of thexylboronic ester **4.2**, however, there seemed to be 20% of the starting boronic ester which had not been homologated. As mentioned in Section 4.1, primary and secondary alkylboronic esters give near-quantitative yields of homologated product. The most obvious reason for the 20% missing in yield would be incomplete capture of the reactive (bromomethyl)lithium.

In an attempt to ensure that all the (bromomethyl)lithium was captured in the homologation reaction, three additional thexylboronic esters were prepared (Scheme 4.4). These three boronic esters have a more electrophilic boron atom, which should mean that they are more effective at capturing carbenoids such as (bromomethyl)lithium.

Scheme 4.4 Synthesis of more electrophilic thexylboronic esters
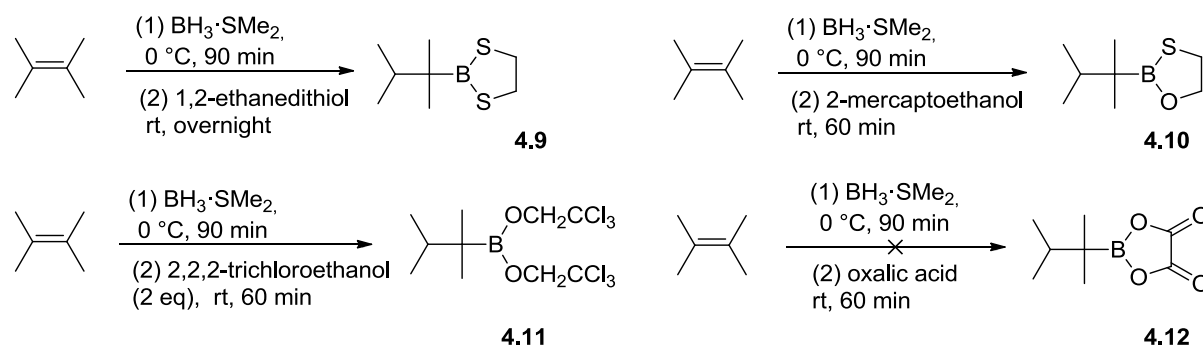
Boronic ester **4.9** was prepared by the addition of 1,2-ethanedithiol to freshly prepared thexylborane, and the reaction mixture was left to stir at room temperature overnight to ensure completion of reaction. The compound was fully characterised, with the data in accordance with those published in the literature,[9] although there was a small amount of thexylborane impurity apparent in the ^{1}H, ^{13}C and ^{11}B NMR spectra (E.S. 4.31e). Boronic

esters **4.10** and **4.11** were prepared in the same manner as boronic esters **4.2** – **4.6** (Scheme 4.3) from 2-mercaptoethanol and 2,2,2-trichloroethanol, respectively, and were both novel compounds. Boronic ester **4.11** seemed particularly susceptible to decomposition, and representative mass spectrometric and IR spectroscopic data could not be measured for this compound. However, all data for both compounds were consistent with the proposed structures (E.S. 4.31d,f).

The chemical shifts seen in the ^{11}B NMR spectra of the boronic esters indicated that, at least two of the boronic esters had boron atoms with increased electrophilicities relative to boronic esters **4.2** – **4.6** (δ = 73.3 ppm for **4.9**, and 53.2 ppm for **4.10**), while boronic ester **4.11** had comparable electrophilicity to boronic esters **4.2** – **4.6** (δ = 29.8 ppm while boronic esters **4.2** – **4.6** ranged from 30.1 – 34.5 ppm). The synthesis of the boronic ester **4.12** from thexylborane and oxalic acid was also attempted (Scheme 4.3), although the ^{1}H/^{13}C NMR spectra of the highly viscous white mass isolated from the reaction pointed towards reduction of the oxalic acid by thexylborane having taken place (the thexyl group was still visible in the ^{1}H NMR spectrum, while the ^{13}C NMR spectrum showed no signal for a carbonyl functionality being present).

Boronic esters **4.9** – **4.11** were prepared again, and taken through to the homologation/oxidation reaction as previously described. Disappointingly, boronic esters **4.9** and **4.10** gave no thexylmethanol (**4.7**) whatsoever, while boronic ester **4.11** gave only a 41% yield of **4.7** (Table 4.4). Having greater electrophilicities, boronic esters **4.9** and **4.10** should have been better at capturing the (bromomethyl)lithium than boronic esters **4.1** – **4.6**. A possible explanation for the lack of homologation could be that the sulfur migrates preferentially to the thexyl group (such sulfur to carbon migrations have been reported for similar reactions).[9] The lower yield of **4.7** from boronic ester **4.11** could be due to either steric hindrance around the boron atom due to the large chlorine atoms present, or the C-Cl bonds might have interacted with the (bromomethyl)lithium or *n*-BuLi.

Table 4.4 Homologation of thexylboronic esters 4.9 –4.11 by *in situ* prepared (bromomethyl)lithium

Thexylboronic ester[a]	Yield (%)[b]	
	thexylmethanol (**4.7**)	thexanol (**4.8**)
4.9	0	100
4.10	0	100
4.11	41	59

[a] Thexyl boronic esters were freshly prepared on the day of the reaction. [b] Yield based on relative integration of the signals for thexylmethanol/thexanol by ^{1}H NMR spectroscopy of the crude product.

Following these disappointing results, it was decided to optimise the reaction conditions and to explore the possible reasons for the 20% loss in yield using the boronic ester **4.2**.

4.22 Study of the homologation/oxidation reaction using boronic ester 4.2

The homologation/oxidation reaction of boronic ester **4.2** with (bromomethyl)lithium was explored using different reaction times (both at low temperature following the addition of *n*-BuLi, and at room temperature following warming) (entries 1 – 4, Table 4.5). All four permutations (usual reaction times, longer time at low temperature, longer time following warming to room temperature and longer time at both temperatures) gave the same result within experimental error.

The fact that there was no increase in yield when leaving the reaction for longer at -78 °C suggests that formation of the 'ate' complex is complete once the addition of *n*-BuLi is complete (entry 5, Table 4.5), but that leaving the reaction mixture at -78 °C has no detrimental effect on the reaction (entry 4, Table 4.5). This second point suggests that the desired 'ate' complex itself is stable (or undergoes the desired rearrangement) over a period of 4 hours at -78 °C.

Table 4.5 Attempts at optimisation of reaction conditions for the homologation/oxidation reaction of boronic ester 4.2

Entry	Description of procedure[a]	Yield (%)[b]	
		thexylmethanol (**4.7**)	thexanol (**4.8**)
1	0.5 h at -78 °C, 1 h at rt	80	20
2	1.5h at -78 °C, 4 h at rt	80	20
3	0.5 h at -78 °C, 4 h at rt	78	22
4	4h at –78 °C, 5 min to warm up	80	20
5	After addition, immediate heating to rt, then 1h at rt	74	26
6	1h –78 °C, 1h –50 °C, 1h at rt	74	26
7	ZnCl$_2$ (1 mmol) to aid migration	67	33

[a] Time at -78 °C does not include the time needed for addition of *n*-BuLi (30 min), time at rt refers to the amount of time the reaction mixture was left for, once the cooling bath was removed; all reactions were on a 5 mmol scale. [b] Yield based on relative integration of the signals for thexylmethanol/thexanol by ^{1}H NMR spectroscopy of the crude product.

Entries 2 and 4 demonstrate that leaving the reaction mixture for 5 minutes after removing the cooling bath or leaving the reaction mixture for 4 hours after removing the cooling bath does not affect the yield of thexylmethanol (**4.7**). These results suggest that whatever the unwanted side-reaction that limits the yield of **4.7** is, the process is complete once the reaction mixture has warmed to room temperature. These results also suggest that the loss of yield is not simply due to slow rearrangement of the desired 'ate' complex. To confirm this, the reaction was repeated and a solution of ZnCl$_2$ (which has previously been shown to speed up such boron – carbon migrations[10]) added following the addition of *n*-BuLi (entry 7, Table 4.5). There was no improvement in the yield of thexylmethanol, suggesting that slow rearrangement of the desired 'ate' complex was not the cause of the 20% drop in yield.

In an attempt to limit the side-reaction, while still allowing the desired homologation to occur (if the unwanted side-reaction was a process that happened at a higher temperature relative to the wanted homologation), the reaction mixture was warmed to an intermediate temperature (entry 6, Table 4.5). However, this reaction also gave a similar result.

As a way of getting around the possible problem of incomplete capture of (bromomethyl)lithium, the reaction was repeated using boronic ester **4.2** and an excess of (bromomethyl)lithium (from 5 eq of CH_2Br_2 and 2 eq of *n*-BuLi). The yield of **4.7** did not improve in this reaction (in actual fact it was slightly lower at 75%), suggesting that incomplete capture of the (bromomethyl)lithium may not be the reason for the 20% loss in yield (at least for this particular thexylboronic ester).

To further confirm that incomplete capture of the (bromomethyl)lithium was not the reason for the observed 20% drop in yield, the homologation of boronic ester **4.2** was completed twice (leaving to warm to room temperature between additions of dibromomethane/*n*-BuLi) before oxidising the reaction mixture (Scheme 4.5). If the problem was simply incomplete capture of the (bromomethyl)lithium, then one would expect 80% of the unreacted boronic ester **4.2** to undergo the homologation in step 2 in Scheme 4.5. However, the ^{1}H NMR spectrum of the oxidised crude product showed 23% thexanol (**4.8**) – which confirmed that incomplete capture of (bromomethyl)lithium was not the problem, and that the boronic ester **4.2** underwent some side reaction to form an organoboron species that was unable to partake further in the homologation reaction.

Interestingly, the second homologation seems to have been slightly less successful than the first (66% migration of the thexylmethyl group), even though the alkyl group bonded to boron following the first homologation step would be a primary alkyl group. Presumably this is because of the various species present in the reaction mixture following the first homologation (*e.g.* it is possible that the organoboron compound produced in the side reaction will still react in some way or other with (bromomethyl)lithium).

Scheme 4.5 Double homologation/oxidation of boronic ester 4.2

| | 4.13 | 51%[a] | | 4.7 | 26% | | 4.8 | 23% |
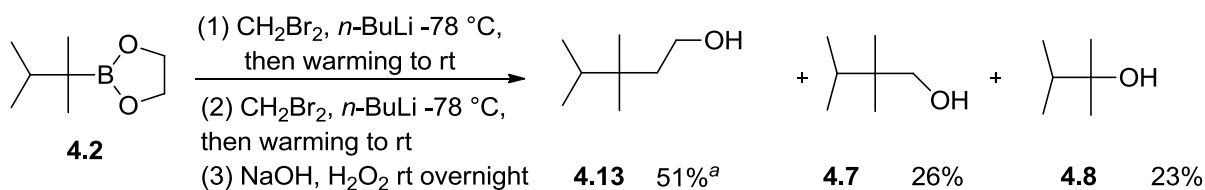
[a] Yield based on relative integration of the signals for thexylethanol/thexylmethanol/thexanol by ^{1}H NMR spectroscopy of the crude product.

4.23 Attempts at identifying the unwanted side-reaction – direct addition of *n*-BuLi

Since it now seemed that incomplete capture of (bromomethyl)lithium was unlikely to be the cause of the observed drop in yield, this prompted us to speculate what the unwanted side reaction might be. One possible explanation was that a percentage of the *n*-BuLi was adding directly to boronic ester **4.2**, forming 'ate' complex **4.16** that cannot rearrange to give the desired product (Scheme 4.6).

Scheme 4.6 Direct addition of *n*-BuLi to boronic ester 4.2 as an explanation for the loss of yield
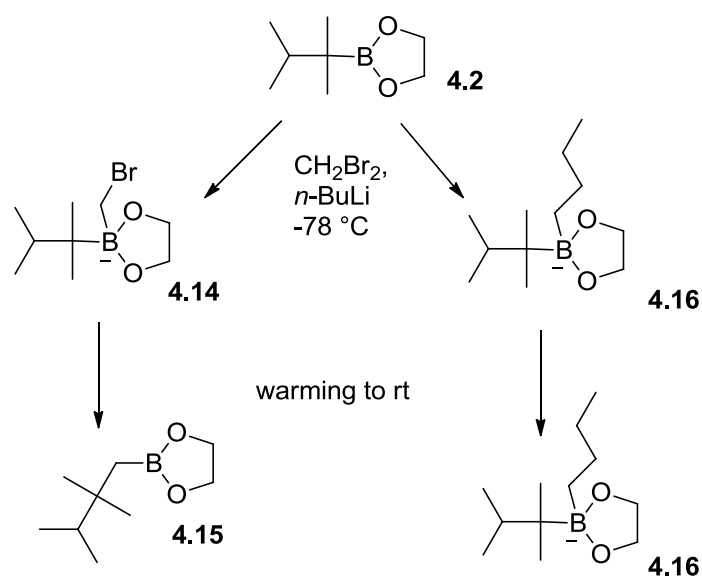
In an attempt to get around this possible problem, the reaction was repeated with both *sec*-BuLi and *tert*-BuLi as the organolithium reagent. We reasoned that a more hindered organolithium reagent should be less prone to direct addition to boronic ester **4.2**.

Table 4.6 Attempts to limit the possible problem of direct addition of *n*-BuLi to boronic ester 4.2

Entry	Description of procedure[a]	Yield (%)[b]	
		thexylmethanol (**4.7**)	thexanol (**4.8**)
1	*sec*-BuLi	39	61
2	*tert*-BuLi	32	68
3	*ex-situ* preparation of LiCH$_2$Br attempt at -100 °C	0	100

[a] All reaction were completed on a 5 mmol scale, using freshly prepared boronic ester **4.2**. [b] Yields based on relative integration of the signals for thexylmethanol/thexanol by ^{1}H NMR spectroscopy of the crude product.

Both *sec*-BuLi and *tert*-BuLi gave lower yields for thexylmethanol (**4.7**, entries 1 and 2, Table 4.6), which may simply suggest that these two organolithium reagents are less effective reagents for the preparation of (bromomethyl)lithium. An attempt was made to prepare the (bromomethyl)lithium *ex-situ* from dibromomethane and *n*-BuLi at -100 °C, followed by the drop-wise addition of a cooled solution of boronic ester **4.2**. If this were successful, then any possible problem of *n*-BuLi adding directly to boronic ester **4.2** would have been overcome. However, no thexylmethanol (**4.7**) was seen in the ^{1}H NMR spectrum of the crude product, highlighting the thermal instability of (bromomethyl)lithium.

Radical anion lithium aryl systems have previously been shown to be effective reagents for Br-Li exchange.[11] Such reagents might be less prone to adding directly to boronate **4.2**, and therefore two such reagents were trialled – lithium naphthalene radical anion (LiN, **4.17**) and lithium-4,4'-di-*tert*-butylbiphenyl radical anion (LiDBB, **4.18**). 4,4'-Di-*tert*-butylbiphenyl **4.19** (for the use in the preparation of LiDBB) (**4.18**) was prepared by the literature procedure[12] from biphenyl, *tert*-butyl chloride and anhydrous iron(III) chloride in 69% isolated yield (Scheme 4.7). The compound was fully characterised, with the data in accordance with those reported in the literature (E.S. 4.33a).[12]

Scheme 4.7 Synthesis of 4,4-di-*tert*-butylbiphenyl (4.19)
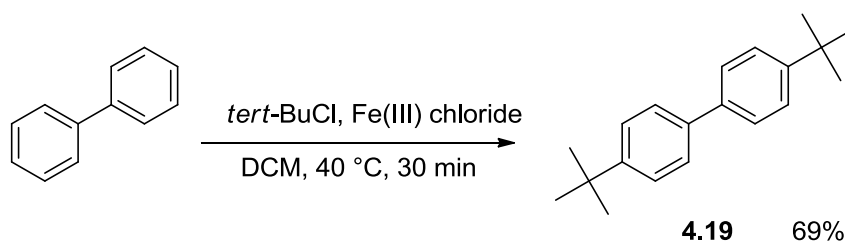
Lithium naphthalene radical anion **4.17** was studied first, and was prepared by the literature procedure,[11] with the dark green colour of the solution an indication of the presence of the radical anion in solution. Adding a solution of boronic ester **4.2** to a solution of LiN (**4.17**) and dibromomethane, and adding a solution of boronic ester **4.2** and dibromomethane to a solution of LiN both resulted in low yields of thexylmethanol (**4.7**) (entries 1 and 2, Table 4.7). The low yield of **4.7** in the first of these reaction is almost certainly because of the decomposition of (bromomethyl)lithium, while it is unclear what the reason for the low yield is for the second of these reactions. However, the addition of a solution of LiN to a solution of boronic ester **4.2** and dibromomethane gave a much more encouraging result (entry 3, Table 4.7). A slower addition of LiN gave a slightly lower yield of thexylmethanol, while a greater excess of LiN and dibromomethane gave a slightly higher yield of thexylmethanol (entries 4 and 5, Table 4.7).

Following these results, we attempted the same reaction using LiDBB (**4.18**), which has been shown in some cases to give higher yields in Br-Li exchange reactions than LiN.[11] An initial reaction with LiDBB (entry 6, Table 4.7) gave a lower yield of thexylmethanol compared to that obtained using the same conditions with LiN. Using excess LiDBB did increase the yield of thexylmethanol to 55% (entry 7, Table 4.7), but it was becoming apparent that using radical lithium aryl reagents was unlikely to give better results than (bromomethyl)lithium prepared with *n*-BuLi. Nevertheless, to our knowledge this is the first use of such radical anion lithium aryl reagents for organoboron reactions involving the generation of a carbanion.
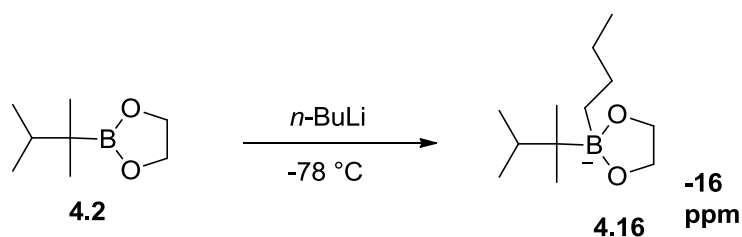
Table 4.7 Homologation of boronic ester 4.2 using radical lithium arene reagents

Entry	Radical lithium arene reagent	Reaction conditions	Yield (%)[a]	
			thexylmethanol (**4.7**)	thexanol (**4.8**)
1	LiN (**4.17**)[b]	boronic ester **4.2** added to LiN + CH$_2$Br$_2$ (2.5 LiN : 1.2 CH$_2$Br$_2$:1 boronate)	5	95
2	**4.17**	boronic ester **4.2** + CH$_2$Br$_2$ added to LiN (2.5 : 1.2 : 1)	10	90
3	**4.17**	LiN added to boronic ester **4.2** + CH$_2$Br$_2$ (2.5 : 1.2 : 1)	40	60
4	**4.17**	As above, slower addition	34	66
5	**4.17**	5: 2.1 : 1 (as entry 3)	44	44
6	LiDBB (**4.18**)[c]	2.5 : 1.2 : 1 (as entry 3)	20	80
7	**4.18**	4.5 : 2.1 : 1 (as entry 3)	55	45
8	**4.18**	5 : 1.1: 1 (as entry 3)	13	87

[a] GC yield using tetradecane as the internal standard. [b] Lithium napthalene radical anion. [c] Lithium 4,4'-di-*tert*-butylbiphenyl radical anion.

## 4.24 Attempts at identifying the unwanted side reaction – ^{11}B NMR investigations

In order to determine definitively whether the drop in yield was due to the direct addition of *n*-BuLi to boronic ester **4.2**, we decided to use ^{11}B NMR spectroscopy as an investigative tool. The *n*-butylboronic ester 'ate' complex **4.16** was prepared by the addition of *n*-BuLi to a solution of boronic ester **4.2** (Scheme 4.8), and a single sharp signal was seen at -16 ppm in the ^{11}B NMR spectrum in the correct region for such an 'ate' complex.

Scheme 4.8 Preparation of *n*-butyl boronic ester 'ate' complex

Following this, the homologation reaction of boronic ester **4.2** was completed as in entry 1 (Table 4.5), and the ^{11}B NMR spectrum taken prior to the oxidation step (Figure 4.1). There were several peaks in the ^{11}B NMR spectrum: the major peak at 33.8 ppm due to the homologated boronic ester **4.15** (and possibly the starting boronic ester **4.2**), and two peaks for unknown substances in the region expected for 'ate' complexes at 6.1 and 9.5 ppm and two further peaks at 51.3 and 55.4 ppm, in the correct region for borinic ester products (possibly resulting from migration of an oxygen-bound substituent, Scheme 4.9). The lack of any peak at -16 ppm strongly suggested that the loss of yield was not due to direct addition of *n*-BuLi to boronic ester **4.2**.

An aliquot from the same reaction mixture prior to the oxidation step was washed with ice-cold water, in an attempt to observe the oxygen-migrated product. Although tentative, ^{1}H NMR signals at 3.57, 3.65 and 4.01 ppm were consistent in multicplicity, integration and chemical shift with the expected oxygen – migrated product **4.20** (Figure 4.2, E.S. 4.32g). The percentage of the apparent oxygen – migrated product could be calculated using these signals and comparing them with the overall integration in the region for thexyl alkyl groups (which suggested around 2% of oxygen migrated product). Although it is possible that some of the oxygen migrated product **4.20** could have decomposed during the washing with ice-cold water, this result is in line with what has twice been observed in the literature[4,5] (*i.e.* that very little oxygen-migrated product is seen when using (bromomethyl)lithium). Further attempts at isolating the oxygen migrated product **4.20** by column chromatography were unsuccessful.

It was also apparent from the ^{11}B NMR spectrum following the washing with ice-cold water that the species responsible for giving the peaks at 6.1 and 9.5 ppm had decomposed, with concomitant increase in the peak at 55.4 ppm.

Figure 4.1 ^{11}B NMR prior to oxidation following homologation reaction of boronic ester 4.2
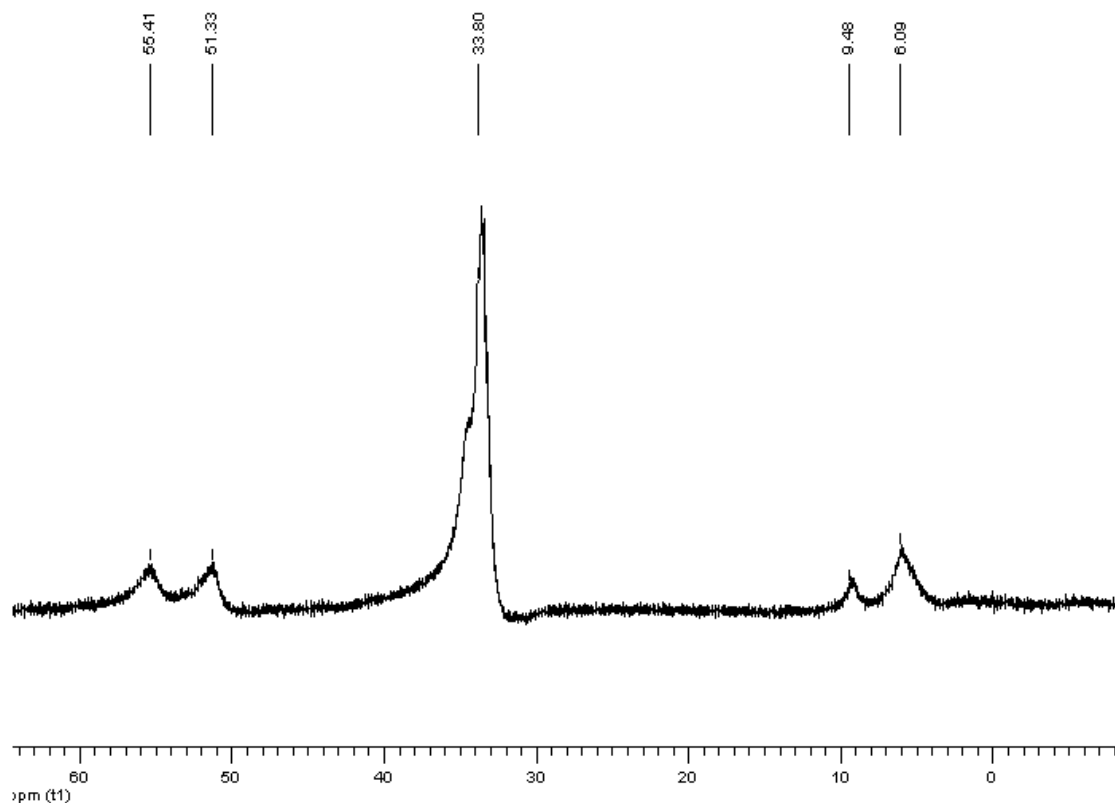
Scheme 4.9 Mechanism for the formation of oxygen-migrated borinic ester 4.20
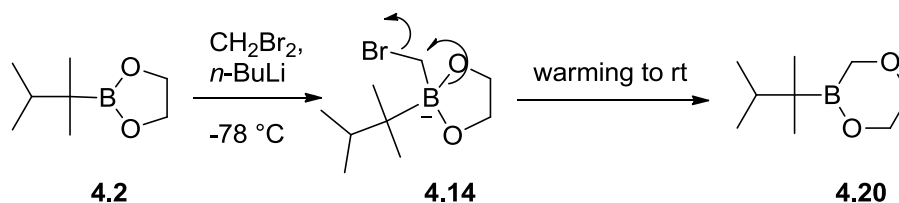
To further confirm the identity of the oxygen migrated product **4.20**, an identical experiment was completed using (chloromethyl)lithium prepared from *n*-BuLi and bromochloromethane *via* a literature procedure,[4] as it has been previously noted that using (chloromethyl)lithium in the reaction results in more oxygen migration.[4,5] The ^{11}B NMR spectrum prior to oxidation showed a larger amount of the two peaks in the borinic ester region (50 – 55 ppm), consistent with a larger amount of oxygen migration having occurred. There also appeared to be a larger amount (5% by relative integrations) of oxygen migrated product **4.20** in the ^{1}H NMR spectrum following washing with ice-cold water, and again it is possible that a portion of the oxygen migrated product had decomposed.

The homologation/oxidation reaction was completed using (chloromethyl)lithium, as in entry 1 (Table 4.5), and gave a lower yield of thexylmethanol (**4.7**) (entry 1, Table 4.8) - presumably due to an increased amount of oxygen migration.

Figure 4.2 ^{1}H NMR spectrum of crude product following ice-cold water washing
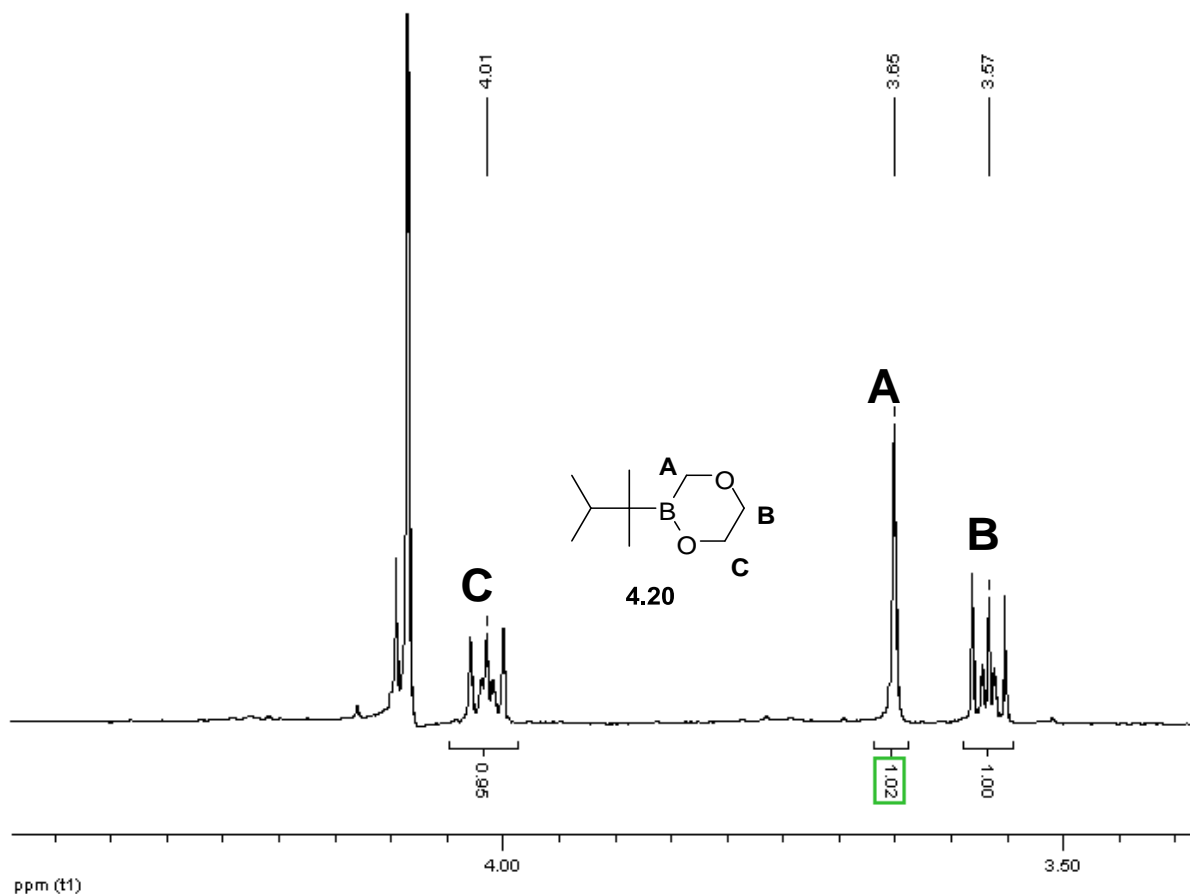
It is conceivable that the oxygen migrated product **4.20**, which seems to account for a portion of the observed 20% loss in yield, could still react in a manner that would give **4.7** if an appropriate 'ate' complex is made (Scheme 4.10). To test this idea, a source of fluoride was added (CsF for entry 2, Table 4.8 and TBAF for entry 3, Table 4.8), and the reaction mixtures were heated in an attempt to promote the desired rearrangement. However, no increase in the yield of thexylmethanol was observed and so this line of research was ceased.

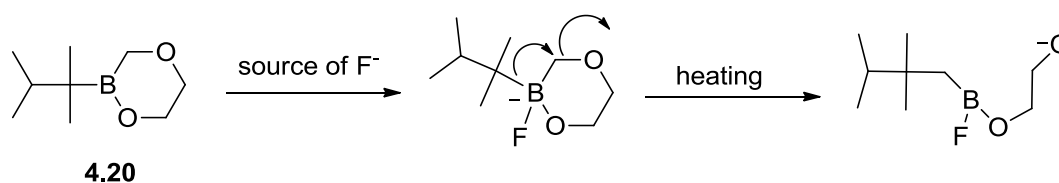**Scheme 4.10 Intended rearrangement of oxygen migrated product**

Table 4.8 Investigative reactions for oxygen migration side reaction

Entry	Reagent	Yield (%)[b]	
		thexylmethanol (**4.7**)	thexanol (**4.8**)
1	(chloromethyl)lithium[a]	47	53
2	BrCH$_2$Li + CsF	79	21
3	BrCH$_2$Li + TBAF	50	50

[a] All reactions were completed on a 5 mmol scale, using freshly prepared boronic ester **4.2**, and (chloromethyl)lithium prepared by the drop-wise addition of *n*-BuLi to bromochloromethane. [b] Yields based on relative integration of the signals for thexylmethanol/thexanol by ^{1}H NMR spectroscopy of the crude product. [c] CsF (2.5 eq) dried over weekend at 200 °C, was added to bent side-arm when flushing apparatus with N$_2$. CsF was added prior to usual oxidation step, then the mixture was refluxed (pot T 74 °C) for 1h. The reaction mixture was then oxidised *etc* in the usual manner.

## 4.25 Attempts at identifying the side products giving rise to ^{11}B signals at 6.1 and 9.5 ppm

Since limiting the production of the oxygen migration product, or attempting to force the intermediate to rearrange to give, after oxidation, thexylmethanol (**4.7**) might not be feasible, it was decided to switch the focus of the research to the other species seen at 6.1 and 9.5 ppm in the ^{11}B NMR spectrum of the homologation reaction of boronic ester **4.2** prior to oxidation (Figure 4.1).

Both peaks are in the region indicative of an organoboron 'ate' complex of some sort. One possibility is simply the bromide 'ate' complex of boronic ester **4.2** (Scheme 4.11). In an attempt to confirm or exclude this possibility, boronic ester **4.2** was stirred with LiBr, and the ^{11}B NMR spectrum taken to see whether any of the bromide 'ate' complex **4.21** had been produced. Only the starting boronic ester **4.2** could be seen, suggesting that bromide 'ate' complex **4.21** is unlikely to be the identity of one of the 'ate' species seen in Figure 4.1.

Two other possibilities result from the reaction of *n*-BuLi with the 'ate' complex **4.21** from the capture of (bromomethyl)lithium with boronic ester **4.2**. If *n*-BuLi displaced the bromide directly, it would result in **4.22**, an *n*-pentyl 'ate' complex of boronate **4.2** that would be unable to undergo homologation. However, this possibility was discounted for two reasons –

no *n*-pentanol was seen in any ^{1}H NMR spectra or GC traces of the homologation/oxidation reactions of boronic ester **4.2**, and also one would expect the 'ate' complex to have a very similar chemical shift in the ^{11}B NMR spectrum to that of the previously discussed *n*-butylboronic ester 'ate' complex **4.16** – and no such signal was observed.

Scheme 4.11 Possible species responsible for the observed 'ate' species in Figure 4.1

4.21 **4.23** **4.22**
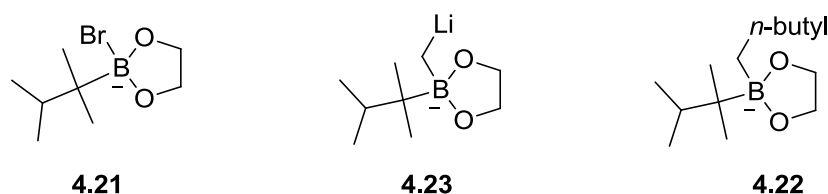
The second mode of reaction of *n*-BuLi with the 'ate' complex **4.14** is that it could perform a Li-Br exchange to give 'ate' complex **4.23**. This species would not be able to take part in the homologation reaction. If this side-reaction were to be the cause of the observed loss in yield of thexylmethanol, then one would expect this to become more of a problem as more *n*-BuLi is added to 'ate' complex **4.14**.

To test this hypothesis, a reaction was carried out using boronic ester **4.2** (as in entry 1, Table 4.5), except that excess *n*-BuLi (2.2 eq) was employed in an attempt to exacerbate the problem of the side reaction (Scheme 4.12).

**Scheme 4.12 Attempt at promoting the unwanted side-reaction**
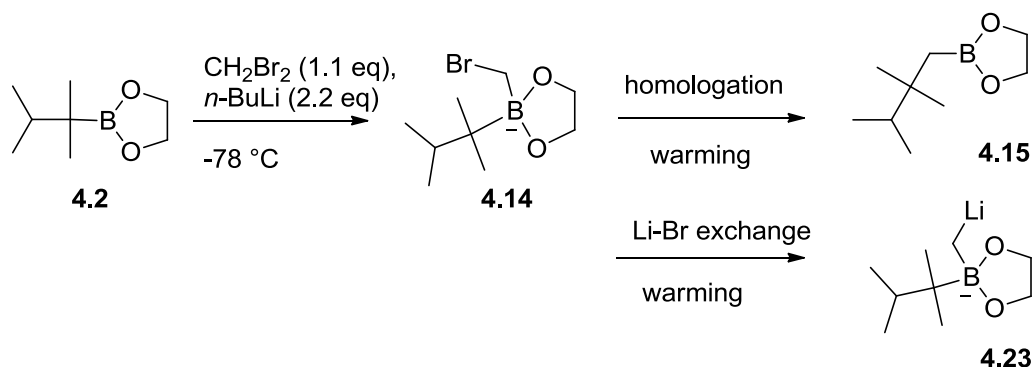
The ^{11}B NMR spectrum prior to oxidation showed that the two 'ate' species at 6.1 and 9.5 ppm were now the predominant species, along with the homologated boronic ester **4.14** and a small amount of what appeared to be oxygen – migrated species **4.20**. The sample was washed quickly with ice cold water and the ^{11}B NMR spectrum taken (Figure 4.3), showing that all the 'ate' species had decomposed to give the peak at 54.6 ppm (which is consistent

with what was reported in Section 3.24. A sample from the same reaction mixture was oxidised, and showed a 34% yield of thexylmethanol – considerably lower than the 80% yield observed when using only 1.1 equivalents of *n*-BuLi.

Although these observations do not prove that the 'ate' species seen at 6.1 and 9.5 ppm are due to the proposed side reaction (Scheme 4.12), the mechanism is at least plausible. Certainly, excess *n*-BuLi increases the amount of 'ate' complex species with concomitant decrease in the yield of thexylmethanol. Another point is that the 'ate' complex decomposes on contact with water to give the observed peak at 54 – 55 ppm, while the peak at 51 ppm is likely to be the oxygen migrated product **4.20**.

Figure 4.3 ^{11}B NMR spectrum from the reaction of boronic ester 4.2 with excess *n*-BuLi, followed by washing with ice cold water
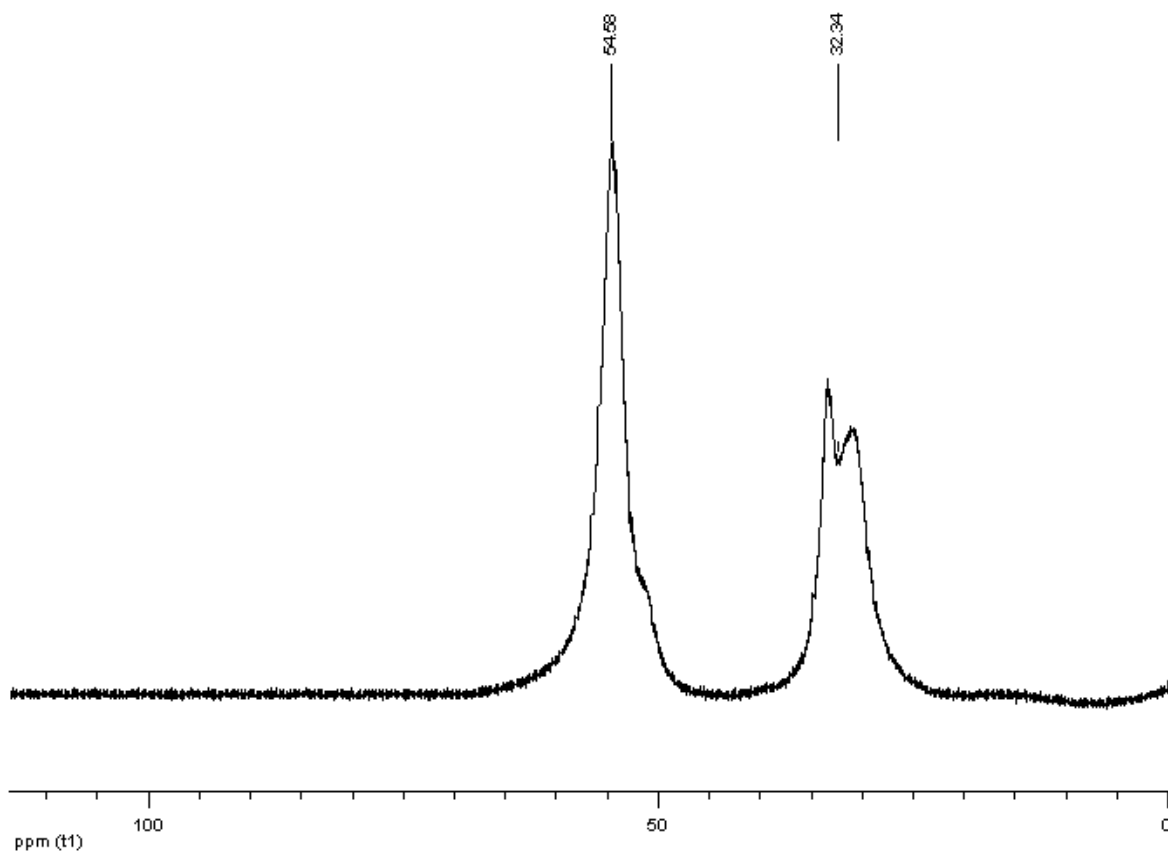
4.26 The use of excess (bromomethyl)lithium for more hindered thexylboronic esters

As discussed in section 4.25, it seems that the majority of the drop in yield observed for the homologation/oxidation of boronic ester **4.2** is due to a side reaction that involves further reaction of *n*-BuLi with the initial 'ate' complex **4.14** formed by (bromomethyl)lithium and

boronic ester **4.2**. It is reasonable to postulate that such a process may be less of an issue for more hindered systems (*n*-BuLi is less likely to react due to steric hindrance around boron). For this reason, along with the fact that the hindered boronic esters are more practical synthetic intermediates (boronic esters derived from 2,2-dimethyl-1,3-propanediol and pinacol tend to be less prone to oxidation or hydrolysis and in most cases can be purified by column chromatography, which is generally not the case for those derived from ethylene glycol/1,3-propanediol), it was decided to take a closer look at boronic esters **4.5** and **4.6**.

In initial reactions, boronic esters **4.5** and **4.6** gave lower yields of thexylmethanol (**4.7**) compared to the less hindered boronic esters **4.1**, **4.2** and **4.3** (70 and 35% respectively, Table 4.3). Although it has been shown in Section 4.22 that incomplete capture of the (bromomethyl)lithium is not the reason for the 20% loss of yield observed with boronic ester **4.2**, it is possible that this is not the case for the more hindered boronic esters **4.5** and **4.6**.

An improvement in the yield of thexylmethanol to 43% was observed when a reaction was performed using the pinacol boronic ester **4.6** and excess (bromomethyl)lithium (5 equivalents of dibromomethane and 3 equivalents of *n*-BuLi, entry 1, Table 4.9). An even better result (59%) was observed by adding just 3 equivalents of the dibromomethane and *n*-BuLi, but in three portions (as opposed to having all the excess dibromomethane present in the reaction mixture prior to the addition of *n*-BuLi). This result may suggest that the excess dibromomethane consumes the (bromomethyl)lithium in some manner.

Buoyed by this result, the same procedure was applied to the 2,2-dimethyl-1,3-propanediol boronic ester **4.5** and the ^{1}H NMR spectrum of the crude product indicated an 84% yield of thexylmethanol (entry 4, Table 4.9) – which is higher than the best result obtained using boronic ester **4.2**. Although perhaps impractical, the procedure was repeated using 5 portions of dibromomethane/*n*-BuLi and gave an even better (89%) yield of thexylmethanol (entry 5, Table 4.9).

It is evident therefore, that for boronic esters **4.5** and **4.6**, a substantial amount of the loss in yield when using only 1 equivalent of (bromomethyl)lithium was due to incomplete capture of (bromomethyl)lithium due to the increased steric hindrance around the boron atom in these more hindered boronic esters.

Table 4.9 The use of excess (bromomethyl)lithium with boronic esters 4.2, 4.5 and 4.6.

Entry	boronic ester	Conditions	Yield (%)[a]	
			thexylmethanol (**4.7**)	thexanol (**4.8**)
1	boronic ester **4.6**	5 eq dibromomethane, 3 eq *n*-BuLi	43	57
2	boronic ester **4.6**	3 × sequential[b]	59	41
3	boronic ester **4.2**	3 × sequential	70	30
4	boronic ester **4.5**	3 × sequential	84 (82)[c]	16 (18)
5	boronic ester **4.5**	5 × sequential	89	11

[a] Yield based on relative integration of the signals for thexylmethanol/thexanol by ^{1}H NMR spectroscopy of the crude product. [b] Dibromomethane (1.2 eq) added drop-wise, followed by *n*-BuLi (1.1 eq), process repeated without warming of the reaction mixture. [c] Experiment repeated to ensure reproducibility of result.

To check whether switching to the more hindered derivatives had been successful in minimising the side reaction to give the 'ate' species seen at 6.1 and 9.5 ppm in the ^{11}B NMR spectrum for the case of boronic ester **4.2** (Figure 4.1), the reaction between boronic ester **4.5** and excess *n*-BuLi (as seen in Scheme 4.12) was completed and the ^{11}B NMR taken prior to the oxidation step. The ^{11}B NMR spectrum showed no evidence of the 'ate' complex peaks at 6.1 and 9.5 ppm, or the borinic species at 51 – 54 ppm, only the homologated boronic ester and/or boronic ester **4.5**. The reaction mixture was oxidised and showed a yield of 71% for thexylmethanol, showing that the excess n-BuLi had not decreased the yield (compared to entry 5, Table 4.3).

This result is a strong indicator that the side reaction(s) observed in the case of boronic ester **4.2** had been supressed by using the more hindered boronic ester **4.5**. It seems that the only factor limiting the yield in this reaction is the incomplete capture of (bromomethyl)lithium as only the homologated and starting boronic esters are seen in the ^{11}B NMR spectrum. This helps to explain why adding excess (bromomethyl)lithium improved the yield of thexylmethanol (entries 4 and 5, Table 4.9).

4.27 Probing the scope of the homologation/oxidation using even more hindered systems

Following the encouraging result for the homologation of boronic ester **4.5**, it was decided to use what was learned for this boronic ester and apply it to the migration of even more hindered tertiary alkyl groups to determine the scope of the homologation/oxidation reaction for tertiary boronic esters.

The first boronic ester to be studied was boronic ester **4.24**, which was prepared using the DCME (dichloromethyl methyl ether) reaction[13] of triethylborane with DCME and lithium triethylcarboxide, followed by reaction with 2,2-dimethyl-1,3-propanediol (Scheme 4.13). The crude product was purified by column chromatography on silica to give the novel boronic ester **4.24** in 45% isolated yield. The compound was fully characterised, with the ^{1}H, ^{13}C and ^{11}B NMR and IR data all consistent with the proposed structure (E.S. 4.35e). The identity of the compound was further confirmed by HRMS.

