Exploring and Exploiting Selectivity in Rhodium-Catalysed Hydroacylation Reactions

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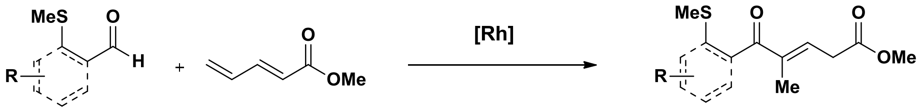
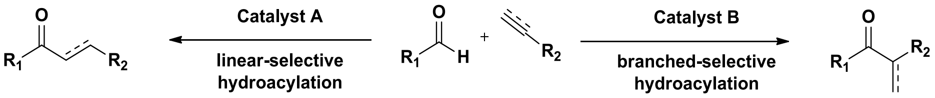
Abstract

Chapter 1 is an overview of the key developments in rhodium-catalysed hydroacylation. The main focus of this chapter is the use of various chelation strategies for the stabilisation of key rhodium-acyl intermediates. In addition, the more recent emergence of regioselective hydroacylation processes has been highlighted.

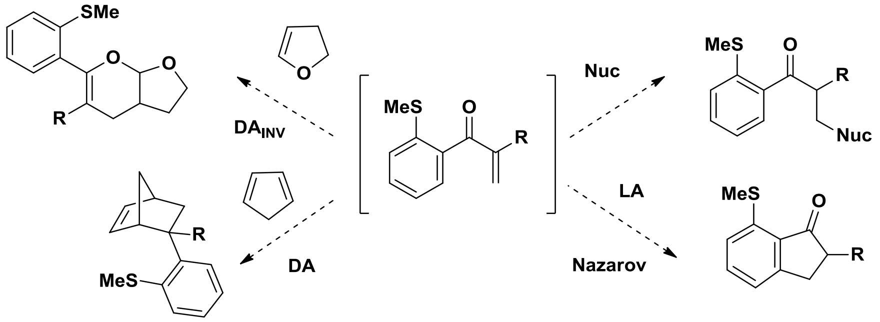
Chapter 2 discloses the branched-selective intermolecular hydroacylation of 1,3-dienes and *S*-chelating aldehydes to afford synthetically useful 1,5-dione products. The evaluation of a number of different phosphine ligands for this process identifies a correlation between ligand bite angle and reaction regioselectivity.



Chapter 3 discusses the development of a linear-selective hydroacylation process for previously challenging alkyne substrates. This, in combination with a complementary branched-selective process, provides a ligand-controlled regioselectivity switch between the branched and linear pathways.



Finally, Chapter 4 details efforts towards the development of multicomponent, tandem processes through exploitation of our synthetically useful branched hydroacylation adducts.



Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated. This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Sarah-Jane Poingdestre

October 2012

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1. Chapter 1 - Introduction 1

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Finally, thank you to Greg – I’m sure I’ve been a nightmare the past few months but I can always rely on you to make me smile. I couldn’t have done it without you.

Abbreviations

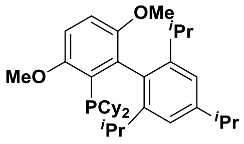
Å	Angstrom
Ac	acetyl
acac	acetylacetonate`
app.	apparent
Ar	aryl
atm.	atmosphere
aq	aqueous
β_n	bite angle
b	branched
$BAr^F{}_4$	$[B[3,5-(CF_3)_2C_6H_3]_4]^-$
br.	broad (spectral)
Bu	butyl
ºC	degrees Celsius
ca.	approximately
cat.	catalytic quantity
Cbz	carbobenzyloxy
cm^{-1}	wavenumber(s)
cod	cyclooctadiene
coe	cyclooctene
cot	cyclooctatriene
cy	cyclohexyl
d	doublet (spectral)
DA	Diels-Alder
DA_{INV}	Inverse electron demand Diels-Alder
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
dcpm	1,1-bis(diphenylcyclohexyl)methane
dcpe	1,1-bis(diphenylcyclohexyl)ethane
dec.	decomposition
DIBK	diisobutylketone

DMAP	dimethylaminopyridine
DMEDA	*N,N'*-dimethylethylenediamine
DMF	*N,N'*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DPEPhos	bis(2-diphenylphosphinophenyl)ether
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppm	1,1-bis(diphenylphosphino)methane
dppp	2-(Diphenylphosphino)pyridine
E	entegen
ee	enantiomeric excess
EDG	electron-donating group
Et	ethyl
ESI	electrospray ionization
eq.	equivalent(s)
EWG	electron-withdrawing group
FI	field ionization
FT	Fourier transform
g	gram(s)
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	hertz
^{i}Bu	*iso*-butyl
^{i}Pr	*iso*-propyl
IR	infrared
J	coupling constant (in NMR spectroscopy)
L	ligand
l	linear
LA	Lewis acid
LDA	lithium diisopropylamide
LRMA	low resolution mass spectroscopy
µw	microwave

m	*meta*
m	multiplet (spectral)
M	molar (moles per liter); mega
M^+	parent molecular ion (in mass spectrometry)
Me	methyl
MHz	megahertz
MIBK	methylisobutylketone
min	minute(s)
mL	millilitre(s)
mol	mole(s)
mmol	millimole(s)
m.p.	melting point
MS	mass spectrometry; molecular sieves
MTM	methylthiomethyl
m/z	mass-to-charge ratio (in mass spectrometry)
$()_n$	number of carbons
nbd	norbornadiene
^{n}Bu	normal butyl
^{n}hex	normal hexyl
nOe	Nuclear Overhauser Effect
NMR	nuclear magnetic resonance
n/r	no reaction
Nuc	nucleophile
[O]	oxidant
o	*ortho*
OA	oxidative addition
p	*para*
PC	propylene carbonate
Ph	phenyl
PHPB	pyridinium hydrobromide perbromide
ppm	part(s) per million
Pr	propyl (normal)
psi	pounds per square inch
q	quartet (spectral)

quant.	quantitative
quin	quintet
rt	room temperature
s	singlet (spectral)
sat.	saturated
sept	septet
SM	starting material
S_NAr	nucleophilic aromatic substitution
sxt	sextet
t	triplet (spectral)
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
Tf	trifluoromethanesulfonate/triflate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOF	turnover frequency
Ts	4-toluenesulfonyl chloride
v/v	volume concentration
w/u	work-up
Z	zusammen

Ligands and Catalysts



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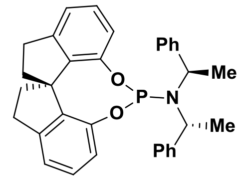

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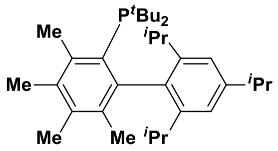

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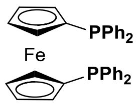

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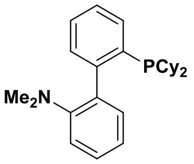

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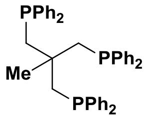

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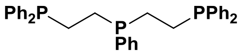

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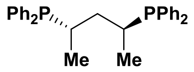

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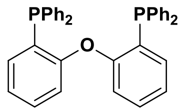

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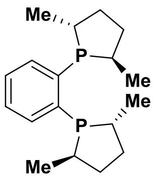

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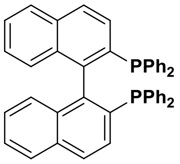

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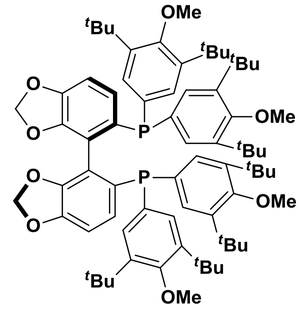

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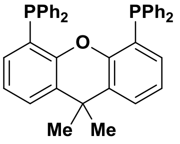

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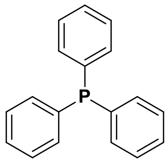

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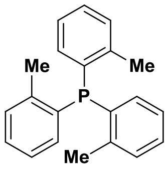

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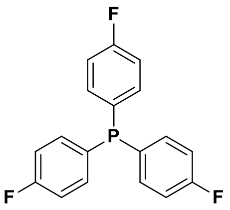

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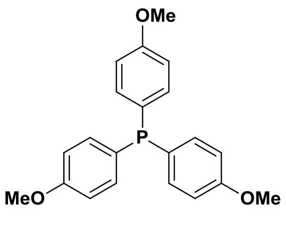

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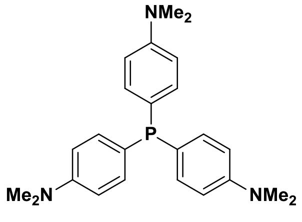

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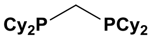

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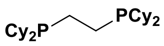

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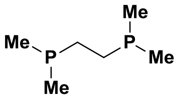

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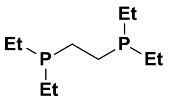

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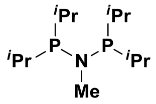

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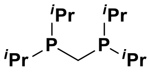

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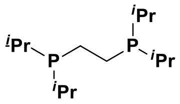

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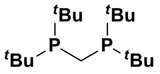

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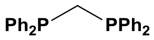

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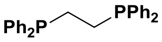

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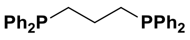

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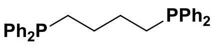

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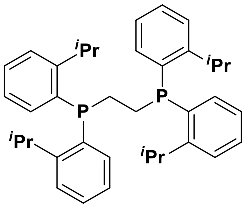
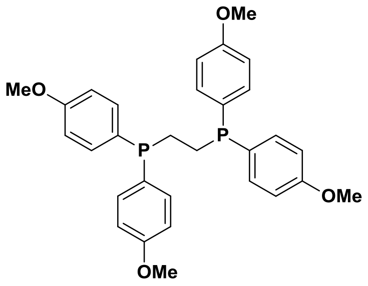


***o*-^{i}Pr-dppe**



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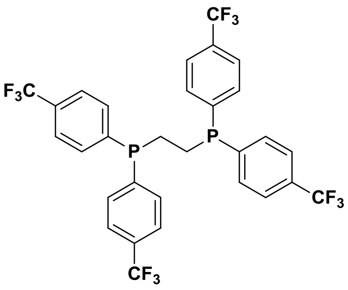
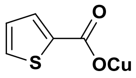


***p*-CF_3-dppe**

$(PPh_3)_3RhCl$

Wilkinson's catalyst



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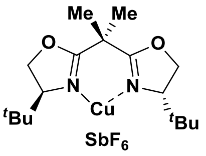

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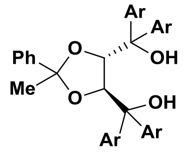
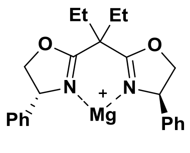
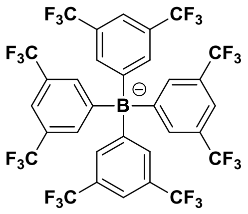


Ar = Ph or *p*-OMePh

TADDOL



Magnesium bis(oxazoline) catalyst



$BAr^F{}_4$

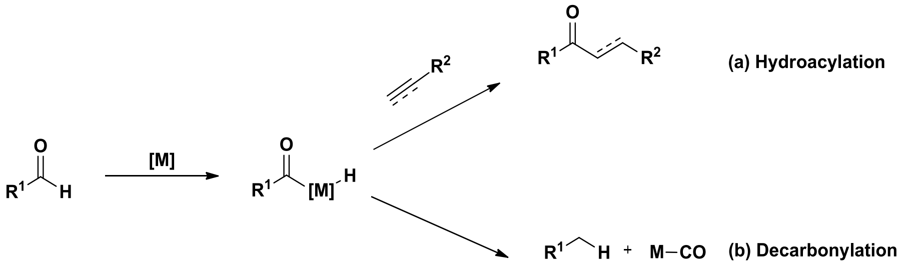
Chapter 1 - Introduction

Metal Catalysed Hydroacylation Reactions

The ability to form C-C bonds with high degrees of atom economy is an increasingly attractive goal for synthetic chemists.[1-3] Recent decades have seen the emergence of multiple catalytic processes for the selective activation and subsequent functionalization of C-H bonds.[4]

Hydroacylation is the formal addition of an acyl unit and a hydride across a C-C unsaturated system - typically an alkene or an alkyne (**Scheme 1.1**). It is an inherently atom-economic process, and can employ very low catalyst loadings to deliver highly functionalised ketone derivatives from readily available starting materials. A number of different metal catalysts can be employed including ruthenium,[5-13] cobalt[14-16] and nickel.[17] However, rhodium catalysts are the most commonly used and will be the focus of this thesis.

Scheme 1.1 - (a) Metal-catalysed hydroacylation; (b) Decarbonylation.



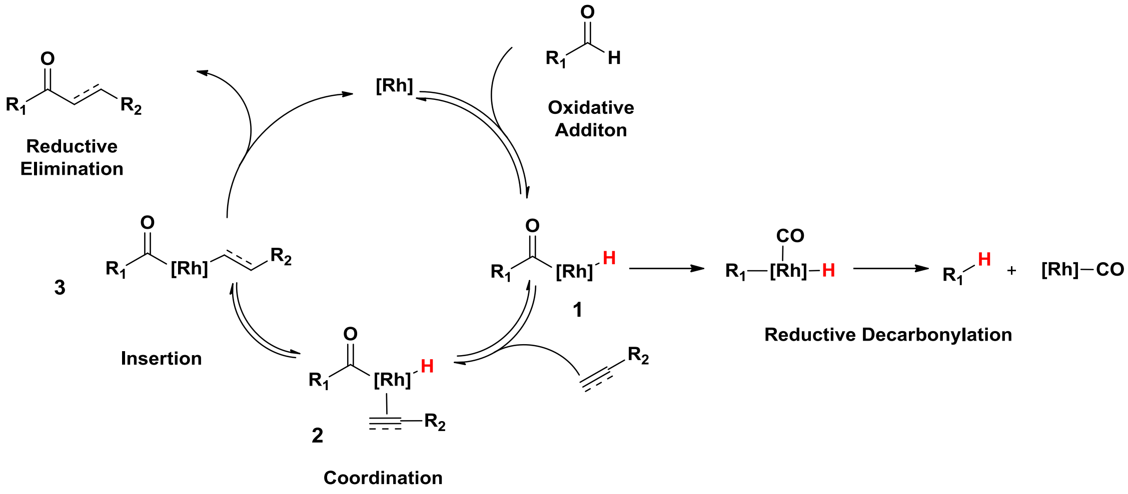
The origins of metal-catalysed hydroacylation lie in decarbonylation reactions. A metal can insert into an aldehyde C-H bond to give a rhodium-acyl species, followed by the steps of carbonyl de-insertion, then reductive elimination to deliver decarbonylated product and a metal carbonyl species. It is this process that has proven to be the main competitive pathway and obstacle in the development of robust hydroacylation processes. Various strategies have been designed to overcome or supress this pathway. This chapter will outline the key developments in rhodium-catalysed hydroacylation chemistry to date. Transition-metal catalysed alkene and alkyne hydroacylation has been subject to a recent comprehensive review by Willis.[18]

Mechanism of Hydroacylation

A number of research groups have investigated the mechanism of transition-metal catalysed hydroacylation reactions. Deuterium labelling studies by Miller[19,20] and extensive NMR studies by Bosnich[21] have provided a widely accepted mechanism for the intramolecular process which has been extended to intermolecular processes. This has been largely supported by computational investigations by Morehead and Sargent,[22] as well as Brookhart's[23] investigative studies into the hydroacylation of vinyl silanes. The following section serves as an overview of the general mechanism of rhodium-catalysed hydroacylation. Further mechanistic details which are specific to individual catalytic systems will be discussed later.

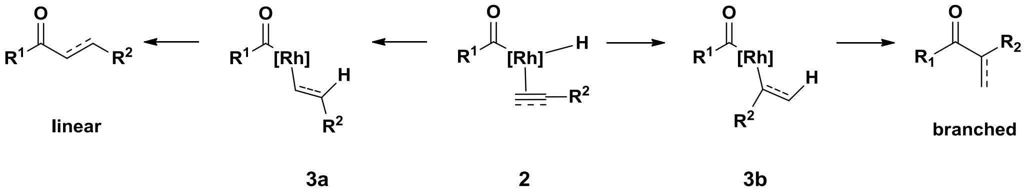
The oxidative addition of the metal species into the aldehyde C-H bond results in a rhodium-acyl hydride **1**. At this stage, two pathways can occur. The first involves carbonyl de-insertion followed by reductive elimination, which leads to the aforementioned decarbonylation pathway and results in catalyst deactivation and reduced substrate. The second consists of coordination of the unsaturated species to the rhodium-acyl to form **2** and subsequent insertion to afford intermediate **3**. This intermediate can then undergo reductive elimination to furnish the ketone adduct and regenerate the metal catalyst. All of the steps in the catalytic cycle, except for reductive elimination to form the product and the equivalent process in the decarbonylation pathway, have been shown to be reversible (**Scheme 1.2**).

Scheme 1.2 – A generally accepted mechanism for Rh-catalysed hydroacylation.



It should also be noted that following the formation of rhodium-acyl intermediate **1**, two modes of insertion of the unsaturated system are possible resulting in either intermediate **3a** or **3b**. Following reductive elimination these intermediates will give rise to either the linear or branched hydroacylation adducts (**Scheme 1.3**).

Scheme 1.3 – Linear and branched hydroacylation pathways.

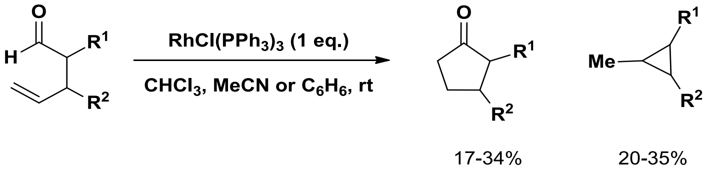


Intramolecular Hydroacylation

Cyclopentanones

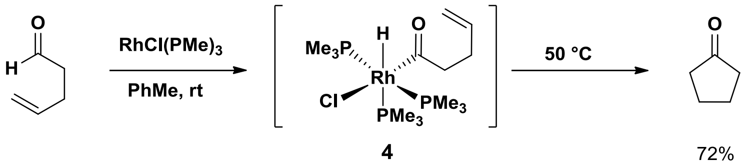
The first example of a rhodium-mediated hydroacylation reaction was reported by Sakai during a study on prostanoid synthesis.[24] A range of 4-enals were treated with stoichiometric amounts of Wilkinson's complex at room temperature to deliver modest yields of cyclopentanones, alongside cyclopropanones resulting from the reductive decarbonylation pathway (**Scheme 1.4**).

Scheme 1.4– The first reported example of a rhodium-mediated hydroacylation.



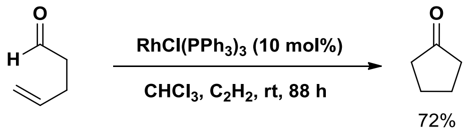
Milstein[25] was able to extend this work through variation of the rhodium complex. The treatment of 4-pentenal with stoichiometric $RhCl(PMe)_3$ enabled the isolation and characterisation of acyl rhodium(III) hydride intermediate **4**, which delivered cyclopentanone when heated in toluene (**Scheme 1.5**). It is important to note that the acyl unit is positioned *trans* to the chloride ligand and that the stability of complex **4** is due to the slow dissociation of the trimethylphosphine ligands. Following isolation of this complex, Milstein postulated a mechanism for this intramolecular hydroacylation process involving fast oxidative addition of 4-pentenal, followed by slow reversible trimethylphosphine dissociation, intramolecular insertion into the Rh-H bond and, finally, reductive elimination.

Scheme 1.5 – Milstein’s cyclopentanone synthesis using $RhCl(PMe)_3$.



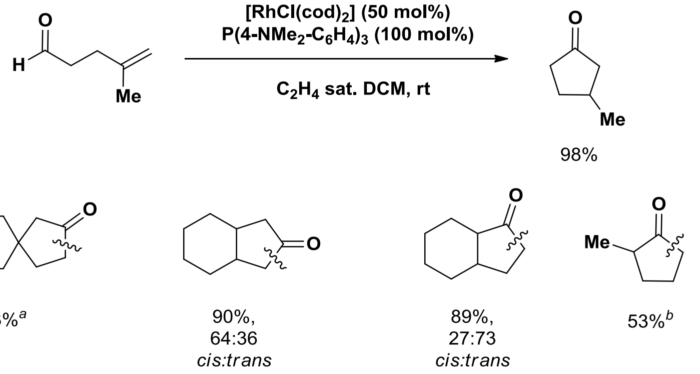
Further work by Milstein demonstrated that complex **4** could also produce three turnovers when used in catalytic quantities - the first example of catalysis that did not rely on the presence of ethene. Miller *et al.* had previously shown that Wilkinson's catalyst could be used in sub-stoichiometric amounts provided that an ethene-saturated solvent was used to supress reductive decarbonylation (**Scheme 1.6**).[26,27] It was postulated that ethene could temporarily occupy a vacant coordination site required for carbonyl de-insertion to occur. This would in turn force the equilibrium towards **2** (See section 1.1), thus reducing the availability of the rhodium-acyl to undergo decarbonylation.

Scheme 1.6 – Miller's catalytic cyclopentanone synthesis using ethene-saturated solvent.



Larock further developed the use of ethene-saturated solvent to increase the efficiency of intramolecular hydroacylation reactions.[28] The use of relatively high catalyst loadings (50 mol%) generated *in situ* from $[Rh(cod)Cl]_2$ and various monophosphine ligands, provided access to a range of substituted, spirocyclic and fused cyclopentanone derivatives. For the more reactive, generally unsubstituted substrates, the catalyst loading could be reduced to 10 mol%. However, the introduction of substitution in the 2- or 5-position of the enal resulted in significantly reduced yields (**Scheme 1.7**).

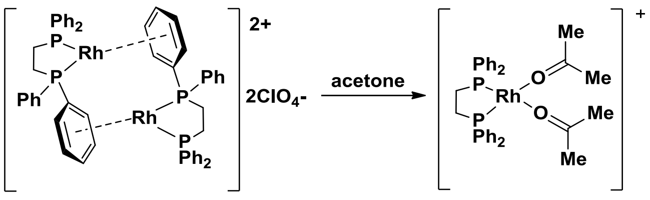
Scheme 1.7 – Larock's synthesis of substituted, fused and spirocyclic cyclopentanones.



^{a} 10 mol% catalyst used. ^{b} $P(4\text{-}OMe\text{-}C_6H_4)_3$ used as ligand

The work by Larock and Miller using *in situ* generated Rh(I) complexes led to extensive development of cationic rhodium complexes with a core structure of [Rh(bis-phosphine)]X (where X = ClO_4, BF_4, OTf or $BAr^F{}_4$) by Bosnich[29,21] (similar complexes had been previously described by Schrock and Osborne[30]). Bosnich identified $[Rh(dppe)ClO_4]$ as the optimum system, which was isolable in the solid state as the catalytically inactive arene-bridged dimer **5a**, and could be generated *in situ* as the disolvated monomer **5b** (**Scheme 1.8**). From a practical standpoint, these complexes are easily accessible through hydrogenation of a solution of [Rh(dppe)(nbd)]ClO_4, which can be prepared from $[Rh(cod)Cl]_2$, dppe and $AgClO_4$.

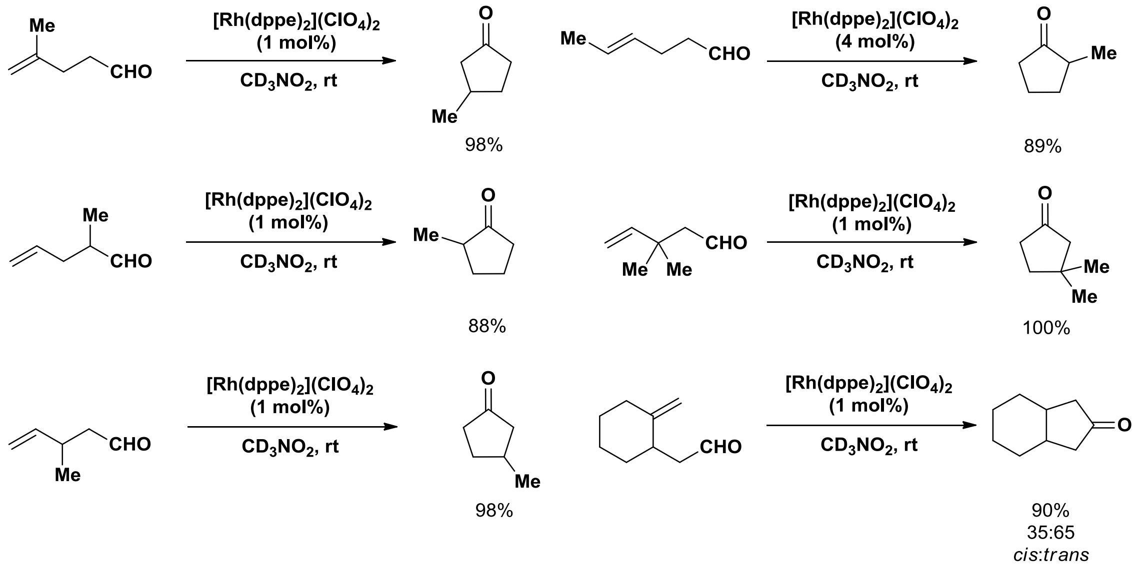
Scheme 1.8 - Structure of arene bridge dimer **5a** and disolvated monomer **5b**.



5a 5b

Bosnich also demonstrated the efficiency of these complexes for the cyclisation of a range of 4-pentenals with varying substitution patterns. Incorporation of substituents at the 2-, 3-, 4- and 5- positions was possible, with catalytic loadings as low as 1 mol% catalyst at 20 °C in CD_3NO_2 (**Scheme 1.9**).

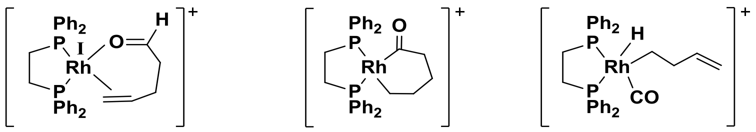
Scheme 1.9 – Bosnich's catalytic formation of cyclopentanones using Rh(I) complexes.



Owing to the high turnover frequency for the hydroacylation pathway, decarbonylation was significantly reduced, although in some cases products resulting from double-bond isomerisation processes were detected. This work represented a significant advance in rhodium-catalysed hydroacylation and initiated the widespread use of these coordinatively unsaturated rhodium complexes.

Following a series of mechanistic studies, Bosnich proposed that the success of these cationic Rh(I) and Rh(III) species was due to the coordinative unsaturation.[21] It was speculated that upon addition of the 4-pentenal substrate, coordination to the rhodium centre would occur to form the catalytically active pre-equilibrium species **6a**. It was proposed that the proximal location of the olefin to the rhodium centre enabled more facile oxidation addition across the aldehyde C-H bond. Owing to the favourable alignment of the metal-hydride bond and the coordinated olefin, Bosnich proposed rapid hydride transfer to afford metallocyclohexanone **6b**, followed by rapid reductive elimination. Despite the fact that a vacant coordination site is also a requirement for rapid decarbonylation of metal-acyl bonds, he suggested that decarbonylation should be relatively supressed due to accelerated hydroacylation, in combination with the relative instability of Rh-CO species **6c**, in comparison to metallacyclohexanone **6b** (**Figure 1.1**).

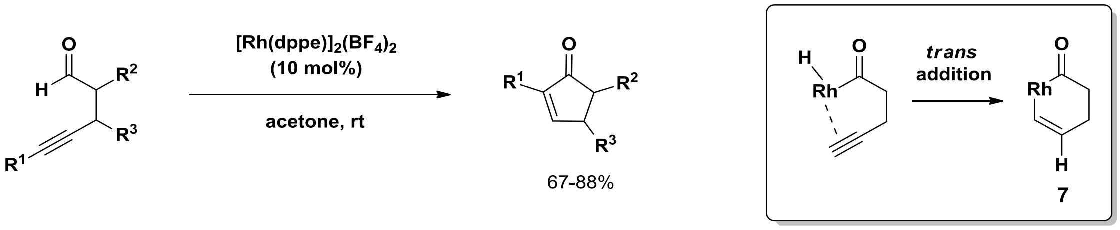
Figure 1.1 – Structures of postulated hydroacylation intermediates.



6a **6b** **6c**

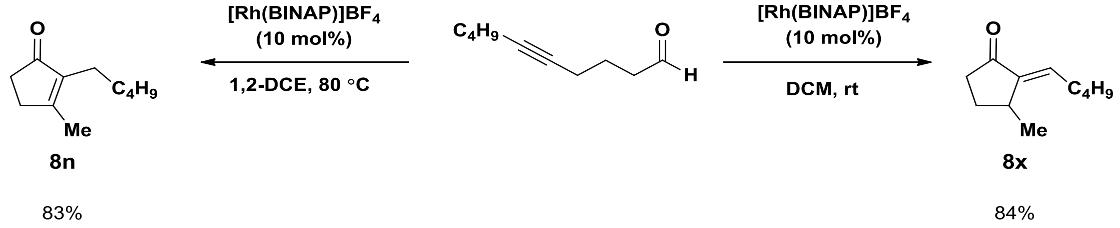
The Fu and Tanaka groups have reported several examples of intramolecular alkyne hydroacylation using cationic rhodium species. Fu[31] *et al.* have reported a synthesis of cyclopentenones which they propose proceeds *via* an unusual *trans* addition of the rhodium hydride to the coordinated alkyne to generate a 6-membered rhodium metallocyclohexene **7** (**Scheme 1.10**).

Scheme 1.10 – Fu’s intramolecular hydroacylation of 5-alkynals.



The Tanaka group[32] have expanded this methodology to the hydroacylation of hexenals and heptenals to give access to both 5- and 6-membered cyclic ketones. Using [Rh(BINAP)]BF_4 they were able to control formation of either the endo- or exocyclic products by variation of reaction temperature: increasing the temperature to 80 °C resulted in double bond isomerisation to afford the endocyclic adduct **8n**, whereas running the reaction at room temperature gave the exocyclic adduct **8x** (**Scheme 1.11**).

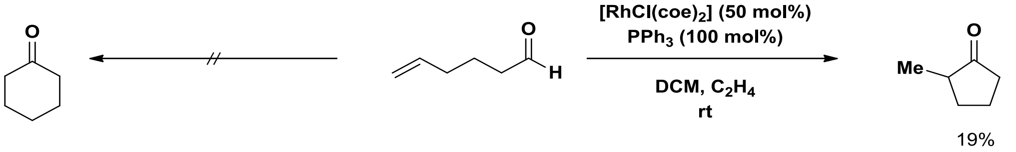
Scheme 1.11 – Tanaka’s hydroacylation/double bond isomerisation.



Larger Rings

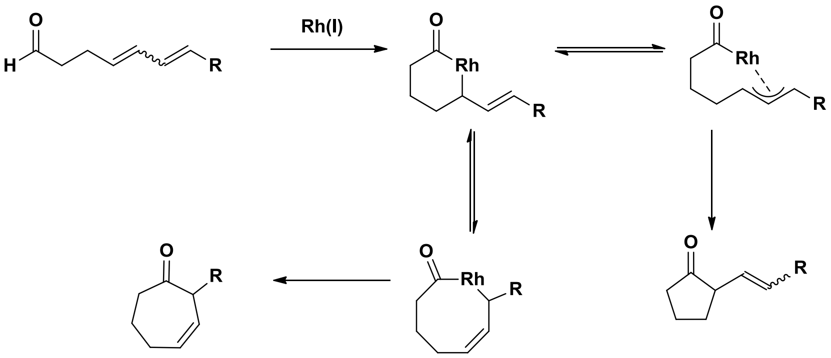
The synthesis of larger ring systems poses several problems. If isomerisation of the rhodium-acyl intermediate to a 6-membered chelate is possible, this pathway will usually predominate. For example, Larock *et al*. isolated exclusively cyclopentanone from the hydroacylation of 5-hexenal (**Scheme 1.12**).[28] In addition, ring closure of larger rings is generally a slower process; hence, the undesired decarbonylation side reaction can prevail.

Scheme 1.12 – Hydroacylation of 5-hexenal.



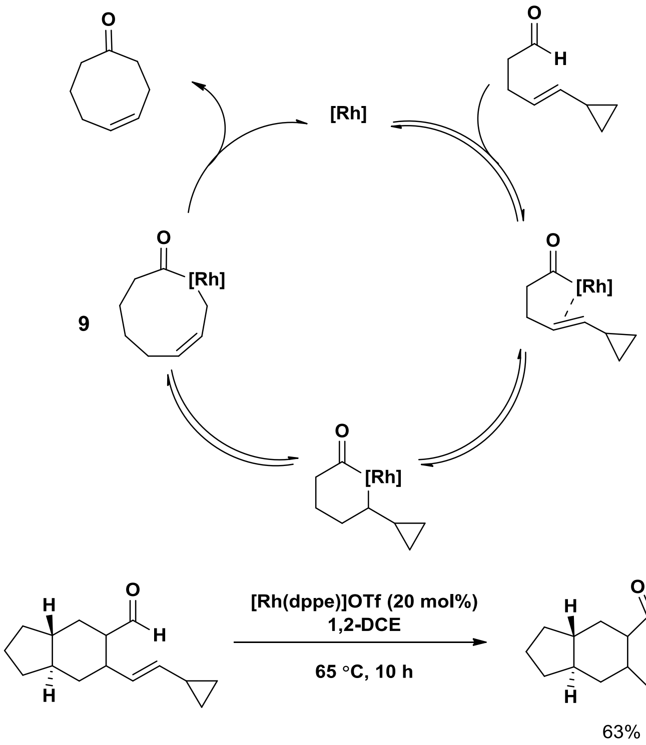
Mori *et al.* employed the cationic rhodium catalyst popularised by Bosnich to construct 7-membered rings from dienal substrates.[33,34] Employing 10 mol% of [Rh(dppe)]ClO_4 in 1,2-DCE at 65 °C gave the desired cycloheptenones in modest yields for a small range of substrates, provided that dienals with *E*-geometry at the C-6 position were employed. It was observed that dienals with *Z*-geometry at the C-6 position favoured formation of the cyclopentanone product. This was rationalised on account of steric repulsions preventing the formation of the π-allyl intermediate (**Scheme 1.13**).

Scheme 1.13 – Mori's cycloheptenone synthesis.



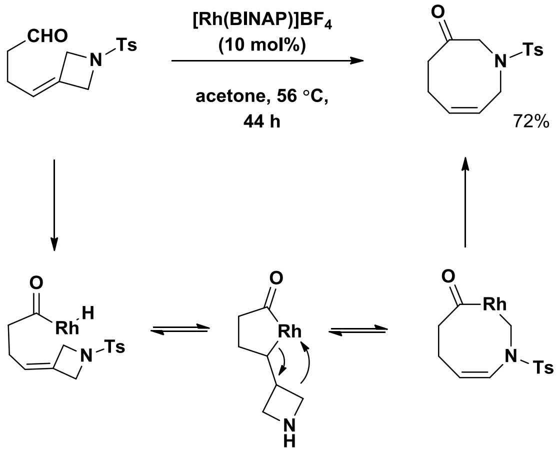
Shair *et al.* demonstrated an interesting cyclooctenone synthesis from substrates incorporating a cyclopropane moiety.[35] Treatment with cationic rhodium complexes under an ethene atmosphere selectively afforded cyclooctenones in moderate yields. A mechanism was proposed involving the key steps of fragmentation of the cyclopropane unit, followed by isomerisation to form a 9-memembered rhodacycle **9** as shown in **Scheme 1.14**.

Scheme 1.14 – Shair’s synthesis of cyclooctenones using cyclopropane tether.



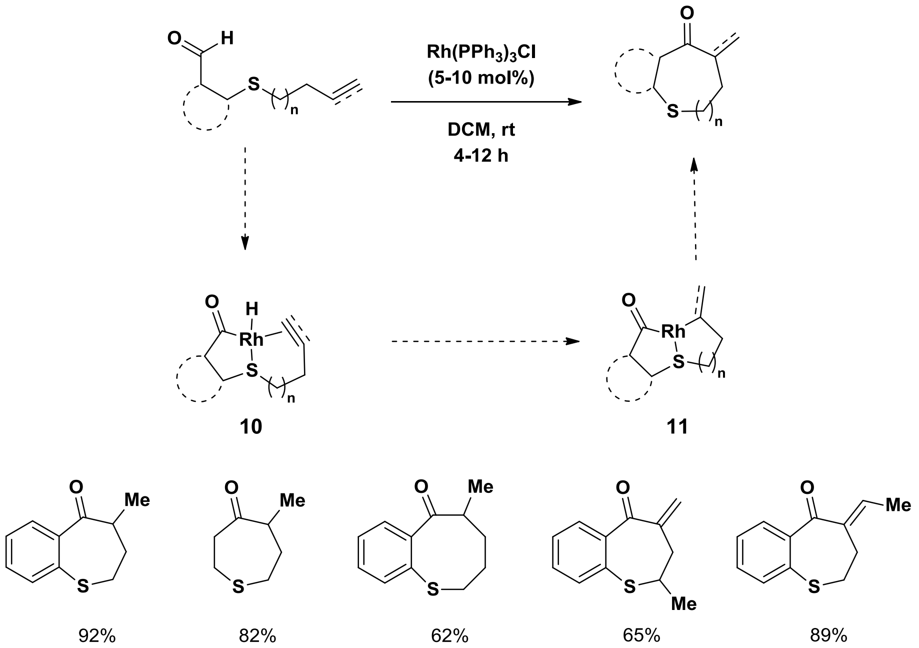
Fürstner and Aïssa used a similar approach to access cycloheptanones and cyclooctenones.[36,37] Through the exploitation of the inherent strain energy of tethered cyclopropanes, cyclobutanes and azetidines, substrates underwent a C-H/C-C activation sequence with the use of *in situ* generated cationic rhodium species. Notably, in the case of the cyclobutanes and azetidines, ethene saturation was not required when using [Rh(BINAP)]BF_4 as catalyst (**Scheme 1.15**).

Scheme 1.15 – Aïssa's C-H/C-C activation sequence using azetidines.



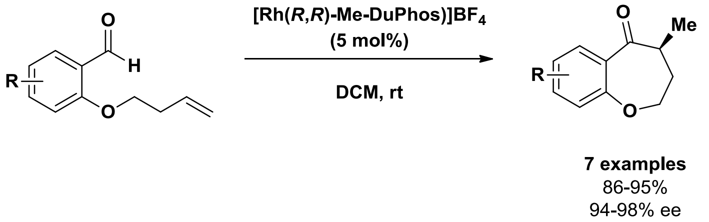
Bendorf and co-workers have used *S*-chelation assisted hydroacylation to synthesise a series of sulfur-containing medium-ring heterocycles in moderate to excellent yields.[38] The use of catalytic Wilkinson's complex at room temperature, afforded a variety of 7- and 8-membered rings from the corresponding ω-alkenals and ω-alkynals, *via* stabilised intermediates **10** and **11** (**Scheme 1.16**). Control experiments using analogous substrates replacing the sulfur with an oxygen or carbon atom proved *S*-chelation to be a prerequisite for hydroacylation. The distance between the sulfur and the alkene or alkyne was found to be crucial to reactivity: homoallylic and bis-homoallylic sulfides performed well whilst their allylic counterparts showed no reactivity.

Scheme 1.16 – Bendorf's *S*-chelation assisted synthesis of medium-sized rings.



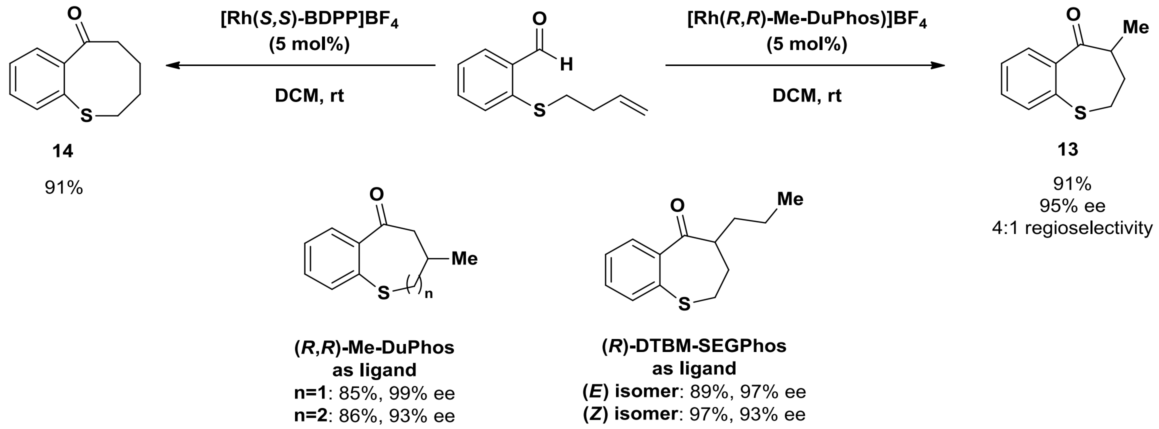
The Dong group have reported an asymmetric variant of Bendorf's 7- and 8-membered ketone synthesis. Using chiral [Rh(*bis*-phosphine)] complexes, excellent yields and selectivities were achieved for a range of benzo-fused heterocycles.[39] As an extension of Bendorf's *S*-chelation strategy, the chelating ability of oxygen was also exploited (**Scheme 1.17**). Notably, Bendorf had previously reported similar ether-linked substrates to be unreactive to Wilkinson's complex.[38]

Scheme 1.17 – Dong's *O*-chelation assisted hydroacylation.



Interestingly, for sulfide-linked enal substrate **12**, it was possible to achieve selectivity for either the 7- or 8-membered ketone with selection of ligand. When the standard MeDuPhos catalyst system was utilised, the 7-membered product **13** was obtained as the major product (4:1 mixture with the 8-membered regioisomer). However, when (*S*,*S*)-BDPP was employed as the ligand, exclusive regioselectivity was observed for the 8-membered heterocycle. The hydroacylation of 1,2- and 1,1-substituted alkenes was also reported, both of which had few previously reported examples (**Scheme 1.18**).

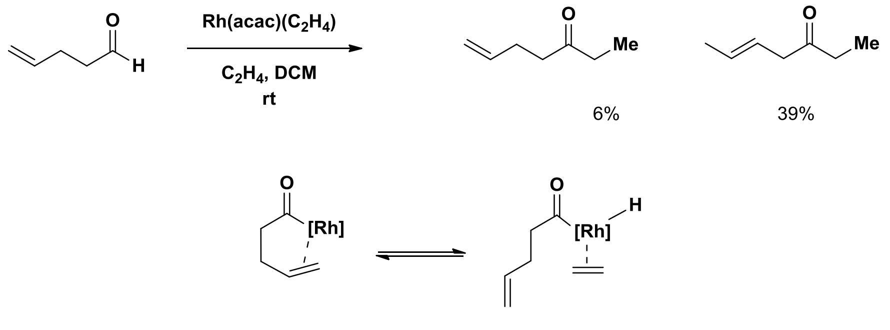
Scheme 1.18- Dong's *S*-chelation assisted hydroacylation.



Intermolecular Hydroacylation

The use of ethene-saturated solvents also led to the first example of intermolecular hydroacylation. In his attempts to suppress the reductive decarbonylation pathway, Miller[26] found that Rh(acac)(C_2H_4)$_2$ also catalysed the intermolecular hydroacylation of 4-pentenal and ethene, to deliver a mixture of isomeric heptanone products alongside trace amounts of cyclopentanone resulting from the intramolecular pathway. This product distribution was explained by the formation of putative intermediates such **15a** and **15b** (**Scheme 1.19**).

Scheme 1.19 – Intermolecular hydroacylation of ethene with 4-pentenal.



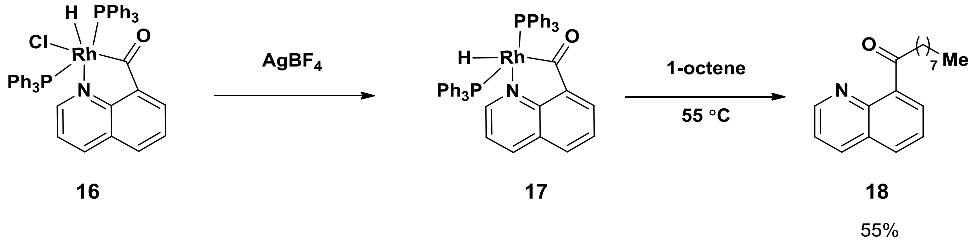
15a **15b**

As previously discussed, ethene saturation of solvents is generally considered to suppress decarbonylation by temporarily occupying a vacant coordination site, which would be required for carbonyl de-insertion to occur. Since such a vacant coordination site is also required for the productive catalytic cycle, the design of catalyst systems which attenuate decarbonylation and also favour product formation remain challenging. Whilst the use of high pressures of ethene cannot be considered as a practically viable method, these results provided a significant insight into the requirement for stabilisation of the rhodium-acyl intermediate, and led to the concept of chelation-assisted hydroacylation. A number of chelation strategies have been developed to overcome the propensity of rhodium-acyl species to undergo reductive decarbonylation.

Chelation Control in Intermolecular Hydroacylation

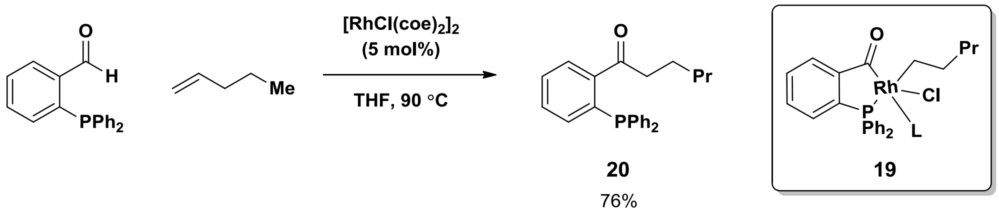
Suggs[40,41] pioneered the use of heteroatom chelation for the stabilisation of rhodium-acyl intermediates. The reaction of one equivalent of quinolone-8-carboxaldehyde and Wilkinson's catalyst enabled isolation of the stable rhodium-acyl intermediate **16** in a 95% yield. The addition of $AgBF_4$ afforded the coordinatively unsaturated species **17**, which then reacted with an excess of 1-octene in THF to deliver the hydroacylated adduct **18** in a 55% yield (**Scheme 1.20**).

Scheme 1.20 – The first example of heteroatom chelation stabilisation of Rh-acyl intermediate.



An alternative chelating strategy was reported by Jun *et al.*: 2-(diphenylphosphino)benzaldehyde was shown to hydroacylate a range of neutral alkenes with the use of catalytic [RhCl(coe)$_2$]$_2$.[42] An example of this reaction is shown below in **Scheme 1.21**. It is proposed that the reaction proceeds *via* Rh(III) acyl intermediate **19**, which then undergoes reductive elimination to deliver ketone **20**.

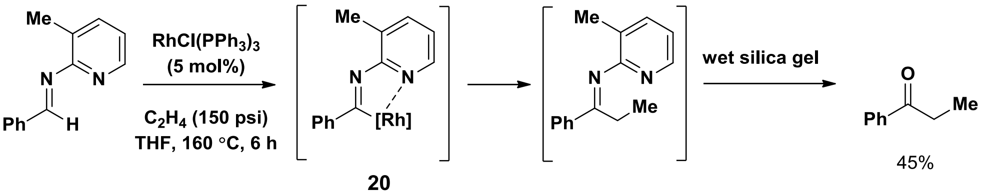
Scheme 1.21 – Jun's use of phosphine chelation.



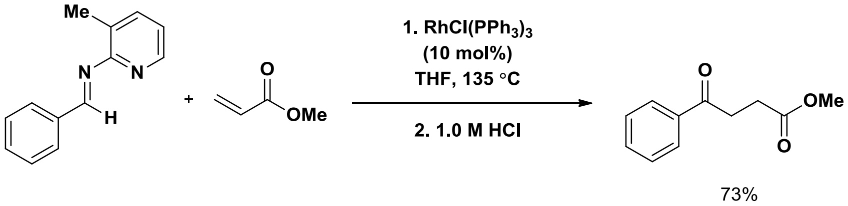
The aforementioned chelation strategies represented a significant advancement in hydroacylation chemistry and provided an understanding of the necessity for a stable rhodium-acyl species. However, the requirement for quinoline and phosphine substituted moieties presented a significant limitation in terms of the generality of this process.

Earlier work by Suggs[43] identified the use of picolylimines as masked aldehydes, which can undergo hydroiminoacylation, followed by hydrolysis of the resultant imine to deliver ketone products (an example is shown below in **Scheme 1.22**). Similarly to the quinoline aldehydes, the pyridyl nitrogen is able to direct metallation to the imine C-H bond, to afford stabilised rhodium-acyl intermediate **21**. When this intermediate is exposed to a high pressure of ethene at an elevated temperature, followed by hydrolysis on silica gel, the ketone product is delivered in a 45% yield. Willis has also exploited the utility of these picolylimine type substrates for the hydroacylation of a range of enoate substrates giving access to synthetically useful 1,4-dicarbonyls (**Scheme 1.23**).[44]

Scheme 1.22 – Suggs' use of picolylimines as masked aldehydes.



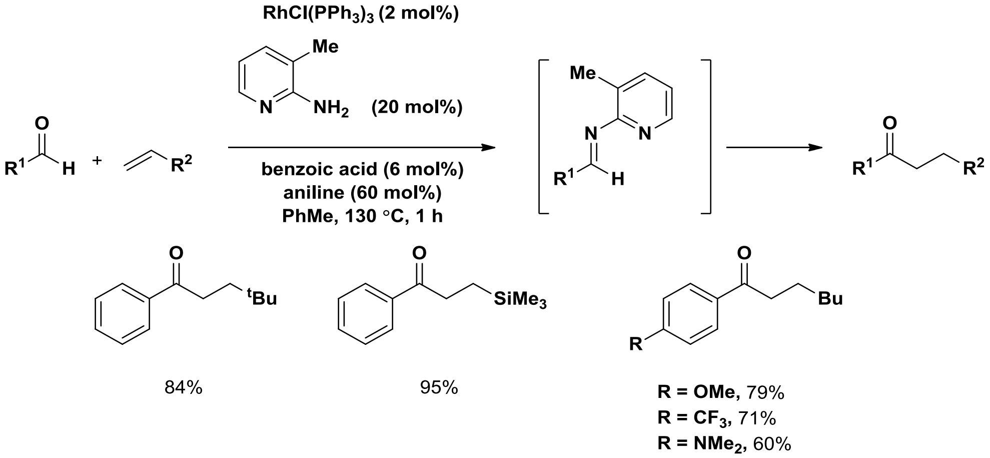
Scheme 1.23 - Willis' picolylimine hydroacylation of enoates.



Jun *et al.*[45] were able to extend upon this work through the use of stoichiometric [RhCl(coe)$_2$]$_2$ as catalyst, followed by treatment with trimethylphosphite to promote reductive elimination.[46] These modifications enabled the application of this process to a range of electronically varied alkenes. Unfortunately, attempts to use substoichiometric loadings of rhodium resulted in very poor turnovers.

A major breakthrough came with the realisation by Jun *et al.* that these picolyl imines could be generated *in situ* from the corresponding aldehydes and amines.[47] Extensive screening and a serendipitous discovery identified a co-catalytic system involving Wilkinson's complex, picolyl amine, benzoic acid and aniline (**Scheme 1.24**).[48]

Scheme 1.24 – Jun's *in situ* generated picolylimines as hydroacylation substrates.

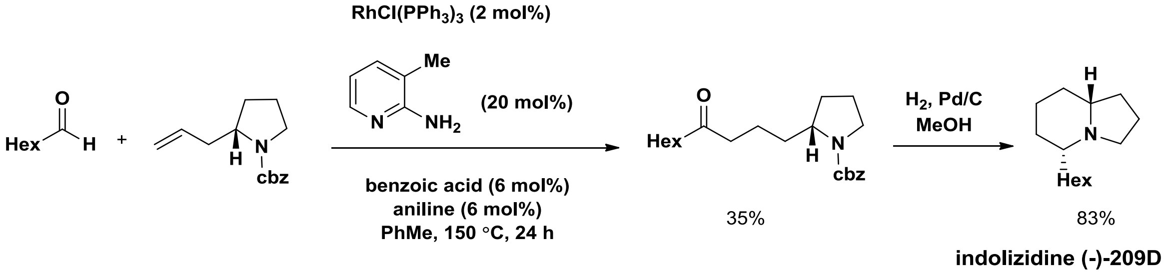


The use of this multicomponent catalyst system enabled the use of low catalyst loadings with a diverse range of alkenes and aldehydes, and delivered ketone products in good to excellent yield using. It was surmised that benzoic acid catalysed the imine formation whilst the aniline facilitated hydrolysis of the imine - the postulated rate determining step of the reaction. Extension of this work to heteroaromatic aldehydes required titanium and zirconium co-catalytic additives.[49] A more recent publication from the Castillon group has demonstrated the use of Montmorillonite K10 clay as a co-catalyst for imine formation.[50]

It is interesting to note that the majority of Jun's publications on picolyl imines use neutral Wilkinson-type catalysts during an era where $[Rh(diphosphine)]^+$ complexes were evolving as superior catalysts. Bo and Castillon conducted a series of computational and NMR studies to ascertain the reasons for the significantly higher conversions observed with Wilkinson's complex.[51] They acknowledged that whilst the overall reaction can be considered a hydroacylation process, the rhodium-catalysed portion proceeds through oxidative addition into the C-H bond of an imine rather than an aldehyde, and hence the metal-catalysed reaction is formally a hydroiminoacylation. They showed this process to be endothermic and hence energetically disfavoured with a cationic rhodium species. In contrast, the oxidative addition was favoured when the neutral Wilkinson's complex was employed.

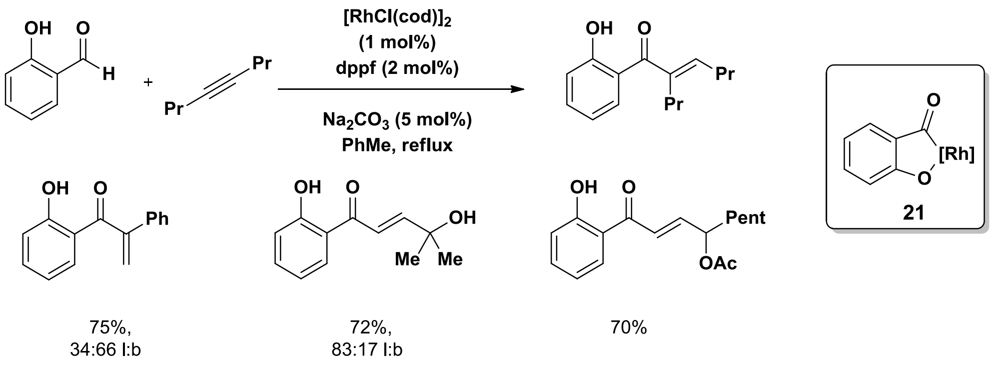
The Kim group have used the conditions developed by the Jun group for the synthesis of indolizidine alkaloids employing commercially available starting materials (**Scheme 1.25**). Although the hydroacylation proceeded in a relatively low yield, total retention of chirality was observed and a natural product was generated in two, simple steps.[52]

Scheme 1.25 – Kim's synthesis of indolizidine (-)-209D.



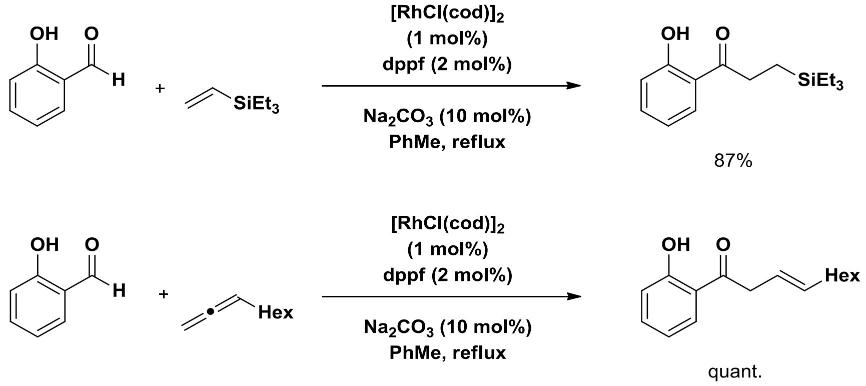
The chelating ability of salicylaldehydes, *via* stabilised intermediates such as **21**, has been exploited by several groups. Miura *et al.* have extensively studied the hydroacylation of alkynes, alkenes and allenes with salicylaldehydes.[53,54] A range of internal and terminal alkynes were hydroacylated in excellent yields. When terminal alkynes were employed, mixtures of the branched and linear regioisomers were observed. An improvement in selectivity was obtained for propargyl alcohols (**Scheme 1.26**).

Scheme 1.26 – Miura's hydroacylation of alkynes with salicylaldehyde.



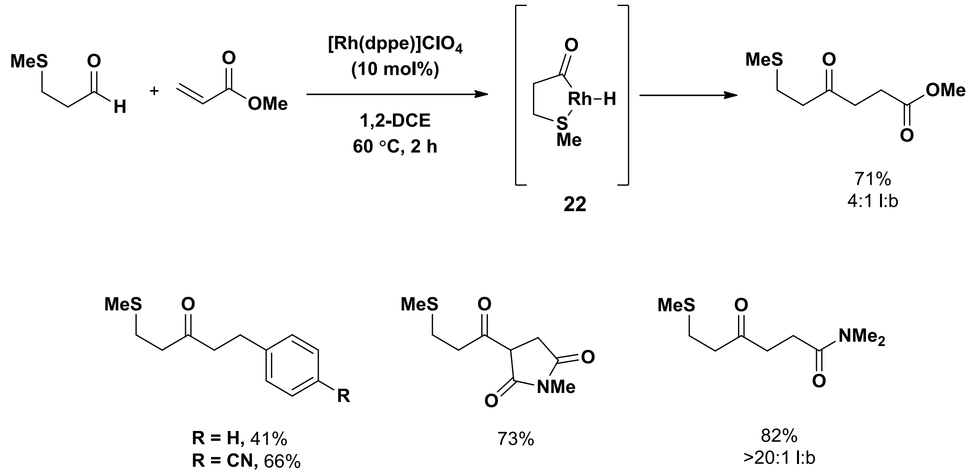
Alkene substrates proved to be more challenging, with triethylvinylsilane the only reactive substrate of those investigated. Finally, several allenes reacted efficiently to afford *α,β*-unsaturated ketone products. Selected examples are shown below in **Scheme 1.27**.

Scheme 1.27 – Selected examples of Miura's hydroacylation of alkenes and allenes.



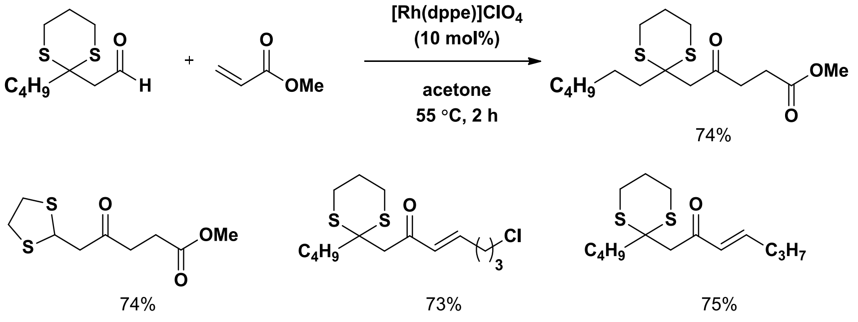
The Willis group have pioneered the use of *S*-chelation in intermolecular hydroacylation chemistry using *β*-sulfur-containing aldehydes and Bosnich-type[29] cationic rhodium complexes. They first reported the hydroacylative coupling of 3-(methylthio)propionaldehyde and a range of functionalised electron-deficient alkenes to afford ketone adducts in good yields (**Scheme 1.28**).[55] The authors rationalised the high reactivity on account of the formation of a stabilised 5-membered rhodium-acyl species **22**. The position of the sulfide proved crucial; for *α*- and γ-substituted aldehydes, reductive decarbonylation was the dominant pathway.

Scheme 1.28– Willis' use of *S*-chelation assisted intermolecular hydroacylation.

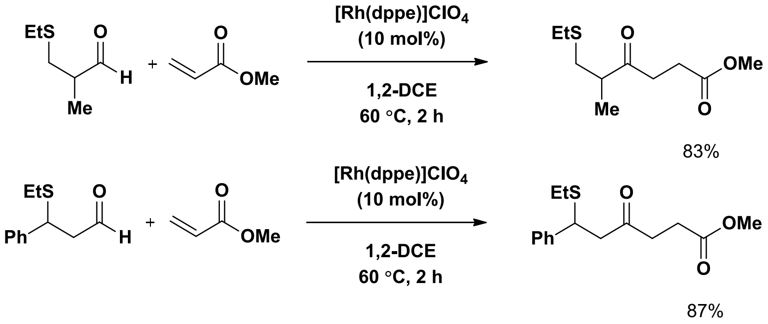


The methodology was extended to include the use of more synthetically useful *β*-thioacetal substrates.[56,57] Through employing the same catalyst system in acetone at 55 °C, both electron-deficient alkenes and a range of electronically varied terminal and internal alkynes were hydroacylated in good yields (**Scheme 1.29**). Both sulfide and thioacetal substrates have also been shown to undergo hydroacylation with 1,2- and 1,3-substituted allenes to deliver *β,γ*-enone products.[58] In addition, *α*- and *β*- branched *β*-thio aldehydes, and various substituted aromatic aldehydes have proved to be reactive substrates (**Scheme 1.30**).[57,59]

Scheme 1.29 – Willis' use of *β*-thioacetals as chelating substrates.

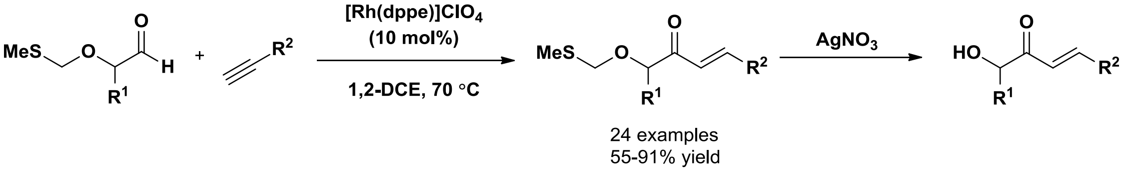


Scheme 1.30 – Willis's use of α- and β- branched β-thio aldehydes



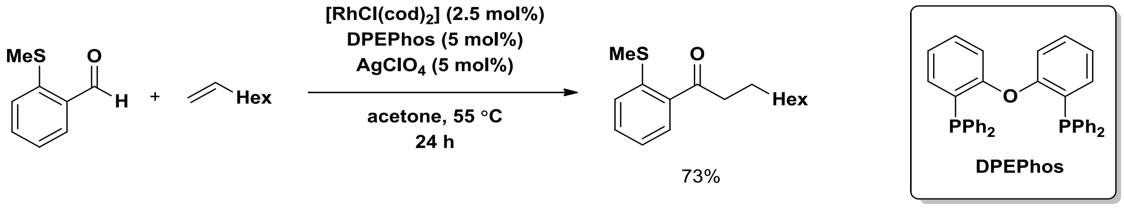
More recently, the aldehyde scope has been broadened to include methylthiomethyl (MTM) ethers as the chelating moiety.[60] These proved to be highly reactive hydroacylation substrates for a range of terminal alkynes (**Scheme 1.31**). The positions of the oxygen and sulfur atoms were found to be fundamental to reactivity; omission of the oxygen resulted in considerably reduced yields whilst replacement of the sulfur with oxygen or carbon led to complete cessation of the reaction. Notably, the product MTM ethers could be converted to the corresponding free alcohols through reaction with silver nitrate.

Scheme 1.31 – Willis' use of MTM ether substituted aldehydes.

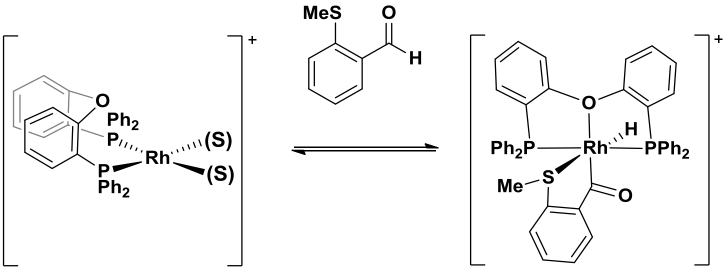


Willis and Weller have since described a "second generation" catalyst system employing DPEPhos as ligand (**Scheme 1.32**).[61,62] This catalyst system showed increased reactivity and greater stability thus enabling efficient hydroacylation of previously poorly reactive electron-neutral alkenes. The authors proposed that the hemi-labile oxygen atom of the DPEPhos ligand allowed coordination to the rhodium centre to form complex **23**, thus providing additional stabilisation for the rhodium-acyl intermediate (**Scheme 1.33**). Previously, for the less reactive electron-neutral alkene species, the decarbonylation pathway had predominated. A practical advantage of this catalyst system is the ability to generate the active species *in situ* by mixing $[Rh(cod)Cl]_2$, DPEPhos and $AgClO_4$, without the requirement for hydrogenation. NMR spectroscopy, mass spectrometry and x-ray crystallography confirmed the structure of the various stabilised intermediates and catalyst species.

Scheme 1.32 - The use of a "second generation" hydroacylation catalyst.



Scheme 1.33 - Stabilisation of the rhodium-acyl intermediate *via* coordination of a hemi-labile oxygen atom.



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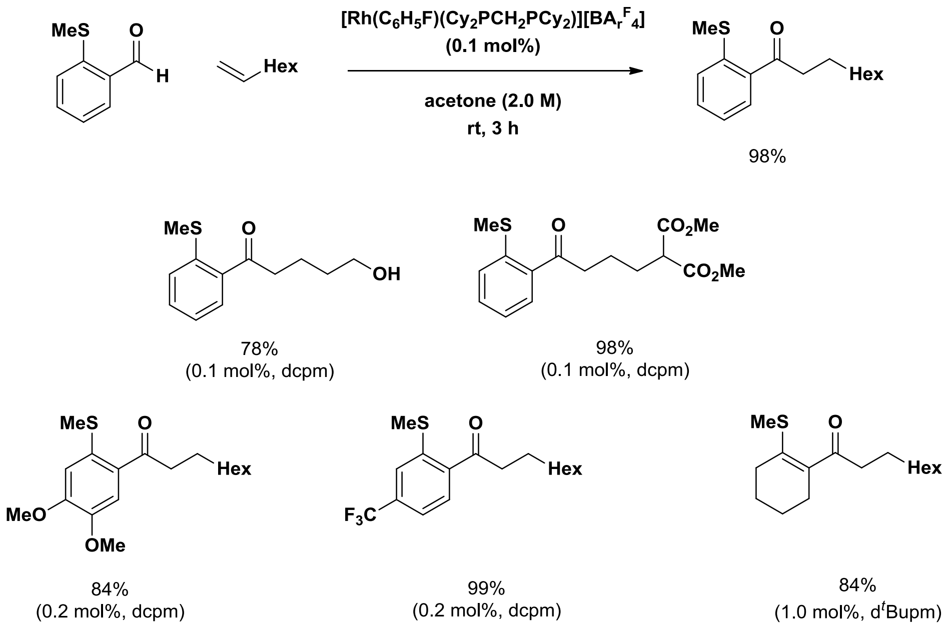
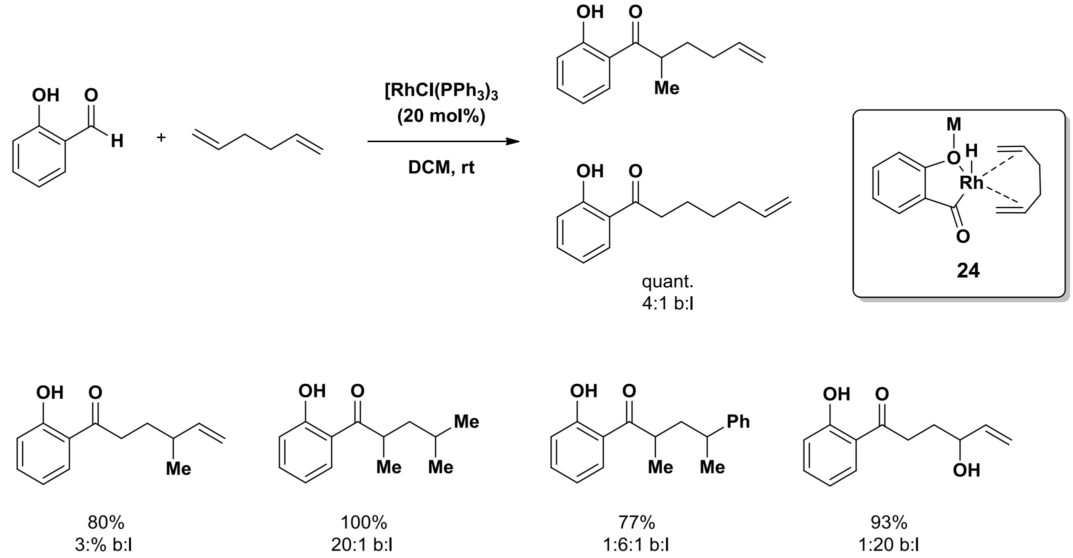
The Willis group has recently reported the use of practical, bench-stable hydroacylation catalysts based on the small bite-angle ligands ${}^tBu_2PCH_2P^tBu_2$ (d^{t}Bupm) and $Cy_2PCH_2PCy_2$ (dcpm).[59] Through careful selection of solvent and concentration, suppression of the competing decarbonylation pathway was achieved, and the rate of hydroacylation was significantly enhanced. This enabled the use of catalyst loadings as low as 0.1 mol% for the combination of a range of β-thio-aldehydes with electronically varied alkenes and alkynes in a linear-selective fashion.[63] Selected examples are shown below in **Scheme 1.34**.

Scheme 1.34 – Hydroacylation using rhodium catalysts with small bite-angle ligands.



Suemune *et al.* have reported a “double chelation assisted” approach for the hydroacylative coupling of a range of salicylaldehydes and dienes (**Scheme 1.35**).[63,64] The use of 20 mol% Wilkinson’s catalyst, under mild reaction conditions facilitated the hydroacylation of a range of 1,4-pentadienes and 1,5-hexadienes in good yields, albeit with varying degrees of regioselectivity. A range of substituted salicylaldehyde derivatives were also tolerated. The hydroxyl group was shown to be essential for reactivity - it was proposed that the reaction proceeded *via* intermediate **24** whereby the rhodium centre is doubly coordinated *via* both the aldehyde and the diene. 1,6-Hexadienes were shown to have poor reactivity, most likely as a result of the larger distance between the two olefins. It was possible to achieve a small degree of selectivity through tuning of the catalyst system: the use of the cationic complex [Rh(*o*-MeC$_6$H$_4$)$_3$P]Cl (formed *in situ* by the addition of AgClO$_4$ to [Rh(coe)Cl]$_2$ and P(*o*-Me MeC$_6$H$_4$)$_3$) afforded the branched isomer, whereas employing neutral [Rh(coe)Cl]$_2$ with NH(^{i}Pr)$_2$ as base delivered the linear isomer.

Scheme 1.35 – Suemune's hydroacylation of 1,5-dienes and salicylaldehydes

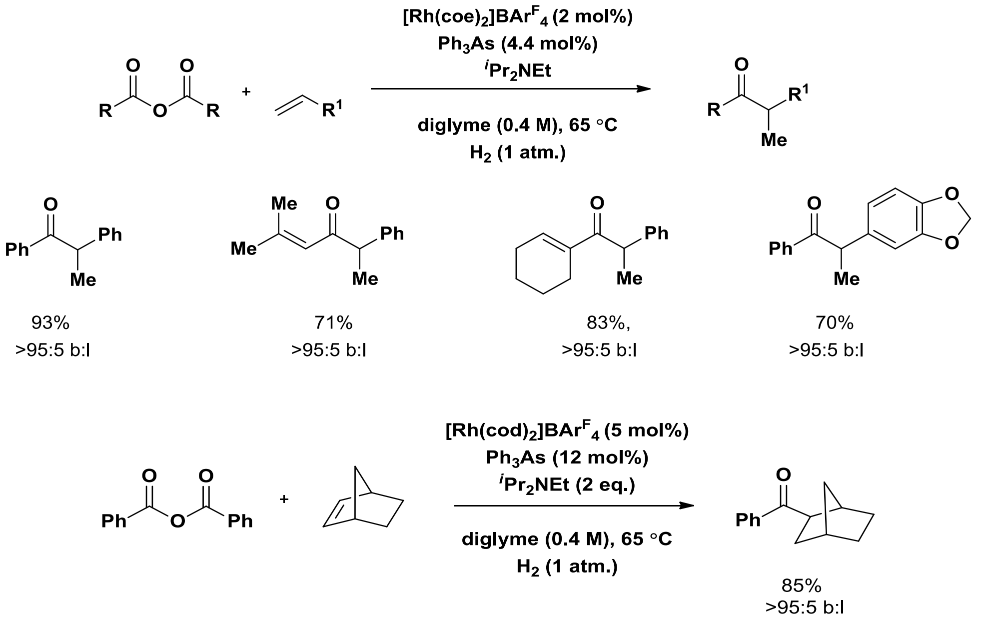


Regioselectivity in Hydroacylation

A number of enantioselective and diastereoselective hydroacylation processes exist; however, the issue of regioselectivity is still relatively unexplored. Linear-selective processes represent the most common outcome for intermolecular hydroacylation, and although recent years have seen the development of branched-selective processes, they often appear contrived or require very specific substrates. Recent examples of regiocontrol in intermolecular hydroacylation processes will be described herein.

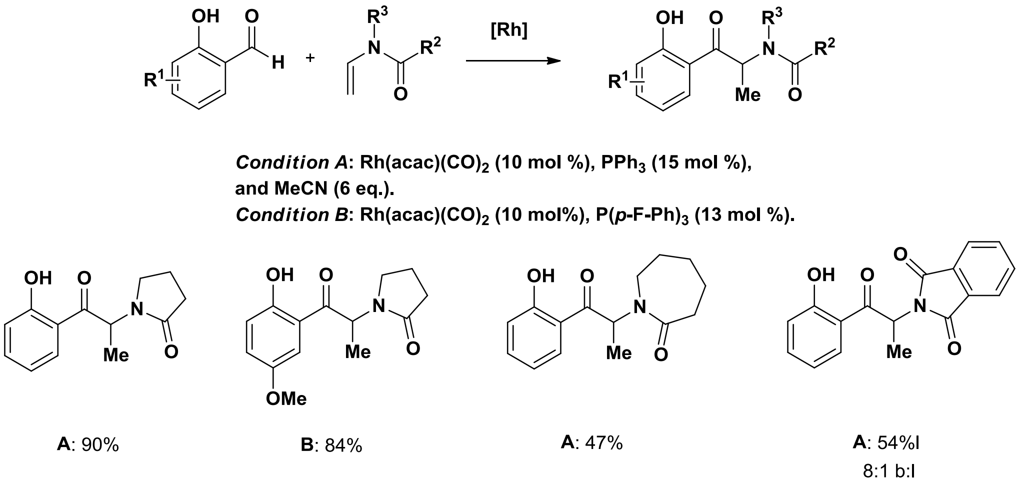
Krische *et al*. demonstrated the branched-selective hydroacylation of a range of styrenes and activated alkenes, employing either symmetrical or mixed carboxylic anhydrides as the acyl donors.[65] Excellent regioselectivities and high yields were obtained with the use of cationic rhodium catalysts and triphenylarsine as ligand (**Scheme 1.36**). The proposed mechanism involved oxidative addition of the anhydride, followed by insertion of styrene, and finally hydrogenolytic cleavage of the rhodium-carbon bond.

Scheme 1.36 – Krische's branched-selective hydroacylation of styrenes with carboxylic anhydrides.



Bolm *et al.* reported the first regioselective hydroacylation of enamides and salicylaldehydes using rhodium catalysis.[66] They observed that the presence of acetonitrile resulted in increased yields. It was also found that monodentate phosphines gave optimum reactivity, with $P(p\text{-}F\text{-}C_6H_5)_3$ proving the most effective for the direct hydroacylation of their standard enamide 1-vinyl-2-pyrrolidinone. Excellent branched selectivity was observed for a range of substituted salicylaldehydes with 1-vinyl-2-pyrrolidinone. However, only a limited number of enamide substrates could be hydroacylated, with *N*-vinylcaprolactam giving only 47% yield and *N*-vinylphthalimide a mixture of regioisomeric products. Selected examples are shown below in **Scheme 1.37**.

Scheme 1.37 – Bolm’s branched-selective hydroacylation of enamides.



Condition A: Rh(acac)(CO)$_2$ (10 mol %), PPh$_3$ (15 mol %), and MeCN (6 eq.).
Condition B: Rh(acac)(CO)$_2$ (10 mol%), P(*p*-F-Ph)$_3$ (13 mol %).

Dong *et al*. described the regio- and enantioselective intermolecular hydroacylation of salicylaldehydes and sulfides using a “double-chelation” approach and exploiting the directing potential of sulfur (**Scheme 1.39**).[67] With the use of a chiral phosphoramidite ligand, they observed excellent yields and enantioselectivities with almost exclusive branched selectivity for the combination of a range of substituted salicylaldehydes and homoallylic sulfides. Interestingly, for the hydroacylation of an allylic sulfide, a reversal in regioselectivity was observed. This was rationalised by the intermediacy of the key structures shown in **Figure 1.2**.

Scheme 1.39 – Dong’s hydroacylative coupling of salicylaldehydes and sulfides.

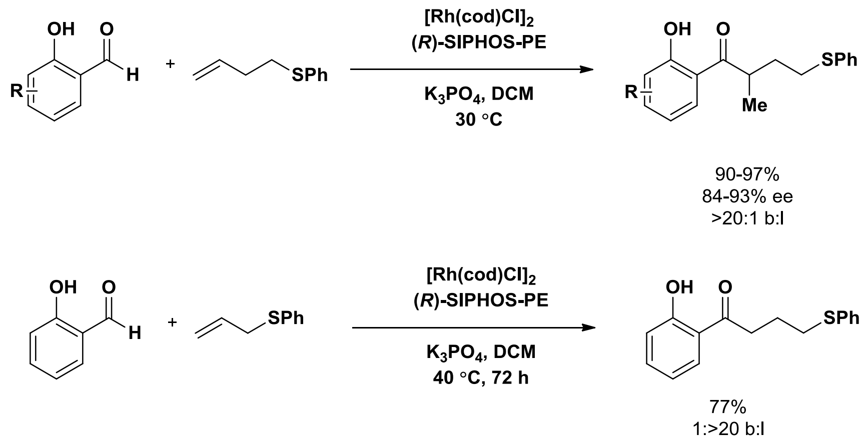
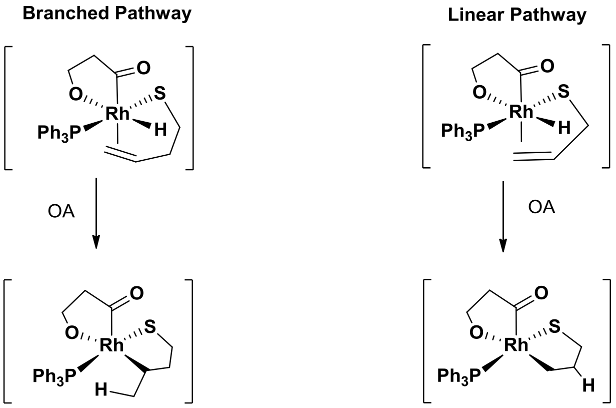
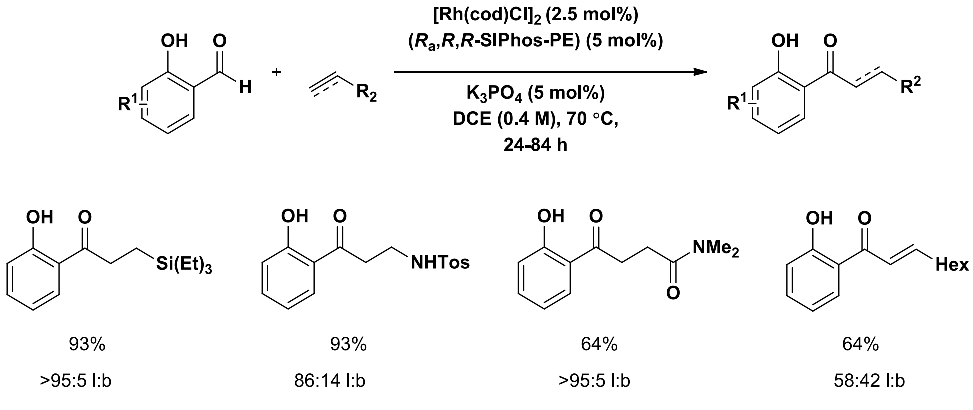


Figure 1.2 –Postulated intermediates for the branched and linear pathways.



The same group have since developed an efficient method for the linear-selective hydroacylation of mono-substituted alkenes with salicylaldehyde derivatives using the same phosphoramidite rhodium catalyst system (**Scheme 1.40**).[67] A range of electron-rich, electron-poor, and neutral salicylaldehydes were hydroacylated in good to excellent yields and, in all cases, with >95:5 linear:branched regioselectivity. In addition, electronically varied alkenes were tolerated with generally high yields and moderate to excellent levels of selectivity.

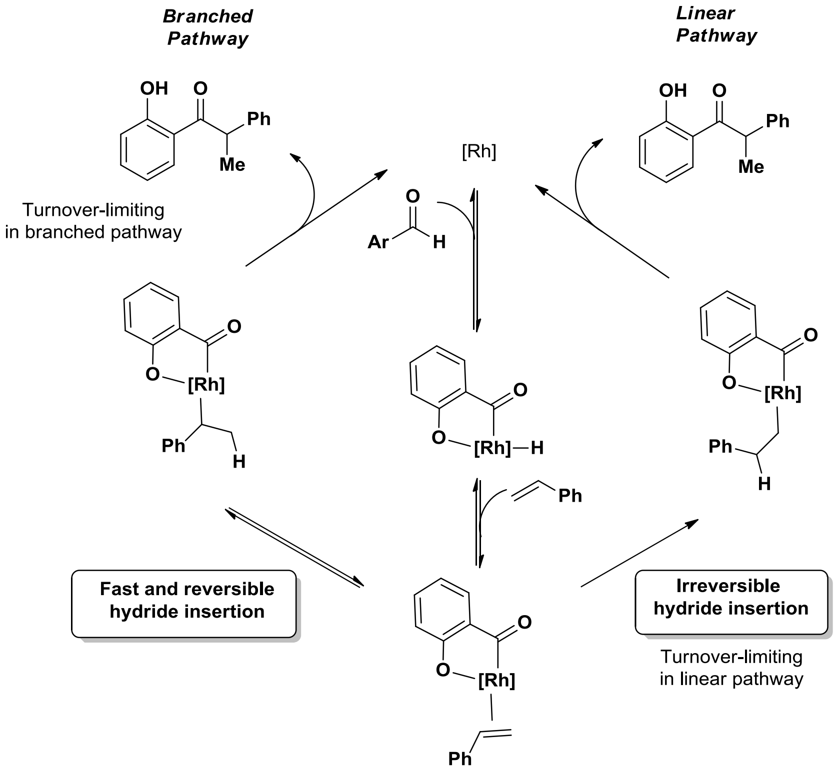
Scheme 1.40 – Linear-selective hydroacylation of mono-substituted alkenes.



The authors established that a precise loading of heterogeneous base was essential in order to achieve high catalytic turnover, the role of the base being to deprotonate the salicylaldehyde to enable coordination to the rhodium centre. The optimum base loading was found to be stoichiometric with respect to rhodium loading; catalytic turnover was in fact inhibited by an excess of base.

A recent publication by Dong and co-workers detailing extensive mechanistic and deuterium labelling studies uncovered some key features of this catalytic system.[68] In accordance with other literature reports, oxidative addition and alkene coordination were found to be rapid and reversible processes. As a general trend, for unactivated alkenes, branched hydride insertion was also rapid and reversible, whereas linear hydride insertion was largely irreversible and turnover-limiting. Additionally, reductive elimination in a branched-selective process was determined as the turnover-limiting step, which is relatively slow in comparison to that of the linear pathway. This is summarised below in **Scheme 1.41** with phenylacetylene as the alkene.

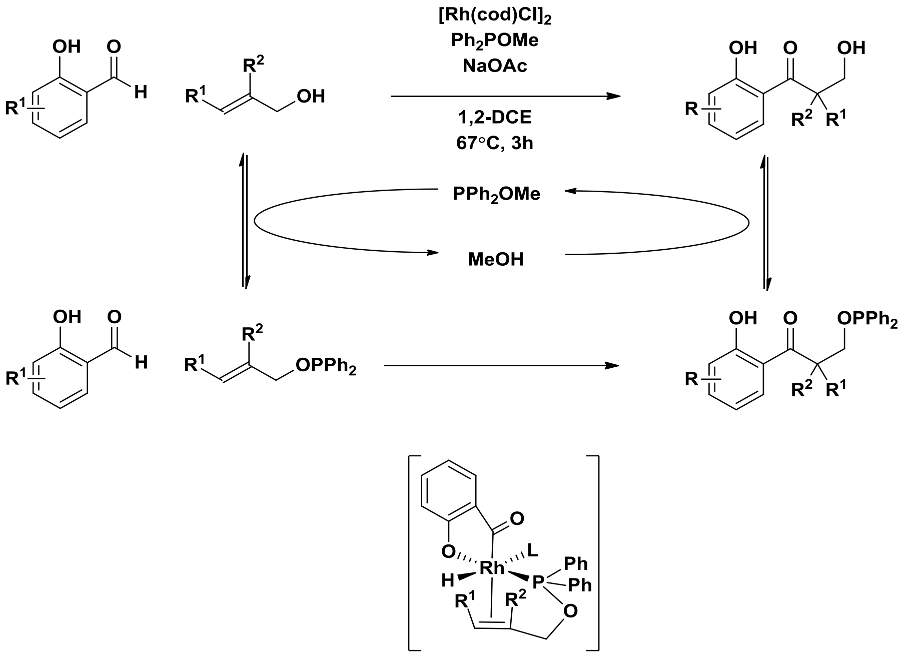
Scheme 1.41 – Dong's proposed catalytic cycle for the branched and linear pathways.



The authors concluded that a combination of steric bulk, a synergistic effect between the three stereogenic elements, and unique stereoelectronic properties enabled (R_a,R,R)-SIPhos-PE to promote both high reactivity and regioselectivity. They suggested that this occurs through suppression of the competing reductive decarbonylation pathway and assistance in favouring turnover-limiting insertion, by lowering the barrier for reductive elimination in the linear-selective pathway. In the case of the previously reported branched-selective hydroacylation of the homoallylic sulfide, these mechanistic studies confirmed a preference for branched hydride insertion. This can be explained by the propensity for the sulfur to chelate the rhodium centre and form a 5-membered rhodacycle.

Dong has most recently reported the branched-selective hydroacylation of allylic alcohols with salicylaldehydes using cooperative catalysis between phosphinite and rhodium (**Scheme 1.42**).[69]

Scheme 1.42 – Dong’s phosphinite and rhodium cooperative catalyst system.



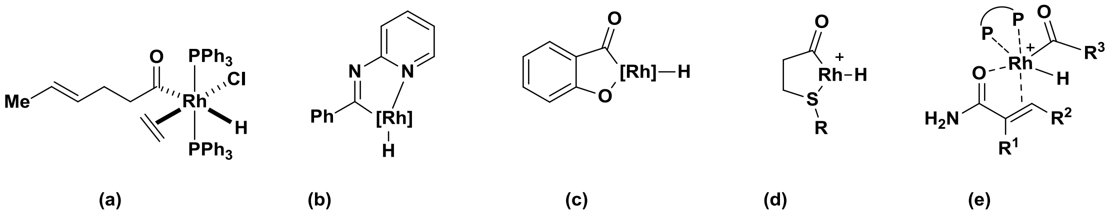
25

It was proposed that a catalytic amount of phosphinite enables the formation of a dynamic covalent bond with the allylic alcohol to form an allylphosphinite. This can then undergo substrate-directed hydroacylation *via* the stabilised rhodium-acyl hydride intermediate **25** and subsequent transesterification. A range of *β*-hydroxy ketones were prepared regioselectively in good to excellent yields. Deuterium labelling studies concluded that oxidative addition and hydride insertion are reversible and reductive elimination the rate-determining step.

Summary

The key developments in rhodium-catalysed hydroacylation have been focussed around the prevention of the undesired decarbonylation pathway through the stabilisation of a key rhodium-acyl intermediate. The various strategies that have been employed are summarised in **Figure 1.3**.

Figure 1.3 - (a) Miller; (b) Jun; (c) Miura, Suemune; (d) Bendorf, Willis; (e) Tanaka



(a) (b) (c) (d) (e)

Intramolecular processes for the synthesis of cyclopentanones are relatively well-established, whilst limitations still exist for the synthesis of larger ring systems. Several stabilisation strategies have been developed for intermolecular hydroacylation processes, through chelation of the aldehyde component, alkene component, or a combination of both. Recent years have seen the emergence of sulfur and oxygen-chelation as a popular strategy and using such methodologies, hydroacylation has evolved as powerful synthetic tool. Linear selectivity represents the most common pathway for intermolecular hydroacylation and relatively few branched-selective processes have been documented. Moreover, these branched-selective processes are often limited by the requirement for a specific combination of substrates.

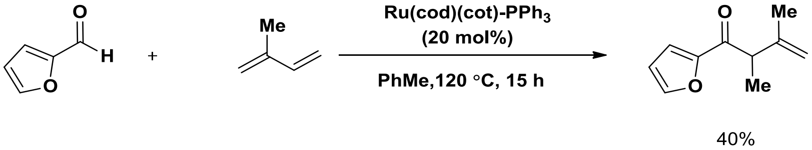
Chapter 2 - Branched-Selective Diene Hydroacylation

Introduction

Background

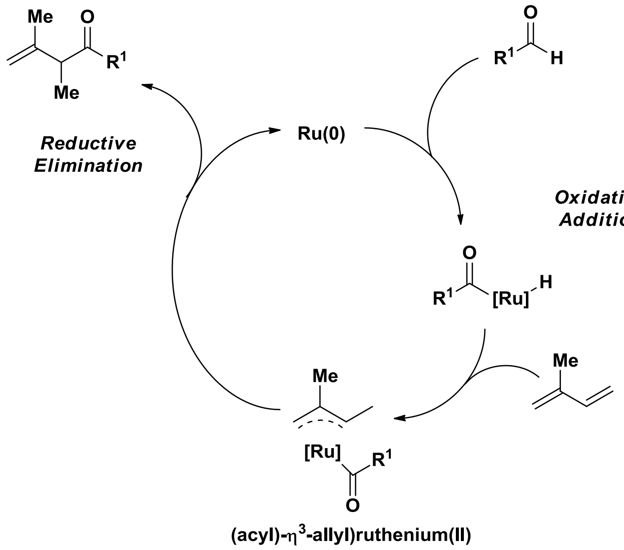
Few examples have been reported for the transition-metal catalysed hydroacylation of 1,3-dienes. To the best of our knowledge, there are no rhodium-catalysed processes; however, several groups have disclosed ruthenium-catalysed variants with exclusive branched selectivity. Kondo *et al.*[10] have reported the ruthenium(0)-catalysed hydroacylation of 1,3-dienes for a limited range of aldehydes in moderate yields (**Scheme 2.1**).

Scheme 2.1 – Ru(0)-catalysed hydroacylation of 1,3-dienes.



They propose a similar mechanism to that of a conventional hydroacylation reaction where the key intermediate is the (acyl)-(η^3-allyl)ruthenium(II) species **26** (**Scheme 2.2**).

Scheme 2.2- Proposed mechanism for Ru(0)-catalysed hydroacylation of 1,3-dienes.



