

Studies on Enolate Directed Carbometallation Reactions

A Thesis Presented by

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Declaration

I, Matthew Penny confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

The present thesis is concerned with the concept of an enolate directed carbometallation reaction.

The first chapter provides a review of the area of heteroatom directed carbometallation of isolated alkynes and allenes as a powerful method for the formation of double bonds and attempts to rationalise the regio and stereochemistry of such additions.

The second chapter begins with the results of a small study on the copper(I) mediated carbometallation reactions of homoallenols. The research into the aforementioned enolate directed carbometallation reaction is then presented and discussed, and especially the efforts made towards efficient formation of a novel “bis-carbanionic” intermediate, possessing both an enolate and a vinyl organometallic reagent. Following on from a preliminary result within the group research was carried out into the carbometallation reactions of enolates derived from carboxylic acids, amides, esters. Whilst amide enolates proved to be problematic, carboxylic acid dianions were found to be suitable substrates for carbometallation and dialkylation of the “bis-carbanion” was successful. After considerable experimentation involving a variety of organometallic reagents and protocols for enolate anion generation, ester enolates were found to be most successful, giving rise to high yields of products and allowing selective reactions of both the vinyl organometallic reagent and the enolate. Finally, very encouraging preliminary results were obtained with an adventurous strategy involving the enolate intermediate obtained from a conjugate addition to an enone. Experiments to probe the reactivity of these novel intermediates, with the aim of selective reaction of only one of the carbanions, are discussed throughout. These results are then summarised and logical conclusions as well as perspectives for future research are drawn.

The thesis concludes with a detailed description of the experimental procedures used and characterisation of the compounds prepared.

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Abbreviations

Ac	acetyl
acac	acetylacetonate
aq	aqueous
Ar	Aryl
BHT	Butylated hydroxytoluene
b.p.	Boiling point
Bu	Butyl
cat.	catalytic
DCC	Dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	Dichloromethane
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
<i>dr</i>	diastereomeric ratio
E	Electrophile
Et	Ethyl
Et ₂ O	Diethyl ether

eq	Equivalents
HMPA	Hexamethylphosphoramide
Hex	Hexyl
IBX	2-Iodoxybenzoic acid
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
LiTMP	Lithium tetramethylpiperidide
Me	Methyl
MeOH	methanol
min	minutes
mL	millilitre
NMM	<i>N</i> -methyldmorpholine
m.p.	Melting point
Ms	Mesyl
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
ppm	Parts per million
R _f	Retention factor
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBAT	Tetra- <i>n</i> -butylammonium triphenyldifluorosilicate
TBS	<i>Tert</i> -butyldimethylsilyl

THF	Tetrahydrofuran
Tf	Trifluoromethanesulfonyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilane

Acknowledgments

First and foremost, I would like to thank Professor William Motherwell for the opportunity to work in his research group and in this exciting area of chemistry. I will be eternally grateful for the guidance, support and confidence he has given me and for his infectious love of chemistry. Secondly, I would like to thank Dr Robyn Motherwell for her expertise, kindness and willingness to help.

Thanks also go to Dr Abil Aliev for help with NMR, John and Lisa in mass spec, Dr Tom Sheppard for helpful advice and Dr Phil Gray for introducing me to carbometallation in the lab.

The Motherwell group has been a fantastic place to be so I am grateful to all members, past and present, for making the last 3 years so enjoyable and rewarding. Special thanks go to my 'year buddy' Josie and Sandy for taking on the challenges of carbometallation.

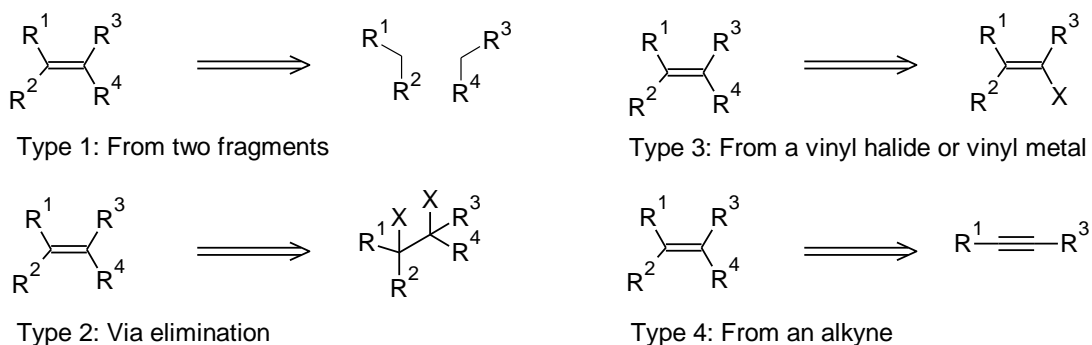
Finally, I would like to thank Mum, Dad and Yumi for their unfailing support and love.

Chapter 1: Introduction

1.1 Principles and Recent Advances in Directed Carbometallation

Since the present thesis is concerned with novel aspects of directed carbometallation the aim of this introductory chapter is to provide a brief overview and discuss the pertinent literature in the field. Due to the nature of our own area of research, this introduction will focus on the regio- and stereospecific synthesis of olefins. As a result, carbometallation of alkenes will not be covered. Although the emphasis will be on directed carbometallation, some non-directed reactions will also be included for perspective and discussion of principles. The review will accordingly concentrate on the additions of organometallic reagents to isolated alkynes and allenes, and so, conjugate additions will not be covered. Although carbometallation reactions using organo- lithium, zinc and aluminium reagents as well as carboboration reactions have been shown to be successful,¹ the majority of directed carbometallation reactions have been carried out with organocopper or Grignard reagents. For this reason and because of the nature of the research carried out, the focus of this chapter will be on the use of these reagents in carbometallation reactions.

Even though the alkene unit is commonplace throughout nature and organic chemistry, be it within a target molecule or as a key intermediate required for further elaboration, methods which provide perfect control over the geometrical isomer formed, especially in the cases of tri- and tetrasubstituted alkenes have remained as a formidable problem for many decades. The following Scheme illustrates four of the possible strategies for disconnection of an alkene in a retrosynthetic fashion (Scheme 1).²



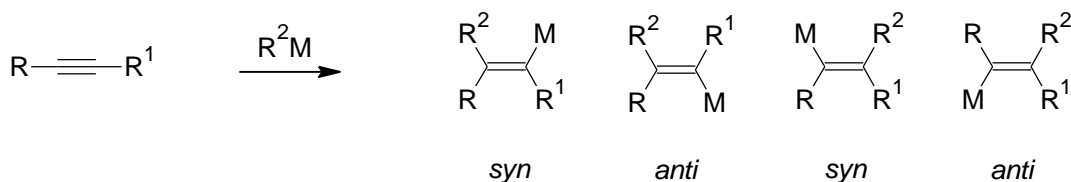
Scheme 1

Type 1 involves the preparation of the alkene from two separate groups and includes the Wittig reaction by way of example. Alternatively the two components can be connected by a single bond and elimination reactions can then take place to form the double bond (Type 2). Type 3 requires a vinyl organometallic species or a halo alkene prepared from another alkene and Type 4 involves functionalization of an acetylene. The synthesis of alkenes by carbometallation falls into Type 4 and, as will be apparent from this chapter, reactions of Type 3 can also be attributed to this manifold.

As indicated above, the synthesis of double bonds of high stereochemical purity remains a challenge in organic chemistry despite the success of the ubiquitous chemistry of Wittig and Horner-Wadsworth-Emmons reactions. Although disubstituted alkenes have been prepared to high degrees of stereochemical purity using various established methodologies, when it comes to constructing tri- and tetrasubstituted double bonds established methods suffer. Carbonyl olefinations in particular, are often unsuccessful, due to steric hindrance³ involved in the transition state. By contrast, carbometallation is known to afford highly substituted olefins

from relatively simple starting materials in good yields and with exceptional stereochemical purity.

Carbometallation involves the addition of an organometallic reagent across a carbon-carbon multiple bond (Scheme 2). The result of the addition is that a new carbon-carbon bond has been formed as well as a new carbon-metal bond. In the cases where the multiple bond substrate is an acetylene or in some cases an allene, a vinyl organometallic reagent is formed. This intermediate can then be reacted with various electrophiles to afford tri and tetrasubstituted olefins. Carbometallation has been reviewed previously^{1,4-6} and has been described as a powerful tool to tackle the important challenge of forming stereospecific olefins. Nevertheless, as indicated in Scheme 2, a variety of regio- and stereochemical outcomes can formally be envisaged.



Scheme 2

The advantage that carbometallation has over other strategies is, that a regio- and stereodefined double bond can be formed, the intermediate alkenyl organometallic reagent from an alkyne or in some cases an allene, can be exploited to form a plethora of complex molecules by various chemistries.⁴ Carbometallation can also be viewed as enthalpically favourable since addition to an alkyne requires only breaking of a relatively weak π bond but gives rise to a new carbon-carbon bond, with both the organometallic reagent and the product possessing a carbon-metal bond.

For ease of discussion the following review will be organised firstly into substrate then further divided into the nature of the organometallic reagent used.

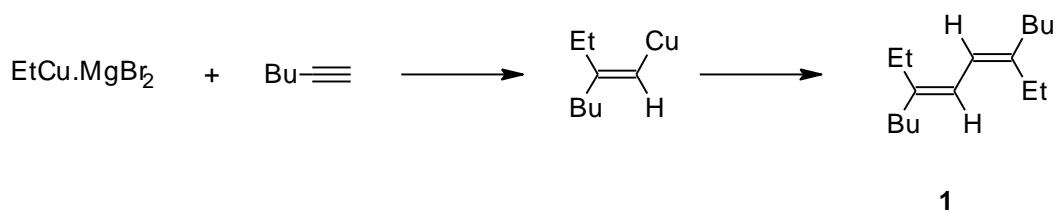
In an early study Normant and co-workers first reported the stereo- and regiospecific *cis* addition of organocopper reagents to terminal alkynes.⁷ Whereas an organocuprate, (formed from two equivalents of organometallic and one equivalent of copper(I) salt) would result in deprotonation of the alkynes, an organocopper species (formed from equimolar amounts of organometallic and copper(I) salt) was shown to add across the triple bond in a *syn* fashion (Scheme 3)



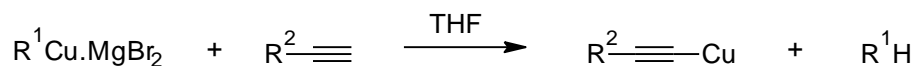
Reagents and conditions: i) Et₂O, -10 °C, 1 h; ii) H₂O

Scheme 3

A side reaction was found to occur due to the instability of the organocopper reagent resulting in the formation of diene **1** (Scheme 4) via oxidative coupling of the vinyl organocopper species. Normant and co-workers noted the deposition of copper metal when this reaction took place. The copper(I) salt was investigated and it was found that copper(I)iodide increased the amount of coupled product as well as liberating iodine which resulted in isomerisation of the diene, whereas copper(I)chloride was less efficient. When investigating the effect of solvent on the reaction it was also observed that THF had the effect of making the organocopper reagent more basic resulting in the formation of the copper acetylide (Scheme 5).

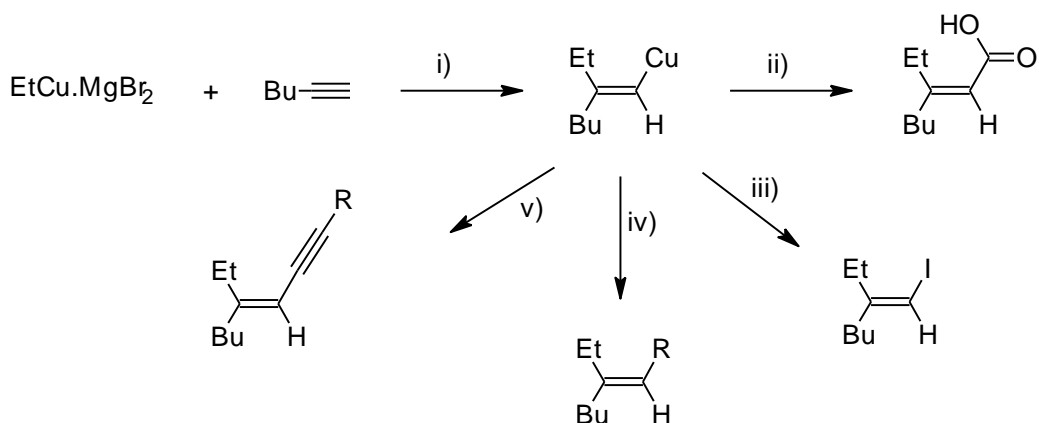


Scheme 4



Scheme 5

The manipulation of the initially formed vinyl organometallic intermediate was investigated briefly in this report and in more depth in subsequent publications⁸⁻¹³ thereby exploiting the power of carbometallation in forming highly functionalised olefins. It was found that the organocopper intermediate took part in alkylation, iodination, carbonation and substitution reactions to give a range of products (Scheme 6).



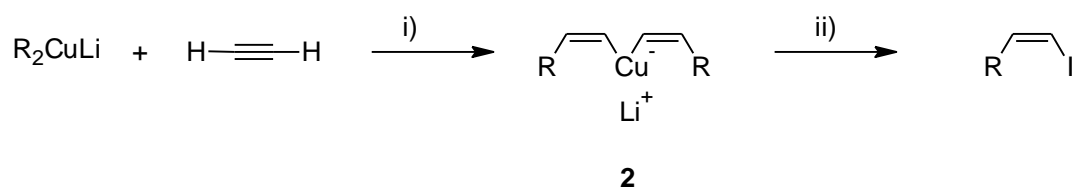
Reagents and conditions: i) Et₂O, -10 °C, 1 h; ii) CO₂, HMPA, 10% P(OEt)₃; iii) I₂, Et₂O, 4 h; iv) RI, HMPA, P(OEt)₃; v) RC≡CCl, HMPA, TMEDA

Scheme 6

With exception of the iodination reaction, the reactivity of the vinylcopper species was greatly enhanced when using HMPA as a cosolvent and catalytic $\text{P}(\text{OEt})_3$ as a ligand. Without these additives the reactions were often low yielding, illustrating the sluggish reactivity of organocopper reagents relative to organocuprates.

Reports on the study of the active species involved in the carbocupration were published by Ashby and co-workers.¹⁴⁻¹⁶ The carbocupration of phenylacetylene was carried out using methyl magnesium bromide and copper(I)bromide in various ratios using THF as a solvent. NMR analysis found that the active species were Cu_4MgMe_6 and Cu_6MgMe_8 in the presence of MgBr_2 . However only methyl magnesium bromide was used to simplify the NMR studies and more importantly the solvent used was THF rather than diethyl ether. It was reported later by Ashby that equimolar methyl magnesium bromide and copper(I)bromide in diethyl ether form MeCu and MgBr_2 and only a small amount of cuprate.¹⁷

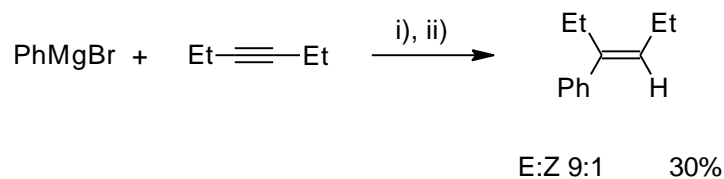
Acetylene itself has also been investigated as a substrate for carbometallation.¹⁸⁻²⁰ Surprisingly, in this instance, it was found that diorgano cuprates are able to add to acetylene to afford (Z)-alkenyl cuprate **2** (Scheme 7). In order to ensure that both alkenyl groups reacted with the selected electrophile, $\text{P}(\text{OEt})_3$ was required as a ligand to stabilise the vinylcopper intermediate and prevent its decomposition at room temperature. The fact that acetylene was not deprotonated by a cuprate suggests that carbometallation was faster than deprotonation.



Reagents and conditions: i) Et₂O, -40 °C; ii) I₂ (2 eq)

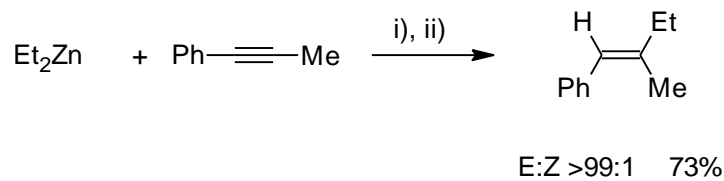
Scheme 7

Non-directed *syn* carbometallation of alkynes has also been mediated by nickel,^{21,22} iron²³ and chromium²⁴ (Schemes 8-9, 10 and 11 respectively) and these methods are likely to benefit from a directing tether to allow an even wider range of non-symmetrical alkynes to be used in potentially regiospecific reactions.



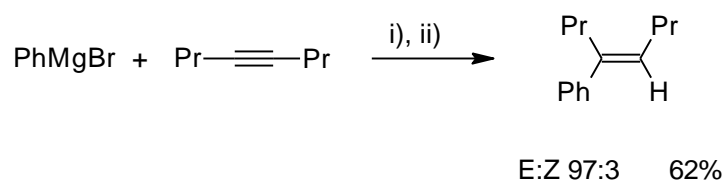
Reagents and conditions: i) (PPh₃)₂NiCl₂, Et₂O, reflux, 72 h; ii) H₂O

Scheme 8



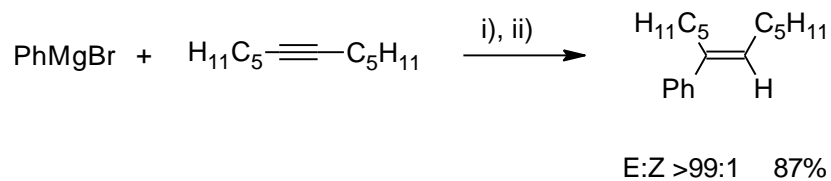
Reagents and conditions: i) Ni(acac)₂ (25 mol%), THF/NMP, -35 °C; ii) H₂O

Scheme 9



Reagents and conditions: i) Fe(acac)₃ (5 mol%), CuBr (10 mol%), PBu₃ (40 mol%), THF, 60 °C, 24 h; ii) H₂O

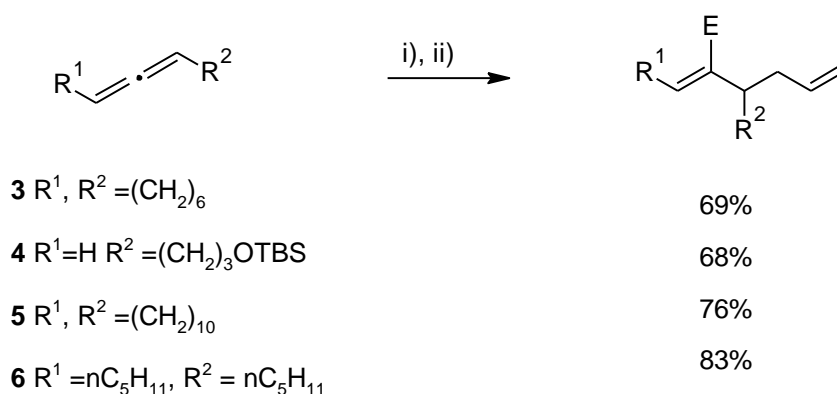
Scheme 10



Reagents and conditions: i) CrCl₂ (7.5 mol%), *t*-BuCO₂H (10 mol%), PhMe, reflux, 15 min; ii) H₂O

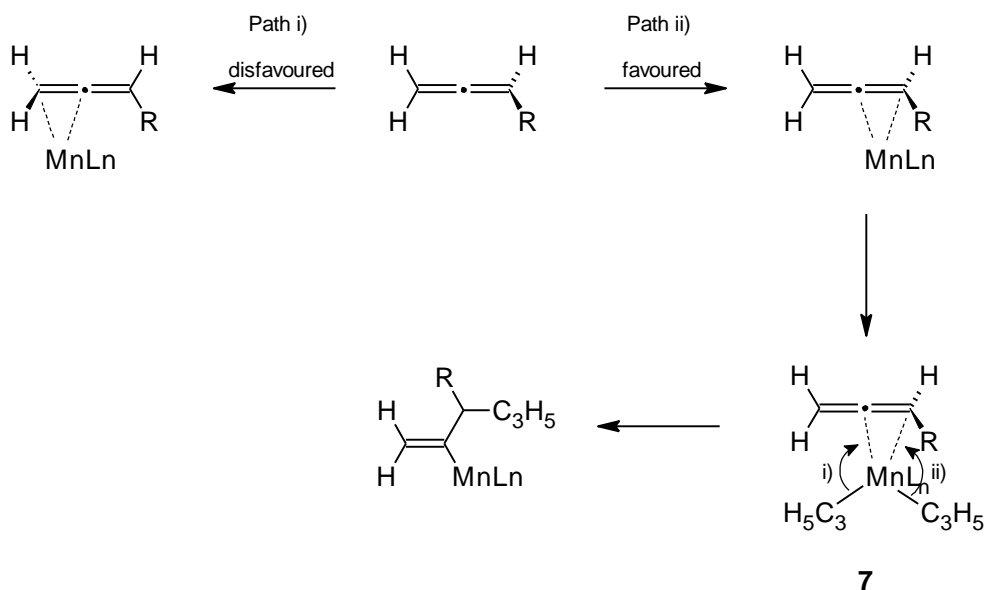
Scheme 11

The carbometallation of allenes was explored by Oshima and co-workers (Scheme 12).²⁵ It was found that tetraallylmanganate added regioselectively to cyclic allene **3** in good yield as well as adding regiospecifically to terminal allene **4** in moderate yield in the presence of HMPA. The addition to acyclic allene **6** was also regioselective however the stereochemistry of the resultant alkene was not determined. The authors then carried out the addition using allyl magnesium chloride and catalytic manganese dichloride which afforded good yields of alkenes when quenched with a range of electrophiles. Cyclic allene **5** gave rise to higher yields but a loss in stereoselectivity most likely due to the fact that the *trans* internal alkene was possible in the larger ring. In the acyclic system there was almost no selectivity. The reactivity of the organometallic towards the more substituted of the two double bonds led to the suggestion that complex **7** (path ii, Scheme 13) was favoured as it avoided the eclipsing interactions of the coplanar hydrogen atoms on the terminus of the allene.



Reagents and conditions: i) (Allyl)₄Mn(MgCl)₂ or AllylMgCl and MnCl₂ (20 mol%), THF, rt; ii) Electrophile

Scheme 12



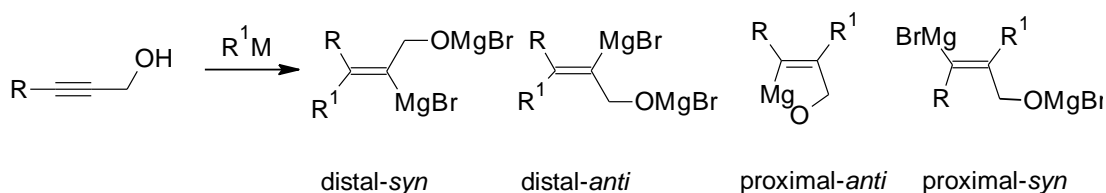
Scheme 13

1.2 Directed carbometallation

As illustrated above, the problem of controlling regioselectivity in carbometallation is a vexatious one and the use of a tether or directing group has provided an often employed solution to this problem for many classes of organic reactions.²⁶ The majority of these directing tethers involve delivery of the reactant to the substrate in a favoured geometry either by way of a noncovalent incipient interaction or by creation of a temporary covalently linked intermediate. This is naturally exploited in stereo- and regiocontrolled reactions. Another aspect to directing tethers is their ability to assist a reaction by bringing both reaction partners together thus creating an intramolecular system which greatly favours any subsequent reaction relative to its formal intermolecular counterpart in which both reaction partners are required to break solvent-solute interactions, as well as overcome any unfavourable repulsive

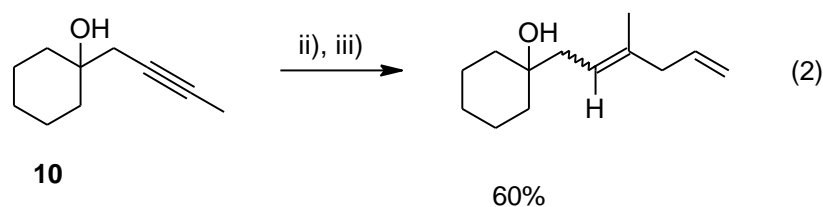
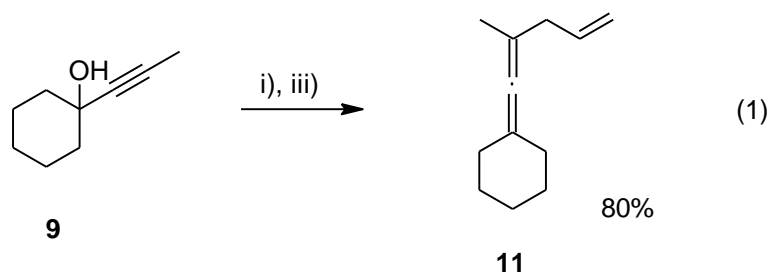
interactions. Both facets of tethers have implications for the chemistry reported in the following survey.

The directed addition of Grignard reagents to propargyl alcohols can, in theory, result in four possible isomers (Scheme 14). It is inconceivable to envisage any intramolecular assistance of the substrate in directing the addition of the organometallic reagent towards the proximal-*syn* isomer. However, this type of addition has in fact been observed in some instances and must therefore be independent of the tether.



Scheme 14

Further to a report of the first addition of a Grignard reagent to a non-conjugated ethylene linkage,²⁷ Eisch and Merkley investigated the validity of intramolecular assistance using the hydroxyl group (Scheme 15).²⁸



Reagents and conditions: i) AllylMgCl (2.5 eq), PhMe, reflux, 96 h; ii) AllylMgCl (2.5 eq), Et₂O, reflux, 96 h, iii) H₂O

Scheme 15

The majority of the reactions reported in this paper and in previous papers use allylic²⁷ and homoallylic²⁹ alcohols as the substrates, however two examples involve refluxing propargylic alcohol **9** and homopropargylic alcohol **10** in toluene and diethyl ether respectively. It is presumed that compound **11** is formed by loss of MgO (or MgO.MgBr₂) as shown in Figure 1.

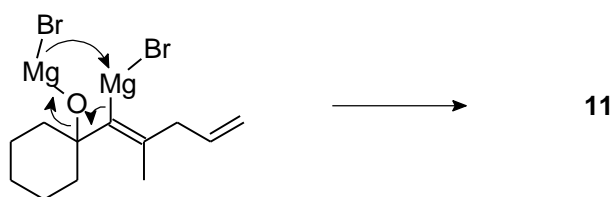


Figure 1

Because of the loss of MgO to give allene **11**, the stereochemistry of the addition cannot be determined. In the second example the carbon-carbon bond has again been formed at the distal carbon of the alkyne. The stereochemistry is not determined but Figure 2 shows two possible metallocycle intermediates that could arise from either a *syn* or *anti* addition. Literature precedent would suggest that in both examples the addition is likely to be *syn*. However, as will be revealed later in this chapter, this is not always the case.

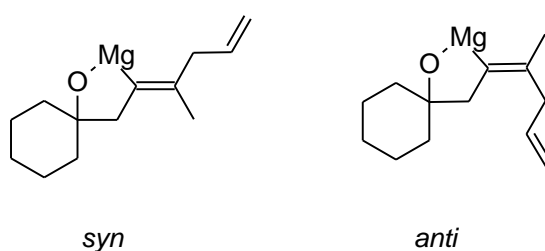
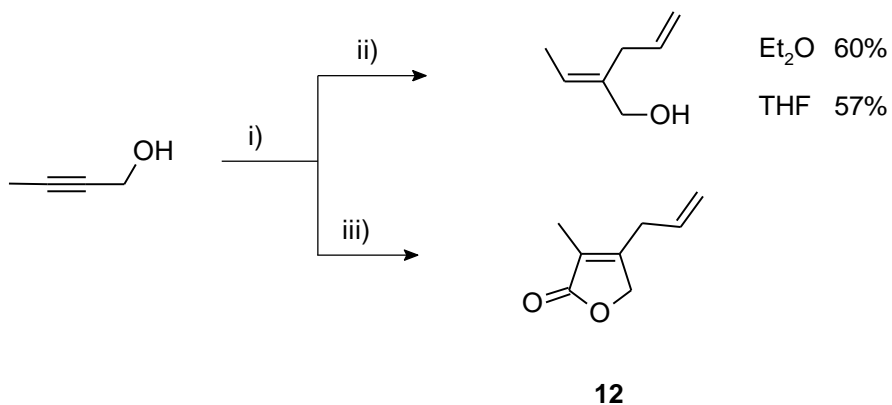


Figure 2

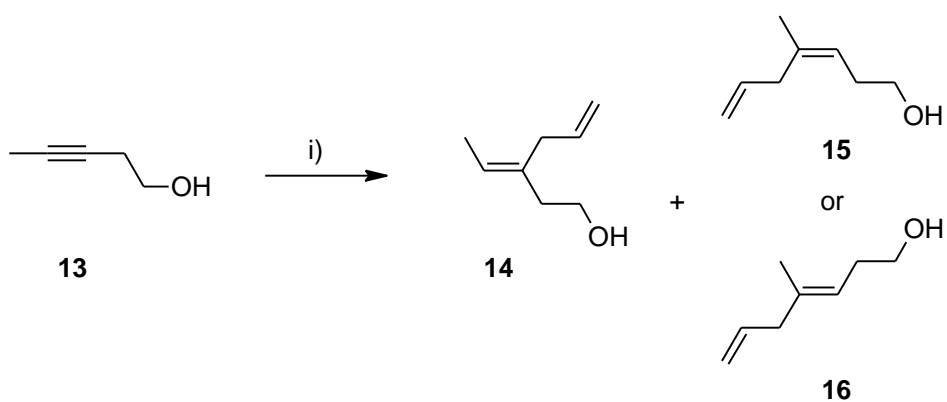
Richey and Von Rein³⁰ subsequently reported additions of allyl and vinyl magnesium chlorides to primary propargylic and homopropargylic alcohols and claimed that the hydroxyl function promoted the addition of the Grignard reagent to those alkynols. Whereas allyl magnesium chloride added to 2-butyne-1-ol in a proximal-*anti* fashion (Scheme 16), no addition products were found from similar reactions with phenyl magnesium bromide, methyl magnesium chloride and *tert*-Butyl magnesium chloride. The value of the intermediate vinyl Grignard was capitalised upon by quenching the reaction with CO₂ to yield the butenolide **12**. In the case of the homopropargylic alcohol **13**, a mixture of products was obtained when it was heated at reflux in diethyl ether with allyl magnesium chloride. Dienols **14** & **15** or **16** were isolated in 30% yield (Scheme 17). The additions were proximal-*anti* (**14**) – as for 2-butyne-1-ol – and either distal-*anti* (**15**) or distal-*syn* (**16**). Interestingly, the reaction of allyl magnesium chloride with 4-phenyl-3-butyne-1-ol

afforded only dienol **17** in 40% yield in which the Grignard had added in a proximal-*anti* fashion (Scheme 18). This could be a consequence of the reaction proceeding through favoured metallocycle **18**.



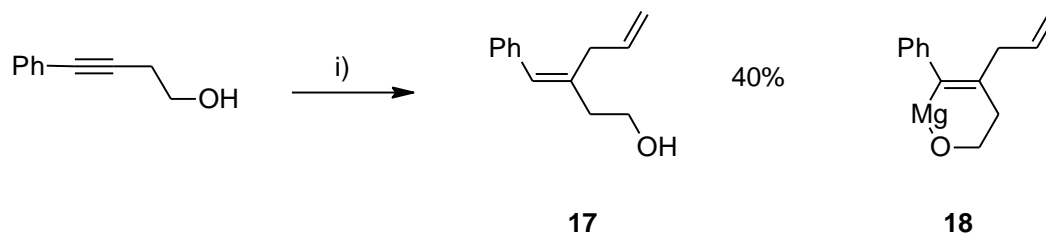
Reagents and conditions: i) AllylMgCl (2 eq), Et₂O or THF, reflux; ii) H₂O; iii) CO₂

Scheme 16



Reagents and conditions: i) AllylMgCl (2 eq), Et₂O, reflux then H₂O

Scheme 17

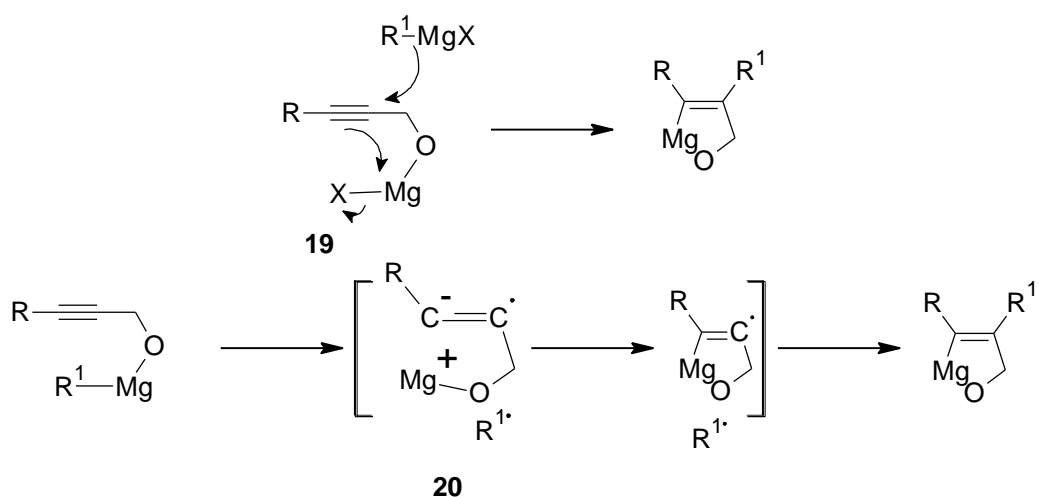


Reagents and conditions: i) AllylMgCl (2 eq), Et₂O, reflux then H₂O

Scheme 18

The possibility that the vinyl Grignard intermediate could have undergone *cis-trans* isomerisation was discounted since previously published work had shown that isomerisation occurred slowly under comparable conditions.³⁰

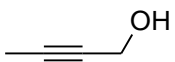
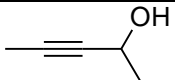
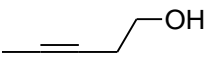
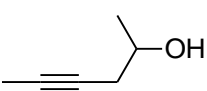
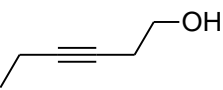
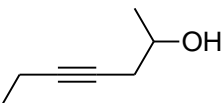
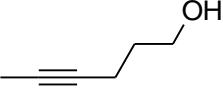
Richey and Von Rein suggested that an intermolecular addition to a species such as **19** would involve close approach of the magnesium to the distal carbon and that this would require considerable distortion. Instead, they postulated a curious single electron transfer mechanism involving intermediate **20** in which a stepwise mechanism forms the new carbon-carbon and carbon-magnesium bonds (Scheme 19).



Scheme 19

Two years later Richey and Von Rein published further work focusing on the stereochemistry of additions to alkynols (Table 1).³¹ The results of their study suggested that additions of allyl magnesium chloride reagents to alkynols are often *trans* and that products corresponding to *cis* addition are from side reactions. The authors noted that additions where the carbon-carbon bond is formed at the proximal carbon are always *trans* additions. When the carbon-carbon bond is formed at the distal carbon additions can be *trans* or *cis*. This correlates with the ability of these additions to be successfully assisted in an intramolecular fashion by the alkoxide tether as discussed earlier. It is observed that *cis* additions are favoured by the use of THF instead of diethyl ether, by a methyl rather than an ethyl substituent on the terminal alkyne carbon, and by an α -methyl substituent (secondary propargyl alcohol). The bis-homopropargyl alcohol affords little product, most likely due to the tether being too far from the alkyne.

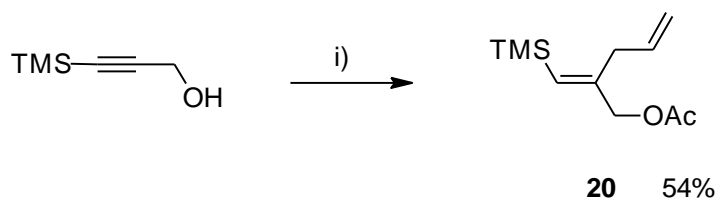
Table 1

Alkynol	Solvent	Time (h)	Procedure	Proximal anti (%)	Distal anti (%)	Distal syn (%)
	Et ₂ O	24	A	85	0	0
	THF	48	A	79	0	0
	THF	54	A	22	0	0
	Et ₂ O	120	A	50	25	0
	THF	120	A	43	10	3
	Et ₂ O	48	A	45	14	16
	THF	48	A	32	8	4
	Et ₂ O	48	B	46	22	0
	THF	48	A	35	13	0
	Et ₂ O	72	B	3	24	0
	THF	168	A	12	13	11
	THF	72	B	0	7	0

Procedure A: 50 °C, analysed by glc and NMR of hydrolysed aliquots; Procedure B: reflux, analysed by glc and NMR of distilled products.

Miller and Reichenbach then extended the work done by Eisch, Merkley, Richey and Von Rein by showing that allyl magnesium chloride can add in a proximal-*anti*

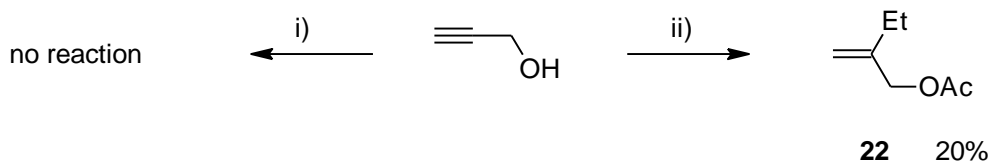
fashion to 3-trimethylsilyl-2-propyn-1-ol in refluxing THF.³² The resulting allylic alcohol was then acetylated to give compound **21** in a 54% yield (Scheme 20). This was an interesting observation as the silicon-carbon bond is known to be labile towards various nucleophiles.³³



Reagents and conditions: i) AllylMgCl, THF, reflux then Ac₂O

Scheme 20

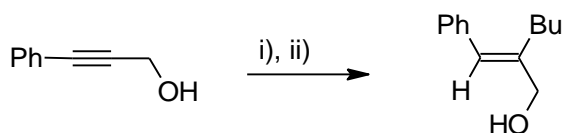
Interestingly, the authors observed that no addition product occurred in the reaction of allyl magnesium chloride with 2-propyn-1-ol. However ethyl magnesium bromide added to propargyl alcohol in refluxing diethyl ether in a proximal-*anti* fashion. The resulting allylic alcohol was again acetylated to afford compound **22** in a 20% yield. The addition of ethyl magnesium bromide to 2-butyne-1-ol and 3-trimethylsilyl-2-propyn-1-ol in either refluxing THF or diethyl ether afforded no addition product (Scheme 21). This highlights the difficulty in reacting alkyl Grignard reagents with propargyl alcohols.



Reagents and conditions: i) AllylMgCl, Et₂O, reflux then Ac₂O; ii) EtMgBr, Et₂O, reflux then Ac₂O

Scheme 21

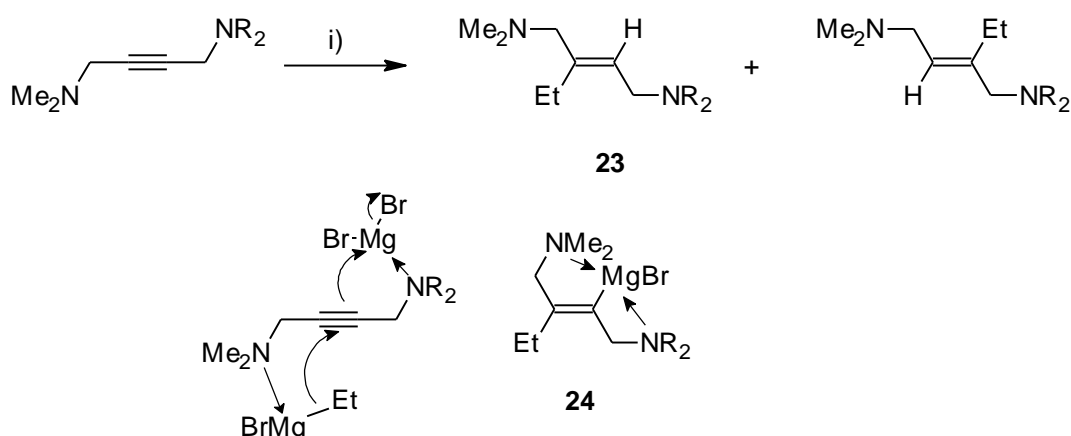
Although this literature review focuses on magnesium and copper containing organometallic reagents, the following example involving an organolithium reagent has been included to illustrate the interesting *anti* addition to propargyl alcohols.³⁴ Olsson and Claesson reacted *n*-butyllithium with 3-phenylpropargyl alcohol in the presence of tetramethylethylenediamine (TMEDA) to afford an allylic alcohol via a proximal-*anti* addition with a single isomer isolated in 90% (Scheme 22). A previous report on the addition of organolithium reagents to allylic alcohols suggests that the TMEDA is involved in breaking up organolithium aggregates and polarizing the carbon-lithium bond.³⁷



Reagents and conditions i) *n*-BuLi (2.5 eq), Et₂O, TMEDA (20 mol%), -30 to 20 °C, 3 h; ii) H₂O

Scheme 22

Amines have also received attention as directing groups for carbometallation.^{35,36} Grignard reagents were shown to add to the triple bond of 1,4-diamino-2-butyne with the regioselectivity depending on the nature of the amine substituents (Scheme 23). When the substituent on the amino group was larger there was an increase in product **23** which could be explained by complexation of the Grignard reagent with the less hindered amine prior to formation of chelate **24**.



Reagents and conditions: i) EtMgBr, PhH, 60 °C, 20 h; ii) H₂O

Scheme 23

1.2.1 Carbocupration and Copper(I) catalysed Grignard additions

Work on the carbocupration of alkynes was applied to a directed system by Normant and co-workers.³⁸ The regioselectivity of the *syn* addition was perturbed by an alkoxide tether to a varying degree. Table 2 shows a study on the effect of solvent and counterion on the selectivity and efficiency of the reaction.

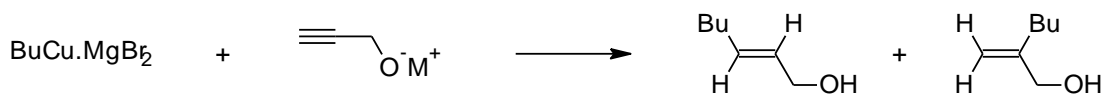
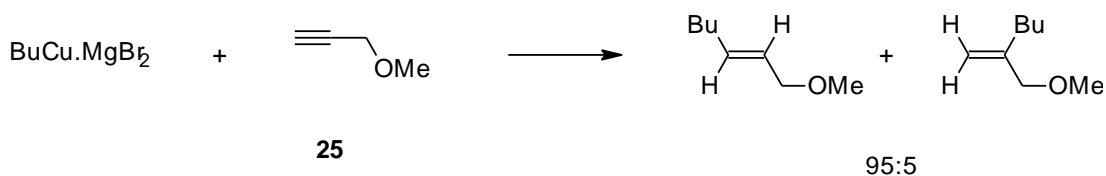


Table 2

M	Solvent	Yield	Distal <i>syn</i> (% rel.)	Proximal <i>syn</i> (% rel.)
Li	Et ₂ O	55	40	60
Li	THF	68	21	79
Na	THF	74	20	80
Na	DME	53	13	87
Na	HMPA	42	9	91

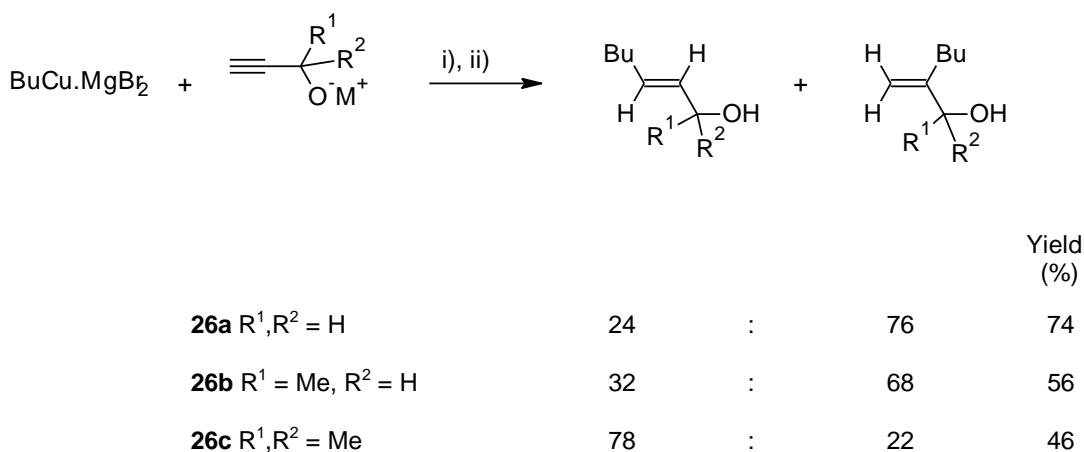
At first glance it appears that the efficiency of the reaction decreases as the polarity of the solvent increases. This could be explained by the organocopper reagent being strongly solvated and less available to react with the alkyne. What is also apparent is the increase in the selectivity for a proximal-*syn* addition and a decrease in the selectivity for a distal-*syn* addition. The proximal-*syn* addition would be the only addition to take place were it not for the alkoxide tether so a greater charge separation has the effect of reducing the capacity for an intramolecular assisted carbometallation giving rise to a proximal-*syn* addition. This is corroborated by the result that ether **25** undergoes a highly selective distal-*syn* addition (Scheme 24). Normant and co-workers offer the explanation that the increased charge separation results in a greater electron donor inductive effect of the alkoxide on the alkyne creating an electronic bias.



Reagents and conditions: i) Et_2O , $-55\text{ }^\circ\text{C}$, 1.5 h; ii) H_2O

Scheme 24

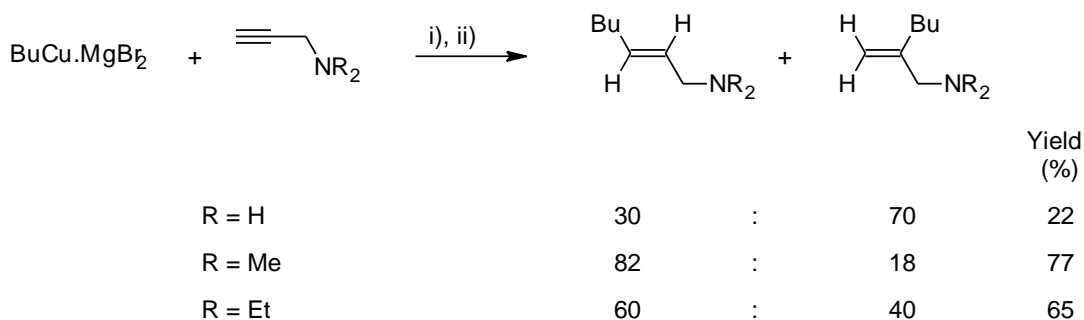
It was also reported that substitution at the propargylic position reduced the amount of proximal-*syn* product and, in the case of alkoxide **26** (Scheme 25), increased the amount of distal-*syn* product which could be explained by an increased electron donor inductive effect as well as the increased steric bulk which could hinder the approach of the organocopper reagent prior to a proximal-*syn* addition.



Reagents and conditions: i) THF , $-40\text{ }^\circ\text{C}$, 3 h; ii) NH_4Cl

Scheme 25

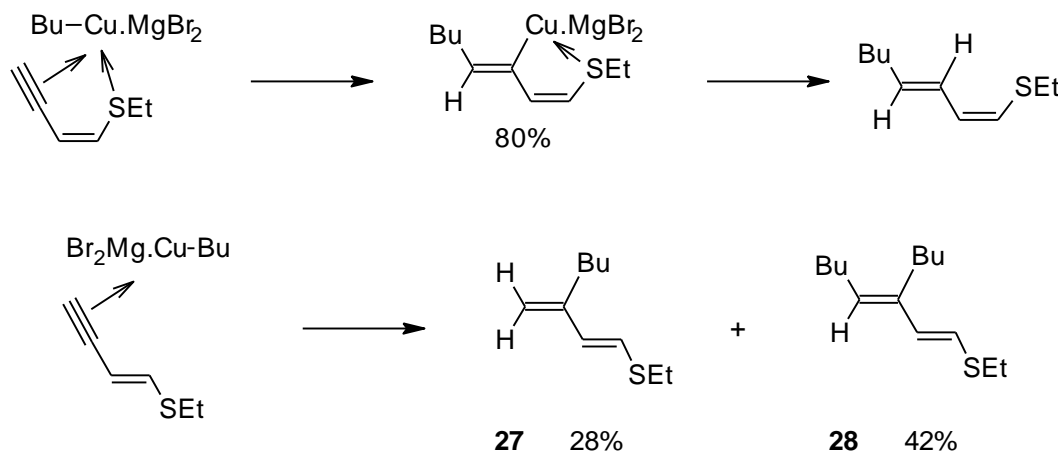
This communication also studied the additions to propargylic amines which gave good yields of allylic amines for dialkyl amino groups. Primary amines however gave poor yields and a greater selectivity for a proximal-*syn* addition. The more coordinating dialkyl amino groups served as better tethers for intramolecular assistance and had selectivity for a distal-*syn* addition as shown in Scheme 26.



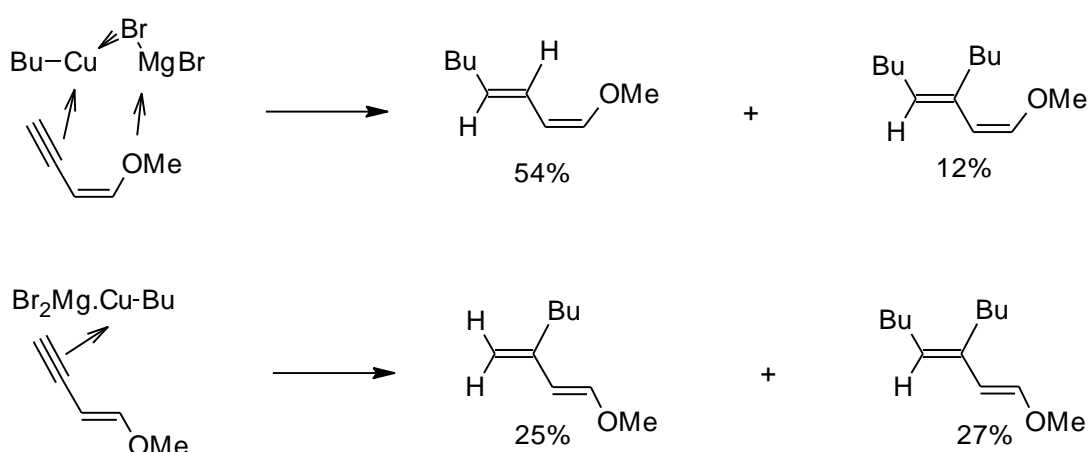
Reagents and conditions: i) THF, -40 °C, 3 h; ii) H₂O

Scheme 26

Normant and coworkers investigated further the effect of tethers on the carbocupration of propargyl systems,^{39,40} looking at ethers, sulfides and amines as well as summarising and rationalising the work from the previous communication. The work, published in 1975, showed that the geometry of the tether affected the efficiency as well as the regioselectivity of the addition. Thioenol ethers (Scheme 27) and enol ethers (Scheme 28) were shown to be successful in directing addition of butylcopper as long as there was a *cis* relationship between the tether and the alkyne.

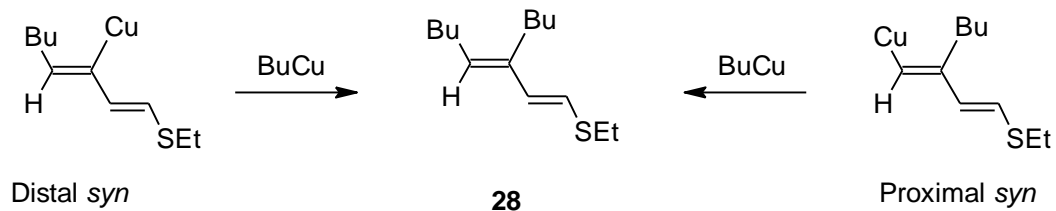


Scheme 27



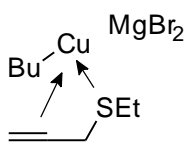
Scheme 28

The authors reported that the proximal-*syn* addition product **27** was accompanied by a side product **28** which came from a reductive coupling of the vinyl copper with butyl copper (*vide supra*). It can be seen that the *cis* relationship of the starting materials not only favours the distal-*syn* product but also reduces the amount of coupled product **28** which could suggest a stabilising effect of the sulfur tether. The greater directing effect of a sulfur ligand as opposed to its oxygen counterpart is also noteworthy. In theory the coupled product could arise from either a distal-*syn* addition or a proximal-*syn* addition (Scheme 29).



Scheme 29

The role of the heteroatom in the tethering chain has also been reinforced in a study of propargyl derivatives. It was suggested that there was a π -copper interaction as well as a heteroatom-copper interaction. The latter interaction was shown to be influenced by the nature of the solvent as shown in Table 3. When the more polar solvent THF was used in place of diethyl ether, the amount of distal-*syn* addition decreased and the amount of proximal-*syn* addition increased. As the butylcopper reagent had been shown to add in proximal-*syn* fashion to terminal alkynes, the results could be rationalised by considering that the heteroatom-MgBr₂-copper interaction was being broken up by the oxygen atom of the THF solvent molecules when the tether was an ether, acetal or an amine. However there was no difference in regioselectivity of addition in the case of thioethers. It was suggested that chelate **29** was too strained and that proximal-*syn* addition would take place with the addition uninfluenced by the sulfide tether.



29

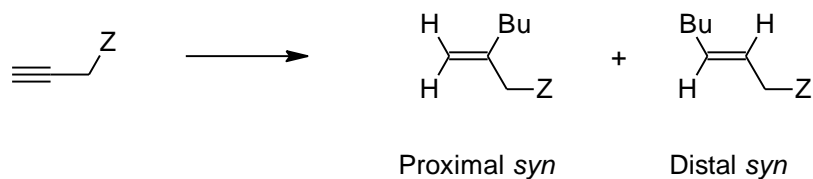
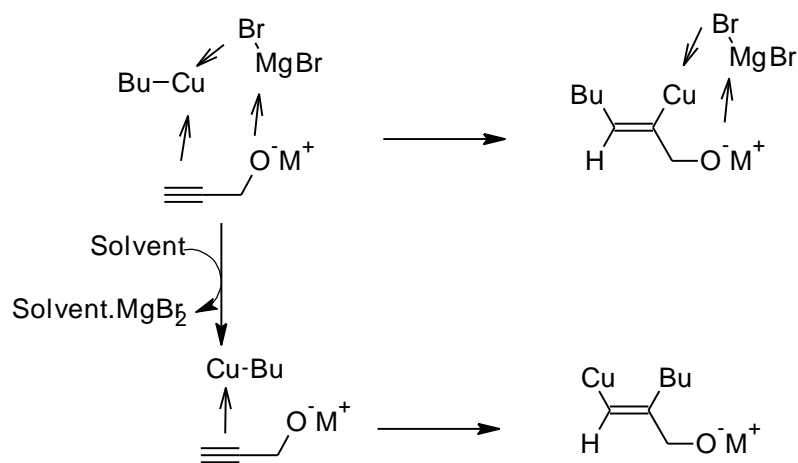


Table 3

Alkyne	Temperature (°C)	Time (h)	Solvent	Yield (%)	Proximal <i>syn</i>	Distal <i>syn</i>
	-15	20	Et ₂ O	44	97	3
	-25	20	THF	32	97	3
	-15	20	Et ₂ O	82	7	93
	-25	20	THF	47	86	14
	-55	1.5	Et ₂ O	65	3	97
	-20	3	THF	42	86	14
	-55	1.5	Et ₂ O	72	15	85
	-50	3	THF	53	100	0

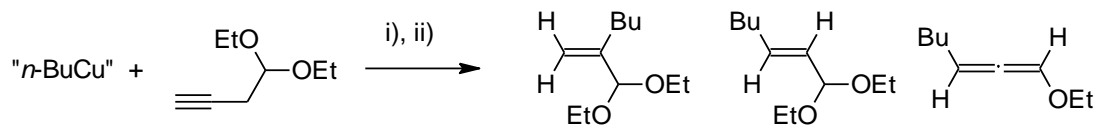
The results from the study on metal alkoxides in the previous communication could also be rationalised by the same argument used above. Scheme 30 shows that if the implied magnesium bromide bridge is solvated by the more polar aprotic solvents then the distal-*syn* addition is disfavoured and the system reverts back to the predisposed proximal-*syn* addition. If the magnesium bromide bridge interaction was not present, the intramolecular assistance would have to arise from an alkoxide-

copper interaction. This would mean that if a polar solvent could disrupt this oxygen-copper interaction to the extent that it is negligible, a stronger solvation of the organocopper reactant would result, and the whole reaction would suffer accordingly. It is worth noting that the increased charge separation of the alkoxide anion and lithium or sodium counterion was affected by a change in solvent which resulted in a less efficient reaction when a polar solvent was used. It would be interesting to consider the use of a potassium counterion in a less polar solvent. This could give the charge separation required for proximal-*syn* selectivity without the detrimental effects of a polar solvent on the efficiency of the reaction.



