The Development and Application of Magnesium Base-mediated Transformations

A thesis submitted to the University of Strathclyde in part fulfilment of the requirements for the degree of Doctor of Philosophy

By

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This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed:

Date:

To my family

Acknowledgement

First and foremost I would like to thank my supervisor Prof. Billy Kerr for his support and encouragement, the discussions, stories, laughs and Oxford commas throughout my PhD. Having been able to return to sunny Glasgow for 4 years has been an incredible opportunity.

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I. Abstract

The exploration of magnesium bases has been the focus of this programme. Utilising the readily prepared Mes_2Mg as a base reagent in a slight excess of 1.5 mol, efficient mediation of the Shapiro reaction has been achieved. A range of easily accessible aryl tosylhydrazones, bearing electron-neutral or –donating substituents, delivered excellent levels of selectivity in electrophilic quench, up to 97:3 (E:H), in conjunction with yields up to 90 % of the corresponding disubstituted alkenes. With only 1.05 equivalents of Weinreb amides as electrophiles, yields as high as 77 % could be obtained. Efforts to utilise more demanding dialkyl tosylhydrazones were of limited success. Mechanistic investigations and attempts to trap key intermediates revealed a substantial lack of reactivity of the carbon-centred base at ambient temperatures and below. Further utilisation of the *in situ* generated vinyl magnesium species within Kumada-type cross-coupling reactions was also briefly explored. Preliminary studies, employing iron(III) chloride as a catalyst and TMEDA as an additive, delivered up to 32 % yield of the desired alkylated product.

Initial investigations into the efficacy of Mes_2Mg in Wittig reactions were focused on the formation of a non-stabilised phosphonium ylide and subsequent reaction with acetophenone. These studies furnished an unusually high *E*-selectivity of 4:1 (*E*:*Z*), albeit in low yields of the alkene product. The conversion of phosphonium salts bearing electron-withdrawing groups delivered yields of up to 93 %.

Extension of the methodology studies utilising magnesium base reagents within the synthesis of the natural product (-)-mucosin was targeted. Efficient preparation of two main fragments, the bicyclic core and the allylic side chain, furnished the desired compounds in 51 % and 41 % yield, respectively. In the key step, enantioselective deprotonation of the *meso*-ketone using a chiral magnesium bisamide produced the enol silane in excellent 92:8 selectivity and up to 87 % yield. Reaction of the silyl

enol ether with the allylic bromide delivered the desired keto ester in a 70 % yield. As an alternative for the alkylation step, utilisation of Tsuji-Trost allylation chemistry was explored. Completion of the natural product focused at first on the reduction of the ketone moiety and subsequent installation of a bromide leaving group. Extensive ^{1}H-NMR studies on the alcohol intermediate validated the proposed route towards (-)-mucosin. Introduction of the final ^{n}butyl side chain was attempted using a range of stoichiometric and catalytic organocuprate-based protocols. A second strategy towards (-)mucosin was devised, concentrating on alkylation of the ketone moiety instead of hydride reduction. However, the hindered position within the molecule prevented the ^{n}butyl group introduction and the completion of the natural product in both routes.

II. Abbreviations

Ac	acetyl
Aq	aqueous
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Cbz	carboxybenzyl
Conv.	conversion
Cp	cyclopentadienyl
c-Hex	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
d.r.	diastereomeric ratio
E	electrophile
EDG	electron-donating group
ee	enantiomeric excess
EQ	external quench
eq	equivalents
e.r.	enantiomeric ratio

Et	ethyl
EWG	electron-withdrawing group
FTIR	Fourier transformation infra-red
G.C.	gas chromatography
GLC	gas liquid chromatography
h	hours
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
HW	Horner-Wittig
HWE	Horner-Wadsworth-Emmons
^{i}Pr	isopropyl
IR	infra red
IQ	internal quench
LAH	lithium aluminium hydride
LDA	lithium di-*iso*-propylamide
M	molar
2-MeTHF	2-methyltetrahydrofuran
Me	methyl
Mes	mesityl
mg	milligrams
MHz	megahertz
min	minutes
ml	millilitres
mmol	millimoles
MOM	methoxymethyl
M.p.	melting point
Ms	methane sulfonyl
Naph	naphthyl

NBS	*N*-bromosuccinimide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
	s singlet
	d doublet
	t triplet
	q quartet
	m multiplet
	br broad
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
ON	overnight experiment
PDC	pyridinium dichromate
PE	petroleum ether
Ph	phenyl
ppm	parts per million
rac	racemic
SM	starting material
rt.	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetrabutylammonium triphenydifluorosilicate
temp.	temperature
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl (*para*-toluenesulfonyl)
Tris	trisyl (2,4,6-tri-*iso*-propylphenylsulfonyl)
UV	ultraviolet

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Chapter 1

Development of a Carbon-centred Magnesium Base-mediated Shapiro Reaction

Contents

1. Introduction

Main-group organometallics have played a major role in modern organic chemistry since the first half of the 20th century and have gained in significance ever since.[1] As the understanding of their properties, behaviour in reactions, and the corresponding mechanistics has continually grown through advances in analytical technologies, their application has now become a fundamentally important element of organic synthesis.

1.1 Lithium Base Reagents

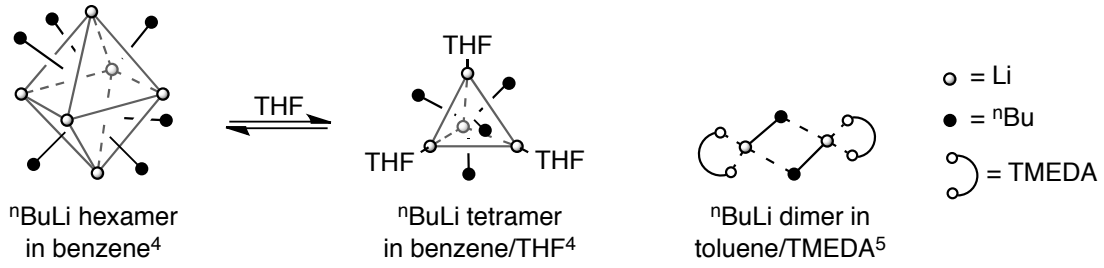
1.1.1 Alkyllithium Reagents

Organolithium reagents have gained enormous importance in synthetic chemistry over the years and are now amongst the most versatile and widely applied metal-based species available to the preparative chemist.[2] Such reagents are highly reactive in both a nucleophilic and basic sense, due to the strongly polarised lithium-carbon bond. In this way, they are employed in a broad spectrum of applications, ranging from simple deprotonation and addition reactions to more complex asymmetric transformations. Generally, they are utilised to facilitate the generation of new carbon-carbon bonds and also function as excellent precursors of other organometallic reagents.

Considering the preparation and handling of alkyllithium species, a number of points have to be taken into account. Firstly, they are air- and moisture-sensitive and must be kept and handled under inert atmospheres. More importantly, their high reactivity make the storage and application at low temperatures a necessity.

Interestingly, a close relationship between the structure and aggregation of the lithium reagents and their reactivity exists.[3,4] In most cases, a sharp increase in reactivity can be observed with a decrease in aggregation and complexity. Therefore, research in this field of study has partly focused on structural elucidation of organolithium compounds and the deaggregation of oligomers with the help of Lewis basic additives.[4] Commonly used donating solvents, such as diethyl ether and THF, and, more importantly, chelating additives, such as nitrogen-based ligands tetramethylethylenediamine (TMEDA) and sparteine, break up the lithium complexes into smaller units through coordination of the electron-deficient metal (**Figure 1.1**, **Scheme 1.1**). Thus, the individual carbon-lithium bonds are more polarised and the basicity and/or nucleophilicity of the organolithium reagent are greatly increased. Moreover, by generating these adducts with Lewis bases, the solubility of the reagents is also generally increased.

Figure 1.1

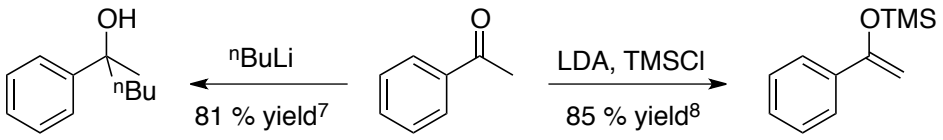


Scheme 1.1

A plethora of organolithium reagents is now available, with ranging reactivity and stability to suit the desired properties required for the envisioned synthetic organic transformation.

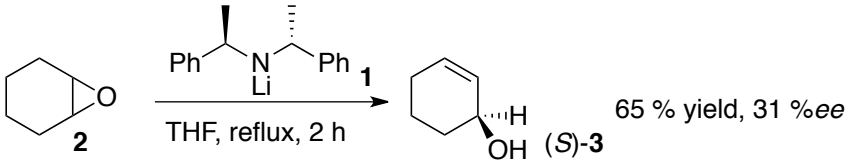
1.1.2 Lithium Amide Bases

An essential class of lithium reagents are lithium amide bases of the general structure $LiNR_2$. Such species have been of much importance as base reagents and act as powerful tools within deprotonation reactions.[6] Most prominent in respect to selective kinetic deprotonation reactions of ketones, as well as within many other processes, is lithium diisopropylamide (LDA). Despite being a strong base, LDA is a weak nucleophile. Based on this, selective α-deprotonation of a carbonyl group to form the corresponding lithium enolate becomes feasible without competitive nucleophilic attack at the carbonyl carbon, as might be observed with the less sterically hindered and consequently more nucleophilic *n*-BuLi (**Scheme 1.2**).[7,8] Having stated this, when utilising aldehydes or certain α-substituted ketones with LDA, addition and reduction reactions are a more common occurrence.[9–12] Nonetheless, LDA has become one of the most widely employed base reagents in organic chemistry.



Scheme 1.2

The first attempts of enantioselective deprotonations using chiral lithium amide bases were performed by Whitesell and Felman in 1980.[13] These workers were able to demonstrate that a chiral base such as **1** could differentiate between enantiotopic hydrogen atoms of a prochiral epoxide, removing one of the two protons *syn* to the oxygen preferentially. Although the rearrangement of epoxide **2** to the corresponding allylic alcohol **3**, as illustrated in **Scheme 1.3**, furnished a low enantiomeric excess of 31 %, it marked the initiation of further in-depth research into asymmetric deprotonation reactions mediated by lithium amides.



Scheme 1.3

The choice of amine ligand and the position of the chiral centre within the ligand are important factors for the degree of enantioselectivity and yield of such asymmetric reactions. Supplementary studies by Asami and O'Brien on the asymmetric rearrangement of epoxides highlight, quite clearly, the sensitivity with which the lithium amide system reacts to alterations in structure, steric bulk, and chirality of the amine employed.[14–16] Using finely tuned (*S*)-proline or norephedrine-derived amines, respectively, enantioselectivity could subsequently be increased up to 94 %*ee* (**Scheme 1.3**, **Figure 1.2**).

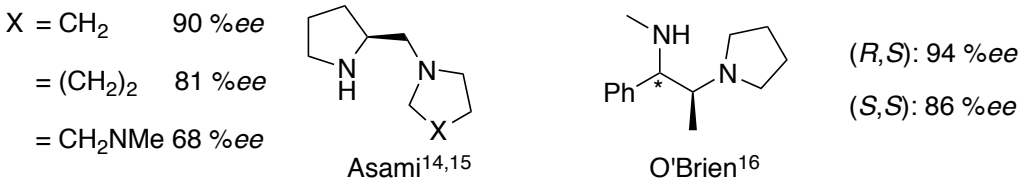


Figure 1.2

Despite the requirement for precisely designed amines, the resulting research emphasises the embedded possibilities for further asymmetric transformations with an optimised system. Accordingly, use of chiral lithium bases was not only restricted to epoxides.

In relation to these first examples of selective deprotonation, alternative substrates such as conformationally locked prochiral ketones, e.g. cyclohexanones, moved into focus very swiftly. The concept for this class of substrates envisages a substituent **R** in the 4-position of the cyclohexanone, thus fixing the symmetrical ketone in the thermodynamically most favoured chair position, with **R** being equatorial (**Figure 1.3**).

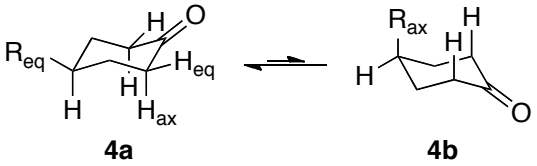
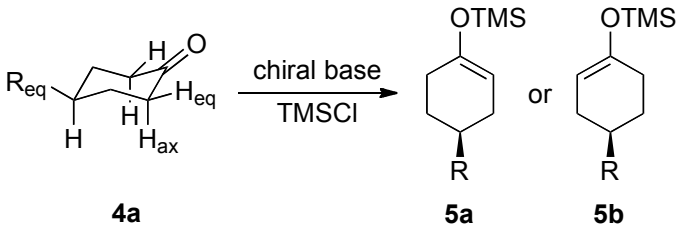


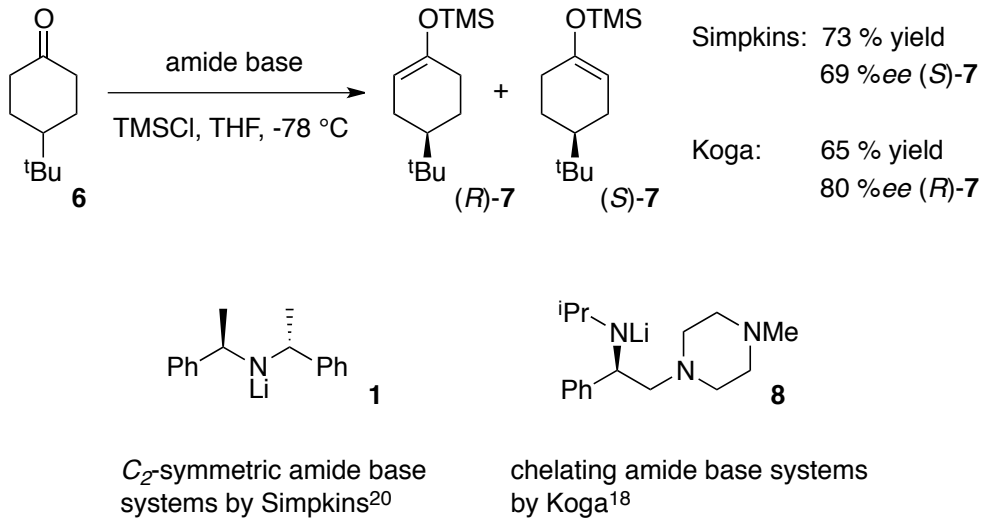
Figure 1.3

Due to stereoelectronic effects, a base reagent abstracts the axial protons α to the carbonyl group in cyclic ketones preferentially.[17] Therefore, a chiral base would be capable of distinguishing between the two enantiotopic protons and, upon trapping the formed lithium enolate with a suitable electrophile like trimethylsilyl chloride (TMSCl), enantiomerically-enriched silyl enol ethers **5** could be formed (**Scheme 1.4**). Indeed, this approach is readily applicable using chiral lithium amide bases and 4-substituted cyclohexanones quickly became standard substrates for assessing the efficacy of chiral amide bases.[18–21]



Scheme 1.4

In the mid-1980s, seminal discoveries and further optimisations on this subject were made by the research teams of Simpkins[19–21] and Koga,[18] focusing on C_2-symmetric and chelating amine ligands, respectively (**Scheme 1.5**).



Scheme 1.5

Respectable enantiomeric excess could be achieved with both chiral systems at this early stage and investigations into the subject pressed on to find the optimum conditions for a more selective and higher yielding asymmetric generation of silyl enol ethers.

Conditions

As with other organolithium reagents, deprotonation reactions with lithium amide bases are generally carried out under inert conditions and at low temperatures (around -78 °C). In this way, the degradation of the lithium species is prevented and the kinetic reaction pathway is favoured, resulting in superior reactivity and selectivity. It can be generalised that the lower the reaction temperatures, the higher the enantioselectivity of the process.

Furthermore, reactivity and selectivity enhancing effects are attributed to donating solvents and Lewis base additives. Reactions carried out in THF provide exceptionally high yields and selectivities. Moreover, independently of the solvent, the inclusion of Lewis bases such as HMPA proved valuable in respect to conversion

and selectivity of the deprotonation process for Koga-type base systems.[22,23] Interestingly, the addition of lithium chloride had an equally beneficial impact, especially when none is formed *in situ* from TMSCl during the course of the reaction, i.e. as part of an external quench process.[24–26] All of these observations can be ascribed to the aggregation state of the lithium species in solution. A number of NMR and X-ray crystallography studies revealed aggregates of differing complexity, depending on the solvents and additives used. Donating solvents and Lewis base additives promote the deaggregation of oligomeric units into dimers or monomers by coordination to the lithium centre.[22,23] In the same sense, lithium chloride is capable of breaking up the larger aggregates to form mixed dimers (**Figure 1.4**).[25–27]

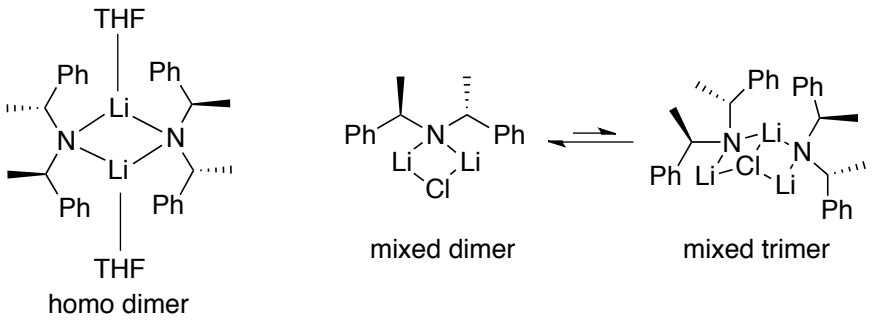
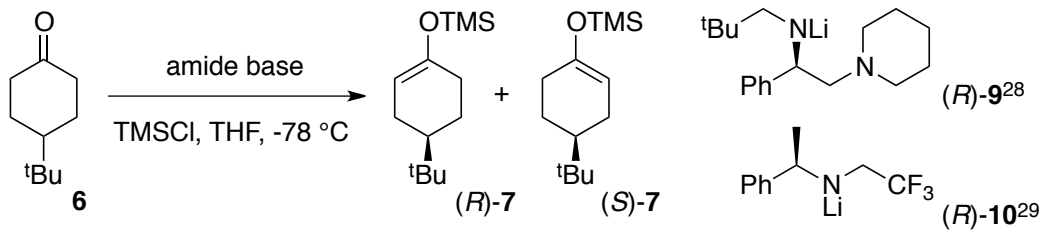


Figure 1.4

Consistent with preceding results, the generated monomeric species exhibit an enhanced reactivity and selectivity compared to the higher aggregates. Moreover, with the progressing structural development of the amide moiety, good conversion and selectivities could be achieved in the formation of silyl enol ether **7** (**Scheme 1.6, Table 1.1**).[28,29]



Scheme 1.6

Entry	*Amide Base*	*Yield* (%)	*E.r.* (*S*:*R*)
1	(*R*)-**9**	93	7:93
2	(*R*)-**10**	98	94.5:5.5

Table 1.1

Enantiomeric excess of up to 89 %*ee* and excellent yields could now be accomplished when employing lithium amide base (*R*)-**10**. As most optimisation studies in lithium-mediated asymmetric deprotonation reactions had mainly focused on 4-substituted ketones, alternative substitution patterns for cyclohexanones were considered, as well as varying ring sizes, in order to broaden the applicability of the developed systems.[11,30–32] Other substrates included sulfoxides,[33] phosphine oxides,[34] bridged bicyclic ketones[35] and imides.[36–38] The majority of these showed good to excellent selectivities and the scope of application is continually growing. As such, chiral lithium amide bases remain valuable reagents in asymmetric transformations.

In view of the progress that has been made since the first discoveries by Whitesell and Felman in 1980,[13] lithium amide bases have been developed to become reliable and frequently used reagents in asymmetric transformations of prochiral substrates.[39,40] Indeed, research is still ongoing to challenge the drawbacks that have emerged over the past decades. In particular, the complex solution behaviour of lithium amides can make it difficult to determine and reproduce the most reactive species of these systems. Moreover, the stability of lithium reagents is limited to low temperatures, which restricts their application considerably and leaves the targeted transformations more cost intensive on an industrial scale.

1.2 Magnesium Reagents

Alkyllithium and lithium amide base systems have shown great efficiency and a wide applicability in synthesis. However, as mentioned above, considerable drawbacks have to be taken into account. Based on this, magnesium analogues were regarded as a suitable alternative.

1.2.1 Magnesium Amide Bases

Organomagnesium compounds have found numerous applications in organic chemistry in the form of Grignard reagents.[2] In contrast, other similar reagents, such as Hauser bases and magnesium bisamides, have gained in significance only recently (**Figure 1.5**).[41,42] Moreover, despite the success of lithium amides, the equivalent magnesium bisamides have been somewhat neglected, even though they exhibit a number of advantages over the corresponding lithium reagents.[43]

R-Mg-X	R_2N-Mg-X	$(R_2N)_2Mg$
Grignard reagents	Hauser bases	Magnesium bisamide

Figure 1.5

Similar to lithium amides, the aggregation states observed in magnesium amides are largely dependent on the solvent employed and the size and nature of the amide ligand. However, the solution behaviour is much less complex, as most species with bulkier ligands are limited to monomers and dimers. Lewis basic additives such as HMPA can further assist in obtaining more predictable and reproducible aggregates.[44,45] At the same time, this helps to furnish reliable and more selective results when applied within organic synthesis. Furthermore, magnesium bisamides display a greater stability at elevated temperatures of -78 °C and above than their lithium equivalents.[46] The enhanced thermal stability allows for heating to moderately

elevated temperatures and reflux without any noticeable amount of degradation. Although this also implies a lowered reactivity compared to lithium amides, enhanced selectivities are potentially attainable through kinetic control.[47]

Another advantage arises from the divalency of magnesium. This opens up the possibility of introducing two ligands, allowing for homo- and heteroleptic species (**Figure 1.6**).

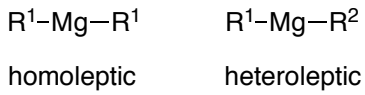
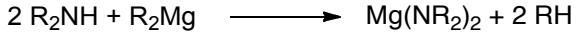


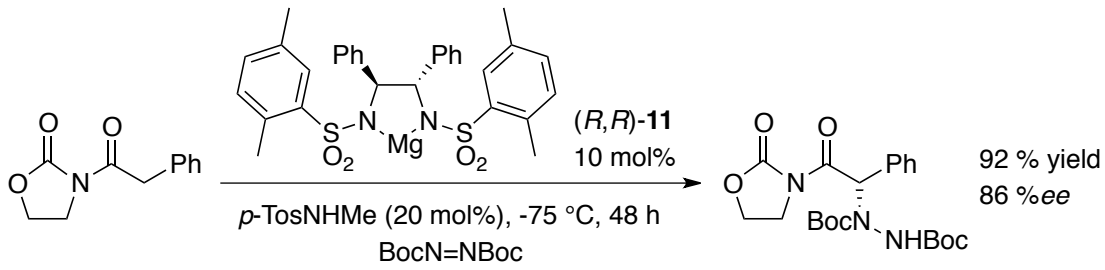
Figure 1.6

In addition, various synthetic routes are now available for the preparation of magnesium bisamides.[43] The most elegant and reliable method involves reacting a dialkylmagnesium species with two equivalents of the appropriate amine at reflux in THF (**Scheme 1.7**).[48] A number of thus generated achiral magnesium bisamides have been applied by Eaton in *ortho*-magnesiations with $Mg(TMP)_2$,[47] and by Bordeau in facilitating the formation of enol silanes with $(^{i}Pr_2N)_2Mg$ and $(TMS_2N)_2Mg$.[49,50]



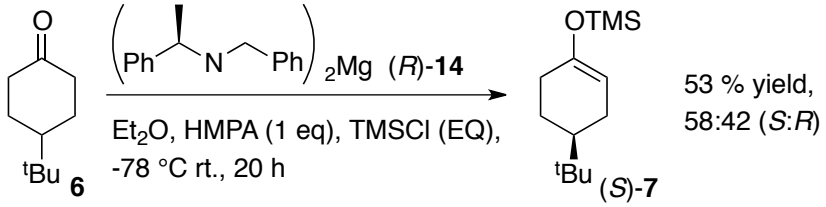
Scheme 1.7

In spite of these promising properties, the first example of a magnesium-mediated asymmetric process *via* an enolate was not reported until Evans' publication on enantioselective amination utilising a chiral sulfonamide complex, (*R*,*R*)-**11**, in 1997 (**Scheme 1.8**).[51] A high 92 % yield and impressive 86 % enantiomeric excess were presented, despite the fact that only catalytic amounts of the chiral amide were used.



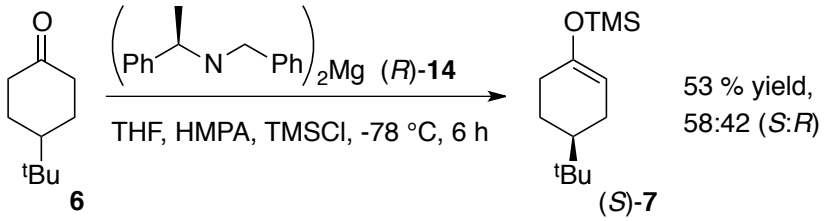
Scheme 1.8

The first steps towards applications of chiral magnesium bisamides in asymmetric deprotonation reactions were taken jointly by the research groups of W. J. Kerr and K. W. Henderson at the University of Strathclyde in 2000.[52,53] The initially conducted experiments quickly showed potential for the proposed application. The magnesium bisamide (*R*)-**14**, prepared from the relatively cheap and structurally simple (*R*)-*N*-benzyl-α-methylbenzylamine and Bu_2Mg, was applied in the desymmetrisation of 4-*tert*-butylcyclohexanone to furnish a 53 % yield of the silyl enol ether in favour of the (*S*)-enantiomer with 58:42 *e.r.* (**Scheme 1.9**).[52] Although these preliminary results are only moderately effective, they represented the first enantioselective deprotonation of a prochiral ketone mediated by a chiral magnesium bisamide.



Scheme 1.9

Following these preliminary observations, substitution of diethyl ether for the more polar solvent THF and employment of an internal quench protocol improved the reactivity and selectivity of the magnesium base system (*R*)-**14** significantly, delivering (*S*)-**7** in good yield and appreciatively enhanced selectivity (**Scheme 1.10**, **Table 1.2**).[52,53] Notably, the equivalent lithium base system at -78 °C furnishes only a conversion of 71 % and an *e.r.* of 75:25 (*S*:*R*).[21]

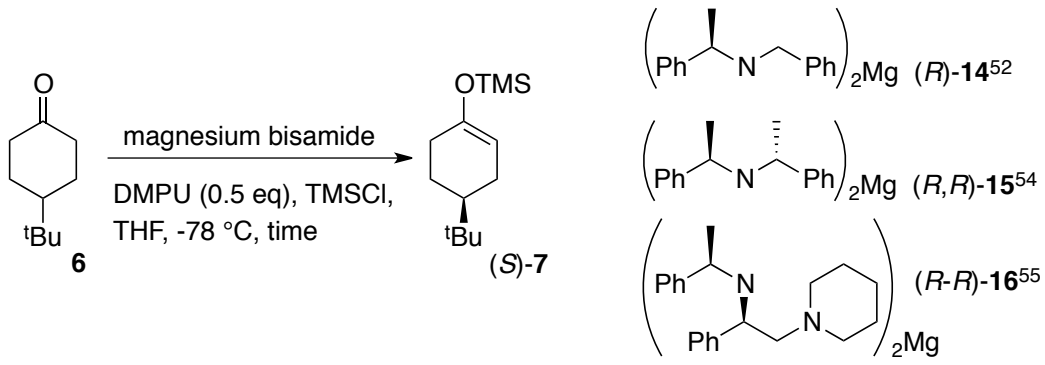


Scheme 1.10

Entry	*HMPA*	*Conversion* (%)	*E.r.* (*S*:*R*)
1	-	33	90:10
2	0.5 eq	82	91:9

Table 1.2

From the above observations, a change in solution aggregation was suggested as the basis of the overall enhancement in effectiveness. Further optimisation of the above system included the substitution of HMPA by the less toxic DMPU as an additive. Additionally, alternative C_2-symmetric and chelating amines were screened as suitable ligands. From these studies, optimised magnesium bisamide systems emerged, capable of furnishing selectivities up to 94:6 *e.r.* with ketone substrate **6** (**Scheme 1.11**, **Table 1.3**).[52,54,55]

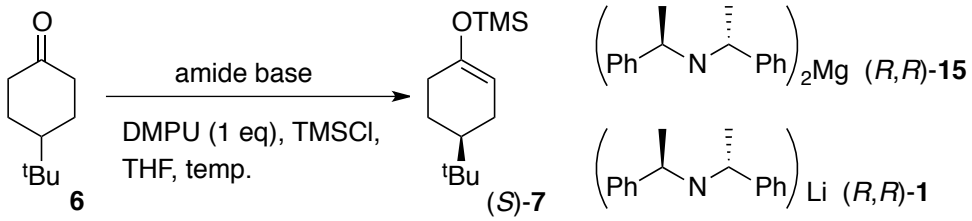


Scheme 1.11

Entry	*Amide Base*	*Time* (h)	*Conv.* (%)	*E.r.* (*S*:*R*)
1	(*R*)-**14**	6	89	90:10
2	(*R*,*R*)-**15**	16	97	94:6
3	(*R*,*R*)-**16**	1.25	90	93:7

Table 1.3

Considering the C_2-symmetric bases further, a very good *e.r.* of 94:6 was obtained at -78 °C. In addition, when the reaction temperature was raised to -20 °C, the *e.r.* observed remained remarkably high (**Scheme 1.12**, **Table 1.4**).[54] Notably, at this temperature and even at 0 °C, the developed magnesium amide-mediated process compares favourably to the analogous lithium amide system using (*R*,*R*)-**1**, which furnishes silyl enol ether **7** in a yield of 73 % and with an *e.r.* of only 85:15 even at -78 °C.[56] Having stated this, only when employing ambient temperatures does the selectivity decrease more significantly with (*R*,*R*)-**15**.



Scheme 1.12

Base	*Temp.* (°C)	*Conv.* (%)	*Yield* (%)	*E.r.* (*S*:*R*)
(*R*,*R*)-**15**	-78	97	88	94:6
(*R*,*R*)-**15**	-20	97	78	88:12
(*R*,*R*)-**15**	0	93	66	86:14
(*R*,*R*)-**15**	25	89	66	75:25

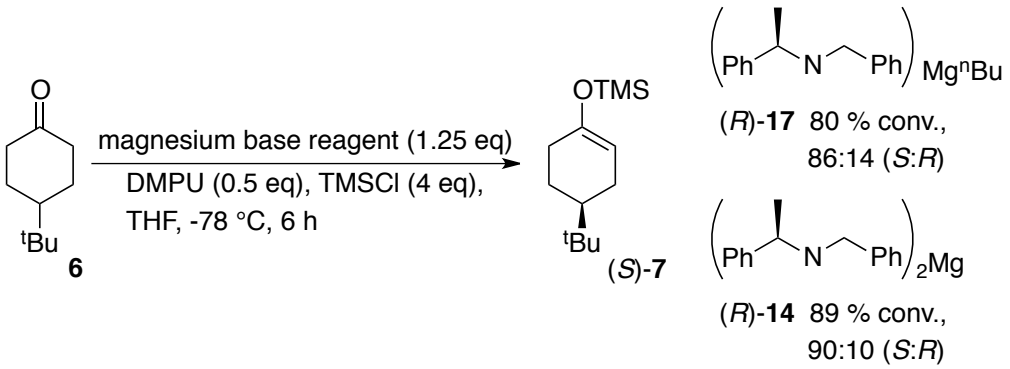
Table 1.4

Based on that detailed above, bisamide (*R*,*R*)-**15** has now emerged as one of the most efficient and versatile magnesium base reagents in asymmetric deprotonation

reactions to date, with a considerable range of substrates being readily transformed, including bridge bicyclic species, to the corresponding silyl enol ethers stereoselectively at both -78 °C and -20 °C, respectively.[54,57] Additionally, computational studies have been conducted to advocate the experimental findings with theoretical data and to allow the design of new efficient amine bases.[57]

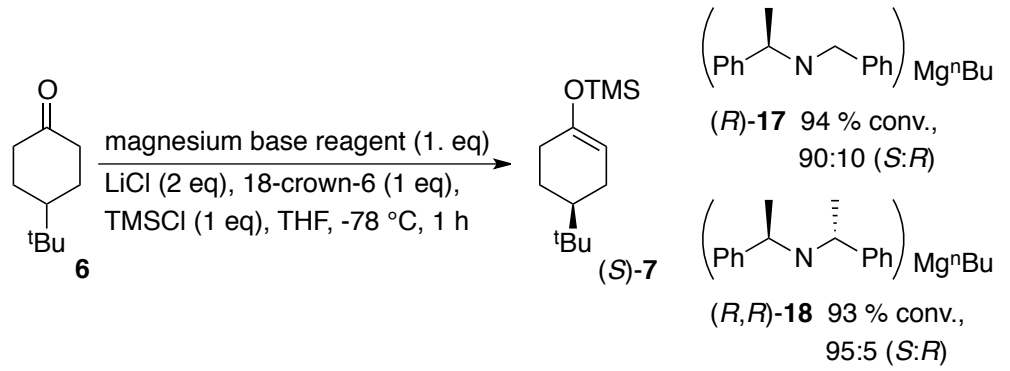
Following these notable achievements, the possibly advantageous divalent nature of magnesium was further explored. In contrast to lithium, and as a major benefit, magnesium can give access to homo- and heteroleptic complexes, opening up a whole new range of possibilities in the design of the base structure. Moreover, by exchanging one amide ligand for an achiral alkyl, alkoxy or halide ligand the amount of the valuable chiral amine could be lowered to 1 equivalent for the described process. In this way, the magnesium-mediated asymmetric deprotonation would become more efficient and cost effective. Various approaches in this area were thus taken, investigating the reactivity and selectivity of alkyl- and alkoxymagnesium amides, as well as Hauser bases.[58–60]

In this regard, alkylmagnesium amide species, which are known to facilitate alkylations,[61,62] enantioselective conjugate additions,[63] reduction of ketones,[64,65] and the deprotonation of carboxamides,[66,67] were probed in the asymmetric deprotonation of **6** under the previously developed conditions for magnesium bisamides. Gratifyingly, *n*-butylmagnesium amide **17** delivered almost equal reactivity and selectivity as the corresponding bisamide system and showed no reduction or alkylation by-products (**Scheme 1.13**).[58]



Scheme 1.13

Further optimised reaction conditions with alkylmagnesium amides (*R*)-**17** and (*R*,*R*)-**18**, which employed 2 eq LiCl and 1 eq 18-*crown*-6 as additives instead of DMPU, delivered excellent selectivities of up to 95:5 (*S*:*R*) within 1 hour reaction time and only 1 equivalent of the TMSCl quench (**Scheme 1.14**).[60] This protocol thus ensures a more economic use of the chiral amine, as it requires only half the quantity, whilst outperforming the system employing analogous lithium amide by far.[21,24]

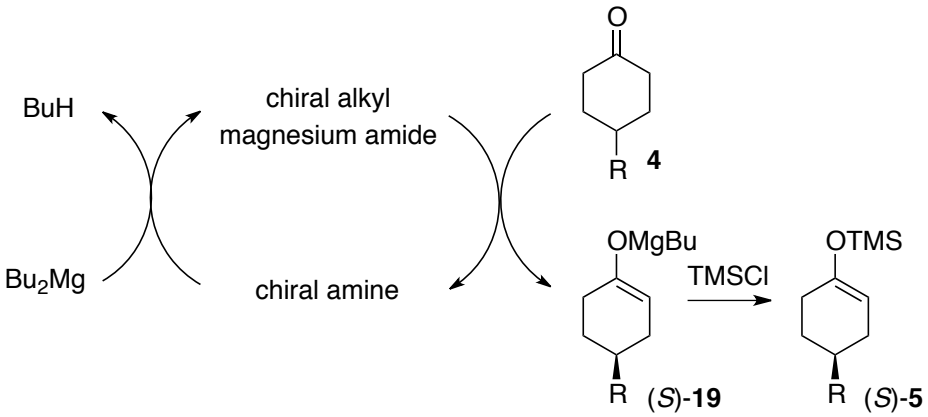


Scheme 1.14

As has been shown above, alkylmagnesium amides provide a more cost-effective process to generate chiral silyl enol ethers compared to the corresponding magnesium bisamide system. To verify which ligand was performing the key deprotonation, ^{1}H-NMR experiments were carried out within our lab, monitoring the disappearance of the NH signal during the initial base formation and its reappearance

during the deprotonation reaction. Moreover, the characteristic signal of the alkyl ligand remained constant throughout, revealing no expulsion of butane. As a whole, the studies confirmed that only the amide portion of the base was carrying out the deprotonation.[59]

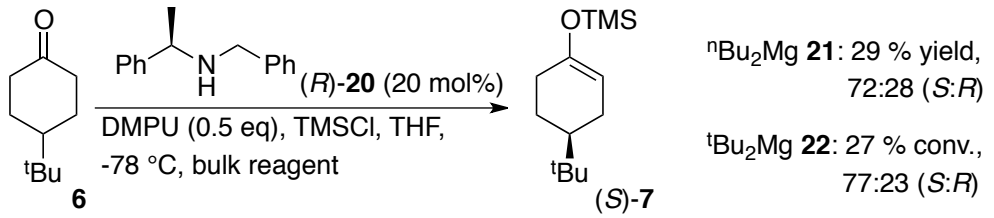
As a consequence of the above, the chiral amine is released into the reaction mixture during the reaction and the regeneration of the alkylmagnesium amide base *in situ* was considered feasible. A catalytic protocol was proposed considering analogous attempts within lithium amide-based deprotonation systems employing sub-stoichiometric amounts of the chiral amine.[68–71] More specifically, the desired chiral heteroleptic complex could be formed from a bulk reagent such as a dialkyl magnesium species and a catalytic amount of the chiral amine. Upon reaction of the introduced ketone **4** to enolate **19** and release of the amine ligand, the reactive species could be regenerated *in situ*, as depicted in **Scheme 1.15**, using the remaining bulk Bu_2Mg reagent.



Scheme 1.15

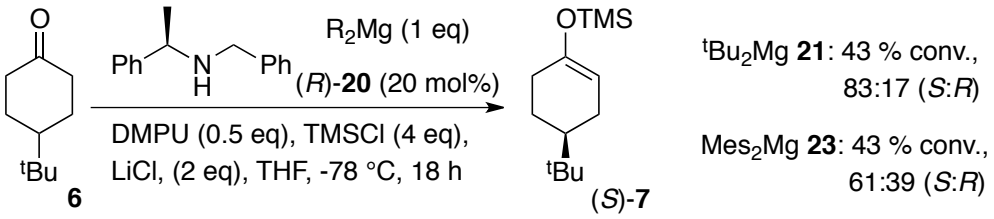
Initial trials confirmed the validity of this protocol, yielding 29 % of the silyl enol ether with 72:28 *e.r.* in favour of the (*S*)-enatiomer, whilst using only 20 mol% of the chiral amine **20** (**Scheme 1.16**).[59] However, competitive alkylation and reduction reactions were observed, rendering the initially employed stock reagent $^{n}Bu_2Mg$ **21** unsuitable for this process. The sterically more encumbered $^{t}Bu_2Mg$ and

Mes_2Mg on the other hand, showed only very small amounts of the alkylation/reduction side products being formed and were subsequently used as stock reagents.



Scheme 1.16

Disappointingly, even after intensive optimisation studies, no substantial increase in reactivity of the bulk reagent at the required low temperatures could be observed, possibly preventing the regeneration of the alkylmagnesium amide. The best conditions found to date for the proposed catalytic protocol are shown in **Scheme 1.17**.[60] Despite only moderate reactivity, the enantiomeric excess could be improved up to 83:17 (*S*:*R*) at -78 °C using 20 mol% of the chiral amine, $^tBu_2Mg$ and, crucially, including LiCl as an additive.

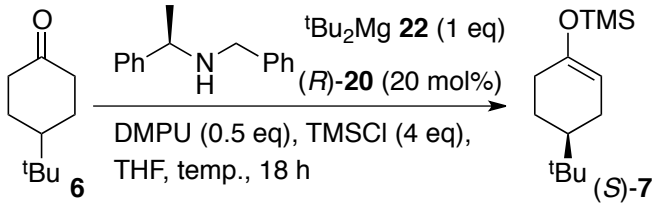


Scheme 1.17

1.2.2 Carbon-centred Magnesium Bases

Amidst the studies of hetero- and homoleptic magnesium amide complexes and especially in the research within the development of a catalytic amide recycling system, the reactivity of another magnesium species became evident.[60] Whilst

employing dialkyl- and diarylmagnesium species as bulk reagents to generate an alkyl-/arylmagnesium amide species *in situ*, a significant rise in yield along with a drop in enantioselectivity could be observed as the reaction temperature was increased (**Scheme 1.18**, **Table 1.5**).[60] It was thus discovered that the stock reagent increasingly deprotonated cyclohexanone **6** unselectively with rising temperatures and did so even in absence of any amine additive.



Scheme 1.18

Entry	*Temp.* (°C)	*Conv.* (%)	*Yield* (%)	*E.r.* (*S*:*R*)
1	-78	43	33	83:17
2	-60	53	42	72:28
3	-40	93	87	58:42

Table 1.5

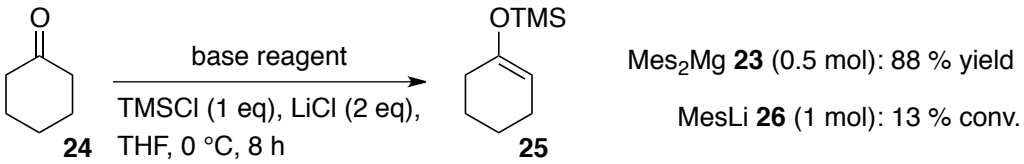
As indicated above, as opposed to the originally used stock reagent $^{n}Bu_2Mg$, $^{t}Bu_2Mg$ and Mes_2Mg exhibit a reduced reactivity and, more importantly, do not lead to addition or reduction of the ketone even at a more elevated temperature of -40 °C. This suggests that the increased steric bulk of those carbon-centred magnesium species inhibits the competitive addition, whereas the lack of β-hydrogens prevents the reduction process, *via* β-hydride elimination, under the employed conditions.

It has to be noted, that very little precedent for intentionally induced enolisation reactions with analogous lithium carbon-centred bases can be found in the literature. In most cases, this is due to the high nucleophilic character and the, consequently, favoured carbonyl addition or reduction process. In those cases, the enolisation

pathway occurs as an undesired side reaction.[2] Thus, only bulky alkyllithium reagents, such as triphenylmethyllithium, can mediate the enolisation of certain ketones more successfully.[72,73] Additionally, highly sterically encumbered ketones, such as trityl ketones, can be transformed to the corresponding enolate with *n*-butyllithium.[74] However, overall the examples in this regard are scarce. Thus, the discovered interesting new nature of carbon-centred magnesium reagents was further investigated to establish their reactivity and determine the scope of their applicability.

Mes_2Mg

Upon optimising the deprotonation of the simpler cyclohexanone **24** with Mes_2Mg, an 88 % yield of the silyl enol ether **25** was achieved (**Scheme 1.19**).[75] Notably, this was accomplished at a more accessible temperature of 0 °C, as opposed to excessive reaction cooling, and with only 1 eq of the TMSCl quench. In comparison, the analogous lithium species **26** gave rise to only 13 % conversion to the desired product, with the major by-product being the *C*-silylated mesitylene.[75] Moreover, as Mes_2Mg is divalent, just 0.5 mol of the base reagent relative to the ketone substrate are required to facilitate the reaction. LiCl proved to be a vital addition to the system as a set up without the additive furnished a conversion of only 62 % even with 4 eq TMSCl.[75]



Scheme 1.19

With these excellent results in hand, the substrate scope was further explored by employing simple cyclic ketones, alternative substituted cyclohexanones, and more functionalised ketones.[75] A small selection of the results achieved is depicted in **Figure 1.7**.

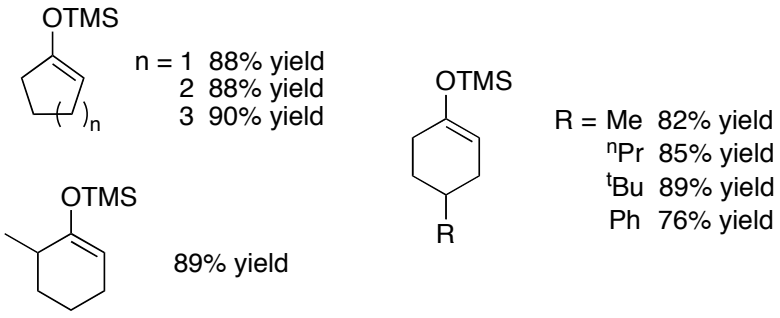
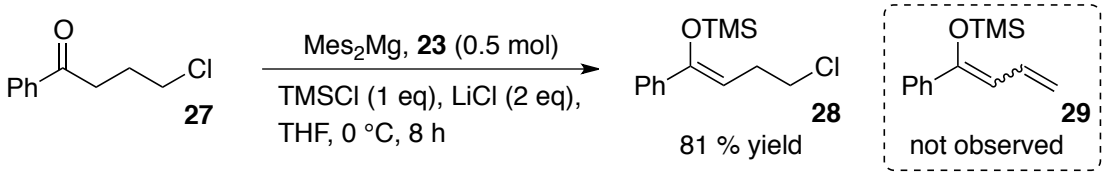


Figure 1.7

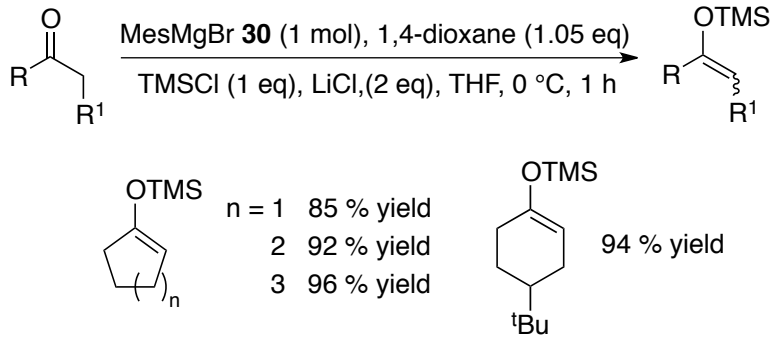
All of the selected ketone substrates were deprotonated readily in good to excellent yields. As was shown with 2-methylcyclohexanone, the kinetic reaction product is delivered exclusively. The developed system proved general and mild even with more sensitive substrates such as **27**, which was transformed to the corresponding silyl enol ether without elimination and as a single isomer (**Scheme 1.20**).[75] This is in contrast to more generally used lithium base reagent LDA, as this promotes the elimination reaction under similar reaction conditions, leading to compound **29** as the major product. Magnesium carbon-centred base **23** has thus been shown to operate very efficiently at a more elevated temperature of 0 °C.



Scheme 1.20

With the establishment of this effective system, further development in relation to the practical handling of the deprotonation reaction was sought. In this regard, the preparation of the diarylmagnesium species is relatively straightforward: stirring a solution of the parent Grignard reagent in THF with 1,4-dioxane affords a stock solution of the dialkyl or diaryl complex in quantitative yield.[76] However, in order to simplify the process and increase its applicability, the development of a one-pot procedure was attempted in which the reactive diaryl species is generated *in situ*

(**Scheme 1.21**).[77] Pleasingly, this could be utilised without difficulty and, upon optimisation, the previously assessed ketones delivered, once more, good to excellent yields of the silyl enol ether products under a similar set of reaction conditions at 0 °C.

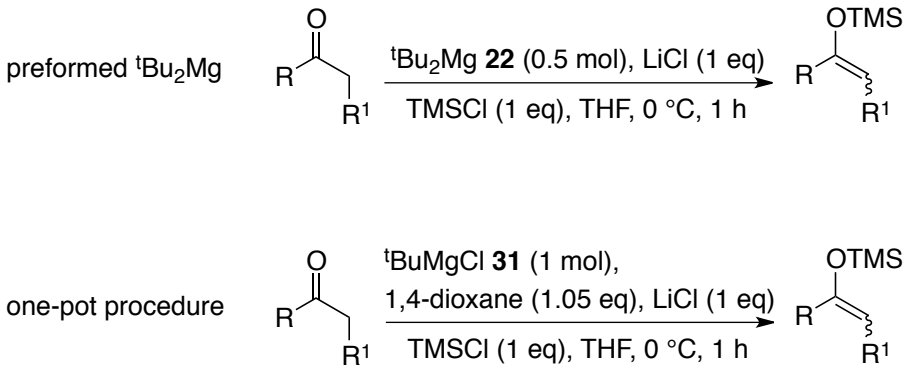


Scheme 1.21

Notably, the reaction time could be shortened to one hour with the *in situ* generated base system, as opposed to 8 hours with preformed Mes_2Mg. In this way, a thermally stable and readily accessible reagent has been developed for use in the achiral deprotonation of ketone substrates without the use of any amide additives or less convenient reaction conditions. Moreover, no further by-products were observed, rendering this reagent virtually non-nucleophilic and non-reductive.

$^tBu_2Mg$

In view of the excellent results obtained by the employment of the carbon-centred base Mes_2Mg, di-*tert*-butylmagnesium **22** was reconsidered as an equally suitable reagent. Accordingly, similar optimisation studies were performed with both preformed and *in situ* generated **22**, and a similar range of ketones was used to screen its reactivity. The optimised conditions for both methods are presented in **Scheme 1.22**.[78]



Scheme 1.22

As opposed to Mes_2Mg, only one equivalent of LiCl was found to be the optimum for both procedures and similarly good yields were obtained for the majority of ketones screened after one hour reaction time. A small range of results, achieved using the one-pot procedure with the di-*tert*-butylmagnesium base, is shown in **Figure 1.8**.[78] Overall, $^tBu_2Mg$ **22** exhibited a greater reactivity at lower temperatures and provides a better atom economy compared to Mes_2Mg. Furthermore, the one-pot protocol gives rise to a cleaner and higher yielding conversion to the desired products.

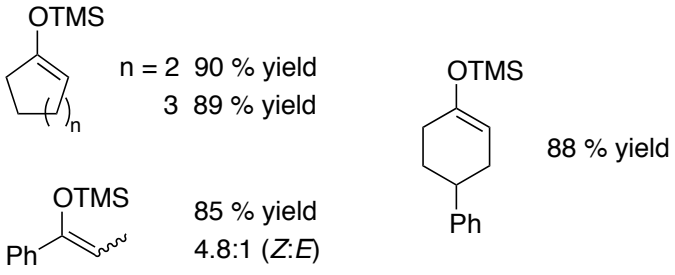


Figure 1.8

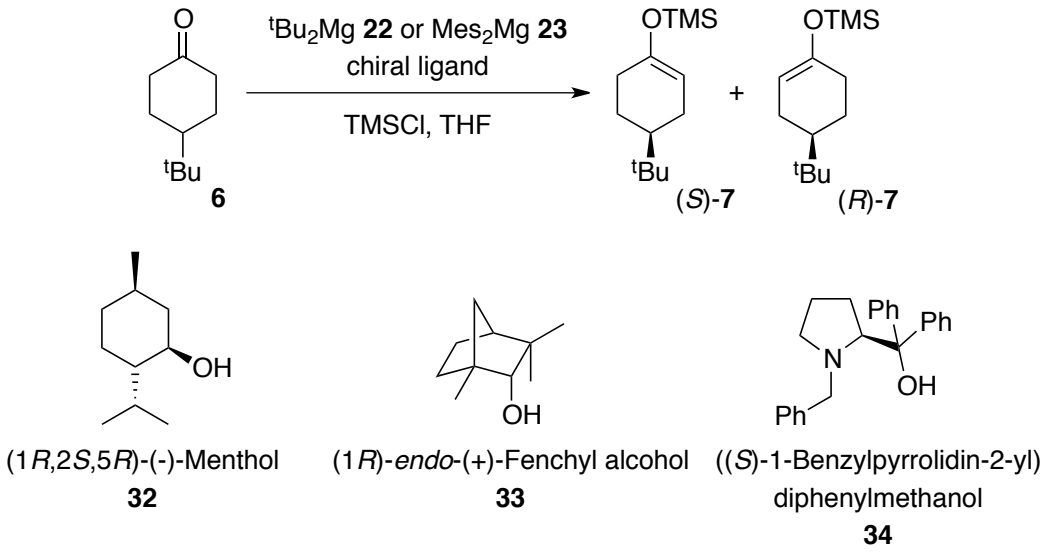
Both novel carbon-centred base species, Mes_2Mg and $^tBu_2Mg$, have proven to be effective reagents for achiral deprotonation reactions. In addition, only 0.5 mol of the reagent is required to complete the reaction, while the practical methods have been improved through the development of a convenient one-pot protocol.

Substrate Scope

To further explore the scope of carbon-centred bases, diarylmagnesium species **23** was subjected to tests with a number of different substrates other than ketones. Disappointingly, the deprotonation of compounds such as aldehydes, esters and carboxylic acids could not be carried out successfully. In most cases, no conversion to the desired products could be observed, returning the starting material almost quantitatively.[60] Further research into the transformation of aldehydes revealed that this class of substrates was prone to self-condensation and nucleophilic attack by the magnesium reagent. Nonetheless, the results obtained from the less electrophilic substrates gave rise to the belief that further optimisation could render the base system more reactive and hence make these transformations possible.

Asymmetric Deprotonation

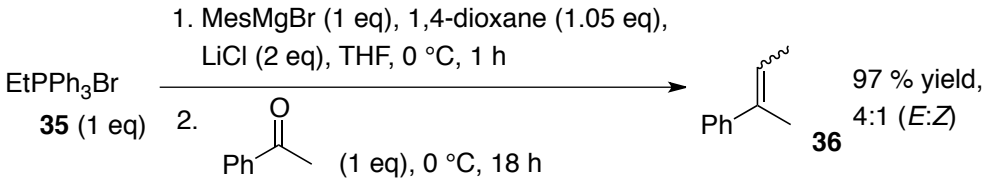
Initial efforts to introduce an asymmetric element to the developed carbon-centred base systems in the deprotonation of prochiral ketone **6** have delivered some small degrees of success. A series of chiral ligands such as amines, alcohols, and carboxylic acids has been screened under a variety of different conditions.[60] A general scheme for the reaction is depicted in **Scheme 1.23**. Alcohols **32**, **33**, and **34** have exhibited the best selectivities, with alcohol **34** delivering an *e.r.* of 19:81 (*S*:*R*). However, to this stage conversions and yields have been consistently low.



Scheme 1.23

Wittig Reaction

As the previously described deprotonations had shown, carbon-centred magnesium species can be successfully applied as base reagents across a selection of ketone substrates. To further explore the utility of the emerging magnesium systems, alternative base-mediated transformations were considered. In this regard, a Wittig-type reaction was envisaged to be feasible. Formation of the reactive phosphonium ylide from phosphonium salts is typically conducted by deprotonation with lithium- or sodium-based reagents.[79,80] The reactivity of *in situ* generated Mes_2Mg towards this deprotonation was thus attempted using $EtPPh_3Br$. As depicted in **Scheme 1.24**, an impressive 97 % yield was attained with a surprisingly 4:1 (*E*:*Z*) selectivity using acetophenone as the ketone moiety.[77] Importantly, the metal cation can have a marked effect on the configuration of the formed double bond and non-stabilised ylides usually furnish predominantly the *Z*-isomer with lithium bases.[80] Further investigations to find optimum conditions and explore the substrate scope have yet to be conducted. Consequently, this area of olefination chemistry remains an attractive target for further development of our alkylmagnesium-mediated deprotonations.



Scheme 1.24

Solution Structure

Many endeavours have been made to elucidate and understand the aggregation state of the discussed lithium and magnesium amide bases in order to be able to systematically optimise the emerging protocols further. On the other hand, little is known about the solution structure of dialkyl- and diarylmagnesium reagents, especially with additives present. Crystallised from a solution of Et_2O and THF, bismesitylmagnesium is proposed to exist as a monomer,[81–83] however the above discussed studies have shown that LiCl is a key additive. Upon consideration of the aggregation of the anticipated reactive species $Mes_2Mg.LiCl$, two possible structures were proposed: 'ate-type complexes **37** and **38** (**Figure 1.9**).[77] Similar complexes of this nature have been observed with dialkylmagnesium reagents and cryptand additives, which exhibit, equally to the $Mes_2Mg.LiCl$ species, an increased reactivity compared to the parent reagents without any additives.[84–86] Literature precedent for a closely related aggregate, formed from $(2,4,6\text{-}^{i}Pr_3C_6H_2)_2Mg$ and $(2,4,6\text{-}^{i}Pr_3C_6H_2)Li$,[82] as well as NMR studies conducted within our laboratories on the discussed $Mes_2Mg.LiCl$ system,[60] led us to favour the bridged complex **38**.

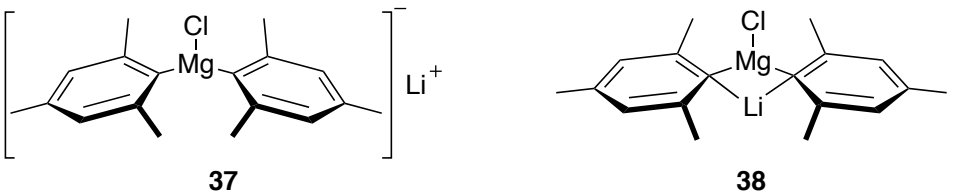


Figure 1.9

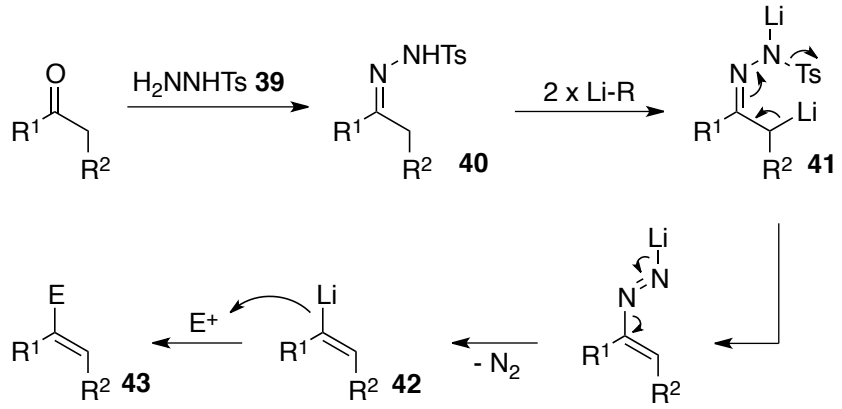
A dimeric complex is suggested for the solid and solution structure of $^{t}Bu_2Mg$.[87] However, no studies have yet been conducted to determine the aggregation of the THF solvated reagent or the corresponding LiCl adduct. As the reactivity and selectivity of these reagents depend largely on their aggregation, further knowledge of these structures, and how they can be influenced, is vital for a systematic improvement of the targeted transformations.

1.3 Shapiro Reaction

Building on the unexpected success of carbon-centred magnesium bases, an alternative reaction has received particular attention within our research team. Within the Shapiro reaction, alkyllithium species are routinely used to facilitate the deprotonation of tosylhydrazones to furnish substituted alkenes.[88] However, this process is known to have a range of practical drawbacks and inefficiencies as will be delineated in this chapter.

Early reports on this type of reaction exploited the use of aprotic and protic solvents, and strong sodium bases, as well as high temperatures in the conversion of tosylhydrazones.[89–91] Conditions employing sodium in ethylene glycol lead to the process known as the Bamford-Stevens reaction. A range of observed side reactions and the generally harsh conditions, however, led to the further development of alternatives to this transformation.

With respect to the application of alkyllithium bases within the Shapiro process, the proposed mechanism is described in **Scheme 1.25**.[88,92,93]

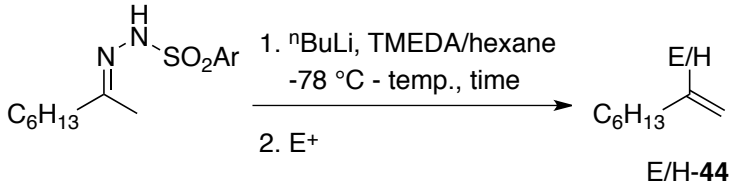


Scheme 1.25

The tosylhydrazone **40**, readily prepared from the parent ketone and tosylhydrazide **39**, is deprotonated twice by the alkyllithium reagent and the formation of a dianionic species **41** is proposed. Along with the N-H moiety, the α–carbon *syn* to the hydrazone functionality is typically deprotonated preferentially.[93] The resulting dianion then collapses to release the sulfinate and nitrogen gas to form the vinyl anion **42**. Upon introduction of an electrophile, **42** is quenched to deliver the functionalised alkene product **43**. Notably, an elaborate temperature protocol is required for the described sequence. More specifically, introduction of the base reagent is commenced at -78 °C, however, warming to ambient temperatures is required to facilitate the fragmentation to vinyl anion **42**. Prior to the electrophile addition, the reaction is typically cooled and later warmed to ambient temperatures to achieve full conversion to the desired product, rendering this process impracticable and cost intensive especially on larger scale.

As stated above, a number of problems are associated with this reaction. Slow fragmentation of intermediate **41** can lead to competitive protonation of the vinyl anion **42** by solvent or tosylhydrazone.[94] Additionally, *ortho*-metallation of the aromatic moiety of the tosyl group can occur *via* the highly reactive lithium base. Both scenarios ultimately lower the yield of the desired alkene, especially if a more precious electrophile (other than H^+) is employed.

Attempts to prevent these side reactions were undertaken. By introducing TMEDA as a solvent or co-solvent the rate of fragmentation was markedly increased, whereas the employment of a large excess of the base reagent compensates for the competing *ortho*-metallation.[94,95] Nevertheless, this procedure calls for an equally high amount of electrophile to quench the reaction completely. As later shown by Bond *et al*., *ortho*-metallation can also be avoided by utilising the more substituted trisyl hydrazones, whilst simultaneously decreasing the stability of the dianionic intermediate and accelerating its collapse to the vinyl anion. Accordingly, the base and electrophile equivalents could be lowered to near stoichiometric quantities (**Scheme 1.26**, **Table 1.6**).[94] As such, reaction times were shortened and competitive proton incorporation further reduced.



Scheme 1.26

Ar	*BuLi* (eq)	*Electrophile*	*Conditions*	*Yield E/H-**44*** (%)	*E-incorporation* (%)
Ts	2	D_2O[a]	rt., 4 h	95-97	< 1
Ts	4.5	D_2O[a]	rt., 4 h	95-97	95
Trs	2	PhCHO[b]	0 °C, 30 min	84	100

[a]Electrophile added at rt., [b]1.2 eq of PhCHO added at 0 °C

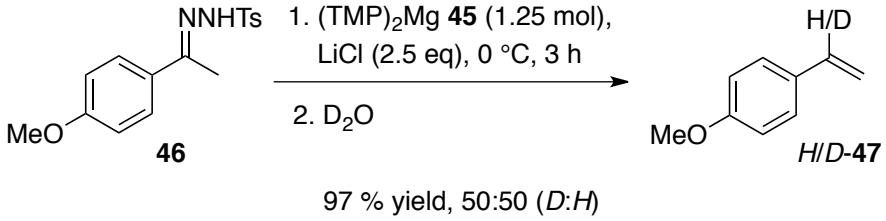
Table 1.6

On the other hand, trisyl hydrazide and the corresponding trisyl hydrazones are considerably more expensive and exhibit an appreciably lowered carbon economy, rendering the process less cost-effective. It should also be noted, that the deprotonation of secondary and tertiary α-carbons requires strong bases in order to facilitate the formation of the dianion.[94] Nonetheless, these vital alterations to the

original Shapiro reaction are now known as the Bond-modification, which has been widely applied in organic synthesis to provide substituted alkenes.[96,97]

Despite the advantages introduced by the Bond-modification, the higher expense and lower atom-economy of trisyl hydrazide, the necessity of co-solvents such as TMEDA, and the more elaborate low temperature protocol, ranging from -78 °C to ambient temperature, still present significant drawbacks within this system. An application of this process on industrial scale seems less than economic. Additionally, the introduction of a wide range of electrophiles has proven rather difficult, especially when employing the more standard tosylhydrazone-based protocols. As such, further optimisation of this transformation was envisaged.

Consequently and in view of the recently developed magnesium-based systems within our research team, a magnesium-mediated Shapiro reaction was envisaged. Experiments assessing the validity of the magnesium bisamide, $(TMP)_2Mg$ **45**, as a base reagent in this reaction revealed good reactivity with a number of different hydrazone substrates. Having stated this, due to *in situ* generated TMP-H, only 50 % of the isolated styrene was deuterated, as it can readily act as a proton source (**Scheme 1.27**).[98,99]



Scheme 1.27

Nonetheless, these conditions were used to screen a series of ketones, all of which gave good to excellent yields of the desired styrene when quenched with water. Representative examples of the styrene products obtained in this way are depicted in **Figure 1.10**.[98]

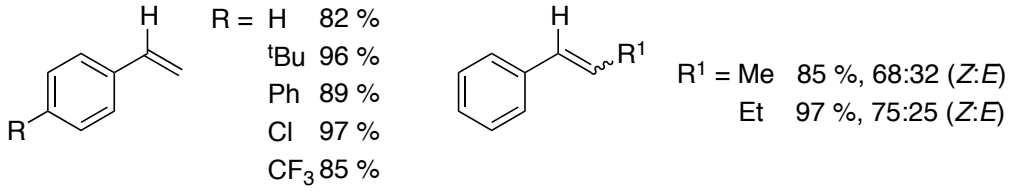
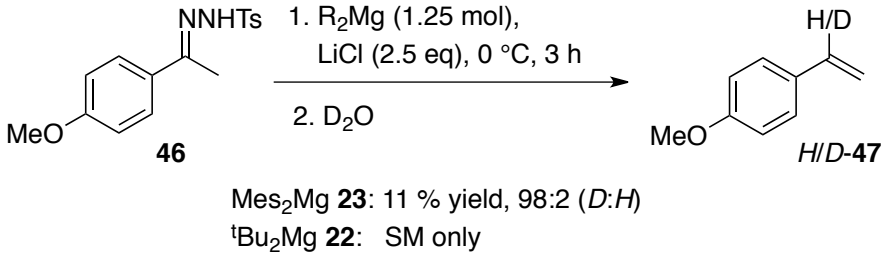


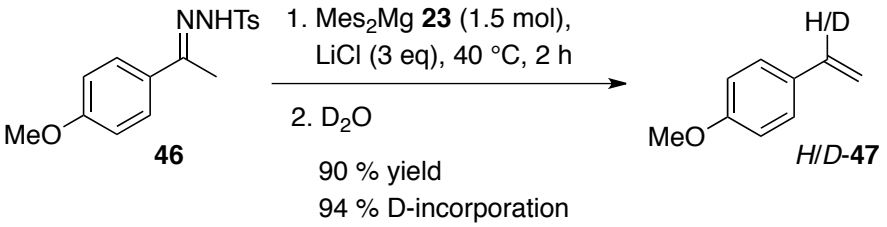
Figure 1.10

In contrast, the aromatic and aliphatic by-products from the carbon-centred magnesium bases were believed to be less aligned to deprotonation and were thus considered as suitable substitutes for $(TMP)_2Mg$. Preliminary results using bismesitylmagnesium **23** and LiCl additive showed an excellent deuterium inclusion of 98 %, albeit displaying a low reactivity at 0 °C, with 84 % of the starting material being recovered (**Scheme 1.28**).[98] In contrast, the di-*tert*-butyl base **22** did not react in the anticipated manner and merely starting material was returned.



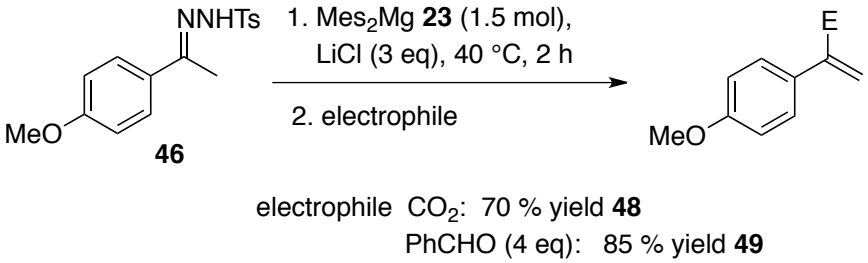
Scheme 1.28

A short preliminary optimisation process ensued, following which the reactivity of **23** was enhanced to furnish an excellent 90 % yield along with 94 % D-incorporation (**Scheme 1.29**).[98]



Scheme 1.29

The improved reaction conditions employed an elevated temperature of 40 °C, which had the possibility of opening up a new range of more sensitive hydrazone substrates that were previously incompatible under lithium-mediated reaction conditions. Following this and again as part of these preliminary investiagtions, different electrophiles were probed, affirming the excellent results attained under the developed conditions with D_2O quench (**Scheme 1.30**).[98] Carbon dioxide and benzaldehyde gave rise to 70 % and 85 % yield of the desired functionalised styrene product, respectively.



Scheme 1.30

In summary, the original lithium-mediated Shapiro reaction has been modified by employing magnesium-based reagents to deliver preliminary results towards revised processes. Moreover, the spectrum of applications for the carbon-centred magnesium bases has thus been potentially extended. Having stated this, to date the emerging protocols are limited and have yet to be fully optimised. Additionally, only a very limited number of electrophiles has been screened, and these had to be employed in a large excess of up to 4 eq to ensure high yields of the desired alkene.

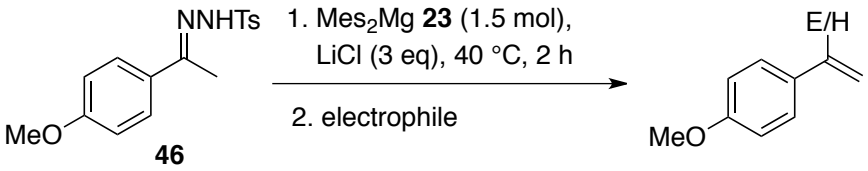
Considering that potentially both aryl ligands of Mes_2Mg should be capable of carrying out the deprotonation of the tosylhydrazone, processes with this base reagent could be further tuned and optimised. Moreover, the application of Mes_2Mg has focused on the hydrazone of 4-methoxyacetophenone only, leaving a whole range of possible substrates to be investigated.

Overall, magnesium base reagents have emerged as valuable alternatives to analogous lithium reagents over recent years. Excellent asymmetric induction in the deprotonation of ketone substrates has been achieved with a number of stoichiometrically employed chiral magnesium bisamides. Similarly, carbon-centred magnesium bases have shown potential as non-nucleophilic and non-reductive base reagents when applied in enolate formation and Shapiro-type reactions.

2. Proposed Work

As described, the application of magnesium amide species in asymmetric deprotonations has been developed very effectively within our laboratory.[53-55] A range of highly selective magnesium bases has been established, giving rise to a true alternative to analogous lithium amide base systems. More importantly, a series of novel carbon-centred bases has emerged from these studies, which are equally applicable in the deprotonation of enolisable ketones, albeit in a non-asymmetric sense.[75,77,78] In contrast to alkyllithium bases, these reagents have been found to be largely non-nucleophilc and non-reductive. It has thus been proposed to further investigate the scope of reactions in which carbon-centred bases could provide a considerable advantage over analogous lithium species.

More specifically, as initial attempts have shown good levels of reactivity in the magnesium base-mediated Shapiro reaction, it was decided that further research into the subject would broaden the practicability and scope of this process. Previously conducted short investigations revealed 1.5 mol of the diarylmagnesium base reagent in conjunction with 3 equivalent LiCl with slight warming to 40 °C over a reaction time of 2 hours to be the conditions which allowed the conversion of tosylhydrazone **46** into functionalised alkenes (**Scheme 1.31**, **Table 1.7**).[98]



Scheme 1.31

Entry	*Electrophile*	*Conv.* (%)[a]	*Yield* (%)	*E*:*H* (%)[a]
1	D_2O	96	90	94:6
2	CO_2	99	70	-
3	PhCHO	94	85	-

[a]Determined by NMR analysis.

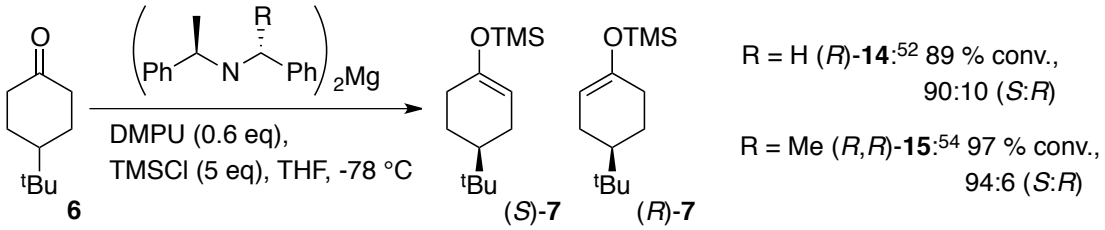
Table 1.7

Only a small number of different electrophiles had been screened, delivering excellent conversion to the desired substituted alkenes. Pleasingly, only a small amount of the competitive proton quench was detected. Based on these initial observations, a robust and effective process with the carbon-centred base Mes_2Mg **23**, would be targeted. Indeeed, it was envisaged that fine-tuning of this system would allow for a wide range of ketones and their corresponding hydrazones to be transformed into functionalised alkene substrates. Particular interest is also placed on the exploration of the electrophile scope for this transformation. In this way, the applicability of the magnesium base-mediated Shapiro process would be established and the limitations elucidated.