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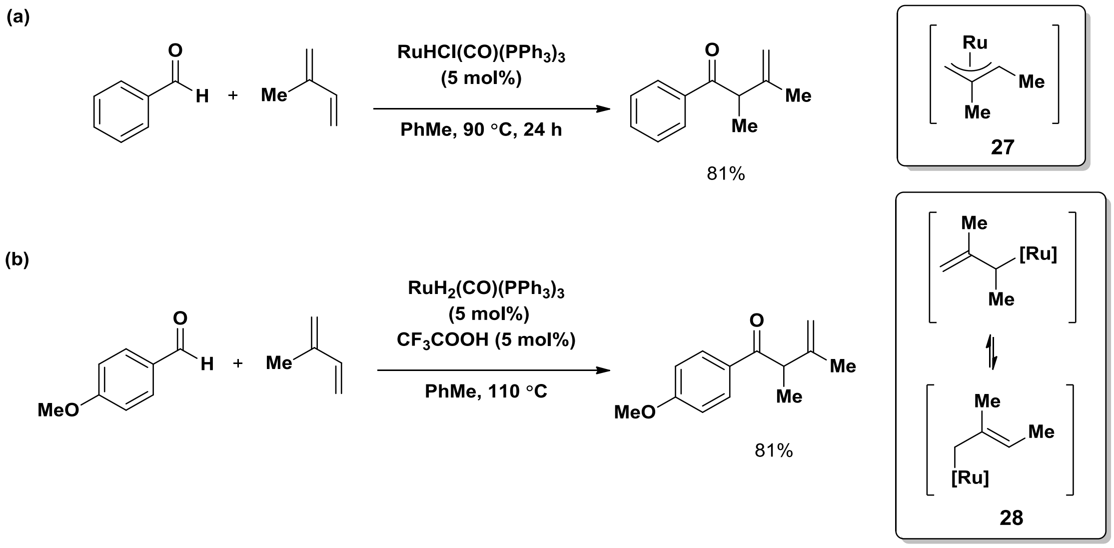
The Ryu[70] and Krische[71] groups have reported the ruthenium hydride-catalysed hydroacylation of various of 1,3-dienes with a range of aromatic and aliphatic aldehydes (**Scheme 2.3**). Both groups propose mechanisms involving initial coordination of the diene to the ruthenium-hydride. The Ryu group postulate generation of the π-allylruthenium intermediate **27** as a result of addition of ruthenium-hydride to the diene. This intermediate can then add to the aldehyde *via* a 6-membered transition state to afford a ruthenium alkoxide species. This then undergoes *β*-hydride elimination to afford the *β*,*γ*-unsaturated ketone. Krische proposes a similar mechanism but suggests that the equilibrating *σ*-ruthenium species **28** is the key intermediate.

Scheme 2.3 – (a) Ryu's and (b) Krische's ruthenium hydride-catalysed hydroacylation of 1,3-dienes.

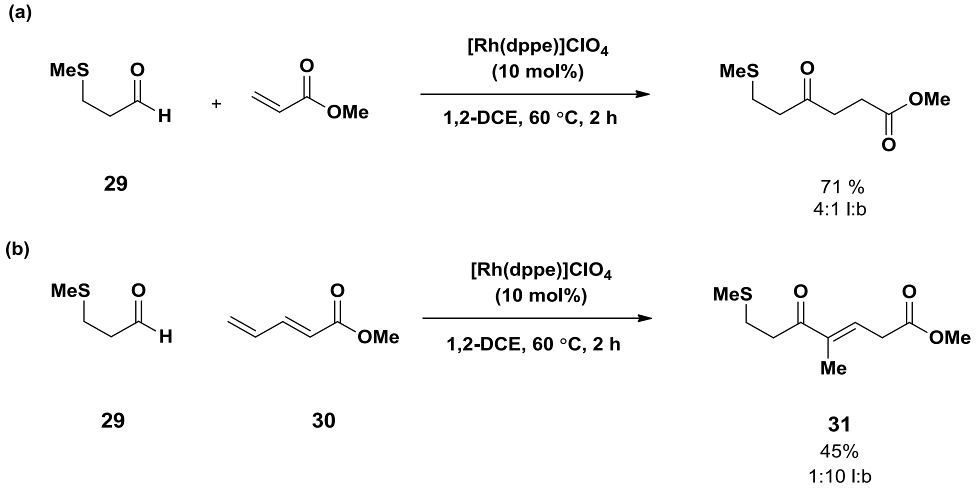


Project aims

As previously discussed, our group research has been primarily focussed on the *S*-chelation assisted hydroacylation of alkenes and alkynes, for which the linear pathway usually predominates (See Section 1.2). It was therefore interesting to observe that when aldehyde **29** and diene **30** were submitted to our standard reaction conditions, a reversal in regioselectivity was observed, forming the branched adduct **31** as the major regioisomer

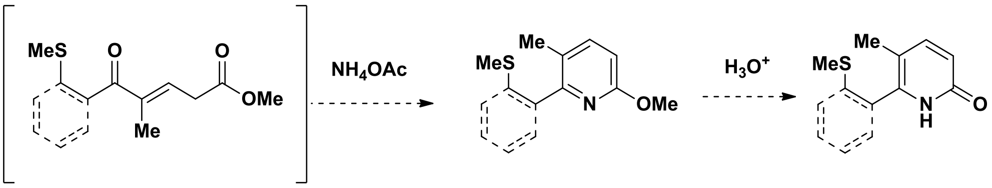
(**Scheme 2.4**).[55] Presumably, the branched regioisomer is formed *via* a rhodium-π-allyl intermediate similar to that proposed by Kondo.[10]

Scheme 2.4 – (a) Linear-selective hydroacylation between aldehyde **29** and methyl acrylate; (b) Branched-selective hydroacylation between aldehyde **29** and diene **30**.



The aim of this project was to investigate the factors involved in determining this unusual regioselectivity in terms of both the substrate and catalyst system. In addition, we sought to establish the scope of the reaction in terms of both the aldehyde and the diene substrates. Finally, we hoped to cyclise the 1,5-dicarbonyl products to furnish the corresponding unusual substituted 2-methoxypyridines or pyridones (**Scheme 2.5**).

Scheme 2.5 – Proposed cyclisation of 1,5-dicarbonyl hydroacylation adducts.

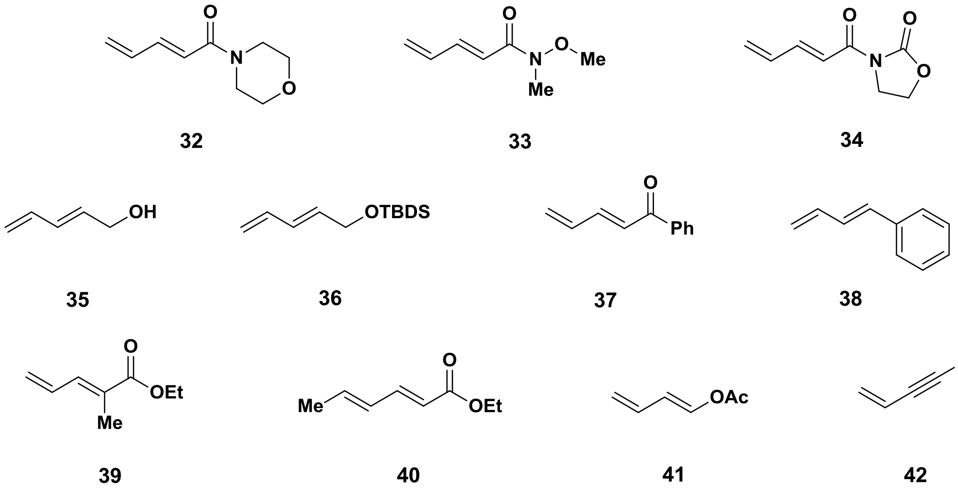


Results and Discussion

Synthesis of Diene Starting Materials

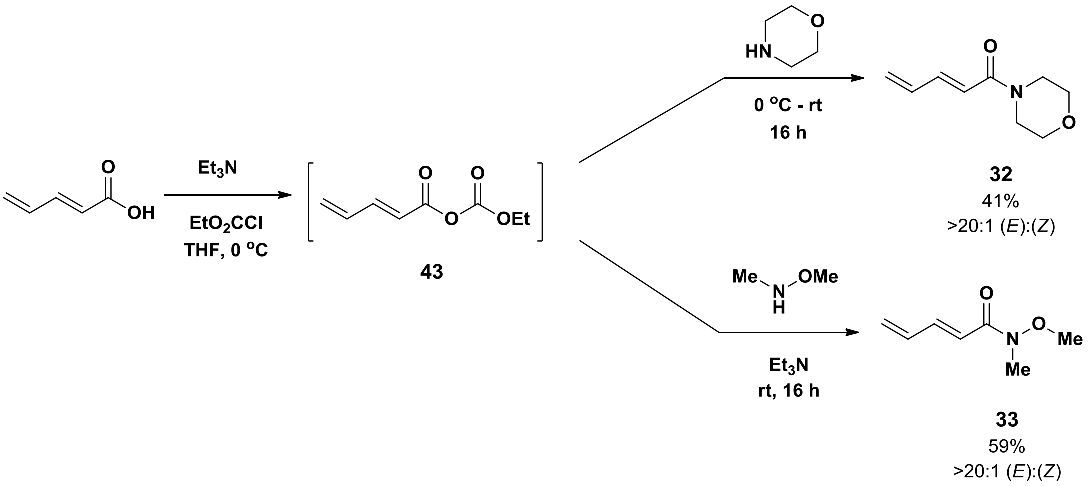
Dienes **32-41** were chosen as potential hydroacylation substrates to evaluate the scope of the reaction in terms of both reactivity and regioselectivity (**Figure 2.1**). In addition, we thought it would be interesting to assess the reactivity of enyne **42** under hydroacylation conditions as this cannot form a rhodium-π-allyl species.

Figure 2.1 – Potential hydroacylation substrates.



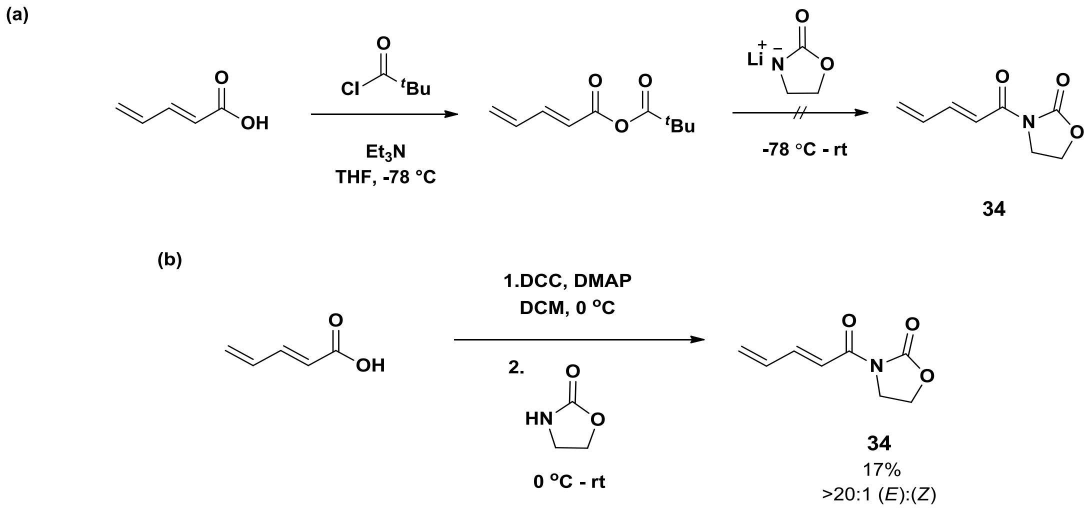
Diene substrates **32** and **33** were synthesised in moderate yields *via* formation of a common mixed carbonic anhydride **43** and subsequent reaction with either morpholine or *N*,*O*-dimethylhydroxylamine (**Scheme 2.6**).

Scheme 2.6 – Synthesis of dienes **32** and **33**.



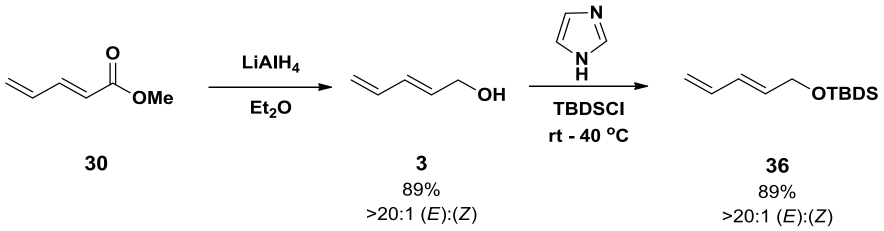
Initial attempts to synthesise oxazolidinone amide **34** *via* formation of a mixed anhydride with pivaloyl chloride then reaction with the lithium salt of oxazolidinone proved unsuccessful. An alternative procedure using DCC coupling afforded the desired product **34** in a low yield. This can be largely be accounted for by difficulties during purification (**Scheme 2.7**).

Scheme 2.7 – (a) Attempted synthesis of **34** *via* a mixed anhydride; (b) Synthesis of **34** using DCC/DMAP coupling reagents.



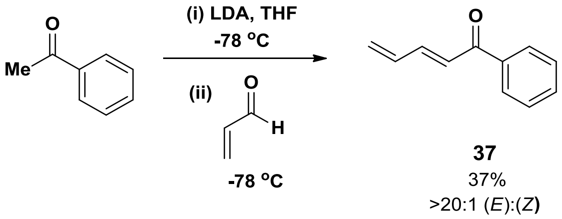
Alcohol **35** was synthesised *via* reduction of methyl ester **30** using $LiAlH_4$, and was subsequently reacted with *tert*-butyldimethylsilylchloride (TBSCl) to form the silyl protected adduct **36** (**Scheme 2.8**).[72]

Scheme 2.8 – Synthesis of alcohol **36** *via* $LiAlH_4$ reduction of methyl ester **30** followed by TBS protection.



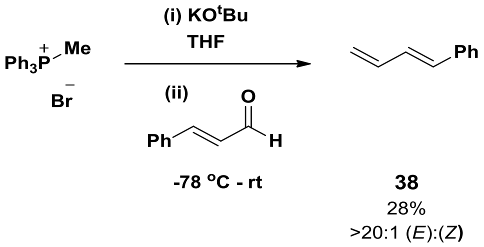
Ketone **37** was synthesised *via* an aldol condensation of acetophenone with acrolein (**Scheme 2.9**).[11,73] Isolation of the desired product was difficult due to problems with polymerisation.

Scheme 2.9 – Synthesis of ketone **37** *via* an aldol reaction of acetophenone and acrolein.



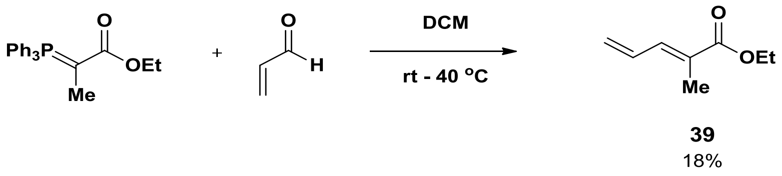
Diene **38** was synthesised *via* a Wittig olefination of cinnamaldehyde as shown in **Scheme 2.10**.[74]

Scheme 2.10 – Wittig olefination of *trans*-cinnamaldehyde to form diene **38**.



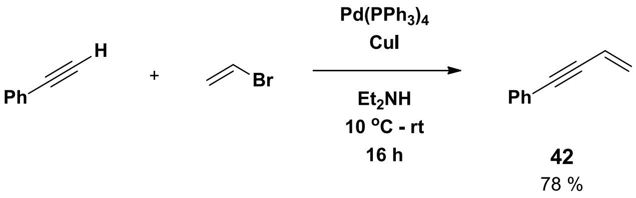
Substituted diene **39** was synthesised according to literature precedent *via* a Wittig reaction between carbethoxyethylidene-(triphenylphosphorane) and acrolein (**Scheme 2.11**). The product was obtained as a single double bond regioisomer; however, the relative stereochemistry was not established.

Scheme 2.11 – Synthesis of substituted diene **39**.



Finally enyne **42** was accessed *via* a Sonagashira coupling of phenylacetylene and vinyl bromide (**Scheme 2.12**).

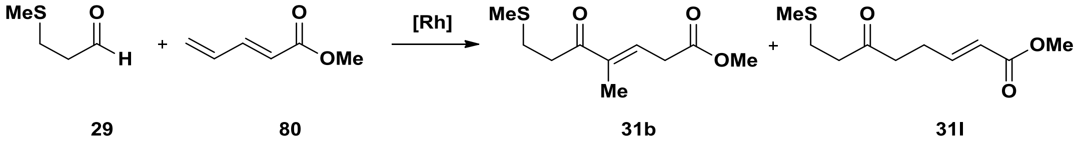
Scheme 2.12 – Synthesis of enyne **42** *via* a Sonagashira coupling.



Initial Optimisation

Initial work focused around the optimisation of the previously reported hydroacylative coupling of aldehyde **29** with diene **30** (**Table 2.1**).[55] Unfortunately, it was not possible to repeat the published yield, with only 18% of the branched product isolated using the literature conditions (**Table 2.1**, entry 1).

Table 2.1 – Optimisation of reaction conditions for the reaction of aldehyde **29** and diene **30.**



Entry No.	Catalyst[a]	Diene eq.	Solvent	Conc. (M)	Temp (°C)	Yield (%)[c]
1	[Rh(dppe)]ClO_4	2.5	1,2-DCE	0.07	60	18
2	[Rh(dppb)]ClO_4	2.5	1,2-DCE	0.07	70	-
3	[Rh(DPEPhos)]ClO_4	2.5	Acetone	0.07	55	-
4	[Rh(dppe)]ClO_4	2.5	1,2-DCE	0.10	90	24
5	[Rh(dppe)]ClO_4	2.5	1,2-DCE	0.20	90	-
6	[Rh(dppe)]ClO_4	2.5	1,2-DCE	0.30	90	-
7	[Rh(dppe)]ClO_4	2.0	1,2-DCE	0.10	90	22
8	[Rh(dppe)]ClO_4	1.5	1,2-DCE	0.10	90	34
9	[Rh(dppe)]BF_4[b]	1.5	1,2-DCE	0.10	90	47

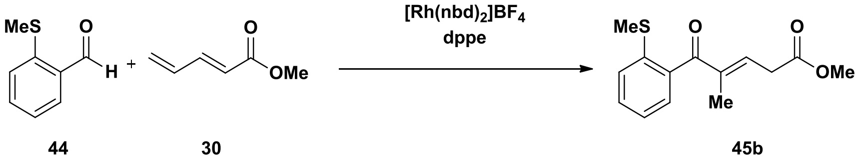
[a] All reactions were performed using 10 mol% of catalyst at the specified temperature for 18 h. The active species was generated *in situ* through hydrogenation of the pre-catalyst complex [Rh(nbd)(ligand)]ClO_4. [b] The active catalyst was generated *in situ* by stirring [Rh$(nbd)_2$]BF_4 and dppe. [c] Isolated yield with >20:1 b:l regioselectivity. In all cases it was difficult to obtain and accurate b:l regioselectivity through analysis of crude ^{1}H NMR spectra.

Variation of the ligand to either dppb or DPEPhos resulted in only recovered starting material (entries 2 & 3). Increasing the reaction temperature to 90 °C and the concentration to 0.1 M produced a slight increase in yield (entry 4). However, increasing the concentration further resulted in no desired product and only a mixture of starting materials and possible decomposition products was observed (entries 5 & 6). Finally, reducing the quantity of diene from 2.5 to 1.5 equivalents resulted in a marginal increase in yield (entry 8). For entries 1-8, the active catalyst species was generated *in situ* through hydrogenation of [Rh(dppe)(nbd)]ClO_4. From a practical perspective, since the majority of this project was to be investigated during an industrial placement, it was hoped that the active species could be generated *in situ* without the requirement for hydrogenation. Gratifyingly, when

[Rh(dppe)]BF_4 was prepared by simply mixing [Rh(nbd)$_2$]BF_4 and dppe in 1,2-DCE, a yield of 47% was obtained (entry 9). These were established as our optimum conditions for this process.

Owing to the relatively capricious nature, poor reactivity and unpleasant odour of aliphatic aldehyde **29**, it was decided to use aromatic aldehyde **44** as our standard aldehyde for further optimisation and screening.

Table 2.2 – Solvent and temperature screen for the hydroacylation of aldehyde **44** and diene **30**.[a]



Entry No.	Solvent	Temp (°C)	H_2/no H_2[b]	Yield (%)[c]	b:l[d]
1	1,2-DCE	90	H_2	72	>20:1
2	1,2-DCE	90	no H_2	68	>20:1
3	1,2-DCE	70	H_2	59	>20:1
4	1,2-DCE	55	H_2	0[e]	-
5	Acetone	55	H_2	56	8:1
6	MIBK	90	no H_2	38	12:1
7	DIBK	90	no H_2	0[e]	-
8	PC	90	no H_2	60	12:1
9	MIBK	120	no H_2	0[f]	-
10	PC	120	no H_2	0[f]	-

[a] Reaction conditions: [Rh(nbd)$_2$]BF_4 (10 mol%), dppe (10 mol%), 0.1 M. [b] Catalyst generated *in situ* either with or without hydrogenation. [c] Isolated yield of both regioisomers. [d] Selectivity determined by analysis of crude ^{1}H NMR spectra. [e] Returned starting material. [f] Complex mixture of decomposition products was obtained.

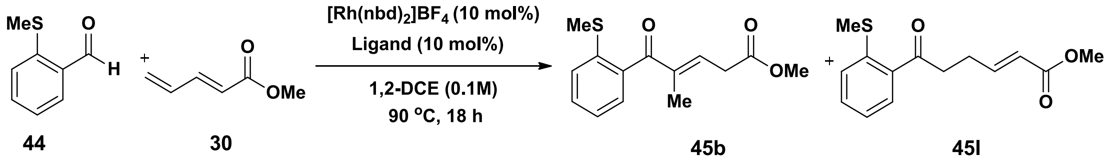
Several higher boiling point solvents were evaluated with the aim to enable the potential for increasing the reaction temperature for more challenging substrates. Unfortunately, no improvement in reactivity was observed: methyl isobutyl ketone (MIBK) gave a 38%

isolated yield and a slight decrease in selectivity of 12:1 (entry 6), whilst performing the reaction in diisobutylketone (DIBK) only returned starting material (entry 7). We were pleased to discover that the reaction performed well using the "green solvent" propylene carbonate (PC)[78] (entry 8), albeit with a reduced branched:linear selectivity of 12:1. Finally, increasing the temperature to 120 °C in both MIBK and PC yielded a complex mixture of decomposition products (entries 9 & 10).

Ligand Evaluation

Next it was decided to screen a range of phosphine ligands to see what effects the nature of the ligand had on reactivity and regioselectivity (**Table 2.3**).

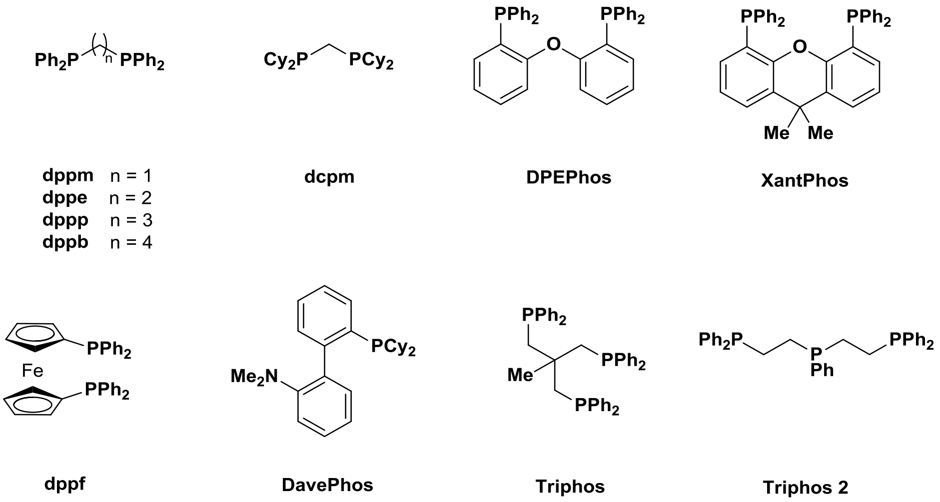
Table 2.3 – Ligand evaluation for the hydroacylation **44** and **30**.



Entry[a] No.	Ligand	Yield (%)[b]	b:l[c]	Bite angle β_n (°)
1	no ligand	0	n/a	n/a
2	dcpm	30	>20:1	70
3	dppm	65	>20:1	73
4	dppe	72	>20:1	86
5	dppp	25	1:1	91
6	dppb	22	1:3	94
7	dppf	10[d]	1:3	99
8	DPEPhos	0	-	104
9	XantPhos	0	-	108
11	DavePhos	0	-	n/a
12	Triphos	0	-	n/a
13	Triphos 2	0	-	n/a
14	BINAP	0	-	93

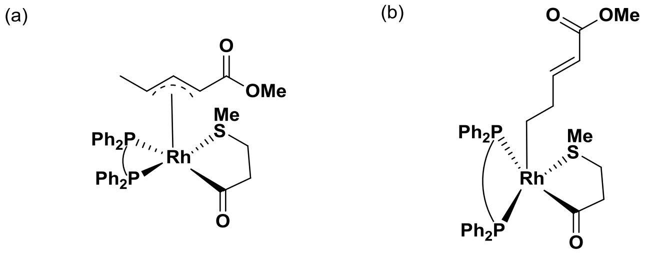
[a] Reactions were performed using stock solutions of catalyst in a Radleys Greenhouse Parallel Synthesiser™. [b] Combined isolated yield of both isomers. [c] Estimated where possible by analysis of the crude ^1H NMR spectra. [d] Reaction conversion determined by analysis of the crude ^1H NMR spectra.

Figure 2.2 –Structures of ligands used in **Table 2.3**



The bite angle (β_n) of a bidentate phosphine ligand can be defined as the ligand-metal-ligand angle. The role of bite angle in cross-coupling reactions has been subject to a recent comprehensive review.[76] Additionally, the steric and electronic influences of ligand bite angle in controlling the regioselectivity of related rhodium-catalysed hydroformylation processes has been extensively studied by van Leeuwen and co-workers.[77-79] We observed a notable decrease in both rate of reaction and branched selectivity with phosphine ligands of increasing chain length and with bite angles of greater than around 90°. A possible explanation for this trend is that the formation of the branched regioisomer proceeds *via* a postulated Rh-π-allyl intermediate **46**, similar to that proposed by Kondo and co-workers.[13] It would be feasible to assume that this intermediate is more favoured for the less bulky and smaller bite angle ligands. Conversely, we expect that for bulkier, larger bite angle ligands, coordination and addition of the rhodium occurs at the terminal carbon (**47**) and thus the linear pathway predominates (**Figure 2.3**). These are only speculative observations and as such we would need to carry out appropriate mechanistic studies along with isolation of key intermediates in order to ascertain the precise mechanisms for the two pathways.

Figure 2.3 – Postulated intermediates **46** and **47** for the (a) branched and (b) linear pathways.



46

47

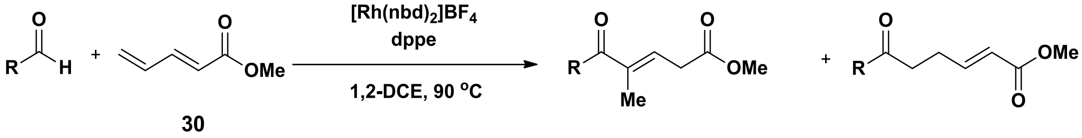
Small bite angle favours formation of a Rh-π-allyl species and formation of branched regioisomer

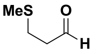
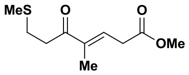
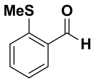
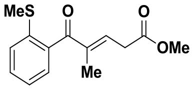
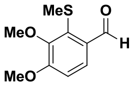
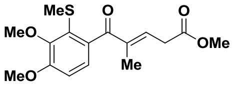
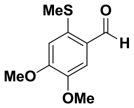
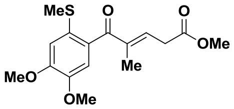
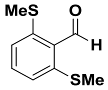
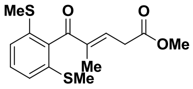
Large bite angle favours coordination and insertion at the terminus of the diene and thus formation of the linear regioisomer

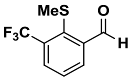
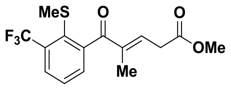
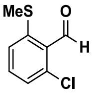
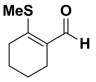
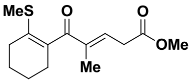
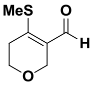
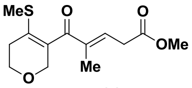
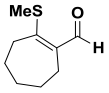
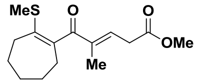
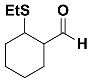
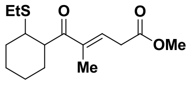
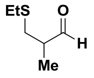
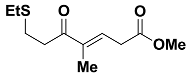
Reaction Scope – Aldehydes

With optimal reaction conditions in hand for a branched-selective diene hydroacylation process, a series of 1,5-dicarbonyls were synthesised through variation of the aldehyde component (**Table 2.4)**. Where possible, regioselectivities were estimated by analysis of the crude ^{1}H NMR spectra, although, in some cases, it was difficult to obtain accurate values due to overlap of signals. Generally, the regioselectivity of the crude reaction mixture was the same as that calculated for the isolated material; however, in certain cases, an improved ratio was obtained upon purification.

Table 2.4 – Aldehyde scope for branched-selective hydroacylation of diene **30**.[a]



Entry	Aldehyde	Product	Yield (%)[b]	Crude b:l[c]	Isolated b:l[d]
1	 **29**	 **31b**	47	10:1	>20:1
2	 **44**	 **45b**	72	>20:1	>20:1
3	 **48**	 **58**	69	>20:1	>20:1
4	 **49**	 **59**	62	-	>20:1
5	 **50**	 **60**	47	11:1	11:1

6	 **51**	 **61**	28	5:1	14:1
7	 **52**	-	0	-	-
8	 **53**	 **62**	89	8:1	8:1
9	 **54**	 **63**	69	-	15:1
10	 **55**	 **64**	35	4:1	>20:1
11[e]	 **56**	 **65**	59[f]	-	3:1
12	 **57**	 **66**	45	1:1	>20:1

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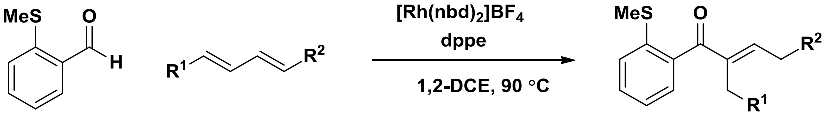
[a] Reaction conditions: [Rh(nbd)$_2$]BF$_4$ (10 mol%), dppe (10 mol%), 1,2-DCE (0.1 M), reflux at 90 °C, 18 h. Active catalyst prepared *in situ* by stirring [Rh(nbd)$_2$]BF$_4$ and dppe. [b] Isolated yield. [c] Estimated through analysis of crude ^{1}H NMR spectra where possible. [d] Estimated through analysis of ^{1}H NMR spectra after column chromatography. [e] Aldehyde used as a 9:1 mixture of *anti*:*syn* diastereomers. [f] Obtained in >20:1 *anti:syn* diastereomeric ratio.

Electron-rich aromatic aldehydes proved to be good hydroacylation substrates: di-methoxy-substituted aldehydes **48** and **49** delivered the branched adducts in good yields and with high selectivities (**Table 2.4**, entries 3 & 4), whilst the di-methylthio-substituted aldehyde **50** afforded branched ketone with a high branched selectivity and modest yield (entry 4). Disappointingly, aldehydes containing electron-withdrawing substituents were poorly tolerated (entries 6 & 7). In particular, 6-chloro substituted aldehyde **52** did not react (entry 7), although this could also be as a result of steric hindrance *ortho* to the aldehyde. We were particularly pleased to find that the *β*-enal substrates **53** and **54** selectively afforded the branched adducts in good yields (entries 8 & 9). However, a compromised yield and poor selectivity was observed for *β*-enal **55** (entry 10). Notably, it is the first time we have utilised the 7-membered carbocyclic and dihydropyran-derived aldehydes in hydroacylation reactions. Finally, decreased selectivities were observed for aliphatic aldehydes **56** and **57**, both of which delivered modest yields of the corresponding branched regioisomers (entries 11 & 12).

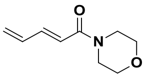
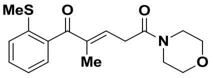
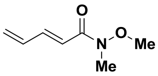
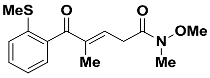
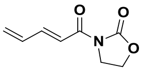
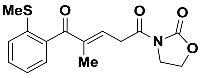
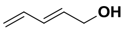
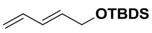
Reaction Scope – Dienes

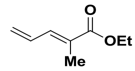
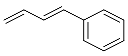
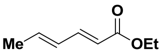
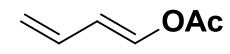
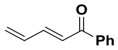
Next, the generality of the reaction in terms of the diene component was evaluated which is summarised below in **Table 2.5**.

Table 2.5 – Diene scope for branched-selective hydroacylation.[a]



44

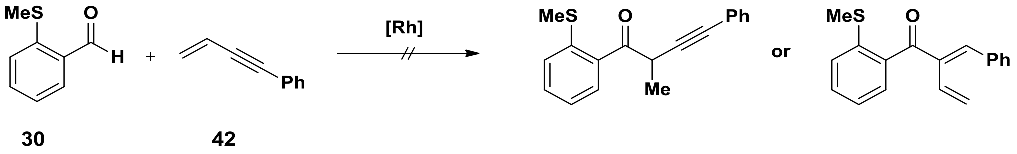
Entry	Diene	Product	Yield (%)[b]
1	 **32**	 **67**	38[c]
2	 **33**	 **68**	47[c]
3	 **34**	 **69**	Trace[e]
4	 **35**	-	0
5	 **36**	-	0

6	 **39**	-	0
7	 **38**	-	0
8	 **40**	-	0
9	 **41**	-	0
10	 **37**	-	0^f

[a] Reaction conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), dppe (10 mol%), 1,2-DCE (0.1 M), reflux at 90 °C, 18 h. Active catalyst prepared *in situ* by hydrogenation of a solution of $[Rh(nbd)_2]BF_4$ and dppe. [b] Isolated yield**.** [c] Obtained in >20:1 b:l . Ratio determined by analysis of crude ^{1}H NMR spectra. [d] Observed by LRMS. [e] Trace amounts of the branched product were observed in ^{1}H NMR spectrum. [f] Diene polymerised under reaction conditions.

It appears that a diene with electron-poor functionality is essential, with moderate yields of the branched ketones obtained with amides **32** and **33** (**Table 2.5**, entries 1 & 2). In both cases the aldehyde was not completely consumed. In addition, it was not possible to determine the regioselectivity through analysis of the crude ^{1}H NMR spectra. Regrettably, all other diene substrates performed poorly. A trace quantity of a possible branched product was observed by analysis of the crude ^{1}H NMR spectrum for the reaction of oxazolidinone diene **34**. In the case of dienes **35**, **36** and **39**, the correct product mass was identified by LRMS, but it was not possible to identify which of the regioisomers were present. For dienes **38**, **40** and **41**, no reaction was observed (entries 7-9). Unfortunately, phenyl ketone substrate **37** polymerised under the reaction conditions (entry 10). Finally we were interested to see how enyne substrate **42** would react: although the aldehyde was completely consumed, no product was isolated under our standard reaction conditions (**Scheme 2.12**).

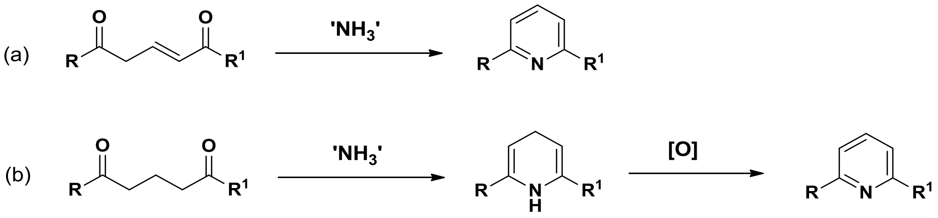
Scheme 2.12 – Attempted hydroacylation of enyne **42**.[a]



Cyclisation of 1,5-dicarbonyl branched hydroacylation products

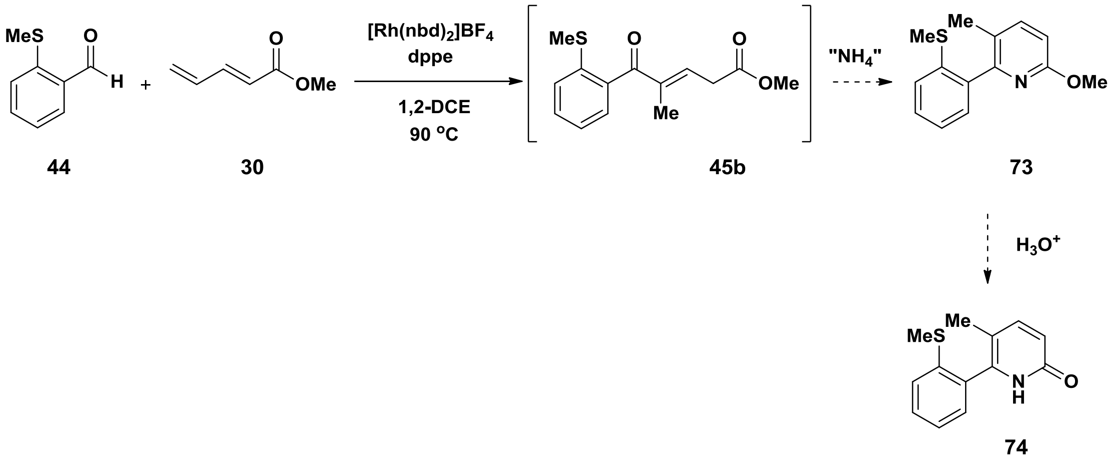
Pyridine derivatives are an important class of heterocycles, which are ubiquitous amongst natural products and pharmaceuticals, and diverse methodologies exist for their synthesis.[80,81] 1,5-Diones[82,83] and 2,3-ene-1,5-diones[84-86] are well-precedented to cyclise to pyridines or pyridones when exposed to an ammonia source such as ammonium acetate (**Scheme 2.13**).

Scheme 2.13 – Cyclisation of (a) 1,5-diones and (b) 2,3-ene-1,5-diones to pyridines.



We hoped that branched enone **45b** would undergo cyclisation to afford either pyridine **73** or hydrolysed pyridone **74**.[87] **Table 2.6** summarises the conditions that have been screened for this cyclisation.

Table 2.6 – Attempted cyclisation of 1,5-dicarbonyl **43b**.[a]



Entry	Ammonia Source (eq.)	Solvent (M)	Temp (°C)	Time (h)	Additive (eq.)	Result
1	NH_4OAc (10)	EtOH (0.1)	55	18	AcOH (10)	n/r
2	NH_4OAc (3)	THF	55	3	-	n/r
3	NH_4OAc (10)	-	120	18	AcOH (10)	<10% unknown product isolated
4[b]	NH_4OAc (10)	-	120	18	AcOH (10)	<10% unknown product isolated
5	NH_4OAc (10)	-	150 (μw)	0.5	*d*$_4$-AcOH (10)	<10% unknown product isolated

[a] Hydroacylation conditions: [Rh(nbd)$_2$]BF$_4$ (10 mol%), dppe (10 mol%), 1,2-DCE (0.1 M), 90 °C, 18 h. Unless otherwise stated, the crude hydroacylation reaction was filtered through Celite® to remove catalyst and concentrated *in vacuo* prior to submission to cyclisation conditions. [b] Rhodium catalyst was not removed by filtration after hydroacylation step.

The first set of conditions applied were based upon a literature procedure for the cyclisation of a similar 1,5-dicarbonyl substrate.[86] The crude hydroacylation product was treated with ammonium acetate and acetic acid in ethanol at 55 °C for 18 h - unfortunately, only starting material was returned (**Table 2.6**, entry 1). An alternative set of literature conditions using THF as solvent[87] and with no acid additive were also tried, again resulting in no reaction (entry 2). Increasing the temperature to 120 °C and running the reaction neat[88] resulted in complete consumption of the 1,5-dicarbonyl but afforded only a complex mixture of products (entry 3). Less than 10% of a potential cyclised product was isolated; however, not all of the data was consistent with expected values. The reaction was repeated without the removal of the rhodium catalyst with the notion that the presence of rhodium might assist with double bond isomerisation. Regrettably, no improvement was observed (entry 4). Finally, the reaction was carried out at 150 °C with microwave heating using deuterated acetic acid so that the reaction could be monitored by ^{1}H NMR spectroscopy. All of the starting material was consumed after 0.5 hours but the result was still a complex mixture of products (entry 5).

Summary

We have developed a branched-selective hydroacylation process for a range of *β*-*S*-substituted aldehydes with (*E*)-methyl penta-2,4-dienoate. Unfortunately, the range of diene substrates tolerated in the reaction was limited. It appears that a diene with electron-poor functionality is a prerequisite for reactivity, although we have little justification for this observation. We have identified a relationship between decreasing branched selectivity and increasing ligand bite angle, and we have postulated intermediates to account for this. Mechanistic studies and the isolation and characterisation of such intermediates would enable a greater understanding of this process. Moreover, computational studies (for example Density Function Theory (DFT) modelling), would provide a further insight into the reaction profile for the two selectivity pathways. Unfortunately, all attempts to cyclise hydroacylation adduct **43b** to the corresponding pyridine or pyridone were unsuccessful, despite the use of a wide range of literature conditions.

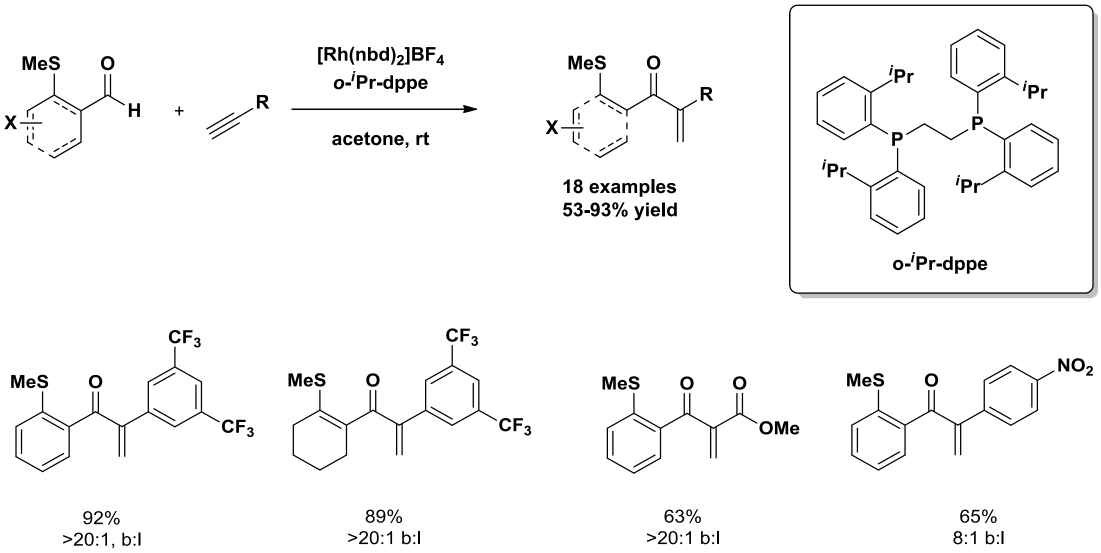
Chapter 3 - *Linear-Selective Alkyne Hydroacylation*

Introduction

Background and Project Aims

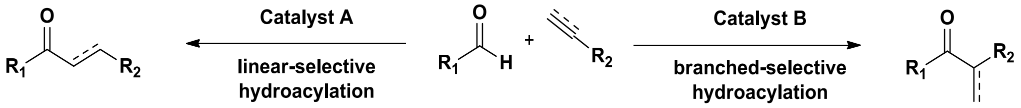
Throughout our group's research into chelation-controlled intermolecular alkyne and alkene hydroacylation, we have observed almost exclusive regioselectivity for the linear regioisomers. As previously discussed, few branched-selective hydroacylation processes exist, and those that do have stringent substrate requirements. Recently, the Willis group has reported a rhodium-catalysed, branched-selective hydroacylation using an *o*-^{i}Pr-dppe derived catalyst system (**Scheme 3.1**).[89] This process enabled the hydroacylative coupling of a range of *β*-*S*-substituted aldehydes and electron-poor alkynes with excellent degrees of regioselectivity.

Scheme 3.1 – Branched-selective hydroacylation using *o*-^{i}Pr-dppe derived catalyst system.



It was surprising to discover that when typically ‘linear-selective’ ligands such as dppe and DPEPhos were employed, it was very difficult to selectively obtain linear adducts with these electron-deficient substrates, particularly with aryl aldehydes. We therefore hoped to develop a catalyst system that would enable selective formation of the linear products, and thus achieve a ligand-controlled regioselectivity switch (**Scheme 2.2**).

Scheme 2.2– Proposed ligand-controlled regioselectivity switch.

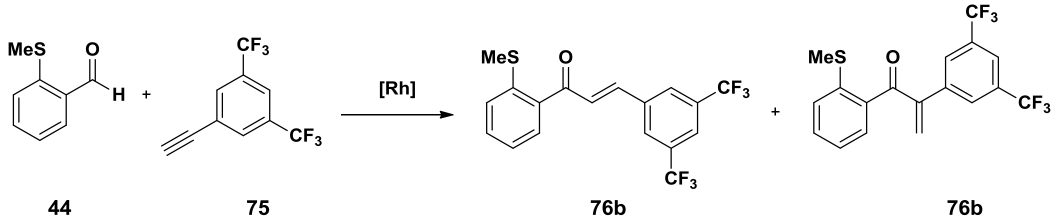


Results and Discussion

Ligand Screening and Optimisation

To investigate the effects of ligand structure on the regioselectivity of alkyne hydroacylation, the coupling of previously challenging aryl aldehyde **44** and electron-deficient alkyne **75** was selected (**Table 3.1**). The chosen reaction conditions were guided by the previously reported branched-selective process.

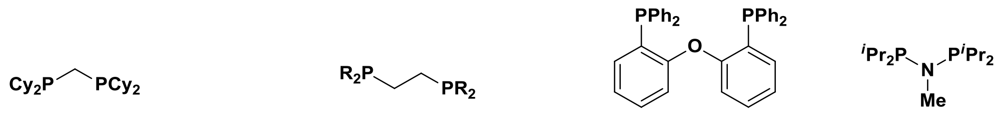
Table 3.1 – Ligand screen for hydroacylation of aldehyde **44** and alkyne **75**.[a]



Entry	Ligand (mol%)	Solvent	Temp (°C)	Conversion (%)[b]	l:b[c]
1	dppe (10)	Acetone	rt	100	2:1
2	DPEPhos (10)	Acetone	50	80	3.8:1
3	DPEPhos (10)	1,2-DCE	70	100	1:1
4	o-^{i}Pr dppe (10)	Acetone	rt	100	>1:20
5	*p*-OMe dppe (10)	Acetone	rt	80	1:1
6	*p*-OMe dppe (10)	1,2-DCE	70	100	2.4:1
7	*p*-CF_3 dppe (10)	Acetone	rt	70	1:1.8
8	*p*-CF_3 dppe (10)	1,2-DCE	70	100	1:1.6
9	dcpm (10)	Acetone	rt	100	>20:1
10	dcpe (10)	Acetone	rt	100	>20:1
11	dcpe (5)	Acetone	rt	100	>20:1
12	dcpe (2.5)	Acetone	rt	100	>20:1
13[d]	dcpe (1)	Acetone	rt	95	>20:1
14[e]	^{i}PrPCCP (10)	Acetone	rt	100	>20:1
15[e]	^{i}PrPNP (10)	Acetone	rt	100	>20:1
16[e]	^{i}PrPCP (10)	Acetone	rt	100	>20:1

[a] Reaction conditions: aldehyde **44** (0.30 mmol), alkyne **75** (0.45 mmol), $[Rh(nbd)_2]BF_4$ (10 mol%), ligand (10 mol%), solvent (2 mL, 0.15 M), 2 h. Catalyst prepared by *in situ* hydrogenation of $[Rh(nbd)_2]BF_4$ and ligand. [b] Determined by analysis of ^1H NMR spectra of crude reaction mixture. [c] Determined by analysis of ^1H or ^{19}F NMR spectra of crude reaction mixture. [d] Reaction performed at 0.3 M. [e] Pre-formed catalyst complex $[Rh(F\text{-}C_6H_5)(ligand)]BAr^F_4$ was employed.

Figure 3.1 – Structures of Ligands



dcpm R = Cy
^{i}Pr-PCP R = ^{i}Pr

dppe R = Ph
dcpe R = Cy
^{i}PrPCCP R = ^{i}Pr
***p*-OMe dppe** R = 4-(OMe)Ph
***p*-CF3 dppe** R = 4-(CF$_3$)Ph
o-iPr dppe R = 2-(^{i}Pr)Ph

DPEphos

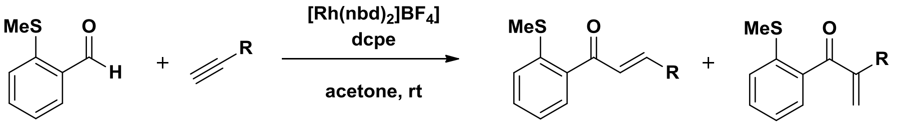
^{i}Pr-PNP

Table 3.1, entry 1 confirms that the use of so called traditional hydroacylation bisphosphine ligands, such as ethylene-bridged dppe, results in very little control of regioselectivity, with only a slight bias for the linear isomer. In order to obtain a good conversion with DPEPhos as the ligand, it was necessary to increase the reaction temperature to 50 °C. This resulted in a 3.8:1 linear-selectivity (entry 2). Unexpectedly, changing the reaction solvent to 1,2-DCE and increasing the temperature to 70 °C led to a complete loss of selectivity (entry 3). The introduction of a bulky *ortho*-substituent onto the phenyl rings of the bisphosphine ligand resulted in complete selectivity for the branched-regioisomer (entry 4). This was in accordance with previously reported results.[89] The use of an electron-rich *para*-methoxy dppe ligand in acetone at room temperature resulted in an 80% conversion and a 1:1 regioselectivity (entry 5). Interestingly, by switching the solvent to 1,2-DCE and increasing the reaction temperature to 70 °C, the linear adduct was favoured (entry 6). Conversely, the electron-poor *para*-CF$_3$ substituted dppe ligand demonstrated a slight preference for the branched regioisomer (entries 7 & 8). We were pleased to discover that electron-rich cyclohexyl-substituted diphosphine ligands dcpm and dcpe produced the linear isomers with excellent linear selectivities of >20:1 (entries 9 & 10). Additionally, by increasing the concentration to 0.3 M, it was possible to significantly reduce the catalyst loading to only 1 mol% (entry 9). Several other electron-rich alkyl-bisphosphines (used as preformed complexes) were also investigated and proved to be highly efficient linear-selective catalysts (entries 14-16). Owing to its structural similarity to the branched-selective ligand *o*-^{i}Pr-dppe ligand, it was decided to proceed with dcpe for further studies. Although significantly lower catalyst loadings were tolerated, a 5 mol% catalyst loading was employed to allow for more challenging substrates.

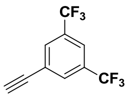
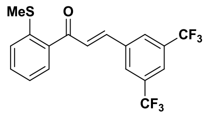
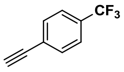
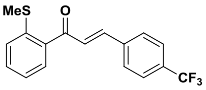
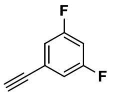
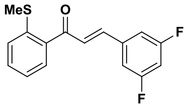
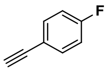
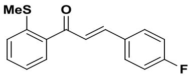
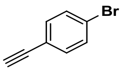
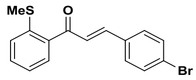
Alkyne Scope

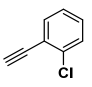
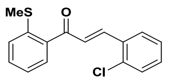
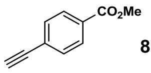
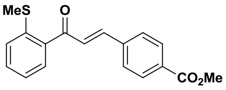
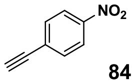
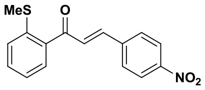
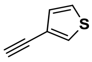
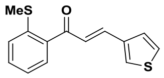
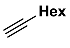
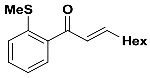
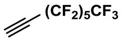
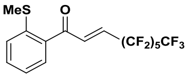
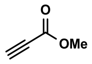
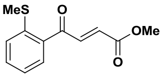
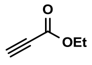
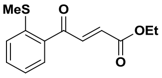
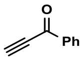
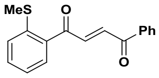
With a linear-selective catalyst system in hand, we sought to assess the reaction scope. **Table 3.2** summarises the generality of the reaction in terms of the alkyne substrate using aldehyde **44** as a common component.

Table 3.2 – Alkyne Scope for branched-selective hydroacylation.[a]



44

Entry	Alkyne	Product	Yield[b]	l:b[c]
1	 **77**	 **91**	93	>20:1
2	 **78**	 **92**	83	>20:1
3	 **79**	 **93**	91	>20:1
4	 **80**	 **94**	91	>20:1
5	 **81**	 **95**	93	>20:1

6	 **82**	 **96**	88	>20:1
7	 **83**	 **97**	74	>20:1
8	 **84**	 **98**	67	7:1
9	 **85**	 **99**	96	>20:1
10	 **86**	 **100**	84[e]	16:1
11[d]	 **87**	 **101**	27	2:1
12[d]	 **88**	 **102**	33	1:1
13[d]	 **89**	 **103**	100[f]	5:1
14[d]	 **90**	 **104**	80[f]	1.2:1

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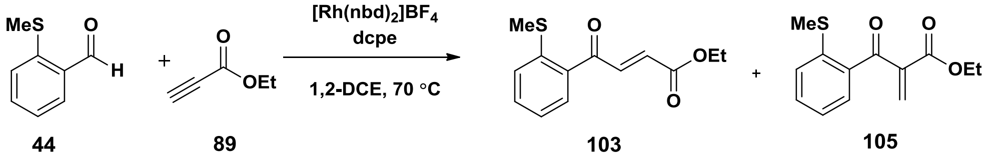
[a] Reaction conditions: Aldehyde (0.3 mmol), alkyne (0.45 mmol), [Rh(nbd)$_2$]BF$_4$ (5 mol%), dcpe (5 mol%), acetone (2 mL, 0.15 M), rt, 2 h. [b] Linear regioisomer isolated in >20:1 l:b. [c] Determined by analysis of ^{1}H NMR spectra of crude reaction mixture. [d] Reaction performed in 1,2-DCE at 70 °C for 18 h. [e] Isolated as a 16:1 mixture of l:b. [f] ^{1}H NMR conversion.

Gratifyingly, a range of previously challenging electron-deficient aryl alkynes delivered the linear adducts with excellent selectivities and isolated yields. Bis- and mono-CF$_3$-substituted aryl alkynes afforded linear adducts in 93% and 83%, respectively, both with >20:1 linear:branched regioselectivities. Entries 3-6 show that it is possible to incorporate halide substituents into the alkyne component. This enables the potential for further functionalization through metal-catalysed cross coupling or simple S_NAr processes. Nitro-substituted alkyne (entry 8) showed a slight decrease in reactivity and a relatively modest linear:branched selectivity of 7:1. However, following column chromatography and recrystallization, pure linear product was obtained. In addition, it was possible to employ an electron-rich heteroaromatic alkyne and the straight chain alkyne, 1-hexyne, with regioselectivities of >20:1 and 16:1, respectively (entries 9 and 10). Entries 11-14 required elevated temperatures and extended reaction times to achieve reactivity; unfortunately poor regioselectivities were obtained for these substrates.

As such poor regioselectivities were obtained with propiolate substrates, a brief ligand screen was carried out for the reaction of ethyl propiolate with aldehyde **44** (**Table 3.2**). Unfortunately, this resulted in no improvement in regioselectivity.

Table 3.2 – Ligand screen for reaction of ethyl propiolate **89** and aldehyde **44**.[a]



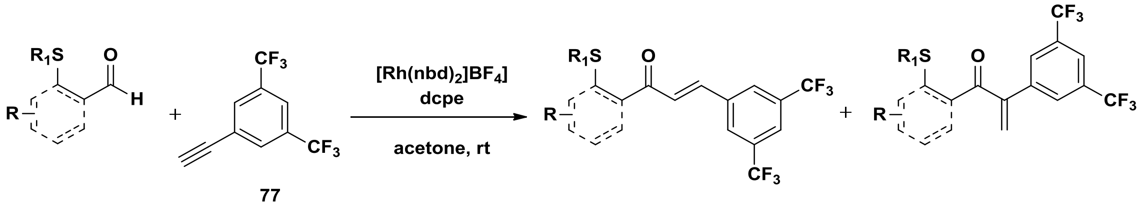
Entry	Ligand	Conversion	l:b[b]
1	dppe	100	1:2
2	DPEPhos	50	1:2
3	^{i}Pr-PCCP[c]	100	1:1

[a] Reaction conditions: Aldehyde **44** (0.30 mmol), ethyl propiolate (0.45 mmol), $[Rh(nbd)_2]BF_4$ (10 mol%), ligand (10 mol%), 1,2-DCE (2 mL, 0.15 mmol), 70 °C, 18 h. [b] Determined by analysis of crude ^{1}H NMR spectra. [c] Pre-formed catalyst complex $[Rh(F\text{-}C_6H_5)(^iPrPCCP)]BAr^F_4$ was employed.

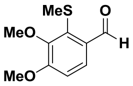
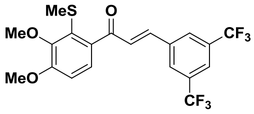
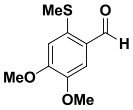
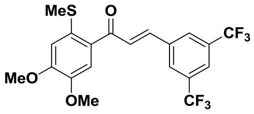
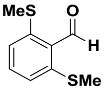
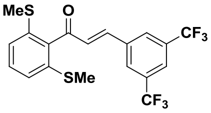
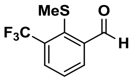
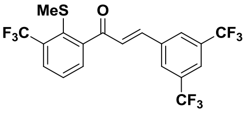
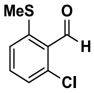
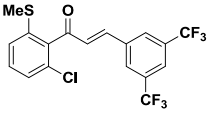
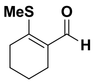
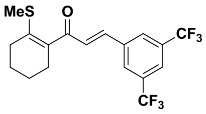
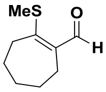
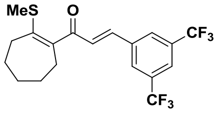
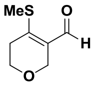
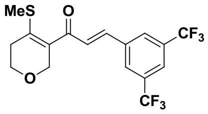
Aldehyde Scope

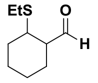
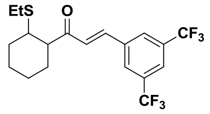
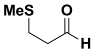
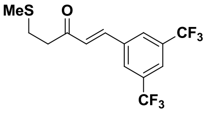
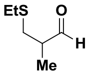
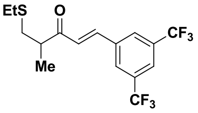
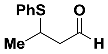
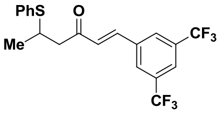
We next investigated the potential for variation of the aldehyde substrate employing electron-poor alkyne **77** as the common alkyne (**Table 3.4**).

Table 3.4 – Aldehyde scope for linear-selective hydroacylation.[a]



77

Entry	Aldehyde	Product	Yield[b]	l:b[c]
1	 **48**	 **107**	82	>20:1
2	 **49**	 **108**	73	>20:1
3	 **50**	 **109**	70	>20:1
4	 **51**	 **110**	94	>20:1
5[d]	 **52**	 **111**	78	>20:1
6	 **53**	 **112**	85	>20:1
7	 **55**	 **113**	63	>20:1
8	 **54**	 **114**	84	>20:1

9[e]	 **56**	 **115**	80[f]	>20:1
10	 **29**	 **116**	74	>20:1
11	 **57**	 **117**	54	>20:1
12[d]	 **106**	 **119**	58[g]	4.5:1

Reaction conditions: Aldehyde (0.3 mmol), alkyne (0.45 mmol), $[Rh(nbd)_2]BF_4$ (5 mol%), dcpe (5 mol%), acetone (2 mL, 0.15 M), RT, 2 h. [b] Isolated yield in >20:1 l:b. [c] Determined by analysis of ^{1}H NMR spectra of crude reaction mixture. [d] Aldehyde used as a 9:1 mixture of *anti:syn* diastereomers. [e] Reaction performed at 50 °C for 18 h. [f] Obtained as a 9:1 mixture of *anti*:*syn* diastereomers. [g] Obtained as a 4.5:1 mixture of l:b.

We were pleased to observe that a variety of both electron-rich and electron-poor aromatic aldehydes delivered the linear enone products in good to excellent isolated yields and with very high selectivities (**Table 3.4,** entries 1-5). Electron-rich aryl aldehydes **48** and **49** (entries 1 & 2) proved to be excellent substrates for the reaction and the unusual di-methylthio substituted aromatic aldehyde **50** also delivered a high yield of the linear adduct (entry 3). Entries 4 and 5 show good tolerance for electron-deficient aromatic aldehydes. Although the 6-chloro substituted aldehyde **52** required a slightly elevated reaction temperature and longer reaction time, the incorporation of a halide at this position provides the opportunity for further functionalization (entry 5). The *β*-enals employed in entries 6-8 performed equally well, allowing access to synthetically interesting bis-enones **112-114**. A number of substituted alkyl aldehydes performed well and maintained excellent selectivities (entries 9-11). The ability to tolerate an *α*-substituent (entry 10) enables the possibility for the development of an asymmetric process. *β*-Substituted aldehyde **106** proved to be a more challenging substrate with a moderate yield and compromised regioselectivity of 4.5:1 linear:branched.

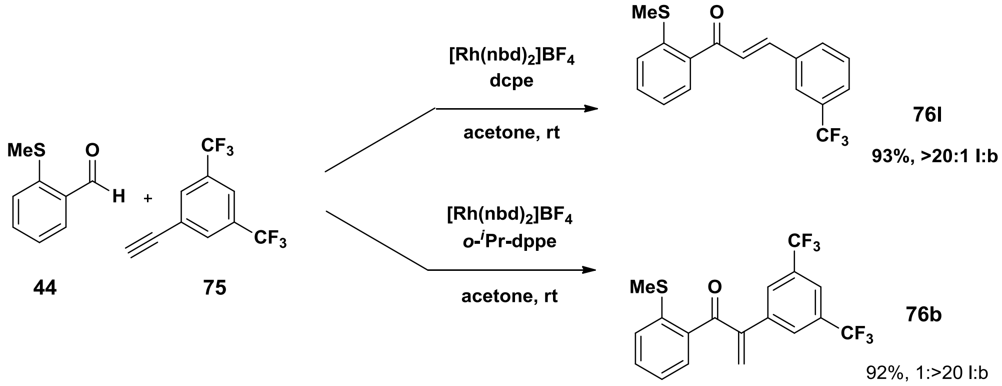
Summary and Future Work

The development of a linear-selective hydroacylation process for the combination of aryl aldehydes and electron-deficient alkynes has previously proved problematic, with ‘traditional’ hydroacylation bisphosphine ligands, such as ethylene-bridged dppe, offering poor regiocontrol.

Following a brief ligand screen, we identified that a range of *electron-rich* alkyl bis-phosphine ligands delivered hydroacylation adducts with excellent linear selectivity, for previously challenging aryl aldehyde and alkyne combinations.[90] Through the use of a dcpe-derived catalyst, excellent yields and regioselectivities were obtained for a range of electronically varied aromatic aldehydes. In addition, alkyl aldehydes and synthetically interesting enal substrates were tolerated. Excellent reactivities and selectivities were also observed for a range of electron-deficient aromatic alkynes, as well as more electron-rich examples.

This methodology can be considered a complimentary process to our previously reported branched-selective chemistry. The combination of the two processes provides a ligand-controlled regioselectivity switch between the branched and linear pathways (**Scheme 2.3**).

Scheme 2.3 – Ligand controlled regioselectivity switch.



We have not established the origin of this ligand-controlled selectivity; however, it appears to be largely influenced by the electronic rather than the steric nature of the phosphine ligand. It is postulated that the electron-rich bisphosphine ligand pushes electron density onto the rhodium centre. This causes a degree of polarisation of the Rh-H bond, and could subsequently impact the mode of addition of the Rh-H bond across the alkyne bond, in this case, favouring addition in a linear-selective manner.

In order to probe whether this selectivity was influenced by the electronic properties of the ligand, electron-rich and electron-poor dppe-derived ligands were evaluated. Unfortunately, this proved to be inconclusive, with no significant bias for the branched or linear pathways observed. It would be interesting to evaluate the regioselectivity using less bulky, electron-rich bis-phosphine ligands such as MePCCP and EtPCCP. The use of these ligands would provide an insight as to whether the regioselectivity is influenced by electronic or steric factors or, a combination of the two (**Figure 3.2**). However, owing to the potentially pyrophoric nature of such ligands, handing outside of a glove box could prove problematic. Mechanistic studies and the isolation of reaction and catalytic intermediates would hopefully provide a greater understanding of the unusual regioselective nature of this process.

Figure 3.2 – Structures of small, electron-rich bis-phosphine ligands.

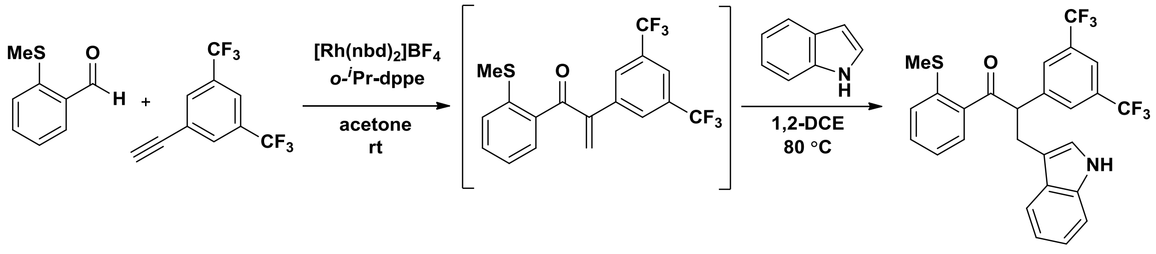
MePCCP **EtPCCP**

Chapter 4 - Exploiting Branched Hydroacylation Intermediates

Background and Project Aims

As discussed in Chapter 3, a branched-selective alkyne hydroacylation process has previously been developed by the Willis group.[89] This process provided access to products containing a synthetically useful *α,β*-unsaturated carbonyl motif. We therefore wished to exploit the inherent reactivity of these *exo*-methylene containing hydroacylation products through development of multi-component tandem processes. Previously published preliminary experiments have begun to address the utility of these branched hydroacylation adducts in a simple one-pot, three-component processes. The *in situ* 1,4-addition of indole to branched hydroacylation adduct **76b** afforded substituted ketone **119** in an excellent yield over two steps (**Scheme 4.1**).

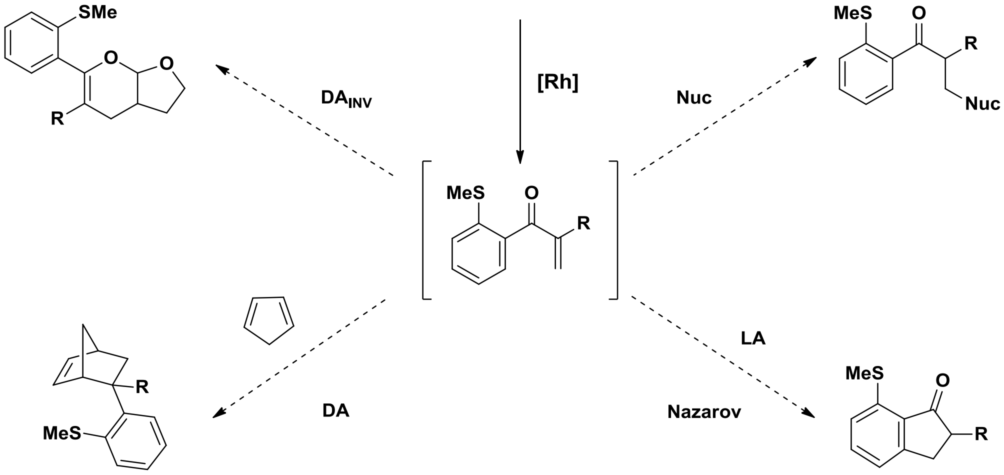
Scheme 4.1 - One-pot, two-step, three-component reaction.



44 **75** **119** **88%**

The aim of this project was to extend this methodology to include a range of different nucleophiles, and provide access to a diverse range of highly functionalised ketone products from simple, readily available starting materials. In addition, we wished to demonstrate the potential utility of these *exo*-methylene containing products in other processes such as Diels-Alder cycloaddition reactions and Nazarov cyclisations (**Scheme 4.2**).

Scheme 4.2 – Potential derivitization of branched hydroacylation adducts.



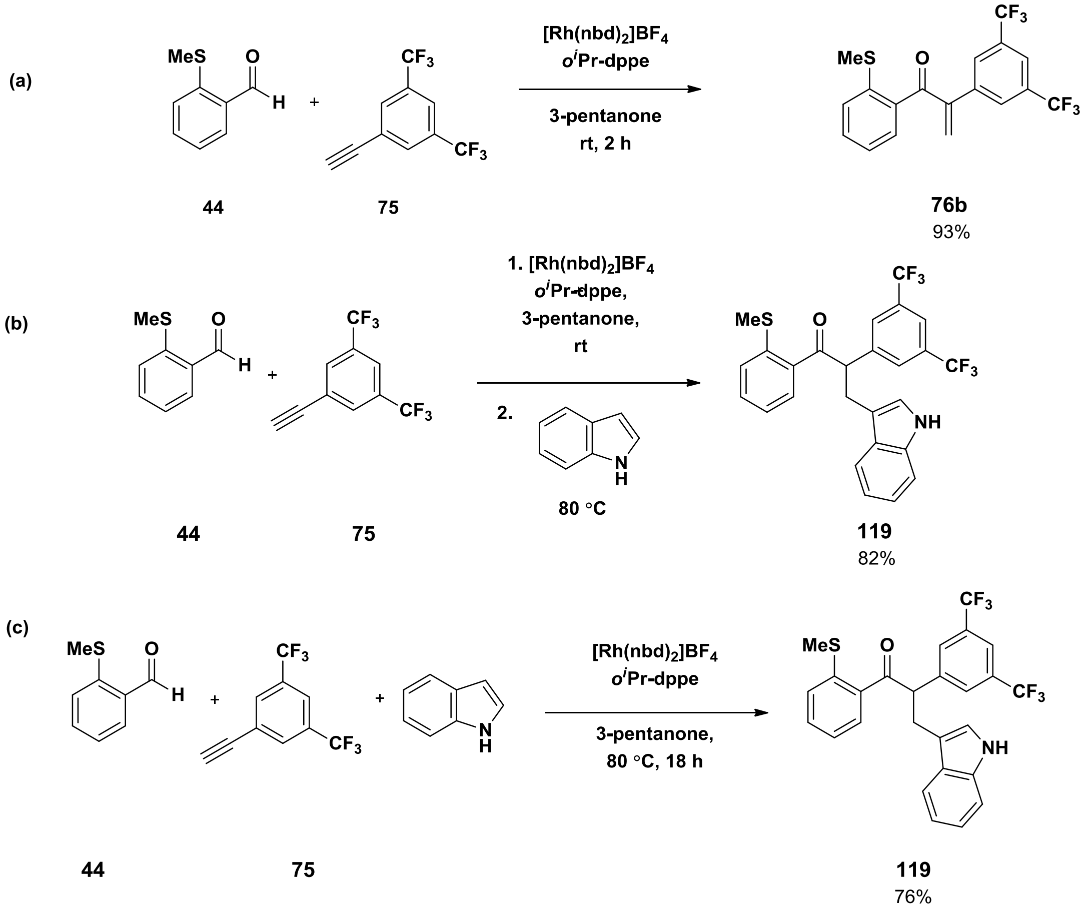
Results and Discussion

Conjugate Addition

The conjugate addition of nucleophiles to *α,β*-unsaturated carbonyls is a powerful synthetic tool.[87] A wide range of *α,β*-unsaturated substrates and nucleophiles can be employed and thus generate a diverse array of products.[92-95] In addition, comprehensive investigations into the development of efficient enantioselective and diastereoselective variants have been reported.[96-101]

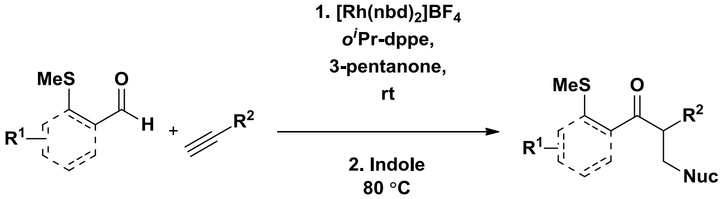
A number of processes exist for the 1,4-addition of indoles[102-106] and pyrroles[107-111] to *α,β*-unsaturated carbonyls, often catalysed by a range of protic and Lewis acids. We were pleased to discover that the 1,4-addition of indole to our hydroacylation adduct **76b** did not require an acidic additive;[112] simply performing the reaction at an elevated temperature of 80 °C afforded the desired product in excellent yield over the two-step process. Since the conjugate addition process was performed in a one-pot process, it is possible that the rhodium was able to act as a catalyst for this process. It should be noted that the since the hydroacylation was performed in acetone, a solvent switch to the higher boiling 1,2-DCE was required. A more attractive procedure would utilise a common solvent for the two steps. Unfortunately, to obtain a high conversion for the hydroacylation process in 1,2-DCE, the reaction must be performed at 50 °C for several hours. We were therefore pleased to discover that the hydroacylative coupling of **44** and **75** was complete after only 2 hours at room temperature using the higher boiling ketone solvent 3-pentanone. This reaction yielded hydroacylation adduct **76b** in a 93% yield (**Scheme 4.3, a)**. Moreover, the direct conjugate addition of indole to the branched hydroacylation adduct proceeded smoothly to afford ketone **119** in high yield (**Scheme 4.3, b**). Finally, the hydroacylation step was not compromised using a one-pot, one-step process, affording ketone **119** in a 76% yield (**Scheme 4.3, c**).

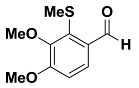
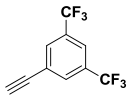
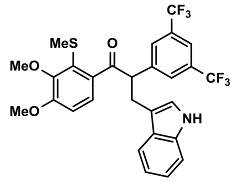
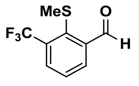
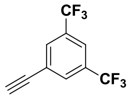
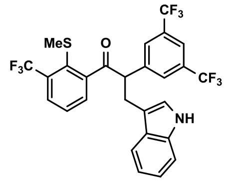
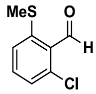
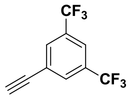
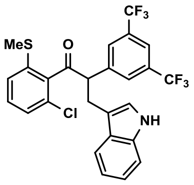
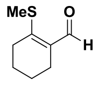
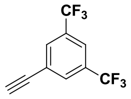
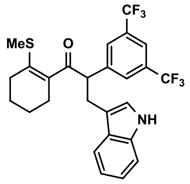
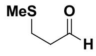
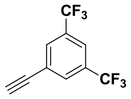
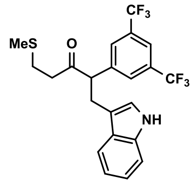
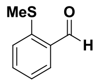
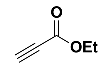
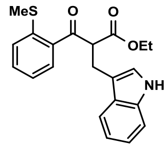
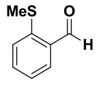
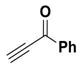
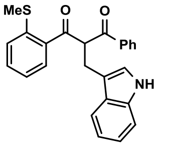
Scheme 4.3 – Use of 3-pentanone as the reaction solvent.



With optimised conditions in hand, we next explored the potential for variation of the functionality originating from the aldehyde and alkyne components (**Table 4.1**).

Table 4.1- Three-component coupling of various aldehydes and alkynes with indole as the nucleophile.[a]



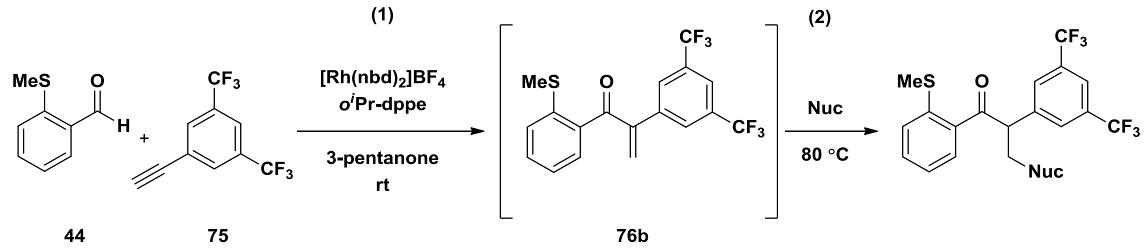
Entry	Aldehyde	Ketone	Product	Yield (%)[b]
1	 **48**	 **75**	 **120**	71
2	 **51**	 **75**	 **121**	44
3	 **52**	 **75**	 **122**	22
4	 **53**	 **75**	 **123**	54
5	 **29**	 **75**	 **124**	40
6[c]	 **44**	 **89**	 **125**	69
7[c]	 **44**	 **90**	 **126**	77

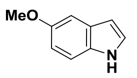
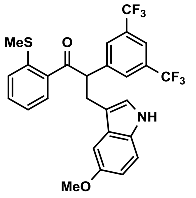
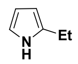
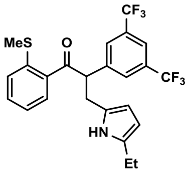
[a] Reaction conditions: **(1)** [Rh(nbd)$_2$]BF$_4$ (10 mol%), *o*-^{i}Pr-dppe (10 mol%), aldehyde (0.30 mmol), alkyne (0.45 mmol), 3-pentanone (2.0 mL, 0.15 M), 2 h. **(2)** Indole (0.60 mmol), 80 °C, 18 h. [b] Isolated yield over two steps. [c] Conjugate addition step performed at 50 °C.

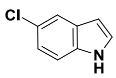
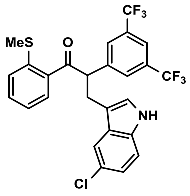
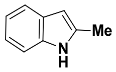
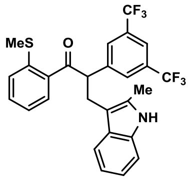
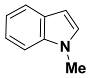
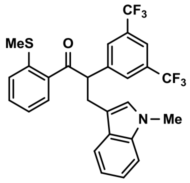
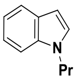
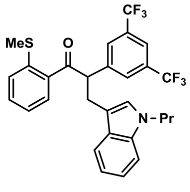
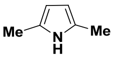
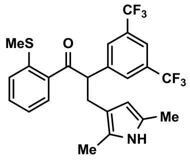
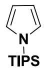
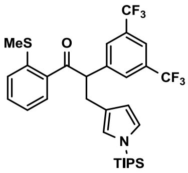
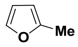
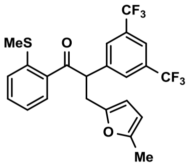
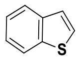
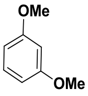
Electron-rich substitution on the left-hand ring maintained high reactivity (**Table 4.1**, entry 1), whilst reduced yields were observed for electron-poor variants (entries 2 & 3). The significantly reduced yield obtained for the 6-chloro substrate could possibly be explained by steric hindrance resulting from the proximity of the large chlorine atom to the *exo* double bond. The hydroacylation step for alkyl aldehyde **29** and enal **53** required the use of acetone as solvent in order to obtain a cleaner reaction. A solvent switch to 1,2-DCE was therefore required for the conjugate addition step and afforded ketone adducts **123** and **123** in moderate yields (entries 4 & 5). Finally, the hydroacylation adducts of aldehyde **44** with either ethyl propiolate or ynone **90** underwent this tandem process furnishing the ketone adducts in excellent yields over two steps (entries 7 & 8). Notably, owing to the increased electrophilicity of these enone intermediates, a reduced reaction temperature could be employed for the conjugate addition step.

We next extended this multicomponent process to include a range of simple heterocyclic carbon nucleophiles as summarised below in **Table 4.2**.

Table 4.2 – Three-component coupling of aldehyde **44**, alkyne **75** and various heterocyclic nucleophiles.[a]



Entry	Nuc	Product	Yield (%)[b]	Entry	Nuc	Product	Yield (%)[b]
1	 **127**	 **138**	56	7	 **133**	 **144**	71

2	 **128**	 **139**	52
3	 **129**	 **140**	71
4	 **130**	 **141**	45
5	 **131**	 **142**	77
6	 **132**	 **143**	64
8	 **134**	 **145**	51[c]
9	 **135**	 **146**	77
10	 **136**	-	0
12	 137	-	0

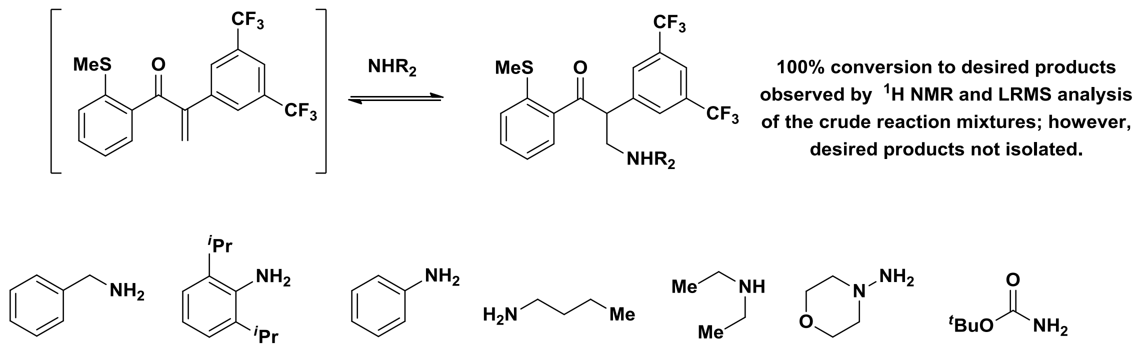
[a] Reaction conditions: **(1)** [Rh(nbd)$_2$]BF$_4$ (10 mol%), *o*-^{i}Pr-dppe (10 mol%), aldehyde (0.30 mmol), alkyne (0.45 mmol), 3-pentanone (2.0 mL, 0.15 M), 2 h. **(2)** Nucleophile (2 equiv.), 80 °C, 18 h. [b] Isolated yield over two steps. [c] Obtained as a 13:1 mixture of 3-position:2-position isomers. The regiochemistry was confirmed by nOe difference experiments.

The hydroacylative coupling of aldehyde **44** and alkyne **76**, and subsequent 1,4-addition of a range of variously substituted indoles was achieved in moderate to good yields with exclusive reactivity at the 3-position for 1*H*-indoles (**Table 4.2**, entries 1-5). Employing 2,4-

dimethylpyrrole and 2-ethylpyrrole as nucleophiles also delivered the desired ketone products in good yields (entries 6 & 7). The introduction of a bulky TIPS protecting group onto the pyrrole nitrogen enabled an unusual regioselective reaction at the 3-position (entry 8). It was not possible to conclusively establish the regiochemistry by analysis of the ^{1}H NMR coupling constants and 2D NMR spectra; therefore, the regiochemistry was confirmed by nOe difference experiments (See Appendix). The 1,4-addition of oxygen containing heterocycles was also possible, with the product resulting from addition of 2-methylfuran isolated in a 51% yield (entry 9). Finally, benzothiophene and 1,3-dimethoxybenzene proved to be poor substrates for this process, with none of the desired products observed (entries 10 & 11).

Attempts to use nitrogen nucleophiles were largely unsuccessful (**Scheme 4.4**). A range of primary and secondary amines along with *N*-aminomorpholine were subjected to the reaction conditions and appeared to undergo 1,4-addition to the enone by analysis of the crude reaction mixtures LRMS and ^{1}H NMR spectroscopy. However, significant difficulties in isolation by column chromatography, presumably due to the reversibility of the conjugate addition process, resulted in only trace quantities of the desired products. Notably, the 1,4-addition of *N*-Boc amine failed completely, only returning the enone intermediate.

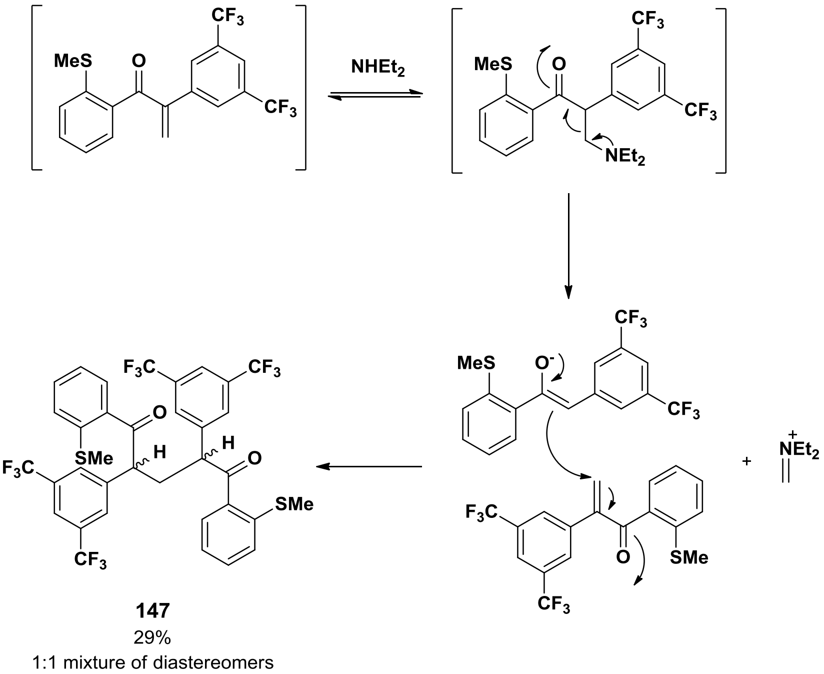
Scheme 4.4 – Failed attempts to use nitrogen nucleophiles.



100% conversion to desired products observed by ^{1}H NMR and LRMS analysis of the crude reaction mixtures; however, desired products not isolated.

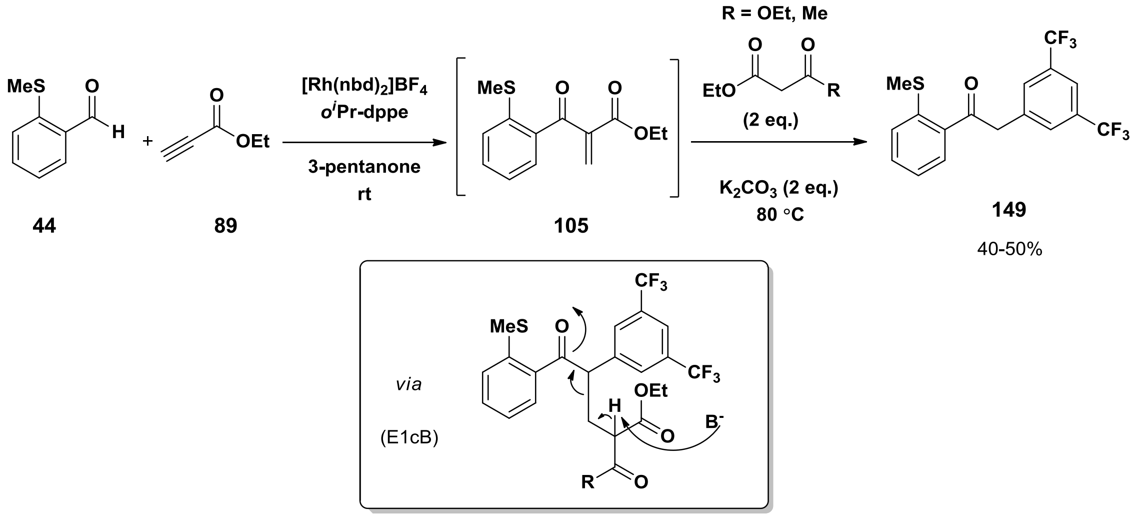
Furthermore, a common side product **147** was observed which we have identified by NMR spectroscopy and mass spectroscopy. This product was consistently isolated in reactions with various different amines in yields of between 20 and 30% as a 1:1 mixture of diastereomers. As shown in **Scheme 4.5**, we postulate that this product results from a retro-Mannich fragmentation of the 1,4-addition product and subsequent addition of the resulting enolate into a second molecule of the branched hydroacylation adduct.

Scheme 4.5 - Proposed formation of side product **147** *via* retro-Mannich and 1,4-addition of enolate.



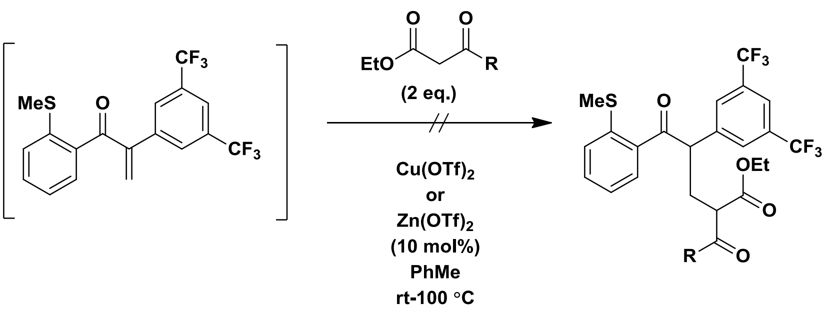
The Michael addition of *β*-carbonyl compounds to activated π-systems is an extremely useful C-C bond forming methodology.[91,113,114] A number of enol nucleophiles can be employed in such transformations including malonate esters,[115] *β*-ketoesters and 1,3-diketones.[116-118] Traditionally these reactions are catalysed by bases such as alkali metal hydroxides or carbonates, or alternatively by a number of Lewis acids. We hoped enone **105** would undergo Michael addition with diethyl malonate or *β*-ketoester **148** using potassium carbonate as base. However, only trace quantities of the desired products were observed alongside modest quantities of ketone **149** presumably, generated *via* the de-protonation and elimination sequence shown in Scheme **4.6**.

Scheme 4.6 – Attempted conjugate addition of diethyl malonate using K_2CO_3 as base.



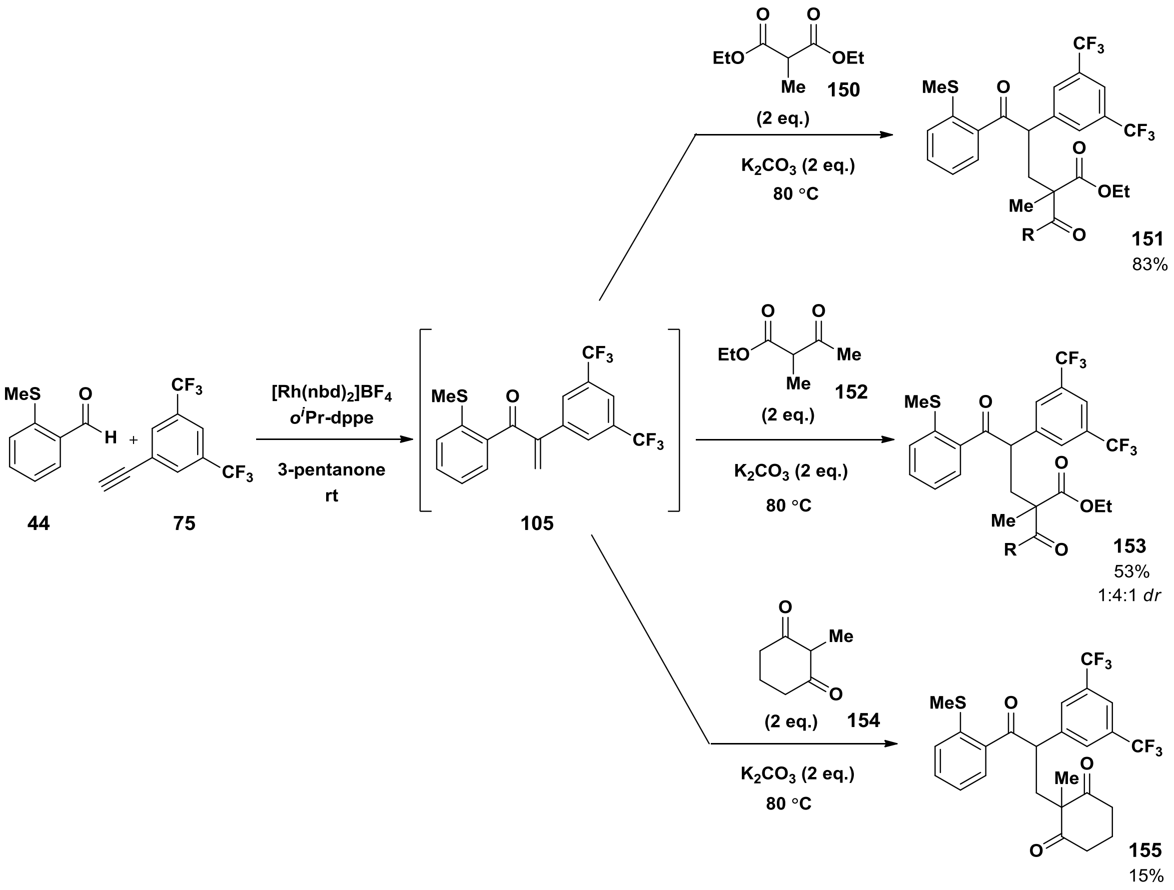
Attempts to use Lewis acid catalysis were also unsuccessful (**Scheme 4.7**): a 10 mol% loading of either copper(II) or zinc(II) triflate resulted in no reaction. In the interest of time, no further Lewis acids were screened. However it has been reported for the addition of these *β*-carbonyl nucleophiles to a range cyclic *α,β*-unsaturated ketones that the nature of the Lewis acid has a significant effect in determining the efficiency of the reaction for different nucleophile-electrophile combinations.[113]

Scheme 4.7 – Attempted conjugate addition of diethyl malonate using catalytic $Cu(OTf)_2$ or $Zn(OTf)_2$.