Scheme 30

As discussed previously it was found that basic lower order diorganocuprates deprotonate terminal alkynes and therefore did not undergo carbometallation. Surprisingly this was found not to be the case when the substrate had an acetal tether.^{41,42} The results from Normant and co-workers found that lithium diorganocuprates gave a higher conversion and greater selectivity of the addition products as shown in Table 4. The low temperature of the reaction was necessary to avoid decomposition of the distal-*syn* product to the allene.



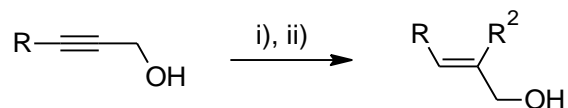
Reagents and conditions: i) Solvent; ii) H₂O

Table 4

	Solvent	Temperature (°C)	Time (h)	Distal <i>syn</i>	Proximal <i>syn</i>	Allene	Conv. (%)
R ₂ Cu ⁻	Et ₂ O	-50	0.5	2	98	0	99
Li ⁺	THF	-50 to +20	4	0	0	0	0
RCu.	Et ₂ O	-45	1	26	74	0	95
LiX	THF	-30	4	53	47	0	74
R ₂ Cu ⁻	Et ₂ O	-40	0.5	8	52	40	99
⁺ MgX	THF	-25	0.5	78	0	22	86
RCu.	Et ₂ O	-40	1	22	64	14	84
MgX ₂	THF	-25	4	59	38	3	81

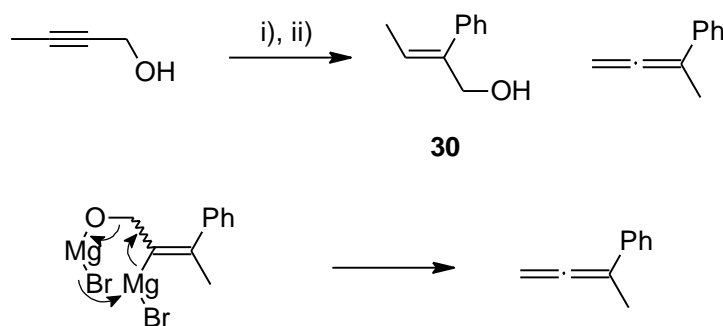
The additions of Grignard reagents to propargylic alcohols also attracted the attention of Jousseau and Duboudin in their 1975 communication on the additions of Grignard reagents with catalytic copper(I)iodide.⁴³ In general the Grignard reagent added regioselectively and stereospecifically in a proximal-*anti* fashion in moderate to high yields (Scheme 31). There were two exceptions however. When R¹ = Me and

the Grignard used was phenyl magnesium bromide two products were observed. The expected proximal-*anti* addition product **30** was formed as well as phenyl-3-buta-1,2-diene in a 30% yield (Scheme 32).



Reagents and conditions: i) R^2MgBr (3 eq), CuI (10 mol%), Et_2O , 0 °C to rt; ii) H_2O

Scheme 31

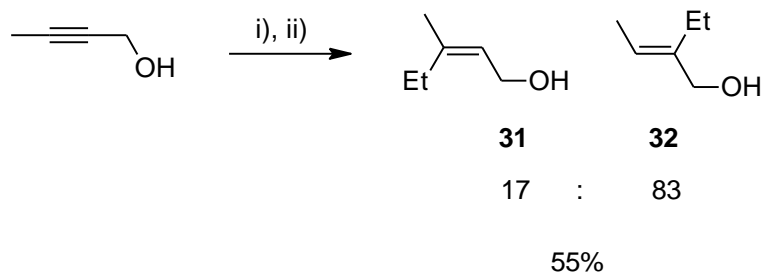


Reagents and conditions: i) $PhMgBr$ (3 eq), CuI (10 mol%), Et_2O , 0 °C to rt; ii) H_2O

Scheme 32

This allene could have been formed by the loss of MgO from the vinyl Grignard intermediate as previously noted in the work of Eisch and Merkley²⁸ and would suggest that phenyl magnesium bromide had added to 2-butyne-1-ol in either a distal-*syn* or distal-*anti* fashion. When ethyl magnesium bromide was left to react with 2-butyne-1-ol for a longer period (Scheme 33), a side product **31** was formed (distal-*syn* or -*anti*) as well as the expected **32** (proximal-*anti*). The comparable result from a shorter reaction time is considerably lower yielding (but regio- and stereoselective)

and it would be interesting to consider whether different selectivity may be observed if other reactions were to be given more time. As the side product **31** was only observed when the reaction was run for a longer time then the rate of the distal *anti* addition must be slower than that of the proximal *anti* addition so a lowering of the reaction temperature could change the proportions of **31** and **32**.



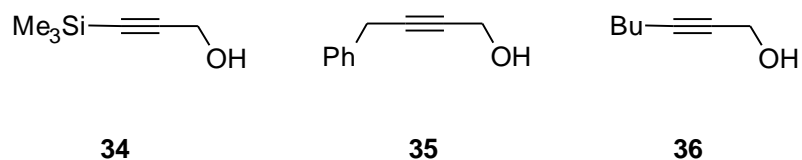
Reagents and conditions: i) EtMgBr (3 eq), CuI (10 mol%), Et₂O, 0 °C to rt; ii) H₂O

Scheme 33

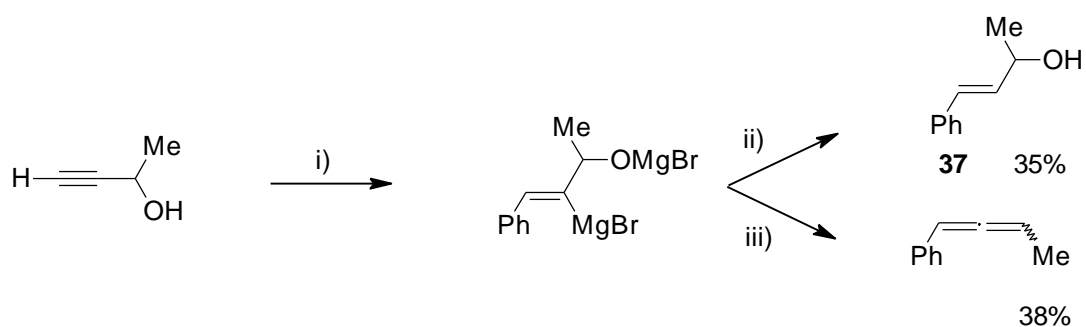
This important development led to the increase in scope of the reaction with respect to Grignard reagent as well as allowing the reaction to proceed under milder conditions.

After their communication in 1975 Duboudin and Jousseume published further work on the additions of Grignard reagents to propargylic alcohols in the presence of cuprous halides.⁴⁴ It was reported that that for primary propargylic alcohols the Grignard reagent adds in a proximal-*anti* fashion. There were however a few exceptions to this general selectivity. These authors also noted a decrease in the reactivity of alcohols **34**, **35** & **36**. Allyl magnesium bromide added regioselectively and stereospecifically to the three alcohols in a proximal-*anti* fashion whereas

phenyl magnesium bromide gave mixtures of proximal-*anti* and distal-*syn/anti* addition products.

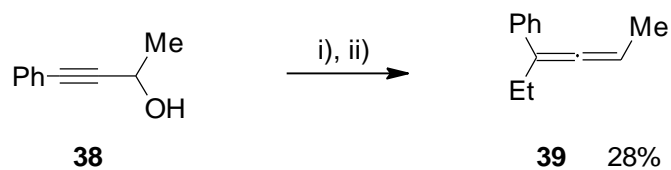


The work on secondary and tertiary propargylic alcohols showed that additions were generally less efficient and depended on the nature of the alcohol and the Grignard. Phenyl magnesium bromide added in a distal-*syn* fashion to 3-butyn-2-ol to give **37** (35%) or when heated produced the resulting allene after loss of MgO (38%) as shown in Scheme 34. With propargylic alcohol **38** and ethyl magnesium bromide allene **39** (from a distal-*anti/syn* addition) was isolated in 28% yield (Scheme 35). However when the same alkynol was treated with phenyl magnesium bromide alcohol **40** was formed in a 22% yield in a proximal-*anti* addition (Scheme 36). Tertiary propargylic alcohol **41** yielded a mixture of **42** and **43** upon reaction with phenyl magnesium bromide both resulting from a distal-*syn* addition (Scheme 37).



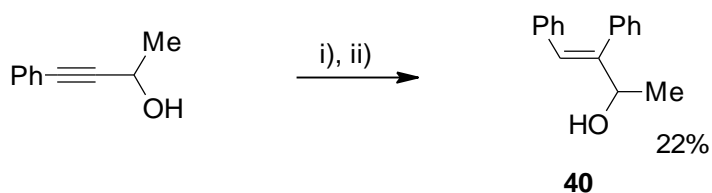
Reagents and conditions: i) PhMgBr, CuI (10 mol%), Et₂O, 0 °C; ii) H₂O; iii) heat

Scheme 34



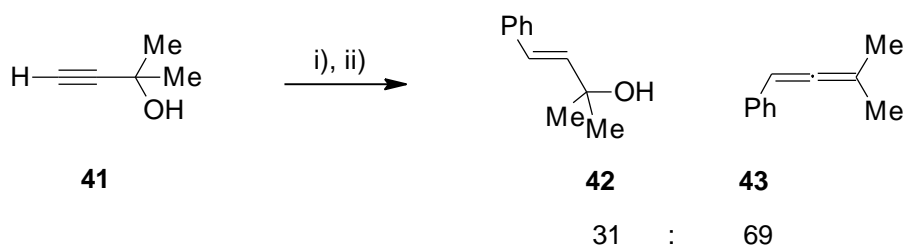
Reagents and conditions: i) EtMgBr, CuI (10 mol%), Et₂O, 0 °C; ii) H₂O

Scheme 35



Reagents and conditions: i) PhMgBr, CuI (10 mol%), Et₂O, 0 °C; ii) H₂O

Scheme 36

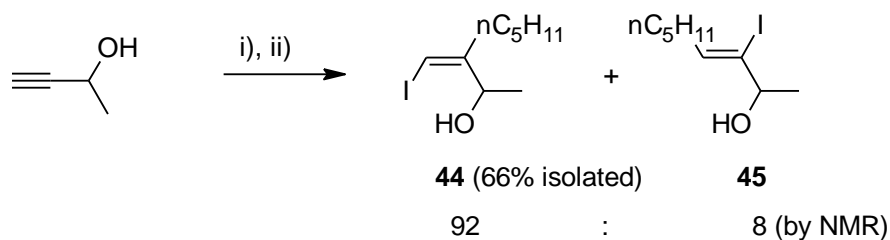


Reagents and conditions: i) PhMgBr, CuI (10 mol%), Et₂O, 0 °C; ii) H₂O

Scheme 37

In summary, it was suggested that there are three factors which affect the stereochemistry of copper catalysed Grignard additions to propargylic alcohols: the degree of substitution at the α position of the alcohol, the substitution of the triple bond and the nature of the Grignard reagent. They explained the proximal-*anti* addition with a mechanism proposed by Richey⁴⁵ and suggested copper iodide is reduced to copper(0) by the Grignard reagent and it is a copper-Grignard species, generated from catalytic copper(0), which reacts with the propargylic magnesium alkoxide.

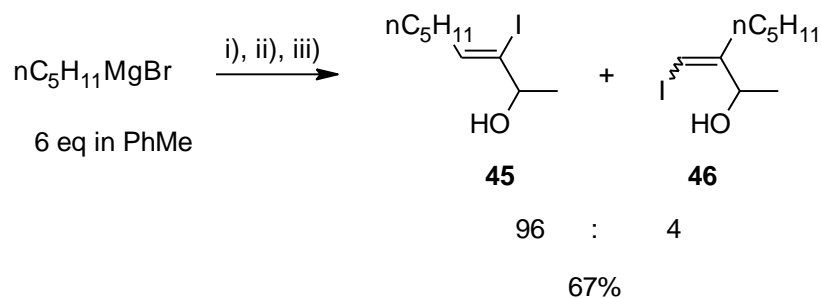
Ma and Lu have provided further insight into the copper(I) mediated additions to secondary and tertiary propargylic alcohols.⁴⁶ It was shown that, with the Grignard reagent in a THF solution, the selectivity of the reaction was reversed, (from distal-*syn* to proximal-*anti*), the yield increased and the time reduced, as compared to the reactions where the Grignard reagent was added in a diethyl ether solution. The yields, selectivity and reaction times were all improved by modifying the temperature, catalyst (counterion and loading) and reaction solvent. The optimised conditions for proximal-*anti* addition are shown in Scheme 38 (44:45 92:8). The study was limited to alkyl Grignard reagents and terminal alkynes. A simple example using phenyl magnesium bromide was also carried out, however the selectivity was completely lost to afford an almost equal mixture of both addition products.



Reagents and conditions: i) $n\text{-C}_5\text{H}_{11}$ (3.5 eq) in THF, CuI (50 mol%), PhMe, $-78\text{ }^\circ\text{C}$ to rt; ii) I_2 in THF (3.5 eq), $-40\text{ }^\circ\text{C}$

Scheme 38

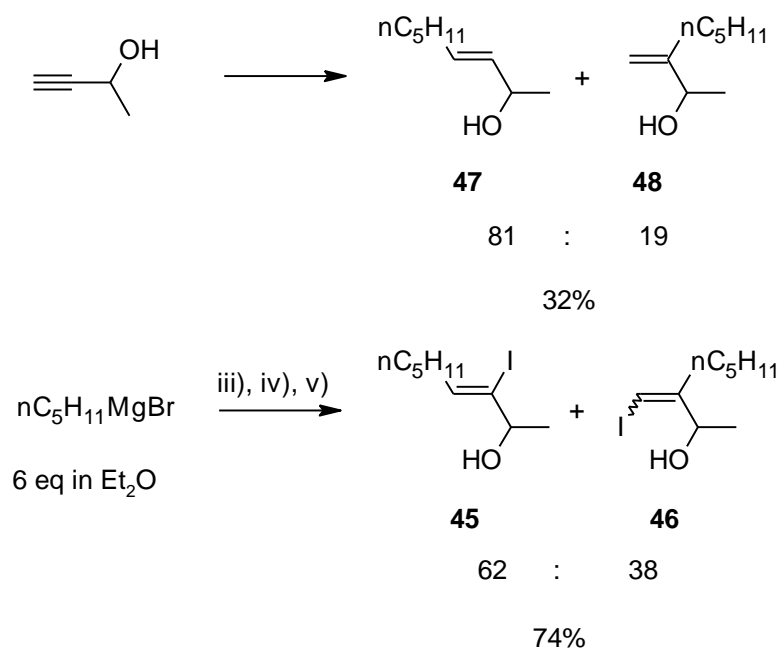
Ma and Lu then investigated the *syn*-carbometallation of secondary and tertiary propargylic alcohols.⁴⁷ It was shown that if the Grignard was prepared in diethyl ether then azeotroped with toluene it would add in a distal-*syn* fashion with a ratio of **45:46** as high as 96:4 (Scheme 39). They also found that using catalytic copper(I)iodide (0.1 eq instead of 1 eq) gave similar selectivities but a dramatically reduced yield. The use of less than 3.5 equivalents of Grignard reagent resulted in a drop in yield from 75% to 7% and a complete loss of selectivity. As with their previous study on *anti* additions, this paper was limited to alkyl Grignard reagents with one example carried out with phenyl magnesium bromide in diethyl ether solution. The *syn* selectivity is still good (90:10) so it is unclear whether other Grignard reagents would behave in the same way in diethyl ether solution. However it is possible that the reactivity of phenyl Grignard reagents differs from that of alkyl Grignard reagents and different conditions are required to influence the stereochemistry of addition.



Reagents and conditions: i) CuI (1 eq); ii) 3-butyne-2-ol in PhMe -40 °C to rt; iii) I₂
 (3.5 eq) in Et₂O -40 °C

Scheme 39

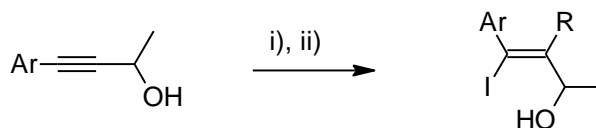
It is both interesting and curious to note that, in the previous related publication from the same two authors⁴⁶ a reaction which only differed in the amount of copper(I)iodide, reaction temperature and quench was included. As a result, the selectivity of the reaction changed from 81:19 **47:48** to 62:38 **45:46** and the combined yield increased from 32% to 74% by adding the Grignard reagent to two equivalents of copper iodide followed by addition of the alcohol at -40 °C to 0 °C instead of at -10 °C to room temperature (Scheme 40). These results highlight the difficulty in manipulating the regio- and stereochemistry of additions as well as the possible overlap in the kinetics of the possible additions.



Reagents and conditions: i) $n\text{-C}_5\text{H}_{11}\text{MgBr}$ (3.5 eq), CuI (10 mol%), Et_2O , $-10\text{ }^\circ\text{C}$ to rt, 17 h; ii) $\text{NH}_4\text{Cl}_{(\text{aq})}$; iii) CuI , (2 eq), rt; iv) 3-butyn-2-ol (1 eq) in Et_2O , $-40\text{ }^\circ\text{C}$ to rt; v) I_2 , $-40\text{ }^\circ\text{C}$

Scheme 40

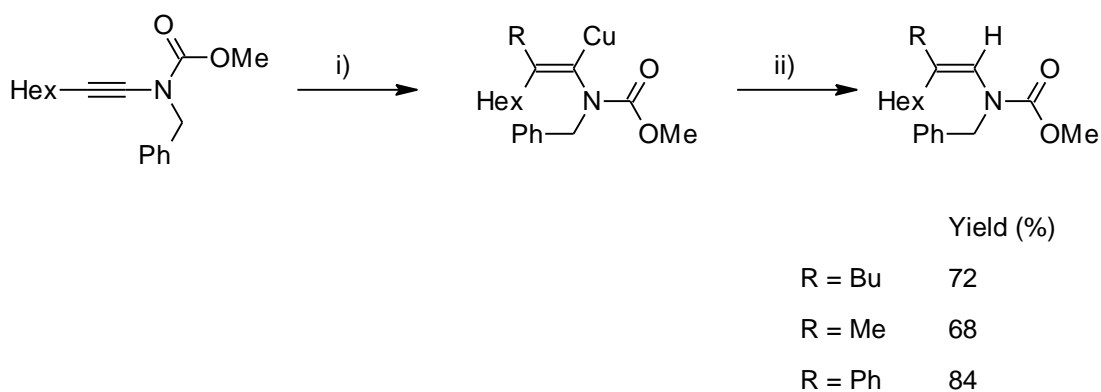
Ma extended the additions of Grignard reagents to aryl substituted secondary alkynols.⁴⁸ The use of stoichiometric copper(I)chloride and a large excess (6 eq) of Grignard gave good yields and excellent selectivity for the proximal-*anti* addition (Scheme 41). Unlike previous reports from the Ma group, this study was applied to a range of Grignard reagents.



Reagents and conditions: i) RMgBr (6 eq in THF), CuCl (1 eq), PhMe, -78 °C to rt;
ii) I₂, -40 °C to rt

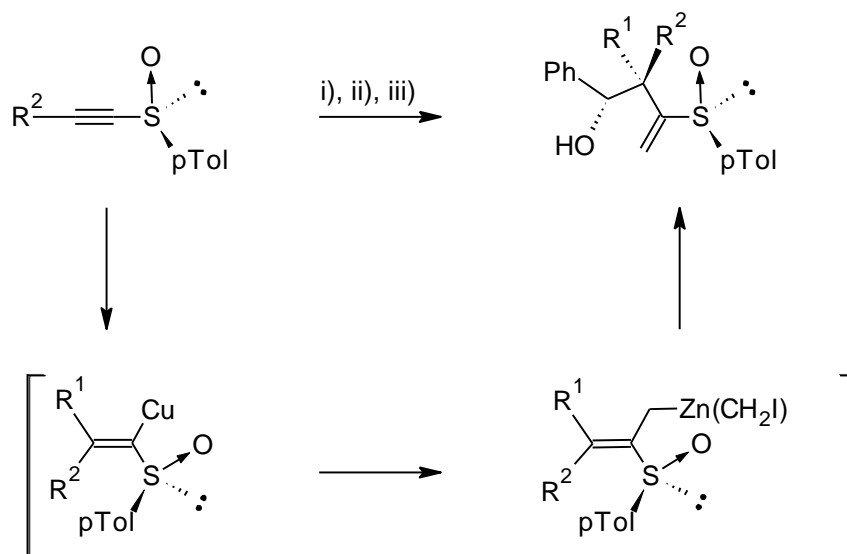
Scheme 41

α -Heteroatom substituted alkynes have been shown to be excellent substrates for directed carbometallation.⁴⁹ Marek et al. have shown that ynamides⁵⁰ (Scheme 42) and sulfoxides⁵¹ (Scheme 43) can direct the addition of organocopper reagents to alkynes in good yields. Marek has also capitalised upon the vinyl copper intermediate to form an all-carbon quaternary stereocentre via a homologation of the vinyl organometallic reagent followed by reaction with an aldehyde.



Reagents and Conditions: i) RCu.MgBr₂, Et₂O, -50 °C to -40 °C or RMgBr, CuI (10 mol%), Et₂O, -30 °C to rt; ii) NH₄Cl/NH₄OH

Scheme 42



R ¹	R ²	dr	Yield (%)
Et	Bu	99:1	81
Me	Hex	99:1	82
Me	Me	98:2	80

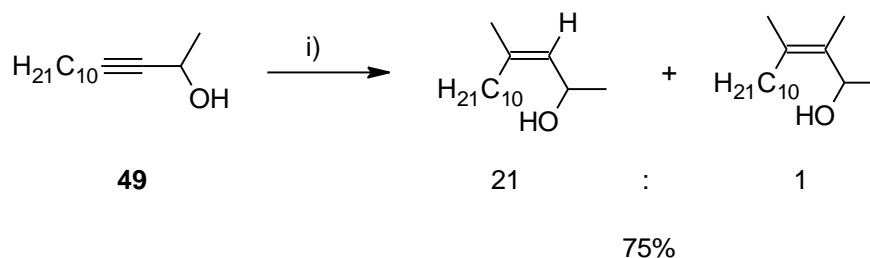
Reagents and Conditions: i) R¹Cu.MgBr₂, THF, -20 °C, 2 h; ii) PhCHO; iii)
Zn(CH₂I)₂

Scheme 43

1.2.2 Transition metal catalysed additions

Whereas the majority of directed carbometallation reactions have been mediated with copper(I) salts, other transition metals have been utilised. In 2006 Zhang and Ready published⁵² a new method of adding Grignard reagents to propargylic and homopropargylic alcohols catalysed by iron. It was shown that a combination of iron(III) acetylacetonate and a 1,2-bis(diphenylphosphino)ethane ligand gave the

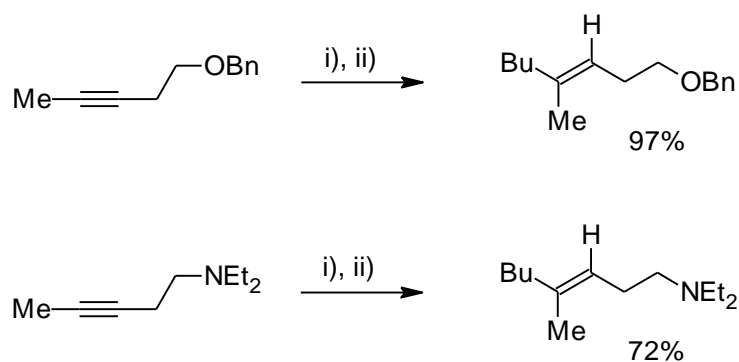
best selectivity for the addition of methyl magnesium bromide to add in a distal-*syn* fashion to **49** (Scheme 44) and reduced the amount of the dimethylated side product.



Reagents and conditions: i) MeMgBr (5 eq), Fe(acac)₃ (20mol%), dppe (20 mol%), THF, -78 °C to 0 °C

Scheme 44

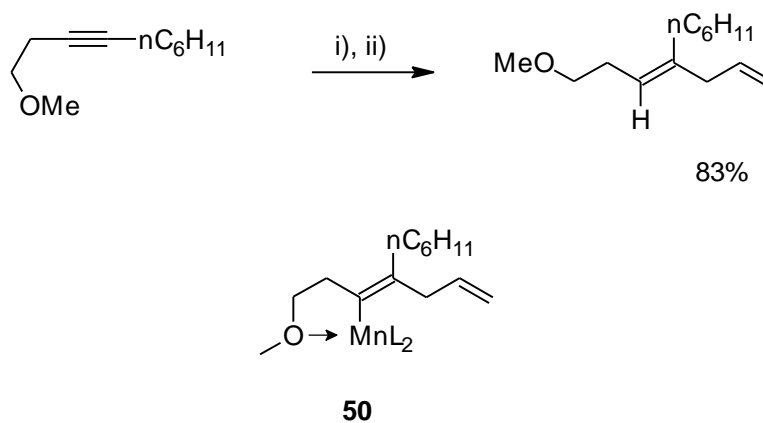
Iron catalysis was exploited again this time with organolithium reagents which were shown to add to homopropargyl ethers and amines in a distal-*syn* fashion in high yields (Scheme 45).⁵³ It was suggested that an iron-ate complex was the active species in the reaction.



Reagents and conditions: i) *n*-BuLi (3 eq), Fe(acac)₃ (10 mol%), PhMe, -20 °C, 4h; ii) H₃O⁺

Scheme 45

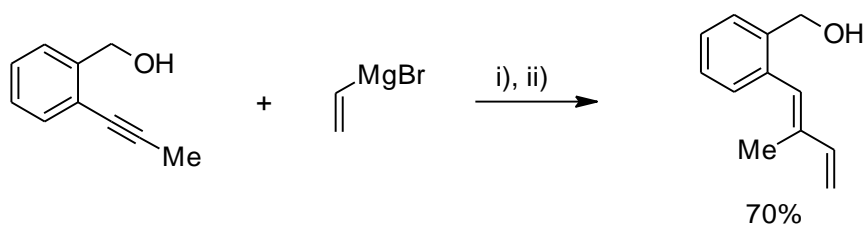
The selective *syn* addition of allyl magnesium bromide to homopropargyl ethers was shown to be catalysed by manganese salts by Oshima and co-workers (Scheme 46).^{54,55} The regio- and stereochemistry could be rationalised by chelate **50**.



Reagents and conditions: i) AllylMgBr, MnI₂ (3 mol%), rt, 3 h; ii) H₃O⁺

Scheme 46

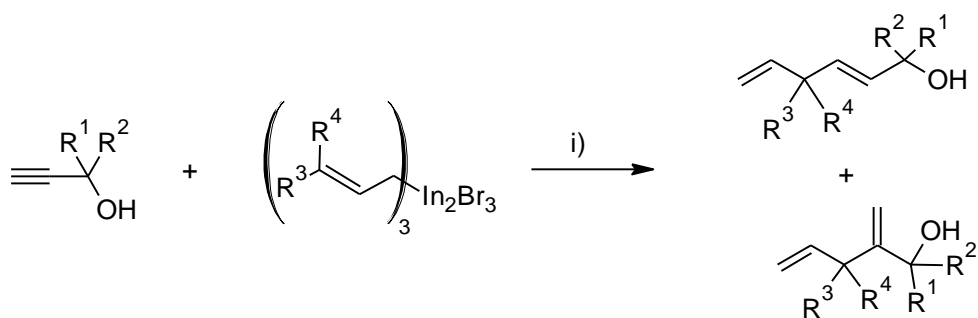
Oshima and co-workers also investigated the nickel catalysed addition of alkenyl Grignard reagents to alkynes with an oxygen tether with distal-*syn* selectivity (Scheme 47).⁵⁶ Alcohol tethers afforded dienes in high yield with ether tethers performing worse. Amine, secondary alcohols and carboxylic acid tethers all failed to direct the addition successfully.



Reagents and conditions: i) NiBr₂(PPh₃)₂ (10 mol%), THF, 50 °C, 2 h; ii) H₃O⁺

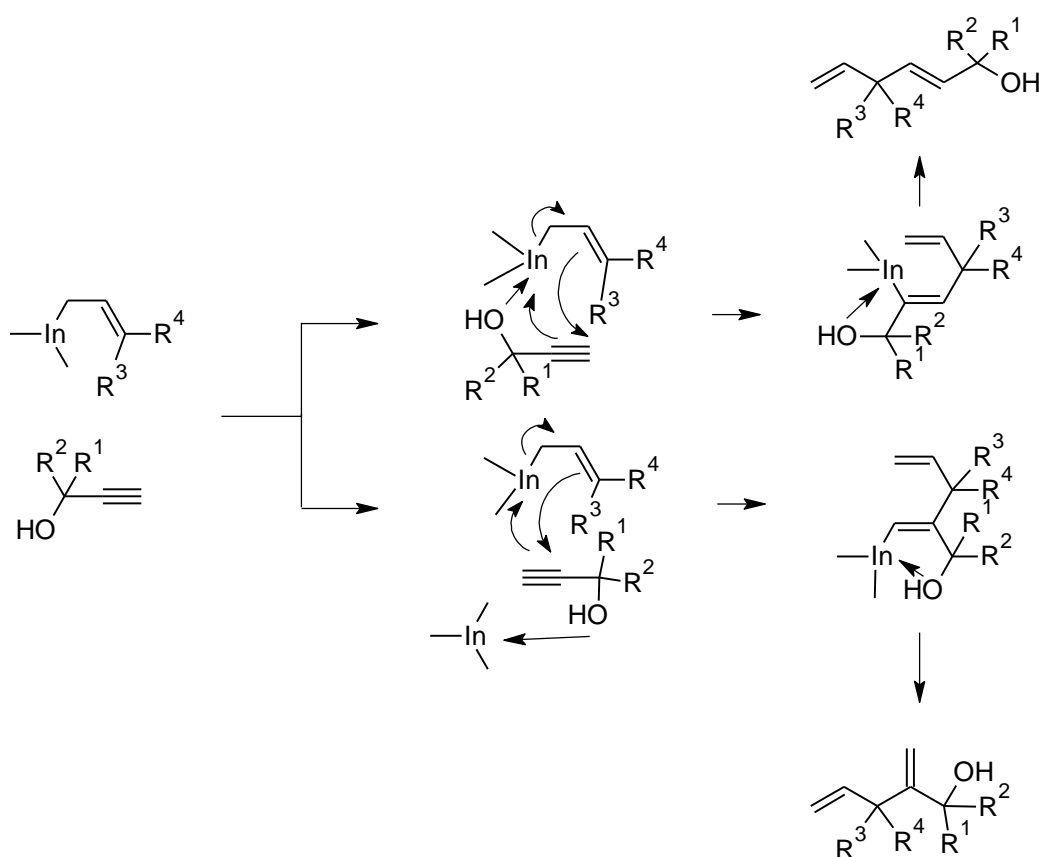
Scheme 47

The directed addition of allylindium sesquihalides to propargyl and homopropargyl alcohols was investigated by Butsugan and co-workers (Scheme 48).⁵⁷ The presence and position of the hydroxyl group was shown to be crucial as, without it, the reaction would not take place under the same conditions, requiring higher temperatures and affording mixtures of products in low yields. The results also showed that the hydroxyl group could be only one or two methylene groups away from the alkyne suggesting significant intramolecular assistance. The reaction differs from those described previously in that the organometallic reagent does not deprotonate the alcohol before addition. This was proven by the use of only 0.5 equivalents of allylindium sesquihalide which, if it were to deprotonate the alkynol, would only give a theoretical maximum yield of 50%. The selectivity of addition was affected by the nature of the alkynol and the allylindium reagent. However reactions always occurred through the γ carbon as shown in the mechanism postulated in the paper (Scheme 49).



Reagents and conditions: i) DMF, 140 °C

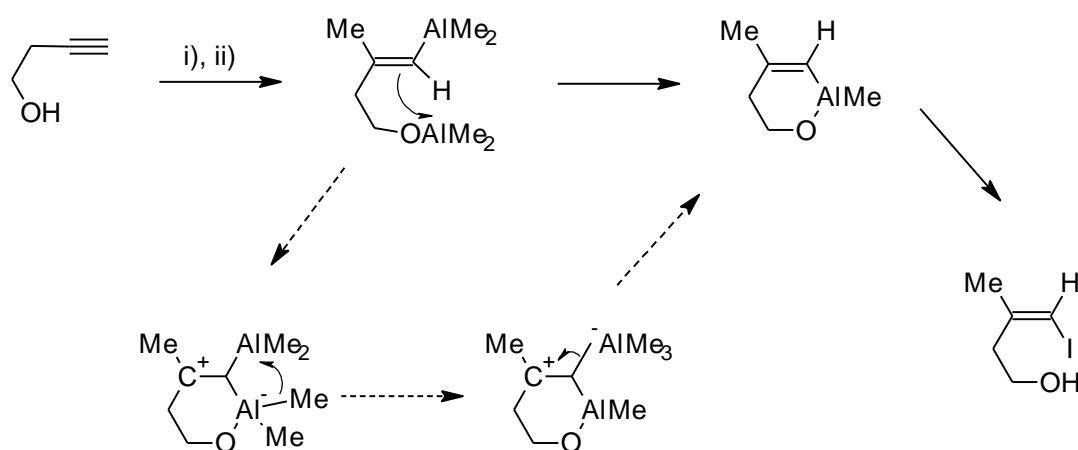
Scheme 48



Scheme 49

A complementary carboalumination of homopropargyl alcohol has been studied by Negishi and co-workers which takes place using Zirconium catalysis (Scheme 50).⁵⁸

Although the initial carbometallation is in a proximal-*syn* fashion and therefore not directed, the use of an oxygen tether affects isomerisation of the double bond giving rise to a postulated metallocycle in which the two fragments of the organometallic end up *anti* to each other. The necessary formation of this metallocycle is rationalised by a necessary chelation control mechanism as the carboalumination product from a simple terminal alkyne does not undergo any isomerisation. Although the initial communication reports the need for 72 hours in refluxing 1,2-dichloroethane to achieve isomerisation, it was reported later⁵⁹ that the use of aluminium trichloride led to complete isomerisation in only 6 hours at 50 °C.



Reagents and conditions: i) Me_3Al , Cl_2ZrCp_2 (cat.), DCE, rt; ii) reflux, 72 h or AlCl_3 , $50\text{ }^\circ\text{C}$, 6 h

Scheme 50

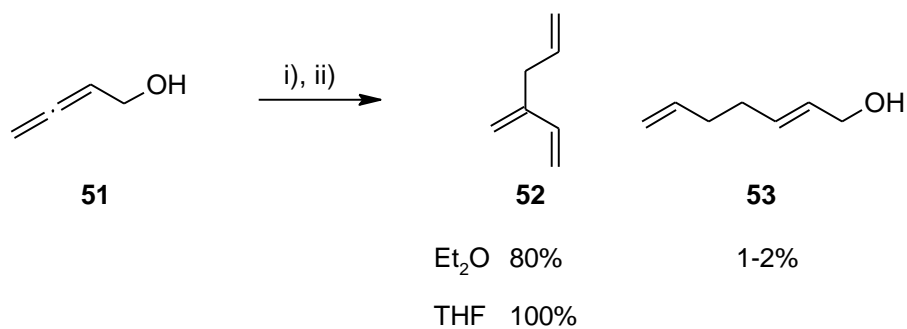
From the forgoing examples, it is clear that the addition of Grignard reagents to propargylic systems is a reaction that has received considerable attention. Nevertheless, the issue of regio- and stereoselectivity is still to be resolved fully to the extent that a set of predictive rules governing selectivity can be drawn up. Primary propargylic alcohols appear to be the most consistent of substrates with

Grignard reagents adding in a proximal-*anti* fashion. However, there are still some exceptions, as for example the copper mediated addition of phenyl magnesium bromide to 2-butyne-1-ol carried out by Duboudin and Jousseume⁴³ as well as the interesting results from Normant³⁸ et al. concerning metal alkoxides. Ma and Lu have made an important contribution in their selective addition of Grignard reagents to secondary and tertiary propargylic alcohols in a distal-*syn* fashion. Unfortunately, a number of variables were changed in the process and it is not entirely clear which factors influence the stereochemical outcome of the additions. It is also not clear where the parallels and distinctions lie between stoichiometric or catalytic carbometallation and the thermally allowed carbomagnesiation.

1.2.3 Additions to allenols

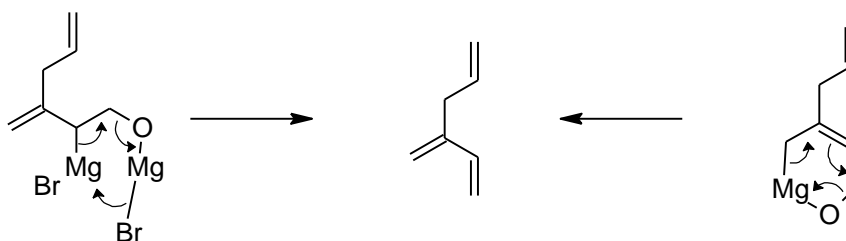
At this stage, it is now appropriate to introduce the allene unit as the second unsaturated functional group which can give rise to regio- and stereoselective creation of a new carbon-carbon double bond. In contrast to the work on propargylic alcohols, the reactions of Grignard reagents with allenols have received less attention. Because of the two cumulated double bonds of the allene unit, there are two additional possibilities in terms of selectivity for a particular regiochemistry.

Richey and Szucs were the first to add allyl magnesium chloride reagents to allenols (Scheme 51).⁶⁰ It was found that addition to allenol **51** resulted in the new carbon-carbon bond being formed at the central carbon atom of the allene with the position of the carbon-magnesium bond unknown since the triene **52** can arise from elimination of MgO or MgO.MgBr₂ from two possible intermediates (Scheme 52). A very small amount of the alternative regioisomeric alcohol **53** was noted when diethyl ether was used as a solvent.



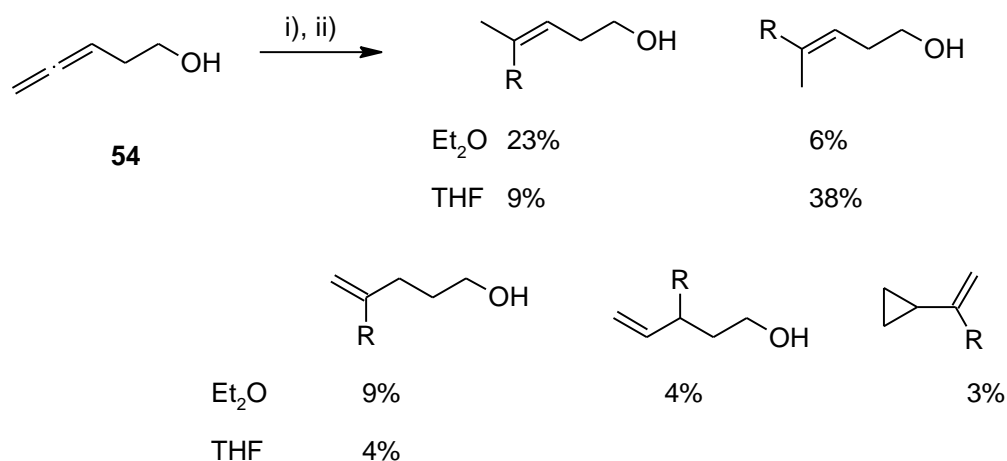
Reagents and conditions: AllylMgCl (3 eq), Et₂O or THF, reflux; i) H₂O

Scheme 51



Scheme 52

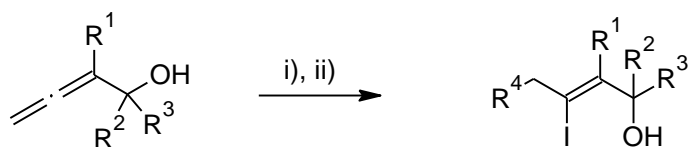
The reactions of the homologous allenol **54** with allyl magnesium bromide however gave a complex mixture of five products as shown in Scheme 53 and Richey and Szucs suggested that there is a possibility that interconversion of the allyl Grignard intermediates occurs.



Reagents and conditions: AllylMgCl (3 eq), Et₂O or THF, reflux; ii) H₂O

Scheme 53

In 1976 Gelin and Albrand reported an extension⁶¹ to carbometallation of allenols with alkyl Grignard reagents by using copper(I)iodide. Ma and Lu then continued this work by studying the reactions of the alcohols shown in Scheme 54.⁶² They reported that when two equivalents of copper(I)chloride were used in place of two equivalents of copper(I)iodide the yield of the product allylic alcohol was increased from 33% to 80%. Less than two equivalents of copper(I)chloride resulted in lower yields. The addition was completely regioselective, presumably as a consequence of the vinyl organometallic intermediate.



	Yield
$R^1 = \text{Ph}, R^2 = \text{Me}, R^3 = \text{H}, R^4 = \text{C}_5\text{H}_{11}$	44%
$R^1 = \text{H}, R^2 = \text{Ph}, R^3 = \text{Me}, R^4 = \text{C}_5\text{H}_{11}$	79%

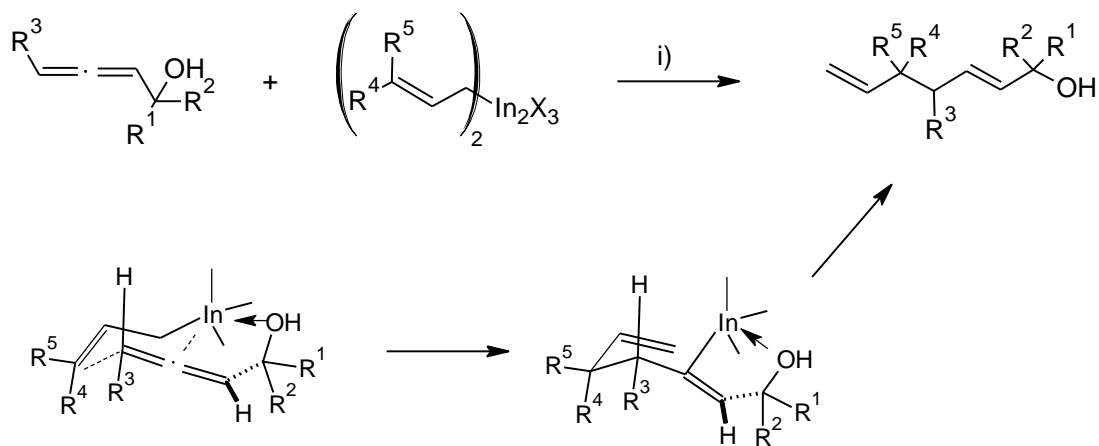
Reagents and conditions: $R^4\text{MgBr}$ (5 eq), CuCl (2 eq), Et_2O , $-78\text{ }^\circ\text{C}$ to rt; ii) I_2 , $-5\text{ }^\circ\text{C}$

Scheme 54

Whereas the use of copper salts in carbometallation reactions with primary propargylic alcohols generally did not affect the regio- or stereochemical outcome, the use of copper salts in the case of allenols altered the regiochemistry. The Grignard reagent added across the distal double bond of the allenol with the new carbon-carbon bond being formed at the terminal allene carbon and the new carbon-metal bond being formed at the central carbon as shown in scheme 54.

The regio- and stereoselective allylindation of allenols has been investigated by Araki and coworkers (Scheme 55).⁶³ In a similar fashion to the study of additions to propargyl alcohols, it was shown that regio and stereoselective allylindation of allenols afforded (*E*) disubstituted allylic alcohols. The new carbon-carbon bond was formed at the terminal allene carbon and the new metal-carbon bond formed at the central allene carbon. Even when the terminus of the allene was substituted by either one or two methyl groups addition still took place with the former affording the products in high yields. The reaction did not tolerate when the hydroxyl was one carbon further from the allene nor when the hydroxyl had been replaced by an ether. In all but one case, the allyl indium reagent attacked through the γ carbon as in the

previous work on propargyl alcohols. A hydroxyl chelated transition state was suggested to be the rationale behind the observed selectivity.

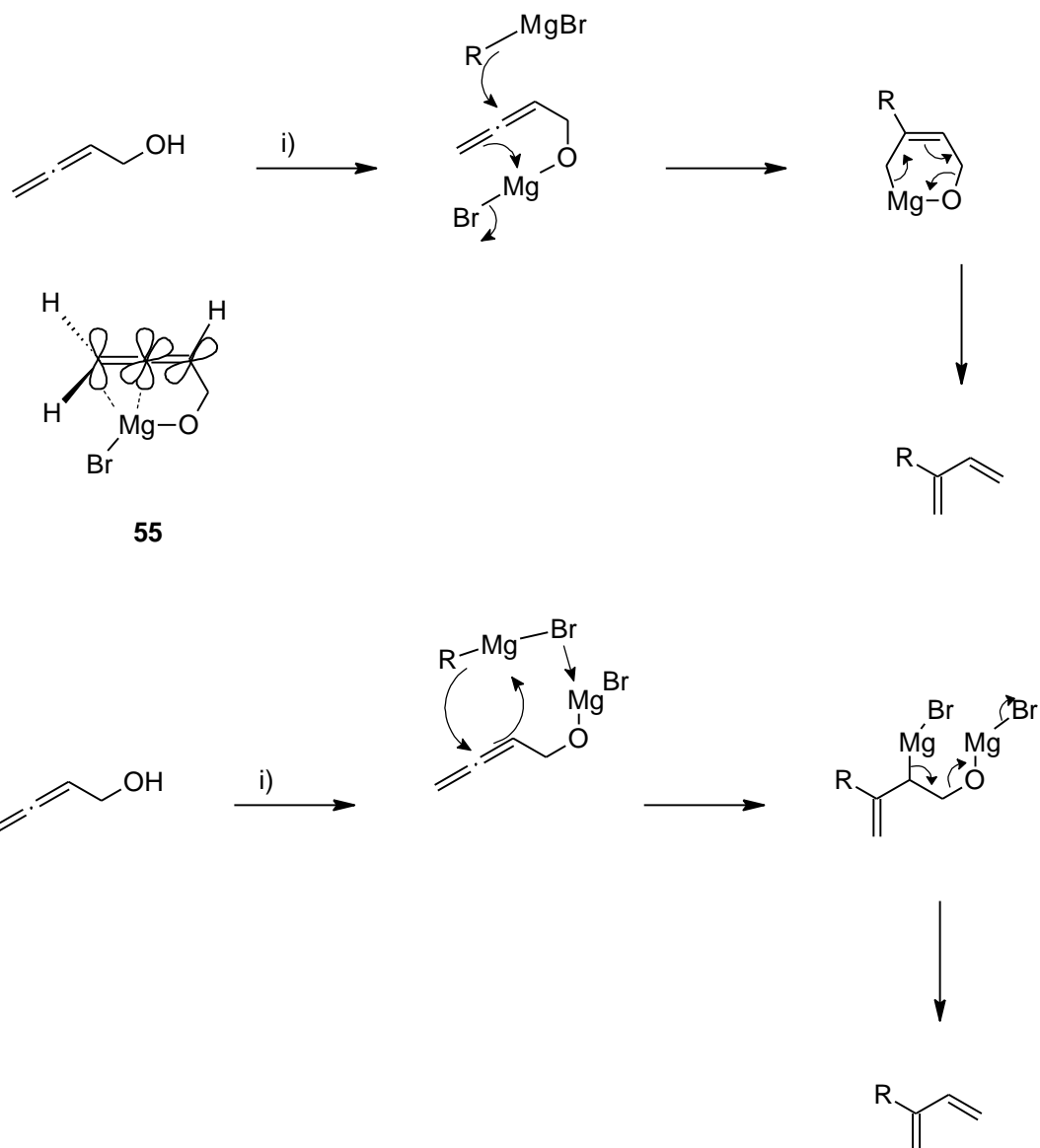


	Yield
$R^1, R^2, R^3, R^4, R^5 = H$	44%
$R^1 R^2 R^3 = H, R^4 R^5 = Me$	79%

Reagents and conditions: i) DMF, 140 °C, 4 h

Scheme 55

The analysis of additions to allenols appears easier than additions to propargylic alcohols. This could be due to less work being published on the subject. However if the possible intermediates are examined the results summarised in this subsection can be justified. The central allene carbon is a relatively hard centre (>210 ppm in ^{13}C NMR) so it is not surprising that when a Grignard reagent is used without any copper catalyst it will attack the harder central allene carbon. The organocopper intermediate would be more likely to react with the softer ends of the allene.

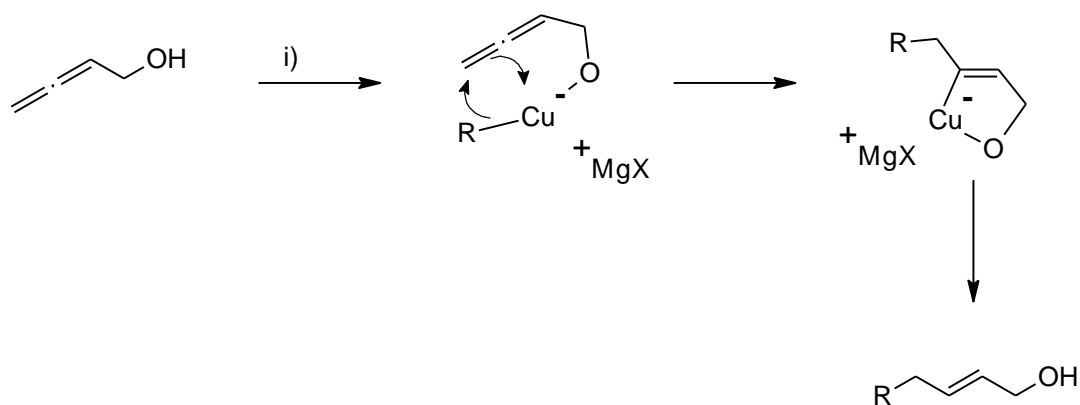


Scheme 56: Possible reaction pathways for non-copper mediated carbometallation of allenols.

Scheme 56 shows the possible intermediates for the non-copper mediated carbometallation of allenols. In the first reaction there is a favourable 6-membered metalocycle, involving the alkoxide, formed as an intermediate. A similar metalocycle in the second reaction is unlikely to be formed as it would involve a 4-membered ring however it is worth noting that the intermediates involved could

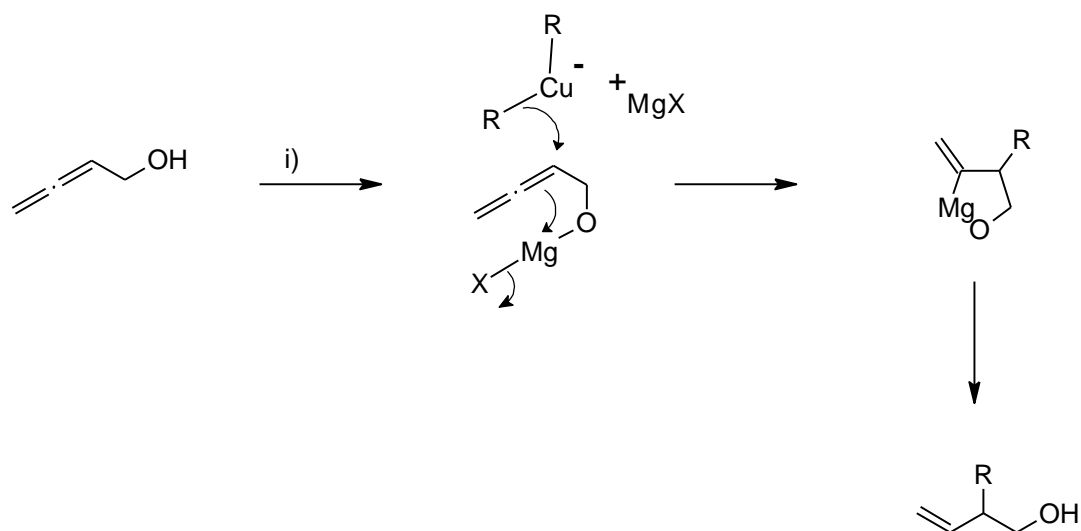
well exist as aggregates rather than as a single species in solution. The first reaction could also be favoured by intermediate **55** which shows a possible interaction between the magnesium alkoxide and the orthogonal terminal π bond.

In the case of a copper mediated reaction the two possibilities are shown in Schemes 57 and 58. The favourable intramolecular addition to the less hindered of the two cumulated alkenes of the allene as shown in Scheme 57 could provide a rationale behind the observed stereo and regiochemistry.



Reagents and conditions: i) RMgX, CuX

Scheme 57: Possible mechanism for copper mediated carbometallation of allenols.

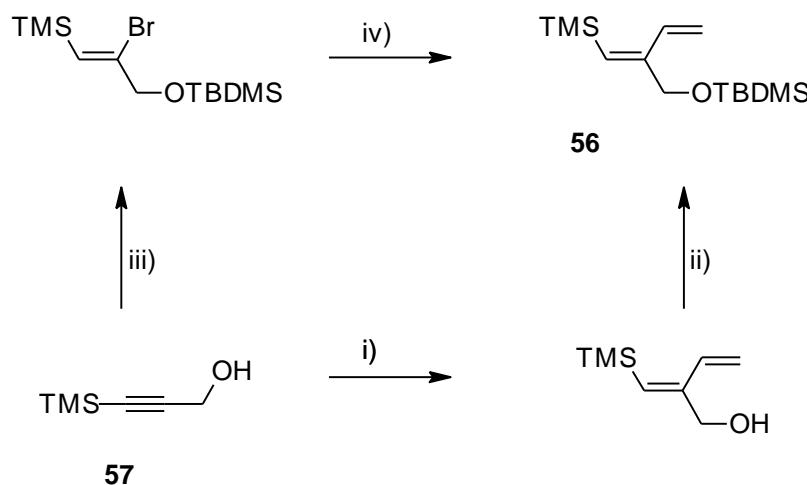


Reagents and conditions: i) RMgX, CuX

Scheme 58: Another possible mechanism for copper mediated carbometallation of allenols

1.3 Applications of carbometallation in synthesis

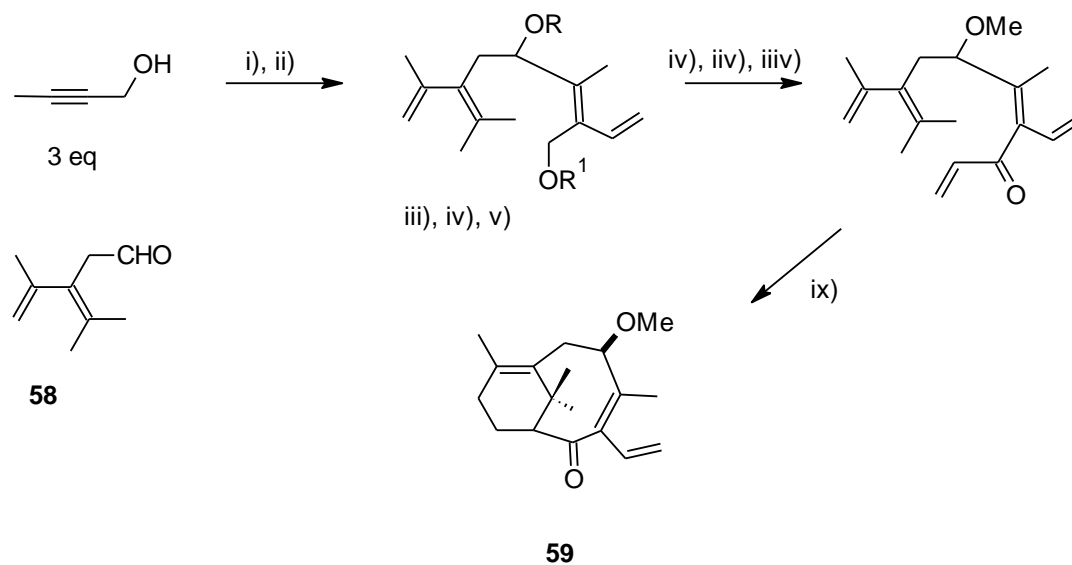
As a result of an intramolecular Diels-Alder strategy for the generation of Taxol analogues, the Fallis group required diene **56** as an important intermediate in their synthesis and hence developed a route involving the carbometallation of propargylic alcohol **57**. This greatly improved the yield to afford the intended diene in 65% overall (Scheme 59).⁶⁴



Reagents and conditions: i) VinylMgCl (3.2 eq), THF, reflux; $\text{NH}_4\text{Cl}_{(\text{aq})}$ (75%); ii) TBDMSCl, imidazole, DCM, rt, (86%); iii) four steps 35% overall; iv) VinylMgBr, $\text{Pd}(\text{PPh}_3)$, THF, reflux (85%)

Scheme 59

Fallis⁶⁵ et al. also developed a tandem carbometallation-intramolecular Diels-Alder strategy for the construction of the AB-Taxane ring system. Carbomagnesiation of 2-butyne-1-ol with vinyl magnesium chloride followed by trapping with aldehyde **58** and further manipulation led to the formation of compound **59**, isolated as a single diastereomer as a result of a chelation controlled intramolecular Diels-Alder (Scheme 60).