3. Results and Discussion

3.1 Asymmetric Deprotonations with Chiral Magnesium Bisamides

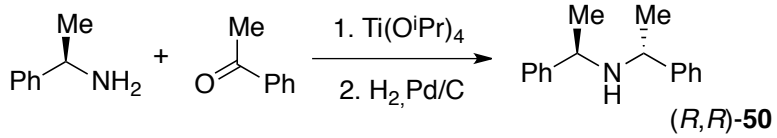
As previously described, it has been shown within our laboratory that chiral magnesium amide bases can be used very successfully in mediating enantioselective deprotonations of cyclic ketones.[52-55,58] Employing the chiral amines (*R*)-(+)-*N*-benzyl-α-methylbenzylamine, (*R*)-**20**, and (*R,R*)-*bis*(1-phenylethyl)amine, (*R,R*)-**50**, as their magnesium bisamide bases (*R*)-**14** and (*R,R*)-**15**, 4-*tert*-butyl-cyclohexanone **6** is deprotonated and trapped with TMSCl to give the silyl enol ether in enantiomerically-enriched form (**Scheme 1.32**). This protocol has since been used as a benchmark reaction within our laboratory in order to acquire the necessary practical skills to carry out the highly sensitive magnesium amide chemistry.



Scheme 1.32

As such, amine (*R,R*)-**50** was prepared in diastereomerically pure form from (*R*)-α-methylbenzylamine and acetophenone as shown in **Scheme 1.33** in 35 % yield. In due course, the above deprotonation reactions were repeated until conversion and selectivity reached the required standard. Intense care had to be taken when preparing the reagents and additives, as they have to be pure as well as air- and moisture-free in order to achieve high levels of selectivity. Accordingly, the chiral amine, DMPU,

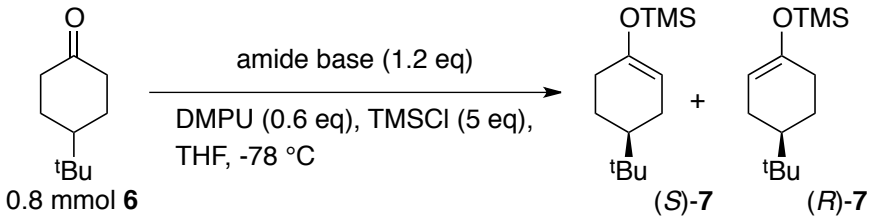
TMSCl and THF were distilled prior to use and the ketone substrate recrystallized. The enantiomeric ratio of the product was determined *via* chiral GC analysis.



35 % yield

Scheme 1.33

Although initial results with amide base (*R*)-**14** did not reach the same elevated level previously recorded, gratifyingly with practice, the yields and selectivities for the deprotonation of cyclohexanone **6** with C_2-symmetric amide base (*R*,*R*)-**15** quickly reached consistency, and yields and selectivities were comparable with the set standard (**Scheme 1.34**, **Table 1.8**, *cf.* **Scheme 1.11**, **Table 1.3**). With the confidence, that the required technique for high yielding and selective deprotonations had been attained, a new section of magnesium base chemistry was focused on.



0.8 mmol **6**

(*S*)-**7** (*R*)-**7**

Scheme 1.34

Entry	*Amide Base*	*Conversion* (%)[a]	*Yield* (%)	*E.r.* (*S*:*R*)[a]
1	(*R*)-**14**	81	62	87:13
2	(*R*,*R*)-**15**	97	84	93:7

[a]Determined by G.C. analysis

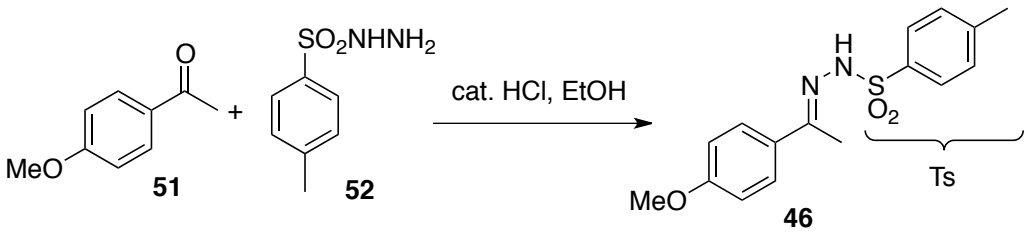
Table 1.8

3.2 Carbon-centred Magnesium Base-mediated Shapiro Reaction

At the outset of this work and in consideration of the very encouraging results concerning the application of carbon-centred magnesium bases, it was decided to further investigate the magnesium-mediated Shapiro reaction as described herein.

3.2.1 Preparation of Substrates and Assessment of Reaction Conditions with Bismesitylmagnesium

The previously studied tosylhydrazone **46** was selected as the substrate of choice for the preliminary investigations. This species was prepared from the commercially available substrates 4-methoxyacetophenone **51** and *para*-toluenesulfonyl hydrazide **52**. More specifically, to a warm, saturated solution of the hydrazide **52** in ethanol was added the ketone, as well as catalytic amounts of hydrochloric acid. The crystalline hydrazone **46**, typically containing a 90:10 mixture of the two stereoisomers, was filtered and recrystallised in ethanol to deliver the *E*-isomer exclusively in 85 % yield (**Scheme 1.35**).

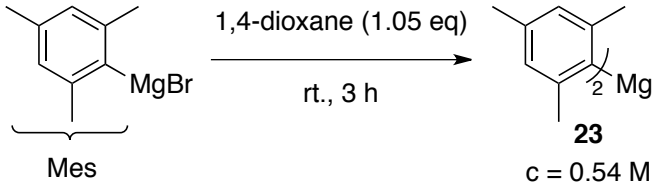


85 % yield *E*-**46**

Scheme 1.35

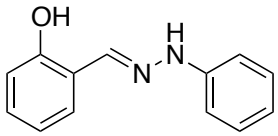
The required organometallic reagent Mes_2Mg was prepared from the parent Grignard reagent in THF solution *via* disproportion induced by 1,4-dioxane.[76] After

stirring the mixture for several hours at room temperature, the formed polymeric $MgBr_2$·1,4-dioxane precipitate was allowed to settle and bismesitylmagnesium was transferred into a flame dried flask *via* cannula and stored under argon (**Scheme 1.36**).



Scheme 1.36

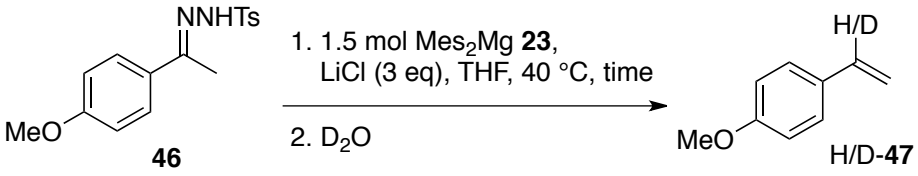
Standardisation of the acquired Mes_2Mg solution was carried out using salicylaldehyde phenyl hydrazone **53** as an indicator (**Figure 1.11**).[100] For this substrate the concentration was typically determined to be around 0.54 M.



53

Figure 1.11

Following the preceding success, the previously employed reaction conditions were adopted and the Shapiro reaction attempted with tosylhydrazone **46** and D_2O as the electrophilic quench. In this way, 1 eq of hydrazone **46** was added slowly to a solution of 1.5 mmol magnesium base **23** in THF and 3 eq LiCl at 40 °C. The reaction was subsequently quenched with D_2O (**Scheme 1.37**, **Table 1.9**). The ratio of deuterated to protonated alkene product were calculated from the crude ^{1}H-NMR.



Scheme 1.37

Entry	*Time* (h)	*Yield* (%)	*D*:*H* (%)[a]
1	1	63	97:3
2	2	60	97:3
3	3	69	95:5
4	3[b]	82	96:4

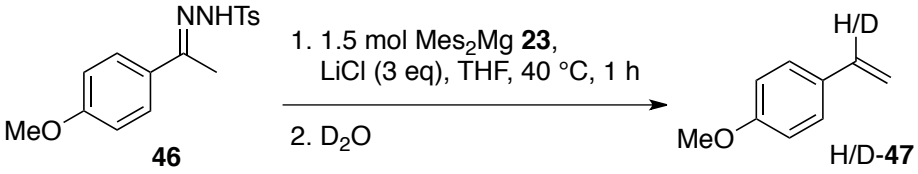
[a]Determined by NMR analysis, [b]2 mol Mes_2Mg were used.

Table 1.9

Surprisingly, even with prolonged reaction times the yield did not reach the high standard of those examples previously reported (*cf.* 2 h, 90 % yield, 94:6 D/H).[98] Despite this, an excellent deuterium quench of the vinyl anion was observed, indicating that the reaction set up was performed correctly and effectively (**Table 1.9**, **Entries 1** to **3**). Longer reaction times of 4 h and more proved to be detrimental for both selectivity and yield. Only with an increased amount of 2 mol of Mes_2Mg could comparable results be achieved (**Table 1.9**, **Entry 4**). As bismesitylmagnesium has two aryl ligands per molecule that can potentially perform the required double deprotonation of the hydrazone substrate, essentially twice the amount of base equivalents had been employed. In consideration of cost effectiveness, this is an undesirable trend. Accordingly the lack of reactivity was further scrutinised.

3.2.2 Optimisation Study with D_2O

As with many organometallic processes, purity and quality of the respective reagents and additives are crucial to provide high conversion and yield. Moreover, solution aggregation can have a marked effect on the reactivity of the organometallic. In view of the importance of the more activated magnesium complex that is formed in solution upon addition of lithium chloride,[77] it was thought that contamination or insufficient drying of LiCl would result in a lowered amount of the essential mixed dimer. As a consequence, the rather hygroscopic LiCl was dried prior to weighing with the intention of removing any absorbed water that would falsify the balance reading. Additionally, a different source to the routinely-used LiCl powder was also investigated and commercially available anhydrous LiCl beads were probed. In both cases, the LiCl was again flamed dried in the Schlenk tube in order to maintain the anhydrous reaction set up. Accordingly, a new series of experiment was conducted, the results of which are presented in **Table 1.10** (**Scheme 1.38**).



Scheme 1.38

Entry	*LiCl source*	*Yield* (%)	*D*:*H* (%)[a]
1	powder[b]	58	98:2
2	beads	53	97:3

[a]Determined by NMR analysis, [b]Dried pre-weighing.

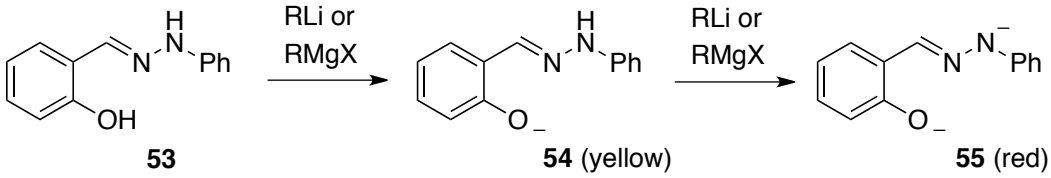
Table 1.10

Despite the more careful handling of lithium chloride, no substantial improvement in respect to the yield could be reported. Moreover, no distinct beneficial effect of the LiCl beads was detected. Nonetheless, deuterium incorporation was consistently high and the best ratio so far of 98:2 was achieved, **Table 1.10**,

Entry 1. Taking these findings into account, all subsequent experiments were conducted using LiCl powder.

Reconsideration of the Standardisation Method for Carbon-centred Magnesium Bases

At this stage in the project, reassessing the standardising method for the base reagent was considered in order to attain a more precise and reliable concentration for the employed base reagent. Salicylaldehyde phenyl hydrazone **53** has been routinely used in our laboratory to standardise organometallic reagents such as phenyllithium, Grignard reagents, and homoleptic amide or alkylmagnesium bases.[100] The first deprotonation of the hydrazone produces the yellow monoanion **54**. Upon addition of one equivalent of base, any excess results in the formation of the red dianion **55** and the solution changes to a bright orange colour (**Scheme 1.39**). This colour change, albeit of no large chromatic shift, is thus used as the end point of the titration. In respect to bismesitylmagnesium, this colour change is somewhat difficult to observe and subjective. Therefore, another way of accurately determining the concentration of organomagnesium compounds was sought.



53 **54** (yellow) **55** (red)

Scheme 1.39

In this respect, an alternative method was introduced, using a procedure as documented by Knochel for the titration of various organomtallic reagents.[101] This technique employs a 0.5 M solution of LiCl in THF as the titration medium. A known amount of iodine is then added to the THF solution, rendering it dark brown in colour. Upon addition of the magnesium reagent, the iodine is used up gradually. The end

point is indicated by the complete consumption of iodine, which results in an instantaneous colour change to a clear colourless solution. With this method being readily applied to Mes_2Mg, a comparison between the two procedures was initiated, the result of which are presented in **Table 1.11**.

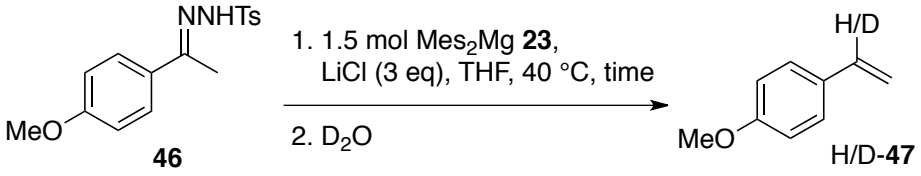
Entry	*Method A* (M THF)	*Method B* (M THF)
1	0.55	0.50
2	0.54	0.49

Method A: with salicylaldehyde phenylhydrazone, Method B: with iodine

Table 1.11

Surprisingly, the results obtained by the Knochel procedure indicated that the concentration of the base reagent used, was indeed lower than initially thought. Consequently, all previous experiments had been carried out with less base reagent than intended. This explains, to some extent, the improved results that were obtained using a larger excess of Mes_2Mg (*cf.* **Table 1.9**, **Entry 4**).

Accordingly, some of the previously gained results were revisited and the reactions repeated. Using Mes_2Mg standardised according to Knochel's method, 1.5 mmol of the base was reacted with tosylhydrazone **46** at 40 °C over a range of reaction times (**Scheme 1.40**, **Table 1.12**).



Scheme 1.40

Entry	*Time* (h)	*Yield* (%)	*D*:*H* (%)[a]
1	1	66	96:4
2	2	79	97:3
3	3	88	97:3

[a]Determined by NMR analysis.

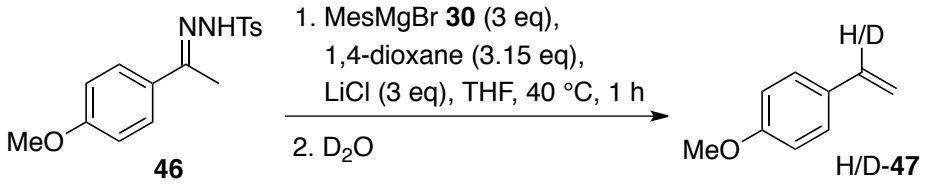
Table 1.12

To our delight, leaving the reaction at 40 °C over 3 hours before quenching with D_2O furnished an excellent 88 % yield of the desired alkene and a ratio of 97:3 of deuterated to protonated species (**Table 1.12**, **Entry 3**). In this regard, an excess of 0.5 mol of the carbon-centred base is sufficient to promote the formation of the vinyl anion near quantitatively whilst giving rise to an outstanding level of electrophilic quench under the stated conditions. The new standardisation procedure[101] was thus applied to determine the concentration of Mes_2Mg and any other carbon-centred base reagents. With the method optimised to this stage, our attention focused on the further exploration of the applicability of the Shapiro reaction.

One-Pot Protocol

Within the previously discussed extensive studies into the achiral deprotonation of enolisable ketones with Mes_2Mg **23**, it emerged that a one-pot approach, in which the base is formed *in situ* from the parent Grignard reagent, is not only feasible, but also more efficient.[77] Moreover, this made isolation of the base reagent unnecessary and subsequently simplified the reaction set up considerably. In consideration of these excellent results and with on-going optimisation of the Shapiro protocol, it was envisaged that such a procedure would be equally beneficial in the magnesium-mediated Shapiro reaction. Therefore, a short assessment into the practicability of this approach was initiated.

On the basis of previous findings, a solution of MesMgBr in THF was treated with a slight excess of 1,4-dioxane in the presence of LiCl to form bismesitylmagnesium. The tosylhydrazone was added to this mixture as a solution in THF and left to stir at 40 °C over 1 hour before adding D_2O to quench the reaction (**Scheme 1.41**, **Table 1.13**).



Scheme 1.41

Entry	*Yield* (%)	*D:H* (%)[a]
1	22	96:4
2	24	97:3

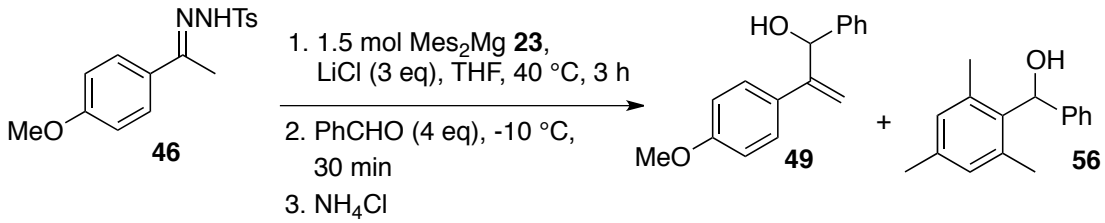
[a]Determined by NMR analysis.

Table 1.13

With respect the above results, a dramatic and detrimental effect on the reactivity of the base was observed. Indeed, the yield of the desired product did not exceed 24 %. In contrast, the level of selectivity was maintained. It is important to note, that the reaction of the one-pot protocol may contain a complex mixture of different species, such as the $MgBr_2$ polymer and other dioxane adducts which might have a damaging effect on the reactivity of the base reagent. As research into the exploration of the electrophile scope of the evolving Shapiro process was ongoing, this particular approach was not pursued any further at this stage.

3.2.3 Optimisation Study with Benzaldehyde

In respect to the newly established conditions within this project and the small range of electrophiles previously screened,[98] it was decided to revisit benzaldehyde as a quench reagent. Tosylhydrazone **46** was thus treated with a solution of Mes_2Mg in THF with LiCl. The reaction was cooled to -10 °C before the quench reagent was added and left to stir for 30 min. Upon work-up the functionalised alkene **49** was isolated (**Scheme 1.42**). The selectivity resulting from either benzaldehyde or a proton source reacting with the vinyl anion is stated as a ratio of electrophilic quench to proton (E:H) in **Table 1.14**.



Scheme 1.42

Entry	*Yield **49*** (%)	*E:H* (%)[a]
1	76	92:8
2	84	92:8

[a]Determined by NMR analysis

Table 1.14

Encouragingly, introduction of PhCHO as the electrophile furnished up to 84 % yield of the desired allyl alcohol **49**. Moreover, only a slight drop in selectivity was observed relative to deuterium pick up, with 92:8 in favour of the added electrophile (**Table 1.14**, **Entries 1** and **2**). Unfortunately, a considerable amount of alcohol **56** was detected, which is formed from reaction of excess Mes_2Mg and the electrophile quench. This suggests that the unreacted **23** can act as a nucleophile, despite earlier reports of its largely non-nucleophilic character.[75,77] Moreover, a large excess of

electrophile is thus necessary to quench the reaction completely. When using more elaborate and expensive electrophiles, this wasteful application of a quench reagent is undesirable. With this in mind, it was decided to focus on the amount of by-product formation during NMR analysis in the course of further optimisations of the emerging protocol.

In the following tables the results are presented as follows: (i) in order to monitor the reactivity of the base, an overall conversion of hydrazone starting material is presented by NMR analysis; this value takes the desired functionalised alkene, as well as the protonated styrene H-**47** into account; (ii) the isolated yield of the functionalised alkene **49** is stated; (iii) the selectivity towards the electrophilic quench reagent is depicted as E:H in (%); and (iv) an NMR-based ratio of **49** and the alcohol by-product **56** is stated in order to be able to detect any changes in the reactivity of the base towards the introduced electrophile.

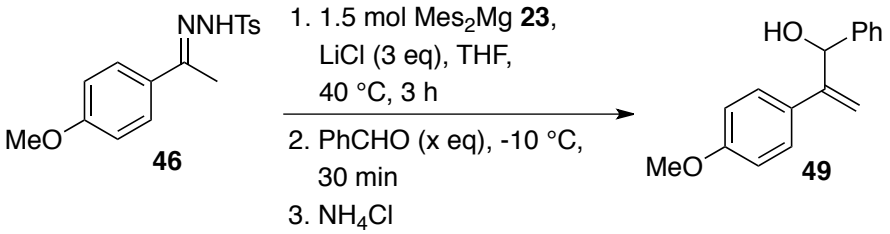
Thus, the initial results using benzaldehyde were re-evaluated (**Table 1.15**).

Entry	*Conv.* (%)[a]	*Yield **49*** (%)	*E:H* (%)[a]	***49*:*56*** (%)[a]
1	86	76	92:8	46:54
2	89	84	92:8	48:52

[a]Determined by NMR analysis

Table 1.15

It was thought to be essential to develop a procedure that would allow for high yields of the desired functionalised alkene whilst generating a minimum amount of addition by-product. At the outset, the quantity of electrophile employed was thus reassessed. To this stage, 4 eq of PhCHO had been added to the reaction after 3 h. Bearing in mind that theoretically only 1 eq is required to quench the generated vinyl anion, the employment of lowered amounts of electrophile was investigated, the results of which are presented in **Scheme 1.43**, **Table 1.16**.



Scheme 1.43

Entry	*PhCHO* (eq)	*Conv.* (%)[a]	*Yield **49*** (%)	*E*:*H* (%)[a]	***49***:***56*** (%)[a]
1	1	87	27	31:69	28:72
2	1.5	83	41	50:50	28:72
3	2	82	74	90:10	40:60
4	3	83	72	89:11	40:60

[a]Determined by NMR analysis

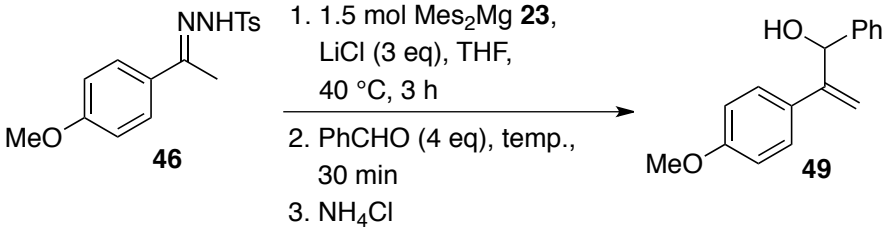
Table 1.16

A distinct drop in yield was observed when less than 2 eq PhCHO were used (**Table 1.16**, **Entries 1** and **2**). The reaction of Mes_2Mg with PhCHO is proposed to be faster than the quench of the vinyl anion by the electrophile, as in all cases a considerable amount of alcohol **56** is generated. The unreacted vinyl anion is quenched upon work up with NH_4Cl and the alkene H-**47** is formed instead. Nonetheless, a lowered amount of 2 eq of the electrophile proved to be sufficient to retain high yields of the desired product and good E:H ratios (**Table 1.16**, **Entry 3**).

Optimisation of Quench Temperature

As part of this on-going optimisation process, it was questioned whether the addition of the electrophile had to be carried out at low temperatures. Moreover, it was envisaged that elevated temperatures could manipulate the reactivity of the remaining magnesium reagent in a favourable way. Accordingly, quenching the

reaction at both ambient temperature (~ 21 °C) and at 40 °C was considered using the original quantity (4 eq) of benzaldehyde (**Scheme 1.44**, **Table 1.17**).



Scheme 1.44

Entry	*Temp.* (°C)	*Conv.* (%)	*Yield **49*** (%)	*E:H* (%)[a]	***49*:*56***[a]
1	21	52	46	89:11	41:59
2	40	17	13	78:22	31:69

[a]Determined by NMR analysis,

Table 1.17

Disappointingly, noticeably lower amounts of the functionalised alkene **49** were isolated. Moreover, the proton pick up by the vinyl anion increased at the higher temperature of 40 °C. Unexpectedly, the conversion of the starting material appeared to be reduced, with only 52 % and 17 %, respectively, of the vinyl anion being formed according to ^{1}H-NMR analysis. As none of the conditions prior to the quench had been altered, high conversion was anticipated. Additionally, a second by-product had emerged and was subsequently identified as benzyl alcohol **57** (**Figure 1.12**).

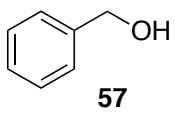
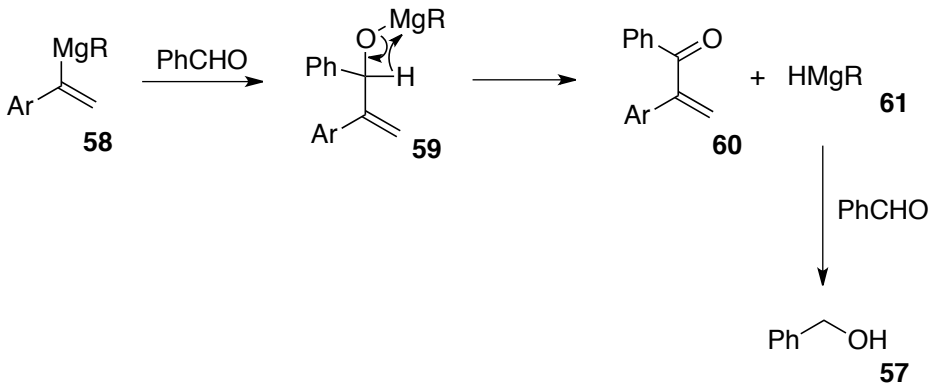


Figure 1.12

At present, it is not fully understood how the benzyl alcohol **57** is formed. However, considering the surprisingly low amount of vinyl anion quenched by either benzaldehyde or protons, a competitive reaction pathway involving β-hydride

elimination is proposed (**Scheme 1.45**). In relation to this, addition of benzaldehyde to the reaction mixture is envisaged to result in the formation of the magnesium alkoxide **59**. It is speculated that this species could then undergo β-hydride elimination across the heteroatom to give α,β-unsaturated ketone **60** and magnesium hydride **61**. Another equivalent of benzaldehyde would then be reduced by the hydride to provide the detected alcohol **57**. Similarly, direct reduction of the aldehyde with alkoxide **59** *via* a mechanism analogous to Meerwein-Ponndorf-Verley reduction could be envisaged, giving rise to enone **60** and alcohol **57**.



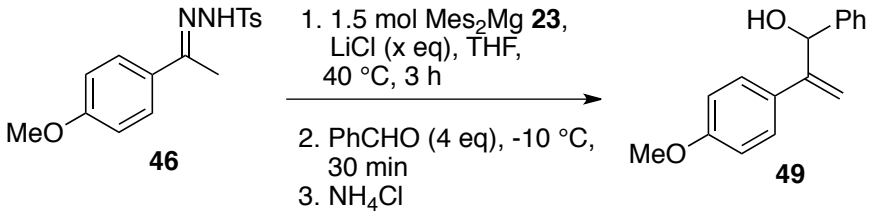
Scheme 1.45

Surprisingly, no other major by-product was found in the crude reaction mixture. Following the proposed mechanisms for the formation of **57**, the observation of equal amounts of the enone **60** were anticipated. Subsequently, no further support for the suggested side reaction could be found and the generation of alcohol **57** remains unclear. The reaction temperature at the time of the quench addition has proved to be crucial. It was thus decided to return to the original method and quench the reaction at -10 °C.

Optimisation of LiCl

In various optimisation studies, it had been shown that the correct amount of LiCl proved vital for the success and selectivity of magnesium base-mediated

transformations.[60,98] Therefore, the quantity of LiCl added to the reaction and its effect on basicity and nucleophilicity of Mes_2Mg was investigated in more detail (**Scheme 1.46**, **Table 1.18**).



Scheme 1.46

Entry	*LiCl* (eq)	*Conv.* (%)[a]	*Yield* ***49*** (%)	*E*:*H* (%)[a]	***49***:***56*** (%)[a]
1	-	27	24	89:11	11:89
2	1.5	86	76	88:12	42:58
3	3	89	82	92:8	48:52
4	4.5	65	60	92:8	45:55

[a]Determined by NMR analysis

Table 1.18

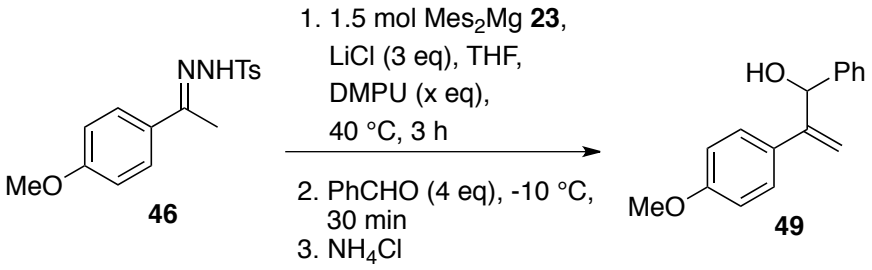
The routinely used 3 mmol LiCl, *i.e.* 2 eq in relation to the amount of base, furnished the best results (**Table 1.18**, **Entry 3**). A slight decrease in yield and selectivity was observed when the quantity of LiCl was reduced by 50 % (**Table 1.18**, **Entry 2**). However, no great improvement in respect to the by-product formation was detected. This suggests that the same reactive species responsible for the excellent results with 3 mmol LiCl is formed to some extent. It came as no surprise that the exclusion of LiCl resulted in a lowered reactivity of the base towards the deprotonation of tosylhydrazone **46**, as none of the proposed reactive mixed dimer is generated in solution (**Table 1.18**, **Entry 1**). At the same time, a higher yield for the addition by-product was expected and confirmed, as more unreacted Mes_2Mg was present in the reaction mixture when the electrophile was added. Upon introducing an extra 50 % of LiCl originally used, a decrease in reactivity was observed. Despite this, the selectivity towards the electrophile quench remained high (**Table 1.18**, **Entry 4**).

Again, no improvement towards the inhibition of formation of the addition by-product **56** could be found from the variation of the quantity of LiCl additive.

In this way, 2 eq of LiCl in respect to the amount of base used has emerged to be the optimum loading for this reaction process. As no considerable improvement could be made in the prevention of addition by-product **56** being formed, other additives were assessed for their effect on carbon-centred base **23**.

Optimisation with Donor Additives

Upon consideration of the results obtained and in view of the sensitivity of magnesium base chemistry towards additives, it was proposed that the addition of a donor additive could modify the basicity and nucleophilicity of the magnesium base reagent. NMR studies have suggested the formation of different aggregates in solution in the presence of such additives and their effect on reactivity.[60] As HMPA and DMPU had been successfully employed in a number of alternative magnesium base-mediated transformations,[53-55] the analysis of the effect of the less toxic DMPU on the studied system was initiated. In this regard, varied quantities of DMPU were introduced to the reaction mixture before addition of hydrazone **46**. The results of this study are summarised in **Scheme 1.47**, **Table 1.19**.



Scheme 1.47

Entry	*DMPU* (eq)	*Conv.* (%)[a]	*Yield* ***49*** (%)	*E*:*H* (%)[a]	***49*****:*****56***[a]
1	0.5	73	65	89:11	35:65
2	0.75	81	63	78:22	36:64
3	1.5	72	60	83:17	40:60

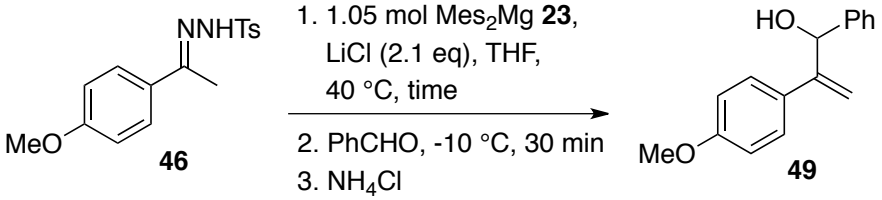
[a]Determined by NMR analysis

Table 1.19

Disappointingly, no appreciable enhanced reactivity and selectivity was observed with varying quantities of DMPU included in the above reaction (**Table 1.19**, **Entries 1-3**). Despite the preserved reactivity, a substantial drop in yield for the desired product **49** became apparent, complete with a rise in the protonated alkene H-**47**. Again, the formation of addition by-product **56** remained high, indicating that the desired distinction between basic and nucleophilic character of **23** had not been achieved. The addition of donor additive DMPU had not provided any advantage for the examined system, rendering these reaction conditions unsuitable.

Optimisation Using Stoichiometric Quantities of Mes_2Mg

In conjunction with previous findings, a drop in conversion and yield to the desired alkene are expected when a stoichiometric amount of Mes_2Mg is employed. However, due to the lower quantity of base reagent, less addition by-product is also anticipated if the reaction can be driven to completion. In this regard, it was felt that a short reinvestigation of base equivalents, with adjusted amounts of LiCl and PhCHO, and the benefit of longer reaction times was required (**Scheme 1.48**, **Table 1.20**).



Scheme 1.48

Entry	*Time* (h)	*Conv.* (%)[a]	*Yield* ***49*** (%)	*E*:*H* (%)[a]	***49***:***56***[a]
1	3	63	51	81:19	62:38
2	6	70	49	76:24	72:28
3	15 h	67	24	36:64	83:17

[a]Determined by NMR analysis

Table 1.20

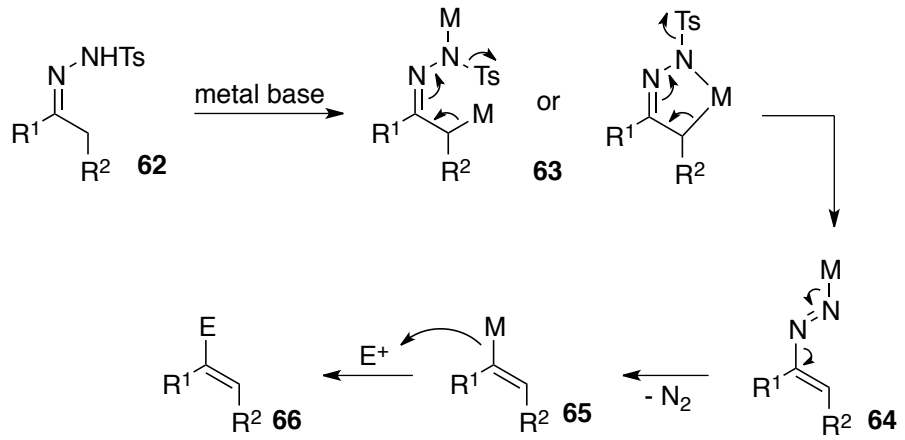
As anticipated, a considerable drop in yield was observed when lowering the base equivalents to near stoichiometric levels (**Table 1.20**, **Entry 1**). In relation to that, a reduction in selectivity (E:H) was detected (*cf.* **Scheme 1.46**, **Table 1.18**, **Entry 3**). Having stated this, a marked difference in the formation of by-product **56** was observed, which is, in part, attributed to the decreased quantity of Mes_2Mg, advocating the proposed approach. In order to achieve higher yields, the reaction time was extended to 6 h and 15 h, respectively (**Table 1.20**, **Entries 2** and **3**). A slight increase in the conversion of tosylhydrazone appeared in both cases, in hand with a drop in by-product **56** formation. The more prominent decrease in E/H-selectivity, and hence lowered yield of **49**, with longer reaction times is thought to arise from the prolonged exposure of the generated vinyl anion to potential proton sources within the reaction mixture. Simultaneously, the quantity of Mes_2Mg is gradually reduced, in turn, leading to a lowered amount of addition by-product.

In summary, the above described studies have been commenced in order to suppress any addition by-product **56** from being formed, while keeping the conversion to product **49** high. The optimal conditions established included the use of 1.5 mmol magnesium base reagent **23** and, in respect to this, 2 eq LiCl. Thus, employing 4 eq PhCHO an excellent 89 % yield of the functionalised alkene **49** and an overall ratio of 92:8 compared to the protonated alkene by-product H-**47** were obtained (*cf.* **Scheme 1.42**, **Table 1.14**, **Entry 2**). Additionally, reducing the amount of electrophile to 2 eq, a respectable 74 % yield of allylic alcohol **49** could be achieved (*cf.* **Scheme 1.43**, **Table 1.16**, **Entry 3**).

Due to the considerable amount of addition by-product generated under the established reaction conditions, investigations into different strategies to diminish these difficulties are ongoing. Indeed, the undesired products may lead to isolation problems of the desired alkene, if electrophiles other than PhCHO are employed. More importantly, the development of a more effective method with less base and stoichiometric amounts of electrophile would give rise to a more economic and efficient system.

3.2.4 Mechanistic Investigations and Isolation of Intermediates

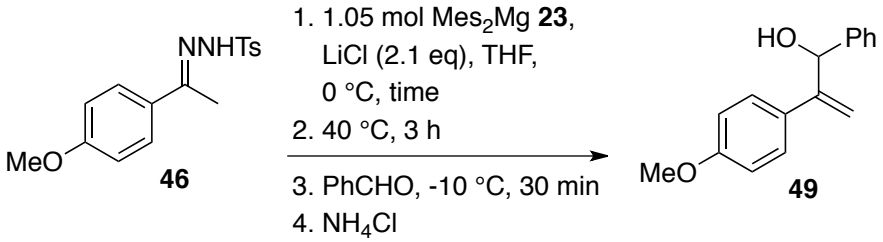
As issues relating to the nucleophilicity of Mes_2Mg and the consequent side product generation persisted and the tuning of reaction conditions did not lead to the anticipated outcome, a different approach was taken. In view of the processes followed as part of the lithium base-mediated Shapiro reaction, an alternative temperature program was considered. Deprotonation of the hydrazone substrate by the lithium base occurs rapidly at lower temperatures. However, the reaction mixture has to be warmed in order to facilitate the collapse of the doubly deprotonated species **63** (**Scheme 1.49**).[88] As mentioned previously, *ortho*-metallation and slow fragmentation of **63** proved detrimental to the reaction in some cases, allowing competing side reactions to occur.[88] With all of this in mind, it was envisaged that a magnesium base-mediated Shapiro reaction with a similar reaction mechanism could be halted or slowed at the stage of intermediate **63** by the application of lower temperatures. As a consequence, it was anticipated that full conversion to dianionic intermediate **63** could be achieved prior to the formation of the vinyl anion **65** and its prolonged exposure to potential proton sources. In turn, if only a small excess of Mes_2Mg could be utilised to realise this proposal, little of the base reagent would remain in the solution before the quench is introduced. Therefore, a large excess of electrophile becomes redundant and the formation of addition by-product would be kept at a minimum.



Scheme 1.49

Optimisation of Low Temperature Protocol

At the outset of this programme, it was thought that a time interval at 0 °C preceding the 3 hours at 40 °C using 1.05 mol of the base reagent would provide an idea of the relevance of the proposal. Thus, the tosylhydrazone was added to the Mes_2Mg solution at 0 °C and later warmed to 40 °C for 3 h before addition of the electrophile (**Scheme 1.50**, **Table 1.21**).



Scheme 1.50

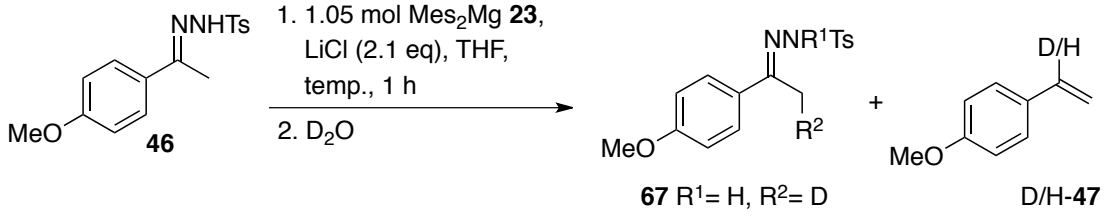
Entry	*Time* (h)	*Conv.* (%)[a]	*Yield* ***49*** (%)	*E*:*H* (%)[a]	***49***:***56***[a]
1	1	58	51	88:12	56:44
2	3	55	48	88:12	59:41

[a]Determined by NMR analysis

Table 1.21

Unfortunately, with this reaction setup, no improved yields of **49** could be detected even under prolonged reaction times at 0 °C. However, a slight increase in the E:H ratio in favour of the functionalised alkene was observed. This could imply that the fragmentation of the dianion is prevented to some extent, and the exposure of the vinyl anion to an environment of potential proton sources is being lowered. On the other hand, no considerable change in addition by-product formation was observed (*cf.* **Scheme 1.48**, **Table 1.20**, **Entry 1**).

In respect to these findings, the reactivity of the magnesium base at low temperatures was questioned and further research was undertaken to investigate this aspect of the process. It was thus proposed to survey the reactivity by quenching the reaction with an electrophile, such as D_2O or MeI, prior to warming to 40 °C (**Scheme 1.51**, **Table 1.22**). In this way, any deprotonation that had occurred at low temperatures would yield the deuterated or methylated starting material derivative if fragmentation of **63** had been prevented. Furthermore, if decomposition to the vinyl anion had taken place, the quench would furnish the corresponding functionalised alkenes. In this manner, the appropriate monitoring of the reaction became possible.



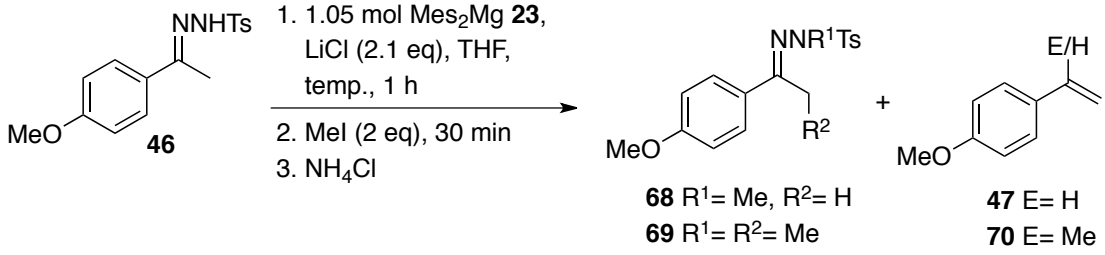
Scheme 1.51

Entry	*Temp.*	***46*** (%)	***67*** (%)	*D/H-**47*** (%)[a]	*D*:*H* (**47**) (%)[a]
1	0 °C	91	-	-	-
2	20 °C	78	-	trace	96:4

[a]Determined by NMR analysis

Table 1.22

Surprisingly, when using D_2O, no or very little deprotonation of the starting material appeared to take place after one hour even at ambient temperatures (**Table 1.22**). Additionally, ^{1}H-NMR analysis showed no indication of deuteration in the recovered starting material (**Table 1.22**, **Entries 1** and **2**) and traces of the deuterated styrene D-**47** were detected when running the reaction at ambient temperatures (**Table 1.22**, **Entry 2**). The reliability of NMR analysis with respect to the deuteration was challenged and it was thus decided to focus on MeI as an electrophile, which provided an easier and more consistent system to analyse (**Scheme 1.52**, **Table 1.23**).



Scheme 1.52

Entry	*Temp.*	***46*** (%)	***68*** (%)	***69*** (%)	*styrene* (%)[a]	*E*:*H* (styrene) (%)[a]
1	0 °C	83	6	-	-	-
2	20 °C	75	3	-	trace	99:1

[a]Determined by NMR analysis

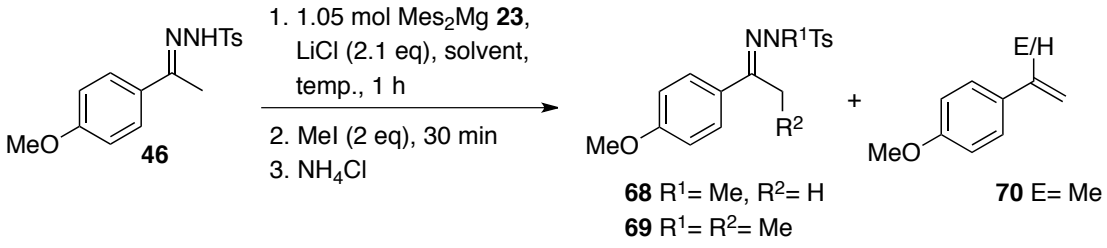
Table 1.23

The obtained results confirmed the suspected inactivity of Mes_2Mg at low temperatures (**Table 1.23**, **Entries 1** and **2**). Frustratingly, most of the starting material was recovered and only a small amount of monomethylation at the nitrogen, **68**, was detected. Once more, ambient temperatures gave rise to traces of methylated alkene **70**. This suggested that upon double deprotonation of the tosylhydrazone the generated dianion decomposes to give the vinyl anion almost immediately. Consequently, trapping of the dianionic species then becomes unfeasible.

Optimisation of Solvent

At this stage within the project, the modification of the reaction medium was considered to be another way to manipulate the reactivity of Mes_2Mg and the stability of the dianion intermediate. Solvents with enhanced or decreased donor abilities compared to the routinely used THF would alter the aggregation of Mes_2Mg and, in turn, its basic and nucleophilic properties.

In relation to this proposal, utilisation of 2-MeTHF as an alternative solvent was considered, as it exhibits a slightly decreased Lewis basicity compared to THF whilst retaining a level of solvent polarity suitable for organometallic transformations.[102] As Mes_2Mg is generally prepared in THF, the solvent had to be removed under high vacuum (~ 0.03 mbar). It was anticipated that solid, almost crystalline Mes_2Mg would remain, as had been observed in the routinely removal of heptane from $^{n}Bu_2Mg$. Instead, a very viscous oil was obtained even after one hour under high vacuum. Nonetheless, this was taken on and dissolved in 2-MeTHF. With regards to hydrazone **46**, solubility difficulties arose and a comparably large amount of solvent was needed for complete solvation. The reaction was then carried out at 0°C and ambient temperature over one hour before MeI was added as a quench (**Scheme 1.53**, **Table 1.24**).



Scheme 1.53

Entry	*Solvent System*	*Temp.* (°C)	***46*** (%)	***68*** (%)	***70*** (%)	*E:H* (%)[a]
1	2-MeTHF	0 °C	57	4	trace	99:1
2	2-MeTHF	20 °C	63	7	17	99:1
3	THF/DMPU 1:1	0	6[a]	80	-	-
4	THF/DMPU 1:1	20	-	90	-	-

[a]Determined by NMR analysis

Table 1.24

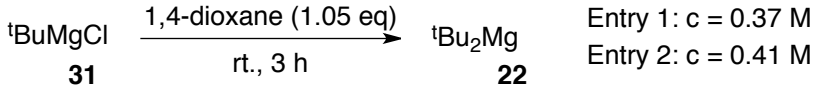
Interestingly, small quantities of the monomethylated species **68**, as well as methylated alkene **70**, were isolated (**Table 1.24**, **Entries 1** and **2**). At ambient temperatures, 63 % of the starting material was recovered and 17 % of the functionalised alkene isolated (**Table 1.24**, **Entry 2**), indicating that the reactivity of the base was indeed increased, however not in the manner anticipated. The same problem with the instability of the dianionic intermediate emerged, as no dimethylated **69** was detected. Considering the poor solubility of the hydrazone and the difficulties encountered while removing THF from the magnesium base solution, this direction of research was not further pursued at the time.

In accordance to the suggested change of solvent, DMPU was proposed to be a suitable candidate for a solvent with increased donor ability. A 1:1 mixture of DMPU and THF was thus employed, circumventing the problematic complete removal of THF from the base reagent solution (**Table 1.24**, **Entries 3** and **4**). Encouragingly, very little of the starting material was recovered and none of the alkene products **47** and **70** could be detected. However, and very much to our disappointment, no second deprotonation had taken place and almost full conversion to the monomethylated species **68** was observed, consequently none of the dianionic intermediate had been trapped. Albeit a partially enhanced reactivity had been achieved, the pursuit of our initial goal to allow for the quantitative formation of the dianion intermediate prior to its fragmentation had not been realised. As this protocol did not render the system more efficient in any anticipated way, this path into the project was abandoned.

3.2.5 Di-*tert*-butylmagnesium-mediated Shapiro Reaction

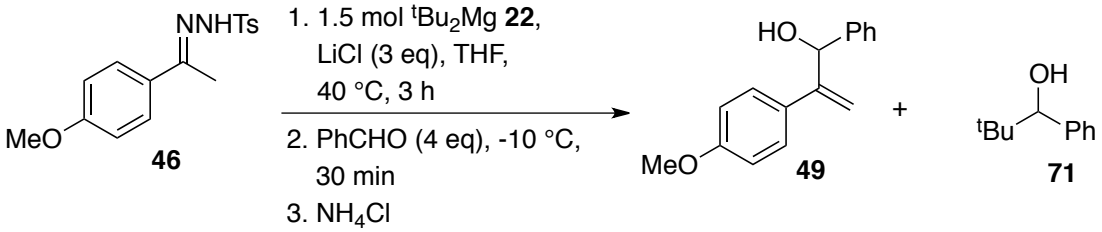
Along with Mes_2Mg, a second carbon-centred base, $^tBu_2Mg$ **22**, has evolved within our research team, which has been successfully applied in the enolisation of ketones.[60,78] Due to a comparable, and, at times, even enhanced reactivity compared to Mes_2Mg, the application of $^tBu_2Mg$ was also probed in the Shapiro reaction. A trial reaction at the outset of the research into this subject with the lithium chloride adduct of $^tBu_2Mg$ had resulted in the complete recovery of the starting material **46**.[98] However, the reaction had been run at 0 °C and a revisit of this reagent was considered to be required.

Preparation of the base reagent was thus undertaken using the parent Grignard reagent, ^{t}BuMgCl, and 1,4-dioxane. The solution was then standardised according to Knochel's method (**Scheme 1.54**).[101]



Scheme 1.54

Firstly, the performance of $^tBu_2Mg$ under the newly established conditions was assessed using 1.5 mol of the base reagent, and benzaldehyde as the electrophilic quench (**Scheme 1.55**, **Table 1.25**).



Scheme 1.55

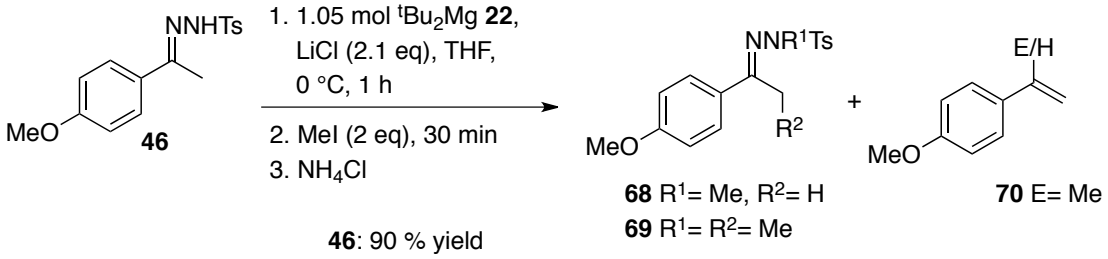
Entry	*Conv.* (%)	*Yield* ***49*** (%)	*E*:*H* (%)[a]	***49***:***71***[a]
1	64	58	91:9	25:75

[a]Determined by NMR analysis

Table 1.25

Much to our surprise a decrease in reactivity was noted as compared to Mes_2Mg, furnishing the desired alkene in 58 % yield (**Table 1.25**, **Entry 1**). Nonetheless, only small amounts of competitive proton pick up could be observed, delivering an excellent ratio of 91:9 (E:H). Lamentably and despite the steric bulk, $^tBu_2Mg$ provided alcohol **71** as the addition by-product in significant quantities.

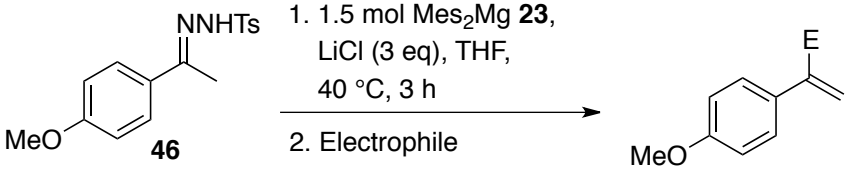
It was decided that the trapping of the dianionic intermediate at lower temperatures should also be reassessed using $^tBu_2Mg$ (**Scheme 1.56**). Disappointingly, only starting material was returned, implying a general lack of reactivity of the base reagent at the lower temperature. This is in line with previous findings, as even 1.05 mol of Mes_2Mg did not give any conversion to the desired product at low temperatures (*cf.* **Scheme 1.52**, **Table 1.23**, **Entry 1**). It was thus decided to undergo no further investigations with $^tBu_2Mg$ and employ the more active Mes_2Mg in all of the following studies within the process under investigation.



Scheme 1.56

3.2.6 Evaluation of Electrophile Scope

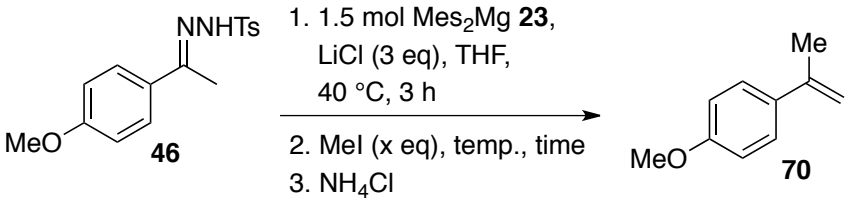
Thorough investigation and optimisation of the Mes_2Mg-mediated Shapiro reaction had delivered a series of positive results with D_2O and benzaldehyde as electrophiles. The standard conditions thus employ 1.5 mol Mes_2Mg and LiCl at 40 °C over 3 h for the efficient deprotonation of the hydrazone starting material and subsequent addition of the desired electrophile (**Scheme 1.57**).



D_2O: 90 % yield, 94:6 (E:H)
PhCHO (2 eq): 74 % yield, 90:10 (E:H)

Scheme 1.57

With these conditions in hand, an exploration of the electrophile scope was targeted, starting with the previously employed iodomethane (**Scheme 1.58**, **Table 1.26**). The short screening of quench conditions revealed that the temperature and time for the electrophile addition had to be slightly increased to achieve full conversion to the desired product. Quenching the reaction at 0 °C with 2 eq MeI delivered a good 81 % isolated yield of **70**, with a 93:7 selectivity in favour of the introduced methyl functionality (**Table 1.26**, **Entry 3**). The corresponding addition by-product 1,3,5-trimethyltoluene was observed, but did not pose a problem for the isolation of **70**.



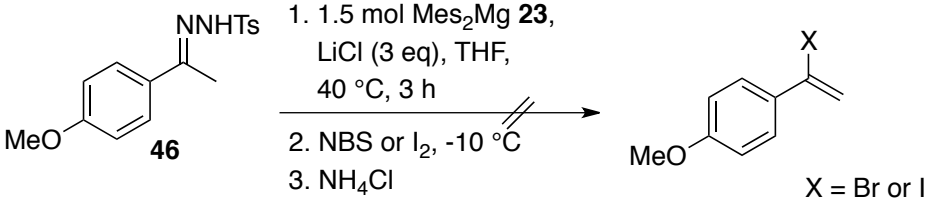
Scheme 1.58

Entry	*MeI*	*Conditions*	*Conv.* (%)[a]	*Yield **70*** (%)	*E:H* (%)[a]
1	4	-10 °C, 30 min	95	54	57:43
2	4	-10 °C, 1 h	97	85	88:12
3	2	0 °C, 1 h	93	81	93:7

[a]Determined by NMR analysis

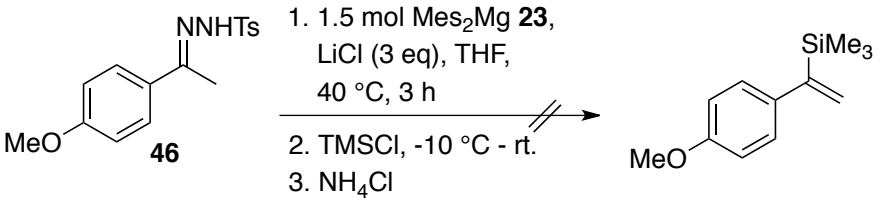
Table 1.26

Another interesting class of substrates that was envisaged to be accessible *via* the developed system from hydrazones are vinyl halides. Their applicability in alkyne formation and, more importantly, in various cross-coupling reactions make them a very desirable target. Electrophilic halides sources such as NBS and I_2 were thus trialled (**Scheme 1.59**). Unfortunately, all conditions employing these electrophiles as quench reagents for the generated vinyl anion were met with failure. Complex mixtures of products were obtained, of which clean isolation of the corresponding vinyl halides was unsuccessful.



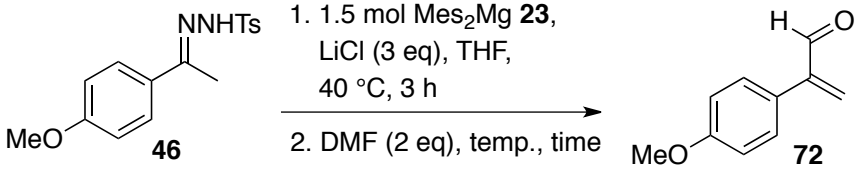
Scheme 1.59

Equally anticipated, but ineffective were attempts to generate α-vinyl silanes *via* the use of chlorotrimethylsilane (TMSCl) as an electrophile (**Scheme 1.60**). These compounds are sufficiently stable and can be activated under mild fluoride conditions for further derivatisation through oxidation or cross coupling.[103,104] However, once again the desired product was not formed as the major component and purification proved to be problematic.



Scheme 1.60

Undaunted by these results, the scope of electrophiles was further explored. Introduction of a carbonyl moiety, by using DMF or acid chlorides to generate the ensuing enal or enones was considered (**Scheme 1.61**, **Table 1.27**).



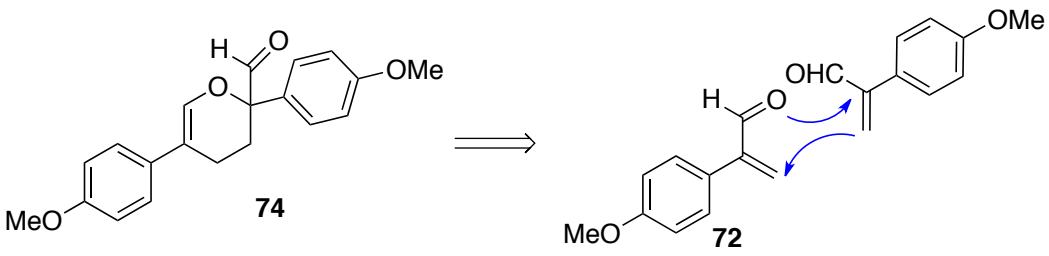
Scheme 1.61

Entry	*Conditions*	*Conv.* (%)	*Yield* ***72*** (%)	*E*:*H* (%)[a]
1	-10 °C, 1 h	95	-	83:17
2	0, 1 h	92	-	87:13

[a]Determined by NMR analysis

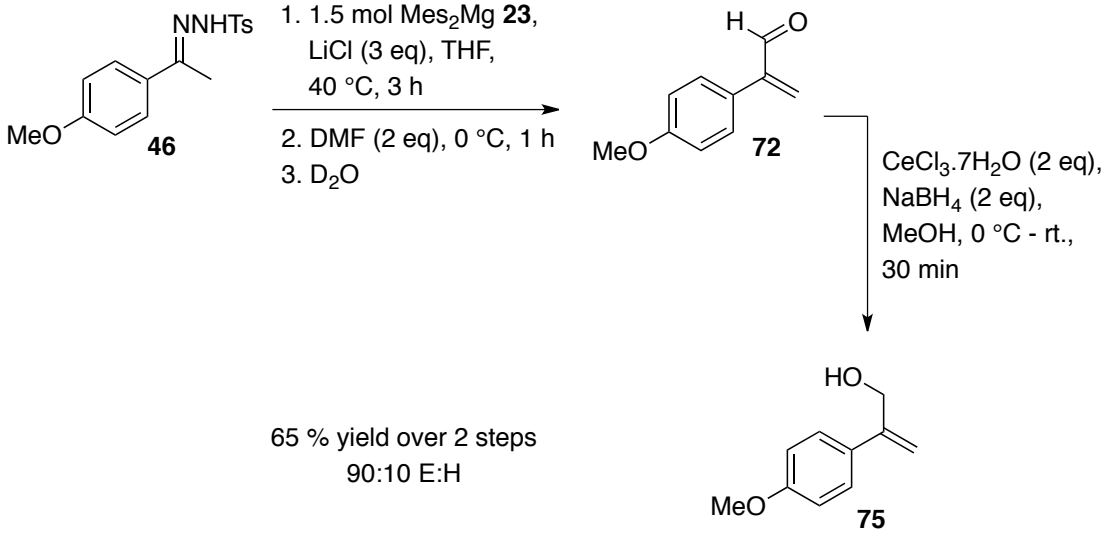
Table 1.27

As expected, conversion of the starting material was high, however acquiring the desired product proved to be more challenging. Despite observing the enal as the main component in the crude mixture when employing DMF with very promising ratios to the protonated alkene by-product of up to 87:13 (**Table 1.27**, **Entry 2**), its instability led to degradation on purification by column chromatography. Additionally, it was found that dimerization to the heterocycle **74** occurred readily upon standing (**Scheme 1.62**).[105]



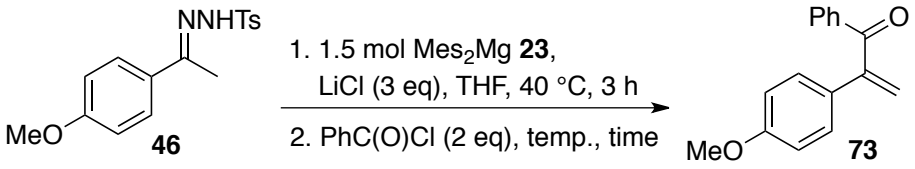
Scheme 1.62

To circumvent the problem, the crude mixture was subjected to Luche reduction conditions and the corresponding allylic alcohol was isolated (**Scheme 1.63**). Telescoping the 2 steps gave rise to an appreciable 65 % yield of the allylic alcohol **75**, thus validating the formation of the initially targeted enal **72**.



Scheme 1.63

In respect to utilising acid chlorides as electrophilic quench reagents, none of the wanted enone could be observed when PhCOCl was added (**Scheme 1.64**, **Table 1.28**).



Scheme 1.64

Entry	*Conditions*	*Yield **73*** (%)	*E*:*H* (%)[a]
1	-10 °C, 30 min	-	-
2	0 °C, 30 min	-	-

[a]Determined by NMR analysis

Table 1.28

Rather than the anticipated outcome, and along with traces of the protonated styrene H-**47**, a white crystalline powder was isolated and identified by X-ray crystallography (**Figure 1.13**).

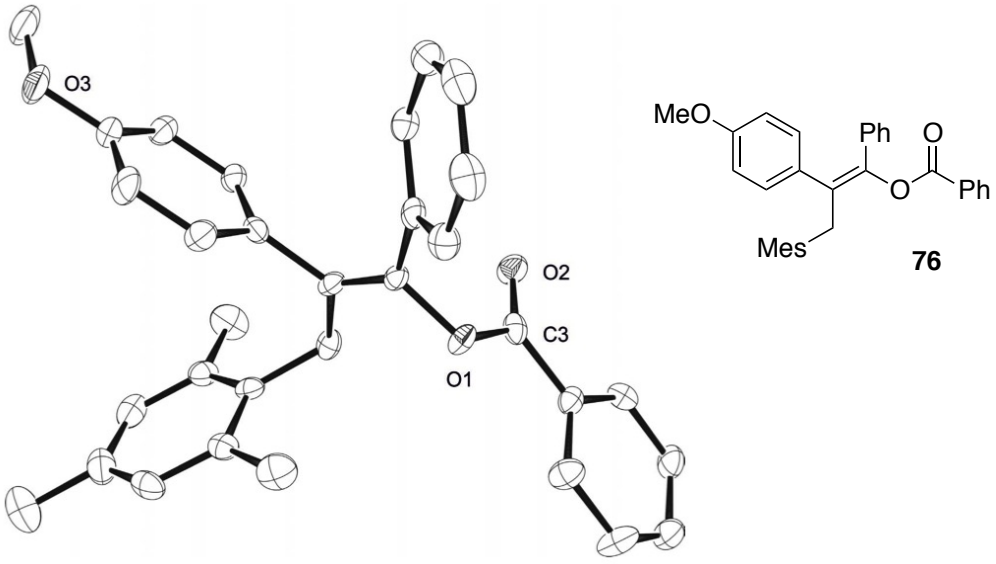
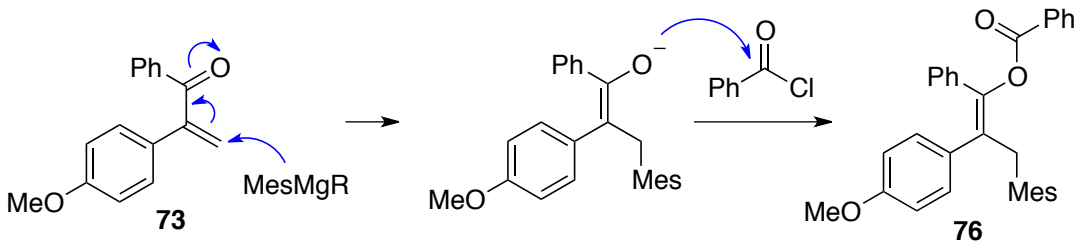


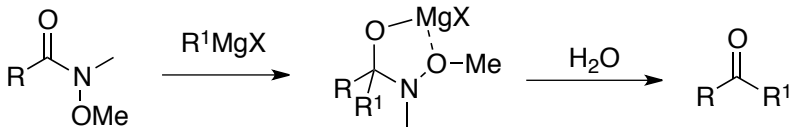
Figure 1.13

The unsaturated ester **76**, obtained in 65 % yield, is believed to arise from the desired enone, **73**, *via* conjugate addition of a mesitylene unit from unreacted base reagent and subsequent reaction with another equivalent of benzoyl chloride through the oxygen anion of the intermediate enolate (**Scheme 1.65**).



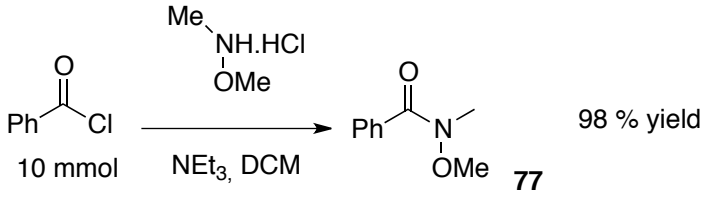
Scheme 1.65

The high yield of ester **76** is evidence for the efficient formation of enone **73** during the reaction but also its instability under the applied conditions. The continuous reaction of reactive ketones when formed from acid chlorides or esters and Grignard reagents to yield the corresponding tertiary alcohol is well known. In such cases, the double addition can be prevented by employing Weinreb amides which release the ketone product only on work up (**Scheme 1.66**).[106,107]



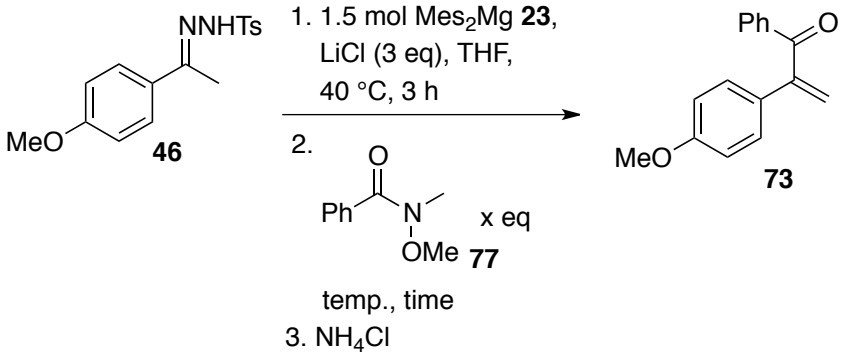
Scheme 1.66

This concept was thought to be applicable within in the developing modified Shapiro system. Accordingly, Weinreb amide **77** was obtained from the parent acid chloride and *N*-methoxy-*N*-methylamine hydrochloride salt in an excellent 98 % yield (**Scheme 1.67**).



Scheme 1.67

With the required electrophile in hand, a series of initial test reactions were explored (**Scheme 1.68**, **Table 1.29**). At low temperatures, as employed previously, only a low conversion to enone **73** was detected and mainly protonated styrene H-**47** was isolated following work-up with aqueous ammonium chloride (**Table 1.29**, **Entry 1**). However, increasing the temperature to ambient and even levelling it to 40 °C gave rise to 69 % and 72 % yield of the functionalised styrene, respectively (**Table 1.29**, **Entries 2** and **3**). More importantly, no addition by-product, as seen with the previously employed electrophiles, was observed. The amount of electrophile was consequently lowered to near stoichiometric quantities (**Table 1.29**, **Entry 4**). Gratifyingly, similarly high yields of up to 75 % could be obtained. The reaction was subsequently scaled up to 5 mmol of hydrazone **46** (1.6 g), delivering a 84 % yield of the enone **73** (**Table 1.29**, **Entry 5**). Similarly to the enal **72**, obtained when using a DMF quench (*cf.* **Scheme 1.62**), dimerisation of **73** occurred upon prolonged standing (*see Experimental section for further details*).



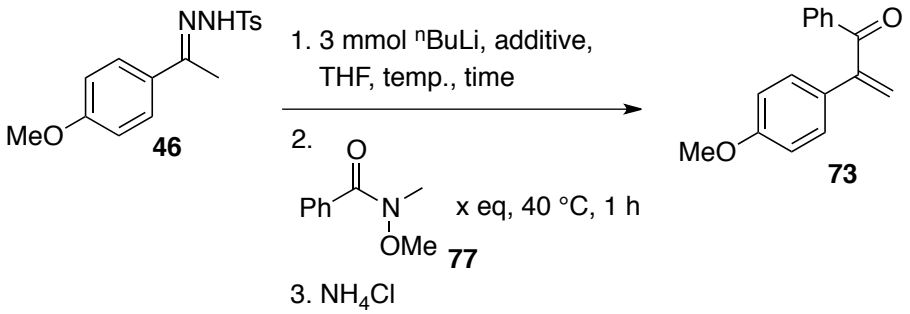
Scheme 1.68

Entry	***77*** (eq)	*Conditions*	*Yield **73*** (%)	*H-**47*** (%)	*E:H* (%)[a]
1	2	-10 °C, 1 h	10	68	12:88
2	2	rt., 1 h	69	9	91:9
3	2	40 °C, 30 min	72	7	97:7
4	1.05	40 °C, 1 h	75	-	93:7
5[b]	1.05	40 °C, 1 h	84	5	93:7

[a]Determined by NMR analysis, [b]scale up to 5 mmol of **46**

Table 1.29

This further improvement with Weinreb amide **73** significantly increases the efficiency of the developed magnesium-mediated Shapiro process. In contrast, the more commonly used lithium-based conditions require expensive trisiylhydrazone derivatives and elaborate low temperature protocols to allow for such low quantities of electrophile. A direct comparison employing *n*-BuLi as a base reagent and Weinreb amide **77** was sought to advocate our arguments (**Scheme 1.69**, **Table 1.30**).



Scheme 1.69

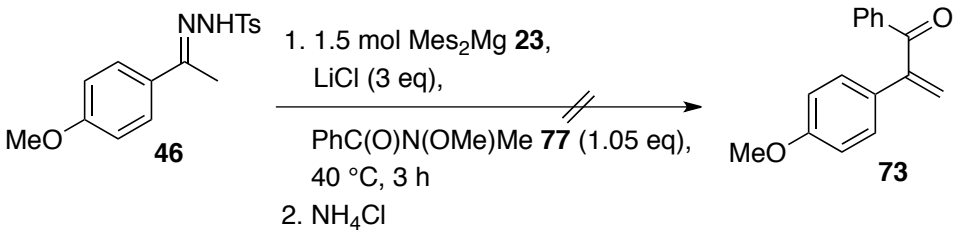
Entry	*Conditions*	*Additive*	***77***	*Quench Conditions*	***73*** (%)	*E:H* (%)[a]
1	40 °C, 3 h	LiCl	1.05 eq	40 °C, 1 h	10	79:21
2	-50 °C - rt., 2 h	TMEDA	4 eq	-78 °C-rt., 1 h	42	64:36

[a]Determined by NMR analysis

Table 1.30

As anticipated, reaction conditions in analogy to the Mes_2Mg-mediated process delivered inferior results, possibly due to degradation at elevated temperatures (**Table 1.30**, **Entry 1**). Subjecting the reaction to a low temperature protocol similar to Bond's first modification[95] with addition of TMEDA and a large excess of electrophile furnished a slightly increased yield of 42 % (**Table 1.30**, **Entry 2**). The timing for this reaction is not optimised and the yield could most likely be further improved for this substrate. Nonetheless, these control reactions emphasise the advancement the magnesium-mediated Shapiro process, which employs a more accessible and constant temperature protocol with only a slight excess of Mes_2Mg and a near stoichiometric amount of Weinreb amide.