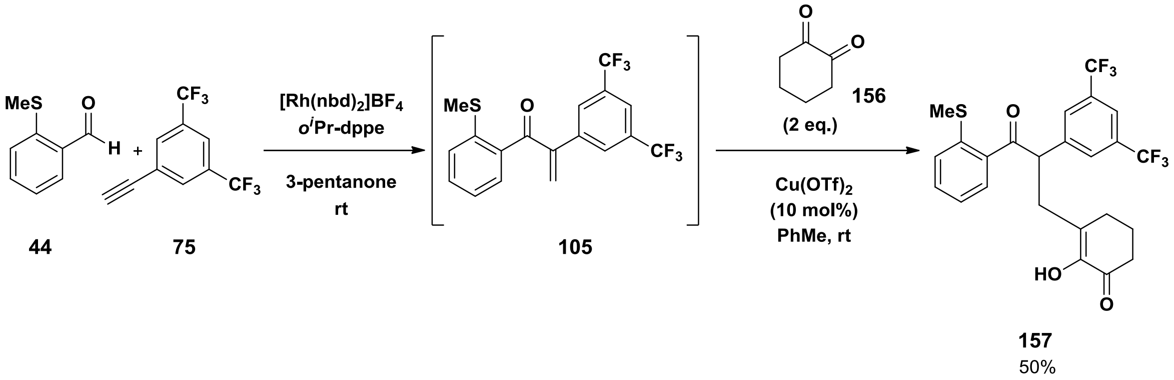
The introduction of an α-methyl group to the dicarbonyl removed the potential for a deprotonation and elimination sequence. Pleasingly, diethyl-2-methyl malonate **150** underwent conjugate addition to hydroacylation adduct **76b** to afford ketone **151** in an excellent yield. In addition, employing *β*-ketoester **152** as the nucleophile afforded the highly functionalised adduct**153** as an inseparable 1.4:1 mixture of diastereomers. Unfortunately, cyclic diketone **154** proved a more challenging substrate for this process with only 15% of the desired product **155** isolated (**Scheme 4.8**).

Scheme 4.8 – Three-component coupling of aldehyde **44,** alkyne **75** and various *β*-carbon nucleophiles.



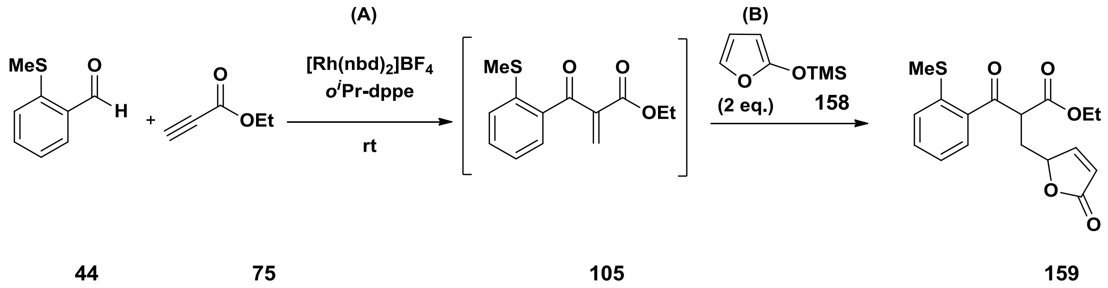
Although attempts to employ Lewis acid catalysis for malonate-type substrates were unsuccessful (**Scheme 4.7**), we were able to demonstrate the copper(II) triflate catalysed addition of cyclohexane-1,2-dione **156**, giving rise to the interesting enol product **157** in a 50% yield. Through analysis of the ^{1}H and ^{13}C NMR spectra, and comparison to the spectroscopic data of a similar literature compound,[113] we believe the product exists as the *α*-hydroxy-enone (**Scheme 4.9**).

Scheme 4.9- Three component coupling of aldehyde **44**, alkyne **75** and cyclohexane-1,2-dione.



Efficient methods towards the construction of γ-butenolide ring systems have received much attention owing to the presence of these structural motifs amongst numerous natural products.[119-121] The Mukaiyama-Michael addition of 2-(trialkylsilyloxy) furans to *α,β*-unsaturated ketones has emerged as an attractive methodology for the installation of these synthetically useful moieties.[122-125] Initial attempts at the 1,4-addition of 2-(trimethylsilyloxy)furan **158** to hydroacylation intermediate **105** under our standard reaction conditions were unsuccessful, leading to a complex mixture of decomposition products (**Table 4.3**, entry 1). The introduction of catalytic copper(II) triflate and a weakly acidic work-up resulted in trace amounts of the desired product alongside unknown side products and with considerable quantities of enone. The application of literature conditions[125] at a reduced temperature, gratifyingly led to a modest 52% yield of the diastereomeric product **159** (entry 4). Stirring in 1 N HCl/THF (1:1 v/v) proved crucial to obtaining good yields (compare entries 3 & 4).

Table 4.3 – Mukaiyama-Michael addition of 2-(trimethylsilyloxy)furan.[a]



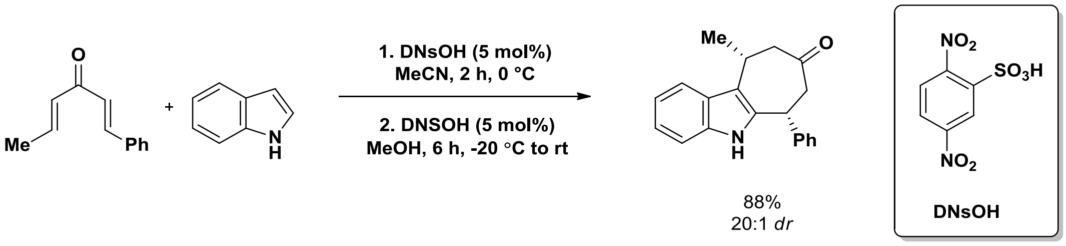
Entry	Solvent (step A)	Conditions (step B)	Yield (%)[b]
1	3-pentanone	3-pentanone, 80 °C, 18 h	Decomposition
2	3-pentanone	f)$_2$ (10 mol%), 3-pentanone, 80 °C, 2. (ii) 1N HCl w/u	trace
3	Acetone	(i) Cu(OTf)$_2$ (10 mol%), DCM, -78 °C, 2 h (ii) $NH_4Cl_{(aq)}$ w/u	29
4	Acetone	(i) Cu(OTf)$_2$ (10 mol%), DCM, -78 °C, 2 h (ii) 1 N HCl/THF (1:1), 0.5 h	52[c]

[a] Hydroacylation conditions: [Rh(nbd)$_2$]BF$_4$ (10 mol%), *o*-^{i}Pr-dppe (10 mol%), aldehyde (0.30 mmol), alkyne (0.45 mmol), solvent (2.0 mL, 0.15 M), 2 h. [b] Isolated yield. [c] Obtained in a 1:1 *dr*.

Double Addition Processes

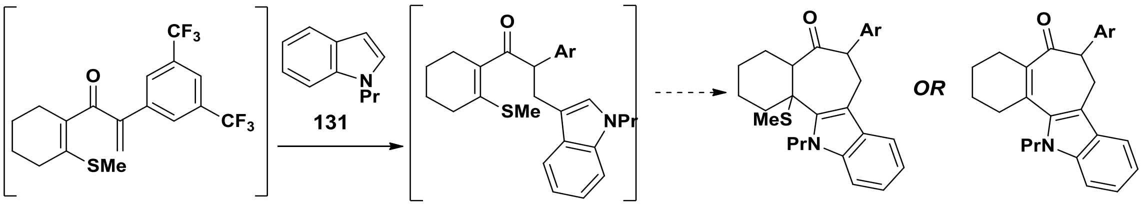
A recent publication by the Carbery group documents the double Friedel-Crafts alkylation of indoles with divinyl ketones using 2,4-dinitrobenzenesulfonic acid (DNsOH).[125] This methodology utilises the ability of divinyl ketones to behave as double electrophiles and that of indoles as double nucleophiles (**Scheme 4.10**).

Scheme 4.10 – Carbery's double Friedel-Crafts alkylation of indoles with divinyl ketones.



The hydroacylation adduct **160** of aldehyde **44** and alkyne **75** could also be considered a double electrophile. We therefore envisioned that it may undergo double addition of nucleophilic *N*-propylindole **131** to afford interesting tricyclic scaffolds **161** or **162** (**Scheme 4.11**).

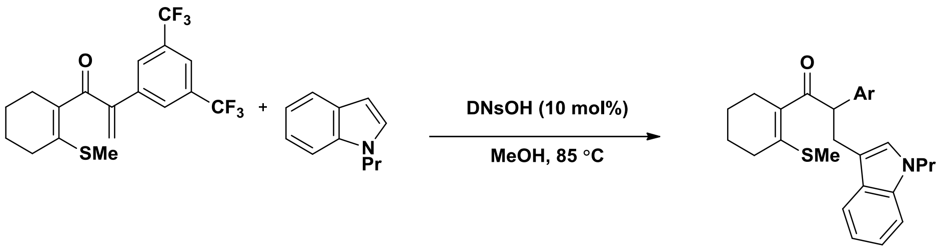
Scheme 4.11 – Potential double addition of *N*-propylindole **131** to enone **105**.



160 **161** **162**

The application of literature conditions to our system, which purportedly favour formation of the bis-adduct, resulted only in isolation of 76% of the mono-addition product **163**.

Scheme 4.12 – Attempted double-addition of indole to the double electrophile **160**.



160 **131** **163**
76%

We decided to focus our attention on the potential for the double addition of a primary amine, which would give access to interesting bicyclic piperidone derivatives. Similar processes exist in the literature[68] and we anticipated that the formation of a 6-membered ring would be more favourable (**Scheme 4.13**).

Scheme 4.13 – Postulated double-addition of indole to double electrophile **160**.

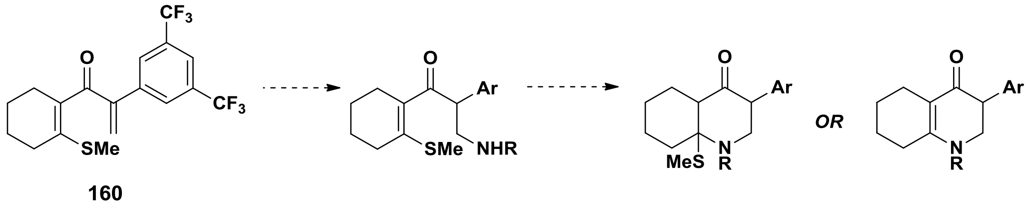
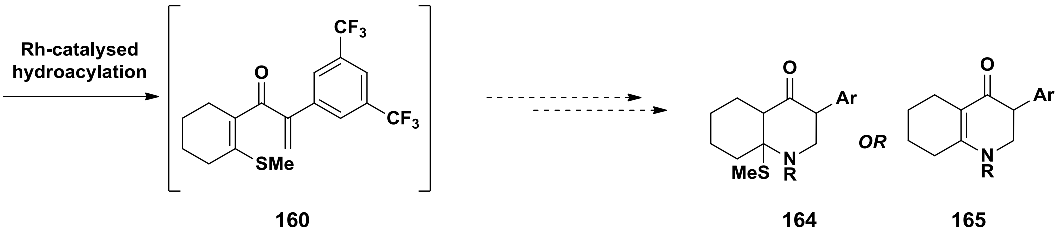


Table 4.4 documents preliminary screening of conditions for this process. We hoped that the addition of copper salts would potentially assist in the elimination of sulfide to afford the unsaturated product. We also evaluated the effect of the addition of an inorganic base and Lewis acid. Unfortunately, only complex mixtures of inseparable products were observed. The sterically hindered tetra-substituted cyclic alkene is a poor Michael acceptor, and thus could explain the difficulties in formation of the desired cyclised adducts.

Table 4.4 – Attempted double-addition of *n*-butylamine to enone **160**

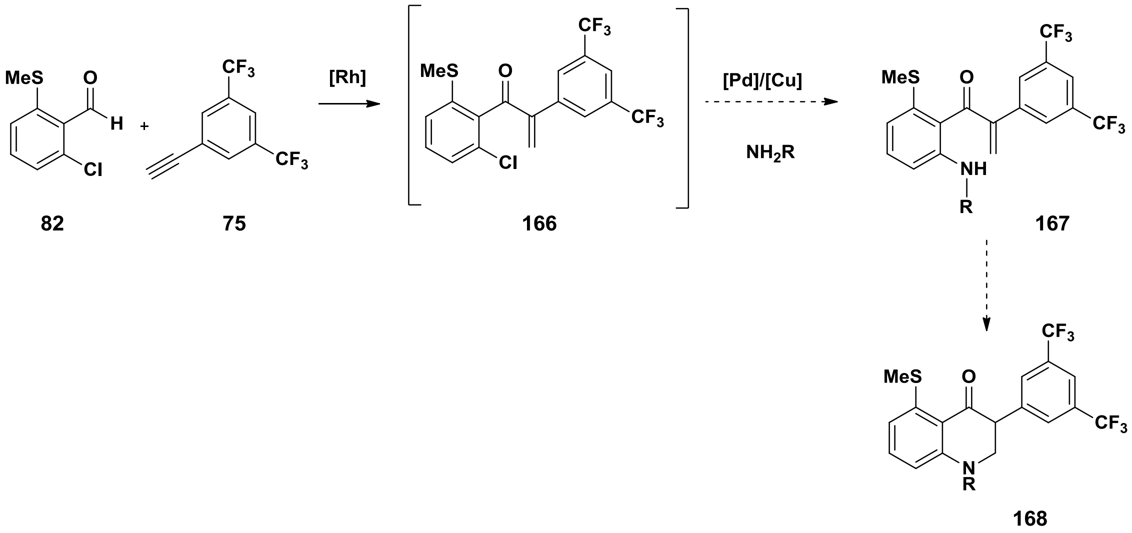


Entry	Conditions	Result
1	toluene, 100 °C	complex mixture
2	$Cu(OAc)_2$ (1 eq.), toluene, 100 °C	complex mixture
3	CuTC (1 eq.), toluene, 100 °C	complex mixture
4	K_2CO_3 (2 eq.), toluene, 100 °C	complex mixture
5	$BF_3(OEt)_2$ (1 eq.), toluene, 100 °C	complex mixture

[a] Hydroacylation conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), *o*-^{i}Pr-dppe (10 mol%), aldehyde **83** (0.30 mmol), alkyne **75** (0.45 mmol), acetone (2.0 mL, 0.15 M), 2 h.

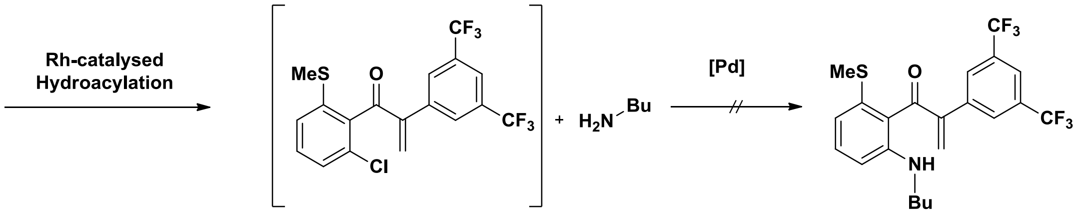
An alternative approach to obtain cyclic adducts such as **164** and **165** would be to incorporate a halide substituent onto the aldehyde derived component, which could then be manipulated *via* metal-catalysed coupling, such as the enone **166** derived from hydroacylation of aldehyde **82** and alkyne **75**. A Buchwald-Hartwig amination would deliver **167** which could be envisaged to undergo cyclisation to bicyclic adduct **168** (**Scheme 4.14**).

Scheme 4.14 – Envisaged Buchwald-Hartwig amination-cyclisation sequence.



Preliminary evaluation of conditions[126] for the Pd-catalysed coupling of 6-chloro-substituted hydroacylation adduct **166** and *n*-butylamine proved unsuccessful: complex mixtures of inseparable products were obtained in all cases with the predominant process appearing to be 1,4-addition into the enone (**Table 4.5**).

Table 4.5 – Attempted Buchwald-Hartwig coupling of **166** and *n*-butylamine.



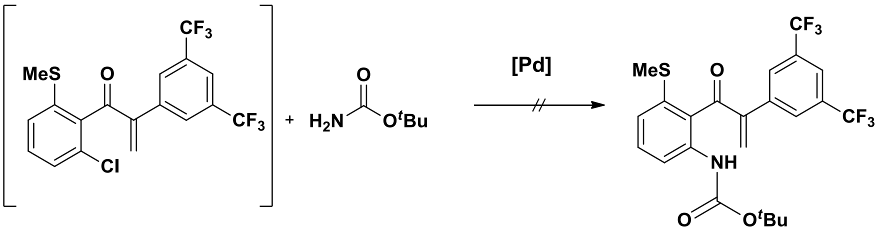
166 167

Entry	Pd Source (mol%)	Ligand (mol%)	Solvent (M)	Base (eq.)	Temp (°C)	Result
1	$Pd(OAc)_2$ (5)	BrettPhos (10)	1,4-dioxane	Na^{t}BuO (2)	100	Complex mixture[b]
2	$Pd(OAc)_2$ (5)	Me$_4$^{t}BuXPhos (10)	1,4-dioxane	Na^{t}BuO (2)	100	Complex mixture[b]

[a] Hydroacylation conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), *o*-^{i}Pr-dppe (10 mol%), aldehyde **82** (0.30 mmol), alkyne **75** (0.45 mmol), acetone (2.0 mL, 0.15 M), 2 h. [b] A complex mixture of products was observed by NMR spectroscopy alongside product of 1,4-addition to enone.

We have previously shown that *N*-Boc amine is a poor nucleophile for the 1,4-addition reaction. We therefore thought it might be a superior substrate for the Buchwald-Hartwig reaction owing to poor susceptibility for the competing 1,4-addition pathway. However, the coupling of enone **166** with of *N*-Boc amine, under both copper and palladium catalysis conditions resulted in no reaction (**Table 4.6** & **Scheme 4.15**).

Table 4.6 –Attempted Pd-catalysed Buchwald-Hartwig amination of enone **166** with *N*-Boc amine.

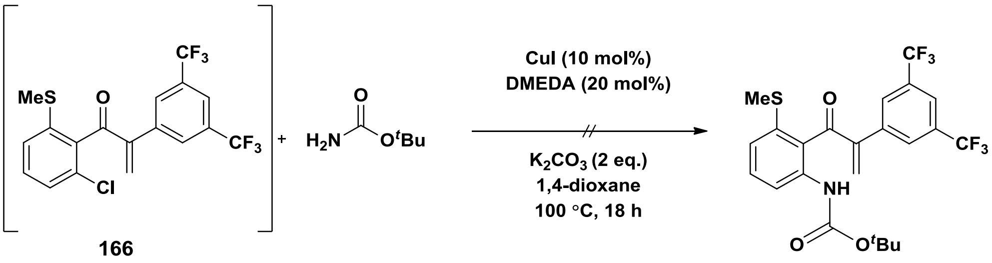


166

Entry	Pd Source (mol%)	Ligand (mol%)	Solvent (M)	Base (eq.)	Temp (°C)	Result
1	$Pd_2(dba)_3$ (5)	XantPhos (10)	1,4-dioxane	Na^{t}BuO (2)	100	n/r
2	$Pd(OAc)_2$ (5)	Me$_4$^{t}BuXPhos (10)	1,4-dioxane	Na^{t}BuO (2)	100	n/r

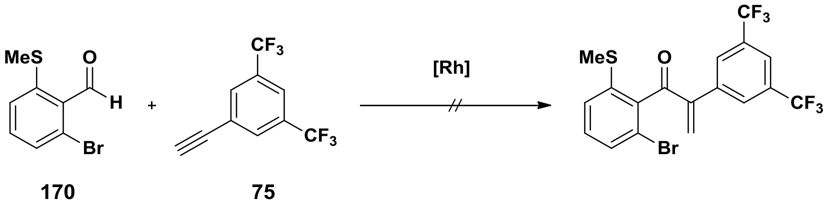
[a] Hydroacylation conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), *o*-^{i}Pr-dppe (10 mol%), aldehyde **82** (0.30 mmol), alkyne **75** (0.45 mmol), acetone (2.0 mL, 0.15 M), 2 h.

Scheme 4.15 –Attempted Cu-catalysed amination of enone **166** and *N*-Boc amine.



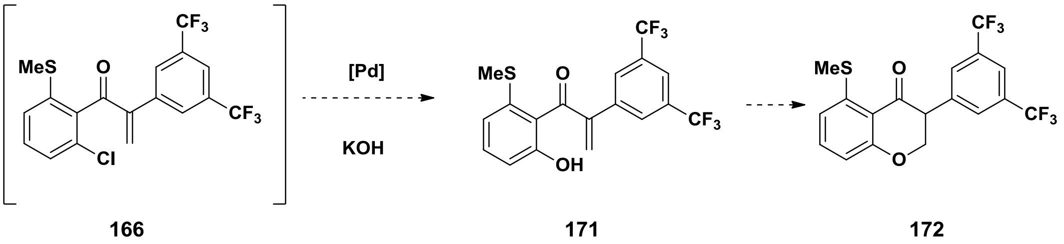
Copper-catalysed coupling is generally more successful with aryl bromides than aryl chlorides[127] and so we hoped to be able to access 6-bromo substituted enone **169**. To this end, we attempted the branched-selective hydroacylation of aldehyde **170** and alkyne **75**. However, only trace amounts of the desired product were observed (**Scheme 4.16**). This is presumably as a result of steric interference of the large bromine atom.

Scheme 4.16 – Attempted branched-selective hydroacylation of aldehyde **170** and alkyne **75.**



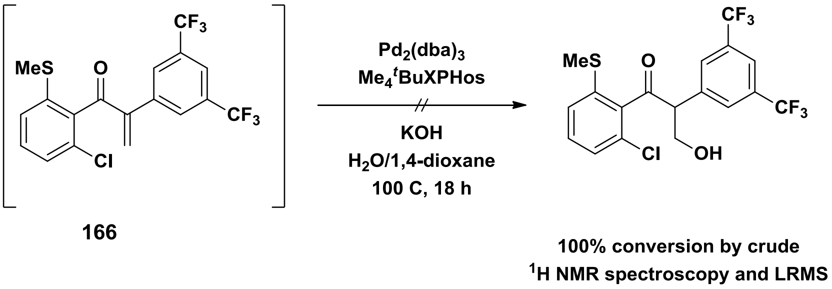
The reaction of aryl halides with KOH is also a well-documented process.[128] It was postulated that the synthesis of phenol **171** would result in cyclisation to form chromanone **172** (**Scheme 4.17**).

Scheme 4.17 – Proposed synthesis of chromanone **172**.



The attempted Pd-catalysed coupling of **166** with KOH under literature conditions resulted instead in a 100% conversion to the product of 1,4-addition as observed by LRMS and ^{1}H NMR analysis of the crude reaction mixture. The product was not isolated (**Scheme 4.18**).

Scheme 4.18 – Attempted reaction of aryl chloride **166** with KOH.



It should be noted that these are all preliminary screening results. Although no success has been achieved as yet, it is conceivable that further investigation would identify potential reaction conditions for these processes.

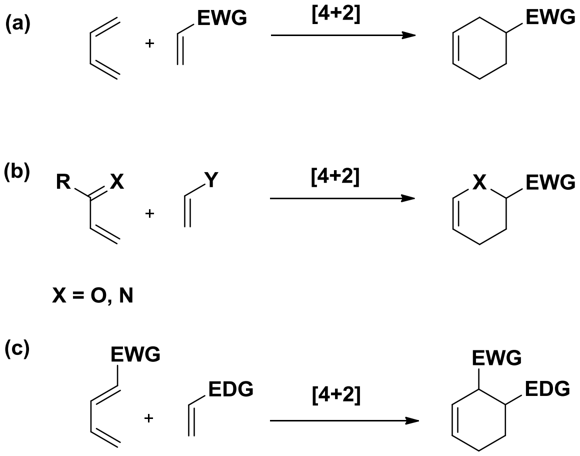
Diels-Alder

Introduction

The Diels-Alder reaction remains one of the most powerful methods for the preparation of six-membered ring systems since it was first reported over 80 years ago.[129] It is a [4+2] cycloaddition reaction whereby a conjugated diene reacts with a typically electron-deficient alkene or alkyne, commonly referred to as the dienophile. A variant of this is the hetero-

Diels-Alder reaction, in which either the diene or dienophile contains a heteroatom, most often oxygen or nitrogen. In addition, the inverse electron-demand Diels-Alder (DA_{INV}) involves the cycloaddition between an electron-rich dienophile and an electron-poor diene.[130]

Scheme 4.19 – (a) Diels-Alder (b) Hetero-Diels-Alder; (c) DA_{INV}



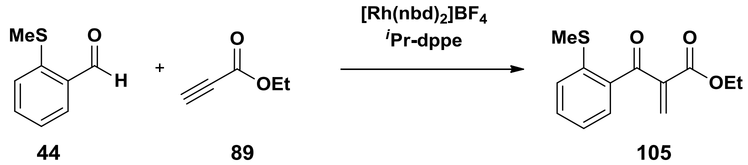
The Diels-Alder reaction can be considered a highly atom economical process and allows in principle the formation of four contiguous stereocentres. As such, numerous asymmetric variants have been developed using a range of different catalysts with broad substrate scope.[131-139] High degrees of stereoselectivity are typically observed owing to "*cis*" principle which states that Diels-Alder reactions require that both ends of the diene attack from the same face of the dienophile in a *syn* fashion.

A number of examples exist for the use of enones as dienophiles in Diels-Alder reaction.[140-145] We were therefore interested in testing our branched hydroacylation products as substrates for both normal and inverse electron-demand Diels-Alder reactions.

Solvent Evaluation

We noted that a number of Diels-Alder processes are performed in DCM or toluene. Since we typically perform our branched-selective hydroacylation process in acetone, we would therefore require a solvent switch for the Diels-Alder step. We sought to evaluate the branched-selective hydroacylation of aldehyde **44** and alkyne **75** in commonly used Diels-Alder solvents (**Table 4.7**).

Table 4.7 – Evaluation of solvents for hydroacylation process.



Entry	Solvent	Temp (°C)	Time (h)	Conversion (%)
1	DCM	40	18	100%
2	1,2-DCE	50	4	100%
3	Toluene	50	18	20%

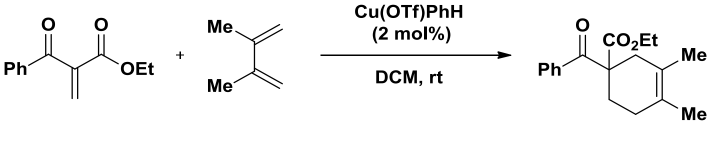
[a] Hydroacylation conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), *o*-^{i}Pr-dppe (10 mol%), aldehyde **44** (0.30 mmol), alkyne **89** (0.45 mmol), solvent (2.0 mL).

Unfortunately, our hydroacylation catalyst suffers from poor solubility in toluene leading to a poor conversion (entry 1). Whilst the hydroacylation proceeded to completion in DCM, elevated temperatures and extended reaction times were required (entry 2). The use of chlorinated solvent 1,2-DCE on the other hand was faster, but required elevated temperature compared to acetone (entry 3). Where possible, 1,2-DCE was employed for both the hydroacylation and Diels-Alder processes. In some cases, in order to maintain close analogy to literature conditions, a solvent switch from acetone to DCM was employed.

Normal Electron Demand Diels-Alder Reactions

Enone **173** has been reported to undergo a copper(II)-catalysed cycloaddition with 2,3-dimethylbutadiene (**Scheme 4.20**).[142]

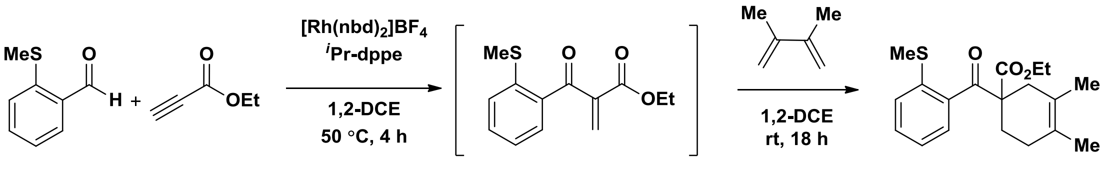
Scheme 4.20 – Diels-Alder of enone **173** and 2,3-dimethylbutadiene



173

Pleasingly, our analogous enone **150** underwent cycloaddition with 2,3-dimethylbutadiene in the absence of a copper catalyst to deliver the highly functionalised *β*-ketoester product in a modest 63% yield (Scheme **4.21**).

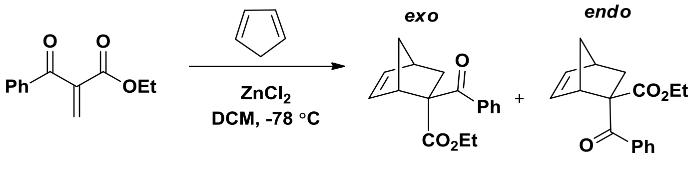
Scheme 4.21- Diels-Alder reaction of enone **105** with 2,3-dimethylbutadiene.



44 **89** **105** **174**
63%

The same *β*-ketoester enone **173** has been reported to undergo the stereoselective zinc(II) chloride-catalysed cycloaddition to form the *exo* bicyclic product **175x** (**Scheme 4.22**).[144]

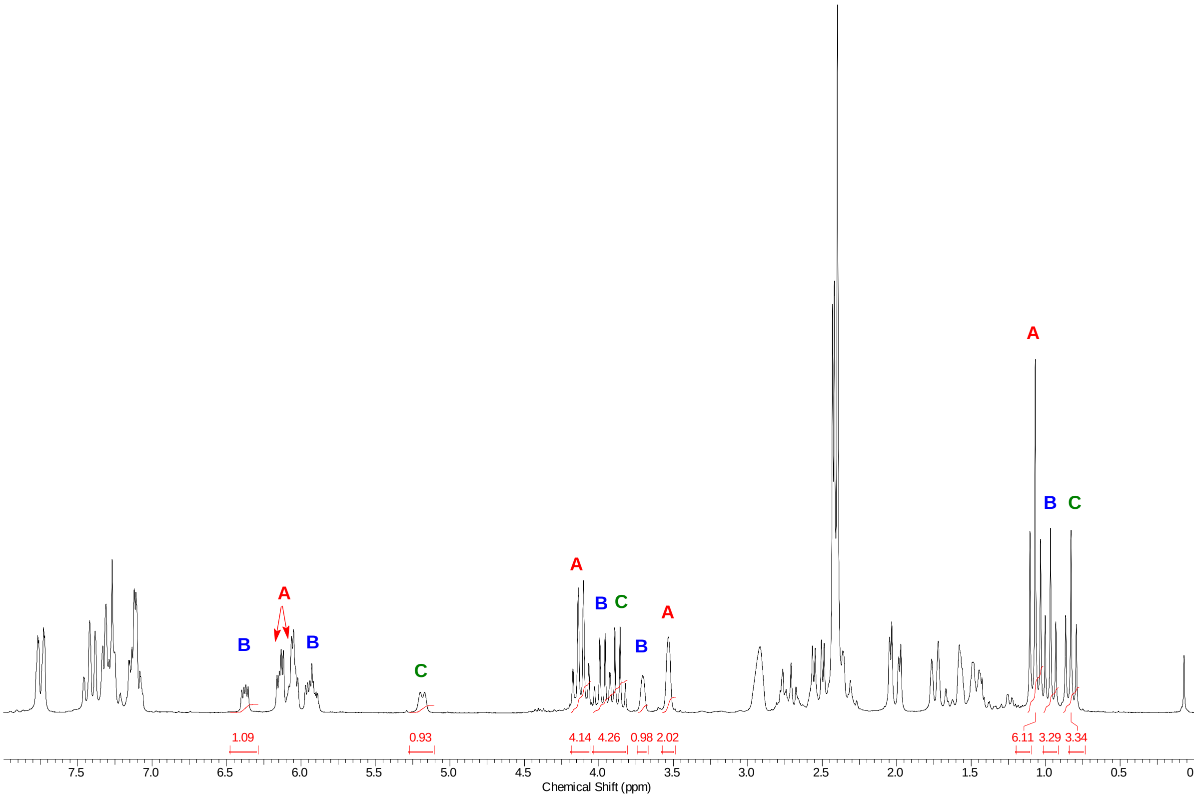
Scheme 4.22 - Stereoselective zinc(II) chloride-catalysed cycloaddition of *β*-ketoester enone **173** and cyclopentadiene.



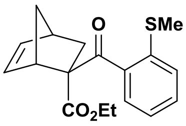
173 **175x** **175n**
73%
96:4 *exo*:*endo*

Our hydroacylation adduct **105** underwent facile reaction with cyclopentadiene in DCM in the absence of a Lewis acid to afford a mixture of three main products, as observed by both 1D and 2D NMR spectroscopy (**Table 4.8**, entry 1). An example of a crude ^{1}H NMR spectra in which three distinct products signals can be identified is shown below in **Figure 4.1**.

Figure 4.1 – Crude ^{1}H NMR spectra from the reaction of enone **105** with cyclopentadiene.

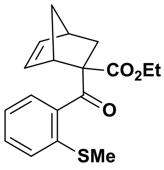


A



176n
"*endo*"

B

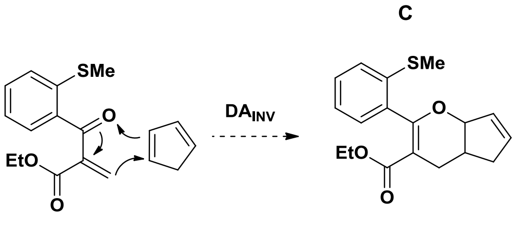


176x
"*exo*"

It is postulated that the signals labelled as A and B correspond to the *endo* (**176n**) and *exo* (**176x**) Diels-Alder adducts, respectively. The *endo* and *exo* assignments were made by comparison of the ^{1}H NMR signals for the alkenyl protons to those of similar literature compounds.

It is proposed that the signals labelled as C correspond to the product resulting from the unusual inverse electron demand Diels-Alder (DA$_{INV}$) of enone **105** with cyclopentadiene (**Scheme 4.23**).

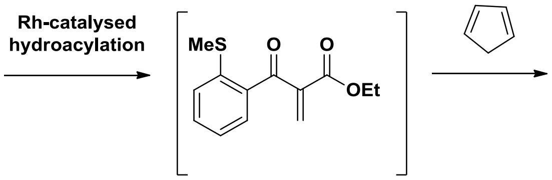
Scheme 4.23 – Postulated cycloaddition product **177** resulting from DA$_{INV}$ of enone **105** with cyclopentadiene



105 **177**

Since the products were inseparable by column chromatography, it was not possible to unequivocally confirm the identity of the reaction products. However, based upon the hypothesis outlined above, ratios of the proposed products were exterminated by analysis of crude the crude ^{1}H NMR and COSY spectra (**Table 4.8**). Unfortunately, the use of zinc(II) chloride at -78 °C resulted in only a 32% yield and a 1:1 *exo*:*endo* selectivity (entry 2). The use of copper(II) triflate led to no notable improvement in either yield or selectivity (entries 3 & 4).

Table 4.8 – Diels-Alder reaction of enone **105** with cyclopentadiene.



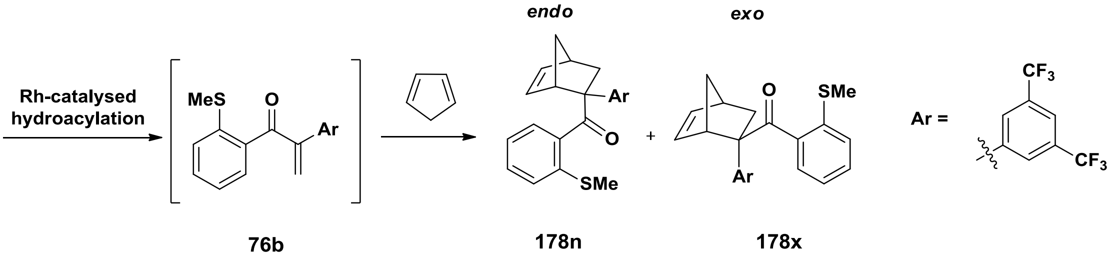
105

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Yield (%)	A:B:C
1	**-**	1,2-DCE	rt	100(conv.)	3.7:1.7:1
2	$ZnCl_2$ (150)	DCM	-78	32	1: 1: trace
3	$Cu(OTf)_2$ (50)	DCM	-78	39	2 : 1: 1
4	$Cu(OTf)_2$ (50)	DCM	-40	54	1.2:1:trace

[a] Hydroacylation conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), *o*-^{i}Pr-dppe (10 mol%), aldehyde **44** (0.30 mmol), alkyne **89** (0.45 mmol), acetone (2.0 mL, 0.15 M), 2 h.

We hoped to achieve improved stereoselectivity for the Diels-Alder of cyclopentadiene with enone **76b** as we expected there would be a more significant differentiation between the ketone and the aromatic ring. In addition, there is only one possible mode of coordination for the Lewis acid. To our disappointment, the use of copper(II) triflate resulted in a 71% overall yield and only 2:1 *endo*:*exo* selectivity (**Table 4.9**, entry 1) Additionally, the use of zinc(II) chloride resulted in a slight increase in selectivity to 3:1, in favour of the *endo* product (entry 2).

Table 4.9 – Diels-Alder reaction of enone **76b** and cyclopentadiene.[a]



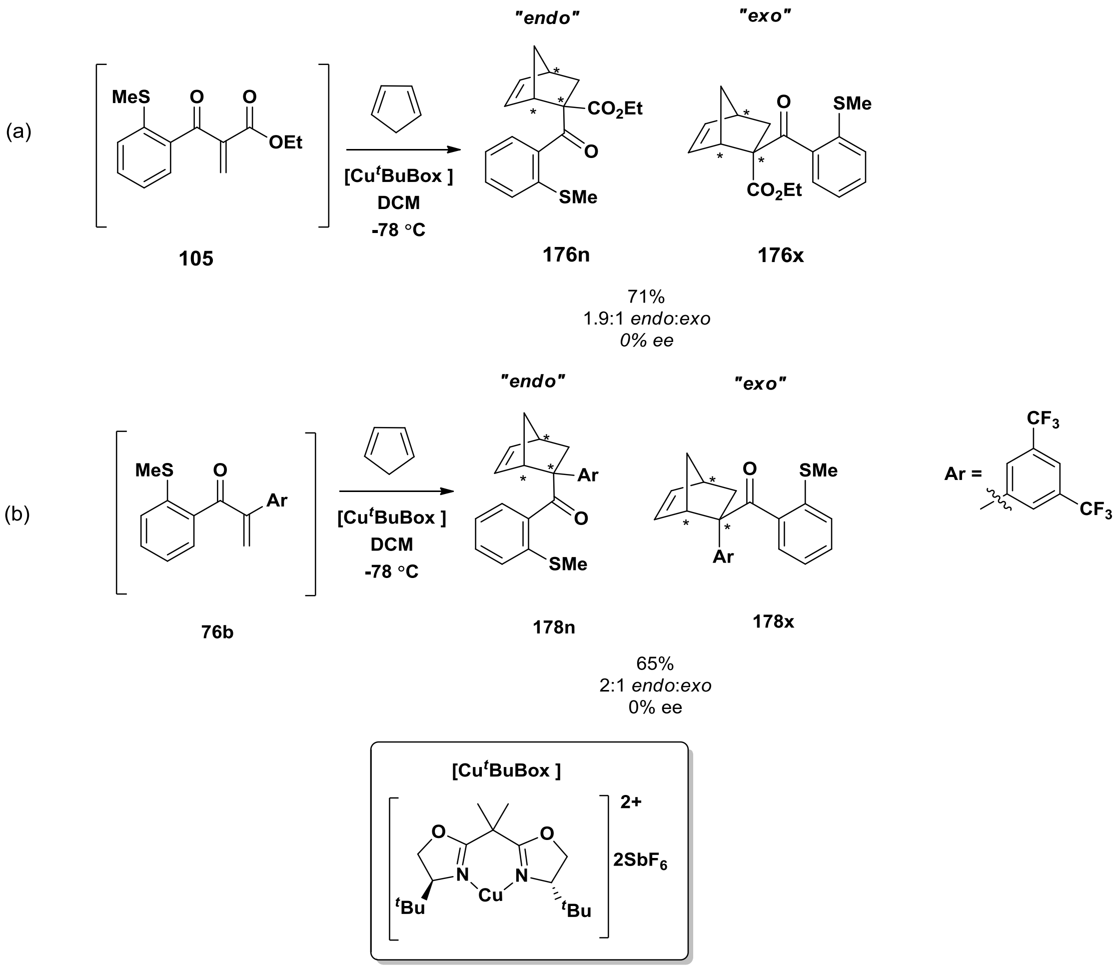
Entry	Catalyst (mol%)	Solvent	Temp (°C)	Yield (%)[b]	*Endo*:*Exo*[c]
1	$Cu(OTf)_2$ (50)	DCM	-78	71	2:1
2	$ZnCl_2$ (150)	DCM	-78	58[c]	3:1

[a] Hydroacylation conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), *o*-^{i}Pr-dppe (10 mol%), aldehyde **44** (0.30 mmol), alkyne **75** (0.45 mmol), acetone (2.0 mL, 0.15 M), 2 h. [b] Yield of both diastereomers. [b] Determined by analysis of crude ^{1}H NMR spectra. [c] Isolated in a >20:1 *endo*:*exo* diastereoselectivity.

A number of asymmetric variants of Diels-Alder reaction of enone **105** with cyclopentadiene also exist. Examples include Ti-TADDOL complexes[143] or magnesium-based oxazolidinone catalysts.[141] The Evans group has published the use of C_2-symmetric bis(oxazoline)-Cu(II) complexes as excellent catalysts for asymmetric Diels-Alder reactions for chelating dienes.[131,138] Although, to the best of our knowledge, no examples exist for their use in the cycloaddition of enones such as **105**, we hoped to be able to employ them in our system.

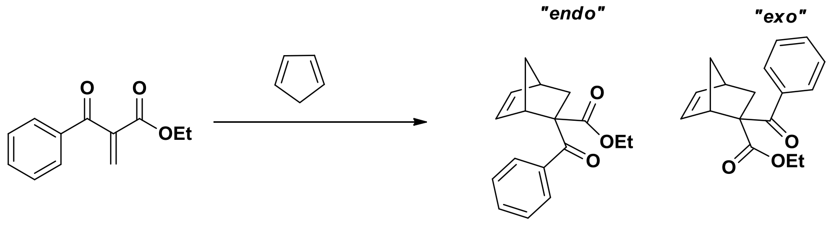
Disappointingly, the use of [Cu((*S*,*S*)-*tert*-Bu-box)]SbF_6 ([Cu^{t}BuBox]), under literature reaction conditions, resulted in poor selectivity of 1.9:1 *endo*:*exo* and no enantiomeric excess (*ee*) for the cycloaddition of **105** with cyclopentadiene, albeit with a slight improvement in yield and trace quantities of the inverse electron demand adduct (**Scheme 4.24, a**). Similarly, the application of the chiral catalyst [Cu^{t}BuBox], to the cycloaddition of **76b** with cyclopentadiene resulted in a racemic process, again with a poor 2:1 *endo*:*exo* selectivity (**Scheme 4.24, b**).

Scheme 4.24 – Attempts at asymmetric processes using [Cu^{t}BuBox].



We rationalised the poor enantiocontrol as a result of the interference of the Lewis basic sulfur chelating group on the aryl ketone. Presumably, the copper can doubly chelate either to the two carbonyl oxygen atoms, or alternatively, between the ketone carbonyl and the sulfur atom. To test our hypothesis we subjected the analogous enone **173** to our racemic and asymmetric conditions (**Table 4.9**).

Table 4.10 – Diels-Alder reaction of enone **173** with cyclopentadiene.



173 **175n** **175x**

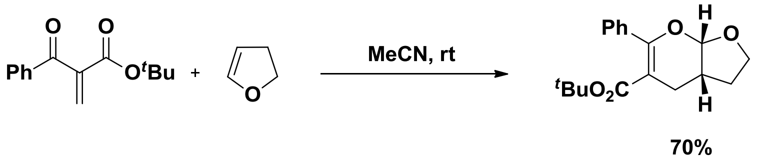
Entry	Conditions	Result
1	$ZnCl_2$ (1.5 eq.), DCM, -78 °C, 4 h	71% (16:1 *exo*:*endo*)
2	[Cu^{t}BuBox], DCM, -78 °C, 2 h	68% (9:1 exo:endo), 47% *ee*

With the use of zinc(II) chloride, complete selectivity for observed for the *exo* isomer which was in accordance with the literature (**Table 4.10**, entry 1). Employing [Cu^{t}BuBox] again resulted in exclusive formation of the *exo* diastereomer with a modest 47% enantiomeric excess (entry 2). Although complete enantiocontrol was not observed, these are un-optimised conditions for this system and we believe this result confirms the detrimental effect of the sulfide substituent.

Inverse Electron Demand Diels-Alder (DA$_{INV}$)

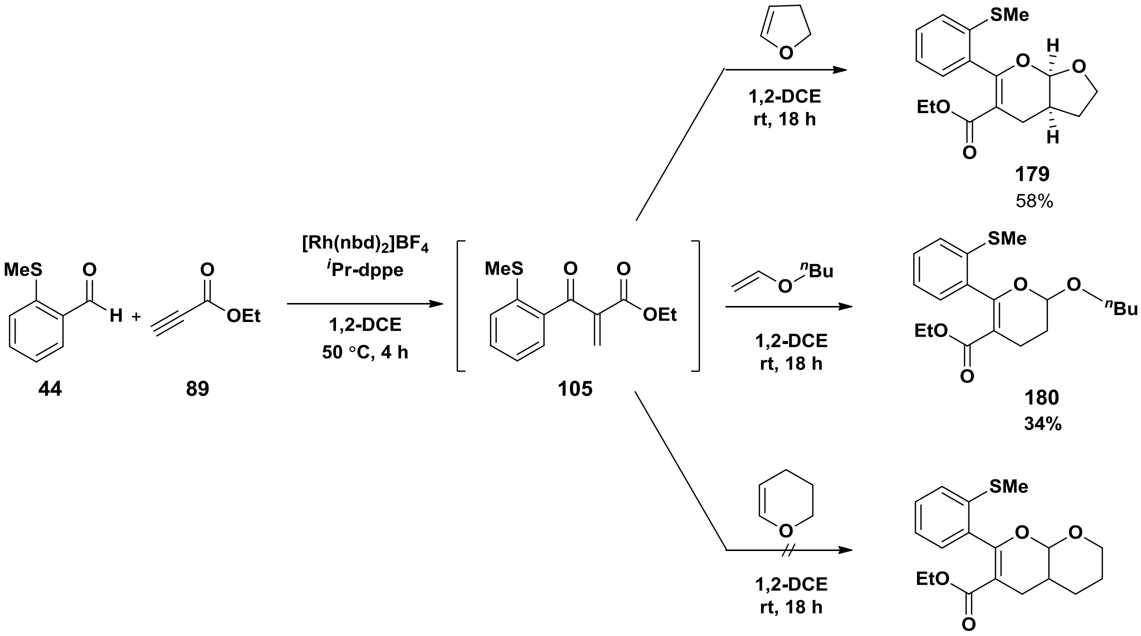
Analogous enones are also precedented to undergo inverse electron demand Diels-Alder reactions (DA$_{INV}$) such as the example shown in Scheme **4.25**.[146]

Scheme 4.25 – Literature example of DA$_{INV}$ with 2,3-dihydrofuran.



We were pleased to observe that the DA$_{INV}$ of enone intermediate **105** with 2,3-dihydrofuran proceeded smoothly in 1,2-DCE at room temperature, affording the interesting bicyclic product **179** in a 58% yield over the two-steps. The two rings are assumed to be *cis*-fused by comparison of the coupling constants for the bridging protons with those for similar literature compounds (^3J = 4.0 Hz). Enone **105** also underwent DA_{INV} with butylvinylether, albeit in a reduced overall yield of 34% of **180** (**Scheme 4.26**). Unfortunately, 3,4-dihydropyran proved to be unreactive under the same reaction conditions, unsurprisingly since 3,4-dihydropyran is known to be an inferior dienophile.[147]

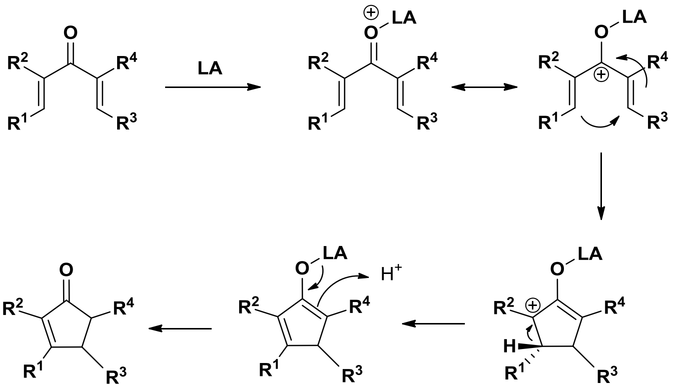
Scheme 4.26 – Tandem hydroacylation - DA_{INV} process.



Nazarov Cyclisations

The Nazarov cyclisation involves the 4π-electrocyclic ring closure of divinyl ketones to cyclopentenones (**Scheme 4.27**).[148,149] This transformation has been extensively studied owing to the synthetic utility of cyclopentenones and their ubiquity of cyclopentenones amongst natural products.[150-153]

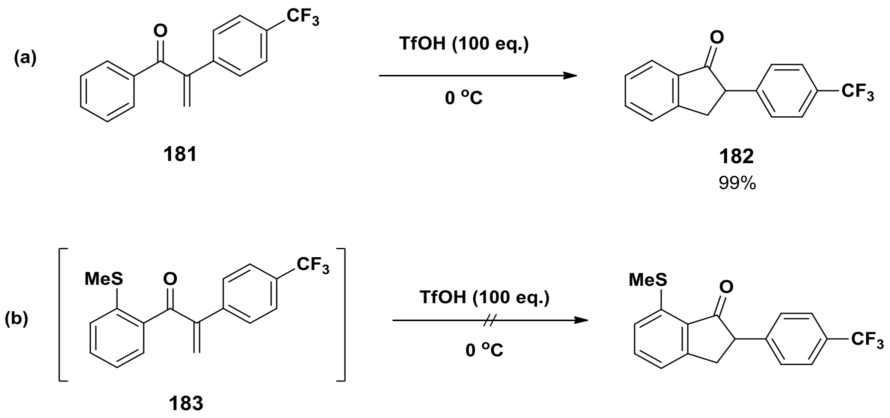
Scheme 4.27 – Nazarov Cyclisation mechanism.



It is traditionally a Lewis acid-catalysed process; however, significant advances in catalysis have led to the use of other promoters such as Brønsted acids, organocatalysts, and transition metal catalysts.[149,154-156]

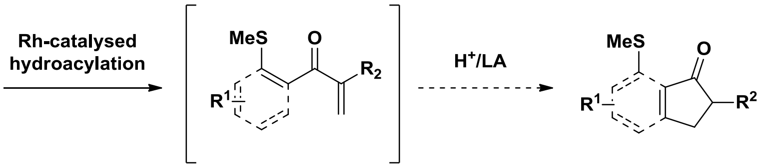
Ohwada *et al*. have reported the Nazarov cyclisation of aryl vinyl ketone **181** with the use of excess triflic acid at 0 °C (**Scheme 4.27, a**).[157] We envisaged that our analogous sulfide containing aryl vinyl ketone **183** would undergo a similar transformation under the same conditions. Unfortunately, no reaction was observed, with large quantities of enone returned alongside decomposition products (**Scheme 4.28, b**).

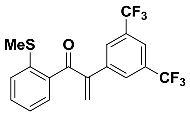
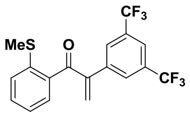
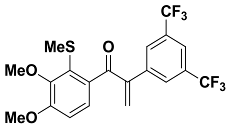
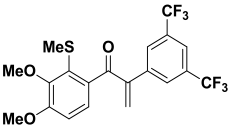
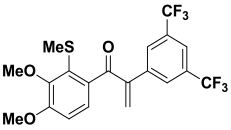
Scheme 4.28 – (a) Ohwada's Nazarov cyclisation of analogous enone'(b) Failed attempt to apply conditions to our substrate.

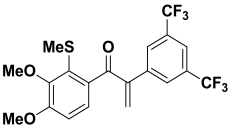
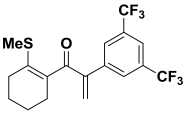
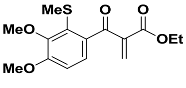
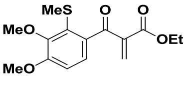
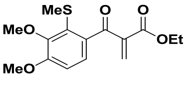
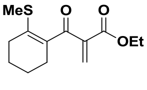
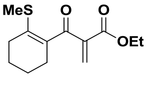
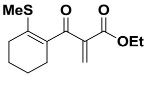
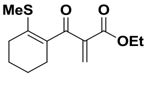


After consultation of the extensive literature surrounding this reaction, we then proceeded to evaluate a range of different Brønsted and Lewis acids using literature conditions for similar substrates (**Table 4.10**).

Table 4.10 – Evaluation of acidic conditions for Nazarov cyclisation of hydroacylation adducts.



Entry	Substrate	Conditions	Result
1		TfOH (100 eq.), 0 °C	SM + Decomposition
2		TMSOTf, $MeNO_2$, 105 °C^{c}	SM
3		TMSOTf, 1,2-DCE, rt^{c}	SM
4		$AgSbF_6$, 1,2-DCE, 80 °C^{c}	SM
5		H_2SO_4, 0 °C^{c}	SM

6		PhCl, 130 °C[c]	SM
7		Cu(OTf)$_2$, DCM, rt	SM
8[b]		TfOH (100 eq.), 0 °C	SM + Decomposition
9[b]		TfOH (4 eq.), DCM, rt	SM + Decomposition
10[b]		Cu(OTf)$_2$, DCM, 100 C, μw, 3 h	Decomposition
11[b]		TfOH (100 eq.), 0 °C	SM + Decomposition
12[b]		TfOH (4 eq.), DCM, rt	SM + Decomposition
13[b]		Cu(OTf)$_2$, DCM, rt	SM
14[b]		Cu(OTf)$_2$, DCM, 100 °C, μw, 3 h	Decomposition

[a] Hydroacylation conditions: [Rh(nbd)$_2$]BF$_4$ (10 mol%), *o*-^{i}Pr-dppe (10 mol%), aldehyde (0.30 mmol), alkyne (0.45 mmol), acetone (2.0 mL, 0.15 M), 2 h. [b] Hydroacylation step performed at 50 °C. [c] Reactions performed by Dr Carlos Gonzalez-Rodriguez.

Disappointingly, all attempts proved unsuccessful with either recovered starting material or decomposition products being observed in all cases. We have not ascertained the exact reasons for this poor reactivity; however, it is evident that the methyl sulfide substituent is having a detrimental effect on the electrocyclisation.

4.2 Summary and Future Work

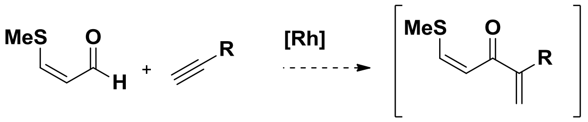
In summary, we have exploited the synthetic utility of our branched hydroacylation adducts through the development of several tandem processes. We have developed a versatile multicomponent process whereby a variety of readily available aldehydes, alkynes and nucleophiles can be coupled in one-pot to deliver highly functionalised ketone derivatives.

Furthermore, we have demonstrated the utility of these enone intermediates as substrates for both normal and inverse electron-demand Diels-Alder cycloadditions. We have identified that the presence of the chelating Lewis basic sulfur atom, which we require for stabilisation of our hydroacylation intermediate, has a detrimental effect on the diastereo- and enantioselectivity of these processes.

Finally, we have reported our efforts towards the development of a tandem hydroacylation-Nazarov cyclisation through the application of a wide range of literature conditions for similar substrates. Unfortunately, all attempts thus far have proved unsuccessful. Again we attribute this to the presence of a sulfide substituent on the aromatic ring.

We have begun to explore the potential for double nucleophilic addition to hydroacylation adducts which can behave as double electrophiles. This has not been realised thus far, most likely as a result of a challenging tetra-substituted Michael acceptor. The extension of our hydroacylation process to include enal substrates such as **184** would give access to intermediates such as **185** which could be envisaged to be significantly more susceptible to a double 1,4-addition.

Scheme 4.29 – The extension of our branched-selective hydroacylation to enals such as **184**.



184 **186**

Chapter 5 - Experimental

General Considerations

Chemicals were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics Ltd., or Strem Chemicals Inc. and used as supplied with the exception of 2-methylthiobenzaldehyde **1a** which was purified by flash column chromatography on silica gel (5% Et_2O/petrol) and distilled (145 °C, 13 mmHg) prior to use. Anhydrous (where stated), HPLC grade solvents were purchased from Sigma Aldrich, Fisher Scientific or Rathburn and used directly without further purification with the exception of acetone which was distilled from Drierite® and 1,2-DCE which was distilled over calcium hydride. DCM, THF and Et_2O were obtained dry from an in-house solvent purification system (Innovative Technology Inc. PS-400-7) having passed through anhydrous alumina columns. 'Petrol' refers to the fraction of light petroleum ether boiling in the range 40-60 °C. Aldehydes **29, 44** and diene **30** were commercially available and distilled prior to use.

Reactions were performed with continuous magnetic stirring, under an atmosphere of nitrogen, unless otherwise stated, using standard Schlenk techniques and all glassware was oven-dried overnight (>200 °C) and allowed to cool under a flow of nitrogen (passed through a Drierite® filled tube) prior to use. Flash column chromatography was performed using Merck Geduran silica gel 60 (particle size 0.040-0.063 nm) with the indicated eluents. Thin Layer Chromatography (TLC) analysis was carried out on Merck Kieselgel 60 PF254 pre-coated aluminium backed sheets and visualised either by UV fluorescence (254 nm) and/or by staining with vanillin or potassium permanganate ($KMnO_4$).

NMR spectra were recorded at ambient temperature on either Brüker DPX200 (200 MHz), DQX400 (400 MHz) or AVC500 (500 MHz) spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and referenced relative to the residual solvent peak(s) (as specified). Coupling constants (*J*) are given in Hertz (Hz) and rounded to the nearest 0.5 Hz. Assignments were made on the basis of chemical shifts, coupling constants, DEPT, COSY, HSQC and comparison with spectra of related compounds. Signal multiplicities are denoted as: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sxt, sextet; sept, septet; m, multiplet; br., broad; app., apparent.

Melting points were measured using a Leica Gallen III hot-stage microscope. Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ESI). High resolution mass spectra were measured by the internal service at the University of Oxford using a Bruker Daltronics microTOF spectrometer. *m/z* ratio values are reported in Daltons; high resolution values are calculated to four decimal places from the molecular formula, all found within a tolerance of 5 ppm. Infrared spectra were determined neat using a Bruker Tensor 27 FT spectrometer with an internal range of 600-4000 cm^{-1}.

Chiral HPLC analysis was carried out using a Dionex HPLC system using Diacel Chiral columns. HPLC grade solvents were purchased from Fisher Scientific and were use as supplied.

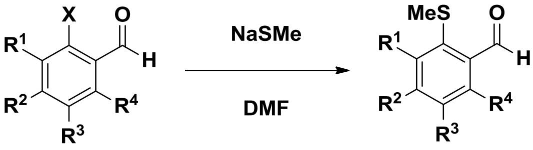
[Cu((*S*,*S*)-*tert*-Bu-box)]$\mathrm{SbF_6}$ ([Cu^{t}BuBox])[138] and [Rh(nbd)$_2$]$\mathrm{BF_4}$[51] were synthesised according to literature procedures. [Rh(F-$\mathrm{C_6H_5}$)(ligand)]$\mathrm{BAr^F{}_4}$ complexes were prepared by Indrek Pernik from the Weller group.

Experimental Procedures and Data

Synthesis of Aldehyde Starting Materials

Aldehydes **48**, **49**, **50**, **82**, **50**, **170** were prepared from the corresponding 2-haloaldehydes following General Procedure **A** (Scheme 5.1).

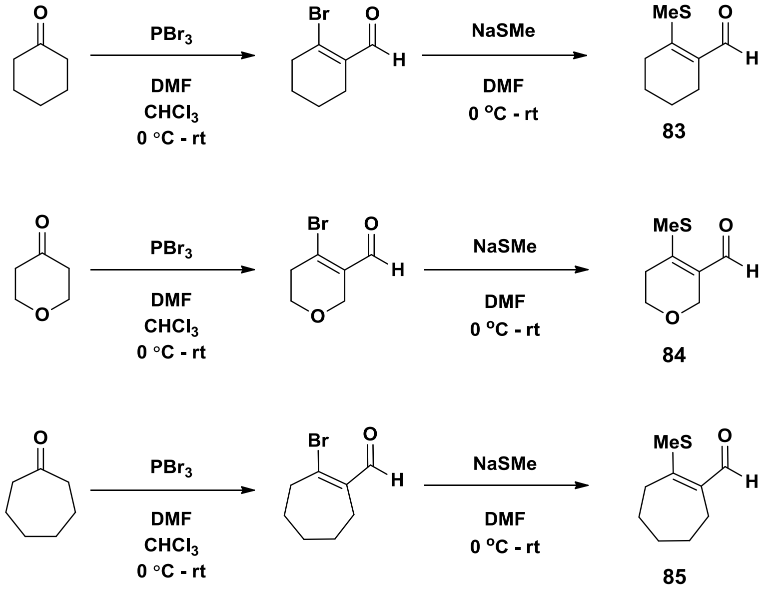
Scheme 5.1 – General Procedure **A** for the preparation of aldehydes **48, 49, 50, 51, 82, 170**



48, $R^1 = R^2 = OMe$, $R^3 = R^4 = H$
49, $R^2 = R^3 = OMe$, $R^1 = R^4 = H$
50, $R^4 = SMe$, $R^1 = R^2 = R^3 = H$
51, $R^1 = CF_3$, $R^2 = R^3 = R^4 = H$
82, $R^4 = Cl$, $R^1 = R^2 = R^3 = H$
170, $R^4 = Br$, $R^1 = R^2 = R^3 = H$

Aldehydes **83, 84** and **85** were synthesised in two steps from the corresponding cyclic ketones *via* a Vilsmeier-Haack bromoformylation[158] and a subsequent nucleophilic addition-elimination reaction (**Scheme 5.2**).

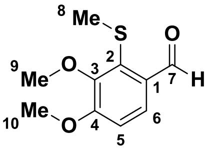
Scheme 5.2 – Synthesis of aldehydes **83**, **84** and **85**.



General Procedure A – Synthesis of *β*-S-aldehydes

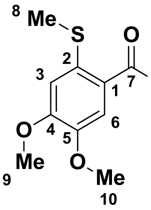
To a solution of the 2-haloaldehyde (1.0 eq.) in DMF at 0 ºC was added NaSMe (1.2 eq.) and the resulting solution stirred at the specified temperature for between 18-24 h. The reaction mixture was diluted with EtOAc and washed with 10% $LiCl_{(aq)}$ then sat. $NaCl_{(aq)}$. The organic layer was dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography.

3,4-Dimethoxy-2-(methylthio)benzaldehyde (48)



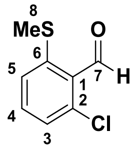
Prepared according to General Procedure **A** using 2-chloro-3,4-dimethoxybenzaldehyde (3.0 g, 14.9 mmol), NaSMe (1.3 g, 19.9 mmol) and DMF (15 mL) at 70 °C for 18 h. Purification by flash column chromatography (20% EtOAc/petrol) afforded the aldehyde **48** as a yellow oil (1.54 g, 49%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (1H, s, C*H*O), 7.73 (1H, d, *J* 8.5, *H-6*), 6.98 (1H, d, *J* 8.5, *H-5*), 3.94 (3H, s, OC*H₃*), 3.91 (3H, s, OC*H₃*), 2.46 (3H, s, *H-8*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3 (*C*HO), 157.9 (Ar*C*OCH₃), 150.2 (Ar*C*OCH₃), 135.4 (*C-2*), 130.6 (*C-1*), 125.6 (*C-6*), 111.8 (*C-5*), 60.7 (ArCO*C*H₃), 56.1 (ArCO*C*H₃), 19.6 (*C-8*); LRMS (ESI) *m/z* 267 (100%, $[M+Na+MeOH]^+$), 235 (45%, $[M+Na]^+$), 213 (10%, $[M+H]^+$). Data is in accordance with the literature.[89]

4,5-Dimethoxy-2-(methylthio)benzaldehyde (49)

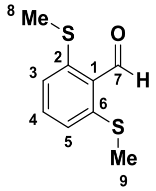


Prepared according to General Procedure **A** using 2-bromo-4,5-dimethoxybenzaldehyde (3.0 g, 11.8 mmol), NaSMe (343 mg, 15.0 mmol) and DMF (15 mL) at 70 °C for 18 h. Purification by flash column chromatography (20% EtOAc/petrol) afforded the aldehyde **49** as a pale yellow solid (1.54 g, 67%); ^{1}H NMR (400 MHz, CDCl$_3$), δ 10.38 (1H, s, C*H*O), 7.38 (1H, s, *H-6*), 6.91 (1H, s, *H-3*), 3.98 (3H, s, ArCOC*H$_3$*), 3.92 (3H, s, ArCOC*H$_3$*), 2.50 (3H, s, SC*H$_3$*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 189.8 (*C*HO), 154.0 (Ar*C*OCH$_3$), 147.9 (Ar*C*OCH$_3$), 136.6 (*C*-*2*), 128.0 (*C*-*1*), 111.9 (*C*-*6*), 111.5 (*C*-*3*), 56.2 (ArCO*C*H$_3$), 56.1 (ArCO*C*H$_3$), 18.4 (*C-8*); LRMS (ESI) *m/z* 267 (100%, [M+Na+MeOH]$^+$), 235 (75%, [M+Na]$^+$), 213 (20%, [M+H]$^+$). Data is in accordance with the literature.[159]

2-Chloro-6-(methylthio)benzaldehyde (52) and 2,6-bis(Methylthio)benzaldehyde (50)



52



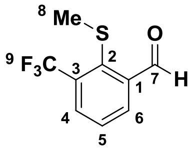
50

Prepared according to General Procedure **A** using 2,6-dichlorobenzaldehyde (1.0 g, 5.7 mmol), NaSMe (360 mg, 5.1 mmol) and DMF (10 mL) at 90 °C for 18 h. Purification by flash column chromatography (20% Et_2O/petrol) afforded in order of elution aldehyde **52** as a pale yellow solid (279 mg, 26%) and aldehyde **50** as a yellow solid (135 mg, 12%);

Data for aldehyde **52**: m.p. (DCM) 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (1H, s, C*H*O), 7.43-7.38 (1H, m, Ar*H*), 7.23-7.17 (2H, m, 2×Ar*H*), 2.45 (3H, s, *H-8*); ^{13}C NMR (101 MHz, $CDCl_3$), δ 192.0 (*C*HO), 146.8 (Ar*C*), 140.3 (Ar*C*), 133.6 (Ar*C*), 128.1 (Ar*C*H) 125.6 (Ar*C*H), 123.0 (Ar*C*H), 15.5 (*C-8*); LRMS (ESI) *m/z* 241 (95%, $[M+Na+MeOH]^+$), 209 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 208.9797 ($[M+Na]^+$), $C_8H_7{}^{35}ClNaOS^+$ requires 208.9797; ν_{max} (neat)/cm^{-1} 3097, 3068, 2924, 2987, 2275, 1668 (C=O), 1571, 1543.

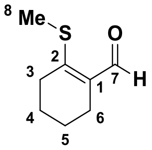
Data for aldehyde **50**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 10.73 (1H, s, C*H*O), 7.49-7.38 (1H, m), 7.13-7.08 (2H, d, *J* 8.0, *H-3* and *H-5*), 2.49 (6H, s, 2×SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0 (*C*HO), 145.8 (*C-2* and *C-6*), 132.9 (*C-1*), 129.2 (*C-4*), 121.9, (*C-3* and *C-5*), 16.2 (*C-8* and *C-9*); LRMS (ESI) *m/z* 221 (100%, $[M+Na]^+$). Data is in accordance with the literature.[160]

2-(Methylthio)-3-(trifluoromethyl)benzaldehyde (51)



Prepared according to General Procedure **A** using 2-fluoro-3-(trifluoromethyl)benzaldehyde (1.0 mL, 7.3 mmol), NaSMe (610 mg, 8.7 mmol) and DMF (15 mL) at 90 °C for 18 h. Purification by flash column chromatography (20% Et_2O/petrol) afforded the aldehyde **51** as a pale yellow solid (1.17 g, 73%); ^{1}H NMR (400 MHz, $CDCl_3$), δ 10.83 (1H, s, C*H*O), 8.10 (1H, app. d, *J* 8.0, *H-4*), 7.96 (1H, dd, *J* 8.0, 1.0, *H-6*), 7.60 (1H, t, *J* 8.0, *H-6*), 2.42 (3H, s, S*CH₃*); ^{13}C NMR (101 MHz, $CDCl_3$), δ 192.0 (*C*HO), 139.9 (Ar*C*), 139.4 (Ar*C*), 135.2 (q, $J_{C\text{-}F}$ 29.0, *C-3*), 132.1 (*C-5*), 131.7 (q, $J_{C\text{-}F}$ 5.5, C-*4*), 129.2 (*C-6*), 123.2 (q, $J_{C\text{-}F}$ 274.0, *C-9*), 23.0 (*C-8*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.5 (3F, s); LRMS (ESI) *m/z* 219 (100%, $[M\text{-}H]^-$). Data is in accordance with the literature.[89]

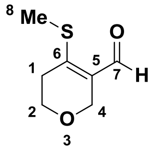
2-(Methylthio)cyclohex-1-enecarbaldehyde (83)



Prepared according to a literature procedure.[151] PBr_3 (13.7 mL, 146 mmol) was added drop-wise to a solution of DMF (12.6 mL, 179 mmol) in $CHCl_3$ (80 mL) at 0 °C and the mixture stirred for 1 h at the same temperature. A solution of cyclohexanone (6.3 mL, 54 mmol) in $CHCl_3$ (10.5 mL) was added drop-wise at 0 °C resulting in the formation of a dark yellow precipitate. The reaction mixture was allowed to warm to room temperature and stirred for 20 h resulting in an orange solution. The reaction mixture was poured onto ice H_2O (300 mL) and neutralised by the addition of $NaHCO_{3(s)}$. The layers were separated and the aqueous layer extracted with DCM (3×100 mL). The combined organic extracts were washed with 10% $LiCl_{(aq)}$ (150 mL) then sat. $NaCl_{(aq)}$ (150 mL), dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (5% Et_2O/petrol) afforded the 2-bromoaldehyde as a yellow oil (1.4 g, 14%) which was used immediately.

To a solution of 2-bromoaldehyde (1.4 g, 7.5 mmol) in DMF (15 mL) at 0 ºC was added NaSMe (630 mg, 9.0 mmol) and the resulting solution stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with 10% $LiCl_{(aq)}$ (2×100 mL), then sat. $NaCl_{(aq)}$ (2×100 mL). The organic layer was dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (20% Et_2O/petrol) afforded the aldehyde **83** as an off-white solid (534 mg, 46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (1H, s, C*H*O), 2.49 (2H, m, *H-6*), 2.28 (3H, s, SC*H₃*), 2.23 (2H, m, *H-3*), 1.74-1.65 (2H, m, C*H₂*), 1.63-1.54 (2H, m, C*H₂*); ^{13}C NMR (101 MHz, $CDCl_3$), δ 189.5 (*C*HO), 157.0 (*C-2*), 134.8 (*C-1*), 30.7 (*C*H₂), 23.9 (*C*H₂), 23.0 (*C*H₂), 21.3 (*C*H₂), 14.0 (*C*H₃); LRMS (ESI) *m/z* 211 (85%, $[M+Na+MeOH]^+$), 179 (100%, $[M+Na]^+$), 157 (45%, $[M+H]^+$). Data is in accordance with the literature.[89]

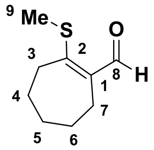
4-(Methylthio)-5,6-dihydro-2H-pyran-3-carbaldehyde (84)



Prepared according to a literature procedure.[151] PBr_3 (8.4 mL, 88 mmol) was added drop-wise to a solution of DMF (7.4 mL, 98 mmol) in $CHCl_3$ (45 mL) at 0 °C and the mixture stirred for 1 h at the same temperature. A solution of dihydro-2*H*-pyran-4(3*H*)-one (3.0 mL, 33 mmol) in $CHCl_3$ (6.0 mL) was added drop-wise at 0 °C resulting in the formation of a yellow precipitate. The reaction mixture was allowed to warm to room temperature and stirred for 20 h resulting in a dark red solution. The reaction mixture was poured onto ice H_2O (150 mL) and neutralised by the addition of $NaHCO_{3(s)}$. The layers were separated and the aqueous layer extracted with DCM (3×50 mL). The combined organic extracts were washed with 10% $LiCl_{(aq)}$ (100 mL) then sat. $NaCl_{(aq)}$ (100 mL), dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (20% Et_2O/petrol) afforded the 2-bromoaldehyde as a yellow oil (2.3 g, 38%), which was used immediately.

To a solution of 2-bromoaldehyde (2.0 g, 10.6 mmol) in DMF (30 mL) at 0 ºC was added NaSMe (890 mg, 12.7 mmol) and the resulting solution stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (75 mL) and washed with 10% $LiCl_{(aq)}$ (2×100 mL) then sat. $NaCl_{(aq)}$ (2×100 mL). The organic layer was dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O/petrol) afforded the aldehyde **84** as an off-white solid (646 mg, 39%); m.p. (DCM) 48-52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (1H, s, C*H*O), 4.33 (2H, t, *J* 2.0, *H-4*), 3.84 (2H, t, *J* 5.5, *H-1*), 2.58 (2H, tt, *J* 5.5, 2.0, *H-2*), 2.36 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.1 (*C*HO), 154.4 (*C-6*), 132.7 (*C-5*), 65.0 (*C*H_2), 64.1 (*C*H_2), 29.6 (*C-1*), 13.3 (*C-8*); LRMS (ESI) *m/z* 213 (65%, $[M+Na+MeOH]^+$), 181 (65%, $[M+Na]^+$); HRMS (ESI) found *m/z* 181.0303 ($[M+Na]^+$), $C_7H_{10}NaO_2S^+$ requires 181.0294; ν_{max} (neat)/cm^{-1} 3004, 2987, 2941, 2904, 2863, 2850, 2827, 2740, 1641 (C=O), 1572.

2-(Methylthio)cyclohept-1-enecarbaldehyde (85)

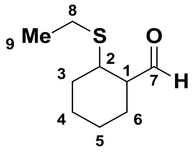


Prepared according to a literature procedure.[151] PBr_3 (13.7 mL, 146 mmol) was added drop-wise to a solution of DMF (12.6 mL, 179 mmol) in $CHCl_3$ (80 mL) at 0 °C and the mixture stirred for 1 h at the same temperature. A solution of cycloheptanone (6.4 mL, 54 mmol) in $CHCl_3$ (10.5 mL) was added drop-wise at 0 °C resulting in the formation of a dark yellow precipitate. The reaction mixture was allowed to warm to room temperature and stirred for 20 h resulting in an orange solution. The reaction mixture was poured onto ice H_2O (300 mL) and neutralised by the addition of $NaHCO_{3(s)}$. The layers were separated and the aqueous layer extracted with DCM (3×100 mL). The combined organic extracts were washed with 10% $LiCl_{(aq)}$ (150 mL) then sat. $NaCl_{(aq)}$ (150 mL), dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (10% Et_2O/petrol) afforded the 2-bromoaldehyde as a yellow oil (2.3 g, 38%), which was used immediately.

To a solution of 2-bromoaldehyde (700 mg, 4.2 mmol) in DMF (15 mL) at 0 ºC was added NaSMe (293 mg, 3.5 mmol) and the resulting solution stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with 10% $LiCl_{(aq)}$ (2×100 mL) then $NaCl_{(aq)}$ (2×100 mL). The organic layer was dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (15% Et_2O/petrol) afforded the aldehyde **85** as yellow oil (412 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (1H, s, C*H*O), 2.75-2.69 (2H, m, C*H₂*), 2.56-2.50 (2H, m, C*H₂*), 2.33 (3H, s, SC*H₃*), 1.83-1.76 (2H, m, C*H₂*), 1.65-1.57 (2H, m, C*H₂*), 1.46-1.39 (2H, m, C*H₂*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0 (*C*HO), 163.0 (*C-2*), 142.5 (*C-1*), 34.7 (*C*H₂), 32.0 (*C*H₂), 26.0

(*C*H$_2$), 25.8 (*C*H$_2$), 25.7 (*C*H$_2$), 15.4 (*C-9*); LRMS (ESI) *m/z* 241 (55%, [M+K+MeOH]$^+$), 209 (50%, [M+K]$^+$), 193 (30%, [M+Na]$^+$); HRMS (ESI) found *m/z* 193.0661 ([M+Na]$^+$), $C_9H_{14}NaOS^+$ requires 193.0658; ν_{max} (neat)/cm^{-1} 2922, 2850, 2729, 1654 (C=O), 1567.

2-(Ethylthio)cyclohexanecarbaldehyde (56)

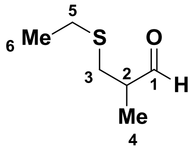


Et_3N (1.5 mL, 11.0 mmol) was added to a solution of EtSH (0.6 mL, 8.9 mmol) and 2-cyclohex-1-enecarbaldehyde (0.5 mL, 4.4 mmol) in DCM (2.5 mL) at 0 ºC and the resulting solution was stirred for 18 h at room temperature. The volatiles were removed *in vacuo* and the crude residue was purified by flash column chromatography (20% Et_2O/petrol) to afford the aldehyde **56** as a colourless oil (467 mg, 62%, 9:1 mixture of *anti:syn* diastereomers).

Anti diastereomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.62 (1H, d, *J* 3.5, C*H*O), 2.79 (1H, dt, *J* 10.5, 4.0, *H-2*), 2.58 (2H, q, *J* 7.5, *H-8*), 2.26 (1H, app. tt, *J* 10.5, 3.5, *H-1*), 2.13-2.04 (1H, m, Alkyl*H*), 1.86-1.64 (4H, m, 4×Alkyl*H*), 1.51-1.32 (3H, m, 3×Alkyl*H*), 1.21 (3H, t, *J* 7.5, *H-9*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 193.0 (*C-7*), 54.5 (*C-1*), 42.4 (*C-2*), 33.1 (*C*H$_2$), 26.9 (*C*H$_2$), 25.4 (*C*H$_2$), 24.3 (*C*H$_2$), 24.1 (*C*H$_2$) 15.4 (*C-9*); LRMS (ESI) m/z 227 (80%, [M+Na+MeOH]$^+$), 211 (50%, [M+K]$^+$), 195 (25%, [M+Na]$^+$). Data is in accordance with the literature.[154]

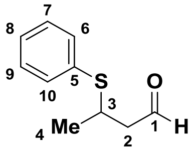
The following signals are consistent with the minor *syn* diastereomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.72 (1H, s, C*H*O), 3.31-3.26 (1H, m, *H-2*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 203.9 (*C-7*), 52.2 (*C-1*), 43.5 (*C-2*), 31.6 (*C*H$_2$), 26.2 (*C*H$_2$), 23.8 (*C*H$_2$), 23.5 (*C*H$_2$), 22.3 (*C*H$_2$), 14.9 (*C-9*).

3-(Ethylthio)-2-methylpropanal (57)



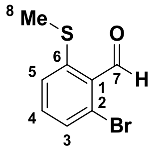
A solution of EtSH (2.7 mL, 36.6 mmol) and 2-methylprop-2-enal (2.0 mL, 29.3 mmol) in DCM (10 mL) was added drop-wise to Et_3N (5.1 mL, 36.6 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 48 h before removal of volatiles *in vacuo* and purification by flash column chromatography to afford the aldehyde **57** as a yellow oil (1.4 g, 44%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, d, *J* 1.5, C*H*O), 2.86-2.82 (1H, m, *H-2*), 2.62-2.50 (4H, m, *H-3* and *H-5*), 1.25 (3H, t, *J* 7.5, *H-6*), 1.20 (3H, d, *J* 7.0, *H-4*); ^{13}C NMR (101 MHz, $CDCl_3$) 203.4 (*C*HO), 46.3 (*C-2*), 32.3 (*C-3*), 26.6 (*C-5*), 14.6 (*C-6*), 13.5 (*C-4*); LRMS (ESI) *m/z* 203 (100%, $[M+K+MeOH]^+$). Data is in accordance with the literature.[62]

3-(Phenylthio)butanal (106)



A solution of (*2E*)-but-2-enal (2.0 mL, 33 mmol) and PhSH (6.8 mL, 66 mmol) was stirred at 30 °C for 1.5 h. Purification by flash column chromatography (10% Et_2O/petrol) afforded the aldehyde **106** as a colourless liquid (1.4 g, 24%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, app. t, *J* 2.0, C*H*O), 7.45-7.41 (2H, dd, *J* 8.0, 1.5, *H-6* and *H-10*), 7.36-7.22 (3H, m, *H-7*, *H-8*, and *H-9*), 3.70 (1H, app. sxt, *J* 7.0, *H-3*), 2.71 (1H, ddd, *J* 17.5, 6.0, 1.5, $H\text{-}2_a$), 2.58 (1H, ddd, *J* 17.5, 7.5, 1.5, $H\text{-}2_b$), 1.36 (3H, d, *J* 7.0, *H-4*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5 (*C-1*), 133.5 (*C-5*), 132.9 (*C-6*, *C-10*), 129.1 (*C-7*, *C-9*), 127.7 (*C-8*), 50.0 (*C-2*), 37.6 (*C-3*), 21.1 (*C-4*); LRMS (ESI) *m/z* 203 (100%, $[M+Na]^+$); Data is in accordance with the literature.[62]

2-Bromo-6-(methylthio)benzaldehyde (170)

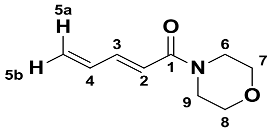


Prepared according to General Procedure **A** using 2-bromo-6-fluorobenzaldehyde (1.0 g, 4.9 mmol), NaSMe (350 mg, 4.9 mmol) and DMF (10 mL) at -40 °C for 18 h. Purification by flash column chromatography (15% Et_2O/petrol afforded the aldehyde **170** as a yellow solid (525 mg, 47%); m.p. (DCM) 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (1H, s, C*H*O) 7.40 (1H, app. d, *J* 7.5, *H-3*), 7.31 (1H, app. t, *J* 8.0, *H-4*), 7.24 (1H, app. d, *J* 8.0, *H-5*), 2.44 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7 (*C-7*), 147.0 (*C-6*), 133.7 (*C-4*), 129.6 (*C-1*), 129.0 (*C-3*), 128.8 (*C-2*), 123.7 (*C-5*), 15.5 (*C-8*); LRMS (ESI) *m/z* 252 (100%,

$[M+Na]^+$); HRMS (ESI) found *m/z* 252.9292 $[M+Na]^+$, $C_8H_7{}^{79}BrNaOS^+$ requires 252.9293; ν_{max} (neat)/cm^{-1} 2922, 2881, 1703, 1681 (C=O), 1567, 1536, 1430, 1408, 1393, 1189, 1083.

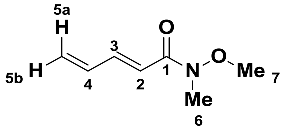
Miscellaneous Starting Materials Synthesis

(*E*)-1-Morpholinopenta-2,4-dien-1-one (32)



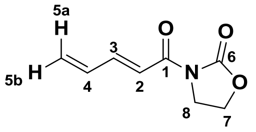
To a stirring solution of 2,4-pentadienoic acid (2.0 g, 20.4 mmol) in THF (60 mL) at 0 °C was added Et_3N (8.5 mL, 61.2 mmol) and ethyl chloroformate (2.1 mL, 22.4 mmol) and the mixture stirred at 0 °C for 0.5 h. Morpholine (2.2 mL, 24.5 mmol) was added drop-wise and the reaction mixture stirred at 0 °C for a further 0.5 h before allowing to warm to room temperature and stirring for 16 h. The crude reaction mixture was partitioned between DCM (100 mL) and H_2O (100 mL) and the organic layer was extracted and then filtered through a pad of Celite® to remove the solid residue. The filtrate was washed with H_2O (2×100 mL) then sat. $NaCl_{(aq)}$ (2×100 mL), dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (80-90% Et_2O/petrol) afforded the morpholine amide **32** as an off-white solid (1.4 g, 41%, >20:1 (*E*):(*Z*)); m.p. (DCM) 83-84°C; ^{1}H NMR (d$_6$-DMSO, 500 MHz, 363 K) 7.09 (1H, dd, *J* 15.0, 4.0, *H-3*), 6.60 (1H, d, *J* 15.0, *H-2*), 6.55 (1H, app. dt, *J* 17.0, 10.0, *H-4*), 5.59 (1H, dd, *J* 17.0, 0.5, *H-5$_a$*), 5.43 (1H, app. d, *J* 10.0, *H-5$_b$*), 3.62-3.58 (4H, m, *H-7*, and *H-8*), 3.57-3.54 (4H, m, *H-6* and *H-9*); ^{13}C NMR (d$_6$-DMSO, 101 MHz) 165.2 (*C-1*), 142.9 (*C-3*), 136.3 (*C-4*), 124.9 (*C-5*), 122.8 (*C-2*), 67.1 (*C-7*), 67.0 (*C-8*), 46.4 (*C-9*), 42.8 (*C-6*); LRMS (ESI) *m/z* 190 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 190.0845 $[M+Na]^+$, $C_9H_{13}NNaO_2^+$ requires 190.0838; ν_{max} (neat)/cm^{-1} 2966, 1860, 1650 (C=O), 1598, 1439, 1411, 1253, 1224, 1112, 1042.

(*E*)-*N*-Methoxy-*N*-methylpenta-2,4-dienamide (33)



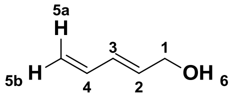
Ethyl chloroformate (1.7 mL, 17.6 mmol) was added drop-wise to a solution of 2,4-pentadienoic acid (2.0 g, 20.4 mmol) and Et_3N (2.8 mL, 20.1 mmol) in THF (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h, upon which *N,O*-dimethylhydroxylamine (3.0 g, 30.1 mmol) and Et_3N (4.3 mL, 30.6 mmol) were added. The reaction mixture was stirred at room temperature for a further 16 h. The crude reaction mixture was partitioned between H_2O (120 mL) and DCM (120 mL) and the phases separated. The aqueous layer was further extracted with DCM (2×100 mL) and the combined organic extracts were washed with sat. $NaCl_{(aq)}$ (2×100 mL), dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo* to afford the Weinreb amide **33** as a brown viscous liquid (1.7 g, 59%, >20:1 (*E*):(*Z*)) which was used without further purification; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (1H, dd, *J* 15.5, 11.0, *H-3*), 6.50 (2H, m, *H-2* and *H-4*), 5.61 (1H, app. d, *J* 17.0, $H\text{-}5_a$), 5.47 (1H, app. d, *J* 10.5, $H\text{-}5_b$), 3.72 (3H, s, OCH_3), 3.42 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8 (*C-1*), 143.5 (*C-3*), 135.2 (*C-4*), 124.9 (*C-5*), 119.7 (*C-2*), 61.9 (*C-7*), 32.6 (*C-6*); LRMS (ESI) *m/z* 164 (100%, $[M+Na]^+$). Data is in accordance with the literature.[165]

(*E*)-3-(Penta-2,4-dienoyl)oxazolidin-2-one (34)



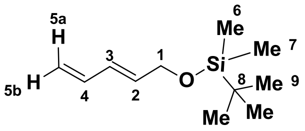
To a solution of 2,4-pentadienoic acid (0.5 g, 5.1 mmol) in DCM (35 mL) at 0 °C was added DMAP (1.0 g, 10.7 mmol) and DCC (1.1 g, 5.1 mmol) and the mixture stirred at 0 °C for 0.5 h. 2-Oxazolidinone (440 mg, 5.1 mmol) was added and the reaction mixture was stirred at room temperature for 20 h. The crude reaction mixture was filtered and the solid residue discarded. Purification by flash column chromatography (*via* Flash Companion; 40 g RediSepColumn; gradient 5-35% EtOAc/cyclohexane) afforded the title compound **34** as an off-white solid (145 mg, 17%, >20:1 (*E*):(*Z*)); m.p. (DCM) 96°C (dec.); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.56-7.29 (2H, m, *H-2*, *H-3*), 6.58 (1H, app. dt, *J* 16.0, 10.0, *H-4*), 5.70 (1H, dd, *J* 17.0, 1.5, $H\text{-}5_a$), 5.59 (1H, dd, *J* 10.0, 1.5, $H\text{-}5_b$), 4.53-4.35 (2H, m, *H-7*), 4.17-4.01 (2H, m, *H-8*); ^{13}C NMR ($CDCl_3$, 101 MHz) 165.4 (*C-1*), 153.8 (*C-6*), 146.6 (*C-3*), 133.3 (*C-4*), 127.2 (*C-2*), 120.9 (*C-5*), 62.2 (*C-7*), 42.1 (*C-8*); LRMS (ESI) *m/z* 220 (100%, $[M+Na+MeOH]^+$), 190 (30%, $[M+Na]^+$); HRMS (ESI) found *m/z* 190.0476 $[M+Na]^+$, $C_8H_9NNaO_3^+$ requires 190.0475; ν_{max} (neat)/cm^{-1} 1767 (C=O), 1682 (C=O), 1626, 1574, 1386, 1219, 1112, 1037.