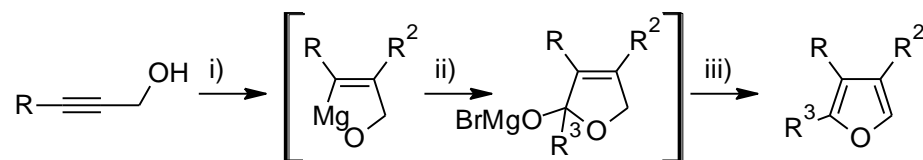


Reagents and conditions: i) VinylMgCl (5 eq), PhMe, 110 °C, 20 h; ii) **58** (1 eq), -78 °C to 0 °C, 71%; iii), TBSCl, DCM, DMAP, 24 h, 92%; iv) NaH, MeI, 18 h, 82%, v) TBAF, THF, 18 h, 99%; vi) Swern Oxidation, 0 °C, 1 h; vii) VinylMgCl, 0 to 21 °C, 18 h, 72%; viii) IBX, DMSO, 3 h, 77%; ix) Et₂AlCl, DCM, -78 °C to 0 °C, 5 min, 76%

Scheme 60

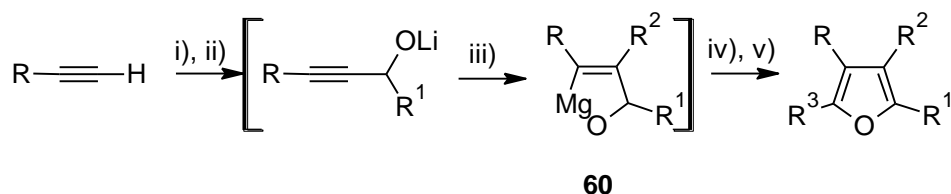
Work on carbometallation by Fallis⁶⁶ et al. allowed tetrasubstituted furans to be synthesised by quenching a carbometallated propargyl alcohol with DMF or aryl nitriles (Scheme 61). The group also managed to extend the scope and versatility of the reaction by constructing the propargyl systems *in situ* (Scheme 62) followed by the carbometallation to generate metallocycle **60**. An impressive four bonds were able to be formed in one pot using this procedure with three of them being valuable carbon-carbon bonds. Fallis also shows that phenyl magnesium chloride will add to propargyl alcohols when refluxing in cyclohexane. The choice of halide in the Grignard, the solvent and the temperature (or a combination of all three) could be responsible for the successful addition when compared with the unsuccessful attempt

to react phenyl magnesium bromide with 2-butyne-1-ol by Richey and Von Rein³⁰ *vide supra*.



Reagents and conditions: i) R_2MgCl (3.2 eq), cyclohexane, 80 °C; ii) DMF or R_3CN , 0 °C to rt; iii) *p*-TsOH, cyclohexane, rt

Scheme 61

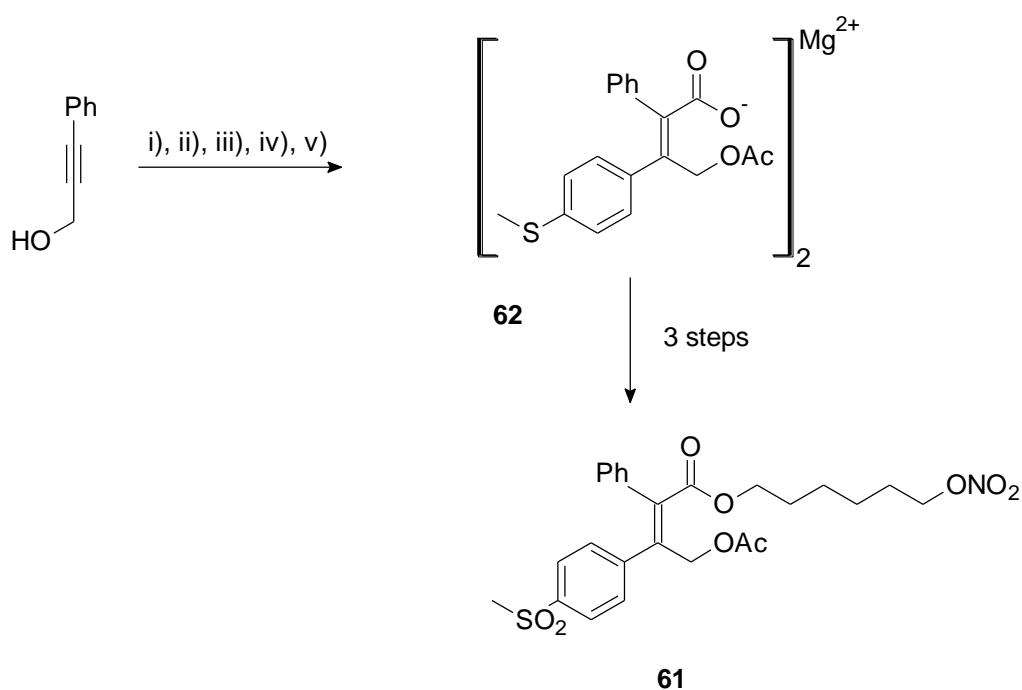


Reagents and conditions: i) *n*-BuLi; ii) R_1CHO ; iii) R_2MgCl , cyclohexane, 80 °C; iv) DMF or R_3CN ; v) *p*-TsOH, cyclohexane, rt

Scheme 62

The prodrug **61** of the Merck COX-2 selective inhibitor rofecoxib (VIOXX) has a tetrasubstituted alkene as the core. Since initial attempts to synthesis the prodrug from the butenolide rofecoxib proved unsuccessful, Engelhardt⁶⁷ et al. adopted the method developed by Fallis⁶⁵ of preparing 2,3-butenolides. The synthesis of the magnesium salt **62** was carried out in 82% and the synthesis of the prodrug **61** was carried out in overall 64% yield (Scheme 63). Importantly Engelhardt et al. noted that the chloride derived Grignard reagent reacted more rapidly than the corresponding bromo Grignard to give the vinyl Grignard reagent. The high yield of

82% demonstrates the power of heteroatom directed carbometallation in constructing tetrasubstituted olefins in a stereospecific manner.

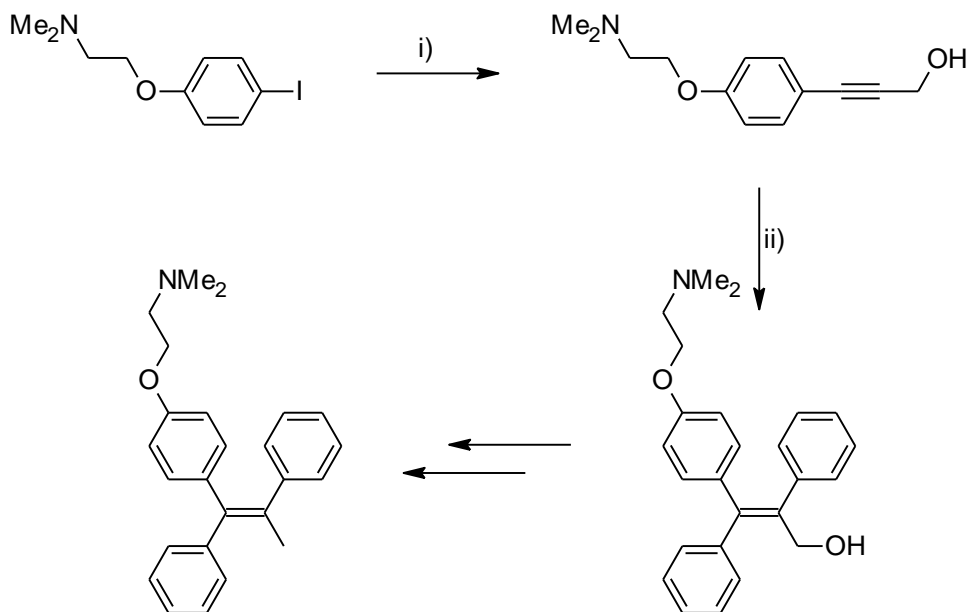


Reagents and conditions: i) MeMgCl (1 eq); ii) 4-thiomethylphenyl magnesium chloride (1 eq), THF, reflux; iii) CO₂; iv) KO^t-Bu (0.5 eq); v) Ac₂O, 82% overall

Scheme 63

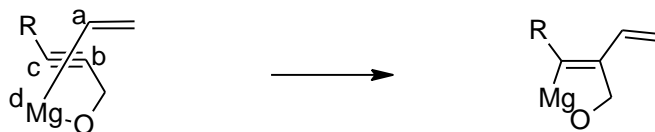
Carbometallation was also applied to the synthesis of the breast cancer drug Tamoxifen. Fallis and co-workers investigated the palladium catalysed coupling of iodides and bromides to the intermediate vinyl Grignard following carbomagnesiation.⁶⁸ Pure (*Z*)-Tamoxifen was prepared according to Scheme 64. It was found that, when investigating the carbometallation, alkyl Grignard reagents afforded very low yields of addition products compared to vinyl, phenyl and allyl reagents. It was suggested that the π counterpart of the latter group of reagents was important to the success of the reaction. In the case of vinyl Grignard it was

postulated (Scheme 65) that intramolecular delivery of the vinyl group involves bonding a-b and c-d to occur in a synchronous manner. However this involves considerable distortion of the triple bond.



Reagents and conditions: i) Propargyl alcohol, $\text{PdCl}_2(\text{PPh}_3)_2$ (10 mol%), CuI (10 mol%), Et_3N , THF, rt, 18 h, 83%; ii) PhMgCl (3.2 eq), MePh, reflux, 16 h then $\text{Pd}(\text{PPh}_3)_4$ (5 mol%), PhI, 72%

Scheme 64



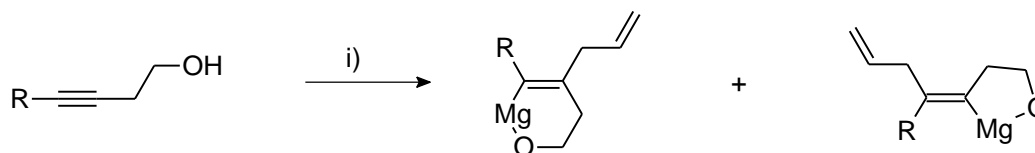
Scheme 65

1.4 Overview

The foregoing review has hopefully highlighted the power that directed carbometallation can offer the synthetic organic chemist for the synthesis of highly substituted olefins. However there remains a dearth of detailed predictive power which restricts the widespread application and the establishment of directed carbometallation as a very well known method. Further understanding at a fundamental level is certainly required to allow logical links to be made between all relevant reactions.

Analysis of the results presented is clearer with the additions to allenols than with any other group of substrates and was discussed above. The carbomagnesiation reaction would benefit from more attention as it is not known how well other Grignard reagents perform but more importantly where the carbon-magnesium bond is formed as well as how to prevent the loss of magnesium oxide so that the valuable carbon-magnesium bond can be preserved for further elaboration.

The additions of organometallic reagents to homopropargylic substrates can be analysed. However, in order to do so, there needs to be a separation into thermally allowed carbomagnesiation and catalytic systems. Although less work into the uncatalysed additions of Grignard reagents to homopropargylic alcohols has been carried out, the stereochemistry is always *anti* if there is no substitution between the alkyne and the oxygen atom in the tether. The regioselectivity is low due to the fact that the two possible outcomes can both be rationalised by metallocycle intermediates (Scheme 66).



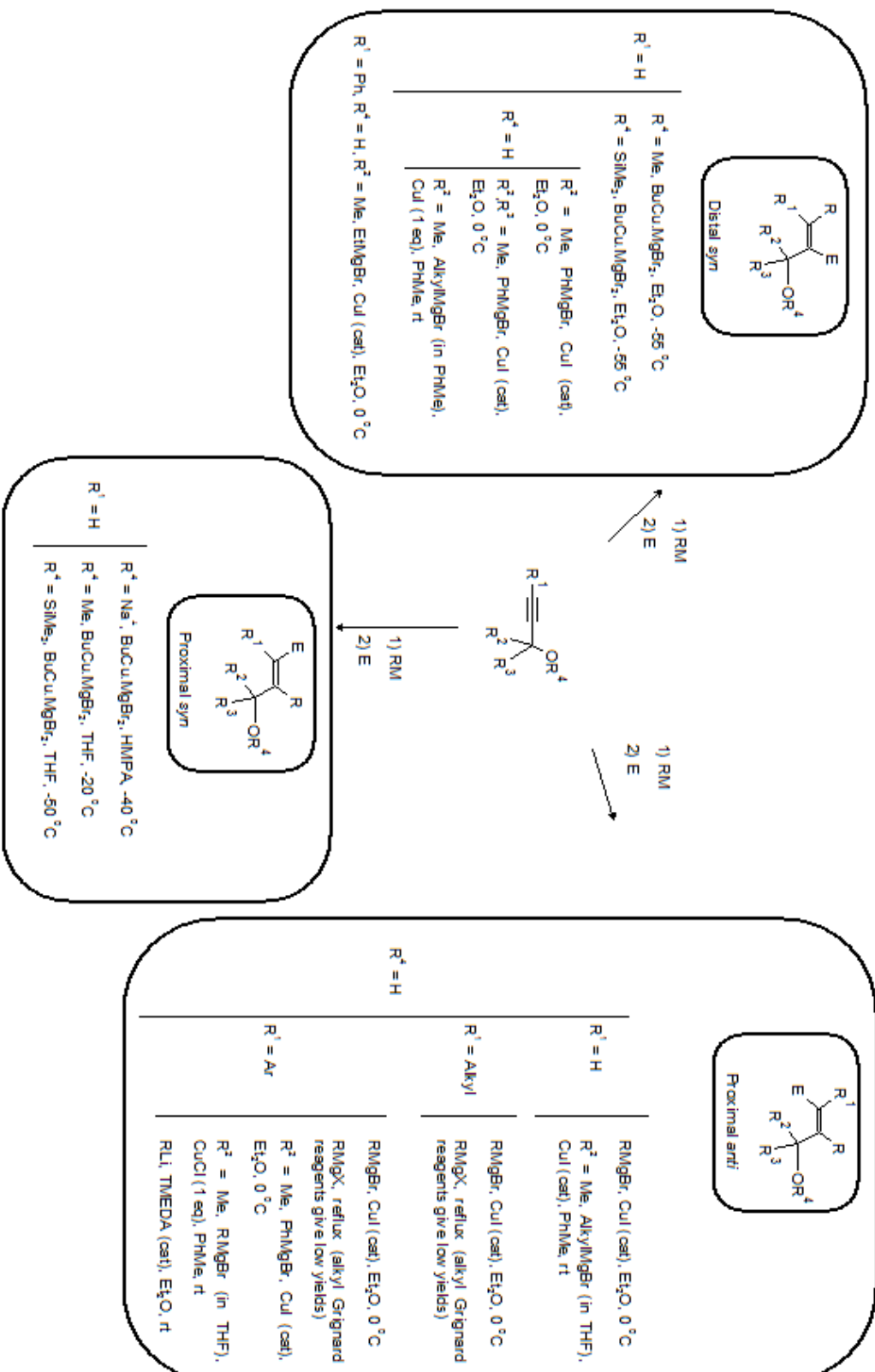
Reagents and conditions: i) AllylMgCl, Et₂O, reflux

Scheme 66

In the case where R = Ph, it was found that the addition of allyl magnesium chloride was regiospecific. It is possible that the phenyl group could have a stabilising effect on the formation of a partial negative charge on the distal carbon similar to the mechanism of carbomagnesiation proposed by Richey and Von Rein (Scheme 18).³⁰ This charge dominated mechanism could be supported by the known hard reactivity of Grignard reagents. Conversely the reactions catalysed by iron(III) (Schemes 44 & 45) and manganese(II) (Scheme 46) are more likely to be orbital dominated. Both metals catalyse a distal-*syn* addition to homopropargyl ethers and iron(III) catalyses additions to homopropargyl alcohols. It would be interesting to investigate the carbomagnesiation of homopropargyl ethers to give a direct comparison. It must also be stressed that less work on the directed additions to homopropargyl systems has been carried out relative to propargyl systems, and analysis of the results in order to make predictions may be premature.

As illustrated throughout, additions to propargyl alcohols have benefited from a lot of attention. The same separation into catalytic and non-catalytic systems as with homopropargyl systems is beneficial for analysis. Phenyl, allyl and vinyl Grignard reagents perform well in the thermally allowed carbomagnesiation reactions giving proximal-*anti* additions with primary, secondary and tertiary alcohols although yields decrease with increased substitution between the alkoxy tether and the alkyne. The addition also benefits when chloro-derived Grignard reagents and higher boiling and, perhaps more significantly, less polar solvents are used. Although the catalysed reactions increase the scope to alkyl Grignard reagents the regio- and

stereochemistry of additions is not straightforward. Phenyl Grignard reagents with a copper(I) catalyst give proximal-*anti* additions to primary terminal and substituted propargyl alcohols with the notable anomaly observed by Duboudin and Jousseume (Scheme 32).⁴³ A distal-*syn* addition is favoured when a phenyl Grignard reagent is used with either a secondary terminal or substituted propargyl alcohol or a tertiary terminal propargyl alcohol. Alkyl Grignard reagents with a copper(I) catalyst give proximal-*anti* additions to primary terminal and substituted propargyl alcohols again with an anomaly observed by Duboudin and Jousseume (Scheme 33). When a secondary propargyl alcohol is used the regio- and stereoselectivity in a diethyl ether solvent is lost. Ma and co-workers solved this issue by showing that alkyl Grignard reagents in a THF solution will add in a proximal-*anti* fashion to terminal and aryl substituted secondary alcohols. When the alkyl Grignard reagent was in a diethyl ether/toluene solution the addition to terminal secondary propargyl alcohols was distal-*syn*. Iron(III) catalysis was also shown to affect a distal-*syn* addition to a secondary substituted propargyl alcohol in a THF solution. Scheme 67 shows the conditions required to achieve three of the four possible modes of addition as outlined previously.

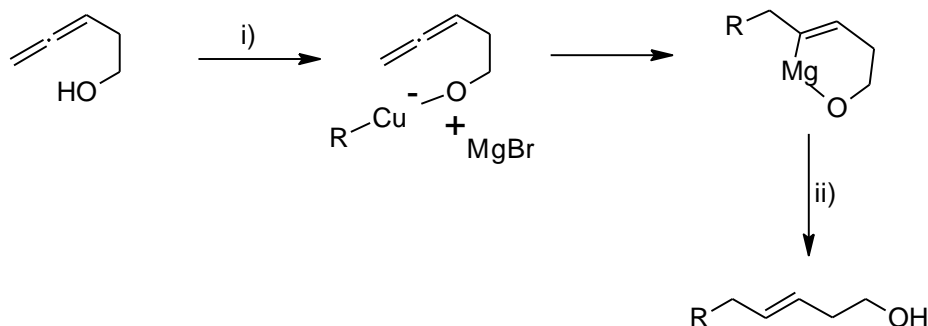


Scheme 67

Chapter 2: Results and Discussion

2.1 Carbometallation Reactions of homoallenols

As a prelude to our major objective, and also as a “test bed” carbometallation reaction, the opportunity was taken to investigate the copper mediated addition reactions of Grignard reagents to homoallenols since a preliminary experiment had been performed by a previous member of the research group.⁶⁹ As mentioned in the preceding chapter (page 56) an interesting change in regioselectivity was observed when a copper(I) salt was used to effect the addition of a Grignard reagent to a simple allenol. It was therefore predicted that the same regiochemistry of addition would be observed when the alkoxide tether was one methylene unit further away from the allene (Scheme 68), since this would result in a 6-membered metallocycle rather than the 5-membered metallocycle generated in the case of an allenol.



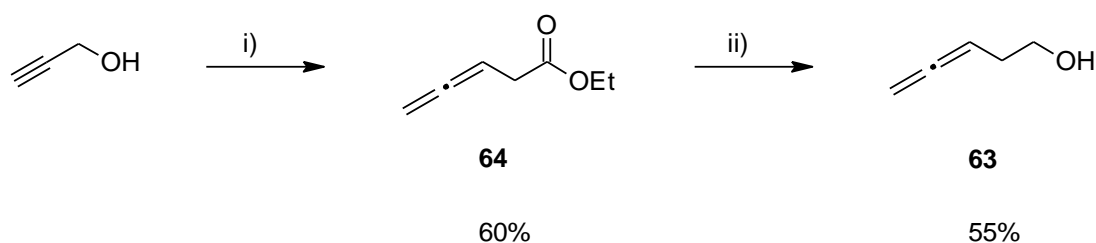
Reagents and conditions: i) RMgBr, CuBr (cat.); ii) NH₄Cl

Scheme 68

Richey and Von Rein⁶⁰ had previously carried out a brief study of additions to homoallenols and the mixture of compounds obtained suggested that homoallenols were not suitable substrates. However, the benefit of a copper mediated reaction is that the addition takes place at a much lower temperature and hence competing side

reactions can possibly be avoided. It was envisaged that the regio and stereoselectivity of addition observed with copper(I) mediated additions of Grignard reagents to allenols would be translated to homoallenols.^{61,62}

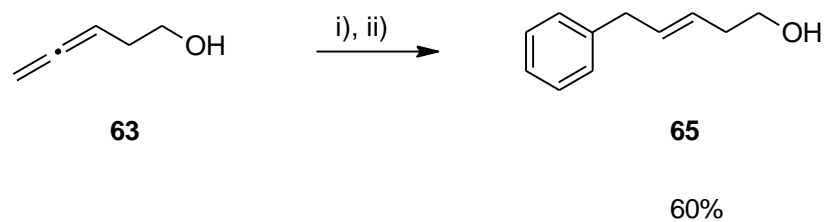
The required homoallenol **63** was prepared in two steps from propargyl alcohol. A Johnson-Claisen rearrangement afforded ester **64** which was then reduced with lithium aluminium hydride (Scheme 69).



Reagents and conditions: i) MeC(OEt)₃, EtCO₂H (cat.), 160 °C; ii) LiAlH₄, THF, 0 °C

Scheme 69

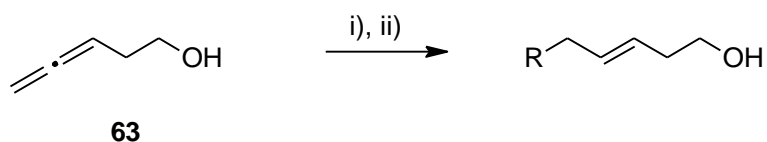
The conditions used by Ma⁶² were initially selected for the copper(I) mediated addition of phenyl magnesium bromide to homoallenol **63** which afforded homoallylic alcohol **65** as a single geometrical isomer in 60% yield (Scheme 70).



Reagents and conditions: PhMgBr (3.5 eq), CuI (50 mol%), PhMe, -78 °C to rt, 12 h;
ii) NH₄Cl_(aq)

Scheme 70

In order to investigate the most suitable “organocopper” reagent a small study was carried out, the results of which are shown in Table 5.



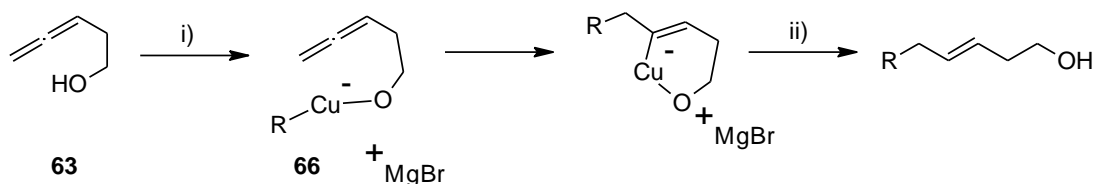
Reagents and conditions: i) RM, solvent, -78 °C to rt; ii) NH₄Cl_(aq)

Table 5

Entry	RM	Solvent	Yield (%)
1	MeMgBr (3.5 eq), CuI (50 mol%)	THF	0
2	MeMgBr (3.5 eq), CuI (50 mol%)	Toluene	30
3	1) BuLi (1 eq); 2) Me ₂ CuLi (2.5 eq)	Toluene	28
4	1) MeMgBr (1 eq); 2) Me ₂ CuLi (2.5 eq)	Toluene	18
5	Me ₂ CuLi (3.5 eq)	Toluene	35

Examination of the results in the Table, albeit that yields are low, provided some valuable insights. Thus, comparison of Entries 2 and 3 would immediately suggest that a stoichiometric organocopper reagent is almost equally efficient to that of a catalytic system, whilst comparison of Entries 3 and 4 would imply that a lithium alkoxide is a better directing group than a magnesium alkoxide. In the event, as shown by Entry 5 the simple Gilman cuprate reagent proved to be most successful.

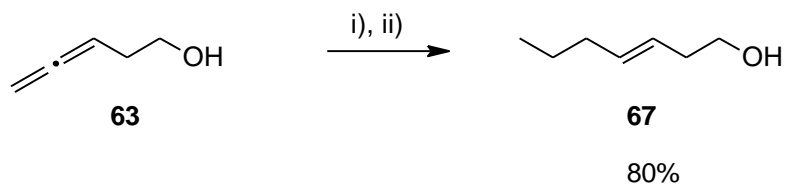
In light of these results, and in view of the success of the organocopper reagent used in the carbocupration reactions investigated by Normant et al.,³⁸ it was decided to investigate this organocuprate, which would first deprotonate the homoallenol to give an intermediate mixed heterocuprate **66**, which could be ideally set-up for carbocupration as shown in Scheme 71.



Reagents and conditions: i) R₂CuMgBr; ii) NH₄Cl_(aq)

Scheme 71

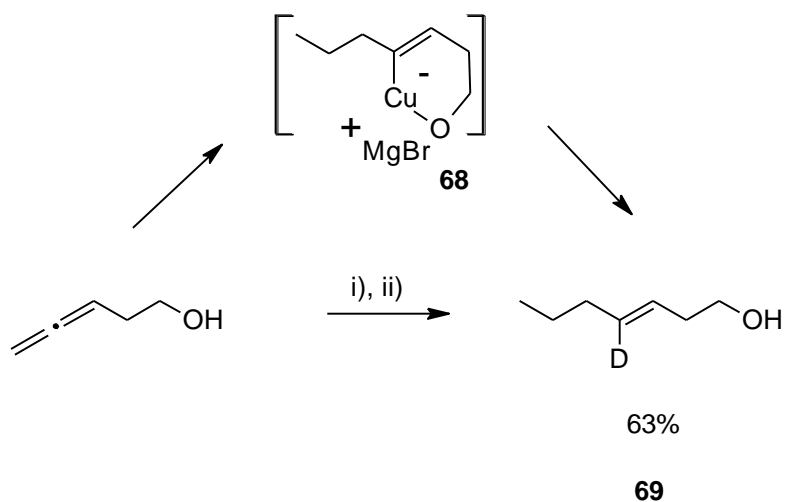
Pleasingly, when homoallenol **63** was treated with preformed bromomagnesium diethylcuprate, homoallylic alcohol **67** was formed in 80% yield (Scheme 72).



Reagents and conditions: i) Et_2CuMgBr , Et_2O , $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 4 h; ii) $\text{NH}_4\text{Cl}_{(\text{aq})}$

Scheme 72

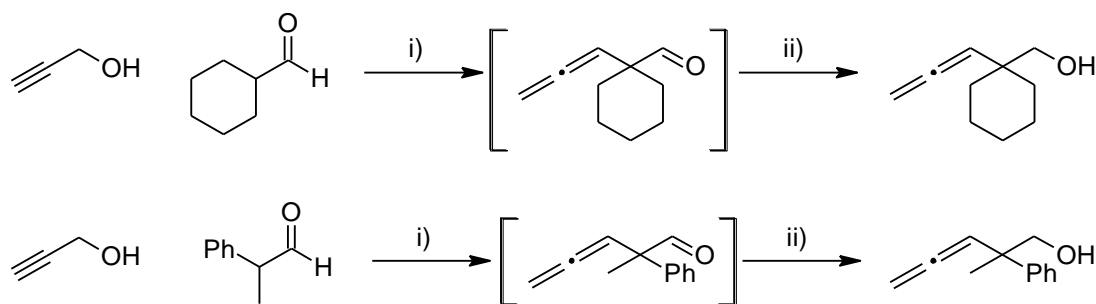
The presence of the vinylcopper intermediate **68** was then proved by a deuterium quench which afforded the deuterated alcohol **69** in 63% yield (Scheme 73).



Reagents and conditions: i) Et_2CuMgBr , Et_2O , $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 4 h; ii) D_2O

Scheme 73

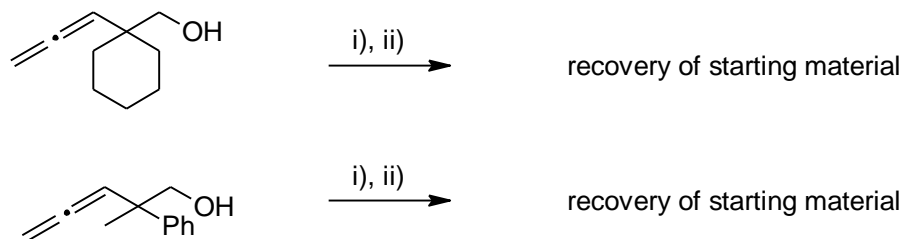
In order to explore the scope of the reaction two additional alcohols were then synthesised via Claisen rearrangement followed by *in situ* reduction of the aldehyde (Scheme 74).



Reagents and conditions: i) PTSA (5 mol%), PhMe, Dean & Stark, 20 h; ii) NaBH_4 , EtOH, 0 °C, 6 h

Scheme 74

In this instance however, as indicated in Scheme 75 no carbometallation products could be detected and only starting material was recovered.



Reagents and conditions: i) Et_2CuMgBr , Et_2O , -78 °C to 0 °C, 4 h; ii) $\text{NH}_4\text{Cl}_{(\text{aq})}$

Scheme 75

Although disappointing, the failure of the reactions shown in Scheme 75 raises issues over the reaction mechanism as substitution at the β position of the alcohol was anticipated to favour the formation of the postulated metallocycle **70** by virtue

of a Thorpe-Ingold effect⁷⁰ as well as the literature precedent for carbometallation of tertiary allenols (Figure 2).⁶²

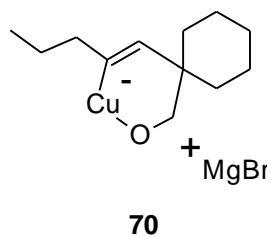
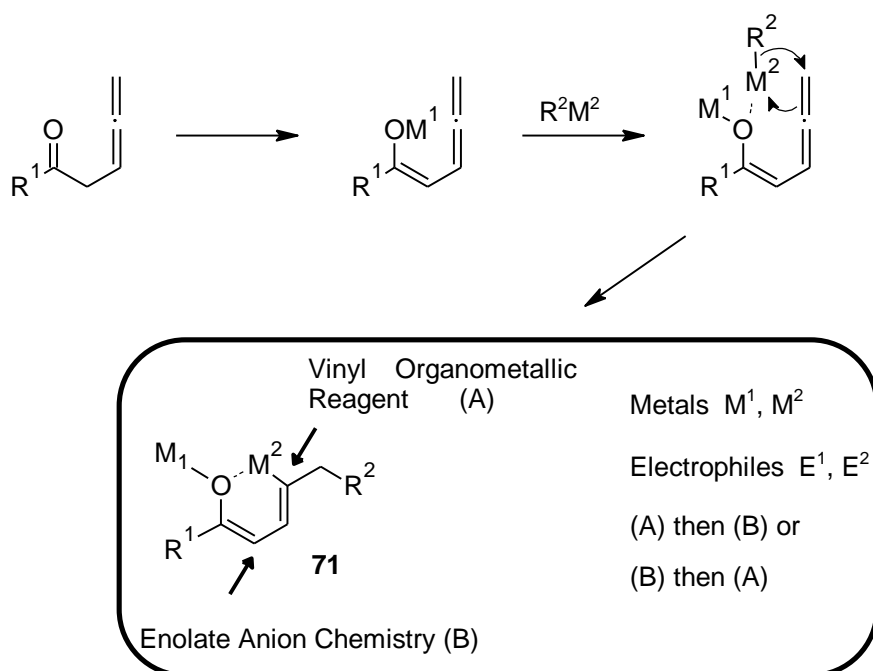


Figure 2

Although this limited study has given encouraging results for the parent system, much further work is necessary on the substitution around the allene and the tethering chain as well as investigating the effect of other organometallic species.

2.2 Enolate anion directed carbometallation: A New Concept

Albeit that the isolated example of carbocupration of the parent primary homoallenol had proceeded in good yield, and that it was possible to extend this study, it can hardly be considered as a conceptual advance in the area of directed carbometallation. Our attention was therefore directed towards the possibility of using a suitably disposed enolate anion as a tether to direct the carbometallation of a pendant alkyne or allene (Scheme 76), by analogy with the known ability of an alkoxide tether to direct similar addition reactions. The resulting postulated intermediate **71** would possess a “bis-carbanionic” character since it is both a vinyl organometallic reagent and an enolate anion. It was envisaged that, as a function of the electrophile chosen, sequential quenching with two different electrophiles could be achieved. Accordingly, the aim of this research programme was to investigate the reactivity of this novel intermediate, as well as its efficient formation. As encapsulated in Scheme 76, a very considerable number of permutations exist within this “simple” idea.

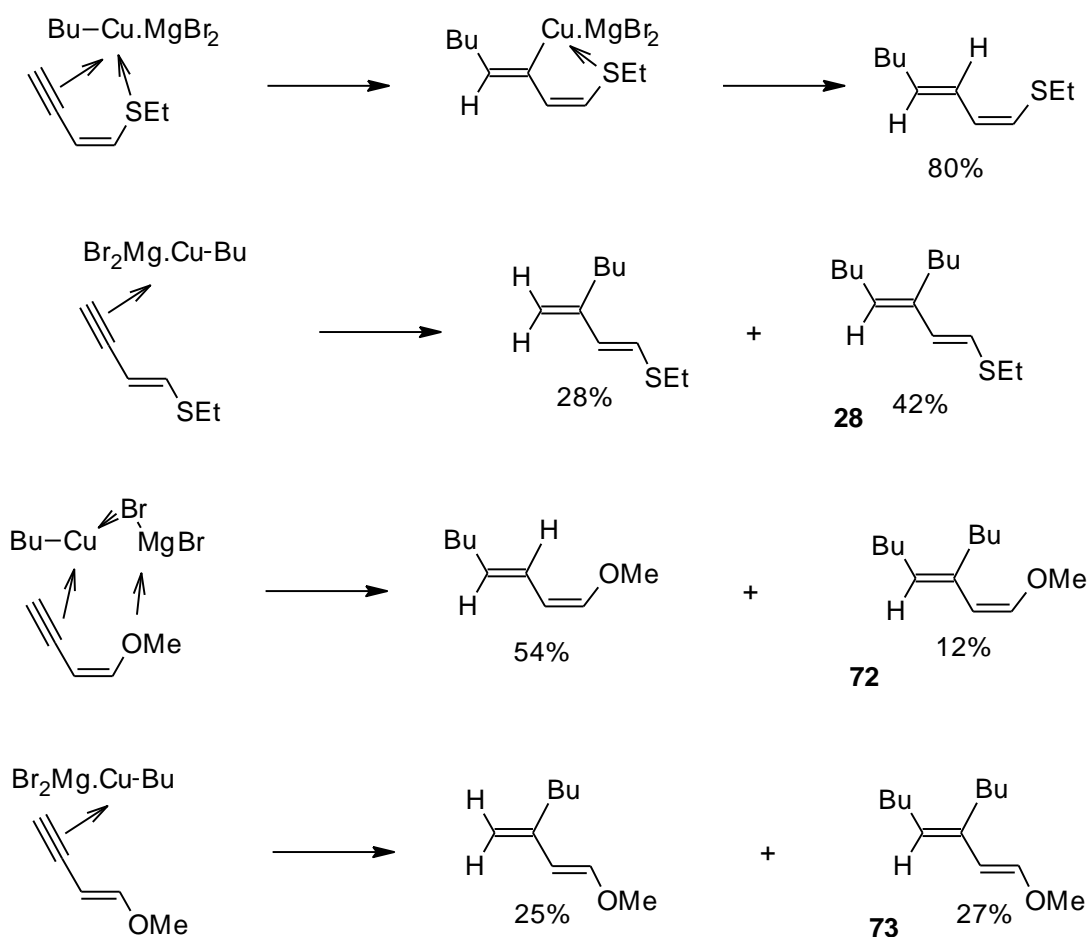


Scheme 76

If successfully controlled, this one-pot sequence could lead to the formation of three new carbon-carbon bonds in a single reaction, and moreover to stereospecific construction of a highly substituted carbon-carbon double bond as well as the further stereochemistry which could arise as a function of the enolate anion geometry.

The overall *modus operandi* required for this objective therefore needed to address the three perceived stages of the transformation: *viz.*, the formation of the enolate anion from the substrate, the enolate directed carbometallation step and the final differentiation of the resultant “bis- carbanionic” reagent. As depicted in Scheme 76 only one geometry of enolate is drawn. This *cisoid* relationship is inferred to be the correct geometry for an intramolecular assisted carbometallation. However, enolates are known to exist as aggregates⁷¹ and it is not inconceivable that carbometallation could be directed from another molecule within the oligomer in “intermolecular” fashion. Nonetheless an enolate of (*Z*) geometry was regarded as a suitable starting point since it could not only influence the carbometallation stage, but also, as will be discussed, affect the subsequent reactivity of the bis-nucleophilic intermediate. A highly efficient carbometallation step was essential not only in terms of a high yielding overall transformation, but, as subsequent exploration of the reactivity of the bis-carbanion **71** follows, any additional side reactions involving substrate enolate or organometallic reagent with electrophiles would only serve to complicate matters. Whilst the reactions of both enolates and vinyl organometallics are extensively documented, no methods seem to involve the presence of the two species at the same time. In consequence, selective reaction of one of the carbanions required a careful selection of electrophile. All three stages were likely to be affected by temperature and a balance between reactivity and stability throughout the entire sequence of events was crucial to the success of the overall transformation.

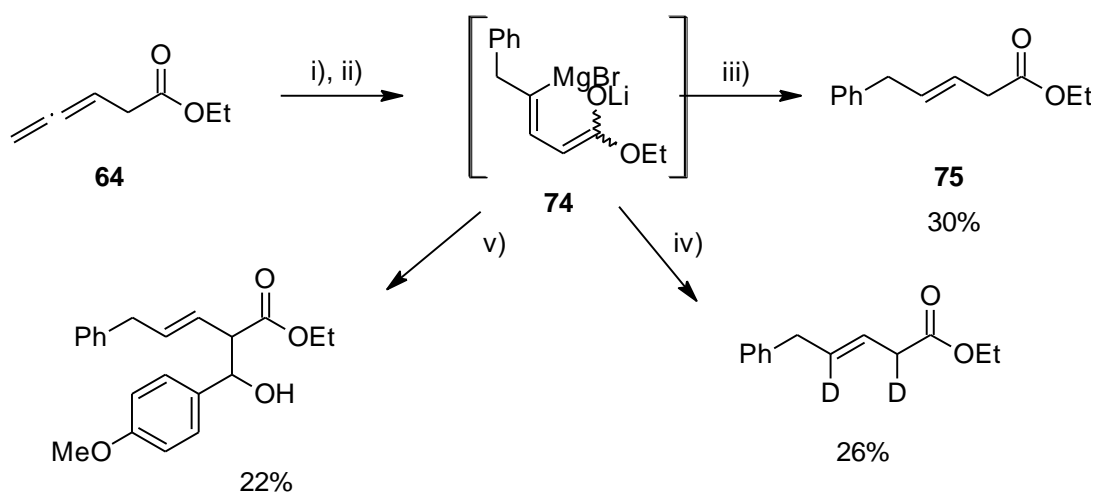
To the best of our knowledge, as mentioned earlier (page 33) the closest literature precedent can be found in the work of Normant and co-workers who reported the addition of a butylcopper reagent to terminal alkynes with geometrically defined enol ether or thioenol ether tethers (Scheme 28).³⁹ It was found that the *cis* relationship between the tether and the alkyne was essential for the reaction to take place. In addition, the reactivity of the vinylcopper intermediate was also affected by the nature of the tether. Where the tether was in the “wrong position” for intramolecular assistance, the yields of oxidative coupling products **28**, **72** and **73** were greater, suggesting that chelation from the sulfur or oxygen atom also has the effect of stabilising the vinylcopper intermediate.



Scheme 28

2.2.1 Prior Observations within the Research Group

The first experiments to provide “proof of concept” within our own research group were carried out by my predecessor, Mr Phillip Gray⁶⁹ and involved sequential treatment of the allenic ester **64** with LDA to form the ester enolate followed by carbometallation with phenyl magnesium bromide in the presence of cuprous iodide. This was successful in affording (*E*) alkene **75** as a single isomer albeit in low yield. Preliminary evidence for the intermediacy of a bis-cabanionic species **74** was also adduced by quenching the reaction with deuterium oxide and the potential for further selective reactions was also demonstrated by an ester enolate aldol reaction with anisaldehyde (Scheme 77).



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) PhMgBr (1.5 eq), CuI (50 mol%), -78 °C to rt, 12 h; iii) NH₄Cl_(aq); iv) D₂O; v) anisaldehyde

Scheme 77

2.2.2 Preliminary studies on carboxylic acid dianions and amide enolates

The selection of ester **64** was initially made because of its ready availability as well as the positive results obtained with the copper(I) mediated additions of Grignard reagents to the parent homoallenol.

Although promising, the yields from these preliminary reactions were low. The issue of enolate geometry was initially thought to be problematic as esters are known to give enolates of (*E*) geometry when deprotonated with LDA at -78°C .⁷² However literature precedent also suggests that either the lithium alkoxide or the ether moiety of the ester enolate could be able to direct a carbometallation.

Hence, in order to ensure a *cis* relationship between the metal alkoxide anion of the enolate and the allene moiety an investigation into the ability of a carboxylic acid dianion to direct a carbometallation was carried out since this selection would negate the issue of enolate geometry (**76**, Figure 3). Acid **77** was simply prepared by acid hydrolysis of ester **64** (Scheme 78).

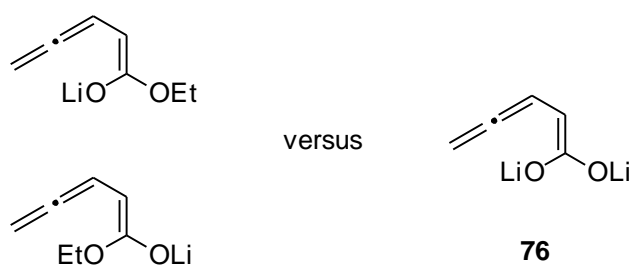
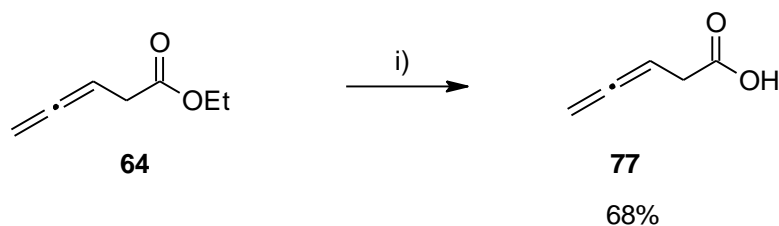


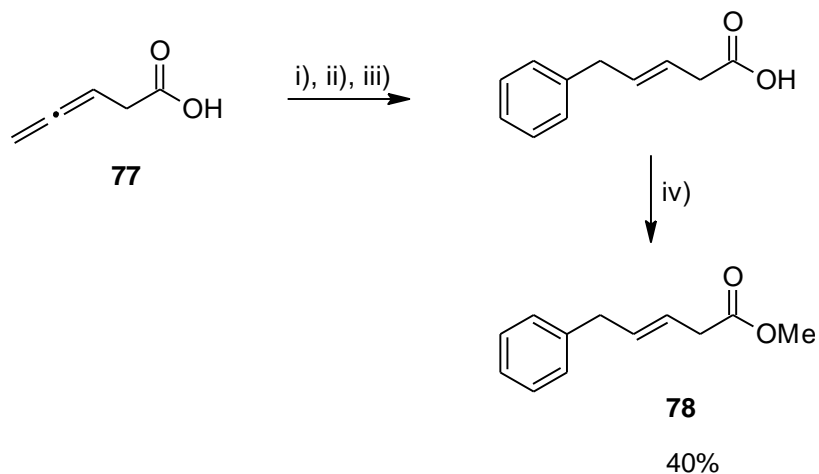
Figure 3



Reagents and conditions: i) 20% HCl, Acetone, rt, 3 days

Scheme 78

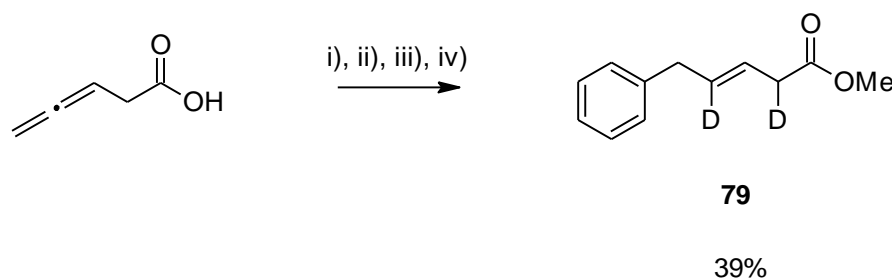
Following the normal literature protocol, acid **77** was deprotonated with 2.0 molar equivalents of LDA to form the dilithio dianion. Subsequent addition of phenyl magnesium bromide in the presence of a catalytic quantity of cuprous iodide followed by protic work up gave a crude reaction mixture whose ^1H NMR revealed signals relating to the two alkene peaks. For ease of purification, the crude acid was then converted into the ester using methanolic hydrochloric acid (Scheme 79) to furnish the desired carbometallated product **78** in an encouraging 40% overall yield.



Reagents and conditions: i) LDA (2 eq), Et_2O , $-78\text{ }^\circ\text{C}$ to rt; 1 h; ii) PhMgBr (1.5 eq), CuI (50 mol%), $-78\text{ }^\circ\text{C}$ to rt, 16 h; iii) $\text{NH}_4\text{Cl}_{(\text{aq})}$; iv) HCl/MeOH

Scheme 79

The nature of the dianionic intermediate was once again proven by a deuterium oxide work up which afforded ester **79** in 39% after conversion to the methyl ester with methanolic HCl (Scheme 80).

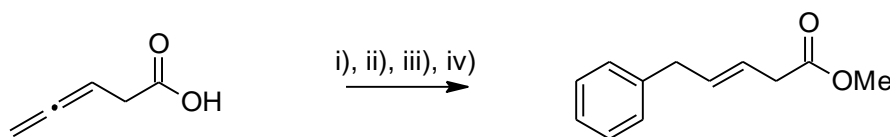


Reagents and conditions: LDA (2 eq), Et₂O, -78 °C to rt; 1 h; ii) PhMgBr (1.5 eq), CuI (50 mol%), -78 °C to rt, 16 h; iii) D₂O; iv) HCl/MeOH

Scheme 80

Table 6 shows the results of an optimisation study for this reaction which reveals that a catalytic copper(I) system (Entry 1) gave better yields than a stoichiometric organocopper system (Entries 2 and 3) in contrast to reports which indicate that the latter is superior for carbometallation of alkynes.⁷³ It was then found that the amount of copper(I)iodide could be reduced to 10 mol% and consequently the amount of phenyl magnesium bromide reduced to 1.1 equivalents (Entry 4). The amount of diisopropylamine was also reduced to sub-stoichiometric levels so that it would form the carboxylic acid dianion in a catalytic cycle (Scheme 81). Finally, it was also found that if more *n*-butyllithium was added to deprotonate the diisopropylamine left over after deprotonation then the yield improved from 40% to 50% (Entry 5) presumably by avoiding the parasitic reaction between diisopropylamine and the Grignard reagent or enolate. The low yield from Entry 6 could be attributed to the

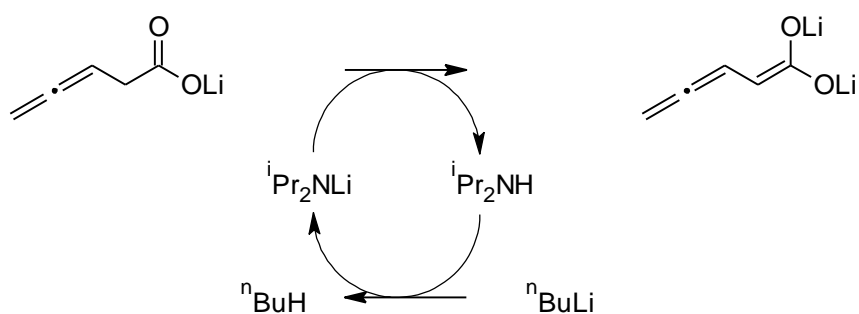
fact that the reaction mixture was extremely heterogeneous which may have hampered an efficient carbometallation reaction.



Reagents and conditions: i) Base, Et₂O, -78 °C to rt, 1h; ii) PhMgBr, CuI, -78 °C to rt, 16 h; iii) NH₄Cl_(aq), iv) HCl/MeOH

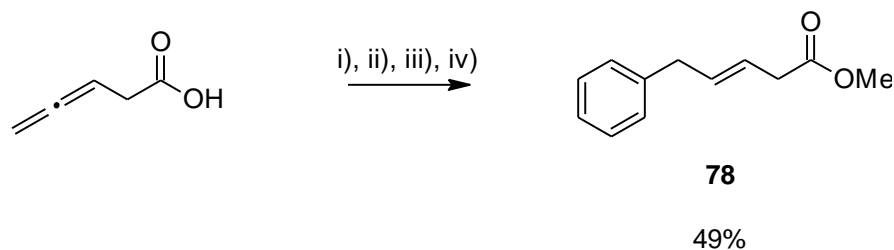
Table 6

Entry	Base	PhMgBr (eq)	CuI	Yield (%)
1	LDA (2 eq)	1.5	50 mol%	40
2	LDA (2 eq)	2	2	34
3	LDA (2 eq)	1.1	1.1	17
4	ⁿ BuLi (2 eq), ⁱ Pr ₂ NH (50 mol%)	1.1	10 mol%	36
5	ⁿ BuLi (2.5 eq), ⁱ Pr ₂ NH (50 mol%)	1.1	10 mol%	50
6	1) NaH (1 eq); 2) EtMgBr (1 eq)	1.1	10 mol%	7



Scheme 81

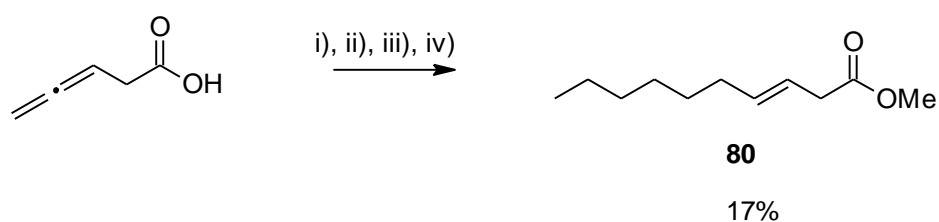
Although methylation with methanolic hydrochloric acid is known to be an efficient protocol it was thought that milder conditions would be more suitable for the application to more complex carbometallation products. Methylation with methyl iodide and potassium carbonate in acetone as the final step thus afforded ester **78** in 49% yield (Scheme 82).



Reagents and conditions: i) $n\text{BuLi}$ (2.5 eq), $i\text{Pr}_2\text{NH}$ (50 mol%), Et_2O , $-78\text{ }^\circ\text{C}$ to rt, 1 h; ii) PhMgBr (1.1 eq), CuI (10 mol%), $-78\text{ }^\circ\text{C}$ to rt, 16 h; iii) $\text{NH}_4\text{Cl}_{(\text{aq})}$; iv) MeI (3 eq), K_2CO_3 (5 eq), acetone, rt, 20 h

Scheme 82

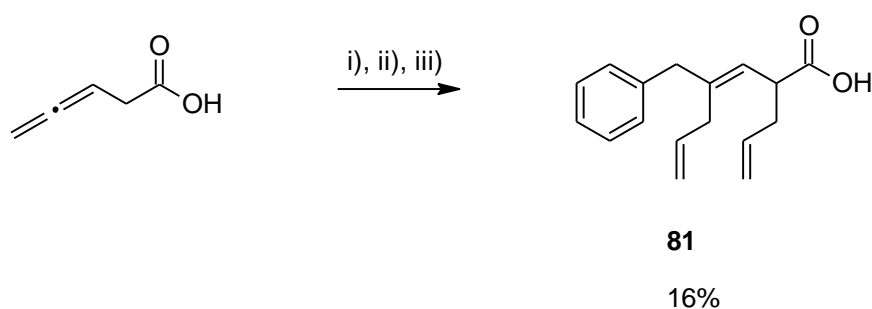
To our disappointment however, when the optimised protocol was applied to another Grignard reagent, pentyl magnesium bromide, ester **80** was isolated in only 19% yield (Scheme 83).



Reagents and conditions: i) $n\text{BuLi}$ (2.5 eq), $i\text{Pr}_2\text{NH}$ (50 mol%), Et_2O , $-78\text{ }^\circ\text{C}$ to rt, 1 h; ii) $\text{C}_5\text{H}_{11}\text{MgBr}$ (1.1 eq), CuI (10 mol%), $-78\text{ }^\circ\text{C}$ to rt, 16 h; iii) $\text{NH}_4\text{Cl}_{(\text{aq})}$; iv) MeI (3 eq), K_2CO_3 (5 eq), acetone, rt, 20 h

Scheme 83

The reactivity of the “bis-carbanion” intermediate was also probed in a preliminary experiment at this stage wherein the reaction mixture was quenched with an excess of allyl bromide with the intention of reacting the vinyl anion, the enolate dianion and finally the carboxylate. Pleasingly, even though the allyl ester was not formed, two additional carbon-carbon bonds were generated in this reaction and the acid **81** was isolated in 16% yield (Scheme 84) with no other discernable products isolated.

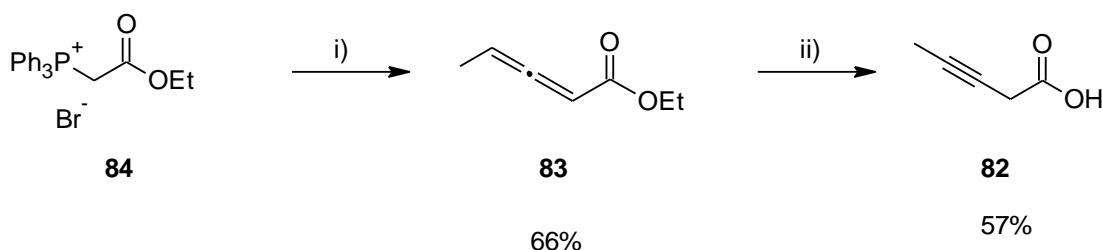


Reagents and conditions: i) ⁿBuLi (2.5 eq), ⁱPr₂NH (50 mol%), Et₂O, -78 °C to rt, 1 h; ii) PhMgBr (1.1 eq), CuI (10 mol%), -78 °C to rt, 16 h; iii) AllylBr (5 eq), 0 °C to rt, 20 h

Scheme 84

Although allenes had only been used for enolate directed carbometallation thus far, the application to alkynes was also conceivable. Due to the greater amount of published work concerning carbometallation of alkynes it was thought that reaction conditions used with propargyl alcohols would be applicable to alkynes with an enolate tether.

Accordingly, acid **82** was prepared by a saponification-isomerisation sequence from ester **83** which, in turn, was prepared from the commercially available phosphonium salt **84** and propionyl chloride (Scheme 85).



Reagents and conditions: i) EtCOCl (1 eq), Et₃N (2 eq), DCM, 0 °C, 2 h; ii) LiOH (5 eq), THF/H₂O (1:1), rt, 45 min

Scheme 85

Unfortunately, when acid **82** was deprotonated with two equivalents of LDA to form the dianion followed by addition of catalytic copper(I)iodide and phenyl magnesium bromide only starting material was recovered. The fact that there is no literature precedent for the copper(I) mediated carbometallation of homopropargylic alcohols may be the reason why the attempted carbometallation of acid **82** was unsuccessful. It would however be interesting to consider how the reaction would fare using iron(III) catalysis since this combination has been used to effect the carbomagnesiation of homopropargylic alcohols as discussed in the previous chapter (page 48).⁵² In light of these results it was decided that, although ideally the concept could eventually be applied to alkynes, allenes had, thus far, proven to be more successful and would therefore be given a higher priority.

At this stage, comparison of the results obtained from both the ester enolate and the carboxylic acid dianion suggested that the carbometallation step was proceeding with

approximately equal efficiency in both cases. As highlighted in Figure 4 however, whilst the symmetrical nature of the carboxylic acid dianion can only offer a lithium alkoxide as a tethering atom, the preferred (*E*) geometry preceded for ester enolates⁷² could lead to a carbometallation which is directed either by the lithium alkoxide or by the “ether” unit, and, as noted in the seminal studies by Normant³⁹ on enol ethers, a *cisoid* relationship between the tethering heteroatom and the unsaturated alkyne is beneficial. Hence, in the initial carbometallation study of an ester enolate, the oxygen atom which had hopefully directed the reaction could not be ascertained, and arguments both for and against each of the two oxygen atoms could be made as to which was the more effective chelating ligand (Figure 4) and even whether intramolecular monomeric delivery was indeed involved.