Reviewing the largely inert character of amide **77** towards the base reagent Mes_2Mg, an internal quench protocol was proposed. With the aim of developing a more practicable procedure, the electrophile was added at the beginning of the reaction set up (**Scheme 1.70**).



Scheme 1.70

Unfortunately, none of the desired enone **73** was isolated, but a crystalline solid. X-ray analysis revealed the formation of the pyrrazole salt **78** (**Figure 1.14**).

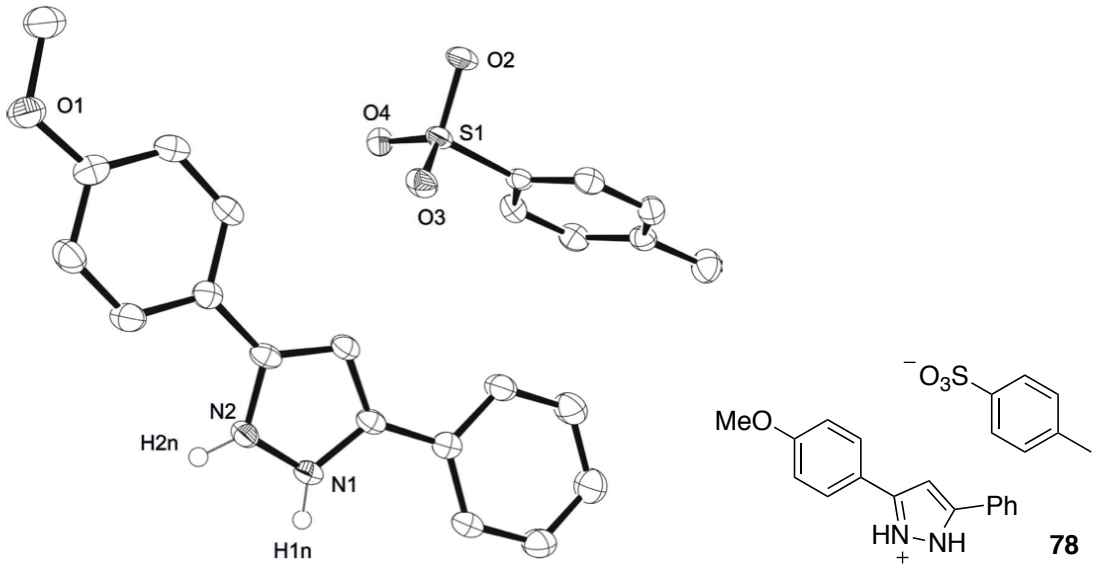
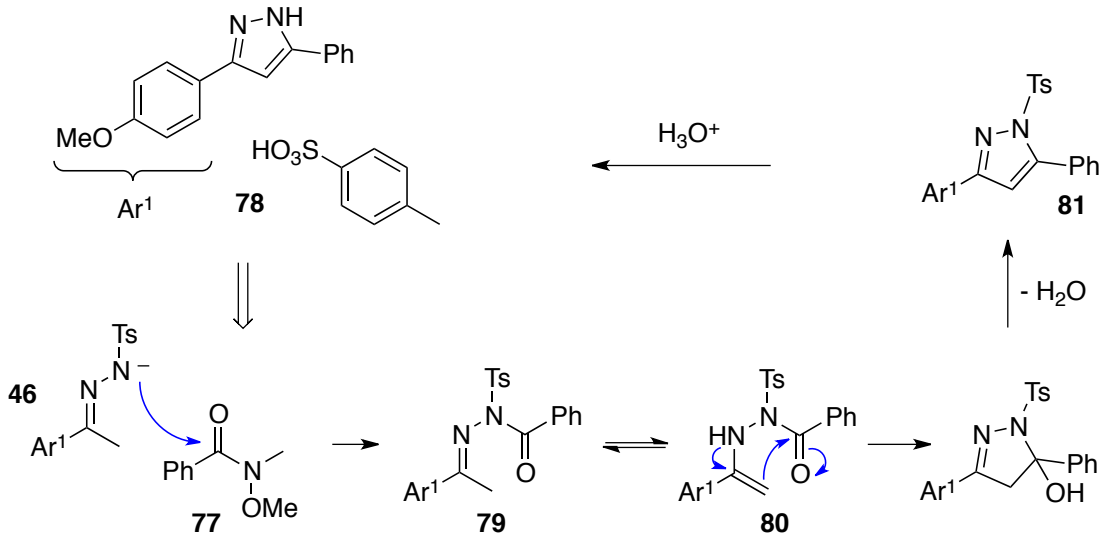


Figure 1.14

Generation of this major product in 31 % yield could be explained as depicted in **Scheme 1.71**.

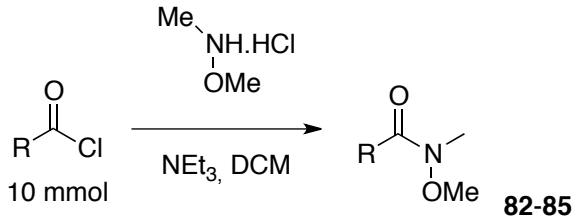


Scheme 1.71

The first deprotonation of hydrazone **46** leads to an immediate nucleophilic attack of the Weinreb amide **77**, which could form the amide **79**, or its magnesium

complexed tetrahedral intermediate prior to the expulsion of *N*-methyl-*N*-methoxy amine (not shown in **Scheme 1.71**). Tautomerisation to enamine **80** allows for cyclisation and subsequent loss of water to form the aromatic pyrazole **81**. As the X-ray analysis confirmed a sulfonate salt, the cleavage of the sulfonamide bond in **81** by the mild acid is proposed. Despite these interesting findings, an internal quench protocol had to be ruled out and was not further investigated.

With optimised conditions for an electrophilic quench with Weinreb amide **77** to produce the corresponding enones in hand, a small range of differently substituted Weinreb amides was synthesised from the corresponding acid chlorides in high yields (**Scheme 1.72**, **Table 1.31**).



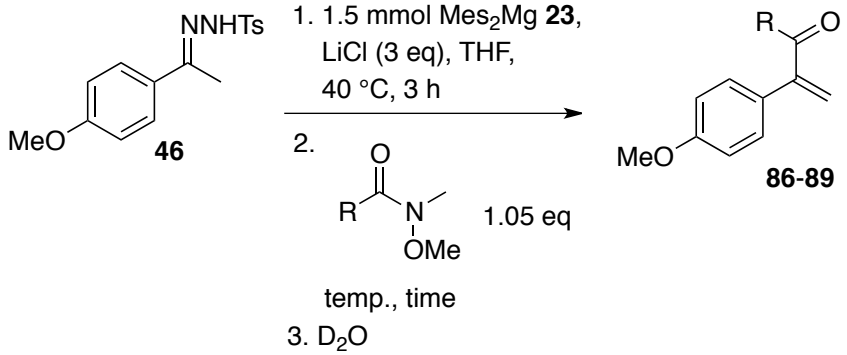
Scheme 1.72

Entry	*R*	*Yield* (%)
1	^{t}Bu	96 (**82**)
2	^{i}Pr	98 (**83**)
3	Et	94 (**84**)
4	Me	98 (**85**)

Table 1.31

Previously, the ratio of desired product to protonated styrene H-**47** (E:H) had been an effective indicator for the efficiency of the electrophile pick up by the vinyl anion. With more complex electrophiles, competitive deprotonation of these species becomes possible and it was decided to add D_2O to the reaction prior to the standard work up. Unreacted vinyl anion is thus converted to the deuterated styrene D-**47**, whereas observed *H*-styrene H-**47** implies a proton source has quenched the reaction

in situ (E:H:D). In this way, analysis of the reaction progression and reactivity of the vinyl anion is easily monitored and optimisation of the quench conditions is more readily rationalised. In respect to the assessment of the synthesised Weinreb amides, the following results have been obtained when applied in the newly developed Shapiro process (**Scheme 1.73**, **Table 1.32**). Notably, all of the obtained enone products were prone to dimerisation as described with enone **73** and enal **72** (*cf.* **Scheme 1.62**), and two of the heterocyclic products could be isolated cleanly (*see Experimental section for further details*).



Scheme 1.73

Entry	*R*	*Conditions*	*Yield* (%)	*H/D -styrene **47** (%)*	*E:H:D* (%)[a]
1	Me[b] (**85**)	0 °C, 2 h	45 (**86**)	22	65:35:0
2	Et[c] (**84**)	40 °C, 1 h	77 (**87**)	8	92:8:0
3	^{i}Pr[c] (**83**)	40 °C, 30 min	72 (**88**)	11	93:7:0
4	^{t}Bu (**82**)	40 °C, 1 h	46 (**89**)	20	58:12:30
5	^{t}Bu (**82**)	40 °C, 16 h	64 (**89**)	12	83:17:0

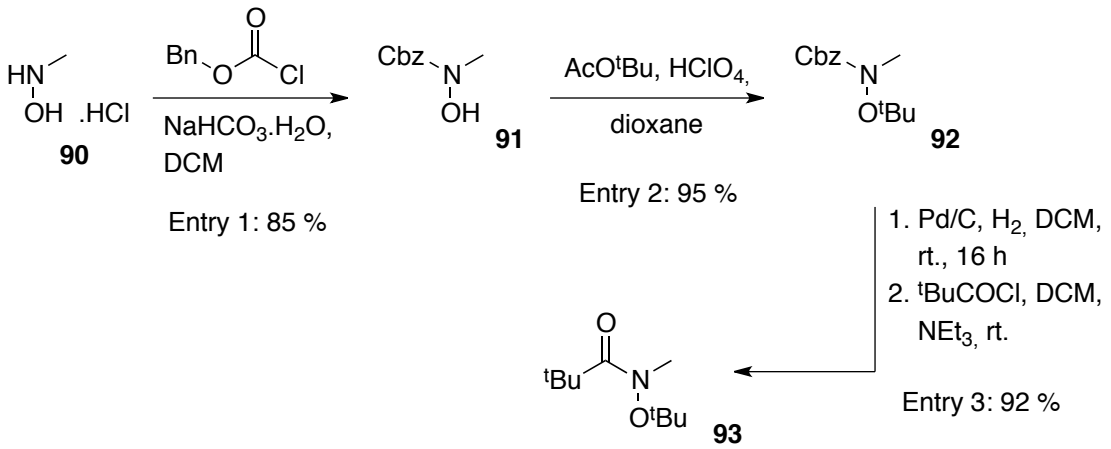
[a]Determined by NMR analysis, [b]2 eq of electrophile were used, [c]dimerised product isolated.

Table 1.32

Under the established standard conditions, methyl Weinreb amide **85** furnished only moderate yields, even when employing 2 equivalent of the amide (**Table 1.32**, **Entry 1**). Optimised conditions for Et- and ^{i}Pr-Weinreb amides, **84** and **83**, were quickly found to be analogous to the phenyl Weinreb amide **77** and delivered

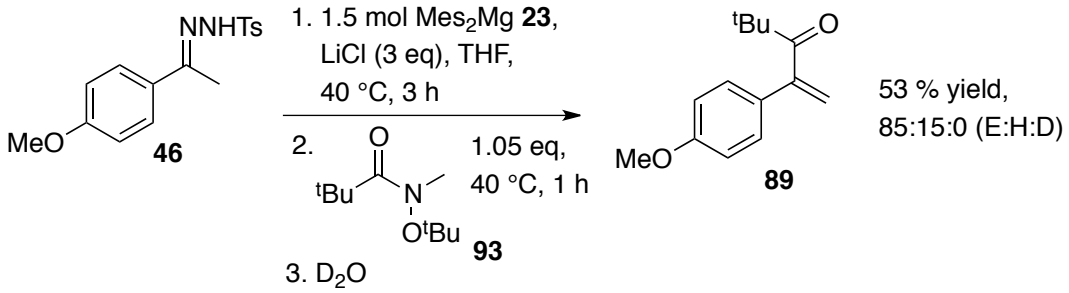
appreciable yields of the desired enones **87** and **88**, respectively (**Table 1.32**, **Entries 2** and **3**). The more bulky *t*-butyl amide **82** on the other hand delivered a much lower yield of 46 % of **89** (**Table 1.32**, **Entry 4**). The large amount of D-**47** identified, however, indicated that the vinyl anion reacted more slowly with this electrophile. Consequently, extending the reaction time to 16 h drove the reaction to completion and delivered the desired enone in 64 % yield. Overall, a range of enone products had been efficiently accessed using the developed Shapiro techniques in moderate to good yields.

Returning to the transformation with *t*-butyl Weinreb amide **82**, the much poorer ratio of 83:17:0 in respect to H-**47** and lower yield of **89** compared to other Weinreb amides was thought to arise from competitive demethoxylation. This can occur quite readily with sterically more encumbered Weinreb amides.[107,108] To confirm this, the exchange of the *N*-methoxy for a *N*-*t*-butoxy group was considered and the corresponding amide **93** was synthesised,[109] starting from hydroxyamine salt **90** (**Scheme 1.74**). Protection of the amine salt and subsequent *O*-alkylation provided amide **92** in high yield. Contrary to the original procedure,[109] the deprotection *via* hydrogenation and further *N*-alkylation could conveniently be telescoped using DCM as a solvent, delivering the final product in 92 % yield.



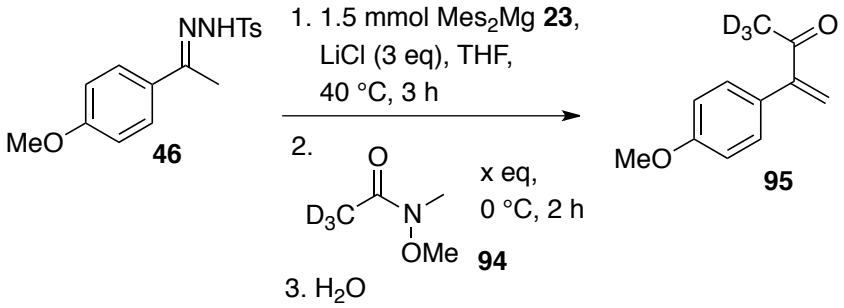
Scheme 1.74

Application of this newly generated electrophile **93** in the Shapiro reaction, led to complete conversion of the starting material after 1 h at 40 °C (**Scheme 1.75**), compared with 16 h reaction time with Weinreb amide **82** (*cf.* **Table 1.32**, **Entry 5**). Although the reaction time was reduced, a comparably low yield of 53 % was obtained. It was reasoned that due to steric bulk (i.e. the release of steric strain) the enone could be formed prematurely, thus allowing for conjugate addition, as observed with benzoyl chloride, and resulting in a decreased yield. Indeed, traces of the corresponding by-product were detected by ^{1}H-NMR (*see Experimental for further details*).



Scheme 1.75

Surprisingly, using methyl Weinreb amide **85** at the standard temperature of 40 °C ensued in very inconsistent and decreased yields even with 2 eq of the electrophile. Best results were obtained at 0 °C, where 45 % of the desired enone **86** could be isolated (*cf.* **Table 1.32**, **Entry 1**). Additionally, a considerable amount of H-**47** was detected, 65:35:0 (E:H:D). Deprotonation of the α-methyl group was believed to be the cause, therefore, the deuterated amide **94** was synthesised and used as an electrophile for verification (**Scheme 1.76**, **Table 1.33**).



Scheme 1.76

Entry	***94*** (eq)	*Yield **95*** (%)	*H*/*D*-***47*** (%)	*E*:*H*:*D* (%)[a]
1	2	75	12	85:15:0
2	1.05	72	15	84:16:0

[a]Determined by NMR analysis

Table 1.33

The addition of D_2O was omitted in these reactions in order to still obtain a diagnostic set of product to by-product ratios. Unexpectantly, no D-**47** was detected and a much increased yield of 75 % of **95** was obtained. This suggests that no deuterium abstraction had occurred due to a small but pivotal kinetic isotope effect. Subsequently, the quantity of the amide electrophile could be lowered to 1.05 equivalents, delivering comparable yields of the enone **95** (**Table 1.33**, **Entry 2**).

Overall, a series of enone products has thus been accessed efficiently when employing Weinreb amides as electrophiles in the newly developed Shapiro process. Notably, this has been achieved with comparably low base quantities and 1.05 equivalent of the electrophile (**Figure 1.15**)

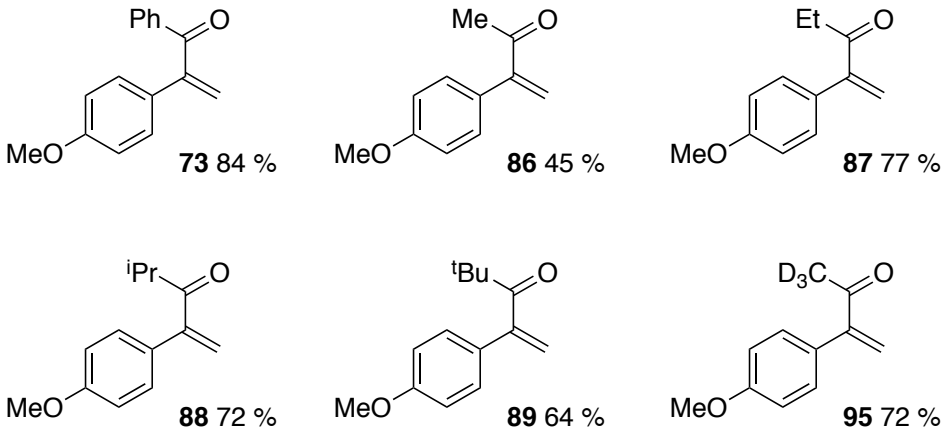


Figure 1.15

Reviewing the efficiency of the electrophile quench with the various Weinreb amide electrophiles, the slow conversion of **82** to form **89** stands out (*cf.* **Table 1.32**, **Entries 4** and **5**). Moreover, since the equally bulky *O*-*t*-butyl derivative **93** reacts much faster, steric encumbrance cannot be the sole reason for this reduced reaction rate (*cf.* **Scheme 1.75**). It was proposed that the *cis*/*trans*-conformation of the amide bond may have an effect and density functional theory (DFT) calculations to determine the most stable conformation in each case were conducted to validate this argument (**Figure 1.16**, **Table 1.34**).

Figure 1.16

R/R[1]	*Ph/Me* ***77***	*^{t}Bu/Me* ***82***	*^{t}Bu/^{t}Bu* ***93***	*^{i}Pr/Me* ***83***	*Et/Me* ***84***	*Me/Me* ***85***
ΔE (kcal/mol)	-0.82	+2.38	-1.51	-2.08	-2.61	-1.81
O=C-N-OR[1]	153.2°	9.4°	174.2°	164.9°	165.4°	165.5°
preferred conformer	*trans*	*cis*	*trans*	*trans*	*trans*	*trans*

Table 1.34

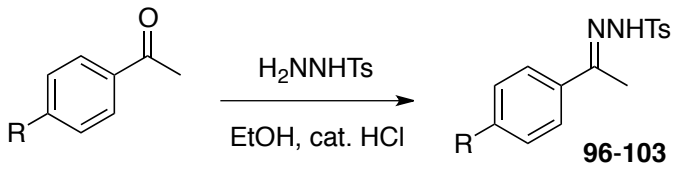
Albeit with a small energy difference, the calculations clearly show a preference for a *cis*-conformation in amide **82**, whereas the remainder prefer a *trans*-arrangement of the carbonyl and the alkoxide moieties. Based on electrostatic repulsion between the carbonyl oxygen and the alkoxy oxygen, the *trans*-conformer is typically favoured, as emphasised by the dihedral angle of O=C-N-OR^1.[110] However, in respect to **82** this may suggest a steric clash between R and R^1, which forces the amide to rotate across the O=C-N bond into a *cis* arrangement.[111] With regards to Weinreb amide **93**, this may not be beneficial due to the equally bulky *t*-butoxide moiety, resulting in electronic factors dominating the conformation.

It seems feasible that the nucleophilic attack of a magnesium coordinated vinyl anion is directed by the oxygen of the *N*-methoxy or *N*-*t*-butoxy group in *trans*-Weinreb amides. This could possibly accelerate the nucleophilic attack considerably compared to the *cis*-conformation and explain the elevated reactivity. It has also been shown that the rotation between *cis*- and *trans*-**82** has an energy barrier of 11 kcal/mol, which can be overcome under the reaction conditions employed. A prolonged reaction time would thus allow for the switch to the faster reacting *trans*-**82** and deliver an increased yield (*cf.* **Table 1.32**, **Entry 5**).

With the screening of quench reagents complete, the generality of the modified Shapiro protocol with Weinreb amides and alternative electrophiles has been established. A range of functionalised styrene derivatives have been made accessible under comparably mild reaction conditions and with only low excess of the respective electrophile.

3.2.7 Evaluation of Substrate Scope

Having extended the scope of electrophiles suitable for the magnesium-mediated Shapiro reaction, a broadening of the substrate range was pursued. First the substitution pattern on the aryl moiety was investigated and a small series of *para*-substituted phenylmethyl hydrazones were prepared (**Scheme 1.77**, **Table 1.35**).

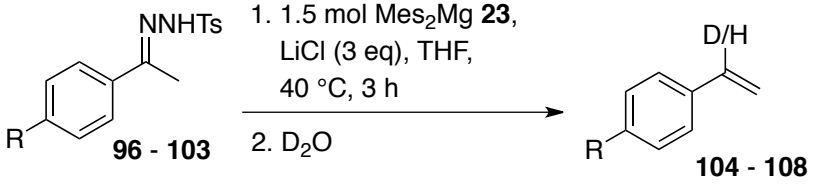


Scheme 1.77

Entry	*R*	*Yield* (%)
1	H	65 (**96**)
2	^{t}Bu	74 (**97**)
3	Ph	87 (**98**)
4	Cl	81 (**99**)
5	$N(CH_2)_4$	92 (**100**)
6	CF_3	90 (**101**)
7	NO_2	94 (**102**)
8	CN	95 (**103**)

Table 1.35

In all cases high yields of the *E*-isomer of the requisite hydrazone could be obtained after recrystallisation in hot ethanol. Accordingly, each substrate was subjected to the optimised reaction conditions and quenched with D_2O to examine their applicability (**Scheme 1.78**, **Table 1.36**).



Scheme 1.78

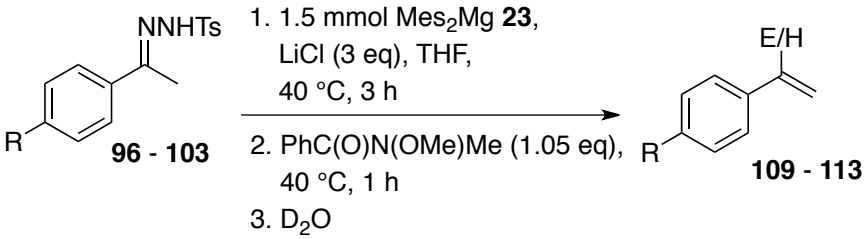
Entry	R^1	*Yield* (%)	*D:H* (%)[a]
1	H (**96**)	57[b] (**104**)	92:8
2	^{t}Bu (**97**)	91[b] (**105**)	91:9
3	Ph (**98**)	85[c] (**106**)	96:4
4	Cl (**99**)	94[b] (**107**)	97:3
5	$N(CH_2)_4$ (**100**)	63[c] (**108**)	90:10
6	CF_3 (**101**)[d]	-	-
7	NO_2 (**102**)	-	-
8	CN (**103**)	-	-

[a]Determined by NMR analysis, [b]yield calculate from ^{1}H-NMR, [c]isolated yield, [d]87 % of **101** recovered when run at 0 °C.

Table 1.36

As anticipated, in the majority of cases a darkening of the reaction mixture was observed over time prior to the electrophile addition, which is generally indicative for the generation of the corresponding vinyl anion. Hydrazones **96** – **100**, with electron-neutral or -donating substituents, delivered good to high yields (up to 94 %) of the deuterated styrene (**Table 1.36**, **Entries 1** to **5**). Disappointingly, more strongly electron-withdrawing groups proved to be more challenging. A rapid or instantaneous colour change to dark brown upon hydrazone addition to the Mes_2Mg solution was detected in each case and no starting material or product could be isolated under the standard conditions (**Table 1.36**, **Entries 6** to **8**). Lowering the reaction temperature to 0 °C and shortening the reaction time was equally unsuccessful. With respect to hydrazones **102** and **103**, the degradation of the material could be explained by competitive attack of Mes_2Mg on the nitrile or nitro substituent. Similarly, such functional groups tend to be incompatible with Grignard reagents, and only recently have conditions been developed under which they remain intact.[112,113] Hydrazone **101**, on the other hand, does not have such a strongly electrophilic substituent. Moreover, running the reaction at 0 °C, the base reagent **23** seems largely ineffective and 87 % starting material were recovered with substrates **101**-**103**. None of the conditions employed provided any appreciable amount of styrene product.

The observed trends of the reactivity of hydrazone **96** to **103** were confirmed when employing Weinreb amide **77** (**Scheme 1.79**, **Table 1.37**). In this regard, hydrazones with electron-neutral or -donating substituents delivered good yields of the corresponding enone products (**Table 1.37**, **Entries 1** to **5**), whereas electron-deficient hydrozones degraded (**Table 1.37**, **Entries 6** to **8**).



Scheme 1.79

Entry	*R*[1]	*Yield* (%)	*E:D:H* (%)[a]
1	H (**96**)	79[c] (**109**)	95:0:5
2	^{t}Bu (**97**)	75[c] (**110**)	94:0:6
3	Ph (**98**)	91[c] (**111**)	93:0:7
4	Cl (**99**)	70[c] (**112**)	97:0:3
5	$N(CH_2)_4$ (**100**)	52[c] (**113**)	95:0:5
6	CF_3 (**101**)	-	-
7	NO_2 (**102**)	-	-
8	CN (**103**)	-	-

[a]Determined by NMR analysis, [b]yield calculate from ^{1}H-NMR, [c]isolated yield.

Table 1.37

In this regard, a range of aryl hydrazones was successfully applied in this newly developed protocol, giving efficient access to a variety of the corresponding deuterated derivatives and enone products (**Figure 1.17**).

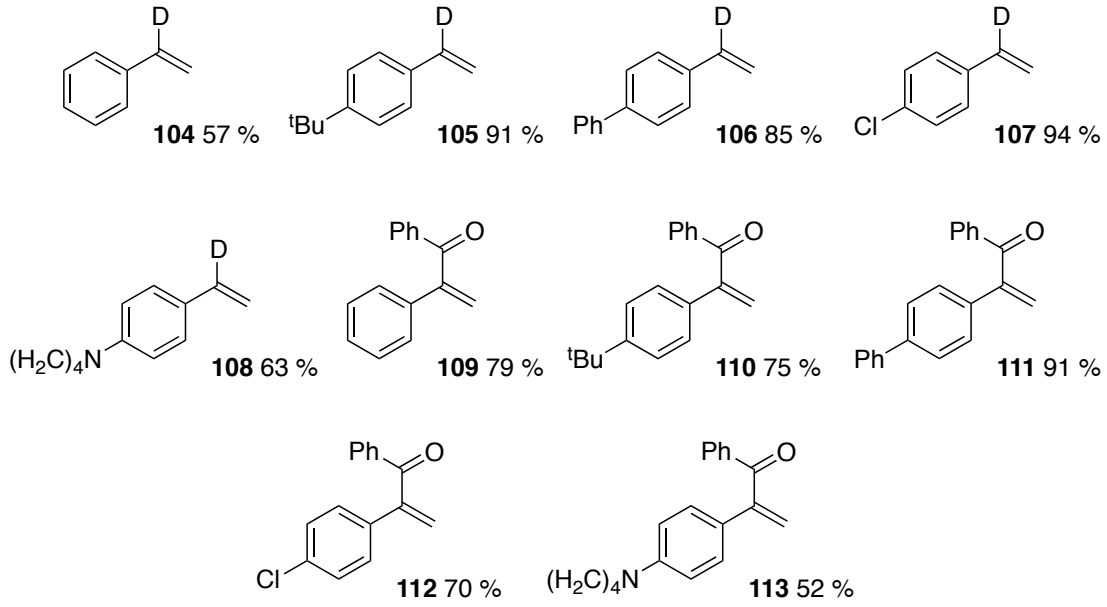


Figure 1.17

Having conducted a brief study of variable aryl substituents, attention focused on more challenging hydrazones without an aryl group and/or secondary alkyl substituents instead of the simple methyl group. All of the required substrates were made from the parent ketones as described previously (**Figure 1.18**).

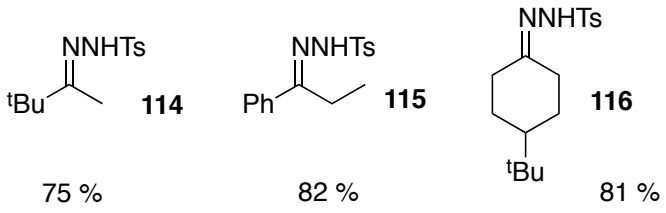
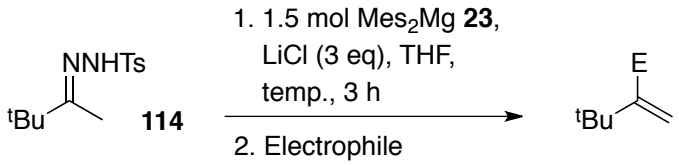


Figure 1.18

At the outset, *tert*-butyl methyl hydrazone **114** was examined, using Weinreb amide **77** as an electrophilic quench (**Scheme 1.80**, **Table 1.38**). Due to their high volatility, the corresponding *H*- or *D*-alkene were not investigated.



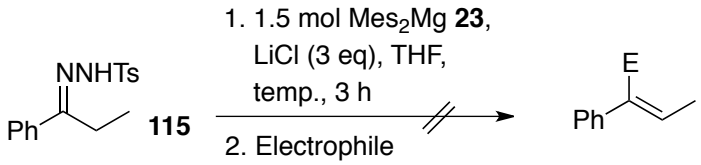
Scheme 1.80

Entry	*Temp.*	*Electrophile*	***114*** (%)	*Yield of E-alkene* (%)
1	40 °C	PhC(O)N(OMe)Me	44	-
2	65 °C	PhC(O)N(OMe)Me	-	-
3	65 °C	PhCHO	-	46 (**117**)

Table 1.38

With regards to the above results, no typical colour change for the vinyl anion formation was observed at the standard reaction temperature of 40 °C and 44 % of the starting material was recovered (**Table 1.38**, **Entry 1**). The reaction temperature was consequently increased to reflux. Despite the appearance of a ruby red colour, no enone product could be isolated when utilising 1.05 equivalents of Weinreb amide **77** (**Table 1.38**, **Entry 2**). The steric encumbrance of both vinyl anion and Weinreb amide may be accountable for this outcome and thus the more reactive benzaldehyde was employed, leading to an encouraging 46 % yield of the allylic alcohol **117** (**Table 1.38**, **Entry 3**). Unfortunately, this could not be further improved under various modified conditions.

In analogy to **114** the phenylethyl hydrazone **115** returned starting material when reacted at 40 °C and quenched with benzyldehyde. Upon warming the reaction to reflux, neither PhCHO nor Weinreb amide **77** resulted in the formation of the desired products or H/D-styrene by-products (**Scheme 1.81**, **Table 1.39**).

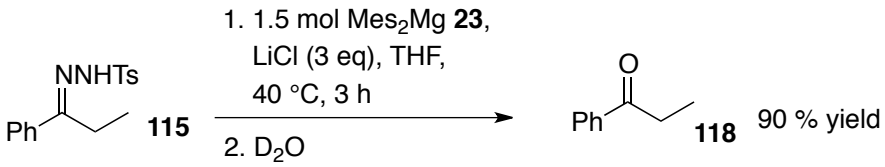


Scheme 1.81

Entry	*Temp.*	*Electrophile*	***115*** (%)	*Yield of E-alkene* (%)
1	40 °C	PhCHO	58	-
2	65 °C	PhCHO	-	-
3	65 °C	PhC(O)N(OMe)Me	-	-

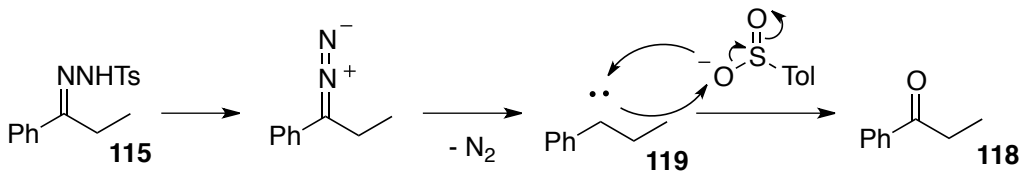
Table 1.39

In all of the above reactions (**Table 1.39**), the corresponding ketone was observed in each case. Further, when omitting the employed electrophiles and quenching the reaction with D_2O only, an astonishing 90 % yield of **118** was obtained (**Scheme 1.82**).



Scheme 1.82

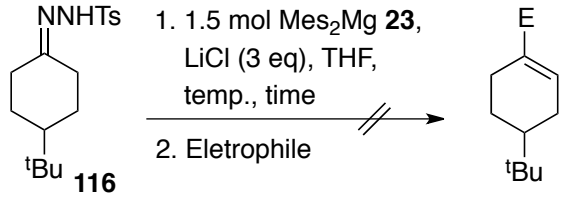
Reviewing the reaction conditions and the surprising outcomes, it was proposed that the double deprotonation of **115** had not occurred, due to the decreased acidity of the α-CH_2. A carbene, **119**, is thought to have been generated *via* the aprotic Bamford Stevens reaction instead (**Scheme 1.83**).[88] The only oxygen source available under the applied reactions conditions and prior to work up is the released sulfinate. In this regard, the formation of near quantitative amounts of ketone **118** could be explained. Additionally, in an attempt to confirm this, ^{18}O-labelled water was explored as a quench. Subsequent analysis of the isolated ketone did not indicate any inclusion of ^{18}O in the ketone, thus supporting the initial theory.



Scheme 1.83

To circumvent this problem, introduction of an electron-withdrawing group, such as chloride or an ester, in the α-position is envisaged. Lamentably, time restriction prevented the more in depth inspection of this idea.

As an alternative substrate, hydrazone **116** was subjected to the developed conditions (**Scheme 1.84**). Disappointingly, a range of conditions and electrophiles did not lead to a positive result and mainly degradation of the starting material was observed at temperatures of 40 °C and above.

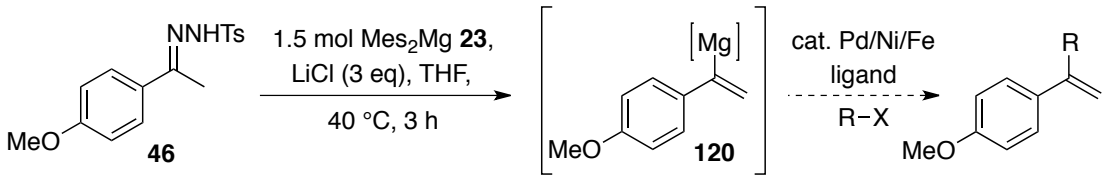


Scheme 1.84

Despite these latter less than satisfying outcomes, the reaction protocol for the magnesium carbon-centred base Shapiro process has been thoroughly explored and optimised. Additionally, the applicable substrate range has been broadened. In this regard, a series of aryl hydrazones are now available for the efficient generation of functionalised styrenes. An opening into further expansion has been made with *t*-butylmethyl hydrazone **114**. More importantly, comparably milder reaction conditions can be employed and only a slight excess of base reagent Mes_2Mg is required. Thus, an improved modification of the commonly used lithium-mediated Shapiro reaction has been introduced, circumventing an inefficient temperature protocol and expensive hydrazine reagents.

3.3 Investigations into Kumada-type Cross-coupling Reactions

Extensive investigations into optimising and extending the Mes_2Mg-mediated Shapiro reaction for a number of different electrophiles had been conducted. However, it was felt that the *in situ* generated vinyl anion, or alkenyl magnesium species, had more potential and cross-coupling reactions were considered (**Scheme 1.85**).

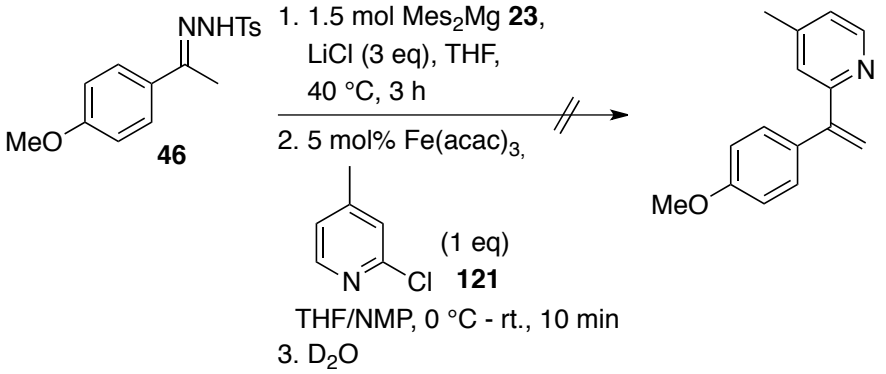


Scheme 1.85

During the early 1970's, Kumada and Corriu published seminal papers on the transition metal catalysed C-C bond formation of aryl and alkenyl halides with Grignard reagents and nickel catalysts.[114,115] This field of study developed appreciably over the following decades, extending both nickel- and palladium-catalysed transformations.[116,117] However, in 1976 Kumada had reported on the sluggish reactivity of alkenyl Grignards with Ni-based catalysts and only a few publications followed.[115,116,118] More recently, and based on results first documented by Kochi,[119,120] the use of simple, inexpensive and toxicologically benign iron catalysts in Kumada-type cross-couplings has moved into focus.[121,122,123] Other key advantages of this transition metal are the mild reaction conditions employed, generally short reaction times, and conveniently applied low temperatures between 0 °C and room temperature. In this regard, even esters are tolerated as additional functional groups.[124]

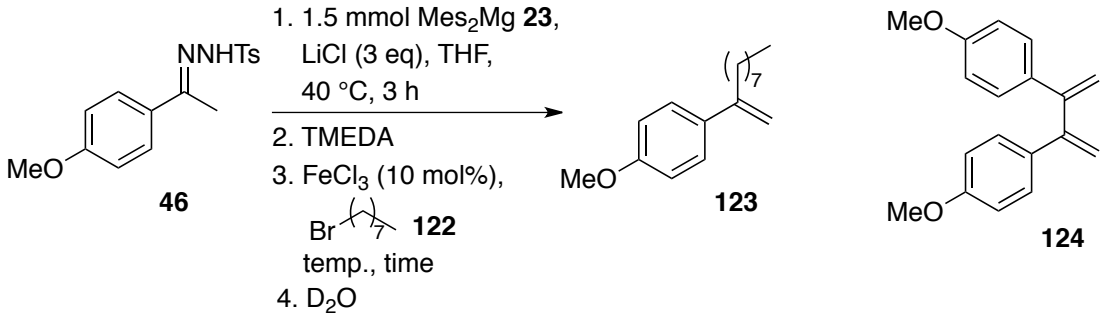
With this in mind, a very brief study concentrating on iron catalysts for the cross-coupling of the generated vinyl magnesium species *via* our modified Shapiro reactions was initiated. Cahiez, and later but more prominently Fürstner, had studied a system employing the air- and moisture-stable $Fe(acac)_3$ (acac = acetylacetonate) as a

catalyst and NMP as a co-solvent.[123,125] Unfortunately, such conditions are tailored to alkyl and aryl Grignard reagents and direct application to the generated vinyl species with pyridine **121** as a coupling partner was unsuccessful, delivering 37 % of the H/D-styrene **47** and returning 95 % of the pyridine **121** (**Scheme 1.86**).



Scheme 1.86

Further minor manipulations of the reaction conditions did not yield any of the desired product. A different, more appropriate system, developed by Cossy and co-workers,[126] was investigated next. A small range of simple alkenyl Grignards had been successfully coupled with primary and secondary alkyl as well as aryl bromides using anhydrous $FeCl_3$ and TMEDA as an additive. Accordingly, after addition of TMEDA to the cooled vinyl magnesium solution, it was transferred dropwise *via* cannula to a solution of $FeCl_3$ and bromooctane in THF (**Scheme 1.87**, **Table 1.40**).



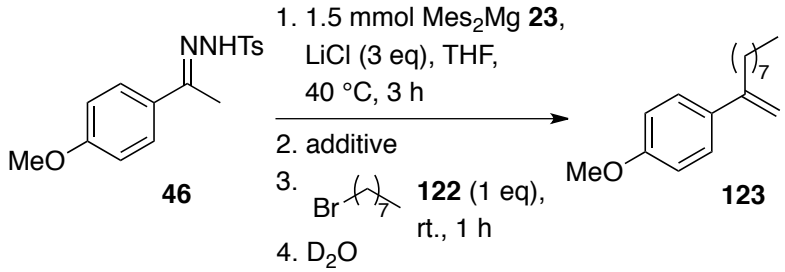
Scheme 1.87

Entry	*Conditions*	*Yield **123*** (%)	*H/D-**47*** (%)[a] (H:D)	*Homocoupling **124*** (%)
1	0 °C, 90 min	25	23 (62:38)	22
2	rt., 90 min	32	10 (67:33)	20

[a]Determined by NMR analysis

Table 1.40

Gratifyingly, under the above described conditions up to 32 % yield of the cross-coupled product **123** was obtained, albeit along with H/D-styrene **47** and homocoupled by-product **124**. To exclude the possibility of simple substitution of the bromide, control reactions without the catalyst and TMEDA were conducted (**Scheme 1.88**, **Table 1.41**). Without $FeCl_3$ as a catalyst, no alkylation product has been observed.



Scheme 1.88

Entry	*Additive*	*Yield **123*** (%)	*H/D-**47*** (%)[a] (H:D)	*Homocoupling* (%)
1	TMEDA	-	75 (13:87)	-
2	-	-	85 (10:90)	-

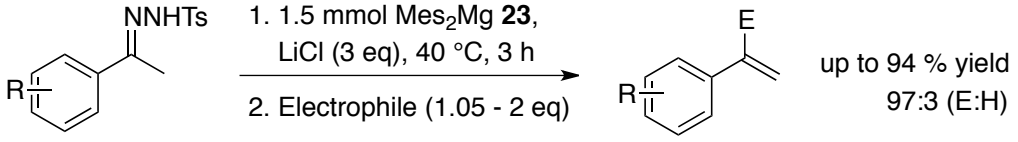
[a]Determined by NMR analysis

Table 1.41

This proof of concept may, with further optimisation, allow for the efficient cross-coupling of more complex alkenyl species and consequently broaden the scope for iron-catalysed Kumada-type couplings. A more thorough screening of alkyl halides is additionally required to ascertain which substrates react *via* substitution or cross-coupling, as MeI had reacted in the absence of a catalyst to furnish the alkylated alkene in high yields (*cf.* **Scheme 1.58**, **Table 1.26**).

4. Conclusions and Future Work

Significant insight into the reactivity of carbon-centred bases **22** and **23** in relation to the magnesium base-mediated Shapiro reaction has been gained. In summary, after optimisation, an efficient protocol has been established to furnish functionalised alkenes from electron-rich or -neutral aryl tosylhydrazones and a number of different electrophiles in excellent yields up to 94 % using Mes_2Mg as a base reagent (**Scheme 1.89**).



Scheme 1.89

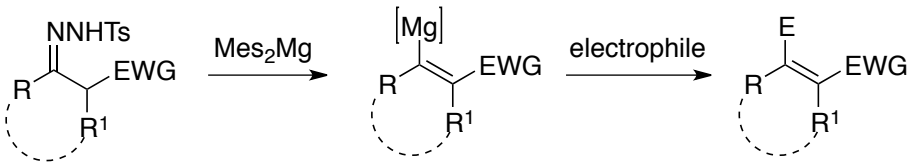
Importantly, the modified Shapiro reaction is run with a more cost effective and convenient temperature protocol (at 40 °C) in opposition to the more commonly used lithium-mediated process. Moreover, the desired products are obtained with only trace amounts of the competitively formed protonated styrene species. A further advancement has been the application of approximately stoichiometric quantities of Weinreb amides as electrophiles, giving access to valuable enone substrates in up to 77 % yield. Under standard lithium-based conditions, the significantly more expensive trisylhydrazine is required to furnish high yields if similarly low quantities of the base and electrophile are applied. In addition, our process requires only a slight excess of two equivalents with the other electrophiles applied, to compensate for competitive addition of the remaining magnesium base reagent. The main body of this work has recently led to a publication in Organic Letters.[99]

As the formation of addition by-product is a prominent occurrence, a survey was performed in attempts to achieve full consumption of the starting material at

lower temperatures with stoichiometric amounts of the base reagent prior to the collapse of dianionic intermediate. Lamentably, various attempts have failed to successfully establish this approach, as the base reagent Mes_2Mg displays a significantly reduced reactivity at temperatures below 10 °C.

With regard to the alternative base, di-*t*-butylmagnesium **22**, only a low reactivity within the Shapiro transformation was observed at various temperatures, rendering the base reagent inferior in comparison to Mes_2Mg.

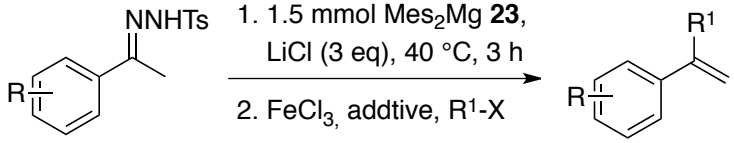
Overall, a considerable range of aryl hydrazones has been successfully utilised in the developed process. Having stated this, investigations to broaden the substrate scope further were met with only limited success. Substrates without aromatic substituents, such as *t*-butyl methyl hydrazone **114**, require more forcing conditions for the generation of the corresponding vinyl anion. Furthermore, substrates with less acidic protons on secondary α-carbons do not deliver the anticipated unsaturated products at all, but lead to the recovery of starting material or degradation instead. In this regard, and as future work, it is envisaged that the introduction of an electron withdrawing α-substituent might increase the acidity of the adjacent proton sufficiently to allow for the conversion to corresponding vinyl anion and thus facilitate the transformation to the desired functionalised alkene (**Scheme 1.90**).



Scheme 1.90

Additionally, research into utilising the *in situ* generated vinyl anion of the discussed process as an alkenyl Grignard analogue in transition metal catalysed cross-coupling reactions has been commenced. Gratifyingly, a brief screening revealed the

simple, inexpensive and toxicologically benign $FeCl_3$ as a suitable catalyst for the coupling of alkyl bromide **122**, providing the disubstituted terminal alkene in 32 % yield. None of the desired product was formed in absence of the catalyst. With further optimisation of this protocol, an efficient process for Kumada-type couplings could be developed using the carbon-centred base reagent **23** (**Scheme 1.91**). In this regard, future work should focus on the detailed screening of alkyl, alkenyl and aryl halides, as well as additives and alternative catalysts to assess the scope and limitations of this transformation.



Scheme 1.91

5. Experimental

5.1 General

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[127]

- THF was dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen.

- ^{t}BuMgCl and MesMgBr, obtained as 1 M solution in THF, were standardised using salicylaldehyde phenylhydrazone[100] or iodine in a saturated solution of LiCl in THF as an indicator.[101]

- DMPU, DMF, Weinreb amides and (*R,R*)-*bis*(α-methylbenzyl)amine were dried by heating to reflux over calcium hydride and distilled under reduced pressure, then purged with and stored under argon over 4 Å molecular sieves.

- Benzaldehyde, benzoyl chloride and TMSCl were dried by distillation under argon and stored under argon over 4 Å molecular sieves.

- Lithium chloride was flame-dried under high vacuum, then purged with and stored under argon.

- 4-*tert*-Butylcyclohexanone was purified by recrystallisation from hexane at 4 ^{o}C and stored under argon.

- MeI was dried by heating to reflux over calcium chloride, then distilled and stored under argon.

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254. This was analysed using a Mineralight UVGL-25 lamp and developed using potassium permanganate or vanillin solution.

Flash chromatography was carried out using Prolabo silica gel (230-400 mesh).

Gas chromatography was carried out using a Carlo Erba HRGC 5300 gas chromatograph fitted with (i) a CP SIL-19CB column or (ii) a CP-Chirasil-DEX CB column. Detection was by flame ionisation and the chromatograph was interpreted using JLC 6000 computer software.

^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX 400 spectrometer at 400 MHz unless otherwise stated. Chemical shifts are reported in ppm, and coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions unless otherwise specified.

High-resolution mass spectra were obtained on a Finnigan MAT900XLT instrument at the EPSRC National Mass Spectrometry Services Centre, University of Wales, Swansea.

FTIR spectra were obtained on a Nicolet Impact 400D machine.

Elemental analysis was obtained using a Carlo Erba 1106 CHN analyser.

Optical rotation was obtained on Perkin Elmer 341 polarimeter using a cell with a path length of 1 dm. Concentration is expressed in g/100 cm^3.

Air-sensitive reactions were carried out using Schlenk apparatus, which was initially evacuated and flame-dried, then purged with argon.

The structures of all Weinreb amides were optimised using density functional theory [128, 129] (DFT) with the B3LYP[2] functional in conjunction with the 6-311G+(d,p)[130,131] basis set, implemented in the Gaussian09[132] program. B3LYP is a hybrid functional which contains the Becke three parameter exchange functional[133] along with Lee-Yang-Parr correlation;[134] this functional is known to produce accurate results for main group chemistry.

5.2 General Experimental Procedures

Typical Procedure A for the Preparation of Magnesium Bisamide Reagents

(*R*)-**14**: $^{n/s}Bu_2Mg$ (1 mmol, 1 M solution in heptane) was transferred into a Schlenk tube and the solvent removed *in vacuo* until the appearance of a white solid, before THF (10 ml) was added. (*R*)-*N*-Benzyl-α-methylbenzylamine, (*R*)-**20**, (0.42 ml, 2 mmol) was then added and the mixture allowed to stir at reflux for 90 min under an atmosphere of argon, after which time quantitative formation of chiral magnesium bisamide (*R*)-**14** was assumed (1 mmol). During magnesium bisamide base formation the reaction vessel was kept under argon.

Typical Procedure B for the Enantioselective Deprotonation of Cyclic Ketones

Table 1.8, **Entry 1**: A solution of chiral magnesium bisamide base (*R*)-**14** (1 mmol, see *Typical Procedure A*) in THF (10 ml) was cooled to -78°C under argon. The Schlenk flask was then charged with DMPU (60 µl, 0.4 mmol) and TMSCl (0.5 ml, 4 mmol) and the mixture stirred for 20 min at -78 °C. 4-*tert*-Butylcyclohexanone **6** (123 mg, 0.8 mmol) was dissolved in freshly distilled THF (2 ml) and then added to the mixture over a period of 1 h using a syringe pump. The resulting solution was

allowed to stir at -78 °C overnight for 18 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution (10 ml) at -78 °C. After warming to room temperature, the reaction mixture was extracted with diethyl ether (2 x 15 ml) and washed with saturated aqueous $NaHCO_3$ (2 × 5 ml). The combined organic layers were dried over Na_2SO_4 and then concentrated *in vacuo* to give a pale yellow oil. The reaction conversion was determined at this stage as 81 % by G.C. analysis. The silyl enol ether product was purified *via* flash chromatography, eluting with petroleum ether (30-40 °C) and diethyl ether (9:1). The combined product fractions were concentrated under vacuum. The product silyl enol ether **7** was isolated as colourless oil (114 mg, 0.5 mmol, 62 % yield). The enantiomeric ratio was determined using G.C. analysis with a chiral stationary phase (87:13, (*S*:*R*)) (*see individual experimental procedures for more detail*).

Typical Procedure C for the Preparation of Dialkyl- or Diarylmagnesium Reagents

To a solution of MesMgBr or ^{t}BuMgCl (100 ml, 100 mmol, 1 M solution in THF) in a flame-dried Schlenk tube, under argon atmosphere at room temperature, was added 1,4-dioxane (8.95 ml, 105 mmol) steadily over 5 minutes. The mixture was stirred vigorously for 3 h. The formed, white precipitate within the pale yellow solution was allowed to settle for 72 h and the clear dialkyl- or diarylmagnesium solution was then removed *via* cannula to a previously flame-dried and purged flask. Care was taken to avoid withdrawing any of the precipitate. The dialkyl- or diarylmagnesium solution was standardised either by using salicylaldehyde phenylhydrazone **53**[99] in THF or iodine in a saturated solution of LiCl in THF as indicator before use.[100] The molarity of the Mes_2Mg solution was typically approximately 0.50 M, whereas the $^{t}Bu_2Mg$ solution was typically approximately 0.45 M.

*Standardising Method A: Using Salicylaldehyde Phenylhydrazone **53***[100]

Table 1.11, **Entry 2A**: A flame dried and argon-flushed Schlenk tube was charged with accurately weighed salicylaldehyde phenylhydrazone **53** (0.95 mmol, 201 mg) and 2 ml of THF. The solution was stirred at ambient temperature until **53** was completely dissolved to give a pale yellow solution. The diarylmagnesium reagent was added dropwise *via* a 1 ml syringe until a colour change to orange was observed. The amount consumed (0.89 ml) contains 0.5 eq of the magnesium reagent relative to **61** and the molarity was thus determined as 0.54 M.

Standardising Method B: Using Iodine[101]

Table 1.11, **Entry 2B**: Anhydrous LiCl (10 mmol, 424 mg) was placed in flame-dried and argon-flushed 50 ml flask with a stirrer bar and was flame-dried under high vacuum. Care was taken not to melt the LiCl. After purging with argon cooling to room temperature, THF (20 ml) was added and the mixture was stirred for 24 h at ambient temperature until the LiCl was completely dissolved, resulting in the formation of a 0.5 M solution of LiCl in THF. A separate flame-dried and argon-flushed Schlenk tube was charged with accurately weighed I_2 (0.93 mmol, 237 mg) and 3 ml of the prepared saturated LiCl solution. The dark brown solution was stirred and cooled to 0 °C in an ice-bath. The diarylmagnesium reagent was added dropwise *via* a 1 ml syringe until the brown colour disappeared to give a clear, colourless solution. The amount consumed (0.94 ml) contains 0.5 eq of the magnesium reagent relative to iodine and the molarity was determined as 0.49 M.

Typical Procedure D for the Preparation of Tosylhydrazones

Scheme 1.35: (*E*)-4-Methoxyacetophenone tosylhydrazone **46**:[135,136] To a warm saturated solution of *p*-tosylhydrazide (3.64 g, 19.6 mmol) in ethanol was added neat 4-methoxyacetophenone (2.45 g, 16.3 mmol) and catalytic amounts of concentrated

HCl (1-2 drops). The reaction mixture was stirred at room temperature for 3 h, despite the rapid formation of a white precipitate. The precipitate was filtered, washed with cold ethanol, and dried under high vacuum. The isolated solid typically contained a mixture of the *E*- and *Z*-isomers of hydrazone **46** (4.75 g, 92 % yield). Further purification was carried out by slow recrystallisation from ethanol, yielding the *E*-isomer of 4-methoxyacetophenone tosylhydrazone **46** exclusively (4.39 g, 16.7 mmol, 85 %).

Typical Procedure E for Magnesium-mediated Shapiro Reaction with D_2O Quench

Table 1.9, **Entry 1**, 4-(1-ethenyl)anisole **47**:[137] To a flame-dried Schlenk tube, under argon, containing dry LiCl (127 mg, 3 mmol) was added a solution of Mes_2Mg in THF (2.73 ml, 1.5 mmol, 0.55 M in THF). The mixture was stirred at 40 °C for 20 min to dissolve the LiCl. In a separate flame-dried 10 ml flask 4-methoxyacetophenone tosylhydrazone **46** (318 mg, 1 mmol) was dissolved in THF (5 ml) under gentle heating. The solution of the tosylhydrazone was then transferred dropwise into the Schlenk flask at 40 °C and stirred at this temperature for 3 h. A colour change from pale yellow to dark brown was observed along with evolution of nitrogen gas. The reaction mixture was quenched by addition of D_2O (0.2 ml, 11 mmol) and diluted with saturated aqueous $NaHCO_3$ solution (10 ml). The product was extracted with diethyl ether (3 x 15 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The conversion and ratio of deuterated to protonated alkene was determined at this stage as 97:3 by ^{1}H-NMR analysis, using the proton signals of the terminal alkene functionality of each compound for comparison (*see individual entries for further details*). Further purification was carried out by flash chromatography eluting the silica gel column with a gradient of Et_2O in petroleum ether (0-30 %). The product H/D-**47** was isolated as a mixture of the deuterated and protonated alkene as a colourless oil (85 mg, 0.63 mmol, 63 % yield).

Typical Procedure F for Magnesium-mediated Shapiro Reaction with Electrophiles Other Than D_2O

Table 1.14, **Entry 1**, 2-(4-Methoxyphenyl)-1-phenylprop-2-enol **49**:[98] To a flame-dried Schlenk tube, under argon, containing LiCl (127 mg, 3 mmol) was added a solution of Mes_2Mg (3 ml, 1.5 mmol, 0.51 M in THF). The mixture was stirred at 40 °C for 20 min to dissolve LiCl. In a separate flame-dried 10 ml flask, 4-methoxyacetophenone tosylhydrazone **46** (318 mg, 1 mmol) was dissolved in THF (5 ml) under gentle heating. The solution of tosylhydrazone was then transferred dropwise into the Schlenk flask at 40 °C and stirred at this temperature for 3 hours. A colour change from pale yellow to dark brown was observed along with evolution of nitrogen gas. The reaction mixture was cooled to -10 °C and quenched by addition of PhCHO (406 μl, 4 mmol). The reaction mixture was left to stir at this temperature for 30 min before addition of NH_4Cl (4 ml) and further dilution with a saturated aqueous $NaHCO_3$ solution (10 ml). The product was extracted with diethyl ether (3 x 15 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The ratios of allyl alcohol **49** to protonated alkene and to addition by-product **56** were determined at this stage as 92:8 and 46:54, respectively, by ^{1}H-NMR analysis (*see individual entries for further details*). The product **49** was isolated by flash chromatography eluting the silica gel column (15-20 g) with a gradient of Et_2O in petroleum ether-diethyl (0-30%) (190 mg, 0.76 mmol, 76 % yield).

Typical Procedure G for the Preparation of Weinreb Amides:

Scheme 1.67, *N*-Methoxy-*N*-methylbenzamide, **77**:[138] To a stirred suspension of *N*-methoxymethylamine hydrochloride salt (976 mg, 10 mmol) in DCM (25 ml) at 0 °C was slowly added triethylamine (2.8 ml, 20 mmol). Benzoyl chloride (1.16 ml, 10 mmol) was then added dropwise to the solution. The temperature was monitored at all stages with an internal thermometer and kept below 4 °C. The solution was then allowed to warm to room temperature and stirred for one hour before quenching with

saturated aqueous $NaHCO_3$ solution (15 ml). The two layers were separated and the organic phase was washed with 1 M HCl (5 ml) and brine (5 ml) and dried over Na_2SO_4 before being concentrated *in vacuo*. The product, *N*-methoxy-*N*-methylbenzamide **77**, was isolated by flash chromatography eluting the silica gel column with a gradient of Et_2O in petroleum ether-diethyl (0-40%) as a clear oil (1.65 g, 98 % yield).

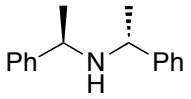
5.3 Asymmetric Deprotonation of 4-*tert*-Butyl-cyclohexanone 6

Preparation of (R,R)-Bis(a-methylbenzyl)amine, **50**:

Scheme 1.33: A mixture of (*R*)-α-methylbenzylamine (20 g, 0.17 mol), acetophenone (19.8 g, 0.17 mol) and titanium (IV) isopropoxide (141 g, 0.5 mol) was stirred at room temperature for 30 min before addition of 10 % palladium on carbon (720 mg, 8.5 mmol). The reaction vessel was then evacuated and purged with hydrogen (x3) and hydrogenated under H_2 (8 bar) with shaking. A small aliquot was removed after 42 h, revealing complete conversion by ^{1}H-NMR analysis. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide, followed by extraction with ethyl acetate. The combined organics were filtered through Celite, dried over Na_2SO_4 and the solvent removed *in vacuo* to leave a pale yellow oil. The oil was dissolved in ethyl acetate and treated with TFA to immediately precipitate a white solid. The crude solid was isolated by filtration, washed with ethyl acetate and recrystallised with IPA, ensuring isolation of the desired (*R*,*R*)-diastereoisomer only by ^{1}H NMR analysis. The diastereomerically pure solid was subsequently treated with an aqueous solution of NaOH and extracted with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to leave (*R,R*)-*bis*(α-methylbenzyl)amine (*R*,*R*)-**50** as a colourless oil (13.1 g, 59.5 mmol, 35 %). The product was dried by heating to 100 °C under vacuum (0.1 mbar) over

calcium hydride, then distilled and stored over 4 Å molecular sieves under a nitrogen atmosphere.

(*R*,*R*)-*Bis(1-phenylethyl)amine*, (*R*,*R*)-**50**:[20]



Colourless oil; IR ($CHCl_3$): 1202, 1493, 1603, 2960, 3061 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.31 (d, 6H, *J* = 6.7, C*H*$_3$), 1.72 (br-s, 1H, N*H*), 3.54 (q, 2H, *J* = 6.6, C*H*), 7.24-7.32 (m, 6H, Ar*H*), 7.34-7.40 (m, 4H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 25.0, 55.2, 126.7, 126.9, 128.5, 145.9; $[\alpha]_D^{20}$ = +204.3 (*R*,*R*) (c = 6.71, $CHCl_3$), Lit: $[\alpha]_D^{20}$ = -171.6 (*S*,*S*) (c = 6.71, $CHCl_3$).

The data observed are in accordance with literature values.

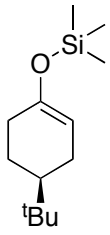
Asymmetric Deprotonation of 4-tert-*Butylcyclohexanone*, **6**:

The following experiments were carried out according to *Typical Procedure B*. Data are reported as (a) chiral Mg amide base *Typical Procedure A*, (b) Lewis base additive, (c) TMSCl, (d) ketone, (e) addition time of ketone, (f) temperature, (g) reaction time, (h) conversion, (i) isolated yield of (*S*)-**7**, and (j) e.r. (*S*:*R*).

Table 1.8, **Entry 1**: (a) Bis-(*R*)- α-methylbenzylmagnesium amide (*R*)-**14**, 1 mmol, (b) DMPU, 60 µl, 0.4 mmol, (c) 500 µl, 4 mmol, (d) 4-*tert*-butylcyclohexanone **6**, 123 mg, 0.8 mmol, (e) 1 h, (f) -78 °C, (g) 18 h, (h) 81 %, (i) 113 mg, 0.5 mmol, 62 %, and (j) 87:13.

Table 1.8, **Entry 2**: (a) Bis-(*R,R*)-*bis*(1-phenylethyl)magnesium amide (*R*,*R*)-**15**, 1 mmol, (b) DMPU, 60 µl, 0.4 mmol, (c) 500 µl, 4 mmol, (d) 4-*tert*-butylcyclohexanone **6**, 123 mg, 0.8 mmol, (e) 1 h, (f) -78 °C, (g) 18 h, (h) 97 %, (i) 152 mg, 0.67 mmol, 84 %, and (j) 97:3.

*(S)-4-*tert-*Butyl-trimethylsiloxycyclohexene*, (*S*)-**7**[20,52]



Colourless Oil; IR ($CHCl_3$): 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 0.18 (s, 9H, $Si(CH_3)_3$), 0.87 (s, 9H, $C(CH_3)_3$), 1.17-1.31 (m, 2H, CH_2), 1.75-1.86 (m, 2H, CH_2), 1.95-2.14 (m, 3H, $CHC(CH_3)_3$ + CH_2), 4.83-4.87 (m, 1H, C=C*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 0.44 ($Si(CH_3)_3$), 24.5, 25.2, 27.4, 31.1, 32.2, 44.1, 104.1, 150.4; Achiral G.C. analysis [CP SIL-19 CB capillary column; carrier gas H_2 (80 kPa); 45 °C (1 min)-190 °C; temperature gradient; 45 °C min^{-1}]; t_R = 5.07 min (**6**), t_R = 5.28 min (**7**). Chiral G.C. analysis [Chiralsil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70-120 °C; temperature gradient; 5 °C min^{-1}]; t_R = 26.25 min ((*S*)-**7**), t_R = 26.78 min ((*R*)-**7**); $[\alpha]_D$ -54.3 (c = 1.5, $CHCl_3$) for **Table 1.8**, **Entry 1**.

The data observed are in accordance with literature values.

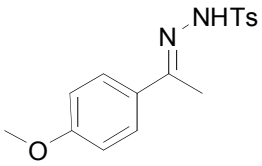
5.4 Carbon-centred Magnesium Base-mediated Shapiro Reaction

5.4.1 Preparation of Substrates and Reagents

Preparation of Tosylhydrazones

The following experiments were carried out according to *Typical Procedure D*. Data are reported as: (a) *p*-tosylhydrazide, (b) ketone, and (c) isolated yield after recrystallisation in warm ethanol. Individual analysis for each hydrazone compound is given below.

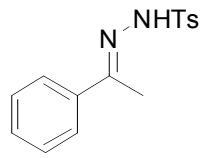
Scheme 1.35: *(E)-4-Methoxyacetophenone tosylhydrazone*, **46**:[135,136] (a) 3.54 g, 19.6 mmol, (b) 4-methoxyacetophenone, 2.45 g, 16.3 mmol, and (c) 4.39 g, 13.9 mmol, 85 %.



Colourless crystals, M.p.: 168-169 °C (lit. 166-168 °C); IR ($CHCl_3$): 1166, 1253, 1604, 3207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.12 (s, 3H, C*H*$_3$), 2.42 (s, 3H, Ts-C*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 6.87 (d, 2H, *J* = 8.9 Hz, Ar*H*), 7.29 (br s, 1H, N*H*, partially obscured by solvent peak), 7.33 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.62 (d, 2H, *J* = 8.9 Hz, Ar*H*), 7.92 (d, 2H, *J* = 8.4 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 13.5, 21.7, 55.4, 113.7, 127.8, 128.2, 129.7, 130.0, 135.6, 144.1, 152.9, 160.9.

The data observed are in accordance with literature values.

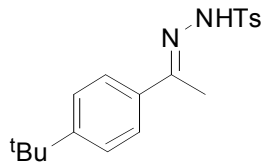
Table 1.35, **Entry 1**: *Acetophenone tosylhydrazone*, **96**:[135,136] (a) 1.23 g, 6.6 mmol, (b) acetophenone, 0.7 ml, 6.0 mmol, and (c) 1.12 g, 3.9 mmol, 65 %.



Colourless crystals, M.p.: 132-134 °C (lit. 133-135 °C); IR ($CHCl_3$): 3221, 1674, 1598, 1338, 1166, 908 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ(ppm) 2.15 (s, 3H, C*H*$_3$), 2.43 (s, 3H, Ts-C*H*$_3$), 7.29-7.40 (m, 6H, Ar*H*, N*H*), 7.63-7.68 (m, 2H, Ar*H*), 7.92 (d, 2H, *J* = 8.3 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 13.0, 21.1, 125.8, 127.7, 127.8, 129.0, 129.1, 135.0, 136.8, 143.7, 152.2.

The data observed are in accordance with literature values.

Table 1.35, **Entry 2**: *4*-Tert-*butylacetophenone tosylhydrazone*, **97**: (a) 1.16 g, 6.2 mmol, (b) 4-*tert*-butylacetophenone, 1.00 g, 5.7 mmol, and (c) 1.44 g, 4.2 mmol, 74 %.

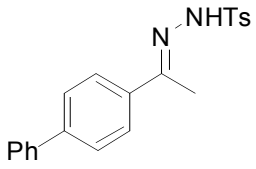


Colourless crystals, M.p.: 148-150 °C (lit. 148-150 °C); IR ($CHCl_3$): 1163, 1594, 2967, 3214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.32 (s, 9H, C(C*H*$_3$)$_3$), 2.17 (s, 3H, C*H*$_3$), 2.42

(s, 3H, Ts-*CH*$_3$), 7.29-7.40 (m, 4H, Ar*H*), 7.59 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.95 (d, 2H, *J* = 8.3 Hz, Ar*H*), 8.06 (br s, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 13.5, 21.6, 31.2, 34.7, 125.3, 126.1, 128.2, 129.6, 134.5, 135.5, 144.1, 152.9, 153.0.

The data observed are in accordance with literature values.

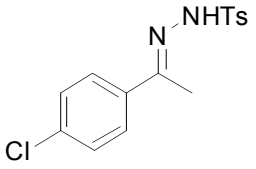
Table 1.35, **Entry 3**: *4-Phenylacetophenone tosylhydrazone*, **98**:[98] (a) 1.23 g, 6.6 mmol, (b) 4-phenylacetophenone, 1.18 g, 6 mmol, and (c) 1.9 g, 5.2 mmol, 87 %.



Colourless crystals, M.p.: 177-179 °C (lit. 176-179 °C); IR ($CHCl_3$): 1166, 1599, 3202 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.19 (s, 3H, C*H*$_3$), 2.43 (s, 3H, Ts-C*H*$_3$), 7.32-7.40 (m, 3H, Ar*H*), 7.42-7.48 (m, 2H, Ar*H*), 7.55-7.63 (m, 4H, Ar*H*), 7.66 (s, 1H, N*H*), 7.74 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.95 (d, 2H, *J* = 8.3 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 13.2, 21.6, 126.7, 127.0, 127.3, 127.7, 128.2, 128.8, 129.6, 135.4, 136.1, 140.2, 142.3, 144.2, 152.0.

The data observed are in accordance with literature values.

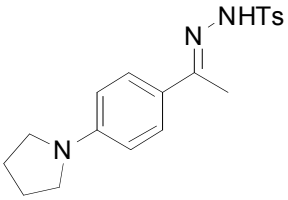
Table 1.35, **Entry 4**: *4-Chloroacetophenone tosylhydrazone*, **99**:[98] (a) 2.05 g, 11.0 mmol, (b) 4-chloroacetophenone, 1.3 ml, 10.1 mmol, and (c) 2.62 g, 8.2 mmol, 81 %.



Colourless crystals, M.p.: 155-157 °C (lit. 156-158 °C); IR ($CHCl_3$): 1166, 1596, 3211 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.13 (s, 3H, C*H*$_3$), 2.43 (s, 3H, Ts-C*H*$_3$), 7.30-7.35 (m, 4H, Ar*H*), 7.46 (br s, 1H, N*H*), 7.59 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.91 (d, 2H, *J* = 8.3 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.9, 21.1, 127.0, 127.6, 128.0, 129.2, 134.8, 135.1, 135.3, 143.8, 151.0.

The data observed are in accordance with literature values.

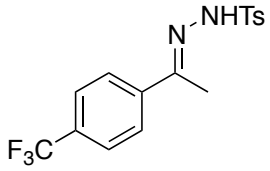
Table 1.35, **Entry 5**: *4-(*N-*Pyrrolidino)acetophenone tosylhydrazone*, **100**:[98] (a) 1.23 g, 6.6 mmol, (b) 4-(*N*-pyrrolidino)acetophenone, 1.14 g, 6 mmol, and (c) 1.98 g, 5.5 mmol, 92 %.



Colourless crystals, M.p.: 200-202 °C (lit. 200-203 °C); IR ($CHCl_3$): 1164, 1611, 2969 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.97-2.04 (m, 4H, C*H*$_2$), 2.10 (s, 3H, C*H*$_3$), 2.41 (s, 3H, Ts-C*H*$_3$), 3.28-3.34 (m, 4H, C*H*$_2$), 6.49 (d, 2H, *J* = 8.9 Hz, Ar*H*), 7.15 (br s, 1H, N*H*), 7.31 (d, 2H, *J* = 8.1 Hz, Ar*H*), 7.57 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.92 (d, 2H, *J* = 8.3 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 12.9, 21.6, 25.4, 47.5, 111.0, 124.0, 127.6, 128.2, 129.4, 135.6, 143.8, 148.8, 153.9.

The data observed are in accordance with literature values.

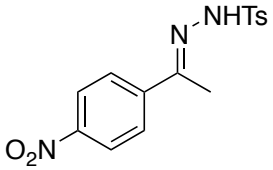
Table 1.35, **Entry 6**: *4-(Trifluoromethyl)acetophenone tosylhydrazone*, **101**:[98] (a) 2.05 g, 11 mmol, (b) 4-(trifluoromethyl)acetophenone, 1.88 g, 10 mmol, and (c) 3.20 g, 9.0 mmol, 90 %.