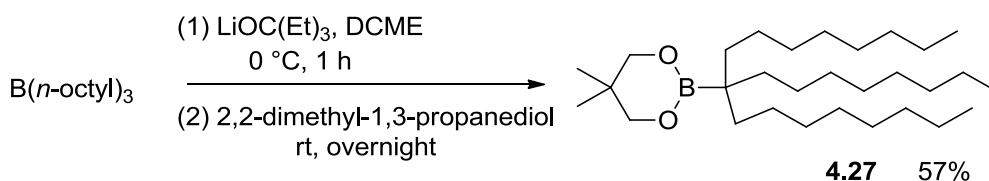**Scheme 4.13 Synthesis of boronic ester 4.24**
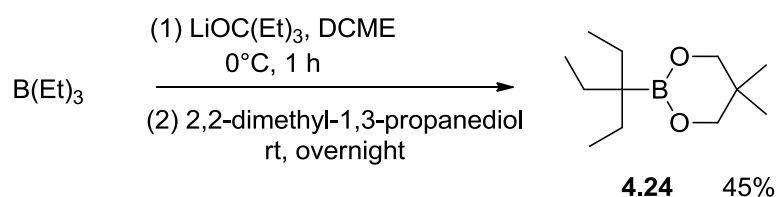
Boronic ester **4.24** was homologated with dibromomethane (1.2 equivalents) and *n*-BuLi and then oxidised (as for entry 1, Table 4.5) (Scheme 4.14). The peaks for the oxidised homologated product and the oxidised starting material were separate and distinct in the ^{1}H NMR spectrum of the crude product, and showed a yield of 26% for the homologated product (2,2-diethylbutan-1-ol, **4.25**). This is substantially lower than was observed for boronic ester **4.5**, and reflects the increased steric hindrance of boronic ester **4.24**.

Applying what was learned in section 4.26, the reaction was repeated using three portions of dibromomethane and *n*-BuLi. The ^{1}H NMR spectrum of the crude product showed a substantial increase in the amount of alcohol **4.25** (72% by ^{1}H NMR spectroscopy, Scheme 4.13), showing that incomplete capture of the (bromomethyl)lithium had limited the yield of the reaction when employing only one equivalent of bromomethyl)lithium. The homologated product **4.25** was purified by column chromatography to give 2,2-diethylbutanol (**4.25**, 36% isolated yield), with the characterisation data in accordance with the literature for this compound (E.S. 4.35g).[14]

Scheme 4.14 Homologation/oxidation reaction of boronic ester 4.24

(1) CH_2Br_2, *n*-BuLi

(2) NaOH, H_2O_2

4.24

26%[a]   74%[a]

72%[b]   28%[b]

4.25   **4.26**
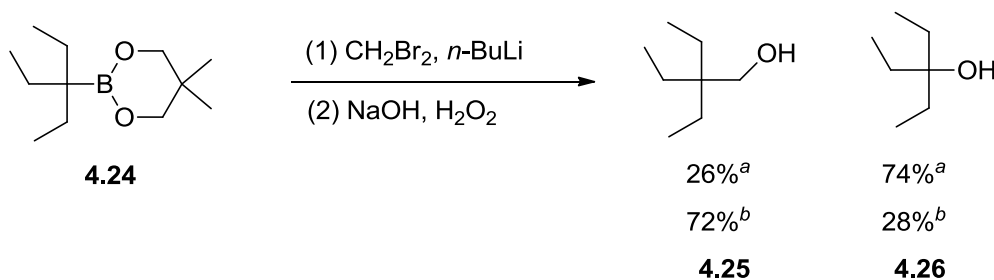
[a] Single addition of CH_2Br_2 (1.2 eq)/*n*-BuLi (1.1 eq). [b] Three sequential additions of CH_2Br_2 (1.2 eq)/*n*-BuLi (1.1 eq) without warming of the reaction mixture.

Moving on to a yet more hindered system, the novel boronic ester **4.27** was produced in the same manner as boronic ester **4.24** (Scheme 4.15). The compound was purified by column chromatography to give pure boronic ester **4.27** (57% isolated yield). The compound was fully characterised, with the ^1H, ^{13}C and ^{11}B NMR spectra along with the IR data and HRMS consistent with the proposed structure (E.S. 4.35b).

Scheme 4.15 Synthesis of boronic ester 4.27

B(*n*-octyl)$_3$

(1) LiOC(Et)$_3$, DCME
0 °C, 1 h

(2) 2,2-dimethyl-1,3-propanediol
rt, overnight

4.27   57%

Two homologation reactions were run, as for boronic ester **4.24** – one reaction using a single portion of (bromomethyl)lithium, and a second reaction using three portions of (bromomethyl)lithium. Using the integration for the CH_2 next to oxygen for the homologated product in the ^1H NMR spectrum of the crude product, it was calculated that the yield of homologated product using a single portion of (bromomethyl)lithium was 18%. Despite several attempts, the homologated alcohol could not be separated from the non-homologated alcohol due to their very close behaviour on silica.

The lower yield of homologated product relative to boronic ester **4.24** is an indicator that this is a more hindered system; it must also be remembered that due to the characteristics of the hydroboration of 1-octene, a small amount of the octyl groups bonded to boron in boronic ester **4.27** will be secondary octyl groups due to hydroboration at the internal position (in the case of tri-*n*-alkylboranes *ca.* 82:18 for terminal: internal respectively).[15]

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The same reaction was run using three portions of (bromomethyl)lithium, and the ^{1}H NMR spectrum of the crude product showed a 36% yield of homologated alcohol. This result shows that excess (bromomethyl)lithium has a positive effect, although the increase in yield is not as marked as for boronic ester **4.24**. It is likely that adding several more portions of (bromomethyl)lithium would result in even higher yields of the homologated alcohol.

Due to the increase in the steric hindrance as a result of the nature of the tertiary alkyl group bonded to boron in boronic ester **4.27**, we reasoned that using a less hindered diol functionality would make the system less hindered (and therefore aid with the capture of (bromomethyl)lithium) while still being hindered enough to avoid the side reactions observed when using boronic ester **4.2**. To test this hypothesis, the novel boronic ester **4.28** was produced using the same procedure as boronic ester **4.27**, except that ethylene glycol was used in place of 2,2-dimethyl-1,3-propanediol (Scheme 4.16).

Scheme 4.16 Synthesis of boronic ester 4.28
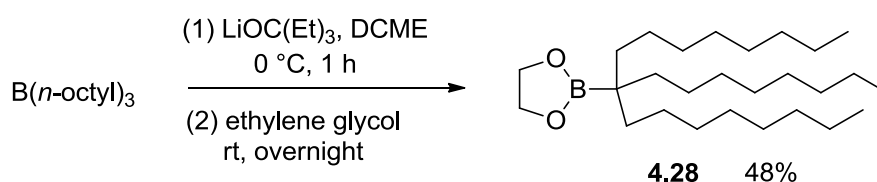
Boronic ester **4.28** was not stable to purification by column chromatography on silica, with hydrolysis of the boronic ester occurring as evident by the disappearance of the singlet for the 2 CH_2 groups next to oxygen in the ^{1}H NMR spectrum. The product was therefore purified by dissolving the crude product in hexane, and washing it several times with methanol in a separating funnel. The hexane layers were kept, and concentration under reduced pressure gave near pure boronic ester **4.28** (48% isolated yield, E.S. 4.35a).
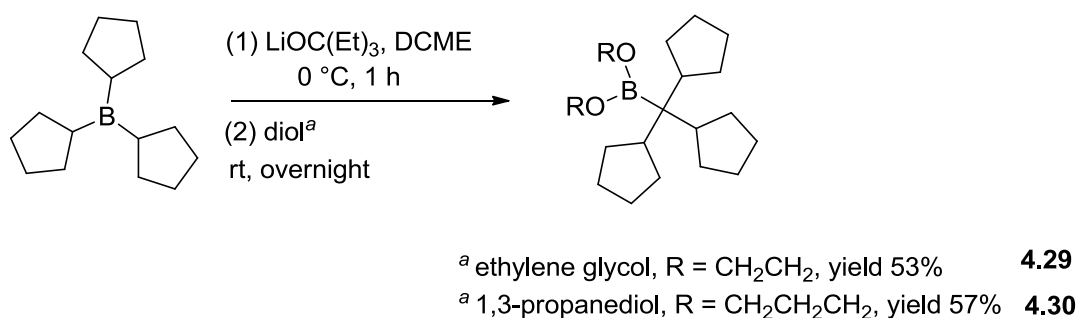
The homologation/oxidation reactions were performed on boronic ester **4.28** using both a single and three portions of (bromomethyl)lithium. Using the ^{1}H NMR spectra of the crude products, it was estimated that the single addition reaction gave a 28% yield of homologated alcohol, while the triple addition gave a 40% yield.

Both of these results are better than their corresponding analogues using boronic ester **4.27**, showing that using a less hindered diol aids in the capture of (bromomethyl)lithium. The 40% yield of homologated alcohol when using three portions of (bromomethyl)lithium and

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boronic ester **4.28** shows that synthetically useful yields can be realised, even when using highly hindered tertiary alkyl groups.

The final hindered boronic esters to be tested were the novel boronic esters **4.29** and **4.30**, both derived from tricyclopentylborane. It was decided to use the least hindered diols due to the increase in steric hindrance of the tertiary alkyl group bonded to boron. Boronic esters **4.29** and **4.30** were prepared using the DCME reaction (Scheme 4.17), with both being stable to purification by column chromatography on silica. However, it was found that pure boronic esters **4.29** and **4.30** could be precipitated directly from the crude reaction mixture by triturating with methanol to give the products in 53 and 57% yields respectively. Both boronic esters were fully characterised, with the data in accordance with the proposed structures (E.S. 4.35c-d); the x-ray crystal structure data for boronic ester **4.29** were also taken.

Scheme 4.17 Synthesis of boronic esters 4.29 and 4.30

(1) LiOC(Et)$_3$, DCME
    0 °C, 1 h

(2) diol^a
    rt, overnight

^{a} ethylene glycol, R = CH$_2$CH$_2$, yield 53%   **4.29**
^{a} 1,3-propanediol, R = CH$_2$CH$_2$CH$_2$, yield 57%   **4.30**

Both boronic esters **4.29** and **4.30** were subjected to the homologation/oxidation reaction conditions using a single portion of (bromomethyl)lithium. The ^{1}H NMR spectra of the crude products for both reactions showed no presence of the expected homologated alcohol, only tricyclopentylmethanol resulting from oxidation of the starting boronic esters.

In a final attempt to homologate boronic ester **4.29**, the reaction was repeated using three portions of (bromomethyl)lithium at a temperature of -95 °C (to give the 'ate' complex the best possible chance of forming). However, no homologated alcohol whatsoever could be seen in the ^{1}H NMR spectrum of the crude product.

It appears that in these highly hindered tricyclopentylmethylboronic esters, the upper limit of the homologation/oxidation reaction has been reached. It is likely that no (bromomethyl)lithium whatsoever is captured due to the steric hindrance around the boron atom. The stability of boronic esters **4.29** and **4.30** to both oxidation and purification using

silica are also indicators of the non-reactive nature of these tricyclopentylmethylboronic esters.

The homologation/oxidation reaction of the boronic esters prepared *via* the DCME reaction are summarised in Table 4.10, and show that as expected, the yield of homologated alcohol decreases as the tertiary alkyl group gets more hindered. Additionally, in every case (bar the tricyclopentylmethylboronic esters **4.29** and **4.30**), the use of three portions of (bromomethyl)lithium increases the yield of homologated alcohol. This suggests that for these highly hindered boronic esters, the capture of the (bromomethyl)lithium is the limiting factor.

Table 4.10 Homologation/oxidation reaction of various hindered boronic esters prepared *via* the DCME reaction

boronic ester	migrating group	single addition		triple addition	
		Yield of homologated alcohol^a	Yield of non-homologated alcohol	Yield of homologated alcohol	Yield of non-homologated alcohol
4.24	triethylmethyl	28	72	74 (36)^b	26
4.27	tri-(*n*-octyl)methyl	18	82	36	64
4.28	tri-(*n*-octyl)methyl	28	72	40	60
4.29	tricyclopentylmethyl	0	100 (82)	0^c	100 (76)
4.30	tricyclopentylmethyl	0	100 (63)	-	-

^{a} Yield based on relative integration of the signals for homologated/non-homologated product by ^{1}H NMR spectroscopy of the crude product. ^{b} Isolated yields in parentheses. ^{c} Initial addition of n-BuLi was carried out at -95 °C.

4.28 Application of the homologation/oxidation reaction to a chiral boronic ester

To demonstrate the importance of the homologation/oxidation reaction of tertiary boronic esters, it was decided to apply what was learned to a previously examined chiral boronic ester. In a recent piece of work by V. Aggarwal *et al.*, boronic ester **4.31** had given low yields of homologated product using *in situ* prepared (bromomethyl)lithium (Scheme 4.18).[5]

Scheme 4.18 Homologation of boronic ester 31 as reported in the literature

(1) CH$_2$Br$_2$, *n*-BuLi

(2) NaOH, H$_2$O$_2$

4.31   37%
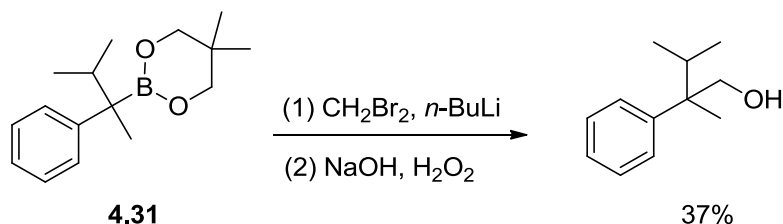
This boronic ester and other boronic esters containing the same tertiary alkyl group but derived from different diols, were chosen to be studied. The intended route for these boronic esters were by the literature method (Scheme 4.19).[16]

Scheme 4.19 Intended route for the synthesis of boronic esters 4.31, 4.37 and 4.38

(1) *sec*-BuLi, -78 °C, 20 min

(2)

4.32   **4.31**, **4.37**, and **4.38**
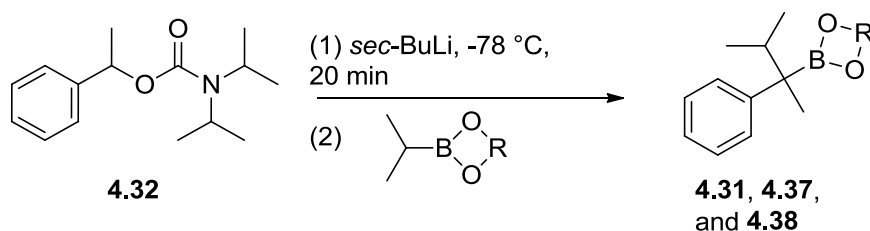
The starting carbamate **4.32** was prepared according to the literature procedure,[16] and purified by column chromatography on silica to give the pure racemic carbamate **4.32** (71% isolated yield, Scheme 4.20, E.S. 4.34a). The compound was fully characterised, with the data consistent with the literature values.[16]

Scheme 4.20 Synthesis of carbamate 4.32


DCM

reflux, 24 h

4.32   71%
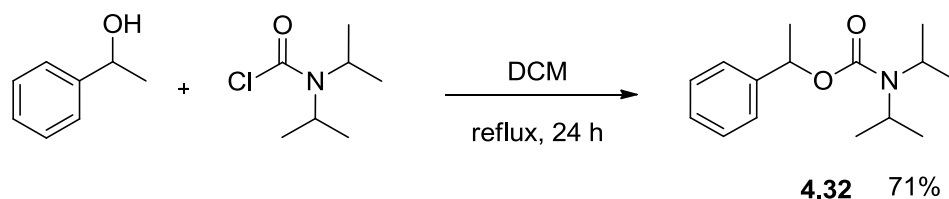
The synthesis of various isopropylboronic esters ranging in the steric hindrance of the diol component was explored, using the corresponding diols and isopropyl boronic acid (Table 4.11). Despite several attempts, the reaction between isopropylboronic acid and ethylene glycol to produce boronic ester **4.33** was unsuccessful. It seemed that solvation of the two starting materials was a problem, but the addition of magnesium sulfate or refluxing the reaction mixture did not improve matters.

The other diols however, reacted smoothly with isopropylboronic acid to give the corresponding isopropyl boronic esters (Table 4.11). The boronic esters **4.34**, **4.35** and **4.36** were purified by simply drying their pentane solutions over magnesium sulfate, filtering and concentrating under reduced pressure. The boronic esters were fully characterised, with the data in accordance with the literature (E.S. 4.34c-e).[16,17] In all but one case, the isopropyl CH signal was missing from the ^{1}H NMR spectrum due to the boron atom's influence on the relaxation time of these protons.

With the starting materials at hand, the synthesis of boronic esters **4.37**, **4.38** and **4.31** was attempted using the literature procedure (Table 4.12).

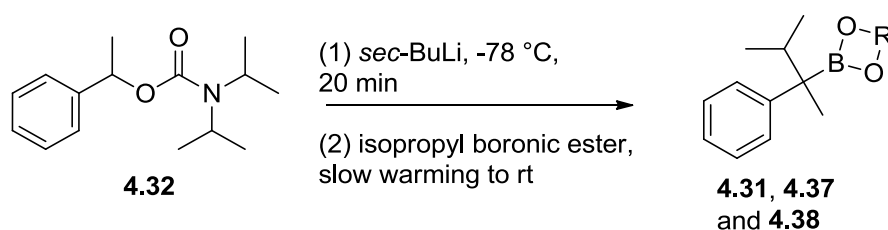**Table 4.11 Synthesis of isopropyl boronic esters 4.33 – 4.36**
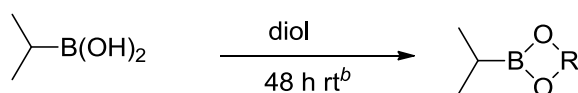
product boronic ester	Diol used	R	Yield (%)^a
4.33	ethylene glycol	CH_2CH_2	trace^b
4.34	1,3-propanediol	$CH_2CH_2CH_2$	46
4.35	pinacol	$C(CH_3)_2C(CH_3)_2$	82
4.36	2,2-dimethyl-1,3-propanediol	$CH_2C(CH_3)_2CH_2$	51

^{a} Isolated yields. ^{b} Reaction was stirred at rt overnight.

The novel racemic boronic ester **4.37** was produced from carbamate **4.32** and boronic ester **4.34**. In the first attempt, the crude product following work up showed the presence of the

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boronic ester **4.37** along with both starting materials. Attempts to purify boronic ester **4.37** by column chromatography on silica, neutral alumina or by simply washing with aqueous 2M HCl solution all led to the decomposition of the product. However, by repeating the reaction with a larger excess of *sec*-BuLi, a clean sample of racemic **4.37** was isolated in 77% yield. The compound was fully characterised (including HRMS), with all data consistent with the proposed structure (E.S. 4.34f).

Table 4.12 Synthesis of boronic esters 4.37, 4.38 and 4.31

(1) *sec*-BuLi, -78 °C, 20 min

(2) isopropyl boronic ester, slow warming to rt

4.32

4.31, **4.37** and **4.38**

product boronic ester	Diol used	R	Yield (%)^a
4.37	1,3-propanediol	$CH_2CH_2CH_2$	77
4.38	pinacol	$C(CH_3)_2C(CH_3)_2$	trace
4.31	2,2-dimethyl-1,3-propanediol	$CH_2C(CH_3)_2CH_2$	73

^{a} Isolated yields.

The synthesis of boronic ester **4.38** was attempted, however only a trace amount of the desired product could be seen in the ^{1}H NMR spectrum of the crude product following work up (Table 4.12). This disappointing result may be a result of the increased steric hindrance in the isopropylboronic ester **4.35** starting material.

Racemic boronic ester **4.31** was prepared in the same manner, and was purified by column chromatography on silica to give the pure boronic ester **4.31** in 73% isolated yield (Table 4.12). The compound was fully characterised, with all the data in accordance with that reported in the literature (E.S. 4.34g).[5]

Boronic ester **4.31** was the first to be studied in the homologation/oxidation reaction. To begin with, a test reaction using a single portion of (bromomethyl)lithium was completed. The

^{1}H NMR spectrum of the crude product following work up showed an approximately equimolar mixture of 2,3-dimethyl-2-phenylbutan-1-ol (**4.39**) to 3-methyl-2-phenylbutan-2-ol (**4.40**). Purification of the products by column chromatography gave the alcohol **4.39** (38% isolated yield, Table 4.13), along with the alcohol **4.40** (24% isolated yield, Table 4.13). Both alcohols were fully characterised, with the data in accordance with the literature (E.S. 4.34h-i).[5] The result for this reaction is essentially the same as is reported in the literature[5] (37% isolated yield of **4.39**), showing that the result is reproducible and that the starting materials and reagents were in good shape.

The reaction was repeated using three portions of (bromomethyl)lithium added in a step-wise manner, and the ^{1}H NMR spectrum of the crude product following work up showed a 64% yield of alcohol **4.39**. The products were purified by column chromatography to give a 43% isolated yield of alcohol **4.39** and 30% isolated yield of alcohol **4.40** (Table 4.13).

Although there is only a small difference in the isolated yield of the alcohol **4.39** from this procedure compared to the analogous reaction using only one portion of (bromomethyl)lithium, the ratios of products seen in the ^{1}H NMR spectrum of the crude product showed that there was an increase in the amount of alcohol **4.39**, proving that the three portion procedure had improved matters.

Table 4.13 Homologation of boronic esters 4.37 and 4.31
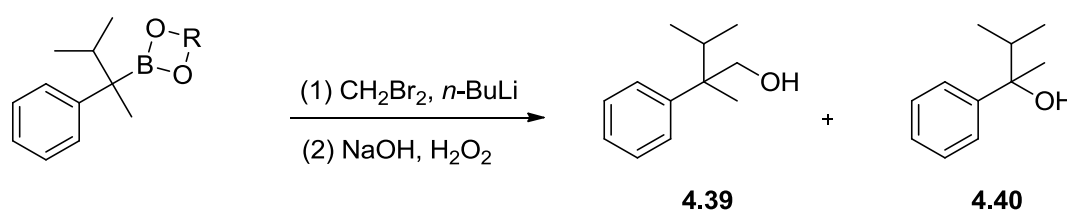
starting boronic ester	R	conditions	Yield (%)^a	
			4.39	**4.40**
4.31	CH$_2$C(CH$_3$)$_2$CH$_2$	single addition	50 (38)^b	50 (24)
4.31	CH$_2$C(CH$_3$)$_2$CH$_2$	triple addition	64 (43)	36 (30)
4.37	CH$_2$CH$_2$CH$_2$	single addition	85 (73)	15

^{a} Yield based on relative integration of the signals of homologated/non-homologated product. ^{b} Isolated yields in parentheses.

The homologation/oxidation reaction was repeated using the less hindered boronic ester **4.37** and a single portion of (bromomethyl)lithium. The ^{1}H NMR spectrum of the crude product following work-up showed a sizable improvement in the amount of homologated alcohol **4.39** (Table 4.13), and following purification by column chromatography on silica a 73% yield of homologated alcohol **4.39** was isolated. The increase in yield can be attributed to the fact that the boronic ester is less hindered, and therefore the capture of the (bromomethyl)lithium is more effective than for boronic ester **4.31**.

4.29 Conclusions on the homologation of tertiary boronic esters using (bromomethyl)lithium

By using various thexylboronic esters, the homologation reaction of tertiary-alkylboronic esters using *in situ* prepared (bromomethyl)lithium has been thoroughly investigated. As a general rule of thumb, the boronic esters derived from less hindered diols give better results under standard conditions (with one equivalent of (bromomethyllithium) due to more effective capture of the reactive (bromomethyl)lithium, although they are difficult to handle. In the case of thexylboronic ester **4.2**, a side reaction that generates 'ate' complex side products limits the yield of the homologated alcohol. This side reaction is not seen in more hindered thexylboronic esters **4.5** and **4.6**.

Using excess (bromomethyl)lithium (especially when added in three sequential portions) improves the yield of homologated product in most cases – except for boronic ester **4.2**, where it seems to promote the aforementioned side reactions. Therefore, from a practical point of view the thexylboronic ester derived from 2,2-dimethyl-1,3-propanediol seems to be the best, with excess (bromomethyl)lithium giving good yields of homologated alcohol while being stable enough to be purified by column chromatography.

Highly hindered boronic esters have been shown to take part in the homologation/oxidation reaction, including boronic esters **4.24**, **4.27** and **4.28**; although there does seem to be an upper limit to the steric hindrance of the boronic ester starting material, with boronic esters **4.29** and **4.30** not giving any homologated product.

The potential importance of the reaction was demonstrated by using the homologation reaction to synthesise a racemic chiral quaternary centre (although if the sequence were carried out using a chiral secondary alcohol, then one could produce a single enantiomer), as

shown recently by V. Aggarwal *et al.*[5] Using what was learned about the reaction when studying the thexylboronic esters, the yield of the homologated alcohol **4.39** containing a chiral quaternary centre was greatly improved compared to the reported yield.[5] This greater understanding of the reaction no doubt makes it a more useful and effective tool for the generation of chiral quaternary centres.

4.30 Experimental Section

4.31 Synthesis of various thexylborane derivatives

4.31a Synthesis of boronic ester 4.2.
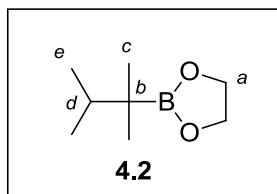
4.2

A dry 50 mL round bottomed flask equipped with a magnetic stirrer bar and septum was assembled when hot, and flushed with N_2 for 10 min. Borane dimethyl sulfide complex (10.5 M, 0.48 mL, 5.0 mmol) was added, and the flask immersed in an ice bath. 2,3-Dimethyl-2-butene (0.59 mL, 5.0 mmol) was added drop-wise with stirring over 5 min. The mixture was left to stir at 0 °C for 90 min. Dry ethylene glycol (0.28 mL, 5.0 mmol) was added drop-wise with safe venting of the evolved hydrogen gas. The cooling bath was removed, and the mixture left to stir for a further 1 h. Excess dimethyl sulfide was removed under a fast stream of N_2 to give boronic ester **4.2**[8] in quantitative yield as a colourless liquid; δ^1H (500 MHz; CDCl$_3$): 4.10 (4H, s, CH$_2$*a*), 1.50 (1H, m, CH*d*), 0.85 (6H, s, CH$_3$*c*), 0.80 (6H, m, CH$_3$*e*); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 65.4 (CH$_2$, C*a*), 35.1 (CH, C*d*), 21.6 (CH$_3$), 18.5 (CH$_3$); δ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 34.5; LR - EI+-MS m/z (%): 155 (M$^+$-1, 85%) 141 (100), 141 (100), 99 (95), 84 (92), 66 (95), 55 (94); ν_{max} (neat/cm^{-1}): 2958, 1465, 1393, 1315, 1280, 1213, 1161, 1127.

4.31b Synthesis of boronic ester 4.3.

4.3
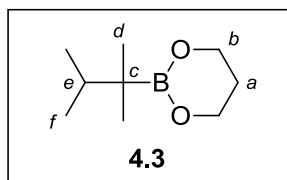
Procedure 4.31a was repeated using 1,3-propanediol (0.36 mL, 5.0 mmol) to give boronic ester **4.3**[8] in quantitative yield as a colourless liquid; δ^1H (400 MHz; CDCl$_3$): 3.90 (4H, app t, $J = 5.2$ Hz, CH$_2$*b*), 1.85 (2H, m, CH$_2$*a*), 1.50 (1H, sept, $J = 6.8$ Hz, CH*e*), 0.75 (12H, m, CH$_3$*d, f*); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 61.5 (CH$_2$, C*b*), 34.4 (CH, C*e*), 27.4 (CH$_2$, C*a*), 21.1 (CH$_3$), 18.3 (CH$_3$); δ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 30.4; LR - EI+-

MS m/z (%): 169 (M$^+$-1, 50%) 155 (100), 143 (60), 126 (100), 113 (100), 99 (100), 85 (100), 75 (94), 69 (100), 59 (96); v_{max} (neat/cm^{-1}): 2955, 2892, 1483, 1416, 1343, 1301, 1272.

### 4.31c Synthesis of boronic ester 4.6.

4.6
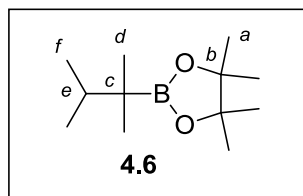
Procedure 4.31a was repeated using a solution of pinacol in dry THF (0.59 g, 5.0 mmol in 5 mL THF) to give boronic ester **4.6**[8] in quantitative yield as a colourless liquid; δ^1H (400 MHz; CDCl$_3$): 1.50 (1H, sept, J = 6.8 Hz, CHe), 1.15 (12H, s, CH$_3a$), 0.70 – 0.85 (12H, m, CH$_3d$, f); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 82.7 (quat C, Cb), 34.6 (CHe), 24.7 (CH$_3$), 21.3 (CH$_3$), 18.5 (CH$_3$); δ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 33.9; LR - EI+-MS m/z (%): 212 (M$^+$, 20%), 197 (25), 170 (20), 153 (32), 129 (35), 113 (33), 101 (63), 97 (53), 83 (100), 69 (87), 55 (59); v_{max} (neat/cm^{-1}): 2958, 1566, 1466, 1304, 1146.

4.31d Synthesis of boronic ester 4.10.

4.10
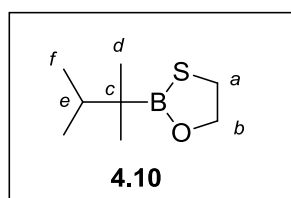
Procedure 4.31a was repeated using 2-mercaptoethanol (0.35 mL, 5.0 mmol) to give boronic ester **4.10** in near quantitative yield as a colourless liquid; δ^1H (500 MHz; CDCl$_3$): 4.30 (2H, app t, J = 7.4 Hz, CH$_2b$), 2.95 (2H, app t, J = 7.4 Hz, CH$_2a$), 1.60 (1H, sept, J = 6.8 Hz, CHe), 0.85 (6H, s, CH$_3d$), 0.80 (6H, d, J = 6.8 Hz, CH$_3f$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 72.5 (CH$_2$, Cb), 35.4 (CH, Ce), 30.0 (CH$_2$, Ca), 22.3 (CH$_3$), 18.5 (CH$_3$); δ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 53.2; HR EI$^+$-MS m/z: calculated for C$_8$H$_{17}$OS^{11}B 172.1093, found 172.1097 (M$^+$, 8%); v_{max} (neat/cm^{-1}): 2956, 1567, 1393, 1180, 1131.

4.31e Synthesis of boronic ester 4.9.

4.9
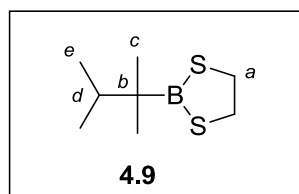
Procedure 4.31d was repeated using 1,2-ethanedithiol (0.42 mL, 5.0 mmol) and the reaction mixture was left to stir overnight for completion of reaction to give fairly pure boronic ester **4.9**[9] as a foul – smelling colourless liquid, contaminated by another thexylborane derivative; δ^1H (500 MHz; CDCl$_3$): 3.10 (4H, s, CH$_2$*a*), 1.70 (1H, m, CH*d*), 0.95 (6H, s, CH$_3$*c*), 0.80 (6H, d, J = 6.9 Hz, CH$_3$*e*); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 38.0 (CH$_2$, C*a*), 24.9 (CH, C*d*), 24.0 (CH$_3$), 18.5 (CH$_3$); δ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 73.3; LR - EI+-MS m/z (%): 188 (M$^+$, 57%), 146 (100), 118 (67), 104 (83), 94 (79), 84 (87), 61 (100); ν_{max} (neat/cm^{-1}): 2955, 2517, 1567, 1463, 1376, 1281, 1100.

4.31f Synthesis of boronic ester 4.11.

4.11
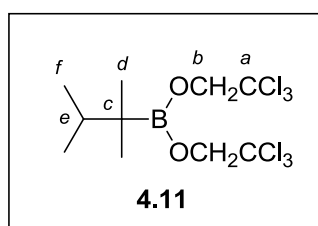
Procedure 4.31a was repeated using 2,2,2-trichloroethanol (0.96 mL, 10.0 mmol) to give boronic ester **4.11** in near quantitative yield as a particularly air-sensitive colourless liquid; δ^1H (250 MHz; CDCl$_3$): 4.40 (4H, s, CH$_2$*b*), 1.70 (1H, sept, J = 6.8 Hz, CH*e*), 0.95 (6H, s, CH$_3$*d*), 0.85 (6H, d, J = 6.8 Hz, CH$_3$*f*); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 97.4 (quat C, C*a*), 76.0 (CH$_2$, C*b*), 33.8 (CH, C*e*), 21.1 (CH$_3$), 18.0 (CH$_3$); δ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 29.8; unable to get representative IR + MS spectra due to the compound's instability.

4.31f Reaction of thexylborane with oxalic acid.
Procedure 4.31a was repeated using a solution of anhydrous oxalic acid (0.47 g, 5.25 mmol) in THF (1 mL). The reaction was left to stir for 2 h, and gave a milky – white oil. ^{1}H and ^{13}C NMR analysis did not correspond to the expected boronic ester product.

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4.31h Synthesis of boronic ester 4.5.

4.5
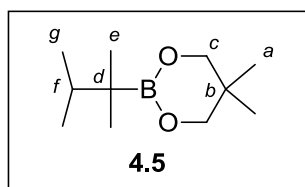
Procedure 4.31a was repeated using a solution of 2,2-dimethyl-1,3-propanediol (0.55 g, 1.05 eq, 5.25 mmol) in dry THF (2 mL) to give boronic ester **4.5** as a colourless liquid; δ^1H (400 MHz; CDCl$_3$): 3.50 (4H, s, CH$_2c$), 1.55 (1H, sept, $J = 6.8$ Hz, CHf), 0.87 (6H, s, CH$_3$), 0.72 – 0.76 (12H, m, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 71.9 (CH$_2$, Cc), 34.3 (quat C, Cb), 31.4 (CH, Cf), 21.9 (CH$_3$), 21.3 (CH$_3$), 18.4 (CH$_3$); δ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 30.1; HR EI$^+$-MS m/z: calculated for C$_{11}$H$_{22}$O$_2$^{11}B 197.1713, found 197.1708 (M$^+$, 5%); ν_{max} (neat/cm^{-1}): 2952, 2873, 1476.

4.31i Synthesis of boronic ester 4.4.

4.4
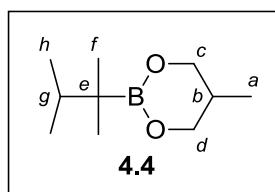
Procedure 4.31a was repeated using 2-methyl-1,3-propanediol (0.44 mL, 5.0 mmol) to give near-pure boronic ester **4.4** as a colourless liquid; δ^1H (400 MHz; CDCl$_3$): 3.87 (2H, dd, $J = 10.8, 4.4$ Hz, CH from diastereotopic CH$_2c$, d), 3.45 (2H, app t, $J = 10.0$ Hz, CH from diastereotopic CH$_2c$, d), 1.95 (1H, app sept, $J = 6.9$ Hz, CHb), 1.51 (1H, sept, $J = 6.8$ Hz, CHg), 0.80 (3H, d, $J = 6.8$ Hz, CH$_3a$), 0.71 – 0.75 (12H, m, CH$_3f$, h); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 67.5 (CH$_2$, Cc, d), 34.5 (CH), 31.3 (CH), 21.1 (CH$_3$), 18.3 (CH$_3$), 12.7 (CH$_3$); δ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 30.2; LR EI$^+$-MS m/z: *molecular ion not seen* 170.1 (M$^+$ - CH$_3$ + 1, 55%), 155 (52), 129 (34), 84 (100), 55 (40); ν_{max} (neat/cm^{-1}) 2956, 1478, 1412, 1347, 1307, 1247, 1182.

4.32 Attempts at thexyl group migration using various thexylborane derivatives and *in situ* formation of LiCH₂Br by reaction of *n*-BuLi and dibromomethane
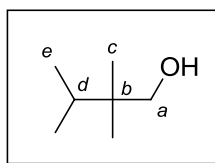

4.32a Typical procedure for thexyl group migration. Boronic ester **4.2** (5.0 mmol) was prepared according to procedure 4.31a. Dry THF (15 mL) was added, followed by dibromomethane (0.42 mL, 1.2 eq, 6.0 mmol). The solution was cooled to -78 °C using a dry ice – acetone bath. *n*-Butyllithium in hexanes (2.5 M, 2.2 mL, 1.1 eq, 5.5 mmol) was added drop-wise over 25 – 30 min with vigorous stirring of the reaction solution. The mixture was left to stir for an additional 30 min, and the cooling bath was then removed. The mixture was left to come up to rt naturally over an hour, before being cooled to 0 °C. Excess sodium hydroxide (1.2 g in 10 mL water) was added drop-wise, followed by excess hydrogen peroxide (30% by weight, 6 mL). Once the initial exothermic reaction subsided, the cooling bath was removed and the reaction left to stir overnight. The aqueous layer was saturated with potassium carbonate, and the mixture was extracted with diethyl ether (3 × 25 mL). The organic extract was washed with brine (2 × 20 mL) and distilled water (2 × 20 mL), dried over magnesium sulfate and filtered. The solvent was evaporated carefully under reduced pressure to around 120% of the maximum theoretical yield to give a mixture of thexylmethanol and thexanol, which was monitored by ^{1}H NMR spectroscopy or GC. The migrated product could be purified by column chromatography on silica (4:1 hexane: diethyl ether), although this was not carried out for each experiment. Such chromatography gave pure thexylmethanol (**4.7**, 2,2,3-trimethylbutan-1-ol) as a colourless liquid; δ^1H (400 MHz; CDCl₃): 3.30 (2H, s, CH₂*a*), 1.55 (1H, sept, $J = 6.9$ Hz, CH*d*), 1.50 (1H, s, OH), 0.80 (6H, d, $J = 7.0$ Hz, CH₃*e*), 0.75 (6H, s, CH₃*c*); δ^{13}C (125 MHz; CDCl₃): 70.6 (CH₂, C*a*), 37.2 (quat C, C*b*), 32.5 (CH, C*d*), 20.9 (CH₃), 17.3 (CH₃); LR EI+-MS m/z (%): 85 (M⁺- CH₂OH, 100%), 73 (78), 69 (37), 55 (72); ν_{max} (neat/cm⁻¹): 3367 (OH), 2957, 1472, 1489, 1038; Rf = 0.45 in 4:1 hexane: diethyl ether.

4.32b Typical procedure for thexyl group migration (triple addition). Procedure 4.32a was repeated, except that the addition of dibromomethane (1.2 eq) /*n*-BuLi (1.1 eq) and subsequent stirring at -78 °C for 30 min were completed three times. The reaction mixture

was not warmed in between additions, and the dibromomethane for each addition was added slowly drop-wise before addition of the *n*-BuLi over a period of 25-30 min. Following the third addition, the reaction mixture was left to stir for an additional 30 min, and then warmed and oxidised as in procedure 4.32a.

4.32c Double migration of thexyl group.
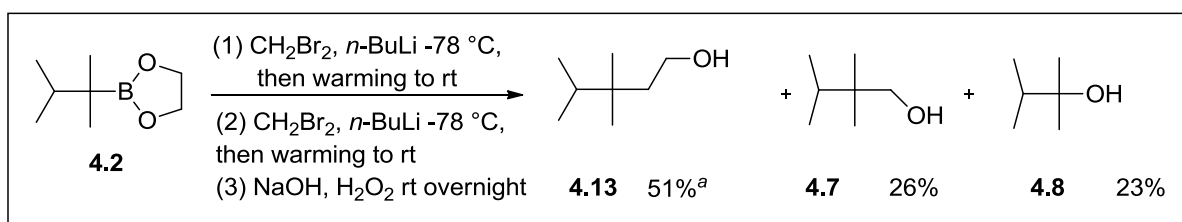
Procedure 4.32a was repeated, except instead of oxidising the reaction mixture, it was cooled back down to -78 °C. Dibromomethane (0.42 mL, 1.2 eq, 6 mmol) was added drop-wise, followed by the drop-wise addition of *n*-BuLi (2.5 M, 2.2 mL, 1.1 eq, 5.5 mmol) over 25-30 min. The reaction mixture was stirred for 30 min at -78 °C, the reaction mixture was thereafter warmed and oxidised as in procedure 4.32a. The ^{1}H NMR spectrum of the crude product showed the presence of thexylethanol (**4.13**), thexylmethanol (**4.7**) and thexanol (**4.8**) (51:26:23 by relative integrations in the ^{1}H NMR spectrum). Attempts were made to purify thexylethanol by column chromatography, but a pure sample was not obtained due to its close behaviour on silica relative to thexylmethanol.

4.32d Typical procedure for investigative ^{11}B NMR reactions. The reactions were completed using modified versions of procedure 4.32a as described in Section 4.24. The reaction mixture was concentrated using a stream of N_2 and the ^{11}B NMR spectrum recorded as soon as possible while the sample was maintained under a N_2 atmosphere.

4.32e Direct reaction of boronic ester 4.2 with *n*-BuLi. Boronic ester **4.2** was prepared as in procedure 4.31a. Dry THF (15 mL) was added, and the mixture cooled to -78 °C. *n*-BuLi (5 mmol) was added drop-wise over 10 min, and the cooling bath removed. The mixture was concentrated under a fast stream of N_2, and the boron NMR spectrum of the 'ate' complex (**4.16**) under N_2 was recorded. δ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): -16.

4.32f Treatment of boronic ester 4.2 with lithium bromide. Procedure 4.32a was repeated, except anhydrous lithium bromide (0.52 g, 6 mmol) was added as a solution in THF (15 mL)

in place of *n*-BuLi. The reaction mixture was not oxidised, but concentrated under a fast N_2 stream. The ^{11}B NMR spectrum was taken, and showed the presence of only the boronic ester **4.15** (34 ppm).

4.32g Gaining information on possible oxygen migrated product (4.20).
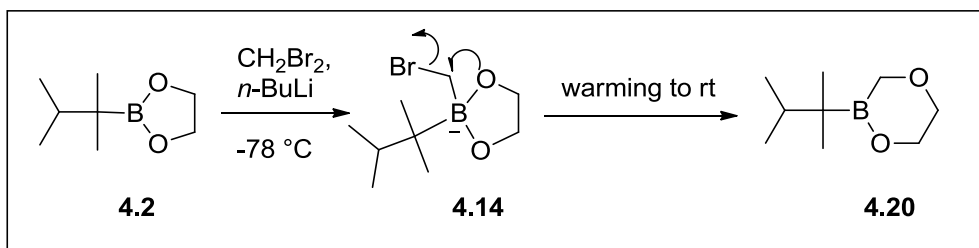
Procedure 4.32a was repeated, except the reaction mixture was not oxidised. The reaction mixture was diluted with diethyl ether (20 mL), and washed twice with cold distilled water (2 × 10mL) dried over magnesium sulfate, filtered and evaporated under reduced pressure to give a colourless liquid, which seemed to show the presence of the the thexyl substituted borinic ester **4.20** arising from oxygen migration. δ^1H (500 MHz; CDCl$_3$): 4.01 (2H, m, CH$_2$), 3.65 (2H, br s, CH$_2$), 3.57 (2H, m, CH$_2$), *thexyl peaks merged with boronic ester* **4.15**.

4.33 Attempts at thexyl group migration using radical lithium aryl systems

4.33a Synthesis of 4,4-di-*tert*-butylbiphenyl (4.19).
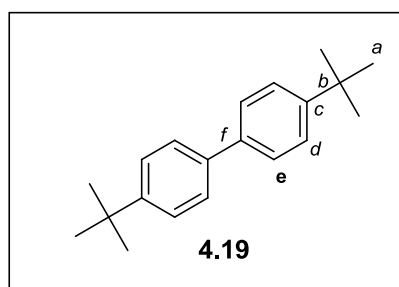
To a dry 250 mL round bottomed flask equipped with a magnetic stirrer bar was added biphenyl (7.70 g, 50.0 mmol), *tert*-butyl chloride (11.6 mL, 110.0 mol) and dry dichloromethane (20 mL). A suspension of iron (III) chloride (40 mg) in dichloromethane (5 mL) was added slowly with stirring, and evolution of HCl gas was observed. The green mixture was warmed to 40 °C and stirred for an additional 30 min. Methanol (10 mL) was added to quench the reaction, and the reaction mixture was washed with water (20 mL) and a saturated solution of sodium bicarbonate (10 mL) and dried over magnesium sulfate. The

solution was filtered, and the dichloromethane evaporated under reduced pressure to give the crude product, which was recrystallized from hot ethanol to give pure 4,4-di-*tert*-butylbiphenyl[12] (**4.19**, 9.18 g, 69%) as colourless needles; m.p 127-128 °C (lit. 127-128 °C[12]); δ^1H (400 MHz; CDCl$_3$): 7.45 (4H, d, J = 8.4 Hz, CH), 7.35 (4H, d, J = 8.4 Hz, CH), 1.25 (18H, s, CH$_3a$); δ^{13}C (125 MHz; CDCl$_3$): 150.0 (quat C, Cc), 138.2 (quat C, Cf), 126.7 (CH), 125.7 (CH), 34.5 (quat C, Cb), 31.4 (CH$_3$, Ca); LR EI+-MS m/z (%): 266 (M$^+$, 67%), 251 (100), 83 (56); ν_{max} (thin film/cm^{-1}): 3019, 2966, 2905, 2869, 1467, 1268, 1216.