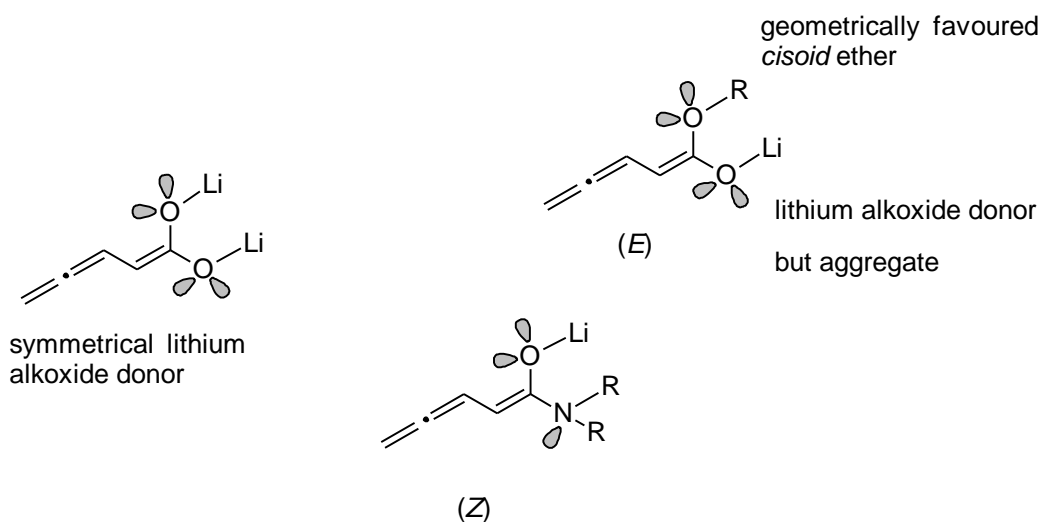
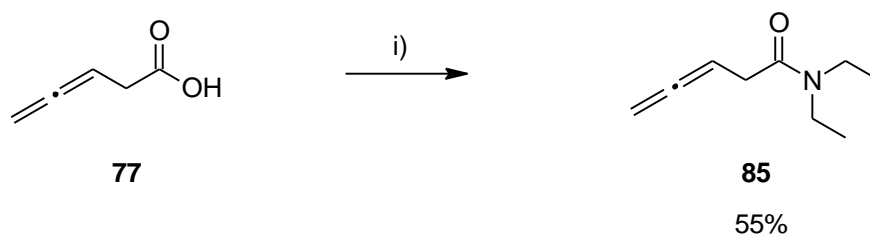


Figure 4

Given that deprotonation of an amide with LDA at $-78\text{ }^{\circ}\text{C}$ is known to favour formation of a (*Z*) enolate, and in the true spirit of blind exploration, it was therefore of considerable interest to “weigh” the virtues of the favourably disposed lithium alkoxide against the tethering nitrogen lone pair as implied in Figure 4. The required

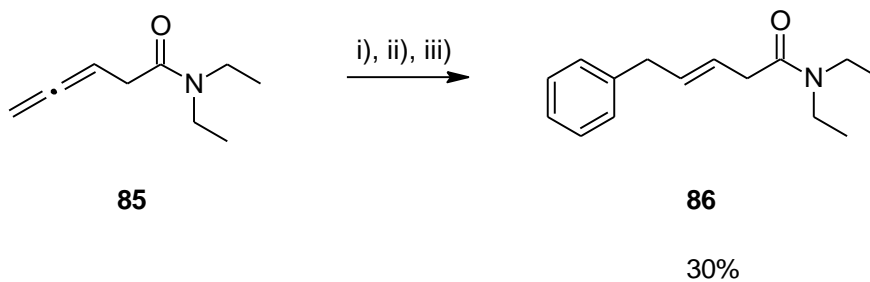
amide **85** was accordingly prepared by a standard dicyclohexylcarbodiimide coupling of acid **77** with diethylamine (Scheme 86).



Reagents and conditions: i) DCC, diethylamine, DCM, rt, 16 h

Scheme 86

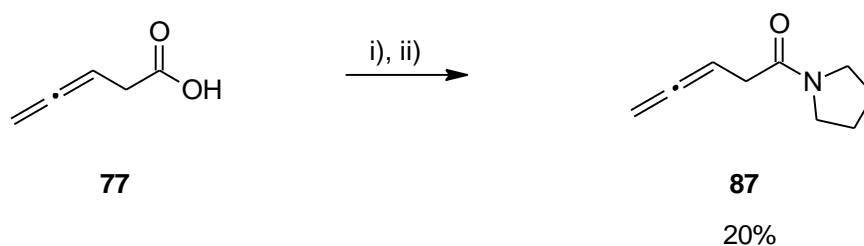
In the event, when amide **85** was deprotonated with LDA and then treated with copper(I)iodide and phenyl magnesium bromide amide **86** was isolated in 30% yield as a single geometrical isomer (Scheme 87).



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) PhMgBr (3.5 eq), CuI (50 mol%), -78 °C to rt, 16 h; iii) NH₄Cl_(aq)

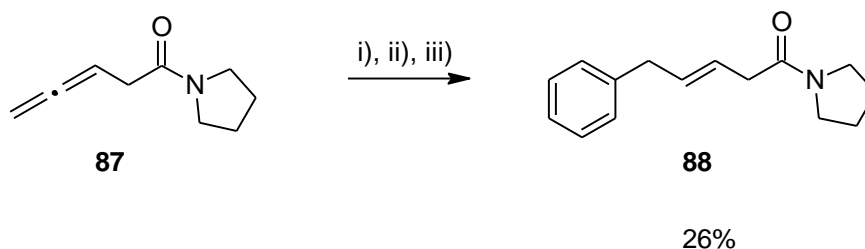
Scheme 87

It was thought that restricting the free rotation of alkyl groups in the amide would help to minimise any unfavourable steric interactions that could have had a detrimental effect on the carbometallation. The cyclic amide **87** was therefore prepared from acid **77** and pyrrolidine (Scheme 88) using ethylchloroformate and *N*-methylmorpholine. However, when amide **87** was then subjected to the same carbometallation conditions shown in Scheme 87, the product **88** was isolated in a comparable 26% yield (Scheme 89).



Reagents and conditions: i) EtOCOCl, NMM, DCM, 0 °C; ii) NMM, Pyrrolidine, 0 °C to rt, 16 h

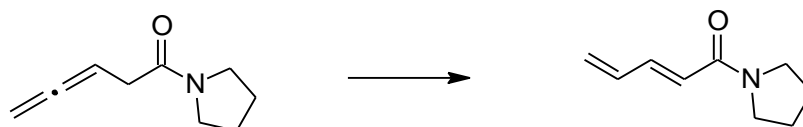
Scheme 88



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) PhMgBr (3.5 eq), CuI (50 mol%), -78 °C to rt, 16 h; iii) NH₄Cl_(aq)

Scheme 89

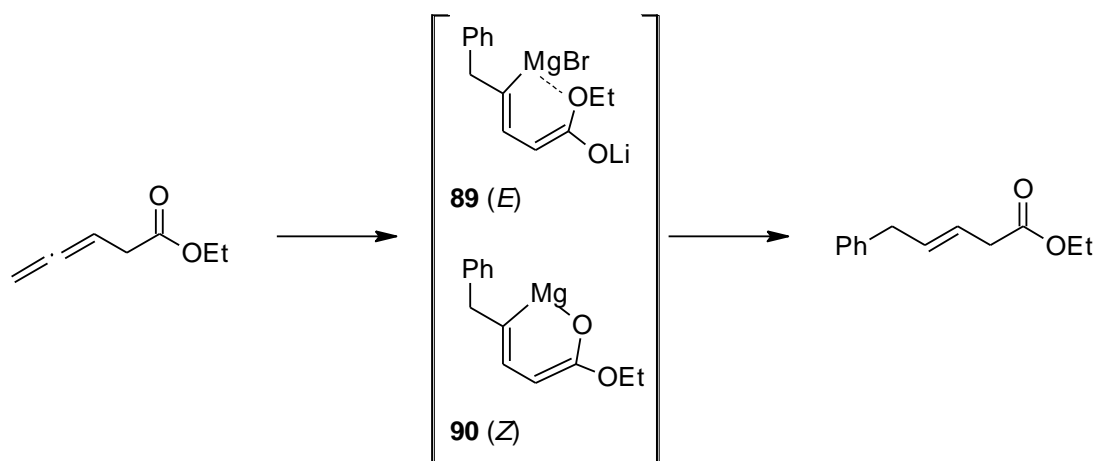
The lower yields from amides **86** and **88** with respect to the corresponding reaction of the carboxylic acid dianion could be interpreted in terms of preferential chelation between the nitrogen atom of the amide and the organometallic reagent. However, it was also of considerable concern that the amount of material recovered from the reaction mixture was significantly lower than expected. Test alkylation and aldol reactions of the first formed lithium amide enolate from **87** without carbometallation resulted in complex mixtures and a considerable amount of insoluble material. It has been reported that the α -anions of β - γ unsaturated amides can isomerise easily⁷⁴ and, for the cases of the allenic amides **85** and **87**, such a process would be even more favourable as a consequence of the extra double bond (Scheme 90). The isomerisation product could then be susceptible to conjugate addition by diisopropylamine.



Scheme 90

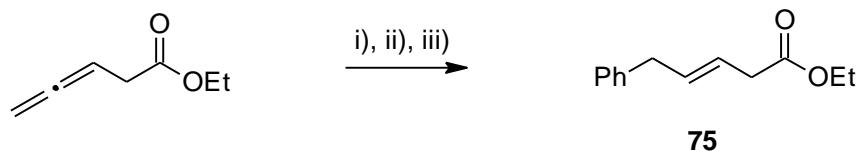
2.2.3 Ester enolates

Since the behaviour of lithium amide enolates was proving to be more problematic than expected, it was decided that a more detailed study of ester enolates as directing tethers for carbometallation was required. As we have noted, irrespective of whether a (*Z*) or an (*E*) enolate is formed, either can be successful in directing a carbometallation. The two enolate geometries would however give rise to two entirely different carbanionic intermediates **89** and **90**, as emphasised in Scheme 91.



Scheme 91

Firstly, it seemed prudent to re-examine the earlier preliminary experiment shown in Scheme 77. It was found that, if followed closely by analytical TLC, the reaction was complete after 2 hours and 30 minutes. Not only had the reaction time been reduced from 12 hours but the yield had also increased from 30% to 79%! The results of a small screening study of the reaction are shown in Table 7. Increasing the reaction time had the effect of decreasing the overall yield of ester **75**. This is most probably due to the unstable nature of ester enolates at higher temperatures. It was also found that only 1.1 equivalents of phenyl magnesium bromide were required which means that further elaboration of the carbometallated intermediate would not be complicated by unwanted reactions arising from excess Grignard reagent.



Reagents and conditions: i) LDA (1 eq), Solvent, -78 °C, 30 min; ii) PhMgBr (1.1 eq), catalyst, -78 °C to Temp; iii) NH₄Cl_(aq), -78 °C

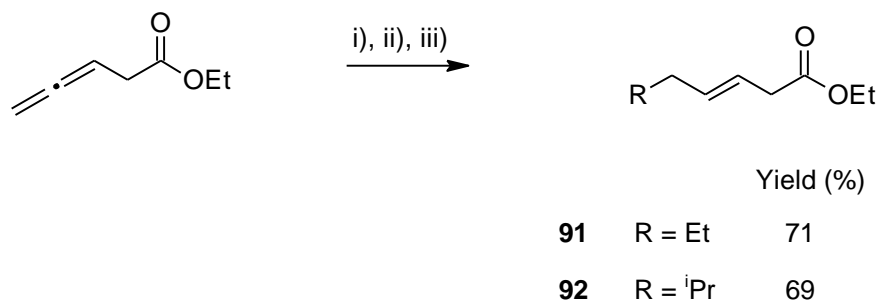
Table 7

Solvent	Catalyst	Temperature	Time	Yield (%)
Et ₂ O	CuI (50 mol%)	rt	12 h	30 ^(a)
Et ₂ O	CuI (10 mol%)	0 °C	2 h 30	79
THF	CuI (10 mol%)	0 °C	4 h	0
Et ₂ O	No catalyst	0 °C	4 h	0

^(a) Experiment performed by Mr P. Gray⁶⁹

Et₂O and copper(I) were shown to be essential for the reaction to take place with THF giving no observed product which agrees with the results from the carbometallation of allenols⁶² and homoallenols as reported earlier.

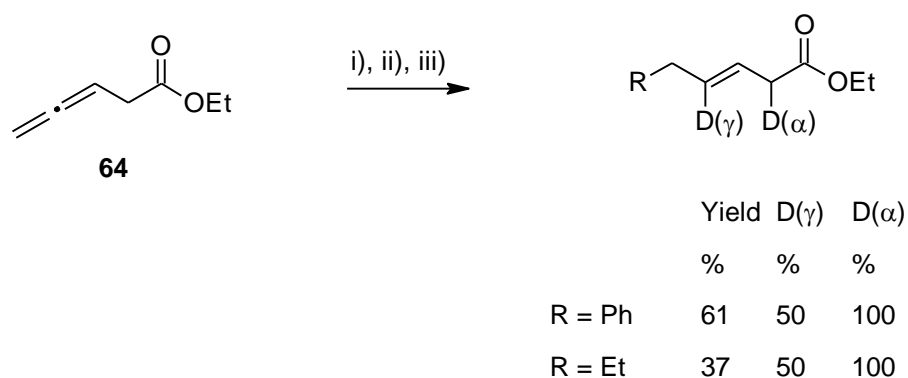
The reaction was also shown to be successful using other Grignard reagents. Both ethyl magnesium bromide and even the more bulky isopropyl magnesium bromide afforded esters **91** and **92** respectively in good yields and as single geometrical isomers (Scheme 92).



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) RMgBr (1.1 eq), CuI (10 mol%), -78 °C to 0 °C, 2 h 30; iii) NH₄Cl_(aq), -78 °C

Scheme 92

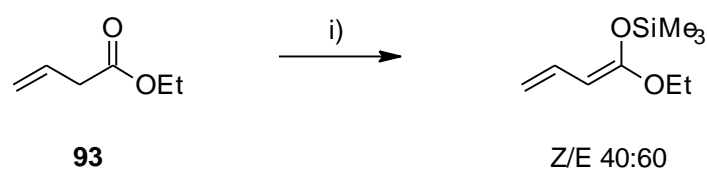
Although these results were very encouraging it was paramount to capitalise on the subsequent reactivity of the bis-carbanionic intermediate in order to realise the full potential of this chemistry. As with previous substrates, the carbometallated ester intermediate was therefore subjected to a deuterium quench to prove the presence of the novel bis-carbanion intermediate. Surprisingly, when the reaction mixture was treated with deuterium chloride and deuterium acetate in deuterium oxide, there was full incorporation of deuterium into the α position but just 50% incorporation into the γ position (Scheme 93).



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) RMgBr (1.1 eq), CuI (10 mol%), -78 °C to 0 °C, 2 h 30; iii) DCl/AcOD/D₂O, -78 °C

Scheme 93

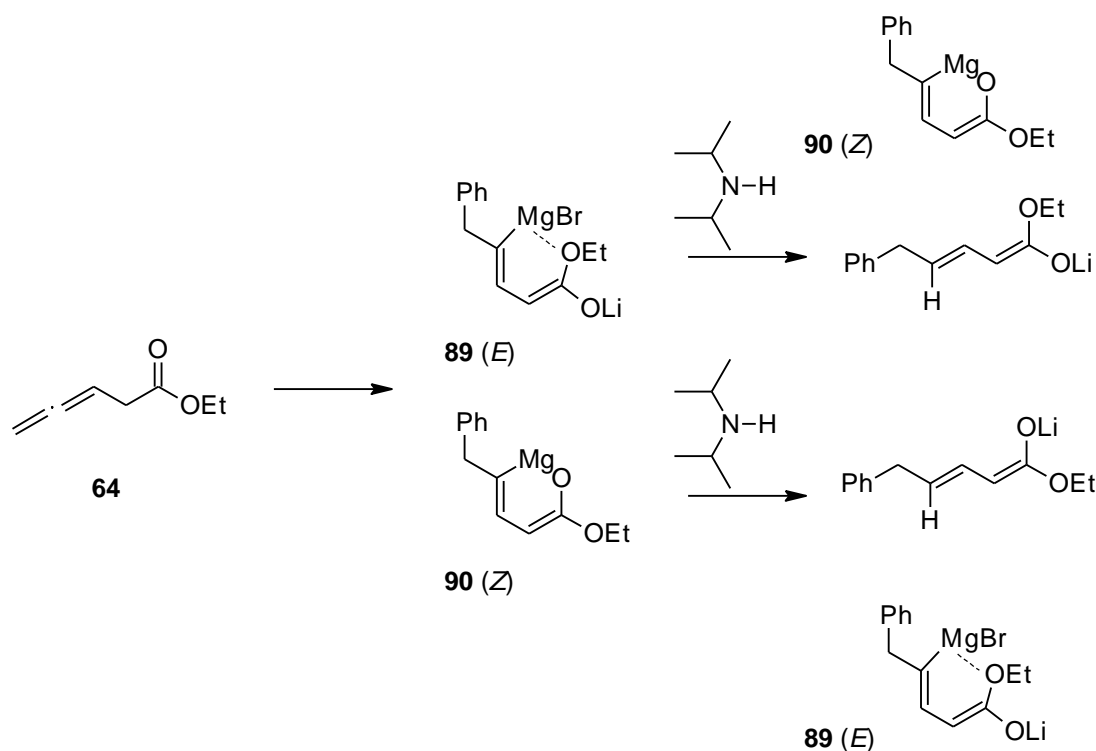
In general, kinetic deprotonation of esters affords enolates of (*E*) geometry.⁷² However, ester **93**, which is closely related to ester **64**, gives a mixture of both *E* and *Z* enolates (Scheme 94),⁷⁵ and hence if two different enolate geometries are also formed with ester **64**, two distinctly different carbometallated intermediates will be generated from these respective enolate geometries, **89** (*E*) and **90** (*Z*) (Scheme 95).



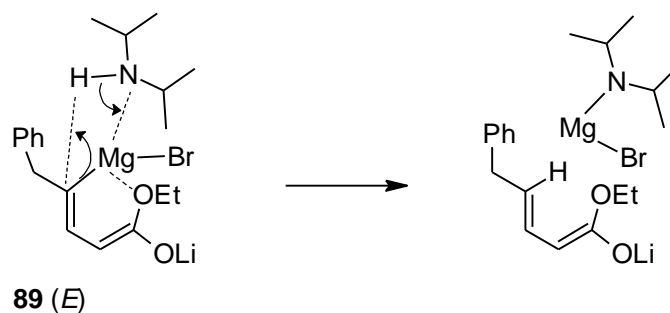
Reagents and conditions: i) LDA, -78 °C

Scheme 94

The 50% incorporation of deuterium in the γ position was thought to be brought about by only one of these, either **89** (*E*) or **90** (*Z*), which were likely to be present in equal proportions, when diisopropylamine was used as the proton source (Scheme 95). Intermediate **90**, with the enolate oxygen anion acting as a ligand, could have shown the reduced reactivity of the heterocuprates developed by Posner.⁷⁶ The reactivity of intermediate **89** was more likely akin to that of an isolated Grignard reagent which can be used to form halo magnesium amide bases. It could also be suggested that the diisopropylamine acted as a ligand for the intermediate vinyl Grignard in the (*E*) enolate intermediate, whilst the (*Z*) enolate possesses an oxy-anion ligand (Scheme 96). The result obtained from the deuteration experiment in the carboxylic acid series (*vide supra*) shows full incorporation of deuterium in the γ position which suggests that the oxy-anion of the lithium enolate prohibits protonation of the vinyl organometallic moiety by diisopropylamine.

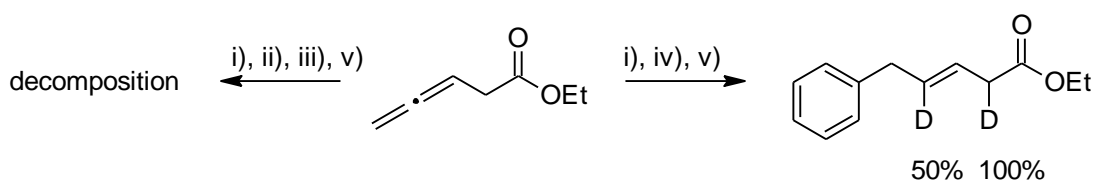


Scheme 95



Scheme 96

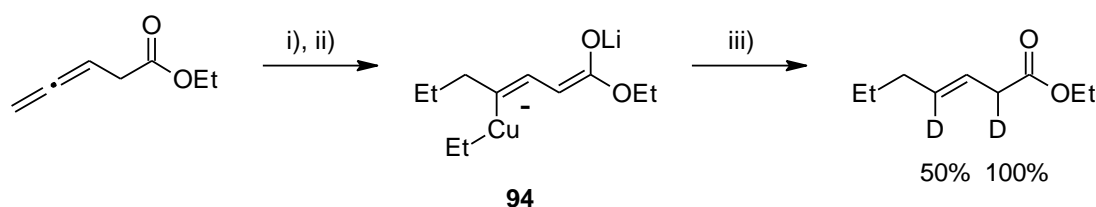
It was therefore imperative that a solution to the low deuterium incorporation problem be found as it was destroying the desired potential of the “bis-carbanion” intermediate. The simplest solution that was first attempted was to increase the amount of Grignard reagent present in the reaction so that it would deprotonate the diisopropylamine in preference before taking part in the carbometallation (Scheme 97). Unfortunately this approach was not successful and afforded the same result of 50% deuterium incorporation. Using a similar tactic it was thought that a second deprotonation of liberated diisopropylamine by *n*-butyllithium would solve the problem. However, in order to do so, the reaction was warmed to 0 °C, and this led to decomposition of the ester enolate (Scheme 97).



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) ⁿBuLi (1 eq), 0 °C, 15 min; iii) PhMgBr (1.1 eq), CuI (10 mol%), -78 °C to 0 °C, 2 h 30; iv) PhMgBr (3.1 eq), CuI (10 mol%), -78 °C to 0 °C, 2 h 30; v) DCl/AcOD/D₂O, -78 °C

Scheme 97

In similar vein to previous experiments, the use of a stoichiometric cuprate reagent was attempted since it was thought to give rise to intermediate **94** (Scheme 98) which would possess both an ethyl and a vinyl ligand on the copper metal such that the ethyl carbanion would be more likely to deprotonate diisopropylamine than the vinyl carbanion (sp^3 versus sp^2). When this hypothesis was tested, the deuterium incorporation was identical to previous experiments (Scheme 98). One reason behind this interesting result could be that the vinyl carbanion is electron rich as a result of the enolate and therefore more basic than an “isolated” vinyl carbanion.

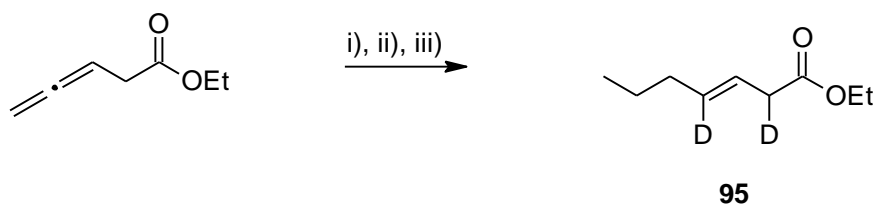


Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) Et₂CuMgBr.MgBr₂, -78 °C to 0 °C, 2 h 30; iii) DCl/AcOD/D₂O, -78 °C

Scheme 98

Lithium aryl amide bases have been shown by Xie et al.⁷⁷ to selectively form (*Z*) ketone enolates due to a more stable carbanion which results in a looser transition state, and therefore a move away from an Ireland deprotonation model.⁷⁸ It was thought that if this (*Z*) selectivity could be translated to ester enolates then intermediate **90** (*Z*) (Scheme 95) would be preferentially formed, and that this species might not undergo protonation by diisopropylamine. It was found that when employing lithium trimethylsilylanilide to form the ester enolate followed by 1.1 equivalents of Grignard reagent and 10 mol% of copper(I)iodide that there was no reaction and only starting material was recovered (Entry 1, Table 8). This was believed to be due to the weaker N-H bond consuming the Grignard reagent which

led to the idea that using an extra equivalent of Grignard reagent would achieve the goal set out above (Scheme 97) of re-deprotonating the secondary amine base. Using 2.1 equivalents of ethyl magnesium bromide afforded ester **95** albeit in 17% yield but more importantly the incorporation of deuterium into the γ position had increased to 70% (Entry 2, Table 8). The increase in deuterium incorporation from 50% to 70% is an indication that either there was a preference for the formation of the (Z) enolate (and therefore a “protected” vinyl organometallic intermediate) or that the trimethylsilylaniline was once again deprotonated. The latter is more likely because of the previous result using only 1.1 equivalents of Grignard reagent. However, it is clear that the second consecutive deprotonation reaction overlapped with the carbometallation reaction, illustrating the very delicate balance required in this research.

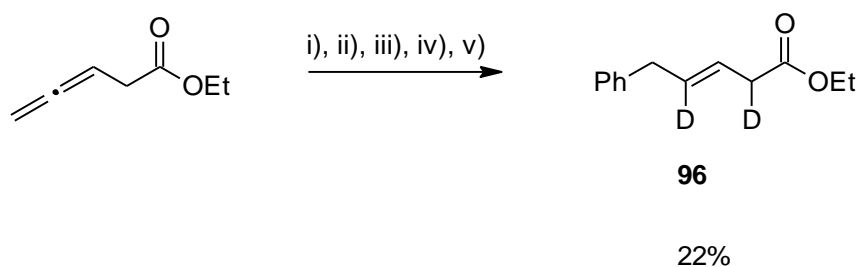


Reagents and conditions: i) LiN(TMS)Ph (1 eq), Et₂O, -78 °C, 30 min; ii) EtMgBr, -78 °C to 0 °C, 2 h 30; iii) DCl/AcOD/D₂O, -78 °C

Table 8

Entry	EtMgBr (eq)	Yield (%)	D incorporation (%)	
			α	γ
1	1.1	0	N/A	N/A
2	2.1	17	100	70

In order to prove that diisopropylamine was the proton source that was responsible for quenching the vinylic carbanion the reaction shown in Scheme 99 was carried out. Following deprotonation with LDA, a high vacuum was applied to remove diisopropylamine. Diethyl ether was then added and the reaction carried out as in previous experiments. After deuteration ester **96** was isolated in 22% yield, but with ^1H NMR analysis showing complete incorporation of deuterium at both sites.



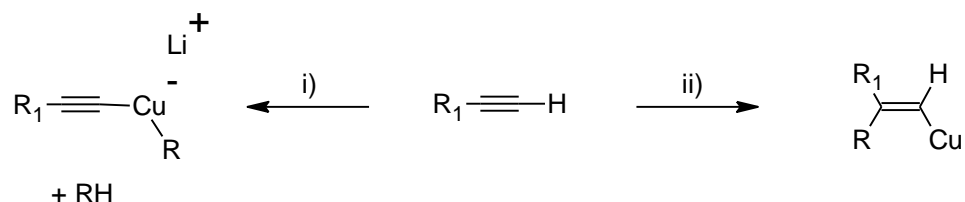
Reagents and conditions: i) LDA (1 eq), Et_2O , $-78\text{ }^\circ\text{C}$, 30 min; ii) high vacuum, $0\text{ }^\circ\text{C}$,
iii) Et_2O , $0\text{ }^\circ\text{C}$ to $-78\text{ }^\circ\text{C}$; iv) PhMgBr (1.1 eq), CuI (10 mol%), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$,
2 h 30; v) $\text{DCl}/\text{AcOD}/\text{D}_2\text{O}$, $-78\text{ }^\circ\text{C}$

Scheme 99

Due to the impracticality of removing diisopropylamine by high vacuum, as well as the poor yield attained, a solution to avoid LDA or to adapt the reaction conditions was highly desirable.

Consideration of the behaviour of terminal alkynes with organometallic reagents suggested a possible solution. It is known that Grignard reagents and diorganocuprates are sufficiently basic to deprotonate a terminal acetylene. However, as indicated in the introductory chapter, organocopper reagents do not

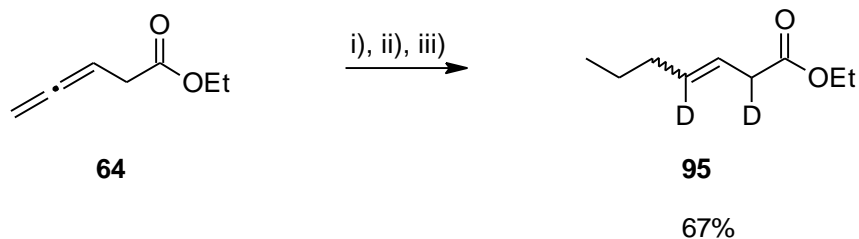
deprotonate terminal alkynes but add across the triple bond in a *syn* fashion, as shown in Scheme 100.⁷⁹



Reagents and conditions: i) R_2CuLi ; ii) RCu

Scheme 100

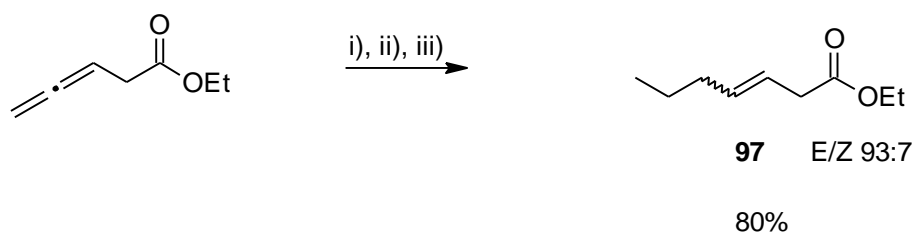
Whereas the pKa of a terminal acetylene is approximately 25, the pKa of diisopropylamine is approximately 36. If an organocopper reagent does not deprotonate a terminal acetylene, it is unlikely therefore to deprotonate diisopropylamine. A reaction to test this hypothesis was accordingly carried out by treating the lithium enolate derived from ester **64** with 1.1 equivalents of ethylcopper, formed from equimolar amounts of ethyl magnesium bromide and copper(I)iodide. Pleasingly, the reaction proceeded in very good yield and, on deuteration, NMR analysis of ester **95** indicated full incorporation of deuterium into both α and γ positions (Scheme 101).



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) EtCu.MgBrI (1.1 eq), -25 °C to -20 °C, 3 h; iii) DCl/AcOD/D₂O, -78 °C

Scheme 101

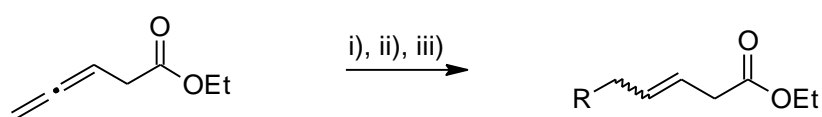
The reaction was repeated to compare the performance of the organocopper reagent as opposed to the catalytic copper(I) salt and Grignard reagent system. Although the latter reaction proceeded in very good yield, NMR analysis of the ester product **97** now showed a mixture of (*E*) and (*Z*) isomers in a ratio of 93:7 (Scheme 102). Hence, by switching from a catalytic copper(I) and Grignard reagent system to a stoichiometric organocopper reagent, the reaction was rendered stereoselective instead of stereospecific.



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) EtCu.MgBrI (1.1 eq), -25 °C to -20 °C, 3 h; iii) NH₄Cl_(aq), -78 °C

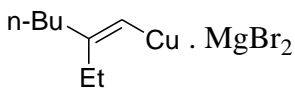
Scheme 102

A number of other organocopper reagents were also examined, the results of which are summarised in Table 9. It was found that the smaller the organic group of the organocopper reagent the better the stereoselectivity. In the case of phenylcopper (Entry 6), the selectivity changed dramatically from (*E*) to (*Z*), which suggests a significant steric interaction that is strongly disfavoured by the larger phenyl group. The use of a simple Grignard reagent (Entry 3) or the selection of THF (Entry 2) as solvent led to recovery of starting material.

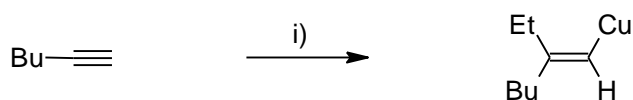


Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) RM (1.1 eq), -25 °C to -20 °C; iii) NH₄Cl_(aq), -78 °C

Table 9

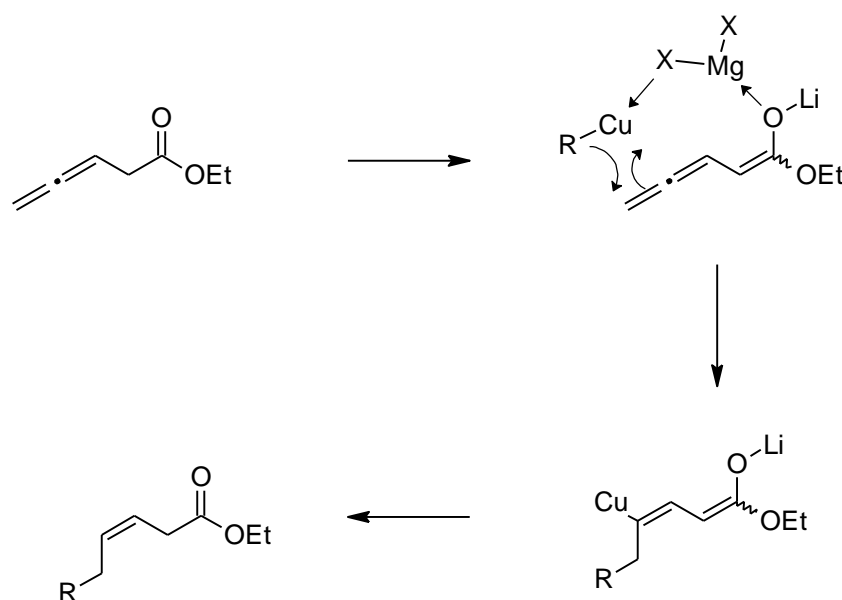
Entry	RM	Solvent	Time	<i>E/Z</i>	Yield (%)
1	EtCu (EtMgBr + CuI)	Et ₂ O	2h	93:7	80
2	EtCu (EtMgBr + CuI)	THF	3h	N/A	0
3	EtMgBr	Et ₂ O	3h	N/A	0
4	ⁱ PrCu (ⁱ PrMgBr + CuI)	Et ₂ O	2h45	83:17	81
5	ⁿ BuCu (ⁿ BuLi + CuBr)	Et ₂ O	2h30	74:26	56
6	PhCu (PhLi + CuBr)	Et ₂ O	2h30	33:67	52
7	 (a)	Et ₂ O	4h	N/A	0

(a) The vinylcopper shown in the last entry was prepared *in situ* via a literature procedure shown in the Scheme below.



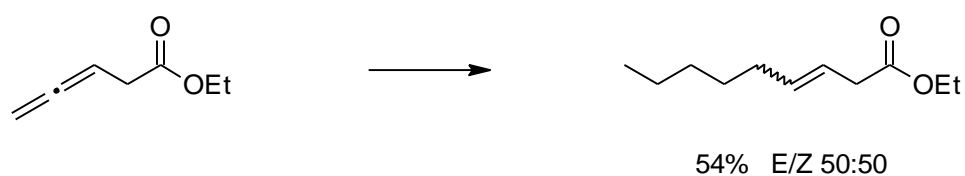
Reagents and conditions: i) EtCu.MgBr₂ (1 eq), Et₂O, -20 °C, 2 h

A rationale for the formation of the (*Z*) alkene is shown in Scheme 103 and invokes a magnesium salt bridge in the transition state. Unfortunately this does not explain the results of the reactions where the organocopper species was derived from an organolithium reagent. In these reactions, the yield was significantly lower when compared with the use of Grignard reagents. It was believed to be due to the absence of the magnesium salt, which has been shown to be crucial for reactions involving organocopper reagents in general,⁷³ as well as being implicated in the carbometallation reactions of terminal alkynes carried out by Normant et al.³⁹



Scheme 103

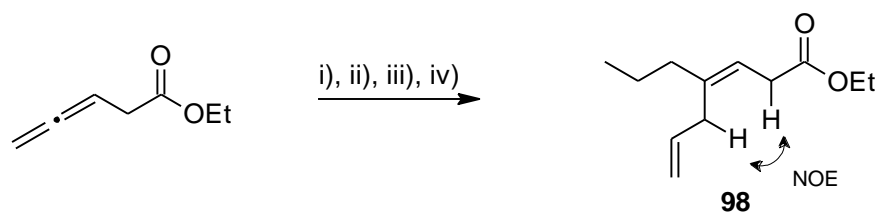
This theory was tested by an experiment where butylcopper was preformed with *n*-butyllithium and copper(I) iodide and then followed by addition of magnesium bromide (Scheme 104). The conversion of the reaction by ^1H NMR analysis of the crude mixture was higher than when the reaction was carried out in the absence of any magnesium salt. However, there was little difference in the isolated yield. Interestingly the (*E*):(*Z*) ratio changed dramatically from 74:26 to 50:50 in accord with the mechanism postulated in Scheme 103.



Reagents and conditions: i) LDA (1 eq), Et_2O , $-78\text{ }^\circ\text{C}$, 30 min; ii) MgBr_2 (1.1 eq);
 iii) $^n\text{BuCu}\cdot\text{LiI}$ (1.1 eq), $-25\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$; iii) $\text{NH}_4\text{Cl}_{(\text{aq})}$, $-78\text{ }^\circ\text{C}$

Scheme 104

With some greater degree of understanding of the first two facets of the strategic aims for this methodology, attention then focused on the possibilities for exploitation of the new dianionic intermediate and especially on the important formation of new carbon-carbon bonds. Initially an alkylation reaction was attempted on both the ester enolate and vinylcopper sites at the same time. For simplicity, an excess of allyl bromide was used. Interestingly, alkylation only took place on the vinylcopper moiety to afford the trisubstituted olefin **98** in 44% yield, the stereochemistry of which was confirmed by NOE. Table 10 shows the results of a study on this alkylation reaction.



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) EtCu.MgBrI (1.1 eq), -25 °C to -20 °C, 3 h; iii) AllylBr, -20 °C, 2 h; iv) NH₄Cl_(aq), -78 °C

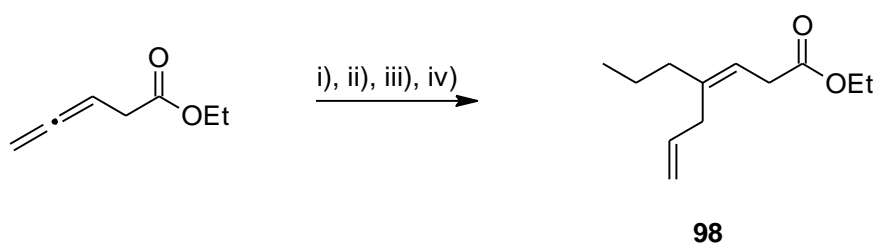
Table 10

Entry	AllylBr (eq)	Additive	Conversion (%)
1	3.1	None	81 (44) ^(a)
2	1.1	None	15
3	2.1	None	52
4	1.1	P(OEt) ₃ , 10 mol%	25
5	1.1	P(OEt) ₃ , 1.1 eq	49

^(a) isolated yield (%)

The alkylation of ester enolates is known to require HMPA as a cosolvent.¹¹ However, when the safer alternative DMPU was added to the reaction mixture prior to addition of the electrophile an intractable and highly viscous substance was formed from which no discernable products could be isolated. Lowering the amount of allyl bromide added resulted in a lower yield of coupled product (Entries 2 and 3). The use of triethyl phosphite as a ligand for a vinyl copper intermediate has been shown to improve reactivity¹¹ in conjunction with HMPA. No such improvement was found in the present instance (Entries 4 and 5) and this could be due to the difficulty in breaking up the complex mixed organometallic aggregates.

Since a key objective of the research programme was to form three carbon-carbon bonds it was decided to find out if the ester enolate was completely unaffected by the alkylation reaction. The carbocupration-alkylation sequence was therefore repeated with a deuterium quench, and to our initial surprise, afforded ester **98** with no observed deuterium incorporation in the α position suggesting that the ester enolate had been quenched internally by a proton source (Scheme 105).

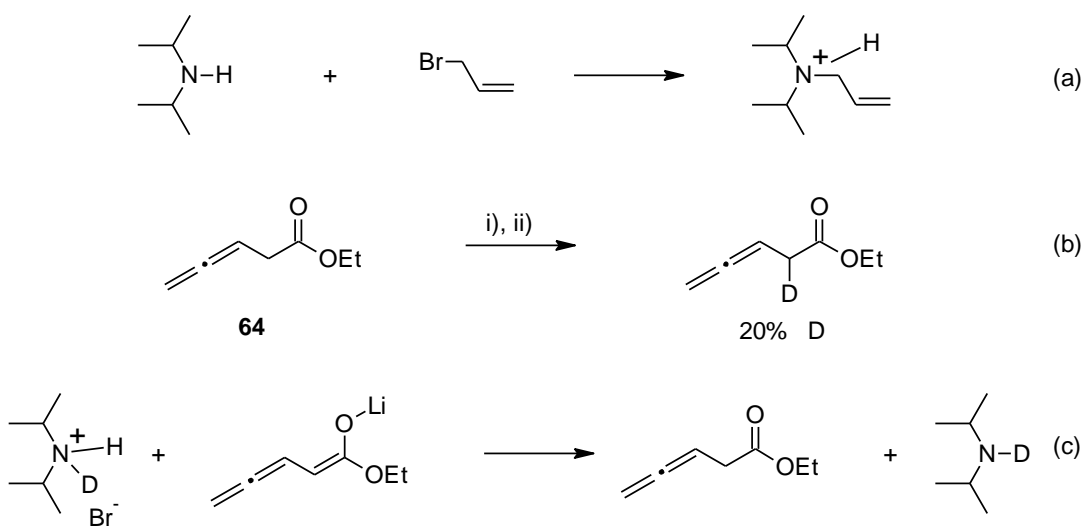


Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) EtCu.MgBrI (1.1 eq), -25 °C to -20 °C, 3 h; iii) AllylBr, -20 °C, 2 h; iv) DCl/AcOD/D₂O, -78 °C

Scheme 105

Initially, it was thought that diisopropylamine was alkylated by allyl bromide to produce the quaternary ammonium hydrobromide which then destroyed the ester enolate (Scheme 106 (a)). However an experiment carried out by another member of the research group shed light on another possibility. When ester **64** was simply deprotonated with LDA at -78°C and then quenched with deuterium chloride, ¹H NMR analysis showed only 20% deuterium incorporation (Scheme 106 (b)). Both of these observations can be explained by a kinetic isotope effect where an acid-base reaction between deuterium chloride and diisopropylamine forms a mono deuterated diisopropylammonium cation with one N-H bond and one N-D bond. Of the two bonds, the N-H bond is significantly weaker and is broken by attack of the enolate,

resulting in protonation of the enolate in preference to deuteration (Scheme 106 (c)). Diisopropylamine is known to be associated with the enolate aggregate, linked via N-Li complexation.⁷¹ As a successful full incorporation of deuterium was found in both the catalytic copper(I) and stoichiometric carbocupration reactions involving the same ester enolate (Schemes 93 and 101) it could be suggested that this association of diisopropylamine is weaker in these cases.

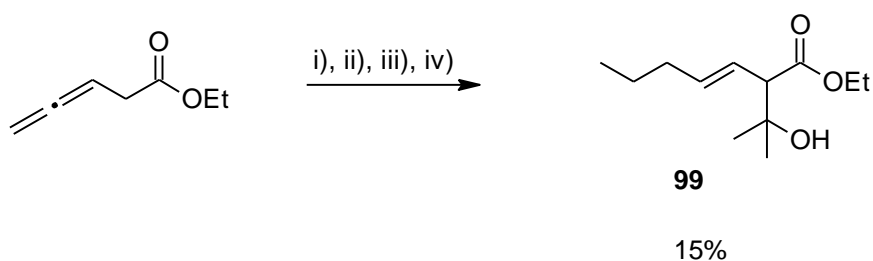


Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) DCl/AcOD/D₂O, -78 °C

Scheme 106

If the second argument that a kinetic isotope effect was the cause of the lack of deuterium incorporation then subsequent reactions of the enolate following the organocopper coupling should be possible. However the fact that there is no deuterium incorporation whatsoever is cause for concern.

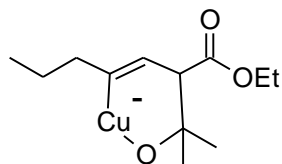
The alternative scenario of achieving reactivity at the ester enolate site prior to an organocopper reaction was therefore initiated. It is known from the work by Normant et al.¹¹ on carbocupration that organocopper reagents are sluggish in reactivity when compared to organocuprate, Grignard and copper(I) catalysed systems. This means that, in moving from a copper(I) catalysed reaction to a stoichiometric organocopper reaction there would be a greater ‘window’ for preferential reaction of the enolate. Since organocopper reagents are known to be unreactive towards ketones acetone was accordingly employed as the electrophile in an ester enolate-aldol reaction to afford the β -hydroxy ester **99** (Scheme 107).



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) EtCu.MgBrI (1.1 eq), -25 °C to -20 °C, 3 h; iii) Acetone (1.1 eq), -20 °C, 2 h; iv) NH₄Cl(aq), -78 °C

Scheme 107

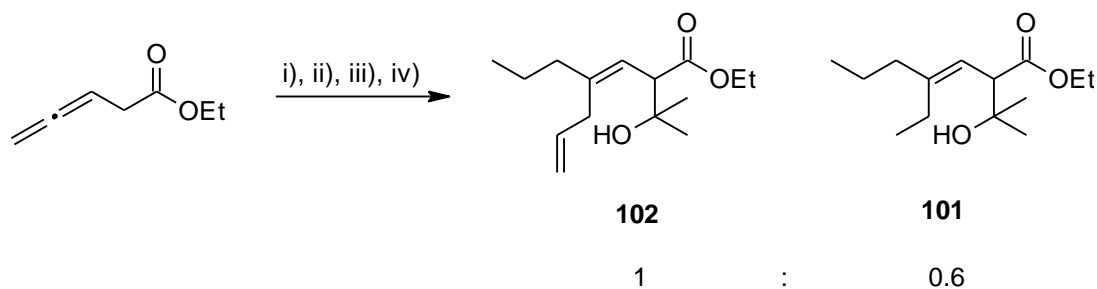
Formation of chelate **100** (Figure 5) was thought to be favoured in this reaction as the alkoxide could behave as a ligand for the vinylcopper moiety and, in so doing, convert it into a mixed heterocuprate which was likely to change the reactivity to that of a cuprate akin to those developed by Posner.⁷⁶



100

Figure 5

In an adventurous effort to combine the two successful selective reactions discussed above it was thought that both acetone and allyl bromide could be added at the same time and, if the ester enolate reacted first, then the organocopper coupling could follow in a three carbon-carbon bond forming process. A reaction to investigate this hypothesis was carried out (Scheme 108). However, a side reaction involving the coupling of excess ethylcopper and the vinylcopper intermediate resulted in the formation of ester **101** which, due to the similarity in structure to the intended product **102**, was not separated. Nevertheless tentative assignment of the ^1H NMR spectra of the reaction mixture suggested that ester **102** had been formed with the stereochemistry of **102** and **101** based upon that of ester **98** (Table 10).

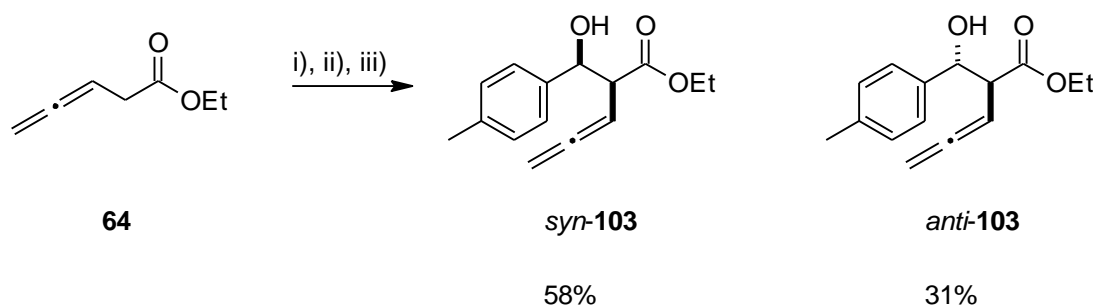


Reagents and conditions: i) LDA (1 eq), Et_2O , $-78\text{ }^\circ\text{C}$, 30 min; ii) EtCu.MgBrI (1.1 eq), $-25\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$, 3 h; iii) Acetone (1 eq), AllylBr (3 eq), $-20\text{ }^\circ\text{C}$, 2 h; iv)



Scheme 108

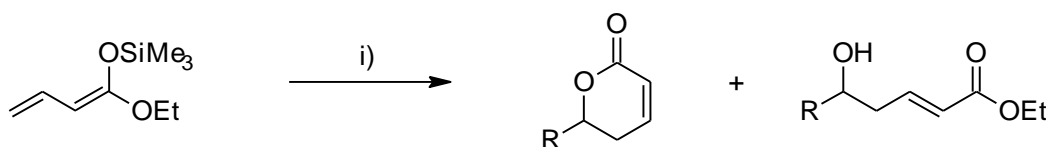
As discussed earlier, the choice of electrophile was crucial for selective stepwise reactions of each “carbanion” one at a time. A reaction that is known to be fast is likely to help this selection of electrophile. One such reaction is the kinetic aldol reactions of ester enolates. The chemo-selectivity of this reaction would be likely to benefit from the fact that the ester enolate aldol can be conducted at $-78\text{ }^{\circ}\text{C}$. Before attempting the more complex sequence a test aldol reaction on the starting ester **64** was carried out in order to ascertain its efficiency as well as to examine the diastereoselectivity. It was unlikely that there would be much diastereoselectivity as any stereochemical information in the geometry of an ester enolate is not translated to the aldol product. It has been reported that in order to achieve diastereoselectivity in an ester enolate aldol reaction a bulky or chelating ester group is required.⁷² In the event, the kinetic aldol reaction of the enolate from ester **64** afforded a diastereoisomeric mixture of *syn*-**103** and *anti*-**103** products in a ratio of 2.2:1 (Scheme 109).



Reagents and conditions: i) LDA (1 eq), Et₂O, $-78\text{ }^{\circ}\text{C}$, 30 min; ii) *p*-MeC₆H₄CHO, $-78\text{ }^{\circ}\text{C}$, 10 min; iii) NH₄Cl(aq), $-78\text{ }^{\circ}\text{C}$

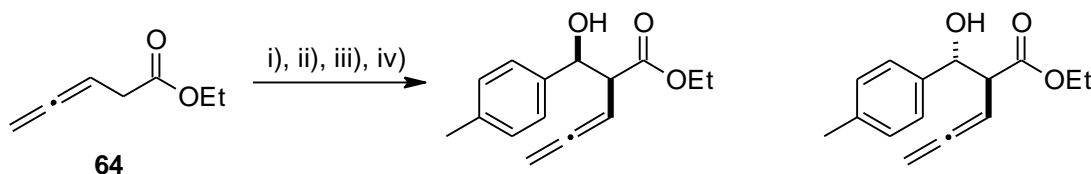
Scheme 109

It is known that copper dienolates formed by desilylation of a silyl ketene acetal⁷⁵ react at the γ position as shown in Scheme 110. It was remotely possible that this conjugate attack of the enolate could be influenced by the presence of copper in the ‘bis-carbanion’ carbometallation intermediate. For this reason an experiment was carried out to investigate the role of a copper(I) salt on the aldol reaction of the starting ester **64**. The reaction shown in Scheme 111 afforded identical products to the reaction carried out without copper(I) by analysis of the ¹H NMR spectrum of the crude material and the diastereoselectivity was also unchanged.



Reagents and conditions: i) PhCHO, Cu(OTf)₂ or CuCl (10 mol%), TBAT or NaO^tBu (10 mol%), THF, rt

Scheme 110

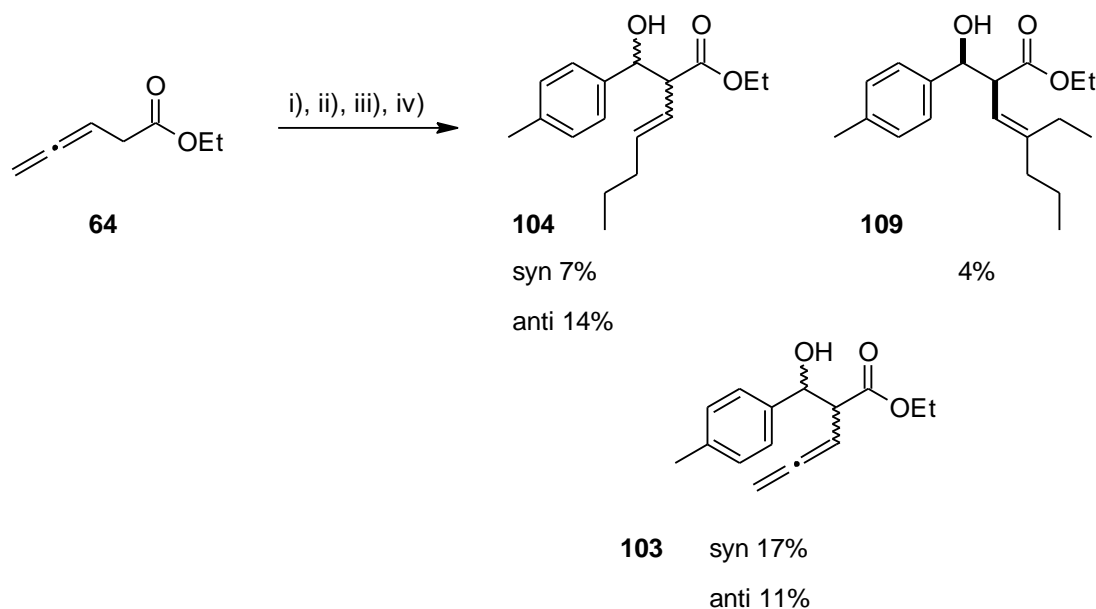


Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) CuI (1 eq), 15 min; iii) *p*-MeC₆H₄CHO, -78 °C, 10 min; iv) NH₄Cl_(aq), -78 °C

Scheme 111

A kinetic aldol reaction was then attempted on the carbometallation intermediate from ester **64** and ethylcopper (Scheme 112). The ester enolate was shown to be more reactive than the vinyl copper as no products suggesting reaction of the latter

were found although it should be noted that the mass balance for the aldol products was surprisingly low so it does not rule out any formation of unstable products.