Colourless crystals, M.p.: 181-183 °C (lit. 180-182 °C); IR ($CHCl_3$): 1163, 1597, 3213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.18 (s, 3H, C*H*$_3$), 2.43 (s, 3H, Ts-C*H*$_3$), 7.34 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.58-7.63 (m, 3H, N*H*, Ar*H*), 7.76 (d, 2H, *J* = 8.2 Hz, Ar*H*), 7.92 (d, 2H, *J* = 8.3 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 13.2, 21.8, 125.3, 126.5, 128.1, 128.6 129.7, 131.2 (q, *J* = 34 Hz, CF_3), 135.2, 140.5, 144.5, 150.5.

The data observed are in accordance with literature values.

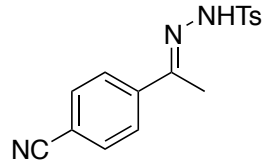
Table 1.35, **Entry 7**: *4-Nitroacetophenone tosylhydrazone*, **102**:[98] (a) 1.56 g, 8.4 mmol, (b) 4'-nitroacetophenone, 1.16 g, 7 mmol, and (c) 2.19 g, 6.57 mmol, 94 %.



Colourless crystals, M.p.: 197-199 °C (lit. 197-200 °C); IR ($CHCl_3$): 1156, 1523, 3244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.20 (s, 3H, C*H*$_3$), 2.44 (s, 3H, Ts-C*H*$_3$), 7.35 (d, 2H, *J* = 8.1 Hz, Ar*H*), 7.76-7.94 (m, 5H, Ar*H*, N*H*), 8.21 (d, 2H, *J* = 8.1 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 13.2, 21.6, 123.6, 124.0, 128.1, 129.8, 135.1, 143.0, 144.6, 148.3, 149.2.

The data observed are in accordance with literature values.

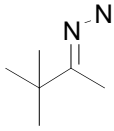
Table 1.35, **Entry 8**: *4-Cyanoacetophenone tosylhydrazone*, **103**:[98] (a) 2.05 g, 11 mmol, (b) 4-acetylbenzonitrile, 1.45 g, 10 mmol, and (c) 2.97 g, 9.5 mmol, 95 %.



Colourless crystals, M.p.: 200-201 °C (lit. 200-202 °C); IR (CH_2Cl_2): 1169, 1597, 2225, 3220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ(ppm) 2.19 (s, 3H, CH3), 2.34 (s, 3H, Ts-CH3), 7.39 (d, 2H, *J* = 8.0 Hz, Ar), 7.77-7.83 (m, 6H, Ar), 10.83 (br s, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 14.6, 21.5, 112.1, 119.1, 127.1, 128.0, 130.0, 132.8, 136.6, 142.1, 144.0, 151.5.

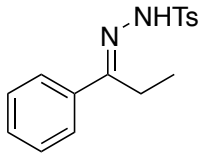
The data observed are in accordance with literature values.

Figure 1.18: Tert-*butylmethylketone tosylhydrazone*, **114**: (a) 2.05 g, 11 mmol, (b) pinacolone, 1.25 ml, 10 mmol, and (c) 2.01 g, 7.5 mmol, 75 %.



Colourless crystals, M.p.: 156-158 °C; IR ($CHCl_3$): 1170, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.05 (s, 9H, C(C*H*$_3$)$_3$), 1.71 (s, 3H, C*H*$_3$), 2.44 (s, 3H, Ts-C*H*$_3$), 7.03 (br s, 1H, N*H*), 7.30 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.86 (d, 2H, *J* = 8.3 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 11.3, 21.1, 26.9, 38.3, 127.7, 128.7, 134.9, 143.3, 163.3; HRMS *m/z* (ESI) Calc. for $C_{13}H_{21}N_2O_2S$ $(M+H)^+$: 269.1318. Found: 269.1320.

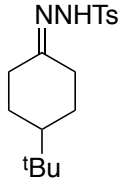
Figure 1.18: *Propiophenone tosylhydrazone*, **115**:[139] (a) 2.05 g, 11 mmol, (b) propiophenone, 1.33 ml, 10 mmol, and (c) 2.48 g, 8.2 mmol, 82 %.



Colourless crystals, M.p.: 114-116 °C (lit. 115-116 °C); IR ($CHCl_3$): 1167, 1598, 3217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.11 (t, 3H, *J* = 7.7 Hz, CH_2CH_3), 2.43 (s, 3H, Ts-CH_3), 2.59 (q, 2H, *J* = 7.8 Hz, CH_2CH_3), 7.30-7.39 (m, 5H, Ar*H*), 7.62-7.69 (m, 3H, Ar*H*, N*H*), 7.92 (d, 2H, *J* = 8.3 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 10.2, 19.9, 21.6, 126.3, 126.8, 128.1, 128.4, 129.6, 135.4, 136.1, 144.2, 157.0.

The data observed are in accordance with literature values.

Figure 1.16: 4-Tert-*butyl-cyclohexanone tosylhydrazone*, **116**:[98] (a) 2.05 g, 11 mmol, (b) 4-*tert*-butyl-cyclohexanone, 1.54 g, 10 mmol, and (c) 2.62 g, 8.13 mmol, 81 %.



Colourless crystals, M.p.: 148-150 °C (lit. 149-150 °C); IR ($CHCl_3$): 1165, 1597, 2963 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 0.83 (s, 9H, $C(CH_3)_3$), 1.02-1.24 (m, 3H, aliphatic ring protons), 1.69-1.79 (m, 1H, aliphatic ring proton), 1.86-1.92 (m, 2H, aliphatic ring protons), 1.98-2.13 (m, 1H, aliphatic ring proton), 2.42 (s, 3H, Ts-CH_3), 2.47-2.49 (m, 1H, aliphatic ring proton), 2.72-2.80 (m, 1H, aliphatic ring proton), 7.31 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.59 (br s, 1H, N*H*), 7.86 (d, 2H, *J* = 8.0 Hz, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 21.5, 26.4, 26.6, 27.4, 32.5, 34.9, 47.2, 128.1, 129.6, 135.6, 143.8, 162.8.

The data observed are in accordance with literature values.

Preparation of Carbon-centred Base Reagents

The following experiments were carried out according to *Typical Procedure C*. Data are reported as (a) Grignard reagent, (b) 1,4-dioxane, (c) time, (d) settling time (e) indicator for standardisation, and (f) concentration.

Scheme 1.36: (a) 2-mesitylmagnesium bromide **30**, 0.1 mol, 100 ml (b) 8.95 ml, 0.105 mol, (c) 3 h, (d) 72 h, (e) salicylaldehyde phenylhydrazone **53**, and (f) **23**, 0.54 M.

Table 1.11, **Entry 1**: (a) 2-mesitylmagnesium bromide **30**, 0.1 mol, 100 ml (b) 8.95 ml, 0.105 mol, (c) 3 h, (d) 72 h, (e) A: salicylaldehyde phenylhydrazone, B: iodine in THF/LiCl solution, and (f) **23**, A: 0.55, B: 0.50 M.

Table 1.11, **Entry 2**: (a) 2-mesitylmagnesium bromide **30**, 0.1 mol, 100 ml (b) 8.95 ml, 0.105 mol, (c) 3 h, (d) 72 h, (e) A: salicylaldehyde phenylhydrazone, B: iodine in THF/LiCl solution, and (f) **23**, A: 0.54, B: 0.49 M.

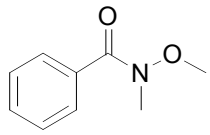
Scheme 1.54, **Entry 1**: (a) *tert*-butylmagnesium chloride **31**, 50 mmol, 50 ml (b) 4.48 ml, 52.5 mmol, (c) 3 h, (d) 72 h, (e) iodine in THF/LiCl solution, and (f) **22**, 0.37 M.

Scheme 1.54, **Entry 2**: (a) *tert*-butylmagnesium chloride **31**, 50 mmol, 50 ml (b) 4.48 ml, 52.5 mmol, (c) 3 h, (d) 72 h, (e) iodine in THF/LiCl solution, and (f) **22**, 0.41 M.

Preparation of Weinreb Amides:

The following experiments were carried out according to *Typical Procedure G*. Data are reported as: (a) *N*-methoxymethylamine hydrochloride salt, (b) NEt_3, (c) volume of DCM, (d) acid chloride, and (e) yield. Individual analysis for each Weinreb amide compound is given below.

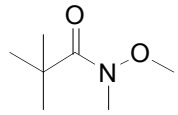
Scheme 1.67, N-*Methoxy*-N-*methylbenzamide*, **77**:[138] (a) 976 mg, 10 mmol, (b) 2.8 ml, 20 mmol, (c) DCM, 25 ml, (d) benzoyl chloride, 1.16 ml, 10 mmol, and (e) 1.65 g, 9.8 mmol, 98 %.



Colourless oil; IR ($CHCl_3$): 1379, 1642, 2934 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.37 (s, 3H, NCH_3), 3.56 (s, 3H, OCH_3), 7.35-7.47 (m, 3H, ArH), 7.67 (d, 2H, J = 8.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 33.8, 61.0, 128.0, 128.1, 130.5, 134.1, 170.0.

The data observed are in accordance with literature values.

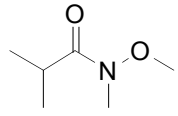
Table 1.31, **Entry 1**, N-*Methoxy*-N-*methyltrimethylacetamide*, **82**:[140] (a) 976 mg, 10 mmol, (b) 2.8 ml, 20 mmol, (c) DCM, 25 ml, (d) pivaloyl chloride, 1.23 ml, 10 mmol, and (e) 1.40 g, 9.6 mmol, 96 %.



Colourless oil; IR ($CHCl_3$): 1359, 1654, 2967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.24 (s, 9H, C(CH_3)$_3$), 3.17 (s, 3H, NCH_3), 3.67 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 27.1, 33.7, 39.4, 60.6, 179.2.

The data observed are in accordance with literature values.

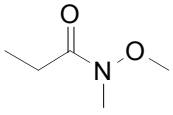
Table 1.31, **Entry 2**, N-*Methoxy*-N-*methylisobutyramide*, **83**:[141] (a) 976 mg, 10 mmol, (b) 2.8 ml, 20 mmol, (c) DCM, 25 ml, (d) isobutyryl chloride, 1.05 ml, 10 mmol, and (e) 1.29 g, 9.8 mmol, 98 %.



Colourless oil; IR ($CHCl_3$): 1385, 1666, 2972 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.09 (d, 6H, J = 6.8 Hz, CH(CH_3)$_2$), 2.94 (septet, 1H, J = 6.5 Hz, CH(CH$_3$)$_2$), 3.15 (s, 3H, NCH_3), 3.67 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 18.6, 29.3, 31.8, 60.9, 177.9.

The data observed are in accordance with literature values.

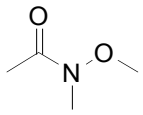
Table 1.31, **Entry 3**, N-*Methoxy*-N-*methylpropionamide*, **84**:[142] (a) 976 mg, 10 mmol, (b) 2.8 ml, 20 mmol, (c) DCM, 25 ml, (d) propionyl chloride; 0.87 ml, 10 mmol, and (e) 1.09 g, 9.4 mmol, 94 %.



Colourless oil; IR ($CHCl_3$): 1380, 1667, 2977 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.13 (t, 3H, J = 6.0 Hz, CH_2CH_3), 2.44 (q, 2H, J = 6.0 Hz, CH_2CH_3), 3.18 (s, 3H, NCH_3), 3.68 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 8.8, 25.2, 32.3, 61.2, 175.4.

The data observed are in accordance with literature values.

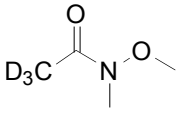
Table 1.31, **Entry 4**, N-*Methoxy*-N-*methylacetamide*, **85**:[143] (a) 976 mg, 10 mmol, (b) 2.8 ml, 20 mmol, (c) DCM, 25 ml, (d) acetyl chloride; 0.71 ml, 10 mmol, and (e) 1.01 g, 9.8 mmol, 98 %.



Colourless oil; IR ($CHCl_3$): 1383, 1667, 2941 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.03 (s, 3H, CH_3), 3.09 (s, 3H, NCH_3), 3.61 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 19.8, 32.0, 61.1, 171.9.

The data observed are in accordance with literature values.

Scheme 1.76: N-*Methoxy*-N-*methylacet-d*^{3}*-amide*, **94**: (a) 976 mg, 10 mmol, (b) 2.8 ml, 20 mmol, (c) DCM, 25 ml, (d) acetyl-d^3 chloride; 0.71 ml, 10 mmol, and (e) 1.04 g, 9.8 mmol, 98 %.



Colourless oil; IR ($CHCl_3$): 1383, 1667, 2941 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.13 (s, 3H, NCH_3), 3.64 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 19.3 (m, CD_3), 31.9, 61.1, 171.9;

HRMS *m*/*z* (ESI) Calc. for $C_4H_7D_3NO_2$ $(M+H)^+$: 106.0816. Found: 106.0817.

5.4.2 Optimisation Study with D_2O

The following experiments were carried out according to *Typical Procedure E*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone **46** (e) time and temperature protocol, (f) D_2O, (g) conversion, (h) yield of **47**, and (i) D:H.

Table 1.9, **Entry 1**: (a) 127 mg, 3 mmol, (b) 2.73 ml, 1.5 mmol, 0.55 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml (e) 40 °C, 1 h, (f) 0.2 ml, 11 mmol, (g) 66 %, (h) **47**, 85 mg, 0.63 mmol, 63 %, and (i) 97:3.

Table 1.9, **Entry 2**: (a) 127 mg, 3 mmol, (b) 2.73 ml, 1.5 mmol, 0.55 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml (e) 40 °C, 2 h, (f) 2 ml, 11 mmol, (g) 90 %, (h) **47**, 81 mg, 0.60 mmol, 60 %, and (i) 97:3.

Table 1.9, **Entry 3**: (a) 127 mg, 3 mmol, (b) 2.73 ml, 1.5 mmol, 0.55 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml (e) 40 °C, 3 h, (f) 2 ml, 11 mmol, (g) 93 %, (h) **47**, 93 mg, 0.69 mmol, 69 %, and (i) 95:5.

Table 1.9, **Entry 4**: (a) 169 mg, 4 mmol, (b) 3.64 ml, 2 mmol, 0.55 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml (e) 40 °C, 3 h, (f) 2 ml, 11 mmol, (g) quant., (h) **47**, 111 mg, 0.82 mmol, 82 %, and (i) 96:4.

Table 1.10, **Entry 1**: (a) powder, 127 mg, 3 mmol, (b) 2.82 ml, 1.5 mmol, 0.53 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml (e) 40 °C, 1 h, (f) 2 ml, 11 mmol, (g) 97 %, (h) **47**, 78 mg, 0.58 mmol, 58 %, and (i) 98:2.

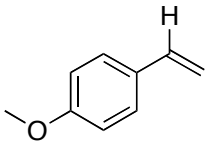
Table 1.10, **Entry 2**: (a) beads, 127 mg, 3 mmol, (b) 2.78 ml, 1.5 mmol, 0.54 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml (e) 40 °C, 1 h, (f) 2 ml, 11 mmol, (g) 93 %, (h) **47**, 72 mg, 0.53 mmol, 53 %, and (i) 97:3.

Table 1.12, **Entry 1**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml (e) 40 °C, 1 h, (f) 2 ml, 11 mmol, (g) 99%, (h) **47**, 89 mg, 0.66 mmol, 66 %, and (i) 96:4.

Table 1.12, **Entry 2**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml (e) 40 °C, 2 h, (f) 2 ml, 11 mmol, (g) 92 %, (h) **47**, 107 mg, 0.79 mmol, 79 %, and (i) 97:3.

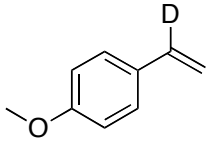
Table 1.12, **Entry 3**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml (e) 40 °C, 3 h, (f) 2 ml, 11 mmol, (g) 97 %, (h) **47**, 119 mg, 0.88 mmol, 88 %, and (i) 97:3.

4-Ethenylanisole, H-**47**:[137,144]



Colourless oil; IR ($CHCl_3$); 1034, 1509, 2939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.83 (s, 3H, OCH_3), 5.13 (dd, 1H, J = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, J = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 6.67 (dd, 1H, J = 17.5 Hz, J = 11.0 Hz, CHCH$_2$), 6.87 (d, 2H, J = 8.6 Hz, ArH), 7.36 (d, 2H, J = 8.6 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 55.3, 111.6, 114.0, 127.5, 130.5, 136.3, 159.5.

4-Ethenylanisole, D-**47**:[137]



Colourless oil; IR ($CHCl_3$): 1034, 1509, 2940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.83 (s, 3H, CH_3), 5.13-5.15 (m, 1H, CH_2), 5.62-5.63 (m, 1H, CH_2), 6.88 (d, 2H, J = 8.8 Hz, ArH), 7.37 (d, 2H,

J = 8.8 Hz, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 55.2, 111.4, 113.9, 127.4, 130.4, 136.0 (t, *J* = 24 Hz, CD), 159.4.

The data observed are in accordance with literature values.

The following ^{1}H-NMR signals were used to calculate the reaction conversion: starting material **46**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.92 (d, 2H, *J* = 8.4 Hz, Ar*H*); alkene products H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.62 (dd, 1H, *J* = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2); and D-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ((ppm) 5.62-5.63 (m, 1H, CH_2).

The following ^{1}H-NMR signals were used to calculate the ratio of protonated to deuterated alkene H/D-**47**: H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, *J* = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, *J* = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2); and D-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13-5.15 (m, 1H, CH_2), 5.62-5.63 (m, 1H, CH_2).

Procedure for Magnesium-mediated Shapiro Reaction - One-pot Protocol

Table 1.13, **Entry 1**: 4-(1-Ethenyl)anisole **47**:[137] To a flame-dried Schlenk tube, under argon, containing dry LiCl (127 mg, 3 mmol) was added a solution of MesMgBr (3 ml, 3 mmol, 0.1 M in THF) and 1,4-dioxane (268 ml, 3.15 mmol). The mixture was stirred at 40 °C for 15 min to dissolve LiCl. In a separate flame-dried 10 ml flask 4-methoxyacetophenone tosylhydrazone **46** (318 mg, 1.00 mmol) was dissolved in THF (5 ml) under gentle heating. The solution of tosylhydrazone was then transferred dropwise into the Schlenk flask at 40 °C and stirred at this temperature for 1 hour. The reaction mixture was quenched by addition of D_2O (0.2 ml, 11 mmol) and diluted with saturated $NaHCO_3$ solution (10 ml). The product was extracted with diethyl ether (3 x 15 ml) and the combined organic layers were dried

over Na_2SO_4 and concentrated *in vacuo*. The conversion and the ratio of deuterated to protonated alkene was determined at this stage as 31 % and 96:4 by ^1H-NMR analysis respectively, using the proton signals of the terminal alkene functionality of each compound for comparison. The product **51** was isolated by flash chromatography eluting the silica gel column (15-20 g) with a gradient of Et_2O in petroleum ether (0-30 %) (30 mg, 0.22 mmol, 22 % yield).

The following experiment was carried out according to the above procedure. Data are reported as (a) LiCl, (b) MesMgBr, (c) 1,4-dioxane, (d) 4-methoxyacetophenone tosylhydrazone **46**, (e) solvent to dissolve hydrazone **46** (f) time and temperature protocol, (g) D_2O, (h) conversion, (i) yield of **47**, and (j) D:H.

Table 1.13, **Entry 2**: (a) 127 mg, 3 mmol, (b) 3 ml, 3 mmol, 0.1 M in THF, (c) 268 ml, 3.15 mmol, (d) 318 mg, 1 mmol, (e) THF, 5 ml (f) 40 °C, 1 h, (g) 2 ml, 11 mmol, (h) 30%, (i) **47**, 32 mg, 0.24 mmol, 24 %, and (j) 97:3.

Data are consistent with that described for compound H/D-**47** on pages 114 and 115.

5.4.3 Optimisation Study with Benzaldehyde

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) PhCHO, (g) quench conditions, (h) conversion, (i) yield of **49**, (j) E:H, and (k) **49**:**56** (addition by-product).

Table 1.14/**Table 1.15**, **Entry 1**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.51 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 406 μl, 4 mmol, (g) -10 °C, 30 min, (h) 86 %, (i) **49**, 125 mg, 0.76 mmol, 76 %, (j) 92:8, and (k) 46:54.

Table 1.14/**Table 1.15**, **Entry 2**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.51 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h (f) 406 µl, 4 mmol, (g) -10 °C, 30 min, (h) 89 %, (i) **49**, 138 mg, 0.84 mmol, 84 %, (j) 92:8, and (k) 48:52.

Table 1.16, **Entry 1**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 102 µl, 1 mmol, (g) -10 °C, 30 min, (h) 87 %, (i) **49**, 44 mg, 0.27 mmol, 27 %, (j) 31:69, and (k) 28:72.

Table 1.16, **Entry 2**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 152 µl, 1.5 mmol, (g) -10 °C, 30 min, (h) 83 %, (i) **49**, 67 mg, 0.41 mmol, 41 %, (j) 50:50, and (k) 28:72.

Table 1.16, **Entry 3**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 204 µl, 2 mmol, (g) -10 °C, 30 min, (h) 82 %, (i) **49**, 122 mg, 0.74 mmol, 74 %, (j) 90:10, and (k) 40:60.

Table 1.16, **Entry 4**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 305 µl, 3 mmol, (g) -10 °C, 30 min, (h) 83 %, (i) **49**, 118 mg, 0.72 mmol, 72 %, (j) 89:11, and (k) 40:60.

Table 1.17, **Entry 1**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) (f) 406 µl, 4 mmol, (g) 21 °C, 30 min, (h) 52 %, (i) **49**, 76 mg, 0.46 mmol, 46 %, (j) 89:11, and (k) 41:59.

Table 1.17, **Entry 2**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 406 µl, 4 mmol, (g) 40 °C, 30 min, (h) 17 %, (i) **49**, 21 mg, 0.13 mmol, 13 %, (j) 78:22, and (k) 31:69.

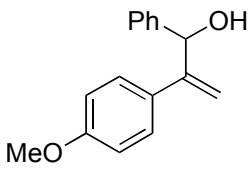
Table 1.18, **Entry 1**: (a) -, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 406 µl, 4 mmol, (g) -10 °C, 30 min, (h) 27 %, (i) **49**, 39 mg, 0.24 mmol, 24 %, (j) 89:11, and (k) 11:89.

Table 1.18, **Entry 2**: (a) 64 mg, 1.5 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 406 μl, 4 mmol, (g) -10 °C, 30 min, (h) 86%, (i) **49**, 125 mg, 0.76 mmol, 76%, (j) 88:12, and (k) 42:58.

Table 1.18, **Entry 3**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 406 μl, 4 mmol, (g) -10 °C, 30 min, (h) 89%, (i) 135 mg, 0.82 mmol, 82%, (j) 92:8, and (k) 48:52.

Table 1.18, **Entry 4**: (a) 191 mg, 4.5 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 406 μl, 4 mmol, (g) -10 °C, 30 min, (h) 65%, (i) **49**, 99 mg, 0.60 mmol, 60%, (j) 92:8, and (k) 45:55.

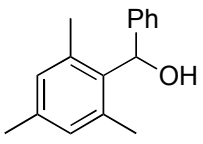
2-(4-Methoxyphenyl)-1-phenylprop-2-enol, **49**:[98]



Colourless oil, IR ($CHCl_3$): 1177, 1605, 3593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.06 (d, 1H, *J* = 4.1 Hz, O*H*), 3.78 (s, 3H, CH_3), 5.41 (d, 1H, *J* = 4.1 Hz, C*H*OH), 5.46 (s, 1H, C=CH_2), 5.69 (s, 1H, C=CH_2), 6.80 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.23-7.29 (m, 3H, Ar*H*, partially obscured by $CDCl_3$ peak), 7.29-7.35 (m, 2H, Ar*H*), 7.39-7.43 (m, 2H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 55.2, 76.0, 112.8, 113.7, 127.0, 127.7, 128.2, 128.5, 131.7, 142.1, 149.7, 159.2.

The data observed are in accordance with literature values.

1-Phenyl-mesitylmethanol, **56**:[145,146]



Colourless oil, IR ($CHCl_3$): 1008, 1611, 3452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.13 (d, 1H, *J* = 4.1 Hz, O*H*), 2.25 (s, 6H, CH_3), 2.28 (s, 3H, CH_3), 6.31 (d, 1H, *J* = 4.1 Hz, C*H*OH), 6.87 (s,

2H, Ar*H*), 7.21-7.34 (m, 5H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 20.6, 21.0, 71.2, 125.5, 126.6, 128.2, 130.0, 136.6, 137.2, 137.4, 143.2.

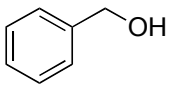
The data observed are in accordance with literature values.

The following ^{1}H-NMR signals were used to calculate the reaction conversion: starting material **46**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.92 (d, 2H, J = 8.4 Hz, Ar*H*); allyl alcohol **49** ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.41 (d, 1H, J = 4.1 Hz, CH), 5.46 (s, 1H, CH_2); H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, J = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, J = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2).

The following ^{1}H-NMR signals were used to calculate the ratio of allyl alcohol **49** to protonated alkene H-**47**: **49**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.41 (d, 1H, J = 4.1 Hz, CH), 5.46 (s, 1H, CH_2); H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, J = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, J = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2).

The following ^{1}H-NMR signals were used to determine the formation of **56** relative to allyl alcohol **49**: **49**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.41 (s, 1H, CH_2), 5.46 (s, 1H, CH_2); by-product **56**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 6.31 (d, 1H, J = 4.1 Hz, C*H*OH).

Benzyl alcohol, **57**:[147,148]



Colourless oil, IR ($CHCl_3$): 1007, 1384, 3033, 3609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.68 (br s, 1H, O*H*), 4.71 (s, 2H, CH_2), 7.29-7.36 (m, 1H, Ar*H*), 7.37-7.39 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 65.4, 127.0, 127.7, 128.6, 140.9.

The data observed are in accordance with literature values.

Optimisation with DMPU as an Additive

The following experiments were carried out according to *Typical Procedure F* with the supplement of adding neat DMPU to the $Mes_2Mg.LiCl$ solution prior to the hydrazone, but after stirring $Mes_2Mg.LiCl$ at 40 °C for 20 min. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) Additive, (d) 4-methoxyacetophenone tosylhydrazone **46**, (e) solvent to dissolve hydrazone (f) time and temperature protocol, (g) PhCHO, (h) quench conditions, (i) conversion, (j) yield of **49**, (k) E:H, and (l) **49**:**56** (addition by-product).

Table 1.19, **Entry 1**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) DMPU, 60 μl, 0.5 mmol, (d) 318 mg, 1 mmol, (e) THF, 5 ml (f) 40 °C, 3 h, (g) 406 μl, 4 mmol, (h) -10 °C, 30 min, (i) 73 %, (j) **49**, 107 mg, 0.65 mmol, 65 %, (k) 89:11, and (l) 35:65.

Table 1.19, **Entry 2**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) DMPU, 90 μl, 0.75 mmol, (d) 318 mg, 1 mmol, (f) THF, 5 ml (e) 40 °C, 3 h, (g) 406 μl, 4 mmol, (h) -10 °C, 30 min, (i) 81 %, (j) **49**, 103 mg, 0.63 mmol, 63 %, (k) 78:22, and (l) 36:64.

Table 1.19, **Entry 3**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) DMPU, 180 μl, 1.5 mmol, (d) 318 mg, 1 mmol, (e) THF, 5 ml (f) 40 °C, 3 h, (g) 406 μl, 4 mmol, (h) -10 °C, 30 min, (i) 72 %, (j) **49**, 99 mg, 0.60 mmol, 60 %, (k) 83:17, and (l) 40:60.

Data are consistent with that described for compounds **49** and **56** on pages 118 and 119.

Optimisation with Stoichiometric Quantities of Mes_2Mg

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone **46**, (e) time and temperature protocol, (f) PhCHO, (g) quench conditions, (h) conversion, (i) yield of **49**, (j) E:H, and (k) **49**:**56** (addition by-product).

Table 1.20, **Entry 1**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.51 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) 284 μl, 2.8 mmol, (g) -10 °C, 30 min, (h) 63 %, (i) **49**, 84 mg, 0.51 mmol, 51 %, (j) 81:19, and (k) 62:38.

Table 1.20, **Entry 2**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.51 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 6 h, (f) 284 μl, 2.8 mmol, (g) -10 °C, 30 min, (h) 70 %, (i) **49**, 80 mg, 0.49 mmol, 49 %, (j) 76:24, and (k) 72:28.

Table 1.20, **Entry 3**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.51 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 15 h, (f) 284 μl, 2.8 mmol, (g) -10 °C, 30 min, (h) 67 %, (i) **49**, 39 mg, 0.24 mmol, 24 %, (j) 36:64, and (k) 83:17.

Data are consistent with that described for compounds **49** and **56** on pages 118 and 119.

Low Temperature Protocol

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) PhCHO, (g) quench conditions, (h) conversion, (i) yield of **49**, (j) E:H, and (k) **49**:**56** (addition by-product).

Table 1.21, **Entry 1**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 0 °C, 1 h; 40 °C, 3 h (f) 206 µl, 2 mmol, (g) -10 °C, 30 min, (h) **49**, 95 mg, 0.58 mmol, 58 %, (i) 51 %, (j) 88:12, and (k) 56:44.

Table 1.21, **Entry 2**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 0 °C, 3 h; 40 °C, 3 h (f) 206 µl, 2 mmol, (g) -10 °C, 30 min, (h) 55 %, (i) **49**, 79 mg, 0.48 mmol, 48 %, (j) 88:12, and (k) 59:41.

Data are consistent with that described for compounds **49** and **56** on pages 118 and 119.

5.4.4 Mechanistic Investigations and Isolation of Intermediates

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) recovered **46**, (i) **67**, (j) E-alkene, and (k) E:H.

Table 1.22, **Entry 1**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 0 °C, 1 h, (f) D_2O, 0.2 ml, 11 mmol, (g) 0 °C, 30 min, (h) **46**, 289 mg, 0.91 mmol, 91 %, (i) -, (j) -, and (k) -.

Table 1.22, **Entry 2**: (a) 2.1 ml, 1.05 mmol, 0.50 M in THF, (b) 89 mg, 2.1 mmol, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 20 °C, 1 h, (f) D_2O, 0.2 ml, 11 mmol, (g) 20 °C, 30 min, (h) **46**, 248 mg, 0.78 mmol, 78 %, (i) -, (j) trace of **47**, and (k) 96:4.

Data are consistent with that described for compound **46** on page 105 and for H/D-**47** on pages 114 and 115.

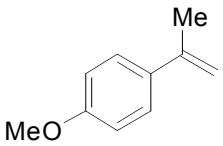
The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) recovered **46**, (i) **68**, (j) **69**, (k) E-alkene, and (l) E:H.

Table 1.23, **Entry 1**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 0 °C, 1 h, (f) MeI, 0.12 ml, 2 mmol, (g) 0 °C, 30 min, (h) **46**, 264 mg, 0.83 mmol, 83 %, (i) **68**, 20 mg, 0.06 mmol, 6 %, (j) -, (k) -, and (l) -.

Table 1.23, **Entry 2**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 20 °C, 1 h, (f) MeI, 0.12 ml, 2 mmol, (g) 20 °C, 30 min, (h) **46**, 238 mg, 0.75 mmol, 75 %, (i) **68**, 10 mg, 0.03 mmol, 3 %, (j) -, (k) trace of **70**, and (l) 99:1.

Data are consistent with that described for compound **46** on page 105 and for H-**47** on page 114.

1-Methoxy-4-(prop-1-enyl)benzene, **70**:[149]



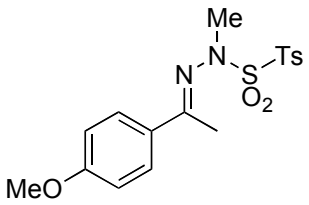
Colourless oil, IR ($CHCl_3$): 1030, 1624, 2956 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.14 (s, 3H, C*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 5.00 (s, 1H, C*H*$_2$), 5.30 (s, 1H, C*H*$_2$), 6.87 (d, 2H, *J* = 8.9 Hz, Ar*H*), 7.43 (d, 2H, *J* = 8.9 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 22.1, 55.5, 110.8, 113.4, 126.8, 134.0, 142.8, 159.3.

The data observed are in accordance with literature values.

The following ^1H-NMR signals were used to calculate the ratio of alkene **70** to protonated alkene H-**47**: **70**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.00 (s, 1H, C*H*$_2$),

5.30 (s, 1H, C*H*$_2$); and H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, *J* = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$), 5.62 (dd, 1H, *J* = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$).

N-*Methyl-4-methoxyacetophenone tosylhydrazone*, **68**:



Colourless crystals, M.p.: 160-162 °C; IR ($CHCl_3$): 1162, 1600, 2929 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.47 (s, 3H, C*H*$_3$), 2.55 (s, 3H, C*H*$_3$), 2.80 (s, 3H, C*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 6.91 (d, 2H, *J* = 8.9 Hz, Ar*H*), 7.37 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.76-7.79 (m, 4H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 16.6, 21.6, 39.4, 55.4, 113.7, 128.9, 129.1, 129.3, 129.5, 131.0, 144.0, 161.9, 173.7; HRMS *m*/*z* (ESI) Calc. for $C_{17}H_{21}O_3N_2S$ $(M+H)^+$: 333.1267. Found: 333.1266.

Solvent Study

Table 1.24, **Entry 1**: To a flame-dried Schlenk tube, under argon, containing LiCl (89 mg, 2.1 mmol) was added a solution of Mes_2Mg (2.1 ml, 1.05 mmol, 0.50 M). The solvent was removed *in vacuo* until the appearance of a viscous oil, before 2-MeTHF (10 ml) was added. The mixture was stirred at 0°C for 20 min to dissolve LiCl. In a separate flame-dried 10 ml flask 4-methoxyacetophenone tosylhydrazone **46** (318 mg, 1.00 mmol) was dissolved in 2-MeTHF (10 ml) under gentle heating. The solution of tosylhydrazone was then transferred dropwise into the Schlenk flask at 0 °C and stirred at this temperature for 1 hour. The reaction mixture was quenched by addition of MeI (0.12 ml, 2 mmol) and left to stir for another 30 min before adding NH_4Cl (4 ml) and diluting with a saturated aqueous $NaHCO_3$ solution (10 ml). The product was extracted with diethyl ether (3 x 15 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The ratio of methylated to protonated alkene was determined at this stage as 99:1 by ^{1}H-NMR analysis, using the

proton signals of the terminal alkene functionality of each compound for comparison. The starting material **46** and intermediate **68** were isolated by flash chromatography eluting the silica gel column (15-20 g) with a gradient of Et_2O in petroleum ether (0-30 %) (181 mg, 0.57 mmol, 57 % and 13 mg, 0.04 mmol, 4 %, respectively).

Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent, (e) solvent to dissolve hydrazone, (f) time and temperature protocol, (g) electrophile, (h) quench time and temperature, (i) recovered starting material, (j) **68**, (k) E-alkene, and (l) E:H.

Table 1.24, **Entry 2**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) 2-MeTHF, 10 ml (e) 2-MeTHF, 10 ml, (f) 20 °C, 1 h, (g) MeI, 0.12 ml, 2 mmol, (h) 20 °C, 30 min, (i) **46**, 200 mg, 0.63 mmol, 63 %, (j) **68**, 23 mg, 0.07 mmol, 7 %, (k) **70**, 25 mg, 0.17 mmol, 17%, and (l) 99:1.

Data are consistent with that described for compound **46** on page 105, H-**47** on page 114 and for **68** and **70** on pages 123 and 124.

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) recovered starting material, (i) **68**, (j) E-alkene, and (k) E:H.

Table 1.24, **Entry 3**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF/DMPU 1:2, 7 ml (e) 0 °C, 1 h, (f) MeI, 0.12 ml, 2 mmol, (g) 0 °C, 30 min, (h) 6 %, (i) **68**, 266 mg, 0.80 mmol, 80 %, (j) -, and (k) -.

Table 1.24, **Entry 4**: (a) 89 mg, 2.1 mmol, (b) 2.1 ml, 1.05 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF/DMPU 1:2, 7 ml, (e) 20 °C, 1 h, (f) MeI, 0.12 ml, 2 mmol, (g) 20 °C, 30 min, (h) -, (i) **68**, 299 mg, 0.90 mmol, 90 %, (j) -, and (k) -.

Data are consistent with that described for compound **46** on page 105, H-**47** on page 114 and for **68** and **70** on pages 123 and 124.

5.4.5 Di-*tert*-butylmagnesium-mediated Shapiro Reaction

The following experiment was carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) $^{t}Bu_2Mg$, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) PhCHO, (g) quench conditions, (h) conversion, (i) yield of **49**, (j) E:H, and (k) **49**:**71** (addition by-product).

Table 1.25, **Entry 1**: (a) 127 mg, 3 mmol, (b) 3.66 ml, 1.5 mmol, 0.41 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 3 h, 40 °C, (f) 406 ml, 4 mmol, (g) -10 °C, 30 min, (h) 64 %, (i) **49**, 95 mg, 0.58 mmol, 58 %, (j) 91:9, and (k) 25:75.

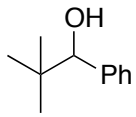
Data is consistent with that described for compound H-**47** on page 114 and for **49** on page 118.

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) $^{t}Bu_2Mg$, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve ketone, (e) time and temperature protocol, (f) electrophile, (g) quench time and temperature, (h) recovered starting material, (i) **68**, (j) E-alkene, and (k) E:H.

Scheme 1.56: (a) 89 mg, 2.1 mmol, (b) 2.56 ml, 1.05 mmol, 0.41 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 0 °C, 1 h, (f) MeI, 0.12 ml, 2 mmol, (g) 0 °C, 30 min, (h) 286 mg, 0.90 mmol, 90 %, (i) -, (j) -, and (k) -.

Data are consistent with that described for compound **46** on page 105.

2,2-Dimethyl-1-phenyl-1-propanol[150]



Colourless oil; IR ($CHCl_3$): 1043, 1605, 3435 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 0.89 (s, 9H, $(CH_3)_3$), 2.54 (s, 1H, O*H*), 4.37 (s, 1H, C*H*), 7.18-7.26 (m, 5H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 25.7, 35.7, 82.1, 125.9, 127.5, 127.9, 143.1.

The data observed are in accordance with literature values.

5.4.6 Evaluation of Electrophile Scope

Preparation of 1-Methoxy-4-(prop-1-enyl)benzene, **70**:

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) conversion, (i) yield of E-alkene, and (j) E:H.

Table 1.26, **Entry 1**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) MeI, 0.25 ml, 4 mmol, (g) -10 °C, 30 min, (h) 95 %, (i) **70**, 80 mg, 0.54 mmol, 54 %, and (j) 57:43.

Table 1.26, **Entry 2**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) MeI, 0.25 ml, 4 mmol, (g) -10 °C, 1 h, (h) 97 %, (i) **70**, 126 mg, 0.85 mmol, 85 %, and (j) 88:12.

Table 1.26, **Entry 3**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (b) 127 mg, 3 mmol, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) MeI, 0.13 ml, 2 mmol, (g) 0 °C, 1 h, (h) 93 %, (i) **70**, 123 mg, 0.81 mmol, 81 %, and (j) 93:7.

Data are consistent with that described for compound **70** on page 123.

Attempted Shapiro Reaction Using NBS, I_2 and TMSCl as Electrophiles

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) conversion, (i) yield of E-alkene, and (j) E:H.

Scheme 1.59, **Entry 1**, **X** = Br: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) *N*-bromosuccinimide as a solution in THF (2 ml), 356 ml, 2 mmol, (g) -10 °C, 1 h, (h) -, (i) **-** and (j) -.

Scheme 1.59, **Entry 2**, **X** = I: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) I_2 as a solution in THF (2 ml), 508 mg, 2 mmol, (g) -10 °C, 30 min, (h) -, (i) **-** and (j) -.

Scheme 1.60: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) TMSCl, 0.25 ml, 2 mmol, (g) -10 °C, 1 h, (h) -, (i) **-** and (j) -.

Attempted Preparation of 2-(4-Methoxyphenyl)acrylaldehyde, **72**:

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) conversion, (i) yield of E-alkene, and (j) E:H.

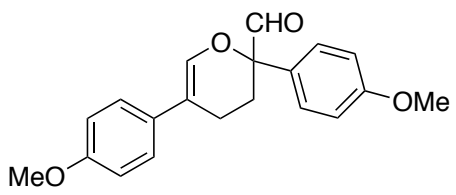
Table 1.27, **Entry 1**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) DMF, 0.16 ml, 2 mmol, (g) -10 °C, 1 h, (h) 95 %, (i) **72**, -, (j) 83:17.

Table 1.27, **Entry 2**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) DMF, 0.16 ml, 2 mmol, (g) 0 °C, 1 h, (h) 92 %, (i) **72**, -, (j) 87:13.

The following ^{1}H-NMR signals were used to calculate the reaction conversion: starting material **46**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.92 (d, 2H, J = 8.4 Hz, Ar*H*); known aldehyde **72**:[103] ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 6.12 (s, 1H, C=CH_2), 9.82 (s, 1H, C*H*O); H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, J = 11.0 Hz, $^{2}J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, J = 17.5 Hz, $^{2}J_{H\text{-}H}$ = 1.0 Hz, CH_2).

The following ^{1}H-NMR signals were used to calculate the ratio of known aldehyde **72**[103] to protonated alkene H-**47**: **72**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 6.12 (s, 1H, C=CH_2), 9.82 (s, 1H, C*H*O); H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, J = 11.0 Hz, $^{2}J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, J = 17.5 Hz, $^{2}J_{H\text{-}H}$ = 1.0 Hz, CH_2).

Dimerised product **74 (Scheme 1.62)**[105]



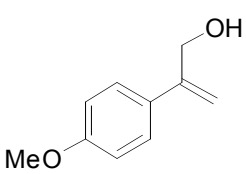
Colourless oil; IR ($CHCl_3$): 1023, 1637, 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.09-2.26 (m, 2H, aliphatic ring protons), 2.28-2.39 (m, 1H, aliphatic ring proton), 2.48-2.56 (m, 1H, aliphatic ring proton), 3.68 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 6.75 (d, 2H, J = 8.9 Hz, Ar*H*), 6.84 (d, 2H, J = 8.9 Hz, Ar*H*), 7.00 (s, 1H, C*H*), 7.10 (d, 2H, J = 8.9 Hz, Ar*H*), 7.33 (d, 2H, J = 8.9 Hz, Ar*H*), 9.44 (s, 1H, C*H*O); ^{13}C NMR (100 MHz,

$CDCl_3$): δ(ppm) 20.6, 27.6, 55.4, 55.5, 83.9, 114.0, 114.3, 114.6, 125.4, 127.1, 128.4, 130.9, 139.1, 158.3, 159.6, 199.8.

The data observed are in accordance with literature values.

Preparation of 2-(4-Methoxyphenyl)-2-propenol, **75**:[151]

Scheme 1.63: Preparation of the enal **75** was carried out according to *Typical Procedure F*: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-methoxyacetophenone tosylhydrazone **46**, 318 mg, 1 mmol, (d) solvent to dissolve hydrazone, THF, 5 ml, (e) time and temperature protocol, 40 °C, 3 h, (f) electrophile, dimethylformamide, 0.16 ml, 2 mmol, (g) quench conditions, 0 °C, 1 h. After workup, extraction and concentration, the crude mixture was dissolved in MeOH (10 ml) and $CeCl_3.7H_2O$ (820 mg, 2.2 mmol, 2.2 eq) was added. The clear yellow solution was cooled to 0 °C before the portion wise addition of $NaBH_4$ (83.2 mg, 2.2 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred for another 30 min before quenching the reaction with saturated NH_4Cl solution (5 ml). The product was extracted with DCM (3 x 5 ml) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The ratio of allyl alcohol **75** to protonated alkene H-**47** was determined at this stage as 90:10 by ^{1}H-NMR analysis, using the proton signals of the terminal alkene functionality of each compound for comparison. The product **75** was isolated by flash chromatography eluting the silica gel column (15-20 g) with a gradient of Et_2O in petroleum ether (0-50 %) (107 mg, 0.65 mmol, 65 % yield).



Colourless oil; IR ($CHCl_3$): 1029, 1516, 2957, 3234 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.55 (t, 1H, *J* = 6.2 Hz, O*H*), 3.83 (s, 3H, OCH_3), 4.53 (d, 2H, *J* = 6.1 Hz, CH_2OH), 5.27 (s, 1H, CH_2), 5.40 (s, 1H, CH_2), 6.90 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.41 (d, 2H, *J* = 8.9 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 55.3, 65.2, 111.1, 113.9, 127.2, 130.9, 146.6, 159.5.

The data observed are in accordance with literature values.

The following ^{1}H-NMR signals were used to calculate the ratio of allyl alcohol **75** to protonated alkene H-**47**: **75**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.27 (s, 1H, CH_2), 5.40 (s, 1H, CH_2); H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, J = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, J = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2).

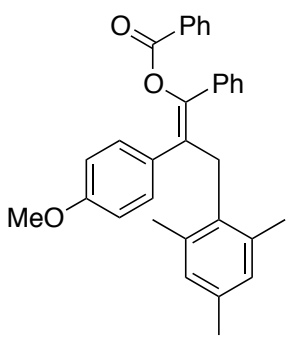
Attempted Preparation of 2-(4-Methoxyphenyl)-1-phenylprop-2-enone, **73**:

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, (i) E:H, and (j) major product isolated.

Table 1.28, **Entry 1**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) benzoyl chloride, 0.23 ml, 2 mmol, (g) -10 °C, 30 min, (h) **73**, - , (i) -, and (j) **76**, 143 mg, 0.31 mmol, 31 % .

Table 1.28, **Entry 2**: (a) 127 mg, 3 mmol, (b) 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) benzoyl chloride, 0.23 ml, 2 mmol, (g) 0 °C, 30 min, (h) **73**, - , (i) -, and (j) **76**, 301 mg, 0.65 mmol, 65 %.

(Z)-3-Mesityl-2-(4-methoxyphenyl)-1-phenylprop-1-en-1-yl benzoate, **76**:



Colourless Solid; M.p.: 125-126 °C; IR ($CHCl_3$): 1093, 1607, 1733, 2954 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 2.17 (s, 9H, ArCH_3), 3.72 (s, 3H, OCH_3), 3.83 (s, 2H, CH_2), 6.60 (d, 2H, J = 8.8 Hz, ArH), 6.68 (s, 2H, Mes$H$), 6.77 (d, 2H, J = 8.8 Hz, ArH), 7.05-7.9 (m, 3H,

Ar*H*), 7.11-7.17 (m, 2H, Ar*H*), 7.50 (t, 2H, *J* = 7.9 Hz, Ar*H*), 7.63 (t, 1H, *J* = 7.4 Hz, Ar*H*), 8.16 (d, 2H, *J* = 7.1 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 20.3, 29.8, 32.9, 55.0, 113.2, 127.3, 127.7, 128.5, 128.6, 128.7, 129.1, 129.6, 130.1, 130.7, 130.9, 131.9, 133.4, 135.4, 135.8, 137.3, 143.2, 158.4, 164.7. HRMS *m*/*z* (ESI) Calc. for $C_{32}H_{31}O_3$ $(M+H)^+$: 463.2268. Found: 463.2262.

Preparation of 2-(4-Methoxyphenyl)-1-phenylprop-2-enone, **73**:

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, (i) yield of H-**47**, and (j) E:H.

Table 1.29, **Entry 1**: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol; (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.31 ml, 2 mmol, (g) -10 °C, 1 h, (h) **73**, 25 mg, 0.10 mmol, 10 %, (i) 92 mg, 0.68 mmol, 68 %, and (j) 12:88.

Table 1.29, **Entry 2**: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol; (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.31 ml, 2 mmol, (g) rt., 1 h, (h) **73**, 165 mg, 0.69 mmol, 69 %, (i) 12 mg, 0.09 mmol, 9 %, and (j) 91:9.

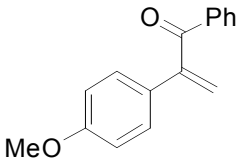
Table 1.29, **Entry 3**: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.31 ml, 2 mmol, (g) 40 °C, 30 min, (h) **73**, 172 mg, 0.72 mmol, 72 %, (i) 9 mg, 0.07 mmol, 7 %, and (j) 97:3.

Table 1.29, **Entry 4**: (a) 127 mg, 3 mmol (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5ml (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**,

0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, (h) **73**, 179 mg, 0.75 mmol, 75 %, (i) -, and (j) 93:7.

Table 1.29, **Entry 5**: (a) 635 mg, 15 mmol, (b) Mes_2Mg, 16 ml, 7.5 mmol, 0.50 M in THF, (c) 1.58 g, 5 mmol, (d) THF, 15 ml (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.8 ml, 5.25 mmol, (g) 40 °C, 1 h, (h) **73**, 996 mg, 0.84 mmol, 84 %, (i) 34 mg, 0.05 mmol, 5 %, and (j) 93:7.

2-(4-Methoxyphenyl)-1-phenylprop-2-enone, **73**:

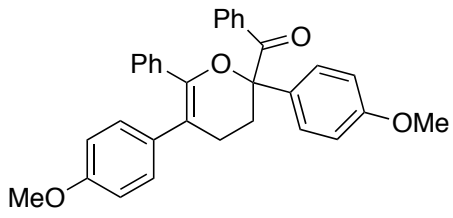


Colourless oil; IR ($CHCl_3$): 1245, 1692, 2963 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.82 (s, 3H, OCH_3), 5.54 (s, 1H, CH_2), 5.99 (s, 1H, CH_2), 6.88 (d, 2H, J = 8.9 Hz, Ar*H*), 7.37 (d, 2H, J = 8.9 Hz, Ar*H*), 7.41-7.46 (m, 2H, Ar*H*), 7.53-7.58 (m, 1H, Ar*H*), 7.92 (d, 2H, J = 7.1 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 55.3, 114.0, 119.0, 128.3, 128.4, 129.5, 130.0, 133.1, 137.2, 147.7, 159.8, 197.9; HRMS *m*/*z* (ESI) Calc. for $C_{16}H_{15}O_2$ $(M+H)^+$: 239.1067. Found: 239.1066.

The following ^1H-NMR signals were used to calculate the ratio of E-alkene to protonated alkene H-**47**: **73**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.54 (s, 1H, CH_2), 5.99 (s, 1H, CH_2); and H-**47**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, J = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, J = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2).

*Dimerised Product of **73***

(2,5-Bis(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2H-pyran-2-yl)(phenyl)methanone



Colourless crystals, M.p.: 167-169 °C; IR ($CHCl_3$): 1175, 1680, 2931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.09-2.20 (m, 1H, CH_2),

2.51-2.59 (m, 2H, C*H*$_2$), 2.89-2.99 (m, 1H, C*H*$_2$), 3.74 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 6.67 (d, 2H, *J* = 8.6 Hz, Ar*H*), 6.82-6.87 (m, 4H, Ar*H*), 7.01 (t, 2H, *J* = 10.8 Hz, Ar*H*), 7.02 (d, 2H, *J* = 7.7 Hz, Ar*H*), 7.09 (t, 1H, *J* = 7.0 Hz, Ar*H*), 7.33 (t, 2H, *J* = 7.7 Hz, Ar*H*), 7.46 (t, 1H, *J* = 7.2 Hz, Ar*H*), 7.57 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.77 (d, 2H, *J* = 7.6 Hz, Ar*H*). ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 26.3, 33.8, 55.1, 55.3, 86.0, 113.5, 114.2, 126.1, 127.3, 127.4, 127.8, 129.4, 129.5, 129.6, 130.2, 132.4, 132.7, 133.4, 136.2, 136.6, 147.9, 157.9, 159.2, 202.2. HRMS *m*/*z* (ESI) Calc. for $C_{32}H_{29}O_4$ $(M+H)^+$: 477.2060. Found: 477.2071.

Lithium-mediated Control Reactions

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) ^{n}BuLi, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, (i) yield of H-**47**, and (j) E:H.

Table 1.30, **Entry 1**: (a) 127 mg, 3 mmol, (b) ^{n}BuLi, 1.24 ml, 3 mmol, 2.43 M in hexane, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, (h) **73**, 24 mg, 0.10 mmol, 10 %, (i) -, and (j) 79:21.

Table 1.30, **Entry 2**: To a flame-dried Schlenk tube, under argon, containing 4-methoxyacetophenone tosylhydrazone **46** (318 mg, 1.00 mmol) and hexane (2 ml) was added TMEDA (0.8 ml, 5.3 mmol) and the mixture cooled to -50 °C before dropwise addition of *n*-BuLi (1.17 ml, 3 mmol, 2.56 M in hexane). The reaction mixture was allowed to warm to ambient temperature and stirred for another 2 h. It was then cooled to -78 °C and PhCON(OMe)Me (406 μl, 4 mmol) was added. The reaction mixture was warmed to ambient temperature and stirred for another hour before addition of NH_4Cl (4 ml) and further dilution with saturated $NaHCO_3$ solution

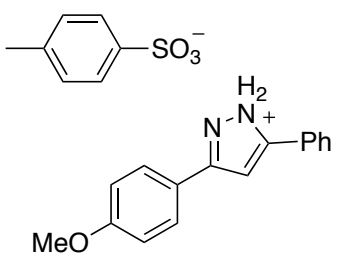
(10 ml). The product was extracted with diethyl ether (3 x 15 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The ratio of enone **73** to protonated alkene was determined at this stage as 64:36 by NMR analysis, using the proton signals of the terminal alkene functionality of each compound for comparison. The product **73** was isolated by flash chromatography eluting the silica gel column (15-20 g) with a gradient of Et_2O in petroleum ether (0-30 %) (99 mg, 0.42 mmol, 42 % yield).

Data are consistent with that described for compound H-**47** on page 114 and for **73** on page 133.

Internal Quench with Weinreb Amide 77

Scheme 1.70: To a flame-dried Schlenk tube, under argon, containing LiCl (127 mg, 3 mmol) was added a solution of Mes_2Mg (3 ml, 1.5 mmol, 0.51 M). The mixture was stirred at 40 °C for 20 min to dissolve LiCl. In a separate flame-dried 10 ml flask 4-methoxyacetophenone tosylhydrazone **46** (318 mg, 1.00 mmol) was dissolved in THF (5 ml) under gentle heating. First, PhCON(OMe)Me (0.16 ml, 1.05 mmol) was added to the Schlenk flask containing the $Mes_2Mg.2LiCl$ solution, and then the tosylhydrazone solution was transferred into the Schlenk flask *via* syringe. The reaction mixture was stirred at 40 °C for 3 hours before quenching with a saturated aqueous solution of NH_4Cl (4 ml) and further diluting with a saturated aqueous $NaHCO_3$ solution (10 ml). The product was extracted with diethyl ether (3 x 15 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude was dissolved in diethyl ether and triturated with petroleum ether to yield a white solid. Recrystallisation from DCM and petroleum ether yielded the product **78** as colourless crystals (56 mg, 0.31 mmol, 31 % yield).

3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazol-1-ium 4-methylbenzenesulfonate, **78**:



Colourless crystals, M.p.: 97-98 °C; IR ($CHCl_3$): 1177, 1381, 1612, 2363 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.41 (s, 3H, TsC*H*$_3$), 3.31-3.39 (m, 1H, N*H*), 3.57-3.65 (m, 1H, N*H*), 3.84 (s, 3H, OC*H*$_3$), 4.09 (s, 1H, C*H*), 6.89 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.20-7.28 (m, 2H, Ar*H*, partially obscured by solvent peak), 7.31-7.41 (m, 3H, Ar*H*), 7.49-7.52 (m, 4H, Ar*H*), 7.77 (d, 2H, *J* = 8.2 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 21.3, 55.8, 114.4, 115.2, 125.3, 126.7, 127.9, 128.0, 128.9, 130.0, 130.1, 134.2, 135.3, 139.6, 154.4, 162.7, 165.6; HRMS *m*/*z* (ESI) for cation Calc. for $C_{16}H_{15}N_2O$ (Cation): 251.1179. Found: 251.1178. HRMS *m*/*z* (ESI) for anion Calc. for $C_7H_7SO_3$ (Anion): 171.0121. Found: 171.0124.

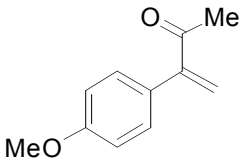
Weinreb Amide Electrophile Scope

See section **5.4.1**, pages 110 to 113, for individual details on the preparation and data of the requisite Weinreb amides.

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, (i) yield of H/D-**47**, and (j) E:H:D. Individual analysis for each enone compound is given below.

2-(4-Methoxyphenyl)buten-3-one, **86**:

Table 1.32, **Entry 1**: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) MeCON(OMe)Me **85**, 0.22 ml, 2 mmol, (g) 0 °C, 2 h, D_2O (0.2 ml, 11 mmol), (h) **86**, 79 mg, 0.45 mmol, 45 %, (i) 30 mg, 0.22 mmol, 22 %, and (j) 65:35:0.

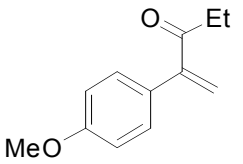


Colourless oil; IR ($CHCl_3$): 1249, 1687, 2937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.45 (s, 3H, C*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 5.93 (s, 1H, C*H*$_2$), 6.10 (s, 1H, C*H*$_2$), 6.90 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.26 (d, 2H, *J* = 8.7 Hz, Ar*H*, partially obscured by solvent peak); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 27.5, 55.3, 113.6, 124.6, 129.4, 129.7, 148.9, 159.6, 199.9; HRMS *m*/*z* (ESI) Calc. for $C_{11}H_{13}O_2$ $(M+H)^+$: 177.0910. Found: 177.0910.

The following ^1H-NMR signals were used to calculate the ratio of E-alkene to protonated and deuterated alkene H/D-**47**: **86**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.93 (s, 1H, C*H*$_2$), 6.10 (s, 1H, C*H*$_2$); H-**47**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, *J* = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$), 5.62 (dd, 1H, *J* = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$); and D-**47**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13-5.15 (m, 1H, C*H*$_2$), 5.62-5.63 (m, 1H, C*H*$_2$).

2-(4-Methoxyphenyl)penten-3-one, **87**:

Table 1.32, **Entry 2**: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol (d) THF, 5 ml, (e) 40 °C, 3 h, (f) EtCON(OMe)Me **84**, 0.13 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) **87**, 146 mg, 0.77 mmol, 77 %, (i) 11 mg, 0.08 mmol, 8 %, and (j) 92:8:0.

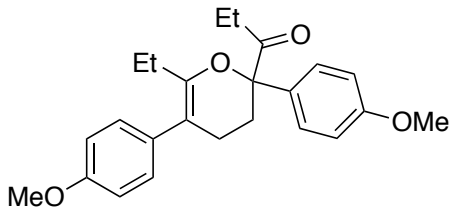


Colourless oil; IR ($CHCl_3$): 1180, 1686, 2937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.15 (t, 3H, *J* = 7.3 Hz, CH_2CH_3), 2.76 (q, 2H, *J* = 7.3 Hz, CH_2CH_3), 3.83 (s, 3H, OC*H*$_3$), 5.82 (s, 1H, C*H*$_2$), 6.01 (s, 1H, C*H*$_2$), 6.89 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.25 (d, 2H, *J* = 8.8 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 7.9, 32.5, 54.8, 113.2, 122.0, 129.0, 129.2, 148.3, 159.1, 202.7; HRMS *m*/*z* (ESI) Calc. for $C_{12}H_{15}O_2$ $(M+H)^+$: 191.1067. Found: 191.1067.

The following ^{1}H-NMR signals were used to calculate the ratio of E-alkene to protonated and deuterated alkene H/D-**47**: **87**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.82 (s, 1H, CH_2), 6.01 (s, 1H, CH_2); H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, J = 11.0 Hz, $^{2}J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, J = 17.5 Hz, $^{2}J_{H\text{-}H}$ = 1.0 Hz, CH_2); and D-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13-5.15 (m, 1H, CH_2), 5.62-5.63 (m, 1H, CH_2).

*Dimerised Product of **87***

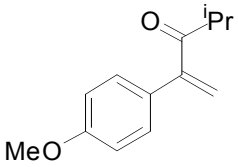
1-(6-Ethyl-2,5-bis(4-methoxyphenyl)-3,4-dihydro-2H-pyran-2-yl)propan-1-one:



Colourless oil; IR ($CHCl_3$): 2936, 2357, 1714, 1608, 1510, 1247, 1177 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 0.96 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.22 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.02-2.12 (m, 2H, aliphatic protons), 2.23-2.39 (m, 3H, aliphatic protons), 2.52-2.71 (m, 3H, aliphatic protons), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.83 (d, 2H, J = 8.8 Hz, ArH), 6.90 (d, 2H, J = 8.9 Hz, ArH), 7.02 (d, 2H, J = 8.8 Hz, ArH), 7.43 (d, 2H, J = 8.9 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 7.8, 12.5, 24.9, 25.2, 29.5, 30.2, 55.2, 85.1, 109.9, 113.5, 113.8, 126.3, 129.7, 131.9, 132.0, 134.0, 149.8, 158.0, 159.1, 212.1; HRMS *m*/*z* (ESI) Calc. for $C_{24}H_{29}O_4$ $(M+H)^+$: 381.2060. Found: 381.2061.

2-(4-Methoxyphenyl)-4-methylpenten-3-one, **88**:

Table 1.32, **Entry 3**: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) ^{i}PrCON(OMe)Me **83**, 0.15 ml, 1.05 mmol, (g) 40 °C, 30 min, D_2O (0.2 ml, 11 mmol), (h) **88**, 147 mg, 0.72 mmol, 72 %, (i) 15 mg, 0.11 mmol, 11 %, and (j) 93:7:0.

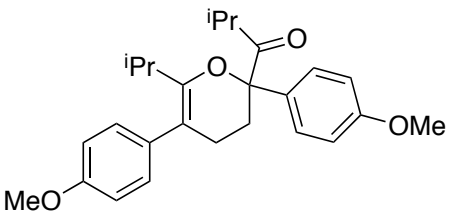


Colourless oil; IR ($CHCl_3$): 1249, 1682, 2971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.14 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$), 3.22 (septet, 1H, J = 6.8 Hz, $CH(CH_3)_2$), 3.83 (s, 3H, OCH_3), 5.79 (s, 1H, CH_2), 5.89 (s, 1H, CH_2), 6.89 (d, 2H, J = 8.8 Hz, Ar*H*), 7.25 (d, 2H, J = 8.8 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 18.2, 36.4, 54.8, 113.2, 120.5, 128.7, 129.4, 148.1, 159.1, 206.9; HRMS *m/z* (EI^+) Calc. for $C_{13}H_{16}O_2$ (M^+): 204.1150. Found: 204.1147.

The following ^1H-NMR signals were used to calculate the ratio of E-alkene to protonated and deuterated alkene H/D-**47**: **88**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.79 (s, 1H, CH_2), 5.89 (s, 1H, CH_2); H-**47**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, J = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, J = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2); and D-**47**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13-5.15 (m, 1H, CH_2), 5.62-5.63 (m, 1H, CH_2).

*Dimerised Product of **88***

1-(6-Isopropyl-2,5-bis(4-methoxyphenyl)-3,4-dihydro-2H-pyran-2-yl)-2-methylpropanone:



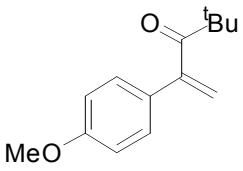
Colourless oil; IR ($CHCl_3$): 2966, 2360, 1712, 1608, 1510, 1247, 1179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 0.80 (d, 3H, J = 6.8 Hz, $CH(CH_3)_2$), 1.07 (d, 3H, J = 6.7 Hz, $CH(CH_3)_2$), 1.19 (d, 3H, J = 6.8 Hz, $CH(CH_3)_2$), 1.26 (d, 3H, J = 6.8 Hz, $CH(CH_3)_2$), 1.97-2.11 (m, 2H, aliphatic ring protons), 2.13-2.22 (m, 1H, aliphatic ring proton), 2.47-2.54 (m, 1H, aliphatic ring proton), 2.75 (septet, 1H, J = 6.8 Hz, $CH(CH_3)_2$), 3.35 (septet, 1H, J = 6.8, $CH(CH_3)_2$), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.83 (d, 2H, J = 8.7 Hz, Ar*H*), 6.89 (d, 2H, J = 8.9 Hz, Ar*H*), 7.01 (d, 2H, J = 8.7 Hz, Ar*H*), 7.44 (d, 2H, J = 8.9 Hz,

Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 19.0, 20.4, 21.3, 25.4, 29.6, 30.3, 33.9, 55.2, 84.9, 108.4, 113.6, 113.8, 126.5, 129.8, 131.9, 134.2, 152.6, 158.0, 159.0, 215.6; HRMS *m*/*z* (ESI) Calc. for $C_{26}H_{33}O_4$ $(M+H)^+$: 409.2373. Found: 409.2372.

2-(4-Methoxyphenyl)-4,4-dimethylpent-1-en-3-one, **89**:

Table 1.32, **Entry 4**: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) ^{t}BuCON(OMe)Me **82**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) **89**, 101 mg, 0.46 mmol, 46 %, (i), 27 mg, 0.20 mmol, 20 %, and (j) 58:12:30.

Table 1.32, **Entry 5**: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) ^{t}BuCON(OMe)Me **82**, 0.16 ml, 1.05 mmol, (g) 40 °C, 16 h, D_2O (0.2 ml, 11 mmol), (h) **89**, 140 mg, 0.64 mmol, 64 %, (i), 16 mg, 0.12 mmol, 12 %, and (j) 83:17:0.



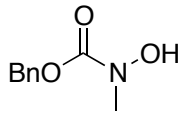
Colourless oil; IR ($CHCl_3$): 1251, 1688, 2968 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 1.16 (s, 9H, C(C*H*$_3$)$_3$), 3.82 (s, 3H, OC*H*$_3$), 5.10 (s, 1H, C*H*$_2$), 5.47 (s, 1H, C*H*$_2$), 6.87 (d, 2H, *J* = 8.9 Hz, Ar*H*), 7.24 (d, 2H, *J* = 8.9 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 27.4, 44.5, 55.3, 111.9, 114.1, 127.4, 129.2, 149.7, 159.8, 213.9; HRMS *m*/*z* (ESI) Calc. for $C_{14}H_{19}O_2$ $(M+H)^+$: 219.1380. Found: 219.1380.

The following ^{1}H-NMR signals were used to calculate the ratio of E-alkene to protonated and deuterated alkene H/D-**47**: **89**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.10 (s, 1H, C*H*$_2$), 5.47 (s, 1H, C*H*$_2$); H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, *J* = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$), 5.62 (dd, 1H, *J* = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$); and D-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13-5.15 (m, 1H, C*H*$_2$), 5.62-5.63 (m, 1H, C*H*$_2$).

Preparation of N-(Tert-*Butoxy*)-N-*methylpivalamide* **93** in 3 steps:

Benzyl hydroxy(methyl)carbamate, **91**:[109]

Scheme 1.74, **Entry 1**: A suspension of *N*-methylhydroxylamine hydrochloride (2.5 g, 30 mmol) and sodium hydrogen carbonate dehydrate (5.0 g, 60 mmol) in water (100 ml) was stirred at 0 °C in an ice bath for 30 min till the solids dissolved. The reaction mixture was then treated with DCM (70 ml) and benzoylchloroformate (4.3 ml, 30 mmol) was added dropwise. The reaction was left to warm to ambient temperature and vigorously stirred over 3 h before separating the layers. The aqueous phase was washed with DCM (2 x 20 ml) and the combined organics were then washed with brine (35 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was further purified by colum chromatography eluting the silica gel column with a gradient of Et_2O in petroleum ether (0-40 %) to give the product **91** as a colourless oil (4.61 g, 26 mmol, 85 % yield).



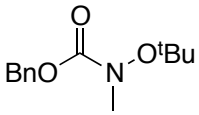
Colourless oil; IR ($CHCl_3$): 1701, 3041, 3304 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.21 (s, 3H, NC*H*$_3$), 5.14 (s, 2H, PhC*H*$_2$), 7.31-7.42 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 38.1, 68.0, 128.0, 128.5, 128.6, 135.3, 158.1.

The data observed are in accordance with literature values.

Benzyl tert-*butoxy(methyl)carbamate*, **92**:[109]

Scheme 1.74, **Entry 2**: Perchloric acid 60 % (0.6 ml, 4.9 mmol) was added to a solution of benzyl hydroxy(methyl)carbamate (4.53 g, 24.9 mmol) and *tert*-butyl acetate (8.4 ml, 62.2 mmol) in dioxane (40 ml) at ambient temperature. The reaction mixture was stirred at this temperature for 15 h before carefully neutralising with saturated aqueous solution of $NaHCO_3$. The two phases were separated and the

aqueous extracted with Et_2O (3 x 30 ml). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The product **92** was isolated by flash chromatography eluting the silica gel column (15-20 g) with a gradient of Et_2O in petroleum ether (0-40 %) as a colourless oil (5.61 g, 23.7 mmol, 95 % yield).

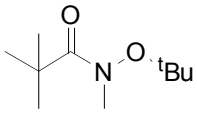


Colourless oil; IR ($CHCl_3$): 1703, 1742, 2927, 3025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.24 (s, 9H, $OC(CH_3)_3$), 3.18 (s, 3H, NCH_3), 5.16 (s, 2H, $PhCH_2$), 7.29-7.40 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 27.2, 41.3, 68.0, 82.1, 128.2, 128.6, 128.9, 136.2, 160.1.

The data observed are in accordance with literature values.

N-*(*Tert-*butoxy)*-N-*methylpivalamide*, **93**:

Scheme 1.74, **Entry 3**: To a solution of benzyl *tert*-butoxy(methyl)carbamate (2.38 g, 10 mmol) in dry DCM was carefully added palladium on activated charcoal (50 mg, 10 % Pd basis). The reaction mixture was evacuated and purged with hydrogen (x3) *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. Upon the final refill, the mixture was stirred at ambient temperature under hydrogen atmosphere for 16 h before removing the palladium by filtration and cooling the remaining clear solution to 0 °C. Triethylamine (1.3 ml, 10 mmol) and pivaloyl chloride (1.23 ml, 10 mmol) were then added slowly to the stirring solution whilst maintaining the low temperature of 0 °C. The reaction mixture was allowed to warm to ambient temperature and left to stir for another 4 h before quenching the reaction with a saturated aqueous $NaHCO_3$ solution (5 ml). The two layers were separated and the organic phase washed with 1M HCl (5 ml) and brine (5 ml), dried over Na_2SO_4, and concentrated *in vacuo*. The product *N*-(*tert*-butoxy)-*N*-methylpivalamide **93** was isolated as a clear oil (1.72 g, 9.2 mmol, 92 % yield).



Colourless oil; IR ($CHCl_3$): 1071, 1685, 2977 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.20-1.25 (m, 18H, $OC(CH_3)_3$, $C(CH_3)_3$), 3.25 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 27.5, 27.9, 39.2, 42.2, 81.8, 181.0; HRMS *m/z* (ESI) Calc. for $C_{10}H_{22}NO_2$ $(M+H)^+$: 188.1645. Found: 188.1640.

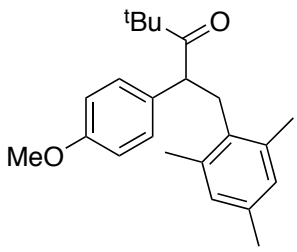
Preparation of 2-(4-Methoxyphenyl)-4,4-dimethylpent-1-en-3-one, **89**:

The following experiment was carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, (i) yield of H/D-**47**, and (j) E:H:D.

Scheme 1.75: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) **46**, 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) $^tBuCON(O^tBu)Me$ **93**, 0.22 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) **89**, 116 mg, 0.53 mmol, 53 %, (i) 12 mg, 0.09 mmol, 9 %, and (i) 85:15:0.

Data and consistent with that described for compound H/D-**47** on page 114 and **89** on page 140.

*By-product Observed in Reaction with Weinreb Amide **93** as Electrophile*



Colourless oil; IR ($CHCl_3$): 1126, 1680, 2958 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 0.94 (s, 9H, $C(CH_3)_3$), 2.10 (s, 6H, Ar-CH_3), 2.22 (s, 3H, Ar-CH_3), 2.93 (dd, 1H, J = 7.2 Hz, $^2J_{H\text{-}H}$ = 14.0, CH_2), 3.27 (dd, 1H, J = 6.6 Hz, $^2J_{H\text{-}H}$ = 14.0 Hz, CH_2), 3.78 (s, 3H, OCH_3), 4.24 (t, 1H, J = 7.0 Hz, C*H*), 6.73-6.80 (m, 4H, Mes*H*, Ar*H*), 7.07 (d, 2H, J = 8.8 Hz, Ar*H*); ^{13}C NMR

(100 MHz, $CDCl_3$): δ(ppm) 20.0 20.8, 26.5, 34.9, 45.0, 51.6, 55.2, 86.3, 113.9, 128.9, 129.2, 131.6, 133.6, 135.2, 136.6, 158.6.

Accurate Mass has yet to be obtained for this compound.

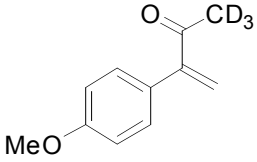
Preparation of 2-(4-Methoxyphenyl)-4-d^3-buten-3-one, **95**:

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, (i) yield of H/D-**47**, and (j) E:H:D.