4.33b Typical procedure for attempts at thexyl group migration using radical lithium aryl systems. A 250 mL two necked flask equipped with a stirrer bar was assembled while hot and flushed with N$_2$. 4,4-Di-*tert*-butylbiphenyl (7.99 g, 30 mmol) was introduced when the reaction flask was around 50 °C, and dry THF (60 mL) was added after flushing with N$_2$ for an additional 5 min. Lithium wire (0.174 g, 25.0 mmol, with 0.5 – 1% sodium) was cut into small pieces with a scalpel, before being pressed to increase surface area with a spatula. The reaction mixture was cooled to 0 °C, and the lithium introduced quickly *via* the side arm under a fast stream of N$_2$ with vigorous stirring of the solution. The solution took the dark green / purple colour of the radical anion within 2 -5 min. The mixture was left to stir vigorously for 5 h, by which time the lithium was fully consumed. The solution was cooled to -78 °C, and transferred drop-wise over 45 min *via* cannula^a to a freshly prepared solution of boronic ester **4.2** in dry THF (5.0 mmol in 15 mL THF, prepared according to procedure 4.1a, also cooled to -78 °C). The reaction mixture was left to stir for an additional 30 min at -78 °C, before removing the cooling bath and leaving the solution to come to rt over 1 h. An accurately weighed portion of hexadecane (typically around 0.5 mL) was introduced as an internal standard for GC, and the mixture was oxidised according to procedure 4.32a. An aliquot was taken from the organic layer, which was analysed by GC and showed the presence of thexylmethanol (**4.7**, 55% by GC) and thexanol (**4.8**, 45% by GC).

4.34 Synthesis and homologation of chiral boronic esters

4.34a Synthesis of racemic 1-phenylethyl *N,N*-diisopropylcarbamate (4.32).

4.32
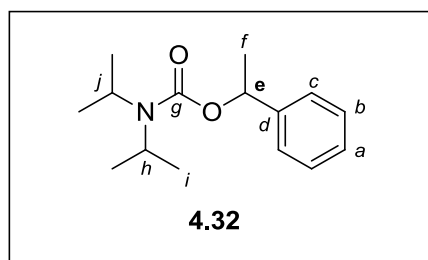
To a dry 100 mL round bottomed flask equipped with a reflux condenser was added 1-phenylethanol (3.51 mL, 29 mmol), diisopropylcarbamoyl chloride (5.00 g, 30 mmol), triethylamine (4.36 mL, 31 mmol) and dry dichloromethane (40 mL). The mixture was refluxed gently (pot temperature 54 °C) for 24 h. The solution was poured into water (50 mL), and extracted with diethyl ether (3 × 30 mL) and the combined organic extracts washed with brine (30 mL) and water (30 mL). The organic extract was dried over magnesium sulfate, filtered and the solvent evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica (10:1 petrol ether: ethyl acetate) to give pure racemic 1-phenylethyl *N,N*-diisopropylcarbamate[16] (**4.32**, 5.36 g, 71%) as a colourless liquid; δ^1H (400 MHz; CDCl$_3$): 7.23 – 7.31 (4H, m, CHc, b), 7.15 (1H, m, CHa), 5.75 (1H, q, J = 6.6 Hz, CHe), 4.0 (1H, br, isopropyl CH), 3.7 (1H, br, isopropyl CH), 1.45 (3H, d, J = 6.6 Hz, CH$_3f$), 1.15 (12H, br, CH$_3i$); δ^{13}C (125 MHz; CDCl$_3$): 155.0 (quat C, Cg), 142.8 (quat C, Cd), 128.4 (CH, Cb), 127.4 (CH, Ca), 126.0 (CH, Cc), 72.7 (CH, Ce), 46.0 (CH, br, Ch), 22.8 (CH$_3$, Cf), 21.0 (CH$_3$, br,Ci); LR - EI+-MS m/z (%): 249 (M$^+$, 22%), 190 (22), 144 (23), 105 (100), 86 (45); v_{max} (neat/cm^{-1}): 2972, 2933, 1687, 1437, 1286, 1213, 1133, 1067; Rf = 0.35 in 10:1 petroleum ether: ethyl acetate.

4.34c Synthesis of boronic ester 4.33.

4.33
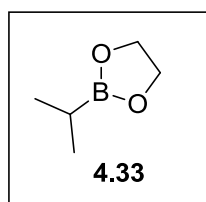
A dry 50 mL round bottomed flask equipped with a magnetic stirrer bar was flushed with N$_2$ for 10 min. Isopropylboronic acid (2.0 g, 22.0 mmol) was added quickly, and the flask

flushed for a further 10 min with N_2. Dry pentane (20 mL) was added, followed by the drop-wise addition of ethylene glycol (1.33 mL, 24.0 mmol). The mixture was stirred overnight at rt, magnesium sulfate (2.0 g) was added, and the mixture left to stir for a further 30 min. The reaction mixture was quickly filtered, and the excess pentane evaporated under a fast N_2 stream to give only a trace amount (*ca*. 5 mg) of boronic ester **4.33** as a colourless liquid; δ^1H (300 MHz; CDCl$_3$): 4.15 (4H, s, CH$_2$O), 1.15 (1H, m, isopropyl CH), 1.0 (6H, br s, CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 34.4 *–not enough sample for further analysis.*

4.34c Synthesis of boronic ester 4.34.

4.34
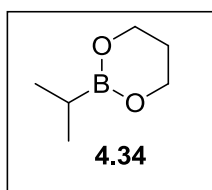
Procedure 4.34b was repeated on a 17.0 mmol scale, using 1,3-propanediol (1.32 mL, 1.05 eq, 18.0 mmol) and the reaction mixture left to stir for 48 h to give boronic ester (**4.34**, 1.01 g, 46%)[17] as a colourless liquid; δ^1H (400 MHz; CDCl$_3$): 3.95 (4H, app t, J = 5.4 Hz, CH$_2$O), 1.85 (2H, m, C*H*$_2$CH$_2$O), 1.15 (1H, m, isopropyl CH – *not always seen*), 0.85 (6H, br, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *CH next to boron not seen*; 61.6 (CH$_2$, CH$_2$O), 27.4 (CH$_2$), 18.1 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 30.1; LR - EI+-MS m/z (%): 127 (M$^+$-1, 100%), 113 (100), 101 (100), 87 (100), 72 (100), 59 (97), 55 (92),*– higher molecular ions seen (141, 155 and 169.)*
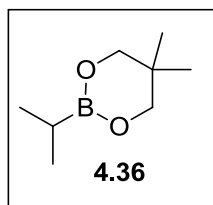
4.34d Synthesis of boronic ester 4.35.

4.35
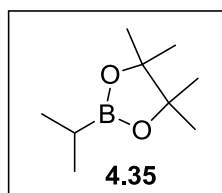
Procedure 4.34c was repeated using a solution of pinacol (2.12 g, 1.05 eq, 18.0 mmol) in dry pentane (5 mL) to give boronic ester **4.35** (2.37 g, 82%)[16] as a light yellow liquid; δ^1H (400 MHz; CDCl$_3$): *CH next to boron not seen* 1.15 (12H, s, CH$_3$), 0.85 – 0.95 (6H, br m, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 82.8 (quat C, OCCH$_3$), 24.7 (CH$_3$), 18.0 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz;

CDCl$_3$): 33.7; LR EI-MS m/z (%): 170 (M$^+$, 19%), 155 (58), 143 (24), 129 (63), 112 (48), 101 (34), 85 (82), 71 (52), 59 (100); v_{max} (neat/cm^{-1}): 2979, 1473, 1389, 1372, 1317.

4.34e Synthesis of boronic ester 4.36.

4.36

Procedure 4.34c was repeated using a solution of 2,2-dimethyl-1,3-propanediol (1.88 g, 1.05 eq, 18.0 mmol) in dry pentane (5 mL). The product was contaminated with what seemed like some oxidised product according to ^{11}B{^{1}H} NMR spectroscopy, and so was taken into diethyl ether (20 mL) and washed with cold water (2 × 20 mL), dried over magnesium sulfate, filtered and the volatiles evaporated under reduced pressure to give pure boronic ester **4.36** (1.35 g, 51%)[16] as a colourless liquid; δ^{1}H (400 MHz; CDCl$_3$): *CH next to boron not seen*; 3.50 (4H, s, CH$_2$O), 0.78 – 0.83 (12 H, br, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *CH next to boron not seen*; 72.0 (CH$_2$, CH$_2$O), 31.6 (quat C), 21.7 (CH$_3$), 18.2 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 29.8; LR - EI-MS m/z (%): 156 (M$^+$, 100%) 141 (34), 126 (33), 113 (90), 99 (43), 84 (37), 73 (26); v_{max} (neat/cm^{-1}): 2960, 2871, 1477, 1414, 1386, 1335.

4.34f Synthesis of racemic boronic ester 4.37.

4.37
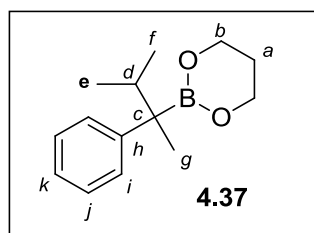
A dry 100 mL flask equipped with a magnetic stirrer bar and stopcock was flushed with N$_2$ for 10 min. Racemic 1-phenylethyl diisopropylcarbamate (1.18 g, 4.74 mmol), and dry diethyl ether (20 mL) were added, and the solution cooled to -78 °C. *s*-BuLi (1.3 M in 92:8 cyclohexane/hexane, 4.0 mL, 5.2 mmol) was added drop-wise over 10 min and the solution stirred for a further 20 min. To this was added a cold solution of 2-isopropyl-1,4,2-dioxaborinane (**4.34**, 0.92 g, 7.19 mmol) in diethyl ether (10 mL) drop-wise over 10 min with vigorous stirring. The solution was left to come to rt slowly overnight as the dry-ice acetone

bath gradually warmed. After stirring for 16 h, the mixture was cooled to 0 °C and saturated ammonium chloride solution (20 mL) was added. The organic layer was kept, and mixed with three extracts (3 × 15 mL diethyl ether) of the aqueous layer. The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. Methanol (20 mL) was added, and the mixture left in the freezer for 1 h, whereupon some impurities precipitated out. After filtration of the impurities and evaporation of the methanol, diethyl ether (20 mL) was added. The supernatant layer was taken, and the diethyl ether evaporated under reduced pressure to give near-pure racemic boronic ester **4.37** (0.85 g, 77%) as a light yellow oil; δ^1H (400 MHz; CDCl$_3$): 7.30 (2H, m, CHj), 7.20 (2H, m, CHi), 7.05 (1H, m, CHk), 3.90 (4H, m, CH$_2$Ob), 2.32 (1H, app sept, J = 6.8 Hz, CHd), 1.80 (2H, m, CH$_2a$), 1.10 (3H, s, CH$_3g$), 0.90 (3H, d, J = 6.8 Hz, CH$_3$), 0.45 (3H, d, J = 6.8 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 147.8 (quat C, Ch), 127.8 (CH), 127.2 (CH), 124.6 (CH, Ck), 61.8 (CH$_2$, Cb), 33.8 (CH, Cd), 27.3 (CH$_2$, Ca), 20.5 (CH$_3$), 16.5 (CH$_3$), 13.4 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 29.5; HR - EI+-MS m/z: calculated for C$_{14}$H$_{21}$O$_2$^{11}B 232.1635, found 232.1634 (M$^+$, 69%); ν_{max} (neat/cm^{-1}): 2963, 1482, 1419, 1274, 1159, 1126.

4.34g Synthesis of boronic ester 4.31.


4.31
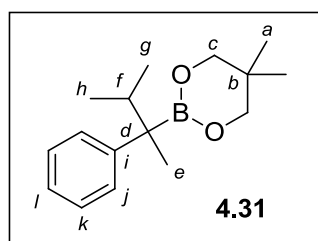
Procedure 4.34f was repeated on a larger scale (5.2 mmol of the carbamate) using boronic ester **4.36**. The crude product was purified by column chromatography on silica (20:1 petroleum ether: diethyl ether) to give pure racemic boronic ester **4.31**[5] (0.99 g, 73%) as a colourless oil; δ^1H (400 MHz; CDCl$_3$): 7.30 (2H, d, J = 8.4, CHj), 7.18 (2H, app t, J = 8.4 Hz, CHk), 7.0 (1H, t, J = 8.4 Hz, CHl), 3.48 (4H, s, CH$_2$Oc), 2.40 (1H, app sept, J = 6.8 Hz, CHf), 1.12 (3H, s, CH$_3e$), 0.92 (3H, d, J = 6.8 Hz, CH$_3$), 0.76 (6H, s, CH$_3a$), 0.47 (3H, d, J = 6.8 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 147.6 (quat C, Ci), 127.9 (CH), 127.2 (CH), 124.7 (CH, Cl), 72.2 (CH$_2$, Cc), 33.5 (CH, Cf), 31.6 (quat C, Cb), 22.0 (CH$_3$), 20.7 (CH$_3$), 16.6 (CH$_3$), 13.3 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 29.7; LR - EI+-

MS m/z (%): 260 (M$^+$, 23%), 217 (95), 131 (31), 117 (36), 84 (100); ν_{max} (neat/cm^{-1}): 2961, 2872, 1476, 1413, 1276, 1248; Rf = 0.85 in 9:1 petroleum ether: ethyl acetate.

The synthesis of the corresponding *tert*-alkylboronic ester from boronic ester **4.35** was attempted, but by applying procedure 4.4f only a trace amount of product was observed in the crude product by ^{1}H NMR analysis.

4.34h Homologation of boronic ester 4.37.
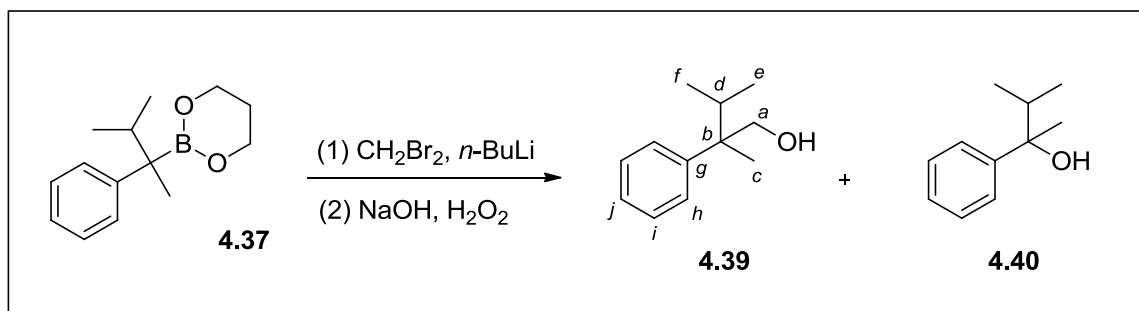
A dry 100 mL round bottomed flask equipped with a stopcock and magnetic stirrer was flushed with N$_2$ for 10 min. Boronic ester **4.37** (0.78 g, 3.37 mmol) was added as a solution in dry THF (15 mL), along with dibromomethane (0.28 mL, 3.99 mmol) and the solution cooled to -78 °C using a dry-ice acetone bath. *n*-BuLi in hexanes (1.5 M, 2.47 mL, 3.71 mmol) was added drop-wise over 30 min with vigorous stirring of the reaction mixture. Once the addition was complete, the solution was left to stir for an additional 30 min, before removal of the cooling bath and stirring for 60 min. The reaction mixture was cooled to 0 °C, and 3 M NaOH (1.2 g in 10 mL distilled water) was added drop-wise. Once the initial vigorous reaction had ceased, hydrogen peroxide (30% by weight, 6 mL) was added drop-wise, and the solution heated to 50 °C for 2 h. The aqueous layer was saturated with potassium carbonate, and products were extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with brine (2 × 20 mL) and distilled water (2 × 20 mL), dried over magnesium sulfate and filtered. The volatiles were evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica (95:5 petroleum ether: ethyl acetate (100 mL), followed by 90:10 petroleum ether: ethyl acetate (200 mL)) to give pure racemic 2,3-dimethyl-2-phenylbutan-1-ol (**4.39**, 0.44 g, 73%)[5] as a colourless oil; δ^{1}H (400 MHz; CDCl$_3$): 7.20 – 7.29 (4H, m, CH*h*, *i*), 7.1 (1H, t, *J* = 6.9 Hz, CH*j*), 3.75 (1H, d, *J* = 10.9 Hz, CH of CH$_2$*a*), 3.45 (1H, d, 10.9 Hz, CH of CH$_2$*a*), 1.95 (1H, app sept, *J* = 6.8 Hz, CH*d*), 1.55 (1H, br s, OH), 1.15 (3H, s, CH$_3$*c*), 0.85 (3H, d, *J* = 6.8 Hz, CH$_3$), 0.55 (3H, d, *J* = 6.8

Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 145.3 (quat C, Cg), 128.3 (CH), 127.1 (CH), 126.0 (CH, Cj), 70.5 (CH$_2$, Ca), 46.3 (quat C, Cb), 34.2 (CH, Cd), 18.0 (CH$_3$), 17.4 (CH$_3$), 15.8 (CH$_3$); LR - EI+-MS m/z (%): 178 (M$^+$, 10%), 147 (100), 134 (100), 117 (100), 106 (100), 91 (100), 83 (100), 77 (88), 65 (34), 57 (75); v_{max} (neat/cm^{-1}): 3399 (OH), 3089, 3058, 2971, 1600, 1498, 1467, 1444, 1374; Rf = 0.22 in 95:5 petroleum ether: ethyl acetate.

4.34i Homologation of boronic ester 4.31.
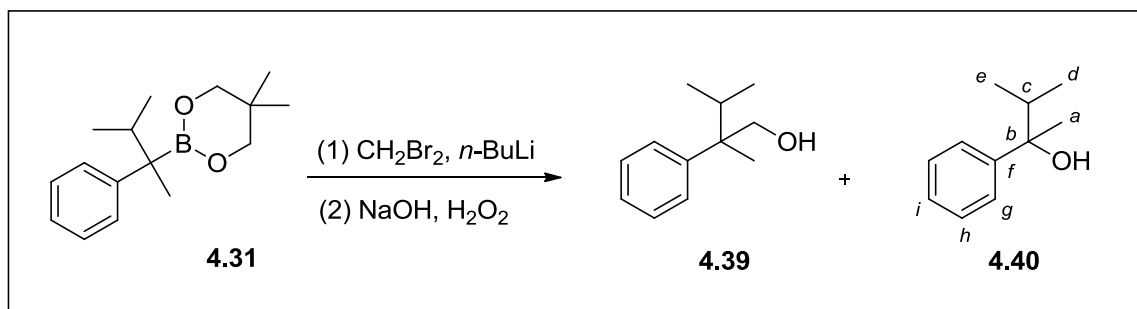
Procedure 4.34h was repeated on a 2.8 mmol scale (with regard to racemic boronic ester **4.31**). The crude product was purified by column chromatography as in procedure 4.34h to give a racemic 2,3-dimethyl-2-phenylbutan-1-ol (**4.39**, 0.19 g, 38%) as a colourless oil and racemic 3-methyl-2-phenylbutan-2-ol[5] (**4.40**, 0.11 g, 24%) as a colourless oil; δ^1H (400 MHz; CDCl$_3$): 7.32 (2H, d, J = 8.6 Hz, CHg), 7.21 (2H, app t, J = 7.4 Hz, CHh), 7.10 (1H, t, J = 7.3 Hz, CHi), 1.92 (1H, app sept, J = 7.3 Hz, CHc), 1.72 (1H, br s, OH), 1.41 (3H, s, CH$_3a$), 0.80 (3H, d, J = 6.8 Hz, CH$_3$), 0.70 (3H, d, J = 6.9 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 147.9 (quat C, Cf), 127.9 (CH), 126.4 (CH, Ci), 125.3 (CH), 76.8 (quat C, Cb), 38.7 (CH, Cc), 26.7 (CH$_3$), 17.5 (CH$_3$), 17.2 (CH$_3$); LR EI+-MS m/z (%): 164 (M$^+$, 4%), 147 (95), 131 (69), 121 (100), 105 (98), 91 (97), 77 (96); v_{max} (neat/cm^{-1}): 3458 (OH), 2973, 1495, 1446, 1373; Rf = 0.45 in 95:5 petroleum ether: ethyl acetate.

4.34j Homologation of boronic ester 4.31. Procedure 4.4i was repeated on a 1.33 mmol scale, except that the addition of n-BuLi and CH$_2$Br$_2$ was repeated 3 times without warming in between additions (1.2 eq CH$_2$Br$_2$ added first, followed by the drop-wise addition of 1.1 eq of n-BuLi). The reaction was worked-up as in procedure 4.4h to give a mixture, consisting of 64:36 of homologated: unhomologated respectively by relative integrations in the ^{1}H NMR spectrum of the crude mixture. The crude mixture was purified by column chromatography on silica as in procedure 4.34h to give racemic 2,3-dimethyl-2-phenylbutan-1-ol (**4.39**, 0.101 g, 43%) and racemic 3-methyl-2-phenylbutan-2-ol (**4.40**, 0.066 g, 30%).

4.35 Synthesis and attempted homologation of *tert*-alkylboronic esters prepared by the DCME reaction

4.35a Synthesis of boronic ester 4.28.

4.28

Procedure 2.32a was repeated on a 10.0 mmol scale, but the reaction mixture was not oxidised. Following the reaction with DCME, ethylene glycol (0.56 mL, 10.0 mmol) was added drop-wise, and the solution left to stir overnight at rt. The volatiles were evaporated under reduced pressure, and hexane (30 mL) was added and the solution filtered. The resulting clear hexane solution was washed in a separating funnel with methanol (2×15 mL). The hexane layer was kept, and concentrated under reduced pressure to give near pure boronic ester **4.28** (2.04 g, 48%) along with some of the isomer due to hydroboration at the 2-position (*ca.* 82:18 by relative integrations in the ^{1}H NMR spectrum) as a colourless oil; δ^1H (400 MHz; CDCl$_3$): 4.10 (4H, s, CH$_2$O), 1.10 – 1.30 (42H, m, CH$_2$), 0.80 (9H, t, $J = 6.6$ Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 65.3 (CH$_2$, *C*H$_2$O), 34.5 (CH$_2$), 31.9 (CH$_2$), 30.8 (CH$_2$), 29.8 (CH$_2$), 29.6 (CH$_2$), 24.7 (CH$_2$), 22.7 (CH$_2$), 14.1 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 29.8; HR - EI+-MS m/z (%): calculated for C$_{27}$H$_{54}$O$_2$^{11}B 422.4295, found 422.4297 (M$^+$-1, 2%); ν_{max} (neat/cm^{-1}): 2924, 2853, 1466, 1389, 1348.

4.35b Synthesis of boronic ester 4.27.

4.27
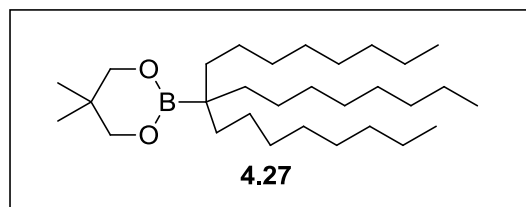
Procedure 4.35a was repeated on a 15.0 mmol scale using a solution of 2,2-dimethyl-1,3-propanediol (1.88 g, 18.0 mmol) in dry THF (5 mL). Following completion of reaction, the product was extracted with diethyl ether (3×20 mL), and the combined organic extracts washed with 2 M HCl (3×15 mL) and water (10 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the crude product, which was purified by

column chromatography (petroleum ether) and concentrated by heating under HV to get rid of residual 1-octene to give pure boronic ester **4.27** (3.98 g, 57%), along with some of the isomer due to hydroboration at the 2-position (*ca.* 82:18 by relative integrations in the ^{1}H NMR spectrum) as a viscous colourless oil; δ^1H (400 MHz; CDCl$_3$): 3.50 (4H, s, CH$_2$O), 1.00 – 1.30 (42H, m, CH$_2$), 0.87 (6H, s, CH$_3$), 0.81 (9H, t, J = 6.8 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 71.8 (CH$_2$, CH$_2$O), 34.3 (CH$_2$), 32.0 (CH$_2$), 31.4 (quat C), 31.0 (CH$_2$), 29.7 (CH$_2$), 29.4 (CH$_2$), 25.0 (CH$_2$), 22.5 (CH$_2$), 22.1 (CH$_3$) 14.1 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 30.6; HR - EI+-MS m/z (%): calculated for C$_{30}$H$_{60}$O$_2$^{11}B 463.4686, found 463.4685 (M$^+$-1, 2%); v_{max} (neat/cm^{-1}): 2923, 2952 , 1467, 1409, 1378, 1246; Rf = 0.90 in 9:1 petroleum ether: ethyl acetate.

4.35c Synthesis of boronic ester 4.29.

4.29
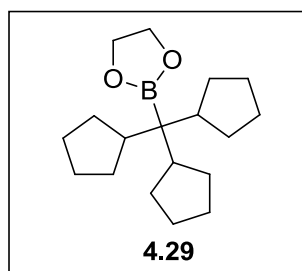
Procedure 4.35a was repeated on a 10.0 mmol scale using cyclopentene (in place of 1-octene), and the reaction mixture left to stir overnight once the ethylene glycol was added. Following completion of reaction, the crude mixture was concentrated under reduced pressure, and methanol (40 mL) was added. The solution was swirled vigorously until the subnatant oil began to form a precipitate. The solution was cooled to 0 °C for 2 h whereupon boronic ester **4.29** (1.53 g, 53%) precipitated as a white solid; m.p 89 – 93 °C; δ^1H (400 MHz; CDCl$_3$): 4.05 (4H, s, CH$_2$O), 1.95 (3H, m, CH), 1.30 – 1.65 (24H, m, CH$_2$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 64.8 (CH$_2$, CH$_2$O), 45.9 (CH), 30.0 (CH$_2$), 25.1 (CH$_2$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 33.8; HR - EI$^+$-MS m/z (%): *molecular ion not seen*, calculated for C$_{13}$H$_{22}$O$_2$^{11}B 221.1713, found 221.1714 (M$^+$-Cp, 100%); v_{max} (thin film/cm^{-1}): 3019, 2952, 2869, 1389, 1215.

4.35d Synthesis of boronic ester 4.30.

4.30
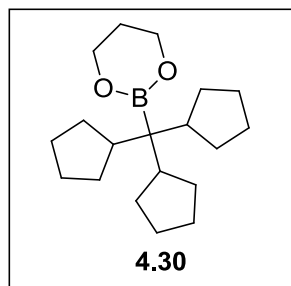
Procedure 4.35c was repeated using 1,3-propanediol to give boronic ester (**4.30**, 1.72 g, 57%) as a white solid; m.p 77 – 79 °C; δ^1H (400 MHz; CDCl$_3$): 3.87 (4H, t, J = 5.4 Hz, CH$_2$O), 1.80 – 1.95 (5H, m, CH and CH$_2$), 1.30 – 1.65 (24H, m, CH$_2$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 61.0 (CH$_2$, CH$_2$O), 46.4 (CH), 30.0 (CH$_2$), 27.5 (CH$_2$), 25.2 (CH$_2$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 29.8; HR - EI$^+$-MS m/z (%): calculated for C$_{19}$H$_{33}$O$_2$^{11}B 304.2574, found 304.2577 (M$^+$, 3%); v_{max} (thin film/cm^{-1}): 3019, 2951, 2868, 1480, 1413, 1267, 1215.

4.35e Synthesis of boronic ester 4.24.
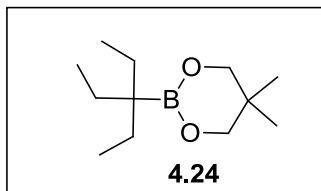
4.24

An oven dried 100 mL round bottomed flask equipped with a magnetic stirrer bar and septum was flushed with N$_2$ for 10 min. Triethylborane solution in dry THF (1.0 M, 15 mL, 15.0 mmol) was added, along with dry THF (15 mL). Thereafter, procedure 4.35b was followed, and the crude product was purified by column chromatography on silica (90:10 petroleum ether: ethyl acetate) to give boronic ester **4.24** (1.43 g, 45%) as a colourless liquid; δ^1H (400 MHz; CDCl$_3$): 3.50 (4H, s, CH$_2$O), 1.27 (6H, q, J = 7.5 Hz, CH$_2$), 0.88 (6H, s, CH$_3$), 0.69 (9H, t, J = 7.5 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 71.8 (CH$_2$, CH$_2$O), 31.4 (quat C), 25.5 (CH$_2$), 22.1 (CH$_3$), 9.2 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 30.3; HR - EI$^+$-MS m/z (%): calculated for C$_{12}$H$_{25}$O$_2$^{11}B 212.1948, found 212.1954 (M$^+$, 3%); v_{max} (neat/cm^{-1}): 2957, 2875, 1476, 1410, 1382, 1358, 1244, 1157; Rf = 0.81 in 9:1 petroleum ether: ethyl acetate.

The *tert*-alkylboronic ester from the DCME reaction with tri(4-methoxyphenylethyl)borane, was prepared as in procedure 4.35a, however the crude product could not be purified, and so was not taken forward to the homologation stage. The *tert*-alkylboronic ester from the DCME reaction with 9-*n*-octyl- 9-BBN was also prepared in a similar manner, but could not be purified and so was not pursued further.

4.35f Attempted homologation of *tert*-alkylboronic esters from the DCME reaction.
Procedure 4.32a or 4.32b was applied to all three *tert*-alkylboronic esters, and the ^{1}H NMR spectra of the crude mixture taken.

4.35g Homologation of boronic ester 4.24.
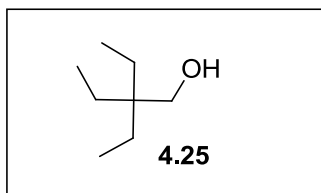
Procedure 4.32b was applied to boronic ester **4.24** (1.8 mmol). A portion of the migrated material, 2,2-diethylbutanol (**4.25**) was separated from triethylmethanol by column chromatography on silica (petroleum ether, followed by 95:5 petroleum ether: ethyl acetate, followed by 80:20 petroleum ether: ethyl acetate) to give 2,2-diethylbutanol[14] (**4.25**, 0.086 g, 36%) as a colourless liquid; δ^1H (400 MHz; CDCl$_3$): 3.29 (2H, s, CH$_2$O), 1.30 (H, br s, OH), 1.18 (6H, q, J = 7.5 Hz, CH$_2$), 0.72 (9H, t, J = 7.5 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 65.9 (CH$_2$, CH$_2$O), 39.5 (quat C), 25.0 (CH$_2$), 7.3 (CH$_3$); LR - EI$^+$-MS m/z (%): 98 (M$^+$- CH$_2$OH, 67%), 86 (100), 74 (100), 69 (61), 59 (100); ν_{max} (neat/cm^{-1}): 3365 (OH), 2965, 2927, 2880, 1465, 1379, 1260.

4.40 References

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Chapter 5: Attempted generation of quaternary carbon centres by use of 3-chloro-1-lithiopropyne

5.1 Aims and introduction

Continuing with our research interests regarding the generation of quaternary carbon centres, we decided to research the reaction of organoboranes with 3-chloro-1-lithiopropyne with a view of modifying the existing methodology to allow efficient migration of *tert*-alkyl groups to generate quaternary carbon centres.

As briefly mentioned at the end of Section 1.44, trialkylboranes react with 3-chloro-1-lithiopropyne (lithiated propargyl chloride) to give, after migration, an allenic organoborane intermediate (Scheme 5.1).[1] This allenic organoborane is a useful synthetic intermediate, and has been shown to undergo protonolysis,[1] allylic rearrangement,[2] and insertion reactions with aldehydes and ketones[2] (Scheme 5.2). With this in mind, if the reaction could be modified to allow efficient migration of *tert*-alkyl groups, then it would constitute a powerful method of generating quaternary carbon centres.

Scheme 5.1 Mechanism of the reaction between trialkylboranes and 3-chloro-1-lithiopropyne
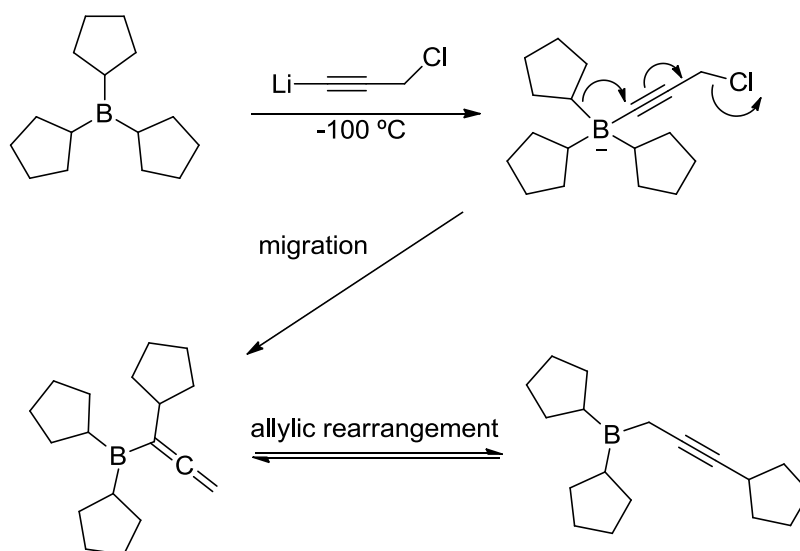
Scheme 5.2 Versatility of the allenic organoborane intermediate
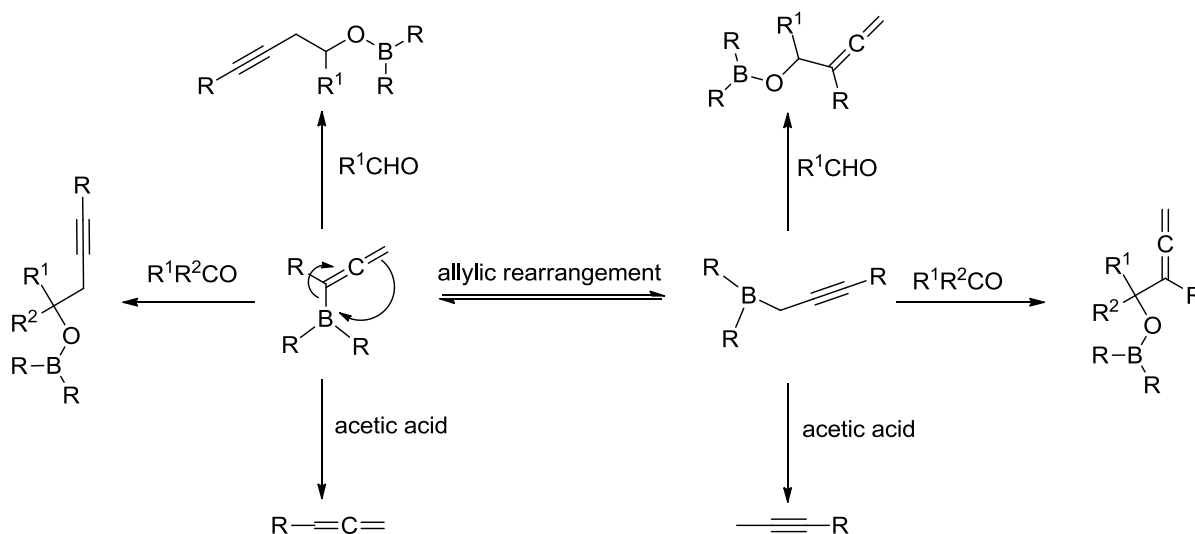
We hoped that by using a similar approach to that reported in Chapter 4, *i.e.* by reacting a *tert*-alkylboronic ester with the 3-chloro-1-lithiopropyne, efficient migration of the *tert*-alkyl group could be achieved to give the desired allenic organoboron intermediate containing the newly-generated quaternary carbon centre (Scheme 5.3). In fact, such an approach has already been shown to be effective for the migration of a silyl group (Scheme 5.4).[3]

Scheme 5.3 Intended migration of *tert*-alkyl group
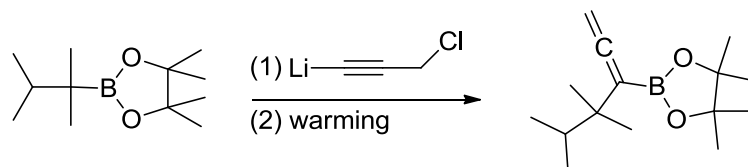
Scheme 5.4 Effective silyl group migration using intended methodology[3]

70%
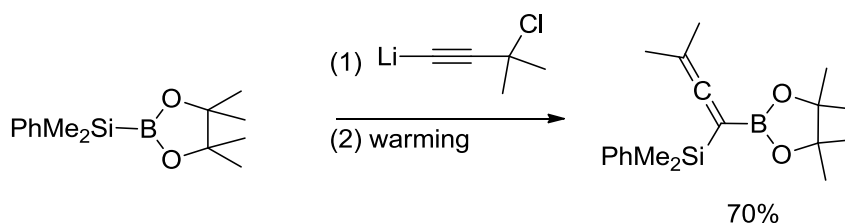
5.2 Results and discussion

5.21 Reaction of trialkylboranes with 3-chloro-1-lithiopropyne
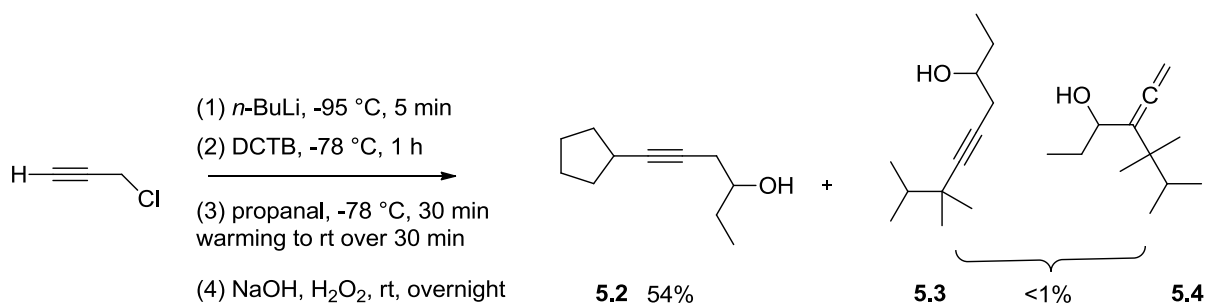
To begin with, it was decided to carry out a test reaction with dicyclopentylthexylborane and 3-chloro-1-lithiopropyne both in order to test the starting materials/procedure and to ascertain whether *sec*-alkyl groups migrate preferentially to *tert*-alkyl groups (it has already been shown that primary-alkyl groups migrate in preference to *tert*-alkyl groups[2])

Scheme 5.5 Synthesis of dicyclopentylthexylborane (5.1)

$BH_3 \cdot SMe_2$ — (1) 2,3-dimethyl-2-butene 0 °C, 1.5 h / (2) cyclopentene (2 eq) rt, 2 h → **5.1** DCTB = dicyclopentylthexylborane
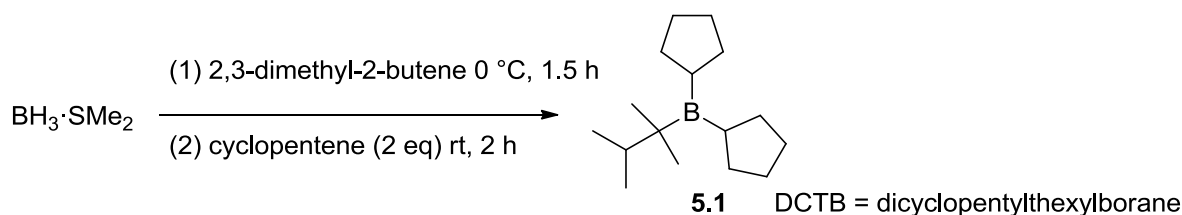
Dicyclopentylthexylborane (**5.1**) was freshly prepared by the monohydroboration of 2,3-dimethyl-2-butene followed by the hydroboration of cyclopentene (Scheme 5.5), and was treated with 3-chloro-1-lithiopropyne (prepared by the drop-wise addition of *n*-BuLi to propargyl chloride at -95 °C). Propanal was added, the reaction mixture oxidised and the crude products purified by column chromatography to give the novel compound 6-cyclopentylhex-5-yn-3ol (**5.2**, 54% isolated yield), and trace amounts of both possible products arising from thexyl group migration (7,7,8-trimethylnon-5-yn-3-ol (**5.3**) and 5,5,6-trimethyl-4-vinylideneheptan-3-ol (**5.4**) in a 52:48 ratio by relative integrations in the ^{1}H NMR spectrum, <1% isolated yield), along with cyclopentanol (57% isolated yield, based on one cyclopentyl unit) (Scheme 5.6). 6-Cyclopentylhex-5-yn-3ol (**5.2**) was fully characterised, with the data in accordance with the proposed structure (E.S. 5.32a).

Scheme 5.6 Reaction of dicyclopentylthexylborane with 3-chloro-1-lithiopropyne and propanal

(1) *n*-BuLi, -95 °C, 5 min
(2) DCTB, -78 °C, 1 h
(3) propanal, -78 °C, 30 min warming to rt over 30 min
(4) NaOH, H$_2$O$_2$, rt, overnight

**5.2** 54% + **5.3** <1% **5.4**

143

From this result, it is clear that *sec*-alkyl groups migrate in preference to *tert*-alkyl groups in the reaction between trialkylboranes and 3-chloro-1-lithiopropyne. Therefore, the use of simple trialkylboranes containing a *tert*-alkyl group in this reaction is unlikely to give good yields of *tert*-alkyl migrated products. Also, it appears that the allenic organoborane intermediate arising from the migration of the thexyl group is more prone to take part in the allenic rearrangement to place the thexyl group further away from the boron atom (as seen by the near-equal mixture of possible thexyl migrated products, while only the product arising from no rearrangement was seen for the cyclopentyl migrated product). It seems that a bulkier allenic organoborane intermediate undergoes the rearrangement faster, as a way of alleviating the greater steric bulk around the boron atom.

The 9-BBN alkyl group has been shown to behave as a 'blocking' group for many organoboron reactions,[4] and so it was decided to repeat the above reaction with 9-thexyl-9-BBN, in the hope that the *tert* thexyl group would migrate preferentially.

9-Thexyl-9-BBN was freshly prepared by the literature procedure,[5] and was treated with 3-chloro-1-lithiopropyne and then propanal (Scheme 5.7).

Scheme 5.7 Reaction of 9-thexyl-9-BBN with 3-chloro-1-lithiopropyne and propanal
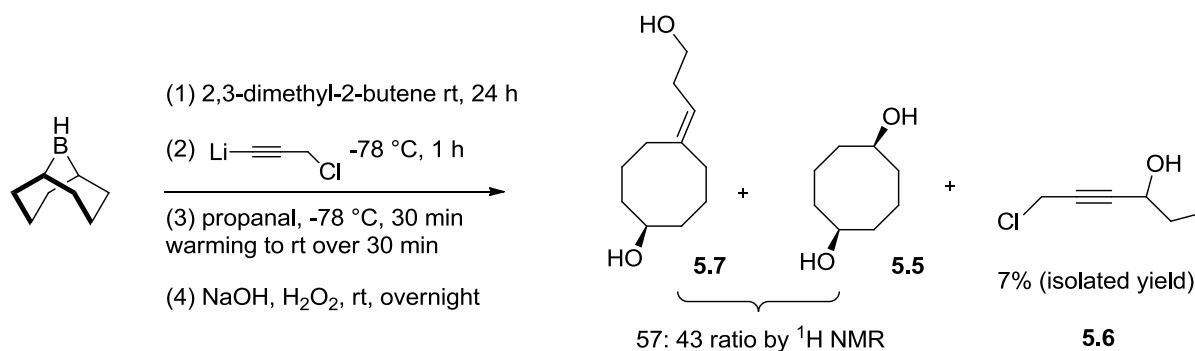
The ^{1}H NMR spectrum of the crude product following work-up showed the presence of (*Z*)-cyclooctane-1,5-diol (**5.5**) and thexanol, along with two unknown species. The crude mixture was purified by column chromatography, and one of the species was isolated and identified as 6-chlorohex-4-yn-3-ol (**5.6**, 7% isolated yield). The compound was fully characterised, with the data in accordance with the literature values (E.S. 5.33b).[6] This side-product is most likely produced when free 3-chloro-1-lithiopropyne attacks propanal (Scheme 5.8), which suggests that not all of the 3-chloro-1-lithiopropyne was coordinated to 9-thexyl-9-BBN (perhaps due to the hindered nature of this particular trialkylborane).

Scheme 5.8 Probable mechanism for the formation of 6-chlorohex-4-yn-3-ol (5.6)
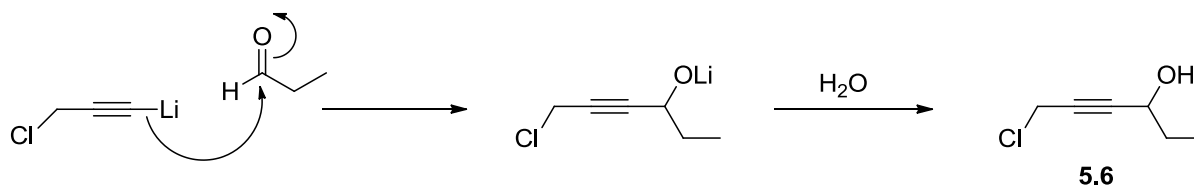
The other unknown species could not be separated from (*Z*)-cyclooctan-1,5-diol (**5.5**) due to their close behaviour on silica gel. The ^{1}H NMR spectrum of the inseparable mixture contained three distinct peaks that were not due to **5.5** – a 1H triplet at 5.40 ppm, a 2H doublet at 4.09 ppm and a 1H multiplet at 3.83 ppm. The corresponding CH, CH$_2$ and CH peaks were also visible in the DEPT ^{13}C NMR spectrum at 125.9 (CH), 71.8 (CH) and 95.1 ppm (CH$_2$), along with a quaternary carbon at 143.9 ppm. Using these data, we proposed that the unknown species was in fact the novel compound (3-hydroxypropylidene)cyclooctan-5-ol (**5.7**, Scheme 5.7), arising from the migration of one end of the 9-BBN alkyl group, followed by some sort of rearrangement. This proposed structure was not the expected product from the migration of the 9-BBN alkyl group (see possible migration products in Scheme 5.2); however all the available evidence pointed towards the proposed structure.