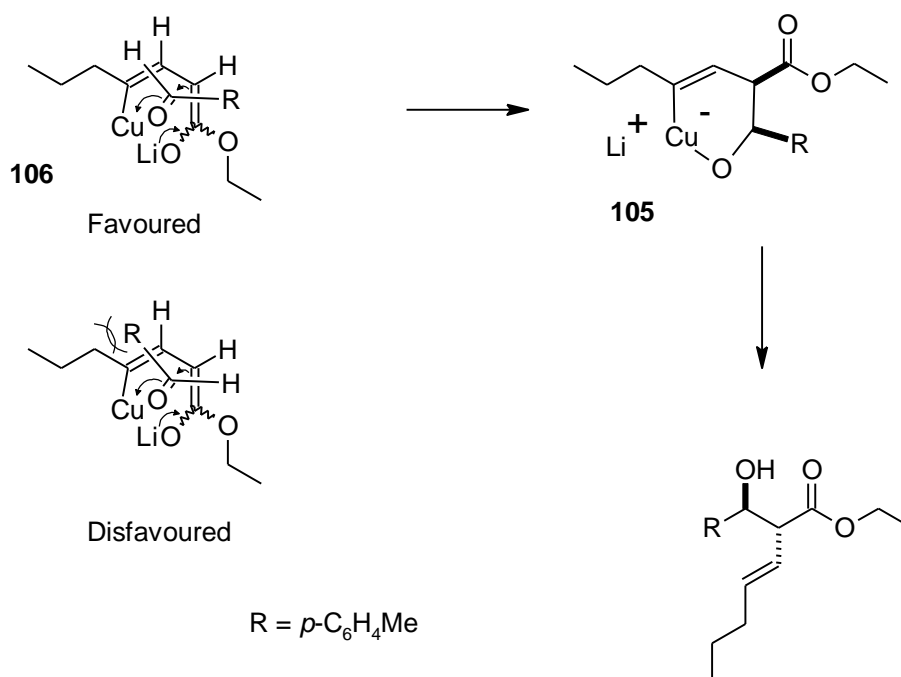


Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) EtCu.MgBrI (1.1 eq), -25 °C to -20 °C, 3 h; iii) *p*-MeC₆H₄CHO, -78 °C, 10 min; iv) NH₄Cl_(aq), -78 °C

Scheme 112

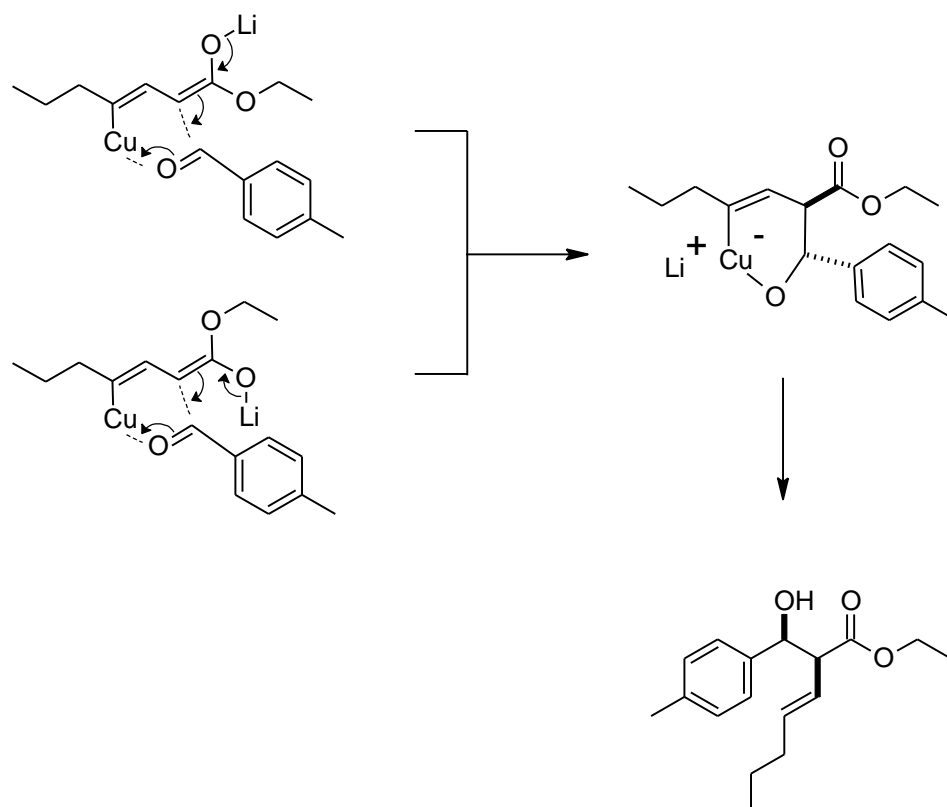
There was also an interesting result in relation to the stereochemistry of the aldol reaction. Whereas the starting ester **64** resulted in a greater amount of *syn* aldol product (2.2:1 *syn:anti*) the two diastereomers of product **104** were found in a ratio of (1:1.9 *syn:anti*) where the selectivity was reversed. This striking result is most probably due to a different transition state which is required by the presence of the vinyl copper atom. Scheme 113 shows the influence of the copper atom in directing the oxygen atom of the aldehyde prior to the possibly favoured formation of metallocycle **105**. The *anti* selectivity can then be rationalised by a preferred

transition state **106** in which an interaction between the propyl group and the aromatic group of the aldehyde is avoided.

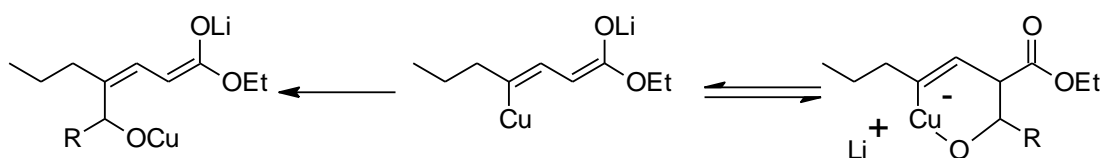


Scheme 113

Although there was a preference for the formation of the *anti* aldol product, some *syn* aldol product was still formed and this product can also be rationalised by a metallocycle involving the copper atom. Scheme 114 shows the *syn* product formed as a result of the ester and aromatic groups in an *anti* relationship to each other. The low temperature of the reaction was chosen not only to investigate any kinetically controlled diastereoselectivity but to avoid any reaction of the vinyl copper with the aldehyde in the event of any retro aldol reaction (Scheme 115).

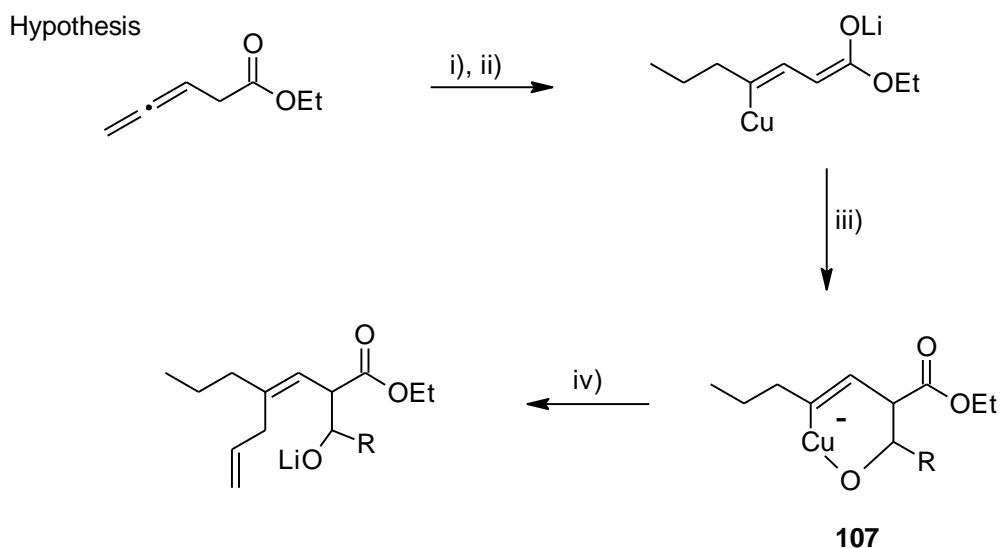


Scheme 114



Scheme 115

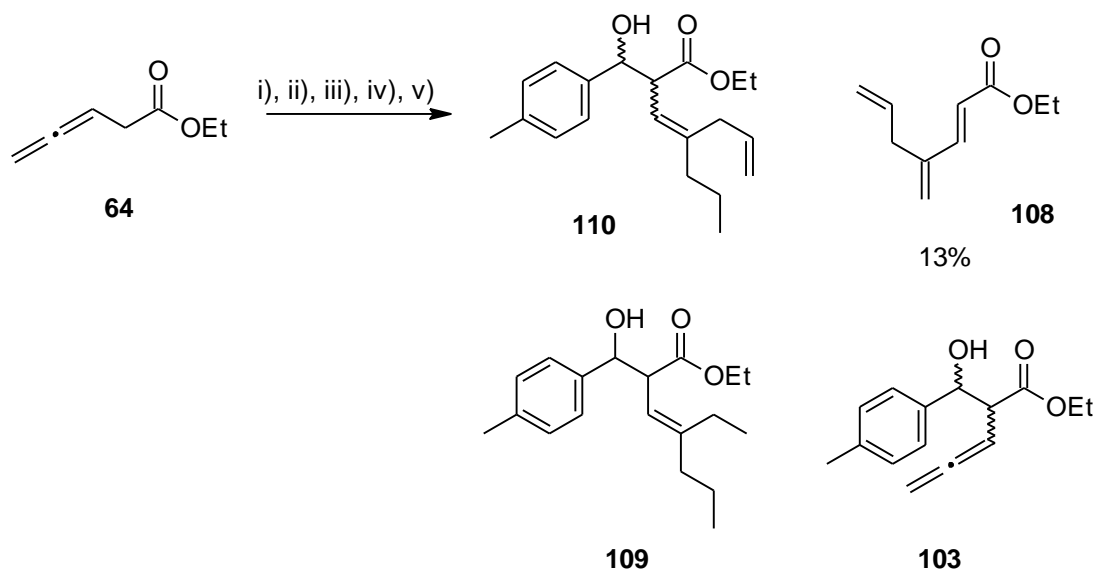
An attempt to marry the successful aldol reaction and the vinylcopper coupling with allyl bromide was thought to be possible if the aldol reaction was carried out first to form cuprate **107** (Scheme 116) which would be likely to be more reactive than the preceding vinylcopper and would hopefully react smoothly with allyl bromide.



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) EtCu.MgBrI (1.1 eq), -25 °C to -20 °C, 3 h; iii) RCHO; iv) AllylBr

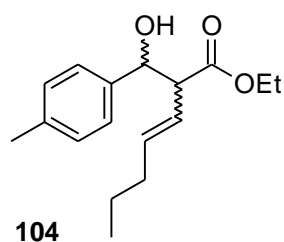
Scheme 116

In the event, as shown in Scheme 117, a complex reaction mixture ensued. Thus, along with the *anti* diastereoisomer of the aldol product **103** derived from the starting ester **64** and ester **108**, two inseparable mixtures were isolated. The first mixture had spectral properties which suggested the presence of side product **109** with the *syn* diastereomer of **110**. The second mixture eluted had spectral properties that suggested the presence of the desired product **110** together with the *syn* diastereoisomer of aldol product **103**. Measurement of the coupling constant of the signal at 3.62 ppm in the ¹H NMR spectrum suggested that the mixture contained the *anti* diastereoisomer of **110**. The tentative assignment of both diastereoisomers of product **110** suggested that the reaction was successful and the failure to find any of aldol product **104** implies that the aldol intermediate **107** was more efficient at reacting with allyl bromide than the vinylcopper as originally hypothesised above (Scheme 116).

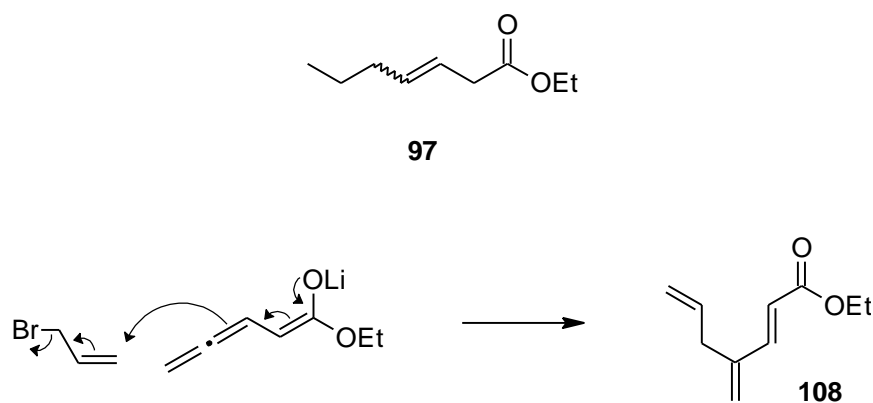


Reagents and conditions: i) : i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) EtCu.MgBrI (1.1 eq), -25 °C to -20 °C, 3 h; iii) *p*-MeC₆H₄CHO, -78 °C, 10 min; iv) AllylBr (3 eq), -20 °C, 2 h; v) NH₄Cl_(aq), -78 °C

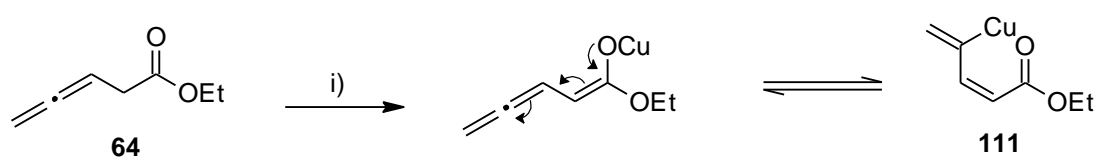
Scheme 117



Interestingly, no carbometallated product **97** was found in the reaction mixture however side product **108** was found in 13% yield. The formation of this product may arise from γ alkylation of the starting ester enolate with allyl bromide (Scheme 118). γ attack of ester dienolates is known⁷⁵ to take place with a copper(I) catalyst and an aldehyde as the electrophile (see Scheme 110) so it is not unreasonable for a copper ester enolate from ester **64** to form tautomeric structure **111** (Scheme 119).



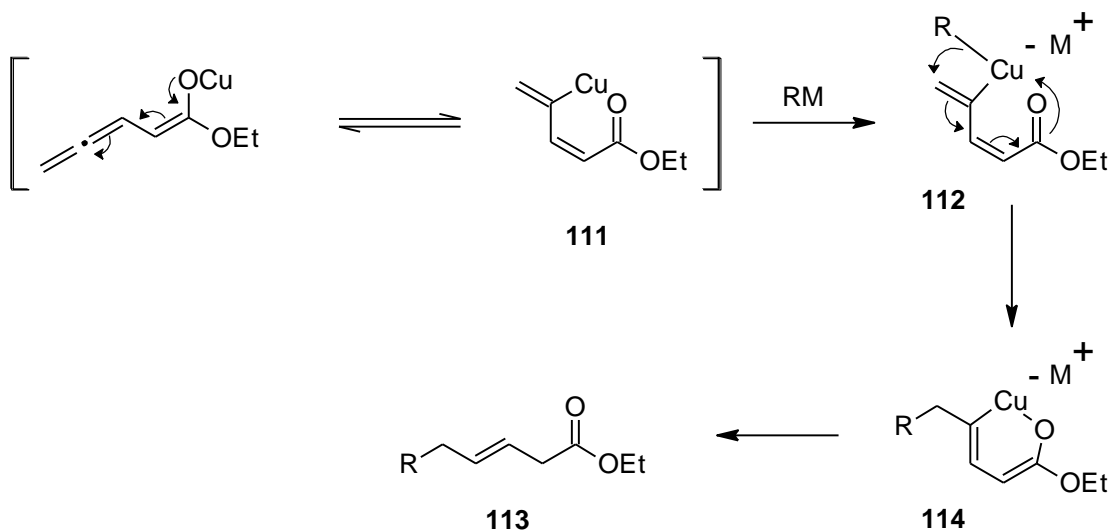
Scheme 118



Reagents and conditions: i) LDA, CuX

Scheme 119

The possibility of the tautomeric structure **111** evokes a possible alternative mechanism whereby addition of an organometallic reagent to **111** forms a cuprate **112** which then undergoes intramolecular conjugate addition of the carbanion 'R'. The stereoselective formation of ester **113** can then be rationalised by the formation of metalocycle **114** (Scheme 120). The fact that this mechanism is not possible for the carbometallation reactions of allenols and homoallenols suggests that it does not take place. However, the carbometallation reactions of ester enolates took considerably less time than those of homoallenols and so the two reactions may proceed via different mechanisms.



Scheme 120

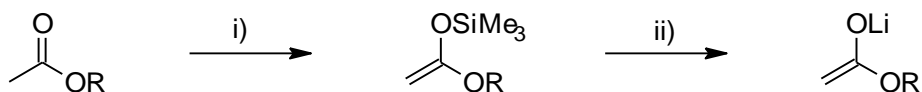
The research carried out into the carbometallation reactions of lithium ester enolates has led to exciting results in the development of enolate directed carbometallation, namely the high yields offered by a variety of Grignard reagents and the observation of the reduced deuterium incorporation which ultimately led to the introduction of organocopper reagents. This has led, in turn, to interesting stereochemical consequences for the geometry of the olefins produced. However, the anticipated reduced reactivity of the vinyl copper intermediate was capitalised upon in the form of selective reactions of the ester enolate with carbonyl substrates. Together with the successful coupling of the vinyl copper and allyl bromide the initial steps in elaboration of the “bis-carbanionic” intermediate were realised and in doing so additional valuable carbon-carbon bonds were formed.

2.2.4 Alternatives to LDA

Although encouraging, the results obtained from the carbometallations of ester substrates were plagued by the fact that the use of LDA as a base had forced us to

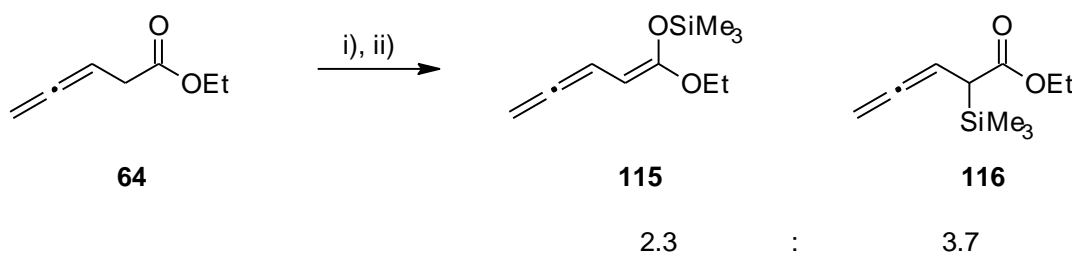
switch from a catalytic copper(I) system to a stoichiometric organocopper reagent and, in so doing, to lose the desirable specificity of the reaction. By far the most common method used to prepare lithium enolates is the use of LDA or another bulky secondary metal amide such as LiHMDS or LiTMP. However these reagents were not ideal for use in this chemistry as they were shown to interfere with the intermediate bis-carbanion. Seebach has reviewed the preparations of metal enolates and reported suggested alternative preparations if avoidance of a secondary amine is necessary.⁷¹

One method used to generate lithium enolates whilst avoiding the use of a secondary amine involves independent preparation of a silyl enol ether, followed by addition of methyllithium to generate a lithium enolate (Scheme 121). This approach is beneficial when using ketone enolates as both thermodynamic and kinetic control can be used to prepare either silyl enol ether from the same substrate. Unfortunately this method was not applicable to ester **64** as attempted preparation of the silyl enol ether resulted in a mixture of *O*-silylation **115** and *C*-silylation **116**, a phenomenon which is known to occur with some other esters (Scheme 122).⁸⁰



Reagents and conditions: i) LDA; ii) MeLi

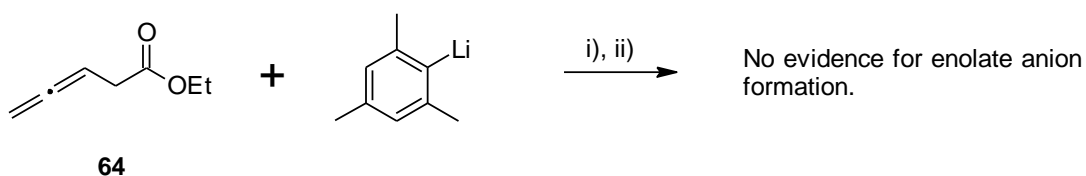
Scheme 121



Reagents and conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) ClSiMe₃, -78 °C to rt

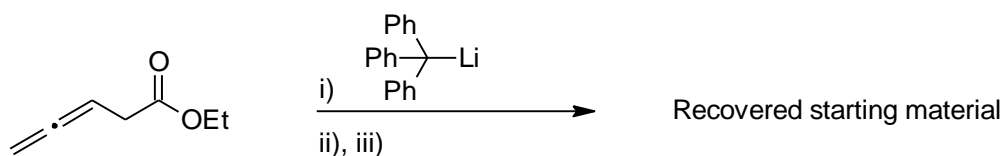
Scheme 122

Another method to form an enolate without LDA uses an organolithium reagent with a bulky carbon fragment such as a mesitylene or a trityl group. Attempted deprotonation of ester **64** with mesityllithium may have resulted in nucleophilic addition to the ester (Scheme 123) which is unsurprising as *tert*-butyllithium is known to preferentially add to ethyl esters rather than deprotonate. The attempted carbometallation using trityllithium afforded only starting material which could be due to the lower pK_a of triphenylmethane allowing it to be deprotonated by the Grignard reagent (Scheme 124).



Reagents and conditions: i) Et₂O, -78 °C; ii) DCl/AcOD/D₂O, -78 °C

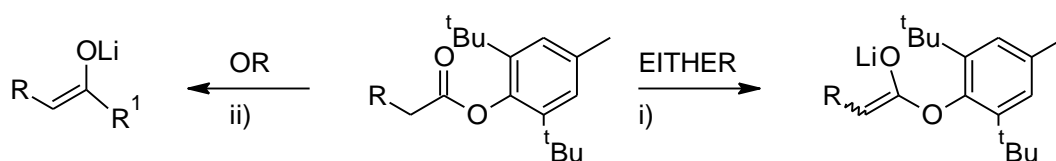
Scheme 123



Reagents and conditions: i) Et_2O , $-78\text{ }^\circ\text{C}$, 30 min; ii) PhMgBr (1.1 eq), CuI (10 mol%), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 2 h 30; iii) $\text{NH}_4\text{Cl}_{(\text{aq})}$, $-78\text{ }^\circ\text{C}$

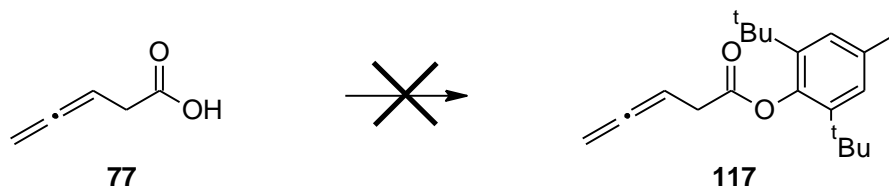
Scheme 124

Rather than adding steric bulk to the base used for enolate formation, it has been reported that the selection of a bulky ester can provide sufficient steric hindrance, such that an organolithium reagent can be used for deprotonation. One such bulky group used is the butylated hydroxytoluene (BHT) group which has been shown to react with normally nucleophilic *n*-butyllithium and deprotonate at the α position rather than add to the ester.⁸¹ One of the added benefits of the BHT group is that, due to its size, it is one of the few ester groups that will allow diastereo-controlled aldol reactions to take place.⁷² Another potential benefit of this choice is that an alternative mechanistic pathway via a ketene intermediate could also occur and hence give rise to a ketone enolate (Scheme 125).



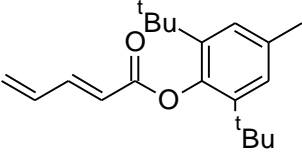
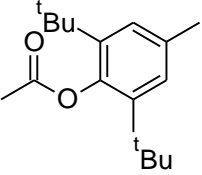
Reagents and conditions: i) ${}^n\text{BuLi}$; ii) R^1Li , $> -20\text{ }^\circ\text{C}$

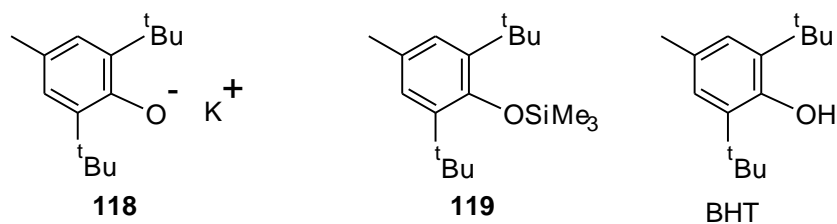
Scheme 125



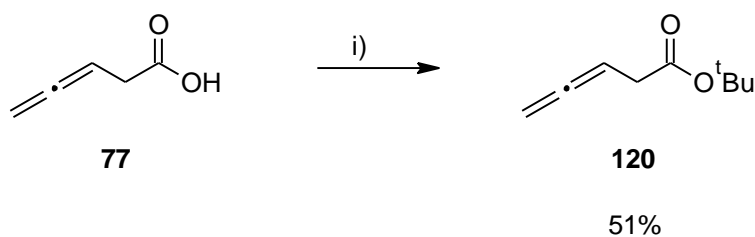
Scheme 126

Table 11

Starting material	Conditions	Result
77	1) (COCl) ₂ , DMF (cat.), DCM, 0 °C to rt; 2) 118	
77	1) EtOCOC ₂ H ₅ , NMM, DCM 0 °C; 2) 118	Trace product
77	1) DCC, DIPEA, DMAP (cat.), BHT, DCM, 0 °C to rt	No reaction
77	1) (TFA) ₂ O, PhMe, rt; 2) BHT	Trace product
	1) ⁿ BuLi, THF, -78 °C; 2) CuI, -78 °C; 3) <chem>C#CC(=O)OS(=O)(=O)c1ccc(C)cc1</chem> , -78 °C	Recovery of starting material
77	1) (COCl) ₂ , DMF (cat.), DCM, 0 °C to rt; 2) 119 , P ⁿ Bu ₃	No reaction
77	1) (COCl) ₂ , DMF (cat.), DCM, 0 °C to rt; 2) 119	No reaction



Unfortunately ester **117** could not be formed (Scheme 126) in spite of several attempts. These are documented in Table 11. Further consultation of the literature at this stage revealed a report from Dubois and co-workers⁸² which showed that isopropyl magnesium bromide was able to deprotonate *tert*-butyl esters without any undesirable addition occurring. The *tert*-butyl ester **120** was accordingly prepared from acid **77** with trifluoroacetic anhydride and *tert*-butanol (Scheme 127).

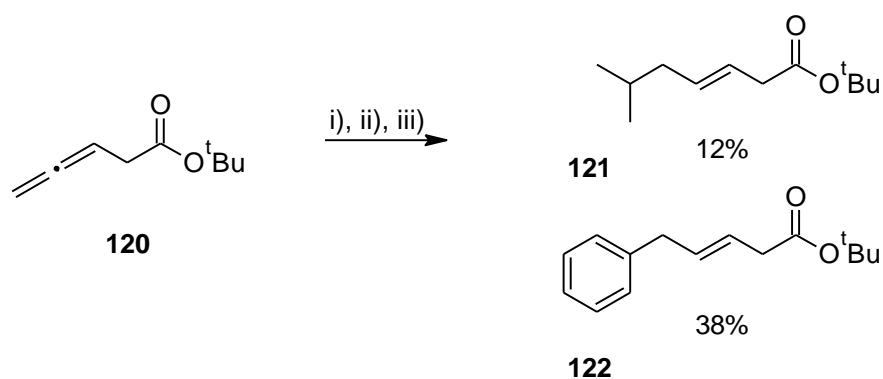


Reagents and conditions: i) *t*BuOH, (TFA)₂O, 0 °C, 35 min

Scheme 127

Ester **120** was treated with isopropyl magnesium bromide at -20 °C for 30 minutes followed by addition of copper(I)iodide and phenyl magnesium bromide to afford a mixture of esters **121** and **122** in respective yields of 12% and 38% (Scheme 128). It is not clear whether the competing carbometallation with isopropyl magnesium bromide was occurring at a similar rate to deprotonation with isopropyl magnesium

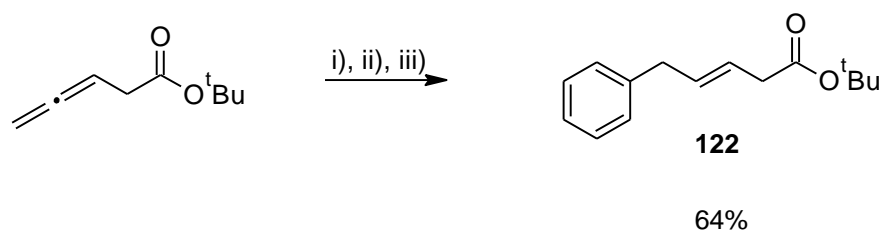
bromide or whether the deprotonation was not complete before addition of the copper(I)iodide and phenyl magnesium bromide.



Reagents and conditions: i) $^i\text{PrMgBr}$ (1 eq), Et_2O , $-20\text{ }^\circ\text{C}$, 30 min; ii) PhMgBr (1.1 eq), CuI (10 mol%), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 1 h 30; iii) $\text{NH}_4\text{Cl}_{(\text{aq})}$, $-78\text{ }^\circ\text{C}$

Scheme 128

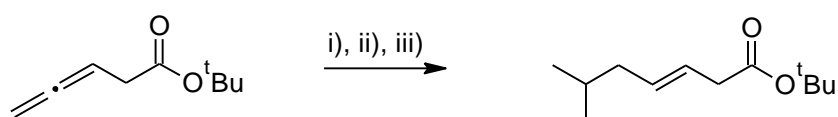
It was thought that by using phenyl magnesium bromide to deprotonate the ester as well as take part in the carbometallation the above mixture of products would be avoided and, as planned, ester **122** was isolated in good yield (64%) using this method (Scheme 129).



Reagents and conditions: i) PhMgBr (1 eq), Et_2O , $-20\text{ }^\circ\text{C}$; ii) PhMgBr (1.1 eq), CuI (10 mol%), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 2 h; iii) $\text{NH}_4\text{Cl}_{(\text{aq})}$, $-78\text{ }^\circ\text{C}$

Scheme 129

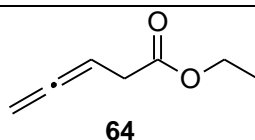
It was possible that the mixture of esters **121** and **122** (Scheme 128) arose because isopropyl magnesium bromide did not add as efficiently to the allene as phenyl magnesium bromide. This was unlikely as the additions of the two Grignard reagents to the lithium enolate of ethyl ester **64** (Table 7 and Scheme 92) were equally efficient, with both reactions giving high yields of products. Nevertheless a study was undertaken to investigate this efficiency as well as the stability of the reaction to temperature, the results of which are summarised in Table 12.



Reagents and conditions: i) ⁱPrMgBr (1 eq), Et₂O, Temp., 30 min; ii) CuI (10 mol%), ⁱPrMgBr (1.1 eq), -78 °C to Temp.; iii) NH₄Cl_(aq), -78 °C

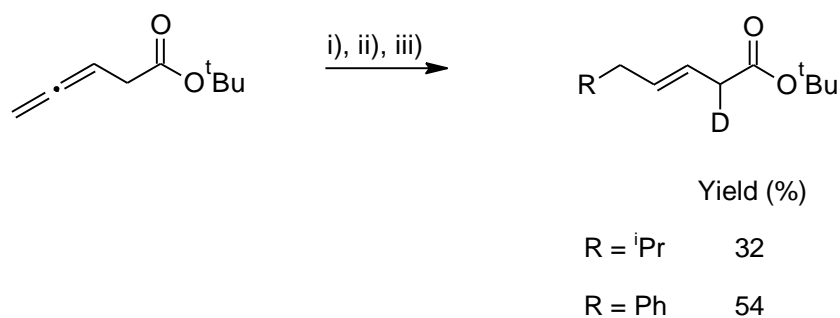
Table 12

Entry	Deprotonation Temperature (°C)	Reaction Temperature (°C)	Time (h)	Conversion by ¹ H NMR (%)
1	-20	0	4	33
2	0	0	4	29
3	-78	0 to rt	6	53
4	-20	0 to rt	6	51
5	-20	rt	7	74 (28 isolated yield)



The results from Table 12 show that the yields from carbometallation of *tert*-butyl esters with isopropyl magnesium bromide is significantly lower than with the other ester enolates. The more bulky *tert*-butyl ester enolate is also a magnesium bromide enolate rather than the lithium enolate in the case of the ethyl ester. Conversion to product was low unless the temperature was raised and the reaction left for a longer time. However, this resulted in significant loss of material as illustrated by the low isolated yield compared with the high conversion in Entry 5. With respect to the issue of ester enolate stability at higher temperatures it should be noted that *tert*-butyl esters are known to be more stable as demonstrated by the fact that lithium *tert*-butyl acetate is an air-stable white solid.⁸³

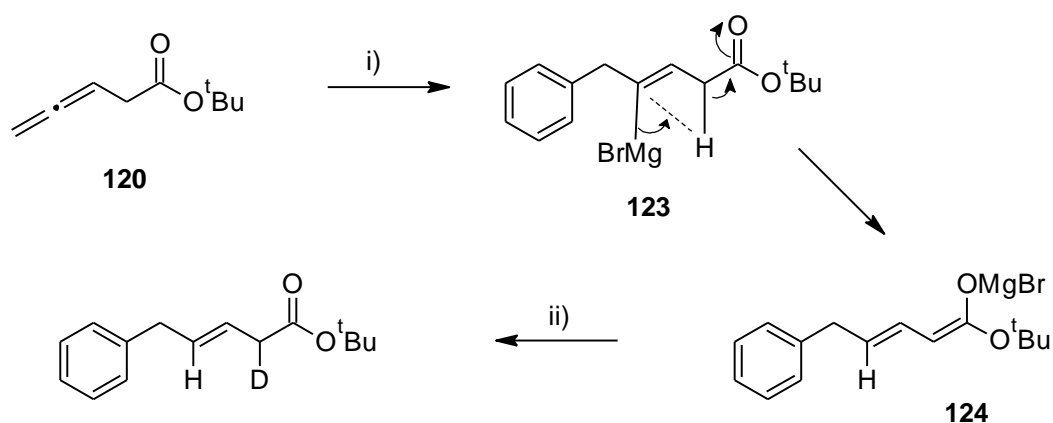
In order to probe the carbanionic nature of the intermediate the deuterium experiment was then carried out as had been done for other substrates. Surprisingly there was no deuterium incorporation in the γ position and full deuterium incorporation in the α position (Scheme 130). The deuteration experiment was repeated using phenyl magnesium bromide (Scheme 130) as it had been shown to give a higher yield of carbometallation product and the result was identical to that observed in the reaction with isopropyl magnesium bromide.



Reagents and conditions: i) RMgBr (1 eq), Et₂O, -20 °C, 30 min; ii) RMgBr (1.1 eq), CuI (10 mol%), -78 °C to rt, 7 h; iii) DCl/AcOD/D₂O

Scheme 130

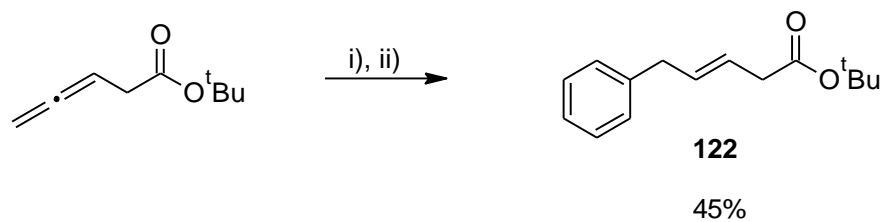
From the results shown in Scheme 130 it was thought that a possible reason for the absence of deuterium in the γ position was because carbometallation was occurring at a faster rate than the competing deprotonation of the α proton. The reaction was thought to proceed as depicted in Scheme 131 whereby carbometallation of the allenic ester **120** by phenyl magnesium bromide leads to intermediate **123**. Because the pKa of the vinylic proton is higher than that of the ester, the α proton can be removed by the vinylic Grignard reagent either in an intra (as shown) or in an intermolecular fashion, leading to intermediate **124** where the enolate was been fully formed as demonstrated by full incorporation of deuterium in the α position.



Reagents and conditions: i) PhMgBr; ii) D⁺

Scheme 131

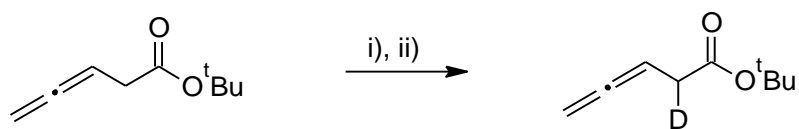
This hypothesis was further supported by the reaction shown in Scheme 132 where only 1.1 equivalents of phenyl magnesium bromide was used. Formation of ester **122** in 45% yield proved that carbometallation of the allene was competing at a faster rate than deprotonation, and it is certainly possible that the directing tether for this reaction is the carbonyl group.



Reagents and conditions: PhMgBr (1.1 eq), CuI (10 mol%), Et₂O, -78 °C to 0 °C, 2 h; ii) NH₄Cl_(aq)

Scheme 132

It was thought that allowing deprotonation of the ester with the more basic isopropyl magnesium bromide to take place for a longer time would ensure that the enolate was formed prior to the carbometallation. A control reaction was therefore performed in order to understand the efficiency of enolate anion formation, whereby a reaction was quenched with deuterium oxide resulting in the incorporation of 40% deuterium in the α position (Scheme 133).

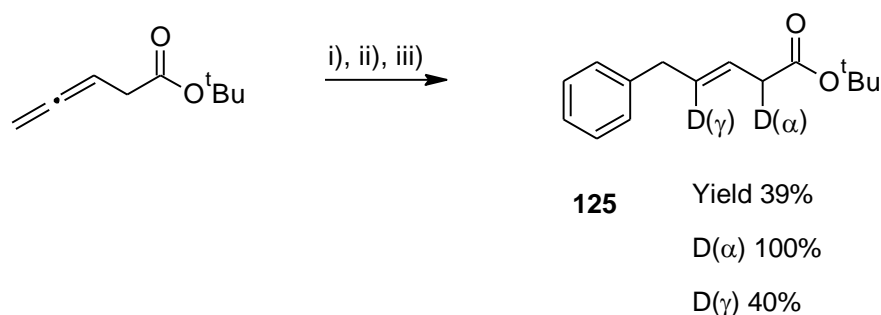


Reagents and conditions: i) ⁱPrMgBr, Et₂O, -20 °C, 1 h; ii) DCl/AcOD/D₂O, -78 °C

Scheme 133

The carbometallation experiment was then repeated using the “improved” enolate formation conditions and a deuterium quench and resulted in affording ester **125** in

39% yield with 100% deuterium incorporation in the α position and 40% incorporation in the γ position (Scheme 134).



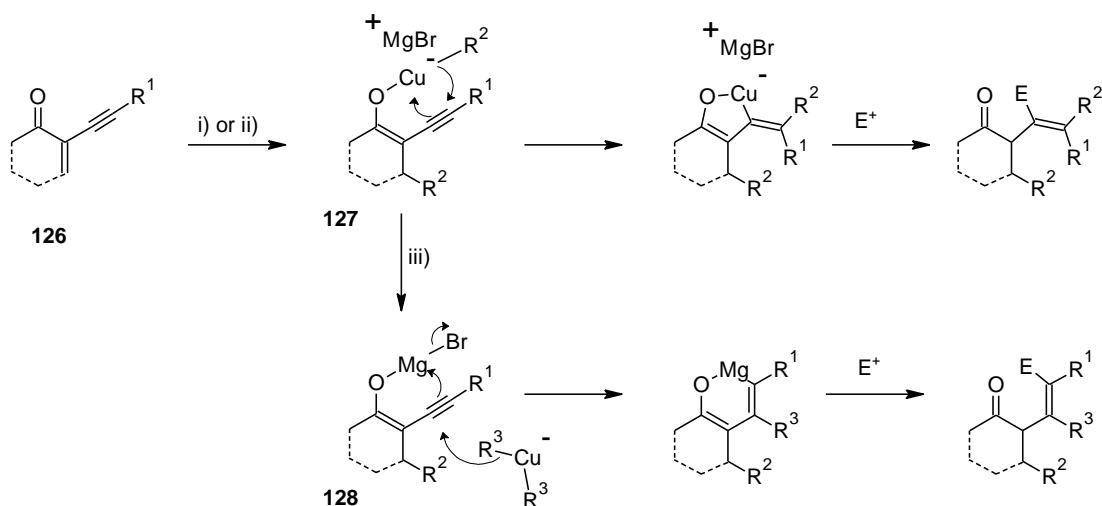
Reagents and conditions: i) $i\text{-PrMgBr}$ (1 eq), Et_2O , $-20\text{ }^\circ\text{C}$, 1 h; ii) PhMgBr (1.1 eq), CuI (10 mol%), $-78\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$, 5 h; iii) $\text{DCI/AcOD/D}_2\text{O}$, $-78\text{ }^\circ\text{C}$

Scheme 134

The most significant result from this brief investigation into the addition reactions of *tert*-butyl esters was the failure of any deuterium to be incorporated in the vinylic position, which, if the mechanism in Scheme 131 is correct, highlights the potential efficiency of carbonyl directed carbometallation of allenic esters. The relatively slow deprotonation is of concern if further research involving *tert*-butyl ester enolates is to take place and is an interesting result considering that *tert*-butyl esters are commonly deprotonated at $-78\text{ }^\circ\text{C}$ using LDA. Sequential stoichiometric carbocupration followed either by ester enolate formation or by quenching of the vinyl copper intermediate and subsequent deprotonation may also prove to be possible.

2.2.5 Enone substrates

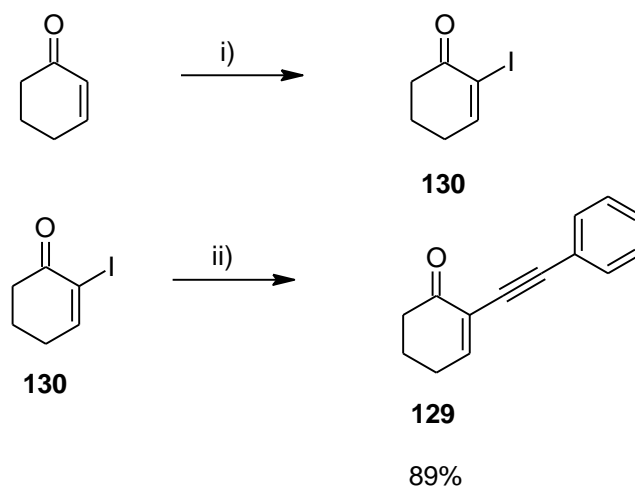
In parallel with the above studies, and with the same objective of using an enolate tether whilst avoiding the use of LDA as a base, an adventurous strategy involving enone substrates was being investigated. The essence of the idea was based on the fact that the conjugate addition of organocuprates or the copper(I) catalysed addition of Grignard reagents to enones are known to proceed through an enolate intermediate. Not only would this enolate forming reaction avoid the use of LDA but also, as shown in Scheme 135, the envisaged transformation involving conjugate addition to enone **126** would also add yet another carbon-carbon bond forming step. Depending on whether a stoichiometric cuprate or a copper(I) catalyst was used intermediates **127** and **128** respectively, would be formed. A further exciting possibility in this approach was to use a chiral transition metal catalysed conjugate addition in the first step (e.g. Feringa⁸⁴).



Reagents and conditions: i) $R^2_2CuMgBr$; ii) R^2MgBr , Cu(I) cat.; iii) R^3MgBr

Scheme 135

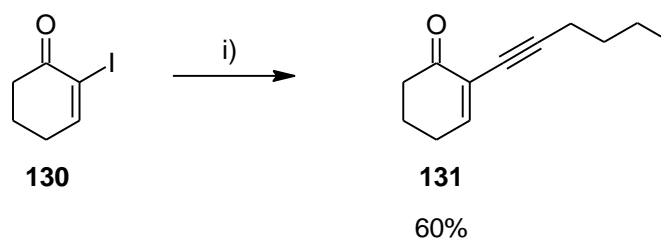
Enone **129**, chosen for its ease of synthesis, was thus prepared via a Sonogoshira coupling of iodo-enone **130** with phenylacetylene (Scheme 136). Unfortunately attempted carbometallation using either phenyl or ethyl magnesium bromide with a copper(I)iodide catalyst afforded a complex mixture.



Reagents and conditions: i) I_2 , K_2CO_3 , DMAP, THF/ H_2O , rt, 2 h 30; ii) $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%), CuI (10 mol%), PhCCH (2 eq), $^i\text{Pr}_2\text{NH}$ (3 eq), THF, 0 °C, 45 min

Scheme 136

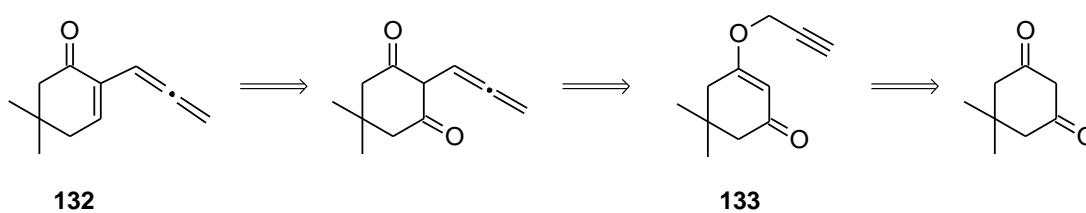
Enone **131** was then prepared from the same iodide **130** (Scheme 137) as it was thought that the *n*-butyl group would pose less problems of steric hindrance. However, the attempted carbometallation using either phenyl or ethyl magnesium bromide and catalytic copper(I)iodide again afforded a complex mixture.



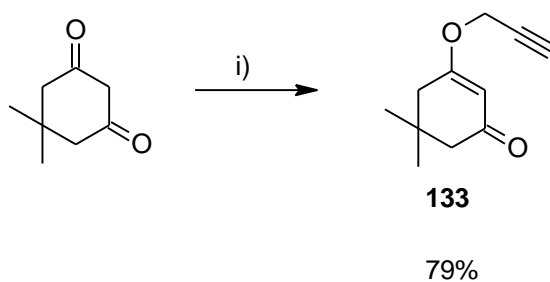
Reagents and conditions: i) $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%), CuI (10 mol%), ${}^n\text{BuCCH}$ (2 eq), ${}^i\text{Pr}_2\text{NH}$ (3 eq), THF, 0 °C, 45 min

Scheme 137

Because of the success of the carbometallation of allenes in the literature as well as the results reported in this chapter it was thought that an enone bearing an appended allene would be more likely to undergo carbometallation. A route to enone **132** was therefore proposed involving a [3,3 σ] sigmatropic rearrangement of vinylogous ester **133** followed by reduction and dehydration (Scheme 138). Vinylogous ester **133** was prepared according to a modified literature procedure from propargyl alcohol and dimedone under Dean and Stark conditions (Scheme 139).



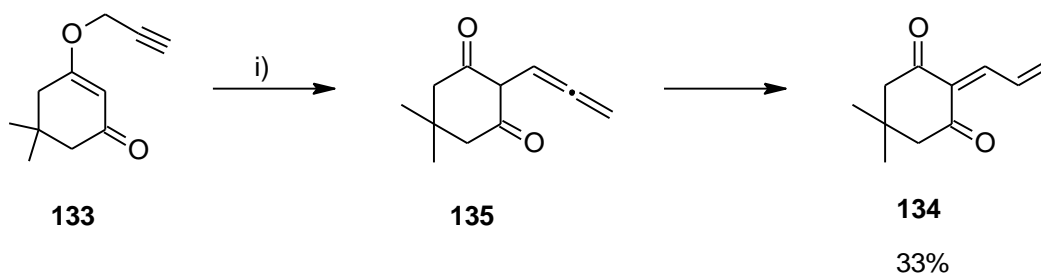
Scheme 138



Reagents and conditions: i) Propargyl alcohol (2 eq), PTSA (5 mol%), Benzene, reflux, Dean & Stark, 2 h

Scheme 139

The Claisen rearrangement of **133** was then attempted by refluxing in xylene (Scheme 140). Unfortunately ^1H NMR analysis of the purified material indicated that, whilst the rearrangement was successful, a subsequent rapid isomerisation to the conjugated diene **134** had occurred.

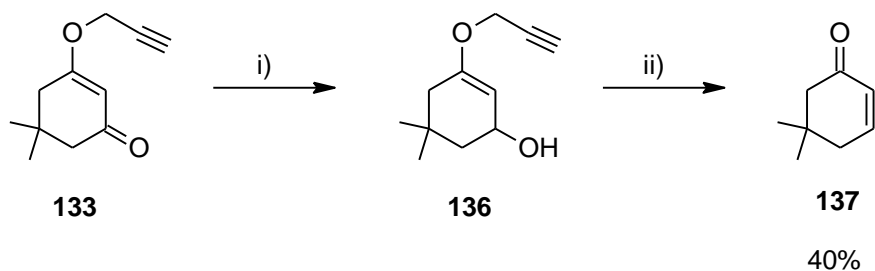


Reagents and conditions: i) Xylene, reflux, 3 h

Scheme 140

To circumvent this problem it was thought that reduction of the carbonyl group would lead to a rearrangement product which would not be susceptible to

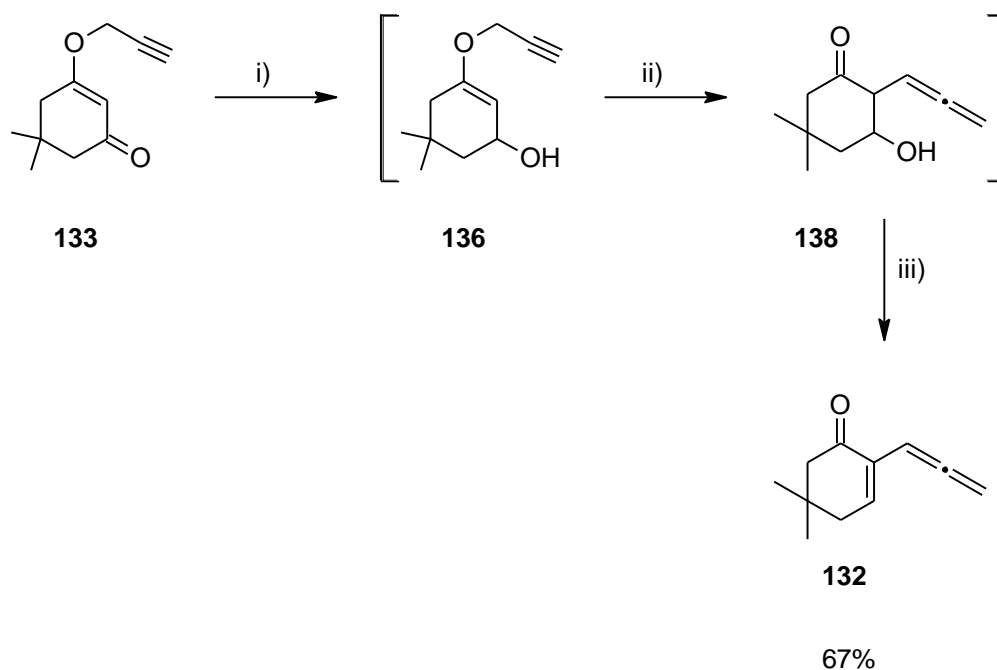
isomerisation since the α proton would not be as acidic as in diketone **135**. Accordingly, reduction of vinylogous ester **133** with lithium aluminium hydride afforded alcohol **136**. However, attempted purification by column chromatography resulted in unwanted dehydration and hydrolysis of the enol ether to give enone **137** (Scheme 141).



Reagents and conditions: i) LiAlH_4 , Et_2O , 0°C , 1h then H_2O and workup; ii) Silica gel

Scheme 141

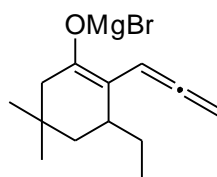
In order to avoid the disastrous formation of enone **137**, it was then decided that alcohol **136** be used directly without purification in the rearrangement step. Pleasingly, reduction of vinylogous ester **133** followed by reflux in xylene for 3 hours gave allene **138** as evidenced by an infrared spectrum of the crude material showing an absorbance at 1957.8 cm^{-1} . The crude product was treated with *para*-toluene sulfonic acid under Dean and Stark conditions to afford the target allene **132** in a very efficient 53% overall yield starting from dimedone (Scheme 142).



Reagents and conditions: i) LiAlH_4 , Et_2O , $0\text{ }^\circ\text{C}$, 1 h then H_2O and workup; ii) xylene, reflux, 3 h; iii) PTSA (5 mol%), Benzene, Dean & Stark, 30 min

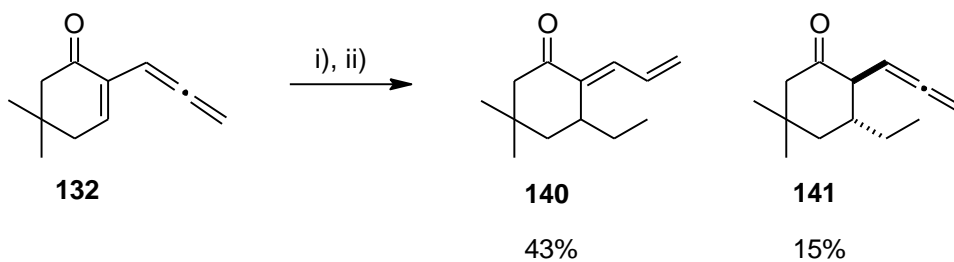
Scheme 142

As in the case of earlier substrates, the efficiency of the formation of enolate intermediate **139** (Figure 6) was studied. Enone **132** was added to a mixture of ethyl magnesium bromide and catalytic copper(I)iodide at $-78\text{ }^\circ\text{C}$. TLC analysis indicated the consumption of starting material after 30 minutes and, on work up the reaction afforded a mixture of ketones **140** and **141** which arose from protonation at either the α position or the γ positions respectively of enolate **139** (Scheme 143).



139

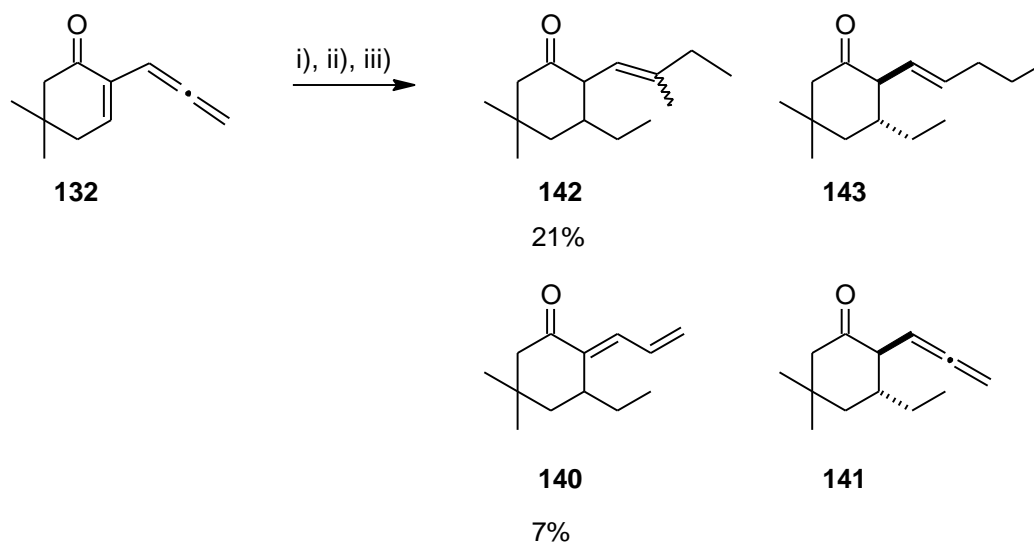
Figure 6



Reagents and conditions: i) EtMgBr (1.1 eq), CuI (10 mol%), Et₂O, -78 °C, 45 min;
ii) NH₄Cl_(aq)

Scheme 143

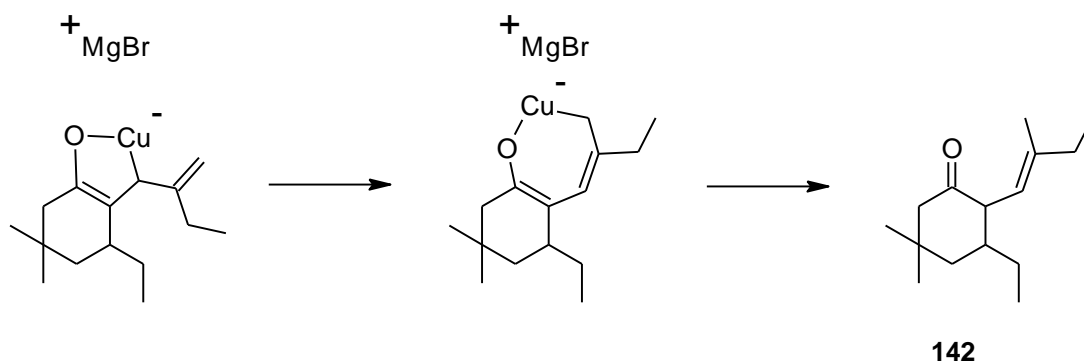
Although the reaction did not give a high combined yield of **140** and **141** the conditions were thought to be a suitable starting point for investigation of a subsequent carbometallation reaction. Enone **132** was therefore treated with 2.1 equivalents of ethyl magnesium bromide and 10 mol% of copper(I)iodide at -78 °C to generate the enolate intermediate followed by warming to 0 °C in an attempt to affect carbometallation. Quenching with ammonium chloride followed by chromatography afforded **142** along with **140**. A third fraction was thought to be a mixture **141** and **143** with the ¹H NMR spectrum indicating the alkene in **143** to be of (*E*) geometry (Scheme 144).



Reagents and conditions: i) EtMgBr (2.1 eq), CuI (10 mol%), -78 °C, 30 min; ii) -78 °C to 0 °C; iii) NH₄Cl_(aq), -78 °C

Scheme 144

The formation of **142** is very interesting as, although the stereochemistry is not known, the regiochemistry of addition is different from all of the other results with allenes in this chapter. The carbon-carbon bond has been formed at the central carbon of the allene with the carbon-metal bond at the terminus. No other examples of ketone enolates or α -substituted enolates have been carried out so it is not known if one of these caused this striking result. Perhaps the geometry of alkene is (*E*) as, if the addition is assisted in an intramolecular fashion, a 7-membered ring can be postulated. The possibility of a 5-membered ring by a 1,3 metal migration should not be overlooked (Scheme 145).