Table 1.33, **Entry 1**: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) **46**, 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) $CD_3CON(OMe)Me$ **94**, 0.22 ml, 2 mmol, (g) 0 °C, 2 h, H_2O (0.2 ml, 11 mmol), (h) **95**, 139 mg, 0.75 mmol 75 %, (i) 16 mg, 0.12 mmol, 12 %, and (j) 85:15:0.

Table 1.33, **Entry 2**: (a) 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) **46**, 318 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) $CD_3CON(OMe)Me$ **94**, 0.12 ml, 1.05 mmol, (g) 0 °C, 2 h, H_2O (0.2 ml, 11 mmol), (h) **95**, 129 mg, 0.72 mmol, 72 %, (i) 20 mg, 0.15 mmol, 15 %, and (j) 84:16:0.

2-(4-Methoxyphenyl)-4-d^3-buten-3-one, **95**:



Colourless oil, IR ($CHCl_3$): 1174, 1678, 2961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.83 (s, 3H, OCH_3), 5.93 (s, 1H, CH_2), 6.09 (s, 1H, CH_2), 6.90 (d, 2H, J = 8.8 Hz, Ar*H*), 7.26 (d, 2H, J = 8.5 Hz, Ar*H*, partially obscured by solvent peak);

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 26.7 (m, CD_3), 55.3, 113.6, 124.6, 129.4, 129.7, 149.0, 159.6, 200.0; HRMS *m/z* (ESI) Calc. for $C_{11}H_{10}D_3O_2$ $(M+H)^+$: 180.1094. Found: 180.1098.

The following ^{1}H-NMR signals were used to calculate the ratio of E-alkene to protonated and deuterated alkene H/D-**47**: **95**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.93 (s, 1H, CH_2), 6.09 (s, 1H, CH_2); H-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13 (dd, 1H, J = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.62 (dd, 1H, J = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2); and D-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.13-5.15 (m, 1H, CH_2), 5.62-5.63 (m, 1H, CH_2).

5.4.7 Evaluation of Substrate Scope

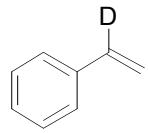
See section **5.4.1**, pages 105 to 109, for individual details on the preparation and data of the requisite tosylhydrazones.

D_2O-Quench

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) tosylhydrazone, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, and (i) E:H or E:H:D where applicable. Individual analysis for each compound is given below.

α-Deuteriostyrene, **104**:[152]

Table 1.36, **Entry 1**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) acetophenone tosylhydrazone **96**, 288 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) D_2O, 0.2 ml, 11 mmol (g) 40 °C, 10 min, (h) **104**, 60 mg, 0.57 mmol, 57 % (NMR yield with mesitylene residues), and (i) 92:8.

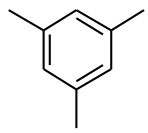


Colourless oil; IR ($CHCl_3$): 1102, 1607, 2963 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.26-5.30 (m, 1H, C*H*$_2$), 5.76-5.81 (m, 1H, C*H*$_2$), 7.29 (d, 1H, *J* = 7.8 Hz, Ar*H*, partially obscured by solvent peak), 7.36 (t, 2H, *J* = 7.3 Hz, Ar*H*), 7.45 (d, 2H, *J* = 7.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 113.7, 126.2, 127.8, 128.5, 137.7. Due to the mesitylene residue, no signal for CD could be identified.

The data observed are in accordance with literature values.

The following ^1H-NMR signals were used to calculate the ratio of known *styrene*, H-**104**,[153] to deuterated alkene D-**104**: H-**104**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.28 (dd, 1H, *J* = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$), 5.77 (dd, 1H, *J* = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$), 6.75 (dd, 1H, *J* = 17.5 Hz, *J* = 11.0 Hz, C*H*CH$_2$); D-**104**: ^1H NMR (400 MHz, $CDCl_3$): 5.26-5.30 (m, 1H, C*H*$_2$), 5.76-5.81 (m, 1H, C*H*$_2$).

Mesitylene:[154,155]

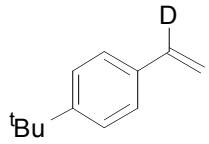


Colourless oil; IR ($CHCl_3$): 3025, 1616, 1485, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.31 (s, 9H, C*H*$_3$), 6.83 (s, 3H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 21.2, 126.9, 137.7.

The data observed are in accordance with literature values.

α-Deuterio-1-ethenyl-4-tert-butylbenzene, D-**105**:

Table 1.36, **Entry 2**: (b) LiCl, 127 mg, 3 mmol, (a) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-*tert*-butylacetophenone tosylhydrazone **97**, 344 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) D_2O, 0.2 ml, 11 mmol, (g) 40 °C, 10 min, (h) D/H-**105**, 147 mg, 0.91 mmol, 91 % (NMR yield with mesitylene residues), and (i) 91:9.

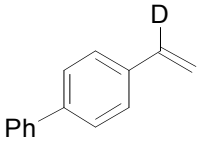


Colourless oil; IR ($CHCl_3$): 1217, 1598, 2961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.34 (s, 9H, C(C*H*$_3$)$_3$), 5.19-5.21 (m, 1H, C*H*$_2$), 5.70-5.72 (m, 1H, C*H*$_2$), 7.34-7.39 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 31.5, 34.8, 113.1, 125.7, 127.2, 135.0, 136.5 (t, J = 30 Hz, CD), 151.2.

The following ^1H-NMR signals were used to calculate the ratio of known *1-ethenyl-4-tert-butylbenzene*, H-**105**,[156] to deuterated alkene D-**105**: H-**105**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.24 (dd, 1H, J = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$), 5.75 (dd, 1H, J = 17.0 Hz, $^2J_{H\text{-}H}$ = 1.2 Hz, C*H*$_2$), 6.75 (dd, 1H, J = 17.3 Hz, J = 11.0 Hz, C*H*CH$_2$); D-**105**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.19-5.21 (m, 1H, C*H*$_2$), 5.70-5.72 (m, 1H, C*H*$_2$).

α-Deuterio-4-vinylbiphenyl, D-**106**:

Table 1.36, **Entry 3**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-phenylacetophenone tosylhydrazone **98**, 364 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) D_2O, 0.2 ml, 11 mmol, (g) 40 °C, 10 min, (h) D/H-**106**, 154 mg, 0.85 mmol, 85 % (isolated), and (i) 96:4.



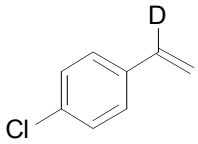
White solid; M.p.: 118-120 °C; IR ($CHCl_3$): 1487, 1613, 3031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.28-5.29 (m, 1H, C*H*$_2$), 5.79-5.81 (m, 1H, C*H*$_2$), 7.33-7.38 (m, 1H, Ar*H*), 7.42-7.47 (m, 2H, Ar*H*), 7.50 (d, 2H, J = 8.4 Hz, Ar*H*), 7.56-7.63 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 113.3, 126.2, 126.5, 126.8, 126.9, 128.3, 135.7 (t, J = 23.5 Hz, CD), 136.1, 140.1, 140.3; HRMS *m/z* (ESI) Calc. for $C_{14}H_{12}D$ $(M+H)^+$: 182.1075. Found: 182.1073.

The following ^1H-NMR signals were used to calculate the ratio of known *4-vinylphenyl*, H-**106**,[157] to deuterated alkene D-**106**: H-**106**: ^1H NMR (400 MHz,

$CDCl_3$): δ(ppm) 5.30 (d, 1H, *J* = 10.8 Hz, C*H*$_2$), 5.80 (d, 1H, *J* = 17.3 Hz, C*H*$_2$), 6.78 (dd, 1H, *J* = 17.4 Hz, *J* = 11.0 Hz, C*H*CH_2); D-**106**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.28-5.29 (m, 1H, C*H*$_2$), 5.79-5.81 (m, 1H, C*H*$_2$).

α-Deuterio-4-chlorostyrene, D-**107**:

Table 1.36, **Entry 4**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-chloroacetophenone tosylhydrazone **99**, 322 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) D_2O, 0.2 ml, 11 mmol, (g) 40 °C, 10 min, (h) D/H-**107**, 131 mg, 0.94 mmol, 94 % (NMR yield with mesitylene residues), and (h) 97:3.

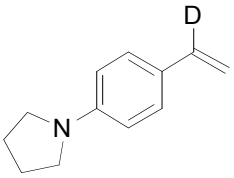


Colourless oil; IR ($CHCl_3$): 1086, 1479, 1625, 3017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.26-5.29 (m, 1H, C*H*$_2$), 5.72-5.74 (m, 1H, C*H*$_2$), 7.28-7.38 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 113.8, 126.9, 128.2, 132.9, 135.5 (t, *J* = 23.4 Hz, CD), 137.2.

The following ^{1}H-NMR signals were used to calculate the ratio of known *4-chlorostyrene*, H-**107**,[158] to deuterated alkene D-**107**: H-**107**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.29 (d, 1H, *J* = 11.0 Hz, C*H*$_2$), 5.74 (d, 1H, *J* = 17.5 Hz, C*H*$_2$), 6.70 (dd, 1H, *J* = 17.5 Hz, *J* = 11.0 Hz, C*H*CH_2); D-**107**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.26-5.29 (m, 1H, C*H*$_2$), 5.72-5.74 (m, 1H, C*H*$_2$).

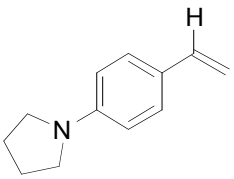
α-Deuterio-1-(4-vinylphenyl)pyrrolidine, D-**108**:

Table 1.36, **Entry 5**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-(*N*-pyrrolidino)acetophenone tosylhydrazone **100**, 357 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) D_2O, 0.2 ml, 11 mmol, (g) 40 °C, 10 min, (h) D/H-**108**, 109 mg, 0.63 mmol, 63 % (isolated), and (i) 90:10.



Colourless oil; IR ($CHCl_3$): 1186, 1520, 1615, 2968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.99-2.20 (m, 4H, C*H*$_2$), 3.31 (m, 4H, NC*H*$_2$), 4.97-4.99 (m, 1H, C*H*$_2$), 5.49-5.51 (m, 1H, C*H*$_2$), 6.53 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.31 (d, 2H, *J* = 8.8 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 25.0, 47.1, 107.8, 111.0, 124.7, 126.8, 136.1 (t, *J* = 27 Hz, CD), 147.2; HRMS *m*/*z* (EI^+) Calc. for $C_{12}H_{14}DN$ (M^+): 174.1267. Found: 174.1269.

1–(4-Vinylphenyl)pyrrolidine, H-**108**:[98]



Colourless oil; IR ($CHCl_3$): 1178, 1515, 1611, 2960 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.98-2.03 (m, 4H, C*H*$_2$), 3.27-3.34 (m, 4H, NC*H*$_2$), 5.00 (dd, 1H, *J* = 10.8 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$), 5.52 (dd, 1H, *J* = 17.6 Hz, $^2J_{H\text{-}H}$ = 1.1 Hz, C*H*$_2$), 6.53 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.64 (dd, 1H, *J* = 17.6 Hz, *J* = 10.9 Hz, C*H*CH_2), 7.31 (d, 2H, *J* = 8.7 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 25.5, 47.6, 108.5, 111.5, 125.2, 127.3, 136.9, 147.7.

The data observed are in accordance with literature values.

The following ^1H-NMR signals were used to calculate the ratio of *1–(4-vinylphenyl)pyrrolidine*, H-**108**,[98] to deuterated alkene D-**108**: H-**108:** ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.00 (dd, 1H, *J* = 10.8 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$), 5.52 (dd, 1H, *J* = 17.6 Hz, $^2J_{H\text{-}H}$ = 1.1 Hz, C*H*$_2$), 6.64 (dd, 1H, *J* = 17.6 Hz, *J* = 10.9 Hz, C*H*CH_2); ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 4.97-4.99 (m, 1H, C*H*$_2$), 5.49-5.51 (m, 1H, C*H*$_2$).

Table 1.36, **Entry 6**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-(Trifluoromethyl)acetophenone tosylhydrazone, **101**, 356 mg, 1

mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) D_2O, 0.2 ml, 11 mmol, (g) 40 °C, 10 min, (h) -, and (i) -.

Table 1.36, **Entry 7**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-nitroacetophenone tosylhydrazone, **102**, 333 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) D_2O, 0.2 ml, 11 mmol, (g) 40 °C, 10 min, (h) -, and (i) -.

Table 1.36, **Entry 8**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-cyanoacetophenone tosylhydrazone, **103**, 313 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) D_2O, 0.2 ml, 11 mmol, (g) 40 °C, 10 min, (h) -, and (i) -.

Variations in the reaction conditions for substrates **101** to **103** were attempted without success.

Reacting tosylhydrazone **101** at 0 °C: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-(trifluoromethyl)acetophenone tosylhydrazone, **101**, 356 mg, 1 mmol, (d) 5 ml, THF, (e) 0 °C, 3 h, (f) D_2O, 0.2 ml, (g) 0 °C, 10 min, (h) -, and (i) -. Recovered **101**: 310 mg, 0.87 mmol, 87 %.

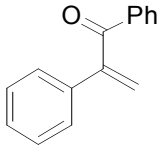
Weinreb Amide Quench

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) tosylhydrazone, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, and (i) E:H or E:D:H where applicable. Individual analysis for each compound is given below.

1,2-Diphenylprop-2-enone, **109**:[159]

Table 1.37, **Entry 1**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) acetophenone tosylhydrazone **96**, 288 mg, 1 mmol, (d) THF, 5 ml, (e)

40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) **109**, 165 mg, 0.79 mmol, 79 %, and (i) 95:0:5.

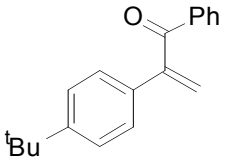


Colourless oil; IR ($CHCl_3$): 1213, 1660, 3062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.66 (s, 1H, CH_2), 6.08 (s, 1H, CH_2), 7.30-7.49 (m, 7H, Ar*H*), 7.57 (t, 1H, *J* = 7.5 Hz, Ar*H*), 7.93 (d, 2H, *J* = 7.3 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 120.4, 126.5, 126.6, 127.9, 128.1, 129.5, 132.6, 136.5, 136.6, 147.8, 197.1.

The following ^1H-NMR signals were used to calculate the ratio of known *styrene*, H-**104**,[153] to enone **109**: H-**104**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.28 (dd, 1H, *J* = 11.0 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.77 (dd, 1H, *J* = 17.5 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, CH_2), 6.75 (dd, 1H, *J* = 17.5 Hz, *J* = 11.0 Hz, C*H*CH_2); **109**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.66 (s, 1H, CH_2), 6.08 (s, 1H, CH_2).

*2-(4-*Tert-*butylphenyl)-1-phenylprop-2-enone*, **110**:

Table 1.37, **Entry 2**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-*tert*-butylacetophenone tosylhydrazone **97**, 344 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) **110**, 209 mg, 0.75 mmol, 75 %, and (i) 94:0:6.

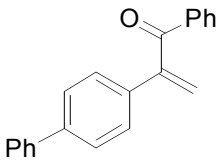


Colourless oil; IR ($CHCl_3$): 1109, 1598, 1683, 2964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1. 33 (s, 9H, C(CH_3)$_3$), 5.58 (s, 1H, CH_2), 6.06 (s, 1H, CH_2), 7.37-7.39 (m, 4H, Ar*H*), 7.45 (t, 2H, *J* = 7.9 Hz, Ar*H*), 7.57 (t, 1H, *J* = 7.4 Hz, Ar*H*), 7.93 (d, 2H, *J* = 7.2 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 30.7, 34.1, 119.5, 125.1, 126.2, 127.9, 129.5, 132.5, 133.5, 136.8, 147.5, 151.1, 197.3; HRMS *m*/*z* (ESI) Calc. for $C_{19}H_{21}O$ $(M+H)^+$: 265.1588. Found: 265.1587.

The following ^{1}H-NMR signals were used to calculate the ratio of known *1-ethenyl-4-tert-butylbenzene*, H-**105**,[156] to enone **110**: H-**105**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.24 (dd, 1H, J = 11.0 Hz, $^{2}J_{H\text{-}H}$ = 1.0 Hz, CH_2), 5.75 (dd, 1H, J = 17.0 Hz, $^{2}J_{H\text{-}H}$ = 1.2 Hz, CH_2), 6.75 (dd, 1H, J = 17.3 Hz, J = 11.0 Hz, CHCH$_2$); **110**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.58 (s, 1H, CH_2), 6.06 (s, 1H, CH_2).

2-(4-Phenylphenyl)-1-phenylprop-2-enone, **111**:

Table 1.37, **Entry 3**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-phenylacetophenone tosylhydrazone **98**, 364 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) **111**, 259 mg, 0.91 mmol, 91 %, and (i) 93:0:7.

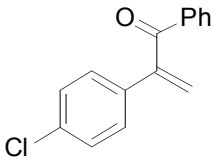


Colourless oil; IR ($CHCl_3$): 1226, 1666, 3034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.67 (s, 1H, CH_2), 6.14 (s, 1H, CH_2), 7.36 (t, 1H, J = 7.4 Hz, ArH), 7.43-7.60 (m, 11H, ArH), 7.95 (d, 2H, J = 7.1 Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 120.8, 127.0, 127.3, 127.4, 127.5, 128.5, 128.8, 130.0, 133.2, 135.9, 137.1, 140.5, 141.3, 147.9, 197.6; HRMS *m*/*z* (ESI) Calc. for $C_{21}H_{17}O$ $(M+H)^{+}$: 285.1274. Found: 285.1274.

The following ^{1}H-NMR signals were used to calculate the ratio of known *4-vinylbiphenyl*, H-**106**,[157] to enone **111**: H-**106**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.30 (d, 1H, J = 10.8 Hz, CH_2), 5.80 (d, 1H, J = 17.3 Hz, CH_2), 6.78 (dd, 1H, J = 17.4 Hz, J = 11.0 Hz, CHCH$_2$); **111**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.67 (s, 1H, CH_2), 6.14 (s, 1H, CH_2).

2-(4-Chlorophenyl)-1-phenylprop-2-enone, **112**:[160]

Table 1.37, **Entry 4**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-chloroacetophenone tosylhydrazone **99**, 323 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) **112**, 170 mg, 0.70 mmol, 70 %, and (i) 97:0:3.



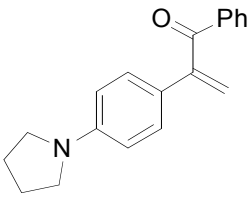
Colourless oil; IR ($CHCl_3$): 1213, 1667, 2925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.69 (s, 1H, CH_2), 6.09 (s, 1H, CH_2), 7.31-7.40 (m, 4H, Ar*H*), 7.46 (t, 2H, *J* = 7.9 Hz, Ar*H*), 7.58 (t, 1H, *J* = 7.5 Hz, Ar*H*), 7.89 (d, 2H, *J* = 8.5 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 121.3, 127.9, 128.0, 128.3, 129.5, 132.7, 134.0, 135.0, 136.5, 146.6, 196.6.

The data observed are in accordance with literature values.

The following ^1H-NMR signals were used to calculate the ratio of known *4-chlorostyrene*, H-**107**,[158] to enone **112**: H-**107**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.29 (d, 1H, *J* = 11.0 Hz, CH_2), 5.74 (d, 1H, *J* = 17.5 Hz, CH_2), 6.70 (dd, 1H, *J* = 17.5 Hz, *J* = 11.0 Hz, C*H*CH_2); **112**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.69 (s, 1H, CH_2), 6.09 (s, 1H, CH_2).

2-(4-Pyrrolidinophenyl)-1-phenylprop-2-enone, **113**:

Table 1.37, **Entry 5**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-pyrrolidinoacetophenone tosylhydrazone **100**, 357 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) **113**, 144 mg, 0.52 mmol, 52 %, and (i) 95:0:5.



Colourless oil; IR ($CHCl_3$): 1222, 1663, 3079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.97-2.02 (m, 4H, C*H*$_2$), 3.27-3.31 (m, 4H, NC*H*$_2$), 5.35 (s, 1H, C*H*$_2$), 5.86 (s, 1H, C*H*$_2$), 6.51 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.26-7.31 (m, 2H, Ar*H*, partially obscured by solvent peak), 7.42 (t, 2H, *J* = 7.8 Hz, Ar*H*), 7.53 (t, 1H, *J* = 7.4 Hz, Ar*H*), 7.94 (d, 2H, *J* = 7.2 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 25.5, 47.5, 111.5, 115.1, 123.8, 127.8, 128.3, 130.0, 132.9, 137.3, 147.9, 148.3, 198.6; HRMS *m*/*z* (ESI) Calc. for $C_{19}H_{20}NO$ $(M+H)^+$: 278.1539. Found: 278.1540.

The following ^1H-NMR signals were used to calculate the ratio of *1–(4-vinylphenyl)pyrrolidine*, H-**108**[97] to enone **113**: H-**108** ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.00 (dd, 1H, *J* = 10.8 Hz, $^2J_{H\text{-}H}$ = 1.0 Hz, C*H*$_2$), 5.52 (dd, 1H, *J* = 17.6 Hz, $^2J_{H\text{-}H}$ = 1.1 Hz, C*H*$_2$), 6.64 (dd, 1H, *J* = 17.6 Hz, *J* = 10.9 Hz, C*H*CH_2); **113**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.35 (s, 1H, C*H*$_2$), 5.86 (s, 1H, C*H*$_2$).

Table 1.37, **Entry 6**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-(trifluoromethyl)acetophenone tosylhydrazone, **101**, 356 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) -, and (i) -.

Table 1.37, **Entry 7**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-nitroacetophenone tosylhydrazone, **102**, 333 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) -, and (i) -.

Table 1.37, **Entry 8**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-cyanoacetophenone tosylhydrazone, **103**, 313 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) -, and (i) -.

Variations in the reaction conditions for substrates **101** to **103** were attempted without success.

Attempted Shapiro Reaction with Tert-*butylmethyl Tosylhydrazone **114***

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) tosylhydrazone, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, and (i) E:H or E:H:D where applicable. Individual analysis for each compound is given below.

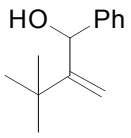
Table 1.38, **Entry 1**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) *tert*-butylmethyl tosylhydrazone **114**, 268 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) only starting **114** recovered, 118 mg, 0.44 mmol, 44 %, and (i) -.

Table 1.38, **Entry 2**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) *tert*-butylmethyl tosylhydrazone **114**, 268 mg, 1 mmol, (d) THF, 5 ml, (e) 65 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) -, and (i) -.

Preparation of 2-(1,1-Dimethylethyl)-1-phenylprop-2-en-1-ol, **117**:

Table 1.38, **Entry 3**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) *tert*-butylmethyl tosylhydrazone **114**, 268 mg, 1 mmol, (d) THF, 5 ml, (e) 65 °C, 3 h, (f) PhCHO, 0.2 ml, 2 mmol, (g) -10 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) **117**, 88 mg, 0.46 mmol, 46 %, and (i) -.

2-(1,1-Dimethylethyl)-1-phenylprop-2-en-1-ol, **117**:



Colourless oil; IR ($CHCl_3$): 1016, 1362, 1454, 3340 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.12 (s, 9H, C(C*H*$_3$)$_3$), 1.76 (d, 1H, *J* = 4.6 Hz, O*H*), 5.19 (s, 1H, C*H*$_2$), 5.24 (s, 1H, C*H*$_2$), 5.43 (d, 1H, *J* = 4.5 Hz, C*H*OH), 7.25-7.31 (m, 1H, Ar*H*, partially obscured by solvent peak), 7.34 (t, 2H, *J* = 7.1 Hz, Ar*H*), 7.41 (d, 2H, *J* = 7.3 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 29.3, 35.1, 72.4, 110.1, 126.4, 126.9, 127.8, 143.2, 160.0; HRMS *m*/*z* (ESI) Calc. for $C_{13}H_{19}O$ $(M+H)^+$: 190.1352. Found: 190.1353.

*Attempted Shapiro Reaction with Phenylethyl Tosylhydrazone **115***

The following experiments were carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) tosylhydrazone, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, and (i) major component isolated.

Table 1.39, **Entry 1**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) phenylethyl tosylhydrazone **115**, 302 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCHO, 0.2 ml, 2 mmol, (g) -10 °C, 1 h, D_2O (0.2 ml), (h) **-**, and (i) **115**, 176 mg, 0.58 mmol, 58 %.

Table 1.39, **Entry 2**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) phenylethyl tosylhydrazone **115**, 302 mg, 1 mmol, (d) THF, 5 ml, (e) 65 °C, 3 h, (f) PhCHO, 0.2 ml, 2 mmol, (g) -10 °C, 1 h, D_2O (0.2 ml), (h) **-**, and (i) **118**, 94 mg, 0.74 mmol, 74 %.

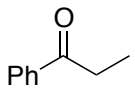
Table 1.39, **Entry 3**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) phenylethyl tosylhydrazone **115**, 302 mg, 1 mmol, (d) THF, 5 ml, (e) 65 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml), (h) **-**, and (i) **118**, 106 mg, 0.79 mmol, 79 %.

Scheme 1.82: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) phenylethyl tosylhydrazone **115**, 302 mg, 1 mmol, (d) THF, 5 ml, (e) 65 °C, 3 h, (f) D_2O, 0.2 ml, 11 mmol, (g) 40 °C, 10 min, (h) **-**, and (i) **118**, 121 mg, 0.90 mmol, 90 %.

Control Reaction with $H_2{}^{18}O$: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) phenylethyl tosylhydrazone **115**, 302 mg, 1 mmol, (d) THF, 5 ml, (e) 65 °C, 3 h, (f) $H_2{}^{18}O$, 0.2 ml, 11 mmol, (g) 40 °C, 10 min, (h) **-**, and (i) **118**, 108 mg, 0.82 mmol, 82 %.

The obtained **118** was analysed for the inclusion of ^{18}O the by mass spectroscopy and ^{13}C-NMR.[161]

Propriophenone, **118**:[162]



Colourless oil; IR ($CHCl_3$): 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.24 (t, 3H, *J* = 7.5 Hz, C*H*$_3$), 3.03 (q, 2H, *J* = 7.5 Hz, C*H*$_2$), 7.39-7.45 (m, 2H, Ar*H*), 7.52-7.58 (m, 1H, Ar*H*), 7.90 (d, 2H, *J* = 8.3 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 9.5, 31.5, 128.2, 128.6, 132.7, 137.1, 200.4.

The data observed are in accordance with literature values.

*Example for an Attempted Shapiro Reaction with 4-*tert*-Butylcyclohexanone Tosylhydrazone **116***

The following experiment was carried out according to *Typical Procedure F*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) tosylhydrazone, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) electrophile, (g) quench conditions, (h) yield of E-alkene, and (i) E:H:D.

Scheme 1.84: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 4-*tert*-butylcyclohexanone tosylhydrazone **116**, 322 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) PhCON(OMe)Me **77**, 0.16 ml, 1.05 mmol, (g) 40 °C, 1 h, D_2O (0.2 ml, 11 mmol), (h) **-**, and (i) **-**.

Variations in the reaction conditions were attempted without success.

5.4.8 Investigations into Kumada-type Cross-coupling Reactions

Scheme 1.86: To a flame-dried Schlenk tube, under argon, containing LiCl (127 mg, 3 mmol) was added a solution of Mes_2Mg (3 ml, 1.5 mmol, 0.51 M). The mixture was stirred at 40 °C for 20 min to dissolve LiCl. In a separate flame-dried 10 ml flask 4-methoxyacetophenone tosylhydrazone **46** (318 mg, 1.00 mmol) was dissolved in THF (5 ml) under gentle heating. The solution of tosylhydrazone was then transferred dropwise into the Schlenk flask at 40 °C and stirred at this temperature for 3 hours. A colour change from pale yellow to dark brown was observed along with evolution of nitrogen gas. The reaction mixture was then cooled to ambient temperature. In a separate flame-dried Schlenk tube, $Fe(acac)_3$ (17.6 mg, 0.05 mmol), 2-chloro-4-methyl-pyridine **121** (0.09 ml, 1 mmol) and NMP (0.56 ml, 6 mmol) were dissolved in THF (5 ml) and cooled to 0 °C in an ice bath before addition of the prepared vinyl magnesium solution *via* syringe. The reaction mixture was stirred for a further 10 min without the ice bath and subsequently quenched with D_2O (0.2 ml, 11 mmol) and 1 M solution of HCl (10 ml). The reaction was extracted with diethyl ether (3 x 15 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude by flash chromatography eluting the silica gel column with a gradient of Et_2O in petroleum ether (0-40 %) returned yielded H-styrene **47** (54 mg, 0.37 mmol, 37 %) and pyridine **121** (121 mg, 0.95 mmol, 95 %) only.

Preparation of 1-(4-Methoxyphenyl)-1-octylethylene, **123**:

General Procedure

To a flame-dried Schlenk tube, under argon, containing LiCl was added a solution of Mes_2Mg. The mixture was stirred at 40 °C for 20 min to dissolve LiCl. In a separate flame-dried 10 ml flask 4-methoxyacetophenone tosylhydrazone **46** was dissolved in THF under gentle heating. The solution of tosylhydrazone was then transferred dropwise into the Schlenk flask at 40 °C and stirred at this temperature for 3 hours. A colour change from pale yellow to dark brown was observed along with evolution of nitrogen gas. The reaction mixture was then cooled to ambient temperature and TMEDA was added. In a separate flame-dried Schlenk tube $FeCl_3$ and bromooctane **122** were taken up in THF (2 ml) and cooled to 0 °C in an ice bath before slow addition of the prepared vinyl magnesium solution *via* cannula over 1 h. The reaction mixture was stirred for a further 30 min at 0 °C and subsequently quenched with D_2O and a saturated aqueous solution of NH_4Cl. The product was extracted with diethyl ether (3 x 15 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The ratio of H-**47** to D-**47** was determined at this stage as by NMR analysis using the proton signals of the terminal alkene functionality of each compound for comparison. The product **123** and homocoupled by-product **124** were isolated by flash chromatography eluting the silica gel column with a gradient of Et_2O in petroleum ether (0-30 %) as colourless oils.

The following experiments were carried out according to the above *General Procedure*. Data are reported as (a) LiCl, (b) Mes_2Mg, (c) 4-methoxyacetophenone tosylhydrazone **46**, (d) solvent to dissolve hydrazone, (e) time and temperature protocol, (f) halide, (g) catalyst, (h) volume of THF for halide and catalyst, (i) TMEDA, (j) quench conditions, (k) yield of **123**, (l) H/D-**47**, and (m) **124**.

Table 1.40, **Entry 1**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 317 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) bromooctane **122**,

0.18 ml, 1 mmol, (g) $FeCl_3$, 16.5 mg, 0.10 mmol, (h) THF, 2ml, (i) 0.14 ml, 0.95 mmol, (j) 0 °C, 90 min, (k) **123**, 62 mg, 0.25 mmol, 25 %, (l) H/D-**47**, 31 mg, 0.23 mmol, 23 %, 62:38, and (m) **124**, 31 mg, 0.11 mmol, 22 %.

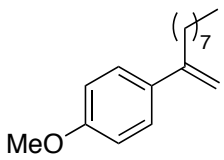
Table 1.40, **Entry 2**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 317 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) bromooctane **122**, 0.18 ml, 1 mmol, (g) $FeCl_3$, 16.5 mg, 0.10 mmol, (h) THF, 2ml, (i) 0.14 ml, 0.95 mmol, (j) rt., 90 min, (k) **123**, 79 mg, 0.32 mmol, 32 %, (l) H/D-**47**, 14 mg, 0.10 mmol, 10 %, 67:33, and (m) **124**, 26 mg, 0.10 mmol, 20 %.

Table 1.41, **Entry 1**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 317 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) bromooctane **122**, 0.18 ml, 1 mmol, (g) -, (h) THF, 2ml, (i) 0.14 ml, 0.95 mmol, (j) rt., 1 h, (k) -, (l) H/D-**47**, 101 mg, 0.75 mmol, 75 %, 13:87, and (m) -.

Table 1.41, **Entry 2**: (a) LiCl, 127 mg, 3 mmol, (b) Mes_2Mg, 3 ml, 1.5 mmol, 0.50 M in THF, (c) 317 mg, 1 mmol, (d) THF, 5 ml, (e) 40 °C, 3 h, (f) bromooctane **122**, 0.18 ml, 1 mmol, (g) -, (h) THF, 2ml, (i) -, (j) rt., 1 h, (k) -, (l) H/D-**47**, 115 mg, 0.85 mmol, 85 %, 10:90, and (m) -.

Data are consistent with that described for compound H/D-**47** on pages 114 and 115.

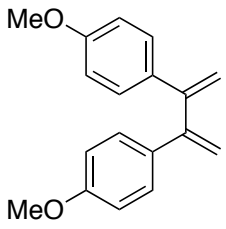
1-(4-Methoxyphenyl)-1-octylethylene, **123**:[163]



Colourless oil; IR ($CHCl_3$): 1245, 1602, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 0.86-0.93 (m, 3H, C*H*$_3$), 1.21-1.39 (m, 10H, aliphatic protons), 1.41-1.49 (m, 2H, C*H*$_3$), 2.47 (t, 2H, *J* = 7 Hz, CC*H*$_2$), 3.82 (s, 3H, OC*H*$_3$), 4.97 (s, 1H, C=C*H*$_2$), 5.20 (s, 1H, C=C*H*$_2$), 6.87 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.36 (d, 2H, *J* = 8.8 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 14.1, 22.8, 28.3, 29.4, 29.7.1, 29.8, 31.9, 35.5, 55.2, 110.3, 113.7, 127.3, 133.8, 148.0, 158.9.

The data observed are in accordance with literature values.

4,4'-(Buta-1,3-diene-2,3-diyl)bis(methoxybenzene), **124**:



Colourless crystals, M.p.: 109-110 °C IR ($CHCl_3$): 1175, 1605, 2931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.78 (s, 6H, OCH_3), 5.25 (d, 2H, $^2J_{H-H}$ = 1.7 Hz, $C=CH_2$), 5.49 (s, 2H, $^2J_{H-H}$ = 1.8 Hz, $C=CH_2$), 6.80 (d, 4H, *J* = 8.9 Hz, Ar*H*), 7.33 (d, 4H, *J* = 8.9 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 55.2, 113.6, 114.3, 128.5, 132.7, 149.4, 159.1; HRMS *m*/*z* (ESI) Calc. for $C_{18}H_{19}O_2$ $(M+H)^+$: 267.1380. Found: 267.1377.

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7. Appendix

X-ray Crystallography Data

(Z)-3-Mesityl-2-(4-methoxyphenyl)-1-phenylprop-1-en-1-yl benzoate, **76**:

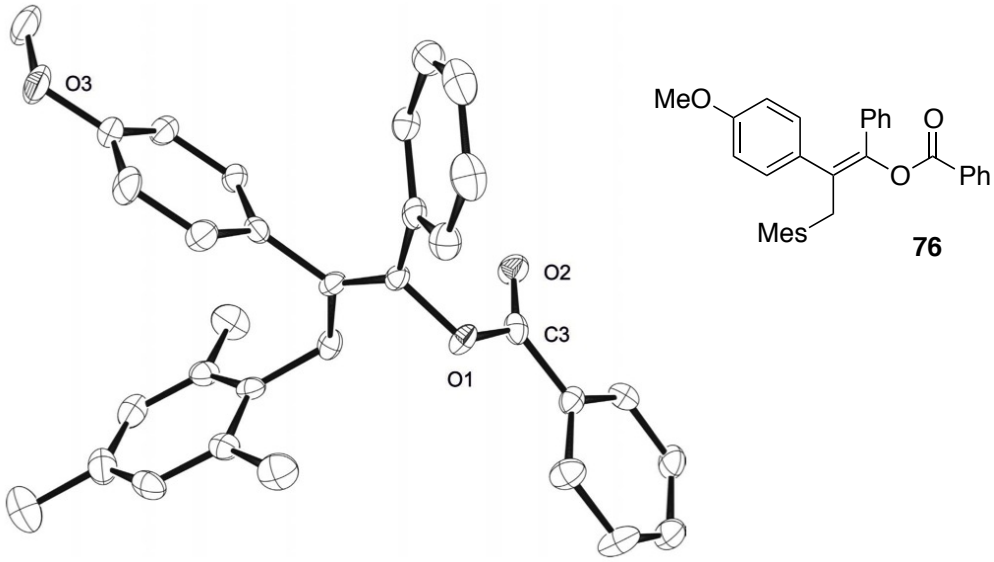


Figure 1.13

Identification code	kerr_tinawibobtr2	
Empirical formula	C32 H30 O3	
Formula weight	462.56	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.9753(4) Å	α = 97.751(5)°.
	b = 12.6243(8) Å	β = 95.047(4)°.
	c = 22.6824(11) Å	γ = 91.032(5)°.

Volume	2535.6(2) $Å^3$
Z	4
Density (calculated)	1.212 Mg/m^3
Absorption coefficient	0.076 mm^{-1}
F(000)	984
Crystal size	0.4 x 0.06 x 0.03 mm^3
Theta range for data collection	2.90 to 26.00°.
Index ranges	-11<=h<=11, -15<=k<=15, -27<=l<=27
Reflections collected	15303
Independent reflections	15303 [R(int) = 0.0000]
Completeness to theta = 26.00°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.85940
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	15303 / 0 / 640
Goodness-of-fit on F^2	0.964
Final R indices [I>2sigma(I)]	R1 = 0.0732, wR2 = 0.1259
R indices (all data)	R1 = 0.1653, wR2 = 0.1529
Largest diff. peak and hole	0.292 and -0.302 $e.Å^{-3}$

3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazol-1-ium 4-methylbenzenesulfonate, **78**:

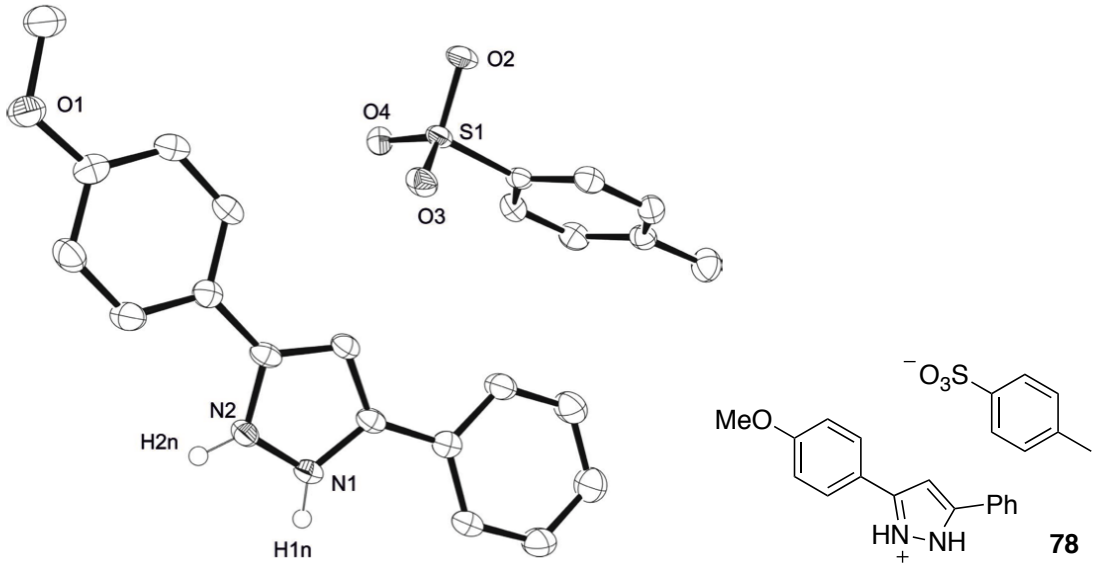


Figure 1.14

Identification code	kerr_tinaw	
Empirical formula	C24 H24 Cl2 N2 O4 S	
Formula weight	507.41	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 10.0946(5) Å	α = 90°.
	b = 17.5868(15) Å	β = 96.493(5)°.
	c = 13.3362(9) Å	γ = 90°.
Volume	2352.4(3) $Å^3$	
Z	4	
Density (calculated)	1.433 Mg/m^3	
Absorption coefficient	0.399 mm^{-1}	

F(000)	1056
Crystal size	0.25 x 0.05 x 0.02 mm^3
Theta range for data collection	2.92 to 27.50°.
Index ranges	-10<=h<=13, -17<=k<=22, -17<=l<=17
Reflections collected	11148
Independent reflections	5189 [R(int) = 0.0397]
Completeness to theta = 26.00°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.99489
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5189 / 0 / 312
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0638, wR2 = 0.1276
R indices (all data)	R1 = 0.1157, wR2 = 0.1533
Largest diff. peak and hole	0.904 and -0.594 e.$Å^{-3}$

Chapter 2

Utilising Bismesitylmagnesium as a Base Reagent in Wittig Reactions

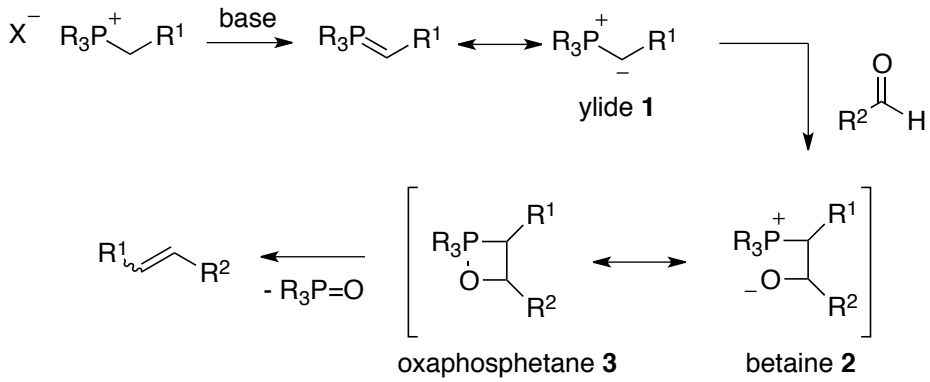
Contents

1. Introduction

From the first application of carbon-centred species R_2Mg as base reagents for the efficient generation of silyl enol ethers from enolisable kektones,[1–3] an exploration of their potential with regards to substrate classes and reactions has been of interest within our laboratory. This previously unobserved reactivity and the generally mild reaction conditions, with respect to silyl enol ether formation, have inspired a number of different research projects, including the development of a modified Shapiro reaction, *cf.* **Chapter 1**,[4] as well as investigations into the deprotonation of esters to form silyl ketene acetals.[5] In an effort to extend the spectrum of applications further, utilising Mes_2Mg as a base reagent in the Wittig reaction was considered.

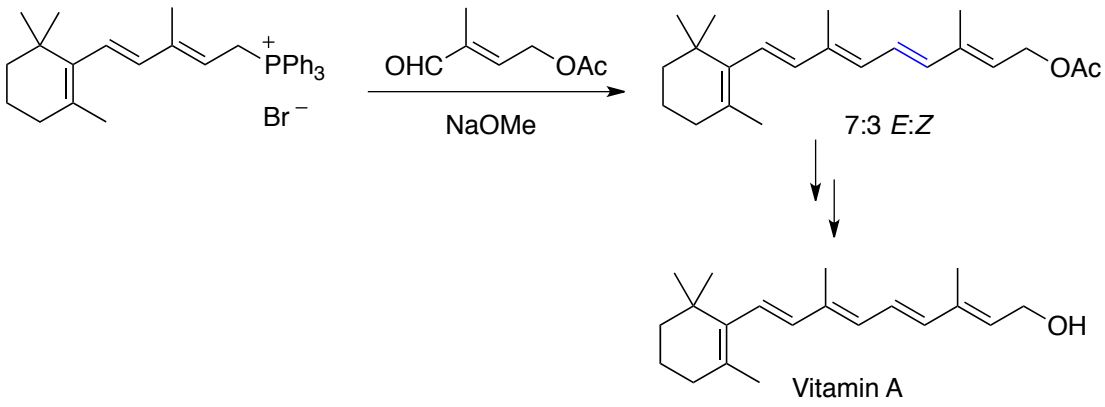
1.1 Wittig Reaction

Within the different olefination techniques in modern organic synthesis, the Wittig reaction has a central role, allowing for the efficient and stereocontrolled generation of multi-substituted alkenes from phosphonium salts and carbonyl compounds *via* a phosphonium ylide, **1** (**Scheme 2.1**). Two intermediate species, zwitter-ionic betaine **2** and oxaphosphetane **3**, are proposed within the reaction mechanism.



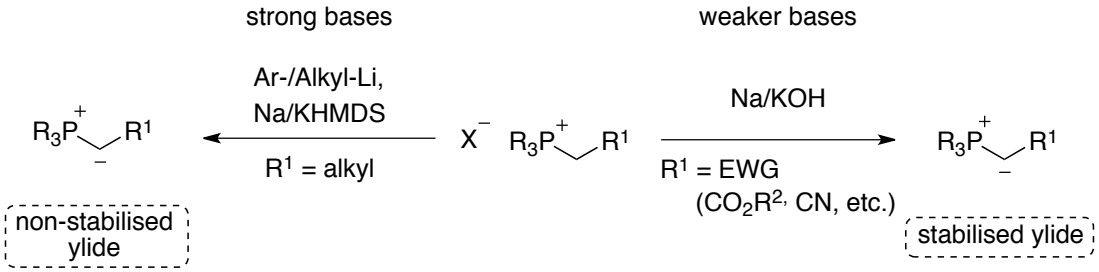
Scheme 2.1

First discovered in 1953,[6–8] the Wittig reaction was enthusiastically acknowledged by the scientific community and, in just over a decade, significant advancements had been made with regard to scope and mechanistic studies, along with two major modifications, later known as the Horner-Wadsworth-Emmons (HWE)[9] and Horner-Wittig (HW)[10] reaction.[11] Illustrating its impact even more, the close collaboration between Universities and industry lead to the large scale application of the Wittig reaction in the manufacturing of Vitamin A and derivatives by BASF only a few years after the first documentation of this olefination method (**Scheme 2.2**).[12–14] The process illustrates complete chemoselectivity for the more reactive aldehyde; the acetate remains intact. In this regard, ketones can also react in the Wittig reaction, although more forcing conditions are required, especially with sterically hindered substrates.[15]



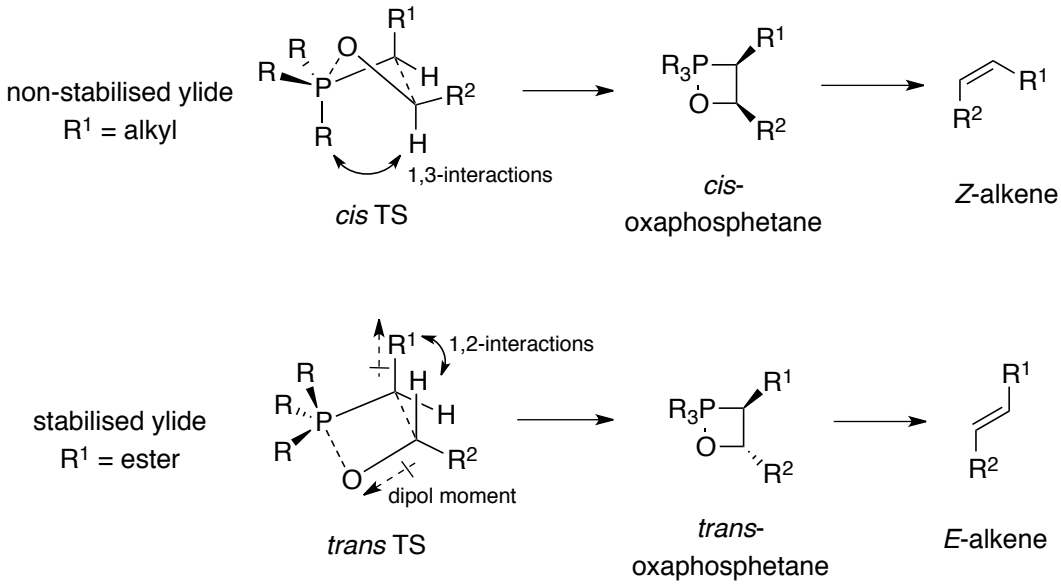
Scheme 2.2

The corresponding phosphonium salt is typically formed from the parent alkyl halide and triphenyl phosphine.[15] Depending on the nature of the phosphonium salt, the base reagent for the ylide formation is selected (**Scheme 2.3**).



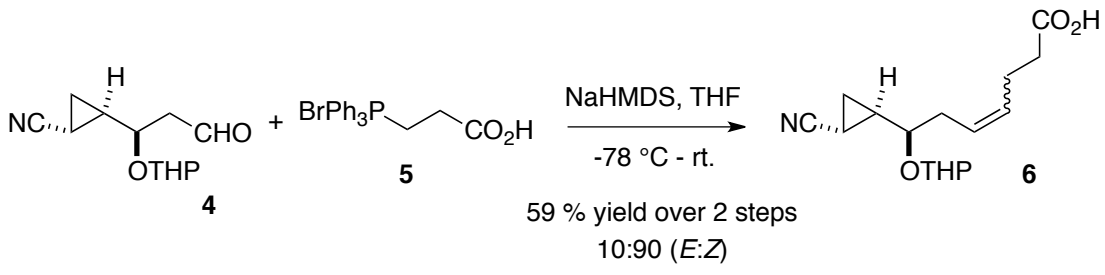
Scheme 2.3

Stronger bases are necessary for phopsphonium salts with electron-donating or neutral substituents, yielding reactive non-stabilised ylides that tend to give high *Z*-selectivities of the alkene product. Electron-withdrawing substituents provide a more acidic proton at the α-carbon and weaker bases are sufficient. Having stated this, they also lower the nucleophilicity of the carbanion and thus deliver less reactive stabilised ylides with a tendency for the formation of *E*-alkenes.[16] The reasoning for the high impact of the ylide nature on the selectivity and the involved intermediates in the mechanism of the reaction has been of much debate, especially the existence of an ionic betaine species **2**, as depicted in **Scheme 2.1**.[8,17,18] At first the betaine was allocated a higher influence, however, more recently ^{31}P-NMR studies and DFT calculations support a model introduced by Vedejs,[11,18–20] which emphasises the role of the oxaphosphetane, a formal [2+2] cycloaddition as the first step, and a stereospecific cycloreversion in the oxaphosphetane decomposition (**Scheme 2.4**).[21,22]



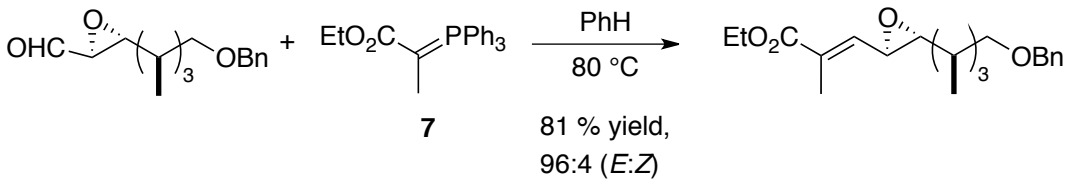
Scheme 2.4

Steric interactions of the substituents in both ylide and carbonyl are decisive factors for the preferential transition states (TS). An early, still flexible, TS is proposed for non-stabilised ylides under kinetic control. To minimise 1,3-interactions between R and R^2, the *cis*-arrangement pictured in **Scheme 2.4** is favoured, leading to a puckered TS, which avoids 1,2-interactions between R^1 and R^2, and therefore gives the *Z*-alkene preferentially. A synthetic example is depicted in **Scheme 2.5**, where a non-stabilised ylide is formed from **5** and reacted with aldehyde **4** under kinetic conditions to yield the disubstituted alkene **6** as the *Z*-isomer preferentially.[23]



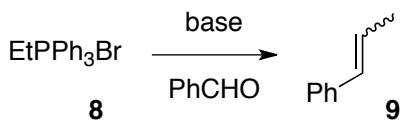
Scheme 2.5

Stabilised ylides on the other hand are thought to have a more rigid and planar TS, with only slight puckering to accommodate the dipolar interactions between carbonyl and electron-withdrawing R[1].[21,22] As these ylides react more slowly, the typically thermodynamic conditions employed allow for equilibration to the preferred *trans*-TS with minimal 1,2-interactions, yielding the *E*-isomer as the major product (*cf.* **Scheme 2.4**). Additionally, due to the extra stabilisation of the carbanion *via* delocalisation, some ylides can be isolated and used directly without base, such as phosphorane **7** in the synthesis of (-)-doliculide (**Scheme 2.6**).[24]



Scheme 2.6

It has been shown, that unless stabilised by a strongly coordinating counterion, such as lithium, the betaine intermediate is not likely to influence the stereoselectivity or even exist.[25,26] Interestingly, the presence of lithium salts, generated by employing lithium bases, goes in hand with a significant drop in selectivity with non-stabilised ylides (**Scheme 2.7**).[17,27] An important modification by Schlosser utilises this observation, specifically employing an excess of lithium base.

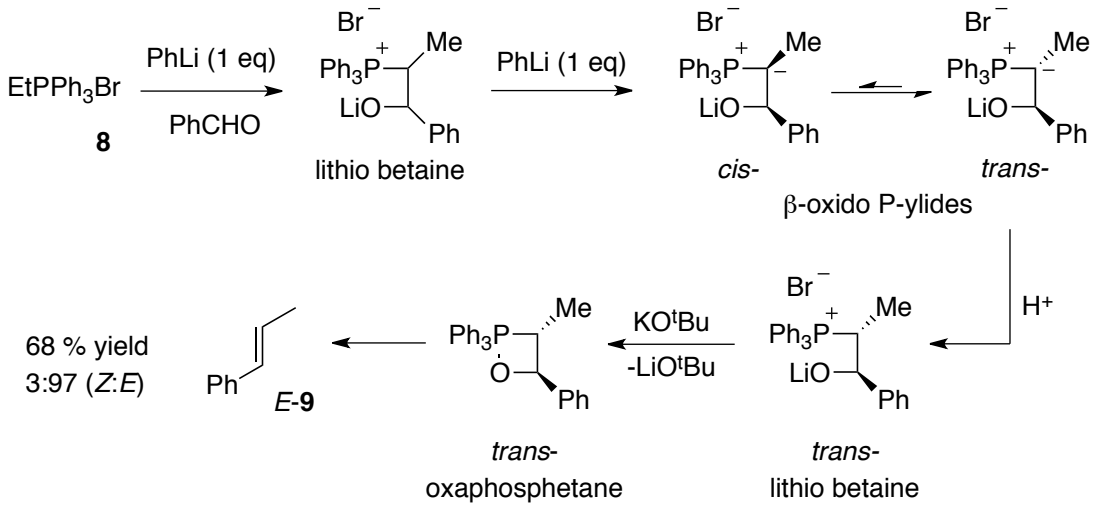


	base	yield	*cis*:*trans*
"classic"	$NaNH_2$ (1 eq)	98 %	87:13
LiBr	BuLi (1 eq)	68 %	61:39
Schlosser	PhLi (2 eq)	68 %	3:97

Scheme 2.7

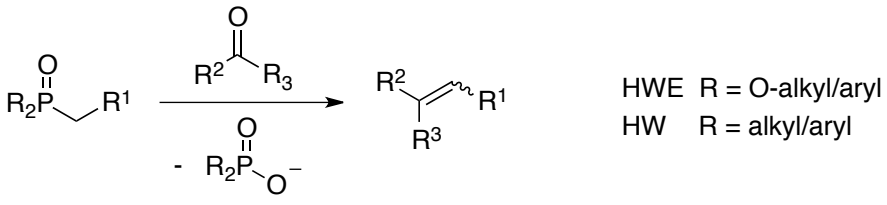
More specifically, addition of one further equivalent of strong base after lithiobetaine formation facilitates the equilibration of the formed β-oxido phosphorus ylide to the less hindered *trans*-isomer and delivers high *E*-selectivities for non-

stabilised ylides, as opposed to the "classic", lithium salt-free conditions (**Scheme 2.8**).[27]



Scheme 2.8

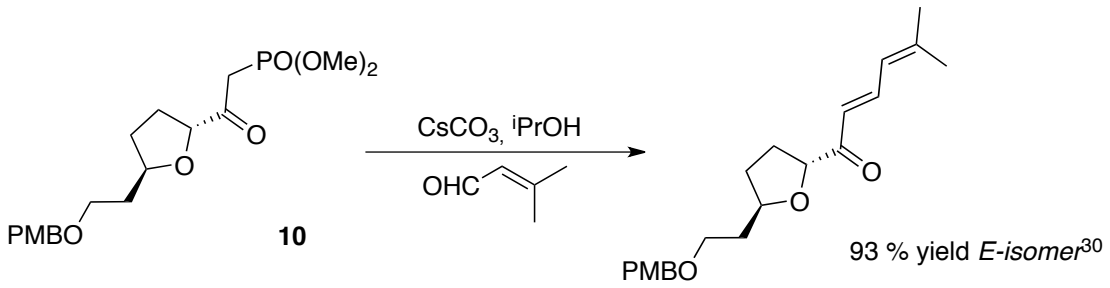
With carefully selected reaction conditions, a range of olefins can be synthesised stereoselectively from phosphonium ylides in high yields, providing an indispensable tool for organic synthesis. Important additions to this methodology are the utilisation of phosphine oxide and phosphonate stabilised anions instead of phosphonium ylides.[11,28] As well as broadening the scope for selective olefin formation, the purification of the reaction mixtures has been significantly simplified, due to the water-soluble phosphorus by-products (**Scheme 2.9**).



Scheme 2.9

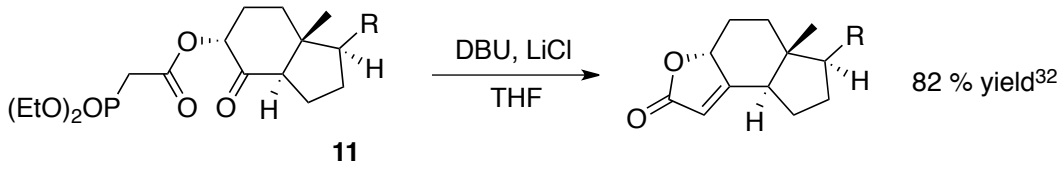
Access to the required alkyl or aryl phosphonates and phosphine oxides is more economic and convenient than for phosphonium salts, and is gained *via* a number of

ways, including the Arbuzov reaction.[15] In both cases, best results are obtained with an electron-withdrawing group as R^1, giving rise to high *E*-selectivity for example α,β-unsaturated esters. Indeed, other substrates, such as ketophosphonate **10**, react equally readily (**Scheme 2.10**).[29,30] The stereoselectivity is mainly based on the steric demand of R and R^1.



Scheme 2.10

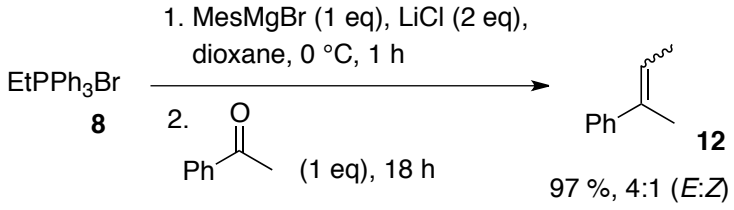
Notably, the carbanions of the discussed species tend to be more reactive than phosphonium ylides and permit milder reaction conditions as well as enabling the conversion of hindered ketones that are either sluggish or do not react at all with Wittig reagents (**Scheme 2.11**).[31,32] A modification by Still and Gennari, employing 2,2-trifluoroethyl phosphonates, has been developed to generate substituted alkenes in high *Z*-selectivity.[33] Additionally, application of diaryl phosphonates, as documented by Ando, deliver α,β-unsaturated esters in high *Z*-selectivities.[15,34–36]



Scheme 2.11

As discussed, the efficiency and selectivity of the Wittig olefination reaction and its variations are dependent on a number of factors, including type of ylide, steric demand of the substrates and, in particular, the base reagent and the counterion it provides for the ylide. Based on the above, the application of the carbon-centred base,

Mes_2Mg, had been considered as a suitable reagent and tested in the deprotonation of phosphonium salt **8** and subsequent reaction of the formed ylide with acetophenone (**Scheme 2.12**).[2] The *in situ* generated base reagent not only seemed to be remarkably efficient, yielding 97 % of the anticipated alkene **12**, but gave also rise to a 4:1 selectivity in favour of the *E*-isomer. In comparison, under the "classic" lithium salt-free conditions the opposite is expected with non-stabilised ylides. In this regard, employing KHMDS instead, 68 % yield of **12** is obtained in an 1:24 (*E*:*Z*)-ratio.[37]



Scheme 2.12

Publications on the use of magnesium salts or Grignard reagents and their effects within Wittig-type transformations are scarce and limited to Horner-Wadsworth-Emmons reactions.[38,39] In such examples, complexation and chelation of the phosphonate anion (**Figure 1**) is key to reactivity and selectivity in the described reactions.

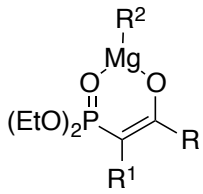
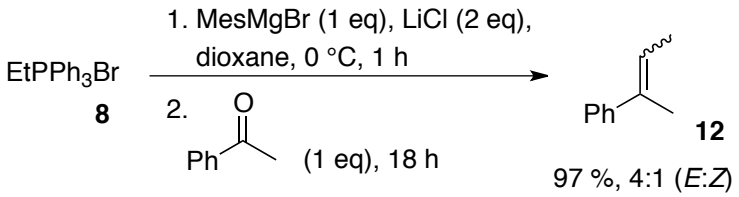


Figure 2.1

With the initial success as described in **Scheme 2.12**, the application of carbon-centred magnesium bases within the olefination arena has been initiated. It is envisaged that milder, more effective reaction conditions could be established, improving on commonly used base reagents in this domain.

2. Proposed Work

In view of the excellent results obtained with Mes_2Mg as a base reagent in the generation of silyl enol ethers from enolisable ketones[1,2] as well as in the formation of 1,1-disubstituted alkenes from aryl hydrazones,[4] further examination of the applicability of the magnesium base reagent is desired. In the transformations described, the employment of carbon-centred magnesium bases has brought significant advancements over the corresponding lithium-mediated processes, especially in terms of efficiency and from an economic viewpoint. The magnesium reagents allow for the reactions to be run at much more convenient temperatures, between 0 °C and 40 °C, without the occurrence of noteworthy quantities of side reactions. While the exploration of the substrate scope for deprotonation of enolisable esters has been inefficient and was met with competitive aldol reaction,[5] utilisation of Mes_2Mg as a base reagent in the Wittig reaction has led to a very interesting and encouraging outcome. More specifically, the first attempt using ethyltriphenylphosphonium bromide and acetophenone delivered the desired alkene in 97 % yield and an *E*:*Z* selectivity of 4:1 when the reaction was run at 0 °C (**Scheme 2.13**).[2]



Scheme 2.13

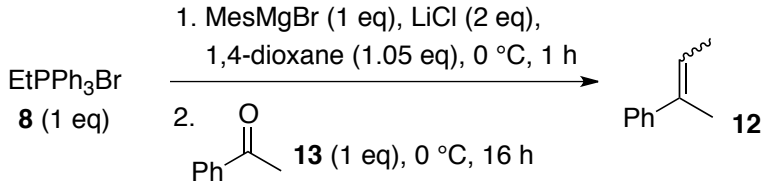
The documented proof of concept in the application of carbon-centred species Mes_2Mg in the Wittig reaction has sparked the interest in more detailed studies in this area. Especially, the previously unobserved high *E*-selectivity of this transformation in conjunction with non-stabilised ylides would complement the more commonly used

reaction conditions, which typically favour the *Z*-isomer. It was thus proposed to reassess and optimise the transformation with regards to reaction conditions and substrate quantities. Moreover, investigations into the generality of the process, with focus on a range of phosphoranes and carbonyl substrates were planned. In due course and with careful analysis of the obtained results, a rationalisation for the detected (*E*)-selectivity would potentially be gained.

3. Results and Discussion

3.1 Revision and Optimisation of Reaction Conditions

At the outset, a repeat of the initial reaction conditions[2] was intended to confirm both the technique and results. In this regard, a $Mes_2Mg.2LiCl$ solution in THF was prepared *in situ* from the parent Grignard reagent, 1,4-dioxane, and anhydrous LiCl. This mixture was subsequently added to a suspension of phosphonium salt **8** in THF to form the requisite ylide (**Scheme 2.14**, **Table 2.1**). A typical colour change from white to bright orange, indicating the generation of ylide, occurred and acetophenone was added slowly. Unexpectedly, a poor conversion of 35 % was observed, yielding the alkene in only 26 %. It has to be noted that the desired alkene co-elutes with the mesitylene formed from the base reagent and the stated yields are based on NMR analysis. Importantly, the reported *E*:*Z* selectivity was approximately comparable to the initial attempt with a ratio of 3.6:1 (*E*:*Z*) being observed (**Table 2.1**, **Entry 1**). Restandardisation of MesMgBr and repurification of all reagents was conducted to eliminate the interference of an impurity, however no significant improvement in conversion or yield could was obtained.



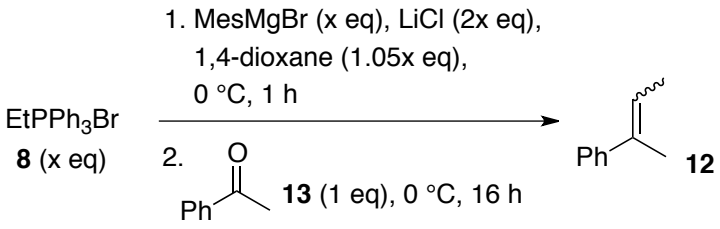
Scheme 2.14

Entry	*Conv.* (%)[a]	*Yield* ***12*** (%)[a]	*E*:*Z*[a]
1	35	26	3.6:1
2	32	23	3.4:1

[a]Determined by NMR analysis

Table 2.1

At this stage, in an attempt to increase the conversion, a brief survey of the ylide equivalents employed was completed (**Scheme 2.15**, **Table 2.2**). Even with a rise in both the number of equivalents of base reagent and phosphonium salt compared to acetophenone, the yields remained at the same level. Interestingly, the orange colour of the ylide disappeared within an hour of the ketone addition, however, reappeared slowly over the following 15 h. This seems to indicate that the ylide formation was not completed after 1 h prior to addition of acetophenone, but a gradual formation over time was occurring.



Scheme 2.15

Entry	*EtPPh₃Br*	*MesMgBr*	*Conv.* (%)[a]	*Yield* ***12*** (%)[a]	*E*:*Z*[a]
1	1.5	1.5	39	28	4.0:1
2	2	2	36	20	4.2:1

[a]Determined by NMR analysis

Table 2.2

Additionally, the β-hydroxyketone **14** was identified as a by-product (**Figure 2.2**), suggesting that excess Mes_2Mg had led to an aldol reaction *via* deprotonation of the ketone **13**.

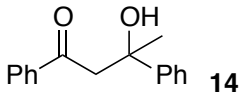
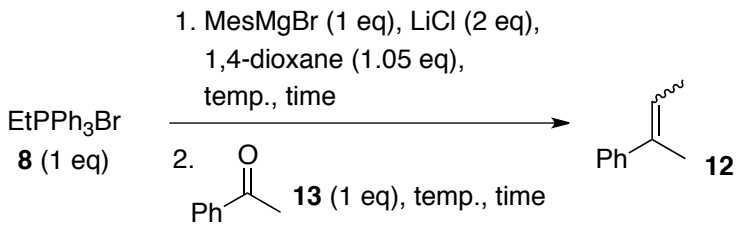


Figure 2.2

Although the previous results imply the deprotonation of **8** is slow, it was still uncertain at which stage the reaction failed to reach the previously described reactivity. As such, a short study concerning the ylide and alkene formation was conducted, investigating reaction time and temperatures (**Scheme 2.16**, **Table 2.3**). To evaluate the deprotonation of the phosphonium salt further, the reaction time for the ylide generation was increased to 3 and 16 h (**Table 2.3**, **Entries 1** and **2**, respectively). A slight increase in conversion and yield was observed when the reaction time was significantly extended, delivering the alkene in an improved 37 % yield (**Table 2.3**, **Entry 2**). However, this was still unacceptably low in comparison to the originally documented result. Additionally, with an increase in reaction time, the selectivity of the process dropped to 2.4:0 (*E*:*Z*).



Scheme 2.16

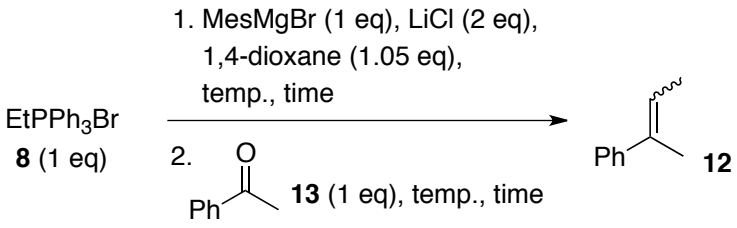
Entry	*Conditions Step 1*	*Conditions Step 2*	*Conv.* (%)[a]	*Yield **12*** (%)[a]	*E*:*Z*[a]
1	0 °C, 3 h	0 °C, 16 h	32	26	4.0:1
2	0 °C, 16 h	0 °C, 16 h	43	37	2.4:1

[a]Determined by NMR analysis

Table 2.3

Indeed, Wittig reactions with ketone substrates can be slow and higher reaction temperatures have been shown to be beneficial.[15] In this regard, the best yield

obtained in this study was achieved when both ylide and alkene formation were run at ambient temperature, albeit with a lowered selectivity of 2.5:1 (*E*:*Z*) (**Scheme 2.17**, **Table 2.4**, **Entry 1**). This appeared to support the idea that alkene formation had a decisive role in the generally low conversion, and further investigation was needed. Despite the improved conversion detected when running the reaction at 40 °C, only 26 % of the desired alkene was isolated and more aldol by-product was again detected, rendering temperatures above ambient unproductive (**Table 2.4**, **Entry 2**).



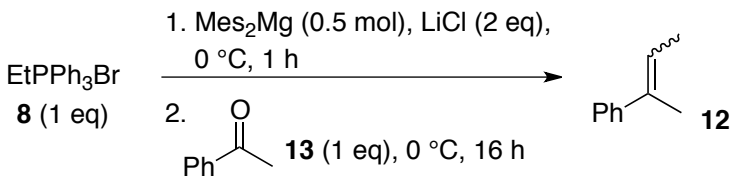
Scheme 2.17

Entry	*Conditions Step 1*	*Conditions Step 2*	*Conv.* (%)[a]	*Yield **12*** (%)[a]	*E*:*Z*[a]
1	rt., 1 h	rt., 16 h	46	43	2.5:1
2	40 °C, 1 h	40 °C, 16 h	52	26	3.0:1

[a]Determined by NMR analysis

Table 2.4

Simultaneously to the above studies, the employment of preformed Mes_2Mg was reconsidered, as isolation and separate standardisation of the solution was thought to be advantageous. Repetition of the documented reaction conditions was performed (**Scheme 2.18**, **Table 2.5**).



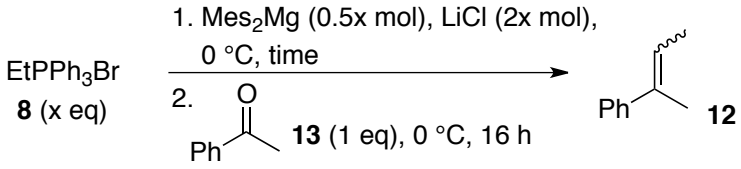
Scheme 2.18

Entry	*Conv.* (%)[a]	*Yield* ***12*** (%)[a]	*E*:*Z* [a]
1	40	30	3.7:1
2	46	35	3.3:1

[a]Determined by NMR analysis

Table 2.5

In comparison to the *in situ* generated Mes_2Mg an increase in yield by approximately 10 % was achieved with similar selectivities of up to 3.7:1 (*E*:*Z*) being observed. With this slight improvement, it was decided to use the preformed carbon-centred base reagent in further optimisation studies and a short revision of the previous trials was performed (**Scheme 2.19**, **Table 2.5**).



Scheme 2.19

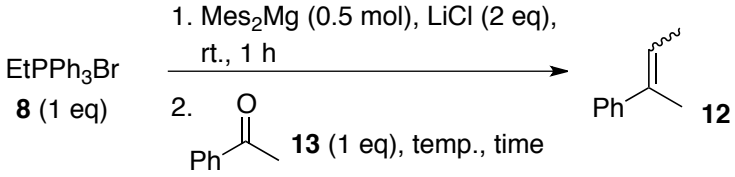
Entry	*Mes₂Mg (mmol)*	*EtPPh₃Br (mmol)*	*Conditions Step 1*	*Conv.* (%)[a]	*Yield* ***12*** (%)[a]	*E*:*Z* [a]
1	0.75	1.5	0 °C, 1 h	77	50	3.2:1
2	1	2	0 °C, 1 h	76	57	3.1:1
3	0.5	1	0 °C, 3 h	68	51	2.6:1

[a]Determined by NMR analysis

Table 2.6

An increase in phosphonium salt and Mes_2Mg led to improved yields, delivering the desired alkene in up to 57 % (**Table 2.6**, **Entries 2**). Similar to the *in situ* prepared Mes_2Mg, an excess of the reagents led to a reappearance of the orange colour over 16 h, indicating the continuous generation of ylide species. Again, stoichiometric use of the preformed reagent in conjunction with an extended time for the ylide formation yielded the alkene in 51 % and 2.6:1 (*E*:*Z*) selectivity, thus giving rise to the assumption that the first step in the Wittig reaction was not reaching completion (**Table 2.6**, **Entry 3**).