Although 9-BBN had failed to serve as a suitable 'blocking group', the reaction was repeated once more and the reaction left for 4 h after the addition of 3-chloro-1-lithiopropyne in an attempt to produce (3-hydroxypropylidene)cyclooctan-5-ol (**5.7**) selectively. Also, the reaction was carried out without the addition of propanal in an attempt to prove that the C$_3$ unit found in the unexpected product, (3-hydroxypropylidene)cyclooctan-5-ol (**5.7**) was originally from the 3-chloro-1-lithiopropyne and not from propanal itself.

The ^{1}H NMR spectrum of the crude product showed the presence of both **5.5** and **5.7** (in a 65:35 ratio respectively by relative integrations in the ^{1}H NMR spectrum), with no presence of 6-chlorohex-4-yn-3-ol (**5.6**). Although this reaction was unsuccessful at producing **5.7** selectively, it did succeed in proving that the C$_3$ unit originated from the 3-chloro-1-lithiopropyne and not propanal.

5.22 Addition of 3-chloro-1-lithiopropyne to thexylboronic esters

Following Shimizu's work,[3] it was decided to try the reaction of boronic esters **5.8** and **5.9** with 3-chloro-1-lithiopropyne to see whether migration of the *tert*-alkyl group would occur to give the desired product.

Boronic esters **5.8** and **5.9** were freshly prepared as in Chapter 4 (from the monohydroboration of 2,3-dimethyl-2-butene and subsequent reaction with ethylene glycol or pinacol, formerly numbered as boronic esters **4.2** and **4.6**). A cold solution of the boronic ester in question was added drop-wise to a cooled solution of 3-chloro-1-lithiopropyne. Following the addition, the reaction mixture was allowed to warm to room temperature and oxidised.
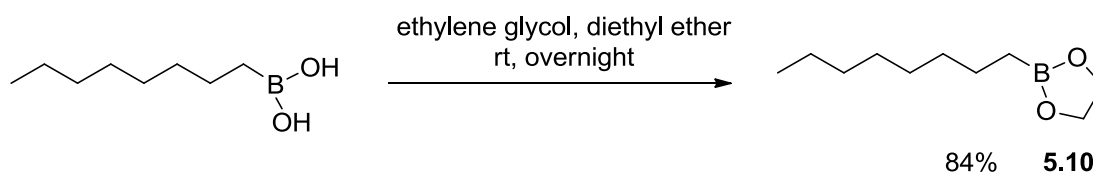
The ^{1}H NMR spectrum of the crude product in both cases showed only the presence of thexanol, presumably from the oxidation of the starting boronic esters (Scheme 5.9). These disappointing results showed that boronic esters do not react in the same manner as trialkylboranes when treated with 3-chloro-1-lithiopropyne. Possible problems include failure to generate the initial 'ate' complex, difficulty with migration of the thexyl group due to steric hindrance, or involvement of some unknown side-reaction.

Scheme 5.9 Reaction of 3-chloro-1-lithiopropyne with boronic esters 5.8 and 5.9
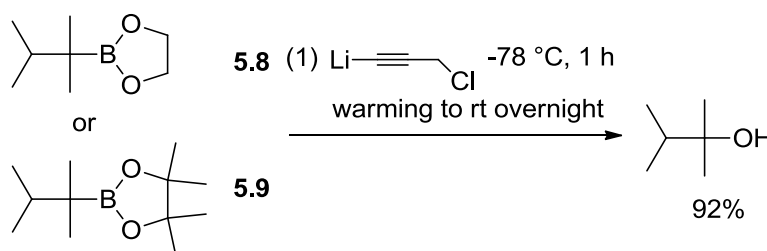
To rule out the second of these, it was decided to try the reaction on a less hindered boronic ester. Boronic ester **5.10** was prepared from *n*-octylboronic acid and ethylene glycol, and was isolated without need for purification in 84% isolated yield (Scheme 5.10). Boronic ester **5.10** was fully characterised, with the data in accordance with the literature values (E.S. 5.31c).[7]

**Scheme 5.10 Synthesis of boronic ester 5.10**

Boronic ester **5.10** was treated with 3-chloro-1-lithiopropyne as for boronic ester **5.8** and **5.9**; however acetic acid was added to cleave off any allenic organoborane compounds present before oxidising the organoboron compounds present as for boronic esters **5.8** and **5.9**. The ^{1}H NMR spectrum of the crude product showed only the presence of 1-octanol (presumably

from oxidation of the starting boronic ester). This result showed that the lack of thexyl-migrated product seen in Scheme 5.9 was not due to the steric hindrance of the boronic esters.

We reasoned that if the capture of the 3-chloro-1-lithiopropyne was the problem, then using a more electrophilic boronic ester might overcome this. Compounds **5.11** and **5.12** were freshly prepared as mentioned in Chapter 4 (from the reaction of thexylborane with 1,2-ethanedithiol and mercaptoethanol respectively, formerly numbered boronic esters **4.9** and **4.10**), and were both treated with 3-chloro-1-lithiopropyne and then oxidised (Scheme 5.11). The ^{1}H NMR spectrum of the crude product in both cases once again showed only thexanol, showing that the migration of the thexyl group had been unsuccessful.

Scheme 5.11 Reaction of 3-chloro-1-lithiopropyne with boronic esters 5.11 and 5.12
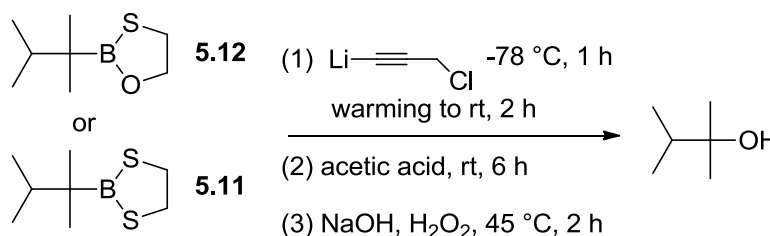
The reaction was repeated once more using a slightly different boronic ester, thexylcatecholborane (**5.13**). Thexylcatecholborane (**5.13**) was freshly prepared by the addition of catechol to thexylborane (Scheme 5.12). The compound was fully characterised, with the data in accordance with the literature values (E.S. 5.31f).[8]

Scheme 5.12 Synthesis of thexylcatecholborane (5.13)
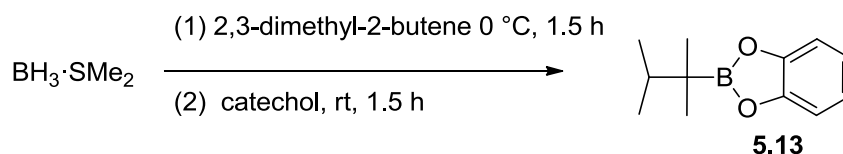
Thexylcatecholborane (**5.13**) was treated with 3-chloro-1-lithiopropyne, followed by the addition of propanal, warming and oxidation. The ^{1}H NMR spectrum of the crude product showed only the presence of thexanol. Surprisingly, there was no sign of 6-chlorohex-4-yn-3-ol (**5.6**) from the reaction of 3-chloro-1-lithiopropyne with propanal. This suggests that, at least at the temperature during the addition of propanal (-78 °C), that the 3-chloro-1-lithiopropyne is in fact coordinated to boron in the desired 'ate' complex. It is possible that the oxygen of the diol component migrates in preference to the thexyl group, although there

was no sign of this product in the ^{1}H NMR spectrum of the crude product. Another possibility is that, although stable at -78 °C, the 'ate' complex disassociates during warming before the desired thexyl group migration takes place (this temperature might be high enough for any 3-chloro-1-lithiopropyne to immediately decompose before being able to react with propanal to give 6-chlorohex-4-yn-3-ol (**5.6**)).

The reaction was repeated, but the reaction mixture left to stir at room temperature overnight to ensure that the problem was not simply due to the 'ate' complex being reluctant to undergo the desired migration. The ^{1}H NMR spectrum of the crude product once again showed only the presence of thexanol.

**5.23 Reaction of 3-chloro-1-lithiopropyne with dichlorothexylborane (5.14)**

It was becoming apparent that the simple reaction of 3-chloro-1-lithiopropyne with *tert*-alkylboronic esters would not give the desired migration product. Therefore, it was decided to take a different approach that followed previous work by Zweifel and Pearson,[9] who showed that they could use thexyl as a 'blocking group', by reacting thexylalkenylchloroboranes with two equivalents of 3-chloro-1-lithiopropyne to give the desired alkenyl migrated product (Scheme 5.13).

Scheme 5.13 Previously reported work on the reaction of 3-chloro-1-lithiopropyne with thexylalkenylchloroboranes[10]
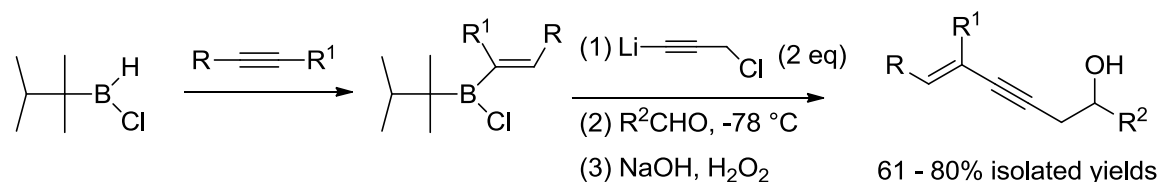

In a similar fashion, we hoped that reacting dichlorothexylborane (**5.14**) with three equivalents of 3-chloro-1-lithiopropyne would give the desired thexyl migrated product (Scheme 5.14).

Scheme 5.14 Intended route for desired thexyl group migration
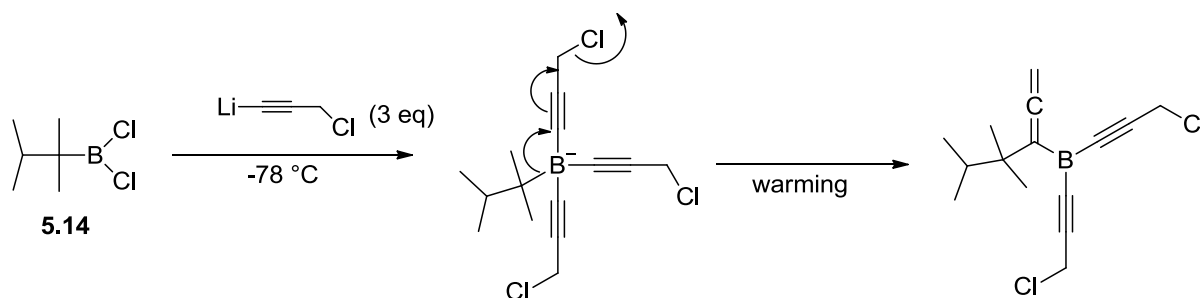
In order to test this intended route, dichlorothexylborane (**5.14**) was prepared by a slightly modified literature procedure[11] by hydroboration of 2,3-dimethyl-2-butene with monochloroborane dimethyl sulfide complex, with the aid of trichloroborane (Scheme 5.15). The compound was isolated in reasonable purity and was fully characterised, with the data in accordance with the literature values,[10] although meaningful IR and MS data were not obtained due to the compound's instability (E.S. 5.33a).

Scheme 5.15 Synthesis of dichlorothexylborane (5.14)
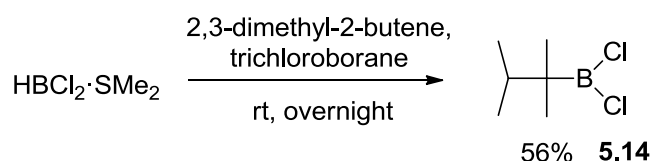
The freshly prepared dichlorothexylborane (**5.14**) was added immediately to three equivalents of 3-chloro-1-lithiopropyne, followed by the addition of propanal and oxidation (Scheme 5.16). The ^{1}H NMR spectrum of the crude product showed the presence of thexanol and 6-chlorohex-4-yn-3-ol (**5.6**), which was purified by column chromatography to give pure **5.6** in 66% isolated yield (based on one propargyl chloride unit).

Scheme 5.16 Reaction of dichlorothexylborane (5.14) with 3-chloro-1-lithiopropyne (3 eq)
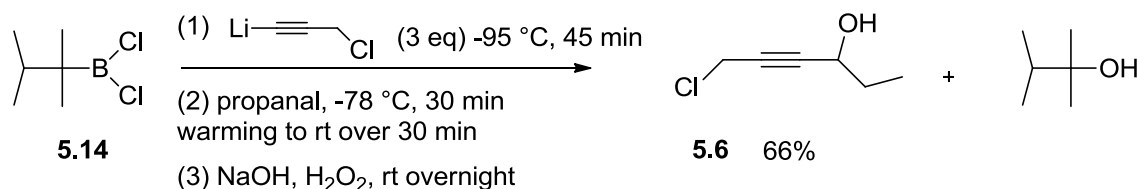

The reaction was repeated, but the reaction mixture left for a longer time after the addition to 3-chloro-3-lithiopropyne (3 hours at -78 °C), before the addition of propanal, in case that the

'ate' complex was slow to undergo the desired migration. However, the ^{1}H NMR spectrum of the crude product for this reaction again showed only the presence of thexanol and 6-chlorohex-4-yn-3-ol (**5.6**).

It was observed that the freshly prepared dichlorothexylborane (**5.14**) fumed when dry THF was added to it. In case the THF was decomposing the dichlorothexylborane (**5.14**) in some way, the above reaction was repeated using dry hexane as the solvent. The ^{1}H NMR spectrum of the crude product still showed thexanol and 6-chlorohex-4-yn-3-ol (**5.6**) as the main components; however a small amount of what appeared to be the thexyl migration product (7,7,8-trimethylnon-5-yn-3-ol (**5.3**)) could be seen with the characteristic signals for the diastereotopic doubled doublets at 2.37 and 2.22 ppm. Attempts were made to purify the compound by column chromatography, but no pure product was obtained.

The reaction was repeated once more using hexane as the solvent, but the reaction mixture was left for a longer time (1 h at -78 °C and 3 h at -40 °C) after the addition to 3-chloro-1-lithiopropyne in an attempt to promote the thexyl group migration. The ^{1}H NMR spectrum of the crude product was very similar to the first attempt using hexane as the solvent (corresponding to around 86% yield of 6-chlorohex-4-yn-3-ol based on one propargyl chloride unit) , although it seemed there was a small increase in the amount of 7,7,8-trimethylnon-5-yn-3-ol (**5.3**), and the thexyl migrated product that had undergone allenic rearrangement (5,5,6-trimethyl-4-vinylideneheptan-3-ol (**5.4**)) was also visible (Scheme 5.17). The reason for the presence of the rearranged product was presumably due to the fact that the reaction mixture was warmed to -40 °C for 3 hours, thus facilitating the allenic rearrangement.

Scheme 5.17 Reaction of dichlorothexylborane (5.14) with 3-chloro-1-lithiopropyne (3 eq) – hexane as solvent
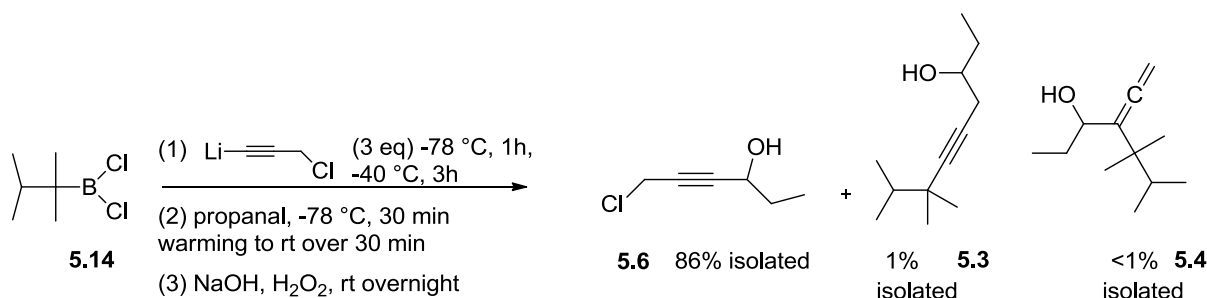
The crude product was purified by column chromatography to give 7,7,8-trimethylnon-5-yn-3-ol (**5.3**, 1% isolated yield), along with impure 5,5,6-trimethyl-4-vinylideneheptan-3-ol (**5.4**, <1% isolated yield) (Scheme 5.17). 7,7,8-Trimethylnon-5-yn-3-ol (**5.3**) was fully characterised (including HRMS), with the data consistent with the proposed structure (E.S. 5.33e). 5,5,6-Trimethyl-4-vinylideneheptan-3-ol (**5.4**) could not be purified, although the ^{1}H and ^{13}C NMR spectra of the impure product were consistent with the proposed structure (especially the characteristic 2H doublet at 4.8 ppm and 1H multiplet and 3.9 ppm in the ^{1}H NMR spectrum, along with two quaternary allenic carbons at 207 and 117 ppm along with the allenic CH$_2$ carbon at 79 ppm in the ^{13}C NMR spectrum).

Although this result showed that the intended route for thexyl group migration could work in principle, it looked like it could not be modified into a synthetically useful method. We therefore pursued a different route of investigation.

5.24 Attempts at carrying out the reaction in an inverse fashion

Due to the lack of thexyl migration reported in Sections 5.21 – 5.23, it was decided to take a different approach. Although not reported in the literature, we wondered whether it was possible to have the propargyl chloride functionality on the boronic ester in the first place, and then add an organometallic reagent to induce the desired migration. If a *tert*-alkyl organometallic reagent was used, then a quaternary carbon centre could be generated (Scheme 5.18).

Scheme 5.18 Intended route for *tert*-alkyl group migration using 'inverse fashion' method
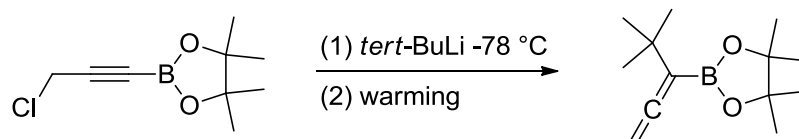
In order to attempt these types of reaction, two novel boronic esters were prepared by adding 3-chloro-1-lithiopropyne to methoxypinacolborane or trimethyl borate followed by a solution of dry HCl (Scheme 5.19). Boronic ester **5.15** was synthesised from methoxypinacolborane and 3-chloro-1-lithiopropyne, and was isolated in 97% yield. Boronic ester **5.16** was synthesised in the same manner from trimethyl borate and 3-chloro-1-lithiopropyne, and was isolated in 59% yield. Both boronic esters were fully characterised, with the data in accordance with the proposed structures (E.S. 5.34a, b).

Scheme 5.19 Synthesis of boronic esters 5.15 and 5.16
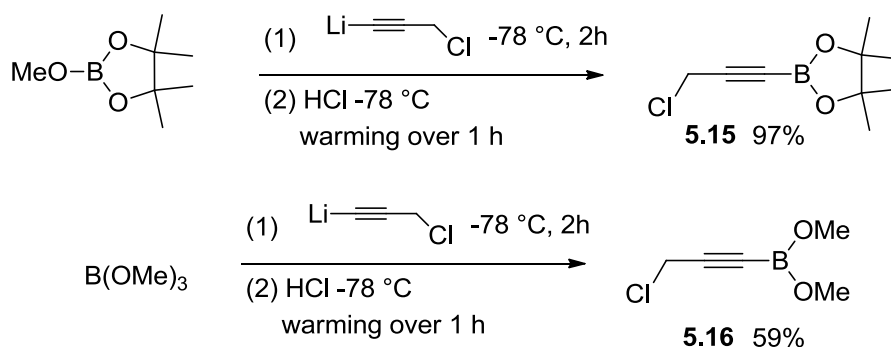
Boronic ester **5.15** was the first to be investigated, and was treated with *n*-BuLi, then propanal, and the mixture oxidised, as shown in Scheme 5.20. The ^{1}H NMR spectrum of the crude product showed the presence of *n*-butanol and pinacol, with no sign of the desired migrated product. The presence of *n*-butanol suggests that the *n*-BuLi had added to boronic ester **5.15** to give the desired 'ate' complex (as any free *n*-BuLi would have either reacted with propanal to give heptan-3-ol or with water during oxidation to give *n*-butane).

Scheme 5.20 Reaction of boronic ester 5.15 with *n*-BuLi, followed by addition of propanal and oxidation
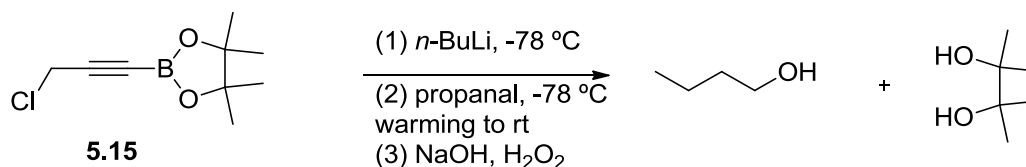
The reaction was repeated with *n*-BuMgCl to see whether a different organometallic reagent would make a difference. The ^{1}H NMR spectrum of the crude product showed the presence of *n*-BuOH, pinacol and possibly a trace amount of the desired product. An attempt was made to isolate the migrated product by column chromatography, but no pure products were isolated.

This reaction was repeated, but the reaction mixture was left to stir for a longer time (5 hours at -78 °C) in an attempt to give the 'ate' complex more of a chance to undergo the desired migration. However, the ^{1}H NMR spectrum of the crude product showed the presence of only *n*-butanol, pinacol and 6-chlorohex-4-yn-3-ol (**5.6**). The presence of **5.6** gives a clue as to

why no migration products were observed – it seems as though the *n*-BuMgCl was adding to the boronic ester to make the 'ate' complex, but that on warming the more stable alkynyl anion disassociated (which is then free to attack propanal, to give the observed 6-chlorohex-4-yn-3-ol (**5.6**), Scheme 5.21).

Scheme 5.21 Possible mechanism for the generation of *n*-butanol and 6-chlorohex-4-yn-3-ol (5.6)
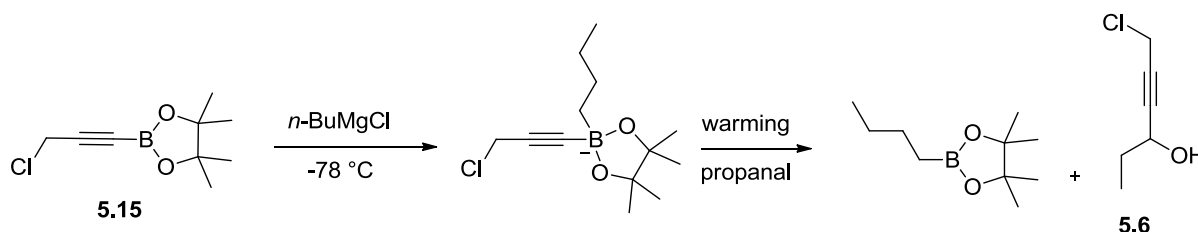

It was hoped that a less hindered boronic ester might lead to a more stable 'ate' complex (due to less steric hindrance), and so the desired migration reaction might take place. Boronic ester **5.16** was reacted with both *n*-BuLi and *n*-BuMgCl, however the ^{1}H NMR spectra for both product mixtures showed the same result as for boronic ester **5.8** (i.e. the presence of *n*-butanol).

From these results, it appeared that an effective method for the migration of *tert*-alkyl groups in this reaction would be difficult to realise. The most likely explanation for the lack of migration reported in Sections 5.22 - 5.24 is that the 'ate' complex in the reaction is not very stable, and that the alkynyl anion disassociates as the reaction mixture is warmed before migration can take place (similar cleavage of boron-alkyne bonds have previously been observed in alkynylboronic esters[11]). For this reason, it was decided to switch the research to the alkenyl analogues of boronic esters **5.15** and **5.16**, in the hope that the desired 'ate' complex of these species would be less likely to disassociate (due to the lower stability of alkenyl anions compared to their alkynyl counterparts). The results for these investigations follow in Chapter 6.

5.3 Experimental Section

5.31 Synthesis and reactions of various boronic esters with 3-chloro-1-lithiopropyne

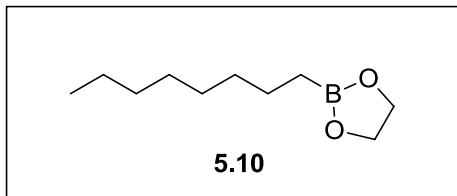#### 5.31a Reaction of 3-chloro-1-lithiopropyne with boronic ester 5.8.
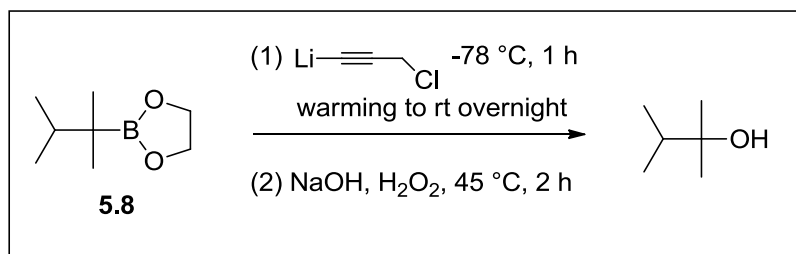
A dry 100 mL round bottomed flask equipped with a stirrer bar and septum was flushed with N_2 for 10 min. Propargyl chloride (0.36 mL, 5.0 mmol) and dry THF (15 mL) were added. The solution was cooled to -95 °C using a liquid N_2/hexane bath, and *n*-BuLi in hexanes (1.6 M, 3.13 mL, 5.0 mmol) was added drop-wise with vigorous stirring of the reaction mixture. The reaction mixture was stirred for an additional 5 min after the addition, and a freshly prepared solution of boronic ester **5.8** (5.0 mmol in 5 mL of dry THF as prepared in procedure 4.1a) was added drop-wise and the reaction mixture was left to come to rt overnight. Excess sodium hydroxide (1.2 g in 10 mL water) was added drop-wise, followed by excess hydrogen peroxide (30% by weight, 6 mL). Once the initial exothermic reaction subsided, the cooling bath was removed and the reaction was heated to 45 °C for 2 h. The reaction mixture was extracted with diethyl ether (2 × 25 mL), and the extract was washed with distilled water and brine, dried over magnesium sulfate, filtered and the solvent evaporated to give a brown liquid (0.47 g, 92% of thexanol). The ^{1}H NMR spectrum of the crude mixture showed no presence of the desired migration product, only thexanol derived from the oxidation of the thexyl group on boron.

#### 5.31b Reaction of 3-chloro-1-lithiopropyne with boronic ester 5.9.
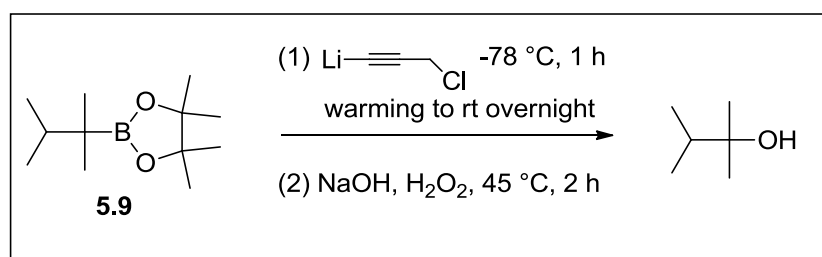
Procedure 5.31a was repeated using boronic ester **5.9** and gave the same result (*i.e* only thexanol was visible in the ^{1}H NMR spectrum following work-up).

5.31c Synthesis of boronic ester 5.10.

5.10

A dry 50 mL round bottomed flask equipped with a stirrer bar and septum was flushed with N$_2$ for 10 min. *n*-Octylboronic acid (1.58 g, 10.0 mmol) was added quickly, and the flask was flushed for an additional 5 min. Dry diethyl ether (15 mL) and ethylene glycol (0.61 mL, 11.0 mmol) were added, and the solution stirred at rt overnight. Excess magnesium sulfate was added, along with additional diethyl ether (10 mL) and the resulting mixture was filtered and the solvent evaporated under reduced pressure to give boronic ester **5.10**[7] as a colourless liquid (1.55 g, 84%); δ^1H (400 MHz; CDCl$_3$): 4.10 (4H, s, OCH$_2$), 1.35 (2H, m, CH$_2$), 1.16 – 1.26 (10H, m, CH$_2$), 0.73 – 0.83 (5H, m, BCH$_2$ and CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 65.3 (CH$_2$, CH$_2$O), 32.4 (CH$_2$), 31.9 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 23.9 (CH$_2$), 22.6 (CH$_2$), 14.0 (CH$_3$), 10.0 (CH$_2$, br - BCH$_2$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 33.8; LR - EI$^+$ MS m/z (%): 184 (M$^+$, 100%), 155 (100), 141 (100), 126 (100), 112 (100), 99 (100), 86 (98), 69 (100), 55 (98); ν_{max} (neat/cm^{-1}): 2906, 1467, 1379, 1229, 1171, 1022.

5.31d Reaction of 3-chloro-1-lithiopropyne with boronic ester 5.10, acetic acid work-up.
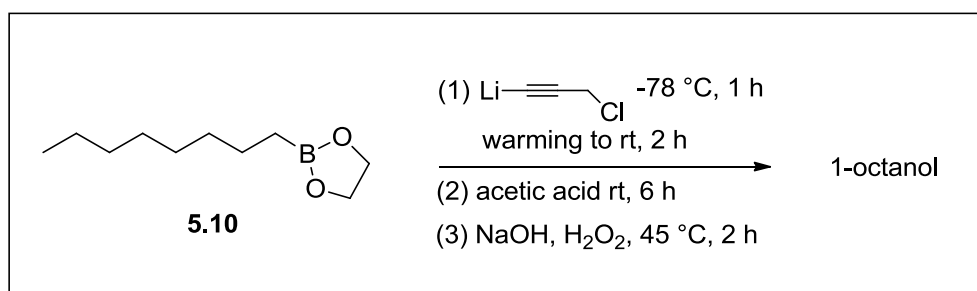
Procedure 5.31a was repeated using boronic ester **5.10** (0.92 g, 5.0 mmol). The mixture was allowed to warm to rt following the addition of the solution of **5.10** over a period of 2 h, and excess acetic acid (2.5 mL, 44.0 mmol) was added drop-wise, and the solution stirred at rt for

a further 6 h. The reaction mixture was then oxidised according to procedure 5.31a to give a light yellow liquid (0.89 g), which was identified as 1-octanol by ^{1}H NMR spectroscopy.

5.31e Reaction of 3-chloro-1-lithiopropyne with 2-thexyl-1,3,2-dithiaborolane (5.11).
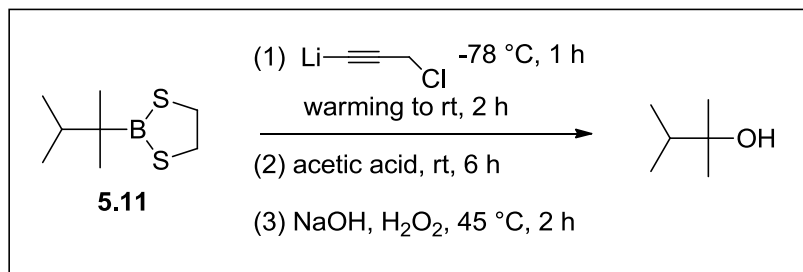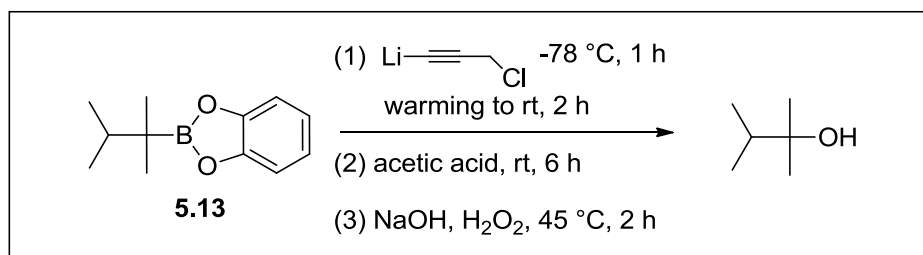

Procedure 5.31d was repeated using a freshly prepared solution of 2-thexyl-1,3,2-dithiaborolane (**5.11,** prepared according to procedure 4.31e) to give a yellow liquid (1.20 g), which consisted of thexanol and THF by ^{1}H NMR spectroscopy.

**5.31f Synthesis of thexylcatecholborane (5.13).**
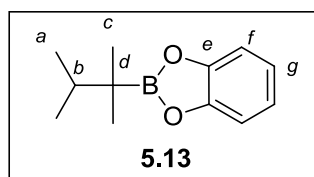
A two-necked 50 mL round bottomed flask equipped with a closed bent side arm charged with catechol (0.55 g, 1.0 eq, 5.0 mmol), magnetic stirrer bar and septum was assembled while hot and flushed with N_2 for 10 min. Borane dimethyl sulfide complex (10.5 M, 0.49 mL, 5.0 mmol) was added, and the reaction flask cooled in an ice bath. 2,3-Dimethyl-2-butene (0.6 mL, 5.0 mmol) was added drop-wise with stirring, and the reaction was left to stir for an additional 1.5 h. Catechol (0.55 g, 5 mmol) was added by rotating the side arm, dry THF (5 mL) was added, and the reaction mixture left to stir at rt for 3 h. THF was removed under a fast stream of N_2 to give quantitative near-pure thexylcatecholborane[8] (**5.13**) as a colourless liquid; δ^1H (400 MHz; CDCl$_3$): 7.16 (2H, m, CH*g*), 7.01 (2H, m, CH*f*), 1.74 (1H, sept, *J* = 6.8 Hz, CH*b*), 1.07 (6H, s, CH$_3$*c*), 0.64 (6H, d, *J* = 6.8 Hz, CH$_3$*a*); δ^{13}C (100 MHz; CDCl$_3$): *quat C next to boron not seen*; 148.2 (quat C, C*e*), 122.4 (CH, C*g*), 112.4 (CH, C*f*), 35.4 (CH, C*b*), 21.8 (CH$_3$), 18.7 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 35.5; LR - EI$^+$ MS m/z (%): 204 (M$^+$, 90%), 189 (20), 161 (95), 134 (100), 120 (92), 84 (48), 72 (95); v_{max} (neat/cm$^-$^{1}): 3201 (decomp OH), 3063, 2958, 1609, 1471, 1373, 1338, 1316, 1235, 1156, 1128, 1005.

5.31g Reaction of 3-chloro-1-lithiopropyne with thexylcatecholborane (5.13).


Procedure 5.31d was repeated using a solution of thexylcatecholborane (5.0 mmol in 10 mL THF) prepared according to procedure 5.31f to give near pure thexanol as a colourless liquid (0.49 g, 96%).

5.31h Reaction of 3-chloro-1-lithiopropyne with thexylcatecholborane (5.13). Procedure 5.31g was repeated, except that the reaction mixture was allowed to come to rt overnight after the addition of thexylcatecholborane. The reaction mixture was then cooled back down to -78 ºC for the addition of propanal, and the procedure was the same thereafter to give near pure thexanol as a colourless liquid (0.42 g, 82%).

5.31i Reaction of 3-chloro-1-lithiopropyne with 2-thexyl-1,3,2-oxathiaborolane.
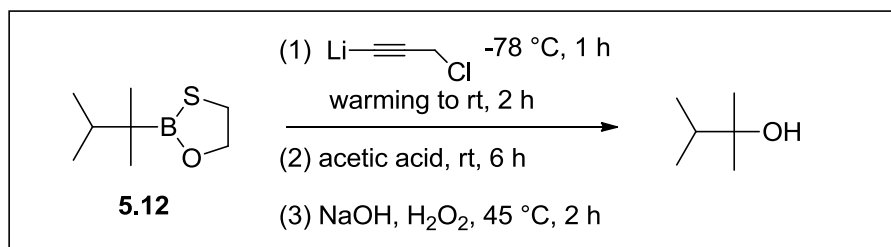
Procedure 5.31a was repeated using 2-thexyl-1,3,2-oxathiaborolane (**5.12**, 5.0 mmol, prepared according to procedure 4.1d) to give a colourless liquid (0.70 g), consisting of thexanol and residual THF by ^{1}H NMR analysis of the crude mixture.

5.32 Synthesis and reactions of various trialkylboranes with 3-chloro-1-lithiopropyne

5.32a Assessment of *sec* vs *tert* alkyl group migration.
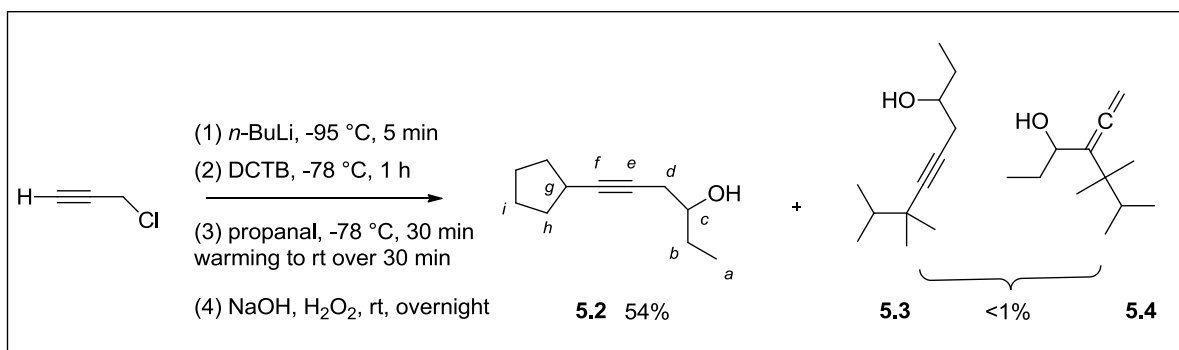
Thexylborane (5.0 mmol) was prepared according to procedure 4.31a. Dry THF (5 mL) was added along with the drop-wise addition of cyclopentene (0.93 mL, 2.1 eq, 10.5 mmol) and the solution left to stir for 2 h at rt. 3-Chloro-1-lithiopropyne was prepared from propargyl chloride (0.4 mL, 1.1 eq, 5.5 mmol), and *n*-butyl lithium in hexanes (1.6 M, 3.44 mL, 1.1 eq, 5.5 mmol) in dry THF (15 mL) at -95 °C according to procedure 5.1a. The resulting solution of thexyldicyclopentylborane in THF was cooled to -78 °C, and transferred slowly *via* cannula to the solution of 3-chloro-1-lithiopropyne. Once the addition was completed, the cooling bath was replaced by an acetone-dry ice bath (-78 °C), and the mixture left to stir for an additional 1 hour. Propanal (0.43 mL, 1.2 eq, 6.0 mmol) was added drop-wise and then the mixture was left to stir for 30 min at this temperature, before removing the cooling bath and allowing the reaction mixture to slowly warm to rt over 30 min. The reaction mixture was removed and the mixture oxidised according to procedure 5.31a to give the crude product, which was purified by column chromatography (95:5 petroleum ether: ethyl acetate, followed by 90:10 and 80:20) to give near-pure 6-cyclopentylhex-5-yn-3ol (**5.2**, 0.45 g, 54%) as a colourless oil; δ^1H (400 MHz; CDCl$_3$): 3.49 (1H, app pent, $J = 5.7$ Hz, CHc), 2.47 (1H, app pent, $J = 7.4$ Hz, CHg), 2.29 (1H, ddd, $J = 16.5, 4.7, 2.2$ Hz, diastereotopic CHd), 2.17 (1H, ddd, $J = 16.5, 6.9, 2.0$ Hz, diastereotopic CHd), 1.93 (1H, br s, OH), 1.77 (2H, m, diastereotopic CHh), 1.59 (2H, m, diastereotopic CHh), 1.37 – 1.48 (6H, m, CH$_2b$, i), 0.83 (3H, t, $J = 6.3$ Hz, CH$_3a$); $\delta^{13}C$ (125 MHz; CDCl$_3$): 87.5 (quat C, Cf), 75.6 (quat C, Ce), 71.5 (CH, Cc), 34.1 (CH$_2$), 30.3 (CH, Cg), 29.0 (CH$_2$), 27.3 (CH$_2$), 24.9 (CH$_2$), 3.9 (CH$_3$, CH$_3a$); HR - EI$^+$ MS m/z (%): calculated for C$_{11}$H$_{18}$O 166.1358, found 166.1355 (M$^+$, 11%); v_{max} (neat/cm^{-1}): 3364 (OH), 2962, 2873, 2238, 1952, 1453; Rf = 0.33 in 4:1 petroleum ether: ethyl acetate, impure products arising from thexyl group migration (7,7,8-trimethylnon-5-yn-

3-ol (**5.3**) and 5,5,6-trimethyl-4-vinylideneheptan-3-ol (**5.4**)) in a 52:48 ratio respectively by relative integrations in the ^{1}H NMR spectrum (8 mg, <1%) and cyclopentanol (0.247 g, 57% based on one cyclopentyl group).

**5.32b Reaction of 3-chloro-1-lithiopropyne with 9-thexyl-9-BBN.**
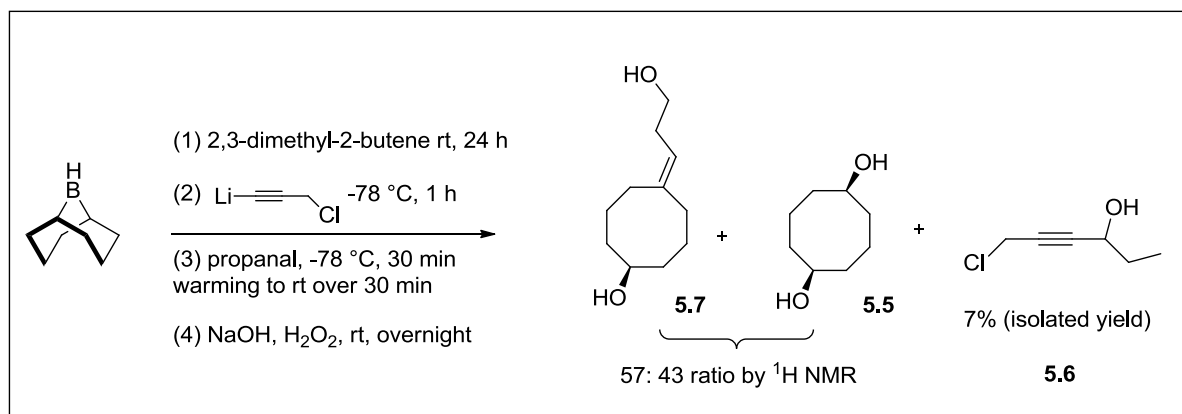
A dry 50 mL round bottomed flask equipped with a stirrer bar and septum was flushed with N$_2$ for 10 min. 9-BBN (0.61 g, 5.0 mmol) was added quickly, and the flask was flushed for an additional 5 min. Dry THF (10 mL) was added, along with 2,3-dimethyl-2-butene (0.59 mL, 5.0 mmol) and the reaction mixture was stirred at rt for 24 h. 3-Chloro-1-lithiopropyne was prepared according to procedure 5.1a from propargyl chloride (0.36 mL, 5.0 mmol) and *n*-BuLi (1.6 M, 3.2 mL, 5.0 mmol) in THF (15 mL). The solution of 9-thexyl-9-BBN was added drop-wise *via* cannula to the reaction mixture (which was cooled to -95°C), and then the reaction mixture was left to stir for an additional hour at -78 °C. Propanal (0.36 mL, 5.0 mmol) was added drop-wise, and the mixture stirred for 15 min, before removing the cooling bath and allowing the reaction mixture to warm to rt over 30 min. The mixture was oxidised as in procedure 5.31a to give a colourless viscous oil (0.43 g), consisting mostly of (*Z*)-cyclooctan-1,5-diol (**5.5**) and an unknown component. The crude product was purified by column chromatography on silica (2:5 petroleum ether: ethyl acetate) to give racemic 6-chlorohex-4-yn-3-ol (**5.6**) as a colourless liquid (60 mg, 7%), and an inseparable mixture of (*Z*)-cyclooctan-1,5-diol (**5.5**) and 5-(3-hydroxypropylidene)cyclooctanol (**5.7**, 0.24 g, in a 43: 57 ratio respectively by relative integrations in the ^{1}H NMR spectrum). 5-(3-Hydroxypropylidene)cyclooctanol was identified by the distinctive peaks in the NMR: δ^{1}H (400 MHz; CDCl$_3$): 5.40 (1H, t, *J* = 6.9 Hz, alkenyl CH), 4.09 (2H, d, *J* = 6.6 Hz, CH$_2$O), 3.83 (1H, m, C*H*OH), other peaks were merged with those for cyclooctane-1,5-diol; δ^{13}C

(125 MHz; CDCl$_3$): 143.9 (quat C, alkenyl C), 125.9 (CH, alkenyl C), 71.8 (CH, CHOH), 59.1 (CH$_2$, CH$_2$OH), other peaks could not be conclusively assigned.

5.32c Reaction of 3-chloro-1-lithiopropyne with 9-thexyl-9-BBN (longer reaction time, no propanal added). Procedure 5.32b was repeated, except that the reaction was stirred for 4 h after the addition of 9-thexyl-9-BBN to the 3-chloro-1-lithiopropyne, and that no propanal was added. The reaction was worked up in the same manner to give a colourless viscous oil (0.55 g), consisting of (Z)-cyclooctane-1,5-diol (**5.5**) and 5-(3-hydroxypropylidene)cyclooctanol (**5.7**, 65:35 ratio respectively by relative integrations in the ^{1}H NMR spectrum).

5.33 Synthesis and reactions of dichlorothexylborane (5.14)

5.33a Synthesis of dichlorothexylborane (5.14).