Scheme 145

The relative amounts of Grignard reagent and copper(I)iodide were then varied and the results of these experiments are shown in Table 13. The conversion to carbometallation products **142** and **143** was higher when an extra equivalent of ethyl magnesium bromide was used which is not surprising. However, when a stoichiometric organocuprate, derived from ethyl magnesium bromide, was used (Entry 3) the conversion was better than that of Entry 2 even though there were fewer equivalents of Grignard reagent. The difference between Entries 2 and 3 being that either a magnesium enolate **139** or the stoichiometric copper enolate **144** is formed (Figure 7).

Table 13

Entry	EtMgBr (eq)	CuI	Relative ratios of products ^(a) 142 : 143 : 140 : 141
1	2.1	10 mol%	2.19 : 1.4 : 1 : 0.3
2	3.1	10 mol%	4.57 : 1.58 : 1 : 0
3	2.2	1.1 eq	1 : 0.4 : 0 : 0

^(a) as indicated by ¹H NMR of crude material

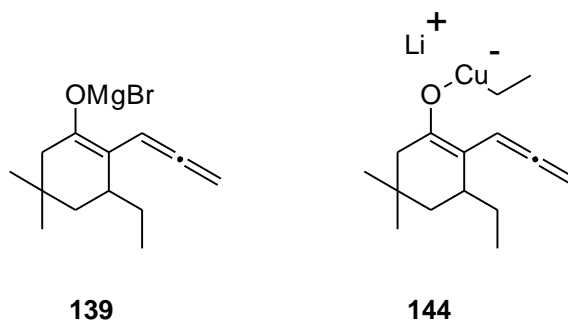
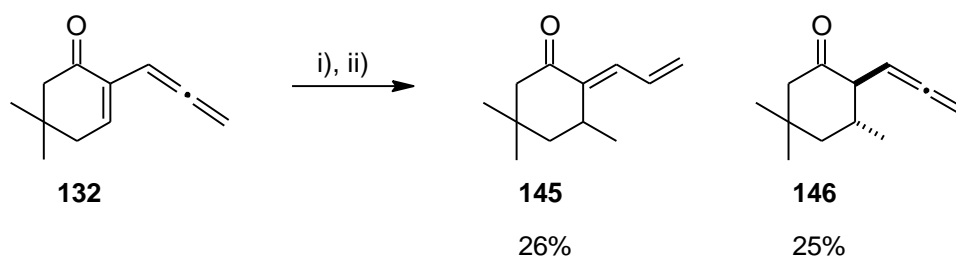


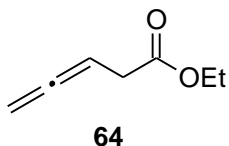
Figure 7

The reactivity of a stoichiometric Gilman cuprate towards enone **132** was also studied. Although an excess of the organometallic reagent was used only the conjugate addition products **145** and **146** were isolated and no carbometallation products were detected (Scheme 146). The implication of a magnesium halide bridge in the carbometallation reactions of Normant et al.³⁹ and the difference in reactivity of organolithium and Grignard derived cuprates (*vide supra*) add to the argument that the use of magnesium salts favours carbometallation. However the reaction depicted in Scheme 146 was conducted at $-20\text{ }^{\circ}\text{C}$ and it is possible that carbometallation of enone **132** requires higher temperatures than for the ethyl ester substrate **64** due to the substitution at the α position.

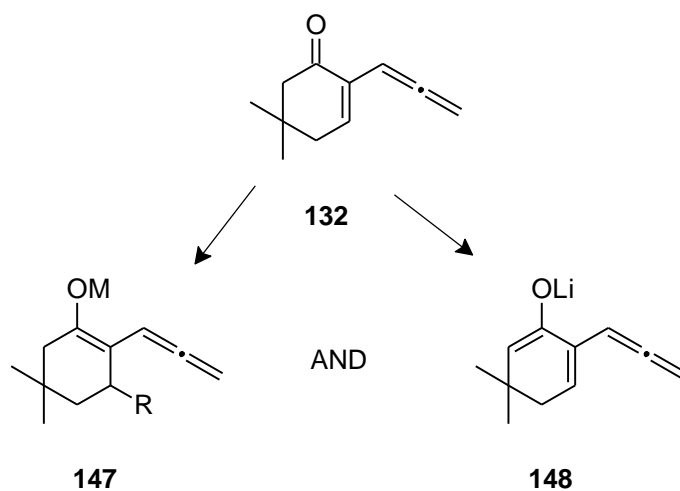


Reagents and conditions: i) $\text{Me}_2\text{CuLi}\cdot\text{LiI}$, $-40\text{ }^{\circ}\text{C}$ to $-20\text{ }^{\circ}\text{C}$, 4 h 30 min; ii) $\text{NH}_4\text{Cl}_{(\text{aq})}$, $-78\text{ }^{\circ}\text{C}$

Scheme 146



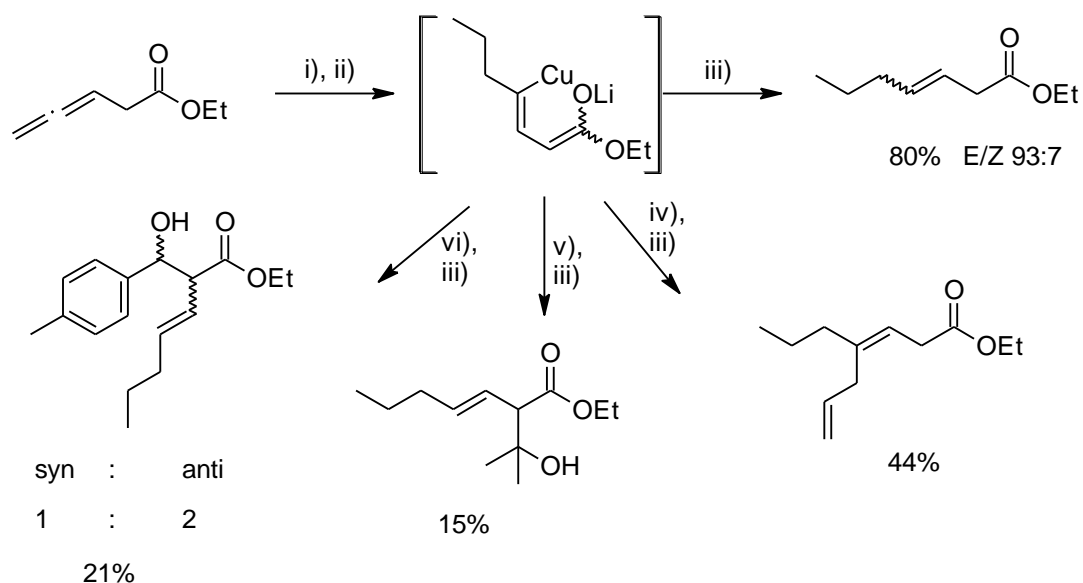
Unfortunately, due to time constraints, further work in this exciting area was not possible. Although the preliminary results suggest that enone **132** is a suitable substrate for enolate directed carbometallation, much more work is required to confirm the tentative structure of **143** as well as to ascertain the stereochemistry and understand the formation of **142** which goes against the regiochemistry of the other copper(I) mediated carbometallation reactions of allenes. The enone **132** can, of course give rise not only to the thermodynamic enolate **147** by conjugate addition, but also to the kinetic enolate **148** by deprotonation and this aspect is also worthy of further investigation (Scheme 147).



Scheme 147

2.3 Summary, Conclusions and Perspectives

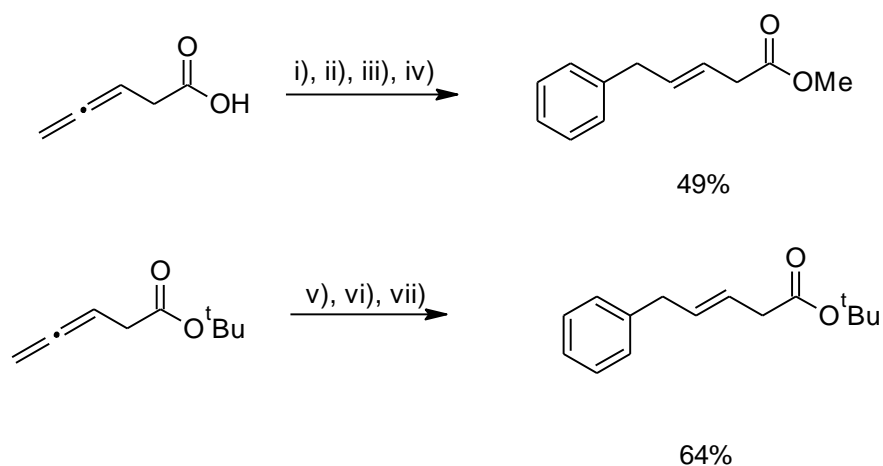
The foregoing discussion of the results obtained during this research programme has not only proven the concept of enolate directed carbometallation but has also demonstrated the synthetic utility of the preparation and exploitation of the novel 'bis-carbanion' intermediate in producing complex products using highly desired carbon-carbon bond forming processes. The efficient carbometallation reactions of the ethyl esters allowed, after the introduction of organocopper reagents, exploratory chemistry to investigate the reactivity of the aforementioned novel intermediate with pleasing results as highlighted in Scheme 148. The careful choice of electrophile was shown to control selective reaction of only one of the carbanions. The results obtained thus far only whet the appetite for further work into this exciting and potentially powerful research area.



Reagents and Conditions: i) LDA (1 eq), Et₂O, -78 °C, 30 min; ii) EtCu.MgBrI (1.1 eq), -20 °C, 3 h; iii) NH₄Cl_(aq), -78 °C; iv) AllylBr (3.1 eq), -20 °C, 2 h; v) Acetone (1.1 eq), -20 °C, 2 h; vi) *p*-MeC₆H₄CHO, -78 °C, 10 min

Scheme 148

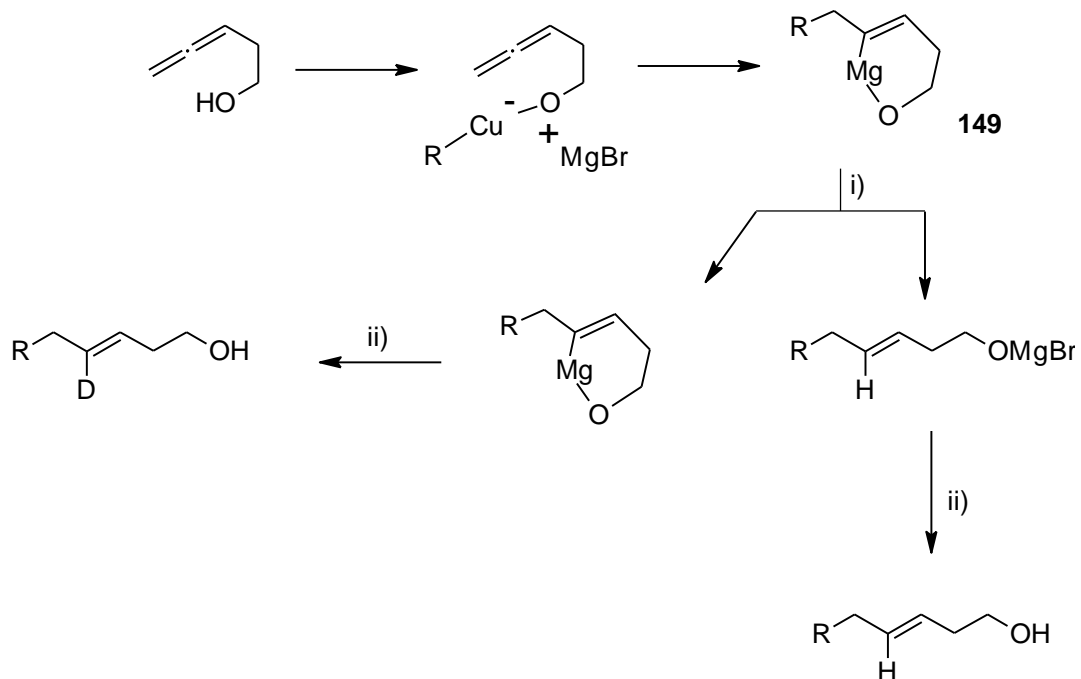
Whereas the carbometallation reactions of the lithium ethyl ester enolates afforded products with high yields with various Grignard reagents, the comparative reactions of carboxylic acid dianions and magnesium *tert*-butyl ester enolates differed in their scope (Scheme 149). Phenyl magnesium bromide was significantly better at addition to the allene unit than alkyl Grignard reagents for the latter two substrates. It was noted that the enolate reaction mixture was heterogeneous in comparison to the homogeneous lithium ester enolate solution. The carbometallation reactions of carboxylic acid dianions and magnesium *tert*-butyl ester enolates may therefore benefit from the use of a more suitable solvent. THF has been shown to be a poor solvent for carbometallation presumably due to it being too coordinating. However, solvents such as methyl *tert*-butyl ether, benzene or toluene or an additive such as dimethyl sulfide may improve the solubility of the reaction mixtures and possibly the efficiency of the reaction. These reactions did not suffer from the unwanted presence of diisopropylamine and the success of these reactions may therefore allow a more rapid advancement of this research.



Reagents and conditions: i) ⁿBuLi (2.5 eq), ⁱPr₂NH (50 mol%), Et₂O, -78 °C to rt, 1 h; ii) PhMgBr (1.1 eq), CuI (10 mol%), -78 °C to rt, 16 h; iii) NH₄Cl_(aq); iv) MeI (3 eq), K₂CO₃ (5 eq), acetone, rt, 20 h; v) PhMgBr (1 eq), Et₂O, -20 °C; vi) PhMgBr (1.1 eq), CuI (10 mol%), -78 °C to 0 °C, 2 h; vii) NH₄Cl_(aq), -78 °C

Scheme 149

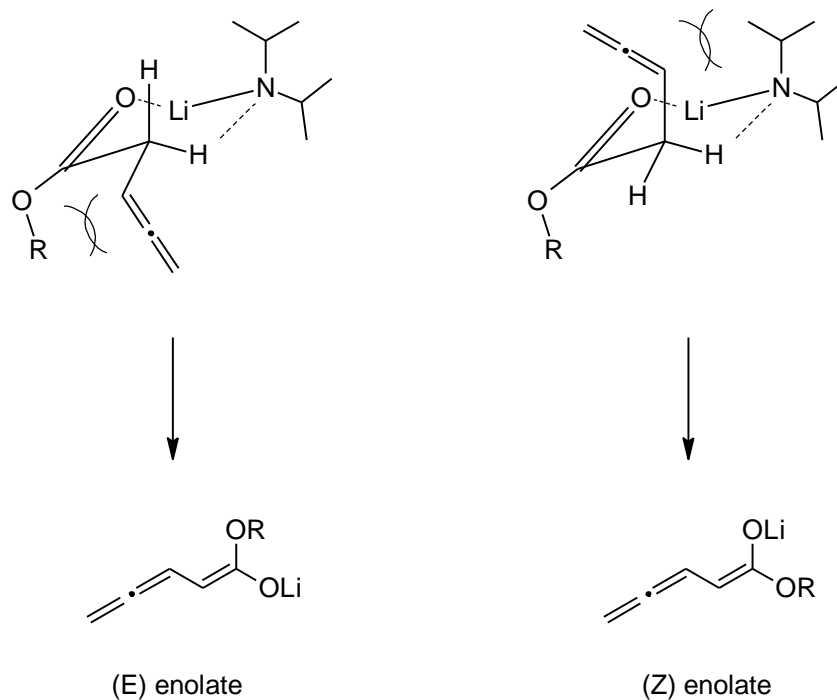
It was suggested that the problems encountered with deuterium incorporation in the carbometallation reactions involving ethyl ester enolates were due one of the two possible intermediates being responsible for protonation by diisopropylamine (Scheme 95, page 96). The experiment depicted in Scheme 150 using the parent homoallenol would examine the basicity of the vinyl Grignard moiety in the postulated metallocycle **149** with respect to diisopropylamine. As the Grignard shown below possesses a metal alkoxide ligand, it would bear some resemblance to the (*Z*) enolate carbometallation intermediate discussed earlier (Scheme 95). It could be ascertained how basic metallocycle **149** is by treatment with diisopropylamine followed by deuterium chloride.



Reagents and conditions: i) iPr_2NH , $0\text{ }^\circ C$; ii) $DCl/AcOD/D_2O$

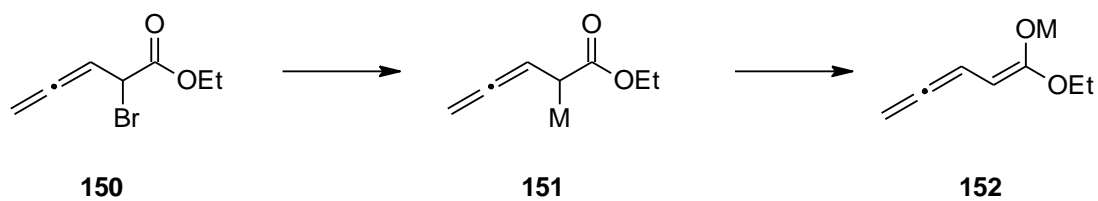
Scheme 150

If a (*Z*) enolate is necessary in order to avoid the problems of diisopropylamine then two possible solutions have been devised. The first, shown in Scheme 151, is concerned with the formation of the ester enolate. The transition states shown below are generated from the Ireland model and show that a bulky ester group could afford a greater proportion of (*Z*) enolate.



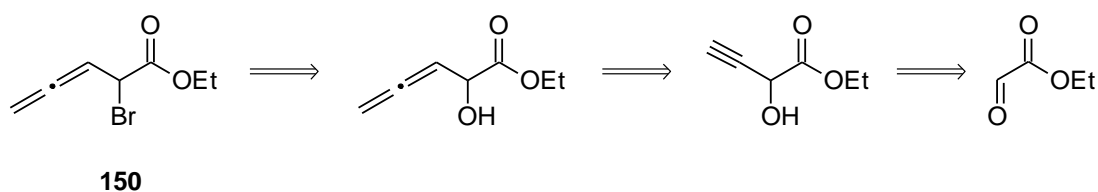
Scheme 151

The second solution involves the preparation of α -halo ester **150** which is proposed to undergo a metal-halogen exchange to give α -metalo ester **151**. This would then rapidly form ester enolate **152** and is thought to be of exclusively (*Z*) geometry based on literature precedent for ketone substrates (Scheme 152).⁷² A proposed retrosynthesis of this ester is shown in Scheme 153 and involves addition of an acetylide anion to ethyl glyoxalate followed by a Crabbé homologation and finally, conversion to the α -halo ester **150**.



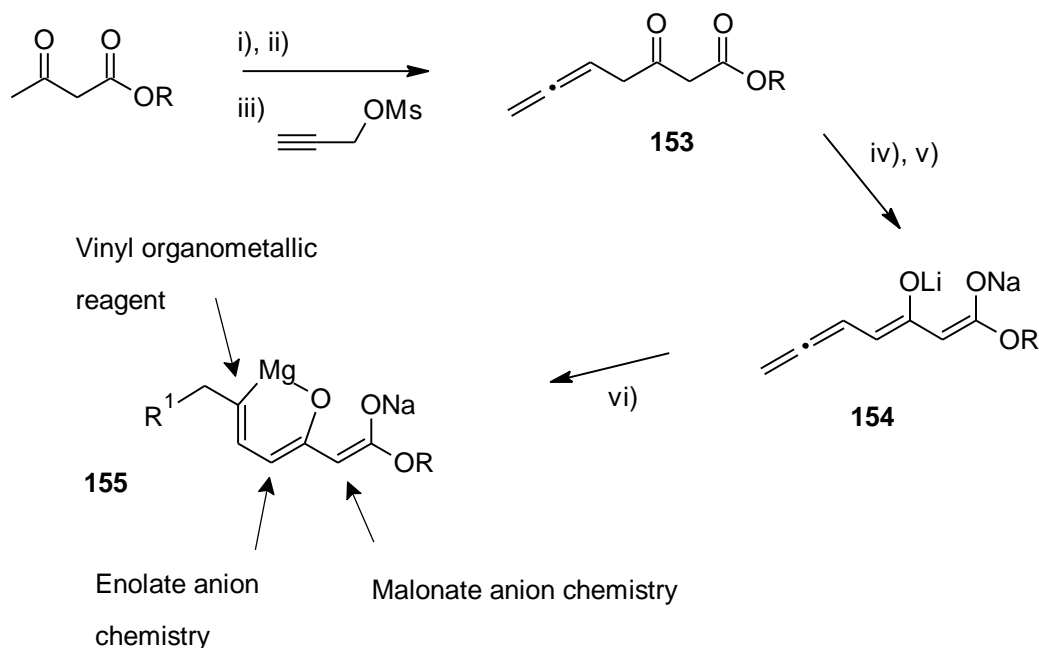
Reagents and conditions: i) ^tBuM

Scheme 152



Scheme 153

An alternative to avoiding the use of LDA is outlined in Scheme 154 and involves the preparation of β -keto ester **153**. Treatment of this β -keto ester with sodium hydride followed by *n*-butyllithium would afford dianion **154** which, after subsequent carbometallation, would give rise to trianion **155**.

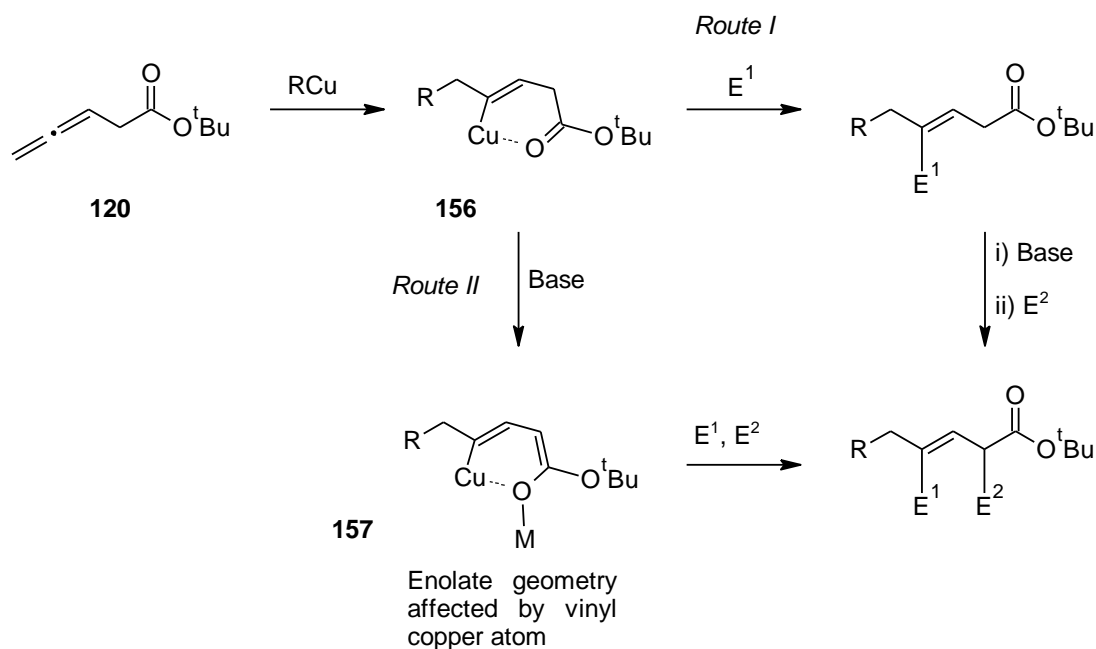


Reagents and Conditions: i) NaH; ii) ${}^n\text{BuLi}$; iii) CuI (cat.); iv) NaH; v) ${}^n\text{BuLi}$; vi) R^1MgBr , CuI (cat.)

Scheme 154

It was suggested that the carbometallation reactions of *tert*-butyl esters were directed by the carbonyl group either prior to enolate formation or at a comparable rate. This suggestion raises a question as to whether an enolate is a prerequisite for directed carbometallation of carbonyl containing allenes or alkynes. The ramification of this question, if the answer is no, is that it is now possible to form and react the vinyl and enolate anions independently of each other. However, the reaction would still have the potential to form 3 carbon-carbon bonds in one pot. This strategy, outlined in Scheme 155, involves the carbometallation of ester **120** with a non-basic organocopper reagent to form an intermediate vinyl copper reagent **156**. Two possibilities now exist. The first of these (Route I) involves reaction of the vinylic carbanion with an electrophile (E^1) followed by formation of an enolate anion and finally, reaction of this enolate with the second electrophile (E^2). The separation of

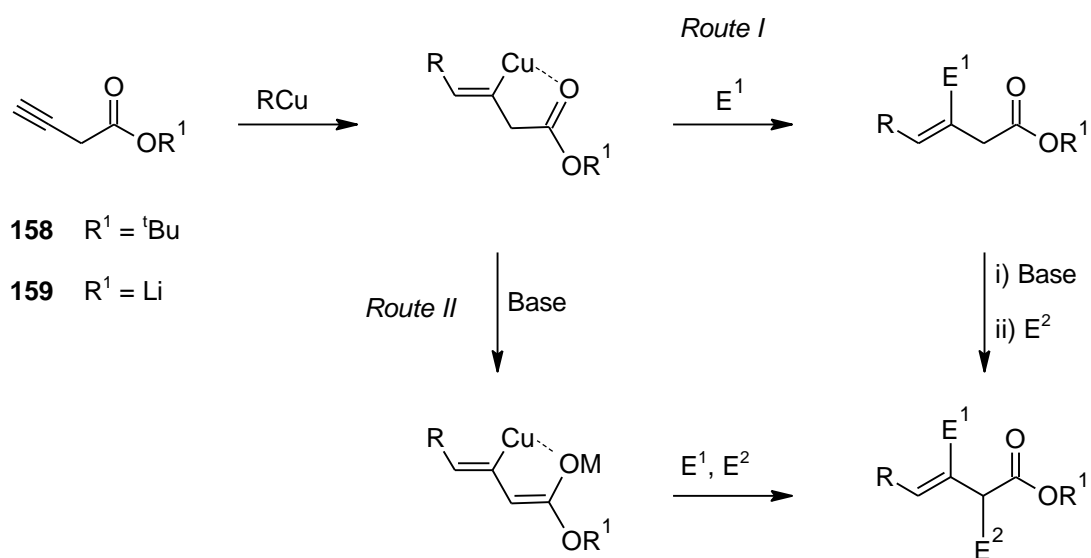
these two reactions (Route I) has the obvious advantage that the objective of selective reacting of only one of the carbanions is circumvented. The second route is, in essence, an alternative method for the formation of a “bis-carbanionic” intermediate by deprotonation of vinyl copper intermediate **156** (Route II). In this case, intermediate **157** could then be further elaborated by reactions with electrophiles (E^1 and E^2). It should be noted that the deprotonation of intermediate **156** is likely to be affected by the presence of the copper atom and could mean that a greater proportion of (*Z*) enolate is formed as a result.



Scheme 155

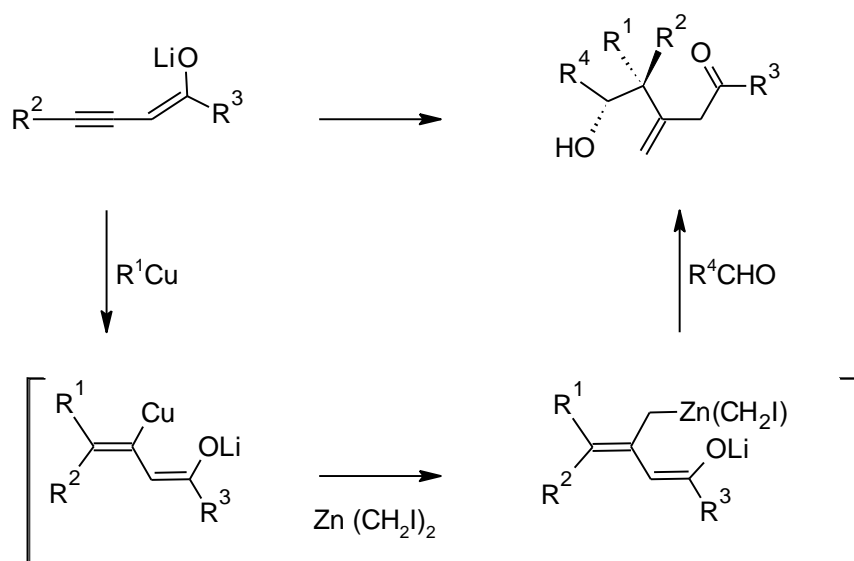
The ideas discussed above can, in principle, also be applied to terminal alkynes as it has been shown by Normant et al.¹¹ that a non-basic organocopper reagent will add stereo- and regioselectively to afford a vinyl organocopper reagent. Esters **158** and **159** possess both a terminal alkyne and a carbonyl group that cannot be deprotonated easily and so it is possible that treatment with an organocopper reagent would afford

a vinyl copper reagent (Scheme 156). This is based on the known ability for heteroatom tethers to direct a distal *syn* addition of organocopper reagents to terminal alkynes.³⁸ There would then be the same choice of the two routes as discussed above.



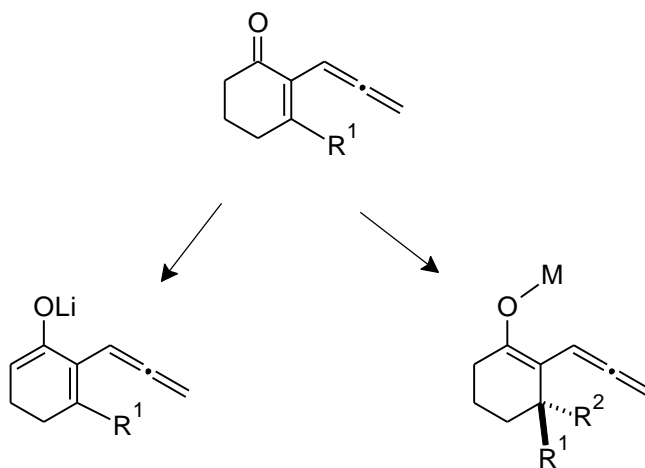
Scheme 156

In all of the above scenarios, it should not be forgotten that the more recent advances in carbometallation such as the use of iron catalysis,^{52,53} indium reagents,⁵⁷ or the elegant transmetallation products illustrated in the work of Marek^{49,85,86} can also be incorporated (Scheme 157).



Scheme 157

Finally, the highly promising results on conjugate addition reactions to the allenic enone system must also be pursued and, as indicated earlier, possibly applied to terminal alkyne congeners (Scheme 158).



Scheme 158

In the final analysis, the research described herein on the directing effects of the carbonyl group and derived enolate anions has highlighted many of the additional factors which must be controlled to implement this “simple concept”. At the same time however, it has also provided many pointers and opened up many exciting possibilities for future research in this area.

Chapter 3: Experimental

General Procedures

All reactions were carried out using dry solvents. Solvents were dried by passing through *Anhydrous Engineering* silica. All reactions were carried out under an atmosphere of nitrogen. All chemicals were purchased from Sigma Aldrich, Alfa Aesar, or Fischer and unless otherwise stated, were used without further purification. Copper(I)bromide was recrystallized from a saturated aqueous solution of sodium bromide, washed sequentially with deionized water, ethanol, ethyl acetate, diethyl ether and petroleum spirits, dried *in vacuo* and stored in a desiccator in the dark. Copper(I)iodide was recrystallized from a saturated solution of sodium iodide, washed sequentially with deionized water, ethanol, ethyl acetate, diethyl ether and petroleum spirits, dried and stored in a desiccator in the dark. Diisopropylamine was distilled from sodium hydroxide and stored over molecular sieves. *p*-Tolualdehyde was dried with calcium sulfate, distilled and stored over molecular sieves. *p*-Toluenesulfonic acid was recrystallized from deionized water. Pyrrolidine was distilled from barium oxide and stored over molecular sieves. Triethylamine was heated at reflux with phthalic anhydride, filtered and the filtrate was distilled from calcium hydride and stored over molecular sieves.

¹H NMR spectra were recorded at 300, 400 and 500 MHz on Bruker AMX300, AV400 and DRX500 spectrometers respectively. The chemical shift (δ) of each peak is given relative to tetramethylsilane (TMS), where δ TMS = 0 ppm. Chemical shifts are quoted using the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad or a combination of these. NMR data are reported as follows: multiplicity, coupling constants (*J* values), number of protons.

^{13}C NMR spectra were recorded at 75, 100 and 125 MHz on Bruker AMX300, AV400, DRX500 spectrometers respectively. The chemical shift (δ) of each peak is given relative to the residual solvent peak.

Infrared (IR) spectra were obtained from a PerkinElmer Spectrum 100 FT-IR machine, and were recorded neat. Absorption maxima are reported in wavenumbers (cm^{-1}), using the following abbreviations: w, weak; m, medium; s, strong; br, broad. Only selected absorbencies are reported.

Mass spectra were obtained using VG ZAB SE instrument at the University College London Chemistry Department either by Electron Impact (EI), Chemical Ionisation (CI) or Fast Atom Bombardment (FAB).

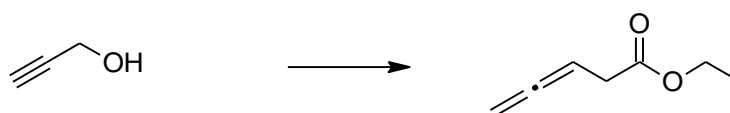
Melting Points were measured on a Reichert Hotstage apparatus for all solids where possible and are quoted to the nearest $^{\circ}\text{C}$ and are uncorrected.

Analytical thin layer chromatography (t.l.c.) was carried out on pre-coated, aluminium backed (Merck 60 F₂₅₄ silica) plates. Visualisation was performed out using short wave (254nm) UV, KMnO_4 solution or DNP solution and gentle heating. Where required, compounds were purified by flash column chromatography using 60A particle size 35 – 70 micron silica gel and eluting with the solvent system specified. Crude mixtures were loaded either in a solution of the eluent or pre-adsorbed onto silica. Pure fractions were combined and the eluted solvent was removed *in vacuo* to afford the purified product.

Brine refers to a saturated aqueous sodium chloride solution.

Grignard reagents were prepared by stirring 1.2 eq of Mg turnings under N₂ for several hours. A small amount of Et₂O was added before adding the relevant bromide in Et₂O dropwise maintaining a constant reflux. After addition was complete the solution was heated at reflux for 30 minutes. The Grignard was then cooled and stored in the fridge and freshly titrated by the method of Love et al.⁸⁷

Ethyl penta-3,4-dienoate

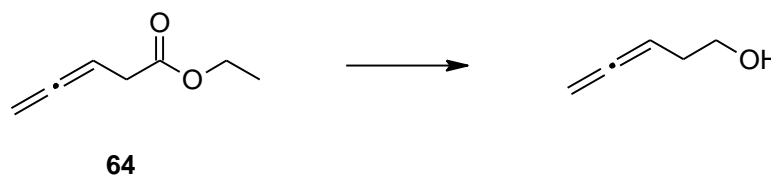


The title allene was prepared *via* a modified literature procedure.⁸⁸ A mixture of propargyl alcohol (9.0 mL, 155 mmol, 1 eq) and triethyl orthoacetate (60 mL, 337 mmol, 2.2 eq) was heated to 100 °C with stirring in a two neck flask fitted with a still head. Propionic acid (0.2 mL, 2.7 mmol, 0.02 eq) was added and the reaction was heated to 160 °C, allowing the steady distillation of ethanol out of the reaction flask. When the distillation had ceased (approx. 2 hours), propargyl alcohol (9.0 mL, 155 mmol, 1 eq) was added over 15 minutes. The reaction was then heated at 160 °C for a further 2 hours. Propionic acid (0.6 mL in 0.2 mol portions) was added slowly. The reaction was cooled to room temperature and 2N HCl (20 mL) was added. The resulting mixture was extracted with Et₂O (3 × 30 mL) and the combined organic fractions washed with a saturated aqueous solution of sodium hydrogen carbonate (20 mL) then brine (20 mL), dried over MgSO₄ and the solvents removed *in vacuo*.

The resultant crude liquid was purified by distillation (65 – 71 °C, 20 mmHg; lit b.p. 65 – 70 °C, 20 mmHg) to afford the title ester as a colourless oil (23.40 g, 60%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2984 (w, C–H), 1960 (w, C=C=C), 1735 (s, C=O); **^1H NMR** (300 MHz, CDCl_3): δ = 1.23 (t, J = 7.1 Hz, COCH_2CH_3 , 3H), 3.00 (m, $\text{CH}_2\text{CO}_2\text{Et}$, 2H), 4.12 (q, J = 7.1 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$, 2H), 4.73 (m, $\text{CH}_2=\text{C}$, 2H), 5.22 (m, $\text{CH}_2=\text{C}=\text{CH}$, 1H); **^{13}C NMR** (75 MHz, CDCl_3): δ = 14.2 (CH_3), 34.2 ($\text{CH}_2\text{CO}_2\text{Et}$), 60.8 (OCH_2), 75.7 ($\text{HC}=\text{C}=\text{CH}_2$), 83.5 ($\text{HC}=\text{C}=\text{CH}_2$), 171.4 (C=O), 209.3 (C=C=C)

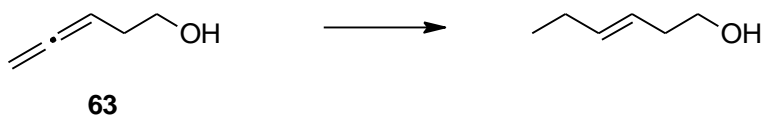
Penta-3,4-dien-1-ol⁸⁹



To a stirred suspension of lithium aluminium hydride (735 mg, 19.4 mmol, 0.7 eq) in THF (10 mL) at 0 °C was added a solution of ester **64** (4 g, 31.8 mmol, 1 eq) in THF (5 mL) over 15 minutes. The reaction was allowed to warm to room temperature and stirred for 16 hours. The reaction was then cooled to 0 °C and a THF/ H_2O mixture (3:1) (20 mL) was added slowly. The resulting solid was filtered off and the filtrate and combined washings were dried (MgSO_4), filtered and the solvents removed *in vacuo*. The crude oil was purified by distillation (72 – 78 °C, 18 mmHg) to afford the title allenol as a colourless oil (1.47 g, 55%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3334 (br, O-H), 2948, 2880 (C-H), 1956 (C=C=C); **^1H NMR** (300 MHz, CDCl_3): δ = 2.16 (br, OH, 1H), 2.23 (m, $\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.67 (t, J = 6.3 Hz, CH_2OH , 2H), 4.69 (m, $\text{H}_2\text{C}=\text{C}=\text{CH}$, 2H), 5.11 (m, $\text{H}_2\text{C}=\text{C}=\text{CH}$, 1H); **^{13}C NMR** (75 MHz, CDCl_3): δ = 31.6 (CH_2), 61.8 (CH_2O), 75.0 ($\text{HC}=\text{C}=\text{CH}_2$), 86.5 ($\text{HC}=\text{C}=\text{CH}_2$), 209.0 (C=C=C)

(3E)-Hex-3-en-1-ol⁹⁰

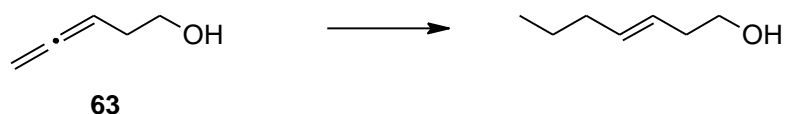


To a mixture of allenol **63** (500 mg, 5.95 mmol, 1 eq) and copper(I)iodide (540 mg, 2.97 mmol, 0.5 eq) in toluene (8 mL) at $-78\text{ }^\circ\text{C}$ was added methyl magnesium bromide (1.54 M in toluene / Et_2O , 13.5 mL, 20.82 mmol, 3.5 eq) dropwise. The reaction was allowed to reach room temperature. After 17 hours the reaction was cooled to $0\text{ }^\circ\text{C}$ and a saturated aqueous solution of ammonium chloride (30 mL) was added dropwise. The resultant mixture was warmed to room temperature and stirred for 15 minutes in air. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et_2O ($3 \times 30\text{ mL}$). The organic fractions were combined, dried over MgSO_4 and mixture concentrated *in vacuo*. The resulting crude liquid was purified by flash column chromatography, eluting with petroleum spirit (b.p. $40 - 60\text{ }^\circ\text{C}$) / EtOAc (1:1) to give the title alcohol as a colourless oil (340 mg, 57%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3346.9 (br, O-H), 2963.1, 2934.7, 2879.3 (C-H); **^1H NMR** (300 MHz, CDCl_3) δ = 0.98 (t, J = 7.4 Hz, CH_3 , 3H), 1.91 (brs, OH, 1H), 1.98 – 2.08 (m, CH_3CH_2 , 2H), 2.21 – 2.32 (m, HOCH_2CH_2 , 2H), 3.61 (t, J = 6.3 Hz, HOCH_2 , 2H),

5.15 (dt, J = 14.9, 9.4 Hz, CH, 1H), 5.45 (dt, J = 14.9, 5.5 Hz, CH, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ = 12.6 (CH_3), 29.9 (CH_2), 35.8 (CH_2), 62.0 (CH_2O), 127.1 (CH), 137.1 (CH)

(3E)-Hept-3-en-1-ol

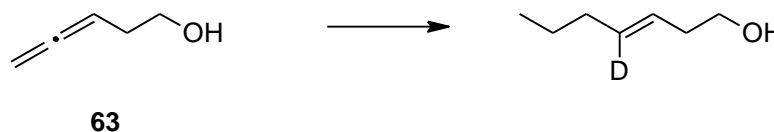


To a stirred suspension of copper(I) bromide (939 mg, 6.54 mmol, 1.1 eq) in Et_2O (10 mL) at $-30\text{ }^\circ\text{C}$ was added an Et_2O solution of EtMgBr (1.3 M in Et_2O , 9.6 mL, 12.50 mmol, 2.1 eq). After 1 hour allenol **63** (500 mg, 5.95 mmol, 1 eq) was added neat, dropwise. The reaction was warmed to $0\text{ }^\circ\text{C}$ and stirred for 4 hours then cooled to $-30\text{ }^\circ\text{C}$ and a saturated aqueous solution of ammonium chloride (8 mL) was added dropwise. The resultant mixture was warmed to room temperature and stirred for 15 minutes in air. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et_2O ($3 \times 30\text{ mL}$). The combined organic fractions were washed with saturated aqueous ammonium chloride (10 mL), dried (MgSO_4), filtered and the solvents removed *in vacuo*. The resulting colourless oil was purified by flash column chromatography, eluting with DCM to afford the title alcohol as a colourless oil (541 mg, 80%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3332.4 (br, O–H), 2957.5, 2928.1, 2873.0 (C–H); **^1H NMR** (500 MHz, CDCl_3): δ = 0.89 (t, J = 7.4 Hz, 3H), 1.34 (qt, J = 7.4, 7.3 Hz, 2H), 1.55 (s, 1H), 1.99 (tdd, J = 7.2, 6.8, 1.1 Hz, 2H), 2.26, (tdd, J = 6.9, 6.3, 1.1 Hz, 2H), 3.61 (t, J = 6.3 Hz, 2H), 5.37 (dtt, J = 15.3, 6.9, 1.3 Hz, 1H), 5.54 (dtt, J = 15.3, 6.7, 1.3 Hz, 1H);

^{13}C NMR (125 MHz, CDCl_3): δ = 13.7 (CH_3), 22.6 (CH_2), 34.8 (CH_2), 36.1 (CH_2), 62.1 (CH_2O), 125.9 (CH), 134.2 (CH)

Deuterated (3E)-hept-3-en-1-ol

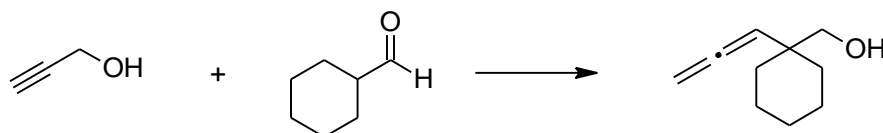


To a stirred suspension of copper(I) bromide (939 mg, 6.54 mmol, 1.1 eq) in Et_2O (10 mL) at $-30\text{ }^\circ\text{C}$ was added an Et_2O solution of EtMgBr (1.4 M in Et_2O , 8.9 mL, 12.50 mmol, 2.1 eq). After 1 hour allenol **63** (500 mg, 5.95 mmol, 1 eq) was added neat, dropwise. The reaction was warmed to $0\text{ }^\circ\text{C}$ and stirred for 4 hours then cooled to $-30\text{ }^\circ\text{C}$ and a solution of DCl and AcOD in D_2O (prepared by adding AcCl (1 mL) to D_2O (5 mL) with stirring) was added dropwise. The resultant mixture was warmed to room temperature, stirred for 15 minutes air. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et_2O ($3 \times 30\text{ mL}$). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO_4), filtered and the solvents removed *in vacuo*. The resulting colourless oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. $40 - 60\text{ }^\circ\text{C}$) / EtOAc (3:1) to afford the title alcohol as a colourless oil (405 mg, 63%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3321.2 (br, O-H), 2957.4, 2926.6, 2873.3 (C-H); **^1H NMR** (300 MHz, CDCl_3): δ = 0.88 (t, J = 7.4 Hz, CH_3 , 3H), 1.37 (sxt, J = 7.3 Hz, CH_3CH_2 , 2H), 1.53 (brs, OH, 1H), 2.00 (m, CDCH_2 , 1H), 2.25 (q, J = 6.5 Hz, CHCH_2 , 2H), 3.61 (t, J =

6.3 Hz, CH₂OH, 2H), 5.36 (m, CH, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 13.6 (CH₃), 22.5 (CH₂), 34.6 (CH₂), 36.0 (CH₂), 62.0 (CH₂O), 125.8 (CH), 133.7 (t, J = 23.5 Hz, CD); MS *m/z* (+ve CI): 115 (10), 98 (100), 97 (40), 96 (20); HRMS: 116.12070 C₇H₁₄OD requires 116.12012

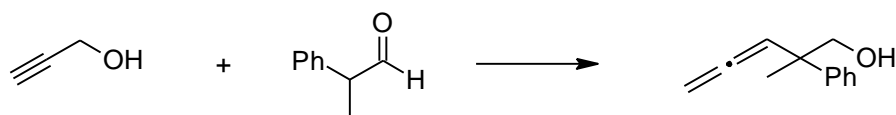
(1-Propadienylcyclohexyl)methanol



A mixture of propargyl alcohol (2.1 mL, 36.00 mmol, 1 eq), cyclohexanecarbaldehyde (4.4 mL, 36.00 mmol, 1 eq) and *para*-toluenesulfonic acid (60 mg) in toluene (60 mL) was heated at reflux with azeotropic removal of water using a Dean & Stark apparatus. After 20 hours the reaction was cooled and concentrated *in vacuo*. The crude oil was dissolved in EtOH (70 mL), cooled to 0 °C and sodium borohydride (1.36 g, 36.00 mmol, 1 eq) was added in portions with stirring. The reaction was warmed to 0 °C and stirred for 6 hours then cooled to 0 °C and acetone (5 mL) was added. The mixture was concentrated *in vacuo* then partitioned between EtOAc (30 mL) and deionized water (30 mL). The mixture was separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic fractions were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (4:1), to afford the title alcohol as a pale yellow oil (763 mg, 14%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3389.7 (br, O-H), 2921.7, 2851.8, (C-H), 1959.5 (C=C=C); **^1H NMR** (300 MHz, CDCl_3): δ = 1.19 – 1.53 (m, $(\text{CH}_2)_5$, 10H), 1.92 (brs, OH, 1H), 3.33 (s, CH_2OH , 2H), 4.74 (d, J = 6.7 Hz, $=\text{CH}_2$, 2H), 4.93 (t, J = 6.7 Hz, $=\text{CH}$, 1H); **^{13}C NMR** (75 MHz, CDCl_3): δ = 22.1 (CH_2), 26.3 (CH_2), 32.7 (CH_2), 40.6 (C), 71.4 (CH_2O), 76.4 ($\text{HC}=\text{C}=\text{CH}_2$), 95.6 ($\text{HC}=\text{C}=\text{CH}_2$), 208.2 (C=C=C); **MS** m/z (+ve CI): 151 (20), 140 (40), 129 (30), 114 (100), 113 (85); **HRMS**: 15111236 $\text{C}_{10}\text{H}_{15}\text{O}$ requires 151.11174

2-Methyl-2-phenylpenta-3,4-dien-1-ol

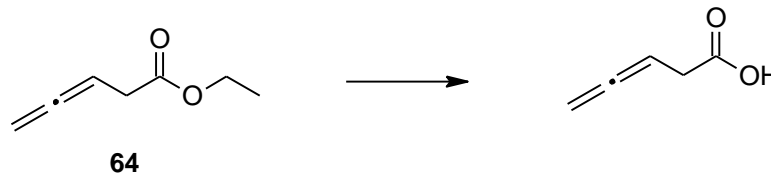


A mixture of propargyl alcohol (2.3 mL, 40.00 mmol, 1 eq), 2-phenylpropanaldehyde (5.4 mL, 40.00 mmol, 1 eq) and *para*-toluenesulfonic acid (60 mg) in toluene (60 mL) was heated at reflux with azeotropic removal of water using a Dean & Stark apparatus. After 20 hours the reaction was cooled and concentrated *in vacuo*. The crude oil was dissolved in EtOH (50 mL), cooled to 0 °C and sodium borohydride (1.51 g, 40.00 mmol, 1 eq) was added in portions with stirring. The reaction was warmed to 0 °C and stirred for 6 hours then cooled to 0 °C and acetone (5 mL) was added. The mixture was concentrated *in vacuo* then partitioned between EtOAc (30 mL) and deionized water (30 mL). The mixture was separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic fractions were washed with brine (20 mL), dried (MgSO_4), filtered and concentrated *in vacuo*. The crude mixture was purified by flash column

chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (4:1), to afford the title alcohol as a colourless oil (1.78 g, 25%).

IR $\nu_{\max}/\text{cm}^{-1}$: 3381.3 (br, O–H), 2982.3, 2915.7, 2853.1 (C–H), 1953.2 (C=C=C); **¹H NMR** (300 MHz, CDCl₃): δ = 1.51 (s, CH₃, 3H), 2.15 (brs, OH, 1H), 3.76 (m, CH₂OH, 2H), 4.93 (dd, J = 6.7, 2.1 Hz, =CH₂, 2H), 5.50 (t, J = 6.7 Hz, =CH, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ = 23.5 (CH₃), 44.5 (C), 71.0 (CH₂O), 77.5 (HC=C=CH₂), 97.0 (HC=C=CH₂), 126.6 (Ar), 126.9 (Ar), 128.5 (Ar), 145.0 (C), 202.4 (C=C=C)

Penta-3,4-dienoic acid⁹¹

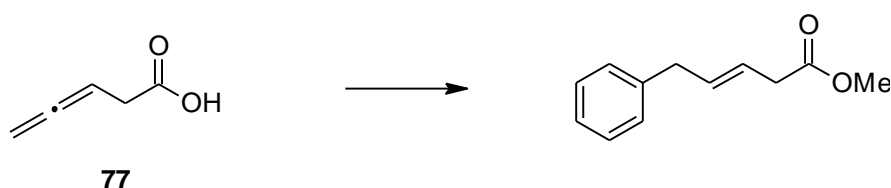


A solution of ester **64** (20 g, 158.5 mmol) was stirred in the mixed solvent of 20% hydrochloric acid (240 mL) and acetone (160 mL) for 3 days. The reaction mixture was extracted with EtOAc (3 × 20 mL) and the organic fractions combined and concentrated *in vacuo*. The crude oil was purified by distillation (56 – 62 °C 2 mmHg; lit b.p. 62°C, 1 mmHg) to afford the title acid as a colourless oil (10.5 g, 68%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2992.3, 2918.84 (br, COOH), 1960.5 (m, C=C=C), 1704.3 (s, C=O), 1404.3; **¹H NMR** (300 MHz, CDCl₃): δ = 3.08 (m, CH₂CO₂H, 2H), 4.78 (m, CH₂=C,

2H), 5.25 (m, CH₂=C=CH, 1H), 11.47 (brs, CO₂H, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 34.1 (CH₂CO₂H), 77.0 (HC=C=CH₂), 82.8 (HC=C=CH₂), 178.0 (C=O), 209.5 (C=C=C)

Methyl (3E)-5-phenylpent-3-enoate⁹²



To a stirred solution of LDA at -78 °C, prepared by the addition of *n*-butyllithium (2.29 M in hexanes, 3.5 mL, 8.15 mmol, 2 eq) to diisopropylamine (1.14 mL, 8.15 mmol, 2 eq) at 0 °C in Et₂O (10 mL), was added a solution of acid **77** (400 mg, 4.08 mmol, 1 eq) in Et₂O (1 mL) dropwise. The reaction was allowed to reach room temperature and stirred for 1 hour. The reaction was then cooled to -78 °C, copper(Diodide (389 mg, 2.04 mmol, 50 mol%) was added followed by phenyl magnesium bromide (2.7 M in Et₂O, 3 mL, 8.15 mmol, 2 eq) dropwise. The reaction was warmed to room temperature and stirred for 16 hours. The reaction was then cooled to 0 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The aqueous phase was acidified with 2M HCl and the resultant mixture filtered *in vacuo*. The mixture was separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic fractions were dried (MgSO₄), filtered and the solvents removed *in vacuo*. A solution of acetyl chloride (2 mL) in methanol (10 mL) was added to the resulting mixture. The reaction was stirred for 16 hours at room temperature. The reaction was concentrated *in vacuo*, diluted with Et₂O (30 mL) and washed with a saturated solution of Na₂S₂O₃. The aqueous washings were back extracted with Et₂O (20 mL), organic fractions

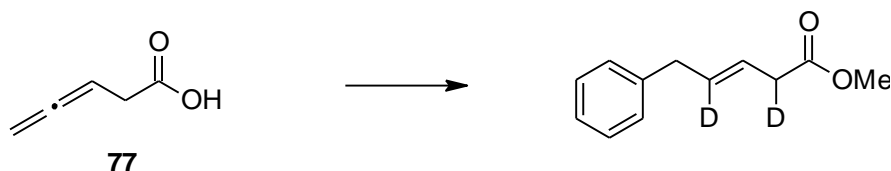
combined, dried over MgSO_4 and solvents removed *in vacuo*. The crude mixture was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et_2O (10:1) to afford the title ester as a colourless oil (285 mg, 40%).