In an effort to enhance the efficiency of the overall transformation without the use of excess of Mes_2Mg or phosphonium salt and to elucidate the cause of the low yield, an investigation of the temperature protocol was executed (**Scheme 2.20**, **Table 2.7**). More specifically, the initial ylide formation in step 1 of this study was commenced at ambient temperature, which had previously proved beneficial with respect to the yield of **12** (*cf.* **Scheme 2.17**, **Table 2.4**, **Entry 1**). When conducting the second step of the reaction at 0 °C and ambient temperature, improved yields up to 57 % were achieved (**Table 2.7**, **Entries 1** and **2**). Further increase of the temperature to 40 °C resulted in a decrease in the isolated yield of **12** (**Table 2.7**, **Entry 3**). Lamentably, in all three attempts, the *E*/*Z*-selectivity was diminished to 2.2:1 (*E*:*Z*) and below.



Scheme 2.20

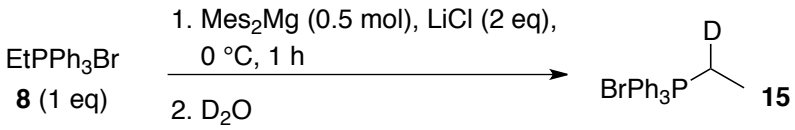
Entry	*Conditions Step 2*	*Conv.* (%)[a]	*Yield **12*** (%)[a]	*E*:*Z*[a]
1	0 °C, 16 h	73	57	1.8:1
2	rt., 16 h	78	57	2.0:1
3	40 °C, 16 h	75	44	2.2:1

[a]Determined by NMR analysis

Table 2.7

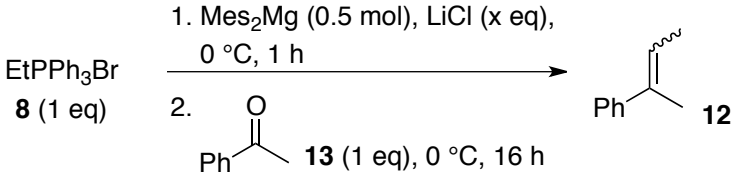
Despite the above attempts, the chemical yield of the desired alkene **12** did not exceed 57 %. At this stage it was questioned whether an alternative method of assigning the effectiveness of the ylide formation could be used. In this regard, an experiment was conducted quenching the reaction with D_2O after 1 h instead of adding the ketone **13**, anticipating the deuterated phosphonium salt **15** as the product (**Scheme 2.21**). Unfortunately, only 34 % of the phosphonium salt **8** was isolated and

no substantial evidence for deuterium inclusion could be found. As the results from this strategy remained inconclusive, it was not further pursued at this point.



Scheme 2.21

In the Wittig reaction, the base reagents employed and the ensuing ions or salts present in the reaction mixture have a marked influence on the reaction, especially regarding the selectivity. With respect to the reactivity of carbon-centred magnesium bases, salt additives have proven equally essential. It was thus decided to explore the dependency of the discussed transformation with Mes_2Mg on LiCl as an additive (**Scheme 2.22**, **Table 2.8**). As anticipated, and as observed with other transformations using Mes_2Mg, omitting LiCl from the reaction was met with a drastic drop in conversion and yield (**Table 2.8**, **Entry 1**). On the other hand, using one equivalent of the additive delivered comparable results to reactions run with the standard two equivalents (*cf.* **Table 2.4, Entry 2**).



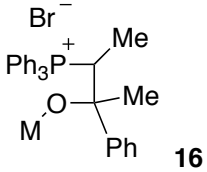
Scheme 2.22

Entry	*LiCl*	*Conv.* (%)[a]	*Yield* ***12*** (%)[a]	*E*:*Z*[a]
1	-	11	9	10:1
2	1 eq	53	38	3.5:1

[a]Determined by NMR analysis

Table 2.8

Surprisingly, reactions with no LiCl showed a much increased selectivity in favour of the *E*-isomer, reaching up to 11:1 (*E*:*Z*). With more commonly used base reagents, such as NaHMDS, non-stabilised ylides yield predominantly the *Z* isomer. The selectivity degrades significantly if lithium bases are used, due to the stabilisation and equilibration of betaine intermediates.[17] Upon consideration of the effect of lithium counterions in "classic" Wittig reactions, a similar influence might be the cause for the observations using Mes_2Mg. Thus, it could be envisaged that the phosphorous-oxygen bond is broken in the formed oxaphosphetane, giving rise to a metal-complexed betaine (**16**) and hence higher *E*-selectivity (**Figure 2.3**).



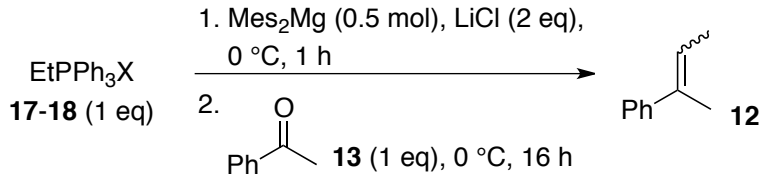
16

Figure 2.3

Additionally, excess base may, as described in the Schlosser modification, lead to a second deprotonation of the stabilised betaine and allow for the equilibration to the less sterically hindered *trans*-arrangement. This could be the case in the presence or absence of LiCl in the magnesium-mediated Wittig reaction, and a fine but complex balance of factors influencing the selectivity is suspected.

With this in mind, a further examination concerning the halide anion of the phosphonium salt was conducted. An analysis by Schlosser documents no significant dependence of the yield of the reaction on varying halide salts when lithium bases are used in conjunction with non-stabilised ylides.[17] However, the selectivity steadily decreases from chloride over bromide to iodide. In view of the impact salt additives or the choice of phosphonium salt can have on the overall outcome of the Wittig reaction, a short study was commenced using the phosphonium halides **17** and **18** (**Scheme 2.23**, **Table 2.9**). The corresponding chloride salt remained unproductive and no conversion to the desired alkene was observed (**Table 2.9**, **Entry 1**), whereas the iodide salt (**Table 2.9**, **Entry 2**) gave rise to a similar yield and selectivity as the

originally used bromide. As no drop in yield was expected with any of the reagents tested, the outcome of **Entry 1** may be an indication of the poorer quality of the respective starting phosphonium salt.



Scheme 2.23

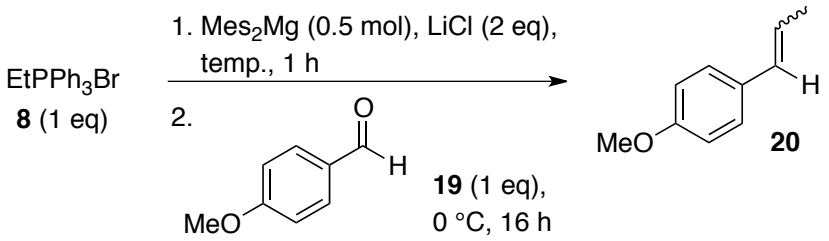
Entry	*EtPPh$_3$X*	*Conv.* (%)[a]	*Yield **12*** (%)[a]	*E:Z* [a]
1	Cl (**17**)	0	-	-
2	1 (**18**)	36	26	4.1:1

[a]Determined by NMR analysis

Table 2.9

As is clear to this stage, the original conditions, as well as the reviewed parameters of the reaction, did not lead to a reproduction of the previously reported result.[2] As mentioned earlier, it has been observed that the Wittig olefination can be difficult with ketone substrates. In this respect, it was envisaged that reacting the formed ylide with a less hindered and more reactive aldehyde substrate instead, should lead to better yields of the corresponding alkene. Aldehyde **19** was thus selected as a suitable candidate and a brief survey was initiated (**Scheme 2.24**, **Table 2.10**). The standard conditions at 0 °C delivered the disubstituted alkene **20** in 41 % yield (**Table 2.10**, **Entry 1**). This is only marginally higher than the yield obtained with acetophenone (*cf.* **Table 2.4**, **Entry 2**) and advocates the suggestion that the ylide formation from **8** is incomplete. Moreover, the selectivity for the *E*-isomer of the alkene dropped to 1.7:1 (*E*:*Z*). Investigations at a higher temperature of 40 °C delivered an encouragingly high conversion of 86 % (**Table 2.4**, **Entry 3**). Disappointingly, alkene **20** was isolated in only 46 % yield, rendering these, and any of the previous attempts to improve the reactivity of the base reagent towards the deprotonation of phosphonium salt **8**, unproductive. It is important to note, that the

increase in conversion is, in part, associated with competitive nucleophilic attack of the aldehyde by excess Mes_2Mg.



Scheme 2.24

Entry	*Conditions Step 1*	*Conv.* (%)[a]	*Yield **20*** (%)[a]	*E*:*Z* [a]
1	0 °C, 1 h	57	41	1.7:1
2	rt., 1 h	64	43	2.0:1
3	40 °C, 1 h	86	46	2.0:1

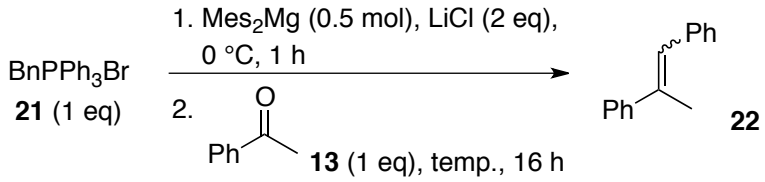
[a]Determined by NMR analysis

Table 2.10

3.2 Employing Semi-stabilised and Stabilised Ylides

Undaunted by these disappointing results, it remained to investigate the generation of more stabilised ylides, which generally involve weaker bases for their formation. Such ylides typically require more forcing reaction conditions, as the corresponding ylides are less reactive, and give high *E*-selectivities.[15] As a readily available phosphonium salt with a mildly electron-withdrawing substituent, that would give rise to a semi-stabilised ylide upon deprotonation, benzyltriphenyl-phosphonium bromide **21** was selected (**Scheme 2.25**, **Table 2.11**). Reacting the obtained ylide with acetophenone resulted in unexpectedly low yields and *E*:*Z*

selectivities, even when the reaction temperature was raised to ambient for the alkene formation (**Table 2.11**, **Entries 1** and **2**).



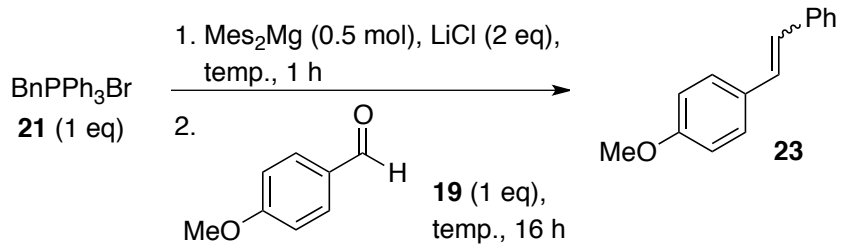
Scheme 2.25

Entry	*Conditions Step2*	*Yield **22*** (%)[a]	*E*:*Z* [a]
1	0 °C, 16 h	13	1.1:1
2	rt., 16 h	14	1:1

[a]Determined by NMR analysis

Table 2.11

Once more, the suitability of ketone substrates was questioned, as the deprotonation of phosphonium salt **21** was not expected to be problematic. To verify this, aldehyde **19** was subjected to the same reaction conditions (**Scheme 2.26**, **Table 2.12**). Satisfyingly, with the more reactive aldehyde substrate and at the low temperature of 0 °C for both stages of the transformation, 86 % yield of the desired alkene **23** was isolated (**Table 2.12**, **Entry 1**), verifying the almost quantitative deprotonation of the phosphonium salt and the efficiency of the carbon-centred base. Moreover, the yield could be increase to 93 % when running the reaction, more conveniently, at ambient temperature (**Table 2.12**, **Entry 2**). Notably, the observed *E*-selectivity of 3.3:1 (*E*:*Z*) compares favourably to reactions with the same substrate and phosphonium salt run at 0 °C with NaHMDS or LiHMDS as base reagents, as they deliver lower selectivities of 1.6:1 (*E*:*Z*) and 1:1.6 (*E*:*Z*), respectively.[40] As such, the emerging Mes_2Mg protocol for the Wittig reaction of semi-stabilised ylides and aldehyde substrates may prove to be a mild and more selective process for the preparation of disubstituted *E*-alkenes.



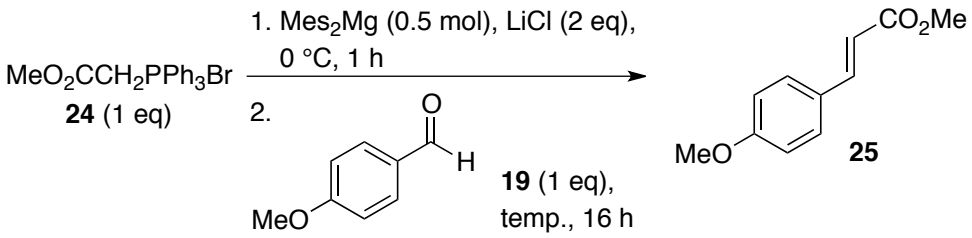
Scheme 2.26

Entry	*Conditions Step 1*	*Conditions Step 2*	*Conv.* (%)[a]	*Yield* ***23*** (%)[a]	*E*:*Z* [a]
1	0 °C, 1 h	0 °C, 16 h	96	86	2.8:1
2	rt., 1h	rt., 16 h	97	93	3.3:1

[a]Determined by NMR analysis

Table 2.12

With these encouraging results in hand, an alternative phosphorane was chosen to complete the series. To represent stabilised ylides, phosphonium salt **24** was chosen as a suitable substrate and further reacted with aldehyde **19** (**Scheme 2.27**, **Table 2.13**). At lower temperatures, 14 % of the corresponding unsaturated ester **19** was isolated, which, considering the known low reactivity of stabilised ylides, came as no great surprise (**Table 2.13**, **Entry 1**). Gratifyingly, upon increasing the reaction temperature to ambient and 40 °C the yield could be gradually enhanced up to 70 % (**Table 2.13**, **Entries 2** and **3**). In all cases, exclusive *E*-selectivity was observed, advocating the typical observation for stabilised ylides.



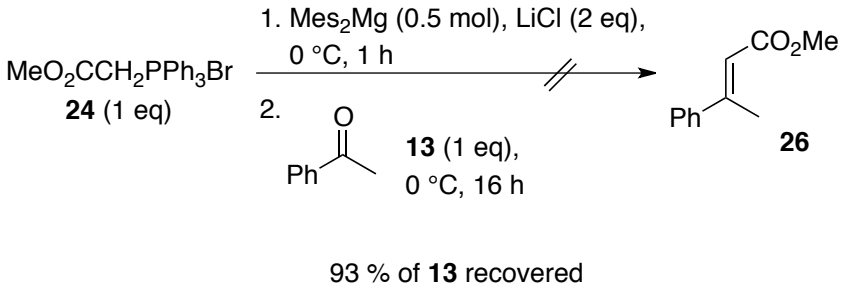
Scheme 2.27

Entry	*Conditions Step 2*	*Conv.* (%)[a]	*Yield* ***25*** (%)[a]	*E*:*Z* [a]
1	0 °C, 16 h	-	14	1:0
2	rt., 16 h	63	54	1:0
3	40 °C, 16 h	81	70	1:0

[a]Determined by NMR analysis

Table 2.13

In turn, reacting the generated ylide with a less reactive ketone, such as acetophenone, returned 93 % of the ketone starting material (**Scheme 2.28**).



Scheme 2.28

It should be noted that throughout this project, control reactions with the employed Mes_2Mg were run on a regular basis in order to monitor the quality of the base reagent and maintain a level of consistency. Although a discolouration of the regularly purchased Grignard reagent MesMgBr had been noticed, yields of silyl enol ethers, from enolisable ketones, or alkenes, *via* the Shapiro reaction, remained unaffected and consultation with the supplier did not offer any satisfactory explanation. A drop in quality of the MesMgBr may be held accountable for the unsatisfyingly low yields in comparison to the initial success of the transformation using carbon-centred magnesium bases. Nevertheless, the efficient preparation of disubstituted alkenes from aldehyde **19** and a small range of electron-deficient phosphonium salts has been achieved with stoichiometric quantities of carbon-centred base Mes_2Mg (**Figure 2.4**).

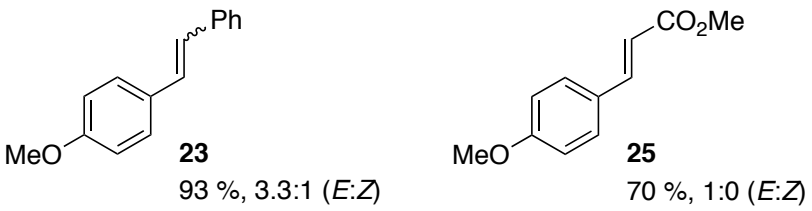


Figure 2.4

The developed techniques are now poised for expansion in terms of aldehyde substrate scope. Particularly interesting will be the *E*/*Z*-selectivity of the thus prepared alkene products which, compared to more commonly employed base reagents, had been improved in favour of the *E*-isomer in the studies conducted with Mes_2Mg. Additionally, it has to be noted that with the application of elevated temperatures, which are possible with our emerging magnesium carbon-centred bases, ketone substrates may also become applicable.

4. Conclusions and Future Work

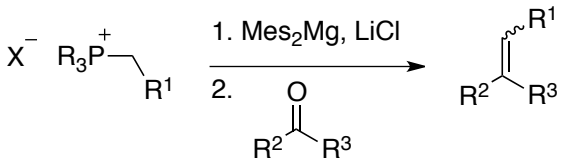
The application of the carbon-centred magnesium base Mes_2Mg in the deprotonation of phosphonium salts to generate the corresponding phosphonium ylide within the Wittig reaction has been investigated. Despite the very encouraging outcome of a previous attempt with ethyltriphenylphosphonium bromide **8** and acetophenone,[2] the result could not be repeated with regards to the documented high yield of 97 % and unusually high *E*:*Z* selectivity of 4:1. Instead, under the reported conditions a low 26 % yield of **12** was observed. Reassessment of the reaction conditions did not deliver the anticipated considerable increase in yield. A small improvement was achieved by switching from *in situ* generated to preformed Mes_2Mg, furnishing the alkene **12** in 35 % yield with comparable *E*:*Z* selectivity being observed. When the reaction temperature was elevated to ambient, the highest yield within this study was obtained with 57 %. Lamentably, this went in hand with a drop in selectivity to 2:0 (*E*:*Z*). Based on these results, it was suspected that the complete deprotonation of the phosphonium salt to the corresponding ylide was not achieved, which was further supported by the low conversion of the more reactive aldehyde **19** when used instead of acetophenone.

The high selectivity for the formation of (*E*)-alkenes with non-stabilised ylides may be attributed to a metal-complexed betaine intermediate. Similarly to observations made by Schlosser, this might allow for the equilibration to the less hindered *trans*-arrangement and furnish the corresponding (*E*)-alkene.

A short study on phosphonium salt derivatives **21** and **24**, bearing more acidic protons, was conducted, leading to much improved results with yields up to 93 % with benzaldehyde as a substrate. The thus generated stabilised ylides show analogous, and notably improved preference for the (*E*)-isomer of the alkene products as observed when more commonly used base reagents are employed. In this regard, α,β-

unsaturated ester **25** was isolated as a single isomer and disubstituted alkene **23** was generated in a 3.3:1 (*E*:*Z*) ratio. With further research into this emerging magnesium-mediated transformation, the thermal stability of the base reagent may be of an advantage with less reactive substrates.

Indeed, it has been shown that the applicability of the carbon-centred magnesium base Mes_2Mg can successfully be extended to the efficient generation of semi- and stabilised phosphonium ylides in Wittig reactions. Further exploration of these substrates with a range of aldehydes and ketones has the potential to expand the developed protocol (**Scheme 2.29**).



Scheme 2.29

Additionally, investigations to elucidate the origin of the selectivity should be conducted to allow for more systematic optimisation studies. In this regard, the efficient formation of non-stabilised ylides should also be revisited. As another aspect, application of the carbon-centred magnesium bases within the arena of Horner-Wadsworth-Emmons and Horner-Wittig reactions on phosphonates and phosphine oxides should be considered and explored.

5. Experimental

5.1 General

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[41]

- THF was dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen.

- MesMgBr, obtained as 1 M solution in THF, was standardised using iodine in a saturated solution of LiCl in THF as an indicator.[42]

- Acetophenone and anisaldehyde were dried by distillation under argon and stored under argon over 4 Å molecular sieves.

- Lithium chloride was flame-dried under high vacuum, then purged with and stored under argon.

- Ethyltriphenylphosphonium bromide, -chloride, and -iodide, as well as benzyltriphenylphosphonium bromide and (carbomethoxymethyl)triphenyl-phosphonium bromide were purified by recrystallisation from DCM and petrol ether and stored under argon.

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254. This was analysed using a Mineralight UVGL-25 lamp and developed using potassium permanganate or vanillin solution.

Flash chromatography was carried out using Prolabo silica gel (230-400 mesh).

Gas chromatography was carried out using a Carlo Erba HRGC 5300 gas chromatograph fitted with (i) a CP SIL-19CB column or (ii) a CP-Chirasil-DEX CB column. Detection was by flame ionisation and the chromatograph was interpreted using JLC 6000 computer software.

^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX 400 spectrometer at 400 MHz, unless otherwise stated. Chemical shifts are reported in ppm, and coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions unless otherwise specified.

High-resolution mass spectra were obtained on a Finnigan MAT900XLT instrument at the EPSRC National Mass Spectrometry Services Centre, University of Wales, Swansea.

FTIR spectra were obtained on a Nicolet Impact 400D machine.

Elemental analysis was obtained using a Carlo Erba 1106 CHN analyser.

Air-sensitive reactions were carried out using Schlenk apparatus, which was initially evacuated and flame-dried, then purged with argon.

5.2 General Experimental Procedures

Typical Procedure A for the Magnesium Base-mediated Wittig Reaction with in situ *Generated Mes_2Mg*

Table 2.1, **Entry 1**: In a flame-dried Schlenk tube under argon ethyltriphenylphosphonium bromide **8** (371 mg, 1 mmol) was dissolved in dry THF (5 ml) and the suspension cooled to 0 °C in an ice bath. To a separate flame-dried Schlenk tube containing dry LiCl (85 mg, 2 mmol) was added a solution of MesMgBr (1 ml, 1 mmol, 1 M in THF), 1,4-dioxane (90 μl, 1.05 mmol) and THF (2 ml). The mixture was stirred at ambient temperature for 30 min before cooling to 0 °C and transferring the solution *via* cannula to the prepared suspension of **8** in THF. The reaction mixture turned a bright orange colour and was stirred at 0 °C for a further hour. A round-bottom flask was flame dried and charged with acetophenone **13** (0.12 ml, 1 mmol) and dry THF (2 ml). The solution was then transferred to the orange reaction mixture *via* syringe pump over 1 h and stirred at 0 °C for 16 h. The reaction mixture was treated with DCM (5 ml) and then concentrated *in vacuo*. The conversion and *E*:*Z* ratio of the product were determined at this stage as 35 % and 3.6:1 by ^{1}H-NMR analysis, using the proton signals of the alkene functionality of each compound for comparison. The crude was then dry loaded and purified *via* flash chromatography, eluting with petroleum ether (30-40 °C). The product **12** was isolated as a colourless oil containing mesitylene residues (34 mg, 0.26 mmol, 26 % yield).

Typical Procedure B for the Preparation of Bismesitylmagnesium

To a solution of MesMgBr (100 ml, 100 mmol, 1 M solution in THF) in a flame dried Schlenk tube under argon atmosphere at room temperature was added 1,4-dioxane (8.95 ml, 105 mmol) steadily over 5 minutes. The mixture was stirred

vigorously for 3 h. The formed, white precipitate within the pale yellow solution was allowed to settle for 72 h and the clear diarylmagnesium solution was then removed *via* cannula to a previously flame-dried and purged flask. Care was taken to avoid withdrawing any of the precipitate. The Mes_2Mg solution was standardised using iodine in a saturated solution of LiCl in THF as indicator before use.[42] The molarity of the Mes_2Mg solution was typically 0.50 M.

Standardising Method: Using Iodine[42]

Table 1.11, **Entry 2B**: Anhydrous LiCl (10 mmol, 424 mg) was placed in flame-dried and argon-flushed 50 ml flask with a stirrer bar and was flame-dried under high vacuum. Care was taken not to melt the LiCl. After purging with argon cooling to room temperature, THF (20 ml) was added and the mixture was stirred for 24 h at ambient temperature until the LiCl was completely dissolved, resulting in the formation of a 0.5 M solution of LiCl in THF. A separate flame-dried and argon-flushed Schlenk tube was charged with accurately weighed I_2 (0.93 mmol, 237 mg) and 3 ml of the prepared saturated LiCl solution. The dark brown solution was stirred and cooled to 0 °C in an ice-bath. The diarylmagnesium reagent was added dropwise *via* a 1 ml syringe until the brown colour disappeared to give a clear, colourless solution. The amount consumed (0.94 ml) contains 0.5 eq of the magnesium reagent relative to iodine and the molarity was determined as 0.49 M.

Typical Procedure C for the Magnesium Base-mediated Wittig Reaction with Preformed Mes_2Mg

Table 2.5, **Entry 1**: In a flame-dried Schlenk tube under argon ethyltriphenylphosphonium bromide **8** (371 mg, 1 mmol) was dissolved in dry THF (5 ml) and the suspension cooled to 0 °C in an ice bath. To a separate flame-dried Schlenk tube containing dry LiCl (85 mg, 2 mmol) was added a solution of Mes_2Mg (1.02 ml, 0.5 mmol, 0.49 M in THF, *see Typical Procedure B*) and THF (2 ml). The

mixture was cooled to 0 °C and transferred *via* cannula to the prepared suspension of **8** in THF. The reaction mixture turned a bright orange colour and was stirred at 0 °C for 1 hour. A round-bottom flask was flame dried and charged with acetophenone **13** (0.12 ml, 1 mmol) and dry THF (2 ml). The solution was then transferred to the orange reaction mixture *via* syringe pump over 1 h and stirred at 0 °C for 16 h. The reaction mixture was treated with DCM (5 ml) and then concentrated *in vacuo*. The conversion and *E*:*Z* ratio of the product were determined at this stage as 40 % and 3.7:1 by ^{1}H-NMR analysis, using the proton signals of the alkene functionality of each compound for comparison. The crude was then adsorbed onto silica and purified *via* flash chromatography, eluting with petroleum ether (30-40 °C). The product **12** was isolated as a colourless oil containing mesitylene residues (40 mg, 0.30 mmol, 30 % yield).

5.3 Carbon-centred Magnesium Base-mediated Wittig Reaction

5.3.1 Revision and Optimisation of Reaction Conditions

Reactions with in situ *Prepared Mes_2Mg*

The following experiments were carried out according to *Typical Procedure A*. Data are reported as: (a) phosphonium bromide **8**, (b) THF for **8**, (c) MesMgBr, (d) 1,4-dioxane, (e) LiCl, (f) THF for Mes_2Mg solution, (g) conditions step 1, (h) acetophenone **13**, (i) THF for **13**, (j) conditions step 2, (k) conversion, (l) yield, and (m) *E*:*Z*. Individual analysis for each compound is given below.

Table 2.1, **Entry 1**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1 ml, 1 mmol, 0.1 M in THF, (d) 90 μl, 1.05 mmol, (e) 85 mg, 2 mmol, (f) THF, 2 ml, (g) 0 °C, 1 h, (h) 0.12

ml, 1 mmol, (i) THF, 2 ml, (j) 0 °C, 16 h, (k) 35 %, (l) **12**, 34 mg, 0.26 mmol, 26 % (NMR yield with mesitylene residues), and (m) 3.6:1.

Table 2.1, **Entry 2**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1 ml, 1 mmol, 0.1 M in THF, (d) 90 µl, 1.05 mmol, (e) 85 mg, 2 mmol, (f) THF, 2 ml, (g) 0 °C, 1 h, (h) 0.12 ml, 1 mmol, (i) THF, 2 ml, (j) 0 °C, 16 h, (k) 32 %, (l) **12**, 30 mg, 0.23 mmol, 23 % (NMR yield with mesitylene residues), and (m) 3.4:1.

Table 2.2, **Entry 1**: (a) 563 mg, 1.5 mmol, (b) THF, 5 ml, (c) 1.5 ml, 1.5 mmol, 0.1 M in THF, (d) 0.14 ml, 1.58 mmol, (e) 127 mg, 3 mmol, (f) THF, 2 ml, (g) 0 °C, 1 h, (h) 0.12 ml, 1 mmol, (i) THF, 2 ml, (j) 0 °C, 16 h, (k) 39 %, (l) **12**, 37 mg, 0.28 mmol, 28 % (NMR yield with mesitylene residues), and (m) 4.0:1.

Table 2.2, **Entry 2**: (a) 742 mg, 2 mmol, (b) THF, 5 ml, (c) 2 ml, 2 mmol, 0.1 M in THF, (d) 0.18 ml, 2.1 mmol, (e) 170 mg, 4 mmol, (f) THF, 2 ml, (g) 0 °C, 1 h, (h) 0.12 ml, 1 mmol, (i) THF, 2 ml, (j) 0 °C, 16 h, (k) 36 %, (l) **12**, 26 mg, 0.20 mmol, 20 % (NMR yield with mesitylene residues), and (m) 4.2:1.

Table 2.3, **Entry 1**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1 ml, 1 mmol, 0.1 M in THF, (d) 90 µl, 1.05 mmol, (e) 85 mg, 2 mmol, (f) THF, 2 ml, (g) 0 °C, 3 h, (h) 0.12 ml, 1 mmol, (i) THF, 2 ml, (j) 0 °C, 16 h, (k) 32 %, (l) **12**, 34 mg, 0.26 mmol, 26 % (NMR yield with mesitylene residues), and (m) 4.0:1.

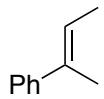
Table 2.3, **Entry 2**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1 ml, 1 mmol, 0.1 M in THF, (d) 90 µl, 1.05 mmol, (e) 85 mg, 2 mmol, (f) THF, 2 ml, (g) 0 °C, 16 h, (h) 0.12 ml, 1 mmol, (i) THF, 2 ml, (j) 0 °C, 16 h, (k) 43 %, (l) **12**, 49 mg, 0.37 mmol, 37 % (NMR yield with mesitylene residues), and (m) 2.4:1.

Table 2.4, **Entry 1**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1 ml, 1 mmol, 0.1 M in THF, (d) 90 µl, 1.05 mmol, (e) 85 mg, 2 mmol, (f) THF, 2 ml, (g) rt., 1 h, (h) 0.12

ml, 1 mmol, (i) THF, 2 ml, (j) rt., 16 h, (k) 46 %, (l) **12**, 57 mg, 0.43 mmol, 43 % (NMR yield with mesitylene residues), and (m) 2.5:1.

Table 2.4, **Entry 2**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1 ml, 1 mmol, 0.1 M in THF, (d) 90 µl, 1.05 mmol, (e) 85 mg, 2 mmol, (f) THF, 2 ml, (g) 40 °C, 1 h, (h) 0.12 ml, 1 mmol, (i) THF, 2 ml, (j) 40 °C, 16 h, (k) 52 %, (l) **12**, 34 mg, 0.26 mmol, 26 % (NMR yield with mesitylene residues), and (m) 3.0:1.

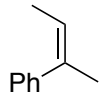
(E)-1-Methyl-(1-propenyl)benzene, (*E*)-**12**:[37]



Colourless oil; IR ($CHCl_3$): 1489, 3030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.82 (d, 3H, *J* = 6.8 Hz, C=CHC*H*$_3$), 2.06 (s, 3H, CC*H*$_3$), 5.88 (q, 1H, *J* = 6.9 Hz, C=C*H*CH$_3$), 7.23 (t, 2H, *J* = 6.7 Hz, Ar*H*), 7.29-7.43 (m, 3H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 19.3, 25.9, 125.8, 126.0, 128.1, 128.8, 134.9, 139.0.

The data observed are in accordance with literature values.

(Z)-1-Methyl-(1-propenyl)benzene, (*Z*)-**12**:[37]



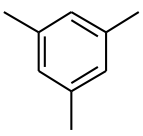
Colourless oil; IR ($CHCl_3$): 1492, 3035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.62 (d, 3H, *J* = 6.9 Hz, C=CHC*H*$_3$), 2.06 (s, 3H, CC*H*$_3$), 5.59 (q, 1H, *J* = 6.9 Hz, C=C*H*CH$_3$), 7.23 (t, 2H, *J* = 6.7 Hz, Ar*H*), 7.29-7.43 (m, 3H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 14.7, 25.4, 121.7, 126.2, 128.0, 128.2, 136.7, 141.9.

The data observed are in accordance with literature values.

The following ^{1}H-NMR signals were used to calculate the ratio of *E*- to *Z*-alkene **12**: *E*-**12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ((ppm) 5.88 (q, 1H, *J* = 6.9 Hz, C=C*H*CH_3); and *Z*-**12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ((ppm) 5.59 (q, 1H, *J* = 6.9 Hz, C=C*H*CH_3).

The following ^{1}H-NMR signals were used to calculate the conversion of **13** to alkene **12**: *E*-**12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.88 (q, 1H, *J* = 6.9 Hz, C=C*H*CH_3); *Z*-**12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.59 (q, 1H, *J* = 6.9 Hz, C=C*H*CH_3); and **13**:[43] ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.56 (s, 3H, CH_3).

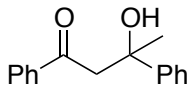
Mesitylene:[44,45]



Colourless oil; IR ($CHCl_3$): 1485, 1616, 3025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 2.31 (s, 9H, CH_3), 6.83 (s, 3H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 21.2, 126.9, 137.7.

The data observed are in accordance with literature values.

1,3-diphenyl-3-hydroxy-1-butanone, **14**:[46]



Colourless oil; IR ($CHCl_3$): 1217, 1668, 3480 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.63 (s, 3H, CH_3), 3.35 (d, 1H, $^2J_{H\text{-}H}$ = 17.4 Hz, CH_2), 3.78 (d, 1H, $^2J_{H\text{-}H}$ = 17.4 Hz, CH_2), 4.85 (s, 1H, O*H*), 7.22 (t, 1H, *J* = 7.3 Hz, Ar*H*), 7.33 (t, 2H, *J* = 7.9 Hz, Ar*H*), 7.42-7.53 (m, 4H, Ar*H*), 7.59 (t, 1H, *J* = 7.4 Hz, Ar*H*), 7.91 (d, 2H, *J* = 7.2 Hz, Ar*H*),; ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 30.9, 48.8, 73.5, 124.4, 126.7, 128.1, 128.3, 128.7, 133.7, 137.0, 147.6, 201.3.

The data observed are in accordance with literature values.

Reactions with Preformed Mes_2Mg

The following experiments were carried out according to *Typical Procedure C*. Data are reported as: (a) phosphonium bromide, (b) THF for phosphonium salt, (c) Mes_2Mg generated according to *Typical Procedure B*, (d) LiCl, (e) THF for Mes_2Mg solution, (f) conditions step 1, (g) acetophenone **13**, (h) THF for **13**, (i) conditions step 2, (j) conversion, (k) yield, and (l) *E*:*Z*.

Table 2.5, **Entry 1**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 40 %, (k) **12**, 40 mg, 0.30 mmol, 30 % (NMR yield with mesitylene residues), and (l) 3.7:1.

Table 2.5, **Entry 2**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 46 %, (k) **12**, 46 mg, 0.35 mmol, 35 % (NMR yield with mesitylene residues), and (l) 3.3:1.

Table 2.6, **Entry 1**: (a) 563 mg, 1.5 mmol, (b) THF, 5 ml, (c) 1.47 ml, 0.75 mmol, 0.51 M in THF, (d) 127 mg, 3 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 77 %, (k) **12**, 66 mg, 0.50 mmol, 50 % (NMR yield with mesitylene residues), and (l) 3.2:1.

Table 2.6, **Entry 2**: (a) 742 mg, 2 mmol, (b) THF, 5 ml, (c) 1.96 ml, 1 mmol, 0.51 M in THF, (d) 170 mg, 4 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 76 %, (k) **12**, 75 mg, 0.57 mmol, 57 % (NMR yield with mesitylene residues), and (l) 3.1:1.

Table 2.6, **Entry 3**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 3 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 68 %, (k) **12**, 67 mg, 0.51 mmol, 51 % (NMR yield with mesitylene residues), and (l) 2.6:1.

Table 2.7, **Entry 1**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) rt., 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 73 %, (k) **12**, 75 mg, 57 % (NMR yield with mesitylene residues), and (l) 1.8:1.

Table 2.7, **Entry 2**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) rt., 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) rt., 16 h, (j) 78 %, (k) **12**, 75 mg, 0.57 mmol, 57 % (NMR yield with mesitylene residues), and (l) 2.0:1.

Table 2.7, **Entry 3**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) rt., 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 40 °C, 16 h, (j) 75 %, (k) **12**, 58 mg, 0.44 mmol, 44 % (NMR yield with mesitylene residues), and (l) 2.2:1.

Analytical data are consistent with that described for compounds *E*- and *Z*-**12** on page 208 and **14** on page 209.

D_2O Quench

Scheme 2.21: In a flame-dried Schlenk tube, under argon, ethyltriphenylphosphonium bromide **8** (371 mg, 1 mmol) was dissolved in dry THF (5 ml) and the suspension cooled to 0 °C in an ice bath. To a separate flame-dried Schlenk tube containing dry LiCl (85 mg, 2 mmol) was added a solution of Mes_2Mg (1.02 ml, 0.5 mmol, 0.49 M in THF) and dry THF (2 ml). The mixture was stirred at ambient temperature for 30 min before cooling it to 0 °C and transferring the solution *via* cannula to the prepared suspension of **8** in THF. The reaction mixture turned a bright orange colour and was stirred at 0 °C for another hour before quenching with D_2O (0.2 ml, 11 mmol) and further diluting with H_2O (5 ml). The two layers were separated and the aqueous extracted with DCM (3 x 5 ml). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The

crude mixture was then recrystallised from DCM and diethyl ether, yielding the phosphonium salt **8** as a white solid (126 mg, 0.34 mmol, 34 % yield). No definite proof was found for the deuteration of the starting material.

LiCl as an Additive

The following experiments were carried out according to *Typical Procedure C*. Data are reported as: (a) phosphonium bromide **8**, (b) THF for **8**, (c) Mes_2Mg generated according to *Typical Procedure B*, (d) LiCl, (e) THF for Mes_2Mg solution, (f) conditions step 1, (g) acetophenone **13**, (h) THF for **13**, (i) conditions step 2, (j) conversion, (k) yield, and (l) *E*:*Z*.

Table 2.8, **Entry 1**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 0.98 ml, 0.5 mmol, 0.51 M in THF, (d) -, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 11 %, (k) **12**, 12 mg, 0.09 mmol, 9 % (NMR yield with mesitylene residues), and (l) 10:1.

Table 2.8, **Entry 2**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 0.98 ml, 0.5 mmol, 0.51 M in THF, (d) 43 mg, 1 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 53 %, (k) **12**, 50 mg, 0.38 mmol, 38 % (NMR yield with mesitylene residues), and (l) 3.5:1.

Analytical data are consistent with that described for compounds *E*- and *Z*-**12** on page 208.

Alternative Phosphonium Salts

The following experiments were carried out according to *Typical Procedure C*. Data are reported as: (a) phosphonium halide, (b) THF for phosphonium halide, (c) Mes_2Mg generated according to *Typical Procedure B*, (d) LiCl, (e) THF for Mes_2Mg

solution, (f) conditions step 1, (g) acetophenone **13**, (h) THF for **13**, (i) conditions step 2, (j) conversion, (k) yield, and (l) *E*:*Z*.

Table 2.9, **Entry 1**: (a) $EtPPh_3Cl$ **17**, 327 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 0 %, (k) -, and (l) -.

Table 2.9, **Entry 2**: (a) $EtPPh_3I$ **18**, 418 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 36 %, (k) **12**, 34 mg, 0.26 mmol, 26 % (NMR yield with mesitylene residues), and (l) 4.1:1.

Analytical data are consistent with that described for compounds *E*- and *Z*-**12** on page 208.

Using Aldehydes

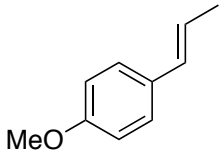
The following experiments were carried out according to *Typical Procedure C*. Data are reported as: (a) phosphonium bromide **8**, (b) THF for **8**, (c) Mes_2Mg generated according to *Typical Procedure B*, (d) LiCl, (e) THF for Mes_2Mg solution, (f) conditions step 1, (g) carbonyl substrate, (h) THF for carbonyl substrate, (i) conditions step 2, (j) conversion, (k) yield, and (l) *E*:*Z*. Individual analysis for each compound is given below.

Table 2.10, **Entry 1**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) 4-methoxybenzaldehyde **19**, 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 57 %, (k) **20**, 56 mg, 0.41 mmol, 41 %, and (l) 1.7:1.

Table 2.10, **Entry 2**: (a) 371 mg, 1 mmol, (b) 1.02 ml, 0.5 mmol, 0.49 M in THF, (c) 85 mg, 2 mmol, (d) rt., 1 h, (e) 4-methoxybenzaldehyde **19**, 0.12 ml, 1 mmol, (f) 0 °C, 16 h, (g) 64 %, (h) **20**, 58 mg, 0.43 mmol, 43 %, and (i) 2.0:1.

Table 2.10, **Entry 3**: (a) 371 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 40 °C, 1 h, (g) 4-methoxybenzaldehyde **19**, 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 86 %, (k) **20**, 56 mg, 0.46 mmol, 46 %, and (l) 2.0:1.

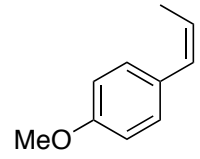
(E)-1-(4-Methoxyphenyl)-1-propene, (*E*)-**20**:[47]



Colourless oil; IR ($CHCl_3$): 1509, 1606, 2958 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.87 (dd, 3H, $^4J_{H\text{-}H}$ = 1.7 Hz, *J* = 6.6 Hz, C*H*$_3$), 3.81 (s, 3H, OC*H*$_3$), 6.11 (dq, 1H, *J* = 6.6 Hz, *J* = 15.7 Hz, CH=C*H*CH$_3$), 6.32-6.40 (m, 1H, C*H*=CHCH$_3$, partially obscured by signal of *Z*-**20**), 6.85 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.23-7.30 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 18.6, 55.3, 114.1, 123.6, 127.1, 130.5, 130.8, 158.7.

The data observed are in accordance with literature values.

(Z)-1-(4-Methoxyphenyl)-1-propene, (*Z*)-**20**:[48]



Colourless oil; IR ($CHCl_3$): 1509, 1606, 2958 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.91 (dd, 3H, $^4J_{H\text{-}H}$ = 1.8 Hz, *J* = 7.2 Hz, C*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 5.72 (dq, 1H, *J* = 7.1 Hz, *J* = 11.6 Hz, CH=C*H*CH$_3$), 6.37-6.40 (m, 1H, C*H*=CHCH$_3$, partially obscured by signal of *E*-**20**), 6.90 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.23-7.30 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 14.6, 55.1, 113.9, 124.9, 129.0, 129.9, 130.4, 158.0.

The data observed are in accordance with literature values.

The following ^{1}H-NMR signals were used to calculate the ratio of *E*- to *Z*-alkene **20**: *E*-**20**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 6.11 (dq, 1H, *J* = 6.6 Hz, *J* = 15.7 Hz, CH=C*H*CH_3); and *Z*-**20**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.72 (dq, 1H, *J* = 7.1 Hz, *J* = 11.6 Hz, CH=C*H*CH_3).

The following ^{1}H-NMR signals were used to calculate the conversion of **19** to alkene **20**: *E*-**20**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 6.11 (dq, 1H, *J* = 6.6 Hz, *J* = 15.7 Hz, CH=C*H*CH_3); *Z*-**20**: ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 5.72 (dq, 1H, *J* = 7.1 Hz, *J* = 11.6 Hz, CH=C*H*CH_3); and **19**:[41] ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 9.82 (s, 1H, C*H*O).

5.3.2 Employing Semi-stabilised and Stabilised Ylides

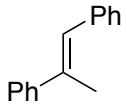
Using Benzyltriphenylphosphonium bromide, **21**:

The following experiments were carried out according to *Typical Procedure C*. Data are reported as: (a) phosphonium bromide **21**, (b) THF for **21**, (c) Mes_2Mg generated according to *Typical Procedure B*, (d) LiCl, (e) THF for Mes_2Mg solution, (f) conditions step 1, (g) carbonyl substrate, (h) THF for carbonyl substrate, (i) conditions step 2, (j) conversion, (k) yield, and (l) *E*:*Z*. Individual analysis for each compound is given below.

Table 2.11, **Entry 1**: (a) **21**, 433 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) **13**, 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) -, (k) **22**, 23 mg, 0.13 mmol, 13 %, and (l) 1.1:1.

Table 2.11, **Entry 2**: (a) **21**, 433 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) **13**, 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) rt., 16 h, (j) -, (k) **22**, 25 mg, 0.14 mmol, 14 %, and (l) 1:1.

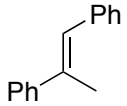
(E)-1,2-Diphenylpropene, (*E*)-**22**:[49]



Colourless oil; IR ($CHCl_3$): 1251, 1589, 3035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.32 (s, 3H, CC*H*$_3$), 6.88 (s, 1H, C=C*H*), 7.27-7.34 (m, 2H, Ar*H*, partially obscured by solvent peak and signals of the *Z*-isomer), 7.37-7.43 (m, 6H, Ar*H*), 7.56 (d, 2H, *J* = 7.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 17.4, 126.4, 126.6, 127.3, 127.8, 128.1, 128.5, 129.3, 137.6, 138.3, 144.0.

The data observed are in accordance with literature values.

(Z)-1,2-Diphenylpropene, (*Z*)-**22**:[50]



Colourless oil; IR ($CHCl_3$): 1251, 1589, 3035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.24 (s, 3H, CC*H*$_3$), 6.51 (s, 1H, C=C*H*), 6.97 (d, 2H, *J* = 7.6 Hz, Ar*H*), 7.05-7.15 (m, 3H, Ar*H*), 7.20-7.23 (m, 2H, Ar*H*), 7.27-7.34 (m, 3H, Ar*H*, partially obscured by solvent peak and signals of the *E*-isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 26.8, 126.1, 126.5, 127.0, 127.5, 128.3, 128.9, 129.2, 137.6, 138.7, 142.2.

The data observed are in accordance with literature values.

The following ^1H-NMR signals were used to calculate the ratio of *E*- to *Z*-alkene **22**: *E*-**22**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.32 (s, 3H, CC*H*$_3$), 6.88 (s, 1H, C=C*H*); and *Z*-**22**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.24 (s, 3H, CC*H*$_3$), 6.51 (s, 1H, C=C*H*).

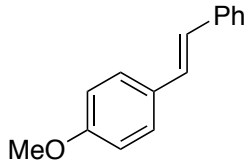
The following ^1H-NMR signals were used to calculate the conversion of **13** to alkene **22**: *E*-**22**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.32 (s, 3H, CC*H*$_3$), 6.88 (s, 1H, C=C*H*); *Z*-**22**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.24 (s, 3H, CC*H*$_3$), 6.51 (s, 1H, C=C*H*); and **13**:[41] ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.56 (s, 3H, C*H*$_3$).

The following experiments were carried out according to *Typical Procedure C*. Data are reported as: (a) phosphonium bromide **21**, (b) THF for **21**, (c) Mes_2Mg generated according to *Typical Procedure B*, (d) LiCl, (e) THF for Mes_2Mg solution, (f) conditions step 1, (g) carbonyl substrate, (h) THF for carbonyl substrate, (i) conditions step 2, (j) conversion, (k) yield, and (l) *E*:*Z*. Individual analysis for each compound is given below.

Table 2.12, **Entry 1**: (a) **21**, 433 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) **19**, 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) 96 %, (k) **23**, 181 mg, 0.86 mmol, 86 %, and (i) 2.8:1.

Table 2.12, **Entry 2**: (a) **21**, 433 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) rt., 1 h, (g) **19**, 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) rt., 16 h, (j) 97 %, (k) **23**, 195 mg, 0.93 mmol, 93 %, and (l) 3.3:1.

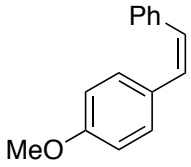
(E)-4-Methoxystilbene, (*E*)-**23**:[51]



Colourless Crystals, M.p. 126-128 °C; IR ($CHCl_3$): 1250, 1602, 3004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.86 (s, 3H, OC*H*$_3$), 6.93 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.01 (d, 1H, *J* = 16.3 Hz, C*H*=CH), 7.10 (d, 1H, *J* = 16.3 Hz, C*H*=CH), 7.27 (t, 1H, *J* = 7.3 Hz, Ar*H*), 7.38 (t, 2H, *J* = 7.4 Hz, Ar*H*). 7.46-7.55 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 55.3, 114.2, 126.3, 126.7, 127.2, 127.8, 128.3, 128.7, 130.2, 137.7, 159.4.

The data observed are in accordance with literature values.

(Z)-4-Methoxystilbene, (*Z*)-**23**:[51]



Colourless Oil; IR ($CHCl_3$): 3004, 1602, 1511, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.80 (s, 3H, OC*H*$_3$), 6.50-6.55 (m, 2H, C*H*=C*H*), 6.76 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.17-7.30 (m, 7H, Ar*H*, partially obscured by solvent peak); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 55.0, 112.9, 126.5, 128.4, 128.6, 129.0, 129.5, 129.7, 130.2, 137.8, 159.0.

The data observed are in accordance with literature values.

The following ^1H-NMR signals were used to calculate the ratio of *E*- to *Z*-alkene **23**: *E*-**23**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.86 (s, 3H, OC*H*$_3$), 6.93 (d, 2H, *J* = 8.8 Hz, Ar*H*); and *Z*-**23**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.80 (s, 3H, OC*H*$_3$), 6.76 (d, 2H, *J* = 8.8 Hz, Ar*H*).

The following ^1H-NMR signals were used to calculate the conversion of **19** to alkene **23**: *E*-**23**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.86 (s, 3H, OC*H*$_3$), 6.93 (d, 2H, *J* = 8.8 Hz, Ar*H*); *Z*-**23**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.80 (s, 3H, OC*H*$_3$), 6.76 (d, 2H, *J* = 8.8 Hz, Ar*H*); and **19**:[41] ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 9.82 (s, 1H, C*H*O).

Using (Carbomethoxymethyl)triphenylphosphonium bromide, **24**:

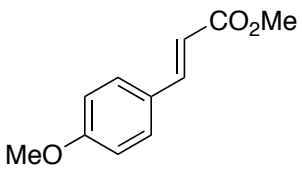
The following experiments were carried out according to *Typical Procedure C*. Data are reported as: (a) phosphonium bromide **24**, (b) THF for **24**, (c) Mes_2Mg generated according to *Typical Procedure B*, (d) LiCl, (e) THF for Mes_2Mg solution, (f) conditions step 1, (g) carbonyl substrate, (h) THF for carbonyl substrate, (i) conditions step 2, (j) conversion, (k) yield, and (l) *E*:*Z*. Individual analysis for each compound is given below

Table 2.13, **Entry 1**: (a) **24**, 415 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) **19**, 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) -, (k) **25**, 27 mg, 0.14 mmol, 14 %, and (l) 1:0.

Table 2.13, **Entry 2**: (a) **24**, 415 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) **19**, 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) rt, 16 h, (j) 63 %, (k) **25**, 104 mg, 0.54 mmol, 54 %, and (l) 1:0.

Table 2.13, **Entry 3**: (a) **24**, 415 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) **19**, 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 40 °C, 16 h, (j) 81 %, (k) **25**, 134 mg, 0.70 mmol, 70 %, and (l) 1:0.

(E)-3-(4-Methoxyphenyl)acrylic acid methyl ester, **25**:[49]



Colourless Crystals, M.p. 85-87 °C; IR ($CHCl_3$): 1161, 1601, 1713, 2947 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.80 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 6.32 (d, 1H, *J* = 16.0 Hz, CH=C*H*CO_2Me), 6.91 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.48 (d, 2H, *J* = 8.6 Hz, Ar*H*), 7.66 (d, 1H, *J* = 16.0 Hz, ArC*H*=CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 51.1, 54.9, 113.8, 114.8, 126.6, 129.2, 144.1, 160.9, 167.3.

The data observed are in accordance with literature values.

The following ^1H-NMR signals were used to calculate the conversion of **19** to alkene **25**: *E*-**25**: ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 6.32 (d, 1H, *J* = 16.0 Hz, CH=C*H*CO_2Me); and **19**:[41] ^1H-NMR (400 MHz, $CDCl_3$): δ(ppm) 9.82 (s, 1H, C*H*O).

The following experiments were carried out according to *Typical Procedure C*. Data are reported as: (a) phosphonium bromide **24**, (b) THF for **24**, (c) Mes_2Mg generated according to *Typical Procedure B*, (d) LiCl, (e) THF for Mes_2Mg solution, (f) conditions step 1, (g) carbonyl substrate, (h) THF for carbonyl substrate, (i) conditions step 2, (j) conversion, (k) yield, and (l) *E*:*Z*. Individual analysis for each compound is given below

Scheme 2.28: (a) **24**, 415 mg, 1 mmol, (b) THF, 5 ml, (c) 1.02 ml, 0.5 mmol, 0.49 M in THF, (d) 85 mg, 2 mmol, (e) THF, 2 ml, (f) 0 °C, 1 h, (g) **13**, 0.12 ml, 1 mmol, (h) THF, 2 ml, (i) 0 °C, 16 h, (j) -, (h) **26**, -, (k) -, and (l) **13**, 112 mg, 0.93 mmol, 93 %

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Chapter 3

Towards the Total Synthesis of (-)-Mucosin

Contents

1. Introduction

The range of magnesium-based reagents developed within our laboratory over the last decade have ensued from considerable efforts in methodological studies. To this end, these have produced highly efficient, reliable and economic base reagents in both, chiral and achiral domains, that offer an exciting alternative to more commonly used reagents and protocols, and in particular to the analogous lithium species.[1–9] Magnesium bisamides, as well as carbon-centred magnesium bases, have shown broad applicability over a number of transformations and substrates, with the main emphasis on the deprotonation of enolisable ketones. Nonetheless, it was envisaged to further probe the emerging asymmetric methodology by applying this within the synthesis of a natural product. In this regard, the eicosanoid (-)-mucosin (**1**) was selected as a suitable target (**Figure 3.1**).

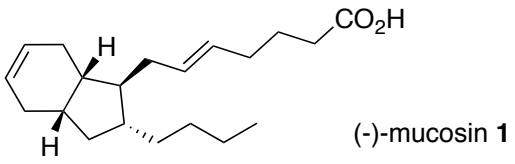
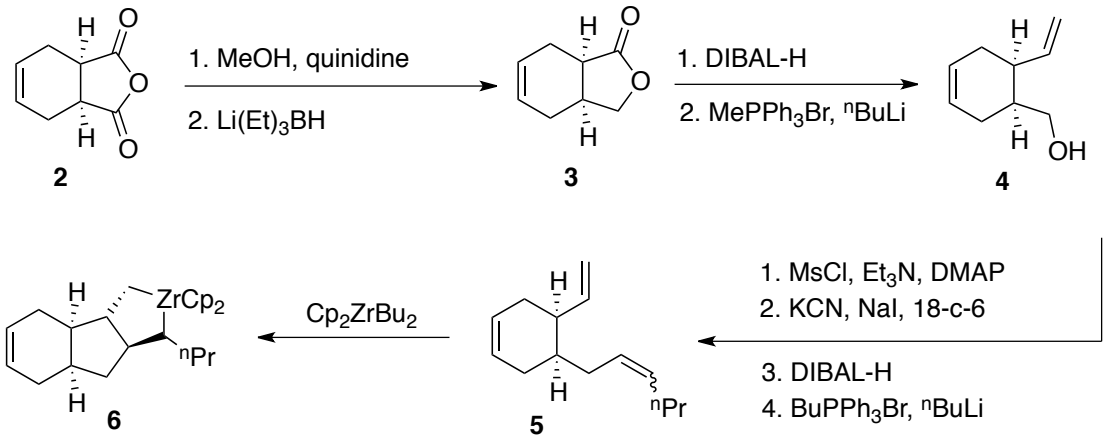


Figure 3.1

1.1 Mucosin

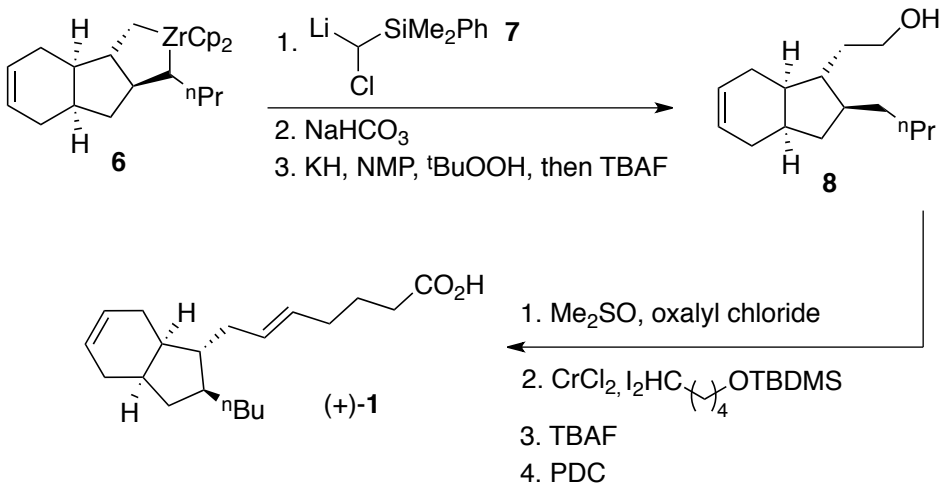
(-)-Mucosin was first isolated from the marine sponge *Reniera mucosa* in 1997 and belongs to the family of eicosanoids, which have a vital role as signalling and messenger molecules in physiological systems of various species, including humans.[10,11] Although its biochemical activity is not known to date, its unusual bicyclic [4.3.0]nonene core with four contiguous stereocentres is extremely intriguing.

The first total synthesis of the unnatural isomer (+)-mucosin was reported by Whitby *et. al* in 2012, employing a zirconium-based co-cyclisation as the key synthetic step to form the bicyclic core and to control the relative stereochemistry of the four chiral centres (**Scheme 3.1**).[12] The absolute stereochemistry is governed by the initial selective ring opening of the starting anhydride **2**, followed by reduction to provide lactone **3** as a single enantiomer.



Scheme 3.1

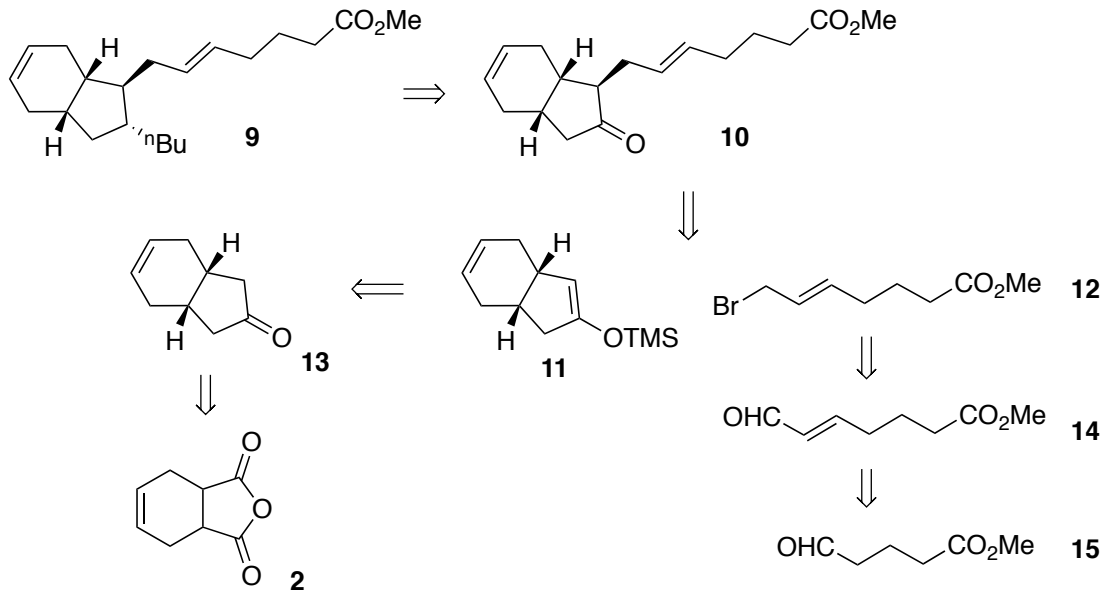
Overall, a series of partial reductions and Wittig olefinations leads to the diene precursor **5** for the key cyclisation, which yields a mixture of isomers with **6** as the major component. Separation of the mixture was performed by HPLC at a later stage within the synthesis. From zirconacycle **6** another 7 steps complete the synthesis to (+)-mucosin in an overall 7 % yield (**Scheme 3.2**).



Scheme 3.2

Despite yielding the unnatural enantiomer, by choosing the correct amine catalyst at the start of the synthesis, the natural isomer of mucosin is proposed to be obtainable following the same series of manipulations.

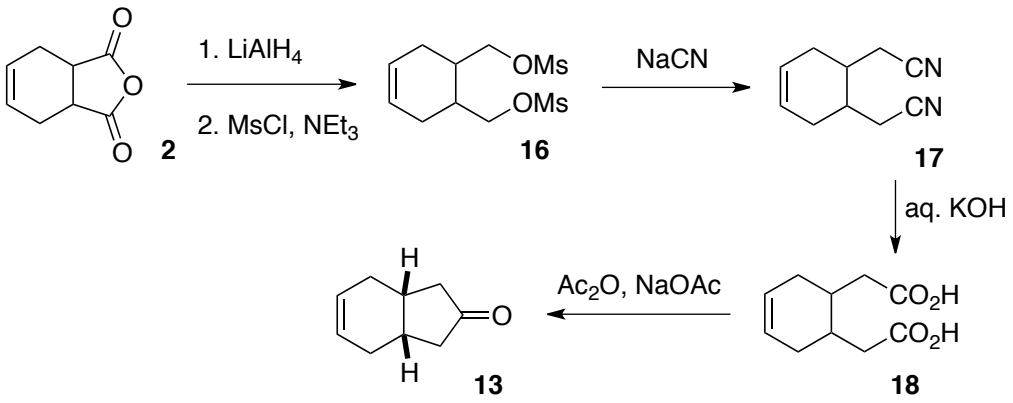
Work within our laboratory towards the synthesis of the naturally occurring (-)-mucosin had commenced prior to the above publication, focusing on an alternative approach with silyl enol ether **11** at its centre (**Scheme 3.3**).[13]



Scheme 3.3

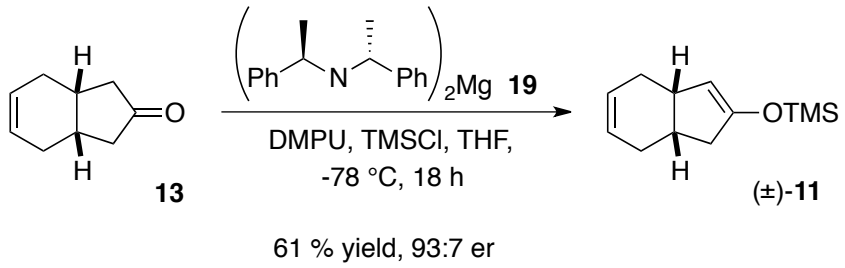
The retrosynthetic analysis of the target molecule started from the corresponding methylester **9**, which was thought to be accessible from the α-substituted ketone **10**. Installation of the allylic side chain was envisaged to be feasible *via* the activation of **11** and consequent substitution of allylic bromide **12**. It was believed that this would proceed stereoselectively, introducing the side chain on the less hindered convex side of the molecule with a *cis*-relationship to the bridgehead protons. Employment of the developed chiral magnesium bisamide bases was anticipated to yield the key silyl enol ether **11** from *meso*-ketone **13** in high selectivity and thus control over the absolute stereochemistry would be gained. In turn, the bicyclic ketone **13** is derived from anhydride **2** over a short series of known steps.[14] Taking the allylic bromide **12** back to the corresponding enal **14**, introduction of the required (*E*)-double bond could be achieved *via* Wittig reaction on aldehyde **15** employing a stabilised yilde.

Initial attempts to access the requisite prochiral ketone **13** were based on reports by Mundy *et. al*[14] and delivered the desired compound in 5 steps (**Scheme 3.4**).[13] Reduction of the cyclic anhydride **2** and subsequent reaction with mesyl chloride furnished the dimesylate **16**. Chain extension was achieved by a substitution reaction with NaCN and hydrolysis delivers the precursor **18** for the final cyclisation. Overall, this short sequence yielded the desired ketone **13** more efficiently than the original route from the commercially available anhydride **2** in 52 % by substituting the previously employed tosylation for the more economic mesylation.[13]



Scheme 3.4

The key desymmetrisation of prochiral *meso*-ketone **13** was conducted utilising chiral magnesium bisamide **19** as a base reagent (**Scheme 3.5**). At -78 °C, the described conditions provided the enol silane in an encouraging 61 % yield. Additionally, HPLC analysis of the product revealed an excellent 93:7 e.r., affirming the synthetic approach as relevant. At this point however, no assignment of the absolute stereochemistry of **11** was possible. From this stage, preliminary efforts to prepare and introduce a suitable derivative for the allylic side chain were conducted.[13]

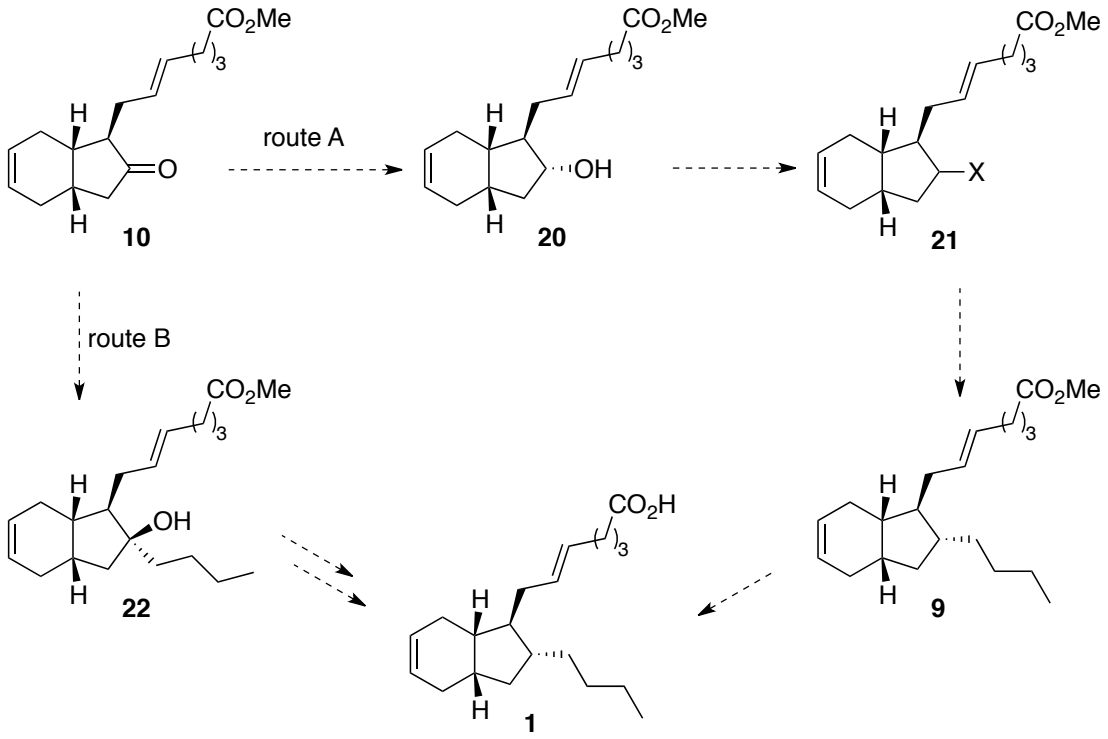


Scheme 3.5

2. Proposed Work

Whilst studies towards the total synthesis of (-)-mucosin had been initiated within our lab, the programme of work presented herein would aim to significantly optimise the emerging route towards the completion of this preparative pathway. In this regard, assessment of a more efficient and scalable access to the key fragments is sought. Additionally, particular emphasis will be placed on the efficient allylation of enol silane **11**.

The work towards (-)-mucosin was also continued in an attempt to complete the synthesis of the natural isomer. More specifically, starting from keto ester **10**, it was envisaged that direct reduction of the ketone functionality to the corresponding alcohol **20** (route A) could be followed by its transformation into an appropriate leaving group (**21**) (**Scheme 3.6**). Nucleophilic displacement by a suitable organometallic reagent is anticipated to yield the desired ester **9**, with only hydrolysis of the methyl ester moiety to complete the synthesis. As an alternative, it is proposed to obtain quaternary alcohol **22** from keto ester **10** by nucleophilic addition (**Scheme 3.6**, route B). Subsequent deoxygenation and hydrolysis of the methyl ester would then provide the desired natural product **1**.



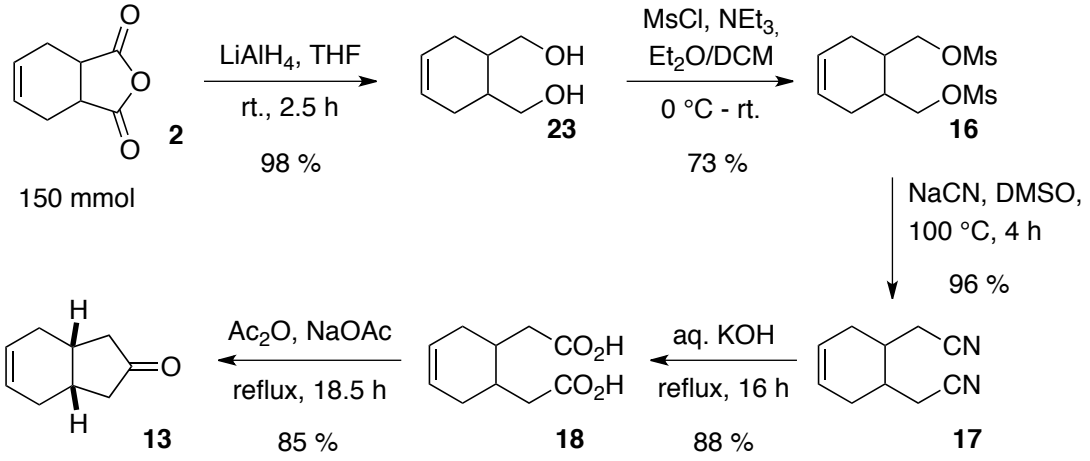
Scheme 3.6

Additionally, the diastereoselectivity of requisite transformations will be investigated, in order to validate the devised route and amend the synthetic sequence if required. It is envisaged that based on the *cis*-arrangement of the two bridgehead protons and the resulting configuration of the bicyclic core in **13**, introduction of the allylic side chain will occur with high diastereoselectivity. In turn, it is proposed that this will then govern the initial construction of the fourth stereocentre. A series of stereospecific reactions will then allow systematic manipulation to generate the targeted (-)-mucosin (**1**) enantioselectively.

3. Results and Discussion

3.1 Preparation and Deprotonation of *meso*-Ketone 13

At the outset of the project, the preparation of bicyclic ketone **13** was embarked upon, based on the initial reports by Mundy.[14] In this regard, anhydride **2** was subjected to a reduction with $LiAlH_4$ to give the desired diol **23** in an excellent 98 % yield after only 2.5 h (**Scheme 3.7**). Direct conversion of **23** with mesyl chloride and triethyl amine delivered the corresponding dimesylate **16** in 73 % yield. Further treatment with NaCN in DMSO resulted in near quantitative formation of diacetonitrile **17**. In turn, the diacid **18** was then obtained by hydrolysis in 88 % yield and was subsequently reacted with acetic anhydride and sodium acetate to furnish the targeted bicyclic ketone **13** in 85 % yield.

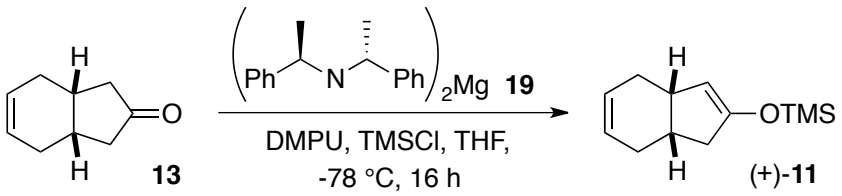


Scheme 3.7

Thus, the *meso*-ketone **13** was very efficiently obtained on large scale in 5 steps and in 51 % overall yield. In this regard, the slightly amended approach towards this key fragment provides a significant advancement to Mundy's route, which furnishes

merely 12 % of **13**.[14] Importantly, purification by column chromatography was only required in the last step, making this protocol very attractive for an application on large scale.