5.14
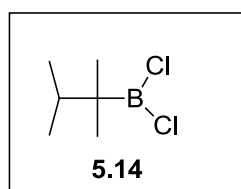
Two 100 mL round bottomed flasks connected with a sintered tube were both equipped with a magnetic stirrer bar, with one equipped with a septum, and the other a septum-capped stopcock, were flushed with N$_2$ for 10 min. Dichloroborane dimethyl sulfide complex (2.31 mL, 20.0 mmol) was added to the septum-capped flask, along with a solution of trichloroborane (20 mL of a 1 M solution in hexane, 20.0 mmol), and the reaction mixture was stirred for 5 min. 2,3-Dimethyl-2-butene (2.4 mL, 20.0 mmol) was added drop-wise and the reaction mixture left to stir overnight. The trichloroborane dimethyl sulfide salt was filtered using the sintered tube using positive N$_2$ pressure. The trichloroborane salt was washed with additional dry pentane (15 mL) before being filtered. The combined filtrates in the second flask were concentrated using a high vacuum pump to give reasonably pure dichlorothexylborane (**5.14**, 1.85 g, 56%) as a colourless liquid; δ^1H (500 MHz; CDCl$_3$): 2.00 (1H, sept, J = 5.9 Hz, CH), 1.00 (6H, s, CH$_3$), 0.85 (6H, d, J = 7.1 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 34.5 (CH), 21.3 (CH$_3$), 18.3 (CH$_3$); ^{11}B$\{^1$H$\}$(96.2 MHz; CDCl$_3$): 64.4; ν_{max} (neat/cm^{-1}): 2963, 2874, 1463, 1372; *a representative mass spectrum could not be obtained due to the compound's instability.*

5.33b Reaction of dichlorothexylborane (5.14) with 3 equivalents of 3-chloro-1-lithiopropyne (THF).
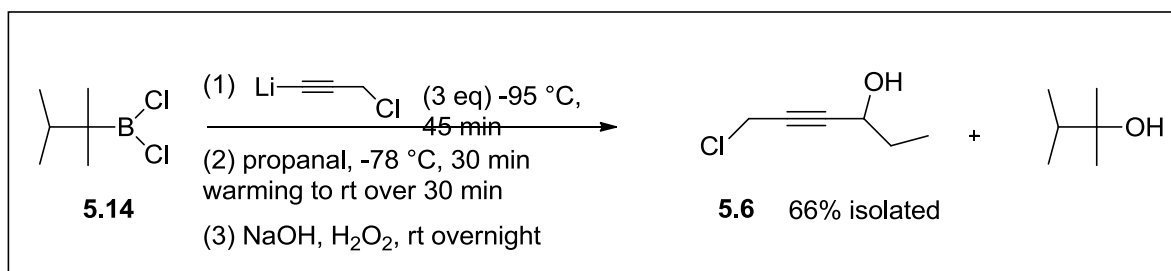
3-Chloro-1-lithiopropyne was prepared according to procedure 5.31a from propargyl chloride (1.04 mL, 14.4 mmol) and *n*-BuLi (1.6 M, 9.0 mL, 14.4 mmol) in dry THF (15 mL). A solution of freshly prepared dichlorothexylborane (**5.14**, prepared according to procedure 5.33a) (0.80 g, 4.8 mmol) in dry THF (10 mL) was added drop-wise *via* cannula, with vigorous stirring of the reaction mixture over a 10 min period. The mixture was stirred for a further 45 min at 95 °C, and propanal (0.36 mL, 5.0 mmol) was added. The mixture was stirred for a further 30 min, before the cooling bath was removed and the mixture was left to warm to rt over a 30 min period. Excess sodium hydroxide (1.2 g in 10 mL water) was added drop-wise, followed by excess hydrogen peroxide (30% by weight, 6 mL). Once the initial exothermic reaction subsided, the cooling bath was removed and the mixture was left to stir overnight at rt. The reaction mixture was then worked up as in procedure 5.31a to give a colourless oil (0.92 g), which consisted primarily of thexanol and an unknown compound by ^{1}H NMR spectroscopy. The crude product was purified by column chromatography on silica (10:1 petroleum ether: ethyl acetate, followed by 10:2) to give racemic 6-chlorohex-4-yn-3-ol[6] (**5.6**, 0.39 g, 66%) as a colourless liquid; δ^1H (500 MHz; CDCl$_3$): 4.23 (1H, m, C*H*OH), 4.06 (2H, d, J = 1.8 Hz, CH$_2$Cl), 2.67 (1H, br s, OH), 1.59 (2H, m, CH$_2$ of Et), 0.86 (3H, app t, J = 7.5 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 87.4 (quat C, alkynyl C), 79.5 (quat C, alkynyl C), 63.5 (CH, CHOH), 30.6 (CH$_2$, CH$_2$Cl), 30.4 (CH$_2$, *C*H$_2$CH$_3$), 9.3 (CH$_3$); LR - EI$^+$ MS m/z (%): *molecular ion not seen*, found 265 (dimer, 49%), 228 (34), 155 (90), 103 (100); v_{max} (neat/cm^{-1}): 3349 (OH), 2970, 2938, 2879, 2325, 1709, 1263, 1154, 1046; Rf = 0.33 in 5:1 petroleum ether: ethyl acetate.
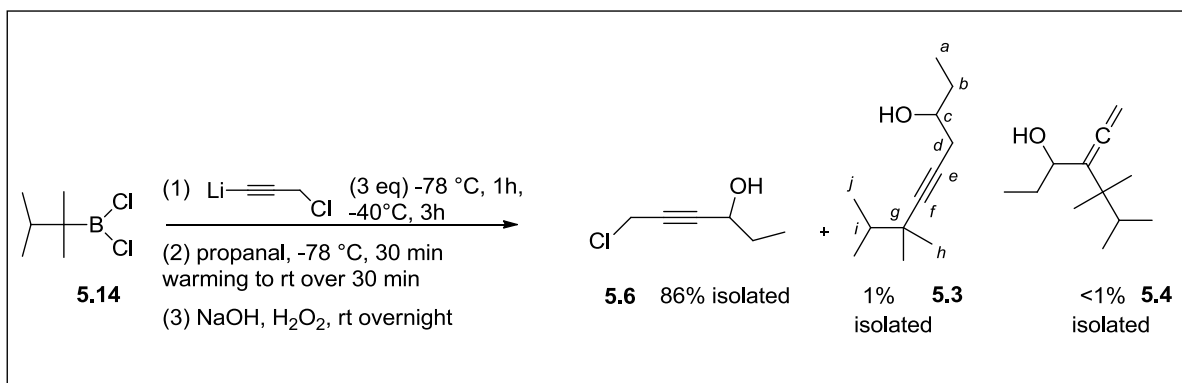
5.33c Reaction of dichlorothexylborane (5.14) with 3 equivalents of 3-chloro-1-lithiopropyne (THF)/longer time before reaction with propanal. 3-Chloro-1-lithiopropyne was prepared according to procedure 5.31a from propargyl chloride (0.65 mL,

9.1 mmol) and *n*-BuLi (1.6 M, 5.7 mL, 9.1 mmol) in dry THF (15 mL). A solution of freshly prepared dichlorothexylborane (prepared according to procedure 5.33a) (0.50 g, 3.0 mmol) in dry THF (10 mL) was added drop-wise *via* cannula, with vigorous stirring of the reaction mixture over a 10 min period. The reaction flask was moved quickly to a dry ice-acetone bath (-78 °C), and the mixture left to stir for 3 h. Propanal (0.22 mL, 1eq, 3.03 mmol) was added drop-wise, and the reaction mixture was then treated as in procedure 5.33b to give a brown oil (0.31 g), consisting of mostly 6-chlorohex-4-yn-3-ol (**5.6**), with no sign of the product arising from thexyl group migration by ^{1}H NMR spectroscopy.

5.33d Reaction of dichlorothexylborane (5.14) with 3 equivalents of 3-chloro-1-lithiopropyne (hexane). Procedure 5.33c was repeated on the same scale, except dry hexane replaced THF as the solvent (dry ice/ethyl acetate -84 °C was used for the lithiation of propargyl chloride to ensure no freezing of the solvent occurred), and 2 eq of propanal was used to give a brown oil (0.42 g) consisting of 6-chlorohex-4-yn-3-ol (**5.6**), thexanol and a trace amount of what seemed like thexyl migrated product by ^{1}H NMR spectroscopy. Attempts at isolating the thexyl migrated product by column chromatography were unsuccessful.

5.33e Reaction of dichlorothexylborane (5.14) with 3 equivalents of 3-chloro-1-lithiopropyne (hexane).


Procedure 5.33c was repeated on a larger scale using propargyl chloride (1.52 mL, 3.3 eq, 21 mmol) in dry hexane (15 mL), *n*-BuLi (1.6 M, 13.1 mL, 3.3 eq, 21.0 mmol) and a solution of dichlorothexylborane (1.06 g, 6.4 mmol) in dry hexane (15 mL). Following the addition of dichlorothexylborane, the mixture was left for 1h at -78 °C, and 3 h at -40 °C before being cooled again to -78 °C for the addition of propanal (1.38 mL, 3 eq, 19.1 mmol). The procedure thereafter was identical to 5.33c, and gave a yellow liquid (0.94 g) which consisted

mostly of 6-chlorohex-4-yn-3-ol (**5.6**) (corresponding to around 86% yield based on 8.26 mmol of propargyl chloride) along with a small amount of thexyl migrated material which was purified by column chromatorgraphy (95:5 petroleum ether: ethyl acetate followed by 90:10 and 80:20) to give near pure 7,7,8-trimethylnon-5-yn-3-ol (**5.3**, 11 mg, 1%) as a colourless oil; δ^1H (400 MHz; CDCl$_3$): 3.55 (1H, m, CH*c*), 2.37 (1H, dd, *J* = 16.4 Hz, 4.7 Hz, CH of CH$_2$*d*), 2.22 (1H, dd, *J* = 16.4 Hz, 4.7 Hz, CH of CH$_2$*d*), 1.93 (1H, b, OH), 1.42 – 1.51 (3H, m, CH$_2$*b*, CH*i*), 1.07 (6H, s, CH$_3$*h*), 0.89 (6H, d, *J* = 6.7 Hz, CH$_3$*j*), 0.80 (3H, m, CH$_3$*a*); δ^{13}C (100 MHz; CDCl$_3$): 90.0 (quat C, alkynyl C), 76.1 (quat C, alkynyl C), 71.6 (CH, C*c*), 37.6 (CH, C*i*), 35.0 (quat C, C*g*), 29.0 (CH$_2$), 27.3 (CH$_3$), 27.3 (CH$_2$), 18.4 (CH$_3$), 10.0 (CH$_3$, C*a*); HR - EI$^+$ MS m/z (%): calculated for C$_{12}$H$_{22}$O 182.1671, found 182.1675; Rf = 0.51 in 5:1 petroleum ether: ethyl acetate; *not enough sample for IR analysis*; along with impure 5,5,6-trimethyl-4-vinylideneheptan-3-ol (**5.4**, 10 mg). - characteristic 2H doublet at 4.8 ppm and 1H multiplet and 3.9 ppm in the ^{1}H spectrum, along with two quaternary allenic carbons at 207 and 117 ppm along with the allenic CH$_2$ carbon at 79 ppm in the DEPT ^{13}C NMR spectrum.

5.34 Investigative reactions for carrying out the reaction in an inverse fashion

5.34a Synthesis of pinacol 2-(3-chloroprop-1-ynyl)boronic acid ester (5.15).

5.15
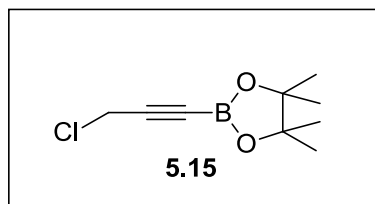
A solution of 3-chloro-1-lithiopropyne was prepared according to procedure 5.31a from propargyl chloride (1.30 mL, 18.0 mmol), *n*-BuLi in hexanes (1.6 M, 11.3 mL, 18.0 mmol) and dry diethyl ether (20 mL). To this was added 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.46 mL, 15.0 mmol) slowly drop-wise. The reaction solution was warmed to -78 ºC, and left to stir for 2 h where the reaction mixture partially solidified and so the reaction flask was occasionally swirled by hand to ensure efficient mixing of the reactants. A solution of HCl in dry diethyl ether (1.0 M, 18 mL, 18.0 mmol) was added drop-wise over a period of 5 min, and the reaction mixture was allowed to warm to rt whereupon the precipitate re-dissolved. The reaction mixture was allowed to stir for an additional h at rt, and then the diethyl ether was evaporated under reduced pressure with the product being

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protected from air. Dry hexane (15 mL) was added, and the solution filtered under N_2 through a glass frit. The hexane was removed at rt under HV to give boronic ester **5.15** as a light yellow powder (2.91 g, 97%); m.p 138-139°C; δ^1H (300 MHz; CDCl$_3$): 4.06 (2H, s, CH$_2$Cl), 1.18 (12H, s, CH$_3$); $\delta^{13}C$ (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 96.5 (quat C, br alkynyl C), 84.6 (quat C, O*C*), 29.9 (CH$_2$, CH$_2$Cl), 24.6 (CH$_3$); $^{11}B\{^1H\}$(96.2 MHz; CDCl$_3$): 22.7; HR - EI$^+$ MS m/z (%): M$^+$ not seen, calculated for C$_8$H$_{11}$O$_2$^{11}B^{35}Cl 185.0541, found 185.0538 (M$^+$ - CH$_3$, 50%); ν_{max} (thin film/cm^{-1}): 2977, 2870, 2219, 1459, 1383, 1339, 1143, 1069.

5.34b Synthesis of boronic ester (5.16).

5.16
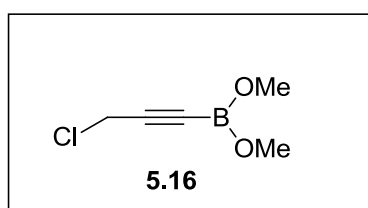
Procedure 5.34a was repeated, except that trimethylborate replaced 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to give near pure boronic ester **5.16**, with some residual hexane, as a deep yellow coloured liquid (1.30 g, 59%); δ^1H (300 MHz; CDCl$_3$): 4.11 (2H, s, CH$_2$Cl), 3.58 (6H, s, OCH$_3$); $\delta^{13}C$ (125 MHz; CDCl$_3$): 97.5 (quat C, br, alkynyl *C*B), 74.5 (quat C, alkynyl *C*C), 52.9 (CH$_3$, OCH$_3$), 30.0 (CH$_2$, CH$_2$Cl); $^{11}B\{^1H\}$ (96.2 MHz; CDCl$_3$): 20.1; ν_{max} (neat/cm^{-1}): 2959, 2871, 2254, 2214, 1484, 1375, 1350, 1307, 1261; *unable to get meaningful mass spectrum due to the compound's instability*.

5.34d Addition of *n*-BuLi to boronic ester 5.15. A 50 mL round bottomed flask equipped with a magnetic stirrer bar and septum was assembled while hot, and flushed with N_2 for 10 min. A solution of boronic ester **5.15** (3.0 mmol) in dry THF (15 mL) was added, and the reaction mixture cooled to -78 °C. *n*-BuLi in hexanes (1.6 M, 2.1 mL, 3.3 mmol) was added drop-wise with vigorous stirring of the reaction mixture over a period of 15 min, and the mixture was stirred for a further 30 min. The reaction mixture was allowed to come to rt over 30 min, before being cooled to -78 °C once more, and propanal (0.26 mL, 3.6 mmol) was added drop-wise. The mixture was left to stir for 30 min, before being allowed to come to rt over 45 min, and oxidised in the usual manner with 3 M NaOH and 30% w/w H$_2$O$_2,$ and worked up as in procedure 5.31a to give a yellow liquid (0.56 g), which consisted of pinacol, *n*-butanol and residual THF by ^1H NMR spectroscopy.

5.34d Addition of *n*-BuMgCl to boronic ester 5.15. Procedure 5.34c was repeated with a solution of boronic ester **5.15** (4.0 mmol) in dry THF (20 mL), except that *n*-butylmagnesium chloride in THF (2.0 M, 2.0 mL, 4.0 mmol) replaced *n*-butyllithium to give a yellow liquid (0.44 g), which consisted of pinacol, *n*-butanol and some unidentified compounds. An attempt was made to isolate the unknown compounds by column chromatography on silica (9:1 petroleum ether: ethyl acetate, followed by 8:2 and 3:1) to give a yellow oil (22 mg) which was a mixture of compounds and seemed to contain some of both possible compounds due to *n*-butyl migration (dec-5-yn-3-ol and 4-vinylideneoctan-3-ol) but no attempts at further purification were made.

5.34e Addition of *n*-BuMgCl to boronic ester 5.15. Procedure 5.34c was repeated using a solution of boronic ester **5.15** (3.0 mmol) in dry THF (15 mL) and *n*-butylmagnesium chloride in THF (2.0 M, 2.0 mL, 4.0 mmol), except that the addition was completed at -95 ℃ and then the solution was stirred for 5 h at -78 ℃ prior to the addition of propanal. The procedure was the same thereafter to give a yellow liquid (0.54 g), which consisted of pinacol, *n*-butanol and 6-chlorohex-4-yn-3-ol (the last two in a 81:19 ratio by relative integrations in the ^{1}H NMR spectrum).

5.34f Addition of *n*-BuMgCl to boronic ester 5.16. Procedure 5.34e was repeated, except using boronic ester **5.16** as a solution in dry THF (4.26 mmol in 6 mL) to give a brown oil (0.41 g), consisting of *n*-butanol, residual THF and a small amount of an unknown compound (by ^{1}H NMR analysis), with a downfield triplet at 5 ppm which did not conform with any expected products.

5.34g Addition of *n*-BuMgCl to boronic ester 5.16. Procedure 5.34f was repeated, except that the Grignard reagent addition was done at 0 ℃, and the mixture was then cooled to -78 ℃ for the subsequent addition of propanal. The procedure was the same thereafter to give a brown oil (0.44 g), which consisted of *n*-butanol, MeOH and residual THF by ^{1}H NMR analysis.

5.4 References

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Chapter 6: Generation of quaternary carbon centres by homologation of tertiary alkylboronic esters using 3-chloro-1-lithio-prop-1-ene

6.1 Aims and introduction

Following the disappointing results of Chapter 5 when attempting to add 3-chloro-1-lithiopropyne to various organoboranes or organometallic reagents to (3-chloropropynyl)boronic esters, it was decided to switch our research efforts towards their alkenyl analogues. The biggest obstacle seen in Chapter 5 was that the (3-chloropropynyl)alkylboronic ester 'ate' complex was not stable, and that this 'ate' complex disassociated before any boron – carbon migration took place (Scheme 6.1).

Scheme 6.1 Instability of (3-chloropropynyl)alkylboronic ester 'ate' complexes
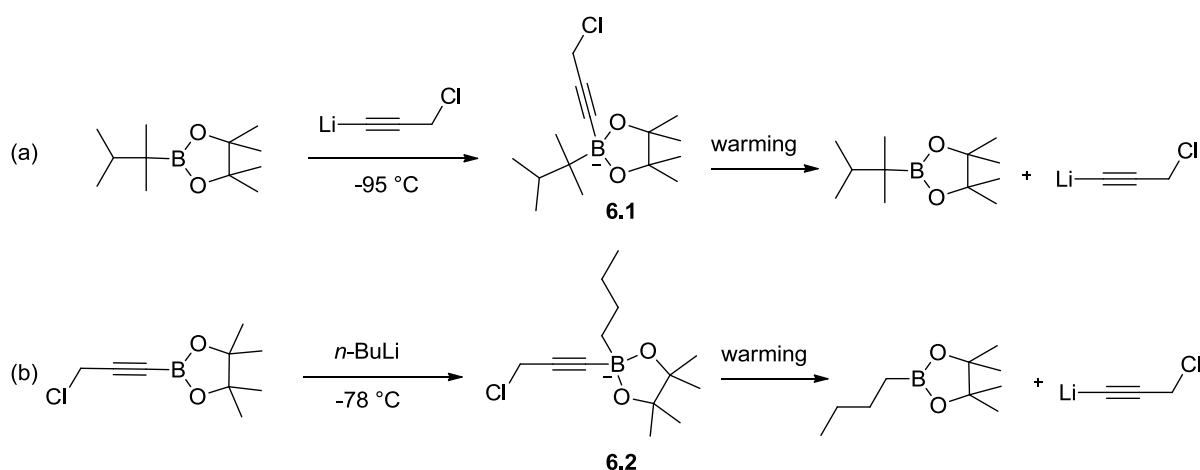

We reasoned that alkenyl analogues to 'ate' complexes **6.1** and **6.2** should be more stable as alkenyl anions are less stable than their alkynyl counterparts, and so might allow the desired boron– carbon migration to take place. A quick literature search revealed that such an approach has already been published for (3-haloprop-1-en-1-yl)organoboranes, although not for the migration of tertiary alkyl groups to give quaternary carbon centres.

A. Pelter and C. R. Harrison published work in 1974 detailing the reaction of trialkylalkynylborates with dihalomethanes *via* a double migration mechanism that involved an intermediate (3-haloprop-1-en-1-yl)organoborane compound (Scheme 6.2).[1] Various examples were explored, with the olefinic products being isolated in moderate to good yields.

C. Trombini *et al.* developed a synthetic route to (3-haloprop-1-en-1-yl)organoboranes through the hydroboration of propargyl chloride/bromide with a dialkylborane (Scheme 6.3).[2] The (3-haloprop-1-en-1-yl)organoboranes were then reacted with aldehydes *via* a cyclic mechanism to give the corresponding homoallylic alcohol products in good yields.

Scheme 6.2 Reaction of trialkylalkynylborates with dibromomethane *via* a (3-haloprop-1-en-1-yl)organoborane intermediate
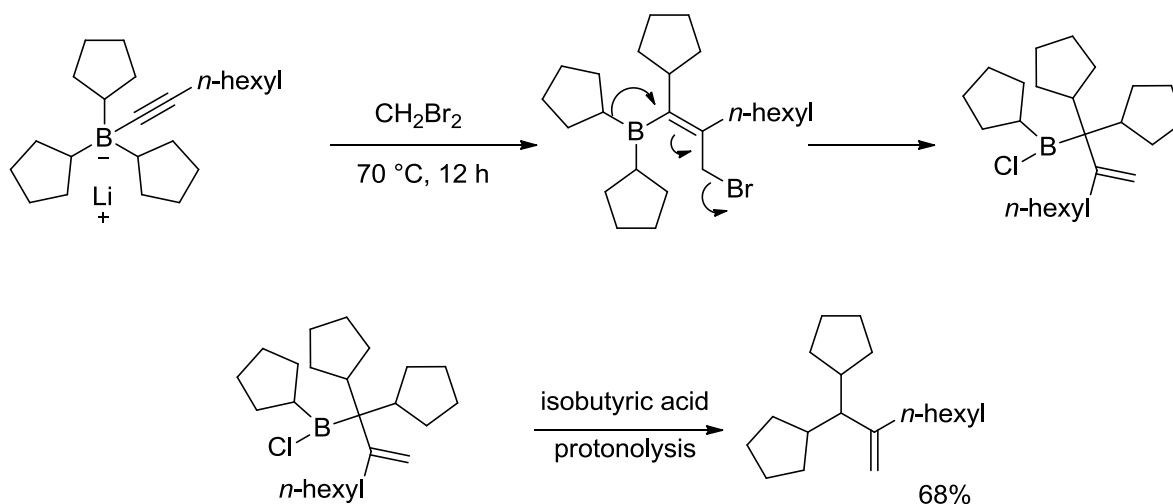

Continuing their interest in the field, Tromboni *et al.* published further work on (3-haloprop-1-en-1-yl)organoboranes in the year 2000, adding methyllithium to generate an 'ate' complex similar to that shown in Scheme 6.1b.[3] The methyl group behaved like a blocking group, with one of the other two alkyl groups undergoing a boron – carbon migration to give an intermediate allylic organoborane which, after undergoing an allylic rearrangement, reacted with aldehydes to give the corresponding homoallylic alcohols in moderate to good yields (Table 6.1).

Scheme 6.3 Synthesis of (3-bromoprop-1-en-1-yl)organoboranes and their reaction with an aldehyde to give homoallylic alcohols

a triethylbenzylammonium bromide
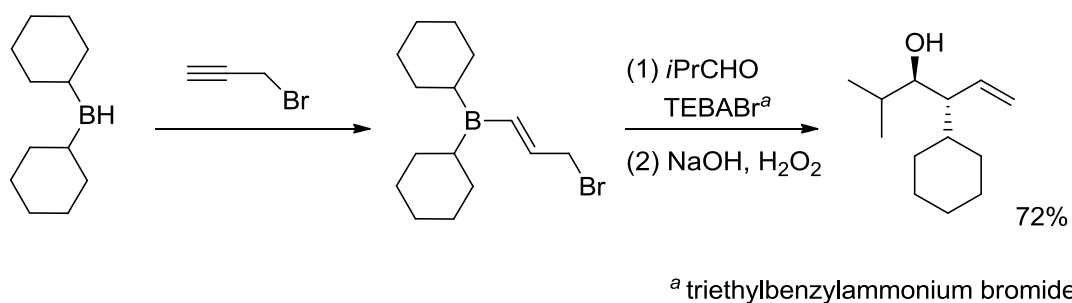
Although this novel methodology gave a new route to homoallylic alcohols, it suffered some drawbacks: dialkylboranes are quite difficult to synthesize (using hydroboration, only a few hindered alkenes stop at the dialkylborane stage), and also the presence of more hindered alkyl groups in the dialkylborane starting materials meant that the allylic rearrangement did not go to completion, resulting in a mixture of products and therefore leading to modest yields.

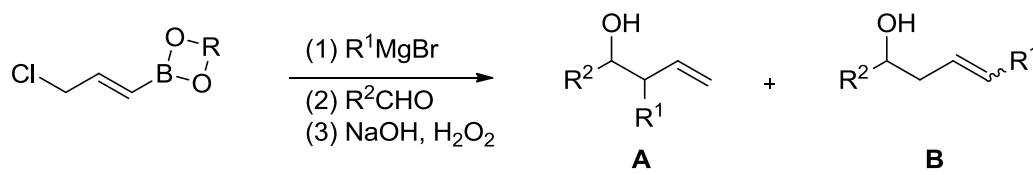**Table 6.1 Synthesis of homoallylic alcohols using (3-bromoprop-1-en-1-yl)organoboranes**
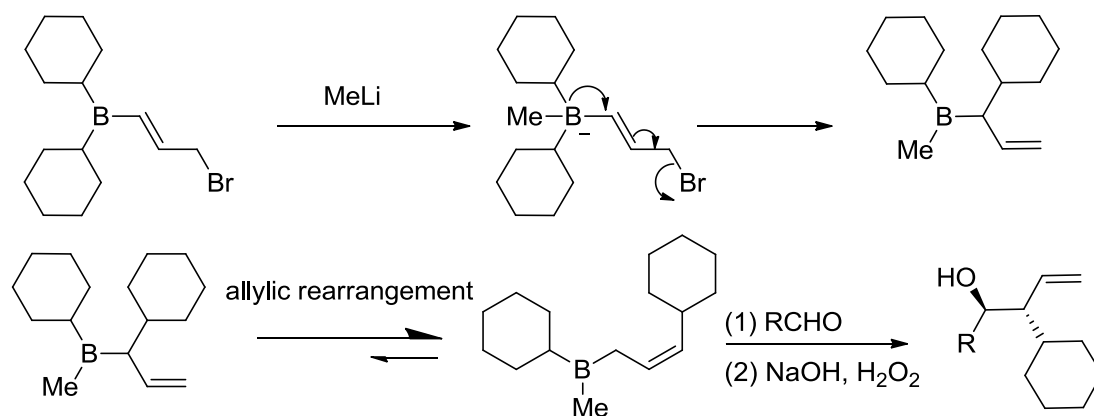
R	Yield (%)[a]
Ph	68
*i*Pr	72
n-hexyl	82

[a]Isolated yields.

In 2002, Trombini *et al.* attempted to address many of these disadvantages by preparing (3-chloroprop-1-en-1-yl)boronic esters.[4] The addition of Grignard reagents to these boronic esters gave 'ate' complexes that rearranged to give allylic boronic esters, which reacted with aldehydes (before, or after undergoing the allylic rearrangement) to give, after oxidation, homoallylic alcohols in moderate yields (Table 6.2).

Using (3-chloroprop-1-en-1-yl)boronic esters meant that the reaction was opened up to any alkyl groups that could be added as a Grignard reagent, rather than only the ones that originated from dialkylboranes. Unfortunately, the allylic rearrangement was not as clean as in their previous work, which meant that there was a mixture of products in most cases, with the rearranged product also being produced as a mixture of (*E*)/(*Z*) isomers (Table 6.2).

Table 6.2 Synthesis of homoallylic alcohols by addition of Grignard reagents to (3-chloroprop-1-en-1-yl)boronic esters, followed by reaction with an aldehyde and oxidation


R	R^1	R^2	Yield (%)[a]	
			A	B
$CH_2CH_2CH_2$	iPr	Ph	13	32 (30:70)[b]
$C(CH_3)_2C(CH_3)_2$	iPr	Ph	trace	55 (30:70)
$C(CH_3)_2C(CH_3)_2$	Ph	$BnOCH_2$	trace	35 (2:98)
$C(CH_3)_2C(CH_3)_2$	n-Bu	Ph	6	59 (20:80)

[a]Isolated yields, [b] numbers in parentheses are (E):(Z) ratios.

Following on from this work, in 2007, L. Carosi and D. G. Hall published work on the same reaction involving (3-chloroprop-1-en-1-yl)boronic esters using chiral phosphoramidite ligands to control the stereochemistry at the newly generated chiral centre (Scheme 6.4).[5] The yields and enantioselectivities of the product homoallylic alcohols were good to excellent, showing that the reaction could be carried out asymmetrically. The (E)/(Z) ratios of the products were also improved by using a stoichiometric amount of $BF_3.Et_2O$.

Scheme 6.4 Asymmetric reaction of a (3-chloroprop-1-en-1-yl)boronic ester with a Grignard reagent and an aldehyde, followed by displacement from boron
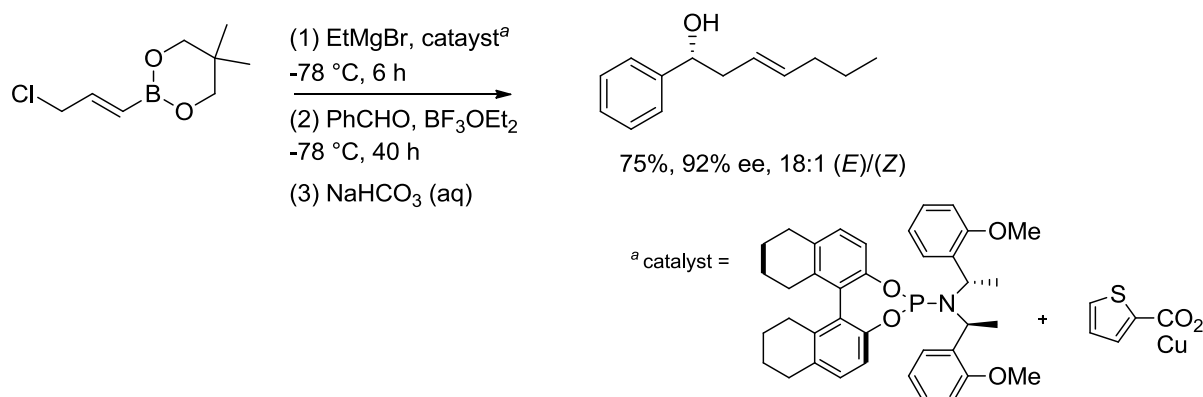
With our continued interest in the generation of quaternary carbon centres, we decided to explore this promising reaction with a view to establishing whether the reaction could be successfully applied to the migration of tertiary alkyl groups. In addition to this, we wondered

if the reaction could be completed in an inverse fashion (*i.e.* adding 1-lithio-3-chloroprop-1-ene to boronic esters), so as to significantly widen the scope of the reaction.

6.2 Results and discussion

6.21 Synthesis and initial reactions of (*E*)-2-(3-chloroprop-1-en-1-yl)boronic acid pinacol ester (**6.3**)

Direct hydroboration of propargyl chloride with pinacolborane[6] gave only very low yields of the desired boronic ester **6.3**. However, using a different literature procedure[7] utilising pinacolborane, propargyl chloride and a catalytic amount of dicyclohexylborane, boronic ester **6.3** was produced in a moderate yield (Scheme 6.5). The boronic ester was purified by column chromatography to give the pure boronic ester **6.3** (49% isolated yield, compared to the literature yield of 84%). Boronic ester **6.3** was fully characterised (E.S. 6.31a; although a representative mass spectrum could not be obtained), with the data in accordance with the literature values.[7]

Scheme 6.5 Synthesis of (*E*)-2-(3-chloroprop-1-en-1-yl)boronic acid pinacol ester (6.3)
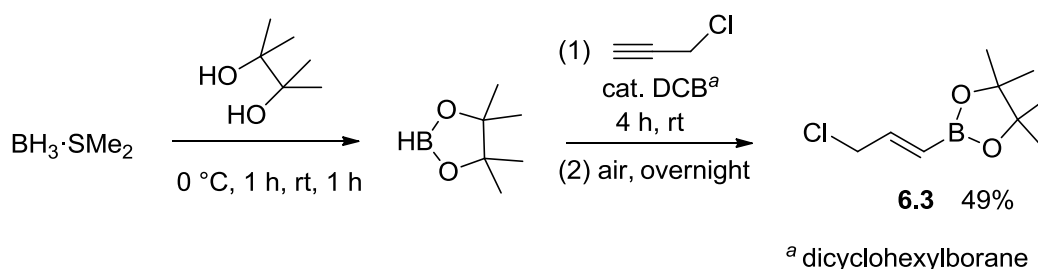
Two test reactions were run to see whether the boronic ester reacted in the way described in the literature,[4] and to check whether there was any difference between using a Grignard or an organolithium reagent. *n*-BuMgCl was added to boronic ester **6.3** at -78°C and the reaction mixture stirred for 30 minutes before the slow addition of propanal, followed by warming to room temperature and oxidation. The crude product following work-up showed a mixture of the three possible migration products: (*E*)/(*Z*) dec-5-en-3-ol (**6.4**, **6.5**) and 4-vinyloctan-3-ol (**6.6**) (in a 70:30 ratio determined by relative integrations seen in the ^{1}H NMR spectrum) (Scheme 6.6), along with some pinacol. The migration products were not isolated; however, both the ^{1}H and ^{13}C NMR spectra of the crude products were in accordance with the proposed structures. This result was in line with the literature, as usually there is a mixture of migration products if the allylic rearrangement has not gone to completion.[4]

The reaction was repeated using *n*-BuLi, where the ^{1}H NMR spectrum following work-up was much cleaner, showing only the migration products arising from completion of the allylic rearrangement ((*E*)/(*Z*) dec-5-en-3-ol (**6.4**, **6.5**)) (Scheme 6.6).

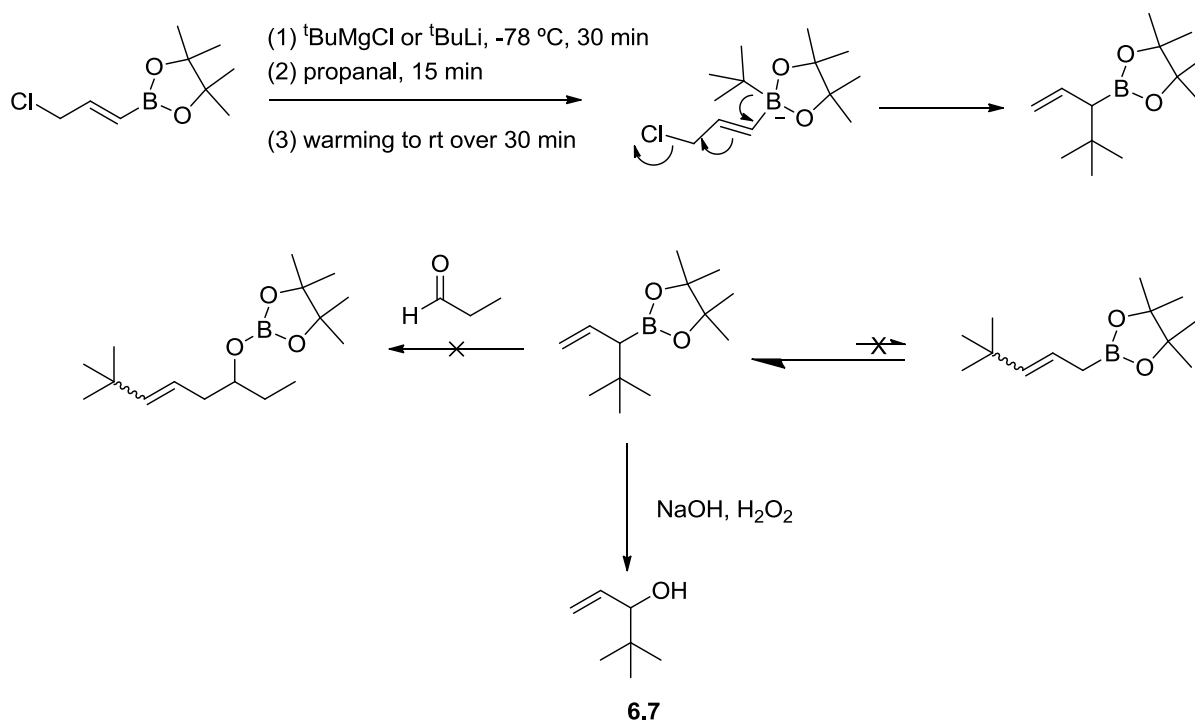**Scheme 6.6 Test reactions of boronic ester 6.3 with *n*-BuMgCl and *n*-BuLi**
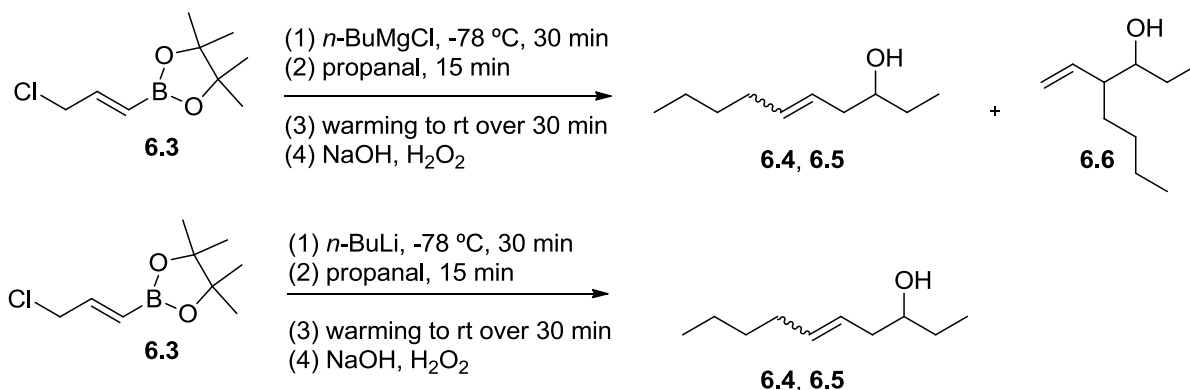
It was then decided to move on to the tertiary Grignard/organolithium reagents to see whether this reaction could be used as a route to quaternary carbon centres. Boronic ester **6.3** was reacted separately with both *tert*-BuMgCl and *tert*-BuLi, with both reactions giving essentially the same result. The ^{1}H NMR spectra following work-up of the reaction mixtures showed what seemed like a single migration product, along with some pinacol. However, the NMR spectra of the product did not correspond to any of the three expected migration products. The unknown compound seemed to have a terminal alkenyl functionality, as shown by two multiplets at 5.9 and 5.2 ppm with an integration of 1:2 respectively.

Attempts at purifying the compound by column chromatography on silica and by dissolving the reaction mixture in diethyl ether and washing several times with water in order to get rid of the pinacol led to decomposition of the unknown compound. It was also noted that the compound was relatively volatile, with the amount of product seen in the ^{1}H NMR spectrum decreasing if the sample was left for a longer time under reduced pressure.

With this information in mind, we proposed that the structure was in fact 4,4-dimethylpent-1-en-3-ol (**6.7**), *i.e.* the direct product arising from oxidation of the intermediate boronic ester following the migration (having not taken part in allylic rearrangement or reaction with propanal) (Scheme 6.7).

Scheme 6.7 Possible explanation and identity of the unknown alkenyl compound

(1) ^{t}BuMgCl or ^{t}BuLi, -78 °C, 30 min
(2) propanal, 15 min
(3) warming to rt over 30 min
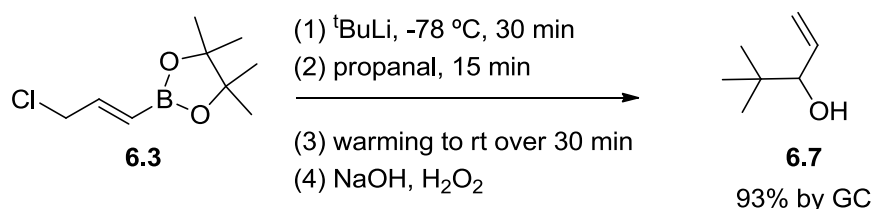
NaOH, H_2O_2

6.7

In order to confirm the identity of the unknown compound, it was decided to synthesise 4,4-dimethylpent-1-en-3-ol (**6.7**) *via* a different route. 4,4-Dimethylpent-1-en-3-ol (**6.7**) was produced by adding vinylmagnesium bromide to a solution of pivaldehyde in THF at -78 °C. Following work-up, the reaction mixture was concentrated under reduced pressure to give pure racemic **6.7** (88% isolated yield, Scheme 6.8). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.31g).[8]

Comparison of the ^{1}H NMR spectrum of the purified compound with the crude products for the previous two reactions containing the unknown compound confirmed that the unknown compound was indeed racemic 4,4-dimethylpent-1-en-3-ol. The identity was further demonstrated by GC analysis, which showed that both the purified compound and the compound seen in the crude reaction mixtures had the same GC retention time.

Scheme 6.8 Synthesis of racemic 4,4-dimethylpent-1-en-3-ol (6.7)

(1) vinylmagnesium bromide,
-78 °C, 30 min, then warming to rt

(2) H_2O

6.7 88%
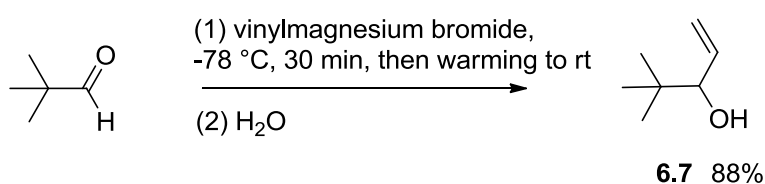
Using the purified racemic 4,4-dimethylpent-1-en-3-ol to calculate the GC response factor with a known weight of internal standard (tetradecane), the reaction between boronic ester **6.3** and *tert*-BuLi was repeated to get a yield by GC analysis. Analysis of the organic layer after oxidation by GC analysis showed a 93% yield of racemic **6.7** (Scheme 6.9).

Scheme 6.9 Reaction of boronic ester 6.3 with *tert*-BuLi

(1) ^{t}BuLi, -78 °C, 30 min
(2) propanal, 15 min

(3) warming to rt over 30 min
(4) NaOH, H$_2$O$_2$

6.3

6.7
93% by GC

The fact that the allylic boronic ester intermediate following migration had not rearranged to give the less hindered allylic boronic ester is surprising, as is the fact that the allylic boronic ester had not reacted with propanal (even after being left overnight with propanal on one occasion). One might expect that a hindered allylic boronic ester such as the one shown in Scheme 6.7, might be more prone to undergo the rearrangement to alleviate the steric strain around boron; however it seems that the system is sufficiently hindered that the rearrangement cannot easily take place.

The reaction was repeated, except that the reaction mixture was heated to reflux overnight in an attempt to force the allylic rearrangement to happen; however, no rearranged product could be seen in the ^{1}H NMR spectrum of the crude product following oxidation. The non-reactivity towards propanal must also be down to the steric hindrance around the boron centre of the allylic boronic ester intermediate. Such a hindered allylic organoboron compound has previously been shown to be less reactive towards allylic rearrangement.[9]

This result was very encouraging, as it showed that the reaction could be used to generate quaternary carbon centres. In addition to this, the yield of the migration product was excellent, and the reaction itself produced only one migration product, making it a much cleaner reaction than seen in previous work.[4]

Exciting as this result was, the methodology is limited by the fact that it requires the preparation of *tert*-organolithium/Grignard reagents. For this reason, it was decided to attempt to complete the reaction in an inverse fashion as already mentioned in Section 6.1 (having the *tert*-alkyl group already bonded to boron as a boronic ester).

6.22 Synthesis and test reaction of 1-bromo-3-chloroprop-1-ene (6.8)

The challenging aspect of completing the reaction in an inverse fashion is to produce the 1-lithio-3-chloroprop-1-enyl organolithium reagent (**6.9**). It was decided that 1-bromo-3-chloroprop-1-ene (**6.8**) might be a possible precursor to **6.9**. One would expect that a Li-Br exchange reaction using 1-bromo-3-chloroprop-1-ene (**6.8**) would be much faster than Li-Cl exchange, and would give the desired organolithium reagent **6.9**. However, even if the difference in reactivity between the two halogens is sufficient that only Li-Br exchange occurs, there are still the additional problems that the organolithium reagent used for the Li-Br exchange could attack the precursor directly with displacement of either chloride or bromide or could affect deprotonation (Scheme 6.10). Even with these possible future hurdles, it was decided to synthesise 1-bromo-3-chloroprop-1-ene (**6.8**).