(*E*)-Penta-2,4-dien-1-ol (35)



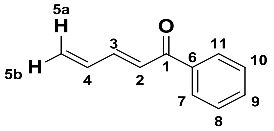
Prepared according to a literature procedure.[160] $LiAlH_4$ (1.3 g, 34.0 mmol) was suspended in Et_2O (60 mL) and cooled to -15 °C. Methyl-2,4-pentadienoate (2.0 mL, 17.2 mmol) was added drop-wise and the mixture stirred at -15 °C for 2 h. The reaction mixture was quenched by the slow addition of ice H_2O (20 mL) and 10% $H_2SO_{4(aq)}$ (40 mL). The phases were separated and the aqueous layer extracted with Et_2O (3×100 mL). The combined organic extracts were washed with sat. $NaCl_{(aq)}$ (2×100 mL), dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo* to afford the alcohol **35** (1.3 g, 89%, >20:1 (*E*):(*Z*)) as a colourless liquid; ^1H NMR ($CDCl_3$, 400 MHz) 6.48-6.19 (2H, m, *H-3* and *H-4*), 5.86 (1H, dt, *J* 14.5, 6.0, *H-2*), 5.24 (1H, dd, *J* 16.0, 2.0, *H-5$_a$*), 5.12 (1H, dd, *J* 10.0, 2.0, *H-5$_b$*), 4.10 (2H, d, *J* 6.0, *H-1*), 1.66 (1H, br. s, *H-6*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 136.2 (*C-4*), 132.5 (*C-3*), 131.8 (*C-2)*, 117.6 (*C-5*), 63.2 (*C-1*); LRMS (ESI) *m/z* 275 (50%, $[3M+Na]^+$), 191 (40%, $[2M+Na]^+$), 107 (100%, $[M+Na]^+$). Data is in accordance with the literature.[168]

(*E*)-*tert*-Butyldimethyl(penta-2,4-dien-1-yloxy)silane (36)



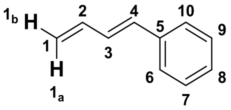
Prepared according to a literature procedure.[72] To a stirring solution of *(E)*-penta-2,4-dien-1-ol (300 mg, 3.6 mmol) and imidazole (0.50 μL, 8.9 mmol) in DMF (10 mL) at room temperature was added a solution of *tert*-butyldimethylsilylchloride (650 mg, 4.3 mmol) in DMF (10 mL) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched by the addition of H_2O (20 mL) and extracted into Et_2O (2×40 mL). The combined organic extracts were washed with sat. $NaCl_{(aq).}$ (2×30 mL), dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (20% Et_2O/petrol) afforded the silyl protected alcohol **36** as a colourless oil (585 mg, 85%, >20:1 (*E*):(*Z*)); ^{1}H NMR ($CDCl_3$, 400 MHz) 6.35 (1H, app. dt, *J* 16.5, 10.0, *H-4*), 6.24 (1H, dd, *J* 15.0, 10.0, *H-3*), 5.79 (1H, dt, *J* 15.0, 5.0, *H-2*), 5.20 (1H, app. d, *J* 16.5, *H-5$_a$*), 5.05 (1H, app. d, 10.0, *H-5$_b$*), 4.24 (2H, d, *J* 5.0, *H-1*), 0.93 (9H, s, *H-9*), 0.08 (6H, s, *H-6* and *H-7*); ^{13}C NMR ($CDCl_3$, 101 MHz) 136.5 (*C-4*), 133.2 (*C-3*), 130.3 (*C-2*), 116.6 (*C-5*), 63.3 (*C-1*), 25.9 (*C-8*), 18.4 (*C-9*), -5.2 (*C-6* and *C-7*); LRMS (ESI) *m/z* 419 (100%, $[2M+Na]^+$). Data in accordance with the literature.[72]

(*E*)-1-Phenylpenta-2,4-dien-1-one (37)



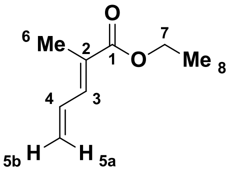
Prepared according to a literature procedure.[12, 68] To a solution of solution of LDA (1.8 mL of 1.8 M solution in THF, 11.2 mmol) at -78 °C was added a solution of acetophenone (1.2 mL, 10.2 mmol) in anhydrous THF (1 mL) and the mixture was stirred at -78 °C for 1 h. Acrolein (0.75 mL, 11.2 mmol) was then added drop-wise, the mixture stirred at -78 °C for 5 min and the reaction mixture quenched by the addition of sat. $NH_4Cl_{(aq)}$ (10 mL). The mixture was then poured onto Et_2O (20 mL), and the organic phase separated, washed with sat. $NaCl_{(aq)}$ (20 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo* to afford the crude aldol product which was used in the next step without further purification. The crude aldol product was redissolved in DCM (10 mL), *p*-TsOH.H_2O (1.0 g, 5.3 mmol) was added and the reaction mixture heated at reflux for 18 h. The reaction mixture was allowed to cool to room temperature and diluted with DCM (20 mL). The organic phase was washed with H_2O (2×50 mL) then sat. $NaCl_{(aq)}$ (2×50 mL), dried over $MgSO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (10% Et_2O/petrol) afforded the ketone **37** (670 mg, 37%, >20:1 (*E*):(*Z*)) as a pale yellow oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (2H, m, *H-7* and *H-11*), 7.60-7.53 (1H, m, *H-9*), 7.51-7.45 (2H, m, *H-8* and *H-10*), 7.40 (1H, dd, *J* 10.0, 14.5, *H-3*), 7.00 (1H, app. d, *J* 15.0, *H-2*), 6.60 (1H, ddd, *J* 17.0, 10.0, 0.5, *H-4*), 5.72 (1H, app. d, *J* 16.0, $H\text{-}5_a$), 5.59 (1H, app. d, *J* 10.0, $H\text{-}5_b$); ^{13}C NMR ($CDCl_3$, 101 MHz) 190.7 (*C-1*), 144.7 (*C-3*), 137.9 (*C-6*), 135.3 (*C-4*), 132.7 (*C-9*), 128.6 (*C-2*), 128.4 (*C-8* and *C-10*), 126.8 (*C-7* and *C-11*), 126.2 (*C-5*); LRMS (ESI) *m/z* 181 (65%, $[M+Na]^+$). Data is in accordance with the literature.[166]

(*E*)-Buta-1,3-dien-1-ylbenzene (38)



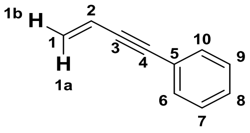
Prepared according to a literature procedure.[74] To a stirring suspension of methyltriphenylphosphonium bromide (2.80 g, 7.8 mmol) in THF (20 mL) at room temperature was added KO^{t}Bu (880 mg, 7.8 mmol) and the mixture stirred at room temperature for 10 min resulting in a yellow suspension. The mixture was cooled to -78 °C and (2*E*)-3-phenylprop-2-enal (0.75 mL, 6.0 mmol) was added drop-wise. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. The reaction mixture was diluted with pentane (150 mL) and filtered to remove triphenylphosphine oxide. This process was repeated 3 times and the solvent removed *in vacuo*. Purification by flash column chromatography (100% pentane) afforded diene **38** as a colourless oil (220 mg, 28%, >20:1 (*E*):(*Z*)); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.42 (2H, app. d. *J* 7.0, *H-6* and *H-10*), 7.33 (2H, app.t, *J* 7.5, *H-7* and *H-9*), 7.26-7.22 (1H, m, *H-8*), 6.80 (1H, dd, *J* 15.5, 10.5, *H-2*), 6.63 (2H, m, *H-3* and *H-4*), 5.37 (1H, app. d, *J* 17.5, $H\text{-}1_a$), 5.20 (1H, app. d, *J* 10.5, $H\text{-}1_b$); ^{13}C NMR (CDCl$_3$, 101 MHz) 137.2 (*C-2*), 137.1 (*C-5*), 132.9 (*C-3*), 129.6 (*C-4*), 128.6 (*C-6* and *C-10*), 127.6 (*C-11* and *C-9*), 126. 4 (*C-8*), 117.4 (*C-1*); LRMS (FI) *m/z* 130.1 [M]$^+$; ν_{max} (neat)/cm^{-1} 2926, 1674, 1627, 1495, 1450, 1126. Data is in accordance with the literature.[74]

(*E*)-Ethyl 2-methylpenta-2,4-dienoate (39)



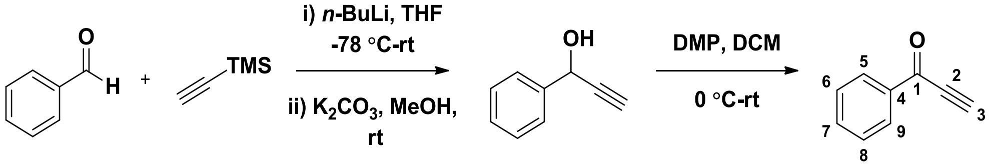
Prepared according to a literature procedure.[169] Acrolein (470 µL, 7.0 mmol) was added drop-wise to a solution of carbethoxyethylidene-(triphenylphosphorane (2.7 g, 7.0 mmol) in DCM (20 mL) and the mixture was stirred at room temperature for 1 h followed by stirring at 40 °C for 2 h. The reaction mixture was allowed to cool to room temperature and concentrated to approximately 2 mL *in vacuo.* The residue was poured into vigorously stirring pentane (150 mL), filtered to remove triphenylphosphine oxide and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (3% Et_2O/petrol) afforded the ester **40** (180 mg, 18%) as a colourless oil. A single isomer was obtained but the double bond geometry was not determined. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.17 (1H, app. dd, *J* 11.5, 0.5, *H-3*), 6.67 (1H, ddd, *J* 16.5, 11.5, 10.0, *H-4*), 5.57 (1H, dd, *J* 16.5, 1.0, *H-5$_a$*), 5.45 (1H, dd, *J* 10.0, 1.0, *H-5$_b$*), 4.22, (2H, q, *J* 7.0, *H-7*), 1.96 (3H, app. s, *H-6*), 1.32 (3H, t, *J* 7.0, *H-8*); ^{13}C NMR ($CDCl_3$, 101 MHz) 168.4 (*C-4*), 138.2 (*C-3*), 132.2 (*C-4*), 128.2 (*C-2*), 124.0 (*C-5*), 60.7 (*C-7*), 14.3 (*C-8*), 12.7 (*C-6*); LRMS (ESI) *m/z* 303 (100%, $[2M +Na]^+$). Data is in accordance with the literature.[169]

But-3-en-1-yn-1-ylbenzene (42)



Prepared according to a literature procedure.[170] CuI (34 mg, 0.09 mmol) and $Pd(PPh_3)_4$ (105 mg, 0.02 mml) were dissolved in Et_2NH (2.3 mL) at 10 °C under an argon atmosphere. Phenylacetylene (0.5 mL, 4.6 mmol) and vinyl bromide (1.0 M in THF, 5.9 mL, 5.9 mmol) were added drop-wise and the resulting suspension was stirred at room temperature for 16 h. The reaction mixture was then poured onto ice H_2O (50 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were then washed with 2.0 M $HCl_{(aq)}$ (2×50 mL), dried over $Na_2SO_{4(s)}$, filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography afforded the enyne **42** (480 mg, 82%) as a colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.49-7.43 (2H, m, *H-6* and *H-10*), 7.35-7.30 (3H, m, *H-7*, *H-8* and *H-9*), 6.04 (1H, dd, *J* 17.5, 11.0, *H-2*), 5.75 (1H, dd, *J* 17.5, 2.0, $H\text{-}1_a$), 5.55 (1H, dd, *J* 11.0, 2.0, $H\text{-}1_b$); ^{13}C NMR ($CDCl_3$, 101 MHz) 131.6 (*C-6* and *C-10*) 128.3 (*C-7* and *C-9*), 128.2 (*C-8*), 126.9 (*C-1*), 123.1 (*C-5*), 117.2 (*C-2*), 90.0 (*C-4*), 88.1 (*C-3*); LRMS (FI) *m/z* 126.1 $[M]^+$; ν_{max} (neat)/cm^{-1} 3081, 3056, 3010, 2219 (C≡C), 1665, 1489, 1443, 1411, 1290, 1262. Data is in accordance with the literature.[170]

1-Phenylprop-2-yn-1-one (90)

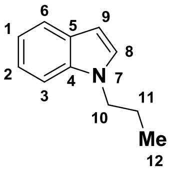


To a solution of trimethysilylacetylene (1.5 mL, 10.4 mmol) in THF (20 mL) at -78 °C was added drop-wise *n*-BuLi (4.1 mL of a 2.4 M solution in hexanes, 9.9 mmol), and the mixture stirred at -78 °C for 1 h. Benzaldehyde (0.95 mL, 9.4 mmol) was added slowly and the reaction mixture stirred for a further 0.5 h at -78 °C before allowing to warm to room temperature over 0.5 h. The reaction mixture was quenched with H_2O (40 mL) and extracted with Et_2O (2×50 mL). Combined organic extracts were washed with sat. $NaCl_{(aq)}$ (100mL), dried over $MgSO_{4(s)}$, filtered and concentrated *in vacuo*. The crude reside was re-dissolved in MeOH (50 mL), K_2CO_3 (6.5 g, 47.2 mmol) was added and the reaction mixture stirred at room temperature for 1.5 h. The reaction mixture was filtered through a pad of Celite$^{®}$ using DCM as eluent (100 mL). The filtrate was washed with sat. $NaCl_{(aq)}$ (2×100 mL), dried over $MgSO_{4(s)}$, filtered and filtrate concentrated *in vacuo*. Purification by flash column chromatography (20% Et_2O/petrol) afforded alcohol as a colourless oil (1.0 g, 82%), which was used immediately.

To a suspension of DMP (1.9 g, 4.5 mmol) at 0 °C was added slowly a solution of alcohol (0.5 g, 3.8 mmol) and the reaction mixture was allowed to warm to room temperature for 2 h. The reaction mixture was quenched with sat. $NaHCO_{3(aq)}$ (50 mL) followed by sat. $Na_2S_2O_{3(aq)}$ and the phases separated. The aqueous layer was further extracted with DCM (3×50 mL) and the combined organic extracts were washed with sat. $NaCl_{(aq)}$ (150 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (15% Et_2O/petrol) afforded the title compound as a pale yellow solid (306 mg, 62%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20-8.11 (2H, m, 2×Ar*H*), 7.68-7.61

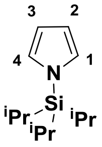
(1H, m, Ar*H*), 7.55-7.48 (2H, m, 2×Ar*H*) 3.45 (1H, s, C≡C*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4 (*C*=O), 136.1 (Ar*C*), 134.5 (Ar*C*H), 129.7 (2×Ar*C*H), 128.7 (2×Ar*C*H), 80.7 (C≡*C*H), 80.3 (*C*≡CH); LRMS (ESI) *m/z* 153.2 (100%, $[M+Na]^+$). Data is in accordance with the literature.[164]

1-Propyl-1*H*-indole (130)



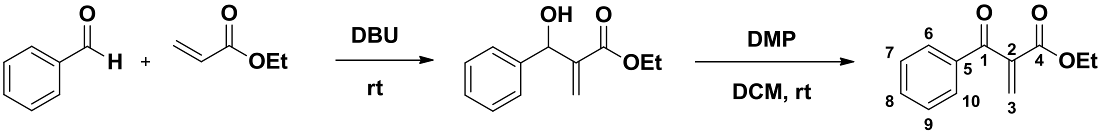
To a suspension of KOH (1.2 g, 21.3 mmol) in DMF (10 mL) was added indole (0.5 g, 4.3 mmol) and the mixture stirred for 1 h at room temperature. 1-Iodopropane (0.6 mL, 6.0 mmol) was added and the reaction mixture heated to 50 °C for 18 h. The reaction mixture was allowed to cool to room temperature, poured onto H_2O (50 mL) and extracted with DCM (2×50 mL). The combined organic extracts were washed 10% $LiCl_{(aq)}$ (100 mL) then sat. $NaCl_{(aq)}$ (100 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification by flash column chromatography afforded indole **130** as a yellow oil (596 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, app. d, *J* 8.0, Ar*H*), 7.41 (1H, app. d, *J* 8.5, Ar*H*), 7.30-7.23 (1H, m, Ar*H*), 7.19-7.13 (2H, m, 2×Ar*H*), 6.55 (1H, dd, *J* 3.0, 0.5, *H-9*), 4.13 (2H, t, *J* 7.0, *H-10*), 1.92 (2H, app. sxt, *J* 7.5, *H-11*), 0.99 (3H, t, *J* 7.5, *H-12*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (*C-4*), 128.6 (*C-5*), 127.9 (*C-8*), 121.3 (*C-1*), 120.9 (*C-6*), 119.2 (*C-2*), 109.4 (*C-3*), 100.8 (*C-9*), 48.1 (*C-10*), 23.6 (*C-11*) 11.6 (*C-12*); LRMS (ESI) *m/z* 357 (100%, $[2M+K]^+$), 341 (80%, $[2M+Na]^+$). Data is in accordance with the literature.[163]

1-(Triisopropylsilyl)-1*H*-pyrrole (134)



Prepared according to a literature procedure.[155] To a solution of pyrrole (1.0 mL, 14.4 mmol) in THF (10 mL) at -78 °C was added drop-wise *n*-BuLi (2.6 M in hexanes, 6.0 mL, 5.9 mmol). After stirring at room temperature for 10 min, TIPS-Cl (3.1 mL, 14.4 mL) was added drop-wise and the reaction mixture stirred at room temperature for 2 h. Volatiles were removed *in vacuo*, and the crude residue partitioned between H_2O (50 mL) and Et_2O (50 mL). The organic layer was extracted and the aqueous layer washed with Et_2O (2×50 mL). The combined organic extracts were washed with sat. $NaCl_{(aq)}$ (150 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification by flash column chromatography afforded silyl protected pyrrole **134** as a yellow oil (3.0 g, 97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (2H, app. t, *J* 2.0, *H-1* and *H-4*), 6.33 (2H, app. t, *J* 2.0), 1.47 (3H, sept, *J* 7.5, C*H*(CH_3)$_2$), 1.11 (18H, d, *J* 7.5, CH(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 124.0 (*C-1* and *C-4*) 110.0 (*C-2* and *C-3*), 17.8 (CH(*C*H$_3$)$_2$), 11.7 (*C*H(CH_3)$_2$); LRMS (ESI) *m/z* 294 (100%, $[M+K+MeOH]^+$), 278 (15%, $[M+Na+MeOH]^+$). Data is in accordance with the literature.[162]

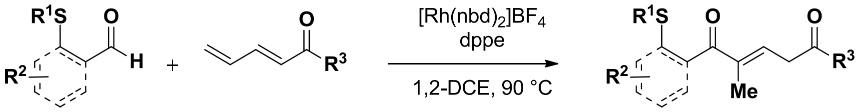
Ethyl 2-benzoylacrylate (173)



Prepared according to a literature procedure.[171] A mixture of ethyl acrylate (1.6 mL, 15.0 mmol), benzaldehyde (1.5 mL, 15.0 mmol) and DBU (2.2 mL, 15.0 mmol) were stirred under N_2 at room temperature for 18 h. The reaction mixture was diluted with Et_2O (30 mL), washed with 3N HCl (2×40 mL) and H_2O (50 mL). The organic phase was extracted, dried over $MgSO_4$, filtered and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O/petrol) afforded the α-hydroxy-enone as a colourless oil (912 mg, 30%) which was used immediately. To a stirring solution of α-hydroxy-enone (200 mg, 0.98 mmol) in DCM (20 mL) at room temperature was added DMP (623 mg, 1.47 mmol) and the reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (30% Et_2O/petrol) afforded enone **173** as a colourless oil (178 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, app. d, *J* 7.5 2×Ar*H*), 7.64-7.55 (1H, m, Ar*H*), 7.53-7.42) (2H, m, 2×Ar*H*), 6.70 (1H, app. s, alkenyl C*H*), 6.07 (1H, app. s, alkenyl C*H*), 4.23 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 1.20 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2 (*C-1*), 164.4 (*C-4*), 141.4 (*C*), 136.3 (*C*), 133.6 (*C*), 131.4 (Ar*C*H), 129.4 (2×Ar*C*H), 128.8 (2×Ar*C*H), 61.5 ($CO_2CH_2CH_3$), 13.9 ($CO_2CH_2CH_3$); LRMS (ESI) *m/z* 259 (100%, $[M+Na+MeOH]^+$). Data is in accordance with the literature.[172]

Branched-Selective Hydroacylation of Dienes

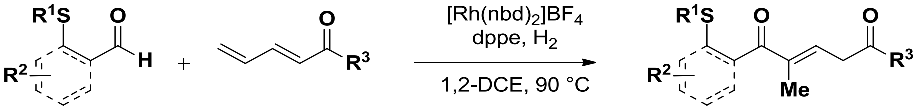
General Procedure B - Branched-Selective Hydroacylation of Dienes



$[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol) and dppe (12 mg, 0.03 mmol) were dissolved in 1,2-DCE (2 mL) and stirred vigorously at room temperature for 5 min. Aldehyde (0.30 mmol) and diene (0.45 mmol) were added as a solution in 1,2-DCE (1 mL) and the reaction mixture was stirred at 90 °C in a Radleys GreenHouse Plus Parallel Synthesiser^{TM} for 18 h. The reaction mixture was diluted with Et_2O, filtered through a pad of Celite$^{®}$ using Et_2O as eluent and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography.

A sample of the crude residue was analysed by ^1H NMR spectroscopy in $CDCl_3$ to determine the branched: linear (b:l) regioselectivity of the reaction. The data for the following compounds is for the branched regioisomer unless otherwise stated. The linear isomer was either not observed or was isolated in insufficient quantities for full analysis by NMR spectroscopy unless otherwise stated.

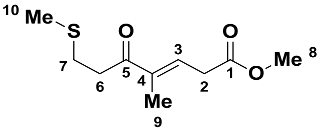
General procedure C - Branched-Selective Hydroacylation of Dienes (Hydrogenation of Catalyst)



$[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol) and dppe (12 mg, 0.03 mmol) were dissolved in 1,2-DCE (2 mL) and stirred vigorously at room temperature for 5 min. $H_{2(g)}$ was bubbled through the solution for 2-3 min. The solution was degassed and purged with $N_{2(g)}$. The aldehyde (0.30 mmol) and diene (0.45 mmol) were added as a solution in 1,2-DCE (1 mL) and the reaction mixture was stirred at 90 °C for 18 h. The reaction mixture was diluted with Et_2O, filtered through a pad of Celite® using Et_2O and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography.

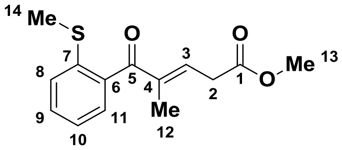
A sample of the crude residue was analysed by ^1H NMR spectroscopy in $CDCl_3$ to determine the branched: linear (b:l) regioselectivity of the reaction. The data for the following compounds is for the branched regioisomer unless otherwise stated. The linear isomer was either not observed or was isolated in insufficient quantities for full analysis by NMR spectroscopy unless otherwise stated.

(*E*)-Methyl 4-methyl-7-(methylthio)-5-oxohept-3-enoate (31b)



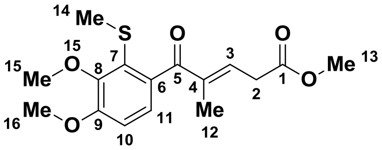
Prepared according to General Procedure **B** using 3-(methylthio)propanal (30 μL, 0.30 mmol) and methyl-2,4-pentadienoate (52 μL, 0.45 mmol). Purification of the crude residue by flash column chromatography (20% Et_2O/petrol) afforded the branched regioisomer **31b** as colourless oil (21 mg, 32%, >20:1 b:l); ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (1H, tq, *J* 7.0, 1.5, *H-3*), 3.68 (3H, s, OCH_3), 3.24 (2H, d, *J* 7.0, *H-2*), 2.96 (2H, t, *J* 7.0, *H-7*), 2.71 (2H, t, *J* 7.0, *H-6*), 2.06 (3H, s, SCH_3), 1.73 (3H, d, *J* 1.5, *H-9*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.2 (*C-5*), 162.0 (*C-1*), 139.7 (*C-3*), 133.6 (*C-4*), 52.6 (*C-6*), 37.7 (*C-2*), 34.6 (*C-7*), 29.2 (*C-8*), 16.2 (*C-10*), 12.1 (*C-9*); LRMS (ESI) *m/z* 255 (100%, $[M+K]^+$). Data is in accordance with the literature.[51]

(*E*)-Methyl 4-methyl-5-(2-(methylthio)phenyl)-5-oxopent-3-enoate (45b)



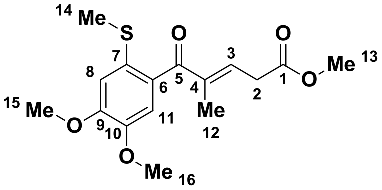
Prepared according to General Procedure **B** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and methyl-2,4-pentadienoate (52 μL, 0.45 mmol). Purification by flash column chromatography (30% Et_2O/petrol) afforded the branched regiosiomer **45b** as a pale yellow oil (57 mg, 72%, >20:1 b:l); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.32 (2H, m, 2×Ar*H*), 7.30-7.23 (1H, m, Ar*H*), 7.22-7.16 (1H, m, Ar*H*), 6.35 (1H, app. td, *J* 7.0, 1.5, *H-3*), 3.70 (3H, s, OC*H₃*), 3.30 (2H, d, *J* 7.0, *H-2*), 2.40 (3H, s, SC*H₃*), 1.92 (3H, app. s, *H-12*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (*C-5*), 170.6 (*C-1*), 139.9, 139.0, 137.9, 137.5 (*C-3*), 130.4 (Ar*C*H), 128.6 (Ar*C*H), 127.7 (Ar*C*H), 124.8 (Ar*C*H), 52.1 (*C-13*), 34.3 (*C-2*), 17.1 (*C-14*), 11.4 (*C-12*); LRMS (ESI) *m/z* 319 (5%, $[M+Na+MeOH]^+$), 303 (100%, $[M+K]^+$), 287 (95%, $[M+Na]^+$), 265 (10%, $[M+H]^+$); HRMS (ESI) found *m/z* 287.0713 $[M+Na]^+$, $C_{14}H_{16}NaO_3S^+$ requires 287.0712; ν_{max} (neat)/cm^{-1} 3059, 2998, 2935, 1735 (C=O ester), 1645 (C=O ketone), 1586, 1435, 1273, 1246, 1201, 1174, 1067, 1010.

(*E*)-Methyl 5-(3,4-dimethoxy-2-(methylthio)phenyl)-4-methyl-5-oxopent-3-enoate (58)



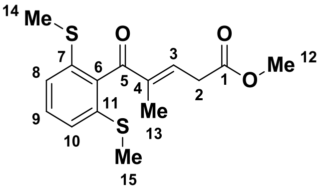
Prepared according to General Procedure **B** using 3,4-dimethoxy-2-(methylthio)benzaldehyde (64 mg, 0.30 mmol) and methyl-2,4-pentadienoate (52 μL, 0.45 mmol). Purification by flash column chromatography (40% Et_2O/petrol) afforded the branched regioisomer **58** as a pale yellow oil (67 mg, 69%, >20:1 b:l); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (1H, d, *J* 8.5, *H-11*), 6.88 (1H, d, *J* 8.5, *H-10*), 6.25 (1H, app. td, *J* 7.0, 1.0, *H-3*), 3.90 (3H, s, ArOC*H*$_3$), 3.89 (3H, s, ArOC*H*$_3$), 3.66 (3H, s, OC*H*$_3$), 3.27 (2H, d, *J* 7.0, *H-2*), 2.32 (3H, s, SC*H*$_3$), 1.97 (3H, app. s, *H-12*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3 (*C-5*), 170.7 (*C-1*), 154.0 (Ar*C*OCH$_3$), 150.3 (Ar*C*OCH$_3$), 141.2 (*C-3*), 136.9, 136.6, 128.8, 123.3 (*C-11*), 111.7 (*C-10*), 60.5 (O*C*H$_3$), 55.9 (O*C*H$_3$), 52.1 (*C-13*), 34.3 (*C-2*), 19.0 (*C-14*), 11.8 (*C-12*); LRMS (ESI) *m/z* 379 (10%, $[M+Na+MeOH]^+$), 363 (50%, $[M+K]^+$), 347 (100%, $[M+Na]^+$), 325 (50%, $[M+H]^+$); HRMS (ESI) found *m/z* 347.0915 $[M+Na]^+$, $C_{16}H_{20}NaO_5S^+$ requires 347.0924; ν_{max} (neat)/cm^{-1} 2951, 2844, 1735 (C=O ester), 1659 (C=O ketone), 1581, 1481, 1438, 1393, 1271, 1043, 1007.

(*E*)-Methyl 5-(4,5-dimethoxy-2-(methylthio)phenyl)-4-methyl-5-oxopent-3-enoate (59)



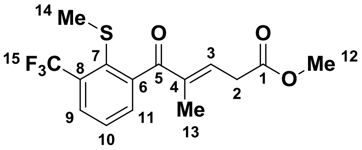
Prepared according to General Procedure **B** using 4,5-dimethoxy-2-(methylthio)benzaldehyde (64 mg, 0.30 mmol) and methyl-2,4-pentadienoate (52 μL, 0.45 mmol). Purification by flash column chromatography (50% Et_2O/petrol) afforded the branched regioisomer **59** as a pale yellow oil (60 mg, 62%, >20:1 b:l); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (1H, s, *H-11*), 6.88 (1H, s, *H-8*), 6.30 (1H, app. td, *J* 7.0, 1.5, *H-3*), 3.93 (3H, s, ArOC*H₃*), 3.85 (3H, s, ArOC*H₃*), 3.67 (3H, s, OC*H₃*), 3.28 (2H, d, *J* 7.0, *H-2*), 2.37 (3H, s, SC*H₃*), 1.96 (3H, app. s, *H-12*); ^{13}C NMR (101 MHz, $CDCl_3$) 0.7 (Ar*C*OCH₃), 147.1 (Ar*C*OCH₃), 140.2, 136.4 (C-*3*), 132.7, 129.5, 112.9 (*C-11*), 112.2 (*C-8*), 56.0 (2×ArO*C*H₃), 52.1 (*C-13*), 34.2 (*C-2*), 18.9 (*C-14*), 12.2 (*C-12*); LRMS (ESI) *m/z* 379 (25%, $[M+Na+MeOH]^+$), 363 (100%, $[M+K]^+$); HRMS (ESI) found *m/z* 347.0911 $[M+Na]^+$, $C_{16}H_{20}NaO_5S^+$ requires 347.0924; ν_{max} (neat)/cm^{-1} 2952, 2845, 1732 (C=O ester), 1643 (C=O ketone), 1591, 1557, 1504, 1462, 1438, 1335, 1269, 1208, 1174, 1029.

(*E*)-Methyl 5-(2,6-bis(methylthio)phenyl)-4-methyl-5-oxopent-3-enoate (60)



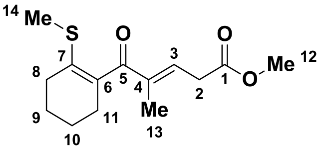
Prepared according to General Procedure **B** using 2,6-bis(methylthio)benzaldehyde (59 mg, 0.30 mmol) and methyl-2,4-pentadienoate (52 µL, 0.45 mmol). Purification by flash column chromatography (40% Et_2O/petrol) afforded the branched regioisomer **60** as a yellow amorphous solid (44 mg, 47%, 11:1 b:l); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (1H, m, *H-9*), 7.22 (2H, app. d, *J* 7.5, *H-8* and *H-10*), 6.40- 6.32 (1H, app. td, *J* 7.0, 1.5, *H-3*), 3.67 (3H, s, OCH_3), 3.31 (2H, d, *J* 7.0, *H-2*), 2.40 (6H, s, *2*×SCH_3), 1.99 (3H, app. s, *H-13*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 197.8 (*C-1*), 170.6 (*C-5*), 141.4, 140.0 (*C-7* and *C-11*), 137.4 (*C-3*), 135.8, 129.6 (*C-9*), 126.7 (*C-8* and *C-10*), 52.1 (*C-12*), 34.4 (*C-2*), 18.0 (*C-14* and *C-15*), 11.1 (*C-13*); LRMS (ESI) *m/z* 349 (100%, $[M+K]^+$), 333 (45%, $[M+Na]^+$), 311 (10%, $[M+H]^+$); HRMS (ESI) found *m/z* 333.0581 $[M+Na]^+$, $C_{15}H_{18}NaO_3S_2^+$ requires 333.0590; ν_{max} (neat)/cm^{-1} 2952, 1733 (C=O ester), 1659 (C=O ketone), 1557, 1432, 1244, 1198, 1172, 1025, 1007.

(*E*)-Methyl4-methyl-5-(2-(methylthio)-3-(trifluoromethyl)phenyl)-5-oxopent-3-enoate (61)



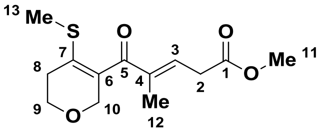
Prepared according to General Procedure **B** using 2-(methylthio)-3-(trifluoromethyl)benzaldehyde (66 mg, 0.30 mmol) and methyl-2,4-pentadienoate (52 µL, 0.45 mmol). Purification of the crude mixture (5:1 b:l) by flash column chromatography (30% Et_2O/petrol) afforded the branched regioisomer **61** as a pale yellow oil (28 mg, 28%, 14:1 b:l); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, app. d, *J* 8.0, *H-9*), 7.52 (1H, app. t, *J* 8.0, *H-10*), 7.39 (1H, app. d, *J* 7.5, *H-11*), 6.22 (1H, app. t, *J* 7.0, *H-3*), 3.69 (3H, s, OCH_3), 3.30 (2H, d, *J* 7.0, *H-2*), 2.30 (3H, s, SCH_3), 2.01 (3H, app. s, *H-13*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3 (*C-5*), 170.4 (*C-1*), 149.3, 140.6, 138.6 (*C-3*), 135.3 (q, J_{C-F} 29.5, *C-8*), 131.7, 130.4 (*C-11*), 128.8 (*C-10*), 127.6 (q, J_{C-F} 5.5, *C-9*), 123.4 (q, J_{C-F} 270.0, *C-15*), 52.2 (*C-12*), 34.3 (*C-2*), 22.2 (*C-14*), 11.5 (*C-13*); ^{19}F NMR (376 MHz, $CDCl_3$) -59.8 (3F, s); LRMS (ESI) *m/z* 355 (100%, $[M+Na]^+$), 333 (30%, $[M+H]^+$); HRMS (ESI) found *m/z* 355.0574 $[M+Na]^+$, $C_{15}H_{15}F_3NaO_3S^+$ requires 355.0586; ν_{max} (neat)/cm^{-1} 2929, 2848, 1742 (C=O) ester, 1662 (C=O ketone), 1437, 1319, 1279, 1130.

(*E*)-Methyl 4-methyl-5-(2-(methylthio)cyclohex-1-en-1-yl)-5-oxopent-3-enoate (62)



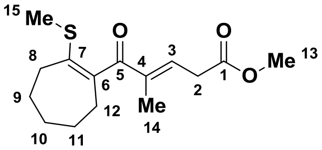
Prepared according to General Procedure **B** using 2-(methylthio)cyclohex-1-enecarbaldehyde (47 mg, 0.30 mmol) and methyl-2,4-pentadienoate (52 μL, 0.45 mmol). Purification of the crude mixture (9:1 b:l) by flash column chromatography (40% Et_2O/petrol) afforded branched regioisomer **62** as colourless oil (68 mg, 85%, >20:1 b:l); ^1H NMR (400 MHz, $CDCl_3$) δ 6.69-6.63 (1H, app. td, *J* 7.0, 1.5, *H-3*), 3.71 (3H, s, OCH_3), 3.30 (2H, d, *J* 7.0, *H-2*), 2.35-2.29 (2H, m, CH_2), 2.25-2.19 (2H, m, CH_2), 2.11 (3H, s, SCH_3), 1.84 (3H, app. s, *C-13*), 1.80-1.72 (2H, m, CH_2), 1.72-1.64 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.8 (*C-5*), 170.9 (*C-1*), 139.0, 138.9, 135.1 (*C-3*), 131.6, 52.1 (*C-12*), 34.2 (*C-2*), 29.0 (2×CH_2), 23.1 (CH_2), 21.7 (CH_2), 17.9 (*C-14*), 11.2 (*C-13*); LRMS (ESI) *m/z* 307 (100%, $[M+K]^+$), 291 (50%, $[M+Na]^+$); HRMS (ESI) found *m/z* 291.1013 $[M+Na]^+$, $C_{14}H_{20}NaO_3S^+$ requires 291.1025; ν_{max} (neat)/cm^{-1} 2937, 1737 (C=O ester), 1650 (C=O ketone), 1436, 1271, 1200.

(*E*)-Methyl 4-methyl-5-(4-(methylthio)-5,6-dihydro-2H-pyran-3-yl)-5-oxopent-3-enoate (63)



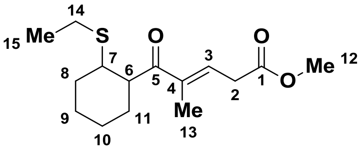
Prepared according to General Procedure **B** using 4-(methylthio)-5,6-dihydro-2H-pyran-3-carbaldehyde (47 mg, 0.30 mmol) and methyl-2,4-pentadienoate (52 µL, 0.45 mmol). Purification by flash column chromatography (60% Et_2O/petrol) afforded the branched regioisomer **63** as colourless oil (56 mg, 69%, 15:1 b:l); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, app. td, *J* 7.0, 1.5, *H-3*), 4.25 (2H, br. s, *H-10*), 3.89 (2H, t, *J* 5.5, *H-9*), 3.72 (3H, s, OC*H$_3$*), 3.30 (2H, d, *J* 7.0, *H-2*), 2.46-2.39 (2H, m, *H-8*), 2.17 (3H, s, SC*H$_3$*), 1.84 (3H, app. s, *H-12*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 197.7 (*C-5*), 170.7 (*C-1*), 148.6, 139.2, 135.7 (*C-3*), 132.5, 67.4 (*C-10*), 64.7 (*C-9*), 52.2 (*C-11*), 34.2 (*C-2*), 28.4 (*C-8*), 14.3 (*C-13*), 11.3 (*C-12*); LRMS (ESI) *m/z* 309 (100%, $[M+K]^+$), 293 (50%, $[M+Na]^+$); HRMS (ESI) found *m/z* 293.0819 $[M+Na]^+$, $C_{13}H_{18}NaO_4S^+$ requires 293.0818; ν_{max} (neat)/cm^{-1} 2954, 2926, 2857, 1737 (C=O ester), 1642 (C=O ketone), 1437, 1383, 1260, 1173.

(*E*)-Methyl 4-methyl-5-(2-(methylthio)cyclohept-1-en-1-yl)-5-oxopent-3-enoate (64)



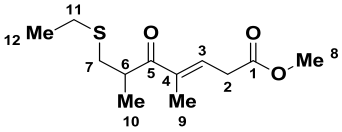
Prepared according to General Procedure **B** using 2-(methylthio)cyclohept-1-enecarbaldehyde (51 mg, 0.30 mmol) and methyl-2,4-pentadienoate (52 μL, 0.45 mmol). Purification of the crude mixture (4:1 b:l) by flash column chromatography (25% Et_2O/petrol) afforded the branched regioisomer **64** as colourless oil (35 mg, 41%, >20:1 b:l). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, app. t, *J* 7.0, *H-3*), 3.72 (3H, s, OC*H*$_3$), 3.31 (2H, d, *J* 7.0, *H-2*), 2.58-2.53 (2H, m, C*H*$_2$), 2.32-2.27 (2H, m, C*H*$_2$), 2.10 (3H, s, SC*H*$_3$), 1.85 (3H, app. s, *H-14*), 1.80 (2H, app. dt, *J* 11.0, 5.5, *H-10*), 1.64 (4H, app. dt, *J* 11.0, 5.5, *H-9* and *H-11*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 200.7 (*C-5*), 171.0 (*C-1*), 144.4, 139.4, 137.8 (*C-3*), 134.2, 52.1 (*C-13*), 34.8 (*C-2*), 34.1 (*C*H$_2$), 32.1 (*C*H$_2$), 32.0 (*C*H$_2$), 26.4 (*C*H$_2$), 26.2 (*C*H$_2$), 15.7 (*C-15*), 11.4 (*C-14*); LRMS (ESI) *m/z* 321 (75%, $[M+K]^+$), 305 (100%, $[M+Na]^+$), 283 (10%, $[M+H]^+$); HRMS (ESI) found *m/z* 305.1181 $[M+Na]^+$, $C_{15}H_{22}NaO_3S^+$ requires 305.1182; ν_{max} (neat)/cm^{-1} 2929, 1724 (C=O ester), 1653 (C=O ketone), 1436, 1261, 1170, 1033.

(*E*)-Methyl 5-(2-(ethylthio)cyclohexyl)-4-methyl-5-oxopent-3-enoate (65)



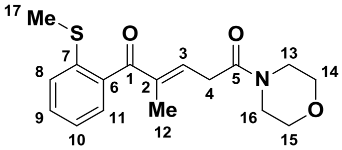
Prepared according to General Procedure **B** using 2-(ethylthio)cyclohexanecarbaldehyde (52 mg, 0.30 mmol, 9:1 *anti:syn*) and methyl-2,4-pentadienoate (52 μL, 0.45 mmol). Purification by flash column chromatography (10% Et$_2$O/petrol) afforded a colourless oil containing an inseparable mixture of regioisomers (50 mg, 59%, 3:1 b:l, >20:1 *anti*:*syn*). **Branched regioisomer:** ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.83-6.75 (1H, m, *H-3*), 3.73 (3H, s, *H-12*), 3.30 (2H, d, *J* 6.5, *H-2*), 3.17 (1H, td, 11.0, 3.0, *H-7*), 2.85 (1H, td, *J* 11.0, 3.0, *H-6*), 2.48 (2H, qd, *J* 7.5, 2.0, *H-14*), 2.21-2.12 (1H, m, Alkyl*H*), 1.81 (3H, app. s, *H*-13), 1.78-1.66 (2H, m, 2×Alkyl*H*), 1.48-1.22 (5H, m, 5×Alkyl*H*), 1.16 (3H, t, *J* 7.5, *H-15*); ^{13}C NMR (CDCl$_3$, 101 MHz) δ 203.9 (*C-5*), 171.0 (*C-1*), 139.7 (*C-4*), 132.3 (*C-3*), 52.1 (*C-12*), 49.6 (*C-11*), 44.7 (*C-6*), 34.4 (*C*H$_2$), 34.2 (*C-2*), 31.6 (*C*H$_2$), 26.2 (*C*H$_2$), 28.3 (*C*H$_2$), 25.0 (*C-14*), 14.9 (*C-15*), 12.1 (*C-13*); LRMS (ESI) *m/z* 323 (100%, [M+K]$^+$), 307 (35%, [M+Na]$^+$), 285 (10%, [M+H]$^+$); HRMS (ESI) found *m/z* 307.1325 [M+Na]$^+$, C$_{15}$H$_{24}$NaO$_3$S$^+$ requires 307.1338; ν_{max} (neat)/cm^{-1} 2931, 2856, 1741 (C=O ester), 1666 (C=O ketone), 1448, 1262, 1170.

(*E*)-Methyl 7-(ethylthio)-4,6-dimethyl-5-oxohept-3-enoate (66)



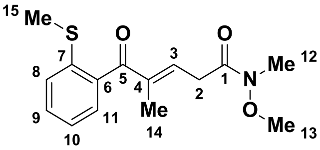
Prepared according to General Procedure **B** using 3-(ethylthio)-2-methylpropanal (40 mg, 0.30 mmol) and methyl-2,4-pentadienoate (52 μL, 0.45 mmol). Purification of the crude mixture (1:1.5 b:l) by flash column chromatography (30% Et_2O/petrol) afforded the branched regioisomer **66** as colourless oil (33 mg, 45%, >20:1 b:l); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (1H, app. t, *J* 6.5, *H-3*), 3.73 (3H, s, OCH_3), 3.74 (1H, app. sxt, *J* 7.0, *H*-6), 3.31 (2H, d, *J* 6.5, *H-2*), 2.85 (1H, dd, *J* 13.0, 7.0, $H\text{-}7_a$), 2.57-2.44 (2H, q, *J* 7.5, *H-11*, overlapping 1H, m, $H\text{-}7_b$), 1.80 (3H, app. s, *H-9*), 1.23 (3H, t, *J* 7.5, *H-12*), 1.17 (3H, d, *J* 7.0, *H-10*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 200.0 (*C-5*), 170.9 (*C-1*), 138.8 (*C-4*), 132.9 (*C-3*), 52.2 (*C-8*), 39.9 (*C-6*), 35.3 (*C-7*), 34.2 (*C-2*), 26.8 (*C-11*), 18.2 (*C-10*), 14.7 (*C-12*), 12.0 (*C-9*); LRMS (ESI) *m/z* 283 (100%, $[M+K]^+$), 267 (45%, $[M+Na]^+$), 245 (10%, $[M+H]^+$); HRMS (ESI) found *m/z* 267.1017 $[M+Na]^+$, $C_{12}H_{20}NaO_3S^+$ requires 267.1025; ν_{max} (neat)/cm^{-1} 2973, 2932, 2876, 1739 (C=O ester), 1668 (C=O ketone), 1455, 1438, 1201, 1173.

(*E*)-2-Methyl-1-(2-(methylthio)phenyl)-5-morpholinopent-2-ene-1,5-dione (67)



Prepared according to General Procedure **C** using 2-methylthiobenzaldehyde (39 μL, 0.30 mmol) and (*E*)-1-morpholinopenta-2,4-dien-1-one (75 mg, 0.45 mmol). Purification by flash column chromatography (40-60% EtOAc/petrol) afforded the branched regioisomer **67** as a pale yellow amorphous solid (38 mg, 40%, >20:1 b:l); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.31 (2H, m, *H-11* and *H-9*), 7.27 (1H, dd, *J* 5.5, 1.5, *H-8*), 7.23-7.13 (1H, m, *H-10*), 6.49-6.37 (1H, m, *H-3*), 3.66-3.61 (4H, m, *H-14* and *H-15*), 3.61-3.56 (2H, m, OCH_2CH_2N), 3.46-3.40 (2H, m, OCH_2CH_2N), 3.31 (2H, d, *J* 7.0, *H-4*), 2.42 (3H, s, SCH_3), 1.99 (3H, app. s, *H-12*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 198.5 (*C-1*), 168.1 (*C-5*), 139.5, 139.4, 139.2 (*C-3*), 137.2, 130.4 (*C-9*), 128.4 (*C-8*), 127.7 (*C-11*), 124.9 (*C-10*), 66.7 (OCH_2CH_2N), 66.5 (OCH_2CH_2N), 46.1 (OCH_2CH_2N), 42.1 (OCH_2CH_2N), 33.9 (*C-4*), 17.1 (*C-17*), 11.9 (*C-12*); LRMS (ESI) *m/z* 358 (100%, $[M+K]^+$), 342 (70%, $[M+Na]^+$); HRMS (ESI) found *m/z* 342.1131 $[M+Na]^+$, $C_{17}H_{21}NNaO_3S^+$ requires 342.1134; ν_{max} (neat)/cm^{-1} 2926, 2923, 1724 (C=O ester), 1644 (C=O ketone), 1435, 1264, 1114.

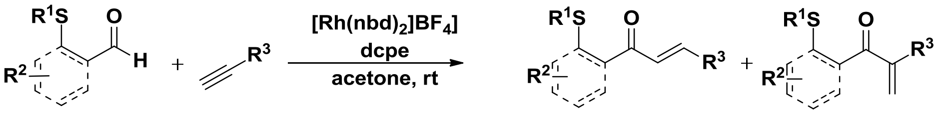
(*E*)-*N*-Methoxy-*N*,4-dimethyl-5-(2-(methylthio)phenyl)-5-oxopent-3-enamide (68)



Prepared according to General Procedure **C** using 2-methylthiobenzaldehyde (39 µL, 0.30 mmol) and (*E*)-*N*-methoxy-*N*-methylpenta-2,4-dienamide (63 mg, 0.45 mmol). Purification by flash column chromatography (40% EtOAc/petrol) afforded the branched regioisomer **68** as a yellow oil (42 mg, 47%, >20:1 b:l); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (2H, m, *H-9* and *H-11*), 7.30-7.24 (1H, m, *H-8*), 7.21-7.15 (1H, m, *H-10*), 6.45 (1H, app. t, *J* 7.0, *H-3*), 3.68 (3H, s, NCH_3), 3.43 (2H, d, *J* 7.0, *H-2*), 3.16 (3H, s, OCH_3), 2.41 (3H, s, SCH_3), 2.00 (3H, app. s, *H-14*); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 198.7 (*C-5*), 171.1 (*C-1*), 139.7, 139.4 (*C-3*), 139.2, 137.3, 130.3 (*C*-9), 128.6 (*C-8*), 127.8 (*C-11*), 124.8 (*C-10*), 61.3 (*C-13*), 32.8 (*C-2*), 32.2 (*C-12*), 17.2 (*C-15*), 11.9 (*C-14*); LRMS (ESI) *m/z* 332 (100%, $[M+K]^+$), 316 (80%, $[M+Na]^+$), 297 (25%, $[M+H]^+$); HRMS (ESI) found *m/z* 316.0965 $[M+Na]^+$, $C_{15}H_{19}NNaO_3S^+$ requires 316.0978; ν_{max} (neat)/cm^{-1} 3010, 2968, 2925, 1723 (C=O ester), 1657 (C=O ketone), 1434, 1385, 1261, 1103.

Linear-Selective Alkyne Hydroacylation

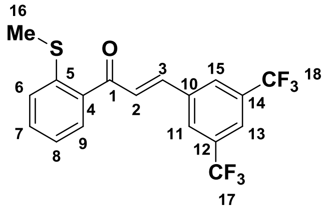
General Procedure D –Linear-Selective Alkyne Hydroacylation



$[Rh(nbd)_2]BF_4$ (5.6 mg, 0.015 mmol) and dcpe (6.3 mg, 0.015 mmol) were dissolved in acetone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. Aldehyde (0.30 mmol) and alkyne (0.45 mmol) were added as a solution in acetone (0.5 mL) and the reaction mixture was stirred at room temperature for the specified time. The reaction mixture was diluted with Et_2O, filtered through a short pad of Celite® using Et_2O as eluent and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography.

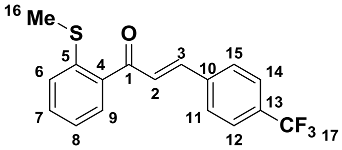
A sample of the crude residue was analysed by ^1H NMR spectroscopy in $CDCl_3$ to determine the linear:branched (l:b) regioselectivity of the reaction. The data for the following compounds is for the linear regioisomers unless otherwise stated. The branched isomer was either not observed or was isolated in insufficient quantities for full analysis by NMR spectroscopy unless otherwise stated. The ^1H NMR signals observed for the branched geminal protons are consistent with those reported in the literature.[89]

(*E*)-3-(3,5-bis(Trifluoromethyl)phenyl)-1-(2-(methylthio)phenyl)prop-2-en-1-one (91)



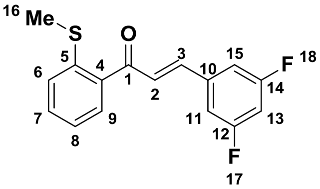
Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) at room temperature for 1 h. Purification by flash column chromatography (20% Et_2O/petrol) afforded the linear regioisomer **91** as a bright yellow solid (109 mg, 93%, >20:1 l:b); m.p. (DCM) 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (2H, s, *H-11* and *H-15*), 7.89 (1H, s, *H-13*), 7.77 (1H, dd, *J* 8.0 and 1.5, *H-9*), 7.68 (1H, d, *J* 16.0, *H-3*), 7.55-7.50 (1H, m, *H-7*), 7.47 (1H, d, *J* 16.0, *H-2*), 7.41 (1H, app. d, *J* 8.0, *H-6*), 7.30-7.25 (1H, m, *H-8*), 2.48 (3H, s, SC*H₃*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4 (*C-1*), 141.3 (Ar*C*), 140.9 (*C-3*), 137.0 (Ar*C*), 136.2 (Ar*C*), 132.5 (q, J_{C-F} 33.5, *C-12* and *C-14*), 132.2 (*C-7*), 129.8 (*C-9*), 127.9 (br. s, *C-11* and *C-15*), 127.8 (*C-2*), 126.2 (*C-6*), 124.2 (*C-8*), 123.5-123.2 (m, *C-13*), 123.0 (q, J_{C-F} 273.0, *C*-17 and C-*18*), 16.4 (*C-16*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (6F, s); LRMS (ESI) *m/z* 803 (100%, $[2M+H]^+$), 413 (10%, $[M+Na]^+$); HRMS (ESI) found *m/z* 413.0405 ($[M+Na]^+$), $C_{18}H_{12}F_6NaOS^+$ requires 413.0411; ν_{max} (neat)/cm^{-1} 3099, 2927, 2851, 1653 (C=O), 1603, 1588, 1554, 1274, 1120, 1047, 1011.

(*E*)-1-(2-(Methylthio)phenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (92)



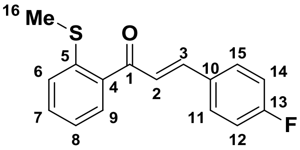
Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (73 μL, 0.45 mmol) at room temperature for 2 h. Purification by flash column chromatography (20% Et_2O/petrol) afforded the linear regiosiomer **92** as a yellow solid (80 mg, 83%, >20:1 l:b); m.p. (DCM) 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.62 (6H, m, *H-3*, *H-7*, *H-11*, *H-12*, *H-14* and *H-15*), 7.53-7.47 (1H, m, Ar*H*), 7.44-7.37 (1H, d, *J* 16.0, *H-2*, overlapping 1H, m, Ar*H*), 7.29-7.22 (1H, m, Ar*H*), 2.47 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1 (*C-1*), 142.8 (Ar*C*), 141.1 (Ar*C*), 138.2 (Ar*C*), 136.6 (Ar*C*), 131.9 (Ar*C*H), 131.8 (q, $J_{\text{C-F}}$ 33.0, *C-13*), 129.7 (Ar*C*H), 128.5 (*C-11* and *C*-15), 126.7 (Ar*C*H), 126.2 (*C*-*2*), 125.9 (app. q, $J_{\text{C-F}}$ 4.0, *C-12* and *C-14*), 124.2 (Ar*C*H), 123.8 (q, $J_{\text{C-F}}$ 272.5, *C-17*), 16.4 (*C-16*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.8, (3F, s); LRMS (ESI) *m/z* 667 (100%, $[2M+Na]^+$), 345 (70%, $[M+Na]^+$), 323 (25%, $[M+H]^+$); HRMS (ESI) found *m/z* 345.0527 ($[M+Na]^+$), $C_{17}H_{13}F_3NaOS^+$ requires 345.0531; ν_{max} (neat)/cm^{-1} 2961, 2923, 1658 (C=O), 1599, 1585, 1577, 1556, 1280.

(*E*)-3-(3,5-Difluorophenyl)-1-(2-(methylthio)phenyl)prop-2-en-1-one (93)



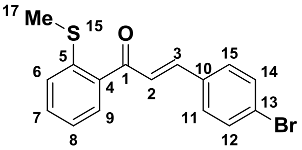
Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-ethynyl-3,5-difluorobenzene (36 μL, 0.45 mmol) at room temperature for 2 h. Purification by flash column chromatography (20% Et_2O/petrol) afforded the linear regioisomer **93** as a yellow solid (74 mg, 91%, >20:1 l:b); m.p. (DCM) 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.71 (1H, m, *H-9*), 7.57-7.46 (2H, m, *H-3* and *H-7*), 7.39 (1H, app. d, *J* 8.0, *H-6*), 7.32 (1H, d, *J* 15.5, *H-2*), 7.28-7.22 (1H, m, *H-8*), 7.14-7.07 (2H, m, *H-11* and *H-15*), 6.85 (1H, app. tt, *J* 8.5, 2.0, *H-13*), 2.48 (3H, s, SC*H₃*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8 (*C-1*), 163.2 (dd, $J_{C\text{-}F}$ 249.0, 13.0, *C-12* and *C-14*), 142.0 (app. t, $J_{C\text{-}F}$ 3.0, *C-3*), 141.1 (Ar*C*), 138.1 (t, $J_{C\text{-}F}$ 9.5, *C-10*), 136.5 (Ar*C*), 132.0 (*C-7*), 129.7 (*C-9*), 126.7 (*C-2*), 126.2 (*C-6*), 124.2 (*C-8*), 110.0 (dd, $J_{C\text{-}F}$ 18.5, 7.0, *C-11* and *C-15*), 105.5 (t, $J_{C\text{-}F}$ 25.0, *C-13*), 16.4 (*C-16*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.9 (2F, s); LRMS (ESI) *m/z* 603 (100%, $[2M+Na]^+$), 329 (45%, $[M+K]^+$), 313 (60%, $[M+Na]^+$), 291 (20%, $[M+H]^+$); HRMS (ESI) found *m/z* 313.0466 ($[M+Na]^+$), $C_{16}H_{12}F_2NaOS^+$ requires 313.0469; ν_{max} (neat)/cm^{-1} 3083, 2922, 1663 (C=O), 1620, 1606, 1588, 1467, 1450, 1274, 1206, 1117.

(*E*)-3-(4-Fluorophenyl)-1-(2-(methylthio)phenyl)prop-2-en-1-one (94)



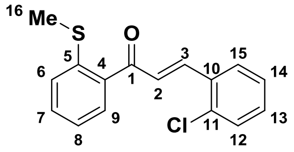
Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-ethynyl-4-fluorobenzene (52 μL, 0.45 mmol) for 2 h at room temperature. Purification by flash column chromatography (30% Et_2O/petrol) afforded linear regioisiomer **94** as a yellow solid (74 mg, 91%,>20:1 l:b); m.p. (DCM) 54-56 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, app. d, *J* 7.5, *H-9*), 7.64-7.53 (3H, m, *H-3* and 2×Ar*H*), 7.51-7.44 (1H, m, Ar*H*), 7.38 (1H, app. d, *J* 8.0, Ar*H*), 7.29-7.20 (2H, m, *H-2* and Ar*H*), 7.09 (2H, app. t, *J* 8.5, 2×Ar*H*), 2.46 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6 (*C-1*), 164.0 (d, J_{C-F} 252.0, *C-13*), 143.9 (*C-3*), 140.6 (Ar*C*), 137.1 (Ar*C*), 131.6 (Ar*C*H), 131.0 (d, J_{C-F} 3.0, *C-10*), 130.4 (d, J_{C-F} 8.0, *C-11* and C-*15*), 129.4 (Ar*C*H), 126.2 (Ar*C*H), 124.4 (d, J_{C-F} 2.0, *C-2*), 124.1 (Ar*C*H), 116.1 (d, J_{C-F} 22.5, *C-12* and *C-14*), 16.4 (*C-16*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.0 (1F, s); LRMS ESI) *m/z* 567 (100%, $[2M+Na]^+$), 295 (65%, $[M+Na]^+$); HRMS (ESI) found *m/z* 295.0561 ($[M+Na]^+$), $C_{16}H_{13}FNaOS^+$ requires 295.0563; ν_{max} (neat)/cm^{-1} 3066, 2977, 2920, 1650 (C=O), 1595, 1586, 1554, 1504, 1461, 1222, 1206.

(*E*)-3-(4-Bromophenyl)-1-(2-(methylthio)phenyl)prop-2-en-1-one (95)



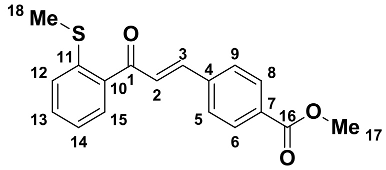
Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-ethynyl-4-bromobenzene (81 mg, 0.45 mmol) at room temperature for 1 h. Purification by flash column chromatography (20% Et_2O/petrol) afforded linear regioisomer **95** as a yellow solid (93 mg, 93%, >20:1 l:b); m.p. (DCM) 77-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, dd, *J* 7.5, 1.5, *H-9*), 7.64-7.44 (1H, d, *J* 16.0, *H-3*, overlapping 5H, m, *H-7*, *H-11*, *H-12*, *H-14* and *H-15*), 7.39 (1H, app. d, *J* 8.0, *H-6*), 7.31 (1H, d, *J* 16.0, *H-2*), 7.28-7.22 (1H, m, *H-8*), 2.46 (3H, s, SC*H$_3$*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5 (*C-1*), 143.7 (*C-3*), 140.7 (Ar*C*), 136.9 (Ar*C*), 133.7 (Ar*C*), 132.2 (*C-11*and *C-15*), 131.7 (*C-7*), 129.8 (*C-12* and *C-14*), 129.5 (*C-9*), 126.2 (*C-6*), 125.1 (*C-2*), 124.8 (Ar*C*), 124.1 (*C-8*), 16.4 (*C-16*); LRMS (ESI) *m/z* 689 (100%, [2M(^{79}Br)+Na]$^+$), 357 (40%, [M+Na]$^+$); HRMS (ESI) found *m/z* 354.9757 ([M(^{79}Br)+Na]$^+$), $C_{16}H_{13}{}^{79}BrNaOS^+$ requires 354.9763; ν_{max} (neat)/cm^{-1} 3096, 2955, 2920, 2853, 1655 (C=O), 1592, 1562, 1461, 1429, 1292, 1143.

(*E*)-3-(2-Chlorophenyl)-1-(2-(methylthio)phenyl)prop-2-en-1-one (96)



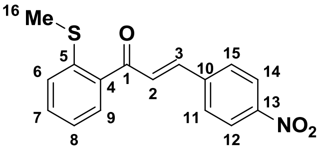
Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-chloro-2-ethynylbenzene (54 μL, 0.45 mmol) at room temperature for 2 h. Purification by flash column chromatography (30% Et_2O/petrol) afforded the linear regioisomer **96** as a yellow solid (76 mg, 88%, >20:1 l:b); m.p. (DCM) 59-62 °C; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.01 (1H, d, *J* 16.0, *H-3*), 7.82-7.73 (2H, m, 2×Ar*H*), 7.56-7.50 (1H, m, Ar*H*), 7.50-7.42 (2H, m, 2×Ar*H*), 7.41-7.26 (1H, d, *J* 16.0, *H-2*, overlapping 3H, m, 3×Ar*H*), 2.49 (3H, s, SC*H$_3$*); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 192.5 (*C-1*), 141.3 (Ar*C*), 140.7 (*C-3*), 137.1 (Ar*C*), 135.6 (Ar*C*), 133.5 (Ar*C*), 132.1 (Ar*C*H), 131.7 (Ar*C*H), 130.6 (Ar*C*H), 130.0 (Ar*C*H), 128.2 (Ar*C*H), 127.7 (Ar*C*H), 127.6 (*C-2*), 126.6 (Ar*C*H), 124.4 (Ar*C*H), 16.6 (*C-16*); LRMS (ESI) *m/z* 599 (100%, $[2M(^{35}Cl)+Na]^+$), 311 (40%, $[M(^{35}Cl)+Na]^+$), 289 (15%, $[M(^{35}Cl)+H]^+$); HRMS (ESI) found *m/z* 311.0265 ($[M(^{35}Cl)+Na]^+$), $C_{16}H_{13}{}^{35}ClNaOS^+$ requires 311.0268; ν_{max} (neat)/cm^{-1} 3065, 2961, 2919, 1650 (C=O), 1592, 1556, 1266, 1208.

(*E*)-Methyl 4-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)benzoate (97)



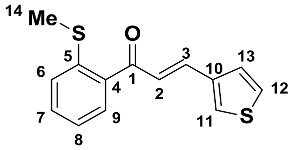
Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and methyl 4-ethynylbenzoate (66 mg, 0.45 mmol) at room temperature for 2 h. Purification by flash column chromatography (20% Et_2O/petrol) afforded the linear regioisomer **97** as a bright yellow solid (69 mg, 74%, >20:1 l:b); m.p. (DCM) 119-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, *J* 8.5, *H-6* and *H-8*), 7.73 (1H, dd, *J* 7.5, 1.5, *H-15*), 7.69-7.62 (3H, m, *H-3, H-5* and *H-8*), 7.52-7.46 (1H, m, *H-13*), 7.43-7.37 (2H, m, *H-2* and *H-12*), 7.28-7.22 (1H, m, *H-14*), 3.93 (3H, s, OCH_3), 2.77 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2 (*C-1*), 166.4 (*C-16*), 143.3 (*C-3*), 140.9 (*C-11*), 139.0 (*C-14*), 136.7 (Ar*C*), 131.8 (Ar*C*), 131.5 (*C-13*), 130.1 (*C-6* and *C-8*), 129.6 (*C-15*), 128.3 (*C-5* and *C-9*), 126.6 (*C-12*), 126.2 (*C-2*), 124.1 (*C-14*), 52.3 (*C-17*), 16.4 (*C-18*); LRMS (ESI) *m/z* 647 (100%, $[2M+Na]^+$), 335 (45%, $[M+Na]^+$), 313 (30%, $[M+H]^+$); HRMS (ESI) found *m/z* 335.0707 ($[M+Na]^+$), $C_{18}H_{16}NaO_3S^+$ requires 335.0712; ν_{max} (neat)/cm^{-1} 3067, 2954, 2913, 1715 (C=O ester) 1655 (C=O ketone), 1603, 1564, 1410, 1281, 1266.

(*E*)-1-(2-(Methylthio)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one (98)



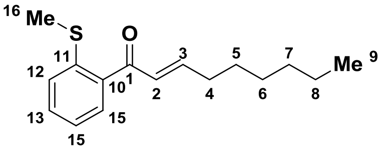
Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-ethynyl-4-nitrobenzene (54 μL, 0.45 mmol) at room temperature for 2 h. Purification of the crude mixture (7:1 l:b) by flash column chromatography (100% DCM), followed by recrystallization from DCM/petrol, afforded the linear regioisomer **98** as a dark yellow crystalline solid (60 mg, 67%, >20:1 l:b); m.p. (DCM/petrol) 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (2H, d, *J* 8.5, *H-12* and *H-14*), 7.78-7.75 (3H, m, *H-9*, *H-11* and *H-15*), 7.68 (1H, d, *J* 16.0, *H-3*), 7.54-7.38 (1H, d, *J* 16.0, *H-2,* overlapping 2H, m, *H-6* and *H-7*), 7.30-7.23 (1H, m, *H-8*), 2.48 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5 (*C-1*), 148.5 (*C-13*), 141.5 (*C-3*), 141.3 (Ar*C*), 141.0 (Ar*C*), 136.3 (Ar*C*), 132.1 (Ar*C*H), 129.8 (Ar*C*), 128.9 (*C-11* and *C-15*), 128.1 (*C-2*), 126.2 (Ar*C*H), 124.2 (*C-8*, *C-12* and C-*14*), 16.4 (*C-16*); LRMS (ESI) *m/z* 354 (20%, $[M+H]^+$), 322 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 322.0507 ($[M+Na]^+$), $C_{16}H_{13}NNaO_3S^+$ requires 322.0508; ν_{max} (neat)/cm^{-1} 2917, 2850, 1651 (C=O), 1604, 1586, 1556, 1513, 1430, 1338 (N=O), 1266, 1207.

(*E*)-1-(2-(Methylthio)phenyl)-3-(thiophen-3-yl)prop-2-en-1-one (99)



Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and 3-ethynylthiophene (42 μL, 0.45 mmol) at room temperature for 2 h. Purification by flash column chromatography (35% Et_2O/petrol) afforded the linear regioisomer **99** as a brown oil (75 mg, 96%, >20:1 l:b); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, dd, *J* 8.0, 1.5, *H-9*), 7.60 (1H, d, *J* 16.0, *H-3*), 7.57-7.54 (1H, m, *H-12*), 7.49-7.43 (1H, m, *H-7*), 7.40-7.34 (3H, m, *H-11*, *H-13* and *H-6*), 7.23 (1H, m *H-8*), 7.12 (1H, d, *J* 16.0, *H-2*), 2.46 (3H, s, SC*H₃*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3 (*C-1*), 140.3 (Ar*C*), 138.8 (*C-3*), 138.1 (Ar*C*), 137.3 (Ar*C*), 131.4 (*C-11*), 129.3 (Ar*C*), 129.1 (*C-7)*, 127.1 (Ar*C*H), 126.3 (Ar*C*), 125.3 (Ar*C*H), 124.7 (*C-2*), 124.2 (*C-12*), 16.5 (*C-14*); LRMS (ESI) *m/z* 543 (100%, $[2M+Na]^+$), 299 (35%, $[M+K]^+$), 283 (45%, $[M+Na]^+$), 261 (10%, $[M+H]^+$); HRMS (ESI) found *m/z* 283.0219 ($[M+Na]^+$), $C_{14}H_{12}NaOS_2^+$ requires 283.0222; ν_{max} (neat)/cm^{-1} 2980, 2919, 1650 (C=O), 1616, 1590, 1432, 1281, 1205.

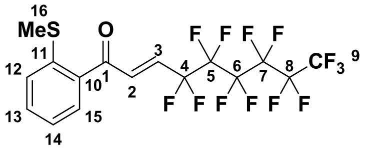
(*E*)-1-(2-(Methylthio)phenyl)non-2-en-1-one (100)



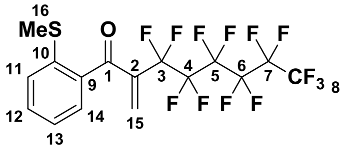
Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 µL, 0.30 mmol) and 1-octyne (66 µL, 0.45 mmol) at room temperature for 2 h. Purification by flash column chromatography (20% Et_2O/petrol) afforded the linear regioisomer **100** as a green oil (66 mg, 84%, >16:1 l:b); ^{1}H NMR (400 MHz, $CDCl_3$) 7.57 (1H, dd, *J* 7.5, 1.5, *H-15*), 7.46-7.41 (1H, m, *H-13*), 7.34 (1H, app. d, *J* 7.5, *H-12*), 7.19 (1H, app. td, *J* 7.5, 1.0, *H-14*), 6.87 (1H, dt, *J* 15.5, 7.0, *H-3*), 6.64 (1H, dt, *J* 15.5, 1.5, *H-2*), 2.43 (3H, s, *H-16*), 2.32-2.24 (2H, m, *H-4*), 1.54-1.42 (2H, m, *H-5*), 1.37-1.25 (6H, m, *H-6*, *H-7* and *H-8*), 0.92-0.83 (3H, m, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5 (*C-1*), 151.2 (*C-3*), 140.2 (Ar*C*), 137.1 (Ar*C*), 131.2 (*C-13*), 129.3 (*C-15*), 128.6 (*C-2*), 126.2 (*C-12*), 124.0 (*C-14*), 32.8 (*C-4*), 31.6 (CH_2), 28.9 (CH_2), 28.0 (*C-5*), 22.5 (CH_2), 16.4 (*C-16*), 14.0 (*C-9*); LRMS (ESI) *m/z* 547 (100%, $[2M+Na]^+$), 285 (50%, $[M+Na]^+$), 263 (20%, $[M+H]^+$); HRMS (ESI) found *m/z* 285.1277 ($[M+Na]^+$), $C_{16}H_{22}NaOS^+$ requires 285.1284; ν_{max} (neat)/cm^{-1} 2924, 2855, 1658 (C=O), 1614, 1585, 1558, 1461, 1433, 1293, 1214.

Linear regioisomer: (*E*)-4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluoro-1-(2-(methylthio)phenyl) non-2-en-1-one (101b) and Branched regioisomer: 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-2-methylene-1-(2-(methylthio)phenyl)octan-1-one (101l)

101l



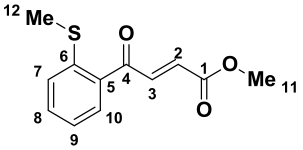
101b



Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 µL, 0.30 mmol) and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooct-1-yne (156 mg, 0.45 mmol) at room temperature for 2.5 h. Purification by flash column chromatography (10% Et_2O/petrol) afforded in order of elution the **linear** regioisomer **101l** as a yellow solid (41 mg, 27%, >20:1 l:b) and the **branched** regioisomer **101b** as a yellow oil (37 mg, 25%, >20:1 b:l).

***Linear regioisomer* 101l:** m.p. (DCM) 51-52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, dd, *J* 7.5, 1.0, *H-15*), 7.58-7.52 (1H, m, *H-13*), 7.49 (1H, dt, *J* 15.5, 2.0, *H-2*), 7.41 (1H, app. d, *J* 8.08, *H-12*), 7.31-7.28 (1H, m, *H-14*), 6.88-6.74 (1H, m, *H-3*), 2.49 (3H, s, SCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.8 (*C-1*), 143.3 (*C-19*), 134.7 (t, *J* 8.0, *C-2*), 134.0 (*C-10*), 133.1 (Ar*C*H), 130.7 (Ar*C*H), 129.1 (t, $J_{C\text{-}F}$ 24.0, *C-3*), 126.0 (Ar*C*H), 124.0 (Ar*C*H), 118.3 (t, $J_{C\text{-}F}$ 33.0), 116.9-115.6 (m), 114.6 (t, $J_{C\text{-}F}$ 31.0), 113.8-112.0 (m), 111.4-109.7 (m), 109.0-107-8 (m), 16.2 (*C-16*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.7 (3F, s, CF_3), -112.9 (2F, s, CF_2), -121.9 (2F, s, CF_2), -122.9 (2F, s, CF_2), 1-23.0 (2F, s, CF_2), -126.1 (2F, s, CF_2); LRMS (ESI) *m/z* 535 (100%, $[M+Na]^+$), 519 (50%, $[M+Na]^+$), 497 (50%, $[M+H]^+$); HRMS (ESI) *m/z* found 519.0049 $[M+Na]^+$, $C_{16}H_9F_{13}NaOS^+$ requires 519.0059; ν_{max} (neat)/cm^{-1} 3066, 2919, 1672 (C=O), 1627, 1587, 1551, 1461, 1430, 1366, 1338. Data for the ***branched regioisomer* 101b** is in accordance with the literature.[89]

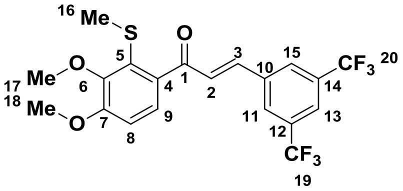
(*E*)-Methyl 4-(2-(methylthio)phenyl)-4-oxobut-2-enoate (102)



Prepared according to General Procedure **D** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol) and methyl propiolate (40 μL, 0.45 mmol) at 70 °C for 18 h. Purification of the crude mixture (1:1 l:b) by flash column chromatography (10% Et_2O/petrol) afforded the linear regioisomer **102** as a yellow crystalline solid (22 mg, 33%, >20:1 l:b). The branched regioisomer was not isolated.

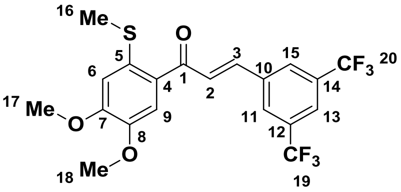
Linear regioisomer 102: m.p. (DCM) 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.75 (2H, m, *H-3* and *H-10),* 7.56-7.47 (1H, m, *H-8*) 7.39 (1H, app. d, *J* 8.0, *H-7*), 7.29-7.20 (1H, m, *H-9*), 6.81 (1H, d, *J* 15.5, *H-2*), 3.84 (3H, s, OC*H$_3$*) 2.47 (3H, s, SC*H$_3$*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5 (*C-4*), 166.1 (*C-1*), 142.9 (Ar*C*), 138.3 (*C-3*), 134.5 (Ar*C*), 132.9 (*C-8*), 131.8 (*C-3*), 130.8 (*C-10*), 125.9 (*C-7*), 123.9 (*C-9*), 52.3 (*C-11*), 16.2 (*C-12*); LRMS (ESI) *m/z* 259 (100%, $[M+Na]^+$); HRMS (ESI) *m/z* found 259.0297 $[M+Na]^+$, $C_{12}H_{12}NaO_3S^+$ requires 259.0299; ν_{max} (neat)/cm^{-1} 2922, 2852, 1714 (C=O ester), 1659 (C=O ketone), 1622, 1286, 1555, 1460, 1433, 1302, 1283, 1189, 1163.

(*E*)-3-(3,5-bis(Trifluoromethyl)phenyl)-1-(3,4-dimethoxy-2-(methylthio)phenyl)prop-2-en-1-one (107)



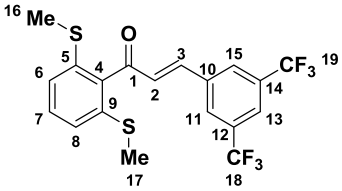
Prepared according to General Procedure **D** using 3,4-dimethoxy-2-(methylthio)benzaldehyde (64 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl) benzene (80 μL, 0.45 mmol) at room temperature for 1 h. Purification by flash column chromatography (30% Et_2O/petrol), followed by recrystallization from petrol, afforded the linear regioisomer **107** as a pale yellow solid (82 mg, 61%, >20:1 l:b); m.p. (petrol) 123-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, s, *H-11* and *H-15*), 7.87 (1H, s, *H-13*), 7.50 (1H, d, *J* 16.0, *H-3*), 7.32 (1H, d, *J* 16.0, *H-2*), 7.27 (1H, d, *J* 8.5, *H-9*), 6.96 (1H, d, *J* 8.5, *H-8*), 3.95 (6H, s, *2*×OC*H₃*), 2.43 (3H, s, SC*H₃*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1 (*C-1*), 155.3 (*C-13*), 150.4 (*C-12*), 138.8 (*C-3*), 137.2 (*C-4*), 136.4 (*C-11*), 132.4 (q, $J_{C\text{-}F}$ 33.5, *C-6* and *C-8*), 130.4 (*C-2*), 129.8 (*C-10*), 127.8 (br. s, *C-5* and *C-9*), 124.8 (*C-15*), 123.0 (q, $J_{C\text{-}F}$ 273.0, *C-16* and *C-17*), 123.4-123.1 (m, *C-7*), 111.7 (*C-14*), 60.5 (*C-19*), 58.0 (*C-20*), 19.4 (*C-18*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.3 (6F, s); LRMS (ESI) *m/z* 923 (100%, $[2M+Na]^+$), 473 (20%, $[M+Na]^+$); HRMS (ESI) found *m/z* 473.0601 ($[M+Na]^+$), $C_{20}H_{16}F_6NaO_3S^+$ requires 473.0617; ν_{max} (neat)/cm^{-1} 3013, 2978, 2943, 2923, 1647 (C=O), 1585, 1480, 1377, 1276, 1185, 1143, 1128.

(*E*)-3-(3,5-bis(Trifluoromethyl)phenyl)-1-(4,5-dimethoxy-2-(methylthio)phenyl)prop-2-en-1-one (108)



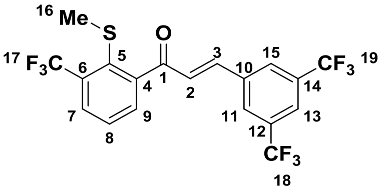
Prepared according to General Procedure **D** using 4,5-dimethoxy-2-(methylthio)benzaldehyde (64 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) at room temperature for 1 h. Purification by flash column chromatography (20% Et$_2$O/petrol) afforded the linear regioisomer **108** as a yellow solid (93 mg, 73%, >20:1 l:b); m.p. (DCM) 140-142 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.00 (2H, s, *H-11* and *H-15*), 7.88 (1H, s, *H-13*), 7.69 (1H, d, *J* 15.5, *H-3*), 7.49 (1H, d, *J* 15.5, *H-2*), 7.26 (1H, s, *H-9*), 6.96 (1H, s, *H-6*), 3.98 (3H, s, ArOC*H$_3$*), 3.94 (3H, s, ArOC*H$_3$*), 3.47 (3H, s, SC*H$_3$*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 190.4 (*C-1*), 152.3 (*C-7*), 146.5 (*C-8*), 139.5 (*C-3*), 137.3 (Ar*C*), 133.7 (Ar*C*), 132.4 (q, $J_{\text{C-F}}$ 34.5, *C-12* and C-*14*), 130.5 (Ar*C*), 128.3 (*C-2*), 127.9-127.7 (m, *C-5* and *C-9*), 123.2 (app. quin, $J_{\text{C-F}}$ 4.0, *C-13*), 123.0 (q, $J_{\text{C-F}}$ 273.0, *C-19*, and *C-20*), 112.9 (*C-9*), 111.0 (*C-6*), 54.4 (O*C*H$_3$), 56.1 (O*C*H$_3$), 19.0 (*C-16*); ^{19}F NMR (376 MHz, CDCl$_3$) δ -63.0 (6F, s); LRMS (ESI) *m/z* 923 (100%, [2M+Na]$^+$), 473 (20%, [M+Na]$^+$), 451 (10%, [M+H]$^+$); HRMS (ESI) found *m/z* 473.0613 ([M+Na]$^+$), $C_{20}H_{16}F_6NaO_3S^+$ requires 473.0617; ν_{max} (neat)/cm^{-1} 3025, 2967, 2914, 2853, 1651 (C=O), 1547, 1430, 1279, 1227, 1195.

(*E*)-1-(2,6-bis(Methylthio)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)prop-2-en-1-one (109)



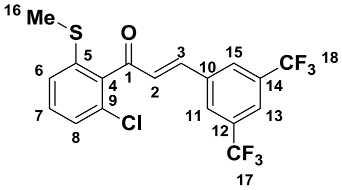
Prepared according to General Procedure **D** using 2,6-bis(methylthio)benzaldehyde (59 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) at room temperature for 2 h. Purification by flash column chromatography (15% Et_2O/petrol) afforded the linear regioisomer **109** as a yellow solid (94 mg, 70%, >20:1 l:b); m.p. (DCM) 116-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, s, *H-11* and *H-15*), 7.87 (1H, s, *H-13*), 7.43-7.37 (1H, m, *H-7*), 7.34 (1H, d, *J* 16.0, *H-3*), 7.27 (2H, d, *J* 8.0, *H-6* and *H-8*), 7.09 (1H, d, *J* 16.0, *H-2*), 2.44 (6H, s, 2×SC*H₃*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1 (*C-1*), 141.2 (*C-3*), 140.3 (*C-5* and *C-9*), 136.8 (Ar*C*), 135.9 (Ar*C*), 132.4 (q, $J_{C\text{-}F}$ 33.5, *C-12* and *C-14*), 130.5 (*C-2*), 130.2 (*C-7*), 128.0 (app. d, $J_{C\text{-}F}$ 3.5, *C-11* and *C-15*), 126.1 (*C-6* and *C-8*), 123.5 (app. quin, $J_{C\text{-}F}$ 4.0, *C-13*), 123.0 (q, $J_{C\text{-}F}$ 273.0, *C-18* and *C-19*), 17.7 (*C-16* and *C-17*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (6F, s); LRMS (ESI) *m/z* 895 (100%, $[2M+Na]^+$), 459 (35%, $[M+Na]^+$), 437 (15%, $[M+H]^+$); HRMS (ESI) found 459.0275 ($[M+Na]^+$), $C_{19}H_{14}F_6NaOS_2^+$ requires 459.0282; ν_{max} (film)/cm^{-1} 3048, 2963, 2924, 1648 (C=O), 1558, 1376, 1276, 1123.

(*E*)-3-(3,5-bis(Trifluoromethyl)phenyl)-1-(2-(methylthio)-3-(trifluoromethyl)phenyl) prop-2-en-1-one (110)



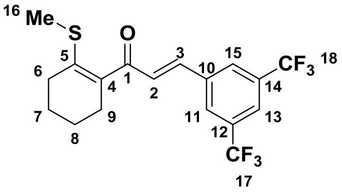
Prepared according to General Procedure **D** using 2-(methylthio)-3-(trifluoromethyl)benzaldehyde (66 mg, 0.30mmol) and 1-ethynyl-3,5-bis(trifluoromethyl) benzene (80 μL, 0.45 mmol) at room temperature for 1.5 h. Purification by flash column chromatography (10% Et_2O/petrol) afforded the linear regioisomer **110** as an off-white solid (129 mg, 94%, >20:1 l:b); m.p. (DCM) 97-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (2H, s, *H-11* and *H-15*), 7.92-7.85 (2H, m, *H-7* and H-*13*), 7.63-7.52 (2H, m, *H-8* and *H-9*), 7.43 (1H, d, *J* 16.0, *H-3*), 7.27 (1H, d, *J* 16.0, *H-2*), 2.34 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2 (*C-18*), 148.6 (Ar*C*), 140.6 (*C-3*), 136.5 (Ar*C*), 135.2 (q, $J_{C\text{-}F}$ 36.5, *C-6*), 132.5 (q, $J_{C\text{-}F}$ 33.5, *C-12* and *C-14*), 132.3 (Ar*C*), 131.0 (ArCH), 130.0 (*C-2*), 129.2 (Ar*C*H), 128.4 (app. q, $J_{C\text{-}F}$ 5.5, *C-7*), 128.0 (app. d. $J_{C\text{-}F}$ 3.5, *C-11* and *C-15*), 123.3 (q, $J_{C\text{-}F}$ 274.0, *C-17*), 122.9 (q, $J_{C\text{-}F}$ 273.0, *C-18* and *C-19*), 123.7 (app. quin, $J_{C\text{-}F}$ 4.0, *C-13*), 22.1 (*C-16*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.7 (3F, s), -63.1 (6F, s); LRMS (ESI) *m/z* 939 (100%, $[2M+Na]^+$), 481 (80%, $[M+Na]^+$); HRMS (ESI) found *m/z* 481.0276 ($[M+Na]^+$), $C_{19}H_{11}F_9NaOS^+$ requires 481.0279; ν_{max} (neat)/cm^{-1} 2961, 2925, 2854, 1649 (C=O), 1632, 1579, 1378, 1332, 1278, 1172, 1129.

(*E*)-3-(3,5-bis(Trifluoromethyl)phenyl)-1-(2-chloro-6-(methylthio)phenyl)prop-2-en-1-one (111)



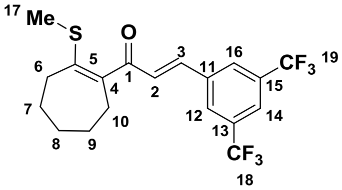
Prepared according to General Procedure **D** using 2-chloro-6-(methylthio)benzaldehyde (56 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) at 50 °C for 18 h. Purification by flash column chromatography (25% Et_2O/petrol) afforded the linear regioisomer **111** as a yellow solid (100 mg, 78%, >20:1 l:b); m.p. (DCM) 96-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, s, *H-11* and *H-15*), 7.89 (1H, s, *H-13*), 7.72-7.24 (4H, m, 3×Ar*H* and *H-3*), 7.33 (1H, d, *J* 16.5, *H-2*), 2.46 (3H, s, SC*H₃*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5 (*C-1*), 142.2 (*C-3*), 138.3 (Ar*C*), 137.8 (Ar*C*), 136.5 (Ar*C*), 132.5 (q, $J_{C\text{-}F}$ 33.5, *C-12* and *C-14*), 130.9 (Ar*C*), 130.7 (Ar*C*H), 129.9 (*C-2*), 128.1 (br. s, *C-11* and *C-15*), 127.0 (Ar*C*H), 126.5 (Ar*C*H), 123.9-123.7 (m, *C-13*), 122.9 (q, $J_{C\text{-}F}$ 273.0, *C-17*, *C-18*), 17.5 (*C-16*); ^{19}F NMR (376 MHz, $CDCl_3$) -63.0 (6F, s); LRMS (ESI) *m/z* 811 (100%, $[2M(^{35}Cl)+Na]^+$), 417 (50%, $[M(^{35}Cl)+Na]^+$), 395 (80%, $[M+H]^+$); HRMS (ESI) found *m/z* 417.0007 ($[M(^{35}Cl)+Na]^+$), $C_{18}H_{11}{}^{35}ClNaOS^+$ requires 417.0016; ν_{max} (neat)/cm^{-1} 3055, 2960, 2927, 1652 (C=O), 1632, 1573, 1557, 1430, 1378, 1320, 1275, 1230, 1109.

(*E*)-3-(3,5-bis(Trifluoromethyl)phenyl)-1-(2-(methylthio)cyclohex-1-en-1-yl)prop-2-en-1-one (112)



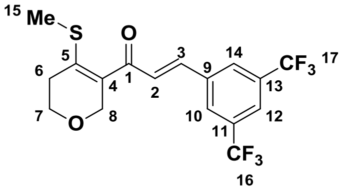
Prepared according to General Procedure **D** using 2-(methylthio)cyclohex-1-enecarbaldehyde (47 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) at room temperature for 2 h. Purification by flash column chromatography (10-15% EtOAc/petrol) afforded the linear regioisomer **112** as a bright yellow solid (100 mg, 85%, >20:1 l:b); m.p. (DCM) 96-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, s, *H-11* and *H-15*), 7.85 (1H, s, *H-13*), 7.63 (1H, d, *J* 15.5, *H-3*), 7.31 (1H, d, *J* 15.5, *H-2*), 2.57-2.49 (4H, m, *H-6* and H-*9*), 2.31 (3H, s, SC*H*$_2$), 1.83-1.70 (4H, m, *H-7* and *H-8*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9 (*C-1*), 148.8 (*C*-*5*), 138.4 (*C*-*3*), 137.6 (*C*-*4*), 132.3 (q, $J_{C\text{-}F}$ 33.5, *C-12* and *C-14*), 131.8 (*C-10*), 128.0 (*C*-*2*), 127.7 (br. s, *C-11* and *C-15*), 123.1 (q, $J_{C\text{-}F}$ 277.0, *C-17* and *C-18*), 123.0-122.7 (m, *C*-*13*), 30.1 (*C*H_2), 28.2 (*C*H_2), 23.0 (*C*H_2), 21.9 (*C*H_2), 15.0 (*C-16*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (6F, s); LRMS (ESI) *m/z* 814 (100%, $[2M+Na]^+$), 417 (50%, $[M+Na]^+$), 395 (80%, $[M+H]^+$); HRMS (ESI) found *m/z* 417.0718 ($[M+Na]^+$), $C_{18}H_{16}F_6NaOS^+$ requires 417.0718; ν_{max} (neat)/cm^{-1} 2926, 2848, 1651 (C=O), 1598, 1333, 1276, 1176, 1134, 1113.

(*E*)-3-(3,5-bis(Trifluoromethyl)phenyl)-1-(2-(methylthio)cyclohept-1-en-1-yl)prop-2-en-1-one (113)



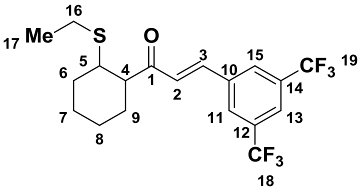
Prepared according to General Procedure **D** using 2-(methylthio)cyclohept-1-enecarbaldehyde (51 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) in acetone (2.0 mL) at room temperature for 1 h. Purification by flash column chromatography (15% Et_2O/petrol) afforded the linear regioisomer **113** as a bright yellow solid (77 mg, 63%, >20:1 l:b); m.p. (DCM) 76-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, s, *H-12* and *H-16*), 7.85 (1H, s, *H-14*), 7.56 (1H, d, *J* 16.0, *H-3*), 7.14 (1H, d, *J* 16.0, *H-2*), 2.71-2.65 (2H, m, C*H₂*), 2.60-2.53 (2H, m, C*H₂*), 2.28 (3H, s, *H-17*), 1.85-1.80 (2H, m C*H₂*), 1.66 (4H, m, 2×C*H₂*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1 (*C-1*), 149.4, 141.8, 137.6, 137.5 (*C-3*), 132.3 (q, $J_{\text{C-F}}$ 33.0, *C-12* and *C-16*), 129.6 (*C-2*), 127.6 (br. s, *C-13* and *C-15*), 123.0 (q, $J_{\text{C-F}}$ 273.0, *C-18* and *C-19*), 122.9-122.7 (m, *C-14*), 33.8 (*C*H₂), 31.8 (*C*H₂), 31.1 (*C*H₂), 26.6 (*C*H₂), 25.8 (*C*H₂), 16.2 (*C-17*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (6F, s); LRMS (ESI) *m/z* 839 (100%, $[2M+Na]^+$), 447 (50%, $[M+K]^+$), 409 (85%, $[M+H]^+$); HRMS (ESI) found *m/z* 431.0871 ($[M+Na]^+$), $C_{19}H_{18}F_6NaOS^+$ requires 431.0875; ν_{max} (neat)/cm^{-1} 2924, 2855, 1663 (C=O), 1602, 1377, 1279, 1169, 1118.

(*E*)-3-(3,5-bis(Trifluoromethyl)phenyl)-1-(4-(methylthio)-5,6-dihydro-2H-pyran-3-yl) prop-2-en-1-one (114)



Prepared according to General Procedure **D** using 4-(methylthio)-5,6-dihydro-2H-pyran-3-carbaldehyde (47 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene at room temperature for 1.5 h. Recrystallization from DCM afforded the linear regioisomer **114** as a bright yellow crystalline solid (100 mg, 84%, >20:1 l:b); m.p. (DCM) 189-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, s, *H-10* and *H-14*), 7.87 (1H, s, *H-12*), 7.69 (1H, d, *J* 15.5, *H-3*), 7.07 (1H, d, *J* 15.5, *H-2*), 4.62 (2H, s, *H-8*), 3.91 (2H, t, *J* 5.5, *H-7*), 2.68-2.61 (2H, m, *H-6*), 2.37 (3H, s, *H-15*); ^{13}C NMR (126 MHz, d_6-DMSO) δ 185.9 (*C-1*), 151.8 (*C-5*), 138.7 (*C-3*) 137.8 (*C-9*), 130.8 (q, $J_{C\text{-}F}$ 33.5, *C-11* and *C-13*), 129.0 (br. s, *C-10* and *C-14*), 127.2 (*C-2*), 127.0 (*C-4*), 123.2 (q, $J_{C\text{-}F}$ 272.0, *C-16* and *C-17*), 123.0-122.7 (m, *C-12*), 66.5 (*C-7*), 63.6 (*C-6*), 28.9 (*C-8*), 13.4 (*C-15*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (6F, s); LRMS (ESI) *m/z* 815 (100%, $[2M+Na]^+$), 419 (20%, $[M+Na]^+$), 397 (30%, $[M+H]^+$); HRMS (ESI) found *m/z* 419.0513 ($[M+Na]^+$), $C_{17}H_{14}F_6NaOS^+$ requires 419.0511; ν_{max} (neat)/cm^{-1} 3093, 2961, 2921, 2851, 1650 (C=O), 1597, 1514, 1380, 1275, 1108.

(*E*)-3-(3,5-bis(Trifluoromethyl)phenyl)-1-(2-(ethylthio)cyclohexyl)prop-2-en-1-one (115)

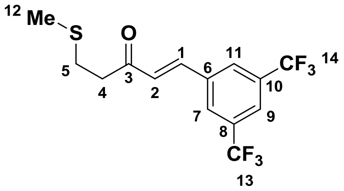


Prepared according to General Procedure **D** using 2-(ethylthio)cyclohexanecarbaldehyde (77 mg, 0.30 mmol, 9:1 *anti:syn*) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) at room temperature for 1.5 h. Purification by flash column chromatography (5% Et_2O/petrol) afforded the linear regioisomer **115** as an off-white solid (95 mg, 80%, >20:1 l:b, 9:1 *anti: syn*); m.p. (DCM) 66-68 °C; LRMS (ESI) *m/z* 843 (100%, $[2M+Na]^+$), 433 (40%, $[M+Na]^+$), 411 (30%, $[M+H]^+$); HRMS (ESI) found *m/z* 433.1027 ($[M+Na]^+$), $C_{19}H_{20}F_6NaOS^+$ requires 433.1031; ν_{max} (neat)/cm^{-1} 3049, 2935, 2859, 1689 (C=O), 1609, 1450, 1273, 1035.