With the *meso*-ketone **13** in hand, conditions for the asymmetric deprotonation using chiral magnesium bisamide **19** were revisited (**Scheme 3.8**, **Table 3.1**).



Scheme 3.8

Entry	*Scale*	*Yield **11*** (%)	$[\alpha]_D^{20}$	*E.r.*[a]
1	0.8 mmol	29	+48.2 °	92:8
2	0.8 mmol	68	+46.9 °	91:9
3[b]	0.8 mmol	87	+45.9 °	90:10
4[b]	1.2 mmol	86	+48.1 °	92:8

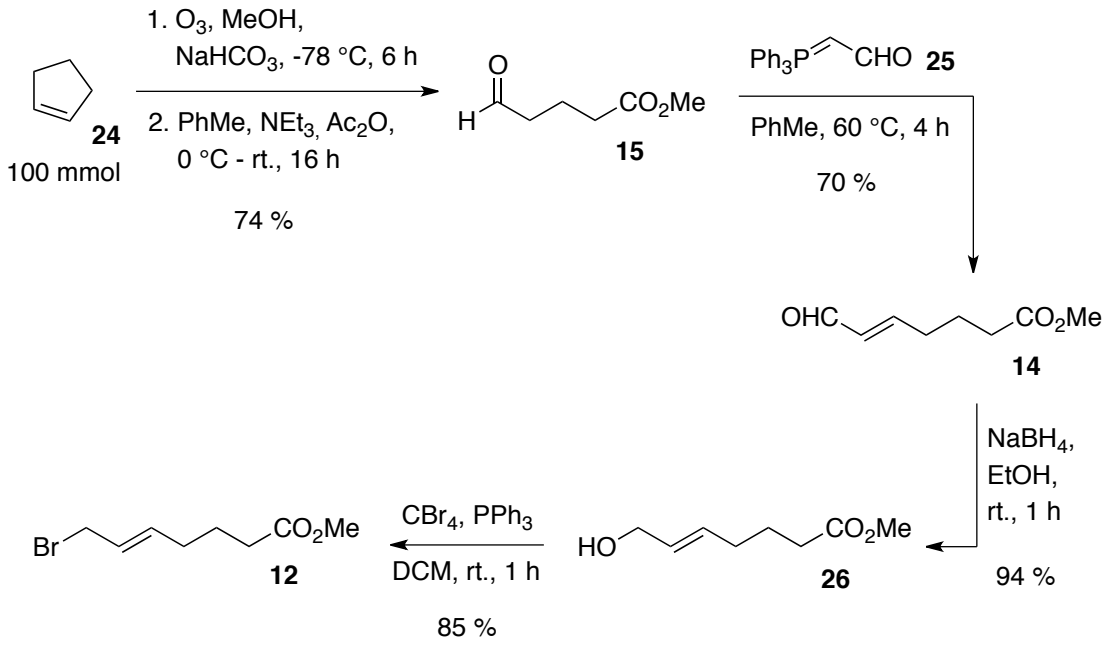
[a]Calculated from Optical Rotation, [b]oven-dried silica.

Table 3.1

Despite observing comparably good to high enantiomeric ratios as seen previously,[13] the yields of the corresponding silyl enol ether **11** were variable and low (**Table 3.1**, **Entries 1** and **2**). It was found, however, that more consistent results could be produced with oven dried silica for column purification (**Table 3.1**, **Entries 3** and **4**). Presumably, residues of moisture in the silica had led to hydrolysis of the enol silane upon purification, decreasing the yields considerably. To this date, the described transformation provides the most efficient process to establish the stereoselectivity in this key intermediate, with excellent yields up to 87 % and an impressive 92:8 e.r. It is worth noting that control reactions with the analogous chiral lithium amide base gave rise to comparable yields and selectivities when using an internal quench protocol, leading to 84 % yield and 93:7 e.r., respectively.

3.2 Preparation of Allylic Bromide 12

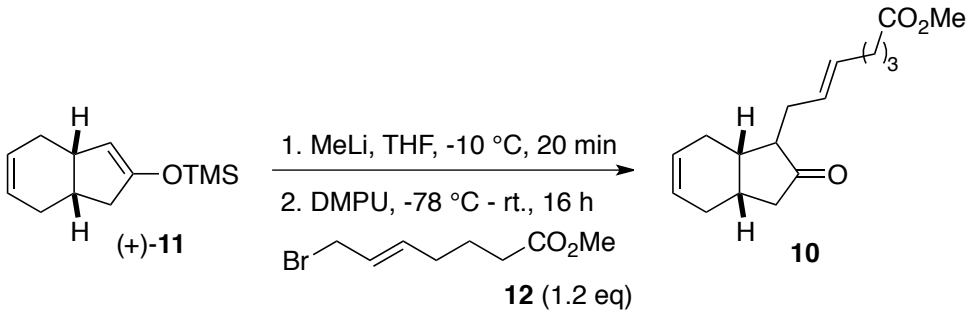
As outlined in the retrosynthetic analysis, access to the second key fragment, allylic bromide **12**, was envisaged to be gained *via* aldehyde **15**. Ozonolysis of the commercially available and inexpensive cyclopentene **24** was thus attempted, providing the targeted aldehyde **15** in 74 % yield as a mixture with residual toluene and acetic anhydride (**Scheme 3.9**). Nonetheless, this mixture could be directly subjected to a Wittig reaction with phosphorane **25**, delivering the enal **14** in 70 % yield with complete *E*-selectivity. Careful monitoring of the selective reduction of **14** utilising $NaBH_4$ allowed the isolation of the desired allylic alcohol **26** in an excellent yield of up to 94 %. Notably, subsequent conversion of **26** to allylic bromide **12** employing the Appel reaction was achieved in 85 % yield. This produced a remarkable overall yield of 41 % over 4 steps of the devised sequence on large scale.



Scheme 3.9

3.3 Assessment of the Preparation of Keto Ester 10

With sufficient quantities of the two central fragments in hand, assessment and optimisation of the allylation of the bicyclic core was focused on. Initially, activation of the silyl enol ether **11** was achieved employing MeLi and subsequent reaction with allylic bromide **12** delivered the alkylated product **10** in moderate 47 % yield (**Scheme 3.10**, **Table 3.2**, **Entry 1**). It is important to highlight that, for each reaction, the enol silane was prepared and used on the same day. Having stated this, further optimisation was sought and in time it was revealed that the quality of bromide **12** had a marked effect on the outcome of the reaction. Despite vigilant purification and routine storage under an argon atmosphere, column chromatography of **12** immediately prior to its addition to the activated enol silane was required to delivered **10** in markedly enhanced yields up to 70 % (**Table 3.2**, **Entry 2**), establishing this transformation as a viable step in the synthesis towards (-)-mucosin (**1**). The diastereoselectivity of the allylation and the stereochemistry of **10** could not be determined at this stage and will be discussed (*vide infra*).

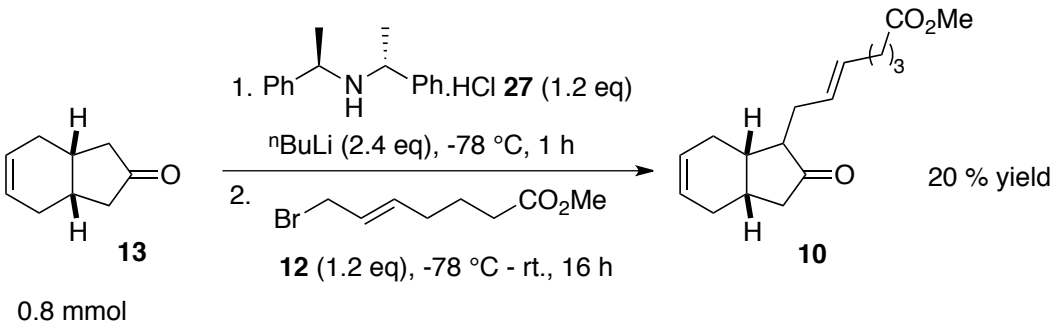


Scheme 3.10

Entry	*Scale*	*Yield **10*** (%)
1	1.26 mmol	47
2	0.66 mmol	70

Table 3.2

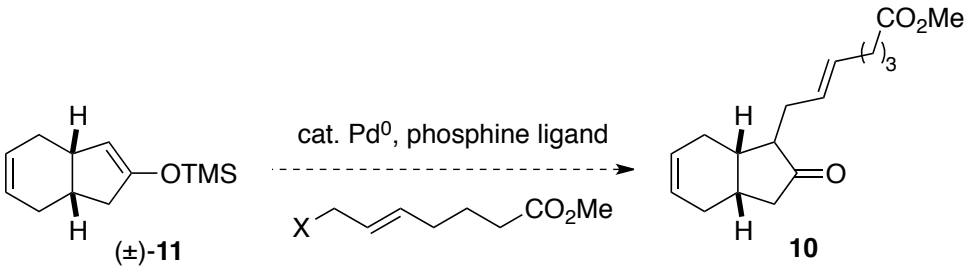
As an alternative, it was also attempted to develop a one-pot procedure for the deprotonation and alkylation of *meso*-ketone **13**, circumventing the formation and isolation of silyl enol ether **11** and utilising the generated enolate directly. In this regard, an external quench protocol with allylic bromide **12** was proposed. This is typically more difficult with regards to the effective and, more importantly, selective deprotonation of the prochiral ketone with both lithium- and magnesium-based reagents.[3,15,16] However, addition of LiCl has repeatedly shown an advantageous effect in externally quenched reactions, especially in lithium-mediated systems.[15] As such, a deviation to the lithium amide reagent was taken. A short investigation was launched, employing chiral amine salt **27** in conjunction with ^{n}BuLi to generate the requisite amide base and LiCl *in situ*, an external quench method described by Majewski (**Scheme 3.11**).[17] After stirring ketone **13** with the formed base at -78 °C for 1 h, allyl bromide **12** was introduced, which furnished the desired keto ester **10** in a poor 20 % yield after 16 h at -78 °C. The remaining bicyclic ketone **13** was recovered, however none of the bromide was returned. Additionally, no analysis could be made on the selectivity of either asymmetric deprotonation or allylation. Subsequently, this method was not further pursued at this point.



Scheme 3.11

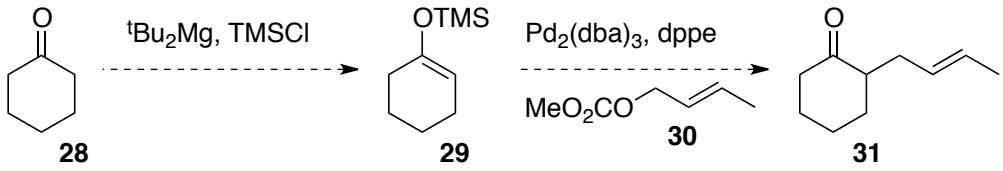
Tsuji-Trost Allylation

Simultaneously, a second approach towards keto ester **13** was pursued. It was considered to utilise Tsuji-Trost-type allylations to access **10** more efficiently (**Scheme 3.12**).



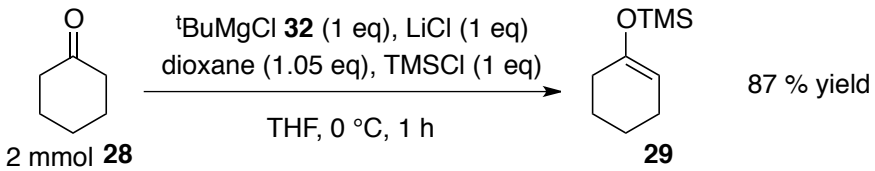
Scheme 3.12

Since the first publication in 1965, the palladium-mediated, and later catalysed, reaction employs predominately allylic acetates and carbonates in the alkylation of a range of nucleophiles and has found widespread application in organic synthesis, especially in its asymmetric variants.[18–22] However, reports relating to non-asymmetric alkylations using silyl enol ethers are less prominent.[23] Notably, when using allyl carbonates no stoichiometric amount of base reagent is required for the efficient palladium-catalysed alkylation. In this regard, a preliminary study on model substrates was proposed, utilising enol silane **29** and allyl carbonate **30** (**Scheme 3.13**).



Scheme 3.13

Generation of the required silyl enol ether was accomplished by employing Grignard reagent **32** to produce the corresponding carbon-centred magnesium base *in situ*. In accordance with previous results using TMSCl,[7] the product was obtained with excellent yields up to 87 % (**Scheme 3.14**).

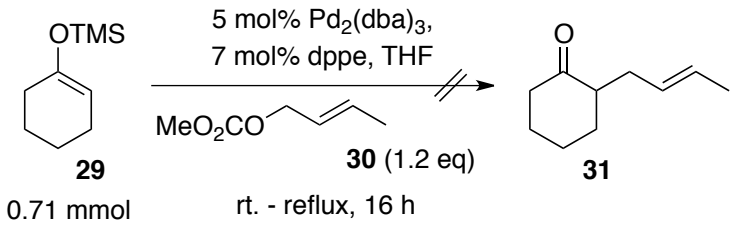


Scheme 3.14

The requisite allylic carbonate **30** was prepared by reacting methylchloroformate with crotyl alcohol **33** in the presence of base in 89 % yield (**Scheme 3.15**).

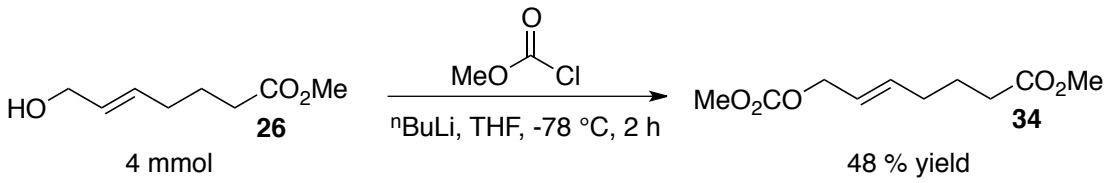
Scheme 3.15

Based on a literature procedure by Tsuji,[23] the chosen palladium source, $Pd_2(dba)_3$, was stirred with 1,2-bis(diphenylphosphino)ethane (dppe) in THF at ambient temperature, before adding the prepared carbonate **30** and silyl ether **29** and heating the reaction to reflux (**Scheme 3.16**). Lamentably, a number of attempts under the above stated conditions resulted in a complex mixture of products, potentially containing the desired ketone **31**, as indicated by ^{1}H-NMR analysis of the crude product mixture and comparison to the known compound. However, ketone **31** could not be isolated in any case.



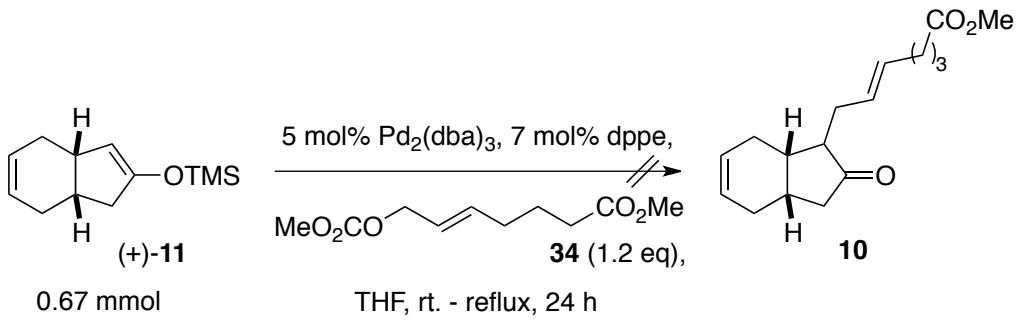
Scheme 3.16

Despite this result, it was still believed that the protocol would pose a feasible attempt in the formation of keto ester **10**, as its isolation from the reaction mixture may not be as challenging. In this regard, preparation of allylic carbonate **34** from alcohol **26** was undertaken (**Scheme 3.17**). Reaction with methylchloroformate delivered the anticipated product in 48 % yield.



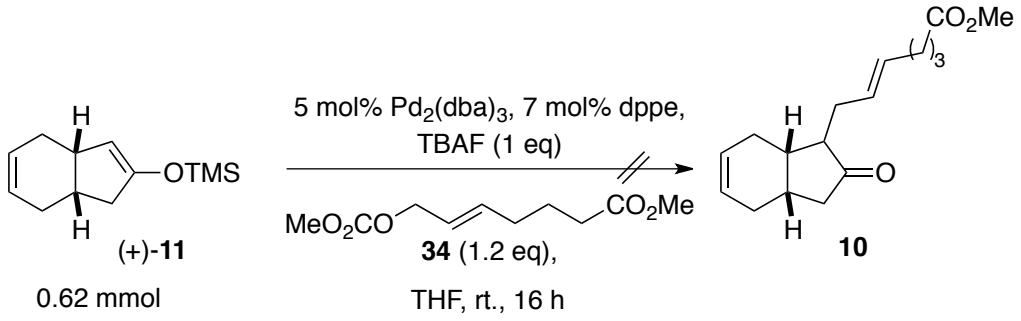
Scheme 3.17

Following the same procedure as employed for the model substrates, silyl enol ether **11** and carbonate **34** were added to a solution of the activated catalyst and heated to reflux (**Scheme 3.18**). Analysis of the crude reaction mixture by TLC prior to work up after 16 h suggested the presence of considerable amounts of enol silane **11** and quenching of the reaction at this stage resulted in the recovery of ketone **13** in 78 % yield.



Scheme 3.18

In this regard, further activation of the masked enolate was considered. It has been shown, that the addition of fluoride sources such as TBAT (tetrabutylammonium difluorotriphenylsilicate) and CsF/ZnF_2 mixtures can influence the reaction positively.[21,24] With only TBAF to hand, a second attempt was commenced with stoichiometric amounts of the fluoride source as an additive (**Scheme 3.19**). Unfortunately, once again, the reaction returned ketone **13** as the major product and none of the allylated species **10** could be detected.

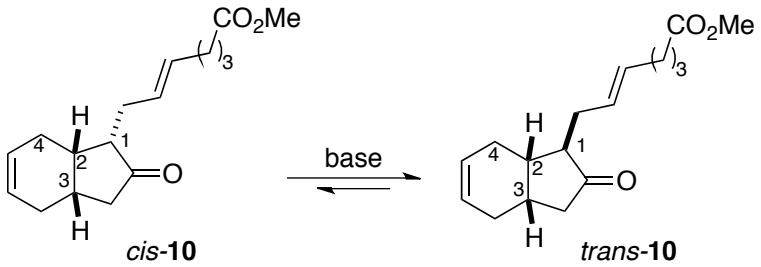


Scheme 3.19

In view of these disappointing results and the significant improvement achieved with the original protocol, further research into the application of the Tsuji-Trost allylation reaction was abandoned at this point.

Diastereoselectivity

In relation to the diastereoselectivity of the allylation reaction, attempted elucidation by extensive NMR analysis on the isolated keto ester **10** and separation of potential isomers by HPLC had been unsuccessful. Due to the *cis*-ring junction of the bicyclic core, a convex and concave side of the molecule may be assigned. Alkylation is envisaged to occur preferentially on the less hindered convex face, furnishing the *trans*-diastereomer as the major product. Having stated this, if a mixture of diastereomers prevailed, it was believed that epimerisation to the less hindered isomer could be achieved under basic conditions (**Scheme 3.20**). Moreover, it was anticipated that this would form the desired *trans*-arrangement of the side chain R and C_4, due to lowered 1,2-interactions (**Figure 3.2**).

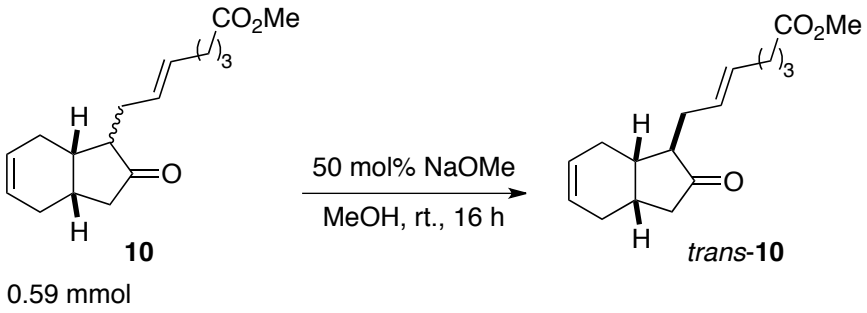


Scheme 3.20

Figure 3.2

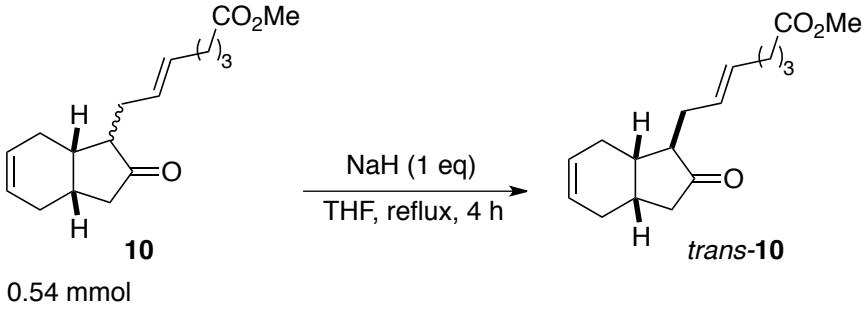
Comparison and interpretation of NMR spectra taken before and after the epimerisation should then reveal a shifting pattern and allow the identification of a respective set of signals for each isomer, although unambiguous assignment as to which diastereomer is formed preferentially may not be possible. In order to prevent hydrolysis of the methyl ester, keto ester **10** was first stirred with NaOMe in methanol

(**Scheme 3.21**). Unfortunately, no significant change in either the ^{1}H- or ^{13}C-NMR spectrum of the recovered material could be detected.



Scheme 3.21

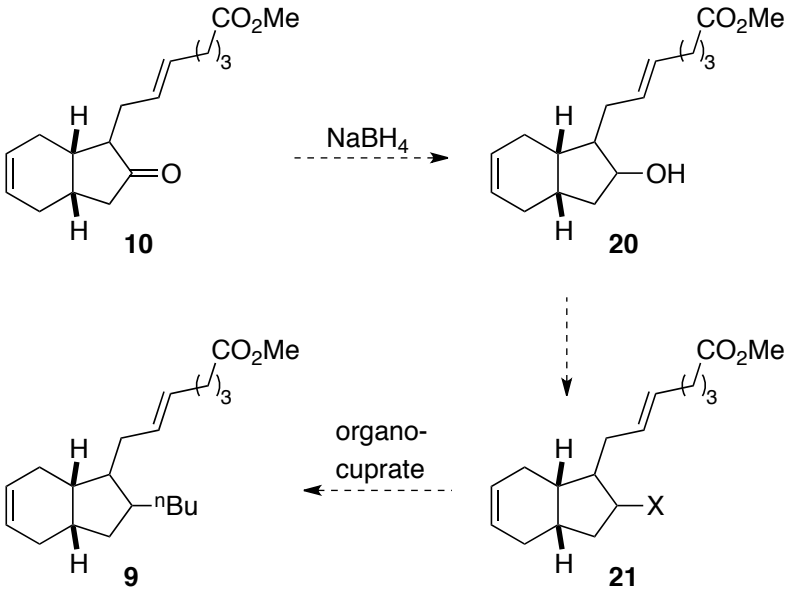
In a second attempt, stoichiometric NaH in THF was employed (**Scheme 3.22**). Once more, no decisive difference was observed after analysis of the ^{1}H-NMR spectra. It remained unclear if the allylation had generated a mixture of diastereomers and whether epimerisation would provide access to a single product preferentially. The stereoselectivity in this and further transformations towards (-)-mucosine will be discussed further (*vide infra*).



Scheme 3.22

3.4 Towards (-)-Mucosin: Route A

Efficient access to the keto ester **10** had now been established in an efficient manner from silyl enol ether **11** and allylic bromide **12** and a route towards the final product was devised. It was envisaged that reduction of ketone **10** would deliver secondary alcohol **20** (**Scheme 3.23**). Due to literature precedent, hydride attack was expected to occur preferentially from the convex face of the bicyclic core.[25] Subsequent transformation of the hydroxyl group into a suitable functional handle was anticipated to allow a direct substitution employing higher order organocuprates, furnishing the desired natural product as the ester derivative (**9**).

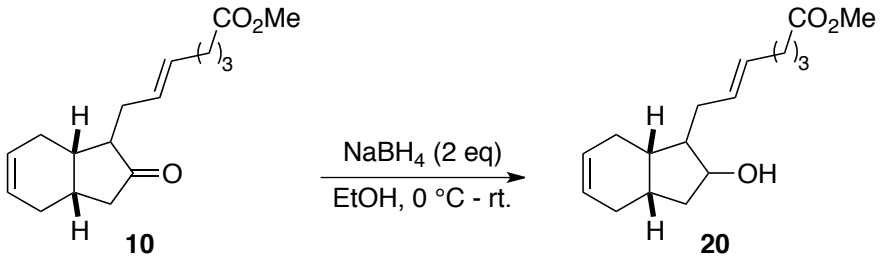


Scheme 3.23

Importantly, with an asymmetric synthesis in mind, the corresponding bromide was favoured over other halides; iodides tend to react *via* a radical mechanism, thus potentially risking the stereochemical outcome at this centre,[26] whereas secondary chlorides exhibit a substantial lack of reactivity in these transformations.[26,27]

As no conclusive results on the stereochemistry of keto ester **10** had been obtained, it was anticipated that further derivatisation of alcohol **20** would help to elucidate the relative stereochemistry of all 4 stereocentres within the molecule at this stage. With the following transformations being stereospecific, a prediction of the relative stereochemistry in the target molecule may be made, and the synthesis further adapted if necessary.

The sequence commenced with the treatment of keto ester **10** with $NaBH_4$ in ethanol at 0 °C to ambient temperature (**Scheme 3.24**, **Table 3.3**). Careful monitoring of the reaction progression by TLC analysis was required as competitive reduction of the ester functionality occurred. Nonetheless, high yields of up to 85 % of the desired alcohol **20** could be isolated in this way.

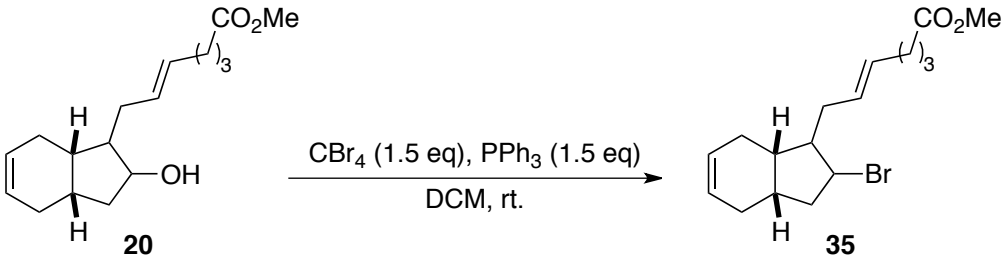


Scheme 3.24

Entry	*Scale*	*Yield **20*** (%)
1	0.42 mmol	65
2	0.27 mmol	85

Table 3.3

With alcohol **20** in hand, installation of the bromide in place of the hydroxyl group was targeted. Employing the Appel reaction, the corresponding bromide **35** could be prepared in excellent yields (**Scheme 3.25**, **Table 3.4**).



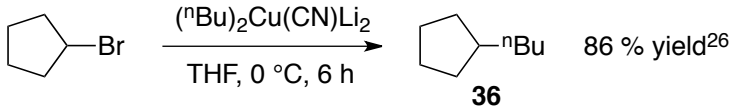
Scheme 3.25

Entry	*Scale*	*Yield **35*** (%)
1	0.34 mmol	91
2	0.29 mmol	95

Table 3.4

Importantly, the above stereospecific reaction would result in an inversion of the stereocentre, allowing for the systematic manipulation within an asymmetric approach towards (-)-mucosin. If necessary a Mitsunobu reaction could be utilised to achieve an inversion of the alcohol, resulting in overall retention of the stereochemistry once the bromide is introduced.

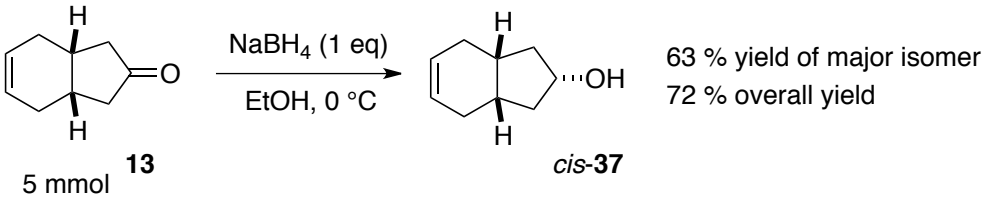
Substitution of the bromide **35** was proposed to take place by employing higher order organocuprate reagents. Despite the unactivated nature of the secondary bromide, literature precedent from Lipshutz *et. al* provided conditions utilising CuCN and ^{n}BuLi for the envisaged transformation on a similar substrate, yielding an excellent 86 % of cycloalkane **36** (**Scheme 3.26**).[26]



Scheme 3.26

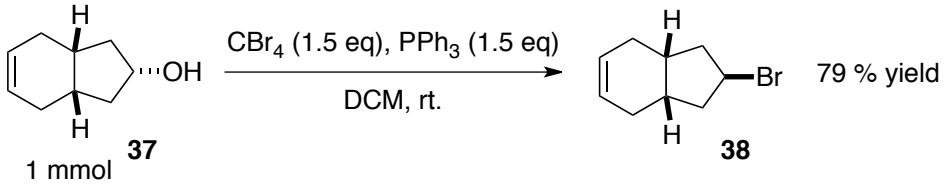
With this in mind, a trial on a model substrate was proposed. In this regard, reduction of ketone **13** and substitution of the corresponding alcohol, following the

same sequence as described above, was targeted. Reduction with $NaBH_4$ afforded the secondary alcohol **37** in 72 % overall yield as a mixture of diastereomers (**Scheme 3.27**). Up to 63 % of the major isomer could be isolated cleanly, which is believed to be the *cis*-isomer due to a sterically less hindered approach of the hydride from the convex face of the bicyclic ketone.



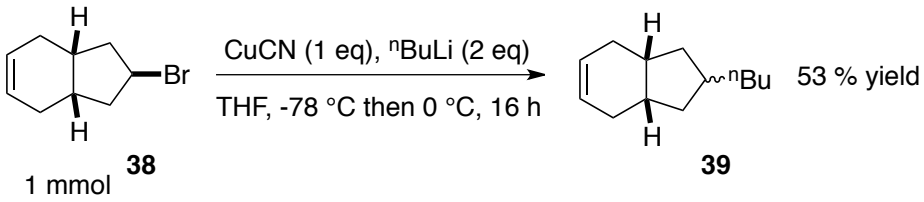
Scheme 3.27

The single isomer was then converted to the desired bromide **38** in 79 % yield. As expected, the Appel reaction proceeded stereospecifically and the single diastereomer was observed, further advocating the devised route towards (-)-mucosin (**Scheme 3.28**).



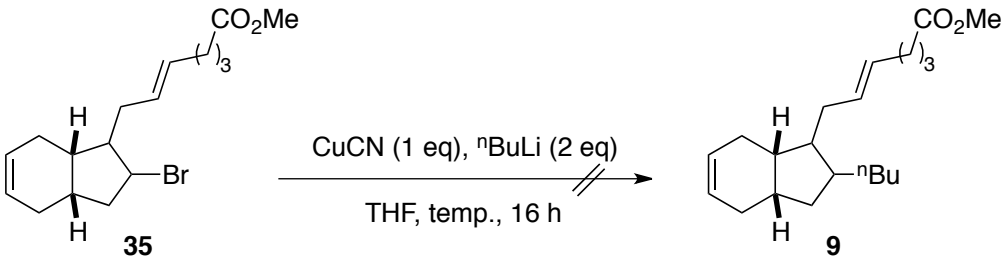
Scheme 3.28

The synthesised bromide **38** was then subjected to the literature conditions, employing cuprous cyanide and *n*-butyllithium to, firstly, generate the organocuprate species, which is then reacted with bromide **38** to yield **39** (**Scheme 3.29**). Introduction of **38** to the reaction mixture at -78 °C with continuous stirring for another 16 h at 0 °C furnished the desired product **39** in an encouraging 53 % yield. Analysis of the product **39** by ^{1}H-NMR was not conclusive with regards whether a single diastereomer had been formed.



Scheme 3.29

With this proof of concept, the transformation of the more complex bromide **35** was attempted under the same reaction conditions (**Scheme 3.30**, **Table 3.5**). Disappointingly, upon careful work up, none of the desired ester **9** was detected. Traces of the starting material were observed, along with a mixture of by-products containing the halide, identified by the chemical shift of the adjacent proton in ^{1}H-NMR, but no ester functionality (**Table 3.5**, **Entry 1**).



Scheme 3.30

Entry	*Scale*	*Temp.*	*Yield **9** (%)*
1	0.10 mmol	-78 – 0 °C	-
2[a]	0.22 mmol	-78 to -10 °C	-
3[b]	0.16 mmol	-78 – 0 °C	-

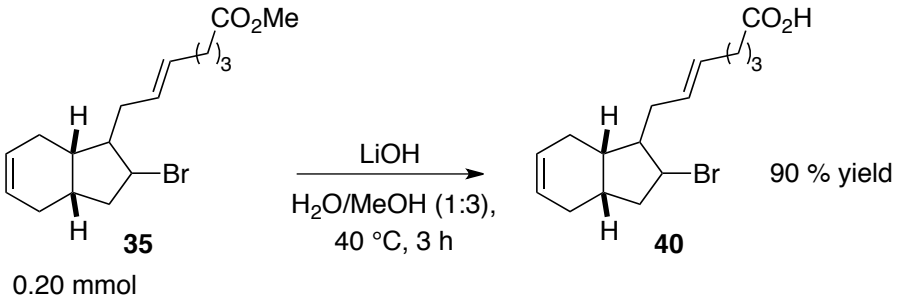
[a]72 % of **35** recovered, [b]2 eq CuCN and 4 eq ^{n}BuLi were used along with a 6 h reaction time.

Table 3.5

Competitive addition of the generated cuprate to the methyl ester was thus suspected and the reaction temperature was kept between -78 °C and -10 °C over 16 h to counteract this undesired reactivity in a second attempt (**Table 3.5**, **Entry 2**). In this instance, 72 % of the starting material was returned intact. An increase in the

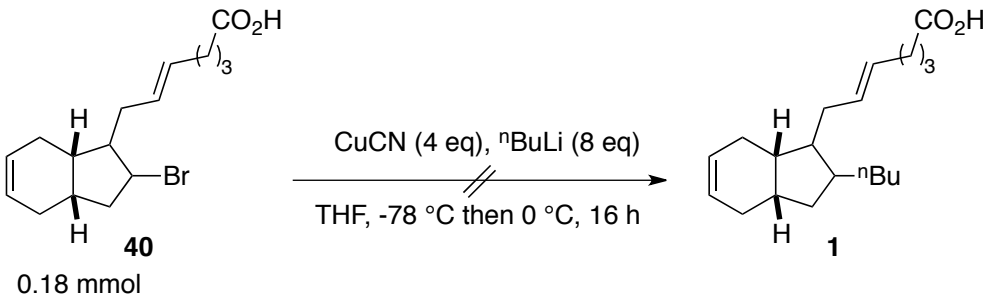
quantity of the organocuprate and a quench of the reaction after 6 h at 0 °C resulted in a combination of starting material and by-products (**Table 3.5**, **Entry 3**).

As the methyl ester seemed a potential hindrance within the above protocol, hydrolysis to the corresponding carboxylic acid was considered. It was envisaged that an extra equivalent of the organometallic reagent would result in fast deprotonation and thus protection of the carbonyl functionality, whilst performing the substitution with the remaining reagent. Accordingly, the bromo ester **35** was reacted with LiOH, affording the carboxylic acid in 90 % yield (**Scheme 3.31**).



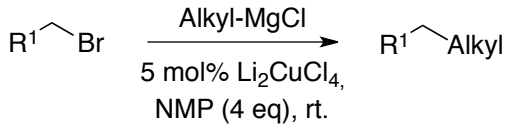
Scheme 3.31

By analogy with the first attempt, **40** was then subjected to the same reaction conditions, this time with an increased amount of cuprous cyanide and ^{n}BuLi (**Scheme 3.32**). Analysis by TLC showed full consumption of the starting material after 16 h. However, it was discovered that once more the halide had been left intact while the carbonyl portion of the substrate had degraded. It is proposed that the very hindered position of the bromide in **35** and **40** reduces the accessibility for the nucleophile and thus competitive side reactions become more prominent.



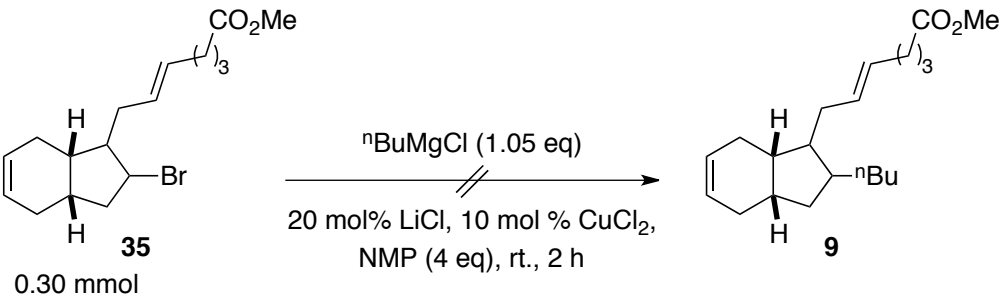
Scheme 3.32

Undaunted by these results, alternative conditions for the proposed transformation were sought. A procedure by Cahiez and co-workers utilises a copper-catalysed Kumada-type reaction to achieve the cross-coupling of sp^3-carbons.[28] Critically, *N*-methylpyrrolidinone (NMP) was employed as an additive in conjunction with cuprous chloride and an appropriate Grignard reagent to furnish high yields of the alkane products (**Scheme 3.33**).



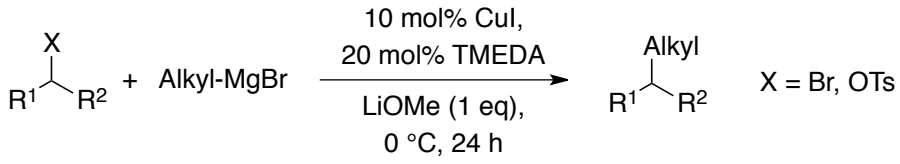
Scheme 3.33

Although these studies are focused on the conversion of primary bromides, the mild reaction conditions employed tolerate a range of functional groups, most notably esters. Based on these promising results, bromo ester **35** was exposed to a mixture of ^{n}BuMgCl, LiCl and $CuCl_2$ under the described conditions (**Scheme 3.34**). Unfortunately, even with prolonged reaction times, none of the desired compound was obtained. In part, this is believed to be due to the less reactive and hindered secondary bromide compared to the primary substrates used in Cahiez's publication.



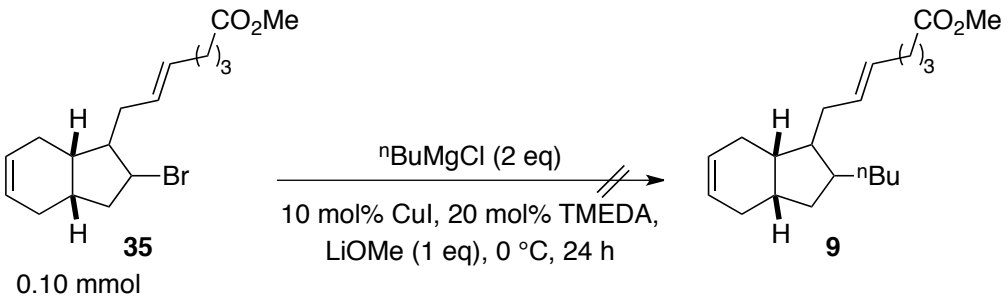
Scheme 3.34

More recently, another set of conditions for the copper-catalysed Kumada reaction on secondary alkyl halides and pseudo-halides by Liu *et. al* has been reported.[29] More specifically, secondary alkyl-Grignard reagents are utilised along with CuI, LiOMe and TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) (**Scheme 3.35**).



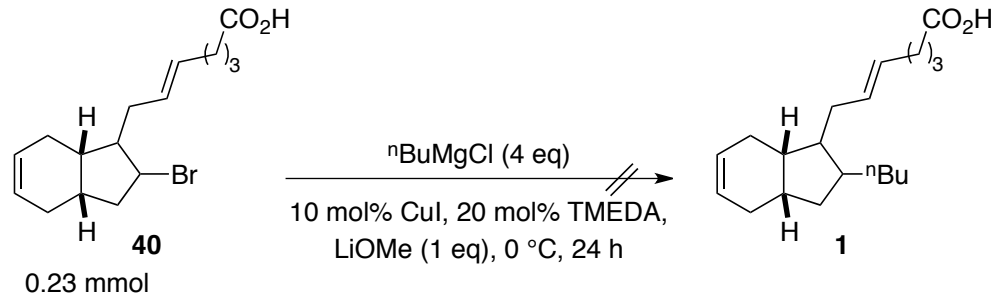
Scheme 3.35

Notably, amongst other functional groups, aryl esters and ketones are tolerated and the process has been found to proceed with inversion at the chiral halide. It was anticipated that with this system, a distinction between the two functional groups in **35** could be achieved (**Scheme 3.36**). Lamentably, once more, a complex mixture of products was obtained, suggesting that elimination and reduction of the bromide had occurred predominantly, along with degradation of the methyl ester.



Scheme 3.36

Subjecting the analogous carboxylic acid **40** to these conditions gave rise to the same disappointing observation (**Scheme 3.37**).



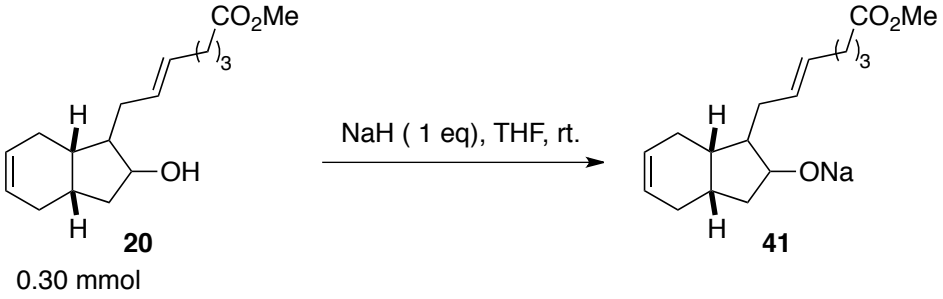
Scheme 3.37

As mentioned, steric hindrance and the unactivated character of the bromide are held accountable for the encountered problems. Alternative cross-coupling methods such as nickel-catalysed Suzuki[30] and Negishi[31] reactions, as documented by Fu *et. al*, have been considered, however, time constraints led to the termination of further research into this route at this point.

3.4.1 Elucidation of Stereochemistry

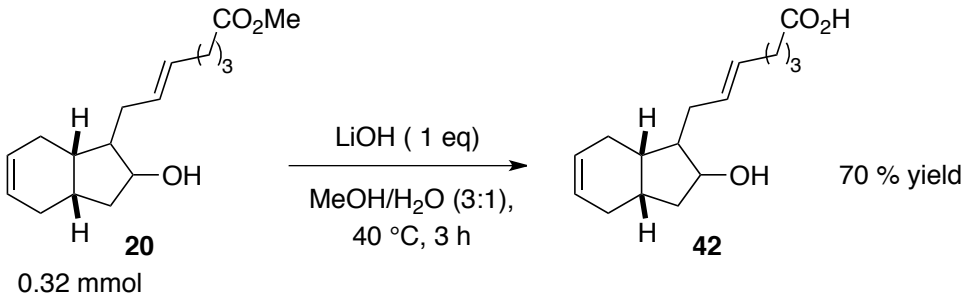
In an effort to determine the absolute stereochemistry installed through asymmetric deprotonation, allylation and subsequent reduction of bicyclic ketone **13** and in order to allow a prediction of the concluding stereochemistry of **1** following the

synthetic sequence as outlined in route A, crystallisation of alcohol ester **20** for X-ray analysis was attempted. At the outset, preparation of the sodium alkoxide **41** from the parent alcohol was considered. In this regard, **20** was treated with NaH in THF and the solvent then removed *in vacuo* (**Scheme 3.38**). Quantitative formation of the alkoxide was assumed. Unfortunately, the resulting thick oil could not be dissolved in any suitable solvent system and crystallisation was unproductive.



Scheme 3.38

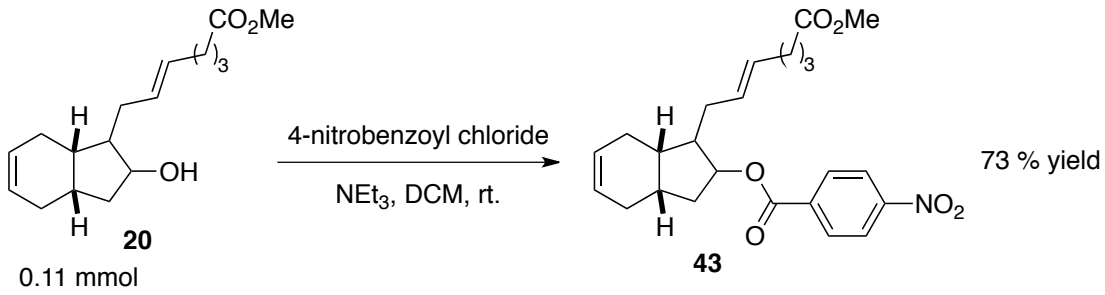
Attention was then focused on the preparation of carboxylic acid **42** *via* hydrolysis of the methyl ester (**Scheme 3.39**). Lamentably, any crystallisation attempt conducted with this material was met with failure and no crystals for X-ray analysis could be obtained.



Scheme 3.39

Undaunted by these results, formation of a bulky aryl ester was considered to be beneficial. As such, alcohol **20** was treated with *p*-nitrobenzoyl chloride to give the corresponding ester **43** in 73 % yield (**Scheme 3.40**). Crystallisation was attempted by slow evaporation of $CHCl_3$, as well as by slow diffusion of hexane into a saturated

solution of **43** in DCM. Once more, no crystals of sufficient quality for the analysis by X-ray could be obtained.



Scheme 3.40

As crystallisation, and thus interpretation of the absolute stereochemistry in **20** and derivatives, had been unproductive, analysis of the relative stereochemistry *via* ^{1}H-NMR analysis was targeted as an alternative. The distinct proton signals for the unsaturated moieties, as well as the signal for the tertiary CH (C_8) bearing the aryl ester, in **43** were envisaged to aid in the identification and assignment of the protons at the crucial stereocentres at C_1, C_6 and C_9 by HMBC and HSQC experiments (**Figure 3.3**). Additionally, nuclear Overhauser effect spectroscopy (NOESY) experiments were proposed to reveal through space interactions of the protons and thus allow for the elucidation of the relative stereochemistry in the 5 membered ring.

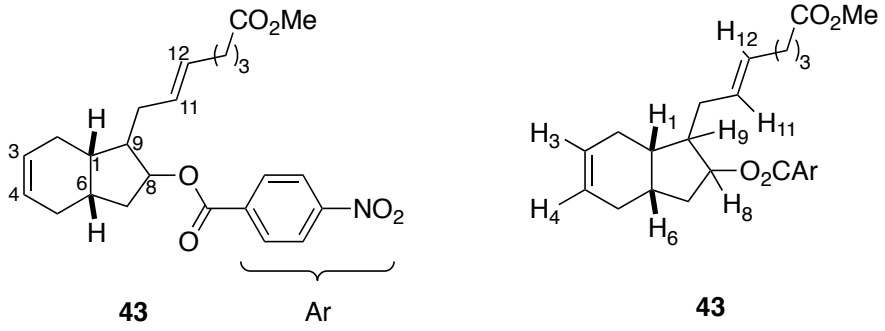


Figure 3.3

Based on NOESY, the *cis*-relationship of the two bridgehead protons H_1 and H_6 was confirmed first (**Figure 3.4 A**). At the same time, a close proximity was observed

between these two protons and H_8, but not to H_9. In this regard, it has been established that H_1, H_6 and H_8 are on the same, convex, face of the bicyclic core.

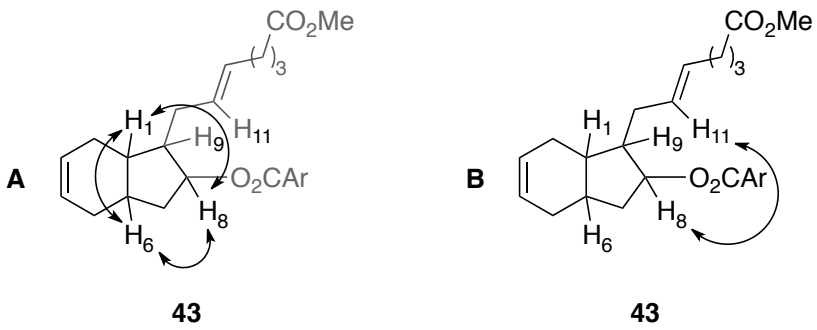


Figure 3.4

Further evidence for a *trans*-relationship of protons 1, 6 and 8 to H_9 was sought. No NOE-based interactions were detected between H_9 and the remaining protons on the concave side of the molecule, however, H_8 showed another NOE to H_{11} in the allylic side chain (**Figure 3.4 B**). It was thus concluded that the allylic side chain is on the convex face of the molecule, *cis* to H_8 and the bridgehead protons, whereas H_9 and the aryl ester are on the opposite, concave face (**Figure 3.5**).

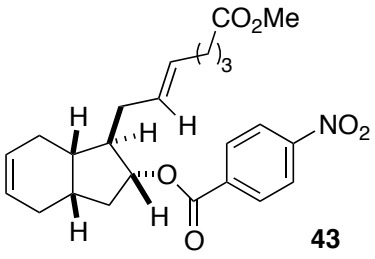
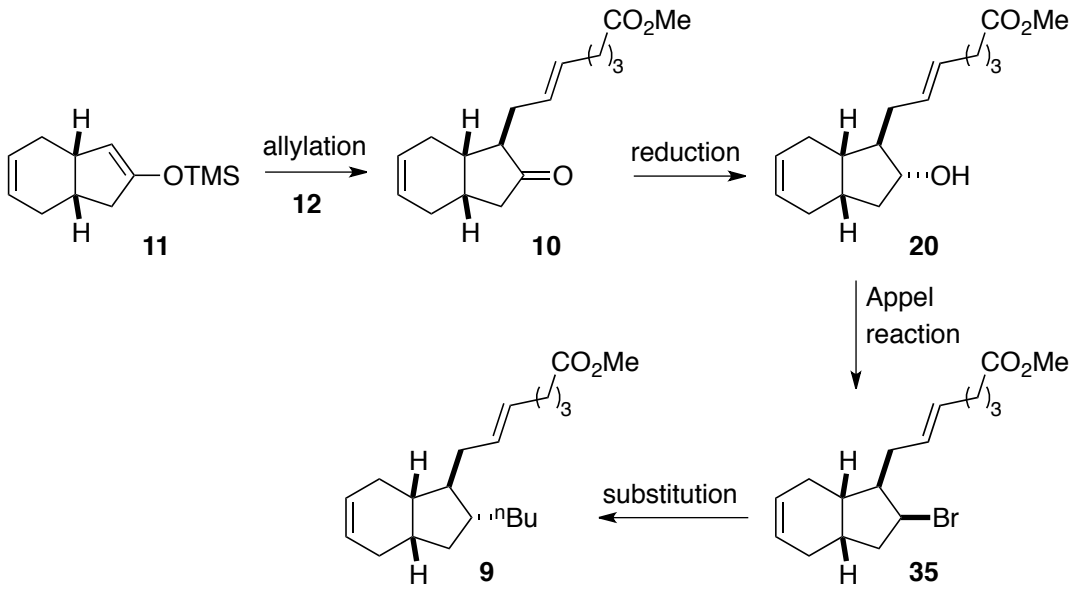


Figure 3.5

Gratifyingly, the assignment of the relative stereochemistry in **43** advocates the initially devised route towards (-)-mucosin. As proposed, allylation of enol silane **11** occurs preferentially from the more accessible convex face (**Scheme 3.41**). Moreover, the reduction of ketone **10** provides alcohol **20** selectively, installing the fourth stereocentre and a *trans*-relationship between allylic side chain and the hydroxyl group as anticipated. Subsequent stereospecific Appel reaction and substitution of the

bromide are envisaged to result in an overall retention of the stereocentre, delivering the correct relative stereochemistry for ester **9**.



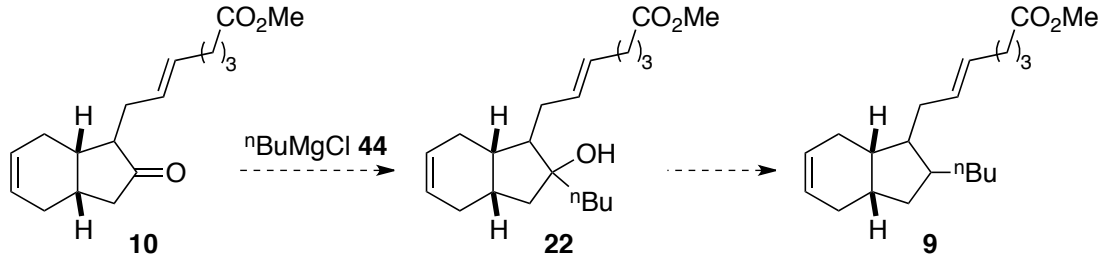
Scheme 3.41

With the relative stereochemistry identified, comparison of the optical rotation of ester **9** to the known value would allow the confirmation of the absolute stereochemistry. As this is governed by the chiral magnesium bisamide base-mediated deprotonation, employment of the appropriate enantiomer of the chiral amine is envisaged to give access to both, the natural and unnatural isomer of mucosin.

3.5 Towards (-)-Mucosin: Route B

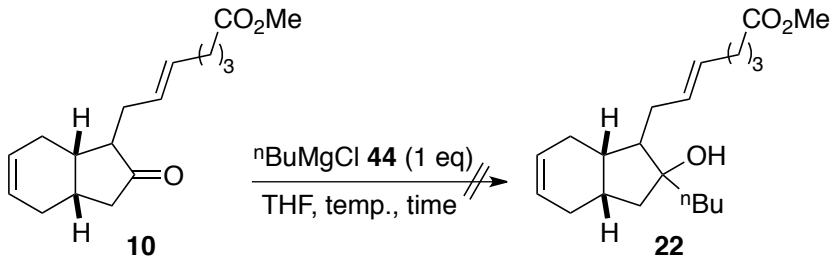
As the introduction of the *n*-butyl side chain in the last step of the synthetic sequence in route A had been unsuccessful, a change in strategy was required. Accordingly, a new approach was taken, focusing on the direct addition of a nucleophile, such as Grignard **44**, to keto ester **10** (**Scheme 3.42**). It was envisaged that the more electrophilic ketone would react preferentially over the present ester

despite the hindering α-substitution. With the quaternary alcohol in hand, a hydride reduction was anticipated to deliver the natural product derivative **9**.



Scheme 3.42

Preliminary attempts using Grignard reagent **44** at 0 °C were conducted as depicted in **Scheme 3.43**, **Table 3.6**. Surprisingly, mainly starting material was returned after 1.5 h. In an effort to increase the reactivity, the reaction was allowed to warm to ambient temperature after the addition of **44**, however this resulted in degradation of the material.



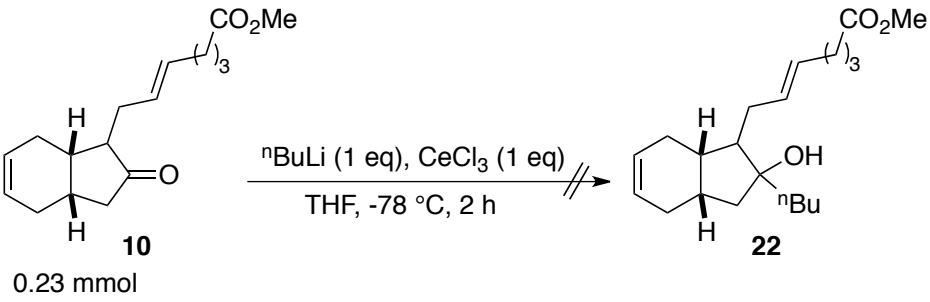
Scheme 3.43

Entry	*Scale*	*Conditions*	*Yield **10*** (%)	*Yield **22*** (%)
1	0.24 mmol	0 °C, 1.5 h	90	-
2	0.22 mmol	0 °C – rt., 16 h	-	-

Table 3.6

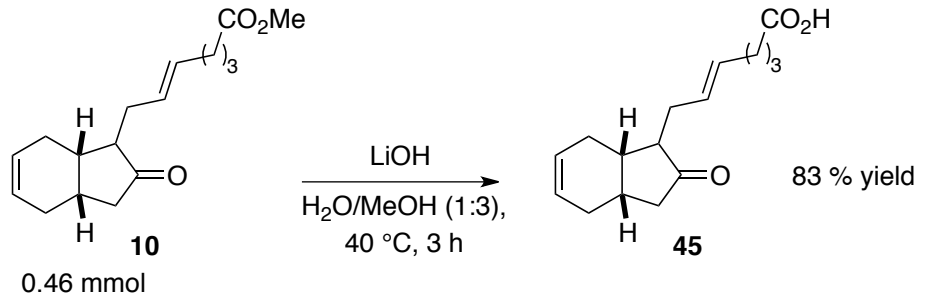
Endeavours were then focused on utilising the analogous lithium reagent with $CeCl_3$ to temper the basicity and increase the nucleophilicity of the alkyl unit. More specifically, ^{n}BuLi and $CeCl_3$ were reacted at -78 °C for 30 min prior to the addition

of keto ester **10** (**Scheme 3.44**). Unfortunately, the above protocol delivered no conversion to alcohol **22**. Instead, by-products with a reduced ester moiety were detected by ^{1}H-NMR analysis. Analogous to the unsuccessful substitution and cross-coupling of bromide **35** in route A, steric encumbrance is proposed to decrease the reactivity to an extent where competitive attack of the methyl ester becomes more accessible.



Scheme 3.44

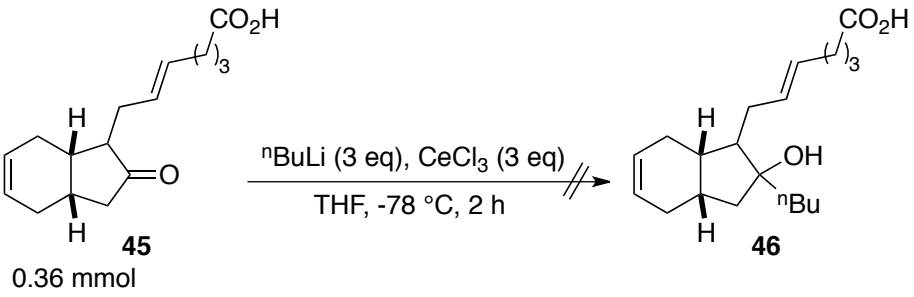
As an alternative, carboxylic acid **45** was anticipated to allow the desired transformation with an increased amount of nucleophile. In this regard, ester **10** was treated with LiOH to yield the hydrolysed product in 83 % yield (**Scheme 3.45**).



Scheme 3.45

Next, the carboxylic acid was subjected to the above described reaction conditions with ^{n}BuLi and $CeCl_3$ (**Scheme 3.46**, **Table 3.7**). Disappointingly, the reaction did not proceed as envisaged. Despite the observation of traces of ketone alkylation, the carboxylic acid did not stay intact and a number of different by-

products were formed. Employing a reverse addition protocol, where $^{n}BuLi/CeCl_3$ was added to the ketone **45**, gave rise to a similarly unsatisfactory mixture and none of the desired product **46** could be isolated. Due to time constraints, further research into this route towards (-)-mucosin was halted at this stage.



Scheme 3.46

Entry	*Scale*	*Yield **46*** (%)
1	0.36 mmol	-
2[a]	0.09 mmol	-

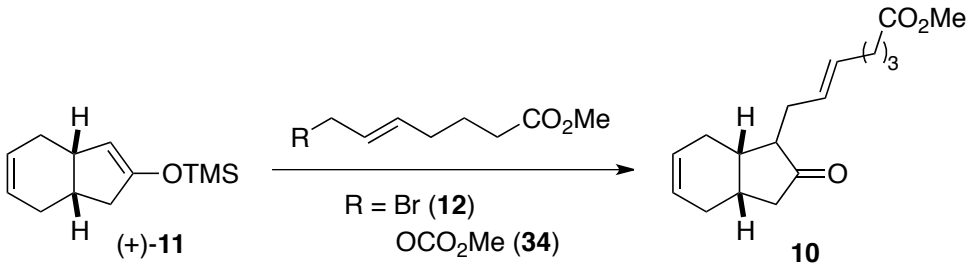
[a]Reversed addition protocol

Table 3.7

4. Conclusions and Future Work

Methodology studies centred around the deprotonation of enolisable ketones with magnesium-based base reagents have been extended and applied towards the synthesis of a natural product, (-)-mucosin **1**. In accordance with the devised routes towards the key fragments, *meso*-ketone **13** has been obtained in a short sequence of synthetic steps in a notable overall yield of 51 %. Subsequent asymmetric formation of enol silane **11** was achieved in an excellent 86 % yield and impressive 92:8 e.r.. Importantly, the second key fragment, allylic bromide **12**, was prepared efficiently on large scale from cyclopentene **24**, furnishing the desired compound in a good 41 % yield over 4 steps. Future work in this part of the synthesis should include more detailed studies on the enantioselective deprotonation of **13**, especially at more convenient temperatures of -40 °C and above.[9]

Particular emphasis has been placed on the efficient access to keto ester **10** (**Scheme 3.47**). In this regard, the original approach employing allylic bromide **12** delivered high yields up to 70 % of the desired product. However, no definite analyses of the diastereoselectivity of the allylation could be made at this stage within the synthesis.

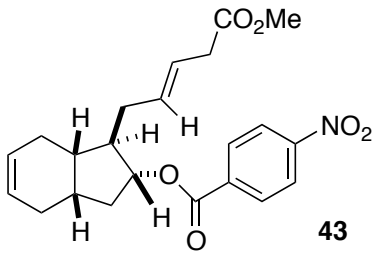


Scheme 3.47

As an alternative to the coupling of enol silane **11** and bromide **12**, investigations into utilising palladium-catalysed Tsuji-Trost allylations with a

respective carbonate have been conducted on both, a model substrate and with enol silane **11** and allylic carbonate **34**. Disappointingly, the proposed transformation did not deliver the anticipated ester **10**. Additionally, a brief exploration of a one-pot procedure, based on the lithium-mediated asymmetric deprotonation of ketone **13** and direct employment of bromide **12** in an external quench protocol, was undertaken. In this instance, a decreased yield of 20 % was observed.

With the bicyclic core including the allylic side chain assembled, attention was focused on completing the natural product synthesis. As such, a strategy including the reduction of the ketone moiety in **10** and the substitution of a suitable leaving group *via* organocurprates or Kumada cross-coupling reactions was pursued. Despite the efficient preparation of bromides **35** and **40**, installation of the *n*-butyl side chain was unsuccessful, which was attributed to the unactivated and very hindered position of the halide. Importantly, derivatisation of the intermediate alcohol **20** to ester **43** and subsequent analysis by NMR experiments allowed the relative stereochemistry of all 4 chiral centres at this stage to be elucidated (**Figure 3.6**), supporting the devised route towards (-)-mucosin. Efforts to establish the absolute stereochemistry *via* X-ray crystallography were unsuccessful.

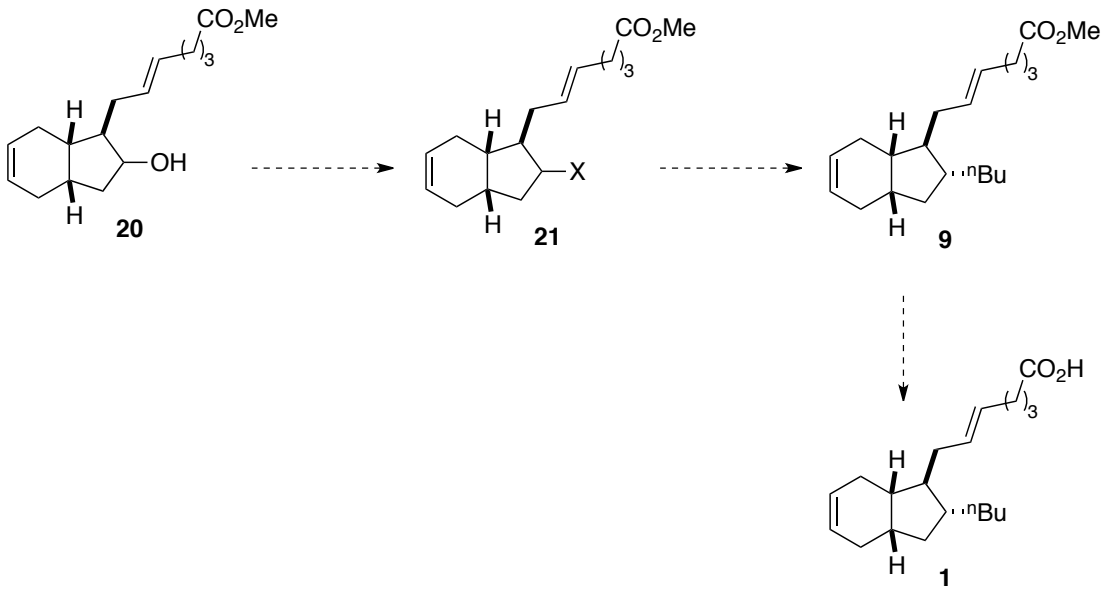


43

Figure 3.6

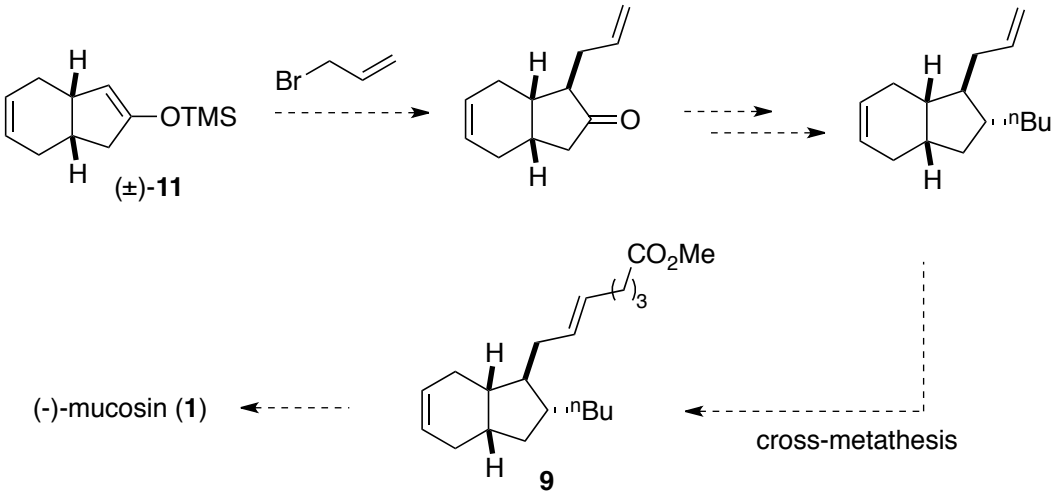
A second approach towards (-)-mucosin has been pursued, focusing on the introduction of the *n*-butyl group at an earlier stage. In this regard, addition of an organometallic reagent to ketone **10** and carboxylic acid derivative **45** has been attempted, however this has been of limited success, due to the more accessible ester or carboxylic acid moieties.

Further research in this area should focus on different strategies to introduce the side chain and completion of the natural product, such as nickel-catalysed Negishi or Suzuki cross-couplings of secondary unactivated halides as precedented by Fu (**Scheme 3.48**).[22,23]



Scheme 3.48

Alternatively, reducing the steric hindrance of the allylic side chain and simultaneously omitting the problematic ester moiety may allow for the installation of the *n*-butyl group *via* the cuprate chemistry described. In this regard, reaction of enol silane **11** with allyl bromide should be considered (**Scheme 3.49**). Cross-metathesis with an appropriate substrate at a later stage may afford the desired natural product efficiently.


H
OTMS
H
(±)-11
Br
H
O
H
H
nBu
H
CO2Me
3
H
nBu
H
9
(-)-mucosin (1)
cross-metathesis

Scheme 3.49

5. Experimental

5.1 General

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[32]

- THF was dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen.

- $^{n}Bu_2Mg$, obtained as 1 M solution in heptane, and $^{n}BuMgCl$, obtained as 2 M solution in THF, were standardised using iodine in a saturated solution of LiCl in THF as an indicator.[33]

- MeLi, obtained as 1.6 M solution in Et_2O, and $^{n}BuLi$, obtained as a 2.5 M solution in THF, were standardised using salicylaldehyde phenylhydrazone as an indicator.[34]

- DMPU, TMEDA and (*R,R*)-*bis*(methylbenzyl)amine were dried by heating to reflux over calcium hydride and distilled under reduced pressure, then purged with and stored under argon over 4 Å molecular sieves.

- DMSO and NMP were dried by distillation under argon and stored under argon.

- Triphenylphosphine was purified by recrystallisation from EtOH and stored under argon.

- CuCN and CuI were dried at 100 °C *in vacuo* over 16 h, then purged with and stored under argon.

- $CeCl_3.7H_2O$ was dried gradually at 60 °C, 80 °C and 140 °C *in vacuo* over 16 h, then purged with and stored under argon.

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254. This was analysed using a Mineralight UVGL-25 lamp and developed using potassium permanganate or vanillin solution.

Flash chromatography was carried out using Prolabo silica gel (230-400 mesh).

Gas chromatography was carried out using a Carlo Erba HRGC 5300 gas chromatograph fitted with (i) a CP SIL-19CB column or (ii) a CP-Chirasil-DEX CB column. Detection was by flame ionisation and the chromatograph was interpreted using JLC 6000 computer software.

^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX 400 spectrometer at 400 MHz if not otherwise stated. Chemical shifts are reported in ppm, and coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions unless otherwise specified.

High-resolution mass spectra were obtained on a Finnigan MAT900XLT instrument at the EPSRC National Mass Spectrometry Services Centre, University of Wales, Swansea.

FTIR spectra were obtained on a Nicolet Impact 400D machine.

Elemental analysis was obtained using a Carlo Erba 1106 CHN analyser.

Air-sensitive reactions were carried out using Schlenk apparatus, which was initially evacuated and flame-dried, then purged with argon.

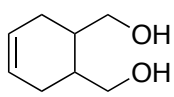
5.2 Experimental Procedures

5.2.1 Preparation and Deprotonation of *meso*-Ketone 13

Preparation of cis-*1,2,3,6-Tetrahydrophthalyl alcohol*, **23**:

Scheme 3.7: $LiAlH_4$ (11.4 g, 300 mmol) was transferred into a flame dried round-bottom flask under an argon atmosphere, dissolved in dry THF (350 ml) and cooled to 0 °C using an ice bath. *cis*-1,2,3,6-Tetrahydrophthalic anhydride (22.8 g, 150 mmol) was added dropwise as a solution in THF (100 ml). The reaction mixture was continuously stirred and allowed to warm to ambient temperature over 2.5 h before being carefully quenched with MeOH and poured into a saturated aqueous solution of Na_2SO_4. The resulting slurry was filtered and the remaining solid washed EtOAc (3 x 300 ml). The two phases of the filtrate were separated and the aqueous washed with EtOAc (3 x 250ml), before drying the combined organics over Na_2SO_4 and concentrating them *in vacuo*. The product was thus obtained as a colourless oil (20.8 g, 147 mmol, 98 %).

cis-*1,2,3,6-Tetrahydrophthalyl alcohol*, **23**:[14]



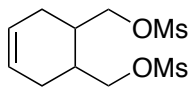
Colourless oil; IR ($CHCl_3$): 1024, 1437, 2887, 3285 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.98-2.21 (m, 6H, aliphatic protons), 2.59 (br s, 2H, O*H*), 3.57-3.65 (m, 2H, OCH_2), 3.71-3.79 (m, 2H, OCH_2), 5.61-5.64 (m, 2H, C*H*=C*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 27.0, 37.8, 64.2, 125.5.

The data observed are in accordance with literature values.