Scheme 6.10 Possible modes of reaction for 1-bromo-3-chloroprop-1-ene (6.8) with an organolithium reagent
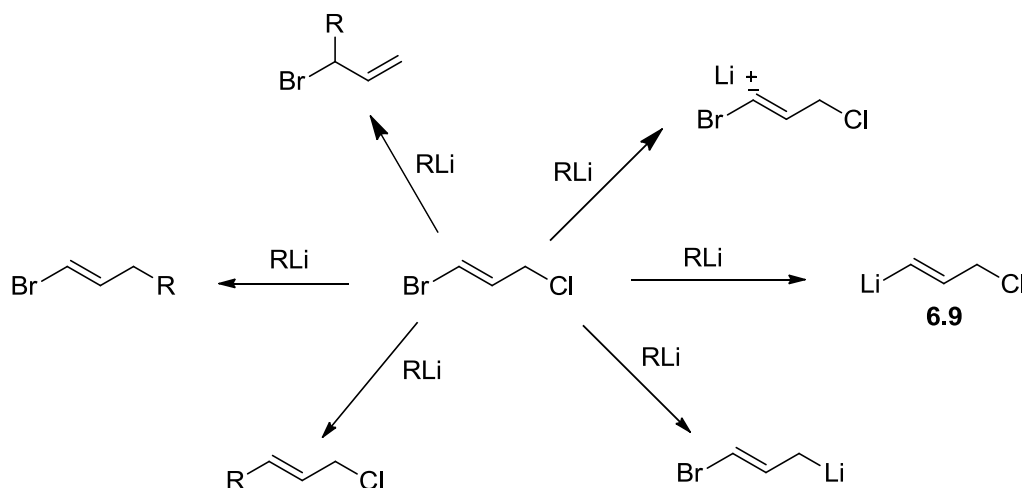

Although Li-Br exchange on 1-bromo-3-chloroprop-1-ene (**6.8**) has to our knowledge never been attempted, the substrate itself has been synthesised previously,[10,11] with the most attractive method being the most recent one.[11] The synthesis consists of reducing (*E*)-3-bromoacrylic acid (**6.10**) to (*E*)-3-bromoprop-2-en-3-ol (**6.11**), and then reacting **6.11** with a mixture of hexachloroacetone/triphenylphosphine to give the (*E*)-1-bromo-3-chloroprop-1-ene (**6.8**).

(*E*)-3-Bromoacrylic acid (**6.10**) was produced by the literature procedure[12] from propiolic acid and an aqueous solution of hydrobromic acid (Scheme 6.11). The (*E*)-3-bromoacrylic acid (**6.10**) was left to crystallise from the reaction mixture overnight, and the crystals were
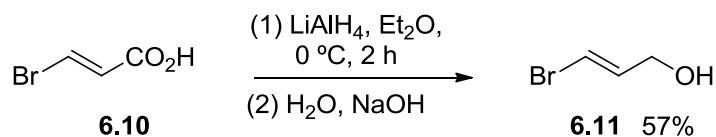
washed with cold water to give pure **6.10** (63% isolated yield, literature yield of 71%). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.32a).[12]

Scheme 6.11 Synthesis of (*E*)-3-bromoacrylic acid (6.10)

$$\equiv\!\!-CO_2H \quad \xrightarrow[\text{95 °C, 2.5 h}]{\text{48\% (aq) HBr}} \quad Br\!\!\diagdown\!\!\diagup\!\!-CO_2H$$

6.10 63%
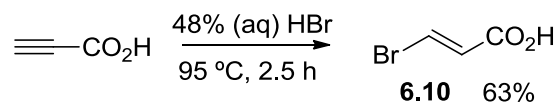
6.10 was reduced using lithium aluminium hydride by the literature procedure.[13] However, in our hands the reaction always gave a lower yield than the reported yield of 70%, and the ^{1}H NMR spectrum of the crude products nearly always showed that some side products were present. Varying the reaction conditions (reaction time, temperature, equivalents of the reducing agent and quenching procedure) did not improve matters. Yields were usually in the region of 45-50%, with the best result being a 57% isolated yield of (*E*)-3-bromoprop-2-en-3-ol (**6.11**) (Scheme 6.12). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.32b).[13] The compound appeared to be sensitive to heating on the rotary evaporator, and as the compound was reasonably pure, no attempts at purification were made.

Scheme 6.12 Synthesis of (*E*)-3-bromoprop-2-en-3-ol (6.11)

$$Br\!\!\diagdown\!\!\diagup\!\!-CO_2H \quad \xrightarrow[\text{(2) H}_2\text{O, NaOH}]{\begin{array}{c}\text{(1) LiAlH}_4\text{, Et}_2\text{O,}\\ \text{0 °C, 2 h}\end{array}} \quad Br\!\!\diagdown\!\!\diagup\!\!\diagdown\!\!OH$$

6.10   **6.11** 57%

The final step was carried out by the literature procedure[11,14] using a triphenylphosphine/hexachloroacetone mixture (Scheme 6.13) (traditional chlorinating reagents, such as thionyl chloride have been shown to introduce a chlorine atom at the incorrect position).[14] The product **6.8** was purified by fractional distillation until no pentachloroacetone was seen in the ^{1}H NMR spectrum of the distillate (usually 2-3 careful fractional distillations were required), to give (*E*)-1-bromo-3-chloroprop-1-ene (**6.8**) in excellent purity, although poor yield (13% isolated yield). The compound was fully characterised, with the data in accordance with the proposed structure (E.S. 6.32c; the NMR spectra have not been previously published). It was noticed that samples of (*E*)-1-bromo-3-chloroprop-1-ene (**6.8**) isomerized to give a mixture of *cis* and *trans* isomers if left in the

presence of light (a previously noted phenomenon[10]), and so samples of (**6.8**) were kept in a foil-wrapped container in the fridge.

Scheme 6.13 Synthesis of (*E*)-1-bromo-3-chloroprop-1-ene (6.8)

a hexachloroacetone
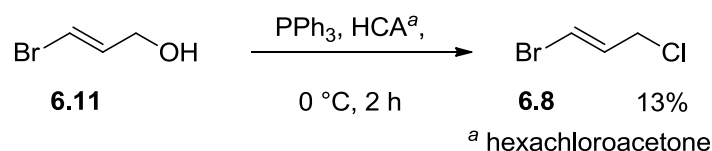
With compound **6.8** at hand, a test reaction (1 mmol) was run to see whether the desired migration reaction would take place. Thexylboronic ethylene glycol ester (**6.12**) was freshly prepared, as in Chapter 4 (previously numbered as boronic ester **4.2**) and was dissolved in THF along with **6.8**. The solution was cooled to -78 °C, and *n*-BuLi was added drop-wise before allowing the reaction mixture to warm to room temperature followed by oxidation.

The ^{1}H NMR spectrum of the crude product after work-up showed some of the starting material **6.8**, thexanol (from no migration), *n*-butanol and what seemed to be the desired migration product. From the relative integrations of the thexanol and desired product peaks, a yield of around 23% migrated product was estimated. The presence of *n*-butanol and **6.8** in the crude product gave an indication of what might be the reason for the low yield: if the *n*-BuLi had added directly to the boronic ester, then this would have led to *n*-butanol, thexanol and unreacted **6.8**. Despite the modest yield of migrated product, this result was encouraging as it showed that it might indeed be possible to complete the reaction in an inverse fashion.

6.23 Synthesis of *tert*-butylboronic esters, and optimisation reactions

Since the test reaction was promising, it was decided to synthesise two *tert*-butylboronic esters to investigate the reaction further, where the yield of the reaction could be checked by GC analysis.

tert-Butylboronic acid (**6.13**) was prepared by the literature procedure from *tert*-BuMgCl and trimethyl borate,[15] and a small aliquot was taken for characterisation purposes. The compound was fully characterised (E.S. 6.33b; a representative MS spectrum could not be obtained due to the compound's instability), and the data was in accordance with the literature values.[16] The boronic acid **6.13** was taken immediately to the next step by the literature procedure involving ethylene glycol to give boronic ester **6.14** in 32% isolated yield

(literature yield 70%,[15] Scheme 6.14). Boronic ester **6.14** was fully characterised, and the data were in accordance with the literature values (E.S. 6.33b).[15]

Scheme 6.14 Synthesis of boronic ester 6.14
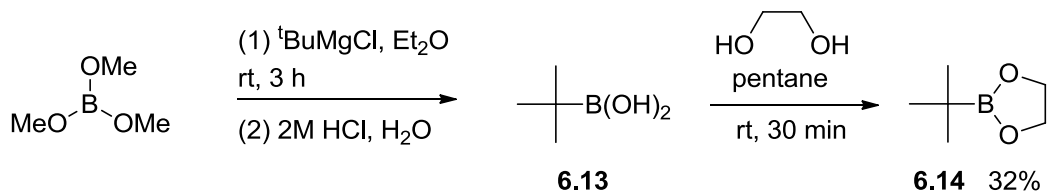
tert-Butylboronic ester **6.15** was produced by the literature method from freshly-prepared pinacolborane and *tert*-BuMgCl (Scheme 6.15).[17] The product was purified by column chromatography on silica to give pure boronic ester **6.15** in 40% isolated yield (literature yield 65%). The compound was fully characterised, with all the data in accordance with the literature values (E.S. 6.33a).[17]

Scheme 6.15 Synthesis of boronic ester 6.15
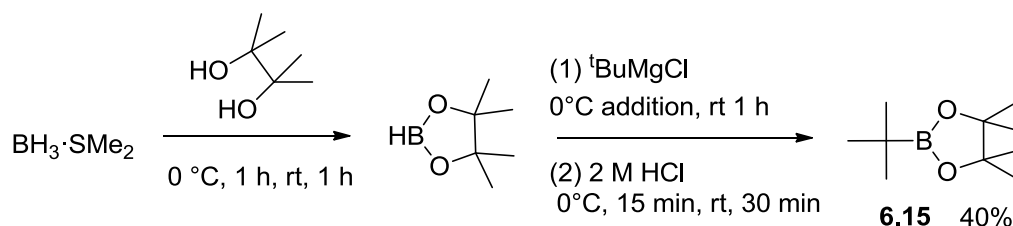
Following the synthesis of boronic esters **6.14** and **6.15**, a number of optimisation reactions were run to see whether good yields of the migrated product **6.7** could be achieved. The results are summarised in Table 6.3.
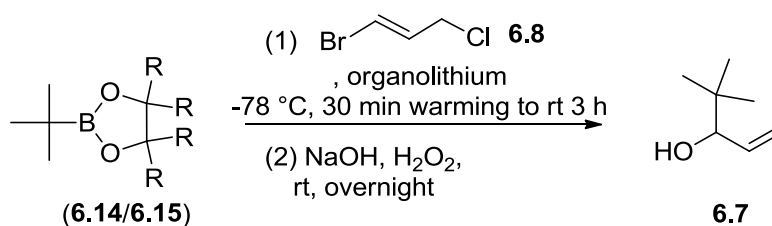
Table 6.3 Optimisation reactions for the migration of a *tert*-butyl alkyl group

Entry	Boronic ester	R	organolithium	Yield of 6.7 (%)[a]
1	**6.14**	H	*n*-BuLi	9
2	**6.14**	H	*tert*-BuLi	42
3	**6.14**	H	*tert*-BuLi (1.25 eq)	27
4	**6.15**	Me	*n*-BuLi	10
5	**6.15**	Me	*n*-BuLi (ex-situ)	0
6	**6.15**	Me	*tert*-BuLi	98
7	**6.15** (excess)	Me	*tert*-BuLi	92
8	**6.15**	Me	*tert*-BuLi	34[b]

[a] Yield by GC analysis hexadecane as the internal standard, [b] 95% pure 1-bromo-3-chloroprop-1-ene (**6.8**) used, instead of 99+% pure, as in other reactions.

Boronic ester **6.14** was studied first, and the initial attempt (entry 1, Table 6.3) was using *n*-BuLi as the organolithium reagent for the Li-Br exchange. The yield by GC analysis was disappointingly low (9%). This result, along with the first test reaction of boronic ester **6.12** led us to postulate that the problem may be direct addition of the *n*-BuLi to boronic ester **6.14**. In fact, the yield appeared to be worse than the test reaction with boronic ester **6.12** which is what one would expect if direct addition of *n*-BuLi is the problem (as *tert*-butylboronic ester **6.14** is less hindered than boronic ester **6.12**).

In an attempt to circumvent this problem, the reaction was repeated but using *tert*-BuLi as the organolithium in the hope that *tert*-BuLi would be less prone to direct addition to boronic ester **6.14** as it is a more hindered organolithium reagent (entry 2, Table 6.3). GC analysis of

the organic layer showed a marked improvement in the yield of **6.7** (42%), showing that using a more hindered organolithium reagent had improved matters. In order to make sure that the yield was not lowered because the *tert*-BuLi used was of lower concentration than had been estimated, the reaction was repeated using 1.25 equivalents of *tert*-BuLi (entry 3, Table 6.3). However, the yield of **6.7** dropped to 27%, hinting that the reaction was quite sensitive to the stoichiometries of the reagents.

Sensing that a more hindered boronic ester might help deter the possible direct addition of the organolithium reagent, we focussed our attention on boronic ester **6.15**. The first attempt, using *n*-BuLi as the organolithium reagent gave the same result within experimental error to the analogous reaction of boronic ester **6.14** (entry 4, Table 6.3).

An attempt was made to generate the anion *ex-situ* (entry 5, Table 6.3), as this would circumvent any possible problem with direct addition of the organolithium reagent to the boronic ester. However, no 4,4-dimethylpent-1-en-3-ol (**6.7**) was detected by GC analysis, highlighting the expected instability of the 1-lithio-3-chloroprop-1-ene intermediate (**6.9**).

Using *tert*-BuLi as the *in-situ* organolithium reagent with boronic ester **6.15** however, improved the yield drastically, giving essentially a quantitative yield of the migrated product **6.7** (entry 6, Table 6.3). This excellent result can be rationalised by the fact that boronic ester **6.15** is more hindered than boronic ester **6.14**, and so would dissuade the organolithium reagent from adding directly (transfer of hydride may also have been a source of the previous drop in yield, especially when using *tert*-BuLi).[18]

In all of the above reactions, 1.1 equivalents of both the organolithium and 1-bromo-3-chloroprop-1-ene (**6.8**) were used. In order to discover whether this excess was needed to achieve good yields, the reaction was repeated with boronic ester **6.15** in excess (entry 7, Table 6.3). GC analysis showed a yield of 92% (based on the amount of **6.8** used), showing that excellent yields could still be achieved when using the boronic ester in excess. However, for all subsequent reactions, the organolithium and 1-bromo-3-chloroprop-1-ene (**6.8**) were used in 1.1 equivalents relative to the boronic ester.

During these optimisation reactions, it was noted that the purity of the 1-bromo-3-chloroprop-1-ene (**6.8**) used was very important to achieve good yields of the migrated product **6.7**. Even very small amounts of pentachloroacetone left from the preparation of **6.8** dropped the yield of **6.7** considerably (entry 8, Table 6.3). In this reaction, 95% pure **6.8** was used

(contaminated by 5% of pentachloroacetone, as seen by relative integrations in the ^{1}H NMR spectrum of the distillate), and only a 34% yield of **6.7** was obtained. It seems that pentachloroacetone was very reactive towards either (or both) *tert*-BuLi or 1-lithio-3-chloroprop-1-ene (**6.9**), and could consume more than stoichiometric amounts of the *tert*-BuLi.

Since these exploratory reactions had shown that it is possible to complete the reaction effectively in an inverse fashion, it was decided to test the scope of the reaction by using a variety of *tert*-alkylboronic esters.

6.24 Synthesis and reactions of various *tert*-alkylboronic esters with 1-lithio-3-chloroprop-1-ene (**6.9**)

Boronic ester **6.16** was prepared as in Chapter 4 (where it was numbered boronic ester **4.6**) from $BH_3.SMe_2$, 2,3-dimethyl-2-butene and pinacol, and was purified by column chromatography. The purified boronic ester **6.16** was then reacted with 1-bromo-3-chloroprop-1-ene (**6.8**)/*tert*-BuLi as in entry 6, Table 6.3. Following work-up, the ^{1}H NMR spectrum of the crude reaction product showed the presence of the expected product (4,4,5-trimethylhex-1-en-3-ol (**6.17**)) and thexanol (in a 66:33 ratio respectively by relative integrations in the ^{1}H NMR spectrum), along with pinacol. Although the ratio of migrated product **6.17** to thexanol was encouraging, the weight of the crude reaction product suggested that loss of thexanol had occurred as a result of concentrating under reduced pressure.

The migrated product **6.17** was purified by column chromatography on NEt$_3$ – neutralised silica, to give pure novel racemic alcohol 4,4,5-trimethylhex-1-en-3-ol (**6.17**) in a 28% isolated yield (Scheme 6.16). The compound was fully characterised, with all the data (including HRMS) in accordance with the proposed structure (E.S. 6.35a). The GC response factor was measured, so that future reactions could be monitored by GC analysis.
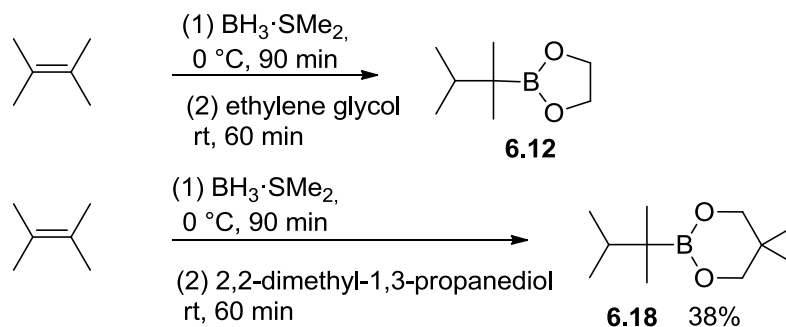
The isolated yield of migrated product **6.17** was a little lower than expected, which might indicate that incomplete capture of the anion was beginning to be a limiting factor with this more hindered boronic ester **6.16**.

Scheme 6.16 Reaction of boronic ester 6.16 with 1-lithio-3-chloroprop-1-ene (6.9)
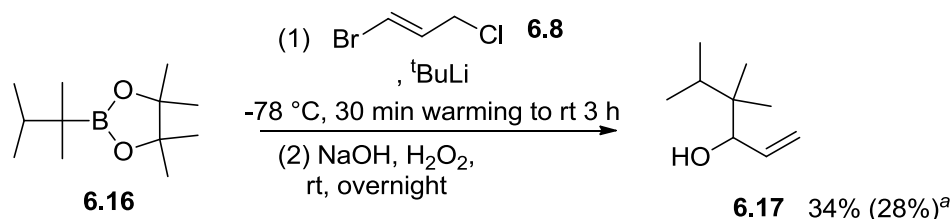
a Yield in parentheses is of isolated product, former is by GC analysis.

The reaction was repeated in order to get a GC yield, and analysis of the organic layer showed a yield of 34%. In an attempt to increase the yield of migrated product, it was decided to produce two less hindered thexylboronic esters.

Boronic esters **6.12** and **6.18** were freshly prepared as in Chapter 4 (Scheme 6.17, where they were numbered boronic esters **4.2** and **4.5**). Boronic ester **6.12** was used directly, while boronic ester **6.18** was purified by column chromatography (38% isolated yield). The reaction was repeated for both boronic esters, and the organic layers analysed by GC. Boronic ester **6.12** gave a 36% yield of **6.17**, while a near quantitative (99%) yield was observed when using boronic ester **6.18**.

**Scheme 6.17 Synthesis of boronic esters 6.12 and 6.18**

The yield of migrated product **6.17** observed with boronic ester **6.12**, while slightly higher than that observed with boronic ester **6.16** was lower than expected. A possible reason for this low yield might have been that the boronic ester **6.12** was now too unhindered – *i.e.* the process that was limiting the yield in the optimisation reactions (Table 6.3) was now at work - in fact the yield was similar to that observed for boronic ester **6.14** (entry 2, Table 6.3).

The yield of migrated product **6.17** when using boronic ester **6.18**, however, was very encouraging. It seemed that this boronic ester was in the 'Goldilocks' zone, neither too

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hindered as to effect incomplete capture of 1-lithio-3-chloroprop-1-ene (**6.9**), nor too unhindered to allow the organolithium to add directly (or possibly to transfer hydride). This result compares favourably with the migration of the thexyl alkyl group discussed in Chapter 4.

It was decided to move on to a yet more hindered *tert*-alkyl group, so boronic ester **6.19** was produced as in Chapter 4 (where it was numbered boronic ester **4.24**) and was purified by column chromatography. The boronic ester was subjected to the usual reaction conditions (entry 6, Table 6.3), and the ^{1}H NMR spectrum of the crude mixture following work-up showed the presence of the expected migrated product **6.20** (as seen by the distinctive signals in the alkenyl region for a terminal alkene). The migrated product was purified by column chromatography to give 4,4-diethylhex-1-en-3ol (**6.20**) in 17% isolated yield (Scheme 6.18). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.35c).[19] The GC response factor was calculated, and analysis of the organic phase of a repeat reaction showed a 25% yield of **6.20** (Scheme 6.18).

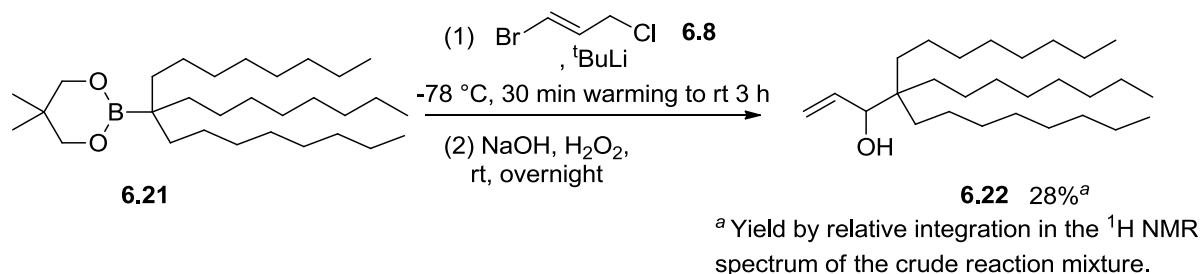**Scheme 6.18 Reaction of boronic ester 6.19 with 1-lithio-3-chloroprop-1-ene (6.9)**
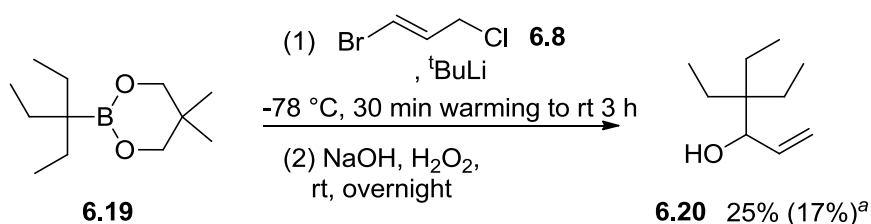
a GC yield, isolated in parentheses.

The low yield of 4,4-diethylhex-1-en-3ol (**6.20**) is an indicator that, just as was the case for the homologation reaction using dibromomethane (Chapter 4), the yield is limited by incomplete capture of the anion due to the steric hindrance around the boron atom. In an attempt to help matters, the reaction was repeated using a threefold excess of *tert*-BuLi and 1-bromo-3-chloroprop-1-ene (**6.8**). GC analysis of the organic layer for this reaction showed a small improvement in the yield of **6.20** (31%). An aliquot was taken from the same reaction mixture prior to the oxidation step for ^{11}B NMR analysis, and showed only a single peak (in the boronic ester region), which suggests that multiple sequential additions (as in Chapter 4) would probably improve the yield of **6.20** yet further.

Moving on to a yet more hindered system, boronic ester **6.21** was prepared as in Chapter 4 and was reacted with 1-lithio-3-chloroprop-1-ene (**6.9**). The ^{1}H NMR spectrum following

work-up showed a 28% yield of the novel migrated product **6.22** (estimated by relative integrations of the migrated product and tri-*n*-octylmethanol) (Scheme 6.19). The product **6.22** could not be separated from tri-*n*-octylmethanol due to their very close behaviour on silica, although the signals seen in the crude ^{1}H and ^{13}C spectra were consistent with the proposed structure.

Scheme 6.19 Reaction of boronic ester 6.21 with 1–lithio-3-chloroprop-1-ene (6.9)

6.21

(1) Br ⟍═⟋ Cl **6.8**
, ^{t}BuLi

-78 °C, 30 min warming to rt 3 h

(2) NaOH, H$_2$O$_2$,
rt, overnight

6.22 28%^{a}

^{a} Yield by relative integration in the ^{1}H NMR spectrum of the crude reaction mixture.

The observed yield of migrated product was in fact slightly better than with boronic ester **6.19**, showing that there wasn't a great deal of difference in the behaviour of the two boronic esters, despite differences in the expected degree of hindrance around boron.

A further two hindered boronic esters were prepared: tricyclopentylmethylboronic ethylene glycol ester **6.23** (Scheme 6.21) (produced in the same manner as mentioned in Chapter 4, where it was numbered boronic ester **4.29**), and the novel boronic ester (*E*)-2-(1,1-dicyclohexyl-3-phenylallyl)-5,5-dimethyl-1,3,2-dioxaborinane (**6.24**) (Scheme 6.20). Boronic ester **6.24** was produced from the dihydroboration of cyclohexene, followed by the hydroboration of phenylacetylene, DCME reaction, and finally reaction with 2,2-dimethyl-1,3-propanediol. The boronic ester was isolated in 20% yield, and was fully characterised with the data in accordance with the proposed structure (E.S. 6.34c). X-Ray analysis further confirmed the structure of **6.24** (Figure 6.1)

Scheme 6.20 Synthesis of boronic ester 6.24

BH$_3$·SMe$_2$

(1) cyclohexene (2 eq)
(2) phenylacetylene

(3) DCME, LiOC(Et)$_3$
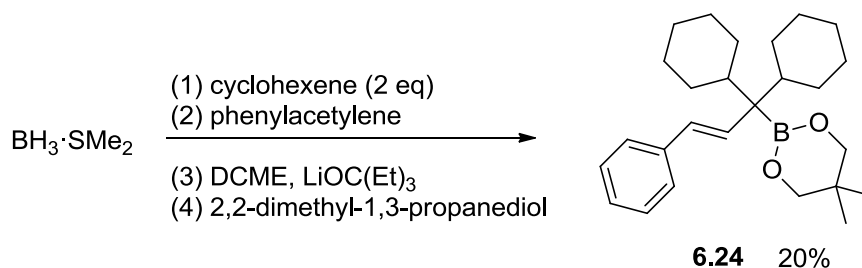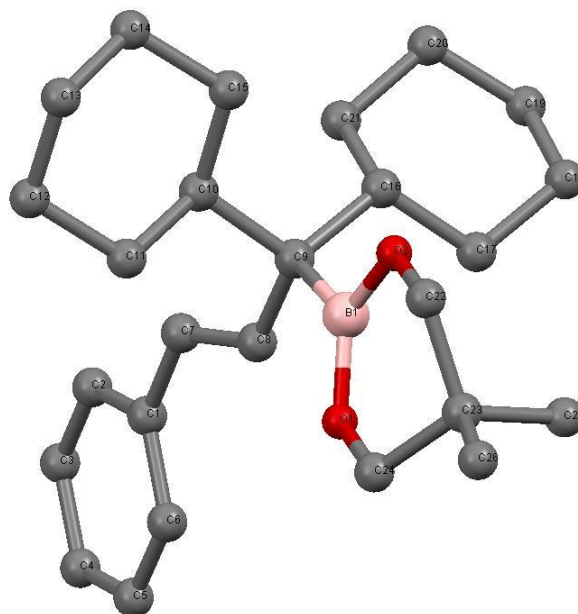(4) 2,2-dimethyl-1,3-propanediol

6.24 20%

Figure 6.1 X-ray structure of boronic ester 6.24

Boronic esters **6.23** and **6.24** were reacted with 1-lithio-3-chloroprop-1-ene (**6.9**), and in both cases none of the expected migration products was seen in the ¹H NMR spectrum of the crude product mixtures; only the corresponding alcohols formed by the direct oxidation of **6.23** and **6.24** (Scheme 6.21). The novel alcohol from the oxidation of boronic ester **6.24** ((*E*)-1,1-dicyclohexyl-3-phenylprop-2-en-1-ol, **6.25**) was purified by column chromatography and fully characterised, with the data in accordance with the proposed structure (Scheme 6.21a, E.S. 6.35d). A small amount of an unknown compound possessing what seemed like alkenyl protons was isolated by column chromatography when purifying **6.25**, but did not correspond to any of the expected migration products.

The fact that these two boronic esters do not take part in the reaction was not a surprise, as they are highly hindered. The cause of the lack of reaction is very likely to be decomposition of 1-lithio-3-chloroprop-1-ene (**6.9**) as a result of the boronic esters being poor trapping reagents due to the steric hindrance around the boron atom. These results are consistent with what was seen in Chapter 4 with (bromomethyl)lithium – *i.e.* there is a point at which the boronic ester is too hindered to trap the anion. The best results for the migration of all the tertiary alkyl groups are summarised in Table 6.4, and show the general trend in this reaction.

Scheme 6.21 Reaction of boronic esters 6.23 and 6.24 with 1-lithio-3-chloroprop-1-ene (6.9)
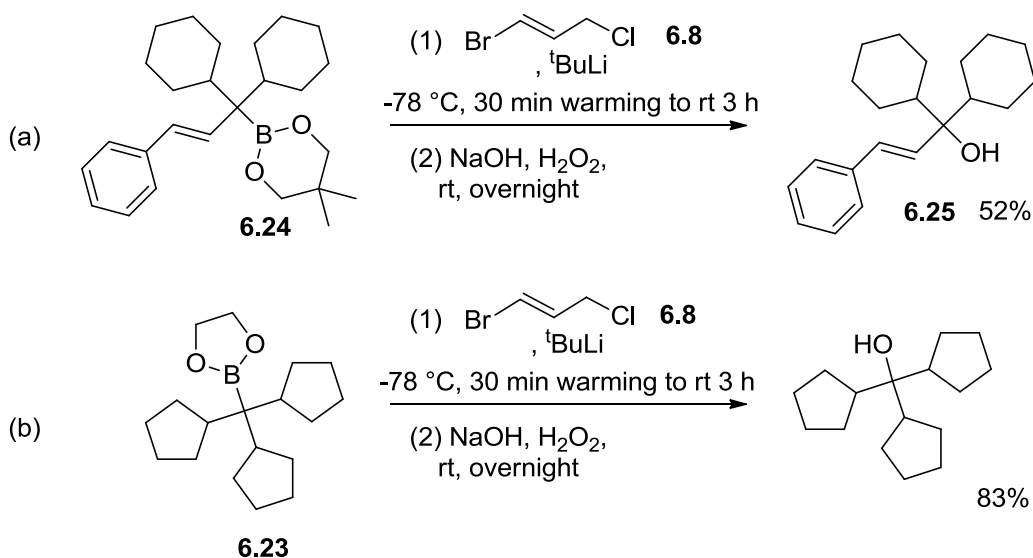
Table 6.4 Reaction of *tert*-alkylboronic esters with 1-lithio-3-chloroprop-1-ene (6.9)

Boronic ester	Migrating *tert*-alkyl group	Yield (%)[a]
6.3	*tert*-butyl	93 (**6.7**)
6.16	*tert*-butyl	98 (**6.7**)
6.18	thexyl	99 (**6.17**)
6.19	triethylmethyl	31[b] (**6.20**)
6.21	tri-(*n*-octyl)methyl	28[c] (**6.21**)
6.24	(1,1-dicyclohexyl)-3-phenylallyl	0
6.23	tricyclopentylmethyl	0

[a] Yields by GC analysis using internal standard (tetradecane), [b] 3 eq of *tert*-BuLi/1-bromo-3-chloroprop-1-ene (**6.8**) used, [c] Yield by relative integrations in the ^{1}H NMR of the crude product.

Although the primary focus of the research contained within this thesis is the synthesis of quaternary carbon centres, it was decided to explore the migration of primary and secondary alkyl groups using the inverse process already established for tertiary alkyl groups. Having the migrating alkyl group present in the starting boronic ester broadens the scope of the reaction compared to the existing method involving addition of an organometallic reagent to

3-chloroprop1-enylboronic esters, and so several primary and secondary boronic esters were synthesised and tested to see whether the reaction would proceed to give a high yield of a single migration product in less hindered systems.

6.25 Synthesis and reactions of primary-alkyl boronic esters with 1-lithio-3-chloroprop-1-ene (6.9)

Boronic ester **6.26** was prepared from *n*-butylboronic acid and 2,2-dimethyl-1,3-propanediol, and was isolated in 76% yield (Scheme 6.22). The boronic ester was fully characterised, with the data in accordance with the literature values (E.S. 6.36a).[20]

Scheme 6.22 Synthesis of boronic ester 6.26
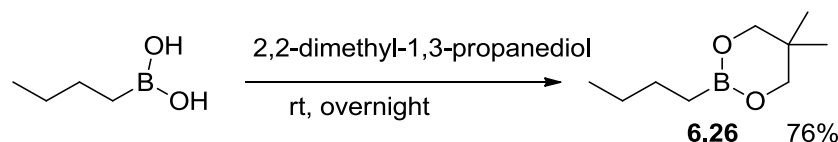
Boronic ester **6.26** was reacted with *tert*-BuLi and 1-bromo-3-chloroprop-1-ene (**6.8**) as described in Section 6.24. The ^{1}H NMR spectrum of the crude product mixture showed the presence of three migration products (Scheme 6.23): hept-1-en-3-ol (**6.27**) from no allylic rearrangement and (*E/Z*)- hept-2-en-1-ol (**6.28**, **6.29**) as a result of allylic rearrangement ((E/Z ratio for **6.28**, **6.29** was 22:78 respectively by relative integrations in the ^{1}H NMR spectrum). The reaction products were purified by column chromatography to give (*E/Z*)-hept-2-en-1-ol (**6.28**, **6.29**, 12% isolated yield) and a trace amount of hept-1-en-3-ol (**6.27**). (*E/Z*)-Hept-2-en-1-ol (**6.28**, **6.29**) was fully characterised, with the data in accordance with the literature values (E.S. 6.37a).[21]

Scheme 6.23 Reaction between boronic ester 6.26 and 1-lithio-3-chloroprop-1-ene (6.9)
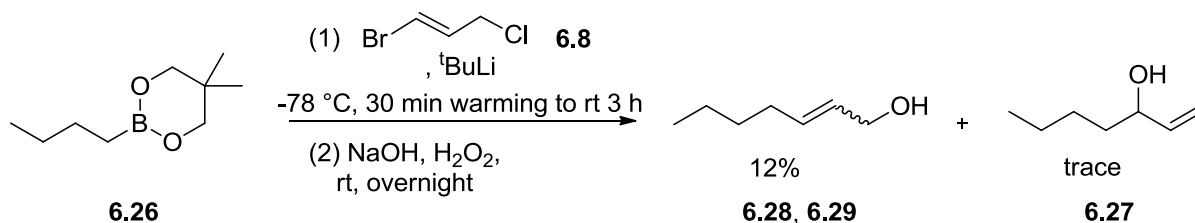

This result was disappointing both in terms of the yield of migrated products, and the fact that the reaction did not proceed to give a single migration product, as seen in all of the *tert*-alkyl boronic esters reported in Section 6.24. The low yield can be tentatively attributed to *tert*-

BuLi adding directly (or transferring hydride) to the starting boronic ester **6.26**, while the mixture of products is almost certainly due to the fact that the allylic intermediate following migration is less hindered – thereby facilitating the allylic rearrangement seen in previous work.[4]

As not enough hept-1-en-3-ol (**6.27**) was isolated from the reaction product mixture to allow a GC response factor to be determined for GC analysis of future reactions, it was decided to synthesise a clean sample by the literature procedure.[22] Valeraldehyde was reacted with vinylmagnesium bromide to give pure racemic **6.27** in 55% isolated yield (Scheme 6.24). The product was fully characterised, with the data in accordance with the literature values (E.S. 6.311a), and the GC response factor was calculated.[23]

Scheme 6.24 Synthesis of racemic hept-1-en-3-ol (6.27)
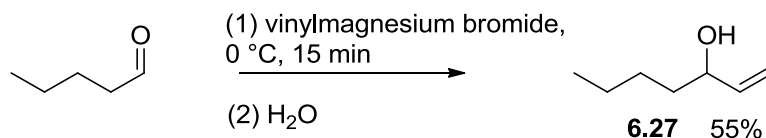
We reasoned that using a more hindered boronic ester might dissuade the possible direct addition/hydride transfer of the *tert*-BuLi, while also stopping the allylic rearrangement. To test this hypothesis, boronic ester **6.30** was synthesised from *n*-butylboronic acid and pinacol in 73% isolated yield (Scheme 6.25). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.36b).[24]

Scheme 6.25 Synthesis of boronic ester 6.30
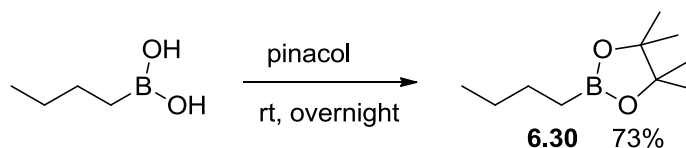
The reaction between boronic ester **6.30**, 1-bromo-3-chloroprop-1-ene (**6.8**) and *tert*-BuLi was carried out, and an aliquot taken from the organic layer for GC analysis. The GC trace showed a 90% yield of racemic hept-1-en-3-ol (**6.27**), with no presence of (*E/Z*)-hept-2-en-1-ol (**6.28**, **6.29**). The ^{1}H NMR spectrum of the crude product confirmed the presence of only **6.27**, along with pinacol and tetradecane (internal GC standard).

This was an encouraging result – showing that even unhindered alkyl groups (in this case *n*-butyl) could migrate efficiently in the inverse reaction to give an excellent yield of only one

migration product. This result highlights the apparent importance of the steric hindrance around boron associated with this reaction – switching from boronic ester **6.26** derived from 2,2-dimethyl-1,3-propanediol to a pinacol boronic ester **6.30** completely changed the nature of the reaction.

Following this result, it was decided to test two more primary boronic esters (boronic esters **6.31** and **6.32**), in order to see whether benzyl alkyl groups would migrate efficiently and whether the reaction was tolerant of an ether functionality. Both boronic esters were commercially available, and were used without further purification.

Boronic ester **6.31** was reacted with 1-bromo-3-chloroprop-1-ene (**6.8**)/*tert*-BuLi in the usual manner, and a small aliquot of the organic layer was taken for subsequent GC analysis while the rest was taken through the normal work-up procedure. The ^{1}H NMR spectrum of the crude reaction product showed the presence of 1-phenylbut-3-en-2-ol (**6.33**) and benzyl alcohol (77% yield of **6.33** by relative integrations in the ^{1}H NMR spectrum), along with tetradecane (internal GC standard) and pinacol. The product was purified by column chromatography on silica to give pure racemic **6.33** in 52% isolated yield (Scheme 6.26). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.37c).[25] The GC response factor was calculated, and analysis of the aliquot taken prior to work-up showed a 75% yield of **6.33** by GC analysis.

**Scheme 6.26 Reaction of boronic ester 6.31 with 1-lithio-3-chloroprop-1-ene (6.9)**
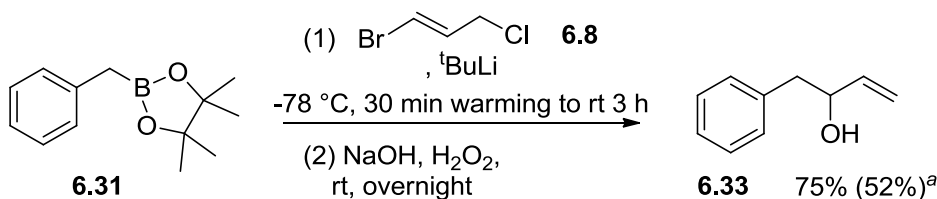
^{a} GC yield, isolated yield in parentheses.

Although the yield of migrated product was lower than when using boronic ester **6.30**, this result showed that there was no problem with the migration of a benzyl alkyl group in this reaction. The drop in yield relative to boronic ester **6.30** may simply have been due to experimental error; some moisture in the solvent or lower than estimated strength of *tert*-BuLi.

Boronic ester **6.32** was taken through the same procedure, and the migration product was purified by column chromatography to give pure racemic 4-methoxyphenylbut-3-en-2-ol (**6.34**) in 52% isolated yield (Scheme 6.27). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.37d).[26] The GC response factor was calculated, and the aliquot taken prior to work-up showed an 84% yield of **6.34** by GC analysis.

Scheme 6.27 Reaction of boronic ester 6.32 with 1-lithio-3-chloroprop-1-ene (6.9)
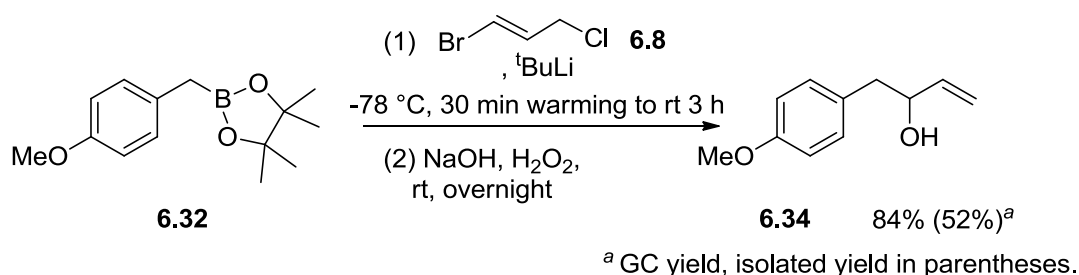
This result again showed that primary alkyl groups (including benzyl alkyl groups) migrate to give only one migration product in good yields, and also showed that the reaction is tolerant of an ether functionality.

6.26 Synthesis and reactions of secondary-alkylboronic esters with 1-lithio-3-chloroprop-1-ene (6.9)

Having demonstrated that the reaction works well for primary alkyl groups (including benzyl alkyl groups), it was decided to check to make sure that the reaction went smoothly for secondary alkyl groups.

Isopropylboronic ester **6.35** was synthesised as in Chapter 4 (when it was numbered boronic ester **4.35**) from isopropylboronic acid and pinacol, and was isolated in 36% yield (Scheme 6.29).

Scheme 6.29 Synthesis of boronic ester 6.35
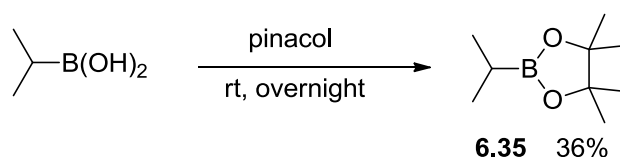
Foreseeing that isolation of the expected migration product of boronic ester **6.35**, 4-methylpent-1-en-3-ol (**6.36**) on a small scale could be problematic due to its volatility, it was

decided to produce a clean sample for GC analysis by the literature procedure from isobutyraldehyde and vinylmagnesium bromide.[22] Racemic 4-methylpent-1-en-3-ol (**6.36**) was isolated without need for further purification in 85% yield (Scheme 6.30). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.311b).[22]

**Scheme 6.30 Synthesis of 4-methylpent-1-en-3-ol (6.36)**
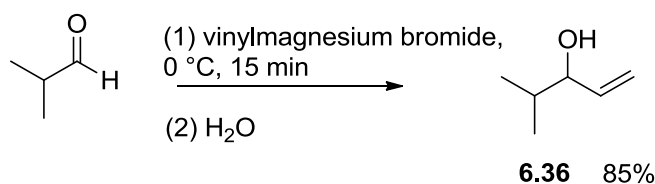
Having calculated the GC response factor of **6.36**, the reaction between boronic ester **6.35** and 1-bromo-3-chloroprop-1-ene (**6.8**)/*tert*-BuLi was completed as for previous examples. GC analysis of the organic layer showed a 94% yield of **6.36** (Scheme 6.31). The ^{1}H NMR spectrum of the crude reaction product showed the presence of only **6.36**, tetradecane (GC internal standard), pinacol and residual THF.

Scheme 6.31 Reaction between boronic ester 6.35 and 1-lithio-3-chloroprop-1-ene (6.9)
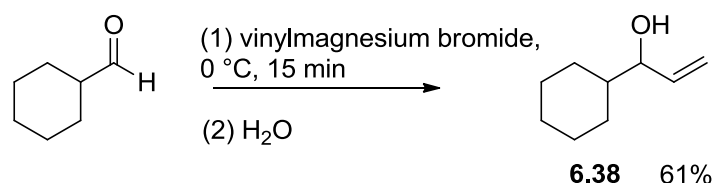

^{a} Yield by GC analysis
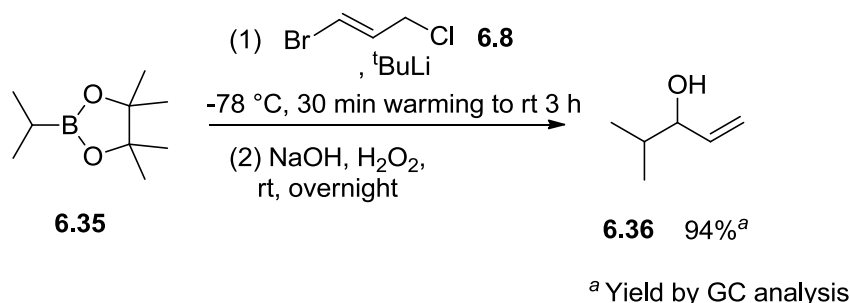
Following this good result, it was decided to check whether cyclic secondary alkyl groups migrate in the same manner. Boronic ester **6.37** was synthesised from cyclohexylboronic acid and pinacol, and was isolated in 32% yield (Scheme 6.32). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.38c).[24]

Scheme 6.32 Synthesis of boronic ester 6.37
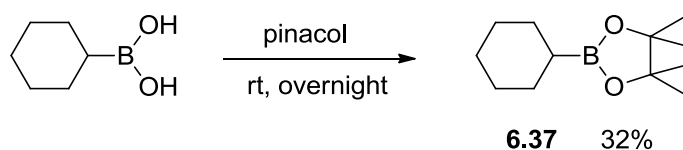
To avoid having to isolate 1-cyclohexylprop-2-en-1-ol (**6.38**) on a small scale, it was decided to synthesise a sample by the literature procedure from cyclohexanecarboxaldehyde and vinylmagnesium bromide.[22] Racemic 1-cyclohexylprop-2-en-1-ol (**6.38**) was isolated in 61% yield, and was fully characterised, with the data in accordance with the literature values (Scheme 6.33, E.S. 6.311c).[27] Its GC response factor with respect to tetradecane was then calculated.