***Anti* diastereomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (2H, s, *H-11* and *H-15*), 7.87 (1H, s, *H-13*), 7.63 (1H, d, *J* 16.0, *H-3*), 6.93 (1H, d, *J* 16.0, *H-2*), 2.95-2.82 (2H, m, *H-4* and *H-5*), 2.60-2.51 (2H, m, *H-18*), 2.26-2.16 (1H, m, Alkyl*H*), 1.92-1.87 (1H, m, Alkyl*H*) 1.86-1.75 (2H, m, 2×Alkyl*H*), 1.53-1.23 (4H, m, 4×Alkyl*H*), 1.20 (3H, t, *J* 7.5, *H-17*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (*C-1*), 138.8 (*C-3*), 136.9 (*C-10*), 132.4 (q, $J_{C\text{-}F}$ 33.5, *C-12* and *C-14*), 129.1 (*C-2*), 127.9 (app. d, $J_{C\text{-}F}$ 3.0, *C-11* and *C-15*), 123.2 (app. quin, $J_{C\text{-}F}$ 4.0, *C-13*), 123.0 (q, $J_{C\text{-}F}$ 273.0, *C-18* and *C-19*), 58.8 (*C-4*), 44.1 (*C-5*), 34.3 (*C*H_2), 30.5 (*C*H_2), 26.0 (*C*H_2), 25.5 (*C-16*), 24.9 (*C*H_2), 14.9 (*C-17*); ^{19}F NMR (376 MHz, $CDCl_3$) -63.1 (6F, s).

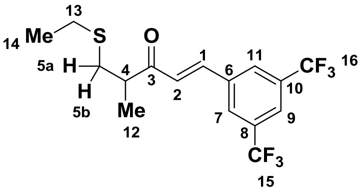
The following NMR signals are consistent with the ***syn* diastereomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, s, *H-11* and *H-15*), 7.64 (1H, d, *J* 16.0, *H-3*), 7.05 (1H, d, *J* 16.0, *H-2*), 2.39-2.32 (1H, m, Alkyl*H*), 2.10-2.03 (1H, m, Alkyl*H*), 1.69-1.64 (1H, m, Alkyl*H*), 1.17 (3H, t, *J* 7.5, *H-17*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2 (*C-1*), 138.4 (*C-3*), 137.0 (*C-10*), 127.7 (d, $J_{C\text{-}F}$ 5.0, *C-11* and *C-15*), 126.8 (*C-2*), 123.2 (app. quin, $J_{C\text{-}F}$ 4.0, *C-13*), 53.1 (*C-4*), 44.6 (*C-5*), 31.9 (*C*H$_2$), 29.7 (*C*H$_2$), 26.4 (*C*H$_2$), 24.2 (*C-16*), 23.0 (*C*H$_2$), 14.8 (*C-17*); ^{19}F NMR (376 MHz, CDCl$_3$) -63.1 (6F, s). The remaining signals are overlapping those for the ***anti*** diastereomer or cannot be observed due to very low intensity.

(*E*)-1-(3,5-bis(Trifluoromethyl)phenyl)-5-(methylthio)pent-1-en-3-one (116)



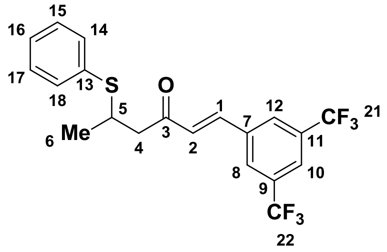
Prepared according to General Procedure **D** using 3-(methylthio)propionaldhehyde (30 μL, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) at room temperature for 2.5 h. Purification by flash column chromatography (5% EtOAc/petrol) afforded the linear regioisomer **116** as an off-white solid (85 mg, 82%, >20:1 l:b); m.p. (DCM) 64-66 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (2H, s, *H*-7 and *H-11*), 7.89 (1H, s, *H-9*), 7.61 (1H, d, *J* 16.0, *H-1*), 6.88 (1H, d, *J* 16.0, *H-2*), 3.05-2.99 (2H, m, *H-4*), 2.88-2.82 (2H, m, *H-5*), 2.16 (3H, s, SC*H$_3$*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 197.4 (*C-3*), 139.0 (*C-2*), 136.6 (*C-6*), 132.5 (q, $J_{\text{C-F}}$ 33.5, *C-8* and *C-10*), 128.7 (*C-1*), 127.8 (m, *C-7* and *C-11*), 123.5 (*C-9*), 122.8 (q, $J_{\text{C-F}}$ 273.0, *C-13* and *C-14*), 40.3 (*C-4*), 27.5 (*C-5*), 14.7 (*C-12*); ^{19}F NMR (376 MHz, CDCl$_3$) δ -63.1 (s, 6F); LRMS (ESI) *m/z* 365 (100%, [M+Na]$^+$); HRMS (ESI) found *m/z* 365.0401 ([M+Na]$^+$), $C_{14}H_{12}F_6NaOS^+$ requires 365.0405; ν_{max} (neat)/cm^{-1} 3044, 2961, 2934, 2888, 1697 (C=O), 1612, 1379, 1280, 1166, 1125.

(*E*)-1-(3,5-bis(Trifluoromethyl)phenyl)-5-(ethylthio)-4-methylpent-1-en-3-one (117)



Prepared according to General Procedure **D** using 3-(ethylthio)-2-methylpropanal (33 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) in acetone (2.0 mL) at room temperature for 4 h. Purification by flash column chromatography (5% Et_2O/petrol) afforded the linear regioisomer **117** as a pale yellow amorphous solid (60 mg, 54% >20:1 l:b); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (2H, s, *H-7* and *H-11*), 7.89 (1H, s, *H-9*), 7.65 (1H, d, *J* 16.0, *H-1*), 6.94 (1H, d, *J* 16.0, *H-2*), 3.15-3.04 (1H, m, *H-4*), 2.95 (1H, dd, *J* 13.0, 7.0, $H\text{-}5_a$), 2.62 (1H, dd, *J* 13.0, 7.0, $H\text{-}5_b$), 2.57 (2H, q, *J* 7.5, *H-13*), 1.32-1.23 (6H, m, *H-12* and *H-14*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2 (*C-3*), 139.2 (*C-1*), 136.7 (*C-6*), 133.5 (q, $J_{C\text{-}F}$ 33.5, *C-8* and *C-10*), 127.9 (br. s, *C-7* and *C-11*), 127.8 (*C-2*), 123.5 (app. quin, $J_{C\text{-}F}$ 3.0, *C-9*), 123.0 (q, $J_{C\text{-}F}$ 273.0, *C-15* and *C-16*), 45.6 (*C-6*), 34.3 (*C-5*), 26.9 (*C-13*), 19.6 (*C-14*), 14.7 (*C-12*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (6F, s); LRMS (ESI) *m/z* 763 (95%, $[2M+Na]^+$), 409 (100%, $[M+K]^+$), 393 (40%, $[M+Na]^+$), 371 (25%, $[M+H]^+$); HRMS (ESI) found *m/z* 393.1710 $[M+Na]^+$), $C_{16}H_{16}F_6NaOS^+$ requires 393.0718; ν_{max} (neat)/cm^{-1} 2975, 2931, 1694 (C=O), 1614, 1379, 1278, 1175, 1131.

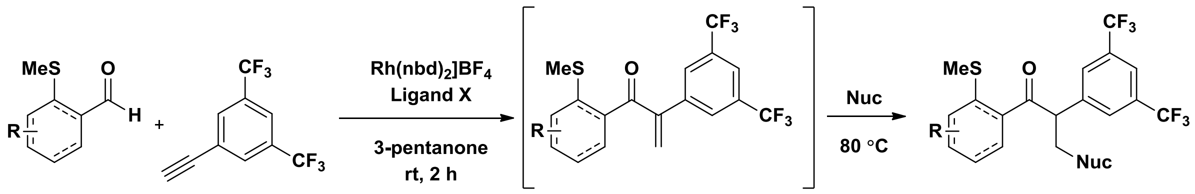
(*E*)-1-(3,5-bis(Trifluoromethyl)phenyl)-5-(phenylthio)hex-1-en-3-one (118l)



Prepared according to General Procedure **D** using 3-(phenylthio)butanal (54 mg, 0.30 mmol) 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) at 50 °C for 18 h. Purification by flash column chromatography (10% Et_2O/petrol) afforded an inseparable mixture of linear regioisomer **118l** and branched regioisomer **118b** as a brown oil (73 mg, 58%, 4.5:1 l:b). The data for the branched regioisomer is in accordance with the literature.[85] **Linear regioisomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, s, *H-8* and *H-12*), 7.89 (1H, s, *H-10*), 7.54-7.44 (1H, d, *J* 16.0, *H-2* overlapping 2H, m, *H-14* and *H-18*) 7.36-7.26 (3H, m, *H-15*, *H-16* and *H-17*), 6.80 (1H, d, *J* 16.0, *H-1*), 3.82 (1H, app. sxt, *J* 6.5, *H-5*), 3.08-3.00 (1H, dd, *J* 16.5, 5.0, $H\text{-}4_a$), 2.83 (1H, dd, *J* 16.5, 8.5, $H\text{-}4_b$), (3H, d, *J* 6.5, *H-6*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1 (*C-3*), 139.1 (*C-1*), 136.6 (Ar*C*), 134.2 (Ar*C*), 132.6 (*C-14*, *C-18*), 132.5 (q, $J_{C\text{-}F}$ 34.0, *C-9* and *C-11*), 129.1 (br. s, *C-2, C-15* and *C-17*), 127.8 (app. d, $J_{C\text{-}F}$ 4.0, *C-8* and *C-12*), 127.5 (*C-16*), 123.6 (app. quin, $J_{C\text{-}F}$ 3.0, *C-10*), 122.9 (q, $J_{C\text{-}F}$ 274.0, *C-21* and *C-22*), 48.2 (*C-5*), 38.3 (*C-4*), 21.0 (*C-6*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1 (6F, s); LRMS (ESI) *m/z* 859 (100%, $[2M+Na]^+$), 441 (40%, $[M+Na]^+$), 419 (15%, $[M+H]^+$)**;** HRMS (ESI) *m/z* found 441.0706 $[M+Na]^+$, $C_{20}H_{16}F_6NaOS^+$ requires 441.0718; ν_{max} (neat)/cm^{-1} 3061, 2968, 2927, 1696 (C=O), 1668, 1585, 1453, 1379, 1278, 1176, 1134. Data for the branched regioisomer is in accordance with the literature.[89]

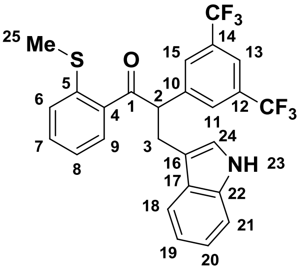
Exploiting Branched Selective Hydroacylation Intermediates

General Procedure E - Tandem Hydroacylation-Nucleophilic Addition



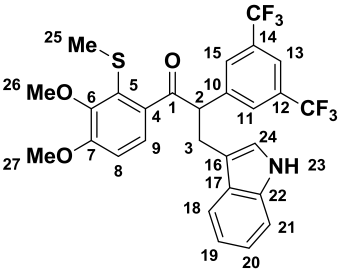
[Rh(nbd)$_2$]BF$_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 3-pentanone (1.5 mL) and stirred at room temperature for 5 min. H$_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with N$_{2(g)}$. The aldehyde (0.30 mmol) and alkyne (0.45 mmol) were added as a solution in 3-pentanone (0.5 mL) and the reaction mixture stirred at room temperature for 2 h. The nucleophile (0.60 mmol) was added and the reaction mixture heated to 80 °C for 18 h. The reaction mixture was allowed to cool to room temperature, filtered through a pad of Celite®, the pad washed with EtOAc and the filtrate concentrated *in vacuo*. Purification by flash column chromatography afforded the desired products.

2-(3,5-bis(Trifluoromethyl)phenyl)-3-(1*H*-indol-3-yl)-1-(2-(methylthio)phenyl)propan-1-one (119)



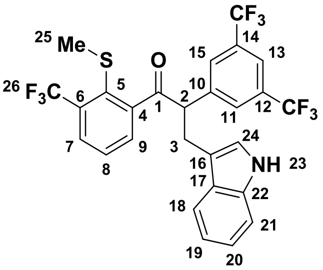
Prepared according to General Procedure **E** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) and indole (70 mg, 0.60 mmol). Purification by flash column chromatography (10% EtOAc/petrol) afforded the title compound **119** as a grey powder (124 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, br. s, N*H*), 7.74 (3H, s, *H-11*, *H-13* and *H-15*), 7.53 (2H, d, *J* 8.0, 2×Ar*H*), 7.45-7.37 (2H, m, 2×Ar*H*), 7.30 (1H, d, *J* 8.0, Ar*H*), 7.23 (1H, d, *J* 8.5, Ar*H*), 7.13 (1H, dd, *J* 8.5, 2.0, Ar*H*), 7.08 (1H, t, *J* 8.0, Ar*H*), 6.81 (1H, d, *J* 2.0, *C-24*), 4.99 (1H, app. t, *J* 7.5, *H-2*), 3.70 (1H, dd, *J* 14.5, 7.0, $H\text{-}3_a$), 3.21 (1H, dd, *J* 14.5, 7.0, $H\text{-}3_b$), 2.42 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9 (*C-1*), 150.1 (ArC), 140.7 (Ar*C*), 136.1 (Ar*C*), 134.9 (Ar*C*H), 132.4 (Ar*C*H), 131.8 (q, $J_{C\text{-}F}$ 34.0, *C-12* and *C-14*), 129.0 (Ar*C*H), 128.5 (br. s, *C-11* and *C-15*), 128.2 (Ar*C*), 125.8 (*C-24*), 123.8 (Ar*C*H), 123.2 (q, $J_{C\text{-}F}$ 273.0, 2×CF_3), 122.9 (Ar*C*), 122.1 (Ar*C*H), 121.4-121.2 (m, *C-13*), 119.6 (Ar*C*H), 118.2 (Ar*C*H), 112.3 (Ar*C*H), 111.1 (*C-16*), 55.3 (*C-2*), 29.8 (*C-3*), 16.1 (*C-25*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8 (6F, s); LRMS (ESI) *m/z* 564 (100%, $[M+Na]^+$). Data is in accordance with the literature.[89]

2-(3,5-bis(Trifluoromethyl)phenyl)-1-(3,4-dimethoxy-2-(methylthio)phenyl)-3-(1*H*-indol-3-yl)propan-1-one (120)



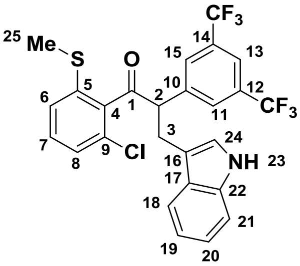
Prepared according to General Procedure **E** using 3,4-dimethoxy-2-(methylthio)benzaldehyde (64 mg, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) and indole (70 mg, 0.60 mmol). Purification by flash column chromatography (40% Et_2O/petrol) afforded the title compound **120** as a dark brown crystalline solid (120 mg, 71%); m.p. (DCM) 57-58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (1H, br. s, *NH*), 7.74-7.66 (3H, m, *H-11*, *H-13* and *H-15*), 7.56 (1H, d, *J* 8.0, *H-18*), 7.32 (1H, app. d, *J* 8.0, *H-21*), 7.19 (1H, app. t, *J* 7.5, *H-20*), 7.15-7.08 (1H, m, *H-20*), 6.84 (1H, d, *J* 8.5, *H-9*), 6.76 (1H, d, *J* 2.0, *H-24*), 6.72 (1H, d, *J* 8.5, *H-8*), 5.01 (1H, app. t, *J* 7.5, *H-2*), 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.78 (1H, dd, *J* 14.5, 7.0, $H\text{-}3_a$), 3.29 (1H, dd, *J* 14.5, 8.0, $H\text{-}3_b$), 2.27 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.3 (*C-1*), 155.0 (Ar*C*OMe), 150.4 (Ar*C*OMe), 141.5 (Ar*C*), 137.0 (Ar*C*), 136.1 (Ar*C*), 131.5 (q, $J_{C\text{-}F}$ 33.5, *C-12* and *C-14*), 129.7 (Ar*C*), 128.9 (br. s, *C-11* and *C-15*), 127.1 (Ar*C*), 124.0 (*C-9*), 123.2 (q, $J_{C\text{-}F}$ 274.0, 2×CF_3), 122.9 (*C-24*), 122.1 (*C-20*), 121.9 (app. quin, $J_{C\text{-}F}$ 4.0, *C-13*), 119.5 (*C-19*) 118.3 (*C-18*), 112.3 (*C-16*), 111.3 (*C-8*), 111.1 (*C-21*), 60.2 (OCH_3), 58.0 (*C*-2), 55.9 (OCH_3), 29.5 (*C-3*), 19.1 (*C-25*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (6F, s); LRMS (ESI) *m/z* 606 (100%, $[M+K]^+$), 590 (70%, $[M+Na]^+$); HRMS (ESI) found *m/z* found 590.1182 $[M+Na]^+$, $C_{28}H_{23}F_6NNaO_3S^+$ requires 590.1195; ν_{max} (neat)/cm^{-1} 3390 (N-H), 2924, 1681 (C=O), 1434, 1371, 1277, 1167, 1126.

2-(3,5-bis(trifluoromethyl)phenyl)-3-(1H-indol-3-yl)-1-(2-(methylthio)-3-(trifluoromethyl)phenyl)propan-1-one (121)



Prepared according to General Procedure **E** using 2-(methylthio)-3-(trifluoromethyl)benzaldehyde (66 mg, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl) benzene (80 µL, 0.45 mmol) and indole (70 mg, 0.60 mmol). Purification by flash column chromatography (40% Et_2O/petrol) afforded the title compound **121** as a pale brown solid (75 mg, 44%); m.p. (DCM) 110-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, br. s, N*H*), 7.75 (1H, s, *H-13*), 7.73-7.65 (1H, m, Ar*H*, overlapping 2H, s, *H-11* and *H-15*), 7.55 (1H, d, *J* 8.0, Ar*H*), 7.35-7.28 (2H, m, 2×Ar*H*), 7.19 (1H, t, *J* 7.5, Ar*H*), 7.15-7.08 (1H, m, Ar*H*), 6.83 (1H, app. d, *J* 8.0, Ar*H*), 6.76 (1H, d, *J* 2.0, *H-24*), 4.99 (1H, dd, *J* 8.5, 6.5, *H-2*), 3.80 (1H, dd, *J* 14.5, 6.5, $H\text{-}3_a$), 3.40 (1H, dd, *J* 14.5, 8.5, $H\text{-}3_b$), 2.15 (3H, s, SC*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.5 (*C-1*), 150.1 (Ar*C*), 140.7 (Ar*C*), 136.1 (Ar*C*), 135.0 (q, $J_{\text{C-F}}$ 29.5, *C-6*), 131.7 (q, $J_{\text{C-F}}$ 33.5, *C-12* and *C-14*), 131.0 (Ar*C*), 130.3 (Ar*C*H), 130.0 (br. s, *C-8*), 128.9 (br. s, *C-11* and *C-15*), 128.0 (q, $J_{\text{C-F}}$ 4.5, *C-7*), 127.0 (Ar*C*), 123.2 (q, $J_{\text{C-F}}$ 274.0, *C*F$_3$), 123.1 (q, $J_{\text{C-F}}$ 273.0, 2×*C*F$_3$), 122.7 (*C-24*), 122.3 (Ar*C*H), 121.5-121.0 (app. quin, $J_{\text{C-F}}$ 3.5, *C-13*), 119.7 (Ar*C*H), 118.4 (Ar*C*H), 111.9 (*C-16*), 111.2 (Ar*C*H), 59.6 (*C-2*), 29.5 (*C-3*), 22.1 (*C-25*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.7 (3F, s,), -62.8 (6F, s); LRMS (ESI) *m/z* 574 (100%, $[M-H]^-$); HRMS (ESI) found *m/z* 598.0840 $[M+Na]^+$, $C_{27}H_{18}F_9NNaOS^+$ requires 598.0858; ν_{max} (neat)/cm^{-1} 3353 (N-H), 1689 (C=O), 1424, 1374, 1321, 1277, 1164, 1119, 1097.

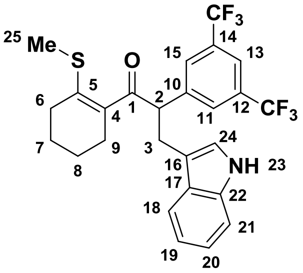
2-(3,5-bis(Trifluoromethyl)phenyl)-1-(2-chloro-6-(methylthio)phenyl)-3-(1H-indol-3-yl)propan-1-one (122)



[Rh(nbd)$_2$]BF$_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in acetone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-Chloro-6-(methylthio)benzaldehyde (45 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) were added as a solution in acetone (0.5 mL) and the reaction mixture heated to 50 °C for 6 h. The reaction mixture was allowed to cool to room temperature, and the solvent removed *in vacuo*. The crude residue was re-dissolved in 1,2-DCE (2 mL), indole (70 mg, 0.60 mmol) was added and the reaction mixture heated to 80 °C for 18 h. The reaction mixture was allowed to cool to room temperature, filtered through a pad of Celite® using EtOAc as eluent and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (40% Et$_2$O/petrol) afforded the title compound **122** as a brown oil (36 mg, 22%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88 (1H, br. s, N*H*), 7.69 (1H, s, *H-13*), 7.65 (2H, s, *H-11* and *H-15*), 7.55 (1H, d, *J* 8.0, Ar*H*), 7.33-7.29 (1H, m, Ar*H*), 7.28-7.24 (1H, m, Ar*H*), 7.23-7.16 (3H, m, 3×Ar*H*), 7.14-7.07 (1H, m, Ar*H*), 6.66 (1H, d, *J* 2.0, *H-24*), 4.85 (1H, dd, *J* 10.0, 4.5, *H-2*), 3.88 (1H, dd, *J* 14.5, 4.5, *H-3$_a$*), 3.48 (1H, dd, *J* 14.5, 10.0, *H-3$_b$*), 2.33-2.24 (3H, s, SC*H$_3$*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 201.8 (*C-1*), 139.7 (Ar*C*), 139.3 (ArC), 137.3 (ArC), 136.1 (ArC), 131.4 (q, $J_{C\text{-}F}$ 32.5, *C-12* and *C-14*), 130.7 (Ar*C*H), 130.1 (Ar*C*), 129.7 (br, s, *C-11* and *C-15*), 127.2 (Ar*C*H), 127.1 (Ar*C*), 126.9 (Ar*C*H), 123.2 (q, $J_{C\text{-}F}$ 272.0, 2×*C*F$_3$), 122.7 (*C-24*), 122.1

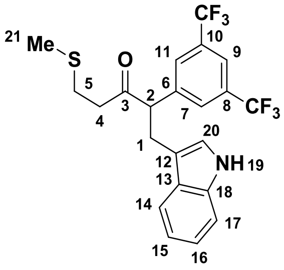
(Ar*C*H), 121.1 (app. quin, $J_{\text{C-F}}$ 3.0, *C-13*), 119.1 (Ar*C*H), 118.4 (Ar*C*H), 111.9 (Ar*C*H), 111.2 (*C-16*), 59.5 (*C-2*), 27.7 (*C-3*), 17.6 (*C-25*); ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.6 (6F, s); LRMS (ESI) *m/z* 580 (50%, $[M+K]^+$), 564 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 564.0593 $[M+Na]^+$, $C_{26}H_{18}ClF_6NNaOS^+$ requires 564.0594; ν_{max} (neat)/cm^{-1} 3481 (N-H), 1703, 1621, 1574, 1556, 1458, 1430, 1374, 1277, 1171, 1132.

2-(3,5-bis(Trifluoromethyl)phenyl)-3-(1*H*-indol-3-yl)-1-(2-(methylthio)cyclohex-1-en-1-yl) propan-1-one (123)



Prepared according to General Procedure **E** using 2-(methylthio)cyclohex-1-enecarbaldehyde (47 mg, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) and indole (70 mg, 0.60 mmol). Purification by flash column chromatography (20% Et_2O/petrol) afforded the title compound **123** as a pale brown powder (82 mg, 54%); m.p. (DCM) 94-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, br. s, N*H*), 7.73 (1H, s, *H-13*), 7.69 (2H, s, *H-11* and *H-15*), 7.53 (1H, app. d, *J* 8.0, *H-18*), 7.34 (1H, app. d, *J* 8.0, *H-21*), 7.24-7.17 (1H, m, *H-20*), 7.16-7.08 (1H, m, *H-19*), 6.73 (1H, d, *J* 2.0, *H-24*), 4.66 (1H, app. t, *J* 7.5, *H-2*), 3.63 (1H, dd, *J* 14.5, 7.0, $H\text{-}3_a$), 3.16 (1H, dd, *J* 14.5, 7.5, $H\text{-}3_b$), 2.45-2.37 (2H, m, CH_2), 2.24 (3H, s, SCH_3), 2.20-2.11 (2H, m, CH_2), 1.58-1.44 (4H, m, 2×CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9 (*C-1*), 151.0 (*C-5*), 142.3 (*C*), 136.1 (*C*), 131.0 (q, $J_{C\text{-}F}$ 33.5, *C-12*, and *C-14*), 130.0 (*C*), 128.7 (br. s, *C-11*, and *C-15*), 127.1 (*C*), 122.8 (*C-24*), 123.3 (q, $J_{C\text{-}F}$ 272.5, 2×CF_3), 121.2 (*C-20*), 120.9-120.7 (m, *C-13*), 119.4 (*C-18*), 118.3 (*C-19*), 112.6 (*C-16*), 111.3 (*C-21*), 54.7 (*C-2*), 30.0 (*C-3*), 29.2 (CH_2), 28.0 (CH_2), 22.6 (CH_2), 21.7 (CH_2), 14.7 (*C-25*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (6F, s); LRMS (ESI) *m/z* 534 (100%, $[M+Na]^+$), 550 (30%, $[M+K]^+$); HRMS (ESI) found *m/z* 534.1276 $[M+Na]^+$, $C_{26}H_{23}F_6NNaOS^+$ requires 534.1297; ν_{max} (neat)/cm^{-1} 3415 (N-H), 2939, 1632 (C=O), 1503, 1458, 1419, 1372, 1276, 1173, 1116, 1006.

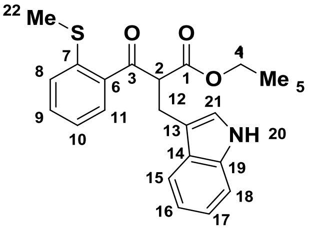
2-(3,5-bis(Trifluoromethyl)phenyl)-1-(1*H*-indol-3-yl)-5-(methylthio)pentan-3-one (124)



[Rh(nbd)$_2$]BF$_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in acetone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 3-Methylthiopropionaldehyde (30 µL, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) were added as a solution in acetone (0.5 mL) and the reaction mixture heated to 50 °C for 6 h. The reaction mixture was allowed to cool to room temperature, and the solvent removed *in vacuo*. The crude residue was re-dissolved in 1,2-DCE (2 mL) before indole (70 mg, 0.60 mmol) was added and the reaction mixture heated to 80 °C for 18 h. The reaction mixture was allowed to cool to room temperature, filtered through a pad of Celite® using EtOAc as eluent and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (20% Et$_2$O/petrol) afforded the title compound **124** as a brown oil (55 mg, 40%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.14 (1H, br. s, *H-19*), 7.80 (1H, s, *H-9*), 7.73 (2H, s, *H-7* and *H-11*), 7.53 (1H, app. d, *J* 8.0, *H-14*), 7.36 (1H, app. d, *J* 8.0, *H-17*), 7.22 (1H, app. t, *J* 7.5, *H-16*), 7.15 (1H, app. t, *J* 8.0, *H-15*), 6.82 (1H, d, *J* 2.0, *H-20*), 4.27 (1H, dd, *J* 8.0, 6.5, *H-2*), 3.62 (1H, dd, *J* 14.5, 8.0, $H\text{-}1_a$), 3.13 (1H, dd, *J* 14.5, 6.5, $H\text{-}1_b$), 2.71-2.46 (4H, m, *H-4* and *H-5*), 1.92 (3H, s, *H-21*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 207.6 (*C-3*), 141.1 (Ar*C*), 136.1 (Ar*C*), 132.0 (q, $J_{\text{C-F}}$ 33.5, *C-8* and *C-10*), 128.5 (Ar*C*), 127.2 (br. s, *C-7* and *C-11*), 123.2 (q, $J_{\text{C-F}}$ 273.5, 2×*C*F$_3$), 122.7 (*C-20*), 122.3 (*C-16*), 121.6-121.3 (m, *C-9*), 119.7 (*C-15*), 118.2 (*C-14*), 112.1 (*C-12*), 111.4 (*C-17*), 58.8 (*C-2*), 42.9 (*C-4*), 29.2 (*C-1*), 27.6 (*C-5*), 15.6 (*C-21*); ^{19}F NMR

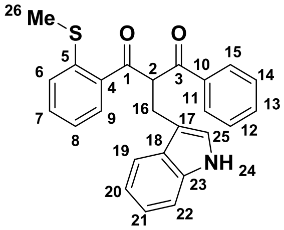
(470 MHz, $CDCl_3$) δ -62.6 (6F, s); LRMS (ESI) *m/z* 482 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 482.0972 $[M+Na]^+$, $C_{22}H_{19}F_6NNaOS^+$ requires 482.0984; ν_{max} (neat)/cm^{-1} 3405 (N-H), 2921, 1710 (C=O), 1620, 1458, 1429, 1373, 1276, 1224, 1169, 1128.

Ethyl 2-((1*H*-indol-3-yl)methyl)-3-(2-(methylthio)phenyl)-3-oxopropanoate (125)



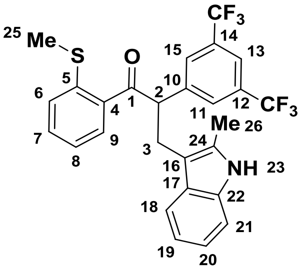
[Rh(nbd)$_2$]BF$_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 3-pentanone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 μL, 0.30 mmol), and ethyl propiolate (61 μL, 0.45 mmol) were added as a solution in 3-pentanone (0.5 mL) and the reaction mixture heated to 50 °C for 4 h. Indole (70 mg, 0.60 mmol) was added and the reaction mixture stirred for a further 18 h at 50 °C. The reaction mixture was allowed to cool to room temperature, filtered through a pad of Celite® using EtOAc as eluent and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (20% Et$_2$O/petrol) afforded the title compound **125** as a brown amorphous solid (85 mg, 77%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.00 (1H, br. s, *H-20*), 7.83-7.70 (1H, app. d, *J* 7.0, *H-11*), 7.62 (1H, app. d, *J* 7.5, *H-15*), 7.49-7.39 (1H, m, *H-9*), 7.37-7.29 (2H, m, *H-8* and *H-18*), 7.19 (1H, app. t, *J* 7.0, *H-10*), 7.16-7.08 (2H, m, *H-16* and *H-17*), 7.06 (1H, d, *J* 2.0, *H-21*), 4.73 (1H, *J* 7.0, *H-2*), 4.12-4.08 (2H, m, *H-4*), 3.51 (2H, d, *J* 7.0, *H-12*), 2.43 (3H, s, SC*H$_3$*) 1.12 (3H, t, *J* 7.0, *H-5*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 195.7 (*C-3*), 169.6 (*C-1*), 143.1 (Ar*C*), 136.1 (Ar*C*), 134.0 (Ar*C*), 132.4 (*C-9*), 130.5 (*C-11*), 127.2 (Ar*C*), 125.3 (*C-8*), 123.5 (*C-17*), 123.0 (*C-21*), 122.0 (*C-10*), 119.4 (*C-16*), 118.5 (*C-15*), 112.5 (*C-13*), 111.1 (*C-18*), 61.4 (*C-4*), 56.3 (*C-2*), 24.5 (*C-12*), 16.1 (*C-22*), 13.9 (*C-5*); LRMS (ESI) *m/z* 366 (100%, [M-H]$^-$); HRMS (ESI) found *m/z* 390.1127 [M+Na]$^+$, $C_{21}H_{21}NNaO_3S^+$ requires 390.1134; ν_{max} (neat)/cm^{-1} 3399 (N-H), 2980, 1728 (C=O ester), 1667 (C=O ketone), 1619, 1587, 1489, 1431, 1339, 1260, 1223, 1173, 1141, 1094.

2-((1*H*-Indol-3-yl)Methyl)-1-(2-(methylthio)phenyl)-3-phenylpropane-1,3-dione (126)



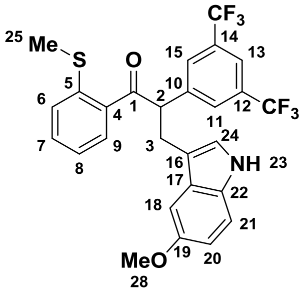
[Rh(nbd)$_2$]BF$_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 3-pentanone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 μL, 0.30 mmol), and 1-phenylprop-2-yn-1-one (59 mg, 0.45 mmol) were added as a solution in 3-pentanone (0.5 mL) and the reaction mixture heated to 50 °C for 4 h. Indole (70 mg, 0.60 mmol) was added and the reaction mixture stirred for a further 18 h at 50 °C. The reaction mixture was allowed to cool to room temperature, filtered through a pad of Celite® using EtOAc as eluent and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (20% Et$_2$O/petrol) afforded the title compound **126** as an orange solid (83 mg, 69%); m.p. (DCM) 138-139 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (1H, br. s, *H-24*), 7.87 (2H, d, *J* 7.5, 2×Ar*H*), 7.60 (2H, t, *J* 8.5, 2×*Ar*H), 7.54-7.46 (1H, m, Ar*H*), 7.43-7.25 (5H, m, 5×Ar*H*), 7.23-7.10 (2H, m, 2×Ar*H*), 7.08-7.03 (2H, m, 2×Ar*H*), 5.63 (1H, app. t, *J* 6.5, *H-2*), 3.69-3.54 (2H, m, *H-16*), 2.36 (3H, s, SC*H$_3$*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 196.8 (*C*=O), 196.0 (*C*=O), 143.0 (Ar*C*-), 136.3 (Ar*C*), 136.1 (Ar*C*), 134.4 (Ar*C*), 133.3 (Ar*C*H), 132.2 (Ar*C*H), 130.0 (Ar*C*H), 128.7 (2×Ar*C*H), 128.6 (2×Ar*C*H), 127.1 (Ar*C*), 125.7 (Ar*C*H), 123.7 (Ar*C*H), 124.4 (Ar*C*H), 121.9 (Ar*C*H), 119.5 (Ar*C*H), 118.4 (Ar*C*H), 112.9 (*C-17*), 111.2 (Ar*C*H), 59.5 (*C-2*), 25.1 (*C-3*), 16.2 (*C-26*), LRMS (ESI) *m/z* 398 (100%, [M-H]$^-$); HRMS (ESI) found *m/z* 422.1178 [M+Na]$^+$, $C_{25}H_{21}NNaO_2^+$ requires 422.1185; ν_{max} (neat)/cm^{-1} 3434 (N-H), 2922, 1687 (C=O), 1659 (C=O), 1585, 1556, 1430, 1323, 1269, 1229, 1189, 1140.

2-(3,5-bis(Trifluoromethyl)phenyl)-3-(2-methyl-1*H*-indol-3-yl)-1-(2-(methylthio) phenyl)propan-1-one (129)



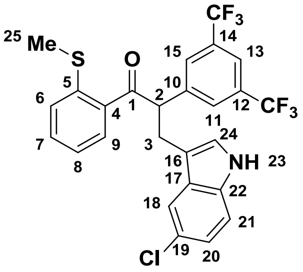
Prepared according to General Procedure **E** using 2-(methylthio)benzaldehyde (39 µL, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) and 2-methylindole (79 mg, 0.60 mmol). Purification by flash column chromatography (20% Et$_2$O/petrol) afforded the title compound **129** as a beige solid (111 mg, 71%); m.p. (DCM) 146-147 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (1H, s, *H-13*), 7.69 (1H, br. s, N*H*), 7.64 (2H, s, *H-11* and *H-15*), 7.48 (2H, t, *J* 7.5, 2×Ar*H*), 7.40 (1H, *J* 8.0, Ar*H*), 7.31 (1H, *J* 8.0, Ar*H*), 7.26 (1H, d, *J* 8.0, Ar*H*), 7.18-7.09 (2H, m, 2×Ar*H*), 7.04 (1H, t, *J* 7.5, Ar*H*), 5.03 (1H, app. t, *J* 7.5, *H-2*), 3.66 (1H, dd, *J* 14.5, 6.5, *H-3$_a$*), 3.17 (1H, dd, *J* 14.5, 8.5, *H-3$_b$*), 2.42 (3H, s, SC*H$_3$*), 1.96 (3H, s, *H-28*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 200.4 (*C-1*), 142.4 (Ar*C*), 141.9 (Ar*C*), 135.4 (Ar*C*), 134.9 (Ar*C*), 132.5 (Ar*C*), 132.3 (Ar*C*H), 131.6 (q, $J_{\text{C-F}}$ 33.5, *C-12* and *C-14*), 129.7 (Ar*C*H), 128.5 (br. s, *C-11* and *C-15*), 128.1 (Ar*C*), 125.8 (Ar*C*H), 123.8 (Ar*C*H), 123.2 (q, $J_{\text{C-F}}$ 273.0, 2×*C*F$_3$), 121.3 (Ar*C*H), 120.9 (app. quin, $J_{\text{C-F}}$ 3.0, *C-13*), 119.5 (Ar*C*H), 117.3 (Ar*C*H), 110.5 (Ar*C*H), 107.6 (*C-16*), 54.9 (*C-2*), 29.4 (*C-3*), 16.2 (*C-25*), 11.1 (*C-26*); ^{19}F NMR (470 MHz, CDCl$_3$) δ -62.8 (6F, s); LRMS (ESI) *m/z* 544.1 (100%, [M+Na]$^+$); HRMS (ESI) found *m/z* 544.1132 [M+Na]$^+$, $C_{27}H_{21}F_6NNaOS^+$ requires 544.1140; ν_{max} (neat)/cm^{-1} 3400 (N-H), 1666 (C=O), 1585, 1460, 1433, 1369, 1278, 1217, 1166, 1124.

2-(3,5-bis(Trifluoromethyl)phenyl)-3-(5-methoxy-1*H*-indol-3-yl)-1-(2-(methylthio) phenyl) propan-1-one (138)



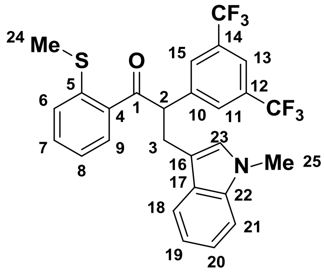
Prepared according to General Procedure **E** using 2-(methylthio)benzaldehyde (39 µL, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) and 5-methoxy-1*H*-indole (88 mg, 0.60 mmol). Purification by flash column chromatography (40% Et_2O/petrol) afforded the title compound **138** as a brown oil (90 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, br. s, N*H*), 7.73 (3H, s, *H-11*, *H-13* and *H-15*), 7.57 (1H, app. d, *J* 7.5, *H-9*), 7.44-7.37 (1H, m, *H-7*), 7.31 (1H, d, *J* 8.0, *H-6*), 7.21 (1H, d, *J* 9.0, *H-21*), 7.07 (1H, app. t, *J* 7.5, *H-8*), 6.93 (1H, br. s, *H-18*), 6.86 (1H, dd, *J* 9.0, 2.0, *H-20*), 6.75 (1H, br. s, *H-24*), 5.03 (1H, app. t, *J* 7.0, *H-2*), 3.85 (3H, s, OCH_3), 3.73 (1H, dd, *J* 14.5, 7.0, $H\text{-}3_a$), 3.23 (1H, dd, *J* 14.5, 7.5, $H\text{-}3_b$), 2.41 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (*C-1*), 154.1 (*C-19*), 142.5 (Ar*C*), 141.9 (Ar*C*), 134.8 (Ar*C*), 132.4 (*C-7*), 131.7 (q, $J_{\text{C-F}}$ 33.5, *C-12*, and *C-14*), 131.3 (Ar*C*), 129.7 (*C-9*), 128.6 (app. d, $J_{\text{C-F}}$ 3.0, *C-11* and *C-15*), 127.5 (Ar*C*), 125.8 (*C-6*), 123.8 (*C-9*), 123.6 (*C-24*), 123.0 (q, $J_{\text{C-F}}$ 273.5, 2×CF_3), 121.1 (app. quin, $J_{\text{C-F}}$ 3.0, *C-13*), 112.1 (*C-20*), 112.0 (br. s, *C-16* and *C-12*), 100.2 (*C-18*), 55.9 (*C-28*), 55.4 (*C-2*), 30.0 (*C-3*), 16.1 (*C-25*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (6F, s); LRMS (ESI) *m/z* 560 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 560.1087 $[M+Na]^+$, $C_{27}H_{21}F_6NNaO_2S^+$ requires 560.1089; ν_{max} (neat)/cm^{-1} 3411 (N-H), 1668 (C=O), 1549, 1468, 1435, 1373, 1278, 1171, 1133.

2-(3,5-bis(Trifluoromethyl)phenyl)-3-(5-chloro-1*H*-indol-3-yl)-1-(2-(methylthio)phenyl) propan-1-one (139)



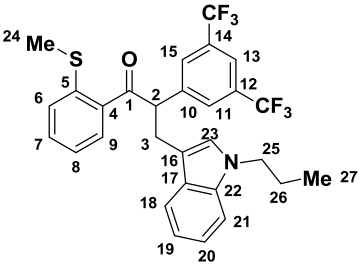
Prepared according to General Procedure **E** using 2-(methylthio)benzaldehyde (39 µL, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) and 5-chloro-1*H*-indole (92 mg, 0.60 mmol). Purification by flash column chromatography (30% Et$_2$O/petrol) afforded the title compound **139** as a pale brown powder (84 mg, 52%); m.p. (DCM) 98-100 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 (1H, br. s, N*H*), 7.73 (1H, s, *H-13*), 7.71 (2H, s, *H-11* and *H-15*), 7.53 (1H, d, *J* 8.0, *H-9*), 7.45-7.37 (2H, m, 2×Ar*H*), 7.30 (1H, d, *J* 8.0, Ar*H*), 7.23 (1H, d, *J* 8.5, Ar*H*), 7.13 (1H, dd, *J* 8.5, 2.0, Ar*H*), 7.08 (1H, t, *J* 8.0, Ar*H*), 6.81 (1H, d, *J* 2.0, *H-24*), 4.99 (1H, app. t, *J* 7.5, *H-2*), 3.70 (1H, dd, *J* 14.5, 7.0, *H-3$_a$*), 3.21 (1H, dd, *J* 14.5, 7.0, *H-3$_b$*), 2.42 (3H, s, SCH_3); ^{13}C NMR (101 MHz, CDCl$_3$) δ 199.9 (*C-1*), 142.4 (Ar*C*), 141.6 (Ar*C*), 134.8 (Ar*C*), 134.4 (Ar*C*), 132.4 (Ar*C*H), 131.8 (q, $J_{\text{C-F}}$ 34.0, *C-12* and *C-14*), 129.6 (Ar*C*H), 128.5 (br. s, *C-11* and *C-15*), 128.2 (Ar*C*H), 125.8 (Ar*C*H), 125.5 (Ar*C*H), 124.4 (Ar*C*H), 123.8 (*C-24*), 123.2 (q, $J_{\text{C-F}}$ 273.0, 2×*C*F$_3$), 122.5 (Ar*C*H) 121.4-121.2 (m, *C-13*), 117.8 (Ar*C*H) 112.2 (Ar*C*H) 112.1 (*C-16*), 55.3 (*C-2*), 29.8 (*C-3*), 16.1 (*C-25*); ^{19}F NMR (376 MHz, CDCl$_3$) δ -62.8 (6F, s); LRMS (ESI) *m/z* 564 (100%, [M+Na]$^+$); HRMS (ESI) found *m/z* 564.0582 [M+Na]$^+$, $C_{26}H_{18}{}^{35}ClF_6NNaOS^+$ requires 564.0594; ν_{max} (neat)/cm^{-1} 3433 (N-H), 1665 (C=O), 1586, 1463, 1431, 1370, 1272, 1173, 1140.

2-(3,5-bis(Trifluoromethyl)phenyl)-3-(1-methyl-1*H*-indol-3-yl)-1-(2-(methylthio)phenyl) propan-1-one (141)



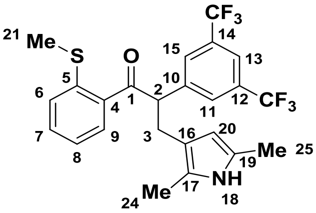
Prepared according to General Procedure **E** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) and 1-methylindole (75 μL, 0.60 mmol). Purification by flash column chromatography (20% Et_2O/petrol) afforded the title compound **141** as green crystalline solid (71 mg, 45%); m.p. (DCM) 129-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (1H, s, *H-13*), 7.72 (2H, s, *H-11* and *H-15*), 7.53 (2H, d, *J* 8.0, 2×ArC*H*), 7.42-7.36 (1H, m, ArC*H*), 7.30 (1H, *J* 8.5, ArC*H*), 7.26-7.10 (3H, m, 3×ArC*H*), 7.06 (1H, t, *J* 7.5, ArC*H*), 6.63 (1H, s, *H-23*), 5.02 (1H, app. t, *J* 7.0, *H-2*), 3.76 (1H, dd, *J* 14.5, 7.5, *H-3$_a$*), 3.66 (3H, s, NCH_3), 3.26 (1H, dd, *J* 14.5, 7.5, *H-3$_b$*), 2.42 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (*C-1*), 142.4 (Ar*C*), 141.9 (Ar*C*), 136.9 (Ar*C*), 135.0 (Ar*C*), 132.3 (Ar*C*H), 131.7 (q, $J_{C\text{-}F}$ 33.5, *C-12* and *C-14*), 129.6 (Ar*C*H), 128.5 (br. s, *C-11* and *C-15*), 127.8 (*C-23*), 127.5 (Ar*C*), 125.8 (Ar*C*H), 123.7 (Ar*C*H), 123.2 (q, $J_{C\text{-}F}$ 273.5, 2×*C*F_3), 121.6 (Ar*C*H), 121.1 (app. quin, $J_{C\text{-}F}$ 4.5, *C-13*), 119.0 (Ar*C*H), 118.3 (Ar*C*H), 110.7 (*C-16*), 109.4 (Ar*C*H), 55.6 (*C-2*), 32.5 (*C-27*), 30.0 (*C-3*), 16.1 (*C-24*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8 (6F, s); LRMS (ESI) *m/z* 544 (60%, $[M+Na]^+$); HRMS (ESI) found *m/z* 544.1139 $[M+Na]^+$, $C_{27}H_{21}F_6NNaOS^+$ requires 544.1140; ν_{max} (neat)/cm^{-1} 2918, 1737, 1661 (C=O), 1554, 1431, 1370, 1279, 1229, 1169, 1111.

2-(3,5-bis(trifluoromethyl)phenyl)-1-(2-(methylthio)phenyl)-3-(1-propyl-1H-indol-3-yl)propan-1-one (142)



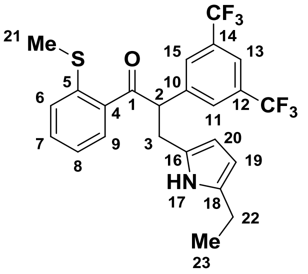
Prepared according to General Procedure **E** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) and 1-methylindole (75 μL, 0.60 mmol). Purification by flash column chromatography (20% Et_2O/petrol) afforded the title compound **142** as brown oil (127 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (3H, s, *H-11*, *H-13* and *H-15*), 7.59-7.52 (2H, m, 2×Ar*H*), 7.40 (1H, t, *J* 7.0, Ar*H*), 7.34-7.26 (2H, m, 2×Ar*H*), 7.21 (1H, t, *J* 7.0, Ar*H*), 7.12 (1H, t, *J* 8.0, Ar*H*), 7.06 (1H, t, *J* 7.0, Ar*H*), 6.66 (1H, s, *H-23*), 5.04 (1H, app. t, *J* 7.5, *H-2*), 4.00-3.87 (2H, m, *H-25*), 3.76 (1H, dd, *J* 14.5, 7.0, $H\text{-}3_a$), 3.27 (1H, dd, *J* 14.5, 8.0, $H\text{-}3_b$), 2.43 (3H, s, SCH_3), 1.78-1.66 (2H, m, *H-26*), 0.77 (3H, t, *J* 7.5, *H-27*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2 (*C-1*), 142.4 (Ar*C*), 141.9 (Ar*C*), 136.2 (Ar*C*), 134.9 (Ar*C*), 132.3 (Ar*C*H), 131.7 (q, $J_{C\text{-}F}$ 34.0, *C-12* and *C-14*), 129.7 (Ar*C*H), 128.6 (br. s, *C-11* and *C-15*), 127.5 (Ar*C*H), 126.8 (*C-23*), 125.7 (Ar*C*H), 123.7 (Ar*C*H), 123.3 (Ar*C*H), 121.5 (Ar*C*H) 121.1 (app. quin, $J_{C\text{-}F}$ 6.0, *C-13*), 118.9 (Ar*C*H), 118.3 (Ar*C*H), 110.4 (*C-16*), 109.6 (Ar*C*H), 55.5 (*C-2*), 47.7 (*C-25*), 30.1 (*C-3*), 23.4 (*C-26*), 16.1 (*C-24*), 11.3 (*C-28*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (6F, s); LRMS (ESI) *m/z* 572 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* found 572.1149 $[M+Na]^+$, $C_{29}H_{25}F_6NNaOS^+$ requires 72.1453; ν_{max} (neat)/cm^{-1} 2966, 2927, 2877, 1668 (C=O), 1615, 1587, 1467, 1433, 1371, 1275, 1167, 1127.

2-(3,5-bis(Trifluoromethyl)phenyl)-3-(2,5-dimethyl-1*H*-pyrrol-3-yl)-1-(2-(methylthio)phenyl) propan-1-one (143)



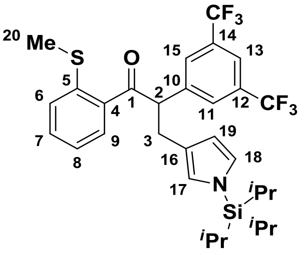
Prepared according to General Procedure **E** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) and 2,5-diemethyl-1H-pyrrole (61 μL, 0.60 mmol). Purification by flash column chromatography (30% Et$_2$O/petrol) afforded the title compound **143** as a rust coloured powder (93 mg, 64%); m.p. (DCM) 116-119 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71 (1H, s, *H-13*), 7.67 (2H, s, *H-11* and *H-15*), 7.64 (1H, dd, *J* 8.0, 1.0, *H-9*), 7.43 (1H, dt, *J 8.0*, *1.5*, *H-7*), 7.35-7.30 (1H, app. d, *J* 8.0, *H-6*), 7.16-7.09 (1H, m, *H-8*), 5.54 (1H, app. d. *J* 2.0, *H-20*), 4.77 (1H, dd, *J* 8.5, 6.0, *H-2*), 3.25 (1H, dd, *J* 14.5, 6.0, *H-3*$_a$), 2.85 (1H, dd, *J* 14.5, 8.5, *H-3*$_b$), 2.42 (3H, s, S*C*H_3), 2.15 (3H, s, CH_3), 1.79 (3H, s, CH_3); ^{13}C NMR (101 MHz, CDCl$_3$) δ 200.5 (*C-1*), 142.5 (Ar*C*), 141.9 (Ar*C*), 135.0 (Ar*C*), 132.2 (*C-7*), 131.3 (q, $J_{\text{C-F}}$ 34.5, *C-12* and *C-14*), 129.7 (*C-9*), 128.7 (br. s, *C-11*, *C-15*), 125.7 (Ar*C*), 125.6 (*C-6*), 123.7 (*C-8*), 123.3 (q, $J_{\text{C-F}}$ 274.0, 2×*C*F$_3$), 123.0 (Ar*C*), 120.8 (app. quin, $J_{\text{C-F}}$ 4.0, C-*13*), 114.9 (*C-16*), 106.2 (*C-20*), 56.5 (*C-2*), 30.9 (*C*-3), 16.1 (*C-21*), 12.8 (*C*H$_3$), 10.4 (*C*H$_3$); ^{19}F NMR (376 MHz, CDCl$_3$) -62.7 (6F, s); LRMS (ESI) *m/z* 540 (20%, [M+Na+MeOH]$^+$), 524 (40%, [M+K]$^+$), 508 (100%, [M+Na]$^+$), 486 (20%, [M+H]$^+$); HRMS (ESI) found *m/z* 508.1125 [M+Na]$^+$, $C_{24}H_{21}F_6NNaOS^+$ requires 508.1140; ν$_{\text{max}}$ (neat)/cm^{-1} 3249 (N-H), 2923, 1670 (C=O), 1587, 1465, 1438, 1372, 1276, 1168, 1127, 1068.

2-(3,5-bis(Trifluoromethyl)phenyl)-3-(5-ethyl-1*H*-pyrrol-2-yl)-1-(2-(methylthio)phenyl)propan-1-one (144)



Prepared according to General Procedure **E** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) and 2-ethylpyrrole (61 μL, 0.60 mmol). Purification by flash column chromatography (10% Et$_2$O/petrol) afforded the title compound **144** as a brown oil (112 mg, 77%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.99 (1H, br. s, N*H*), 7.78-7.67 (3H, m, *H-11*, *H-13* and *H-15*), 7.58 (1H, app. d, *J* 8.0, *H-9*), 7.46-7.38 (1H, m, *H-7*), 7.32 (1H, d, *J* 8.0, *H-6*), 7.10 (1H, app. t, *J* 7.5, *H-8*), 5.80-5.68 (2H, m, *H-19* and *H-20*), 4.89 (1H, dd, *J* 9.5, 4.5, *H-2*), 3.54 (1H, dd, *J* 14.5, 9.5, *H-3$_a$*), 3.02 (1H, dd, *J* 14.5, 4.5, *H-3$_b$*), 2.52 (2H, q, *J* 7.5, *H-24*), 2.44 (3H, s, SC*H$_3$*), 1.17 (3H, t, *J* 7.5, *H-25*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 200.7 (*C-1*), 142.7 (Ar*C*), 141.6 (Ar*C*), 134.7 (Ar*C*), 133.9 (Ar*C*), 132.6 (*C-7*), 132.1 (q, $J_{\text{C-F}}$ 33.5, *C-12* and *C-14*), 129.7 (*C-9*), 128.1 (br. s, *C-11* and *C-15*), 126.9 (Ar*C*), 125.7 (*C-6*), 123.8 (*C-8*), 123.1 (q, $J_{\text{C-F}}$ 273.5, 2×*C*F$_3$), 121.4 (app. quin, $J_{\text{C-F}}$ 3.5, *C-13*), 106.9 (pyrrole Ar*C*H), 105.9 (pyrrole Ar*C*H), 56.7 (*C-2*), 32.9 (*C-3*), 20.8 (*C-22*), 16.0 (*C-21*), 13.6 (*C-23*); ^{19}F NMR (376 MHz, CDCl$_3$) -62.8 (6F, s); LRMS (ESI) *m/z* 524 (10%, [M+K]$^+$), 508 (100%, [M+Na]$^+$); HRMS (ESI) found *m/z* 508.1141 [M+Na]$^+$, $C_{24}H_{21}F_6NNaOS^+$ requires 508.1140; ν_{max} (neat)/cm^{-1} 3369 (N-H), 2970, 2926, 1669 (C=O), 1622, 1586, 1464, 1434, 1372, 1344, 1275, 1168, 1128.

2-(3,5-bis(Trifluoromethyl)phenyl)-1-(2-(methylthio)phenyl)-3-(1-(triisopropylsilyl)-1H-pyrrol-3-yl)propan-1-one (145)

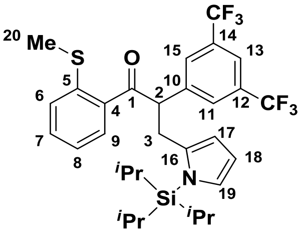


[Rh(nbd)$_2$]BF$_4$ (11 mg, 0.03 mmol) and ligand *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in acetone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-Methylthiobenzaldehyde (39 µL, 0.30 mmol) and (1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) were added as a solution in acetone (0.5 mL) and the reaction mixture stirred at room temperature for 2 h after which the solvent was removed *in* vacuo to afford the crude enone as a brown oil. The crude residue was re-dissolved in 1,2-DCE (2 mL), 1-(triisopropylsilyl)-1*H*-pyrrole (133 mg, 0.60 mmol) was added and the reaction mixture heated to 80 °C for 4 days. The reaction mixture was allowed to cool to room temperature, filtered through a pad of Celite®, the pad washed with EtOAc and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (20% Et_2O/petrol) afforded the title compound **145** as a beige solid (94 mg, 51%, 13:1 3-position: 2-position). m.p (DCM) 83-86 °C; LRMS (ESI) *m/z* 612 (100%, [M-H]$^-$); HRMS (ESI) found *m/z* 636.2172 [M+Na]$^+$, $C_{31}H_{37}F_6NNaOSSi^+$ requires 636.2162; ν_{max} (neat)/cm^{-1} 2948, 2869, 1663 (C=O), 1463, 1431, 1372, 1306, 1273, 1167, 1139, 1097, 1077.

3-position isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, s, *H-11* and *H-15*), 7.70-7.62 (2H, m, *H-13* and *H-9*), 7.46-7.38 (1H, m, *H-7*), 7.31 (1H, app. d, *J* 8.0, *H-6*), 7.17-7.10 (1H, m, *H-8*), 6.61 (1H, app. t, *J* 2.0, *H-18*), 6.28 (1H, s, *H-17*), 6.09-6.00 (1H, m, *H-19*), 4.89 (1H, dd, *J* 8.5, 6.5, *H-2*), 3.43 (1H, dd, *J* 14.0, 6.5, *H-3$_a$*), 3.06 (1H, dd, *J* 14.0, 8.5, *H-*

3$_b$), 2.41 (3H, s, SC*H$_3$*), 1.36-1.21 (3H, m, 3×C*H*(CH$_3$)$_2$), 1.00-0.90 (18H, m, 3×CH(C*H$_3$*)$_2$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 200.4 (*C-1*), 142.2 (Ar*C*), 141.8 (Ar*C*), 135.0 (Ar*C*), 132.2 (*C-7*), 131.4 (q, $J_{\text{C-F}}$ 33.0, *C-21* and *C-22*), 129.7 (*C-9*), 128.7 (br. s, *C-11* and *C-15*), 125.7 (*C-6*), 124.4 (*C-18*), 123.7 (*C-8*), 123.2 (q, $J_{\text{C-F}}$ 274.0, 2×*C*F$_3$), 122.4 (*C-17*), 121.5 (*C-16*), 120.9 (app. quin, $J_{\text{C-F}}$ 4.0, *C-13*), 110.7 (*C-19*), 56.6 (*C-2*), 32.2 (*C-3*), 17.6 (3×CH(*C*H$_3$)$_2$), 16.1 (*C-20*), 11.5 (3×*C*H(CH$_3$)$_2$); ^{19}F NMR (376 MHz, CDCl$_3$) δ -62.7 (6F, s).

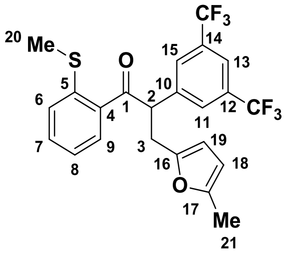
The following ^{1}H NMR signals are consistent with the 2-position isomer:



^{1}H NMR (400 MHz, CDCl$_3$) δ 6.74-6.70 (1H, m, Ar*H*), 6.11 (1H, app. t, *J* 3.0, Ar*H*), 5.92-5.89 (1H, m, Ar*H*), 5.16-5.11 (1H, m, *H-2*), 3.63 (1H, dd, *J* 16.0, 6.0, *H-3$_a$*), 3.20 (1H, dd, *J* 16.0, 8.0, *H-3$_b$*), 1.50-1.40 (3H, m, 3×C*H*(CH$_3$)$_2$), 1.13-1.04 (18H, m, 3×CH(C*H$_3$*)$_2$).

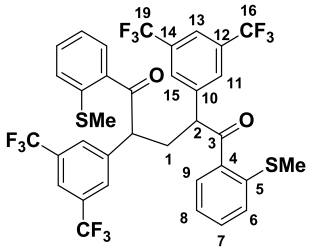
The regiochemistry has been confirmed by nOe difference experiments (See Appendix).

2-(3,5-bis(Trifluoromethyl)phenyl)-3-(5-methylfuran-2-yl)-1-(2-(methylthio)phenyl) propan-1-one (146)



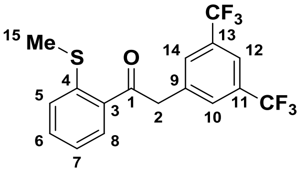
Prepared according to General Procedure **E** using 2-(methylthio)benzaldehyde (39 μL, 0.30 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) and 2-methylfuran (54 μL, 0.60 mmol). Purification by flash column chromatography (10% Et_2O/petrol) afforded the title compound **146** as an amorphous brown solid (101 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.66 (4H, m, *H-9*, *H-11*, *H-13* and *H-15*), 7.44 (1H, m, *H-7*), 7.32 (1H, app. d, *J* 8.0, *H-6*), 7.18-7.12 (1H, m, *H-8*), 5.75 (2H, app. q, *J* 3.0, *H-18* and *H-19*), 5.08 (1H, app. t, *J* 7.5, *H-2*), 3.50 (1H, dd, *J* 15.0, 7.0, $H\text{-}3_a$), 3.11 (1H, dd, *J* 15.0, 8.0, $H\text{-}3_b$), 2.42 (3H, s, SCH_3), 2.19 (3H, s, *H-23*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0 (*C-1*), 151.1 (Ar*C*), 149.7 (Ar*C*), 142.8 (Ar*C*), 141.1 (Ar*C*), 134.5 (Ar*C*), 132.4 (*C-7*), 131.8 (q, $J_{C\text{-}F}$ 33.5, *C-11* and *C-15*), 129.7 (*C-9*), 128.5 (app. d, $J_{C\text{-}F}$ 4.0, *C-10* and *C-12*), 125.8 (*C-6*), 123.7 (*C-8*), 123.1 (q, $J_{C\text{-}F}$ 273.5, 2×CF_3), 121.2 (app. quin, $J_{C\text{-}F}$ 4.0, *C-13*), 108.2 (Ar*C*H), 106.0 (Ar*C*H), 53.4 (*C-2*), 32.6 (*C-3*), 16.1 (*C-20*), 13.3 (*C-23*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8 (6F, s); LRMS (ESI) *m/z* 527 (100%, $[M+Na+MeOH]^+$), 511 (90%, $[M+K]^+$), 495 (75%, $[M+Na]^+$); HRMS (ESI) found *m/z* 495.0823 $[M+Na]^+$, $C_{23}H_{18}F_6NaO_2S^+$ requires 495.0824; ν_{max} (neat)/cm^{-1} 2924, 1681 (C=O), 1434, 1371, 1277, 1167, 1126.

2,4-bis(3,5-bis(Trifluoromethyl)phenyl)-1,5-bis(2-(methylthio)phenyl)pentane-1,5-dione (147)



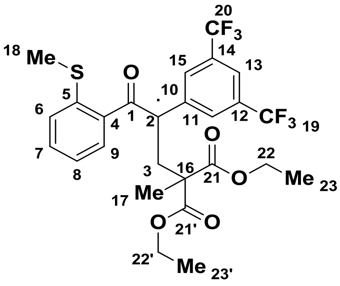
$[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 3-pentanone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 µL, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) were added as a solution in 3-pentanone (0.5 mL) and the reaction mixture stirred at room temperature for 2 h. Diisopropylamine (62 µL, 0.6 mmol) was added and the reaction mixture heated to 80 °C for 18 h. The reaction mixture was allowed to cool to room temperature, filtered through a pad of Celite®, the pad washed with EtOAc and the filtrate concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound **147** as a brown amorphous solid (66 mg, 29%). The product was obtained as a 1:1 mixture of diastereomers **d1** and **d2** which were partially separated. The following data is for both diastereomers and is assigned were possible. In some cases the ^{13}C NMR signals for the two diastereomers overlap.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.72 (8H, m, 8×Ar*H*), 7.66 (4H, s, 4×Ar*H*), 7.57 (2H, app. d, *J* 8.0, 2×Ar*H*), 7.50-7.40 (2H, m, 2×Ar*H*), 7.43-7.31 (6H, m, 6×Ar*H*), 7.30-7.21 (2H, m, 2×Ar*H*), 7.19-7.08 (2H, m, 2×Ar*H*), 7.02 (2H, app. t, *J* 7.5, 2×Ar*H*), 4.81 (2H, t, *J* 7.5, **d1** *H-2*) 4.59 (2H, t, *J* 7.5, **d2** *H-2*), 3.12-3.00 (1H, m, **d2** $H\text{-}1_a$), 2.69 (2H, app. t, *J* 7.5, **d1** *H-1*) 2.51-2.41 (1H, m, **d2** $H\text{-}1_b$ overlapping 6H, s, 2×SCH_3), 2.40 (6H, s, 2×SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7 (*C*=O), 198.9 (*C*=O), 142.9 (Ar*C*), 142.2 (Ar*C*), 141.1 (Ar*C*), 140.5 (Ar*C*), 134.7 (Ar*C*), 134.1 (Ar*C*), 132.8 (Ar*C*H), 132.5 (Ar*C*H), 132.3 (q, $J_{C\text{-}F}$ 33.0, 2×Ar*C*CF$_3$), 132.2 (q, *J*$_{C\text{-}F}$ 34.0, 2×Ar*C*CF$_3$), 129.5 (Ar*C*H), 129.4 (Ar*C*H), 128.5 (br. s, 2×Ar*C*H), 128.3 (br. s, 2×Ar*C*H), 123.0 (q, *J*$_{C\text{-}F}$ 274.0, 2×*C*F$_3$), 122.9 (q, *J*$_{C\text{-}F}$ 273.5, 2×*C*F$_3$), 121.9-121.5 (m, 2×Ar*C*H), 52.2 (*C*H), 51.6 (*C*H), 39.2 (*C*H$_2$), 38.8 (*C*H$_2$), 16.1 (S*C*H$_3$), 16.0 (S*C*H$_3$); ^{19}F NMR (440 MHz, CDCl$_3$) δ –62.8 (6F, s), -62.9 (6F, s); LRMS (ESI) *m/z* 791 (100%, [M+Na]$^+$); HRMS (ESI) *m/z* found 791.0907 [M+Na]$^+$, $C_{35}H_{24}F_{12}NaO_2S_2^+$ requires 791.0918; ν_{max} (neat)/cm^{-1} 2926, 1684 (C=O), 1671 (C=O), 1622, 1588, 1559, 1464, 1435, 1373, 1278, 1172, 1132.

2-(3,5-bis(Trifluoromethyl)phenyl)-1-(2-(methylthio)phenyl)ethanone (149)



$[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 3-pentanone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) were added as a solution in 3-pentanone (0.5 mL) and the reaction mixture stirred at room temperature for 2 h. Ethylacetoacetate (76 μL, 0.6 mmol) and K_2CO_3 (83 mg, 0.6 mmol) were added and the reaction mixture heated to 80 °C for 18 h. The reaction mixture was allowed to cool to room temperature, diluted with Et_2O, filtered through a pad of Celite®, the pad washed with Et_2O and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (40% Et_2O/petrol) and recrystallisation from Et_2O/petrol afforded the title compound **149** as off-white needles (49 mg, 40%); m.p. (DCM) 83-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, dd, *J* 8.0, 1.5, *H-8*), 7.81 (1H, s, *H-12*), 7.73 (2H, s, *H-10* and *H-14*), 7.57–7.49 (1H, m, *H-6*), 7.39 (1H, app. d, *J* 8.0, *H-5*), 7.29-7.23 (1H, m, *H-7*), 4.44 (2H, s, *H-2*), 2.45 (3H, s, *H-15*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5 (*C-1*), 143.2 (Ar*C*), 136.7 (Ar*C*), 133.6 (Ar*C*), 132.8 (*C-6*), 131.6 (q, $J_{C\text{-}F}$ 33.5, *C-11* and *C-13*), 130.2 (br. s, *C-10* and *C-14*), 130.1 (*C-8*), 125.6 (*C-5*), 123.8 (*C-7*), 121.2-120.9 (m, *C-12*), 123.3 (q, $J_{C\text{-}F}$ 272.5, 2×CF_3), 45.9 (*C-2*), 16.0 (*C-15*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (6F, s); LRMS (ESI) *m/z* 401 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 401.0398 $[M+Na]^+$, $C_{17}H_{12}F_6NaOS^+$ requires 401.0398; ν_{max} (neat)/cm^{-1} 2360, 1672 (C=O), 1588, 1557, 1380, 1279, 1174, 1160, 1110.

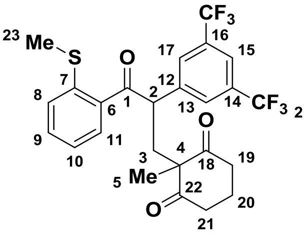
Diethyl 2-(2-(3,5-bis(trifluoromethyl)phenyl)-3-(2-(methylthio)phenyl)-3-oxopropyl)-2-methylmalonate (151)



$[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 3-pentanone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) were added as a solution in 3-pentanone (0.5 mL) and the reaction mixture stirred at room temperature for 2 h. Diethyl-2-methylmalonate (102 μL, 0.6 mmol) and K_2CO_3 (83 mg, 0.6 mmol) were added and the reaction mixture heated to 80 °C for 18 h. The reaction mixture was allowed to cool to room temperature, diluted with Et_2O, filtered through a pad of Celite® using Et_2O as eluent and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/petrol) afforded the title compound **151** as a pale brown solid (140 mg, 83%); m.p. (DCM) 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, dd, *J* 8.0, 1.5, *H-9*), 7.76 (2H, s, *H-11* and *H-15*), 7.70 (1H, s, *H-13*), 7.45-7.38 (1H, m, *H-7*), 7.28 (1H, app. d, *J* 7.5, *H-6*), 7.18-7.12 (1H, m, *H-8*), 5.09 (1H, dd, *J* 8.0, 3.5, *H-2*), 4.14 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 4.09 (1H, dq, *J* 11.0, 7.0, $CO_2CH_aH_bCH_3$), 3.85 (1H, dq, *J* 11.0, 7.0, $CO_2CH_aH_bCH_3$), 3.04 (1H, dd, *J* 14.5, 8.0, *H-3$_a$*), 2.36 (3H, s, SCH_3), 2.24 (1H, dd, *J* 14.5, 3.4, *H-3$_b$*), 1.43 (3H, s, *H-17*), 1.23 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 1.10 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0 (*C-1*), 172.0 (*C*=O), 171.3 (*C*=O), 143.3 (Ar*C*), 142.3 (Ar*C*), 133.9 (Ar*C*), 132.4 (*C-7*), 132.0 (q, J_{C-F} 29.5, *C-12* and *C-14*), 129.7 (*C-9*), 128.4 (br. s, *C-11* and

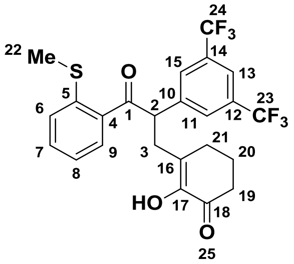
C-15), 125.5 (*C-6*), 123.6 (*C-8*), 123.0 (q, $J_{C\text{-}F}$ 272.0, *C-19* and *C-20*), 121.2 (app. quin, $J_{C\text{-}F}$ 4.0, *C-13*), 61.5 ($CO_2\mathit{C}H_2CH_3$), 61.4 ($CO_2\mathit{C}H_2CH_3$), 53.1 (*C-16*), 50.4 (*C-2*), 39.1 (*C-3*), 21.6 (*C-17*), 15.9 (*C-18*), 13.9 ($CO_2CH_2\mathit{C}H_3$), 13.6 ($CO_2CH_2\mathit{C}H_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8 (6F, s); LRMS (ESI) *m/z* 1152 (100%, $[2M+Na]^+$, 587 (50%, $[M+Na]^+$); HRMS (ESI) found *m/z* 587.1299 $[M+Na]^+$, $C_{26}H_{26}F_6NaO_5S^+$ requires 587.1297; ν_{max} (neat)/cm^{-1} 2990, 2948, 1721 (C=O), 1675 (C=O), 1584, 1558, 1461, 1446, 1443, 1373, 1323, 1278, 1246, 1215, 1184, 1165.

2-(2-(3,5-bis(Trifluoromethyl)phenyl)-3-(2-(methylthio)phenyl)-3-oxopropyl)-2-methylcyclohexane-1,3-dione (155)



$[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 3-pentanone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) were added as a solution in 3-pentanone (0.5 mL) and the reaction mixture stirred at room temperature for 2 h. 2-Methylcyclohexane-1,3-dione (76 mg, 0.6 mmol) and K_2CO_3 (83 mg, 0.6 mmol) were added and the reaction mixture heated to 80 °C for 18 h. The reaction mixture was allowed to cool to room temperature, diluted with Et_2O, filtered through a pad of Celite® using Et_2O as eluent and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (100% DCM) afforded the title compound **155** as a pale yellow oil (24 mg, 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (1H, dd, *J* 8.0, 1.5, *H-11*), 7.70 (1H, s, *H-15*), 7.67 (2H, s, *H-13* and *H-17*), 7.49-7.37 (1H, m, *H-9*), 7.32-7.23 (1H, m, *H-8*), 7.23-7.12 (1H, m, *H-10*), 4.87 (1H, dd, *J* 8.0, 4.5, *H-2*), 3.07 (1H, dd, *J* 14.0, 8.0, *H-3$_a$*), 2.84-2.48 (4H, m, *H-19* and *H-21*), 2.36 (3H, s, SCH_3), 2.08 (1H, dd, *J* 14.25, 4.5, *H-3$_b$*), 2.02-1.81 (2H, m, *H-20*), 1.34 (3H, s, *H-5*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0 (*C*=O), 209.8 (*C*=O), 198.3 (*C-1*), 142.8 (Ar*C*), 141.1 (Ar*C*), 134.2 (Ar*C*), 132.5 (*C-9*), 131.9 (q, $J_{C\text{-}F}$ 33.0, *C-14* and *C-16*), 129.4 (C-11), 128.7 (app. d, $J_{C\text{-}F}$ 3.0, *C-13* and *C-17*), 126.3 (*C-6*), 124.1 (*C-10*), 123.0 (q, $J_{C\text{-}F}$ 273.0, 2×CF_3), 121.4 (app. quin, $J_{C\text{-}F}$ 3.0, *C-15*), 63.8 (*C-4*), 50.1 (*C-2*), 39.2 (*C-3*), 38.0 (C*H$_2$*), 37.7 (C*H$_2$*), 20.4 (*C-5*), 17.4 (C*H$_2$*), 16.0 (*C-23*); ^{19}F NMR (376 MHz, CDCl$_3$) δ -62.8 (6F, s); LRMS (ESI) *m/z* 515 (100%, [M-H]$^-$); HRMS (ESI) found *m/z* found 539.1078 [M+Na]$^+$), $C_{25}H_{22}F_6NaO_3S^+$ requires 539.1086; ν_{max} (neat)/cm^{-1} 2926, 1726 (C=O), 1694 (C=O), 1463, 1434, 1372, 1279, 1172, 1132.

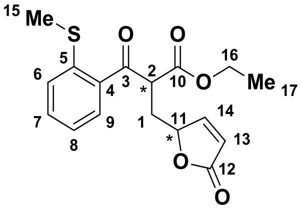
2-(3,5-bis(Trifluoromethyl)phenyl)-3-(2,3-dihydroxycyclohexa-1,3-dien-1-yl)-1-(2-(methylthio) phenyl)propan-1-one (157)



[Rh(nbd)$_2$]BF$_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in acetone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 μL, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 μL, 0.45 mmol) were added as a solution in acetone (0.5 mL) and the reaction mixture stirred at room temperature for 2 h. The reaction mixture was diluted with Et_2O, filtered through a pad of Celite® using Et_2O as eluent and the filtrate concentrated *in vacuo* to afford crude enone. The crude residue was re-dissolved in toluene (1 mL), Cu(OTf)$_2$ (11 mg, 0.03 mmol) was added followed by cyclohexane-1,2-dione (67 mg, 0.60 mmol) and the reaction mixture stirred at room temperature for 18 h. The reaction mixture was diluted with DCM (10 mL) and washed with H_2O (2×10 mL) then sat. $NaCl_{(aq)}$ (20 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (100% DCM) afforded the title compound **157** as a white powder (74 mg, 50%); m.p. (DCM) 122-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, s, *H-13*), 7.51 (2H, s, *H-11* and *H-15*), 7.30-7.24 (1H, m, *H-7*), 7.15 (1H, app. d, *J* 8.0, *H-9*), 7.03-6.94 (2H, m, *H-6* and *H-8*), 5.02 (1H, br. s, O*H*), 3.16 (1H, dd, *J* 16.5, 6.0, *H-2*), 3.04-2.91 (2H, m, CH_aH$_b$), 2.56 (1H, app. d, *J* 14.5, *H-3$_a$*), 2.45 (3H, s, SCH_3), 2.34-2.15 (4H, m, *H-3$_b$*, CH_2, CH$_a$$H_b$), 1.85-1.74 (2H, m, C$H_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8 (*C*=O), 147.1 (Ar*C*), 142.4 (Ar*C*), 133.4 (Ar*C*), 130.8 (Ar*C*H), 130.1 (q, J_{C-}

$_F$ 33.5, *C-12* and *C-14*), 129.6 (*C-7*), 128.5 (br. s, *C-11* and *C-15*), 128.4 (Ar*C*), 124.9 (Ar*C*H), 124.8 (*C-9*), 123.3 (q, J_{C-F} 247.0, 2×*C*F_3), 119.7-119.4 (m, *C-13*), 109.5 (*C*=C), 94.8 (*C*=C), 39.4 (*C-2*), 36.9 (*C-3*), 28.0 (*C*H_2), 27.8 (*C*H_2), 24.8 (*C*H_2), 15.3 (*C-22*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.0 (6F, s); LRMS (ESI) *m/z* 557 (100%, $[M+Na+MeOH]^+$, 525 (40%, $[M+Na]^+$); HRMS (ESI) found *m/z* 525.0928 $[M+Na]^+$, $C_{24}H_{20}F_6NaO_3S^+$ requires 525.0930; ν_{max} (neat)/cm^{-1} 3457 (O-H), 2929, 2870, 1733 (C=O), 1635, 1616, 186, 1467, 1435, 1387, 1278, 1178, 1128.

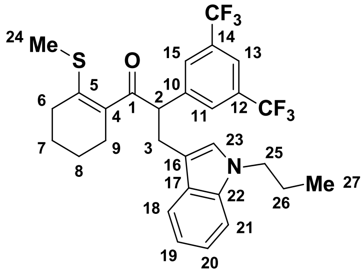
Ethyl 3-(2-(methylthio)phenyl)-3-oxo-2-((5-oxo-2,5-dihydrofuran-2-yl)methyl) propanoate (158)



[Rh(nbd)$_2$]BF$_4$ (5.6 mg, 0.015 mmol) and *o*-^{i}Pr-dppe (8.5 mg, 0.015 mmol) were dissolved in acetone (0.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (19 µL, 0.15 mmol) and ethyl propiolate (23 µL, 0.26 mmol) were added as a solution in acetone (0.5 mL) and the reaction mixture stirred at room temperature for 2 h. The reaction mixture was diluted with Et$_2$O, filtered through a pad of Celite® using Et$_2$O as eluent and the filtrate concentrated *in vacuo* to afford crude enone. In a separate flask, Cu(OTf)$_2$ (5.5 mg, 0.015 mmol) was suspended in DCM (0.3 mL) at room temperature. A solution of crude enone in DCM (0.3 mL) was added *via* cannula and the solution cooled to -78 °C. 2-Trimethylsiloxyfuran (30 µL, 0.18 mmol) was added drop-wise and the reaction mixture stirred at -78 °C for 2 h before quenching with sat. $NH_4Cl_{(aq)}$ (2 mL) and allowing to warm to room temperature. The layers were separated and the aqueous layer extracted with DCM (2×5 mL). Combined organic extracts were washed with sat. $NaCl_{(aq)}$ (10 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. The resulting residue was treated with HCl/THF (4 mL, 1 N, 1:1 v/v) at room temperature 0.5 h before diluting with H$_2$O (10 mL), and extracting with EtOAc (2×20 mL). Combined organic extracts were washed with sat. $NaCl_{(aq)}$ (20 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification by flash chromatography (100% DCM) afforded the title compound **158** as a pale yellow amorphous solid (26 mg, 52%). The product was obtained as an inseparable 1:1 mixture of diastereomers as determined by ^{1}H

NMR spectroscopy. The following NMR signals are for a mixture of the two diastereomers. In certain cases, the signals for the two diastereomers overlap. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.96 (1H, m, *H-9*), 7.92-7.88 (1H, m, *H-9*), 7.55-7.44 (4H, m, *H-7* and *H-14*), 7.38-7.31 (2H, m, *H-6*), 7.29-7.19 (2H, m, *H-8*), 6.11 (1H, dd, *J* 5.5, 2.0, *H-13*), 6.04 (1H, dd, *J* 5.5, 2.0, *H-13*), 5.27-5.22 (1H, m, *H-11*), 5.06-5.00 (1H, m, *H-11*), 4.65 (2H, app. ddd, *J* 14.0, 9.0, 5.0, *H-2*), 4.21-4.07 (4H, m, *H-16*), 2.76 (1H, ddd, *J* 14.5, 9.0, 3.0, $H\text{-}1_a$), 2.68 (1H, ddd, *J* 14.5, 9.0, 3.5 $H\text{-}1_a$), 2.45 (3H, s, SCH_3), 2.44 (3H, s, SCH_3), 2.12-2.03 (2H, m, $H\text{-}1_b$), 1.16 (6H, app. dt, *J* 11.0, 7.0, *H-17*); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 194.0 (*C-3*), 193.9 (*C-3*), 171.3 (*C-12*), 171.3 (*C-12*), 168.1 (br. s, *C-10*), 155.2 (*C-14*), 155.1 (*C-14*), 142.8 (Ar*C*), 142.7 (Ar*C*), 132.8 (Ar*C*H), 132.1 (Ar*C*H), 130.1 (Ar*C*H), 129.9 (Ar*C*H), 124.7 (Ar*C*H), 124.6 (Ar*C*H), 122.9 (br. s, Ar*C*H), 120.9 (*C-13*), 120.8 (*C-13*), 80.1 (*C-11*), 80.0 (*C-11*), 61.1 (*C-16*), 61.0 (*C-16*), 50.1 (*C-2*), 50.0 (*C-2*), 31.6 (*C-1*), 31.4 (*C-1*), 15.1 (*C-15*), 1.0 (*C-15*), 13.0 (*C-17*), 12.9 (*C-17*); LRMS (ESI) *m/z* 691 (100%, $[2M+Na]^+$), 357 (95%, $[M+Na]^+$), 335 (10%, $[M+H]^+$); HRMS (ESI) found *m/z* 357.0757 $[M+Na]^+$, $C_{17}H_{18}NaO_5S^+$ requires 357.0767; ν_{max} (neat)/cm^{-1} 2961, 2927, 2363, 1754 (C=O), 1671 (C=O), 1588, 1558, 1434, 1368, 1260, 1232, 1161.

2-(3,5-bis(Trifluoromethyl)phenyl)-1-(2-(methylthio)cyclohex-1-en-1-yl)-3-(1-propyl-1*H*-indol-3-yl)propan-1-one (163)

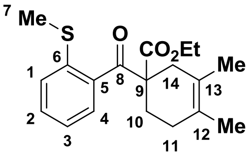


[Rh(nbd)$_2$]BF$_4$ (6 mg, 0.015 mmol) and ligand *o*-^{i}Pr-dppe (8 mg, 0.015 mmol) were dissolved in acetone (0.5 mL) and stirred at room temperature for 5 min. H$_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with N$_{2(g)}$. 2-(Methylthio)cyclohex-1-enecarbaldehyde (24 mg, 0.15 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (40 μL, 0.23 mmol were added as a solution in acetone (0.5 mL) and the reaction mixture stirred at room temperature for 4 h. The solvent was removed *in vacuo* to afford the crude enone as a brown oil. 1-Propyl-1H-indole (44 mg, 0.3 mmol), DNsOH (7 mg, 0.03 mmol) and MeOH (1 mL) were added and the reaction mixture stirred at 85 °C for 18 h before allowing to cool to room temperature. The crude reaction mixture was filtered through a short pad of a mixture Celite® and K$_2$CO$_3$, washed with MeOH and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (40% Et$_2$O/petrol) afforded the title compound **163** as a brown oil (39 mg, 76%); ^{1}H NMR (400 MHz, CDCl$_3$) 7.72 (1H, s, *H-13*) 7.68 (2H, s, *H-11* and *H-15*), 7.52 (1H, app. d, *J* 8.0, *H-18*), 7.32-7.24 (1H, m, *H-21*), 7.23-7.16 (1H, m, *H-20*), 7.14-7.05 (1H, m, *H-19*), 6.59 (1H, s, *H-23*), 4.63 (1H, app. t, *J* 7.5, *H-2*), 4.05-3.83 (2H, m, *H-25*), 3.60 (1H, dd, *J* 14.5, 7.0, *H-3$_a$*), 3.15 (1H, dd, *J* 14.5, 8.0, *H-3$_b$*), 2.46-2.37 (2H, m, C*H$_2$*), 2.25 (3H, s, SC*H$_3$*), 2.23-2.09 (2H, m, C*H$_2$*), 1.73 (2H, app. sxt, *J* 7.0, *H-26*), 1.61-1.46 (4H, m, 2×C*H$_2$*), 0.79 (3H, t, *J* 7.5, *H-27*); ^{13}C NMR (101 MHz, CDCl$_3$) δ 200.2 (*C-1*), 150.7 (C), 142.4 (C), 136.2 (C), 131.4 (q, $J_{C\text{-}F}$ 33.0, *C-12* and *C-14*), 130.1 (C), 128.7 (br. s, *C-11* and *C-15*), 127.6 (C), 126.7 (*C-*

23), 123.2 (q, $J_{C\text{-}F}$ 273.0, 2×*C*F_3*)*, 121.4 (*C-20*), 120.9-120.6 (m, *C-13*), 118.8 (*C-19*), 118.4 (*C-18*), 110.7 (*C-16*), 109.5 (*C-21*), 54.9 (*C-2*), 47.7 (*C-25*), 30.1 (*C-3*), 29.9 (*C*H_2), 28.1 (CH_2), 23.4 (*C-26*), 22.6 (*C*H_2), 21.7 (*C*H_2), 14.7 (*C-24*), 11.3 (*C-29*); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (6F, s); LRMS (ESI) *m/z* 576 (100%, $[M+K]^+$), 590 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* found 576.1751 $[M+Na]^+$, $C_{29}H_{29}F_6NNaOS^+$ requires 576.1766; ν_{max} (neat)/cm^{-1} 2933, 2876, 1680 (C=O), 1642, 1615, 1550, 1501, 1372, 1169, 1130.

Diels-Alder

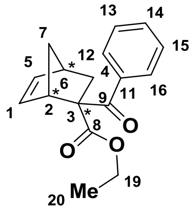
Ethyl 3,4-dimethyl-1-(2-(methylthio)benzoyl)cyclohex-3-enecarboxylate (174)



$[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 1,2-DCE (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 µL, 0.30 mmol) and ethyl propiolate (46 µL, 0.45 mmol) were added as a solution in 1,2-DCE (0.5 mL) and the reaction mixture stirred at 50 °C for 4 h. The reaction mixture was allowed to cool to room temperature, 2,3-dimethylbutadiene (169 µL, 5.0 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with DCM (10 mL), washed with H_2O (2×10 mL) then sat. $NaCl_{(aq)}$ (10 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification by flash chromatography (40-50% Et_2O/petrol) afforded the title compound **174** as an off-white solid (56 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, dd, *J* 8.0, 1.0, *H-4*), 7.41-7.35 (1H, m, *H-2*), 7.35-7.31 (1H, m, *H-1*), 7.15-7.08 (1H, m, *H-3*), 4.12 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 2.59-2.44 (2H, m, *H-14*), 2.41 (3H, s, SCH_3), 2.26-2.18 (2H, m, CH_2), 1.98-1.91 (2H, m, CH_2), 1.58 (6H, s, $CH_3C{=}CCH_3$), 1.12 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9 (*C-8*), 172.8 ($CO_2CH_2CH_3$), 140.3 (*C*), 136.0 (*C*), 130.9 (*C*-2), 127.5 (*C-4*), 126.7 (*C-1*), 124.9 (*C-3*), 123.6 (*C*), 122.9 (*C*), 61.3 ($CO_2CH_2CH_3$), 58.9 (*C-9*), 37.3 (*C-14*), 29.3 (CH_2), 28.6 (CH_2), 19.0 (CH_3), 18.7 (CH_3), 16.7 (*C-7*), 13.4 ($CO_2CH_2CH_3$); LRMS (ESI) *m/z* 387 (90%, $[M+Na+MeOH]^+$), 371 (100%, $[M+K]^+$) 365 (50% $[M+H+MeOH]^+$), 333 (10%, $[M+H]^+$); HRMS (ESI) found *m/z* found

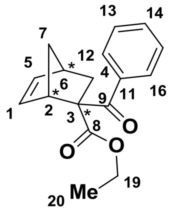
355.1331 [M+Na]$^+$, $C_{19}H_{24}NaO_3S^+$ requires 355.1338; ν_{max} (neat)/cm^{-1} 2979, 2922, 1728 (C=O ester), 1677 (C=O ketone), 1587, 1560, 1434, 1366, 1227, 1179, 1133, 1091, 1070.

(1*S**, 2*S**, 4*S**)- Ethyl 2-benzoylbicyclo[2.2.1]hept-5-ene-2-carboxylate (175)



To a solution of **173** (61 mg, 0.30 mmol) in DCM (1.5 mL) at -78 °C was added $ZnCl_2$ (61 mg, 0.45 mmol) and mixture stirred at the same temperature for 0.5 h. A solution of cyclopentadiene (74 μL, 0.90 mmol) in DCM (0.9 mL) was added drop-wise and the reaction mixture was stirred at 78 °C for 4 h. H_2O (10 mL) was added and the phases separated. The organic phase was washed with H_2O (20 mL) then sat. $NaCl_{(aq)}$, dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (10% Et_2O/petrol) afforded the ***exo*** diastereomer **175x** as an off-white solid (57 mg, 71%, >20:1 *exo*:*endo*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.90 (2H, m, Ar*H*), 7.57-7.47 (1H, m, Ar*H*), 7.46-7.38 (2H, m, 2×Ar*H*), 6.40 (1H, dd, *J* 5.5, 3.0, alkenyl C*H*), 5.97 (1H, dd, *J* 5.5, 3.0, alkenyl C*H*), 4.04-3.94 (2H, m, dq, *J* 7.0, 2.5, *H-19*), 3.68 (1H, br. s, C*H*), 2.98 (1H, br. s, C*H*), 2.43 (1H, dd, *J* 12.0, 2.5, *H-7$_a$*), 2.01 (1H, dd, *J* 12.0, 3.5, *H-7$_b$*), 1.61-1.49 (2H, m, *H-4*), 0.98 (3H, t, *J* 7.0, *H-20*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1 (*C-9*), 172.3 (*C-8*), 140.5 (Alkenyl *C*H), 138.9 (Ar*C*), 135.7 (Ar*C*H), 132.9 (Ar*C*H), 132.5 (Alkenyl *C*H), 130.1 (Ar*C*H), 129.1 (Ar*C*H), 128.4 (Ar*C*H), 64.0 (*C-3*), 61.3 (*C-19*), 50.1 (*C-4*), 49.7 (*C*H), 43.0 (*C*H) 36.1 (*C-7*), 13.8 (*C-20*); LRMS (ESI) *m/z* 293 (100%, [M+Na]$^+$), 271 (10%, [M+H]$^+$). Data is in accordance with the literature.[172]

(1*S,2S*,4S*)- Ethyl 2-benzoylbicyclo[2.2.1]hept-5-ene-2-carboxylate (175)**



[Rh(nbd)$_2$]BF$_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 1,2-acetone (1.5 mL) and stirred at room temperature for 5 min. H$_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with N$_{2(g)}$. 2-(Methylthio)benzaldehyde (39 µL, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) were added as a solution in acetone (0.5 mL) and the reaction mixture stirred at room temperature for 2 h after which volatiles were removed *in vacuo* to afford crude enone.