Preparation of cis-*1,2,3,6-Tetrahydrophthalyl alcohol dimethanesulfonate*, **16**:

Scheme 3.7: A solution of alcohol **23** (20.8 g, 147 mmol) in Et_2O (500 ml) and DCM (150 ml) was cooled to 0 °C in an ice bath before addition of NEt_3 (61.5 ml, 441 mmol). Dropwise addition of mesyl chloride (27.3 ml, 353 mmol) resulted in the formation of a white precipitate, which could be broken up with further addition of DCM (50 ml). The reaction mixture was then stirred at ambient temperature overnight, prior to being concentrated *in vacuo* and subsequently dissolved in H_2O (300 ml) and DCM (300 ml). The biphasic solution was separated and the aqueous extracted with DCM (3 x 150 ml). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield an orange/brown solid, which was repeatedly triturated with MeOH to yield the product as a white solid (32.1 g, 108 mmol, 73 %).

cis-*1,2,3,6-Tetrahydrophthalyl alcohol dimethanesulfonate*, **16**:[35]



Colourless solid, M.p.: 86-87 °C; IR ($CHCl_3$): 947, 1165, 1341 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.99 (dd, 2H, J = 4.9 Hz, J = 16.8 Hz, CHCH_2), 2.25 (dd, 2H, J = 4.9 Hz, J = 16.8 Hz, CHCH_2), 2.38-2.49 (m, 2H, aliphatic protons), 3.05 (s, 6H, SO_2CH_3), 4.17 (dd, 2H, J = 9.9 Hz, J = 7.2 Hz, CH_2OMs), 4.29 (dd, 2H, J = 9.9 Hz, J = 7.2 Hz, CH_2OMs), 5.65-5.72 (m, 2H, C*H*=C*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 26.0, 34.0, 37.4, 69.9, 124.8.

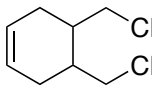
The data observed are in accordance with literature values.

*Preparation of Cyclohexene-4-*cis-*1,2-diacetonitrile*, **17**:

Scheme 3.7: A flame-dried, round-bottom flask, under argon, was charged with methanesulfonate **16** (32.1 g, 108 mmol), NaCN (20 g, 410 mmol) and distilled DMSO (350 ml). The flask was fitted with a condenser and evacuated/purged with

argon (3 x) before heating the reaction to 100 °C for 4 h. The reaction mixture was treated with H_2O (150 ml) and left to cool to ambient temperature. The biphasic solution was then separated and the aqueous extracted with DCM (3x 100 ml). The organic extracts were concentrated *in vacuo*, taken up in EtOAc (150 ml) and repeatedly washed with H_2O (3 x 200 ml). The organics were then dried over Na_2SO_4 and concentrated *in vacuo* to yield the product as a colourless oil (16.6 g, 103 mmol, 96 %).

Cyclohexene-4-cis-*1,2-diacetonitrile*, **17**:[14]



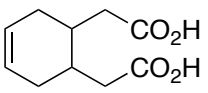
Colourless oil; IR ($CHCl_3$): 1422, 1442, 1653, 2247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.98-2.07 (m, 2H, aliphatic ring protons), 2.31-2.43 (m, 8H, aliphatic ring protons), 5.64-5.72 (m, 2H, C*H*=C*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) 18.0, 28.1, 32.6, 117.8, 123.9.

The data observed are in accordance with literature values.

Preparation of Cyclohexene-4-cis-*1,2-diacetic acid*: **18**:

Scheme 3.7: Diacetonitrile **17** (16.6 g, 103 mmol) was transferred into a round-bottom flask and treated with aqueous KOH (33 %, 100 ml). The reaction was heated to reflux for 16 h before acidifying it with concentrated HCl (60 ml). The white precipitate thus formed was filtered, washed with H_2O (100 ml) and dried *in vacuo*. Residual H_2O was removed by azeotroping with toluene to yield the product as a beige solid (18 g, 91 mmol, 88 %).

Cyclohexene-4-cis-*1,2-diacetic acid*: **18**:[14]



Beige solid; M.p.: 156-158 °C; IR ($CHCl_3$): 1694, 2919 cm^{-1}; ^1H NMR (400 MHz, MeOD): δ(ppm) 1.90 (dd, 2H, J = 4.2 Hz, J =

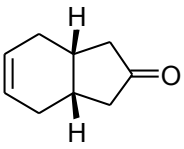
15.6 Hz, aliphatic ring protons), 2.20-2.37 (m, 8H, aliphatic ring protons), 5.03 (s, 2H, CO_2H), 5.62-5.70 (m, 2H, C*H*=C*H*); ^{13}C NMR (400 MHz, MeOD): δ(ppm) 28.4, 32.2, 34.1, 124.4, 175.1.

The data observed are in accordance with literature values.

Preparation of cis-*Bicyclo[4.3.0]non-3-en-8-one*, **13**:

Scheme 3.7: A solution of diacetic acid **18** (9.9 g, 50 mmol) in acetic anhydride (95 ml, 1 mol) was heated to reflux for 2.5 h before the addition of sodium acetate (14 g, 170 mmol) and further refluxing for 16 h. The reaction mixture was then cooled to ambient temperature, diluted with Et_2O (100 ml) and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. Further purification was carried out by flash chromatography eluting the silica gel column with a gradient of Et_2O in petroleum ether (0-40 %). The product was isolated as a colourless oil (5.9 g, 43 mmol, 85 %).

cis-*Bicyclo[4.3.0]non-3-en-8-one*, **13**:[14]



Colourless oil; IR ($CHCl_3$): 1136, 1406, 1736, 2901 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.85 (dd, 2H, J = 3.8 Hz, J = 16.7 Hz, aliphatic ring protons), 2.06 (dd, 2H, J = 6.2 Hz, J = 18.3 Hz, aliphatic ring protons), 2.22-2.36 (m, 4H, aliphatic ring protons), 2.40-2.48 (m, 2H, aliphatic ring protons), 5.64-5.72 (m, 2H, C*H*=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 26.3, 32.3, 44.6, 124.6, 219.5.

The data observed are in accordance with literature values.

*Asymmetric Deprotonation of Bicyclic Ketone **13***

*General Procedure for the Preparation of Magnesium Bisamide (R,R)-**19***:

(*R*,*R*)-**19**: $^{n/s}Bu_2Mg$ (1 ml, 1 mmol, 1 M solution in heptane) was transferred into a flame-dried Schlenk tube, under argon atmosphere, and the solvent removed *in vacuo* until the appearance of a white solid. THF (10 ml) was then added followed by (*R*,*R*)-bis(1-phenylethyl)amine (0.42 ml, 2 mmol) and the mixture was allowed to stir at reflux for 90 min under an atmosphere of argon. After this time quantitative formation of chiral magnesium bisamide (*R*,*R*)-**19** was assumed (1 mmol). During magnesium bisamide base formation the reaction vessel was kept under argon.

Asymmetric Preparation of Enol Silane Intermediate, **11**: *Typical Procedure*

Table 3.1, **Entry 1**: A solution of chiral magnesium bisamide base (*R*,*R*)-**19** (1 mmol, *see General Procedure above*) in THF (10 ml) was cooled to -78°C under argon. The Schlenk flask was then charged with DMPU (60 µl, 0.4 mmol) and TMSCl (0.5 ml, 1 mmol) and the mixture stirred for 20 min at -78 °C. *cis*-Bicyclo(4.3.0)non-3-en-8-one **13** (0.1 ml, 0.8 mmol) was dissolved in freshly distilled THF (2 ml) and then added to the mixture over a period of 1 h using a syringe pump. The resulting solution was allowed to stir at -78 °C overnight for 16 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution (10 ml) at -78 °C. After warming to room temperature, the reaction mixture was extracted with diethyl ether (2 x 15 ml) and washed with saturated aqueous $NaHCO_3$ (2 × 5 ml). The combined organic layers were dried over Na_2SO_4 and then concentrated *in vacuo* to give a pale yellow oil. The silyl enol ether product was purified *via* flash chromatography, eluting with petroleum ether (30-40 °C) and diethyl ether (9:1). The combined product fractions were concentrated *in vacuo*. The product silyl enol ether **11** was isolated as colourless oil (48 mg, 0.23 mmol, 29 % yield). The optical rotation was measured ($[\alpha]_D^{20}$ = +48.2 ° (c = 1, $CHCl_3$)) and used to calculate the er (92:8).

The following experiments were carried out according to the above *Typical Procedure*. Data are reported as: (a) chiral Mg amide base, *General Procedure*, (b) volume of THF, (c) DMPU, (d) TMSCl, (e) *cis*-bicyclo(4.3.0)non-3-en-8-one **13**, (f) volume of THF for **13**, (g) reaction conditions, (h) isolated yield of **11**, and (i) optical rotation/e.r.

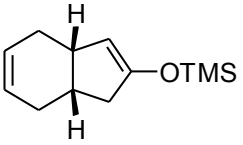
Prior to column chromatography in experiments detailed in **Table 3.1**, **Entries 3** and **4**, the silica gel was dried in an oven and left to cool to ambient temperature in a desiccator under an argon atmosphere.

Table 3.1, **Entry 2**: (a) (*R*,*R*)-**19**, 1 mmol, (b) THF, 10 ml, (c) DMPU, 60 μl, 0.4 mmol, (d) 0.5 ml, 1 mmol, (e) **13**, 0.1 ml, 0.8 mmol, (f) THF, 2 ml), (g) -78 °C, 16 h, (h) 115 mg, 0.55 mmol, 68 %, and (i) 46.9 °, 91:9.

Table 3.1, **Entry 3**: (a) (*R*,*R*)-**19**, 1 mmol, (b) THF, 10 ml, (c) DMPU, 60 μl, 0.4 mmol, (d) 0.5 ml, 1 mmol, (e) **13**, 0.1 ml, 0.8 mmol, (f) THF, 2 ml, (g) -78 °C, 16 h, (h) 145 mg, 0.70 mmol, 87 %, and (i) 45.9 °, 90:10.

Table 3.1, **Entry 4**: (a) (*R*,*R*)-**19**, 1.5 mmol, (b) THF, 10 ml, (c) DMPU, 90 μl, 0.6 mmol, (d) 0.75 ml, 1.5 mmol, (e) **13**, 0.15 ml, 1.2 mmol, (f) THF, 2 ml, (g) -78 °C, 16 h, (h) 215 mg, 1.03 mmol, 86 %, and (i) 48.1 °, 92:8.

Enol silane intermediate, **11**:[13]



Colourless oil; IR ($CHCl_3$): 1200, 1252, 1337, 1644, 2922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 0.21 (s, 9H, $Si(CH_3)_3$), 1.75-1.83 (m, 1H, aliphatic ring proton), 1.85-1.91 (m, 1H, aliphatic ring proton), 1.93-1.99 (m, 1H, aliphatic ring proton), 2.13-2.21 (m, 2H, aliphatic ring protons), 2.39-2.51 (m, 2H, aliphatic ring protons), 2.73-2.80 (m, 1H, aliphatic ring proton), 4.58 (s, 1H, C*H*=COTMS), 5.81-5.91 (m, 2H, C*H*=C*H*); ^{13}C

NMR (400 MHz, $CHCl_3$): δ(ppm) 1.0, 28.8, 29.0, 33.3, 39.4, 41.2, 108.1, 128.0, 128.7, 154.1.

The optical rotation was measured (c = 1, $CHCl_3$) and used to calculate the enantiomeric excess from the literature standard ($[\alpha]_D^{20}$ = +45.8 ° (c = 1, $CHCl_3$), 90:10 e.r.).[13]

The data observed are in accordance with literature values.

Asymmetric Preparation of Enol Silane Intermediate, **11**: *Control Reaction with Chiral Lithium Amide*

A flame-dried flask, under argon, was charged with (*R*,*R*)-bis(1-phenylethyl)amine (0.22 ml, 1 mmol) and THF (7 ml) and cooled to -78 °C before dropwise addition of ^{n}BuLi (0.40 ml, 1 mmol, 2.5 M in THF). The reaction was warmed to ambient temperature and cooled to -78 °C after 5 min. DMPU (0.12 ml, 1 mmol) and TMSCl (0.13 ml, 1 mmol) were added before dropwise addition of *cis*-bicyclo(4.3.0)non-3-en-8-one **13** (0.1 ml, 0.8 mmol) as a solution in THF (2 ml). The reaction stirred for 30 min at -78 °C before being quenched with a saturated aqueous solution of $NaHCO_3$ (10 ml) and extracted with Et_2O (3 x 20 ml). After drying the combined organics over Na_2SO_4 and concentration *in vacuo*, the crude was further purified by flash chromatography on silica, eluting with a gradient of Et_2O in petroleum ether (0-5 %). The product **11** was thus obtained as a colourless oil (140 mg, 0.67 mmol, 84 %). The enantiomeric ratio was calculated using optical rotation analysis (48.7 ° (c = 1, $CHCl_3$), 93:7).

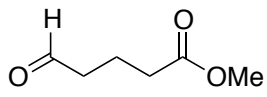
Analytical data are consistent with that described for compound **11** on page 271.

5.2.2 Preparation of Allylic Bromide 12

Preparation of Methyl 5-oxopentanoate, **15**:

Scheme 3.9: A stirred solution of cyclopentene **24** (8.8 ml, 100 mmol) and $NaHCO_3$ (30.2 g, 360 mmol) in MeOH (20 ml) and DCM (130 ml) was cooled to -78 °C and treated with O_3 by bubbling through the solution over 6 h. O_2 was then passed through the solution for another 5 min before diluting the reaction with toluene (450 ml) and concentrating it slowly *in vacuo*. The remaining solution was cooled to 0 °C and NEt_3 (27.8 ml, 200 mmol) and acetic anhydride (37.8 ml, 400 ml) were added. The reaction mixture was allowed to warm to ambient temperature over 16 h before being diluting with DCM and washed with a saturated aqueous $NaHCO_3$ solution. The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo* to give the product as a colourless oil in a mixture of residual toluene and acetic anhydride (9.7 g, 74.3 mmol, 74 % (calculated by ^{1}H-NMR)). The mixture was taken on without further purification.

Methyl 5-oxopentanoate, **15**:[36]



Colourless oil; IR ($CHCl_3$): 1729, 2953 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.92 (pentet, 2H, J = 7.2 Hz, $CH_2CH_2CO_2CH_3$), 2.35 (t, 2H, J = 7.3 Hz, $CH_2CO_2CH_3$), 2.50 (td, 2H, J = 7.3, J = 1.3 Hz, H(O)CCH_2), 3.63 (s, 3H, CO_2CH_3), 9.94 (t, 1H, J = 1.3 Hz, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 17.2, 32.9, 42.8, 51.6, 173.3, 201.3.

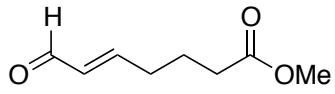
The data observed are in accordance with literature values.

Preparation of (E)-Methyl-7-oxohept-5-enoate, **14**:

Scheme 3.9: Methyl 5-oxopentanoate **15** (6.8 g, 52 mmol) was stirred with (triphenylphosphoranylidene)acetaldehyde **25** (16.7 g, 55 mmol) in toluene (250 ml)

and heated to 60 °C for 4 h. The reaction mixture was then concentrated *in vacuo* and directly loaded onto a silica column, eluting with a gradient of EtOAc in hexane (0-30 %) to give the product as a colourless oil (5.7 g, 36 mmol, 70 %).

(E)-Methyl 7-oxohept-5-enoate, **14**:[37]



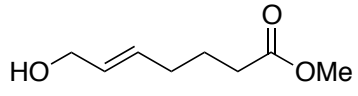
Colourless oil; IR ($CHCl_3$): 1636, 1687, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.86 (pentet, 2H, J = 7.4 Hz, $CH_2CH_2CH_2$), 2.41-2.33 (m, 4H, $CH_2CH_2CH_2$), 3.68 (s, 3H, CO_2CH_3), 6.13 (ddt, 1H, J = 15.8 Hz, J = 8.0 Hz, $^4J_{H\text{-}H}$ = 1.5 Hz, H(O)CC*H*=CH), 6.82 (dt, 1H, J = 15.6 Hz, J = 6.8 Hz, H(O)CCH=C*H*), 9.51 (d, 1H, J = 7.9 Hz, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 23.0, 31.8, 32.9, 51.7, 133.6, 156.9, 173.4, 193.9.

The data observed are in accordance with literature values.

Preparation of (E)-Methyl 7-hydroxyhept-5-enoate, **26**:

Scheme 3.9: To a solution of $NaBH_4$ (794 mg, 21 mmol) in EtOH (60 ml) at 0 °C under an argon atmosphere was added enal **14** (3.5 g, 21 mmol) and the reaction mixture stirred for 1 h at ambient temperature. The reaction was then quenched with H_2O (100 ml) and extracted with DCM (4 x 80 ml). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to yield the product as a colourless oil (3.1 g, 20 mmol, 94 %).

(E)-Methyl 7-hydroxyhept-5-enoate, **26**:[13]



Colourless oil; IR ($CHCl_3$): 1427, 1736, 2951, 3356 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.35 (br s, 1H, O*H*), 1.74 (pentet, 2H, J = 7.4 Hz, $CH_2CH_2CH_2$), 2.05-

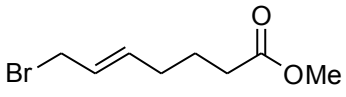
2.13 (m, 2H, CHC*H*$_2$), 2.33 (t, 2H, *J* = 7.5 Hz, C*H*$_2$CO$_2$CH$_3$), 3.66-3.69 (m, 3H, OC*H*$_3$), 4.08-4.12 (m, 2H, CHC*H*$_2$OH), 5.63-5.70 (m, 2H, C*H*=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 24.2, 31.5, 33.4, 51.5, 63.6, 130.0, 131.8, 174.0.

The data observed are in accordance with literature values.

Preparation of (E)-Methyl 7-bromohept-5-enoate, **12**:

Scheme 3.9: Triphenylphosphine (4.3 g, 16 mmol) was added portion wise to a solution of hydroxyheptenoate **26** (1.7 g, 11 mmol) and tetrabromomethane (5.4 g, 16 mmol) in DCM (50 ml). The reaction was stirred at ambient temperature for 1 h before concentrating *in vacuo*. The crude was adsorbed onto silica gel and purified *via* flash chromatography, eluting with a gradient of EtOAc in hexane (0-10 %) to yield the product as a colourless oil (2.0 g, 93.3 mmol, 85 %).

(E)-Methyl 7-bromohept-5-enoate, **12**:[13]



Colourless oil; IR ($CHCl_3$): 1169, 1203, 1435, 1732, 2949 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.74 (pentet, 2H, *J* = 7.4 Hz, CH$_2$C*H*$_2$CH$_2$), 2.06-2.15 (m, 2H, CHC*H*$_2$), 2.33 (t, 2H, *J* = 7.5 Hz, C*H*$_2$CO$_2$CH$_3$), 3.68 (s, 3H, OC*H*$_3$), 3.94 (d, 2H, *J* = 6.1 Hz, CHC*H*$_2$Br), 5.72-5.76 (m, 2H, C*H*=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 23.5, 30.8, 32.5, 32.7, 51.0, 126.9, 134.6, 173.3.

The data observed are in accordance with literature values.

5.2.3 Assessment of the Preparation of Keto Ester 10

*Allylation Employing Allyl Bromide **12***

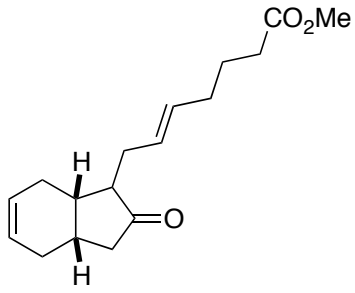
Preparation of (E)-Methyl 7-(2-oxo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl) hept-5-enoate, **10**:

Table 3.2, **Entry 1**: A flame-dried flask, under argon atmosphere, was charged with enol silane **11** (261 mg, 1.26 mmol) and THF (5 ml) and cooled to -10 °C. Methyllithium (0.78 ml, 1.26 mmol, 1.6 M in Et_2O) was added and the reaction stirred at -10 °C for 20 min before adding DMPU (0.75 ml, 5.04 mmol) and cooling to -78 °C. The solution was then treated with bromoheptenoate **12** (0.26 ml, 1.51 mmol) and allowed to warm slowly from -78 °C to ambient temperature over 16 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (10 ml) and extracted with Et_2O (3 x 20 ml). After drying the combined organics and concentration *in vacuo* the crude was further purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-5 %). The product was thus obtained as a colourless oil (163 mg, 0.59 mmol, 47 %).

The following experiment was carried out according to the above procedure. Data are reported as: (a) enol silane **11**, (b) THF, (c) MeLi, (d) DMPU, (e) bromoheptenoate **12**, (f) reaction conditions, and (g) isolated yield **10**.

Table 3.2, **Entry 2**: (a) **11**, 138 mg, 0.66 mmol (b) THF, 5 ml, (c) 0.41 ml, 0.66 mmol, 1.6 M in Et_2O, (d) 0.40 ml, 2.64 mmol, (e) **12**, 0.15 ml, 0.79 mmol (f) -10 °C, 20 min, then -78 °C – rt., 16 h, and (g) **10**, 129 mg, 0.46 mmol, 70 %.

(E)-Methyl 7-(2-oxo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **10**:[13]



Colourless oil; IR ($CHCl_3$): 1435, 1732, 2907 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.63-1.75 (m, 3H, aliphatic protons), 1.97-2.45 (m, 14H, aliphatic protons), 3.67 (s, 3H, O*CH*$_3$), 5.30-5.48 (m, 2H, chain C*H*=C*H*), 5.66-5.74 (m, 2H, ring C*H*=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 24.6, 25.4, 27.1, 29.7, 31.0, 31.8, 33.4, 37.0, 46.3, 50.9, 51.5, 124.5, 125.1, 127.9, 131.8, 174.1, 220.5.

The data observed are in accordance with literature values.

One-pot Protocol

Scheme 3.11: A flame-dried flask, under argon, was charged with (*R*,*R*)-bis(1-phenylethyl)amine hydrochloride salt **27** (262 mg, 1 mmol) and THF (7 ml) and cooled to -78 °C before dropwise addition of ^{n}BuLi (0.80 ml, 2 mmol, 2.5 M in THF). The reaction was warmed to ambient temperature and cooled to -78 °C after 5 min. *cis*-Bicyclo(4.3.0)non-3-en-8-one **13** (0.1 ml, 0.8 mmol) was then added as a solution in THF (2 ml) and the reaction stirred for 1 h at -78 °C before adding bromide **12** (0.18 ml, 1 mmol) as a solution in THF (1 ml). The reaction was allowed to warm to ambient temperature over 16 h, before being quenched with a saturated aqueous solution of NH_4Cl (10 ml) and extracted with Et_2O (3 x 20 ml). After drying the combined organics over $Na2SO_4$ and concentration *in vacuo*, the crude was further purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-5 %). The product **10** was thus obtained as a colourless oil (56 mg, 0.16 mmol, 20 %).

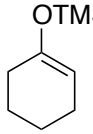
Analytical data are consistent with that described for compound **10** on page 277.

Allylation Employing Tsuji-Trost Protocol – Model Substrate Synthesis

Preparation of (Trimethylsilyloxy)-1-cyclohexene, **29**:

Scheme 3.14: To a flame-dried Schlenk tube, under argon, containing LiCl (85 mg, 2 mmol) were added ^{t}BuMgCl (3.3 ml, 2 mmol, 0.6 M in THF), THF (9 ml) and 1,4-dioxane (0.18 ml, 2.1 mmol). The reaction was stirred at ambient temperature for 15 min before cooling it to 0 °C and adding TMSCl (0.25 ml, 2 mmol). Cyclohexanone (0.21 ml, 2 mmol) was then added as a solution in THF (2 ml) *via* syringe pump over 1 h and the reaction was stirred for 1 h at 0 °C. After this time, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 ml) and extracted with Et_2O (3 x 20 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo*, and further purified by flash chromatography on silica, eluting with a gradient of Et_2O in petrol ether (0-10 %). The product was thus obtained as a colourless oil (296 mg, 1.74 mmol, 87 %).

(Trimethylsilyloxy)-1-cyclohexene, **29**:[38]



Colourless oil; IR ($CHCl_3$): 1668, 2932 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 0.16 (s, 9H, Si(C*H*$_3$)$_3$), 1.43-1.52 (m, 2H, C*H*$_2$), 1.59-1.65 (m, 2H, C*H*$_2$), 1.92-2.01 (m, 4H, 2xC*H*$_2$), 4.80-4.86 (m, 1H, ring C=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 0.4, 22.4, 23.0, 23.5, 29.8, 104.5, 150.6.

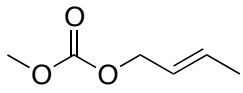
The data observed are in accordance with literature values.

Preparation of (E)-But-2-en-1-yl methyl carbonate, **30**:

Scheme 3.15: A solution of crotyl alcohol **33** (2 ml, 23 mmol) in THF (20 ml) was cooled to -78 °C and treated with ^{n}BuLi (9.36 ml, 23 mmol, 2.5 M in THF). After 10 min methylchloroformate (2.2 ml, 28 mmol) was added and the reaction stirred for a further 2 h before quenching with a saturated aqueous solution of $NaHCO_3$ (20 ml)

and extracting with Et_2O (3 x 40 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and further purified by distillation under argon at ambient pressure at 157-160 °C to yield the product as a colourless oil (2.7 g, 20 mmol, 89 %).

(E)-But-2-en-1-yl methyl carbonate, **30**:[39]



Colourless oil; IR ($CHCl_3$): 1013, 1257, 2960 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.72 (dd, 3H, $^4J_{H\text{-}H}$ = 0.8 Hz, J = 6.4 Hz, CHCH_3), 3.77 (s, 3H, OCH_3), 4.54 (d, 2H, J = 6.6 Hz, OCH_2CH), 5.60 (dt, 1H, J = 15.2 Hz, J = 6.6 Hz, CH_2CHCH), 5.82 (dq, 1H, J = 15.2 Hz, J = 6.6 Hz, C$H$$CH_3$); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 17.2, 54.2, 68.1, 124.0, 131.8, 155.2.

The data observed are in accordance with literature values.

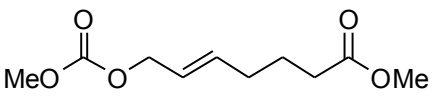
Attempted Allylation Employing Tsuji-Trost Protocol – (E)-2-(But-2-en-1-yl)cyclohexanone, **31**:

Scheme 3.16: In a flame-dried flask, under argon atmosphere, 1,2-bis(diphenylphosphino)ethane (20 mg, 0.05 mmol) and $Pd_2(dba)_3$ (3 mg, 0.04 mmol) were dissolved in dry THF (5 ml) and stirred at ambient temperature. After 20 min, enol silane **29** (121 mg, 0.71 mmol) and carbonate **30** (111 mg, 0.85 mmol) were added as a solution in THF (2 ml) and the reaction was heated to reflux for 16 h. The reaction mixture was then diluted with Et_2O (10 ml) and washed with 1 M HCl (10 ml) and brine, before being dried over Na_2SO_4 and concentrated *in vacuo*. Further purification was attempted by flash chromatography on silica, eluting with a gradient of Et_2O in petroleum ether (0-10 %). The complex mixture of products could not be separated and neither cyclohexanone nor carbonate **30** were detected.

Allylation Employing Tsuji Trost-Protocol – Preparation of (E)-Methyl 7-((methoxycarbonyl)oxy)hept-5-enoate, **34**:

Scheme 3.17: A solution of hydroxyheptenoate **26** (632 mg, 4 mmol) in THF (10 ml) was cooled to -78 °C and treated with ^{n}BuLi (1.6 ml, 4 mmol, 2.5 M in THF). After 10 min methylchloroformate (0.37 ml, 4.8 mmol) was added and the reaction stirred for another 2 h before quenching with a saturated aqueous solution of $NaHCO_3$ (20 ml) and extraction with Et_2O (3 x 40 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and further purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-20 %) to yield the product as a colourless oil (417 mg, 1.93 mmol, 48 %).

(E)-Methyl 7-((methoxycarbonyl)oxy)hept-5-enoate, **34**:



Colourless oil; IR ($CHCl_3$): 1258, 1441, 1738, 2953 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.74 (pentet, 2H, J = 7.4 Hz, $CH_2CH_2CH_2$), 2.06-2.15 (m, 2H, $CHCH_2$), 2.32 (t, 2H, J = 7.5 Hz, $CH_2CO_2CH_3$), 3.67 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.57 (d, 2H, J = 6.4 Hz, $CHCH_2OCO_2CH_3$), 5.62 (dt, 1H, J = 15.4 Hz, J = 6.4 Hz, CH=CH), 5.78 (dt, 1H, J = 15.4 Hz, J = 6.7 Hz, CH=CH); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 23.4, 31.0, 32.8, 51.0, 54.2, 67.9, 123.8, 135.3, 155.1, 173.4. HRMS (ESI) m/z calculated for $C_{10}H_{20}NO_5$ $[M+NH_4]^+$: 234.1336. Found: 234.1336.

The data observed are in accordance with literature values.

Attempted Allylation Employing Tsuji-Trost Protocol – (E)-Methyl 7-(2-oxo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **10**:

Scheme 3.18: In a flame-dried flask, under an argon atmosphere, 1,2-bis(diphenylphosphino)ethane (19 mg, 0.05 mmol) and $Pd_2(dba)_3$ (3 mg, 0.03 mmol)

were dissolved in dry THF (5 ml) and stirred at ambient temperature. After 20 min, enol silane **11** (140 mg, 0.67 mmol) and carbonate **34** (175 mg, 0.81 mmol) were added as a solution in THF (2 ml) and the reaction was heated to reflux for 24 h. Analysis of the crude reaction mixture by TLC during this time revealed mainly unreacted enol silane **11**. The reaction mixture was then diluted with Et_2O (10 ml) and washed with 1 M HCl (10 ml) and brine, before being dried over Na_2SO_4 and concentrated *in vacuo*. Further purification by flash chromatography on silica, eluting with a gradient of Et_2O in petroleum ether (0-10 %) returned ketone **13** (71 mg, 0.52 mmol, 78 %).

Attempted Allylation Employing Tsuji-Trost Protocol with TBAF – (E)-Methyl 7-(2-oxo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **10**:

Scheme 3.19: In a flame-dried flask, under an argon atmosphere, 1,2-bis(diphenylphosphino)ethane (15 mg, 0.04 mmol) and $Pd_2(dba)_3$ (3 mg, 0.03 mmol) were dissolved in dry THF (5 ml) and stirred at ambient temperature. After 20 min, enol silane **11** (129 mg, 0.62 mmol) and carbonate **34** (161 mg, 0.74 mmol) were added as a solution in THF (2 ml) as well as TBAF (0.62 ml, 0.62 mmol, 1M solution in THF) and the reaction was stirred at ambient temperature for 16 h. The reaction mixture was then diluted with Et_2O (10 ml) and washed with 1 M HCl (10 ml) and brine, before being dried over Na_2SO_4 and concentrated *in vacuo*. Further purification by flash chromatography on silica, eluting with a gradient of Et_2O in petrol ether (0-10 %) returned ketone **13** (61 mg, 0.45 mmol, 72 %).

Attempted Epimerisation of (E)-Methyl 7-(2-oxo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **10**:

Scheme 3.21: A solution of keto ester **10** (162 mg, 0.59 mmol) in MeOH (5 ml) was treated with sodium methoxide (16 mg, 0.30 mmol) and stirred at ambient temperature for 16 h. The reaction was then quenched with a saturated aqueous

solution of NH_4Cl (5 ml) and extracted with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield the product as a colourless oil (148 mg, 0.53 mmol, 91 %). Comparison of the ^1H- and ^{13}C-NMR data to the data set reported for compound **10**, page 266, did not show any significant difference.

Scheme 3.22: A solution of keto ester **10** (149 mg, 0.54 mmol) in THF (5 ml) was treated with sodium hydride (19 mg, 0.55 mmol) and heated to reflux for 4 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (5 ml) and extracted with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield the product as a colourless oil (126 mg, 0.45 mmol, 83 %). Comparison of the ^1H- and ^{13}C-NMR data to the data set reported for compound **10**, page 266, did not show any significant difference.

5.2.4 Towards (-)-Mucosin: Route A

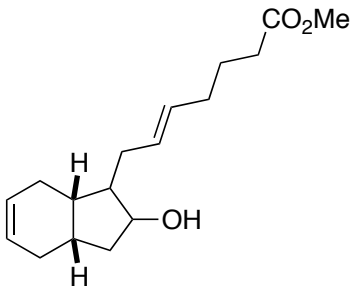
Preparation of (E)-Methyl 7-(2-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **20**:

Table 3.3, **Entry 1**: To a solution of $NaBH_4$ (32 mg, 0.84 mmol) in EtOH (5 ml) at 0 °C was added keto ester **10** (115 mg, 0.42 mmol) as a solution in EtOH (2 ml) and allowed to warm to ambient temperature over 1 h. The reaction was then quenched with H_2O (5 ml) and extracted with DCM (4 x 10 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-30 %) to yield the product as a colourless oil (76 mg, 0.27 mmol, 65 %).

The following experiment was carried out according to the above procedure. Data are reported as: (a) $NaBH_4$, (b) volume of EtOH, (c) keto ester **10**, (d) volume of EtOH for **10**, (e) reaction conditions, and (f) isolated yield of **20**.

Table 3.3, **Entry 2**: (a) 21 mg, 0.54 mmol, (b) EtOH, 5 ml, (c) **10**, 75 mg, 0.27 mmol, (d) EtOH, 2 ml, (e) 0 °C - rt., 1 h, and (f) **20**, 64 mg, 0.23 mmol, 85 %.

(E)-Methyl-7-(2-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **20**:



Colourless oil; IR ($CHCl_3$): 1737, 2907, 3422 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.54-1.73 (m, 5H, aliphatic protons), 1.95-2.37 (m, 12H, aliphatic protons), 3.67 (s, 3H, CO_2CH_3), 3.89-3.96 (m, 1H, C*H*OH), 5.41-5.59 (m, 2H, chain C*H*=C*H*), 5.67-5.78 (m, 2H, ring C*H*=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) major isomer: 24.6, 26.3, 28.0, 31.8, 33.3, 33.4, 35.8, 40.4, 41.1, 51.5, 52.4, 77.0, 125.9, 126.6, 130.0, 130.8, 174.1; HRMS (ESI) m/z calculated for $C_{17}H_{27}O_3$ $[M+H]^+$: 279.1955. Found: 279.1959.

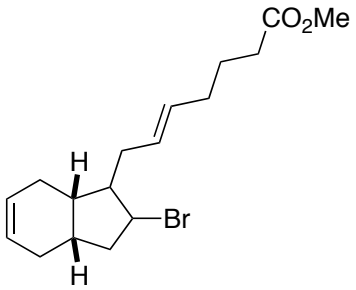
Preparation of (E)-Methyl 7-(2-bromo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **35**:

Table 3.4, **Entry 1**: Triphenylphosphine (134 mg, 0.51 mmol) was added portionwise to a solution of alcohol **20** (95 mg, 0.34 mmol) and tetrabromomethane (169 mg, 0.51 mmol) in DCM (10 ml). The reaction was stirred at ambient temperature for 1 h before concentrating it *in vacuo*. The crude mixture was then adsorbed onto silica and purified *via* flash chromatography, eluting with a gradient of EtOAc in hexane (0-20 %) to yield the product as a colourless oil (105 mg, 0.31 mmol, 91 %).

The following experiment was carried out according to the above procedure. Data are reported as: (a) triphenylphosphine, (b) alcohol **20**, (c) CBr_4, (d) volume of DCM, (e) reaction conditions, and (f) isolated yield of **35**.

Table 3.4, **Entry 2**: (a) 115 mg, 0.44 mmol, (b) **20**, 82 mg, 0.29 mmol, (c) 144 mg, 0.44 mmol, (d) DCM, 10 ml, (e) rt., 1 h, and (f) **35**, 95 mg, 0.28 mmol, 95 %.

(E)-Methyl-7-(2-bromo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **35**:

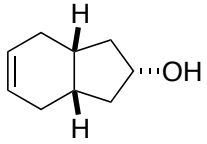


Colourless oil; IR ($CHCl_3$): 1169, 1435, 1735, 2922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.66-1.74 (m, 2H, aliphatic protons), 1.76-1.90 (m, 3H, aliphatic protons), 2.00-2.28 (m, 8H, aliphatic protons), 2.31-2.39 (m, 3H, aliphatic protons), 2.59-70 (m, 1H, aliphatic proton), 3.68 (s, 3H, OC*H*$_3$), 4.50-4.53 (m, 1H, C*H*Br), 5.37-5.55 (m, 2H, chain C*H*=C*H*), 5.89-5.94 (m, 2H, ring C*H*=C*H*). ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) major isomer: 24.1, 25.3, 27.2, 31.4, 32.9, 34.5, 34.7, 39.5, 43.7, 51.0, 51.7, 61.6, 128.6, 128.7, 128.9, 130.3, 173.7; HRMS (ESI) m/z calculated for $C_{17}H_{29}BrNO_2$ $[M+NH_4]^+$: 358.1376. Found: 358.1383.

*Preparation of 2,3,3a,4,7,7a-Hexahydro-1*H*-inden-2-ol*, **37**:

Scheme 3.27: To a solution of $NaBH_4$ (189 mg, 5 mmol) in EtOH (15 ml) at 0 °C was added ketone **13** (680 mg, 5 mmol) as a solution in EtOH (5 ml) and allowed to warm to ambient temperature over 1 h. The reaction was then quenched with H_2O (5 ml) and extracted with DCM (4 x 10 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-30 %) (single major isomer isolated: 431 mg, 3.1 mmol, 63 %; overall yield: 500 mg, 3.6 mmol, 72 %).

*2,3,3a,4,7,7a-Hexahydro-1*H-*inden-2-ol*, **37**: major isomer

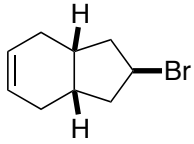


Colourless oil; IR ($CHCl_3$): 1433, 3327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.40-1.48 (m, 2H, aliphatic ring protons), 1.60 (app. s, 1H, O*H*), 1.94-2.07 (m, 4H, aliphatic ring protons), 2.09-2.24 (m, 4H, aliphatic ring protons), 4.35-4.43 (m, 1H, C*H*OH), 5.67-5.72 (m, 2H, C*H*=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 26.7, 34.4, 41.4, 72.9, 125.1. HRMS (ESI) m/z calculated for $C_9H_{15}O$ $[M+H]^+$: 139.1117. Found: 139.1115.

*Preparation of 2-Bromo-2,3,3a,4,7,7a-hexahydro-1*H-*indene*, **38**:

Scheme 3.28: Triphenylphosphine (399 mg, 1.5 mmol) was added portionwise to a solution of alcohol **37** (140 mg, 1 mmol) and carbon tetrabromide (504 mg, 1.5 mmol) in DCM (20 ml). The reaction was stirred at ambient temperature for 1 h before concentrating *in vacuo*. The crude mixture was then adsorbed onto silica and purified *via* flash chromatography, eluting with petroleum ether to yield the product as a colourless oil (160 mg, 0.79 mmol, 79 %).

*2-Bromo-2,3,3a,4,7,7a-hexahydro-1*H-*indene*, **38**:

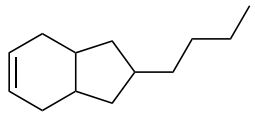


Colourless oil; IR ($CHCl_3$): 1223, 1446, 2920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.71-1.82 (m, 2H, aliphatic ring protons), 2.04-2.18 (m, 2H, aliphatic ring protons), 2.20-2.30 (m, 4H, aliphatic ring protons), 2.38-2.49 (m, 2H, aliphatic ring protons), 4.51-4.58 (m, 1H, C*H*Br), 5.72-5.76 (m, 2H, C*H*=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 26.6, 34.8, 44.5, 51.0, 126.4. HRMS (ESI) m/z calculated for $C_9H_{14}Br$ $[M+H]^+$: 201.0273. Found: 201.0274.

*Preparation of 2-Butyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene*, **39**:

Scheme 3.29: A flame-dried flask, under argon atmosphere, was charged with CuCN (90 mg, 1 mmol) and THF (2 ml) before being cooled to -78 °C and addition of ^{n}BuLi (0.8 ml, 2 mmol, 2.5 M in THF). The reaction mixture was allowed to warm to 0 °C for 5 min, then cooled to -78 °C and bromide **38** (195 mg, 1 mmol) was added as a solution in THF (2 ml). The reaction was allowed to warm to 0 °C over 16 h before being quenched with a solution of 10% NH_4OH in saturated aqueous NH_4Cl (10 ml) and extracted with Et_2O (3 x 15 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of Et_2O in petroleum ether (0-30 %) to yield the product as a colourless oil (92 mg, 0.53 mmol, 53 %).

*2-Butyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene*, **39**:



Colourless oil; IR ($CHCl_3$): 2922, 1460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 0.89 (t, 3H, J = 6.5 Hz, CH_3), 0.97-1.08 (m, 1H, aliphatic proton), 1.20-1.41 (m, 7H, aliphatic protons), 1.77-1.94 (m, 5H, aliphatic protons), 1.96-2.08 (m, 2H, aliphatic protons), 2.10-2.23 (m, 2H, aliphatic protons), 5.62-5.71 (m, 2H, C*H*=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 14.2, 22.9, 28.1, 31.2, 36.1, 38.0, 38.1, 39.0, 126.2. HRMS (ESI) m/z calculated for $C_{13}H_{23}$ $[M+H]^+$: 179.1794. Found: 179.1790.

Attempted Preparation of (E)-Methyl 7-(2-butyl-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **9**:

Table 3.5, **Entry 1**: A flame-dried flask, under argon atmosphere, was charged with CuCN (9 mg, 0.10 mmol) and THF (2 ml) before being cooled to -78 °C and addition of ^{n}BuLi (0.12 ml, 0.20 mmol, 1.58 M in THF). The reaction mixture was allowed to warm to 0 °C for 5 min, then cooled to -78 °C and bromide **35** (32 mg,

0.10 mmol) was added as a solution in THF (2 ml). The reaction was allowed to warm to 0 °C over 16 h before being quenched with a solution of 10% NH_4OH in saturated aqueous NH_4Cl (10 ml) and extracted with Et_2O (3 x 15 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-30 %). The complex mixture of products and starting material could not be separated.

The following experiments were carried out according to the above procedure. Data are reported as: (a) CuCN, (b) volume of THF, (c) ^{n}BuLi, (d) bromide **35**, (e) volume of THF for **35**, (f) reaction conditions, (g) isolated yield of **9**, and (h) recovered starting material (**35**).

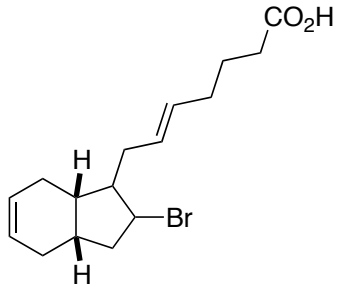
Table 3.5, **Entry 2**: (a) 20 mg, 0.22 mmol, (b) THF, 2 ml, (c) 0.18 ml, 0.44 mmol, 2.5 M in THF, (d) **35**, 74 mg, 0.22 mmol, (e) THF, 2 ml, (f) -78 to -10 °C, 16 h, (g) -, and (h) **35**, 54 mg, 0.16 mmol, 72 %.

Table 3.5, **Entry 3**: (a) 28 mg, 0.32 mmol, (b) THF, 2 ml, (c) 0.25 ml, 0.63 mmol, 2.5 M in THF, (d) **35**, 54 mg, 0.16 mmol, (e) THF, 2 ml, (f) -78 - 0 °C, 6 h, (g) -, and (h) -.

Preparation of (E)-7-(2-Bromo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoic acid, **40**:

Scheme 3.31: A solution of bromide **35** (69 mg, 0.20 mmol) in MeOH (6 ml) and H_2O (2 ml) was treated with LiOH (17 mg, 0.41 mmol) and warmed to 40 °C for 3 h. The reaction was then acidified with 1 M HCl (pH = 2) and extracted with Et_2O (3 x 10 ml). The combined organic extracts were dried over Na_2SO_4, filtered through a short plug of silica and concentrated *in vacuo* to yield the product as a colourless oil (59 mg, 0.18 mmol, 90 %).

(E)-7-(2-Bromo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoic acid, **40**:



Colourless oil; IR ($CHCl_3$): 1242, 1435, 1705, 2922, 3032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.78-1.92 (m, 5H, aliphatic protons), 2.02-2.23 (m, 9H, aliphatic protons, CO_2H), 2.32-2.40 (m, 3H, aliphatic protons), 2.61-70 (m, 1H, aliphatic proton), 4.50-4.54 (m, 1H, C*H*Br), 5.38-5.57 (m, 2H, chain C*H*=C*H*), 5.91-5.95 (m, 2H, ring C*H*=C*H*). ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 24.4, 25.9, 27.7, 31.8, 33.0, 35.0, 35.2, 40.1, 44.2, 52.2, 62.0, 129.1, 129.3, 129.4, 130.7, 178.2; HRMS (ESI) m/z calculated for $C_{16}H_{21}O_2$ $[M-2H-Br]^-$: 245.1547. Found: 245.1540.

Attempted Preparation of (E)-7-(2-Bromo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoic acid, **1**:

Scheme 3.32: A flame-dried flask, under argon atmosphere, was charged with CuCN (64 mg, 0.72 mmol) and THF (2 ml) before being cooled to -78 °C and addition of ^nBuLi (0.57 ml, 1.44 mmol, 2.5 M in THF). The reaction mixture was allowed to warm to 0 °C for 5 min, then cooled to -78 °C and bromide **40** (58 mg, 0.18 mmol) was added as a solution in THF (2 ml). The reaction was allowed to warm to 0 °C over 16 h before being quenched with a solution of 10% NH_4OH in saturated aqueous NH_4Cl (10 ml) and extracted with Et_2O (3 x 15 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-30 %). The complex mixture of products could not be separated.

Attempted Preparation of (E)-Methyl-7-(2-butyl-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **9**:

Scheme 3.34: A flame-dried flask, under argon atmosphere, was charged with $CuCl_2$ (7 mg, 0.03 mmol), LiCl (3 mg, 0.06 mmol), bromide **35** (102 mg, 0.30 mmol), NMP (0.12 ml, 1.2 mmol) and THF (4 ml) before adding ^{n}BuMgCl (0.16 ml, 0.32 mmol, 2 M in THF) dropwise at ambient temperature. The solution was stirred for 2 h before being quenched with a saturated aqueous NH_4Cl solution (10 ml) and extracted with Et_2O (3 x 15 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-30 %). The complex mixture of products and starting material could not be separated.

Attempted Preparation of (E)-Methyl-7-(2-butyl-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **9**:

Scheme 3.36: A flame-dried flask, under argon atmosphere, was charged with CuI (3 mg, 0.01 mmol) and LiOMe (4 mg, 0.10 mmol), evacuated/purged with argon three times and cooled to 0 °C. Bromide **35** (36 mg, 0.10 mmol) was added as a solution in THF (5 ml). TMEDA (10 µl, 0.02 mmol) was then added to the solution before the addition of ^{n}BuMgCl (0.1 ml, 0.20 mmol, 2 M in THF), which turned the clear colourless solution to dark purple colour. The reaction was vigorously stirred at 0 °C for 24 h. The resulting clear yellow solution was then quenched with a saturated aqueous NH_4Cl solution (10 ml) and extracted with Et_2O (3 x 15 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-30 %). The complex mixture of products could not be separated.

Attempted Preparation of (*E)-7-(2-Bromo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoic acid*, **1**:

The following experiment was carried out according to the above procedure. Data are reported as: (a) CuI, (b) LiOMe, (c) bromide **40**, (d) volume of THF, (e) TMEDA, (f) ^{n}BuMgCl, (g) reaction conditions, (h) isolated yield of **1**, and (i) recovered starting material **40**.

Scheme 3.37: (a) 9 mg, 0.03 mmol, (b) 9 mg, 0.23 mmol, (c) **40**, 75 mg, 0.23 mmol, (d) THF, 5 ml, (e) 20 μl, 0.05 mmol, (f) 0.46 ml, 0.92 mmol, 2 M in THF, (g) 0 °C, 24 h, (h) -, and (i) -.

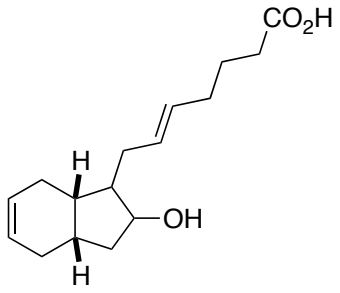
*Attempted Crystallisation of Alcohol **10** as Alkoxide **41***

Scheme 3.38: A flame-dried flask was charged with NaH (8 mg, 0.30 mmol), THF (2 ml) and alcohol **20** (82 mg, 0.30 mmol) as a solution in THF (2 ml) and the reaction stirred for 20 min at ambient temperature. The solvent was then removed *in vacuo* to yield a thick oil. Any efforts to gain crystals were unsuccessful due to poor solubility.

Preparation of (*E)-7-(2-Hydroxy-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoic acid*, **42**:

Scheme 3.39: A solution of alcohol **20** (87 mg, 0.32 mmol) in MeOH (6 ml) and H_2O (2 ml) was treated with LiOH (13 mg, 0.32 mmol) and warmed to 40 °C for 3 h. The reaction was then acidified with 1 M HCl (pH = 2) and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered through a short plug of silica and concentrated *in vacuo* to yield the product as a colourless oil (59 mg, 0.22 mmol, 70 %).

(E)-7-(2-Hydroxy-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoic acid, **42**:

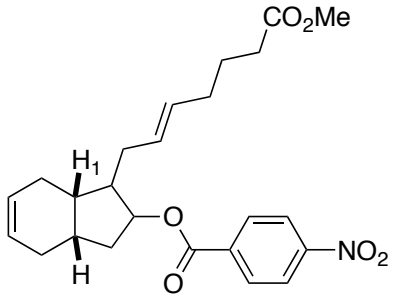


Colourless oil; IR ($CHCl_3$): 1705, 2907, 3331 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.53-1.78 (m, 6H, aliphatic protons), 1.88-2.42 (m, 13H, aliphatic protons), 3.91-3.40 (m, 1H, C*H*OH), 5.41-5.59 (m, 2H, chain C*H*=C*H*), 5.68-5.80 (m, 2H, ring C*H*=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 23.8, 25.8, 27.4, 31.3, 32.7, 32.9, 35.4, 40.1, 40.6, 51.8, 77.5, 125.3, 126.0, 129.7, 130.2, 177.7; HRMS (ESI) m/z calculated for $C_{16}H_{25}O_3$ $[M+H]^+$: 265.1798. Found: 279.1796.

Preparation of (E)-1-(7-Methoxy-7-oxohept-2-en-1-yl)-2,3,3a,4,7,7a-hexahydro-1H-inden-2-yl 4-nitrobenzoate, **43**:

Scheme 3.40: A solution of alcohol **20** (30 mg, 0.11 mmol) in DCM (5 ml) was treated with NEt_3 (0.02 ml, 0.16 mmol) and 4-nitrobenzoyl chloride (30 mg, 0.16 mmol) and the reaction mixture stirred for another 2 h at ambient temperature before being quenched with a saturated aqueous solution of $NaHCO_3$ (5 ml) and extracted with Et_2O (3 x 10 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and further purified *via* flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-30 %) to yield the product as a colourless oil (34 mg, 0.08 mmol, 73 %).

(E)-1-(7-Methoxy-7-oxohept-2-en-1-yl)-2,3,3a,4,7,7a-hexahydro-1H-inden-2-yl-4-nitrobenzoate, **43**:



Colourless oil; IR ($CHCl_3$): 1271, 1525, 1717, 2908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.54-1.60 (m, 3H, aliphatic protons, side chain), 1.76-1.83 (m, 1H, bridgehead H_1), 1.89-2.04 (m, 5H, aliphatic protons), 2.07-2.32 (m, 8H, aliphatic protons), 3.63 (s, 3H, OCH_3), 5.10-5.16 (m, 1H, C*H*OOC), 5.36-5.45 (m, 2H, chain C*H*=C*H*), 5.68-5.74 (m, 2H, ring C*H*=C*H*), 8.16 (d, 2H, J = 8.9 Hz, Ar*H*), 8.28 (d, 2H, J = 8.9 Hz, Ar*H*). ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) 24.4, 25.4, 26.8, 31.3, 32.8, 33.1, 34.5, 38.2, 39.0, 48.6, 50.9, 81.1, 123.0, 124.8, 125.2, 128.1, 130.1, 130.7, 135.6, 150.0, 163.9, 173.4; HRMS (ESI) m/z calculated for $C_{24}H_{30}NO_6$ $[M+H]^+$: 428.2068. Found: 428.2064.

5.2.5 Towards (-)-Mucosin: Route B

Attempted Preparation of (E)-Methyl 7-(2-butyl-2-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoate, **22**:

Table 3.6, **Entry 1**: A flame-dried flask, under argon, charged with ketone **10** (67 mg, 0.24 mmol) and THF (5 ml) and was cooled to 0 °C before addition of ^nBuMgCl (0.12 ml, 0.24 mmol). The reaction was stirred for 1.5 h, then quenched with a saturated aqueous solution of NH_4Cl (10 ml) and extracted with Et_2O (3 x 15 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-30 %). The ketone starting material **10** was recovered (60 mg, 0.22 mmol, 90 %) with none of the desired product being observed.

The following experiment was carried out according to the above procedure. Data are reported as: (a) ketone **10**, (b) volume of THF for **10**, (c) ^{n}BuMgCl, (d) reaction conditions, (e) isolated yield of **22**, and (f) recovered starting material **10**.

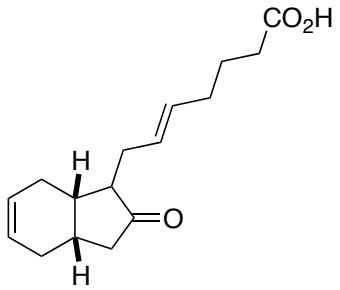
Table 3.6, **Entry 2**: (a) **10**, 60 mg, 0.22 mmol, (b) THF, 5 ml, (c) 0.11 ml, 0.22 mmol, 2 M in THF, (d) 0 °C - rt., 16 h, (e) -, and (f) -.

Scheme 3.44: A flame-dried flask, under argon, was charged with dry $CeCl_3$ (57 mg, 0.23 mmol) and THF (2 ml). The slurry was stirred at ambient temperature for 2 h before cooling it to -78 °C, adding ^{n}BuLi (0.15 ml, 0.23 mmol, 1.58 M in THF) dropwise and stirring the reaction for a further 30 min. After this time, a solution of ketone **10** (62 mg, 0.23 mmol) in THF (3 ml) was added to the reaction dropwise over 15 min. After 2 h at -78 °C the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 ml) and extracted with Et_2O (3 x 15 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-40 %). The complex mixture of products could not be separated. Analysis by IR detected no carbonyl stretch.

Preparation of (E)-7-(2-Oxo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoic acid, **45**:

Scheme 3.45: A solution of keto ester **10** (129 mg, 0.46 mmol) in MeOH (6 ml) and H_2O (2 ml) was treated with LiOH (39 mg, 0.93 mmol) and warmed to 40 °C for 3 h. The reaction was then acidified with 1 M HCl (pH = 2) and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered through a short plug of silica and concentrated *in vacuo* to yield the product as a colourless oil (99 mg, 0.38 mmol, 83 %).

(E)-7-(2-Oxo-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoic acid, **45**:



Colourless oil; IR ($CHCl_3$): 1737, 2907, 3422 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 1.64-1.79 (m, 3H, aliphatic protons), 1.90-2.49 (m, 15H, aliphatic protons), 5.35-5.50 (m, 2H, chain C*H*=C*H*), 5.65-5.75 (m, 2H, ring C*H*=C*H*); ^{13}C NMR (400 MHz, $CHCl_3$): δ(ppm) major isomer: 24.3, 25.4, 27.1, 29.7, 31.0, 31.7, 33.1, 37.0, 46.3, 50.9, 124.5, 125.1, 129.1, 131.9, 178.5, 220.7; HRMS (ESI) m/z calculated for $C_{16}H_{23}O_3$ $[M+H]^+$: 263.1642. Found: 263.1642.

Attempted Preparation of (E)-7-(2-Butyl-2-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)hept-5-enoic acid, **46**:

Table 3.7, **Entry 1**: A flame-dried flask, under argon, was charged with dry $CeCl_3$ (268 mg, 1.09 mmol) and THF (2 ml). The slurry was stirred at ambient temperature for 2 h before cooling it to -78 °C, adding ^{n}BuLi (0.44 ml, 1.09 mmol, 2.5 M in THF) dropwise and stirring the reaction for another 30 min. A solution of ketone **51** (95 mg, 0.36 mmol) in THF (5 ml) was then added to the reaction dropwise over 15 min. After 2 h at -78 °C the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 ml) and extracted with Et_2O (3 x 15 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-40 %). The complex mixture of products could not be separated.

Reversed Addition

Table 3.7, **Entry 2**: A flame-dried flask, under argon, was charged with dry $CeCl_3$ (63 mg, 0.26 mmol) and THF (2 ml). The slurry was stirred at ambient

temperature for 2 h before cooling it to -78 °C, adding ^{n}BuLi (0.10 ml, 0.26 mmol, 2.5 M in THF) dropwise and stirring the reaction for another 30 min. The prepared solution was the transferred *via* cannula to a solution of ketone **10** (22 mg, 0.09 mmol) in THF (3 ml). After 2 h at -78 °C the reaction was quenched with a saturated solution of NH_4Cl (10 ml) and extracted with Et_2O (3 x 15 ml). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica, eluting with a gradient of EtOAc in hexane (0-40 %). The complex mixture of products could not be separated.

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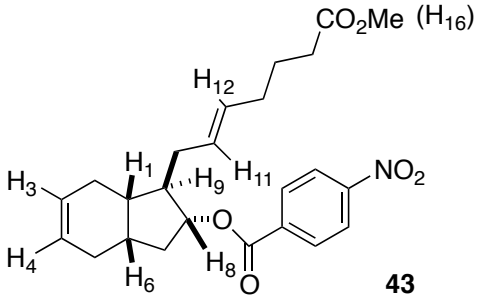
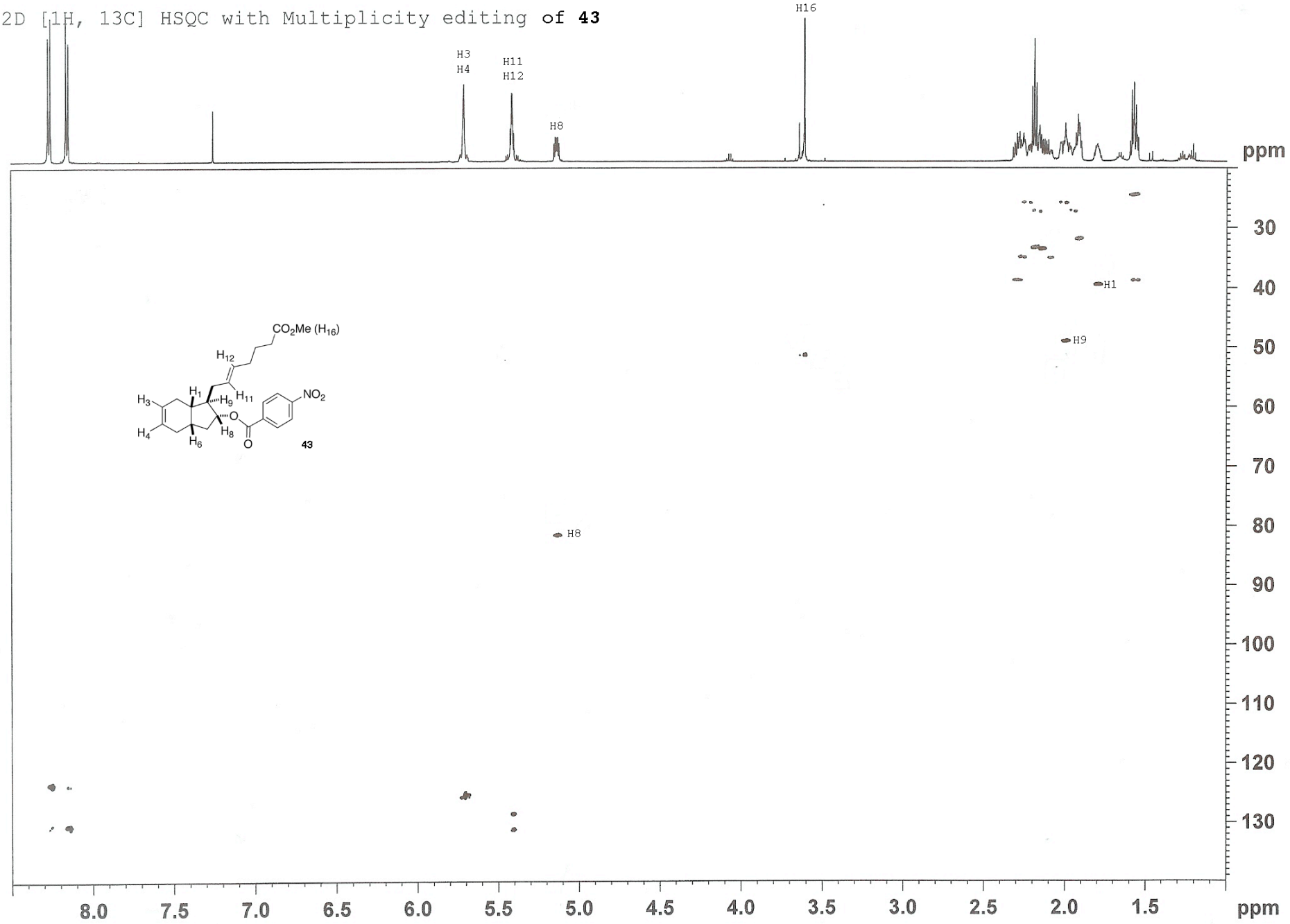
7. Appendix

HSQC and NOESY NMR Data for Bicyclic Ester 43



43

2D [1H, 13C] HSQC with Multiplicity editing of **43**



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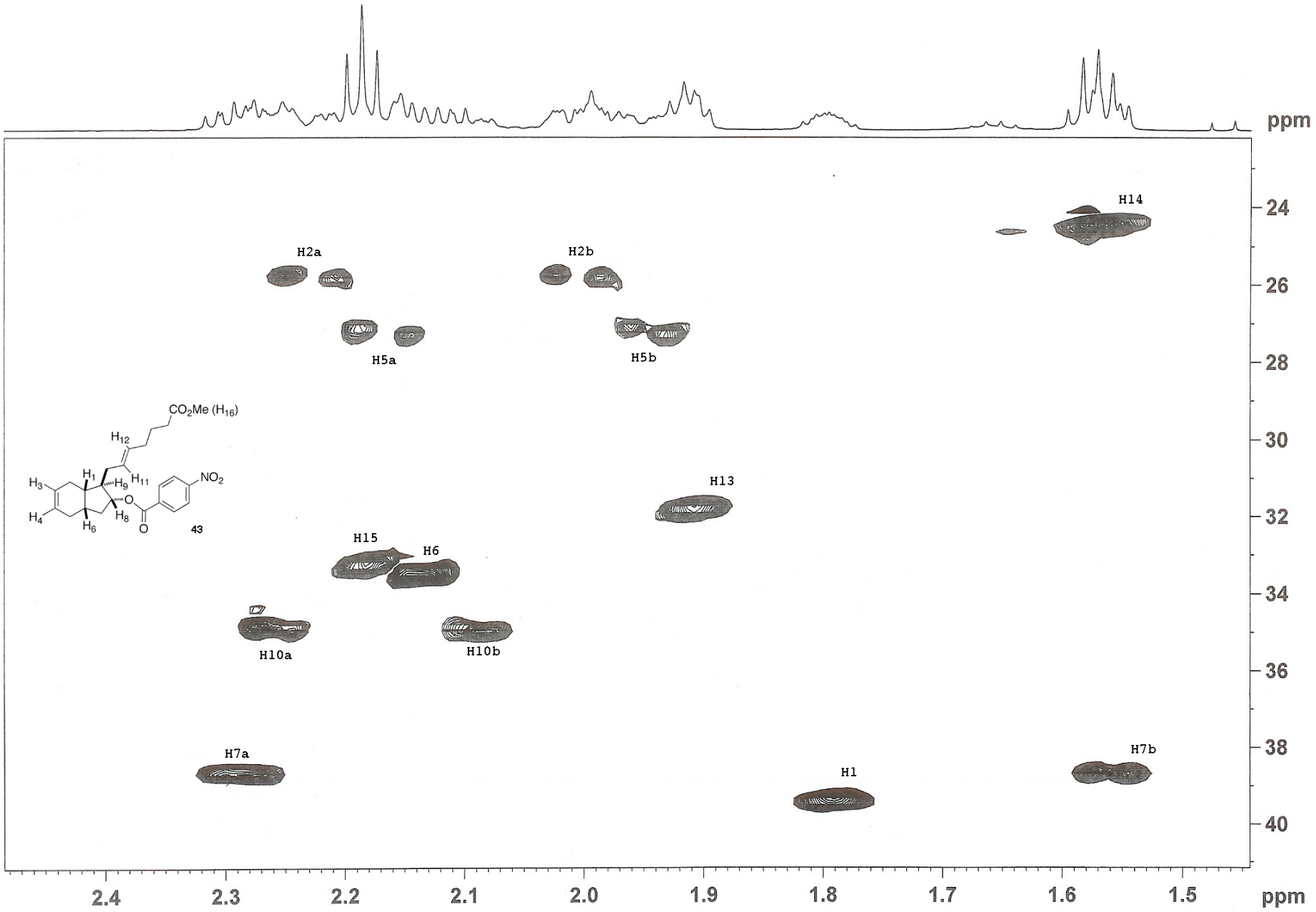

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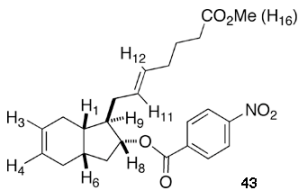

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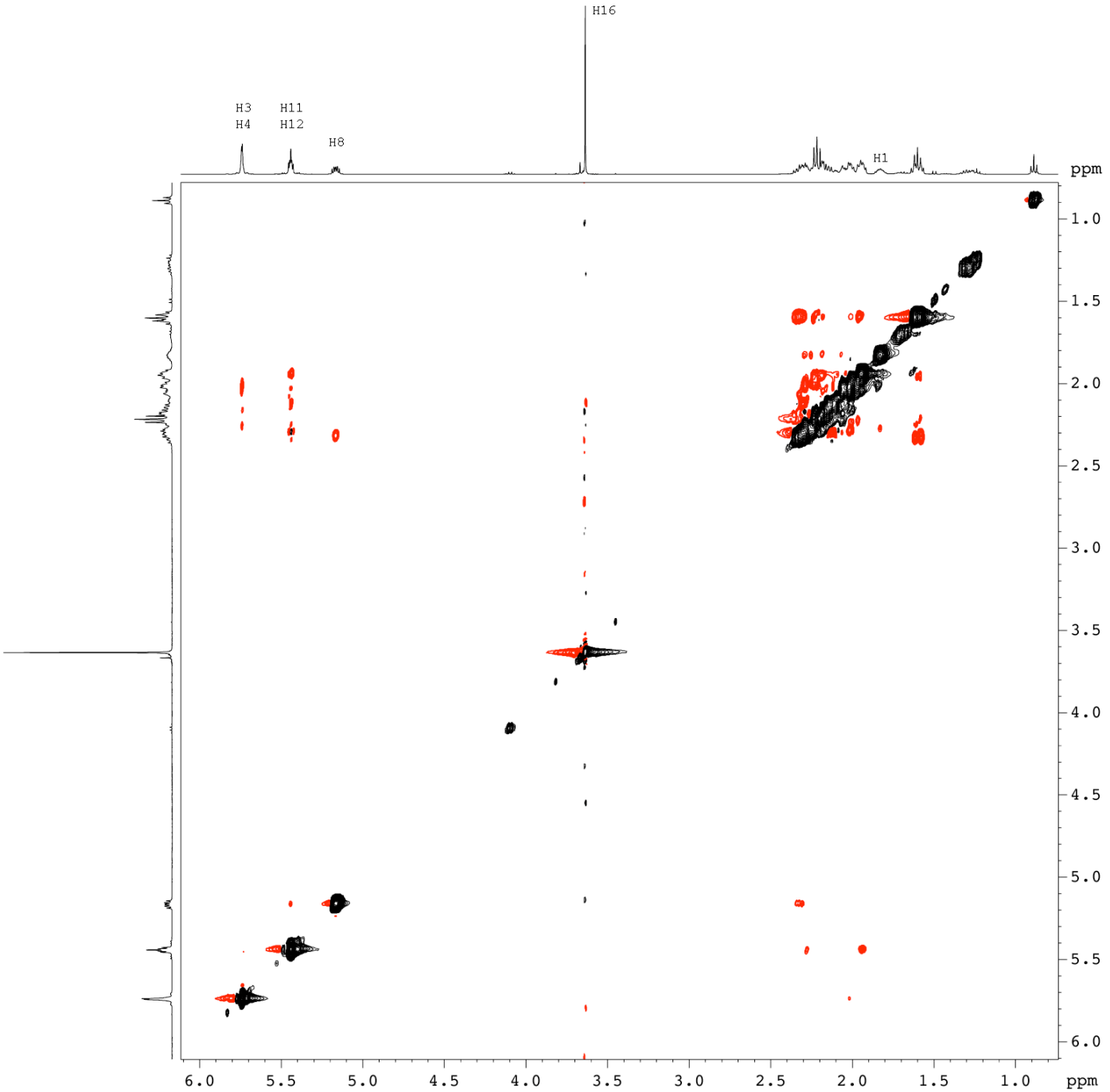

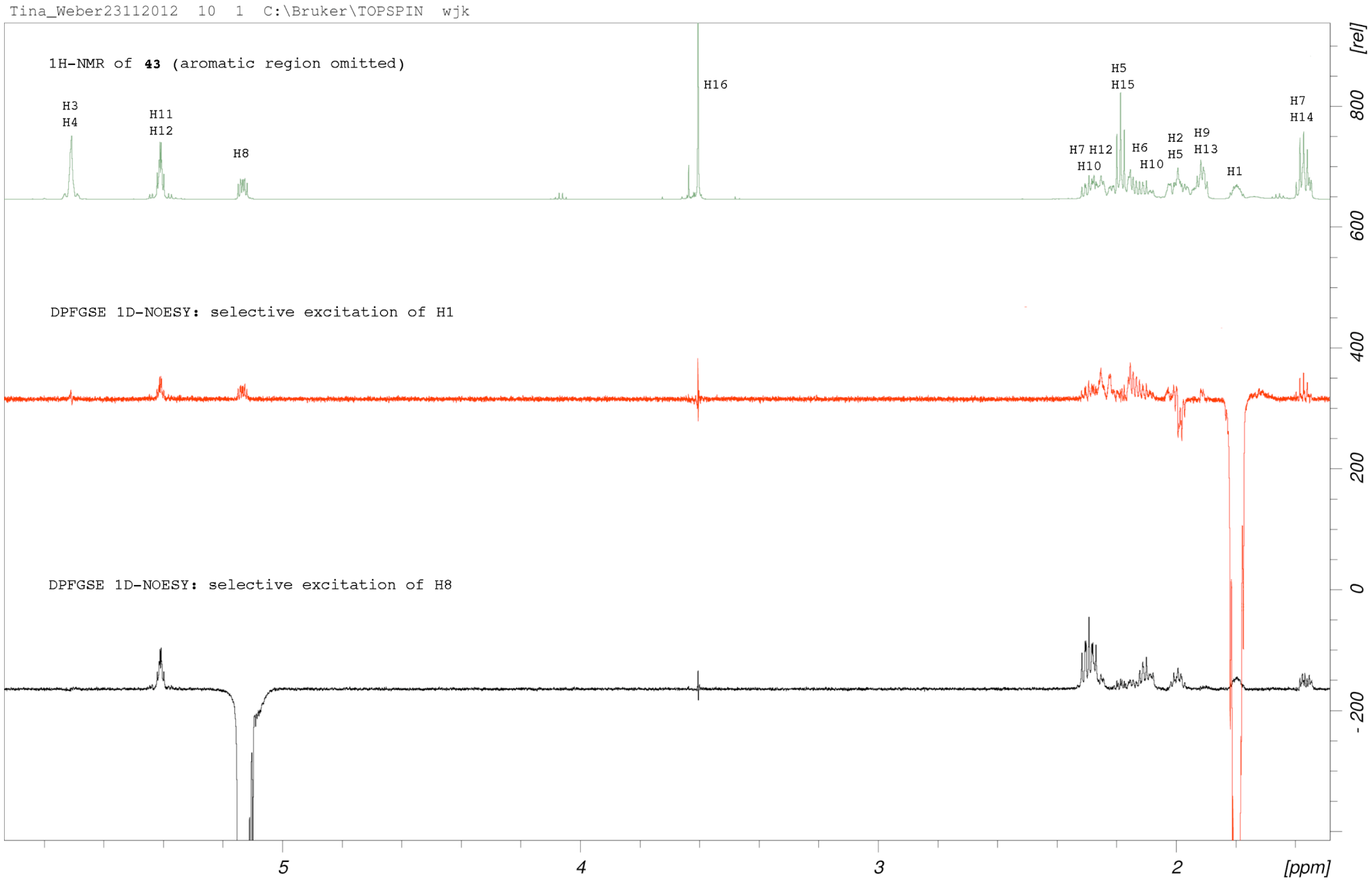
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H12
H8
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H7 H12
H10
H6
H10
H2
H5
H9
H13
H1
H7
H14
DPFGSE 1D-NOESY: selective excitation of H1
DPFGSE 1D-NOESY: selective excitation of H8
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