Scheme 6.33 Synthesis of racemic 1-cyclohexylprop-2-en-1-ol (6.38)

The reaction between boronic ester **6.37** and 1-bromo-3-choroprop-1-ene (**6.8**)/*tert*-BuLi was completed, and GC analysis of the organic layer showed an 83% yield of **6.38** (Scheme 6.34). The ^{1}H NMR spectrum of the crude product following work-up showed the presence of **6.38**, tetradecane (GC internal standard) and pinacol, indicating that the reaction had proceeded cleanly.

This was another strong result, showing that the reaction works well for cyclic secondary alkyl groups.

Scheme 6.34 Reaction of boronic ester 6.37 with 1-lithio-3-chloroprop-1-ene (6.9)
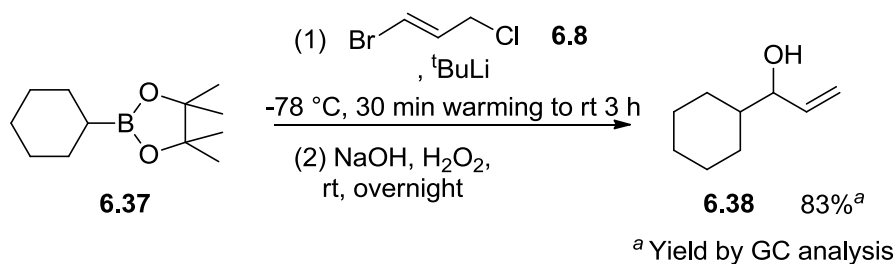
It was decided to test the reaction with a more hindered secondary alkyl group, and so the novel boronic ester **6.39** was synthesised from the reaction of so-called DIB-borane[28] (prepared from the monohydroboration of 2,4,4-trimethyl-2-pentene by $BH_3 \cdot SMe_2$) and 2,2-dimethyl-1,3-propanediol (Scheme 6.35). 2,2-Dimethyl-1,3-propanediol was used as the diol component as the DIB alkyl group has been shown to be a very hindered alkyl group.[28] Racemic boronic ester **6.39** was purified by column chromatography, and was isolated in

48% yield. The compound was fully characterised (including HRMS), with the data in accordance with the proposed structure (E.S. 6.38a).

Scheme 6.35 Synthesis of boronic ester 6.39
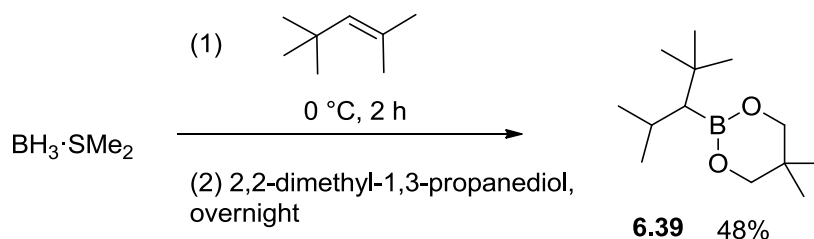
Boronic ester **6.39** was reacted with 1-bromo-3-chloroprop-1-ene (**6.8**)/*tert*-BuLi as with previous examples. However the ^{1}H NMR spectrum of the crude reaction product showed only the presence of pinacol and 2,2,4-trimethylpentan-3-ol (**6.40**) from oxidation of the starting material (Scheme 6.36). The alcohol was purified by column chromatography and was isolated in 17% yield (Scheme 6.35). 2,2,4-Trimethylpentan-3-ol (**6.40**) was fully characterised, with the data in accordance with the proposed structure (E.S. 6.39a).

Scheme 6.36 Reaction of boronic ester 6.39 with 1-lithio-3-chloroprop-1-ene (6.9)
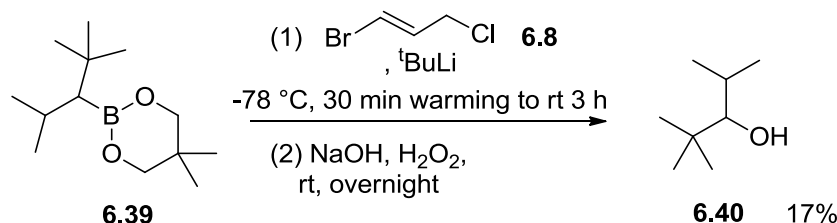

Although disappointing, this result demonstrated how hindered boronic ester **6.39** must be. The low yield of the alcohol **6.40** is likely to be as a result of incomplete oxidation of the boronic ester **6.39** (the boronic ester was left to stir at room temperature overnight, while even DIB-borane itself was oxidised by being heated to 50°C for 2 hours in the literature[28]), and again hints at the highly hindered nature of this boronic ester.

6.27 Synthesis and reactions of unsaturated alkylboronic esters with 1-lithio-3-chloroprop-1-ene (6.9)

In order to learn whether alkenyl alkyl groups would migrate as successfully as primary, secondary and tertiary alkyl groups, it was decided to produce and test the reactivity of a representative alkenylboronic ester. To this end, (*E*)-styrylboronic acid pinacol ester (**6.41**)

was prepared from (*E*)-styrylboronic acid and pinacol. The ^{1}H NMR of the crude product showed some impurities, and so the product was purified by column chromatography to give pure **6.41** in 73% isolated yield (Scheme 6.28). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.310c).[29]
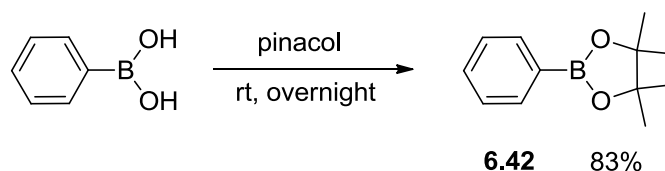
Scheme 6.28 Synthesis of boronic ester 6.41
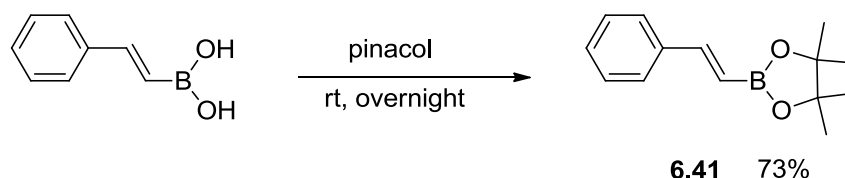
Boronic ester **6.41** was reacted with 1-bromo-3-chloroprop-1-ene (**6.8**)/*tert*-BuLi as in previous examples. The ^{1}H NMR of the crude product however, did not seem to have any of the expected migration products even though aromatic protons were present. Attempts were made to purify the unknown compound by column chromatography on silica; however it seemed that decomposition had occurred, with the ^{1}H NMR spectrum of the major column fractions showing a complex mixture of products displaying both aromatic and alkenyl protons. The GC trace of an aliquot taken prior to work-up also showed multiple species, showing that the reaction was not as clean as it had been with simple alkyl groups (Sections 6.24 – 6.26). No further attempts were made using boronic ester **6.41**.

The final boronic ester to be studied was boronic ester **6.42**. The boronic ester was synthesised from phenylboronic acid and pinacol, and was isolated in 83% yield (Scheme 6.37). The compound was fully characterised, with the data in accordance with the literature values (E.S. 6.310a).[30]

**Scheme 6.37 Synthesis of boronic ester 6.42**

Boronic ester **6.42** was reacted with 1-bromo-3-chloroprop-1-ene (**6.8**)/*tert*-BuLi as for previous examples. The ^{1}H NMR spectrum of the crude reaction product did not seem to correspond to any of the expected migrated products. Attempts were made to purify the unknown component by column chromatography; however it was evident that decomposition

had occurred, with the column fractions containing multiple species just as for boronic ester **6.41**. A GC trace of an aliquot taken prior to work-up also showed the presence of several species.

In case the issue was the steric hindrance around the boron atom of the boronic ester **6.42**, boronic ester **6.43** was synthesised from phenylboronic acid and 2,2-dimethyl-1,3-propanediol. The compound was purified by column chromatography to give the boronic ester in 55% isolated yield (Scheme 6.38). Boronic ester **6.43** was fully characterised, with the data in accordance with the literature values (E.S. 6.310b).[31]

Scheme 6.38 Synthesis of boronic ester 6.43
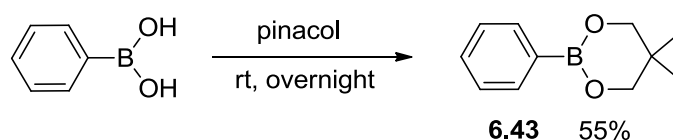
The reaction of boronic ester **6.43** with 1-bromo-3-chloroprop-1-ene (**6.8**)/*tert*-BuLi was carried out. However, the ^{1}H NMR spectrum of the crude reaction product was the same as for the reaction using boronic ester **6.43**. An attempt was made to wash the 2,2-dimethyl-1,3-propanediol out through dissolving the product mixture in diethyl ether and washing several times with water to leave only the unknown compound; however, the ^{1}H NMR spectrum following the washing showed that the unknown compound had decomposed in a similar manner as was seen when attempting to purify the compound by column chromatography in the previous reaction using boronic ester **6.43**.

There must be an issue when using alkenyl or phenyl groups in the reaction; perhaps the *tert*-BuLi or 1-lithio-3-chloroprop-1-ene (**6.9**) reacts with the unsaturated functionality instead of taking their usual roles in the reaction, or the desired migrated product decomposes when exposed to the oxidation or work-up conditions. Whatever the precise reason, the reaction does not appear to follow the same course as with alkylboronic esters, and the products cannot easily be isolated. No further work was conducted with these unsaturated systems.

Despite the disappointing results using the alkenyl and phenyl boronic esters, the results contained in Sections 6.25 and 6.26 are very encouraging – showing the reaction can be applied to both primary and secondary boronic esters, giving good to excellent yields of a single migration product (summarised in Table 6.5). These results significantly broaden the scope of the reaction compared to previously published results.
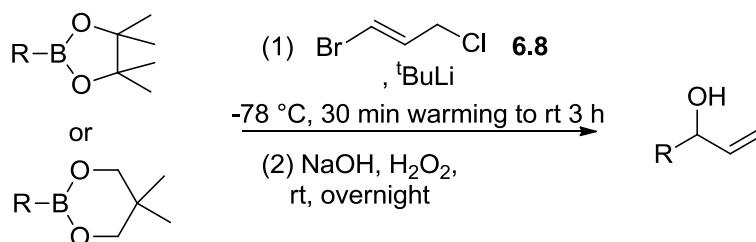
Table 6.5 Reaction of non-tertiary -alkylboronic esters with 1-lithio-3-chloroprop-1-ene (6.9)

Boronic ester	migrating group (R)	Yield (%)^a
6.30	*n*-Bu	90 (**6.27**)
6.31	Bn	75 (52, **6.33**)
6.32	(4-MeO)Bn	84 (52, **6.34**)
6.41	(*E*)-styryl	0^b
6.35	*i*Pr	94 (**6.36**)
6.37	Ch^c	83 (**6.38**)
6.39	DIB^d	0
6.42, 6.43	Ph	0^b

^{a} Yield by GC analysis using an internal standard (tetradecane), isolated yields in parentheses, ^{b} no sign of expected migration products; unknown compounds decomposed when attempts at purification were made, ^{c} cyclohexyl, ^{d} 2-diisobutyl.

6.3 Experimental Section

6.31 Investigative reactions using 3-chloroprop-1-enyl pinacol boronic ester (6.3)
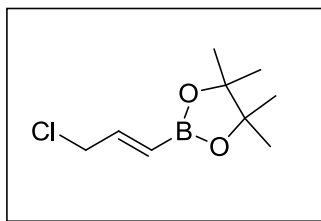
6.31a Synthesis of 3-chloroprop-1-enylboronic acid pinacol ester (6.3). Borane dimethyl sulfide complex (10 M, 0.2 mL, 2.0 mmol) was added to a dry 25 mL round bottomed flask equipped with a magnetic stirrer bar and septum under N_2. The solution was cooled in an ice bath, and cyclohexene (0.41 mL, 4.0 mmol) was added drop-wise with stirring. The reaction mixture was stirred for a further 2 h at 0 ℃ to give a white precipitate, dicyclohexylborane, which was stored under N_2 until needed. Borane dimethyl sulfide complex (10 M, 2.00 mL, 20.0 mmol) was added to a separate 50 mL round bottomed flask under N_2, and cooled in an ice bath. To this was added a solution of pinacol (2.60 g, 22.0 mmol) in dry DCM (2 mL) drop-wise. The reaction mixture was stirred for 1 h at 0 ℃, and 1 h at rt. The mixture was cooled again to 0 ℃, and propargyl chloride (1.45 mL, 20 mmol) was added drop-wise, along with the previously prepared dicyclohexylborane (2.0 mmol) in dry DCM (2 mL). The cooling bath was removed, and the reaction mixture was left to stir for 4 h at rt. A needle was then inserted through the septum to allow air into the reaction, and the mixture was left to stir overnight. The crude product was diluted with petroleum ether (5 mL), and was purified by column chromatography on silica (9:1 petroleum ether: ethyl acetate) to give pure 3-chloroprop-1-enylboronic acid pinacol ester[7] (**6.3**) as a colourless oil (2.05 g, 49%); δ^1H (400 MHz; CDCl$_3$): 6.58 (1H, dt, J = 17.6, 6.1 Hz, CH), 5.68 (1H, d, J = 17.6 Hz, CH), 4.03 (2H, dd, J = 6.1, 1.4 Hz, CH$_2$), 1.20 (12H, s, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *CH next to boron not seen;* 146.6 (CH), 83.5 (quat C, *C*OCH$_3$), 46.0 (CH$_2$), 24.8 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 28.5; LR - EI$^+$ MS m/z (%): *molecular ion/characteristic fragments not seen*; v_{max} (neat/cm^{-1}): 2979, 2929, 2853, 1642, 1358, 1329, 1144; Rf = 0.14 in 9:1 petroleum ether: ethyl acetate.

6.31b Test reaction of 3-chloroprop-1-enylboronic acid pinacol ester with *n*-BuLi. An oven dried 50 mL round bottomed flask equipped with a magnetic stirrer bar and septum was flushed with N_2 for 10 min. 3-Chloroprop-1-enylboronic acid pinacol ester (0.198 g, 0.98

mmol) and dry THF (5 mL) were added and the solution cooled to -78 ºC. *n*-BuLi in hexanes (1.6 M, 0.64 mL, 1.02 mmol) was added drop-wise with vigorous stirring of the reaction mixture. The reaction mixture was stirred for an additional 30 min, and propanal (0.09 mL, 1.27 mmol) was added drop-wise. The reaction mixture was stirred for 15 min before removing the cooling bath, and allowing the reaction mixture to warm to rt over 30 min. The reaction was oxidised and worked - up as in procedure 5.1a to give a colourless oil (0.142 g), consisting of pinacol and a mixture of *cis/trans* isomers of dec-5-en-3-ol (**6.4**, **6.5**; identified by ^{1}H/^{13}C NMR analysis). The products were not purified further.

6.31c Test reaction of 3-chloroprop-1-enylboronic acid pinacol ester with *n*-BuMgCl.
Procedure 6.31b was repeated, except using *n*-butylMgCl in THF (2.0 M, 0.51 mL, 1.02 mmol) instead of *n*-BuLi, to give a colourless oil (0.074 g), consisting of pinacol and all three possible migration product isomers (*cis/trans* isomers of dec-5-en-3-ol (**6.4**, **6.5**) and 4-vinyloctan-3-ol (**6.6**) in a 70:30 ratio respectively by relative integrations in the ^{1}H NMR). The products were not purified further.

6.31d Test reaction of 3-chloroprop-1-enylboronic acid pinacol ester with *tert*-BuLi.
Procedure 6.31b was repeated, using 3-chloroprop-1-enylboronic acid pinacol ester (0.52 g, 2.59 mmol), dry THF (10 mL), *tert*-BuLi (1.9 M, 1.5 mL, 2.85 mmol) and propanal (0.25 mL, 3.49 mmol) to give a colourless oil (0.33 g), consisting of pinacol and 4,4-dimethylpent-1-en-3-ol (**6.7**, identified by ^{1}H NMR spectroscopy).

6.31e Test reaction of 3-chloroprop-1-enylboronic pinacol ester with *tert*-BuMgCl.
Procedure 6.31b was repeated, using 3-chloroprop-1-enylboronic pinacol ester (0.54 g, 2.65 mmol), dry THF (10 mL), *tert*-BuMgCl (1.7 M, 1.71 mL, 2.91 mmol) and propanal (0.25 mL, 3.49 mmol) to give a colourless oil (0.48 g), consisting of pinacol and 4,4-dimethylpent-1-en-3-ol (**6.7**, identified by ^{1}H NMR analysis - see Section 6.31g).

**6.31f Test reaction of 3-chloroprop-1-enylboronic acid pinacol ester with *tert*-BuLi, longer time with propanal.** Procedure 6.31d was repeated, except the reaction was left to stir overnight after the addition of propanal. The reaction was worked up in the same manner to give a colourless oil (0.37 g), consisting of pinacol and 4,4-dimethylpent-1-en-3-ol (**6.7**, identified by ^{1}H NMR analysis - see Section 6.31g).

6.31g Synthesis of 4,4-dimethylpent-1-en-3-ol (6.7).
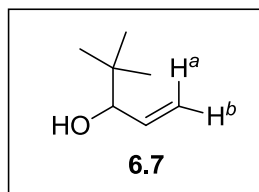
6.7

A dry 50 mL round bottomed flask equipped with a magnetic stirrer bar and septum was flushed with N_2 for 10 min. Pivaldehyde (1.09 mL, 10.0 mmol) and dry THF (10 mL) were added, and the solution cooled to -78 ℃. Vinylmagnesiumbromide solution (0.7 M in THF, 15 mL, 10.5 mmol) was added drop-wise, and the mixture was allowed to stir for 30 min following the completion of addition. The cooling bath was then removed, and the reaction mixture allowed to warm to rt over 3.5 h. Distilled water (10 mL) was added, the organic layer separated and the aqueous layer extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with distilled water (2 × 20 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give pure 4,4-dimethylpent-1-en-3-ol[8] (**6.7**) as a light yellow liquid (1.00 g, 88%); δ^1H (500 MHz; CDCl$_3$): 5.85 (1H, m, alkenyl CH), 5.16 (1H, dd, J = 17.2, 3.0 Hz, CH*a* of CH$_2$), 5.10 (1H, dd, J = 10.5, 2.8 Hz, CH*b* of CH$_2$), 3.68 (1H, d, J = 6.8 Hz, C*H*OH), 1.83 (1H, br s, OH), 0.84 (9H, s, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 138.1 (CH), 116.3 (CH$_2$), 81.2 (CH), 34.7 (quat C), 25.6 (CH$_3$); LR - EI$^+$ MS m/z (%): *molecular ion not seen*; 85 (M$^+$-CH$_3$, OH, 100%); ν_{max} (neat/cm^{-1}): 3435 (br, OH), 3078, 2956, 2907, 2871, 1709 (trace pivaldehyde), 1642, 1480, 1465, 1425, 1364.

6.31h Reaction of 3-chloroprop-1-enylboronic acid pinacol ester with *tert*-BuLi. 3-Chloroprop-1-enylboronic pinacol ester (0.54 g, 2.67 mmol) and dry THF (10 mL) were added to a 50 mL round bottomed flask equipped with a magnetic stirrer bar and septum. The mixture was cooled to -78 ℃, and *tert*-BuLi in hexanes (1.9 M, 1.55 mL, 2.95 mmol) was added very slowly drop-wise with vigorous stirring of the reaction solution. Following the completion of addition, the reaction mixture was stirred for a further 30 min, before removing the cooling bath and allowing the solution to warm to rt over 3 h. Tetradecane (0.3675 g) was added *via* a weighed syringe, and the reaction was oxidised as in procedure 5.1a. Diethyl ether (10 mL) was added to the reaction mixture, along with potassium carbonate (2.5 g) and the solution was stirred for 5 min. An aliquot was taken from the organic layer, and GC analysis showed 4,4-dimethylpent-1-ene-3-ol (**6.7**, 93%).

6.31i Reaction of 3-chloroprop-1-enylboronic acid pinacol ester with *tert*-BuLi, attempt to rearrange the allylic intermediate boron compound (attempt 1).

(1) ᵗBuLi, -78 °C, 30 min
(2) propanal, 15 min
(3) warming to rt over 30 min, reflux, 2 h
(4) NaOH, H₂O₂
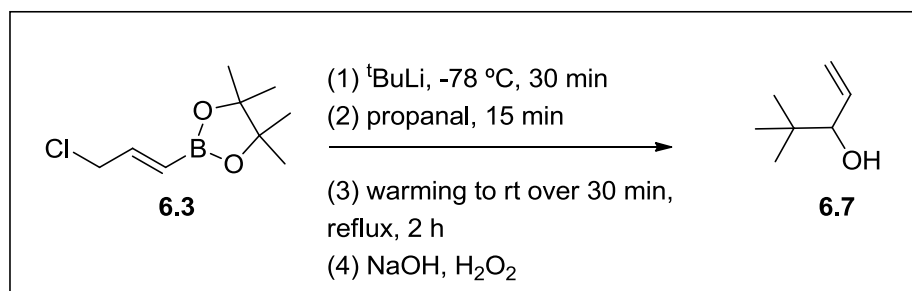
Procedure 6.31h was repeated using 3-chloroprop-1-enylboronic acid pinacol ester (0.446 g, 2.2 mmol), *tert*-BuLi in hexanes (1.9 M, 1.35 mL, 2.57 mmol) and dry THF (10 mL), with the addition of a septum-capped reflux condenser. Prior to the oxidation step, the mixture was refluxed for 2 h, before being cooled to 0 °C and was then oxidised and worked-up as in procedure 6.31h to give a colourless liquid (0.32 g), consisting of pinacol, 4,4-dimethylpent-1-en-3-ol (**6.7**), and residual THF by ^{1}H NMR analysis.

6.31j Reaction of 3-chloroprop-1-enylboronicacid pinacol ester with *tert*-BuLi, attempt to rearrange the allylic intermediate boron compound (attempt 2).
Procedure 6.31i was repeated, using 3-chloroprop-1-enylboronic acid pinacol ester (0.414 g, 2.05 mmol), *tert*-BuLi in hexanes (1.9 M, 1.19 mL, 2.26 mmol), and dry THF (10 mL) except that the mixture prior to oxidation was refluxed overnight to give a colourless liquid (0.233 g), consisting of pinacol and 4,4-dimethylpent-1-en-3-ol (**3.7**) by ^{1}H NMR analysis.

## 6.32 Synthesis and test reaction of 1-bromo-3-chloroprop-1-ene (6.8)

### 6.32a Synthesis of (*E*)-3-bromoacrylic acid (6.10).
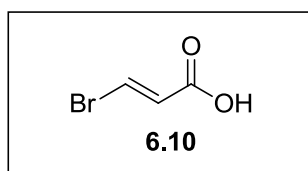
Propiolic acid (8.79 mL, 0.143 mole) and an aqueous solution of HBr (48%, 40 mL, excess) were added to a 250 mL round bottomed flask equipped with a magnetic stirrer bar. The mixture was refluxed at 95 °C for 2.5 h, and then left to cool overnight. The crude product was filtered using a Buchner funnel, and washed with cold distilled water (3 × 25 mL). The

product was transferred to a large clock glass, and left to dry naturally over 2 days to give (*E*)-3-bromoacrylic acid[12] (**6.10**) as colourless needles (13.49 g, 63%); m.p 120–121.5 ℃ (lit.[32] m.p 117.5-118.5 ℃); δ^1H (400 MHz; CDCl$_3$): 10.45 (1H, br s, OH), 7.70 (1H, d, *J* = 13.9 Hz, CHBr), 6.50 (1H, d, *J* = 13.9 Hz, CHC=O); δ^{13}C (100 MHz; CDCl$_3$): 169.6 (quat C), 130.0 (CH), 128.1 (CH); LR - EI$^+$ MS m/z (%): 150 (M$^+$, 93%), 133 (70), 124 (24%), 105 (59), 84 (100), 71 (68%); v_{max} (nujol/cm^{-1}): 3300 (br, OH), 2926, 2727, 2550, 1870, 1809, 1701, 1602, 1456, 1377, 1297.

6.32b Synthesis of (*E*)-3-bromoprop-2-en-3-ol (6.11).

6.11
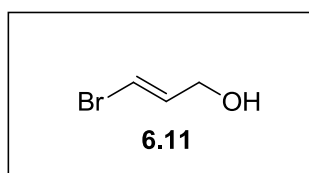
A two necked round bottomed flask, equipped with a magnetic stirrer bar, septum and septum-capped dropping funnel was assembled while hot and flushed with N$_2$ for 10 min. (*E*)-3-Bromoacrylic acid (8.0 g, 53 mmol) was dissolved in dry diethyl ether (40 mL), and transferred *via* syringe to the dropping funnel. Powdered LiAlH$_4$ (4.02 g, 106 mmol) was transferred quickly to the reaction flask, and dry diethyl ether (40 mL) was added carefully. The reaction mixture was cooled in an ice bath, and the solution of 3-bromoacrylic acid was added drop-wise *via* the dropping funnel with vigorous stirring of the reaction mixture. Once the addition was complete, the mixture was left to stir for an additional 2 h. Distilled water (2.5 mL) was added carefully drop-wise, followed by 15% NaOH (aq) solution (5.25 mL) and more distilled water (7.4 mL). The resulting salts were washed with diethyl ether (3 × 50 mL), and the combined extracts dried over sodium sulfate and concentrated under reduced pressure to give fairly pure (*E*)-3-bromoprop-2-en-3-ol[13] (**6.11**) as a yellow liquid (4.16 g, 57%); δ^1H (500 MHz; CDCl$_3$): 6.36 – 6.37 (2H, m, 2 CH), 4.10 (2H, d, *J* = 4.1 Hz, CH$_2$), 2.50 (1H, br s, OH); δ^{13}C (125 MHz; CDCl$_3$): 136.5 (CH, *C*HCH$_2$OH), 107.8 (CH, CHBr), 62.8 (CH$_2$); LR - EI$^+$ MS m/z (%): 137 (M$^+$-1 (^{81}Br), 98%), 135 (M$^+$-1 (^{79}Br), 98%), 87.0 (100), 58 (100); v_{max} (neat/cm^{-1}): 3337 (br, OH), 2926, 2872, 1622, 1454, 1422, 1362, 1279, 1248, 1192, 1082, 1014.

6.32c Synthesis of (*E*)-1-bromo-3-chloroprop-1-ene (6.8).

6.8
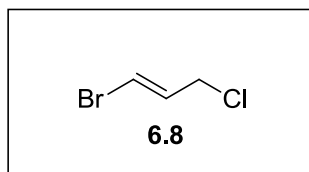
A 50 mL round bottomed flask equipped with a magnetic stirrer bar was charged with (*E*)-3-bromoprop-2-en-3-ol (3.52 g, 25.7 mmol) and cooled using an ice bath. Hexachloroacetone (7.79 mL, 51.4 mmol) was added, and the solution stirred for 5 min. Powdered triphenylphosphine (6.74 g, 25.7 mmol) was added portion-wise carefully over a period of 25 min. The reaction mixture was left to stir for 2 h at 0 °C, before being fractionally distilled under reduced pressure to give 90% pure (*E*)-1-bromo-3-chloroprop-1-ene, which was fractionally distilled a second time to give pure (*E*)-1-bromo-3-chloroprop-1-ene (**6.8**) as a colourless liquid (0.52 g, 13%); δ^1H (500 MHz; CDCl$_3$): 6.49 (1H, d, J = 13.5 Hz, CHBr), 6.37 (1H, m, C*H*CH$_2$Cl), 4.03 (2H, d, J = 7.1 Hz, CH$_2$); δ^{13}C (125 MHz; CDCl$_3$): 133.0 (CH, *C*HCH$_2$Cl), 110.7 (CH, *C*HBr), 43.5 (CH$_2$); LR - EI$^+$ MS m/z (%): 156 (M$^+$+2, 82%), 121 (100), 84 (87), 75 (100); ν_{max} (neat/cm^{-1}): 3010, 2930, 1779 (trace pentachloroacetone), 1102.

6.32d Test reaction of thexylboronic acid ethylene glycol ester with *n*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene. Freshly prepared thexylboronic acid ethylene glycol ester (**6.12**, 0.16 g, 1.0 mmol, prepared according to procedure 4.1a), 1-bromo-3-chloroprop-1-ene (0.16 g, 1.0 mmol) and dry THF (10 mL) were added to a dry 50 mL round bottomed flask equipped with a magnetic stirrer bar and septum. The reaction mixture was cooled to -78 ºC, and *n*-BuLi in hexanes (1.6 M, 0.69 mL, 1.1 mmol) was added drop-wise with vigorous stirring of the reaction mixture, and the mixture was left to stir for an additional 30 min. The cooling bath was removed, and the reaction mixture left to warm to rt over 3 h. The reaction mixture was then oxidised as in procedure 5.1a to give a yellow oil (0.143 g), consisting of thexanol, 1-bromo-3-chloroprop-1-ene, 4,4,5-trimethylhex-1-en-3-ol (**6.17**), *n*-butanol and residual THF. The products were not purified further.

6.33 Synthesis and reactions of *tert*-butylboronic esters

6.33a Synthesis of boronic ester 6.15.

6.15
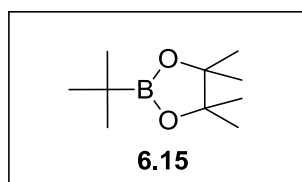
Pinacolborane (20.0 mmol) was prepared from borane dimethyl sulfide complex (10 M, 2.0 mL) and pinacol (2.36 g, 20.0 mmol) in dry DCM (2 mL) according to procedure 6.1a. The reaction mixture was cooled to 0 ℃ using an ice bath, and *tert*-BuMgCl in THF (1.7 M, 11.8 mL, 20.0 mmol) was added drop-wise. The reaction mixture was allowed to warm to rt over an hour, and then cooled back again to 0 ℃ and aqueous HCl (aq) (3 M, 13.5 mL) was added carefully drop-wise. The reaction mixture was left to stir for 15 min at 0 ℃, and then for a further 30 min at rt. The reaction mixture was poured into a separating funnel, and extracted with diethyl ether (3 × 25 mL), the combined organic extracts were washed with water (2 × 15 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (5:1 petroleum ether: ethyl acetate) to give *tert*-butylboronic acid pinacol ester[17] (**6.15**) as a light yellow liquid (1.462 g, 40%); δ^1H (400 MHz; CDCl$_3$): 1.15 (12H, s, CH$_3$), 0.85 (9H, s, *tert*-Bu); δ^{13}C (125 MHz; CDCl$_3$): 82.8 (quat C, COCH$_3$), 26.9 (CH$_3$), 24.6 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 33.9; LR - EI$^+$ MS m/z (%): 184 (M$^+$, 3%), 169 (100), 129 (69), 83 (91); ν_{max} (neat/cm^{-1}): 2979, 2941, 2895, 2863, 1482, 1396, 1372, 1355, 1308, 1175, 1146; Rf = 0.86 in 5:1 petroleum ether: ethyl acetate.

6.33b Synthesis of boronic ester 6.14.
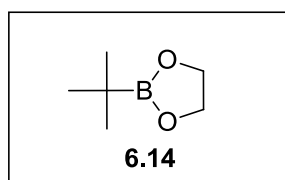
6.14

An oven dried 100 mL round bottomed flask equipped with a magnetic stirrer bar and septum was flushed with N$_2$ for 10 min. Trimethyl borate (8.1 mL, 72 mmol), and dry diethyl ether (20 mL) were added, followed by the drop-wise addition of *tert*-BuMgCl in THF (1.7 M ,14.1 mL, 24 mmol). The reaction mixture was stirred for a further 3 h, and aqueous HCl (2

M, 14 mL) was added carefully drop-wise. The reaction mixture was transferred *via* syringe to a separating funnel equipped with a septum, and already under N_2. Dry diethyl ether (20 mL) was added, and the organic layer was washed with degassed water (3 × 10 mL). The washed organic layer was transferred *via* syringe to a flask under N_2 containing magnesium sulfate (5.0 g), and the solution was swirled for a few min. The mixture was then filtered (using a large upturned funnel to keep an oxygen-free environment), and concentrated under reduced pressure to give a white precipitate, *tert*-butylboronic acid[16] (**6.13**) as a white solid. A small portion was taken for characterisation; m.p. 93-95 °C decomp (lit.[33] m.p 103-105 °C); δ^1H (300 MHz; CDCl$_3$): 0.97 (9H, s, *tert*-Bu); $\delta^{13}C$ (75 MHz; CDCl$_3$): 27.2 (CH$_3$); $^{11}B\{^1H\}$(96.2 MHz; CDCl$_3$): 32.8; v_{max} (thin film/cm^{-1}): 3400 (v.br, OH), 2400, 1216; *a representative MS spectrum could not be obtained due to the compound's instability*. Dry pentane (20 mL) was added, along with ethylene glycol (1.4 mL, 25 mmol), and the reaction was left to stir at rt for 30 min. The mixture was filtered, and the filtrate concentrated under reduced pressure to give boronic ester **6.14** as a colourless liquid[15] (0.98 g, 32%); δ^1H (500 MHz; CDCl$_3$): 4.11 (4H, s, CH$_2$), 0.91 (9H, s, *tert*-Bu); $\delta^{13}C$ (125 MHz; CDCl$_3$): 65.6 (CH$_2$), 27.1 (CH$_3$); $^{11}B\{^1H\}$(96.2 MHz; CDCl$_3$): 34.5; LR - EI$^+$ MS m/z (%): 128 (M$^+$, 12%), 114 (75), 84 (100), 70 (74), 57 (72), *higher mass ions seen*; v_{max} (neat/cm^{-1}): 2943, 2909, 2863, 1482, 1397, 1342, 1262, 1223, 1166.

The reactions in the following Table were completed on boronic esters **6.14** and **6.15** according to procedure 6.32d.
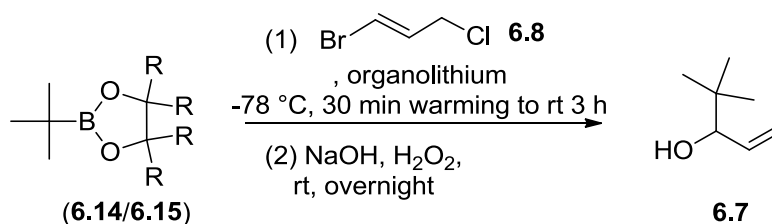

**Table 6.6 Optimisation reactions for the migration of *tert*-butyl alkyl group**

Entry	Boronic ester	R	organolithium	Yield of **6.7** (%)[a]
1	**6.14**	H	*n*-BuLi	9
2	**6.14**	H	*tert*-BuLi	42

3	**6.14**	H	*tert*-BuLi (1.25 eq)	27
4	**6.15**	Me	*n*-BuLi	10
5	**6.15**	Me	*n*-BuLi (*ex-situ*)	0
6	**6.15**	Me	*tert*-BuLi	98
7	**6.15** (excess)	Me	*tert*-BuLi	92
8	**6.15**	Me	*tert*-BuLi	34[b]

a Yield by GC analysis hexadecane as the internal standard. *b* 95% Pure 1-bromo-3-chloroprop-1-ene (**6.8**) used, instead of 99 +% pure, as in other reactions.
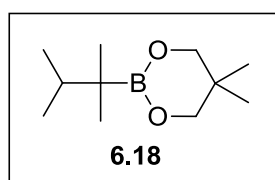
6.34 Synthesis of other *tert*-alkylboronic esters

6.34a Synthesis of boronic ester 6.16.

6.16
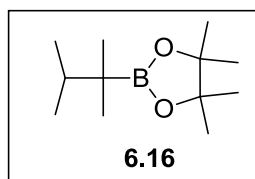
Procedure 4.1c was repeated on a 10 mmol scale. The crude product was dissolved in diethyl ether (25 mL), and the solution was washed with 2 M HCl (aq) (3 × 15 mL) and distilled water (10 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica (95:5 petroleum ether: ethyl acetate) to give pure boronic ester **6.16** (1.03 g, 24%). For characterisation data, see Section 4.1c.

6.34b Synthesis of boronic ester 6.18.

6.18

Procedure 4.1h was repeated on a 10 mmol scale, and the crude product dissolved in diethyl ether (25 mL), and the solution was washed with 2 M HCl (aq) (3 × 15 mL) and distilled water (10 mL), dried over magnesium sulfate, filtered and concentrated under reduced

pressure to give pure boronic ester **6.18** (0.69 g, 38%). For characterisation data, see Section 4.1h.

6.34c Synthesis of boronic ester 6.24.

6.24
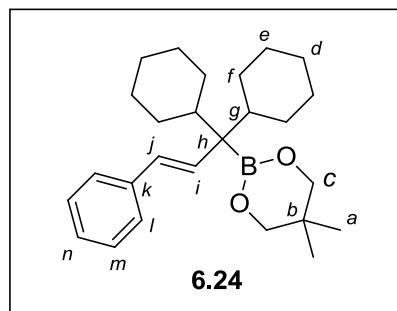
Dicyclohexylborane was prepared according to procedure 6.1a from borane dimethyl sulfide complex (10 M, 1.00 mL, 10.0 mmol) and cyclohexene (2.12 mL, 20.9 mmol). Dry THF (10 mL) was added, and the mixture was kept at 0 °C during the drop-wise addition of phenylacetylene (1.15 mL, 10.5 mmol). The reaction mixture was stirred for 1 h at 0 °C and 1 h at rt. The mixture was subjected to the DCME reaction conditions (procedure 4.5a), using 1.5 eq of DCME, 1.5 eq of *n*-BuLi in hexanes and 1.5 eq of 3-ethyl-3-pentanol. The crude product following work-up was purified by column chromatography on silica (petroleum ether) to give pure (*E*)-2-(1,1-dicyclohexyl-3-phenylallyl)-5,5-dimethyl-1,3,2-dioxaborinane (**6.24**, 1.19 g, 20%) as cubic crystals; m.p. 188-189 °C; δ^1H (400 MHz; CDCl$_3$): 7.43 (2H, d, $J = 7.2$ Hz, CH*l*), 7.31 (2H, app t, $J = 7.8$ Hz, CH*m*), 7.18 (1H, t, $J = 7.3$ Hz, CH*n*), 6.41 (1H, d, $J = 16.7$ Hz, CH*j*), 6.30 (1H, d, $J = 16.7$ Hz, CH*i*), 3.67 (4H, s, CH$_2$*c*), 0.87 − 1.84 (22H, m, CH$_2$*d, e, f* + CH*g*), 1.04 (6H, s, CH$_3$*a*); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 139.2 (quat C), 135.7 (CH), 128.9 (CH), 128.3 (CH), 126.1 (CH), 125.9 (CH), 71.7 (CH$_2$, C*c*), 41.0 (CH), 31.3 (quat C), 30.4 (CH$_2$), 29.1 (CH$_2$), 27.5 (CH$_2$), 27.3 (CH$_2$), 27.1 (CH$_2$), 22.5 (CH$_3$, C*b*); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 33.0; HR - EI$^+$ MS m/z (%): calculated for C$_{26}$H$_{39}$^{11}BO$_2$ 394.3043, found 394.3049 (M$^+$, 39%); ν_{max} (nujol/cm^{-1}): 2907, 1464, 1377, 1255; Crystallography data (petroleum ether): Triclinic, space group: P1, $a = 9.4967(3)$ Å, $b = 11.2837(2)$ Å, $c = 12.0297(4)$ Å, $\alpha = 109.897(2)$, $\beta = 96.388(2)$, $\gamma = 102.048(2)$, 1161.9 Å^3, $Z = 2$, $R_1 = 4.98$; Rf = 0.53 in petroleum ether.

6.35 Reactions of *tert*-alkylboronic esters with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene

6.35a Reaction of thexylboronic acid pinacol ester with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.

a Yield in parentheses is of isolated product, former is by GC analysis.
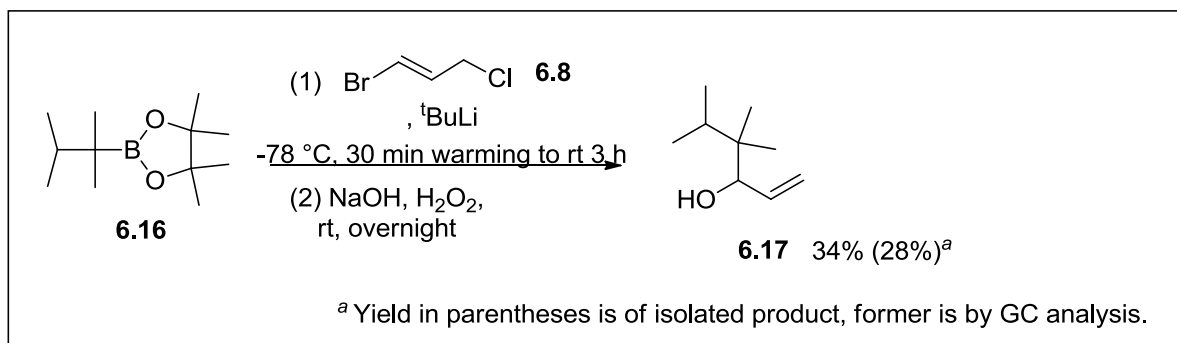
Procedure 6.32d was repeated using boronic ester **6.16** (0.564 g, 2.66 mmol), 1-bromo-3-chloroprop-1-ene (0.416 g, 2.68 mmol), dry THF (15 mL) and *tert*-BuLi in hexanes (1.9 M, 1.41 mL, 2.68 mmol) to give a light yellow liquid (0.56 g), consisting of pinacol, traces of 1-bromo-3-chloroprop-1-ene, 4,4,5-trimethylhex-1-en-3-ol (**6.17**) and thexanol (66:33 ratio of **6.17**:thexanol by relative integrations in the ^{1}H NMR spectrum), which was purified by column chromatography on silica (prewashed with 3% triethylamine in petroleum ether), (90:10 petroleum ether: ethyl acetate, followed by 80:20 and finally 60:30) to give 4,4,5-trimethylhex-1-en-3-ol (**6.17**) as a colourless oil (0.105 g, 28%); δ^1H (400 MHz; CDCl$_3$): 5.88 (1H, m, alkenyl CH), 5.10 – 5.20 (2H, m, alkenyl CH$_2$), 3.94 (1H, d, J = 6.7 Hz, C*H*OH), 1.66 (1H, m, thexyl CH), 1.41 (1H, br s, OH), 0.82 (3H, d, J = 6.9 Hz, diastereotopic CH$_3$), 0.79 (3H, d, J = 5.9 Hz, diastereotopic CH$_3$), 0.77 (3H, s, diastereotopic CH$_3$), 0.66 (3H, s, diastereotopic CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 138.3 (CH), 116.3 (CH$_2$), 78.0 (CH), 39.5 (quat C), 32.7 (CH), 18.9 (CH$_3$), 18.5 (CH$_3$), 17.4 (CH$_3$), 17.3 (CH$_3$); HR - EI$^+$ MS m/z (%): calculated for C$_9$H$_{18}$O 124.1252, found 124.1252 (M$^+$-H$_2$O, 10%); Rf = 0.24 in 9:1 petroleum ether: ethyl acetate.

Procedure 6.32d was repeated several times, using boronic ester **6.12**, boronic ester **6.16** and boronic ester **6.18**. The GC yield was calculated for these reactions, and the results are shown in Table 6.7.

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**Table 6.7 Migration of thexyl alkyl group**

Thexylboronic ester	Scale	organolithium	Yield of **6.17** (%)[a]
6.16	0.897 mmol	*tert*-BuLi	34
6.12	1.123 mmol	*tert*-BuLi	36
6.18	0.844 mmol	*tert*-BuLi	99

[a] Yields by GC analysis using internal standard (tetradecane).

**6.35b Reaction of boronic ester 6.21 with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.**
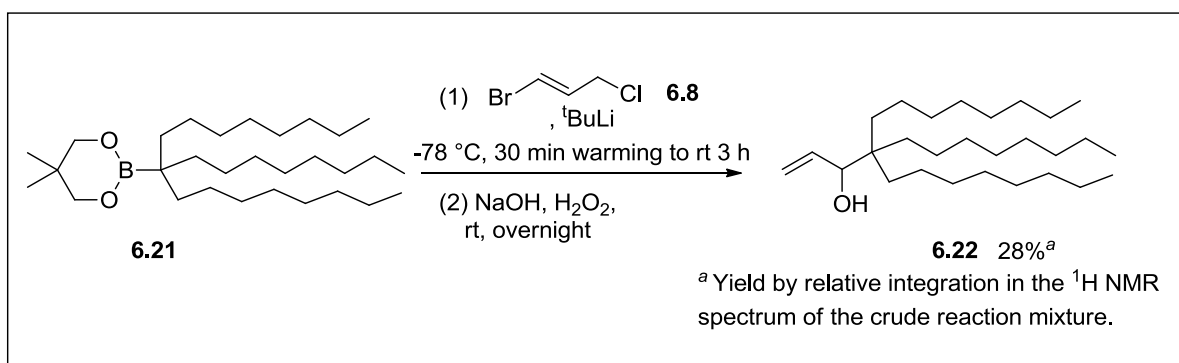
Procedure 6.32d was repeated using boronic ester **6.21** (prepared according to procedure 4.5b) (0.524 g, 1.13 mmol), 1-bromo-3-chloroprop-1-ene (0.200 g, 1.29 mmol), dry THF (10 mL) and *tert*-BuLi in hexanes (1.6 M, 0.81 mL, 1.30 mmol) to give a yellow oil (0.47 g), consisting of tri-*n*-octylmethanol and 4,4-di-*n*-octyldodec-1-en-3-ol (**6.22**) in a 72:28 ratio, respectively, by relative integrations in the ^{1}H NMR spectrum, along with 2,2-dimethyl-1,3-propanediol and residual THF. The crude product was purified by column chromatography (petroleum ether, followed by 95:5 petroleum ether: ethyl acetate) to give an inseparable mixture of tri-*n*-octylmethanol and 4,4-di-*n*-octyldodec-1-en-3-ol (**6.22**). Preparatative TLC was also unsuccessful at separating the two compounds.