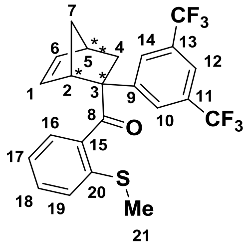
In a separate flask, a solution of [Cu((*S*,S)-*tert*-Bu-box)]Cl$_2$●CH$_2$Cl$_2$ (15 mg, 0.03 mmol) in DCM (1.0 mL) was added *via* cannula to a solution of AgSbF$_6$ (21 mg, 0.06 mmol) in DCM (0.5 mL) at room temperature. The mixture was stirred in the dark for 2 h to produce a green solution with a white AgCl precipitate. The mixture was filtered through an oven dried pad of Celite®, and washed through with DCM (0.5 mL). The resulting turquoise solution was cooled to -78 °C. The crude enone was re-dissolved in DCM (0.5) and added to the catalyst solution *via* cannula along followed by drop-wise addition of solution of cyclopentadiene (75 µL, 0.9 mmol) in DCM (0.5 mL). The reaction mixture was stirred at -78 °C for 2 h. H$_2$O (10 mL) was added and the phases separated. The organic phase was washed with H$_2$O (20 mL) then sat. NaCl$_{(aq)}$, dried over MgSO$_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (10% Et$_2$O/petrol) afforded title compound **175x** as an off-white solid (57 mg, 71%, >9:1 *exo*:*endo*); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98-7.90 (2H, m, Ar*H*), 7.57-7.47 (1H, m, Ar*H*), 7.46-7.38 (2H, m, 2×Ar*H*), 6.40

(1H, dd, *J* 5.5, 3.0, alkenyl C*H*), 5.97 (1H, dd, *J* 5.5, 3.0, alkenyl C*H*), 4.04-3.94 (2H, m, dq, *J* 7.0, 2.5, *H-19*), 3.68 (1H, br. s, C*H*), 2.98 (1H, br. s, C*H*), 2.43 (1H, dd, *J* 12.0, 2.5, $H\text{-}7_a$), 2.01 (1H, dd, *J* 12.0, 3.5, $H\text{-}7_b$), 1.61-1.49 (2H, m, *H-4*), 0.98 (3H, t, *J* 7.0, *H-20*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1 (*C-9*), 172.3 (*C-8*), 140.5 (alkenyl *C*H), 135.7, 132.9 (Ar*C*H), 132.5 (alkenyl *C*H), 129.1 (Ar*C*H), 128.4 (Ar*C*H), 64.0 (*C-3*), 61.3 (*C-19*), 50.1 (*C-4*), 49.7 (*C*H), 43.0 (*C*H) 36.1 (*C-7*), 13.8 (*C-20*); LRMS (ESI) *m/z* 293 (100%, $[M+Na]^+$), 271 (10%, $[M+H]^+$); Data is in accordance with the literature.[173]

Enantiomers of the title compounds were separated by HPLC using Chiralcel OD-H column; eluent 0.1% isopropanol in hexanes; 0.1 ml/min; 47% *ee*.

The absolute stereochemistry has not been established.

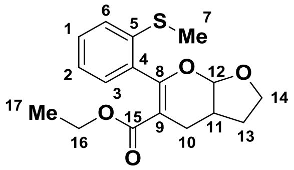
((1*S**, 2*S**, 4*S**)-2-(3,5-bis(trifluoromethyl)phenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-(methylthio)phenyl)methanone (178n)



$[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 1,2-acetone (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 µL, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) were added as a solution in acetone (0.5 mL) and the reaction mixture stirred at room temperature for 2 h after which volatiles were removed *in vacuo*. The crude residue was re-dissolved in DCM, cooled to -78 °C and $ZnCl_2$ (61 mg, 0.45 mmol) was added followed by drop-wise addition of a solution of cyclopentadiene (75 µL, 0.9 mmol) in DCM (0.5 mL). The reaction mixture was stirred at -78 °C for 6 h. The reaction mixture was allowed to warm to room temperature, diluted with H_2O (5 mL) and the phases separated. The organic phase was washed with H_2O (10 mL) then sat. $NaCl_{(aq)}$, dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification of the crude mixture by flash column chromatography (10% Et_2O/petrol) afforded a single diastereomer **178n** as an brown oil (79 mg, 58%, >20:1 *endo*:*exo*); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, s, *H-12*), 7.39 (2H, s, *H-10* and *H-14*), 7.30-7.23 (1H, m, Ar*H*), 7.22-7.15 (1H, m, Ar*H*), 7.05-6.90 (2H, m, 2×Ar*H*), 6.13-6.09 (1H, m, alkenyl *H*), 5.98 (1H, dd, *J* 6.0, 2.0, alkenyl *H*), 5.30 (1H, app. d, *J* 7.0, C*H*), 2.90 (1H, td, *J* 7.0, 4.0, C*H*), 2.76-2.65 (2H, m, 2×C*H*H), 2.52-2.36 (2H, m, 2×C*H*H, overlapping 3H, s, SC*H₃*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6 (Ar*C*), 141.9 (Ar*C*), 138.0 (Ar*C*), 134.2 (Alkenyl *C*H), 133.4 (Ar*C*), 130.4 (Alkenyl *C*H), 129.7 (Ar*C*H), 129.6 (q, $J_{C\text{-}F}$ 32.5, *C-11* and *C-13*), 128.3 (Ar*C*), 126.7 (app. d, $J_{C\text{-}F}$ 3.0, *C-10* and *C-14*), 124.2 (Ar*C*H), 123.7 (Ar*C*H), 122.4 (q, $J_{C\text{-}F}$ 273.5, 2×CF_3), 117.7 (app. quin, $J_{C\text{-}F}$ 3.0, *C-12*), 82.6 (*C*H), 37.7 (*C*H_2), 36.2 (*C*H_2), 28.3 (*C*H), 14.5 (*C-21*); ^{19}F (470 MHz, $CDCl_3$) -62.0; LRMS (ESI) *m/z* 479 (100%, $[M+Na]^+$, 456 (20%, $[M+H]^+$); HRMS (ESI) found *m/z* 479.0870 $[M+Na]^+$, $C_{23}H_{18}F_6NaOS^+$ requires 479.0875; ν_{max} (neat)/cm^{-1} 2928, 1638 (C=O), 1437, 1388, 1275, 1229, 1172, 1126.

The product was assigned as the *endo* diastereomer by analogy to similar literature compounds.[173]

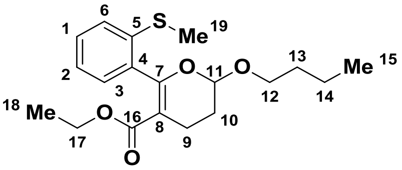
Ethyl 6-(2-(methylthio)phenyl)-3,3a,4,7a-tetrahydro-2H-furo[2,3-b]pyran-5-carboxylate (179)



$[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 1,2-DCE (1.5 mL) and stirred at room temperature for 5 mins. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 mins, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 μL, 0.30 mmol) and ethyl propiolate (46 μL, 0.45 mmol) were added as a solution in 1,2-DCE (0.5 mL) and the reaction mixture stirred at 50 °C for 4 h. The reaction mixture was allowed to cool to room temperature, 2,3-dihydrofuran (45 μL, 0.60 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with DCM (10 mL), washed with H_2O (2×10 mL) then sat. $NaCl_{(aq)}$ (10 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification by flash chromatography afforded the title compound **179** as a yellow oil (62 mg, 63%); m.p. (DCM) 74-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (1H, m, Ar*H*), 7.28-7.22 (1H, m, Ar*H*), 7.18-7.10 (2H, m, 2×Ar*H*), 5.56 (1H, d, *J* 4.0, *H-12*), 4.31-4.20 (1H, m, *H-14$_a$*), 4.03 (1H, app. q, *J* 8.5, *H-14$_b$*), 3.89 (2H, q, *J* 7.0, *H-16*), 2.74 (2H, d, *J* 3.5, *H-10*), 2.64 (1H, app. td, *J* 9.5, 4.0, *H-11*), 2.43 (3H, s, SC*H$_3$*), 2.21-2.04 (2H, m, *H-13*), 0.85 (3H, t, *J* 7.0, *H-17*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (*C-15*), 159.5 (*C-8*), 136.9 (Ar*C*), 136.8 (Ar*C*), 128.0 (Ar*C*H), 128.7 (Ar*C*H), 126.3 (Ar*C*H), 124.8 (Ar*C*H), 102.0 (*C-9*), 101.2 (*C-12*), 68.7 (*C-14*), 59.8 (*C-16*), 36.8 (*C-11*), 27.6 (*C-13*), 22.5 (*C-10*), 16.3 (*C-7*), 13.6 (*C-17*); LRMS (ESI) *m/z* 343 (100%, $[M+Na]^+$), 359 (40%, $[M+K]^+$); HRMS (ESI) found *m/z*; 343.0968 $[M+Na]^+$, $C_{17}H_{20}NaO_4S^+$ requires 343.0975; ν_{max}

(neat)/cm^{-1} 2981, 296, 2903, 281, 1680 (C=O), 1637, 1582, 1467, 1436, 137, 1243, 1210, 1160, 1129.

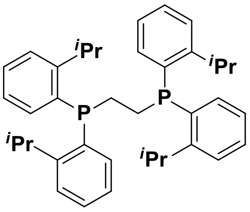
Ethyl 2-butoxy-6-(2-(methylthio)phenyl)-3,4-dihydro-2H-pyran-5-carboxylate (180)



[Rh(nbd)$_2$]BF$_4$ (11 mg, 0.03 mmol) and *o*-^{i}Pr-dppe (17 mg, 0.03 mmol) were dissolved in 1,2-DCE (1.5 mL) and stirred at room temperature for 5 min. $H_{2(g)}$ was bubbled through the pre-catalyst solution for 2 min, then the solution purged with $N_{2(g)}$. 2-(Methylthio)benzaldehyde (39 μL, 0.30 mmol) and ethyl propiolate (46 μL, 0.45 mmol) were added as a solution in 1,2-DCE (0.5 mL) and the reaction mixture stirred at 50 °C for 4 h. The reaction mixture was allowed to cool to room temperature, butyl vinyl ether (81 μL, 0.60 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with DCM (10 mL), washed with H_2O (2×10 mL) then sat. $NaCl_{(aq)}$ (10 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. Purification by flash chromatography (40-50% Et_2O/petrol) afforded the title compound **180** as an off-white solid (36 mg, 34%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (1H, m, Ar*H*), 7.26-7.23 (1H, m, Ar*H*), 7.19-7.11 (2H, m, 2×Ar*H*), 5.21 (1H, dd, *J* 3.5, 2.5, *H-11*), 3.89 (2H, q, *J* 7.0, *H-17*), 3.63-3.52 (1H, m, C*H*H) 2.58-2.51 (2H, m, C*H$_2$*), 2.43 (3H, m, SC*H$_3$*), 2.06-1.98 (1H, m, C*H*H), 1.98-1.88 (1H, m, C*H*H), 1.64-1.58 (2H, m, C*H$_2$*), 1.45-1.34 (2H, m, C*H$_2$*), 1.27-1.25 (1H, m, C*H*H), 0.93 (3H, t, *J* 7.5, *H-15*), 0.86 (3H, t, *J* 7.0, *H-18*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6 (*C-16*), 167.4 (*C-11*), 137.1 (Ar*C*), 136.9 (Ar*C*), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 125.8 (Ar*C*H), 124.7 (Ar*C*H), 106.2 (*C-7*), 98.6 (*C-8*), 68.8 (*C*H$_2$), 59.7 (*C*H$_2$), 31.7 (*C*H$_2$), 31.6 (*C*H$_2$), 25.9 (*C*H$_2$), 19.3 (*C*H$_2$), 16.0 (*C-19*), 13.9 (*C*H$_3$), 13.6 (*C*H$_3$); LRMS (ESI) *m/z* 389 (100, $[M+K]^+$), 373 (95, $[M+Na]^+$); HRMS (ESI) found *m/z* 373.1450 $[M+Na]^+$, $C_{19}H_{26}NaO_4S^+$ requires 373.1444; ν_{max} (neat)/cm^{-1} 2959, 2931, 2871, 1692 (C=O), 1636, 1466, 1436, 1372, 1339, 1293, 1261, 1243, 1156, 1056.

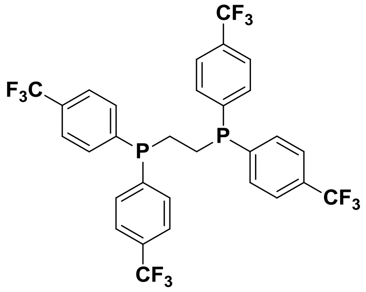
Ligands

1,2-bis(Bis(2-isopropylphenyl)phosphino)ethane (*o*-^{i}Prdppe)



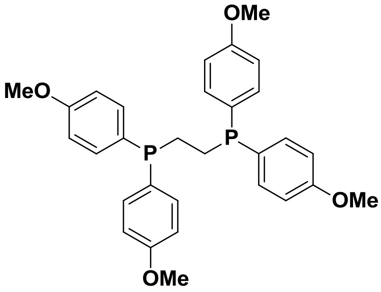
Prepared according to a literature procedure.[89] *n*-BuLi (2.5 M in hexanes, 6.7 mL, 16.7 mmol) was added drop-wise over 30 min to a solution of 1-bromo-2-isopropylbenzene (2.5 mL, 16.7 mmol) in Et_2O (20 mL) under $N_{2(g)}$ at room temperature and the resulting solution was stirred for 20 min at room temperature. The solution was cooled to -50 ºC, and solution of 1,2-bis(dichlorophosphino)ethane (530 µL, 3.5 mmol) in Et_2O (6 mL) was added drop-wise over 15 min. The mixture was allowed to warm to 20 ºC, stirred for 60 min and quenched with H_2O (10 mL), resulting in formation of a white precipitate. The precipitate was collected by filtration, washed with anhydrous MeOH (10 mL) and dried *in vacuo* to afford bisphosphine ligand ***o*-^{i}Pr-dppe** as a white crystalline solid (1.25 g, 63%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (8H, m, 8×Ar*H*), 7.09-7.02 (8H, m, 8×Ar*H*), 3.84-3.72 (4H, m, 2×C*H*$_2$), 2.02 (4H, t, *J* 4.0, 4×C*H*(CH_3)$_2$), 1.22 (12H, d, *J* 6.5, 4×CH_3), 0.95 (12H, d, *J* 6.5, 4×CH_3); ^{13}C NMR (101 MHz, CDCl3), δ 152.9 (app. t, *J* 12.0, 4×*C*), 136.0 (m, 4×*C*-P), 131.4 (4×*C*H), 128.8 (4×*C*H), 125.9 (4×*C*H), 125.4 (4×*C*H), 31.0 (app. t, J_{C-P} 12.0, 4×*C*H), 24.5 (d, J_{C-P} 4.0, 2×*C*H_2), 24.1 (4×*C*H_3), 23.6 (4×*C*H_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ-38.7; HRMS (ESI) *m/z* found 567.3304 $[M+H]^+$, $C_{38}H_{49}P_2^+$ requires 567.3304. Data is in accordance with the literature.[89]

1,2-bis(Bis(4-(trifluoromethyl)phenyl)phosphino)ethane (*p*-CF_3-dppe)



Prepared according to a literature procedure.[46] A solution of 1-bromo-4-(trifluoromethyl)benzene (2.5 mL, 17.8 mmol) was stirred under $N_{2(g)}$ at room temperature. *n*-BuLi (1.8 M in hexanes, 10.0 mL, 17.8 mmol) was added drop-wise over 30 min and the resulting solution stirred for a further 20 min. The solution was cooled to -50 ºC, and a solution of 1,2-bis(dichlorophosphino)ethane (580 µL, 3.8 mmol) in Et_2O (6 mL) was added drop-wise over 15 min. The mixture was allowed to warm to 20 ºC, stirred for 60 min, and quenched with H_2O (20 mL) resulting in the formation of a biphasic mixture with yellow precipitate. The layers were separated and the ethereal layer dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo* to afford a yellow oily solid. The aqueous layer was filtered *in vacuo* to afford a yellow solid. Recrystallisation of both crude residues from DCM/MeOH afforded bisphosphine ligand ***p*-CF_3-dppe** as a white crystalline solid (870 mg, 34%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (8H, d, app. *J* 8.5, 8×Ar*H*), 7.50-7.36 (8H, m, 8×Ar*H*), 2.13 (4H, t, *J* 4.5, 2×C*H₂*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8 (app. t, *J* 8.5, 4×*C*-P), 132.9 (app. t, *J* 9.5, 8×*C*H), 131.3 (q, $J_{C\text{-}F}$ 33.0, 4×Ar*C*CF_3), 125.4 (q, *J* 4.5, 8×*C*H), 123.8 (q, $J_{C\text{-}F}$ 272.5, 4×*C*F_3), 23.5 (2×*C*H_2); ^{31}P NMR (162 MHz, $CDCl_3$) δ -12.4; ^{19}F NMR (376 MHz, $CDCl_3$) -62.8 (12F, s). LRMS (FI) *m/z* 670.1 $[M]^+$; Data is in accordance with the literature.[46]

1,2-bis(Bis(4-methoxyphenyl)phosphino)ethane (*p*-OMe-dppe)



Prepared according to a literature procedure.[46] Magnesium turnings (1.0 g, 41.0 mmol) and a small crystal of iodine were added to an oven-dried reaction vessel. THF (3 mL) was added and the mixture stirred vigorously under $N_{2(g)}$. A THF (10 mL) solution of 4-bromoanisole (4.2 mL, 34.0 mmol) was added drop-wise whilst maintaining the temperature between 40-50 °C (N.B. after addition of 2 mL of the solution the mixture was heated with a heat gun). The reaction mixture was heated to reflux for 18 h after which it was cooled to room temperature and the resulting Grignard (0.83 M) was used immediately.

Grignard (0.83 M solution in THF, 30.8 mL, 25.5 mmol) was cooled to -78 °C. A solution of 1,2-bis(dichlorophosphino)ethane (640 μL, 4.3 mmol) in THF (15 mL) was added drop-wise over 40 min and the reaction mixture allowed to warm to room temperature for 18 h. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ (50 mL) and the organic phase extracted and concentrated *in vacuo*. The crude residue was partitioned between EtOAc (100 mL) and H_2O (100 mL), the organic phase extracted, washed with sat. $NaCl_{(aq)}$ (100 mL), dried over $MgSO_{4(s)}$, filtered and the filtrate concentrated *in vacuo*. The crude residue was dissolved in hot EtOH and allowed to stand at room temperature overnight upon which a white solid precipitated. The solid was collected by filtration and dried *in vacuo* to afford bisphosphine ligand ***p*-OMe-dppe** as a white crystalline solid (616 mg, 28%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (8H, m, 8×Ar*H*), 6.85 (8H, d, *J* 8.5, 8×Ar*H*), 3.80 (12H, s, 4×OC*H₃*), 2.01 (4H, t, *J* 8.0, 2×C*H₂*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (4×Ar*C*OMe), 134.0 (t, *J* 8.5, 8×Ar*C*H), 129.2 (t, *J* 5.0, 8×Ar*C*H), 114.1 (t, *J* 3.0, 4×*C*-P), 55.2 (2×*C*H_2), 24.4 (4×O*C*H_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -15.9. LRMS (ESI) m/z 551 (100%, $[M+H+MeOH]^+$), 519 (20%, $[M+H]^+$). Data is in accordance with the literature.[46]

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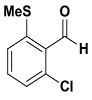
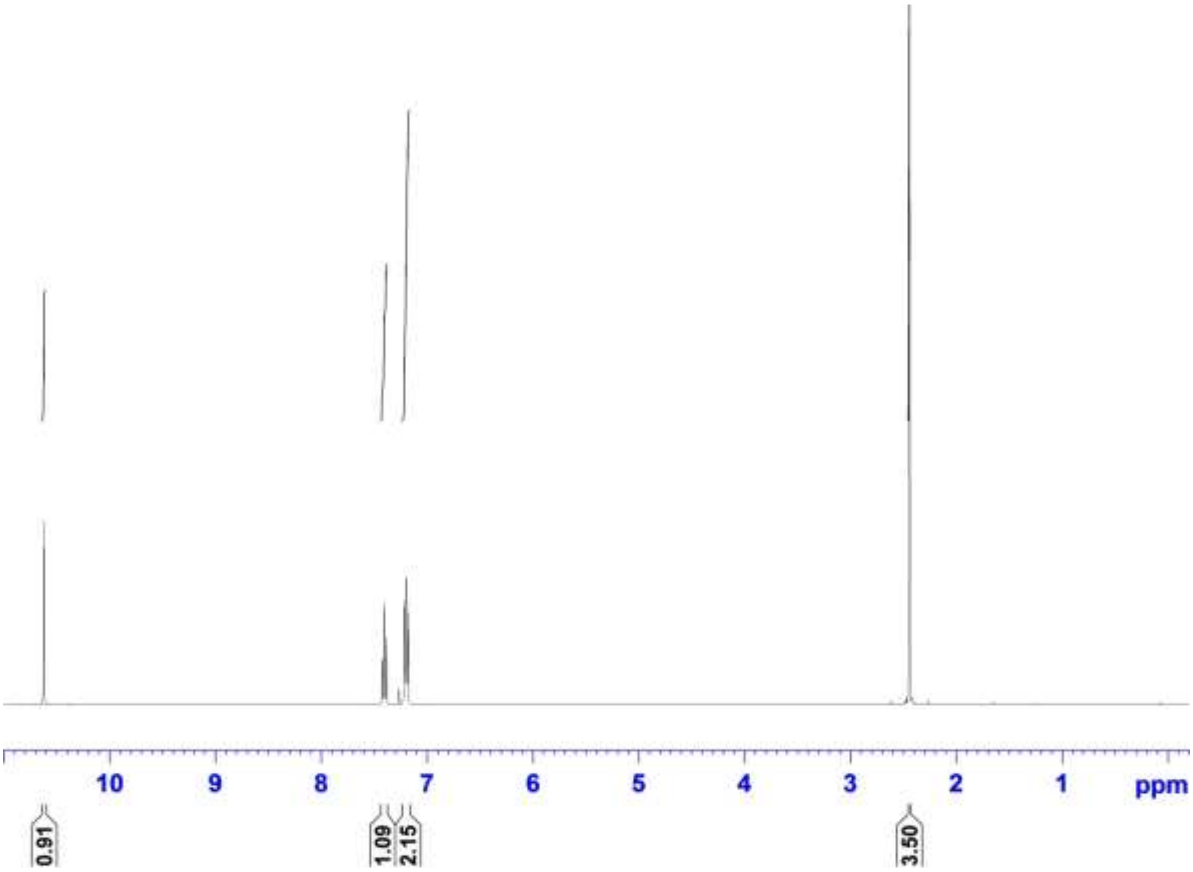
Appendix 1 - Spectral Data for Novel Compounds

Aldehydes

^{1}H NMR (400 MHz, CDCl$_3$)



52



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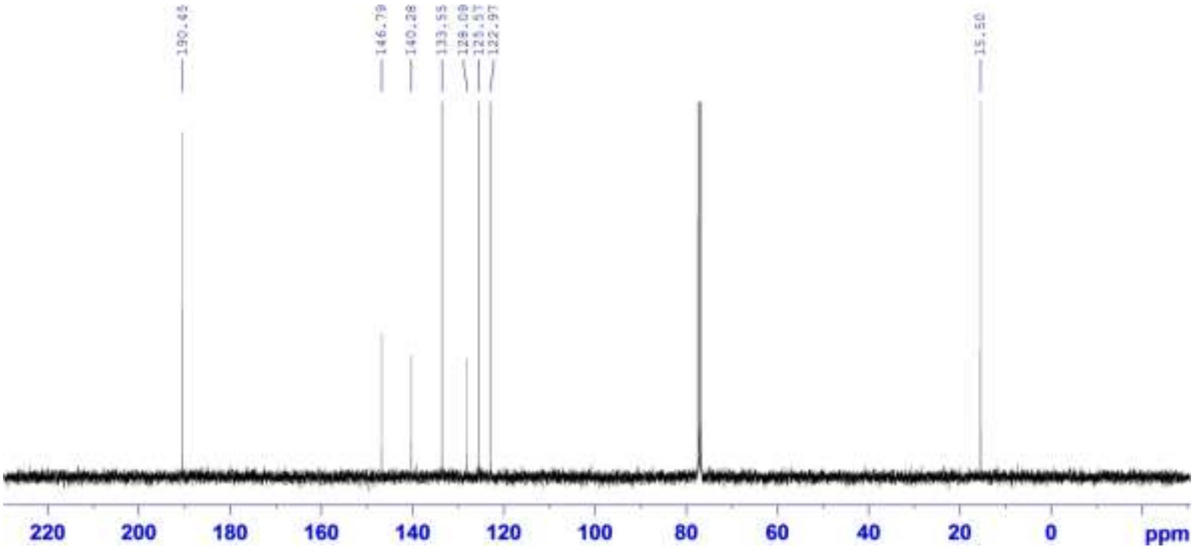

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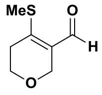
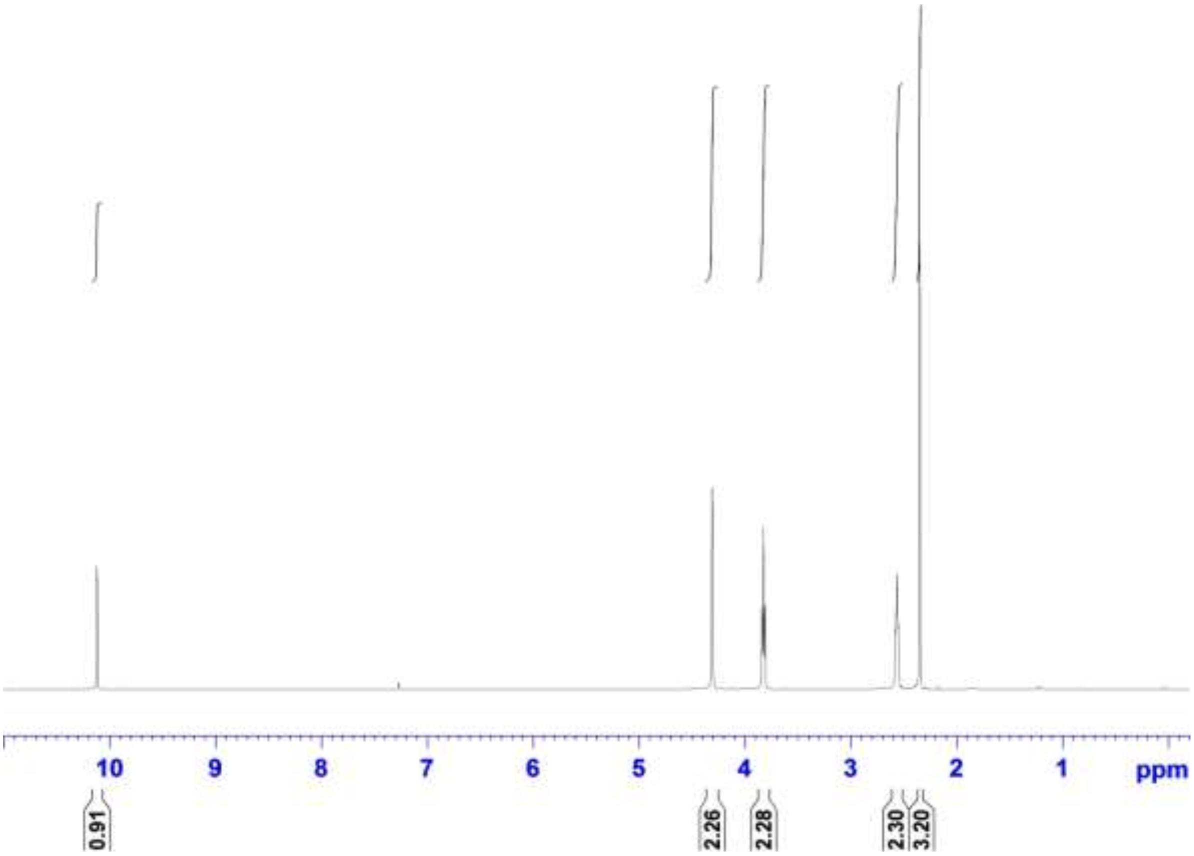


84



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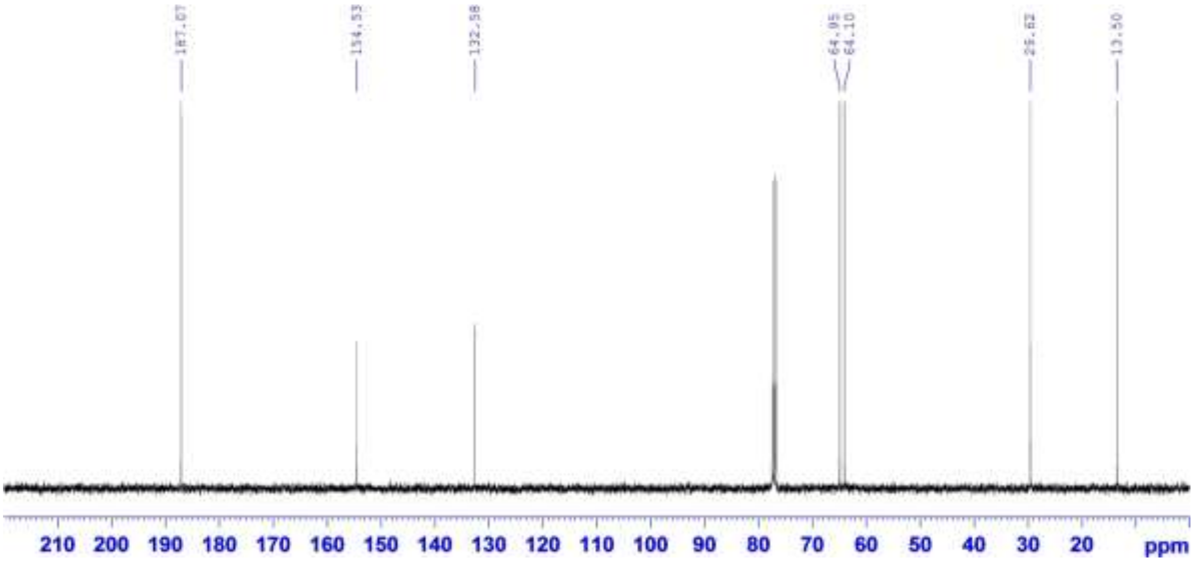

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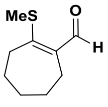

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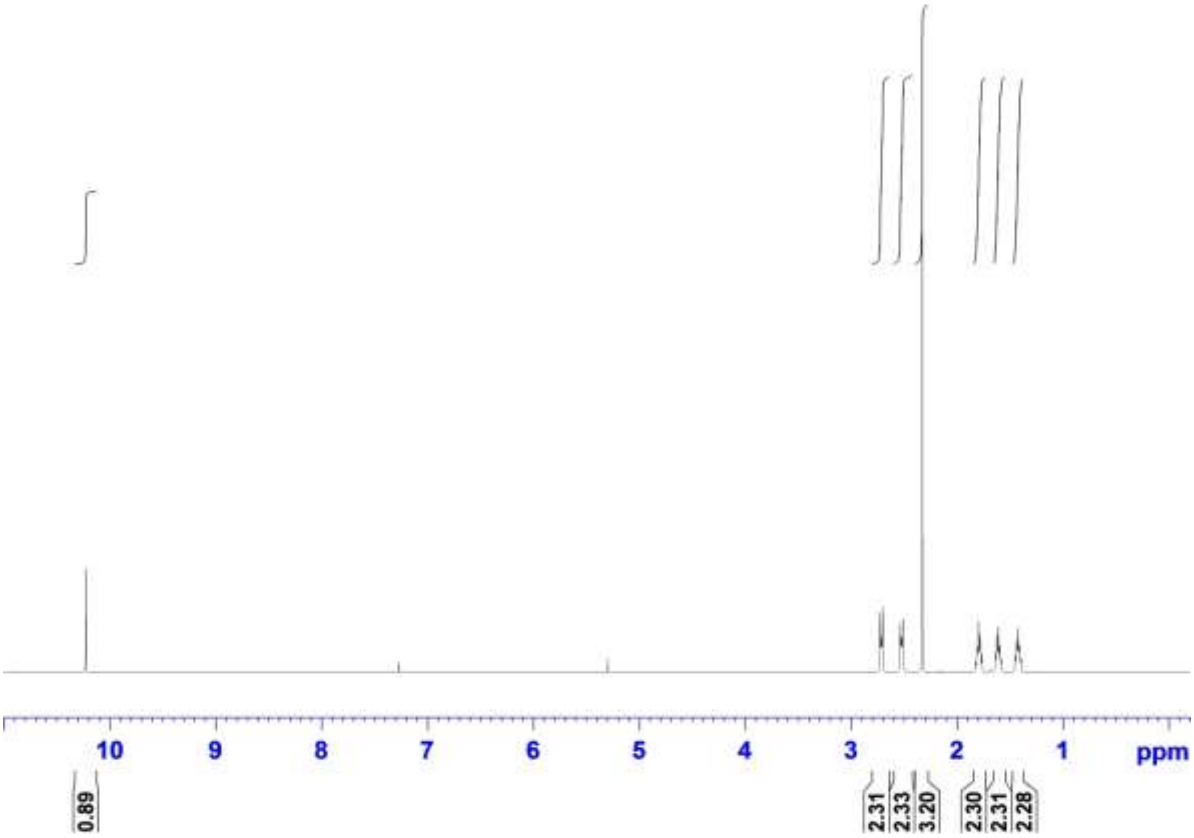

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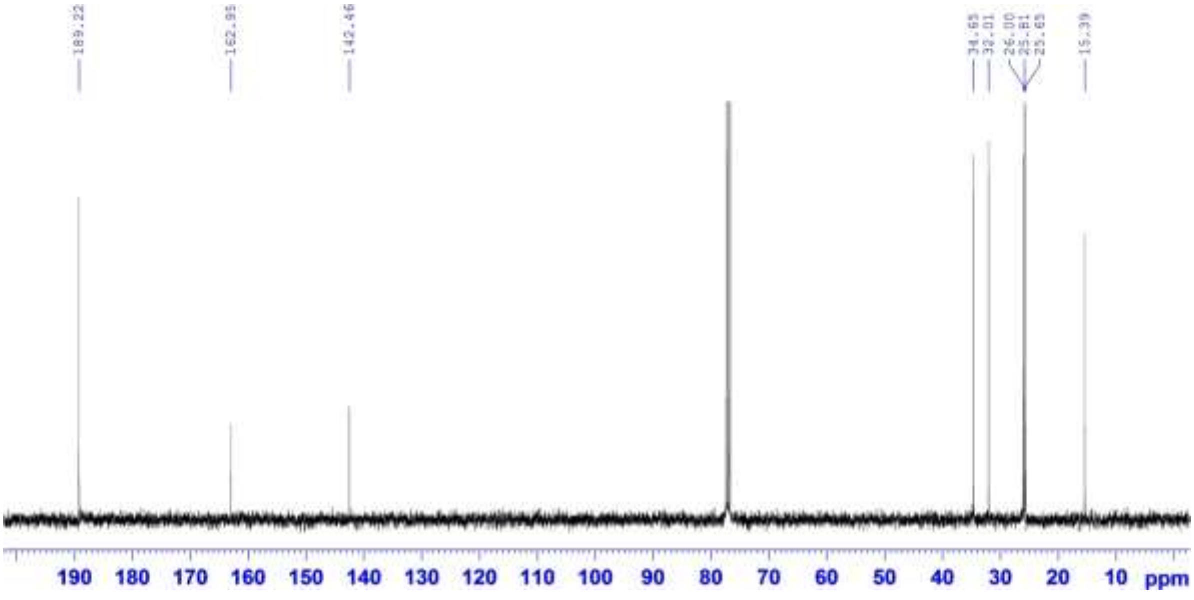
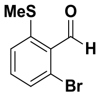


^{1}H NMR (400 MHz, CDCl$_3$)



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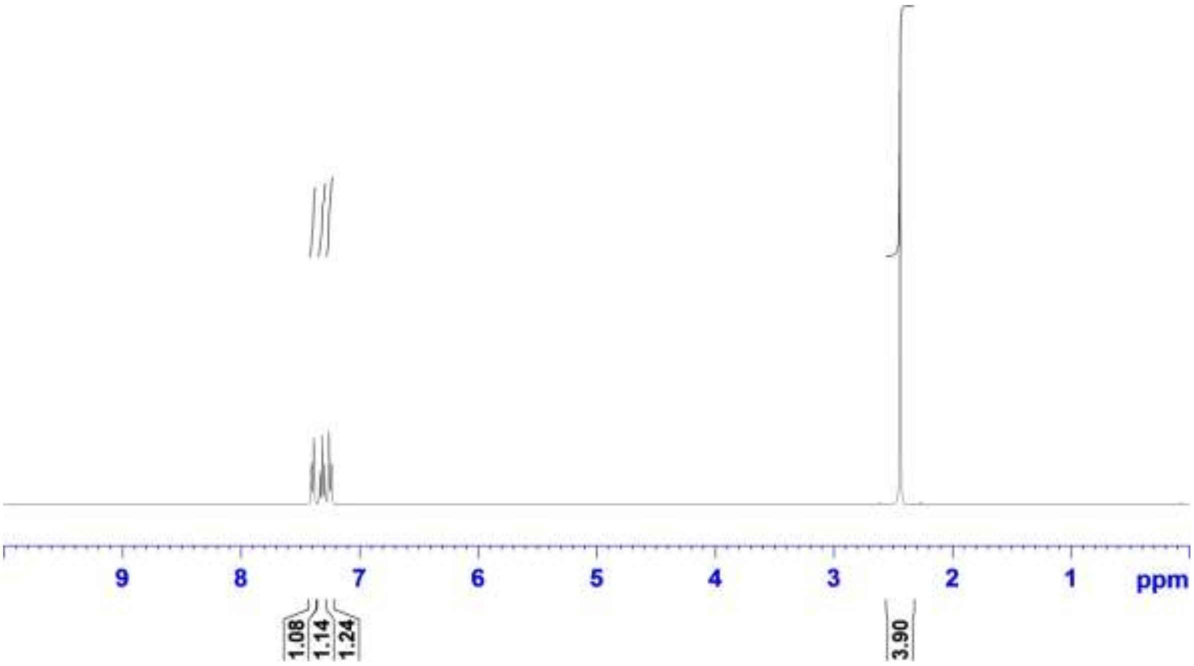
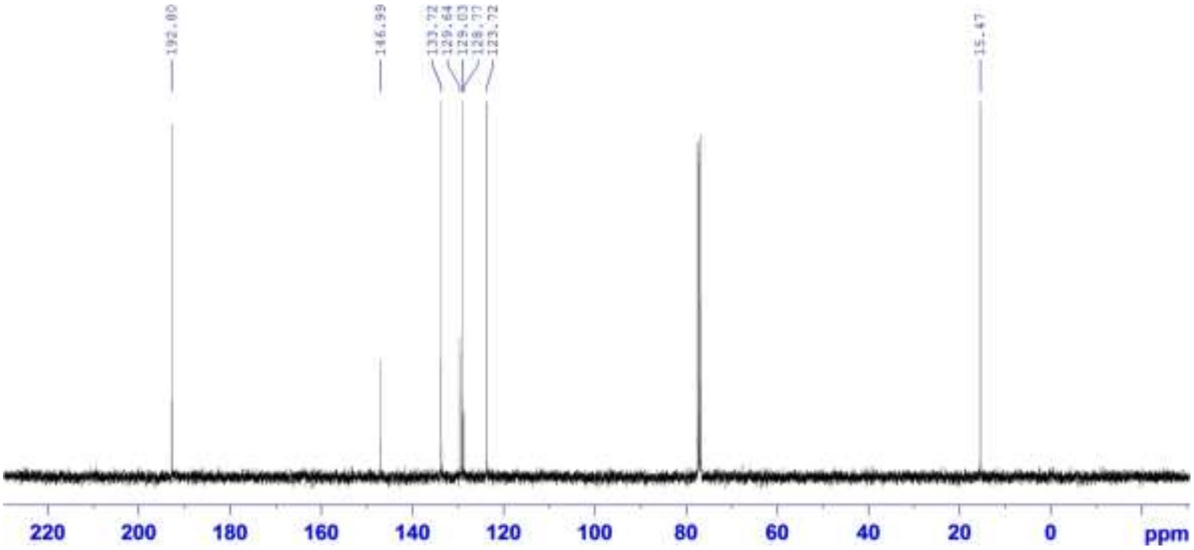
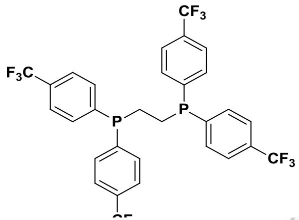


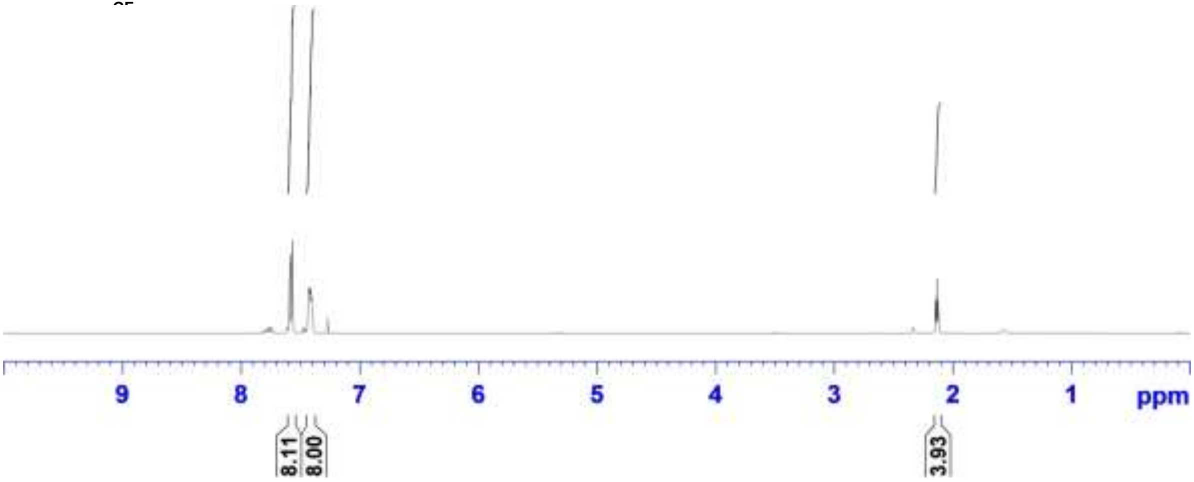
^{13}C NMR (101 MHz, CDCl$_3$)



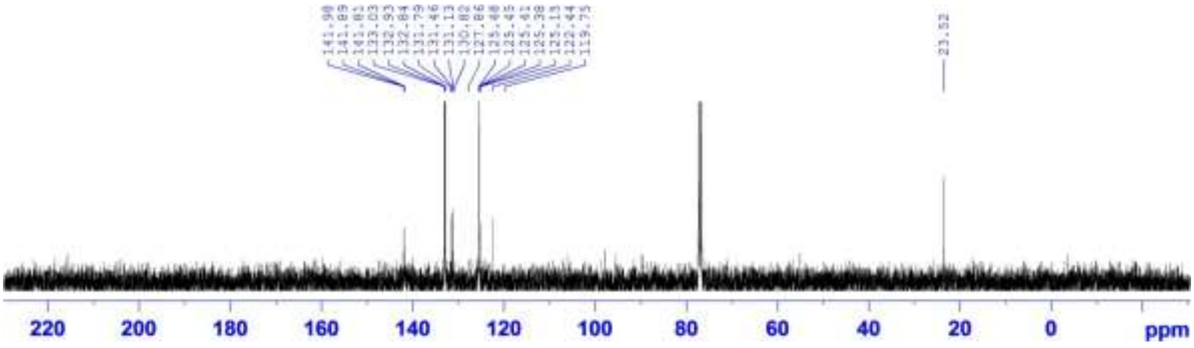
Ligands

^{1}H NMR (400 MHz, CDCl$_3$)

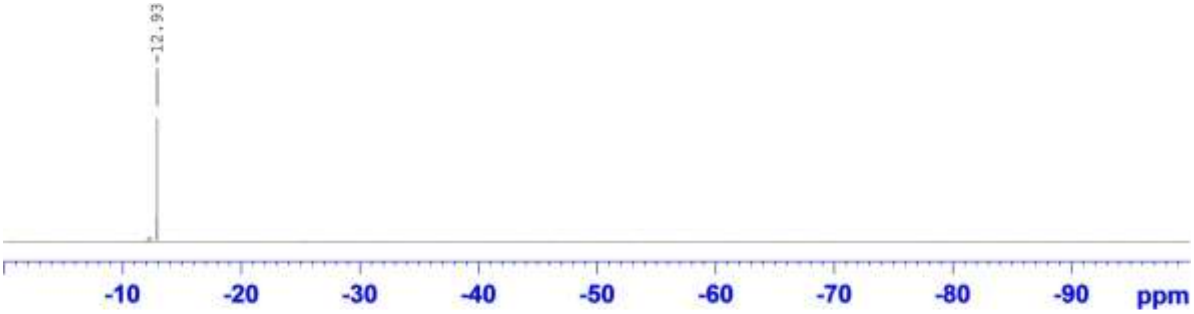




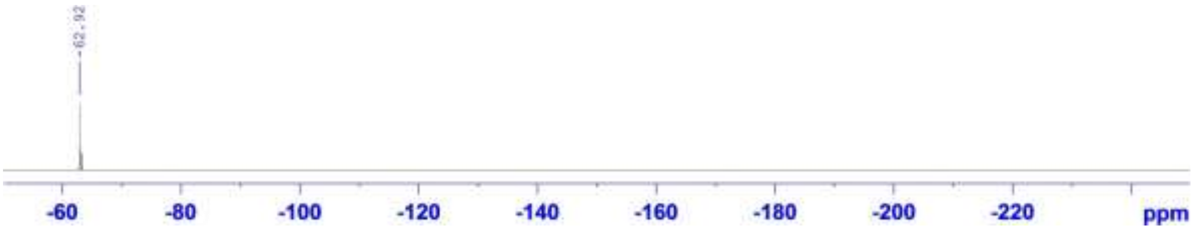
^{13}C NMR (101 MHz, CDCl$_3$)



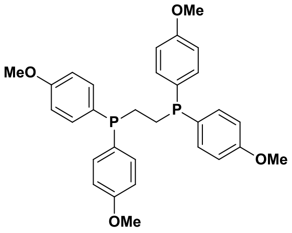
^{31}P NMR (162 MHz, CDCl$_3$)

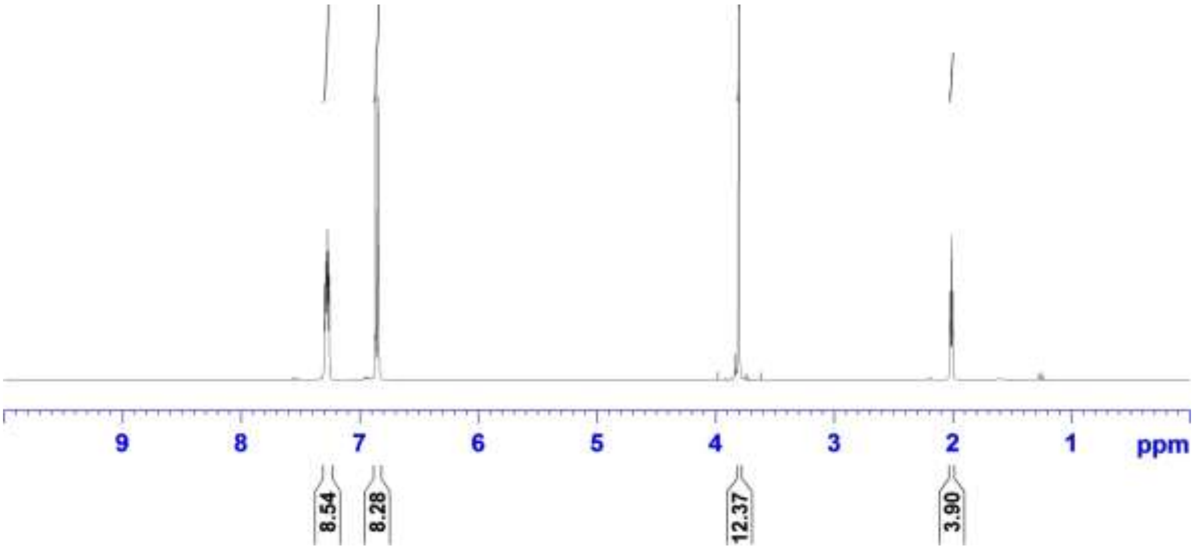


^{19}F NMR (376 MHz, CDCl$_3$)

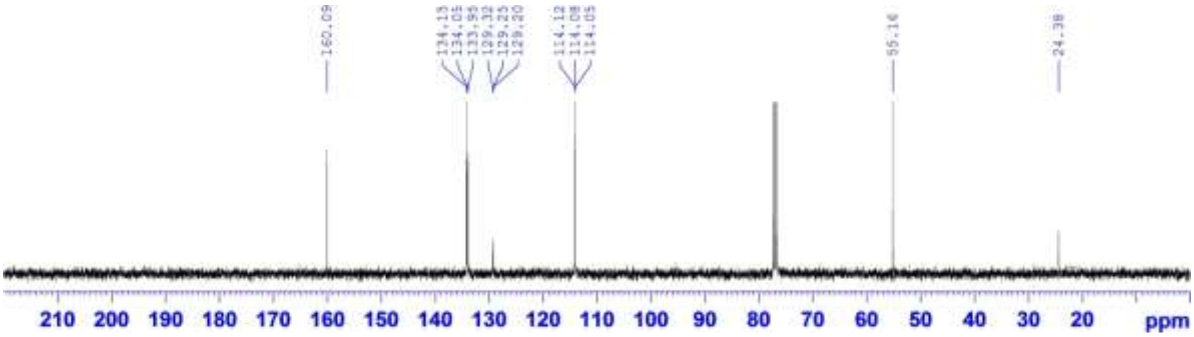


^{1}H NMR (400 MHz, CDCl$_3$)

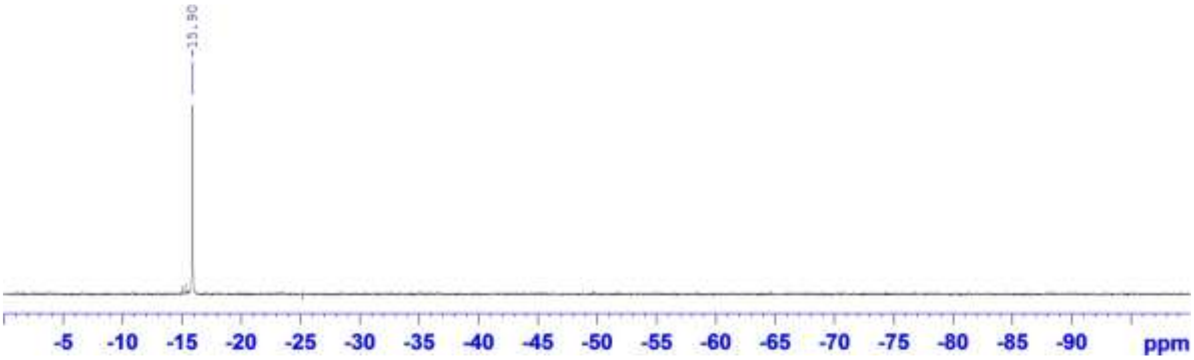




^{13}C NMR (101 MHz, CDCl$_3$)

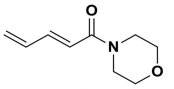


^{31}P NMR (162 MHz, CDCl$_3$)



Miscellaneous Starting Materials

^{1}H NMR (d_6-DMSO, 500 MHz, 363 K)



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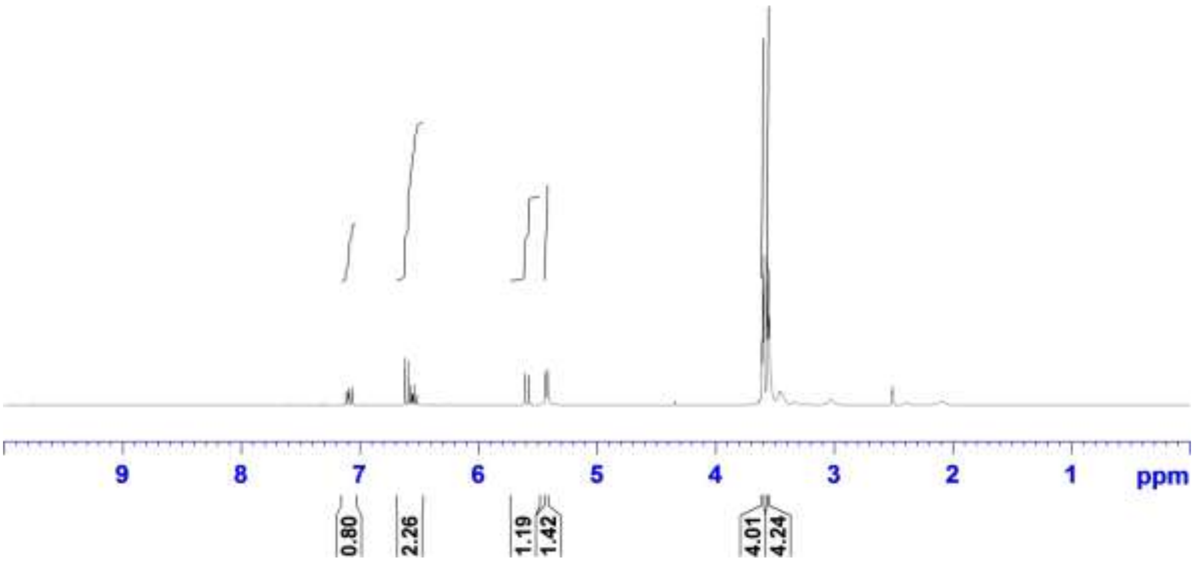
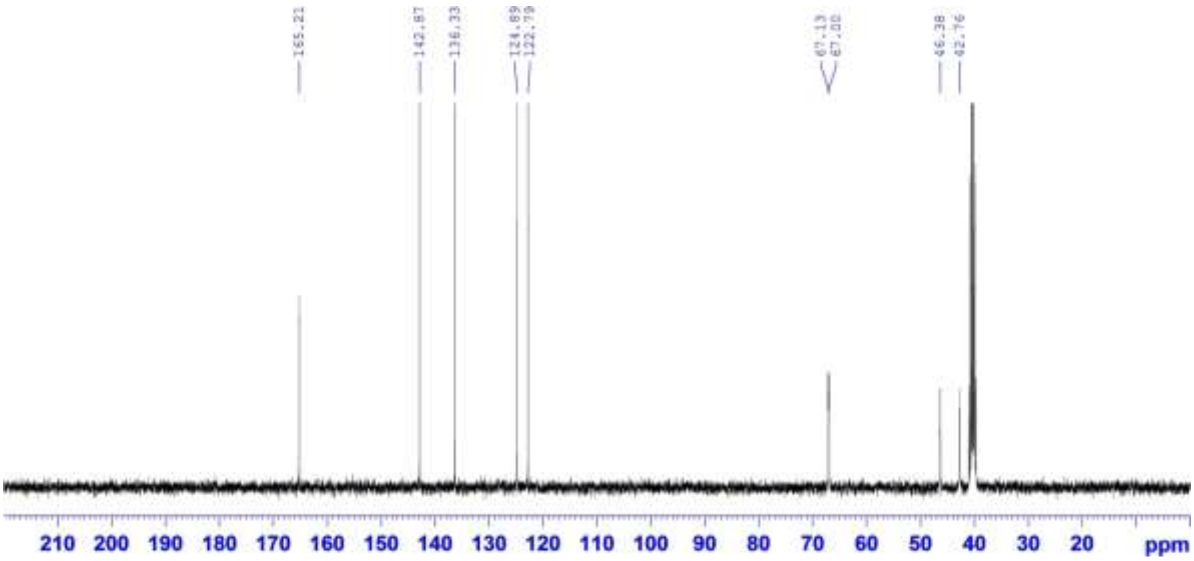
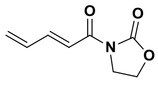


^{13}C NMR (d_6-DMSO, 101 MHz)



^{1}H NMR (CDCl$_3$, 400 MHz)



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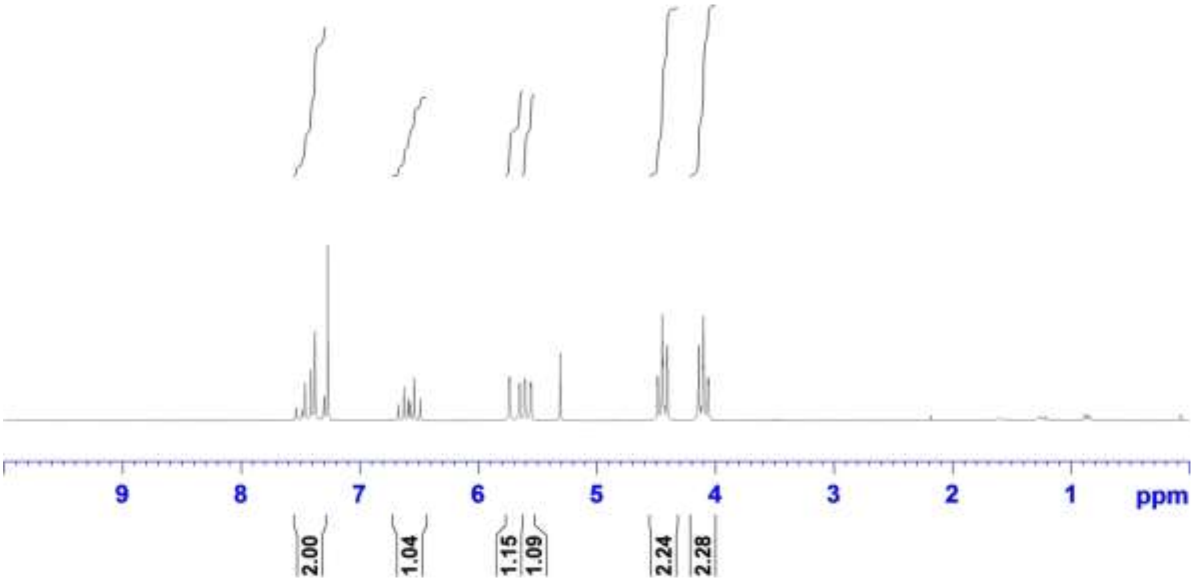
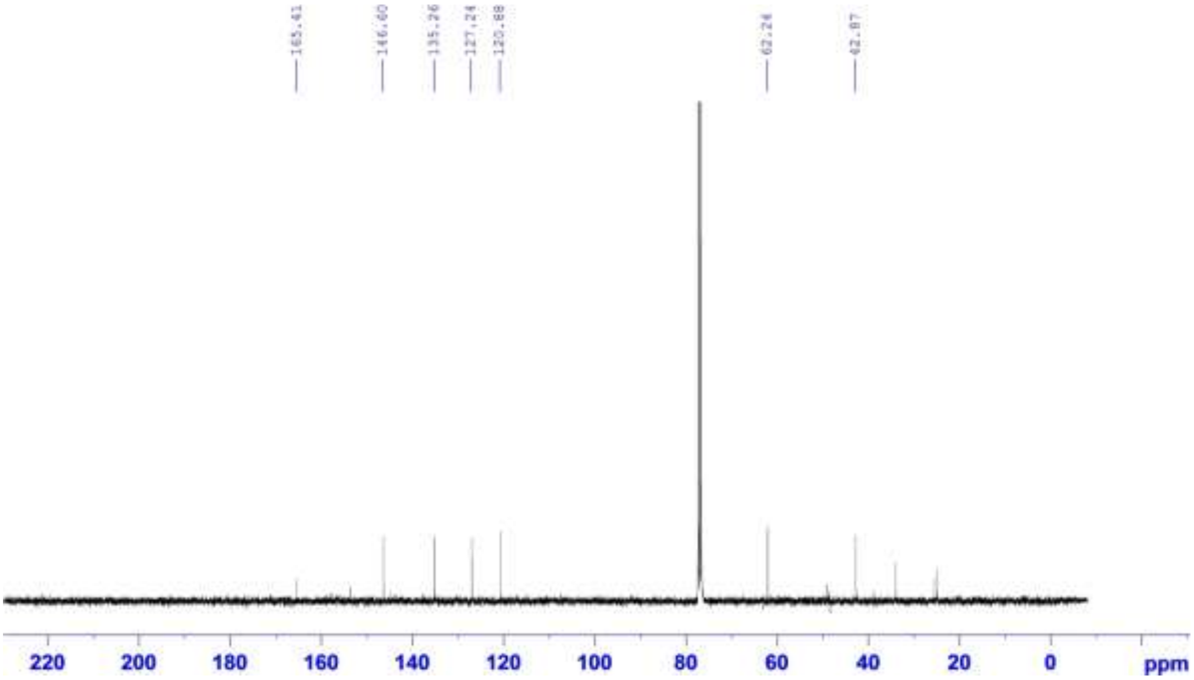
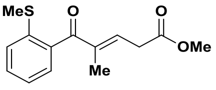


^{13}C NMR (CDCl$_3$, 101 MHz)

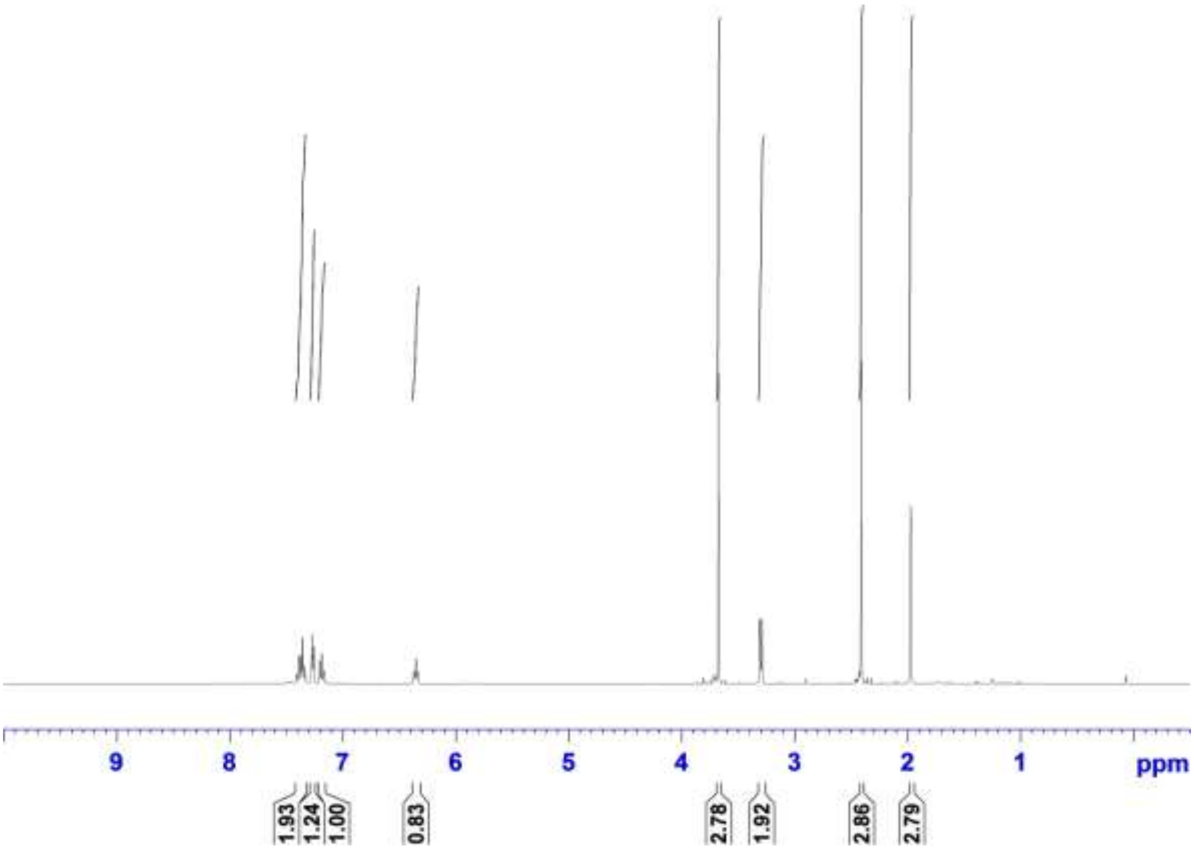


Chapter 2- Branched-Selective Diene Hydroacylation

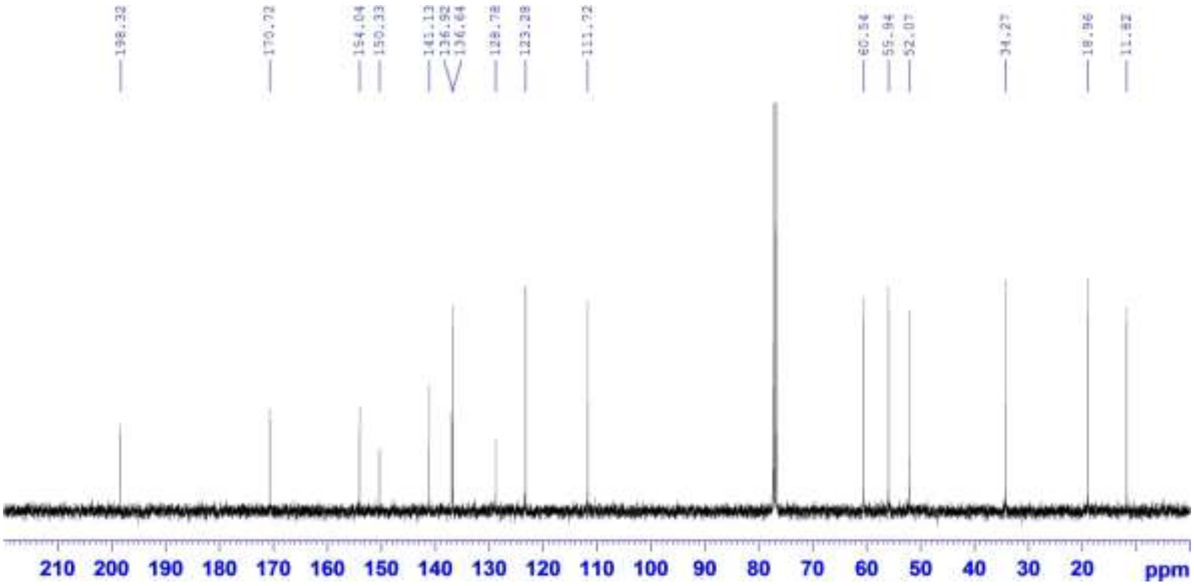
^{1}H NMR (CDCl$_3$, 400 MHz)



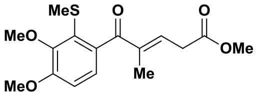
31b



^{13}C NMR (CDCl$_3$, 101 MHz)



^{1}H NMR (CDCl$_3$, 400 MHz)



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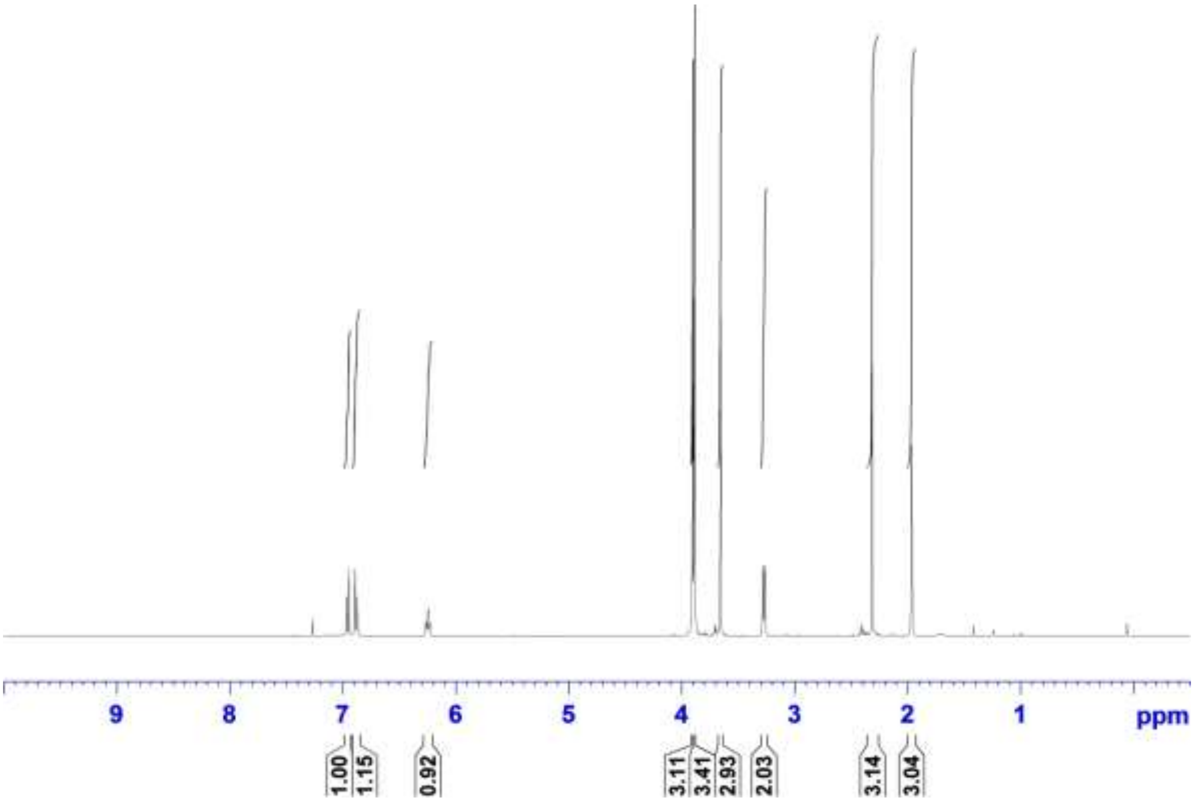
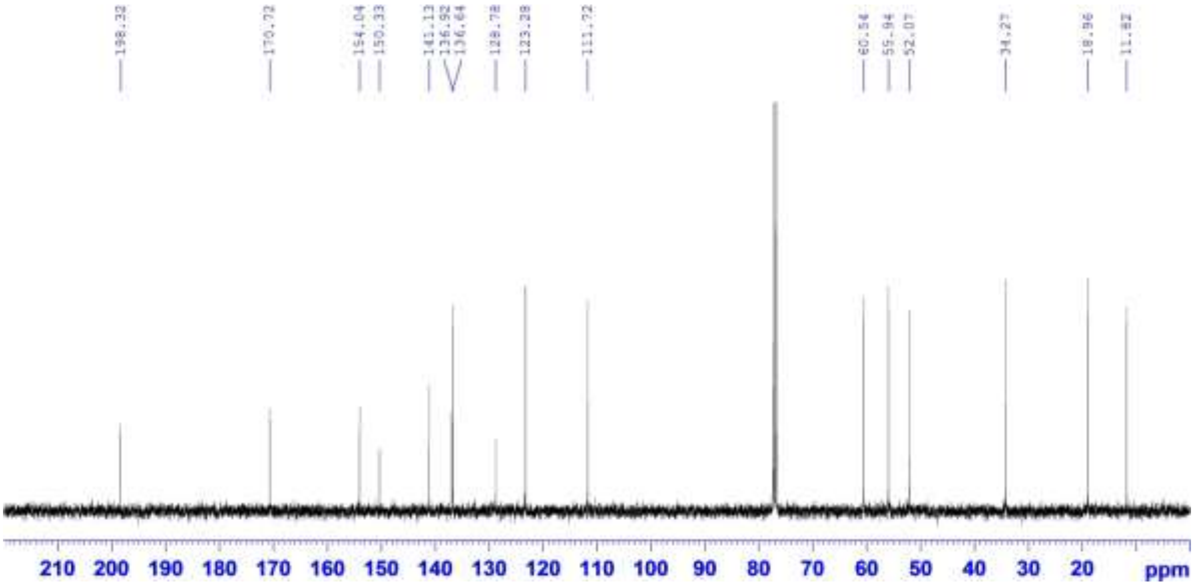
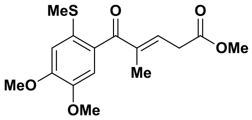


^{13}C NMR (CDCl$_3$, 101 MHz)



^{1}H NMR (CDCl$_3$, 400 MHz)



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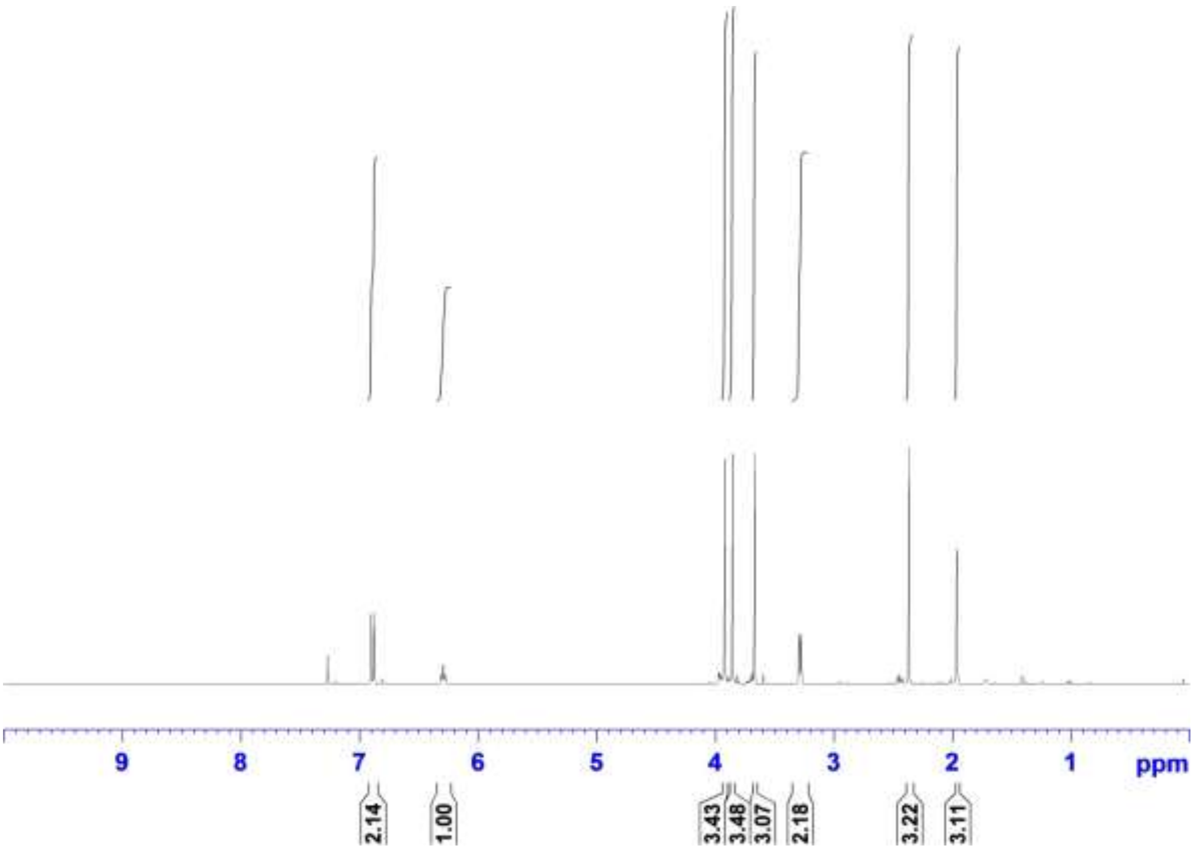
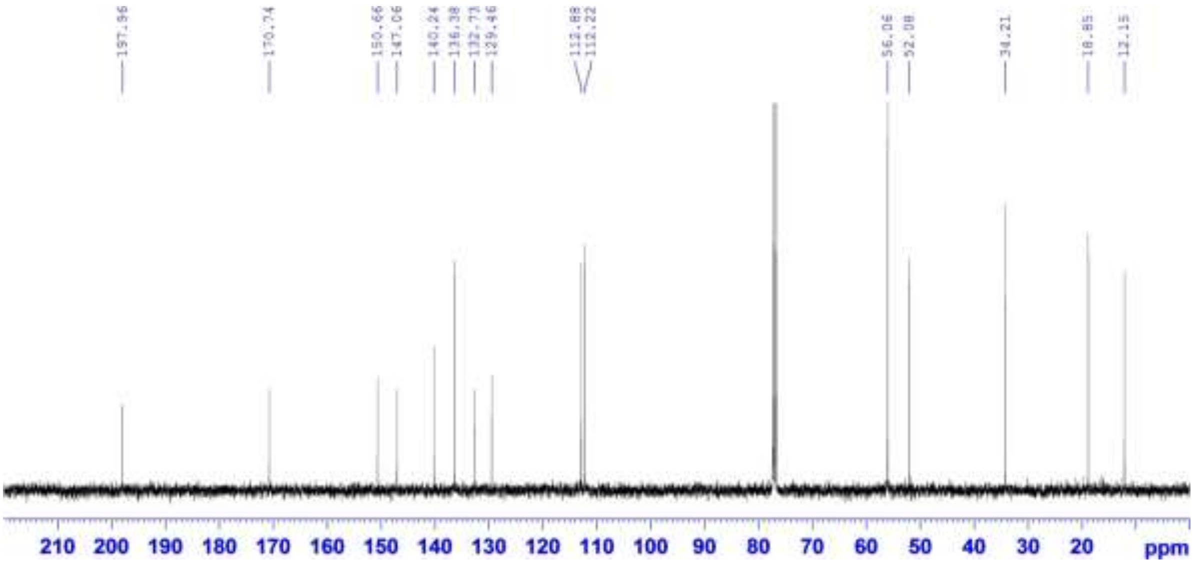
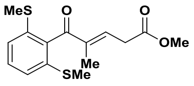


^{13}C NMR (CDCl$_3$, 101 MHz)



^{1}H NMR (CDCl$_3$, 400 MHz



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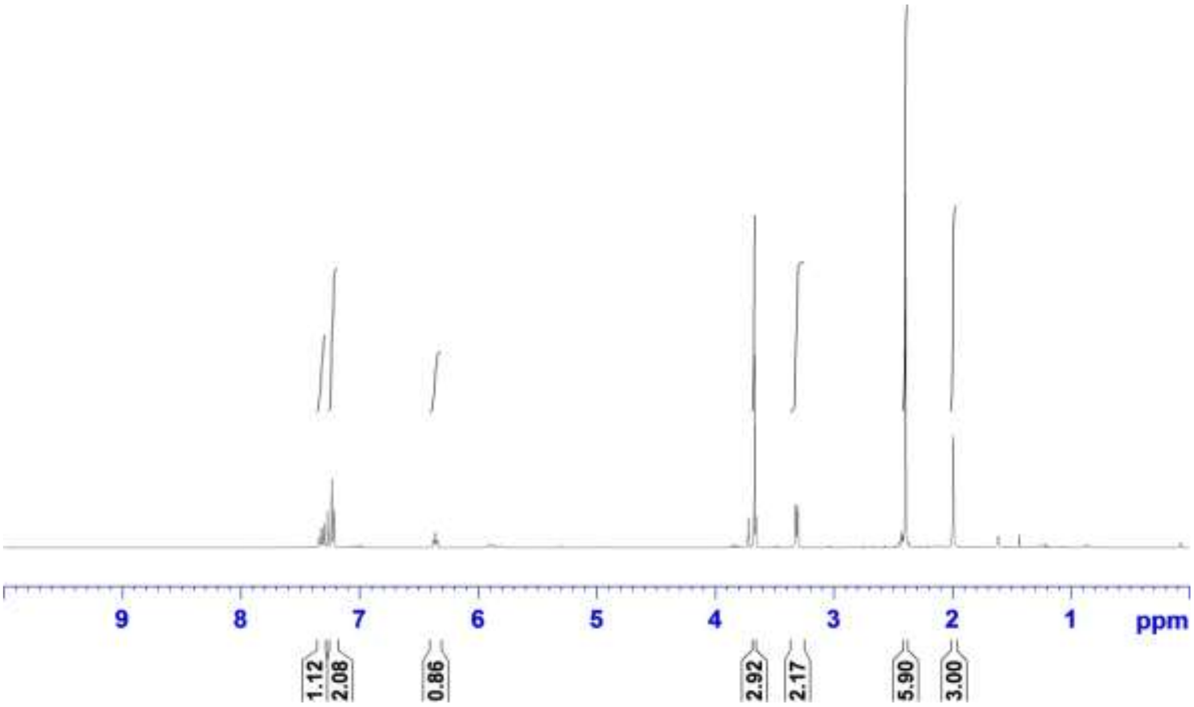
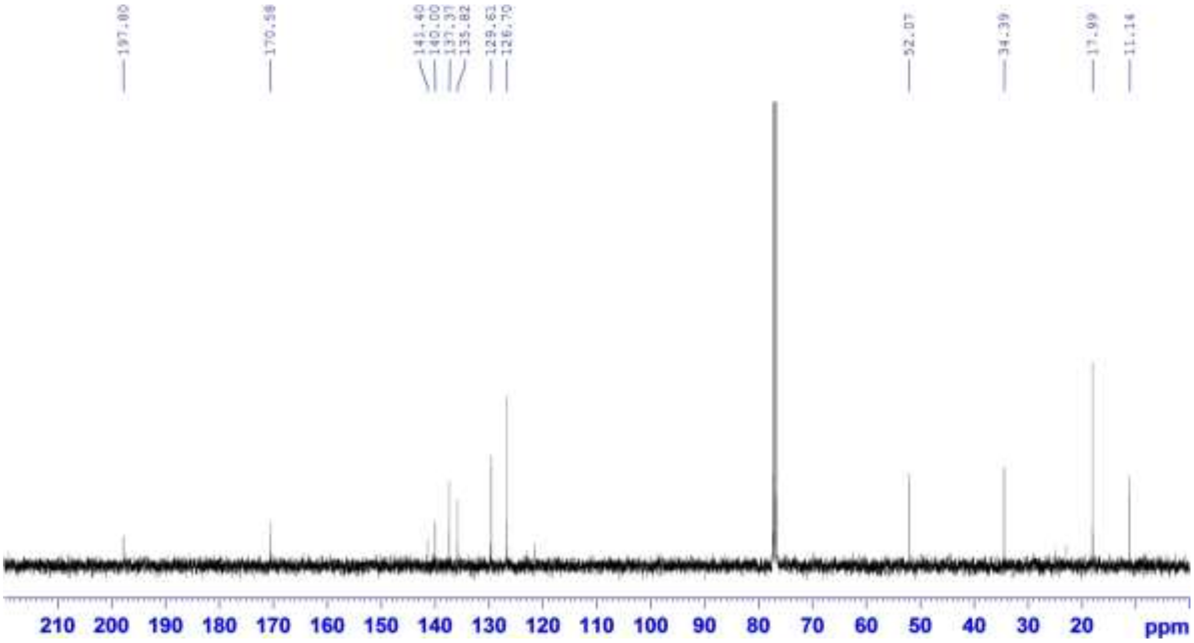
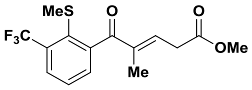


^{13}C NMR (CDCl$_3$, 101 MHz)



^{1}H NMR (CDCl$_3$, 400 MHz)



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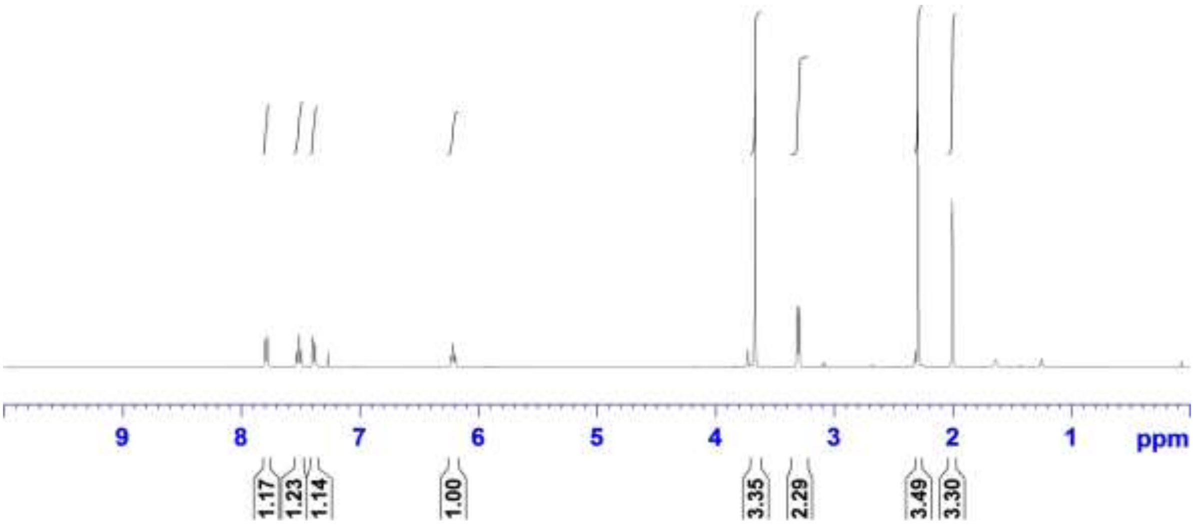
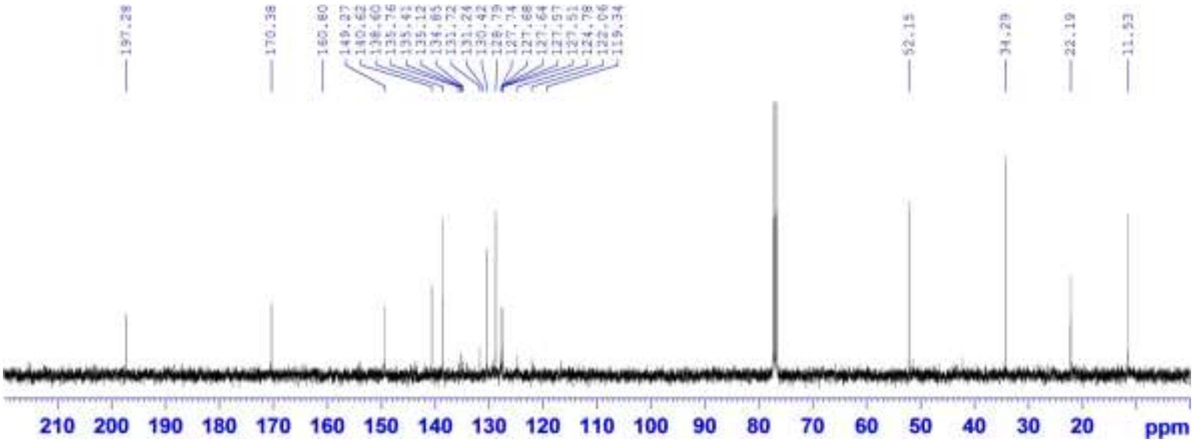
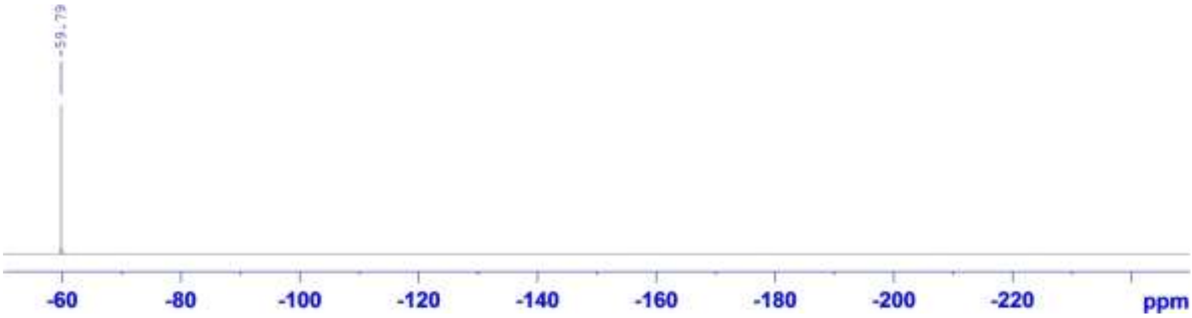


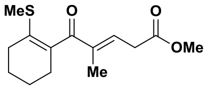
^{13}C NMR (CDCl$_3$, 101 MHz)



^{19}F NMR (CDCl$_3$, 376 MHz)



^{1}H NMR (CDCl$_3$, 400 MHz)



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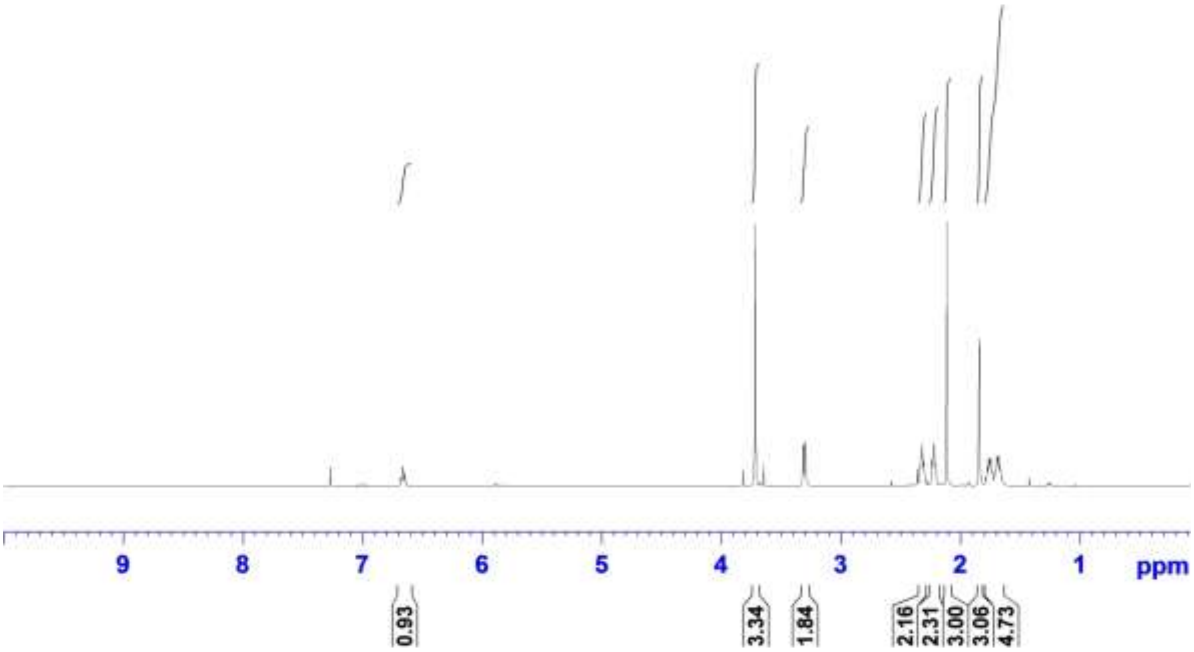
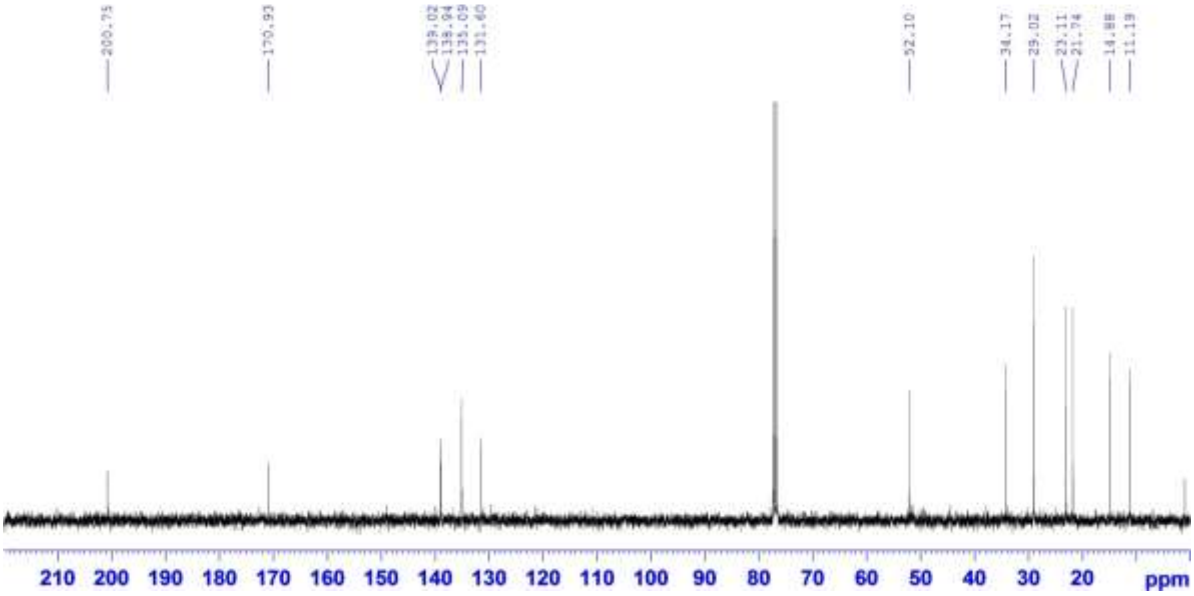
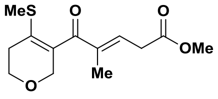


^{13}C NMR (CDCl$_3$, 101 MHz)



^{1}H NMR (CDCl$_3$, 400 MHz)