Alternative method for methylation

The resultant crude acid was dissolved in acetone (30 mL) and potassium carbonate (3.5 g, 25.5 mmol, 5 eq) was added followed by methyl iodide (1 mL, 15.3 mmol, 3 eq) and the reaction stirred at room temperature for 24 hours. Et_2O (30 mL) was added and the resultant precipitate filtered off *in vacuo*. The filtrate was concentrated *in vacuo* and purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et_2O (10:1) to yield the title ester as a colourless oil (471 mg, 49%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3027.9, 2952.2, 2842.2, 1735.3, 1494.9, 1453.4, 1435.1, 1247.9, 1195.6, 1164.2; **^1H NMR** (500 MHz, CDCl_3): δ = 3.10 (dd, J = 6.7, 1.0 Hz, CH_2CO , 2H), 3.40 (d, J = 6.5 Hz, PhCH_2 , 2H), 3.69 (s, CH_3O , 3H), 5.69 (dtt, J = 15.3, 6.7, 1.2 Hz, CHCH_2CO , 1H), 5.73 (dtt, J = 15.3, 6.5, 1.0 Hz, PhCH_2CH , 1H), 7.20 – 7.32 (m, Ph, 5H); **^{13}C NMR** (125 MHz, CDCl_3): δ = 37.8 ($\text{CH}_2\text{CO}_2\text{Me}$), 51.9 (CH_3O), 123.1, 126.2, 128.4, 128.5 (Ar), 128.6 (Ar), 133.3 (CH), 140.2 (C), 171.0 (C=O)

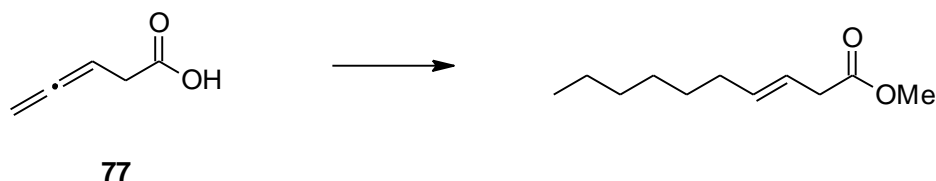
Deuterated methyl (3E)-5-phenylpent-3-enoate



To a stirred solution of LDA at $-78\text{ }^{\circ}\text{C}$, prepared by the addition of *n*-butyllithium (2.29 M in hexanes, 3.5 mL, 8.15 mmol, 2 eq) to diisopropylamine (1.14 mL, 8.15 mmol, 2 eq) at $0\text{ }^{\circ}\text{C}$ in Et_2O (10 mL), was added a solution of acid **77** (400 mg, 4.08 mmol, 1 eq) in Et_2O (1 mL) dropwise. The reaction was allowed to reach room temperature and stirred for 1 hour. The reaction was then cooled to $-78\text{ }^{\circ}\text{C}$, copper(Diodide (389 mg, 2.04 mmol, 50 mol%) was added followed by phenyl magnesium bromide (2.7 M in Et_2O , 3 mL, 8.15 mmol, 2 eq) dropwise. The reaction was warmed to room temperature and stirred for 16 hours. The reaction was then cooled to $0\text{ }^{\circ}\text{C}$ and deuterium oxide (10 mL) was added dropwise. The aqueous phase was acidified with 2M HCl and the resultant mixture filtered *in vacuo*. The mixture was separated and the aqueous phase extracted with EtOAc ($3 \times 20\text{ mL}$). The combined organic fractions were dried (MgSO_4), filtered and the solvents removed *in vacuo*. A solution of acetyl chloride (2 mL) in methanol (10 mL) was added to the resulting mixture. The reaction was stirred overnight at room temperature. The reaction was concentrated *in vacuo*, diluted with Et_2O (30 mL) and washed with a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous washings were back extracted with Et_2O (20 mL), organic fractions combined, dried over MgSO_4 and solvents removed *in vacuo*. The crude mixture was purified by flash column chromatography, eluting with petroleum spirit (b.p. $40 - 60\text{ }^{\circ}\text{C}$) / Et_2O (10:1) to afford the title ester as a colourless oil (280 mg, 39%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3027.8, 2952.3, 2843.2, 1735.8, 1494.8, 1453.5, 1435.0, 1248.0, 1195.1, 1162.9; **^1H NMR** (500 MHz, CDCl_3): $\delta = 3.09$ (d, $J = 6.2\text{ Hz}$, CHDCO_2Me , 1H), 3.40 (d, $J = 6.2\text{ Hz}$, PhCH_2 , 2H), 3.70 (s, CH_3O , 3H), 5.73 (m, $\text{CHCHDCO}_2\text{Me}$, 1H), 7.19 – 7.32 (m, Ph, 5H); **^{13}C NMR** (125 MHz, CDCl_3): $\delta = 37.6$ (CH_2), 38.9 (CH_2), 51.5 (CH_3O), 123.1 (t, $J = 22\text{ Hz}$, CD), 126.2 (Ar), 128.4 (Ar), 128.6 (Ar), 133.3 (CH), 140.2 (C), 172.2 (C=O)

Methyl (3E)-dec-3-enoate⁹³

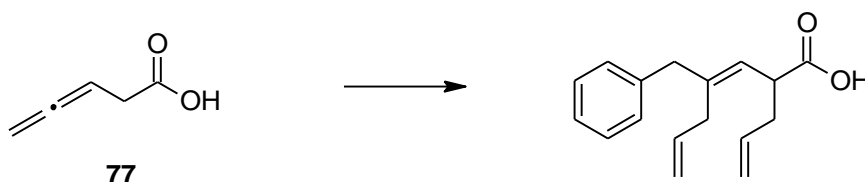


To a stirred solution of diisopropylamine (0.36 mL, 2.55 mmol, 50 mol%) in Et₂O (8 mL) was added *n*-butyllithium (2.33 M in hexanes, 5.5 mL, 12.74 mmol, 2.5 eq) at 0 °C. After 15 minutes the solution was cooled to -78 °C and a solution of acid **77** (500 mg, 5.10 mmol, 1 eq) in Et₂O (1 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 1 hour. The reaction was then cooled to -78 °C and copper(I)iodide (97 mg, 0.51 mmol, 10 mol%) was added followed by dropwise addition of pentyl magnesium bromide (2.1 M in Et₂O, 2.7 mL, 5.61 mmol, 1.1 eq). The reaction was warmed to room temperature and stirred for 16 hours. The reaction was then cooled to 0 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The aqueous phase was acidified with 2M HCl and the resultant mixture filtered *in vacuo*. The mixture was separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic fractions were dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resultant crude acid was dissolved in acetone (30 mL) and potassium carbonate (3.5 g, 25.5 mmol, 5 eq) was added followed by methyl iodide (1 mL, 15.3 mmol, 3 eq) and the reaction stirred at room temperature for 24 hours. Et₂O (30 mL) was added and the resultant precipitate filtered off *in vacuo*. The filtrate was concentrated *in vacuo* and purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to yield the title ester as a colourless oil (176 mg, 19 %).

IR $\nu_{\max}/\text{cm}^{-1}$: 2955.8, 2927.0, 2856.4 (m, C–H), 1742.4 (s, C=O) **¹H NMR** (500 MHz, CDCl₃): δ = 0.88 (t, J = 7.0 Hz, CH₃, 3H), 1.24 – 1.38 (m, CH₃(CH₂)₄CH₂,

8H), 2.02 (J = 7.3, 6.5 Hz, C₅H₁₁CH₂, 2H), 3.03 (d, J = 6.1 Hz, CH₂CO₂CH₃, 2H), 3.68 (s, OCH₃, 3H), 5.51 (dt, J = 15.3, 6.5 Hz, C₆H₁₃CH=CH, 1H), 5.56 (dt, J = 15.3, 6.1 Hz, C₆H₁₃CH=CH, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 14.2 (CH₃), 22.7 (CH₂), 28.9 (CH₂), 29.2 (CH₂), 31.8 (CH₂), 32.5 (CH₂), 38.0 (CH₂), 51.8 (CH₃O), 121.4 (CH), 135.1 (CH), 172.7 (C=O)

Methyl (3E)-4-benzyl-2-(prop-2-en-1-yl)hepta-3,6-dienoate

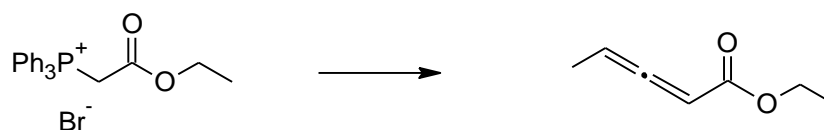


To a stirred solution of diisopropylamine (0.36 mL, 2.35 mmol, 50 mol%) in Et₂O (8 mL) was added *n*-butyllithium (2.34 M in hexanes, 5.4 mL, 12.74 mmol, 2.5 eq) at 0 °C. After 15 minutes the solution was cooled to -78 °C and a solution of acid **77** (500 mg, 5.10 mmol, 1 eq) in Et₂O (1 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 1 hour. The reaction was then cooled to -78 °C and copper(I)iodide (97 mg, 0.51 mmol, 10 mol%) was added followed by dropwise addition of phenyl magnesium bromide (1.6 M in hexanes, 3.5 mL, 5.61 mmol, 1.1 eq). The reaction was warmed to room temperature and stirred for 16 hours. The reaction was then cooled to 0 °C and allyl bromide (1.8 mL, 20.4 mmol, 4 eq) was added dropwise and the reaction warmed to room temperature and stirred for 20 hours. The reaction was then cooled to 0 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The aqueous phase was acidified with 2M HCl and the resultant mixture filtered *in vacuo*. The mixture was separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic fractions were dried (MgSO₄), filtered and the solvents removed *in vacuo*. The crude

material was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (2:1) to yield the title acid as a colourless oil (211 mg, 16%)

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2989.2, 2844.4, 2792.1 (m, C–H), 1705.0 (C=O), 1603.2; **^1H NMR** (300 MHz, CDCl_3): δ = 2.53 (m, $\text{CHCH}_2\text{CH}=\text{CH}_2$, 2H), 2.74 (d, J = 6.4 Hz, $\text{CCH}_2\text{CH}=\text{CH}_2$, 2H) 3.35 (s, PhCH_2 , 2H), 3.42 (m, CHCO , 1H), 5.06 (m, $(\text{CH}=\text{CH}_2)_2$, 4H), 5.32 (d, J = 9.6 Hz, $\text{C}=\text{CH}$, 1H), 5.72 (m, $(\text{CH}=\text{CH}_2)_2$, 2H), 7.14 – 7.30 (m, ArH, 5H); **^{13}C NMR** (75 MHz, CDCl_3): δ = 36.1 (CH_2), 34.5 (CH_2), 37.3 (CH_2), 38.0 (CH_2), 115.8 (CH_2), 116.1 (CH_2), 117.1 (CH), 117.1 (CH), 124.6 (CH), 126.3 (Ar), 128.4 (Ar), 128.5 (Ar), 139.5 (C), 142.9 (C), 174.4 (C=O); **MS** m/z (+ve CI): 257 (60), 256 (30), 239 (50), 211 (65), 169 (100); **HRMS** 257.15317 $\text{C}_{17}\text{H}_{21}\text{O}_2$ requires 257.15415

Ethyl penta-2,3-dienoate

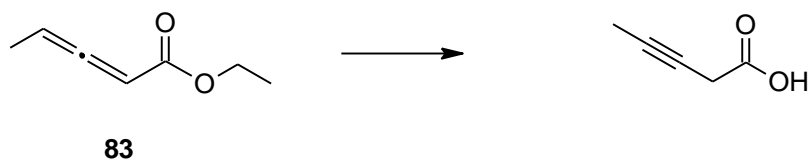


The title allene was prepared via a modified literature procedure.⁹⁴ To a stirred solution of (ethoxycarbonylmethyl)triphenylphosphonium bromide (10 g, 23.3 mmol, 1 eq) in DCM (50 mL) at 0 °C was added triethylamine (6.5 mL, 46.6 mmol, 2 eq) dropwise followed by slow addition of a solution of propionyl chloride (2 mL, 23.3 mmol, 1 eq) in DCM (10 mL). After stirring at this temperature for 2 hours the

reaction was concentrated *in vacuo* to approximately ½ volume. Et₂O (60 mL) was added and the resultant colourless precipitate filtered *in vacuo*. The filtrate was concentrated *in vacuo* and more Et₂O (60 mL) was added. The mixture was filtered through a pad of silica and the filtrate concentrated *in vacuo*. The crude mixture was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (10:1) to afford the title allene as a colourless oil (1.7 g, 66%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2981.5, 2936.5 (m, C–H), 1961.4 (w, C=C=C), 1716.8 (C=O); **¹H NMR** (300 MHz, CDCl₃): δ = 1.27 (t, J = 71 Hz, OCH₂CH₃, 3H), 1.79 (m, =CHCH₃, 3H), 3.20 (m, CHCO₂Et, 1H), 4.17 (q, J = 7.1 Hz, OCH₂CH₃, 2H), 5.56 (m, =CHCH₃, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ = 12.8 (CH₃), 14.2 (CH₃), 26.0, 60.8 (CH₂O), 61.4, 87.7 (CH), 90.2 (CH), 168.2, 169.0 (C=O), 212.9 (C=C=C)

Pent-3-ynoic acid⁹⁵

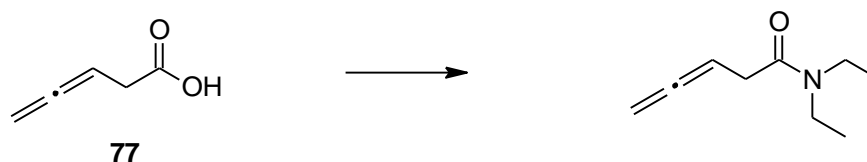


The title acid was prepared via a modified literature procedure. To a stirred solution of ester **83** (1.8 g, 16.35 mmol, 1 eq) in THF (20 mL) at room temperature was added a solution of lithium hydroxide (3.4 g, 81.77 mmol, 5 eq) in deionised water (50 mL). After 45 minutes the mixture was extracted with Et₂O (20 mL) and the organic phase discarded. The aqueous phase was acidified and extracted with Et₂O (3 × 20 mL). The organic fractions were combined, dried (MgSO₄), filtered and

solvents removed *in vacuo* to afford the title acid as a colourless solid (760 mg, 57%).

m.p. 100 – 101 °C (lit. 102 °C); **IR** $\nu_{\max}/\text{cm}^{-1}$: 3332.0 (br, O–H), 2923.1, 2906.0, (m, C–H), 1703.8 (s, C=O); **^1H NMR** (300 MHz, CDCl_3): δ = 1.83 (t, J = 2.4 Hz, CH_3 , 3H), 3.30 (q, J = 2.4 Hz, CH_2 , 2H), 10.34 (br, OH, 1H); **^{13}C NMR** (75 MHz, CDCl_3): δ = 3.6, 25.9, 60.6 (C), 80.0 (C), 125.4 (C=O)

N,N-Diethylpenta-3,4-dienamide

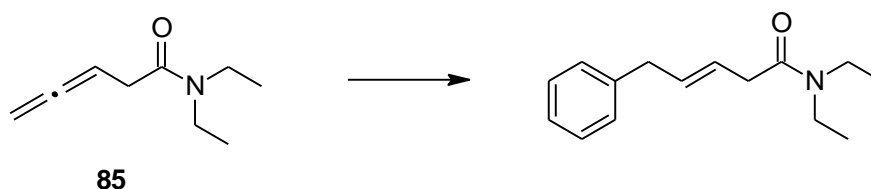


To a stirred solution of acid **77** (2 g, 20.38 mmol, 1 eq) and 1,3-dicyclohexylcarbodiimide (6.3 g, 30.57 mmol, 1.5 eq) in DCM (40 mL) was added diethylamine (2.2 mL, 20.38 mmol, 1 eq) at room temperature. After 16 hours the insoluble material was filtered off and the filtrate washed with a saturated aqueous solution of NaHCO_3 (20 mL), 2M HCl (20 mL) and brine (20 mL). The organic phase was then dried (MgSO_4), filtered and the solvent was removed *in vacuo*. The crude mixture was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (2:1) to afford the title amide as a colourless oil (1.69 g, 55%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2973.9, 2934.1 (C–H), 1959.2 (C=C=C), 1634.5 (C=O); **R_f** = 0.16 (Petroleum spirit / Et_2O ; 2:1); **^1H NMR** (300 MHz, CDCl_3): δ = 1.12 (m,

$N(CH_2CH_3)_2$, 6H), 3.05 (m, CH_2CO , 2H), 3.32 (m, $N(CH_2CH_3)_2$, 4H), 4.71 (m, $CH=C=CH_2$, 2H), 5.33 (m, $CH=C=CH_2$, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.0 (CH_3), 14.3 (CH_3), 33.7 (CH_2), 40.2 (CH_2), 42.1 (CH_2), 75.6($CH=C=CH_2$), 85.0 ($CH=C=CH_2$), 169.7 (C=O), 208.9, (C=C=C); MS m/z (EI): 153 (M^+), 138 (10), 124 (25); HRMS 153.11488 $C_9H_{15}ON$ requires 153.11481

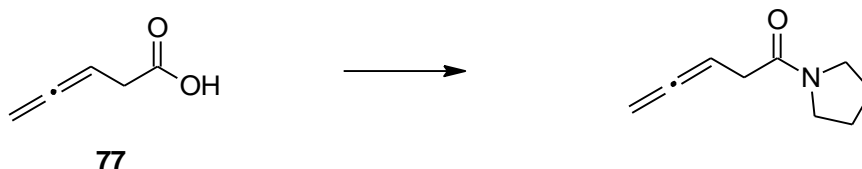
(3E)-N,N-Diethyl-5-phenylpent-3-enamide



To a solution of LDA at -78 °C, prepared by the addition of *n*-butyllithium (2.27 M on hexanes, 1.4 mL, 3.26 mmol, 1 eq) to diisopropylamine (0.46 mL, 3.26 mmol, 1 eq) at 0 °C in Et_2O (15 mL), was added a solution of amide **85** (500 mg, 3.26 mmol, 1 eq) in Et_2O (1 mL) dropwise. After 30 minutes, copper(I)iodide (310 mg, 1.63 mmol, 50 mol%) was added followed by dropwise addition of phenyl magnesium bromide (2.23 M in Et_2O , 5 mL, 11.41 mmol, 3.5 eq). The reaction was warmed to room temperature and stirred for 16 hours. The reaction was then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The mixture was separated and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvents removed *in vacuo*. The resultant crude mixture was purified by flash column chromatography, eluting with petroleum spirit (b.p. $40 - 60$ °C) / $EtOAc$ (2:1) to yield the title amide as a colourless oil (225 mg, 30 %).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2974.2, 2933.1 (C-H), 1633.6 (C=O); **^1H NMR** (300 MHz, CDCl_3): δ = 1.12 (m, $\text{N}(\text{CH}_2\text{CH}_3)_2$, 6H), 3.09 (d, J = 4.8 Hz, CH_2CO , 2H), 3.32 (m, $\text{N}(\text{CH}_2\text{CH}_3)_2$, PhCH_2 , 6H), 5.65 (dt, J = 15.5, 5.4 Hz, $\text{CH}=\text{CH}$, 1H), 5.72 (dt, J = 15.5, 5.4 Hz, $\text{CH}=\text{CH}$, 1H); **^{13}C NMR** (75 MHz, CDCl_3): δ = 13.0 (CH_3), 14.4 (CH_3), 37.4 (CH_2), 38.9 (CH_2), 40.1 (CH_2), 44.2 (CH_2), 124.9 (CH), 125.9 (Ar), 128.5 (Ar), 128.8 (Ar), 130.4 (CH), 140.4 (C), 170.3 (C=O); **MS** m/z (+ve EI): 231 (M^+), 140 (30), 100 (100); **HRMS** 231.16204 $\text{C}_{15}\text{H}_{21}\text{ON}$ requires 231.16177

1-(Pyrrolidin-1-yl)penta-3,4-dien-1-one⁹⁶

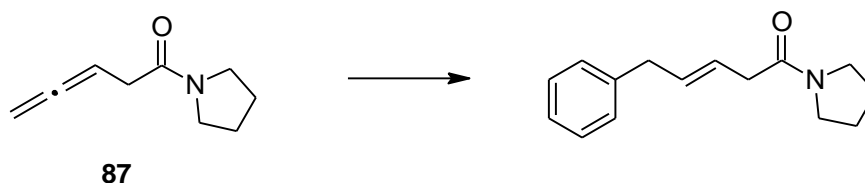


To a stirred solution of acid **77** (9 g, 91.70 mmol, 1 eq) and *N*-methyl morpholine (10 mL, 183.4 mmol, 2 eq) in DCM (60 mL) at 0 °C was added a solution of ethyl chloroformate (8.8 mL, 91.7 mmol, 1 eq) in DCM (15 mL) dropwise. After 20 minutes a solution of pyrrolidine (7.5 mL, 91.7 mmol, 1 eq) in DCM (20 mL) was added slowly. The reaction was warmed to room temperature. After 18 hours the mixture was washed with a saturated aqueous solution of NaHCO_3 (20 mL), 2M HCl (20 mL) and brine (20 mL). The organic phase was then dried (MgSO_4), filtered and the solvent removed *in vacuo*. The crude oil was purified by distillation (110 – 115 °C 1.5 mmHg) to afford the title amide as a colourless oil (2.71 g, 20%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2973.0, 2953.0, 2874 (C-H), 1958.0 (C=C=C), 1631.0 (C=O); **^1H NMR** (300 MHz, CDCl_3): δ = 1.76 – 1.96 (m, $\text{N-CH}_2(\text{CH}_2)\text{CH}_2$ -, 4H), 3.00 (m,

CH₂CO, 2H), 3.41 (m, N-CH₂(CH₂)CH₂-, 4H), 4.69 (m, CH=C=CH₂, 2H), 5.31 (m, CH=C=CH₂, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 24.4 (NCH₂CH₂), 26.1 (NCH₂CH₂), 35.1 (CH₂CO), 45.8 (NCH₂CH₂), 46.6 (NCH₂CH₂), 75.4 (HC=C=CH₂), 84.4 (HC=C=CH₂), 169.0 (C=O), 209.1 (C=C=C)

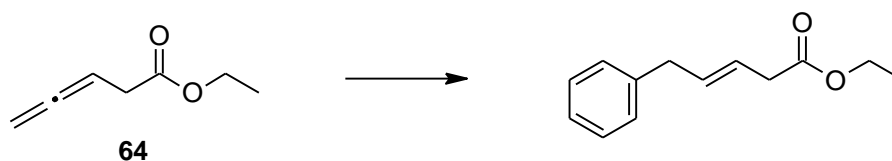
(3E)-5-Phenyl-1-(pyrrolidin-1-yl)pent-3-en-1-one



To a solution of LDA at -78 °C, prepared by the addition of *n*-butyllithium (2.00 M in hexanes, 1.7 mL, 3.41 mmol, 1 eq) to diisopropylamine (0.48 mL, 3.41 mmol, 1 eq) at 0 °C in Et₂O (15 mL), was added a solution of amide **87** (500 mg, 3.41 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 30 minutes, copper(I)iodide (315 mg, 1.66 mol, 50 mol%) was added followed by dropwise addition of phenyl magnesium bromide (2.05 M in Et₂O, 8 mL, 16.55, 3.5 eq). The reaction was warmed to room temperature and stirred for 16 hours. The reaction was then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The mixture was separated and the aqueous phase was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with brine (20 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resultant crude mixture was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (2:1) to yield the title amide as a colourless oil (196 mg, 26%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2972.5, 2952.1, 2874.8 (C–H), 1632.2 (C=O); **^1H NMR** (300 MHz, CDCl_3): δ = 1.80 – 1.93 (m, N- $\text{CH}_2(\text{CH}_2)\text{CH}_2$ -, 4H), 3.05 (d, J = 4.3 Hz, CH_2CO , 2H), 3.37-3.47 (m, N- $\text{CH}_2(\text{CH}_2)\text{CH}_2$ -, PhCH_2 , 6H), 5.66 (dt, J = 15.5, 5.6 Hz, $\text{CH}=\text{CH}$, 1H), 5.69 (dt, J = 15.5, 5.6 Hz, $\text{CH}=\text{CH}$, 1H), 7.16 – 7.26 (m, ArH, 5H); **^{13}C NMR** (75 MHz, CDCl_3): δ = 24.8 (N CH_2CH_2), 25.9 (N CH_2CH_2), 34.7 (CH_2CO), 45.4 (N CH_2CH_2), 46.5 (N CH_2CH_2), 123.5 (CH), 126.0 (Ar), 128.3 (Ar), 128.8 (Ar), 132.3 (CH), 140.1 (C), 170.0 (C=O); **MS** m/z (+ve EI): 229 (40, M^+), 131 (55), 120 (70); **HRMS** 229.16591 $\text{C}_{15}\text{H}_{19}\text{ON}$ requires 229.14666

Ethyl (3E)-5-phenylpent-3-enoate

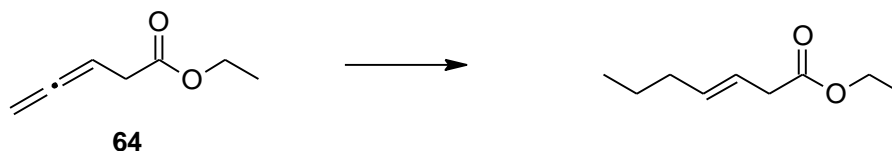


To a solution of LDA at $-78\text{ }^\circ\text{C}$, prepared by the addition of *n*-butyllithium (2.33 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at $0\text{ }^\circ\text{C}$ in Et_2O (7 mL), was added a solution of ester **64** (500 mg, 3.97 mmol, 1 eq) in Et_2O (1 mL) dropwise. After 30 minutes, copper(I)iodide (75 mg, 0.4 mmol, 10 mol%) was added followed by dropwise addition of phenyl magnesium bromide (1.4 M in Et_2O , 3.1 mL, 4.36 mmol, 1.1 eq). The reaction was then warmed to $0\text{ }^\circ\text{C}$ and stirred for 3 hours then cooled to $-78\text{ }^\circ\text{C}$ and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et_2O ($3 \times 20\text{ mL}$). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO_4), filtered and the solvents removed *in vacuo*. The resulting oil

was purified by flash column chromatography eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (10:1) to afford the title ester as a colourless oil (640 mg, 79%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3029.7, 2983.6, 2935.9 (m, C–H), 1718.1 (s, C=O), 1601.9; **¹H NMR** (500 MHz, CDCl₃): δ = 1.26 (t, J = 7.2 Hz, CH₃, 3H), 3.06 (dd, J = 6.8, 1.0 Hz, CH₂CO₂Et, 2H), 3.39 (d, J = 6.6 Hz, PhCH₂, 2H), 4.15 (q, J = 7.2 Hz, CO₂CH₂CH₃, 2H), 5.64 (dt, J = 15.3, 6.8, 1.1 Hz, CHCH₂CO₂Et, 1H), 5.72 (dt, J = 15.3, 6.6, 1.1 Hz, PhCH₂CH, 1H), 7.18 – 7.31 (m, ArH, 5H); **¹³C NMR** (125 MHz, CDCl₃): δ = 14.3 (CH₃), 38.1 (CH₂), 39.0 (CH₂), 60.7 (CH₂O), 123.4 (CH), 126.2 (Ar), 128.5 (Ar), 128.6 (Ar), 133.2 (CH), 140.2 (C), 172.0 (C=O); **MS** m/z (EI): 204 (20), 174 (10), 157 (10), 131 (85); **HRMS**: 204.11405 C₁₃H₁₆O₂ requires 204.11448

Ethyl (3*E*)-hept-3-enoate⁹⁷

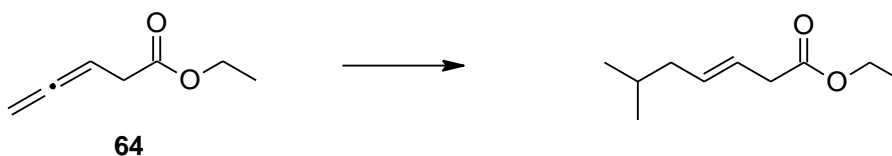


To a solution of LDA at -78 °C, prepared by the addition of *n*-butyllithium (2.33 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C in Et₂O (7 mL), was added a solution of ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 30 minutes, copper(I)iodide (75 mg, 0.4 mmol, 10 mol%) was added followed by dropwise addition of ethyl magnesium bromide (1.4 M in Et₂O, 4.5 mL, 6.34 mmol, 1.6 eq). The reaction was then warmed to 0 °C and stirred for 3 hours then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The mixture was then warmed to

room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to afford the title ester as a colourless oil (473 mg, 71%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2962.1, 2934.5, 2874.8 (m, C–H), 1721.4 (s, C=O), 1660.8 (m, C=C); **R_f** = 0.28 (Petroleum spirit / Et₂O; 20:1); **¹H NMR** (300 MHz, CDCl₃): δ = 0.87 (t, J = 7.2 Hz, CH₃CH₂, 3H), 1.25 (t, J = 7.2 Hz, CH₃CH₂O, 3H), 1.38 (sxt, J = 7.2 Hz, CH₃CH₂, 2H), 2.00 (m, CH₂CH, 2H), 3.01 (d, J = 5.4 Hz, CH₂CO₂Et, 2H), 4.14 (q, J = 7.2 Hz, CH₂O, 2H), 5.51 (dt, J = 15.3, 5.4 Hz, CH=, 1H), 5.55 (dt, J = 15.3, 5.4 Hz, CH=, 1H); **¹³C NMR** (125 MHz, CDCl₃): δ = 13.7 (CH₃), 14.3 (CH₃CH₂O), 22.4 (CH₂), 34.6 (CH₂), 38.3 (CH₂), 60.6 (CH₂O), 121.8 (CH), 134.8 (CH), 172.3 (C=O)

Ethyl (3*E*)-6-methylhept-3-enoate

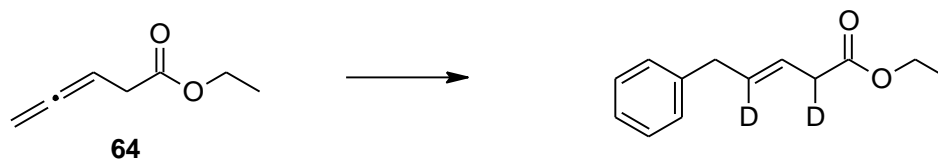


To a solution of LDA at -78 °C, prepared by the addition of *n*-butyllithium (2.15 M in hexanes, 1.8 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C in Et₂O (7 mL), was added a solution of ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 30 minutes, copper(I)iodide (75 mg, 0.4 mmol,

10 mol%) was added followed by dropwise addition of isopropyl magnesium bromide (1.3 M in Et₂O, 3.5 mL, 4.36 mmol, 1.1 eq). The reaction was then warmed to 0 °C and stirred for 3 hours then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (10:1) to afford the title ester as a colourless oil (463 mg, 69%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2985.5, 2872.1 (m, C–H), 1719.5, (s, C=O), 1660.5 (m, C=C); **R_f** = 0.5 (Petroleum spirit / Et₂O; 10:1); **¹H NMR** (300 MHz, CDCl₃): δ = 0.86 (s, CH₃CH, 3H), 0.88 (s, CH₃CH, 3H), 1.25 (t, 7.1 Hz, CH₃CH₂, 3H), 1.61 (spt, J = 6.7 Hz, (CH₃)₂CH, 1H), 1.91 (t, 6.2 Hz, CHCH₂, 2H), 3.02 (d, J = 5.1 Hz, CH₂CO₂Et, 2H), 4.13 (q, J = 7.1 Hz, CH₂CH₃, 2H), 5.50 (dt, J = 15.3, 5.89 Hz, CH=, 1H), 5.84 (dt, J = 15.3, 5.89 Hz, CH=, 1H); **¹³C NMR** (125 MHz, CDCl₃): δ = 14.3 (CH₃CH₂O), 22.3 ((CH₃)₂CH), 28.3 (CH), 38.3 (CH₂CO), 41.9 (CH₂), 60.5 (CH₂O), 122.8 (CH=), 133.6 (CH=), 172.3 (C=O); **MS** *m/z* (+ve CI): 185 (100), 171 (10), 169 (30), 141 (45); **HRMS**: 171.13945 C₁₀H₁₉O₂ requires 171.13850

Deuterated ethyl (3E)-5-phenylpent-3-enoate

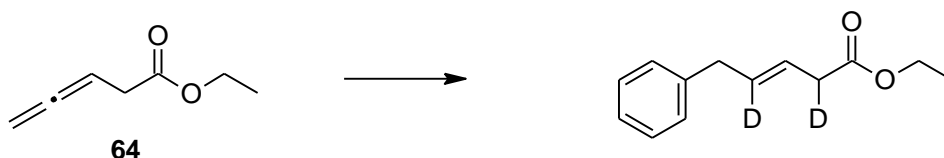


To a solution of LDA at $-78\text{ }^{\circ}\text{C}$, prepared by the addition of *n*-butyllithium (2.15 M in hexanes, 1.8 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at $0\text{ }^{\circ}\text{C}$ in Et_2O (7 mL), was added a solution of ester **64** (500 mg, 3.97 mmol, 1 eq) in Et_2O (1 mL) dropwise. After 30 minutes, copper(I)iodide (75 mg, 0.4 mmol, 10 mol%) was added followed by dropwise addition of phenyl magnesium bromide (1.4 M in Et_2O , 3.1 mL, 4.36 mmol, 1.1 eq). The reaction was then warmed to $0\text{ }^{\circ}\text{C}$ and stirred for 3 hours then cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of DCl and AcOD in D_2O (prepared by adding AcCl (1 mL) to D_2O (5 mL) with stirring) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et_2O (3 x 20 mL). The combined organic fractions were washed with saturated aqueous ammonium chloride (10 mL), dried (MgSO_4), filtered and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography eluting with petroleum spirit (b.p. $40 - 60\text{ }^{\circ}\text{C}$) / Et_2O (10:1) to afford the title compound as a colourless oil (496 mg, 61%). ^1H NMR analysis of the product shows 100% deuterium incorporation into the α position and 50% deuterium incorporation into the γ position.

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3029.6, 2983.7, 2937.4 (C-H), 1726.1 (C=O), 1601.9 (C=C); **^1H NMR** (300 MHz, CDCl_3): δ = 1.26 (t, J = 7.2 Hz, CH_3 , 3H), 3.04 (brs, CHD, 1H), 3.38 (brs, PhCH_2 , 2H), 4.14 (q, J = 7.2 Hz, CH_2CH_3 , 2H), 5.62 – 5.75 (m, $\text{CH}=\text{CD}$, 1.5H), 7.17-7.38 (m, Ar, 5H); **^{13}C NMR** (125 MHz, CDCl_3): δ = 14.2 (CH_3), 37.8 (CH_2),

38.8 (CH₂), 60.7 (CH₂COEt), 123.2 (CH), 126.1 (Ar), 128.5 (Ar), 128.7 (Ar), 133.2 (CD), 140.2 (C), 172.1 (C=O); **MS** *m/z* (+ve CI): 207 (80), 206 (75), 205 (20), 161 (25), 160 (20), 133 (50), 132 (100), 131 (55); **HRMS**: 207.13742 C₁₃H₁₅O₂D₂ requires 207.13850

Deuterated ethyl (3*E*)-5-phenylpent-3-enoate

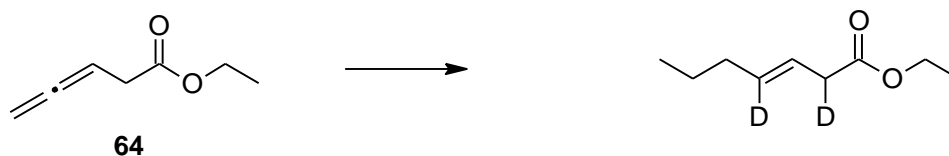


To a solution of LDA at -78 °C, prepared by the addition of *n*-butyllithium (2.15 M in hexanes, 1.8 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C in Et₂O (7 mL), was added a solution of ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 30 minutes a high vacuum was applied and the reaction warmed to 0 °C. When the reaction was evaporated to dryness the reaction flask was filled with nitrogen and Et₂O (7 mL) was added, the reaction stirred for 5 minutes and then the high vacuum applied again. The flask was then filled with nitrogen and Et₂O (7 mL) was added and the reaction cooled to -78°C. Copper(I)iodide (75 mg, 0.4 mmol, 10 mol%) was added followed by dropwise addition of phenyl magnesium bromide (1.4 M in Et₂O, 3.1 mL, 4.36 mmol, 1.1 eq). The reaction was then warmed to 0°C and stirred for 3 hours then cooled to -78 °C and a solution of DCl and AcOD in D₂O (prepared by adding AcCl (1 mL) to D₂O (5 mL) with stirring) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et₂O (3 x 20 mL). The combined organic fractions

were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (10:1) to afford the title compound as a colourless oil (172 mg, 22%). ¹H NMR analysis of the product shows 100% deuterium incorporation into the α position and 100% deuterium incorporation into the γ position.

¹H NMR (300 MHz, CDCl₃): δ = 1.26 (t, J = 7.1 Hz, CH₃, 3H), 3.04 (brs, CHD, 1H), 3.39 (brs, PhCH₂, 2H), 4.14 (q, J = 7.1 Hz, CH₂CH₃, 2H), 5.62 – 5.70 (m, CH=CD, 1 H), 7.17 – 7.32 (m, Ar, 5H)

Deuterated ethyl (3E)-hept-3-enoate

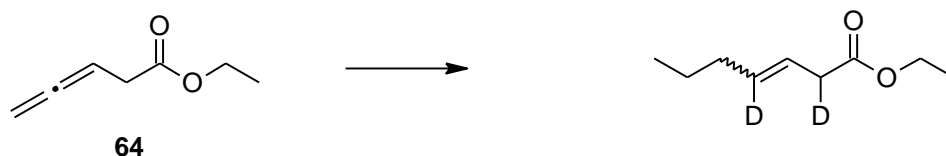


To a solution of LDA at -78 °C, prepared by the addition of *n*-butyllithium (2.28 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C in Et₂O (7 mL), was added a solution of ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 30 minutes, copper(I)iodide (75 mg, 0.4 mmol, 10 mol%) was added followed by dropwise addition of ethyl magnesium bromide (1.4 M in Et₂O, 3.1 mL, 4.36 mmol, 1.6 eq). The reaction was then warmed to 0 °C and stirred for 3 hours then cooled to -78 °C and a solution of DCl and AcOD in D₂O (prepared by adding AcCl (1 mL) to D₂O (5 mL) with stirring) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5

minutes. The mixture was then separated and the aqueous phase extracted with Et₂O (3 x 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to afford the title compound as a colourless oil (228 mg, 37%). ¹H NMR analysis of the product shows 100% deuterium incorporation into the α position and 50% deuterium incorporation into the γ position.

¹H NMR (300 MHz, CDCl₃): δ = 0.89 (t, J = 7.4 Hz, CH₃CH₂CH₂, 3H), 1.25 (t, J = 7.2 Hz, CH₃CH₂O, 3H), 1.38 (m, CH₃CH₂CH₂, 2H), 2.01 (m, CH₃CH₂CH₂, 2H), 3.00 (m, CHD, 1H), 4.15 (q, J = 7.2 Hz, CH₃CH₂, 2H), 5.49 – 5.55 (m, CH=, 1.5H)

Deuterated ethyl (3E)-hept-3-enoate

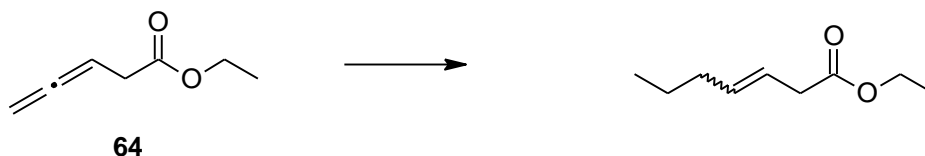


Ethyl magnesium bromide (2.45 M in Et₂O, 1.8 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)iodide (829 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.28 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0°C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was

transferred via a large bore cannula to the organocopper suspension at $-40\text{ }^{\circ}\text{C}$. The reaction was stirred between $-30\text{ }^{\circ}\text{C}$ and $-25\text{ }^{\circ}\text{C}$ for 3 hours then cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of DCl and AcOD in D_2O (prepared by adding AcCl (1 mL) to D_2O (5 mL) with stirring) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et_2O ($3 \times 20\text{ mL}$). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO_4), filtered and the solvents were removed *in vacuo*. The resulting colourless yellow oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. $40 - 60\text{ }^{\circ}\text{C}$) / Et_2O (20:1) to yield the title ester as a colourless oil (417 mg, 67%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2961.1, 2931.4, 2873.9 (C–H), 1736.2 (C=O); **^1H NMR** (500 MHz, CDCl_3): δ = 0.88 (t, $J = 7.4\text{ Hz}$, CH_3CH_2 , 3H), 1.25 (t, $J = 7.2\text{ Hz}$, $\text{CH}_3\text{CH}_2\text{O}$, 3H), 1.38 (sxt, $J = 7.4\text{ Hz}$, CH_3CH_2 , 2H), 2.00 (m, CH_2CH , 2H), 3.00 (brm, CHD, 1H), 4.13 (q, $J = 7.3\text{ Hz}$, CH_2O , 2H), 5.52 (brm, CD, 1H); **^{13}C NMR** (125 MHz, CDCl_3): δ = 13.9 (CH_3), 14.3 (CH_3), 22.4 (CH_2), 34.5 (CH_2), 38.0 (t, $J = 19.3\text{ Hz}$, CHD), 60.6 (CH_2), 121.7 (CH), 134.7 (CD), 172.3 (C=O); **MS** m/z (+ve EI): 158 (M, 65), 157 (95), 156 (41), 128 (57); **HRMS** 158.13074 $\text{C}_9\text{H}_{14}\text{O}_2$ requires 158.13012

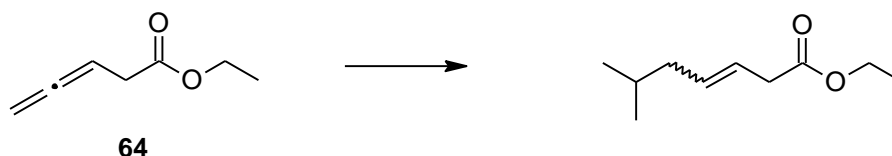
Ethyl hept-3-enoate



Ethyl magnesium bromide (2.45 M in Et₂O, 1.8 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)iodide (829 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.28 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. The reaction was stirred between -30 °C and -25 °C for 3 hours then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to yield the title ester, in an E/Z ratio of 94:6, as a colourless oil (494 mg, 80%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2961.8, 2934.4, 2874.7 (C–H), 1720.7 (C=O), 1660.3 (C=C); **¹H NMR** (500 MHz, CDCl₃): δ = 0.89 (t, J = 7.4 Hz, CH₃CH₂, 3H), 1.26 (t, J = 7.1 Hz, CH₃CH₂O, 3H), 1.39 (s, J = 7.3, CH₃CH₂, 2H), 2.00 (m, CH₂CH, 2H), 3.01 (d, J = 5.4 Hz, CH₂CO₂Et (*E*), 1.7H), 3.08 (d, J = 5.7 Hz, CH₂CO₂Et (*Z*), 0.3H), 4.13 (q, J = 7.3 Hz, CH₂O, 2H), 5.49 – 5.59 (m, CH=CH, 2H); **¹³C NMR** (125 MHz, CDCl₃): δ = 13.7 (CH₃), 14.3 (CH₃), 22.4 (CH₂), 34.6 (CH₂), 38.3 (CH₂), 60.6 (CH₂O), 121.8 (CH), 134.7 (CH), 172.3 (C=O)

Ethyl 6-methylhept-3-enoate

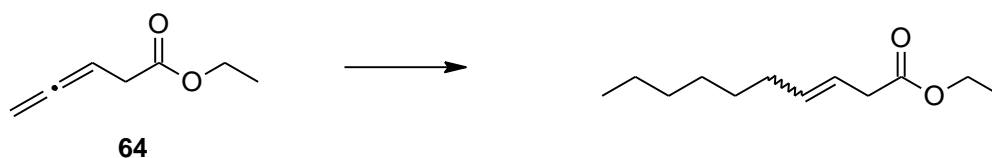


Isopropyl magnesium bromide (1.3 M in Et₂O, 3.4 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)iodide (829 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.28 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. The reaction was stirred between -30 °C and -25 °C for 3 hours then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to yield the title ester, in an E/Z ratio of 83:17, as a colourless oil (547 mg, 81%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2958.7, 2934.4, 2871.3 (C-H), 1720.2 (C=O), 1660.4 (C=C); **¹H NMR** (300 MHz, CDCl₃): δ = 0.86 (s, (CH₃)₂CH, 2.3H), 0.88 (s, (CH₃)₂CH, 0.7H), 0.88 (s, (CH₃)₂CH, 2.3H), 0.90 (s, (CH₃)₂CH, 0.7H), 1.25 (t, J = 7.2 Hz, CH₃CH₂O, 3H),

1.60 (spt, $J = 7.0$ Hz, $(\text{CH}_3)_2\text{CH}$, 1H), 1.92 (m, CHCH_2 , 2H), 3.02 (d, $J = 5.7$ Hz, $\text{CH}_2\text{CO}_2\text{Et}$ (E), 1.5H), 3.08 (d, $J = 5.4$ Hz, $\text{CH}_2\text{CO}_2\text{Et}$ (Z), 0.4H), 4.13 (q, $J = 7.2$ Hz, CH_2O , 2H), 5.52 – 5.54 (m, $\text{CH}=\text{CH}$, 1.5H), 5.89 (m, $\text{CH}=\text{CH}$, 0.4H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 14.3$ (CH_3), 22.3 ($(\text{CH}_3)_2\text{CH}$), 28.3 (CH), 38.3 (CH_2CO), 41.1 (CH_2CH), 60.7 (CH_2O), 122.7 (CH , Z), 123.3 (CH , E), 133.6 (CH), 166.2 ($\text{C}=\text{O}$); MS m/z (+ve EI): 170 (M^+ , 5), 142 (12), 127 (30); HRMS 170.12986 $\text{C}_{10}\text{H}_{18}\text{O}_2$ requires 170.13013

Ethyl dec-3-enoate

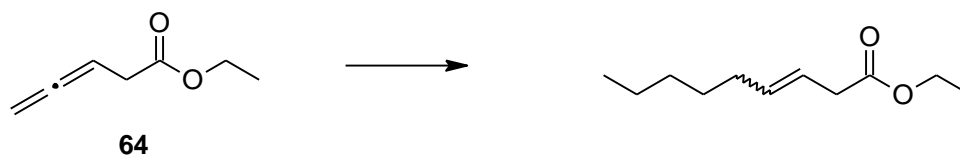


Pentyl magnesium bromide (2.4 M in Et_2O , 1.8 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)iodide (829 mg, 4.36 mmol, 1.1 eq) in Et_2O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et_2O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.28 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C) in Et_2O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. The reaction was stirred between -30 °C and -25 °C for 3 hours then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et_2O (3×20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO_4), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash

column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to yield the title ester, in an E/Z ratio of 70:30, as a colourless oil (276 mg, 35%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2956.9, 2927.3, 2857.5 (C–H), 1721.4 (C=O), 1660.4 (C=C); **¹H NMR** (500 MHz, CDCl₃): δ = 0.93 (t, J = 6.6 Hz, CH₃(CH₂)₅, 3H), 1.27 – 1.40 (m, CH₃(CH₂)₄CH₂, OCH₂CH₃, 11H), 2.05 (m, CH₃(CH₂)₄CH₂, 2H), 3.04 (d, J = 5.7 Hz, CH₂CO₂Et, (*E*), 1.4H), 3.11 (d, J = 5.7 Hz, CH₂CO₂Et, (*Z*), 0.6H), 4.16 (q, J = 7.3 Hz, OCH₂CH₃, 2H), 5.51 – 5.61 (m, CH=CH, 2H); **¹³C NMR** (125 MHz, CDCl₃): δ = 14.3 (CH₃), 14.6 (CH₃) 22.7 (CH₂), 28.9 (CH₂), 29.2 (CH₂), 29.5 (CH₂), 31.8 (CH₂), 38.3 (CH₂), 60.6 (CH₂O), 121.6 (CH), 134.9 (CH), 172.3 (C=O)

Ethyl non-3-enoate



n-Butyllithium (2.3 M in hexanes, 1.9 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)iodide (829 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.3 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. The reaction was stirred between -30 °C and -25 °C for 3 hours then cooled to -78 °C and

saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to yield the title ester, in an E/Z ratio of 74:26, as a colourless oil (410 mg, 56%).

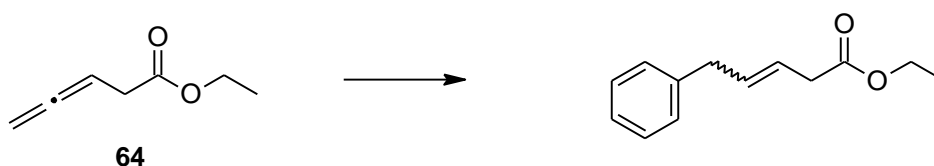
IR $\nu_{\max}/\text{cm}^{-1}$: 2958.2, 2928.5, 2858.5 (C-H), 1735.1 (C=O); **¹H NMR** (300 MHz, CDCl₃): δ = 0.88 (t, J = 6.6 Hz, CH₃(CH₂)₄, 3H), 1.23 – 1.41 (m, CH₃(CH₂)₃CH₂, OCH₂CH₃, 9H), 2.01 (m, CH₃(CH₂)₃CH₂, 2H), 3.01 (d, J = 5.1 Hz, CH₂CO₂Et, (*E*) 1.4H), 3.08 (d, J = 5.6 Hz, CH₂CO₂Et (*Z*), 0.6H), 4.13 (q, J = 7.2 Hz, OCH₂CH₃, 2H), 5.45 – 5.61 (m, CH=CH, 2H); **¹³C NMR** (75 MHz, CDCl₃): δ = 14.1 (CH₃), 14.3 (CH₃), 22.6, 22.6, 27.4, 28.9, 29.1, 31.4, 31.5, 32.5, 33.1, 38.3, 60.6 (CH₂O), 60.6 (CH₂O), 121.6 (*Z*), 120.6 (*E*), 134.9 (*Z*), 133.6 (*E*), 172.2 (C=O), 172.3 (C=O)

Alternative method for the preparation of Ethyl non-3-enoate

n-Butyllithium (2.4 M in hexanes, 1.8 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)diodide (829 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.4 M in hexanes, 1.6 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. Magnesium bromide (415 mg, 4.36 mmol, 1.1 eq) was added and the reaction was stirred between -30 °C and -25 °C for 3 hours then cooled to -78 °C and a saturated

aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to yield the title ester, in an E/Z ratio of 50:50, as a colourless oil (396 mg, 54%).

Ethyl 5-phenylpent-3-enoate

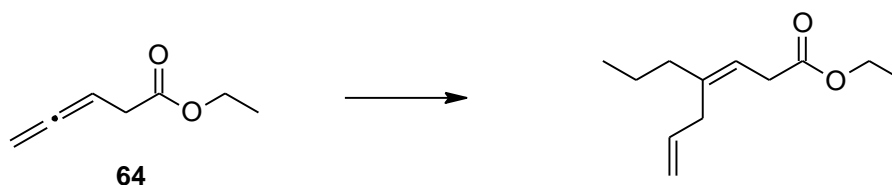


Phenyllithium (2.0 M in Et₂O, 2.2 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)bromide (625 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.3 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0°C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. The reaction was stirred between -30 °C and -25 °C for 3 hours then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with

Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to yield the title ester, in an E/Z ratio of 33:67, as a colourless oil (419 mg, 52%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2957.6, 2929.9, 2860.1 (C-H), 1720.9 (C=O), 1660.0 (C=C); **¹H NMR** (500 MHz, CDCl₃): δ = 1.28 (t, J = 7.1 Hz, CH₃, 3H), 3.06 (dd, J = 6.8, 0.9, Hz, CH₂CO₂Et (*E*), 0.6H), 3.20 (d, 6.9 Hz, CH₂CO₂Et (*Z*), 1.4H), 3.38 (d, J = 6.6 Hz, PhCH₂ (*E*), 0.6H), 3.45 (d, J = 7.3 Hz, PhCH₂ (*Z*), 1.4H), 4.17 (q, J = 7.2 Hz, CO₂CH₂CH₃, 2H), 5.66 – 5.79 (m, CH=CH, 2H), 7.18-7.32 (m, ArH, 5H); **¹³C NMR** (75 MHz, CDCl₃): δ = 14.3 (CH₃), 36.4 (CH₂), 38.1 (CH₂), 61.7 (CH₂O), 123.4 (CH), 125.9 (Ar), 128.1 (Ar), 129.8 (Ar), 132.4 (CH), 134. (CH), 139.7 (C), 176.9 (C=O)

Ethyl (3Z)-4-propylhepta-3,6-dienoate

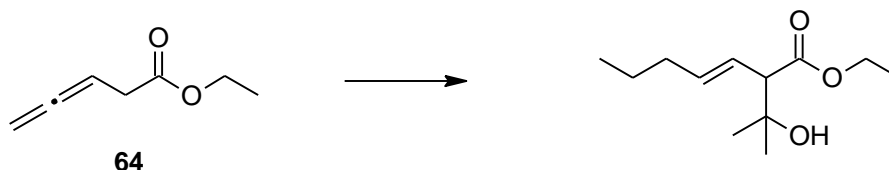


Ethyl magnesium bromide (1.4 M in Et₂O, 3.1 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)iodide (829 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added

dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.28 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. The reaction was stirred between -30 °C and -25 °C for 3 hours then allyl bromide (1.1 mL, 12.28 mmol, 3.1 eq) was added dropwise. After 2 hours the reaction was cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to yield the title ester as a colourless oil (341 mg, 44%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2977.0, 2960.0, 2932.0, 2873.0 (m, C–H), 1738.0 (s, C=O), 1637.0 (w, C=C); **¹H NMR** (500 MHz, CDCl₃): δ = 0.91 (t, J = 7.6 Hz, CH₃CH₂CH₂, 3H), 1.28 (t, J = 7.6 Hz, OCH₂CH₃, 3H), 1.46 (sxt, J = 7.4 Hz, CH₃CH₂CH₂, 2H), 2.03 (t, J = 7.6 Hz, CH₃CH₂CH₂, 2H), 2.80 (d, J = 6.3 Hz, CH₂CH=CH₂, 2H), 3.08 (d, J = 6.9 Hz, CH₂CO₂Et, 2H), 4.16 (q, J = 7.3 Hz, OCH₂CH₃, 2H), 5.04 (ddq, J = 17.0, 10.1, 1.6 Hz, CH=CH₂, 2H), 5.44 (t, J = 7.1 Hz, CHCH₂CO₂Et, 1H), 5.75 (ddt, J = 16.9, 10.2, 6.5 Hz, CH=CH₂, 1H); **¹³C NMR** (125 MHz, CDCl₃): δ = 13.8 (CH₃), 14.3 (CH₃), 20.9 (CH₂), 33.6 (CH₂), 35.0 (CH₂), 39.2 (CH₂), 60.6 (CH₂O), 115.5 (CH), 117.2 (CH), 135.4 (CH), 140.6 (C), 172.4 (C=O); **MS** *m/z* (+ve CI): 197 (M+H, 82), 171 (37), 151 (100); **HRMS** 197.15447 C₁₂H₂₁O₂ requires 197.15415

Ethyl (3E)-2-(2-hydroxypropan-2-yl)hept-3-enoate

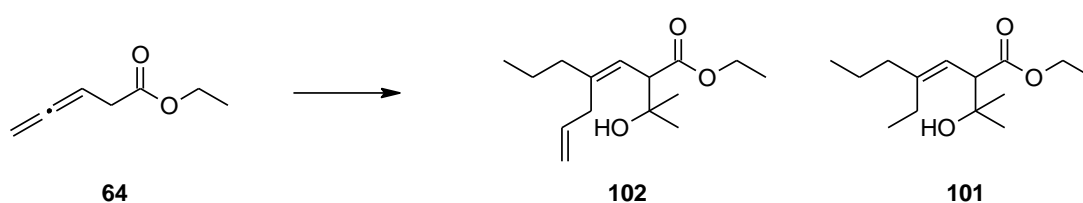


Ethyl magnesium bromide (1.4 M in Et₂O, 3.1 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)iodide (829 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.28 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. The reaction was stirred between -30 °C and -25 °C for 3 hours then acetone (0.32 mL, 4.36 mmol, 1.1 eq) was added dropwise. After 2 hours the reaction was cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (6:1) to yield the title ester as a colourless oil (130 mg, 15%).

IR $\nu_{\max}/\text{cm}^{-1}$: 3491.4 (br, O–H), 2965.1, 2933.5, 2874.2 (m, C–H), 1729.3, (s, C=O);
¹H NMR (600 MHz, CDCl₃): δ = 0.89 (t, J = 7.2 Hz, CH₃CH₂CH₂, 3H), 1.18 (s, CCH₃, 3H), 1.23 (s, CCH₃, 3H), 1.28 (t, J = 6.8 Hz, OCH₂CH₃, 3H), 1.40 (sxt, J =

7.2 Hz, CH₃CH₂CH₂, 2H), 2.03 (td, J = 7.5, 6.0 Hz, CH₃CH₂CH₂, 2H), 2.95 (d, J = 8.7 Hz, CHCO₂Et, 1H), 4.18 (q, J = 6.8 Hz, OCH₂CH₃, 2H), 5.55 – 5.63 (m, CH=CH, 2H); ¹³C NMR (150 MHz, CDCl₃): δ = 13.7 (CH₃), 14.3 (CH₃), 22.4 (CH₂), 26.6 (CH₃), 28.8 (CH₃), 34.7 (CH₂), 59.4 (CH), 60.9 (CH₂O), 71.4 (C), 124.4 (CH), 136.5 (CH), 174.6 (C=O); MS *m/z* (+ve CI): 215 (M+H, 12), 197 (100); HRMS found 215.16395 C₁₂H₂₃O₃ requires 215.16472

Carbometallation-aldol-allylation sequence

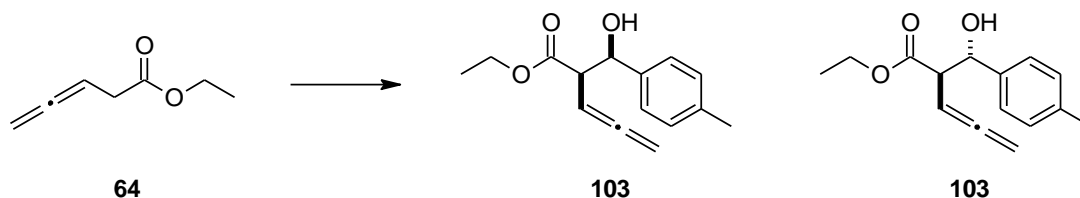


Ethyl magnesium bromide (1.4 M in Et₂O, 3.1 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)iodide (829 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.28 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. The reaction was stirred between -30 °C and -25 °C for 3 hours then acetone (0.9 mL, 11.91 mmol, 1.1 eq) and allyl bromide (1.03 mL, 11.91 mmol, 3 eq) were added dropwise. After 2 hours the reaction was cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture

was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude mixture was partially purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (6:1) to yield a 1:0.6 mixture of **102** and **101**.