6.35c Reaction of boronic ester 6.19 with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.

a GC yield, isolated in parentheses.
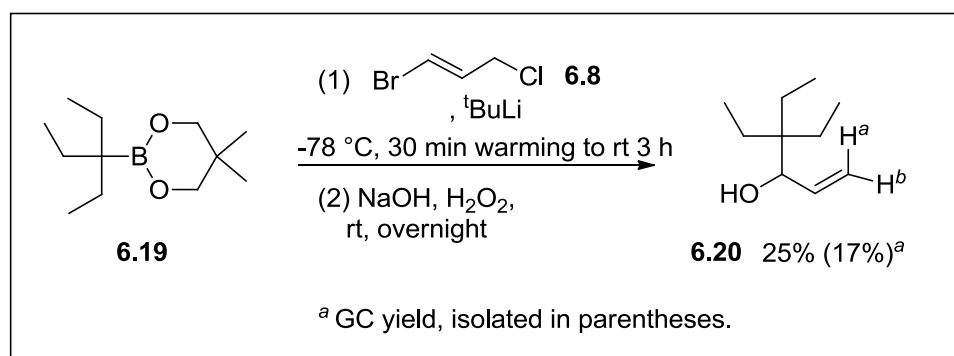
Procedure 6.32d was repeated using boronic ester **6.19** (prepared according to procedure 4.5e) (0.335 g, 1.58 mmol), 1-bromo-3-chloroprop-1-ene (0.274 g, 1.76 mmol), dry THF (10 mL) and *tert*-BuLi in hexanes (1.6 M, 1.09 mL, 1.74 mmol) to give a light yellow oil (0.27 g), consisting of triethylmethanol, 4,4-diethylhex-1-en-3ol (**6.20**, 50:50 ratio by relative integrations in the ^{1}H NMR spectrum) and 2,2-dimethyl-1,3-propanediol. 4,4-Diethylhex-1-en-3ol was purified by column chromatography on silica (prewashed with 3% triethylamine in petroleum ether) (98:2 petroleum ether: ethyl acetate, followed by 95:5) to give 4,4-diethylhex-1-en-3ol (**6.20**, 0.042 g, 17%) as a colourless liquid; δ^1H (500 MHz; CDCl$_3$): 5.95 (1H, m, alkenyl CH), 5.17 (1H, d, *J* = 17.2 Hz, CH*a*), 5.10 (1H, d, *J* = 10.5 Hz, CH*b*), 3.92 (1H, m, C*H*OH), 1.28 (6H, m, CH$_2$), 0.78 (9H, t, *J* = 7.6 Hz, *tert*-Bu); δ^{13}C (125 MHz; CDCl$_3$): 138.7 (CH, alkenyl CH), 115.7 (CH$_2$, alkenyl CH$_2$), 78.3 (CH, *C*HOH), 41.5 (quat C), 25.8 (CH$_2$), 8.3 (CH$_3$); HR - EI$^+$ MS m/z (%): calculated for C$_{10}$H$_{20}$O 156.1514, found 156.1509 (M$^+$, 3%); ν_{max} (neat/cm^{-1}): 3472 (OH), 3078, 2924, 2854, 1466, 1378, 1260; Rf = 0.25 in 9:1 petroleum ether: ethyl acetate.

The above reaction was repeated using boronic ester **6.19** (1.18 mmol), and gave a GC yield of 25%. The reaction was also repeated using a threefold excess of *tert*-BuLi and **6.8**, and gave a 31% GC yield, using boronic ester **6.19** (0.7 mmol).

6.35d Reaction of boronic ester 6.24 with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.
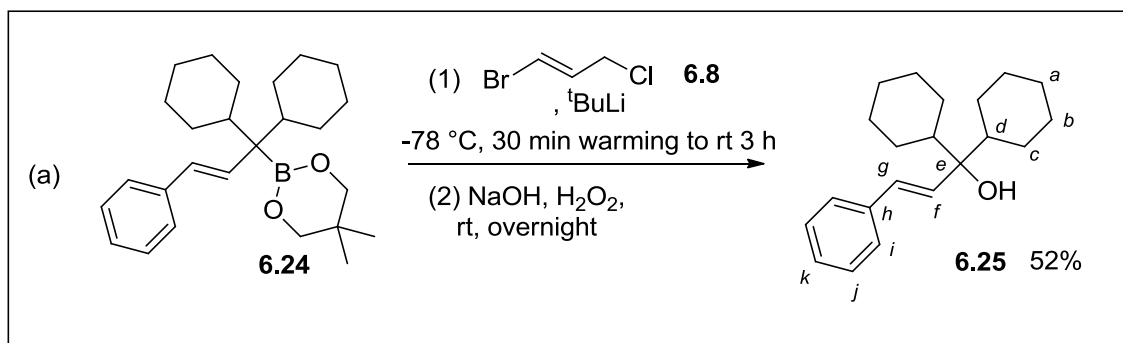

Procedure 6.32d was repeated using boronic ester **6.24** (0.42 g, 1.05 mmol), 1-bromo-3-chloroprop-1-ene (0.187 g, 1.20 mmol), dry THF (10 mL) and *tert*-BuLi in hexanes (1.6 M, 0.75 mL, 1.20 mmol) to give, after work-up, a colourless oil, which was purified by column chromatography (prewashed with 3% triethylamine in petroleum ether) (90:10 petroleum ether: ethyl acetate) to give (*E*)-1,1-dicyclohexyl-3-phenylprop-2-en-1-ol (**6.25**, 0.16 g, 52%) as a waxy-white solid; δ^1H (400 MHz; CDCl$_3$): 7.32 (2H, d, J = 7.3 Hz, CH*i*), 7.24 (2H, app t, J = 7.3 Hz, CH*j*), 7.1 (1H, t, J = 7.3 Hz, CH*k*), 6.50 (1H, d, J = 16.1 Hz, CH*g*), 6.03 (1H, d, J = 16.1 Hz, CH*f*), 1.52 – 1.76 (10H, m, CH*d* + CH$_2$), 0.75 – 1.22 (12H, m, CH$_2$); δ^{13}C (125 MHz; CDCl$_3$): 137.4 (quat C, C*h*), 133.9 (CH), 128.53 (CH), 128.52 (CH), 127.0 (CH), 126.3 (CH), 79.3 (quat C, C*e*), 43.6 (CH, C*d*), 27.6 (CH$_2$), 26.9 (CH$_2$), 26.6 (CH$_2$), 26.3 (CH$_2$); HR - EI$^+$ MS m/z (%): calculated for C$_{21}$H$_{30}$O 298.2297, found 298.2299 (M$^+$, 4%); ν_{max} (neat/cm^{-1}): 3495 (br, OH), 3081, 3059, 3025, 2929, 2851, 1600, 1496, 1448, 1261; Rf = 0.15 in 98:2 petroleum ether: ethyl acetate.

6.35e Reaction of boronic ester 6.23 with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.
Procedure 6.32d was repeated using freshly prepared tricyclopentylboronic acid ethylene glycol ester (**6.23**, procedure 4.5c) (0.294 g, 1.01 mmol), 1-bromo-3-chloroprop-1-ene (0.17 g, 1.11 mmol) in dry THF (15 mL) and *tert*-BuLi in hexanes (1.6 M, 0.69 mL, 1.11 mmol). The reaction was worked-up in the same manner to give a viscous oil (0.197 g), which consisted of tricyclopentylmethanol (see procedure 3.32b) and a trace amount of 1-bromo-3-chloroprop-1-ene by ^{1}H NMR analysis.

6.36 Synthesis of primary-alkylboronic esters

6.36a Synthesis of boronic ester 6.26.
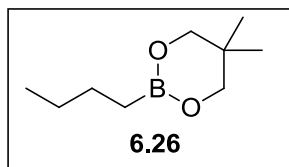
6.26

An oven dried 50 mL round bottomed flask equipped with a magnetic stirrer bar and septum was flushed with N_2 for 10 min. *n*-Butylboronic acid (1.00 g, 9.81 mmol), 2,2,-dimethyl-1,3-propanediol (1.07 g, 10.3 mmol) and dry pentane (15 mL) were added, and the mixture stirred overnight at rt. Magnesium sulfate (5.0 g) was added, along with hexane (20 mL), and the mixture stirred for 5 min before being filtered and concentrated under reduced pressure to give boronic ester **6.26**[20] as a colourless liquid (1.26 g, 76%); δ^1H (400 MHz; CDCl$_3$): 3.51 (4H, s, CH$_2$), 1.17 – 1.31 (4H, m, CH$_2$), 0.88 (6H, s, CH$_3$), 0.81 (3H, t, J = 7.1 Hz, CH$_3$), 0.64 (2H, t, J = 7.7 Hz, CH$_2$); δ^{13}C (125 MHz; CDCl$_3$): *CH$_2$ next to boron not seen*; 71.9 (CH$_2$, *C*H$_2$O), 31.6 (quat C), 26.4 (CH$_2$), 25.5 (CH$_2$), 21.8 (CH$_3$), 13.9 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 29.6; LR - EI+-MS m/z (%): 170 (M$^+$, 22%), 141 (100), 128 (55), 113 (71), 99 (48), 87 (67), 74 (35), 69 (93), 56 (74); v_{max} (neat/cm^{-1}): 2955, 2874, 1476, 1415, 1377, 1334, 1280, 1245, 1180.

6.36b Synthesis of boronic ester 6.30.

6.30
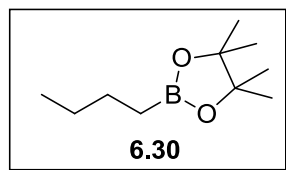
Procedure 6.36a was repeated using *n*-butylboronic acid (1.50 g, 14.7 mmol), pinacol (1.83 g, 15.5 mmol) and dry pentane (20 mL) to give boronic ester **6.30**[24] as a colourless liquid (1.97 g, 73%); δ^1H (400 MHz; CDCl$_3$): 1.17 – 1.35 (4H, m, CH$_2$), 1.17 (12H, s, CH$_3$), 0.81 (3H, t, J = 7.2 Hz, CH$_3$), 0.70 (2H, t, J = 7.8 Hz, CH$_2$); δ^{13}C (125 MHz; CDCl$_3$): *CH$_2$ next to boron not* seen; 82.8 (quat C, *C*OCH$_3$), 26.2 (CH$_2$), 25.4 (CH$_2$), 24.8 (CH$_3$), 13.8 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 33.2; LR - EI$^+$ MS m/z (%): 184 (M$^+$, 3%), 169 (100), 129

(100), 113 (53), 98 (95), 85 (100), 70 (88), 59 (95); v_{max} (neat/cm^{-1}): 2979, 2958, 2929, 2873, 1468, 1408, 1380, 1320, 1147.

### 6.37 Reactions of primary-alkylboronic esters with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene

6.37a Reaction of boronic ester 6.26 with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.
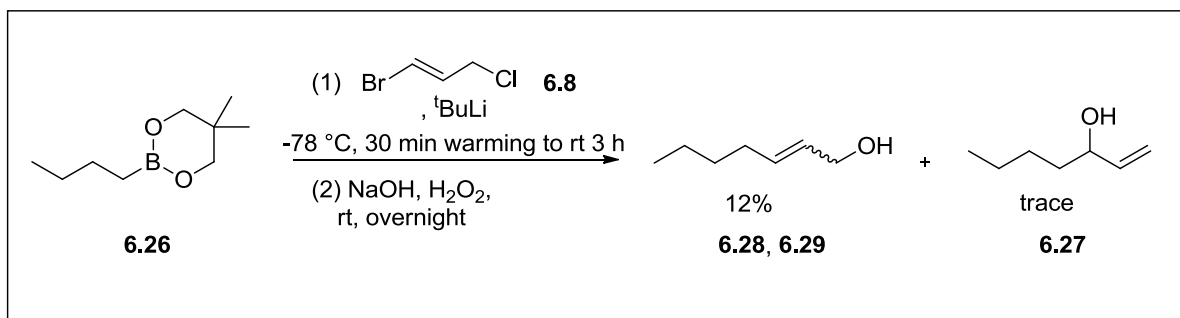
Procedure 6.32d was repeated using boronic ester **6.26** (0.278 g, 1.64 mmol), 1-bromo-3-chloroprop-1-ene (0.280 g, 1.83 mmol), dry THF (10 mL) and *tert*-BuLi in hexanes (1.6 M, 1.14 mL, 1.82 mmol) to give, after work-up, a light yellow liquid (0.37 g), consisting of (*E*)/(*Z*)- hept-2-en-1-ol (**6.28**/**6.29**), hept-1-en-3-ol (**6.27**; 78:22 ratio, respectively, by ^{1}H NMR analysis), THF, 2,2-dimethyl-1,3-propanediol and 1-bromo-3-chloroprop-1-ene. The mixture was purified by column chromatography (prewashed with 3% triethylamine in petroleum ether) (98:2 petroleum ether: ethyl acetate, followed by 95:5, 90:10) to give impure hept-1-en-3-ol (**6.27**, 1 mg) and a mixture of (*E*) and (*Z*)-hept-2-en-1-ols[23] (**6.28** and **6.29**) as a colourless liquid (22 mg, 12%); δ^1H (500 MHz; CDCl$_3$; mixture of **6.28** and **6.29**): 5.44 – 5.66 (2H, m, CH), 4.12 (1.04H, d, *J* = 6.3 Hz, OCH$_2$, one isomer), 4.02 (0.96H, d, J = 6.5 Hz, OCH$_2$, other isomer), 1.95 – 2.05 (2H, m, CH$_2$), 1.39 (1H, br, OH), 1.21 – 1.31 (4H, m, CH$_2$), 0.83 (3H, app t, *J* = 5.9 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 133.5 + 133.2 (CH, =CH, isomers), 128.9 + 128.3 (CH, =CH, isomers), 63.8 + 58.6 (CH$_2$, OCH$_2$, isomers), 31.8 + 31.3 (CH$_2$, CH$_2$ isomers), *following signals for the two isomers could not be differentiated*; 27.1 (CH$_2$), 22.2 (CH$_2$), 13.9 (CH$_3$); LR - EI+-MS m/z (%): 114 (M$^+$, 8%), 96 (98), 84 (100), 74 (85), 68 (88), 57 (97); v_{max} (neat/cm^{-1}): 3350 (OH), 2920, 1467, 1378, 1125.

6.37b Reaction of boronic ester 6.30 with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.
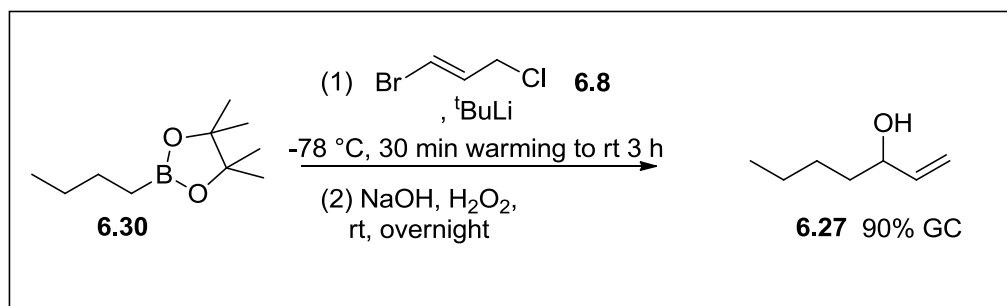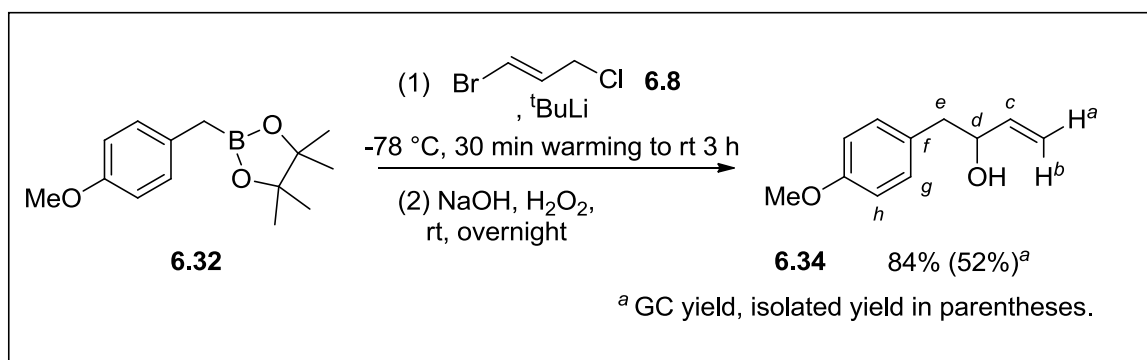

Procedure 6.32d was repeated using boronic ester **6.30** (0.287 g, 1.56 mmol), 1-bromo-3-chloroprop-1-ene (0.272 g, 1.75 mmol), dry THF (10 mL) and *tert*-BuLi in hexanes (1.5 M, 1.17 mL, 1.76 mmol) to give, after work-up, a light yellow liquid (0.56 g), containing hep-1-ene-3-ol (**3.27**), tetradecane (internal standard), pinacol and residual THF according to its ^{1}H NMR spectrum. GC analysis of the organic layer prior to work-up showed the presence of hept-1-ene-3-ol (**6.27**, 90% yield), using tetradecane as the internal standard.

6.37c Reaction of benzylboronic acid pinacol ester (6.31) with *tert*-BuLi/(E)-1-bromo-3-chloroprop-1-ene.
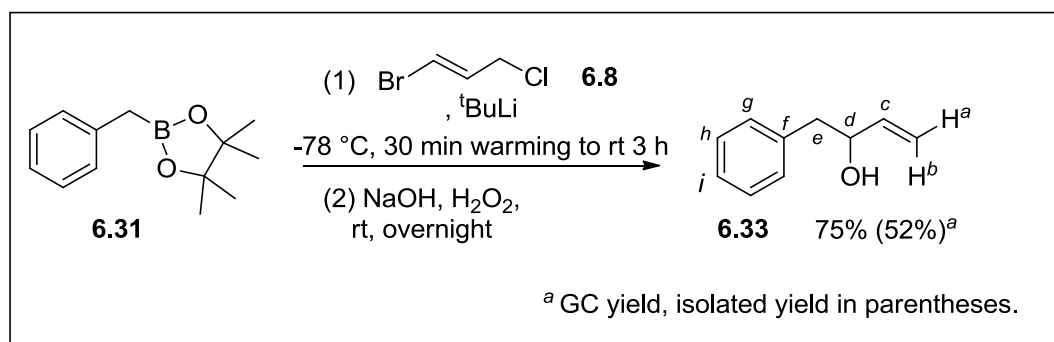
Procedure 6.32d was repeated using benzylboronic acid pinacol ester (0.280 g, 1.28 mmol), 1-bromo-3-chloroprop-1-ene (0.226 g, 1.45 mmol), dry THF (10 mL) and *tert*-BuLi in hexanes (1.5 M, 0.97 mL, 1.46 mmol). GC analysis of the organic layer showed the presence of 1-phenylbut-3-en-2-ol (**6.33**, 75% yield), using tetradecane as the internal standard. The ^{1}H NMR spectrum following work-up showed the presence of **6.33** and benzyl alcohol (in a ratio of 77:33 by relative integration) along with pinacol and tetradecane. The crude product was purified by column chromatography on silica (95:5 petroleum ether: ethyl acetate, followed by 90:10) to give pure 1-phenylbut-3-en-2-ol[25] (**6.33**, 0.097 g, 52%) as a colourless oil; δ^1H (500 MHz; CDCl$_3$): 7.24 (2H, app t, *J* = 6.9 Hz, CH*h*), 7.15 – 7.19 (3H, m, CH*g*, *i*), 5.86 (1H,

m, CH*c*), 5.18 (1H, app dt, *J* = 17.2, 1.4 Hz, CH*b*), 5.06 (1H, app dt, J = 10.5, 1.3 Hz, CH*a*),

4.28 (1H, m, CH*d*), 2.82 (1H, dd, *J* = 13.6, 5.1 Hz, diastereotopic CH of CH_2), 2.72, (1H, dd,

J = 13.6, 8.0 Hz, diastereotopic CH of CH_2), 1.64 (1H, br s, OH); δ^{13}C (125 MHz; CDCl$_3$):

140.0 (CH), 137.6 (quat C, C*f*), 129.4 (CH), 128.4 (CH), 126.5 (CH), 114.9 (CH_2, C*a, b*),

73.5 (CH, C*d*), 43.7 (CH_2, C*e*); LR - EI$^+$ MS m/z (%): 148 (M$^+$, 4%), 129 (46), 115 (33), 92

(100), 84 (37), 74 (35), 65 (34), 59 (40); v_{max} (neat/cm^{-1}): 3399 (OH), 3086, 3065, 3029,

2981, 2922, 2874, 1947, 1873, 1645, 1604, 1496, 1455, 1425; Rf = 0.24 in 8:2 petroleum

ether: ethyl acetate.

6.37d Reaction of 4-methoxybenzylboronic acid pinacol ester with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.


^{a} GC yield, isolated yield in parentheses.

Procedure 6.32d was repeated using 4-methoxybenzylboronic acid pinacol ester (0.292 g,

1.18 mmol), 1-bromo-3-chloroprop-1-ene (0.210 g, 1.35 mmol), dry THF (10 mL) and *tert*-BuLi in hexanes (1.5 M, 0.84 mL, 1.26 mmol). GC analysis of the organic layer showed the

presence of 4-methoxyphenylbut-3-en-2-ol (**6.34**, 84% yield), using tetradecane as the

internal standard. The ^{1}H NMR spectrum following work-up showed the presence of 1-phenylbut-3-en-2-ol (**6.34**) and benzyl alcohol (in a ratio of 68:32 by relative integration)

along with pinacol and tetradecane. The crude product was purified by column

chromatography on silica (90:10 petroleum ether: ethyl acetate, followed by 85:15) to give

pure 4-methoxyphenylbut-3-en-2-ol[26] (**6.34**, 0.185 g, 52%) as a colourless oil; δ^1H (400

MHz; CDCl$_3$): 7.07 (2H, d, *J* = 8.7 Hz, CH*g*), 6.79 (2H, d, *J* = 8.7 Hz, CH*h*), 5.85 (1H, m,

alkenyl CH*c*), 5.17 (1H, app dt, *J* = 17.2, 1.4 Hz, CH*b*), 5.06 (1H, app dt, *J* = 10.5, 1.4 Hz,

CH*a*), 4.23 (1H, m, CH*d*), 3.72 (3H, s, OCH$_3$), 2.74 (1H, dd, *J* = 13.7, 5.1 Hz, diastereotopic

CH of CH_2), 2.66 (1H, dd, *J* = 13.7, 7.9 Hz, diastereotopic CH of CH_2), 1.65 (1H, br s, OH);

δ^{13}C (125 MHz; CDCl$_3$): 158.4 (quat C, Ar C), 140.3 (CH, alkenyl C*c*), 130.5 (CH, Ar CH),

129.7 (quat C, Ar C), 114.8 (CH_2, C*a*), 114.0 (CH, Ar CH), 73.7 (CH, C*d*), 55.3 (CH$_3$, MeO),

42.9 (CH$_2$, C*e*); LR - EI$^+$ MS m/z (%): 178 (M$^+$, 45%), 160 (59), 144 (44), 129 (34), 121 (100), 115 (41), 91 (52), 77 (53), 65 (33); v_{max} (neat/cm^{-1}): 3399, 3076, 3005, 2934, 2835, 2002, 1882, 1612, 1584, 1514, 1465, 1442, 1301, 1249; Rf = 0.29 in 8:2 petroleum ether: ethyl acetate.

6.38 Synthesis of secondary-alkylboronic esters

6.38a Synthesis of boronic ester 6.39.
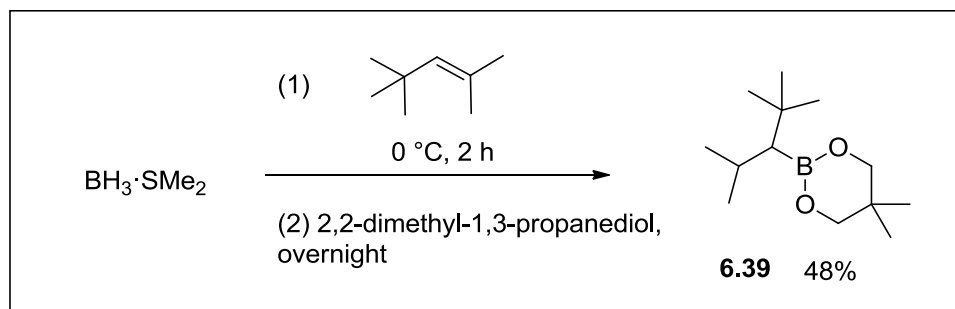
An oven dried 50 mL round bottomed flask equipped with a magnetic stirrer bar and septum was flushed with N$_2$ for 10 min. Borane dimethyl sulfide complex (10.0 M, 1.5 mL, 15.0 mmol) and dry THF (10 mL) were added, and the solution cooled to 0°C using an ice bath. 2,4,4-Trimethyl-2-pentene (2.34 mL, 15.0 mmol) was added drop-wise, and the solution left to stir for 2 h. A solution of 2,2-dimethyl-1,3-propanediol (1.716 g, 16.5 mmol) in dry THF (6 mL) was added drop-wise, and the reaction mixture left to stir overnight at rt. The reaction mixture was concentrated under reduced pressure, and the product purified by column chromatography on silica (98:2 petroleum ether: ethyl acetate) to give pure boronic ester **6.39** as a colourless liquid (1.64 g, 48%); δ^1H (400 MHz; CDCl$_3$): 3.52 (4H, s, CH$_2$O), 1.78 (1H, m, CH of *i*Pr), 0.87 – 0.92 (21H, m, CH$_3$), 0.54 (1H, d, *J* = 3.7 Hz, CHB); δ^{13}C (100 MHz; CDCl$_3$): *CH next to boron not seen*; 71.4 (CH$_2$), 32.7 (quat C), 31.3 (quat C), 30.1 (CH$_3$), 26.8 (CH), 26.4 (CH$_3$), 23.0 (CH$_3$), 22.4 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 29.4; HR - EI$^+$ MS m/z (%): calculated for C$_{13}$H$_{26}$^{11}BO$_2$ 225.2026, found 225.2027 (M$^+$-1, 7%); v_{max} (neat/cm^{-1}): 2955, 1476, 1411, 1366, 1253; Rf = 0.90 in 9:1 petroleum ether: ethyl acetate.

6.38b Synthesis of boronic ester 6.35.

6.35
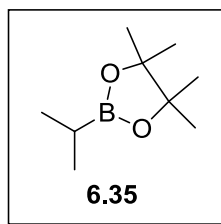
Procedure 4.4d was repeated on a 17 mmol scale, and the product further purified by dissolving in diethyl ether, washing with 2 M HCl (3 × 10 mL), drying over magnesium sulfate, filtering and concentrating under reduced pressure to give pure boronic ester **6.35** (1.04 g, 36%). For spectroscopic data, see Section 4.4d.

6.38c Synthesis of boronic ester 6.37.

6.37
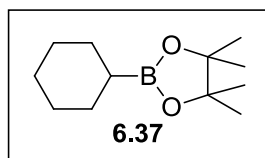
Procedure 6.36a was repeated using cyclohexylboronic acid (2.00 g, 15.6 mmol), pinacol (1.94 g, 16.4 mmol) and dry pentane (20 mL) to give boronic ester **6.37**[24] as a colourless liquid (1.04 g, 32%); δ^1H (400 MHz; CDCl$_3$): 1.50 – 1.60 (4H, m, CH$_2$), 1.20 – 1.31 (6H, m, CH$_2$), 1.16 (12H, s, CH$_3$), 0.91 (1H, m, CHB); δ^{13}C (125 MHz; CDCl$_3$): *CH next to boron not seen*; 82.7 (quat C, *C*OCH$_3$), 28.0 (CH$_2$), 27.1 (CH$_2$), 26.8 (CH$_2$), 24.7 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 33.2; LR - EI+-MS m/z (%): 210 (M$^+$, 5 %), 195 (44), 129 (33), 24 (100), 110 (26), 82 (34), 69 (38); ν_{max} (neat/cm^{-1}): 2978, 2923, 2850, 1448, 1414, 1383, 1310, 1146.

6.39 Reactions of secondary-alkylboronic esters with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene

6.39a Reaction of boronic ester 6.39 with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.
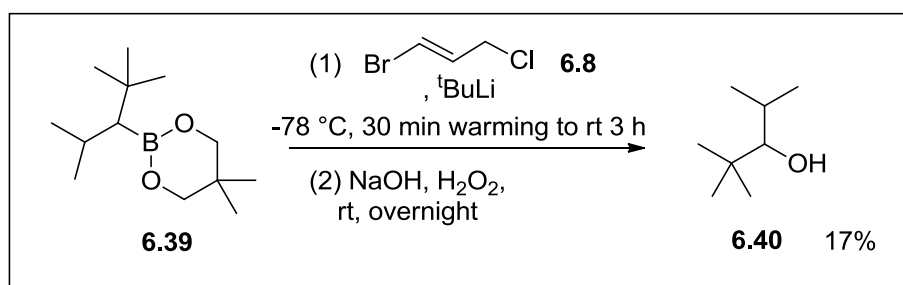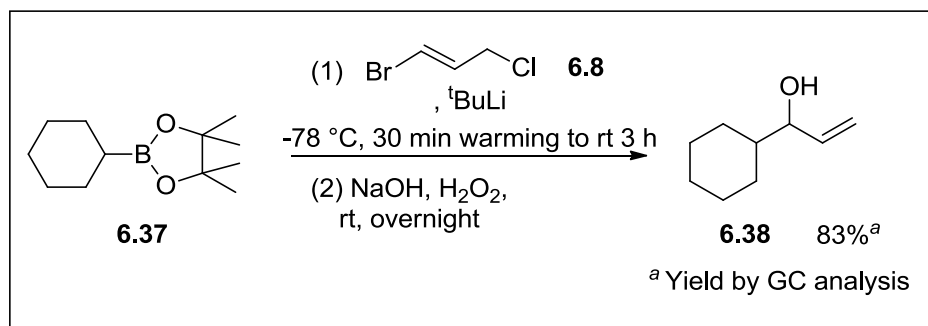
Procedure 6.3a was repeated using boronic ester **6.39** (0.374 g, 1.66 mmol), 1-bromo-3-chloroprop-1-ene (0.291 g, 1.87 mmol), dry THF (10 mL) and *tert*-BuLi in hexanes (1.5 M, 1.25 mL, 1.88 mmol), to give, after work-up, a light yellow liquid (0.379 g), consisting of 2,2-dimethyl-1,3-propanediol, internal standard (tetradecane) and 2,2,4-trimethylpentan-3-ol (**6.40**) by ^{1}H NMR analysis. The mixture was separated by column chromatography on silica (95:5 petroleum ether: ethyl acetate, followed by 90:10 and finally 80:20) to give pure 2,2,4-trimethylpentan-3-ol (**6.40**, 0.037 g, 17%) as a colourless oil; δ^1H (400 MHz; CDCl$_3$): 3.04 (1H, d, J = 2.3 Hz, CHOH), 1.88 (1H, app d sept, J = 6.9, 2.3 Hz, CH), 1.45 (1H, br s, OH), 0.92 (3H, d, J = 7.0, CH$_3$), 0.87 (9H, s, *tert*-Bu), 0.85 (3H, d, J = 6.8 Hz); δ^{13}C (125 MHz; CDCl$_3$): 83.6 (CH, CHOH), 35.8 (quat C), 28.8 (CH, *i*Pr CH), 26.7 (CH$_3$, *tert*-Bu), 23.6 (CH$_3$), 16.5 (CH$_3$); LR - EI$^+$ MS m/z (%): *molecular ion not seen*; 112 (M$^+$ - H$_2$O, 40%), 97 (100), 87 (40), 84 (49), 73 (59), 69 (68), 57 (46), 55 (78); ν_{max} (neat/cm^{-1}): 3478 (OH), 2958, 1730, 1469, 0367, 1261, 1173, 1119, 1037; Rf = 0.38 in 9:1 petroleum ether: ethyl acetate.

6.39b Reaction of isopropylboronic acid pinacol ester (6.35) with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.
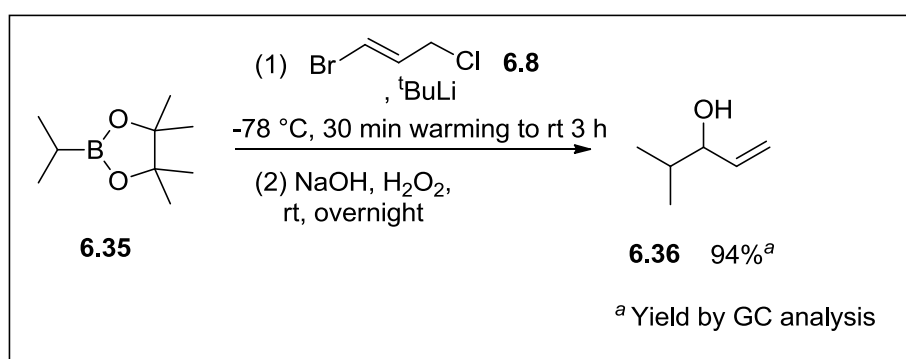
Procedure 6.32d was repeated using boronic ester **6.35** (0.303 g, 1.78 mmol), 1-bromo-3-chloroprop-1-ene (0.303 g, 1.95 mmol), dry THF (10 mL) and *tert*-BuLi in hexanes (1.5 M, 1.30 mL, 1.95 mmol) to give, after work-up, a light yellow liquid (0.53 g), consisting of 4-methyl-pent-1-en-3-ol (**6.36**), 1-bromo-3-chloroprop-1-ene, tetradecane, pinacol and residual THF. GC analysis of the organic layer prior to work-up showed the presence of 4-methyl-pent-1-en-3-ol (**6.36**, 94% yield), using tetradecane as the internal standard.

6.39c Reaction of boronic ester 6.37 with *tert*-BuLi/(*E*)-1-bromo-3-chloroprop-1-ene.
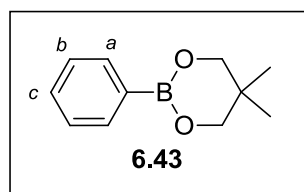

Procedure 6.32d was repeated using boronic ester **6.37** (0.239 g, 1.14 mmol), 1-bromo-3-chloroprop-1-ene (0.188 g, 1.21 mmol), dry THF (10 mL) and *tert*-BuLi in hexanes (1.5 M, 0.81 mL, 1.22 mmol). GC analysis of the organic layer showed the presence of 1-cyclohexylprop-2-en-1-ol (**6.38**, 83% yield), using tetradecane as the internal standard.

6.310 Synthesis of unsaturated boronic esters

6.310a Synthesis of boronic ester 6.42.
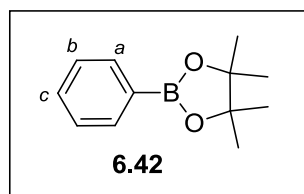
An oven dried 50 mL round bottomed flask equipped with a magnetic stirrer bar and septum was flushed with N_2 for 10 min. Phenylboronic acid (1.83 g, 15.0 mmol), pinacol (1.77 g, 15.0 mmol) and dry pentane (20 mL) were added, and the reaction mixture stirred overnight at rt. Magnesium sulfate (5.0 g) was added, along with hexane (20 mL), and the reaction mixture stirred for 5 min before being filtered and concentrated under reduced pressure to give pure boronic ester **6.42**[30] as a colourless oil, which solidified on standing (2.53 g, 83%); m.p. 29-30 °C (lit m.p. 27-28 °C[34]); δ^1H (400 MHz; CDCl$_3$): 7.73 (2H, d, *J* = 8.0 Hz, CH*a*), 7.37 (1H, t, *J* = 6.2 Hz, CH*c*), 7.29 (2H, app t, *J* = 8.0 Hz, CH*b*), 1.26 (12H, s, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen;* 134.8 (CH, Ar CH), 131.2 (CH, Ar CH), 127.7 (CH, Ar CH), 83.8 (quat C, *C*OCH$_3$), 24.9 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 30.1; LR - EI$^+$ MS m/z (%): 204 (M$^+$, 33%), 189 (80), 118 (62), 105 (100), 84 (51); ν_{max} (heated to an oil/cm^{-1}): 3080, 3056, 2979, 1604, 1499, 1440, 1359.

**6.310b Synthesis of boronic ester 6.43.**

6.43

Procedure 6.310a was repeated using phenylboronic acid (1.22 g, 10.0 mmol), 2,2-dimethyl-1,3-propanediol (1.09 g, 10.5 mmol) and dry pentane (20 mL) to give the crude product, which was purified by column chromatography on silica (90:10 petroleum ether: ethyl acetate) to give pure boronic ester **6.43**[31] as a white solid (1.04 g, 55%); m.p 69–71.5 °C (lit m.p. 65.5 °C[35]); δ^1H (500 MHz; CDCl$_3$): 7.74 (2H, d, J = 7.8 Hz, CHa), 7.35 (1H, t, J = 7.6 Hz, CHc), 7.28 (2H, app t, J = 7.4 Hz, CHb), 3.70 (4H, s, CH$_2$O), 0.95 (6H, s, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): *quat C next to boron not seen*; 133.8 (CH), 130.7 (CH), 127.6 (CH), 72.3 (CH$_2$), 31.9 (quat C), 21.9 (CH$_3$); ^{11}B{^{1}H}(160 MHz; CDCl$_3$): 26.8; LR - EI$^+$ MS m/z (%): 190 (M$^+$, 100%), 147 (30), 118 (35), 105 (50), 56 (93); v_{max} (thin film/cm^{-1}): 3082, 3050, 2955, 2934, 2904, 2874, 1967, 1907, 1600, 1478, 1441, 1416.

6.310c Synthesis of (*E*)-styrylboronic acid pinacol ester (6.41).

6.41
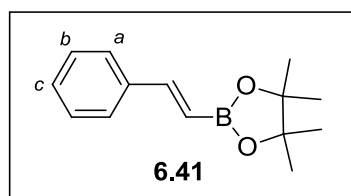
Procedure 6.310a was repeated using (*E*)-styrylboronic acid (1.00 g, 6.76 mmol), pinacol (0.84 g, 7.11 mmol) and dry diethyl ether (10 mL) to give the crude product, which was purified by column chromatography on silica (90:10 petroleum ether: ethyl acetate) to give pure boronic ester **6.41**[29] as a colourless liquid (1.13 g, 73%); δ^1H (500 MHz; CDCl$_3$): 7.24 (2H, d, J = 7.9 Hz, CHa), 7.15 (1H, d, J = 18.4 Hz, alkenyl CH), 7.01 – 7.11 (3H, m, CHb, c), 5.92 (1H, d, J = 18.4 Hz, alkenyl CH), 1.06 (12H, s, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 149.5 (CH), 137.6 (quat C, Ar C), 128.9 (CH), 128.6 (CH), 127.1 (CH), 83.3 (quat C, COCH$_3$), 24.8 (CH$_3$); ^{11}B{^{1}H}(96.2 MHz; CDCl$_3$): 29.9; LR - EI$^+$ MS m/z (%): 231 (M$^+$ +1, 52%), *higher molecular ions seen*; v_{max} (neat/cm^{-1}): 3082, 3060, 3026, 2979, 2930, 1739, 1624, 1577, 1450; Rf = 0.92 in 9:1 petroleum ether: ethyl acetate.

6.311 Synthesis of products for GC standards

6.311a Synthesis of hept-1-en-3-ol (6.27).
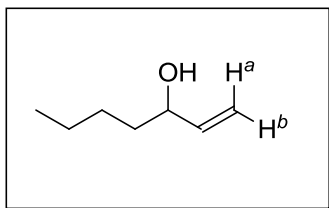
An oven dried 50 mL round bottomed flask equipped with a magnetic stirrer bar and septum was flushed with N_2 for 10 min. Vinyl magnesium bromide solution in THF (0.7 M, 20 mL, 14.0 mmol) was added, and the solution cooled to 0 °C. Valeraldehyde (1.24 mL, 11.7 mmol) was added drop-wise, and the reaction mixture left to stir for 15 min. Distilled water (10 mL) was added carefully, and the product extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with water (2 × 10 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give pure hept-1-en-3-ol[23] (**6.27**, 0.73 g, 55%) as a light yellow liquid; δ^1H (400 MHz; CDCl$_3$): 5.80 (1H, m, alkenyl CH), 5.13 (1H, d, J = 17.2 Hz, CHa), 5.05 (1H, d, J = 10.4 Hz, CHb) 4.03 (1H, app q, J = 6.7 Hz, CHOH), 1.71 (1H, br s, OH), 1.46 (2H, m, CH$_2$), 1.16 – 1.40 (4H, m, CH$_2$), 0.84 (3H, app t, J = 7.2 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 141.4 (CH, alkenyl CH), 114.5 (CH$_2$, alkenyl CH$_2$), 73.3 (CH, CHOH), 36.8 (CH$_2$), 27.5 (CH$_2$), 22.6 (CH$_2$), 14.0 (CH$_3$); LR - EI$^+$ MS m/z (%): *molecular ion not seen*, 101 (64%); ν_{max} (neat/cm^{-1}): 3349 (OH), 3079, 2931, 2861, 1845, 1644, 1467, 1320, 991.

6.311b Synthesis of 4-methyl-pent-1-en-3-ol (6.36).
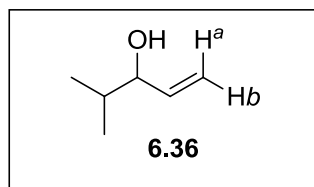
Procedure 6.311a was repeated using vinyl magnesium bromide solution in THF (0.7 M, 30 mL, 21 mmol) and isobutyraldehyde (1.60 mL, 17.5 mmol) to give 4-methyl-pent-1-en-3-ol[22] (**6.36**, 1.49 g, 85%) as a colourless liquid; δ^1H (500 MHz; CDCl$_3$): 5.80 (1H, m, alkenyl CH), 5.16 (1H, app dt, J = 17.2, 1.5 Hz, CHa), 5.10 (1H, app dt, J = 10.5, 1.5 Hz, CHb), 3.79 (1H, app t, J = 6.1 Hz, CHOH), 1.67 (1H, m, CH), 1.51 (1H, br s, OH), 0.87 (3H, d, J = 6.8 Hz,

CH$_3$), 0.83 (3H, d, J = 6.8 Hz, CH$_3$); δ^{13}C (125 MHz; CDCl$_3$): 139.5 (CH, alkenyl CH), 115.6 (CH$_2$, alkenyl CH$_2$), 78.3 (CH, CHOH), 33.6 (CH, *i*Pr CH), 18.1 (CH$_3$), 17.7 (CH$_3$); LR - EI$^+$ MS m/z (%): *molecular ion not seen*; 84 (M$^+$-OH, 100%), *higher molecular ions seen*; ν_{max} (neat/cm^{-1}): 3367 (OH), 3079, 2960, 2875, 1847, 1645, 1470, 1426, 1384, 1367.

6.311c Synthesis of 1-cyclohexylprop-2-en-1-ol (6.38).
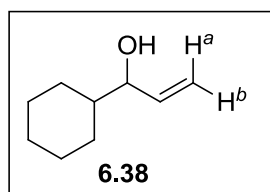
Procedure 6.311a was repeated using vinyl magnesium bromide solution in THF (0.7 M, 10 mL, 7 mmol) and cyclohexanecarboxaldehyde (0.71 mL, 5.9 mmol) to give 1-cyclohexylprop-2-en-1-ol[27] (**6.38**) as a colourless liquid (0.50 g, 61%); δ^1H (500 MHz; CDCl$_3$): 5.79 (1H, m, alkenyl CH), 5.13 (1H, app dt, J = 17.2, 1.6 Hz, CH*a*), 5.08 (1H, app dt, J = 10.4, 1.6 Hz, CH*b*), 3.78 (1H, app t, J = 6.4 Hz, C*H*OH), 1.78 (1H, m, CH), 1.68 (2H, m, cyclohexyl), 1.60 (2H, cyclohexyl), 1.49 (1H, br s, OH), 0.88 – 1.21 (6H, m, cyclohexyl); δ^{13}C (125 MHz; CDCl$_3$): 139.8 (CH, alkenyl CH), 115.4 (CH$_2$, alkenyl CH$_2$), 77.7 (CH, CHOH), 43.5 (CH), 28.8 (CH$_2$), 28.3 (CH$_2$), 26.5 (CH$_2$), 26.14 (CH$_2$), 26.08 (CH$_2$); LR - EI$^+$ MS m/z (%): *higher molecular ions seen, molecular ion not seen*, 122 (M$^+$-H$_2$O, 98%), 110 (100), 95 (90), 83 (100), 67 (96), 55 (94); ν_{max} (neat/cm^{-1}): 3366, 3076, 2926, 1853, 1643, 1450, 1424, 1308, 1261.

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