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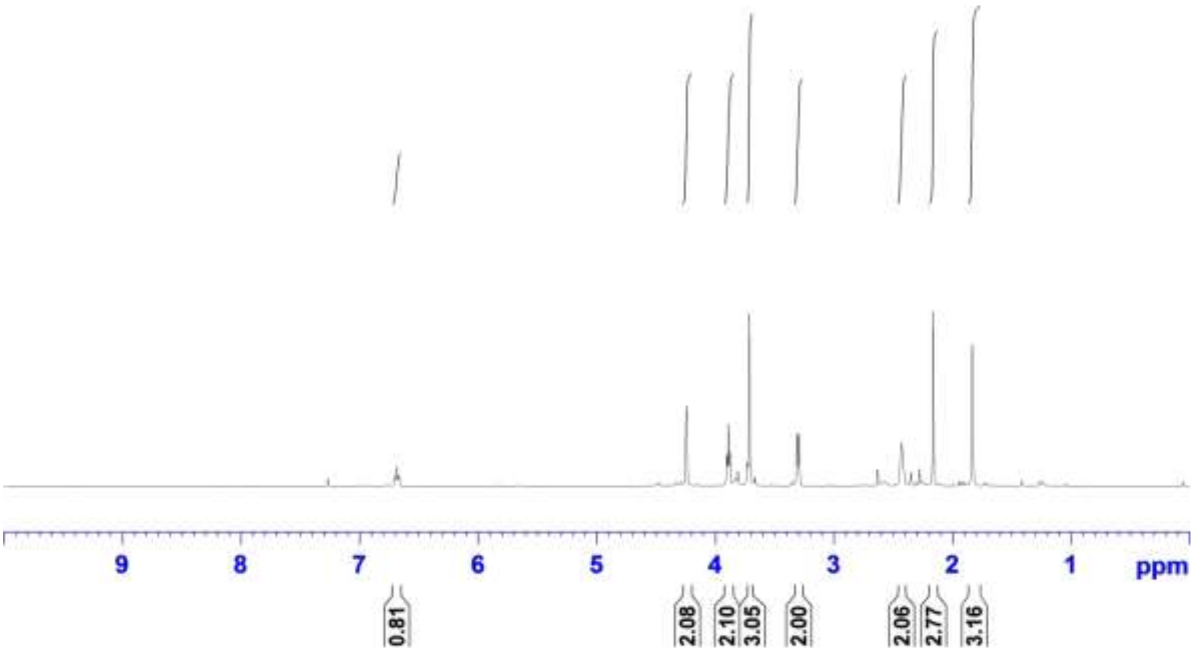
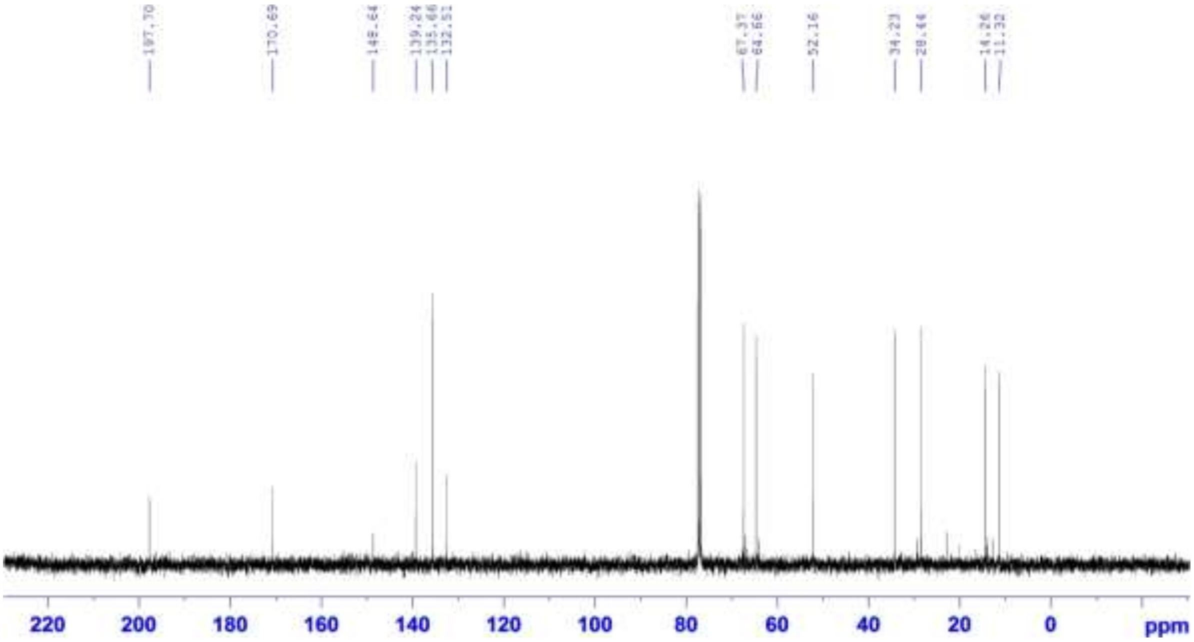
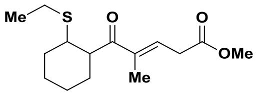


^{13}C NMR (CDCl$_3$, 101 MHz)



^{1}H NMR (CDCl$_3$, 400 MHz)



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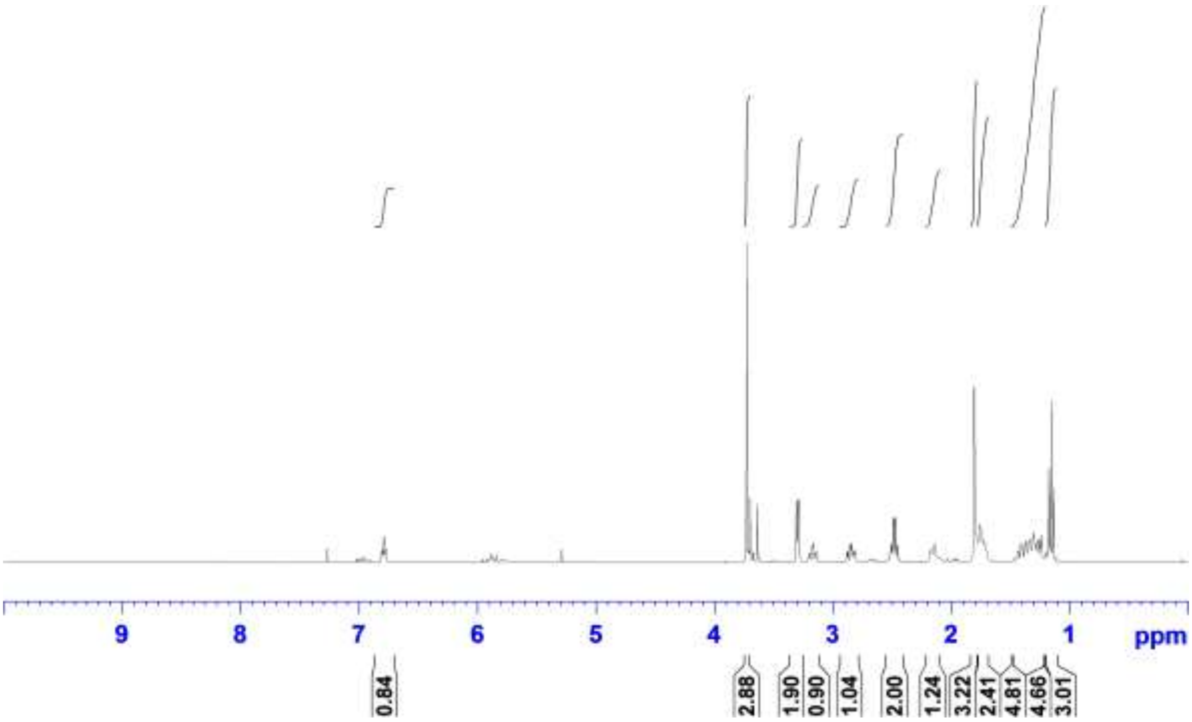
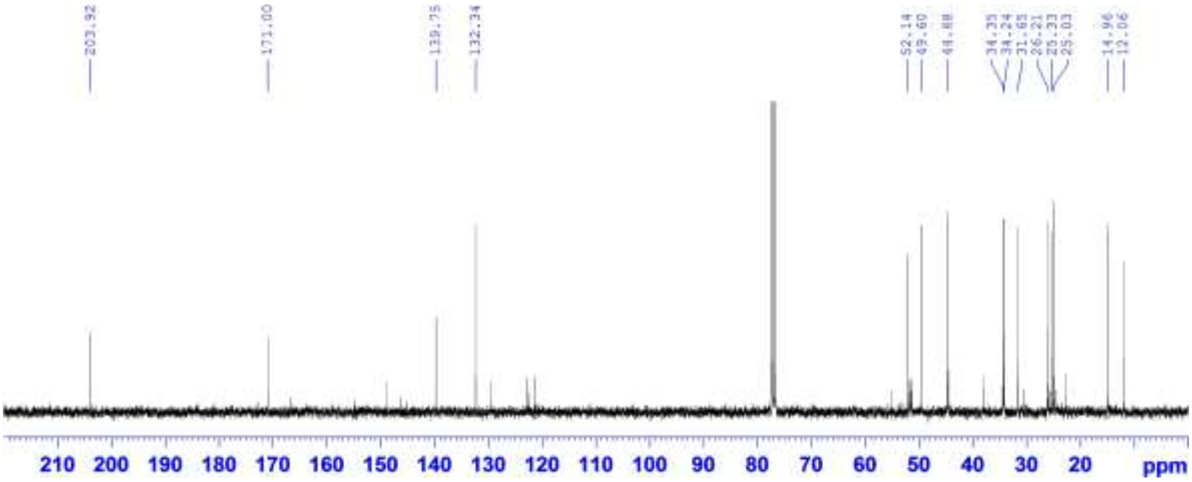
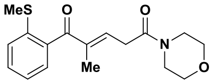


^{13}C NMR (CDCl$_3$, 101 MHz)



^{1}H NMR ($CDCl_3$, 400 MHz)



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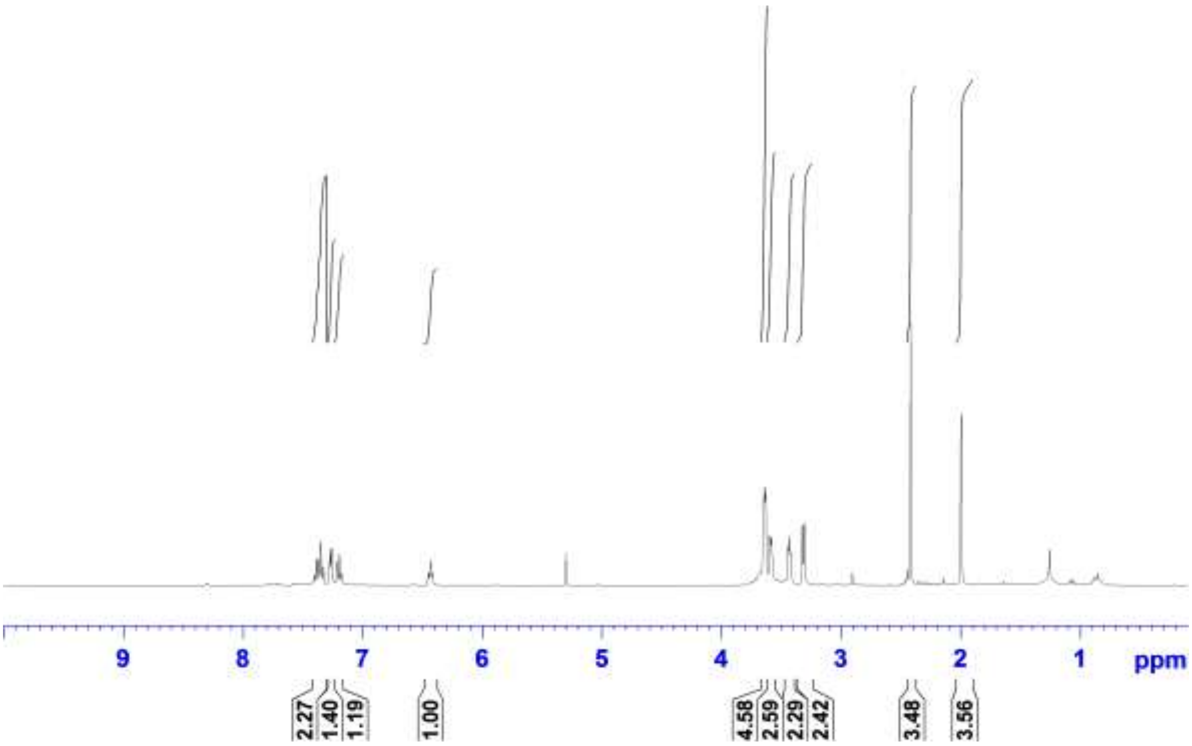
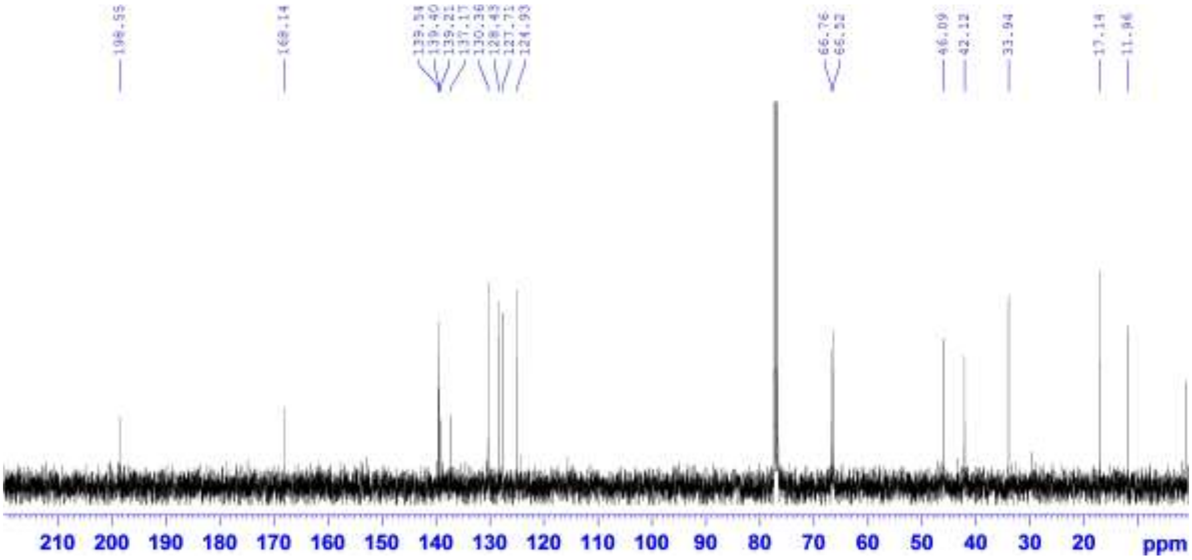
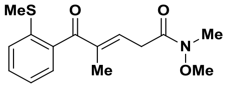


^{13}C NMR ($CDCl_3$, 101 MHz)



^{1}H NMR (CDCl$_3$, 400 MHz)



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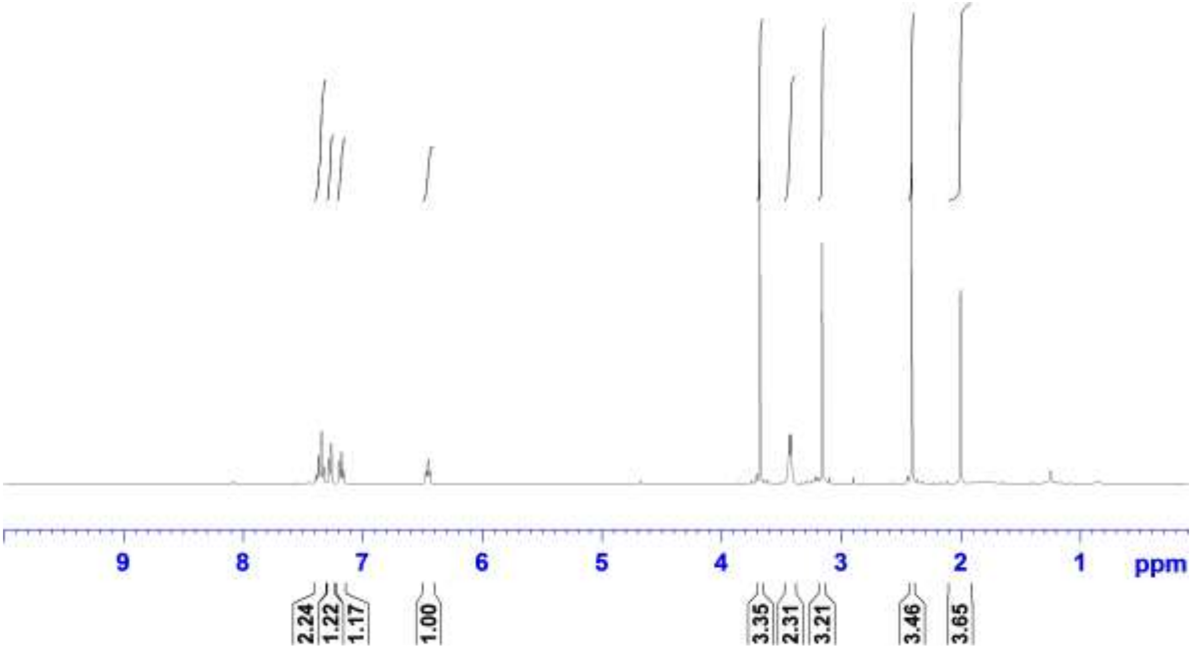
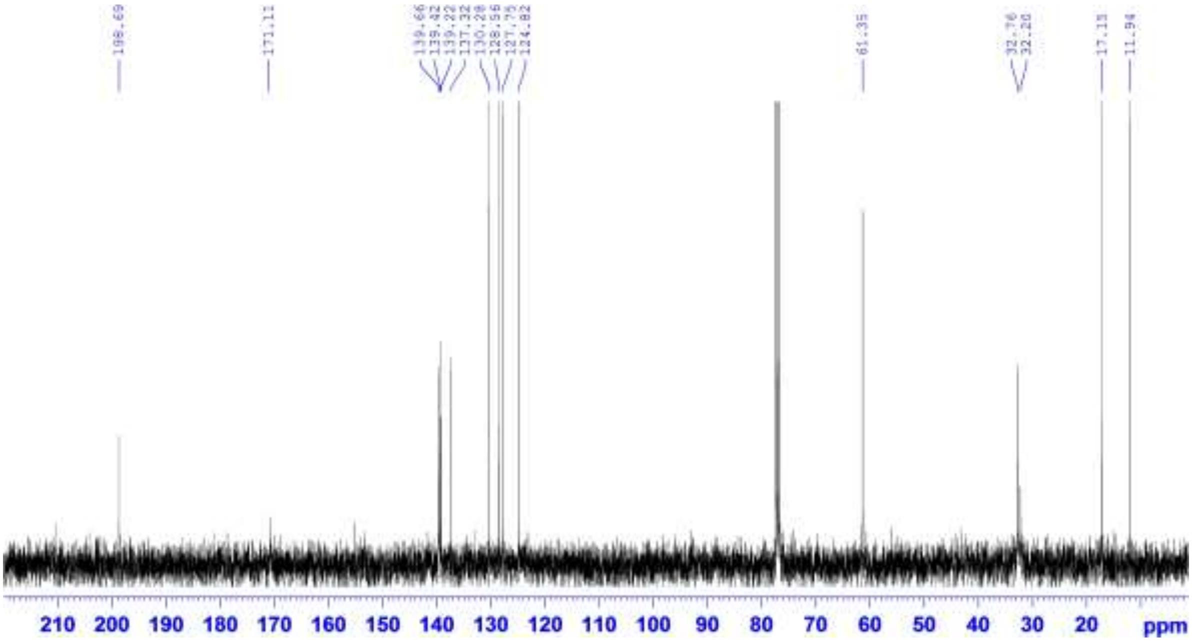
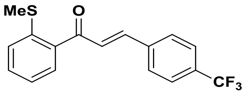


^{13}C NMR (CDCl$_3$, 101 MHz)



Chapter 3 – Linear-Selective Alkyne Hydroacylation

^{1}H NMR (400 MHz, $CDCl_3$)



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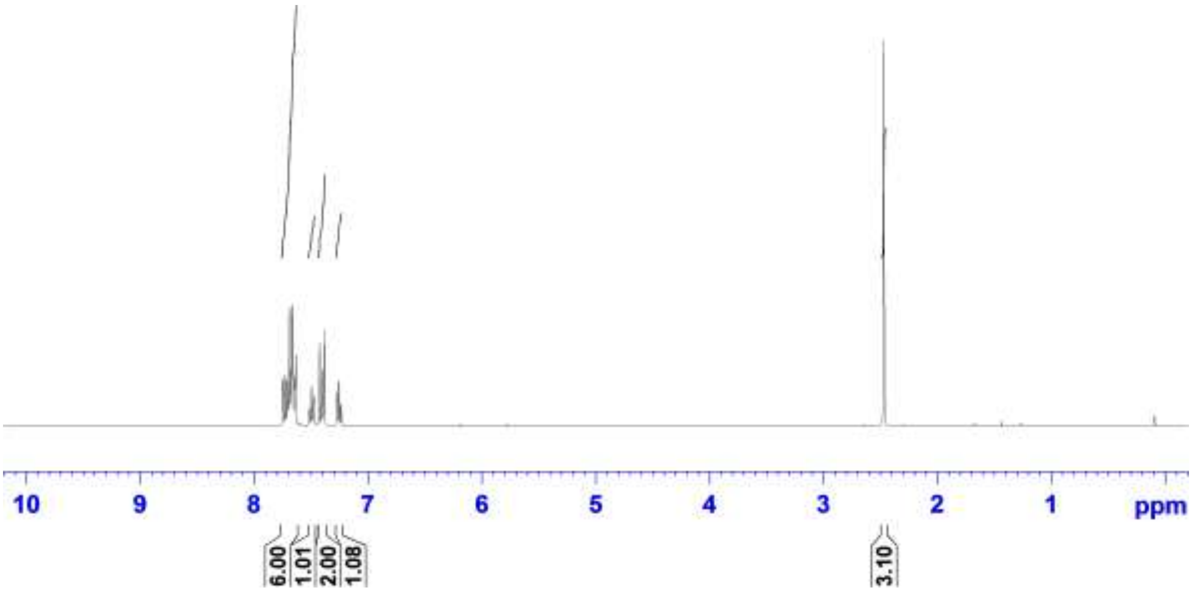
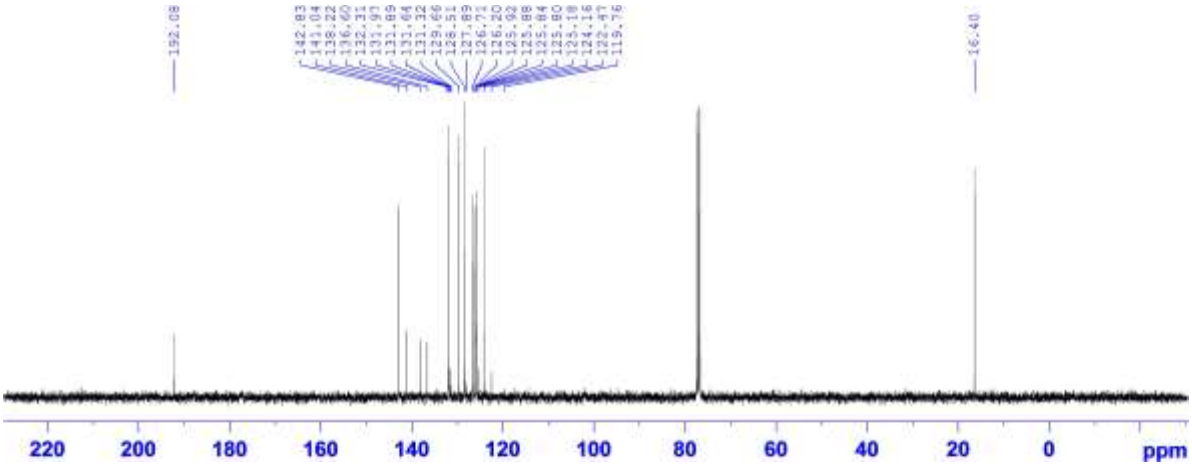
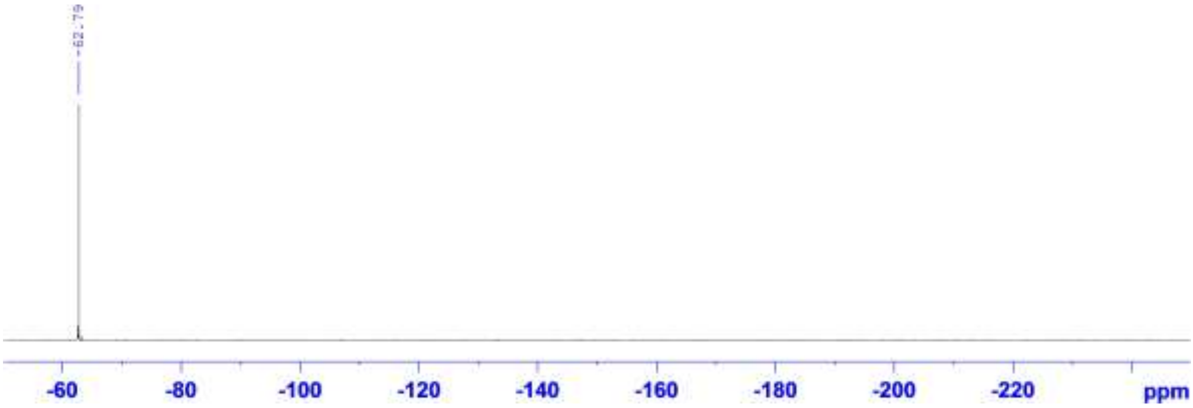


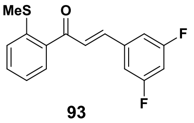
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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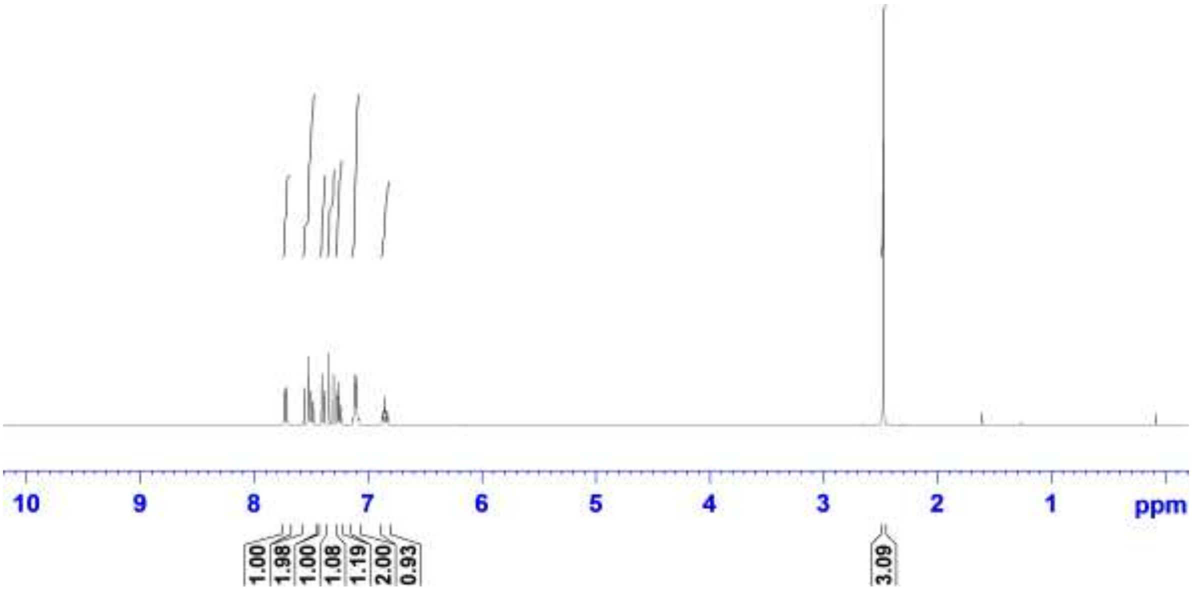
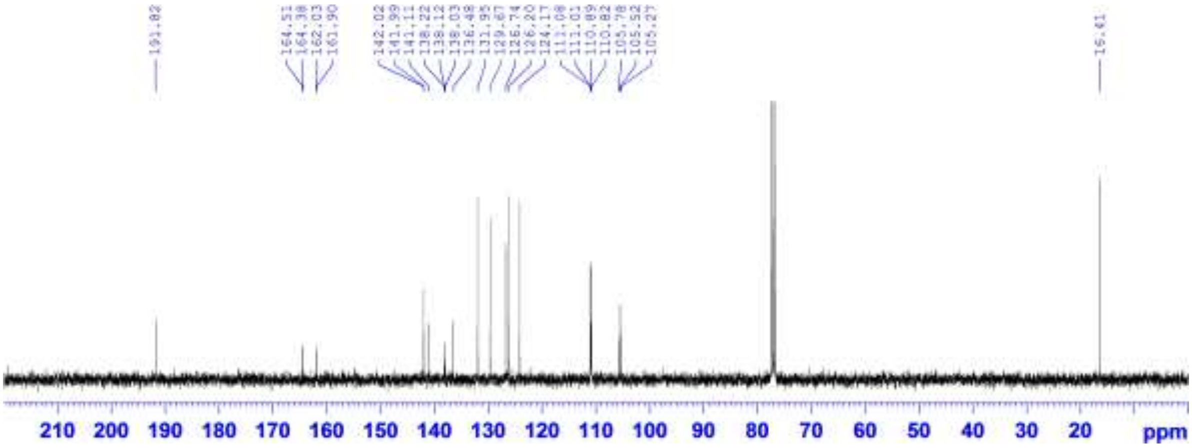
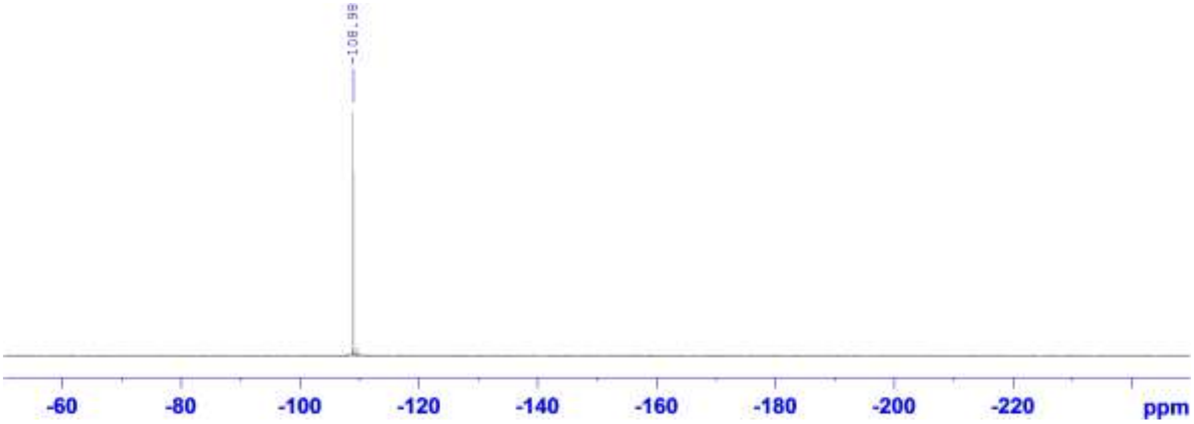


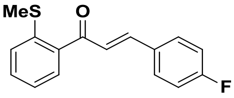
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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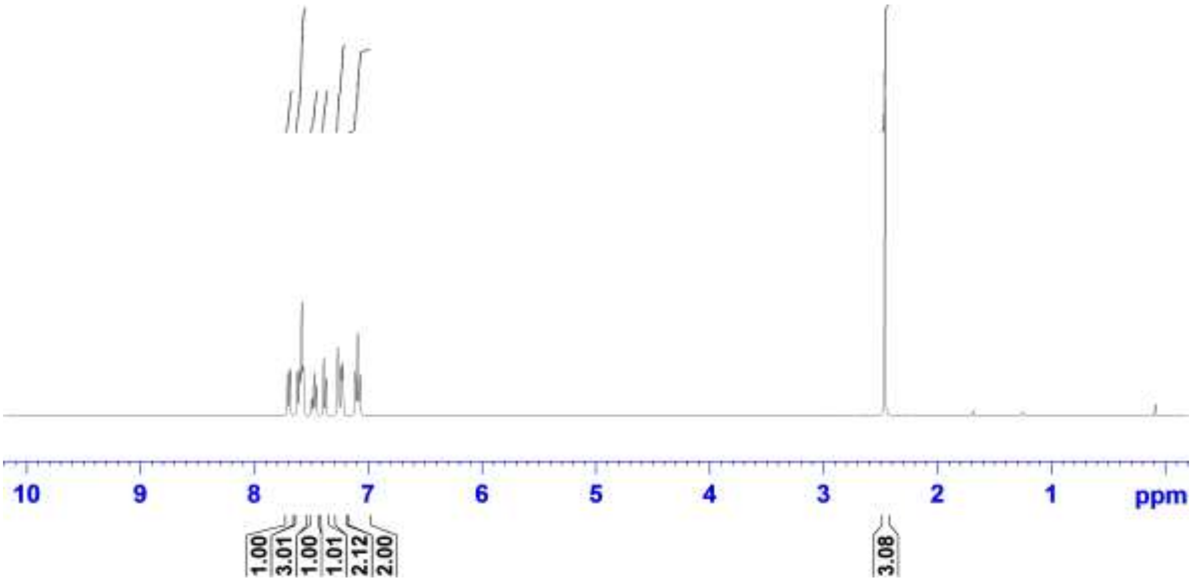
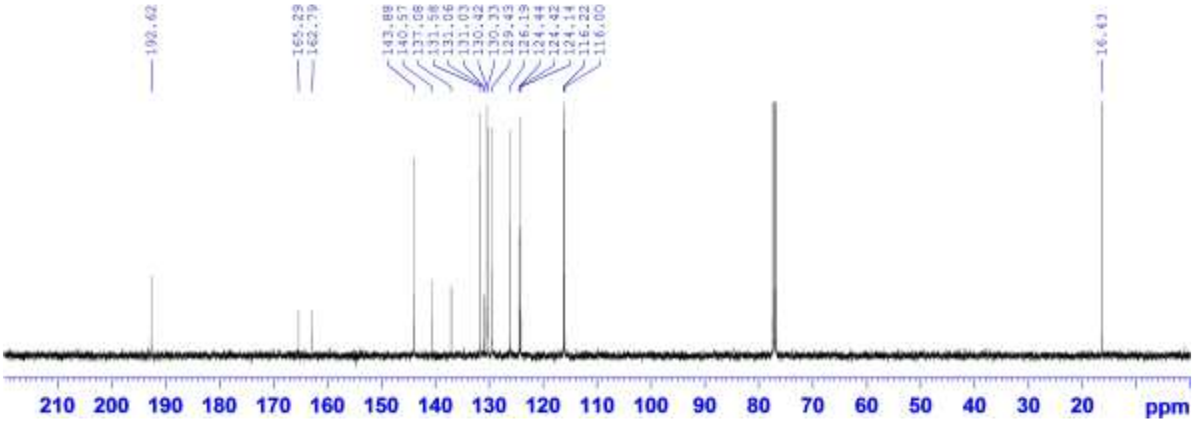
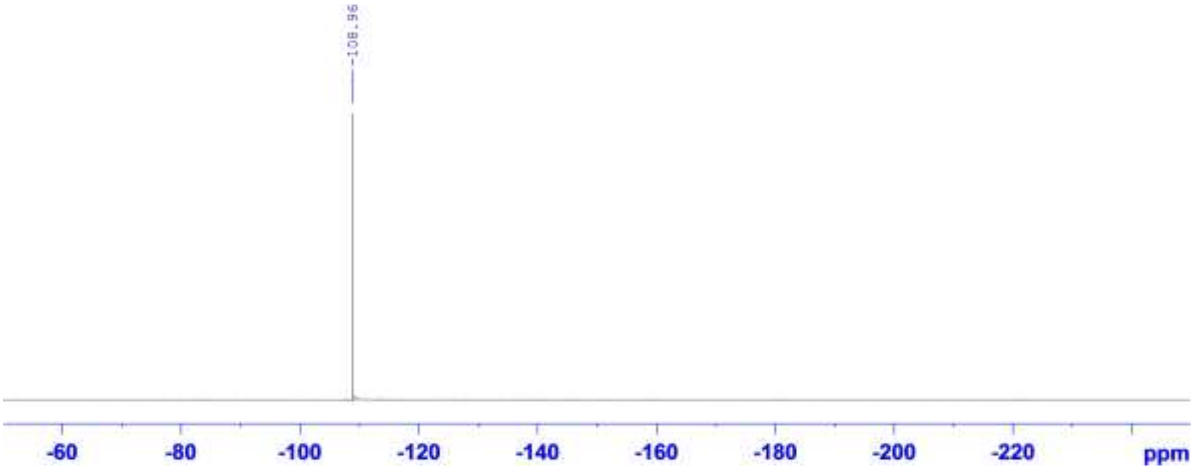


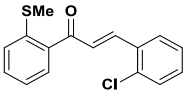
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CD_2Cl_2)



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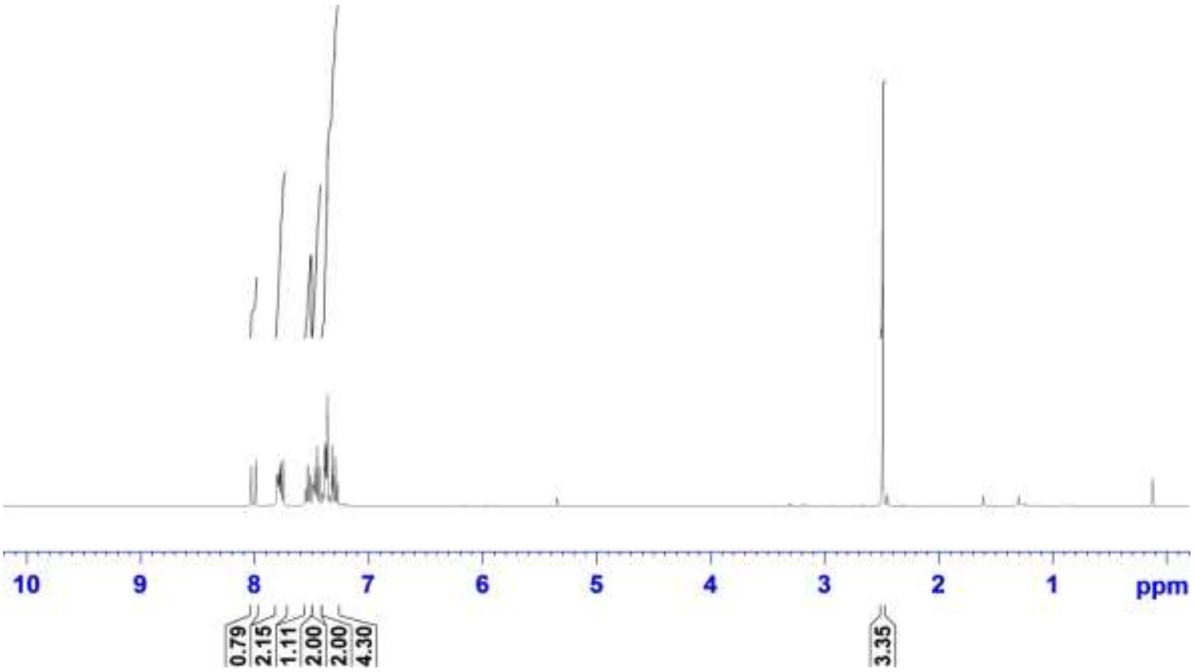
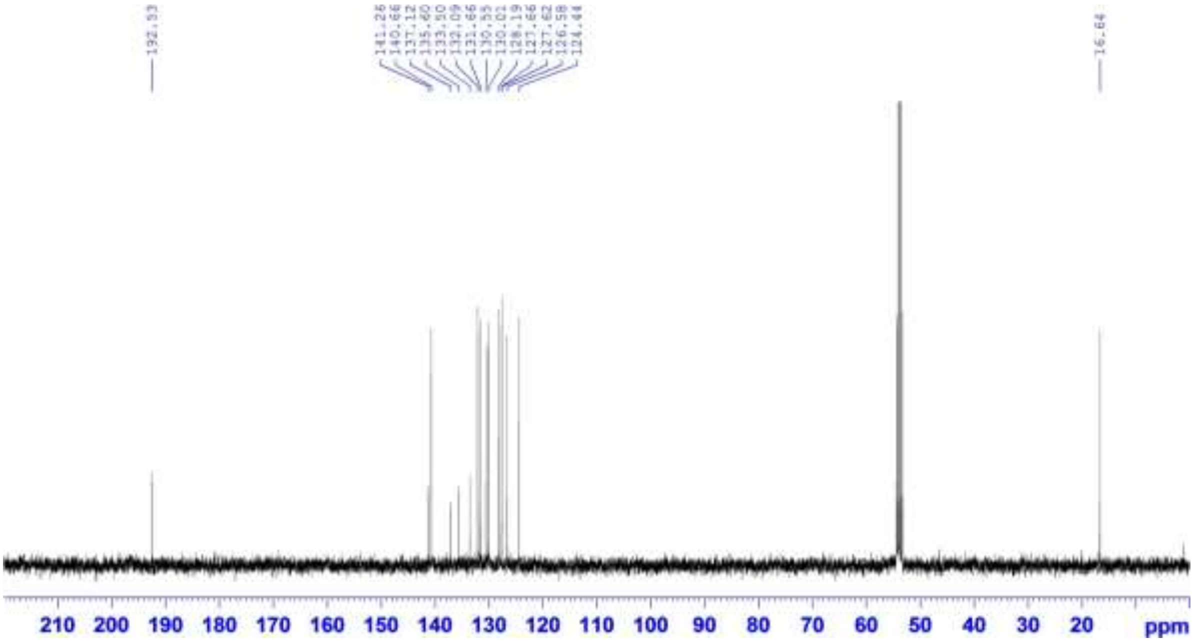
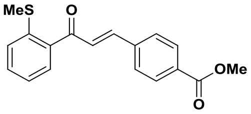


^{13}C NMR (101 MHz, CD_2Cl_2)



^{1}H NMR (400 MHz, CDCl$_3$)



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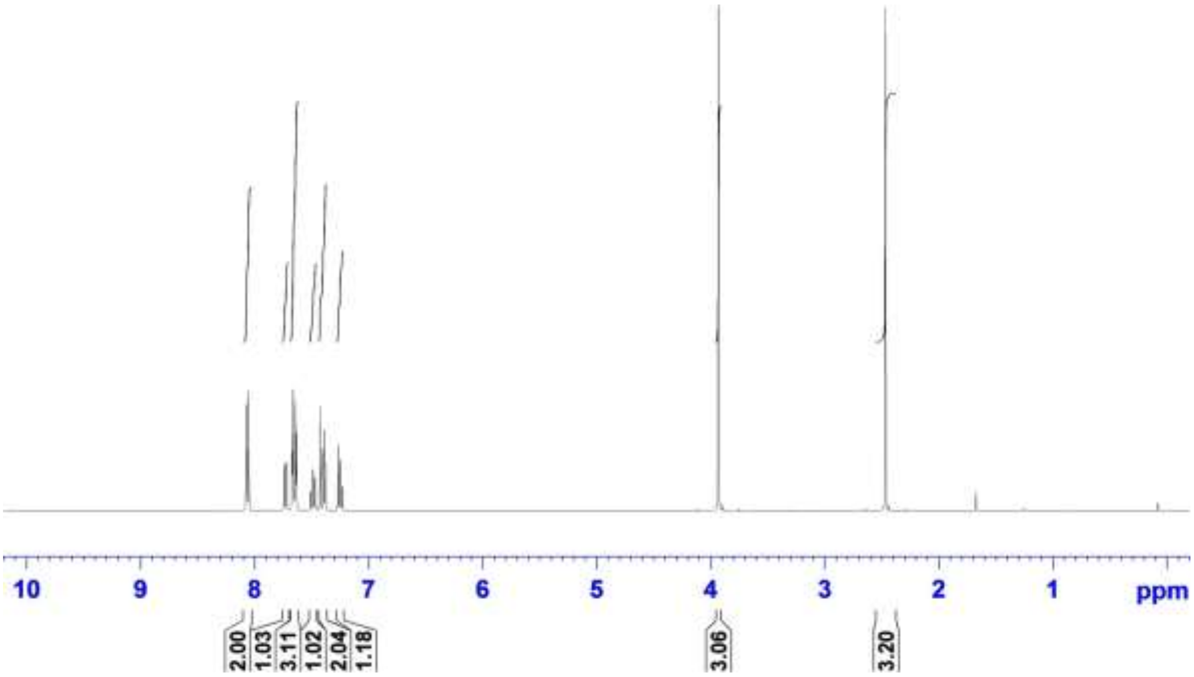
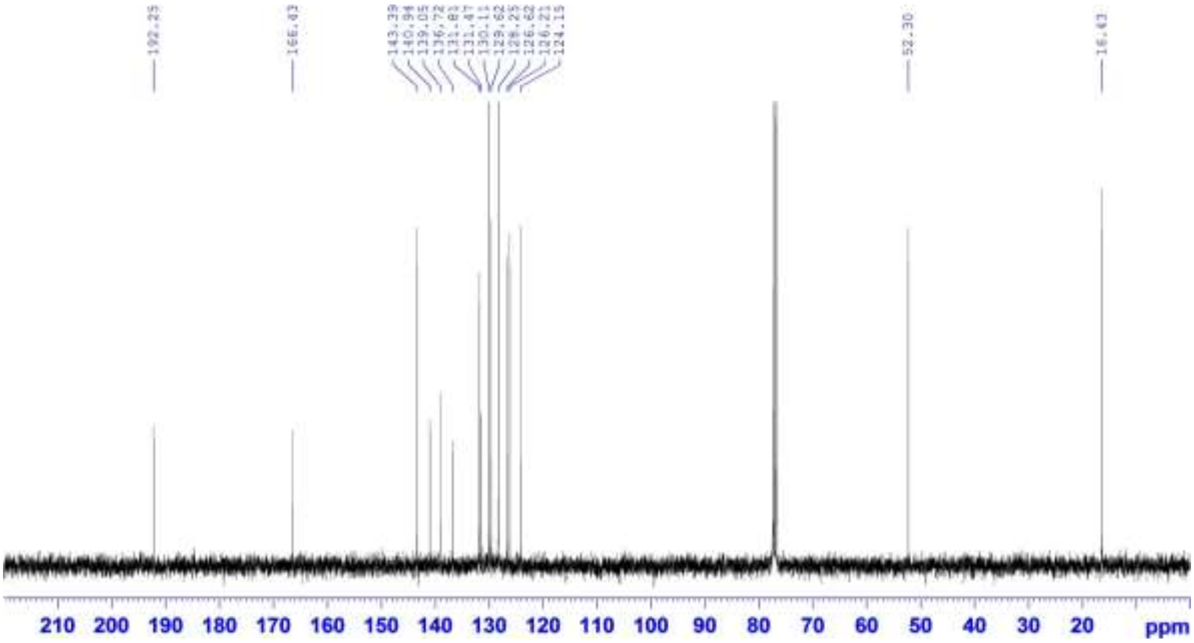
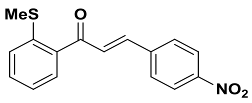


^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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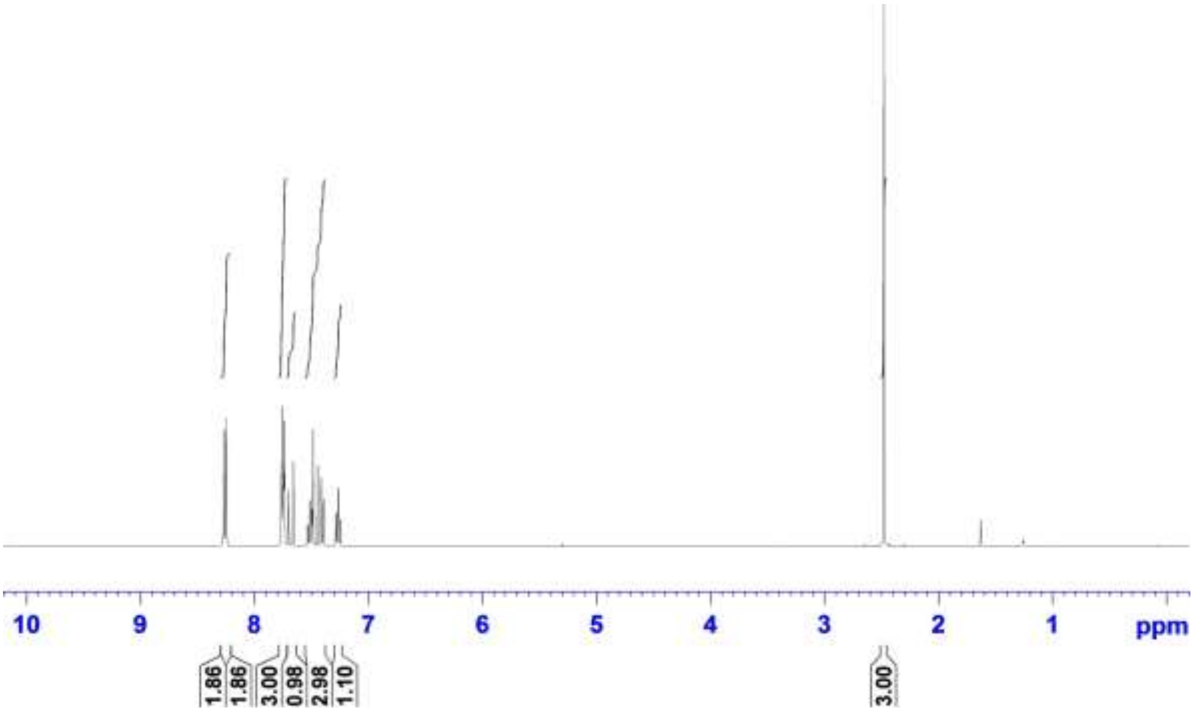
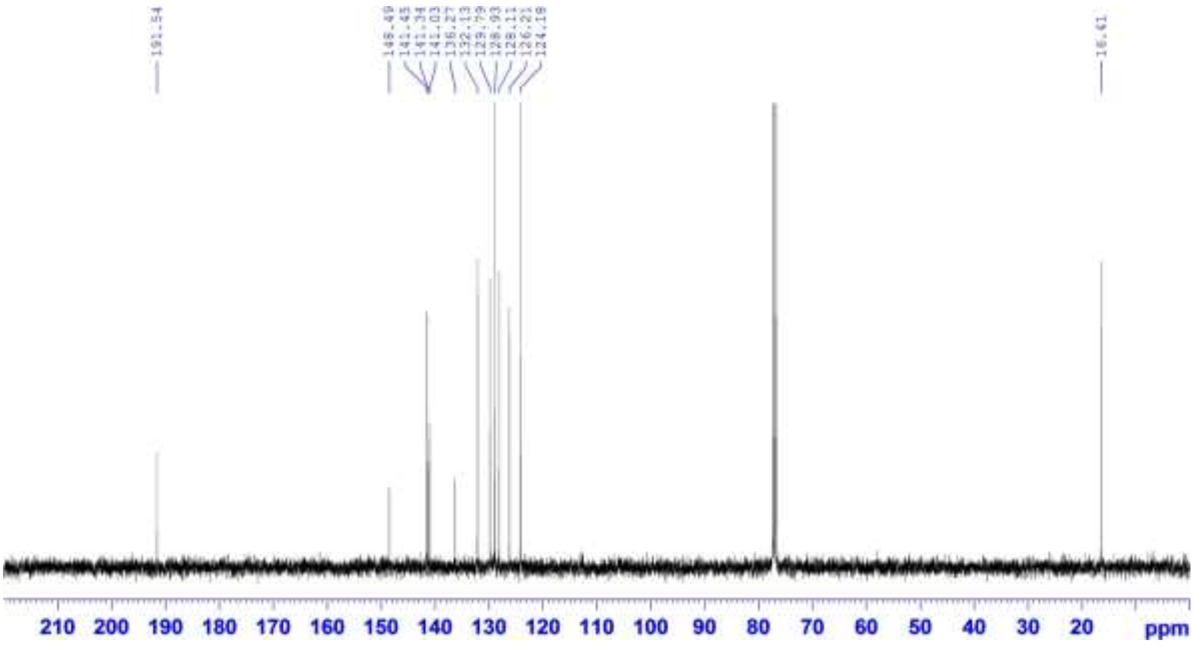
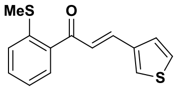


^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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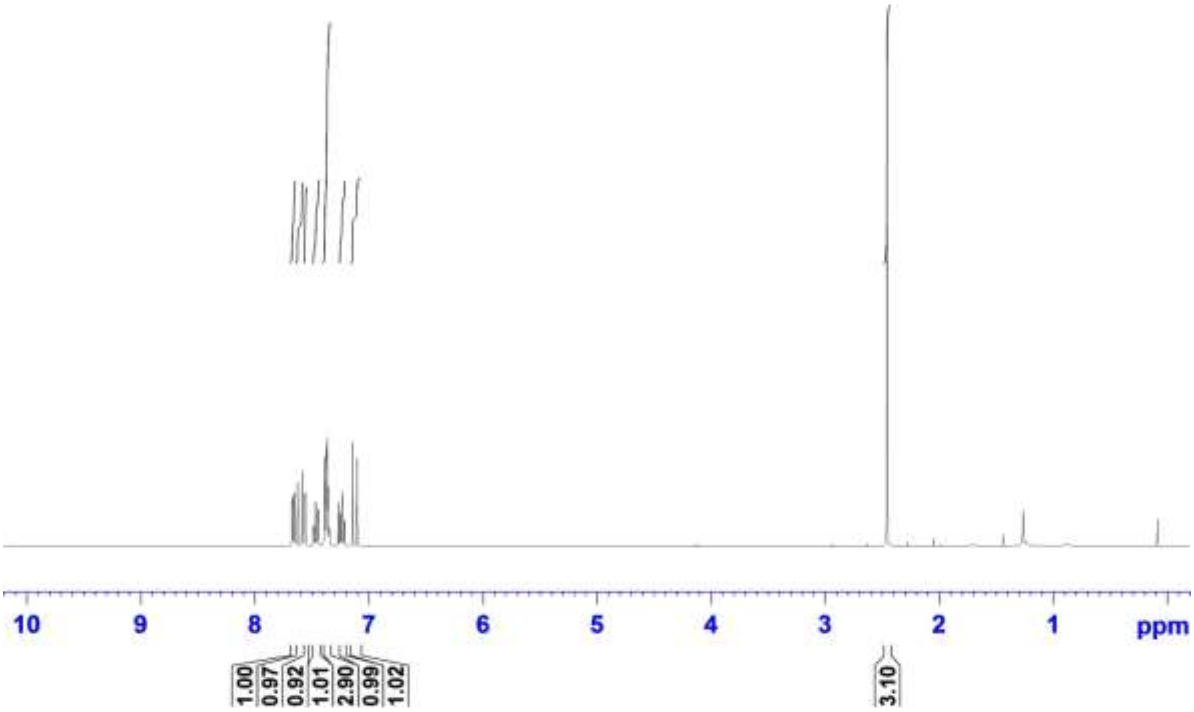
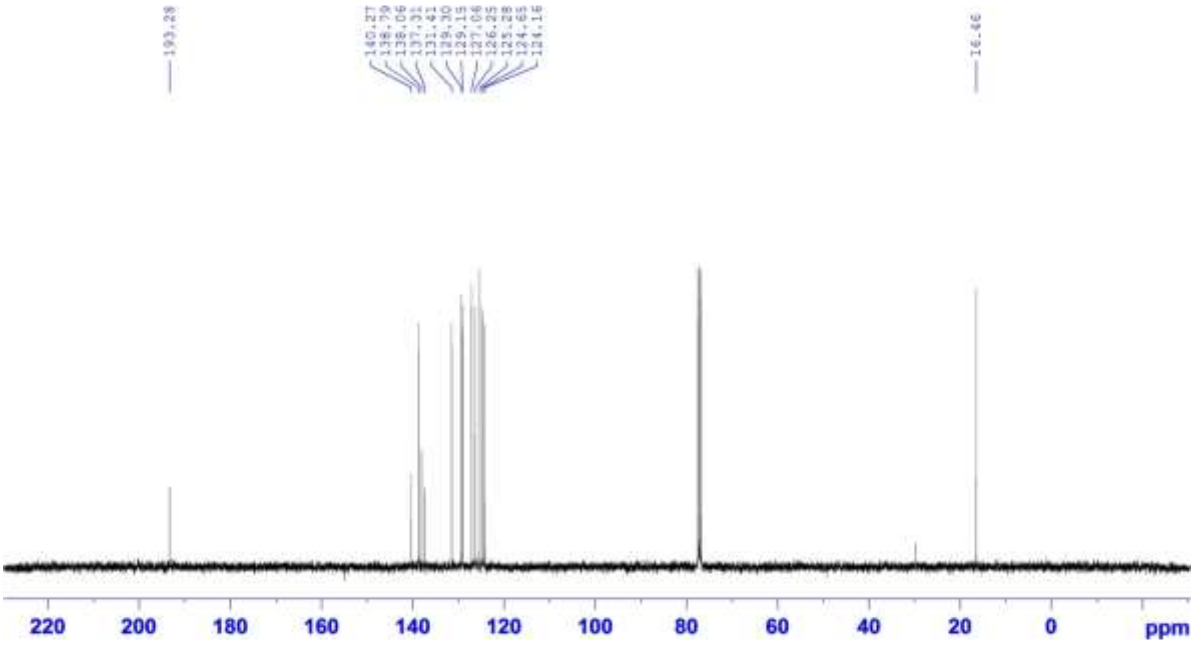
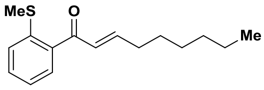


^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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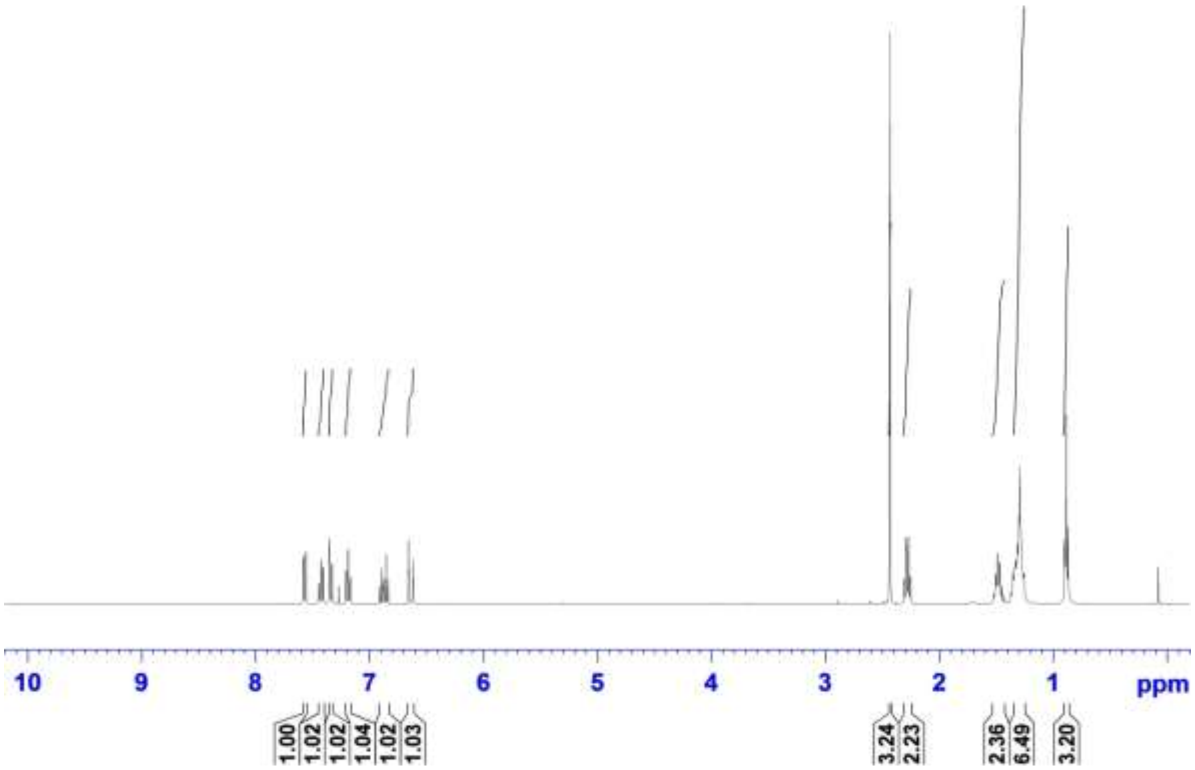
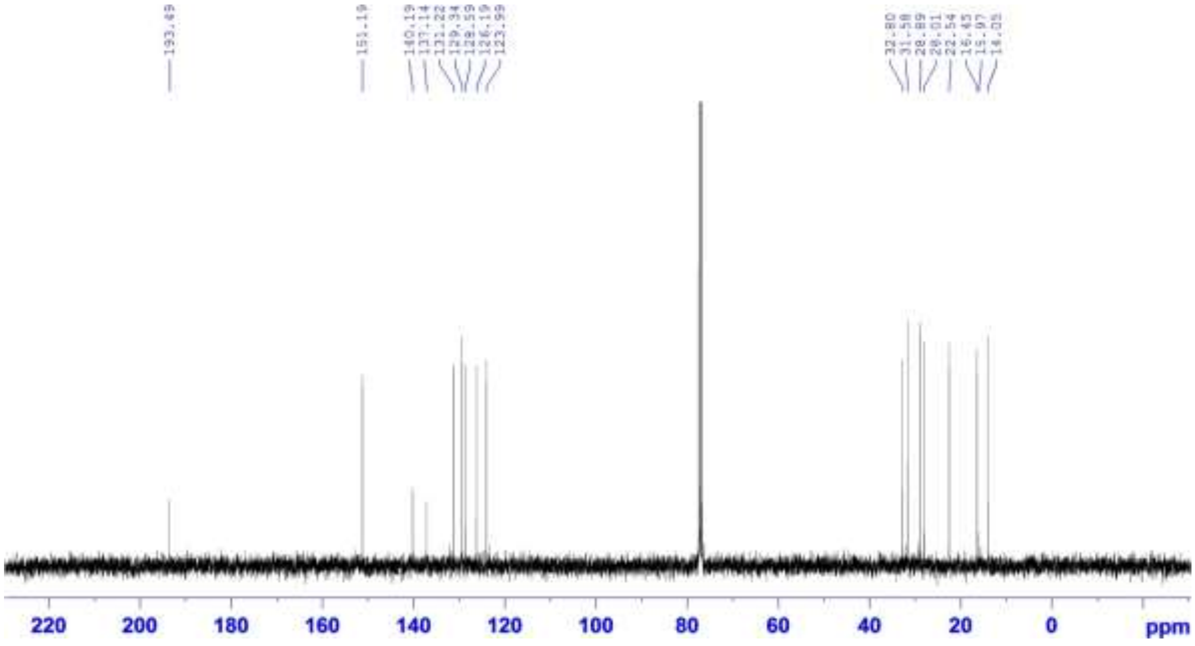
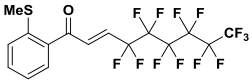


^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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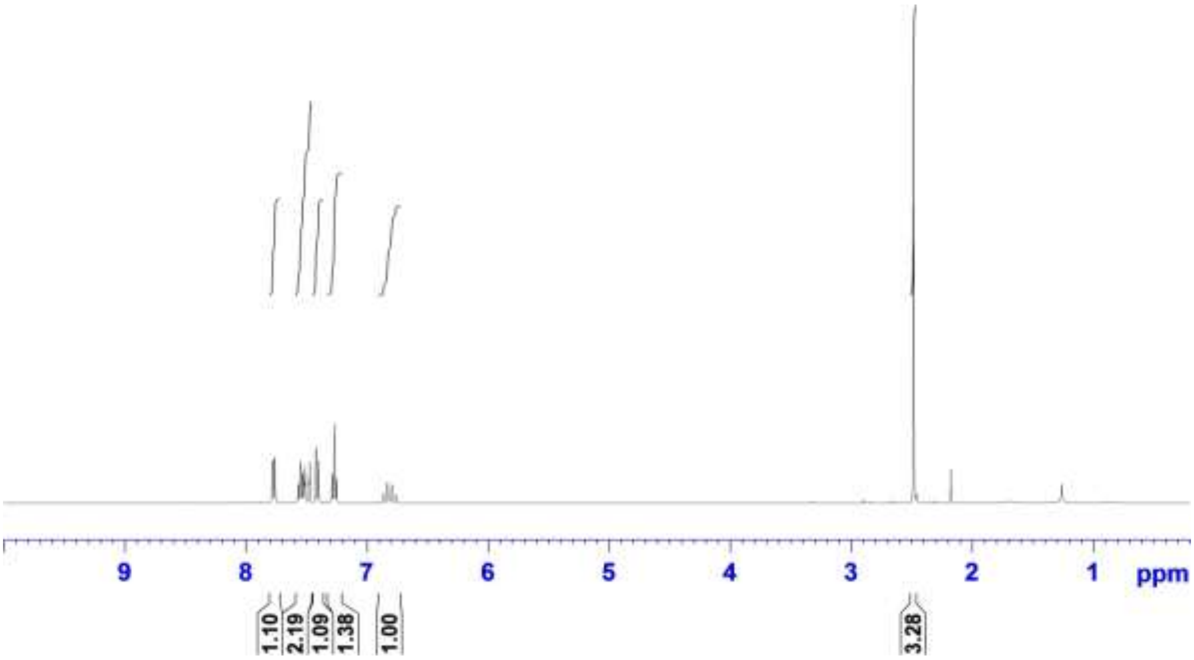
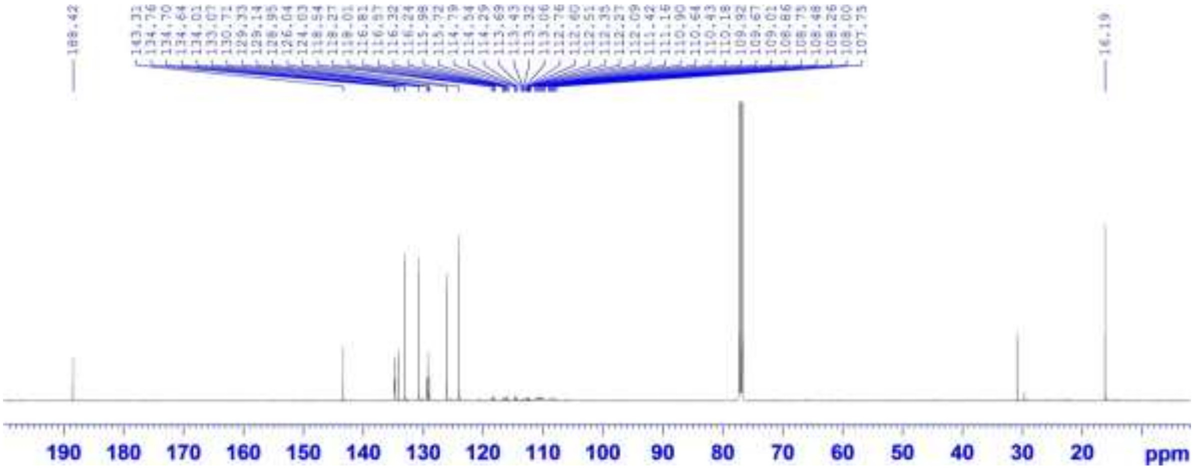


^{13}C NMR (101 MHz, CDCl$_3$)



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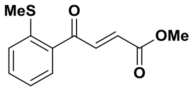

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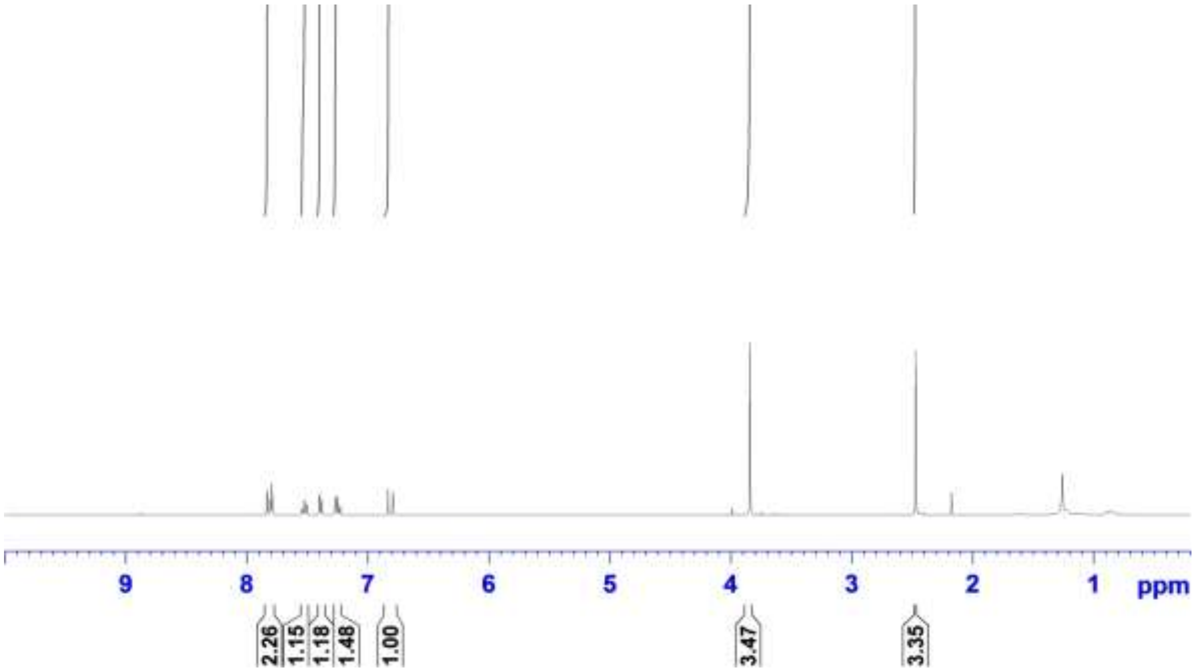
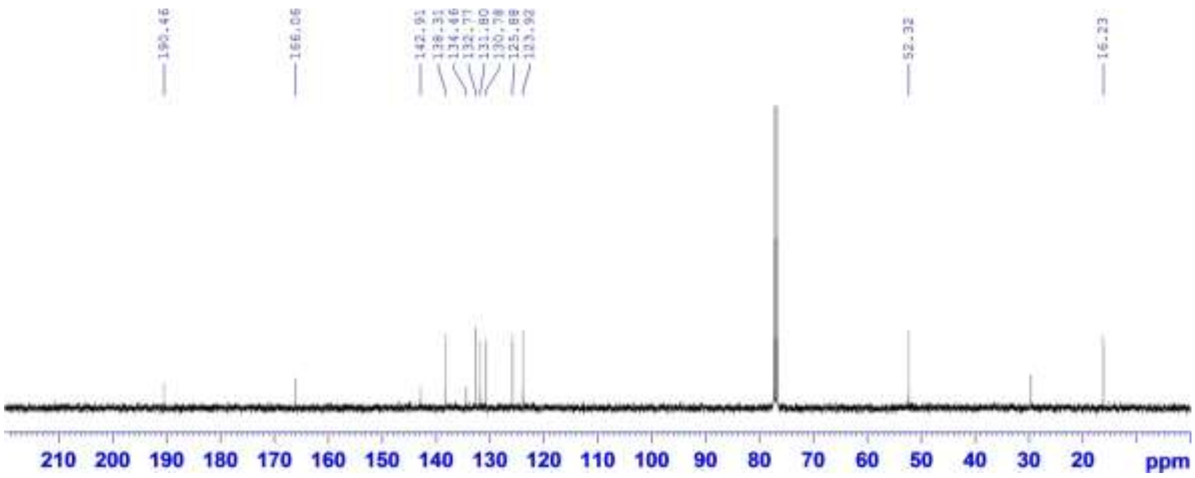
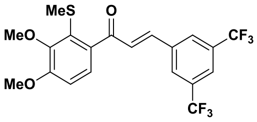


^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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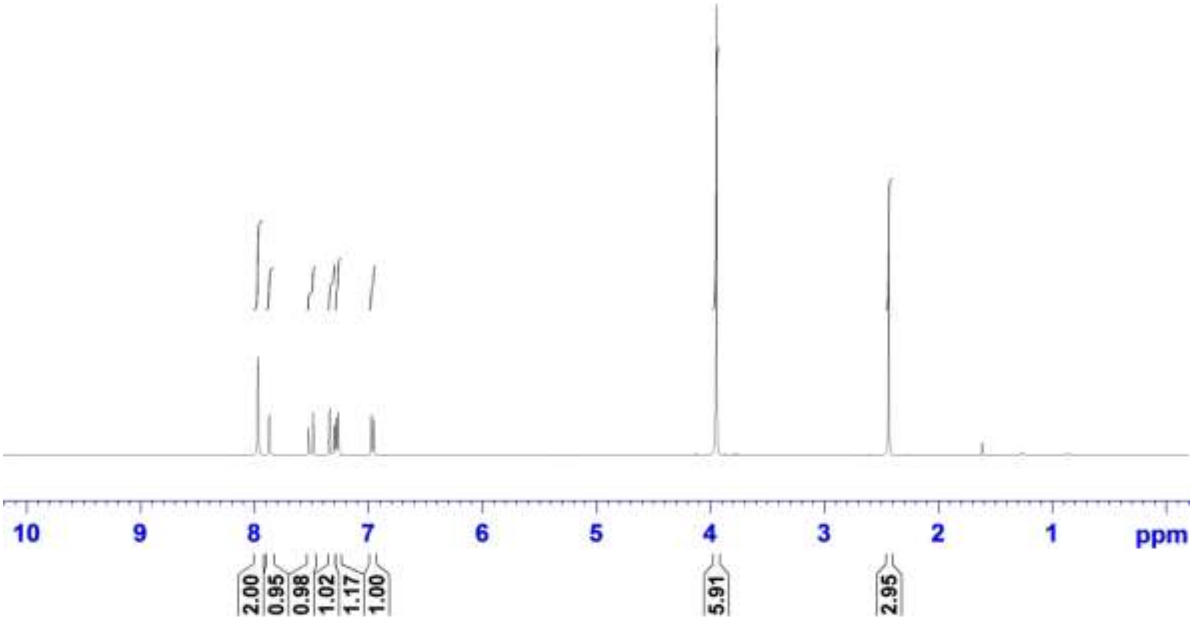
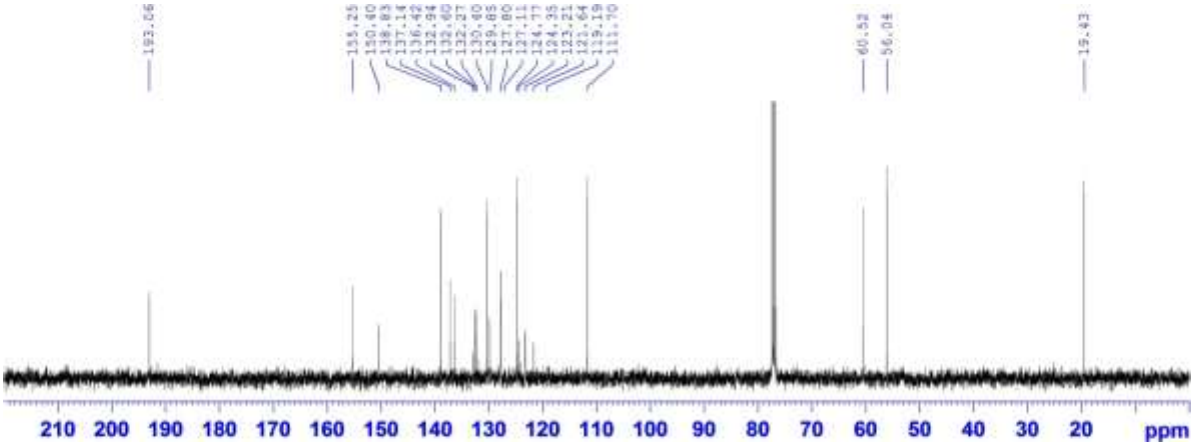
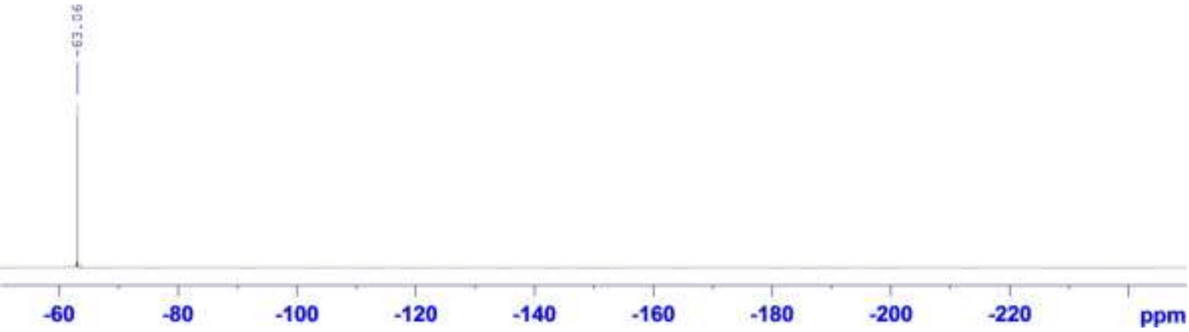


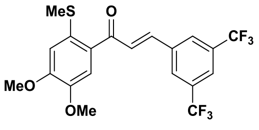
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$



^{1}H NMR (400 MHz, CDCl$_3$)



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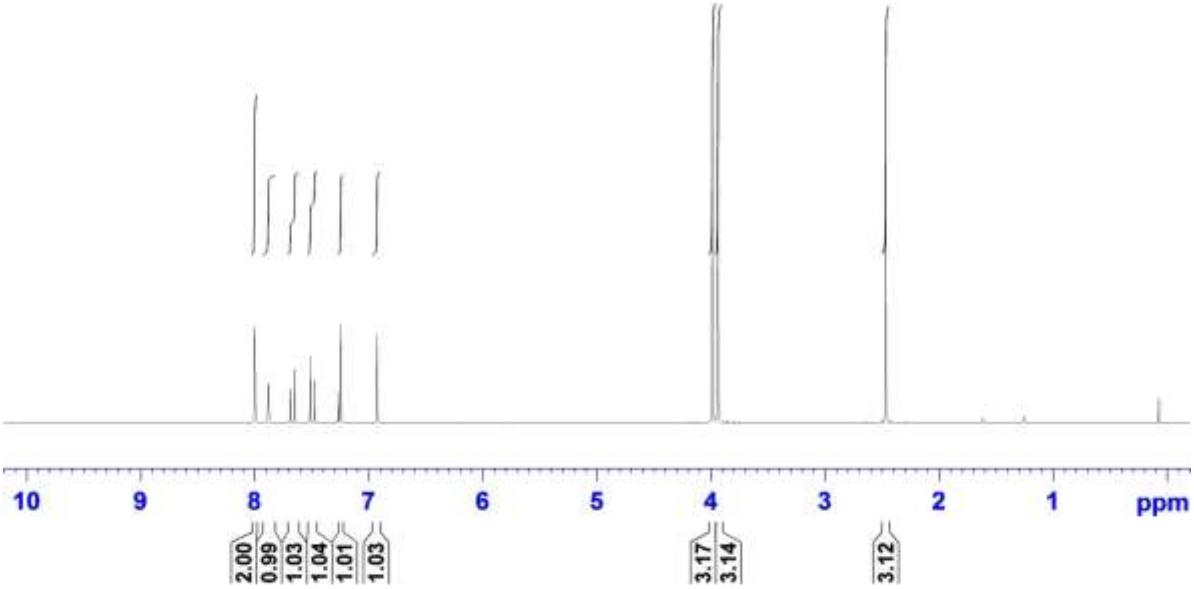
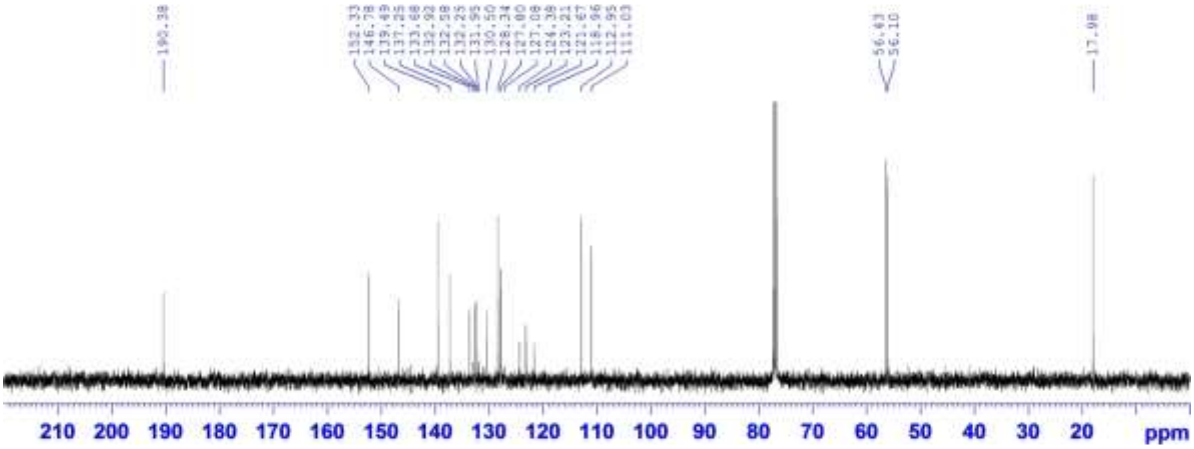
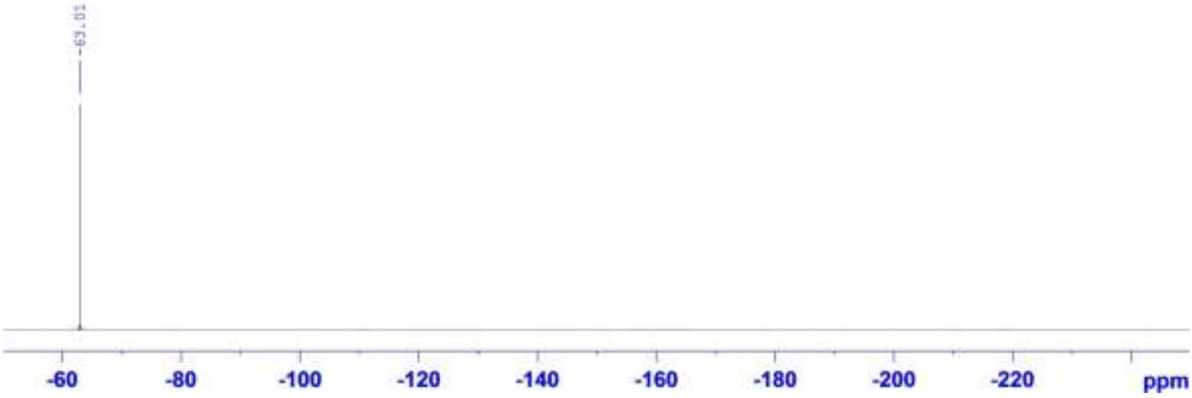


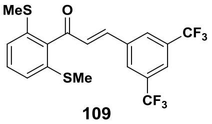
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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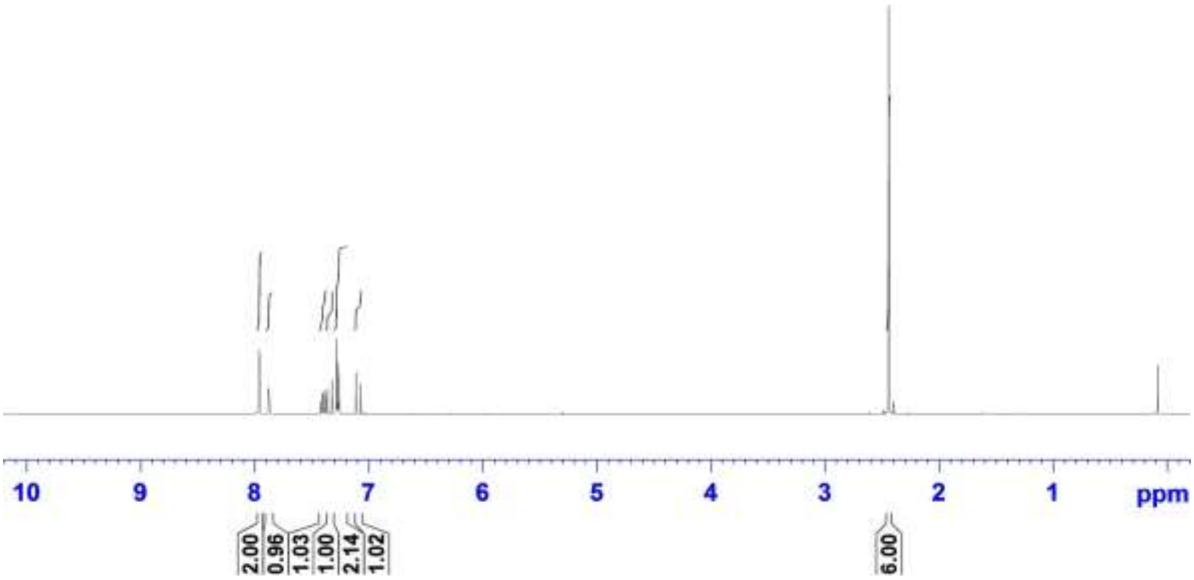
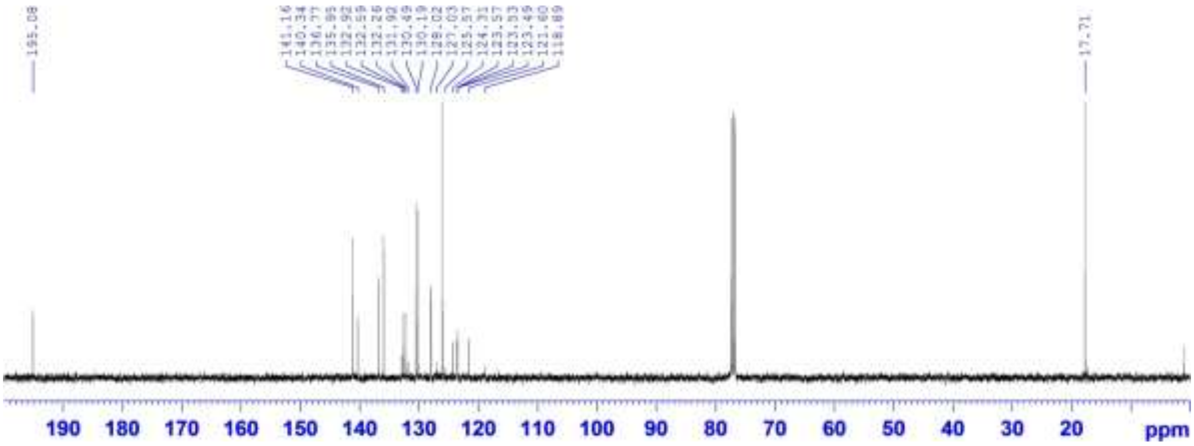


^{13}C NMR (101 MHz, CDCl$_3$)



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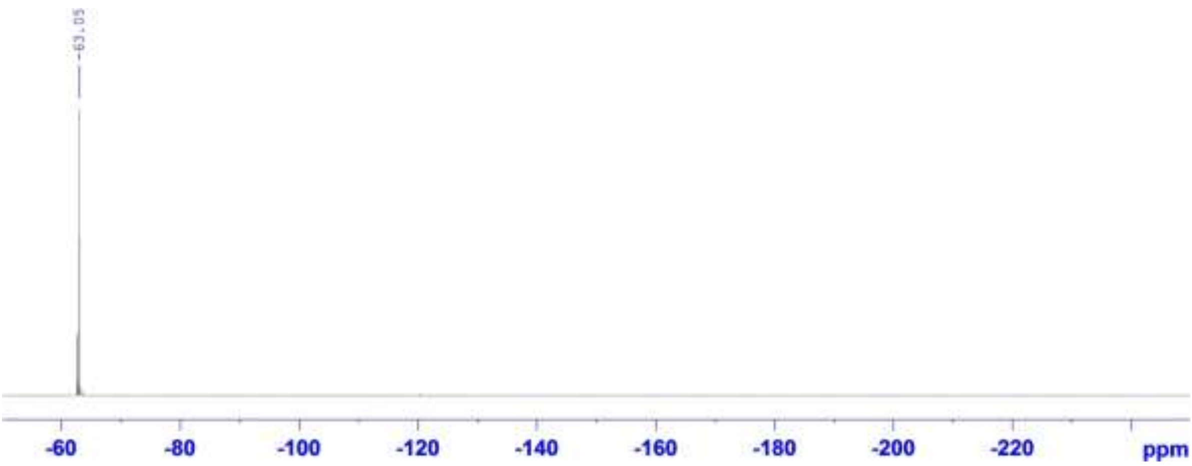

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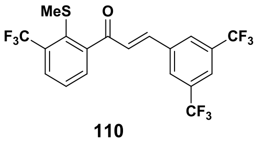

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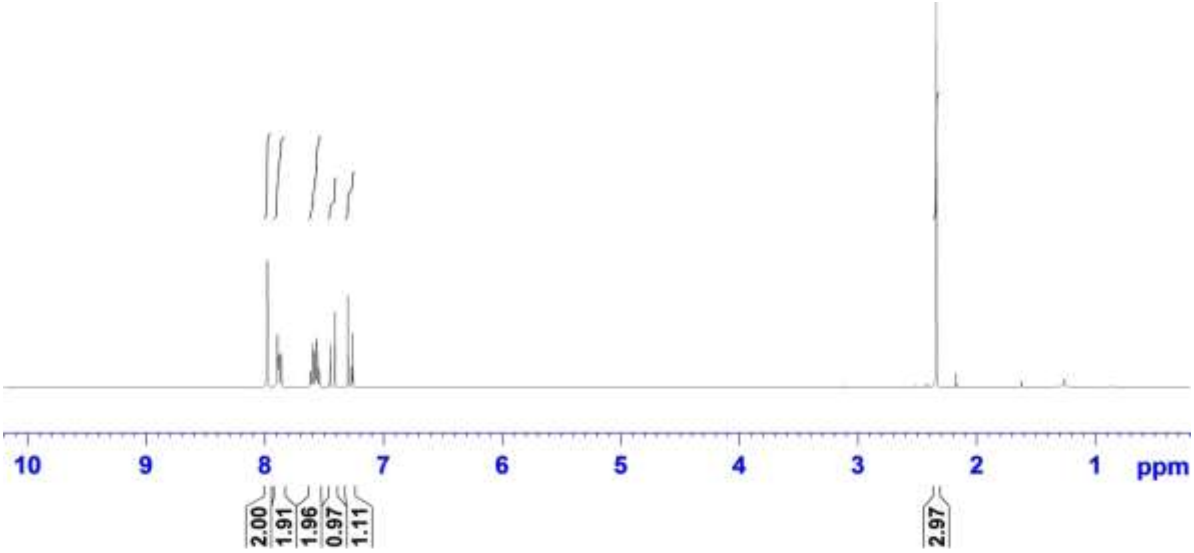
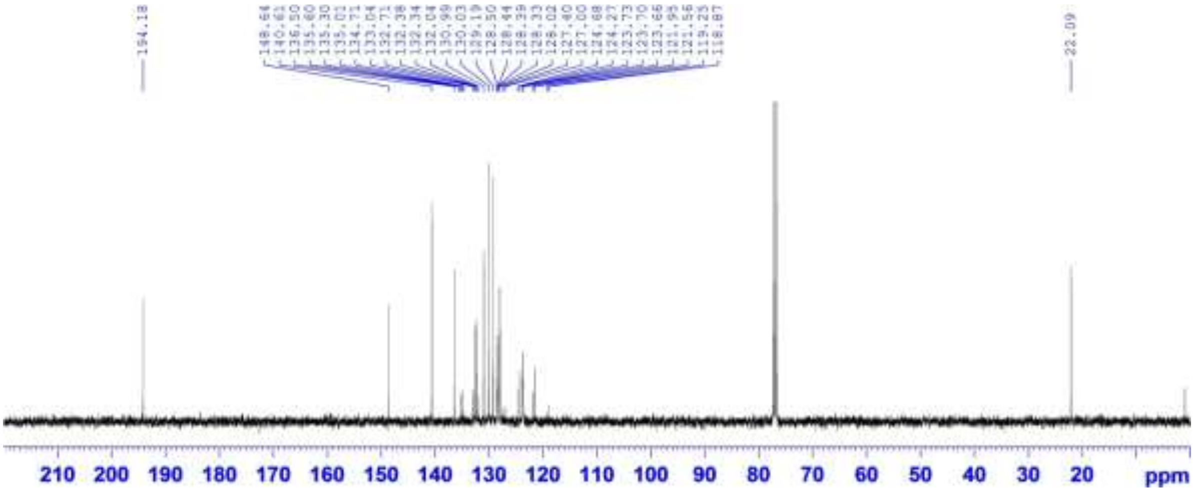