IR $\nu_{\max}/\text{cm}^{-1}$: 3499.1 (O-H), 2967.7, 2937.8, 2871.4 (C-H), 1708.9 (C=O); **¹H NMR** (500 MHz, CDCl₃): δ = 0.87 (t, J = 7.3 Hz, CH₃CH₂CH₂), 1.16 (s, CCH₃), 1.26 (s, CCH₃, OCH₂CH₃), 1.43 (sxt, J = 7.2 Hz, CH₃CH₂CH₂), 1.58 (s, OH), 2.04 (CH₃CH₂CH₂), 2.84 (d, J = 6.4 Hz, CHCO₂Et), 3.28 (m, CH₂CH=CH₂), 4.15 (m, OCH₂CH₃), 5.02 (m, CH=CH₂), 5.48 (d, J = 10.2 Hz, CHCHCO₂Et), 5.73 (m, CH=CH₂); **¹³C NMR** (125 MHz, CDCl₃): δ = 13.2, 13.9, 14.3, 21.1, 21.4, 23.4, 26.5, 26.6, 29.0, 32.5, 35.0, 38.7, 39.1, 41.5, 53.8, 71.6, 115.9, 116.3, 118.2, 120.0, 120.2, 135.8, 136.7, 142.4, 143.3, 146.6, 174.7, 175.0

Ethyl-2-[hydroxy(4-methylphenyl)methyl]penta-3,4-dienoate



To a solution of LDA at -78 °C, prepared by the addition of *n*-butyllithium (2.2 M in hexanes, 1.8 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C in Et₂O (7 mL), was added a solution of ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 30 minutes a solution of *p*-tolualdehyde (0.47 mL, 3.97 mmol, 1 eq) in Et₂O (2 mL) was added dropwise. The reaction was stirred for 10 minutes then a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The mixture was warmed to room temperature, separated and the aqueous phase was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with brine (20 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude mixture was purified by flash column chromatography petroleum spirit (b.p. 40 – 60 °C) / EtOAc (6:1) to afford *syn* ester **103** (618 mg, 58%) and *anti* ester **103** (334 mg, 31%). Analysis of the two diastereoisomers was by ¹H NMR with reference to the reported spectra of *erythro*- and *threo*-ethyl-2-ethenyl-3-hydroxy-3-phenylpropanoate.⁹⁸

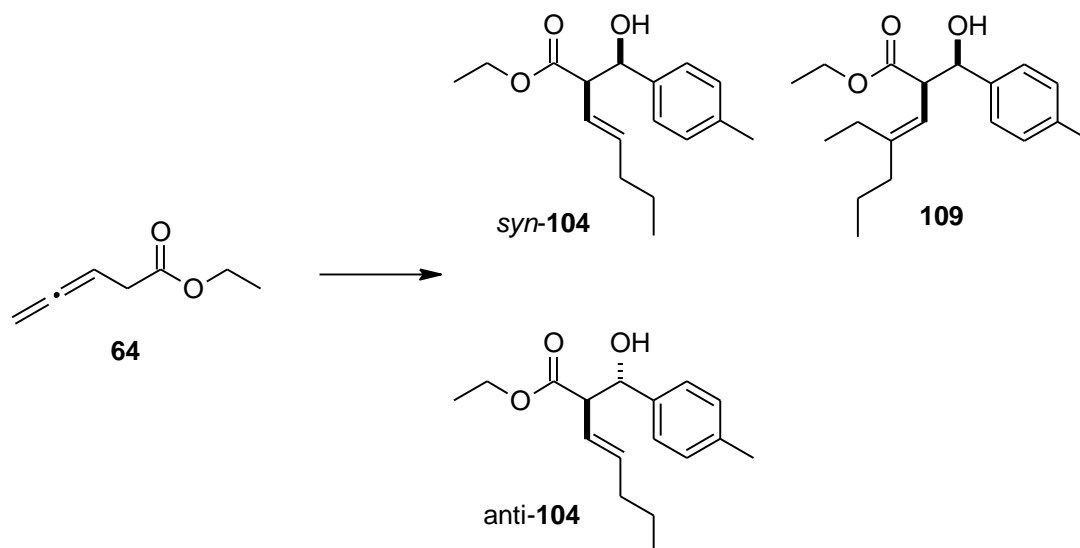
Data for *syn*-**103**

IR $\nu_{\max}/\text{cm}^{-1}$: 3475.0 (br, O–H), 2983.1, 2926.9 (C–H), 1957.9 (C=C=C), 1716.4 (C=O); **¹H NMR** (500 MHz, CDCl₃): δ = 1.15 (t, *J* = 6.9 Hz, CH₃CH₂, 3H), 2.33 (s, ArCH₃, 3H), 2.93 (d, *J* = 2.7 Hz, OH, 1H), 3.34 (ddt, *J* = 8.6, 5.7, 1.7 Hz, CHCO₂Et, 1H), 4.09 (q, *J* = 6.9 Hz, CH₂CH₃, 2H), 4.70 (ddd, *J* = 11, 6.8, 1.7 Hz, CH=C=CH₂, 1H), 4.78 (ddd, *J* = 11, 6.7, 1.7 Hz, CH=C=CH₂, 1H), 5.02 (dd, *J* = 5.6, 2.8 Hz, CHOH, 1H), 5.30 (dt, *J* = 8.5, 6.7 Hz, CH=C=CH₂, 1H), 7.14 (d, *J* = 7.9 Hz, ArH, 2H), 7.24 (d, *J* = 8.0 Hz, ArH, 2H); **¹³C NMR** (125 MHz, CDCl₃): δ = 14.1 (CH₃), 21.2 (CH₃), 27.1 (CH), 49.5 (CH), 61.1 (CH₂O), 76.3 (CH=C=CH₂), 85.2 (CH=C=CH₂), 126.4 (Ar), 129.0 (Ar), 137.6 (C), 137.7 (C), 172.5 (C=O), 209.7 (C=C=C); **MS** *m/z* (+ve ES): 269 (30), 201 (40), 194 (100); **HRMS** found 269.1164 C₁₅H₁₈O₃Na requires 269.1154

Data for *anti*-103

IR $\nu_{\max}/\text{cm}^{-1}$: 3456.9 (br O–H), 2982.6, 2925.1 (C–H), 1957.8 (C=C=C), 1716.9 (C=O); **$^1\text{H NMR}$** (500 MHz, CDCl_3): δ = 1.26 (t, J = 7.2 Hz, CH_3CH_2 , 3H), 2.34 (s, ArCH_3 , 3H), 2.88 (dd, J = 4.9, 1.3 Hz, OH, 1H), 3.40 (tt, J = 8.4, 2.1 Hz, CHCO_2Et , 1H), 4.20 (q, J = 7.1 Hz, CH_2CH_3 , 2H), 4.62 (ddd, J = 11, 6.8, 2 Hz, $\text{CH}=\text{C}=\text{CH}_2$, 1H), 4.72 (ddd, J = 11, 6.7, 2 Hz, $\text{CH}=\text{C}=\text{CH}_2$, 1H), 4.89 (dd, J = 8.3, 5.1 Hz, CHOH , 1H), 5.05 (dt, J = 8.2, 6.7 Hz, $\text{CH}=\text{C}=\text{CH}_2$, 1H), 7.15 (d, J = 7.9 Hz, ArH, 2H), 7.23 (d, J = 8.2 Hz, ArH, 2H); **$^{13}\text{C NMR}$** (125 MHz, CDCl_3): δ = 14.1 (CH_3), 21.3 (CH_3), 27.1 (CH), 49.5 (CH), 61.2 (CH_2O), 75.2 ($\text{CH}=\text{C}=\text{CH}_2$), 86.3 ($\text{CH}=\text{C}=\text{CH}_2$), 126.7 (Ar), 129.1 (Ar), 137.8 (C), 138.1 (C), 172.9 (C=O), 209.2 (C=C=C); **MS** m/z (+ve ES): 269 (100), 242 (75), 229 (30), 201 (80); **HRMS** found 269.1162 $\text{C}_{15}\text{H}_{18}\text{O}_3\text{Na}$ requires 269.1154

Carbometallation-aldol sequence



Ethyl magnesium bromide (2.11 M in Et₂O, 2.1 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)iodide (829 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.33 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. The reaction was stirred between -30 °C and -25 °C for 3 hours then cooled to -78 °C and a solution of *p*-tolualdehyde (0.47 mL, 3.97 mmol, 1 eq) in Et₂O (2 mL) was added dropwise. The reaction was stirred for 10 minutes then a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in vacuo* and the filtrate was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (6:1) to afford esters **109** (54 mg, 4%), *syn*-**104** (82 mg, 7%), *syn*-**103** (163 mg, 17%), *anti*-**104** (154 mg, 14%), *anti*-**103** (103 mg, 11%) as colourless oils. The data for *syn*-**103** and *anti*-**103** is shown above

Data for **109**

IR $\nu_{\max}/\text{cm}^{-1}$: 3498.8 (O–H), 2960.2, 2931.8, 2872.8 (C–H), 1729.7 (C=O), 1636.5; **¹H NMR** (300 MHz, CDCl₃): δ = 0.85 (m, CH₃, 6H), 1.11 (t, J = 7.1 Hz, OCH₂CH₃, 3H), 1.40 (sxt, J = 7.2 Hz, CH₃CH₂CH₂, 2H), 1.98 (m, (CH₂)₂C=, 4H), 2.31 (s, ArCH₃, 3H), 2.83 (d, J = 2.1 Hz, OH, 1H), 3.54 (dd, 10.2, 6.4 Hz, CHCO₂Et, 1H), 4.03 (q, J = 7.2 Hz, OCH₂CH₃, 2H), 4.92 (d, J = 6.2 Hz, CHOH, 1H), 5.3 (d, J = 10.2 Hz, C=CH, 1H), 7.09 – 7.24 (m, ArH, 4H); **¹³C NMR** (125 MHz, CDCl₃): δ = 13.1

(CH₃), 13.9 (CH₃), 14.1 (CH₃), 21.1 (CH₂), 21.2 (CH₂), 23.5 (CH₂), 38.7 (CH₂), 53.0 (CH), 60.7 (CH₂O), 74.4, 117.3 (CH), 126.5 (Ar), 128.1 (Ar), 137.4 (C), 138.1 (C), 148.5 (C), 173.3 (C=O); **MS** *m/z* (+ve CI): 287 (M-OH) (20), 213 (100), 184 (36), 133 (36); **HRMS** found 287.20177 C₁₉H₂₇O₂ (M-OH) requires 287.20111

Data for *syn*-104

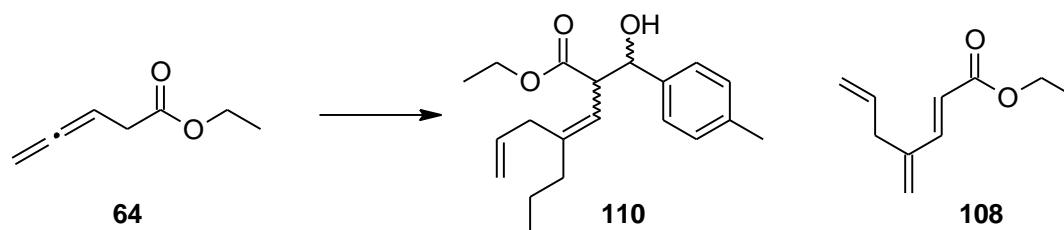
IR $\nu_{\max}/\text{cm}^{-1}$: 3446.8 (O-H), 2961.3, 2927.9, 2872.0 (C-H), 1722.9 (C=O); **¹H NMR** (600 MHz, CDCl₃): δ = 0.85 (t, *J* = 7.5 Hz, CH₃CH₂CH₂, 3H), 1.11 (t, *J* = 7.2 Hz, OCH₂CH₃, 3H), 1.37 (sxt, *J* = 7.5 Hz, CH₃CH₂CH₂, 2H), 2.02 (m, CH₃CH₂CH₂, 2H), 2.32 (s, ArCH₃, 3H), 2.81 (d, *J* = 2.3 Hz, OH, 1H), 3.23 (dd, 7.3, 6.4 Hz, CHCO₂Et, 1H), 4.03 (q, *J* = 6.9 Hz, OCH₂CH₃, 2H), 4.89 (dd, *J* = 6.6, 1.7 Hz, CHOH, 1H), 5.54 – 5.62 (m, CH=CH, 1H), 7.11 – 7.22 (m, ArH, 4H); **¹³C NMR** (150 MHz, CDCl₃): δ = 13.7 (CH₃), 14.1 (CH₃), 21.2 (CH₂), 22.3 (CH₂), 34.8 (CH₂), 57.8 (CH), 60.9 (CH₂O), 74.1, 115.2 (CH), 123.7 (CH), 126.6 (Ar), 129.0 (Ar), 137.4 (C), 173.0 (C=O); **MS** *m/z* (+ve CI): 259 (M-OH) (35), 219 (20), 213 (18), 185 (100), 156 (22); **HRMS** found 259.1702 C₁₇H₂₃O₂ (M-OH) requires 259.16980

Data for *anti*-104

IR $\nu_{\max}/\text{cm}^{-1}$: 3455.9 (O-H), 2961.0, 2931.1, 2868.0 (C-H), 1723.1 (C=O); **¹H NMR** (500 MHz, CDCl₃): δ = 0.75 (t, *J* = 7.6 Hz, CH₃CH₂CH₂, 3H), 1.24 (m, OCH₂CH₃, CH₃CH₂CH₂, 3H), 1.88 (m, CH₃CH₂CH₂, 2H), 2.32 (s, ArCH₃, 3H), 2.84 (d, *J* = 3.8 Hz, OH, 1H), 3.34 (t, *J* = 8.4 Hz, CHCO₂Et, 1H), 4.17 (q, *J* = 7.2 Hz, OCH₂CH₃, 2H), 4.86 (dd, *J* = 7.7, 2.5 Hz, CHOH, 1H), 5.31 (ddt, *J* = 15.6, 8.4, 1.1 Hz, =CHCHCO₂Et, 1H), 5.40 (dt, *J* = 15.4, 6.5 Hz, CH=CHCHCO₂Et, 1H) 7.11 – 7.19 (m, ArH, 4H); **¹³C NMR** (125 MHz, CDCl₃): δ = 13.4 (CH₃), 14.2 (CH₃), 21.2 (CH₂), 22.1 (CH₂), 34.5 (CH₂), 57.0 (CH), 60.9 (CH₂O), 75.5, 124.0 (CH), 126.6 (CH),

129.0 (Ar), 135.8 (Ar), 137.5 (C), 138.3 (C), 173.9 (C=O); **MS** m/z (+ve ES): 299 (100), 259 (10); **HRMS** found 299.1629 C₁₇H₂₄O₃ requires 299.1623

Carbometallation-aldol-allylation sequence



Ethyl magnesium bromide (2.11 M in Et₂O, 2.1 mL, 4.36 mmol, 1.1 eq) was added dropwise to a stirred suspension of copper(I)iodide (829 mg, 4.36 mmol, 1.1 eq) in Et₂O (3 mL) at -30 °C. The reaction was stirred for 1 hour between -30 °C and -25 °C. In a separate flask ester **64** (500 mg, 3.97 mmol, 1 eq) in Et₂O (1 mL) was added dropwise to a solution of LDA (prepared by the addition of *n*-butyllithium (2.33 M in hexanes, 1.7 mL, 3.97 mmol, 1 eq) to diisopropylamine (0.56 mL, 3.97 mmol, 1 eq) at 0 °C) in Et₂O (5 mL) at -78 °C. After 30 minutes the enolate solution was transferred via a large bore cannula to the organocopper suspension at -40 °C. The reaction was stirred between -30 °C and -25 °C for 3 hours then cooled to -78 °C and a solution of *p*-tolualdehyde (0.47 mL, 3.97 mmol, 1 eq) in Et₂O (2 mL) was added dropwise. The reaction was stirred for 10 minutes then allyl bromide (1.1 mL, 12.28 mmol, 3.1 eq) was added dropwise. The reaction was warmed to -20 °C and stirred for 2 hours then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred in the air for 5 minutes. The mixture was then filtered *in*

vacuo and the filtrate was extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / ethyl acetate (6:1) to afford ester **108**. Tentative assignment of other products suggests a mixture of esters **110**, **109** and **103** however the aforementioned products were not able to be separated.

Data for **108**

IR $\nu_{\max}/\text{cm}^{-1}$: 2924.7 (C–H), 1717.9 (C=O), 1368.9; **¹H NMR** (600 MHz, CDCl₃): δ = 1.30 (t, J = 6.8 Hz, CH₃CH₂O, 3H), 2.99 (d, J = 6.6 Hz, CCH₂CH, 2H), 4.21 (q, J = 7.2 Hz, CH₃CH₂O, 2H), 5.10 (m, CH=CH₂, 2H), 5.36 (s, C=CH₂, 1H), 5.44 (s, C=CH₂, 1H), 5.85 (m, CH=CH₂, 1H), 5.93 (d, J = 15.8 Hz, CHCO, 1H), 7.33 (d, J = 16.2 Hz, CHCHCO, 1H); **¹³C NMR** (150 MHz, CDCl₃): δ = 14.4 (CH₃), 36.1 (CH₂), 60.5 (CH₂O), 117.1 (CH₂), 118.8 (CH₂), 124.3 (CH), 135.0 (CH), 142.9 (CH), 146.1 (C), 167.2 (C=O); **MS** m/z (+ve CI): 167 (M+H) (100), 151 (20); **HRMS** found 167.10674 C₁₀H₁₅O₂ requires 167.10720

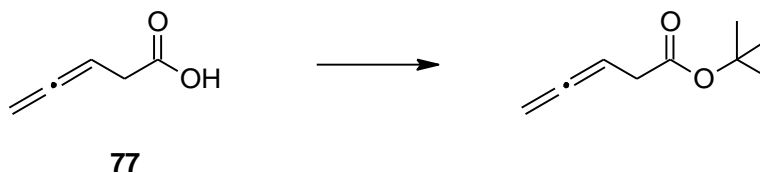
Selected data tentatively assigned to **110**

IR $\nu_{\max}/\text{cm}^{-1}$: 3498.1 (O–H), 2959.8, 2931.0, 2872.1 (C–H), 1728.5, 1711.8 (C=O), 1636.4; **¹H NMR** (600 MHz, CDCl₃): δ = 0.84 (t, CH₃CH₂CH₂), 1.12 (m, OCH₂CH₃), 1.41 (m, CH₃CH₂CH₂), 2.00 (m, CH₃CH₂CH₂), 2.32 (s, ArCH₃), 2.66 (d, J = 6.4 Hz, CH₂CH=CH₂), 3.54 (m, CHCO₂Et), 4.03 (m, OCH₂CH₃), 4.93 (m, CHOH, CH=CH₂), 5.43 (m, C=CH), 5.53 (m, CH=CH₂), 7.11-7.22 (m, ArH)

Selected data tentatively assigned to **110**

IR $\nu_{\max}/\text{cm}^{-1}$: 3464.9 (O–H), 1960.8, 2930.1, 2872.4 (C–H), 1716.2 (C=O), 1636.4;
 ^1H NMR (600 MHz, CDCl_3): δ = 0.71 (t, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.16 (m, OCH_2CH_3), 1.78 (m, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.85 (m, $\text{CH}_3\text{CH}_2\text{CH}_2$), 2.3 (s, ArCH_3), 2.56 (d, J = 6.4 Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.33 (m, CHCO_2Et), 4.1 (m, OCH_2CH_3), 4.87 (m, CHOH , $\text{CH}=\text{CH}_2$), 5.17 (m, $\text{C}=\text{CH}$), 5.39 (m, $\text{CH}=\text{CH}_2$), 7.11-7.24 (m, ArH)

tert-Butyl penta-3,4-dienoate

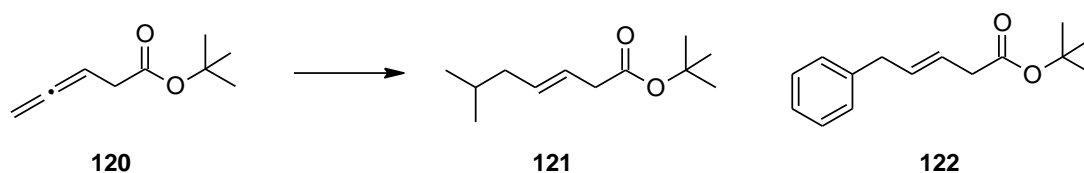


Trifluoroacetic anhydride (18 mL, 127.42 mmol, 2.5 eq) was added dropwise to a mixture of *tert* butanol (50 mL) and acid **77** (5 g, 50.10 mmol, 1 eq) whilst simultaneously cooling to 0 °C in an ice bath. After addition was complete the reaction was stirred for a further 5 minutes at 0 °C then warmed to room temperature and stirred for 30 minutes. The reaction was poured slowly into saturated solution of sodium hydrogen carbonate (100 mL) and the mixture was extracted with Et_2O (3 x 30 mL). The organic fractions were combined and washed with saturated sodium hydrogen carbonate (20 mL) then brine (20 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The resultant crude liquid was purified by distillation (70 – 72 °C, 20mmHg) to afford the title ester as a colourless oil (3.94 g, 51%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2980.5, 2933.0 (m, C–H), 1960.6 (m, C=C=C), 1730.2 (s, C=O); **^1H NMR** (300 MHz, CDCl_3): δ = 1.44 (s, 9H), 2.94 (dt, J = 7.5, 2.9 Hz, 2H), 4.72 (dt, J = 6.7, 2.9 Hz, 2H), 5.22 (m, 1H); **^{13}C NMR** (75 MHz, CDCl_3): δ = 28.1 (CH_3), 35.3

(CH₂), 75.5 (HC=C=CH₂), 83.9 (C), 99.0 (HC=C=CH₂), 170.6 (C=O), 209.2 (C=C=C); **MS** *m/z* (+ve CI): 155 (30), 115 (40), 99 (100); **HRMS** found 155.10621 M⁺ C₉H₁₄O₂ requires 155.10665

tert-Butyl (3E)-6-methylhept-3-enoate and tert-butyl (3E)-5-phenylpent-3-enoate



To a stirred solution of isopropyl magnesium bromide (2.1 M in Et₂O, 1.2 mL, 2.60 mmol, 1 eq) in Et₂O (5 mL) at -20 °C was added a solution of ester **120** (400 mg, 2.60 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 15 minutes the reaction was cooled to -78 °C and copper(I)iodide (49 mg, 0.26 mmol, 10 mol%) was added followed by phenyl magnesium bromide (2.66 M in Et₂O, 1.1 mL, 2.85 mmol, 1.1 eq) dropwise. The reaction was warmed to 0 °C and stirred for 1 hour 30 minutes then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to

afford ester **121** as a colourless oil (63 mg, 12%) and ester **122** as a colourless oil (227 mg, 38%)

Data for **121**

IR $\nu_{\max}/\text{cm}^{-1}$: 2979.4, 2959.0 (m, C–H), 1731.9 (s, C=O), 1368.2; **R_f** = 0.37 (Petroleum spirit / Et₂O; 20:1); **¹H NMR** (500 MHz, CDCl₃): δ = 0.88 (d, J = 6.6 Hz, 2 × CH₃, 6H), 1.44 (s, ^tBu, 9H), 1.61 (m, CH(CH₃)₂, 1H), 1.91 (dt, J = 6.8, 5.8 Hz, CH₂CH(CH₃)₂, 2H), 2.93 (d, J = 5.7 Hz, CH₂CO₂^tBu, 2H), 5.48 (dt, J = 15.3, 5.7 Hz, CHCH₂CO₂^tBu, 1H), 5.52 (dt, J = 15.3, 6.0 Hz, CHCH₂CH(CH₃)₂, 1H); **¹³C NMR** (125 MHz, CDCl₃): δ = 22.3 (CH₃), 28.2 (CH₃), 28.2 (CH₃), 28.3 (CH₂), 39.5 (CH₂), 41.9 (CH), 80.4 (C), 123.4 (CH), 133.1 (CH), 171.7 (C=O); **MS** m/z (+ve FAB): 221 (100), 207 (90); found 221.15072 M⁺ C₁₂H₂₂O₂ requires 221.15174

Data for **122**

IR $\nu_{\max}/\text{cm}^{-1}$: 2979.0, 2932.0, 2908.0 (m, C–H), 1730.0 (s, C=O), 1495.0; **R_f** = 0.26 (Petroleum spirit / Et₂O; 20:1); **¹H NMR** (500 MHz, CDCl₃): δ = 1.45 (s, ^tBu, 9H), 2.98 (dd, J = 6.8, 1.1 Hz, CH₂CO₂^tBu, 2H), 3.38 (d, J = 6.5 Hz, PhCH₂, 2H), 5.62 (dt, J = 15.3, 6.8, 1.3 Hz, CHCH₂CO₂^tBu, 1H), 5.69 (dt, J = 15.3, 6.6, 1.1 Hz, PhCH₂CH, 1H), 7.18 – 7.30 (m, ArH, 5H); **¹³C NMR** (125 MHz, CDCl₃): δ = 28.2 (CH₃), 39.0 (CH₂), 39.3 (CH₂), 80.6 (C), 124.0 (CH), 126.1 (Ar), 128.5 (Ar), 128.6 (Ar), 132.7 (CH), 140.4 (C), 171.4 (C=O); **MS** m/z (EI): 232 (10), 176 (100), 159 (60); **HRMS** found 232.14520 M⁺ C₁₅H₂₀O₂ requires 232.14577

Alternative method for the preparation of **121**

To a stirred solution of isopropyl magnesium bromide (2.33 M in Et₂O, 1.4 mL, 3.24 mmol, 1 eq) in Et₂O (6 mL) at -20 °C was added a solution of ester **120** (500 mg,

3.24 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 30 minutes the reaction was cooled to -78 °C and copper(I)iodide (62 mg, 0.32 mmol, 10 mol%) was added followed by isopropyl magnesium bromide (2.33 M in Et₂O, 1.5 mL, 3.57 mmol, 1.1 eq) dropwise. The reaction was warmed to room temperature and stirred for 7 hours then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to afford ester **121** as a colourless oil (181 mg, 28%).

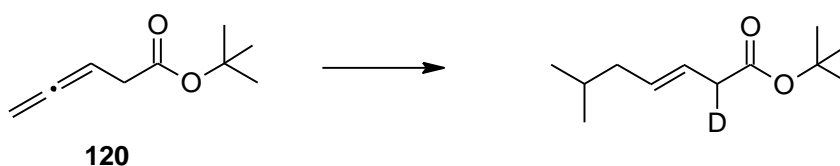
Alternative method for the preparation of **122**

To a stirred solution of phenyl magnesium bromide (2.64 M in Et₂O, 1.2 mL, 3.24 mmol, 1 eq) in Et₂O (5 mL) at -20 °C was added a solution of ester **120** (400 mg, 2.60 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 30 minutes the reaction was cooled to -78 °C and copper(I)iodide (62 mg, 0.32 mmol, 10 mol%) was added followed by phenyl magnesium bromide (2.64 M in Et₂O, 1.4 mL, 3.7 mmol, 1.1 eq) dropwise. The reaction was warmed to 0 °C and stirred for 2 hours then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to afford ester **122** as a colourless oil (480 mg, 64%).

Alternative method for the preparation of ester **122**

To a stirred solution of phenyl magnesium bromide (2.64 M in Et₂O, 1.4 mL, 3.57 mmol, 1.1 eq) in Et₂O (5 mL) and copper(I)iodide (62 mg, 0.32 mmol, 10 mol%) at -78 °C was added a solution of ester **120** (500 mg, 3.24 mmol, 1 eq) in Et₂O (1 mL) dropwise. The reaction was warmed to 0 °C and stirred for 2 hours then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (10 mL) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to afford ester **122** as a colourless oil (338 mg, 45%). The spectral properties of the product were identical to those reported above.

Deuterated tert-butyl (3E)-6-methylhept-3-enoate

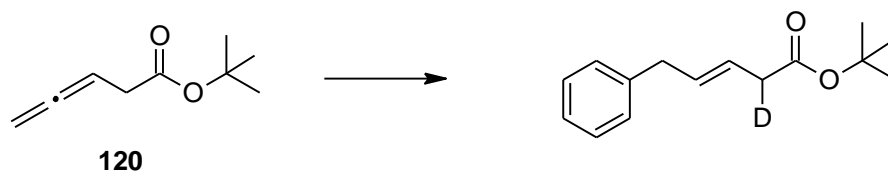


To a stirred solution of isopropyl magnesium bromide (2.33 M in Et₂O, 1.4 mL, 3.24 mmol, 1 eq) in Et₂O (5 mL) at -20 °C was added a solution of ester **120** (500 mg, 3.24 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 30 minutes the reaction was cooled to -78 °C and copper(I)iodide (62 mg, 0.32 mmol, 10 mol%) was added followed by isopropyl magnesium bromide (2.33 M in Et₂O, 1.5 mL, 3.57 mmol, 1.1 eq) dropwise. The reaction was warmed to room temperature and stirred for 7 hours then

cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of DCl and AcOD in D_2O (prepared by adding AcCl (1 mL) to D_2O (5 mL) with stirring) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et_2O ($3 \times 20\text{ mL}$). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO_4), filtered and the solvents were removed *in vacuo*. The resulting oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. $40 - 60\text{ }^{\circ}\text{C}$) / Et_2O (20:1) to afford the title ester as a colourless oil (208 mg, 32%)

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2957.4, 2870.4 (m, C–H), 1731.9 (s, C=O), 1466.5; **$^1\text{H NMR}$** (500 MHz, CDCl_3): $\delta = 0.88$ (d, $J = 6.6\text{ Hz}$, $2 \times \text{CH}_3$, 6H), 1.44 (s, ^tBu , 9H), 1.61 (m, $\text{CH}(\text{CH}_3)_2$, 1H), 1.91 (dt, $J = 6.8, 5.8\text{ Hz}$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, 2H), 2.91 (brs, $\text{CHDCO}_2^t\text{Bu}$, 1H), 5.47 (dd, $J = 15.3, 5.7\text{ Hz}$, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$, 1H), 5.52 (dd, $J = 15.3, 6.6\text{ Hz}$, $\text{CHCHDCO}_2^t\text{Bu}$, 1H); **$^{13}\text{C NMR}$** (125 MHz, CDCl_3): $\delta = 22.3$ (CH_3), 28.1 (CH_3), 28.2 (CH_2) 39.4 (CH_2), 41.9 (CH), 80.4 (C), 123.3 (CH), 133.1 (CH), 171.7 (C=O); **MS** m/z (+ve CI): (100), 185 (46), 178 (96), 177 (44); **HRMS** found 200.17624 ($\text{M}+\text{H}$) $^+$ $\text{C}_{12}\text{H}_{22}\text{D}\text{O}_2$ requires 200.17608

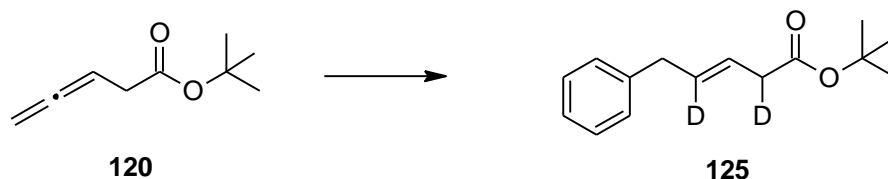
Deuterated tert-butyl (3E)-5-phenylpent-3-enoate



To a stirred solution of phenyl magnesium bromide (2.64 M in Et₂O, 1.2 mL, 3.24 mmol, 1 eq) in Et₂O (5 mL) at -20 °C was added a solution of ester **120** (500 mg, 3.24 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 30 minutes the reaction was cooled to -78 °C and copper(I)iodide (62 mg, 0.32 mmol, 10 mol%) was added followed by phenyl magnesium bromide (2.64 M in Et₂O, 1.4 mL, 3.57 mmol, 1.1 eq) dropwise. The reaction was warmed to 0 °C and stirred for 1 hour 30 minutes then cooled to -78 °C and a solution of DCl and AcOD in D₂O (prepared by adding AcCl (1 mL) to D₂O (5 mL) with stirring) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to afford the title ester as a colourless oil (409 mg, 54%)

IR $\nu_{\max}/\text{cm}^{-1}$: 3027.5, 2978.2, 2932.6 (m, C–H), 1725.6 (s, C=O), 1603.0; **¹H NMR** (500 MHz, CDCl₃): δ = 1.45 (s, ^tBu, 9H), 2.97 (brs, CHDCO₂^tBu, 1H), 3.38 (d, J = 6.5 Hz, PhCH₂, 2H), 5.61 (dd, J = 15.3, 6.6 Hz, PhCH₂CH=CH, 1H), 5.69 (dtt, J = 15.3, 6.6, 1.1 Hz, PhCH₂CH, 1H), 7.18 – 7.34 (m, ArH, 5H); **¹³C NMR** (125 MHz, CDCl₃): δ = 28.2 (C(CH₃)₃), 39.0 (CH₂CO), 80.6 (C), 123.9 (CH), 126.1 (Ar), 128.5 (Ar), 128.6 (Ar), 132.8 (CH), 140.4 (C), 171.4 (C=O); **MS** *m/z* (+ve CI): 234 (37), 178 (100), 177 (61); **HRMS** found 234.16082 (M+H)⁺ C₁₅ H₂₀ O₂ requires 234.16043

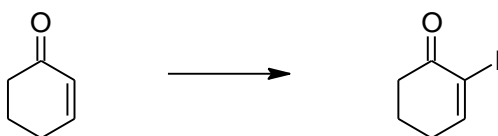
Deuterated tert-butyl (3E)-5-phenylpent-3-enoate



To a stirred solution of isopropyl magnesium bromide (2.41 M in Et₂O, 1.3 mL, 3.24 mmol, 1 eq) in Et₂O (5 mL) at -20 °C was added a solution of ester **120** (500 mg, 3.24 mmol, 1 eq) in Et₂O (1 mL) dropwise. After 1 hour the reaction was cooled to -78 °C and copper(I)iodide (62 mg, 0.32 mmol, 10 mol%) was added followed by phenyl magnesium bromide (2.64 M in Et₂O, 1.4 mL, 3.57 mmol, 1.1 eq) dropwise. The reaction was warmed to 0 °C and stirred for 1 hour 30 minutes then cooled to -78 °C and a solution of DCl and AcOD in D₂O (prepared by adding AcCl (1 mL) to D₂O (5 mL) with stirring) was added dropwise. The mixture was then warmed to room temperature and stirred in air for 5 minutes. The mixture was then separated and the aqueous phase extracted with Et₂O (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography eluting with petroleum spirit (b.p. 40 – 60 °C) / Et₂O (20:1) to afford ester **125** as a colourless oil (298 mg, 39%). ¹H NMR analysis of the product showed 100 % incorporation of deuterium in the α position and 40 % incorporation of deuterium in the γ position.

IR $\nu_{\max}/\text{cm}^{-1}$: 3063.7, 3027.5, 2975.5, 2932.8 (m, C-H), 1729.3 (s, C=O), 1603.3; **¹H NMR** (500 MHz, CDCl₃): δ = 1.45 (s, ^tBu, 9H), 2.96 (brd, J = 6.8 Hz, CHDCO₂^tBu, 1H), 3.38 (d, J = 6.0 Hz, PhCH₂, 2H), 5.59-5.83 (m, CHCHDCO₂^tBu, 1H), 5.69 (dtd, J = 15.3, 6.8, 1.3 Hz, PhCH₂CH, 0.6H), 7.18-7.30 (m, ArH, 5H); **MS** (+ve CI): 178 (20), 177 (25)

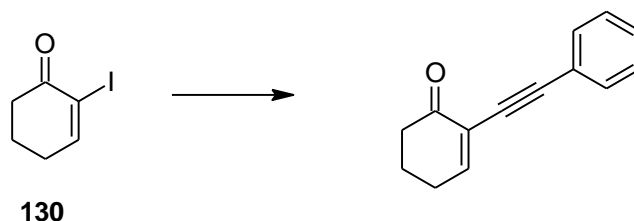
2-Iodocyclohex-2-en-1-one⁹⁹



The iodo enone was prepared via a literature procedure. To a stirred solution of 2-cyclohexene-1-one (10 mL, 103 mmol, 1 eq) in THF/deionized water 1:1 (200 mL) was added iodine (52.3 g, 206 mmol, 2 eq), potassium carbonate (17.1 g, 124 mmol, 1.2 eq) and *n,n*-dimethylaminopyridine (2.5 g, 20.6 mmol, 0.2 eq) at room temperature. After 2 hours 30 minutes the reaction was diluted with EtOAc (50 mL) and washed with a saturated aqueous solution of sodium thiosulfate (100 mL). The organic fraction was washed with a further portion of saturated aqueous solution of sodium thiosulfate (30 mL) and then 0.1 M HCl (30 mL). The organic fraction was then dried (MgSO₄), filtered and solvents removed *in vacuo*. The crude mixture solidified upon standing for approximately 1 hour. The crude solid was recrystallized from Et₂O / pentane to afford the title compound as pale brown crystals in quantitative yield.

m.p. 45 °C (lit. 46 - 47 °C); **R_f** = 0.49 (Petroleum spirit / EtOAc; 6:1); **IR** $\nu_{\max}/\text{cm}^{-1}$: 3036.1, 2935.4, 2867.8 (m, C-H), 1676.0 (s, C=O), 1583.5; **¹H NMR** (300 MHz, CDCl₃): δ = 2.09 (m, COCH₂CH₂CH₂, 2H), 2.44 (m, COCH₂CH₂CH₂, 2H), 2.66 (m, COCH₂CH₂CH₂, 2H), 7.77 (t, J = 4.4 Hz, CH, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ = 22.9 (CH₂), 23.2 (CH₂), 29.9 (CH₂), 137.3 (CH), 159.4 (C), 197.2 (C=O)

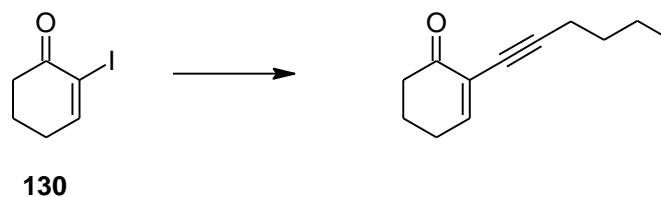
2-(Phenylethynyl)cyclohex-2-en-1-one¹⁰⁰



To a solution of iodoeneone **130** (1 g, 4.50 mmol, 1 eq) in THF (30 mL) at 0 °C was added Bis(triphenylphosphine)palladium(II) dichloride (158 mg, 0.23 mmol, 5 mol%), copper(I)iodide (86 mg, 0.45 mmol, 10 mol%), phenyl acetylene (1 mL, 9.00 mmol, 2 eq) and diisopropylamine (1.9 mL, 13.5 mmol, 3 eq). After 45 minutes stirring the mixture was diluted with Et₂O and washed with 0.1 M HCl (50 mL) and brine (20 mL). The organic phase was dried (MgSO₄), filtered and the solvents removed *in vacuo*. The crude mixture was purified by flash column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (7:1) to afford the title product as a pale brown solid (790 mg 89%).

m.p. 86 °C (lit. 109 - 110 °C); **IR** $\nu_{\max}/\text{cm}^{-1}$: 2998.0, 2913.0, 2885.0 (m, C–H), 2165.5 (w, C≡C), 1683.9 (s, C=O); **¹H NMR** (300 MHz, CDCl₃): δ = 2.07 (m, COCH₂CH₂CH₂, 2H), 2.52 (m, COCH₂CH₂CH₂, 4H), 7.31 (m, ArH, 3H), 7.36 (t, J = 4.4 Hz, CH, 1H), 7.50 (m, ArH, 2H)

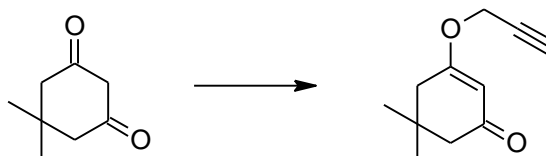
2-(Hex-1-yn-1-yl)cyclohex-2-en-1-one¹⁰¹



To a solution of iodoeneone **130** (2 g, 9.01 mmol, 1 eq) in THF (50 mL) at 0 °C was added Bis(triphenylphosphine)palladium(II) dichloride (316 mg, 0.45 mmol, 5 mol%), copper(I)iodide (172 mg, 0.90 mmol, 10 mol%), 1-hexyne (2.1 mL, 18.02 mmol, 2 eq) and diisopropylamine (3.8 mL, 27.03 mmol, 3 eq). After 45 minutes stirring the mixture was diluted with Et₂O and washed with 0.1 M HCl (50 mL) and brine (20 mL). The organic phase was dried (MgSO₄), filtered and the solvents removed *in vacuo*. The crude mixture was purified by chromatography eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (8:1) to afford the title product as a pale brown oil (952 mg 60%).

IR $\nu_{\max}/\text{cm}^{-1}$: 2956.2, 2871.6 (m, C–H), 2153.8 (w, C≡C), 1681.2 (s, C=O). **¹H NMR** (300 MHz, CDCl₃): δ = 0.91 (t, J = 7.0 Hz, CH₃, 3H), 1.36-1.59 (m, CH₃(CH₂)₂CH₂, 4H), 2.00 (m, CH₃(CH₂)₂CH₂, 2H), 2.34 – 2.50 (m, COCH₂CH₂CH₂, 4H), 7.19 (t, J = 4.4 Hz, CH, 1H)

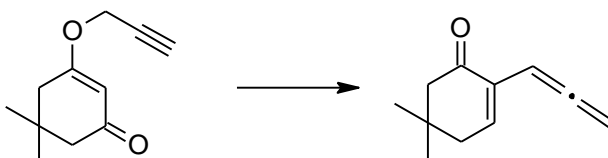
5,5-Dimethyl-3-(prop-2-yn-1-yloxy)cyclohex-2-en-1-one



The title compound was prepared via a modified literature procedure.¹⁰² A mixture of dimedone (15 g, 107.0 mmol, 1 eq), propargyl alcohol (12.6 mL, 214.0 mmol, 2 eq) and *para*-toluenesulfonic acid (1.02 mg, 5.35 mmol, 5 mol%) in benzene (100 mL) was heated at reflux with azeotropic removal of water using a Dean & Stark apparatus. After 2 hours the reaction mixture was cooled, diluted with Et₂O (50 mL) and washed with 5% NaOH (40 mL). The aqueous layer was extracted with Et₂O (20 mL) and the combined organic fractions washed with brine (20 mL), dried over MgSO₄ and the solvents removed *in vacuo*. The crude mixture solidified on cooling in the fridge and was recrystallized from petroleum ether (b.p. 60 – 80 °C) / EtOAc to give the title compound as colourless crystals (15.0 g, 79%).

m.p. 52 – 53 °C (lit 50 – 52 °C) **IR** $\nu_{\max}/\text{cm}^{-1}$: 3238.5, 2959.8, 2872.5 (m, C–H), 2123.5 (w, C≡C), 1653.8 (s, C=O), 1607.4; **¹H NMR** (300 MHz, CDCl₃): δ = 1.06 (s, 6H, 2CH₃), 2.21 (s, 2H), 2.30 (s, 2H), 2.57 (t, J = 2.4 Hz, C≡CH, 1H), 4.53 (d, J = 2.4 Hz, C≡CCH₂, 2H), 5.42 (s, C=CH, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ = 28.2 (CH₃), 32.6 (CH₃), 42.6, 50.7 56.0, 76.5, 76.8, 102.5 (CH), 174.5 (OC=C), 199.2 (C=O)

5,5-Dimethyl-2-propadienylcyclohex-2-en-1-one

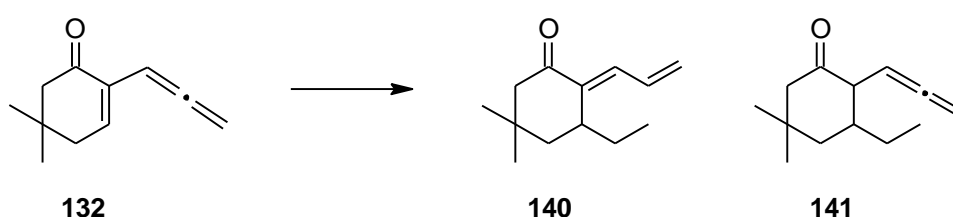


To a stirred suspension of lithium aluminium hydride (1.06 g, 28.10 mmol, 1 eq) in Et₂O (40 mL) at 0 °C was added 5,5-Dimethyl-3-prop-2-ynoxy-cyclohex-2-enone (5 g, 28.10 mmol, 1 eq) slowly. After 1 hour deionised water (15 mL) was added dropwise. The resultant white precipitate was filtered off *in vacuo* and the filtrate separated. The aqueous phase was extracted with Et₂O (20 mL) and the combined organic fractions were washed vigorously with brine (20 mL), dried over MgSO₄, filtered and the solvents removed *in vacuo*. The resultant crude oil was dissolved in xylene (40 mL) and heated at reflux for 3 hours. The reaction was then cooled and the xylene removed *in vacuo*. The resulting crude oil was dissolved in benzene (40 mL), *para*-toluenesulfonic acid (267 mg, 1.41 mmol, 5 mol%) was added and then heated at reflux, using a Dean & Stark apparatus, for 30 minutes. The reaction was then cooled and the solvents were removed *in vacuo*. The crude oil was purified by column chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (25:1) to give the title allene as a colourless oil (3.07 g, 67%).

IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2959.3, 2870.8 (C–H), 1944.0 (C=C=C), 1674.1 (C=O); **¹H NMR** (500 MHz, CDCl₃): δ = 1.05 (s, 2CH₃, 6H), 2.33 (s, CH₂C=O, 2H), 2.34 (brm, CH₂C=C, 2H), 5.00 (m, C=CH₂, 2H), 6.14 (t, J = 7.0 Hz, C=C=CHC, 1H), 6.85 (t, J = 4.0 Hz, CH=C–C=O, 1H); **¹³C NMR** (125 MHz, CDCl₃): δ = 28.4 (CH₃), 34.1 (C(CH₃)₂), 40.5 (CH₂), 52.0 (CH₂), 77.9 (CH=C=CH₂), 86.0 (CH=C=CH₂), 131.5 (C=C–C=O), 143.1 (C=C–C=O), 197.3 (C=O), 209.8 (C=C=C); **MS** m/z (ED): 169

(16), 163 (7), 162 (21), 148 (11), 147 (100), 131 (17); **HRMS** found 162.10425 M⁺
C₁₁ H₁₄ O requires 162.10392

(2E)-3-Ethyl-5,5-dimethyl-2-(prop-2-en-1-ylidene)cyclohexanone and 3-ethyl-5,5-dimethyl-2-propadienylcyclohexanone



To a solution of ethyl magnesium bromide (2.11 M in Et₂O, 0.8 mL, 1.70 mmol, 1.1 eq) and copper(I)iodide (29 mg, 0.15 mmol, 10 mol%) in Et₂O (4 mL) at -78 °C was added a solution of enone **132** (250 mg, 1.54 mmol, 1 eq) in Et₂O (1 mL). After 45 minutes a saturated aqueous solution of ammonium chloride (5 mL) was added dropwise. The mixture was separated and the aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents were removed *in vacuo*. The resulting oil was purified by chromatography eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (30:1) to afford ketone **140** (128 mg, 43%) and ketone **141** (44 mg, 15%).

Data for 140

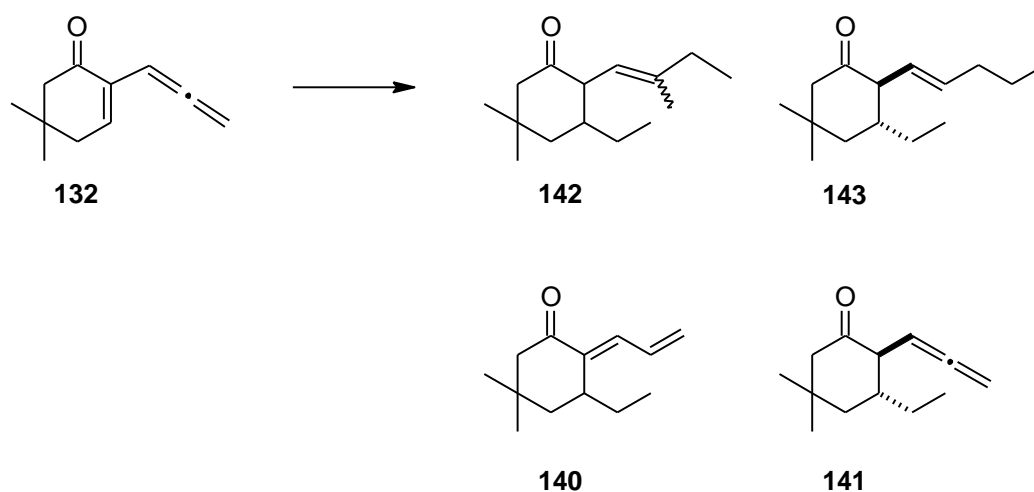
IR $\nu_{\max}/\text{cm}^{-1}$: 2956.8, 2929.0, 2872.1 (C–H), 1688.3 (C=O); **R_f** = 0.3 (Petroleum spirit / Et₂O; 30:1); **¹H NMR** (500 MHz, CDCl₃): δ = 0.96 (t, J = 7.4 Hz, CH₂CH₃, 3H), 1.00, 1.04 (s, C(CH₃)₂, 6H), 1.38 (m, CH₂CH₃, 2H), 1.76 (m, CH₂CHCH₂CH₃,

2H), 2.28 (m, CH₂CO, 2H), 2.47 (m, CH₂CHCH₂CH₃, 1H), 5.27 (dt, J = 9.9, 1 Hz, COCCH, 1H), 5.38 (ddd, J = 16.9, 1.7, 0.8 Hz, COCHCHCH₂, 1H), 6.08 (dd, J = 11, 2.1 Hz, COCHCHCH₂, 1H), 6.95 (ddd, J = 16.9, 10.2, COCHCHCH₂, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 11.5, 26.0, 26.8, 31.9, 33.0, 40.2, 43.9, 55.8, 122.2 (CH₂), 131.2 (CH), 133.6 (CH), 142.2 (C), 205.0 (C=O); MS m/z (+ve EI): 192 (7), 163 (18); HRMS found 192.15006 C₁₃H₂₀O requires 192.15087

Data for 141

IR ν_{max}/cm⁻¹: 2962.9, 2905.4 (C-H), 1719.6 (C=O); R_f = 0.23 (Petroleum spirit / Et₂O; 30:1); ¹H NMR (500 MHz, CDCl₃): δ = 0.90 (t, J = 7.3 Hz, CH₂CH₃, 3H), 1.03, 1.07 (s, C(CH₃)₂, 6H), 1.40 (m, CH₂CH₃, 2H), 1.70 (m, CCH₂CH, 3H), 2.20 (m, CH₂CO, 2H), 2.68 (dd, J = 11.3, 9.3 Hz, CHCO, 1H), 4.70 (m, CH=C=CH₂, 2H), 5.13 (dt, J = 9.3, 6.6 Hz, CH=C=CH₂, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 10.5, 25.7, 27.0, 32.3, 34.1, 41.3, 43.6, 54.6, 55.9, 75.0 (HC=C=CH₂), 87.0 (HC=C=CH₂), 197.3 (C=O), 209.8 (C=C=C); MS m/z (+ve CI): 193 (M+H) (28), 197 (40); HRMS found 193.16011 C₁₃H₂₁O requires 193.15924

Carbometallation of 132



To a solution of ethyl magnesium bromide (3.01 M in Et₂O, 1.3 mL, 3.88 mmol, 2.1 eq) and copper(I)iodide (35 mg, 0.19 mmol, 10 mol%) in Et₂O (4 mL) at -78 °C was added a solution of enone **132** (300 mg, 1.85 mmol, 1 eq) in Et₂O (1 mL). After 30 minutes the reaction was warmed to 0 °C and stirred for 4 hours 30 minutes. The reaction was then cooled to -78 °C and a saturated aqueous solution of ammonium chloride (5 mL) was added dropwise. The mixture was separated and the aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting oil was purified by chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (30:1) to afford **142** (85 mg 21%), **140** (27 mg, 7%) and a mixture that was tentatively assigned to be **143** and **141** (combined yield 60 mg).

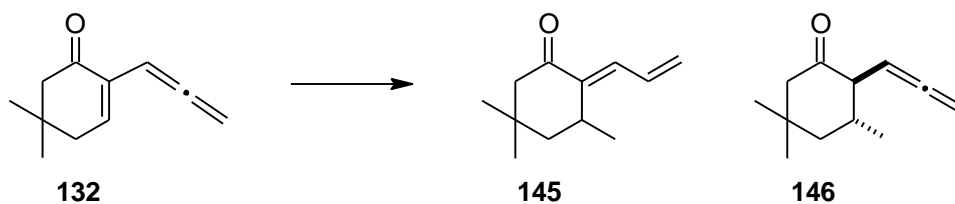
Data for **142**

IR $\nu_{\max}/\text{cm}^{-1}$: 2961.0, 2931.1, 2874.7 (m, C–H), 1712.2 (s, C=O), 1685.7 (s, C=C); **¹H NMR** (500 MHz, CDCl₃): δ = 0.88 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H), 0.98 (s, 3H), 1.02 (s, 3H), 1.32 (m, 6H), 1.68 (ddd, J = 13.2, 7.5, 5.6 Hz, 1H), 1.74 (ddd, J = 13.2, 5.0, 2.1 Hz, 1H), 2.24 (m, 4H), 2.34 (m, 1H), 5.52 (m, 1H); **¹³C NMR** (125 MHz, CDCl₃): δ = 11.5 (CH₃), 14.0 (CH₃), 22.4, 26.0, 26.8, 28.7, 32.0, 32.1, 33.1 (C), 40.2, 44.3, 56.1 (CH), 133.9 (CH), 141.3 (C), 205.8 (C=O); **MS** m/z (+ve CI): 223 (M+H, 20), 193 (20), 175 (10).

Selected peaks for **143**

¹H NMR (500 MHz, CDCl₃): δ = 2.53 (dd, J = 11.7, 7.6 Hz, 1H), 5.31 (dt, J = 15.3, 7.4 Hz, 1H), 5.39 (J = 15.3, 6.1 Hz, 1H)

(2E)-3,5,5-Trimethyl-2-(prop-2-en-1-ylidene)cyclohexanone and 3,5,5-trimethyl-2-propadienylcyclohexanone



To a stirred suspension of copper(I)iodide (528 mg, 2.78 mmol, 1.5 eq), in Et₂O (4 mL) at 0 °C was added a methyl lithium (1.6 M in Et₂O, 3.5 mL, 5.55 mmol, 3 eq) dropwise. The reaction was cooled to -20 °C and a solution of enone **132** (300 mg, 1.85 mmol, 1 eq) in Et₂O (4 mL) was added dropwise. After 4 hours 30 minutes the reaction mixture was poured into a saturated aqueous solution of NH₄Cl (30 mL). The mixture was separated and the aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic fractions were washed with a saturated aqueous solution of ammonium chloride (10 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. The resulting oil was purified by chromatography, eluting with petroleum spirit (b.p. 40 – 60 °C) / EtOAc (30:1) to afford ketone **145** (87 mg, 26%) and ketone **146** (81 mg, 25%).

Data for **145**

IR $\nu_{\max}/\text{cm}^{-1}$: 2958.0, 2871.0 (C–H), 1684.6 (C=O); **R_f** = 0.22 (Petroleum spirit / Et₂O; 30:1); **¹H NMR** (500 MHz, CDCl₃): δ = 1.01, 1.03 (s, C(CH₃)₂, 6H), 1.17 (d, J = 6.5 Hz, CHCH₃, 3H), 1.42 (t, J = 12.8 Hz, CCH₂, 1H), 1.68 (ddd, J = 13.2, 4.7, 4.7 Hz, CCH₂, 1H), 2.28 (m, CH₂CO, 2H), 2.68 (m, CH₃CH, 1H), 5.27 (dd, J = 10.1, 0.9

Hz, C=CH, 1H), 5.39 (ddd, J = 16.9, 1.9, 0.9 Hz, CH=CH₂, 1H), 6.07 (dd, J = 11, 2.4 Hz, CH=CH₂, 1H), 6.93 (ddd, J = 17, 10.7, 10.2 Hz, CH=CH₂, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 18.7 (CH₃), 26.4 (CH₂), 31.8 (CH₂), 33.5 (CH), 47.7 (CH), 56.2 (C), 122.1 (CH₂), 130.9 (CH), 133.5 (CH), 143.3 (C), 204.8 (C=O); MS *m/z* (+ve EI): 178 (35), 163 (39); HRMS found 178.13561 C₁₂H₁₈O requires 178.13522

Data for **146**

IR $\nu_{\max}/\text{cm}^{-1}$: 2956.2, 2906.9, 2870.5 (C-H), 1959.2 (C=C=C), 1711.5 (C=O); R_f = 0.16 (Petroleum spirit / Et₂O; 30:1); ¹H NMR (500 MHz, CDCl₃): δ = 1.01, 1.03 (s, C(CH₃)₂, 6H), 1.07 (d, J = 6.3 Hz, CHCH₃, 3H), 1.46 (dd, J = 12.9, 12.9 Hz, CCH₂, 1H), 1.64 (ddd, J = 13.7, 3.2, 3.2 Hz, CCH₂, 1H), 1.83 (m, CHCH₃, 1H), 2.21 (m, CH₂CO, 2H), 2.57 (dd, J = 11.3, 9.1 Hz, CHCO, 1H), 4.71 (m, CH=C=CH₂, 2H), 5.16 (dt, J = 9, 6.8 Hz, CH=C=CH₂, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 21.1 (CH₃), 25.7 (CH₃), 32.1 (CH₂), 35.6, 35.7, 47.7, 54.5, 57.8, 75.0 (HC=C=CH₂), 87.0 (HC=C=CH₂), 209.3 (C=O), 210.1 (C=C=C); MS *m/z* (+ve CI): 179 (M+H) (100), 161 (25); HRMS found 179.14401 C₁₂H₁₉O requires 179.14359

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