^{13}C NMR (101 MHz, CDCl$_3$)



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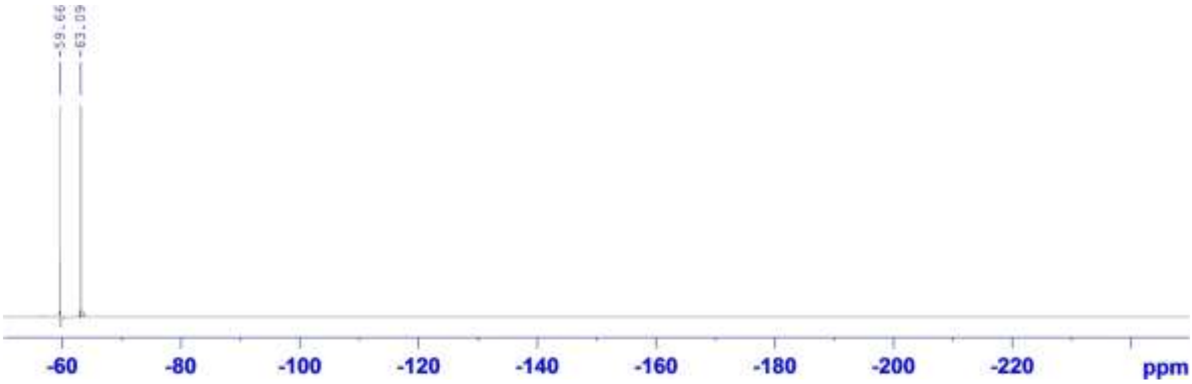

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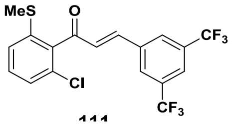

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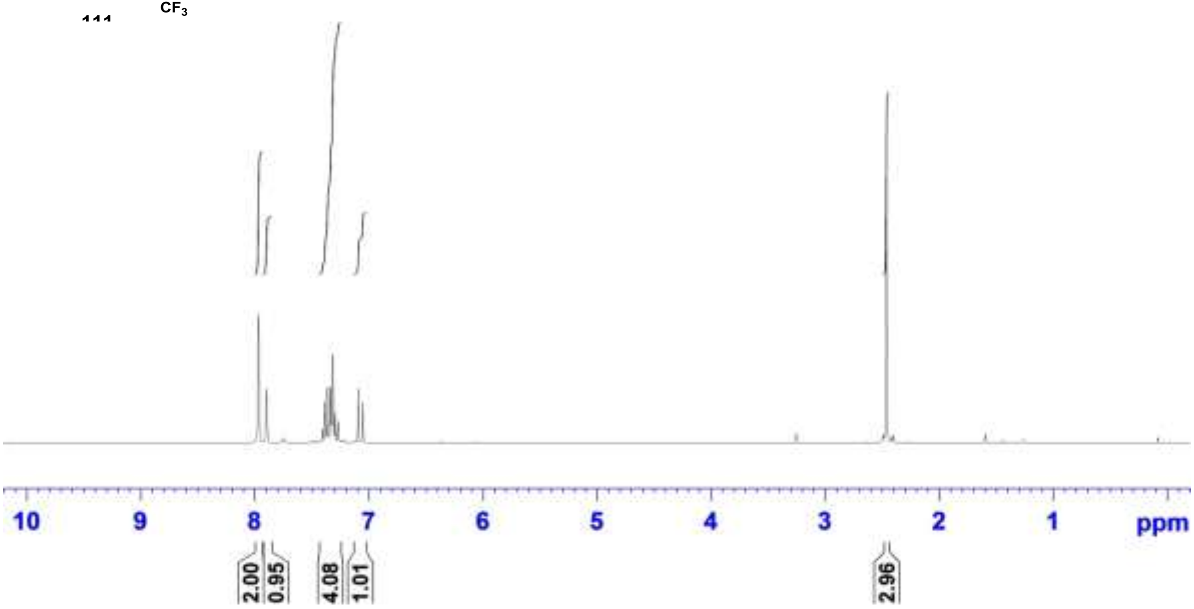
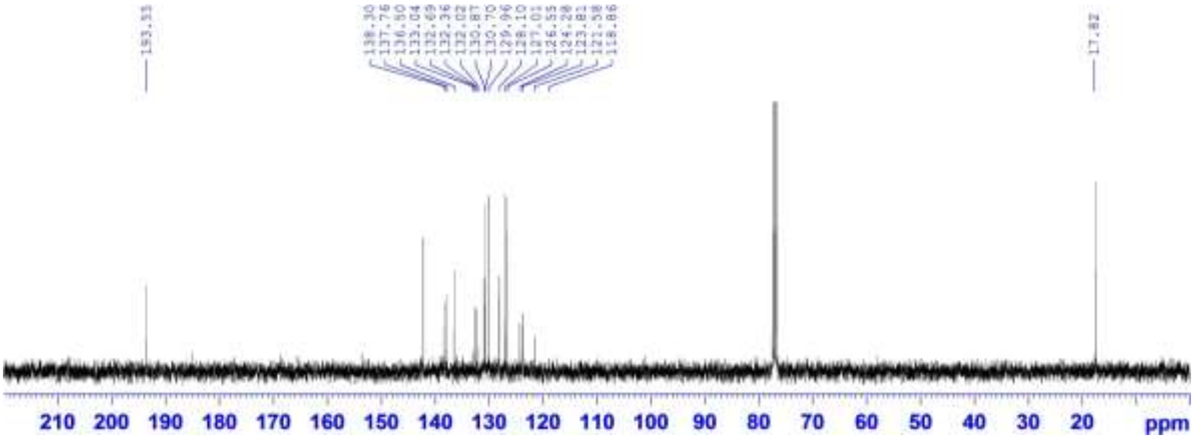
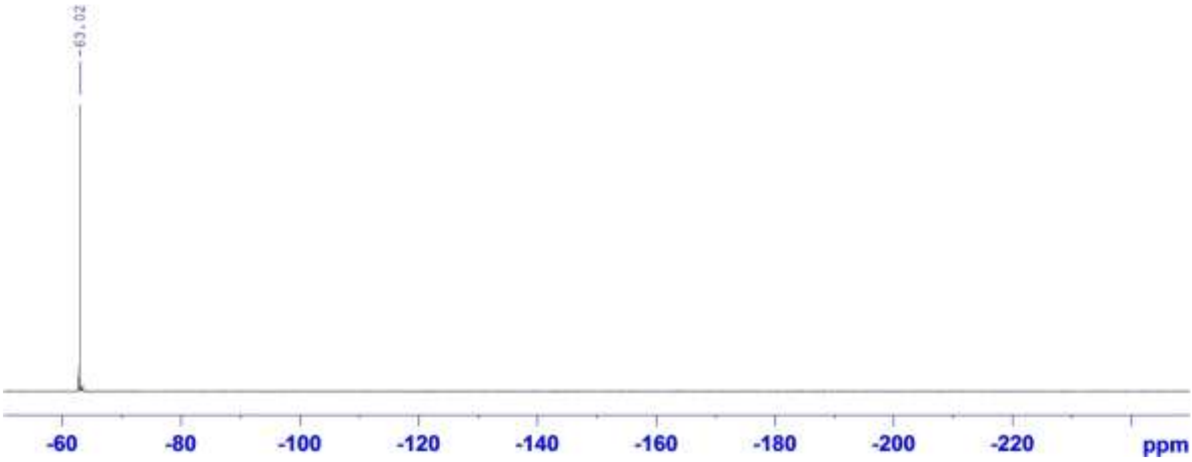


^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



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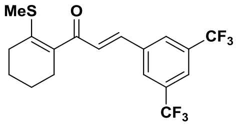

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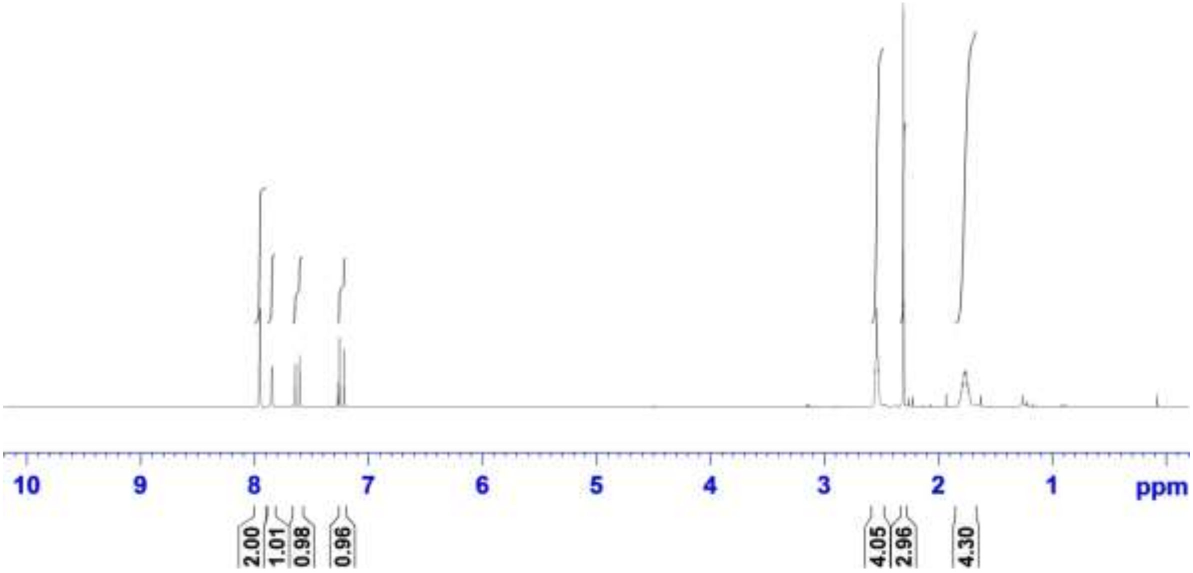
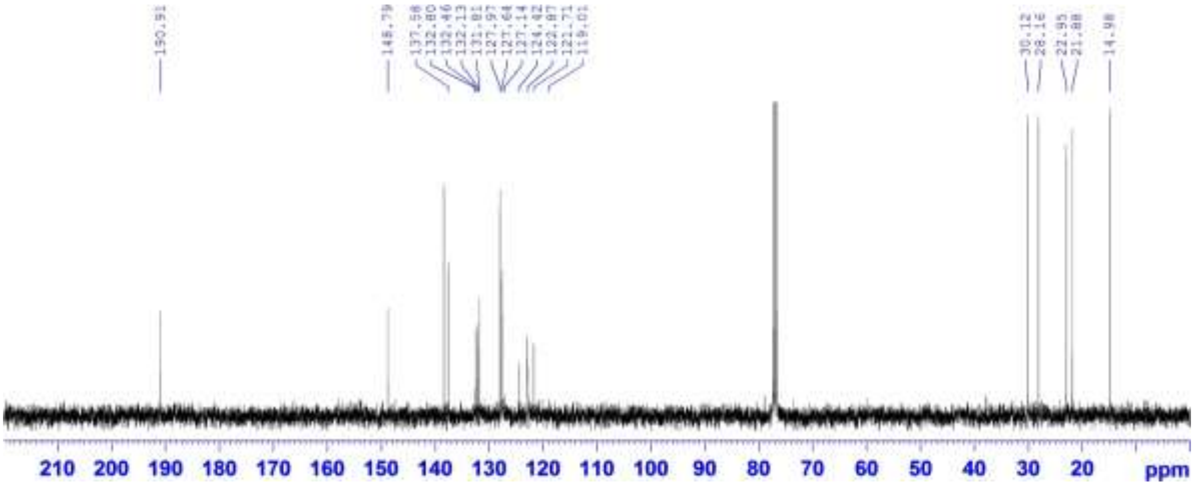
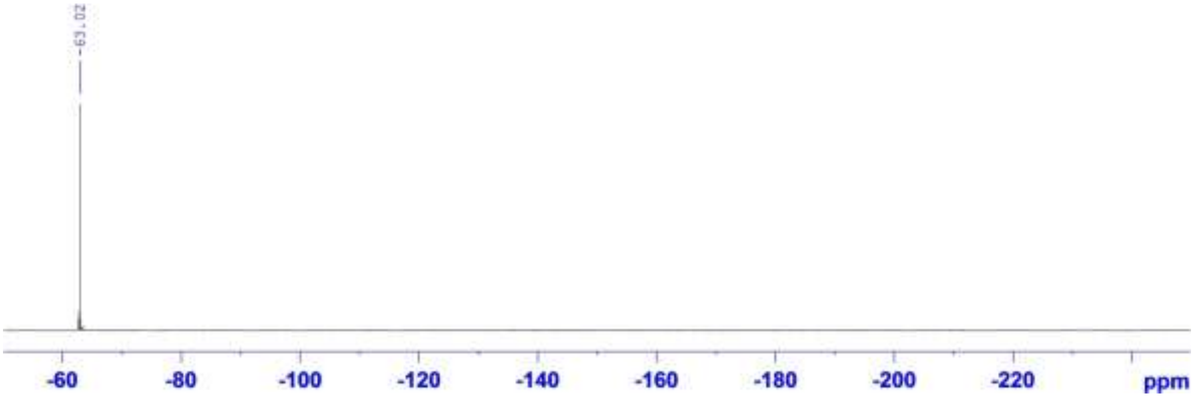


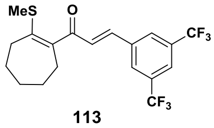
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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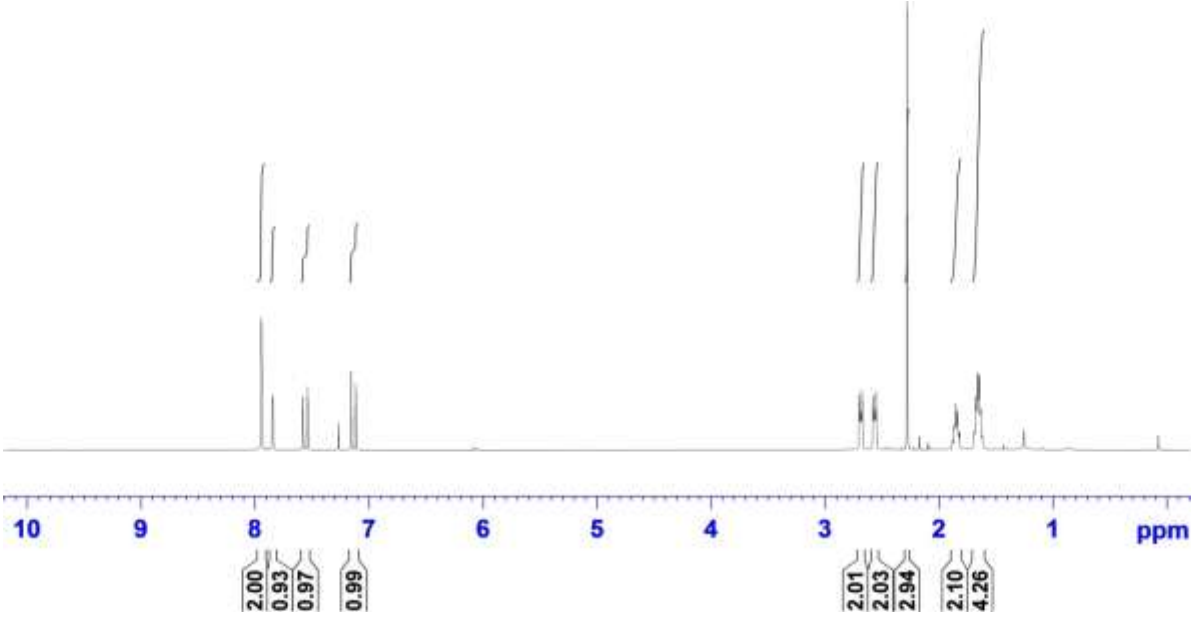
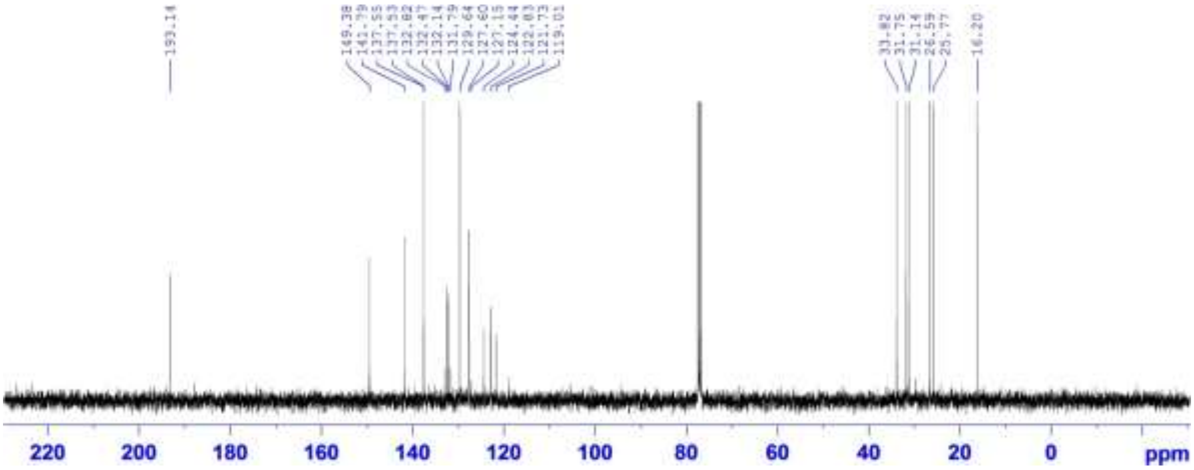
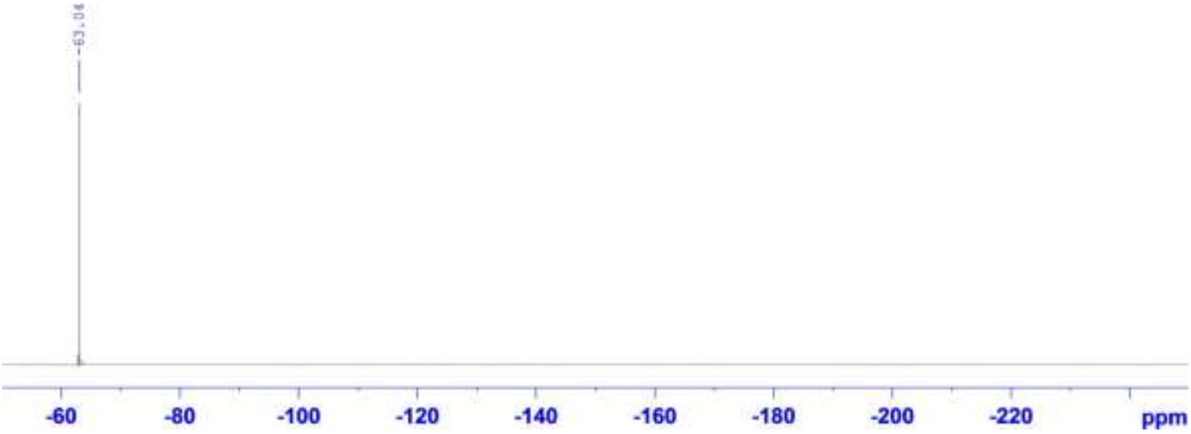


^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)



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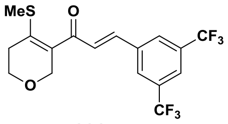

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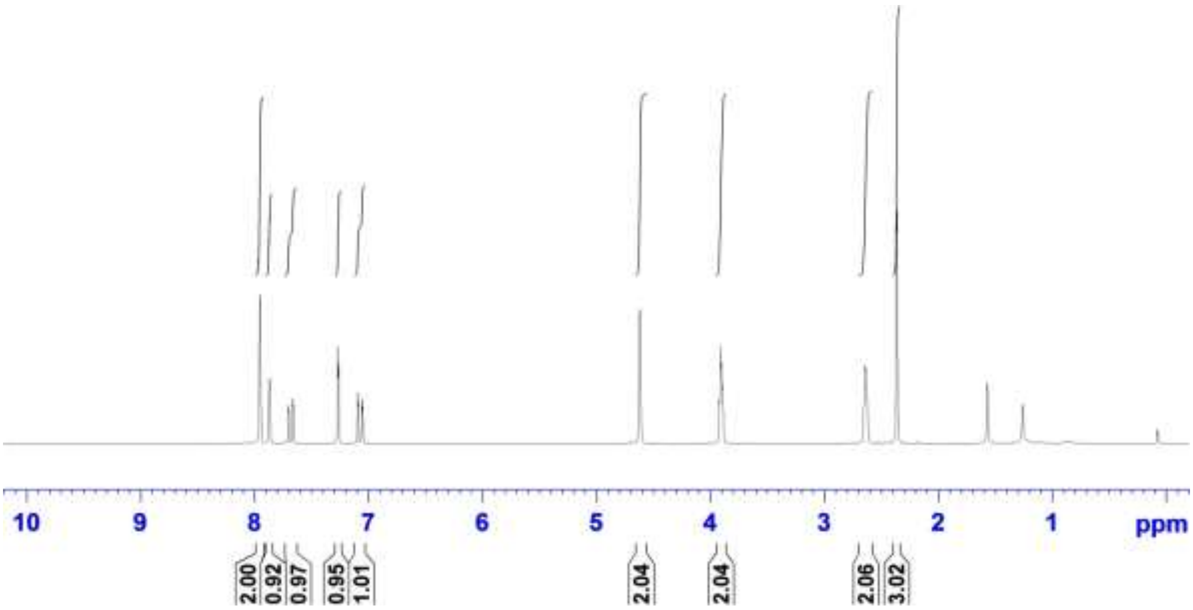
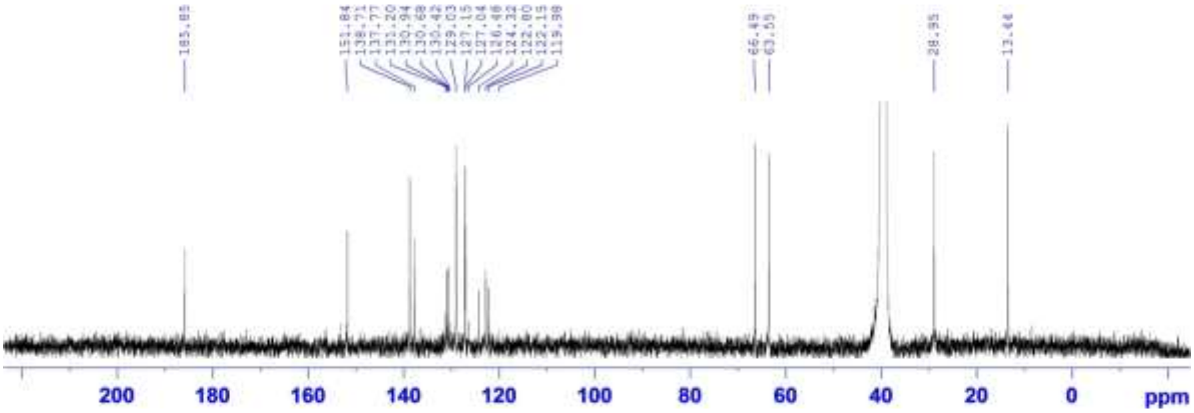
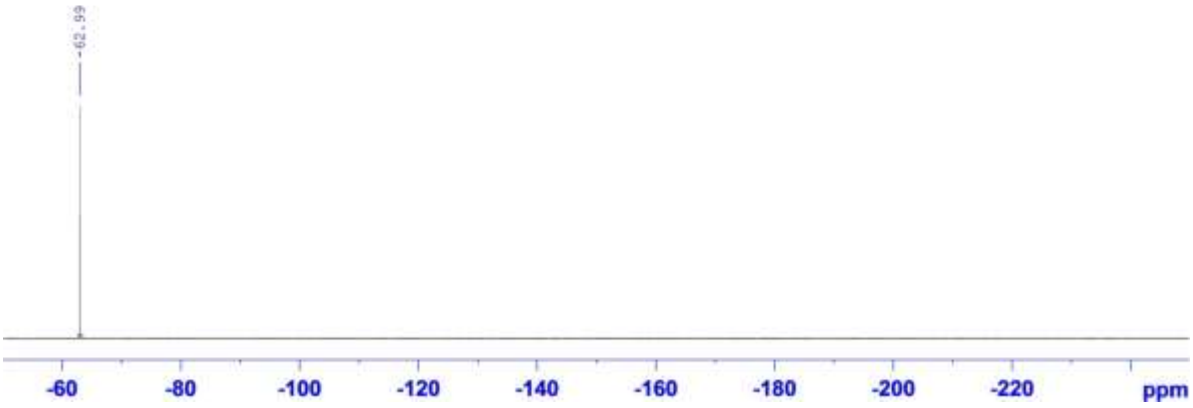


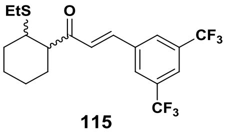
^{13}C NMR (126 MHz, *d$_6$*-DMSO)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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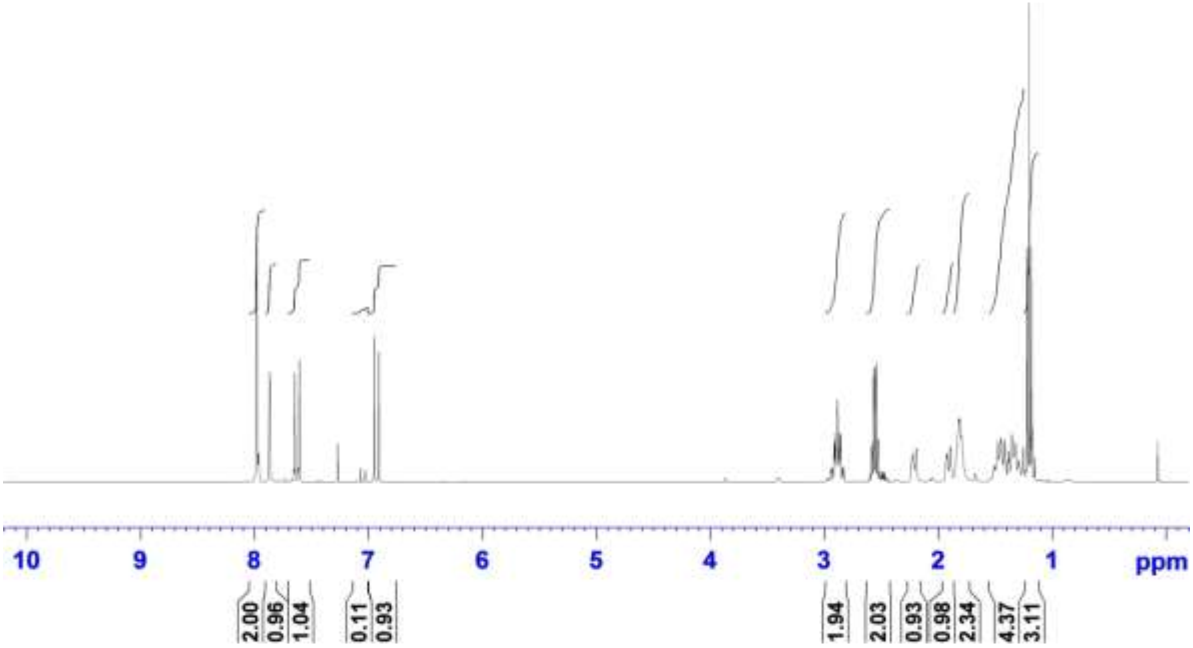
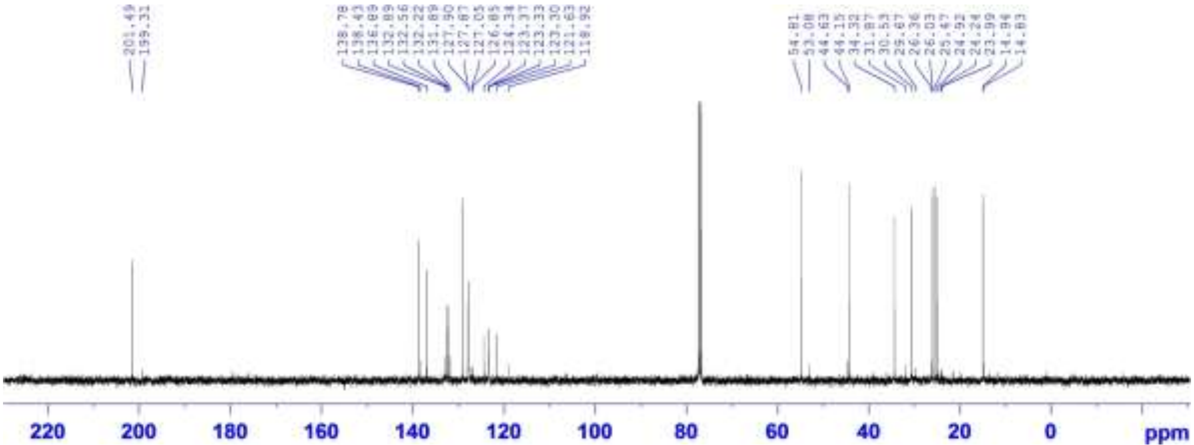
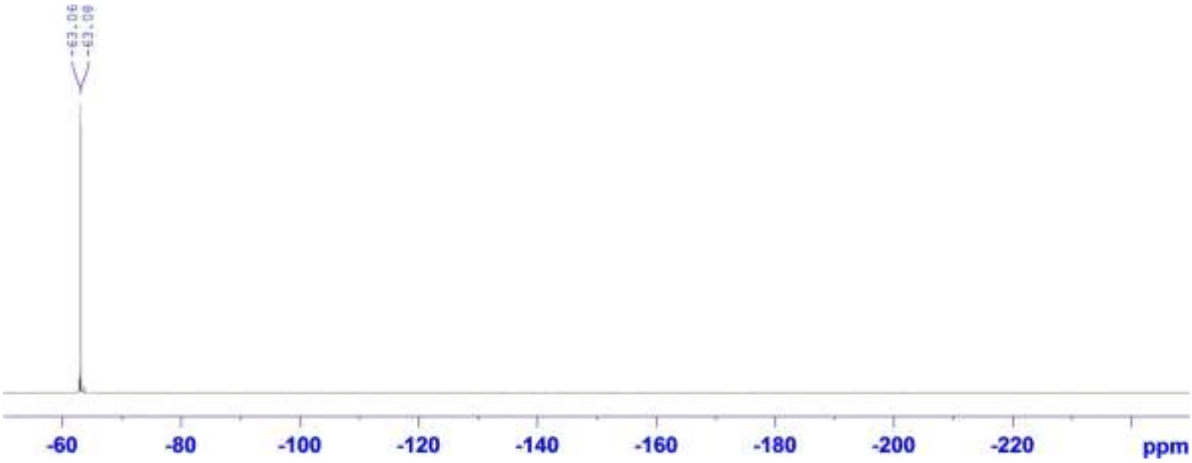


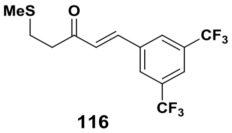
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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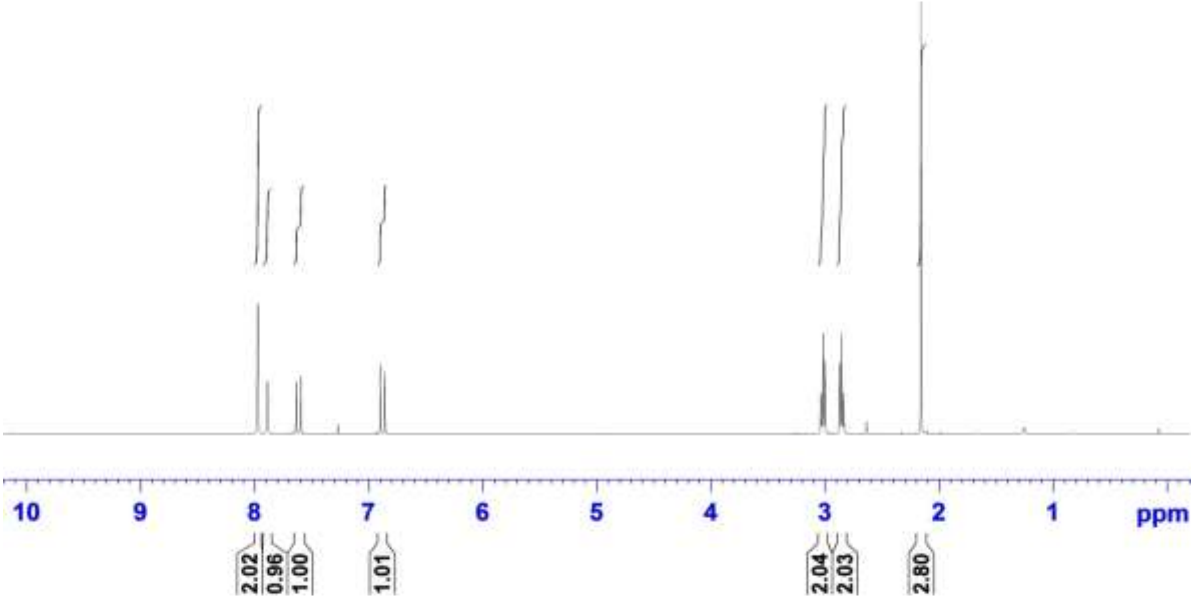
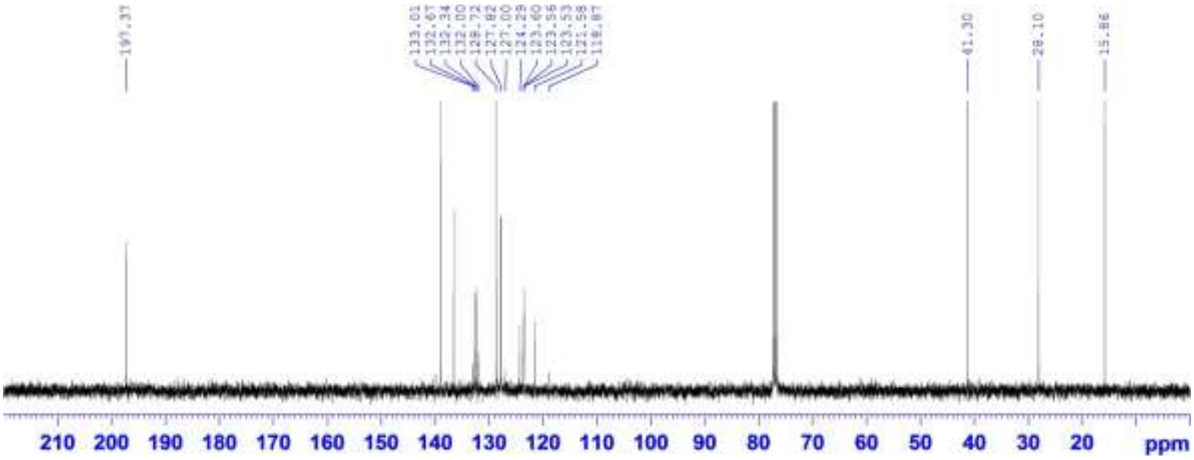
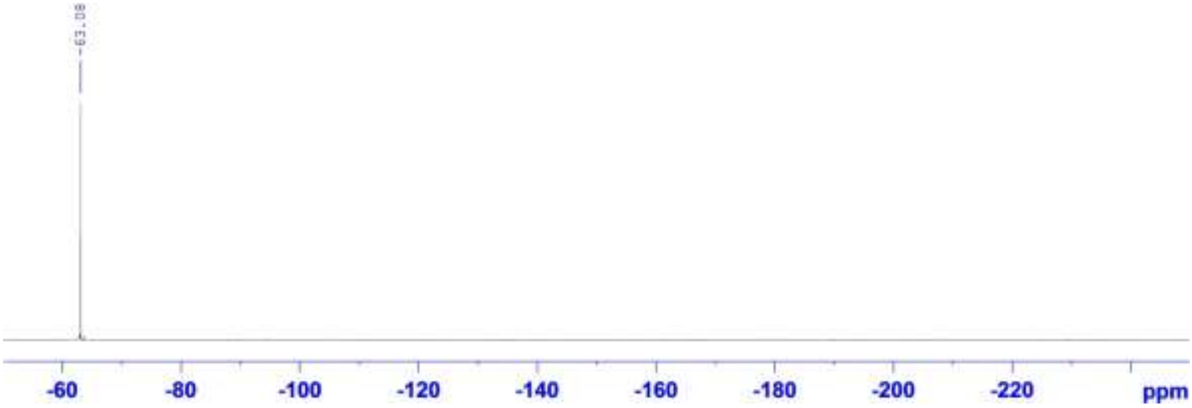


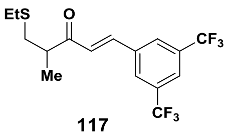
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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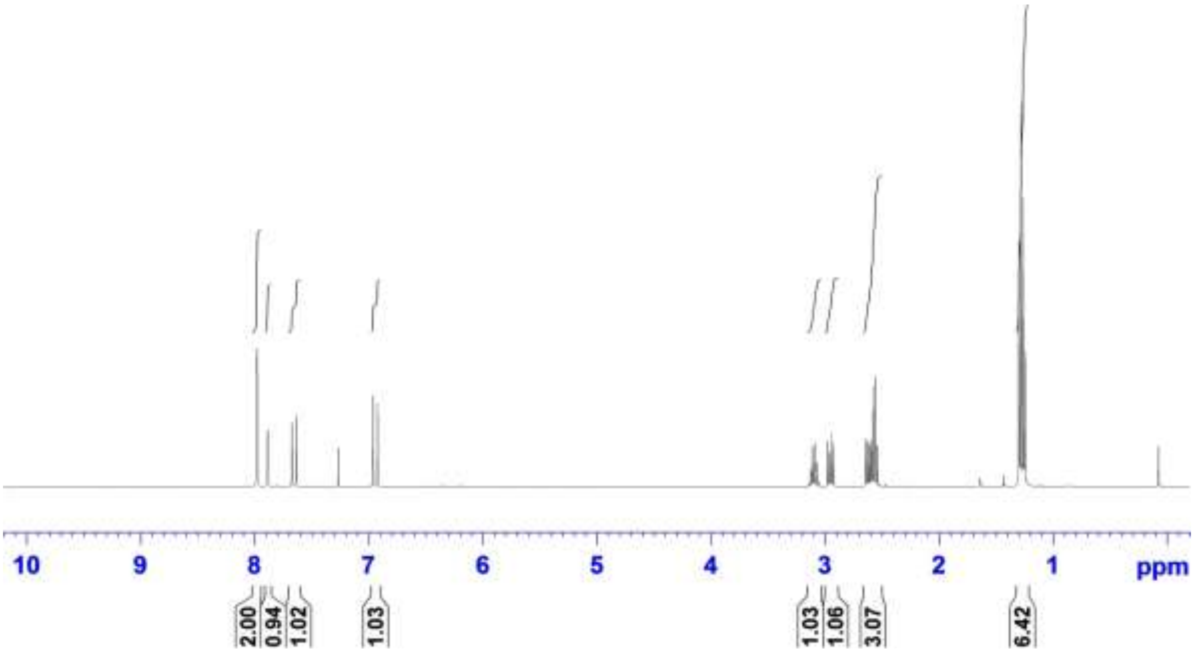
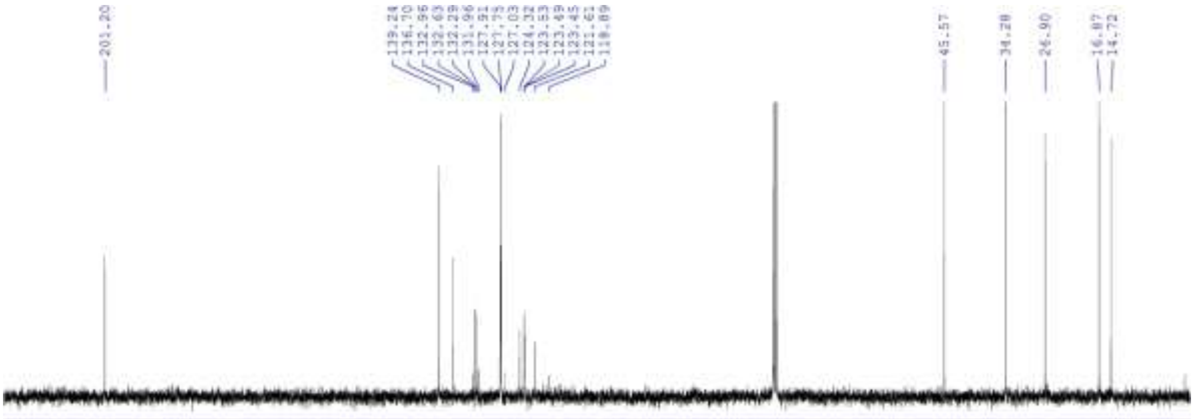
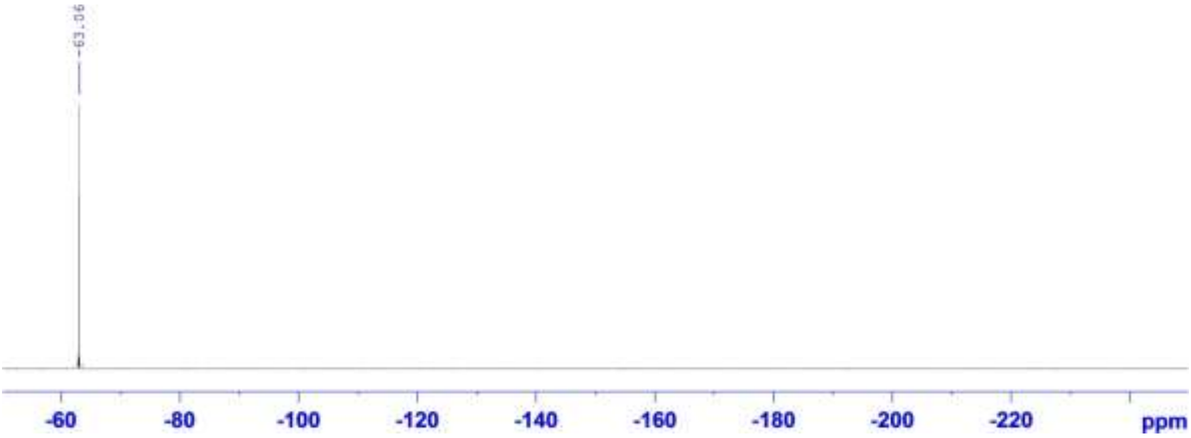


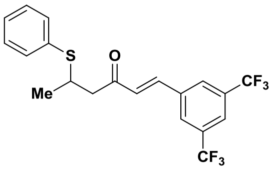
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHx, CDCl$_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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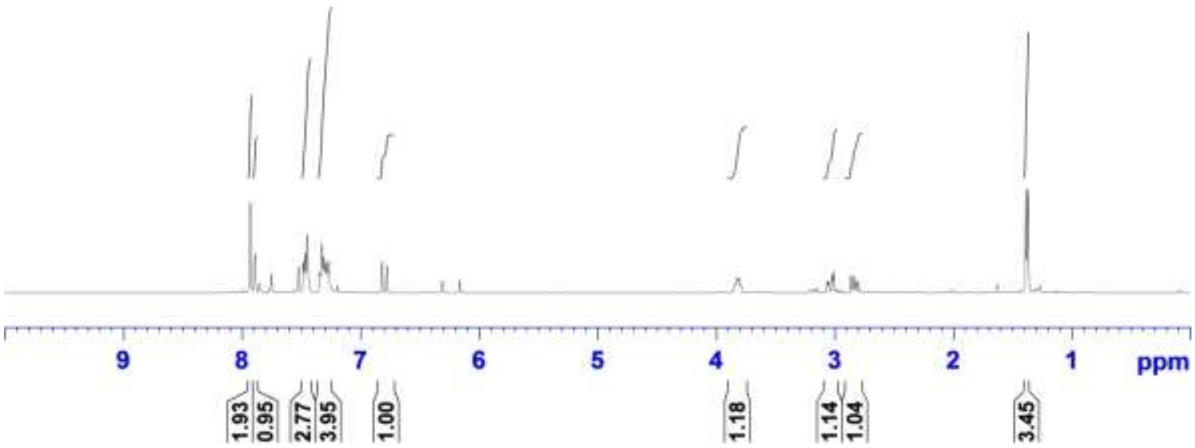
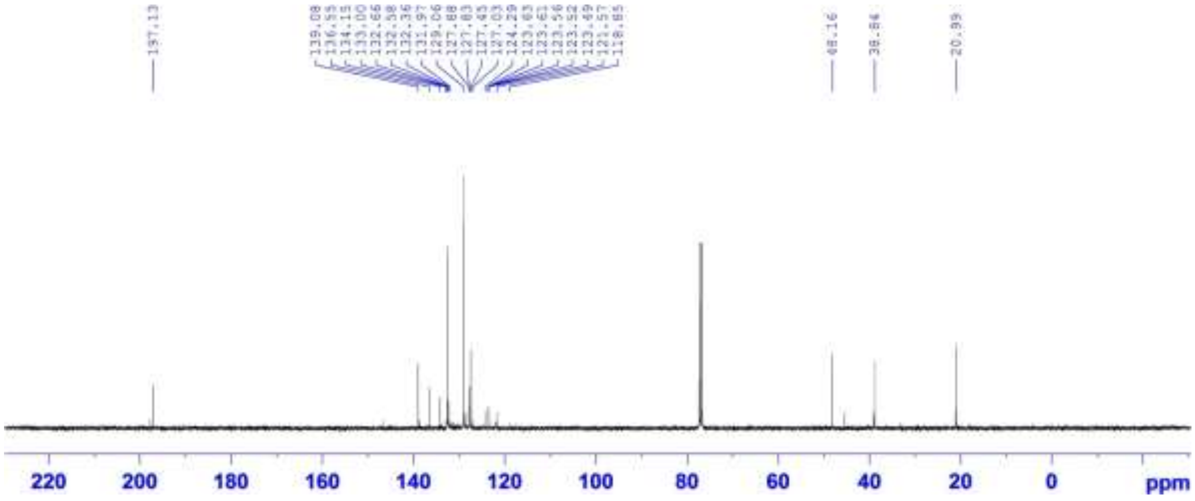
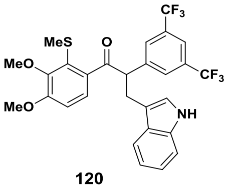


^{13}C NMR (101 MHz, $CDCl_3$)



Chapter 4 - Exploiting Branched Hydroacylation Intermediates

^{1}H NMR (400 MHz, CDCl$_3$)



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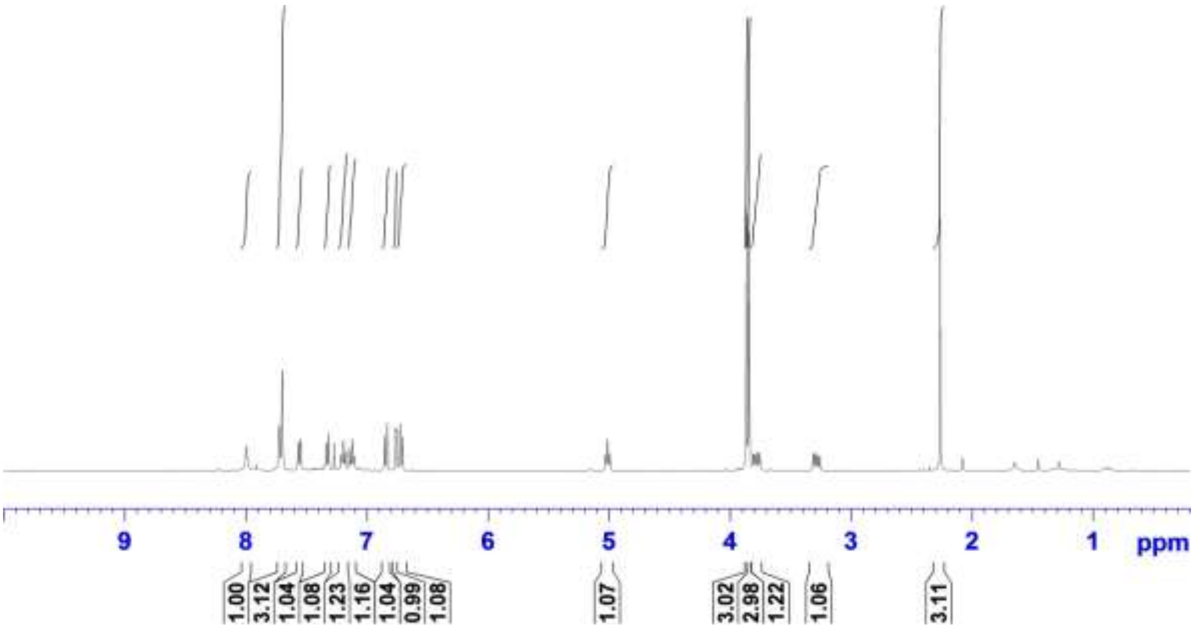
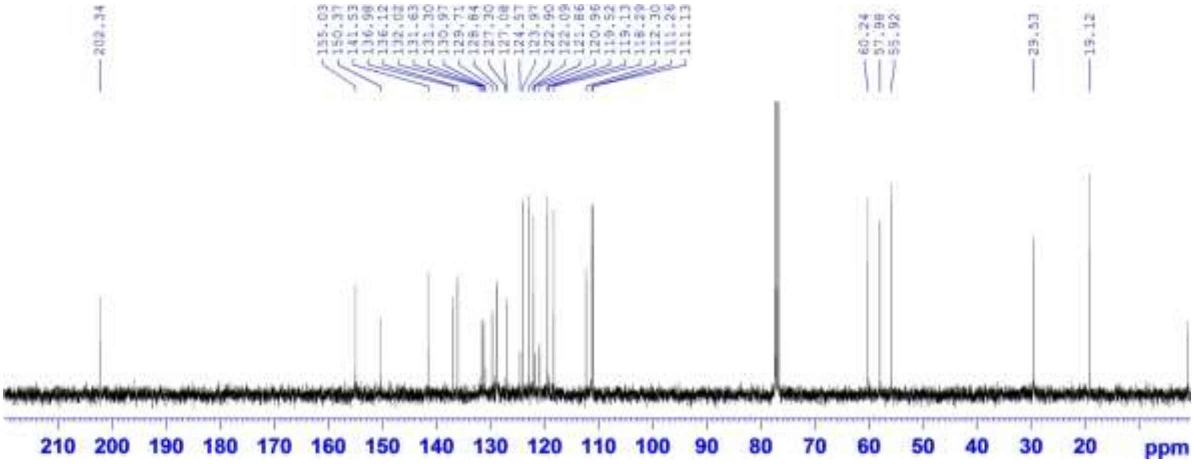
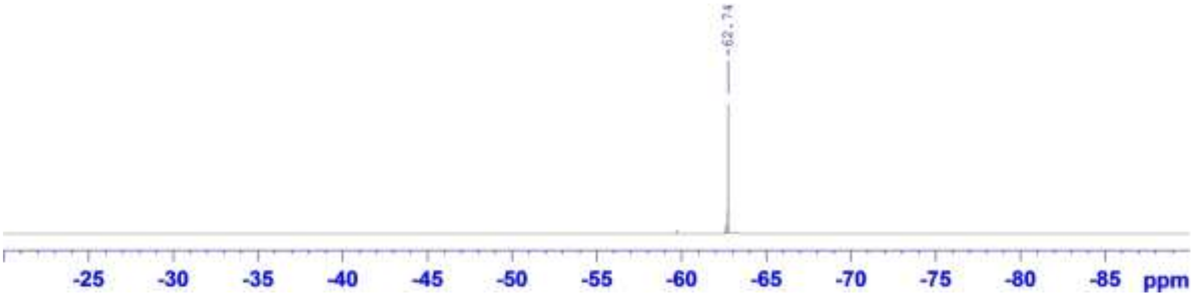


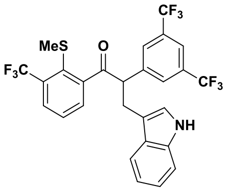
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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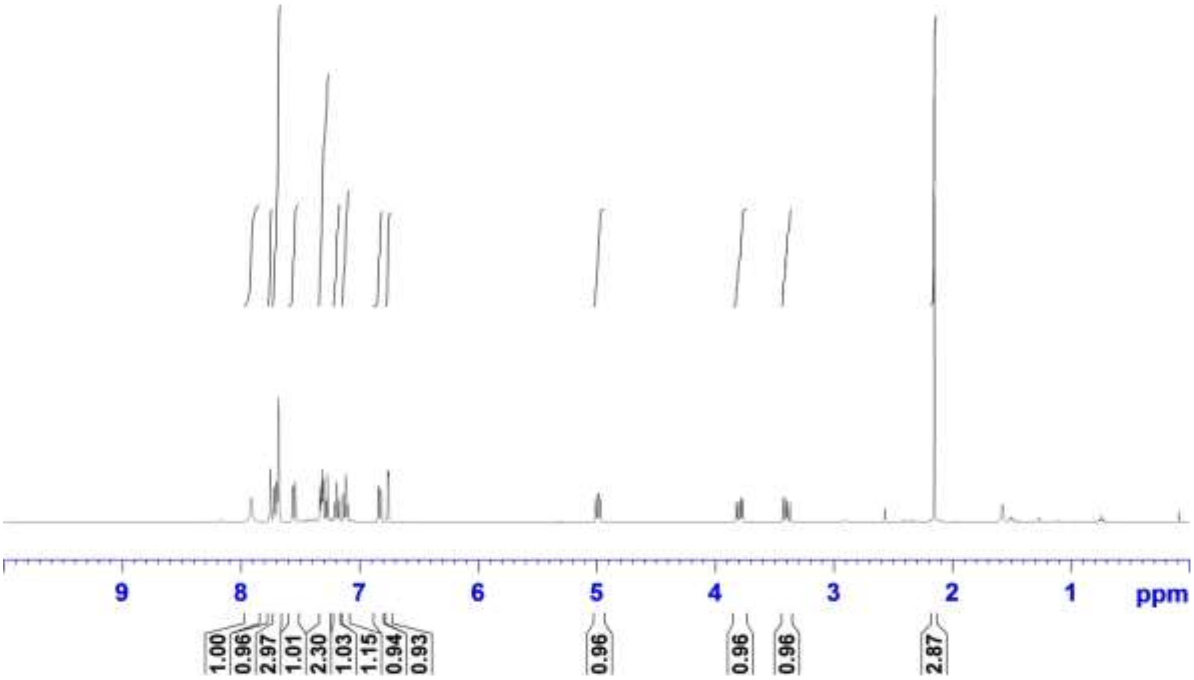
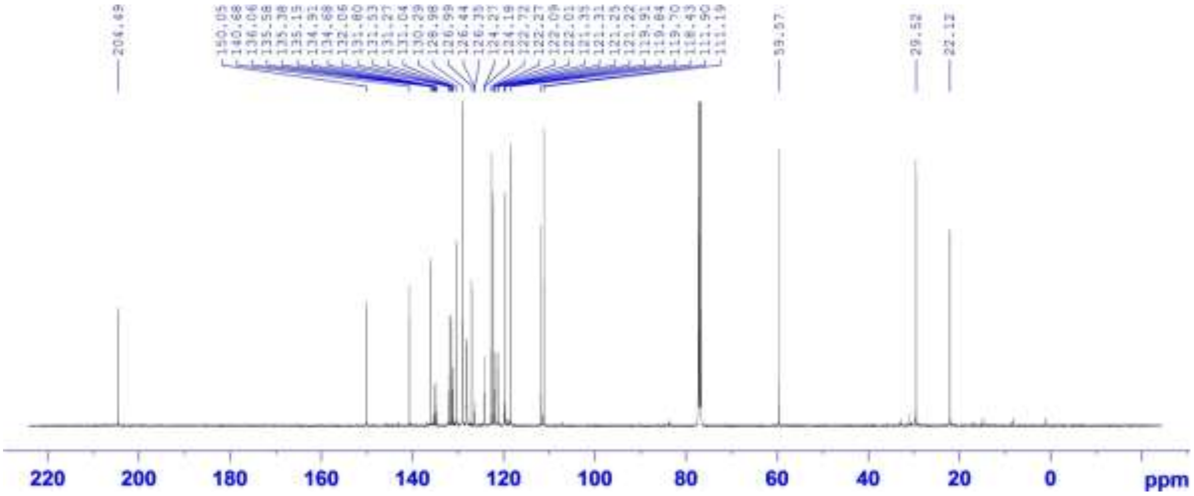
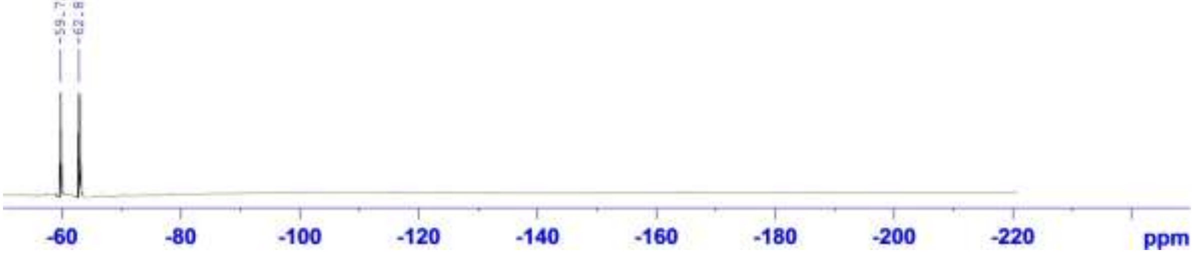


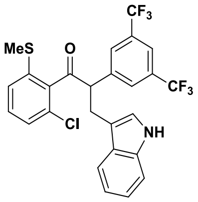
^{13}C NMR (126 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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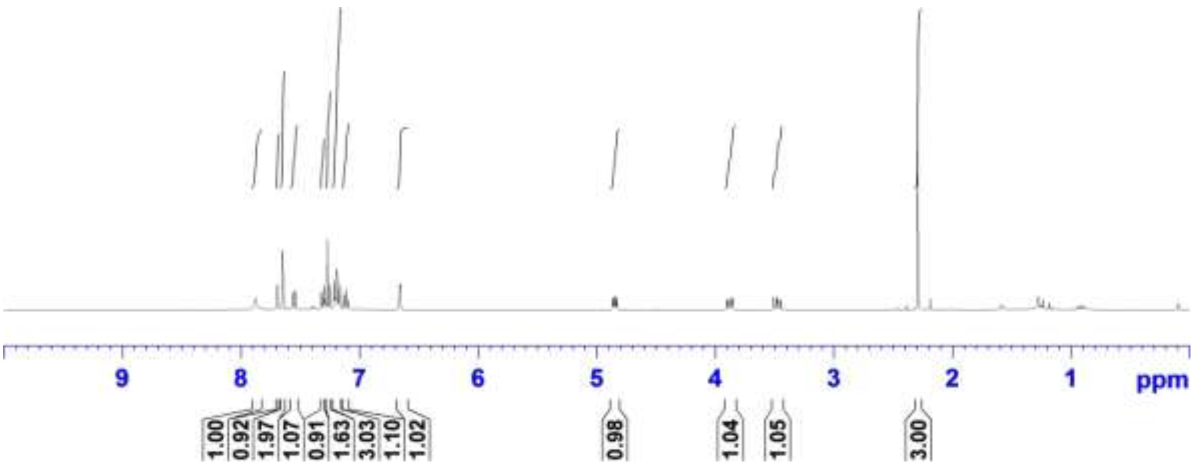
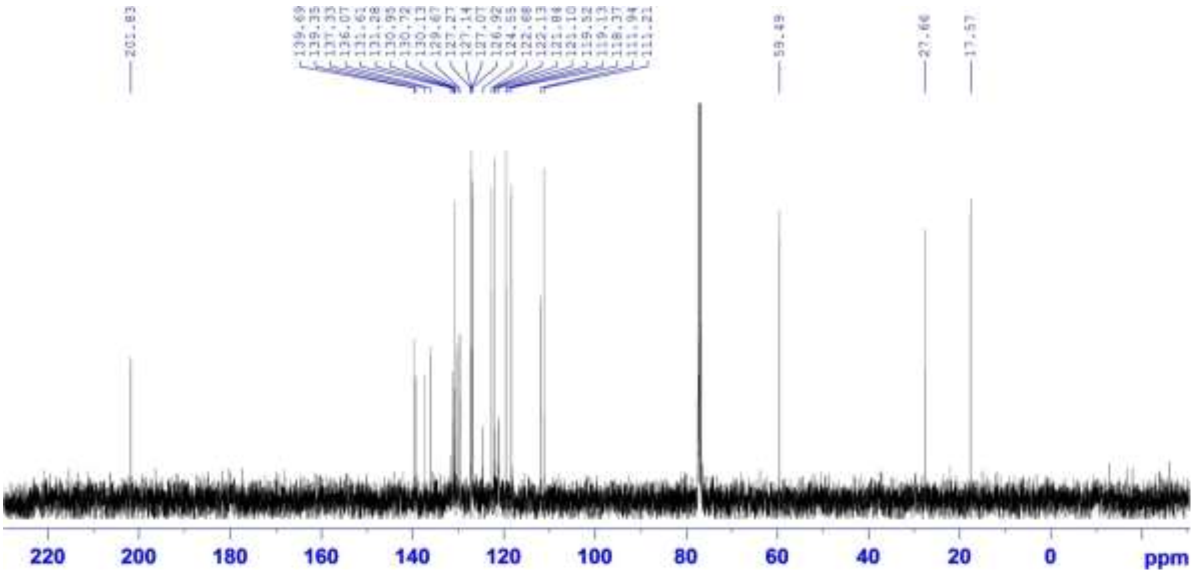
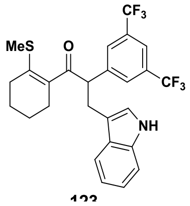


^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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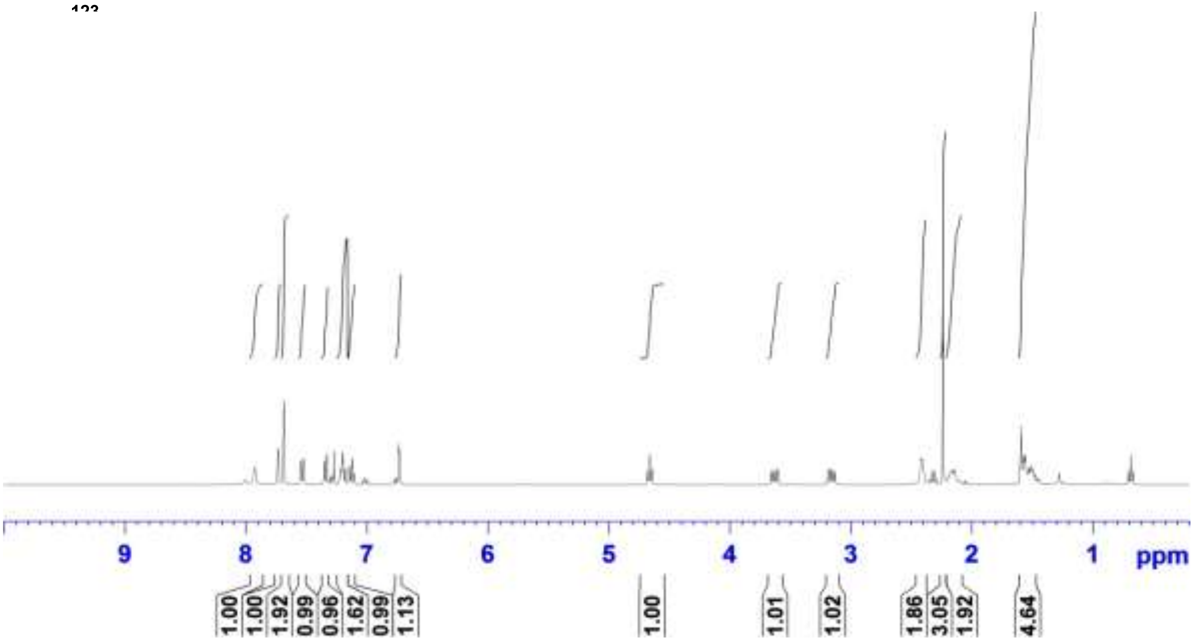
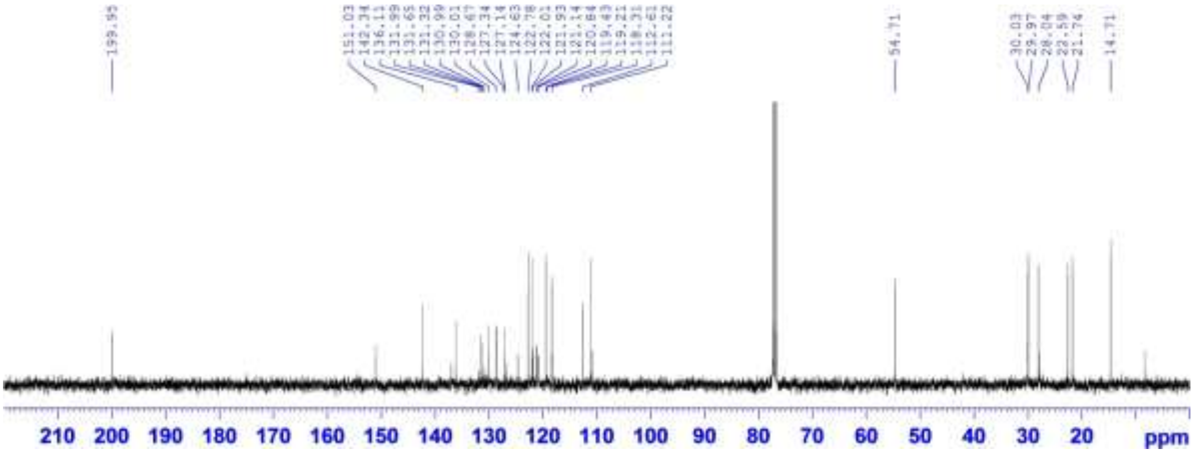
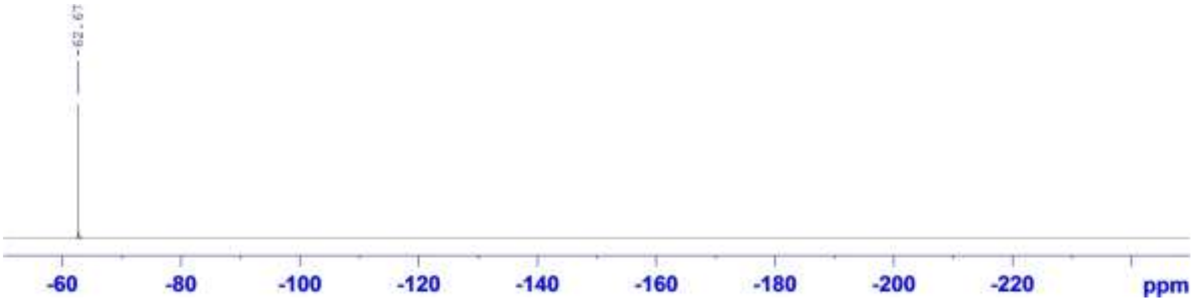


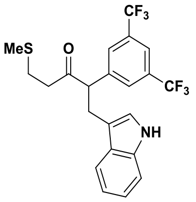
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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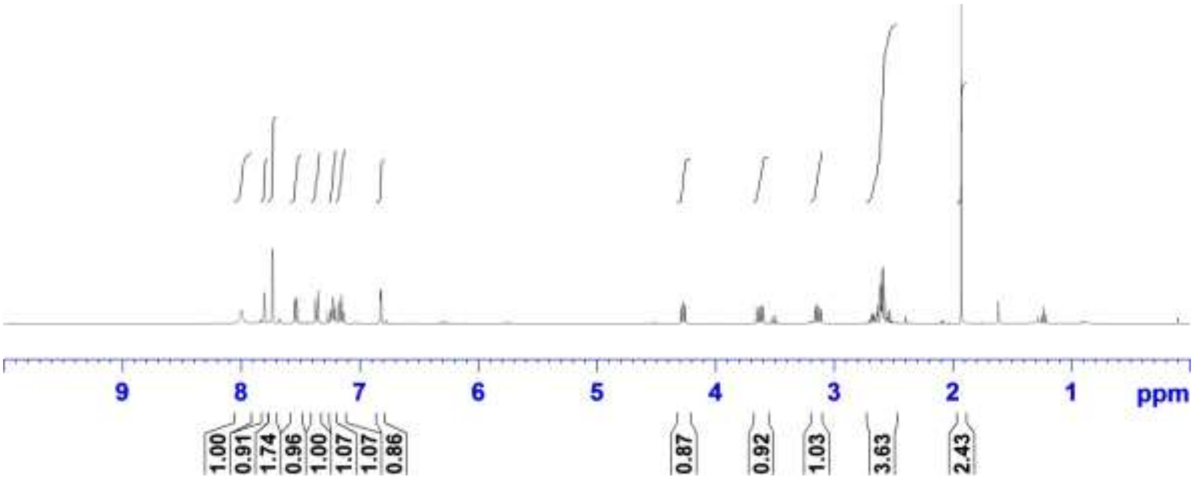

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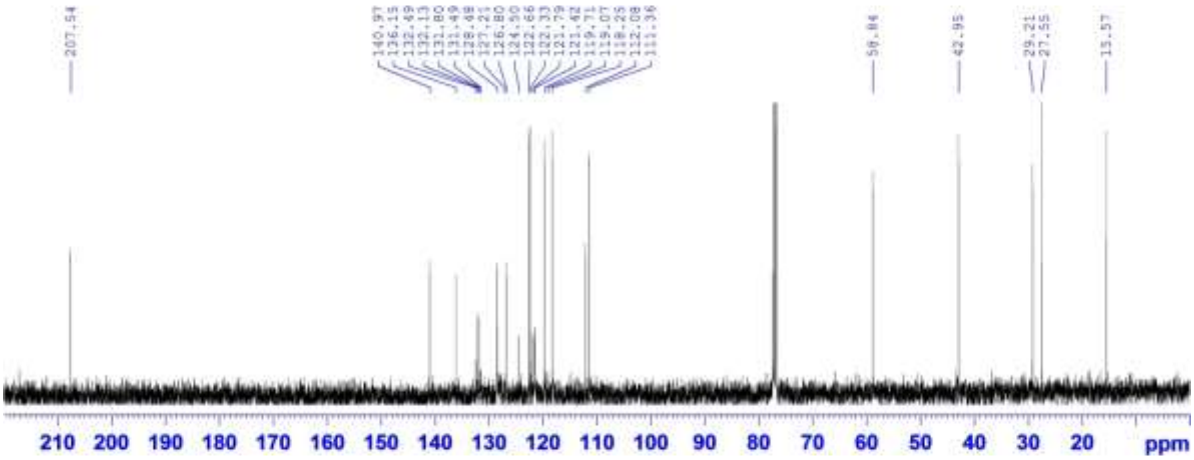
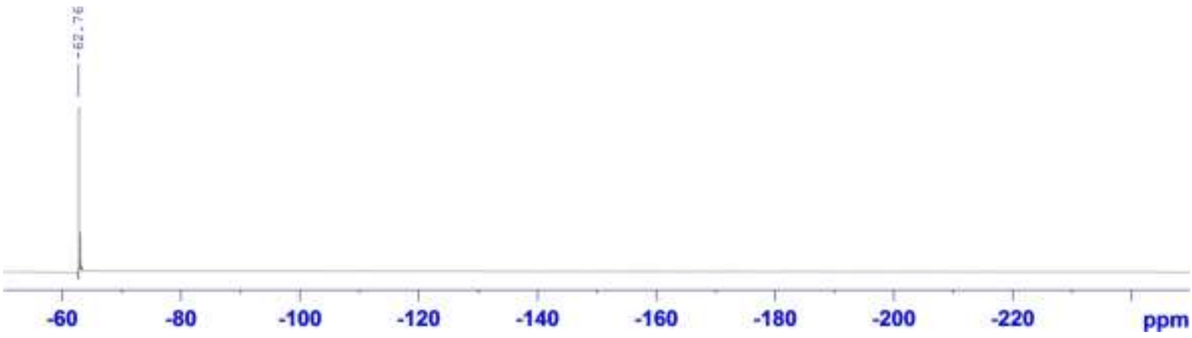


^{19}F NMR (376 MHz, CDCl$_3$)



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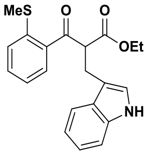

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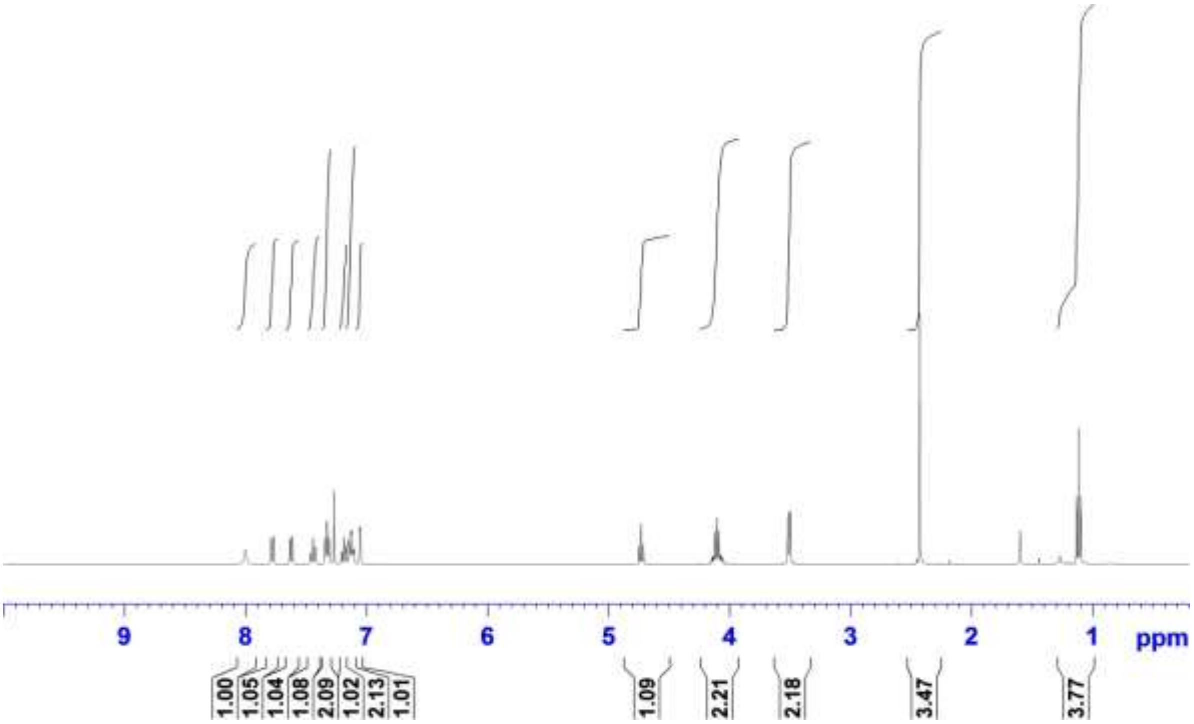

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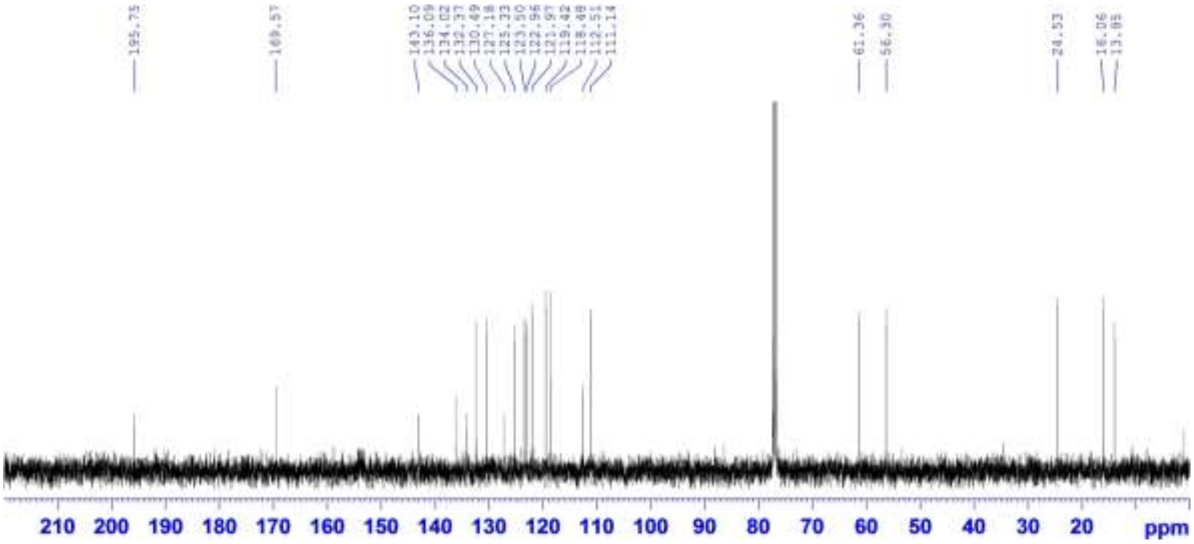

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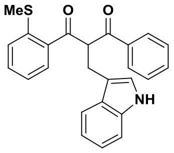

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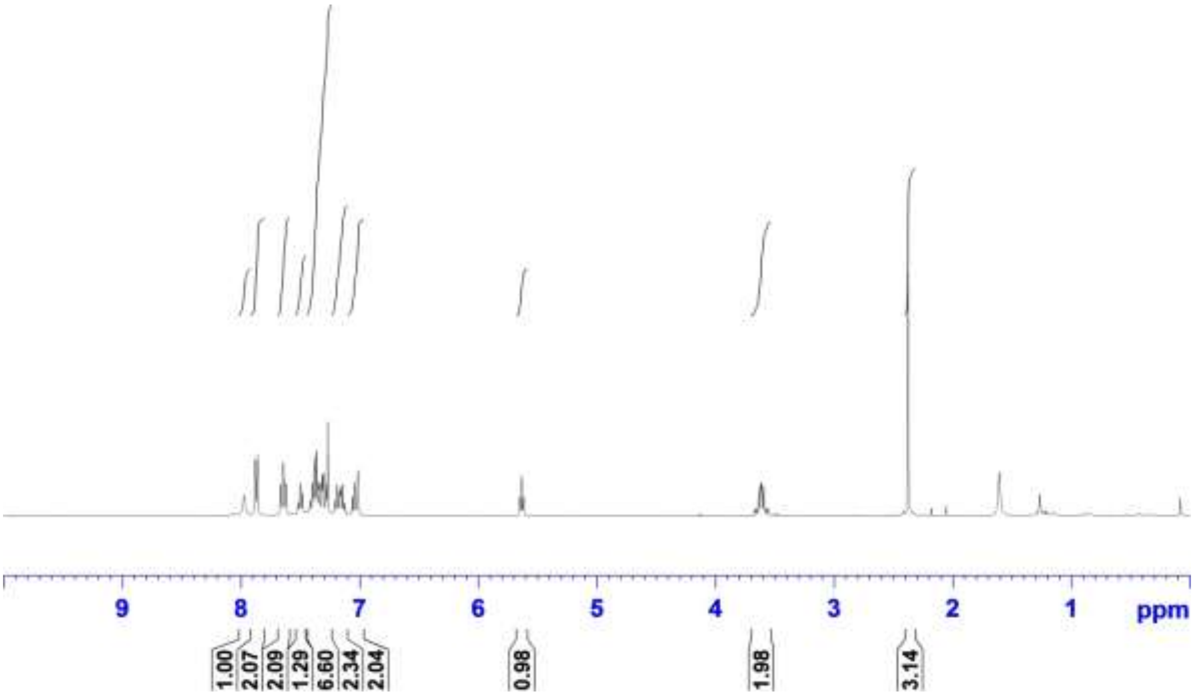

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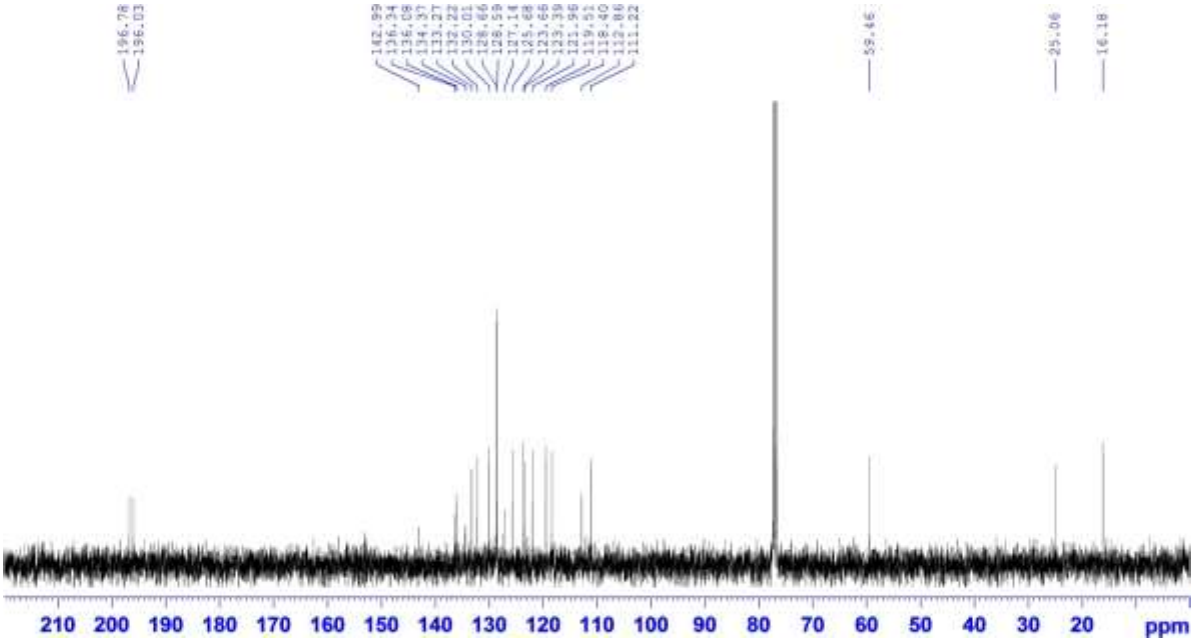

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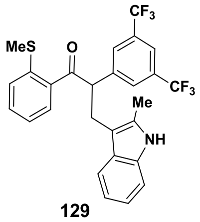

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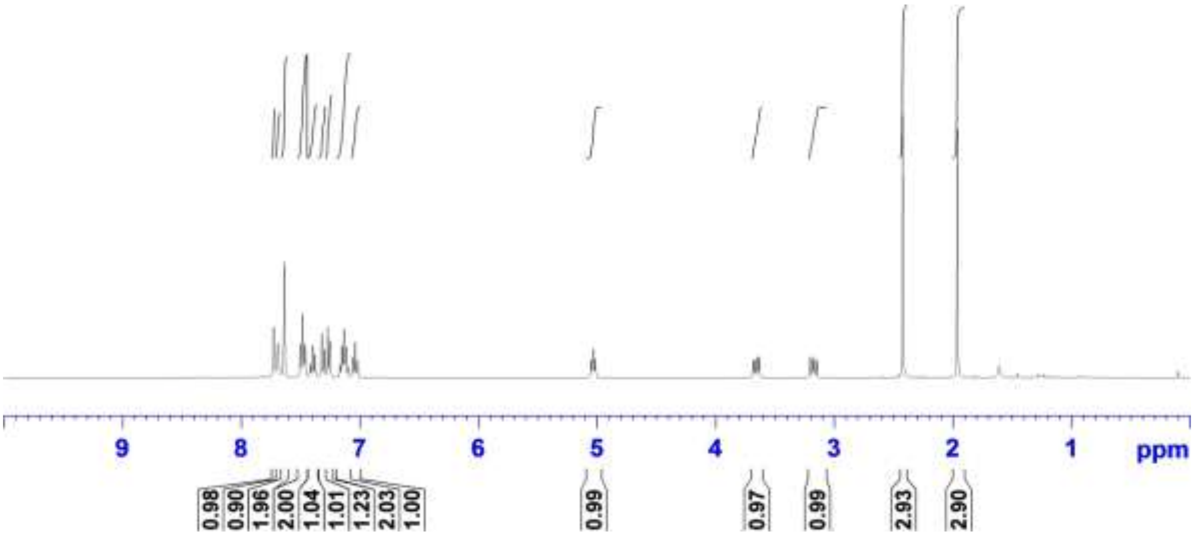
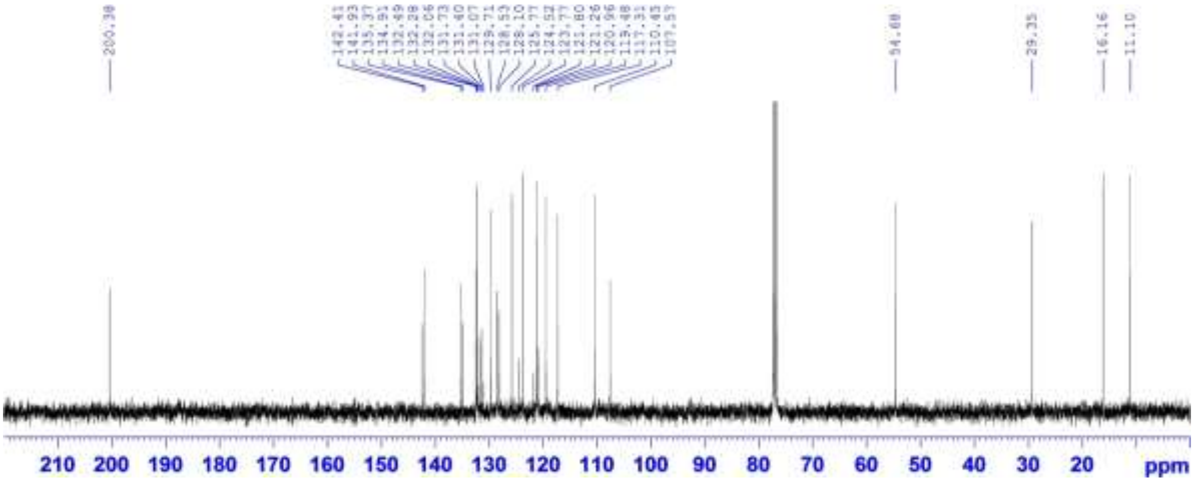
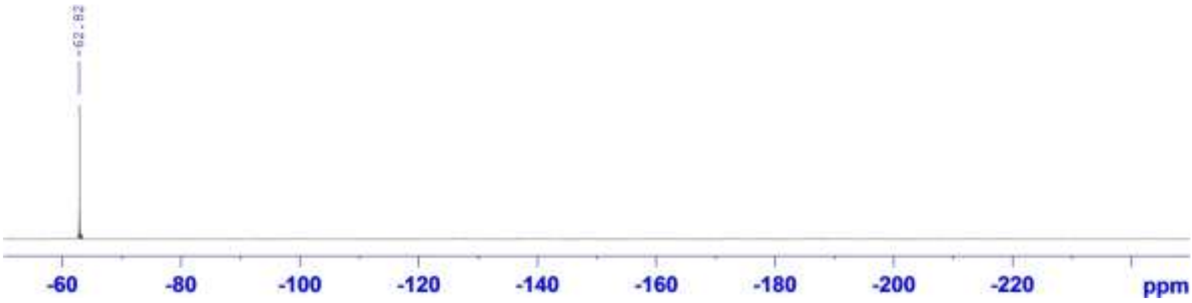


^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (470 MHz, CDCl$_3$)



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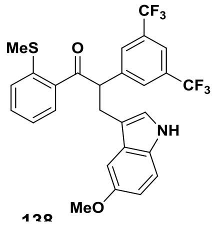

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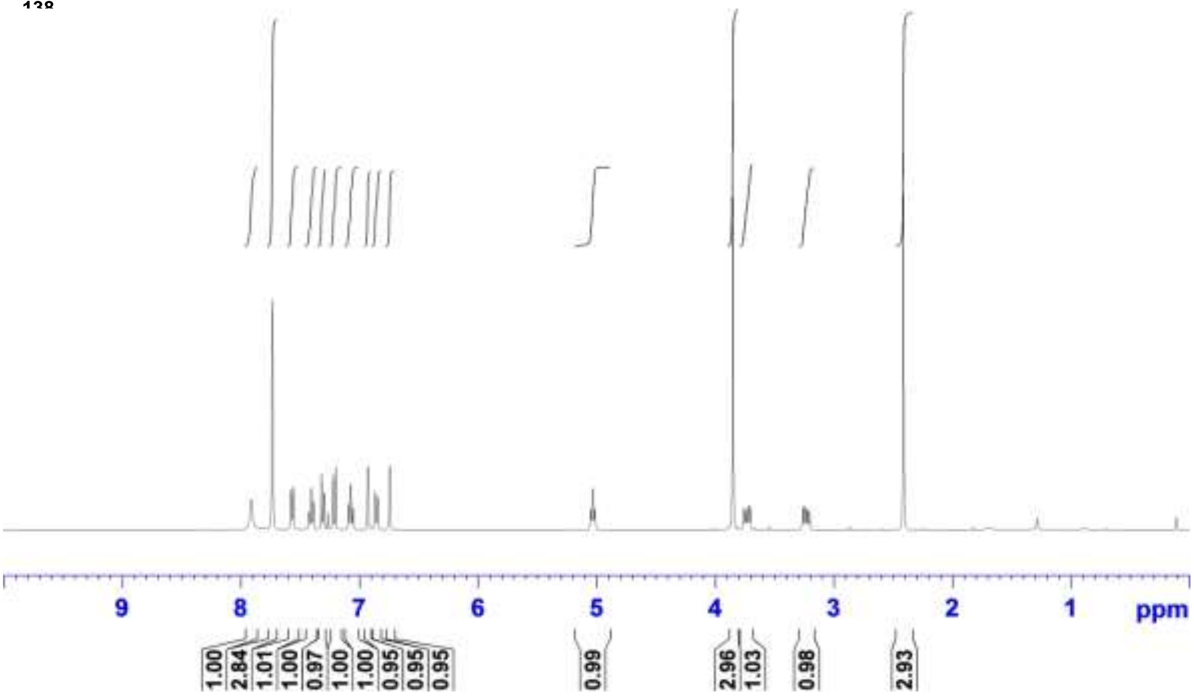

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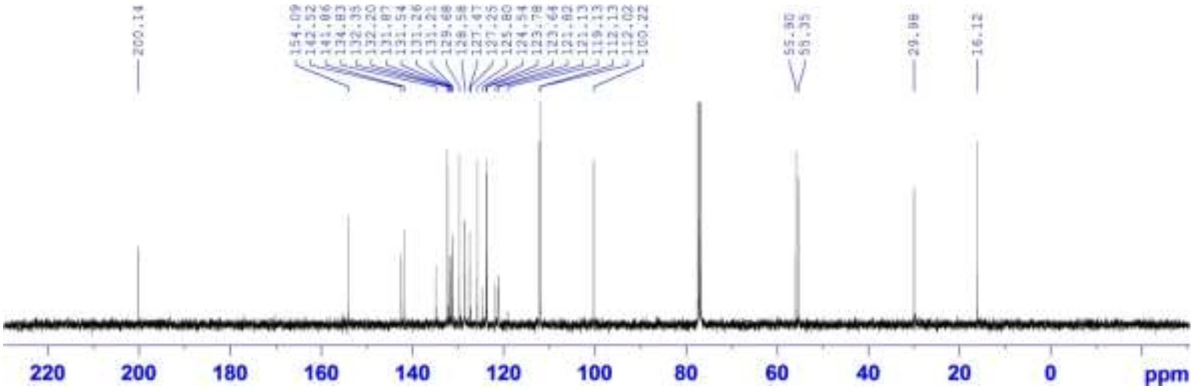
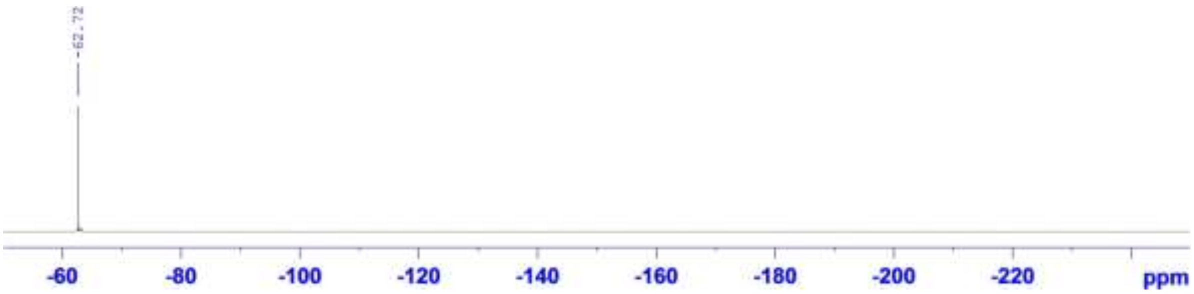
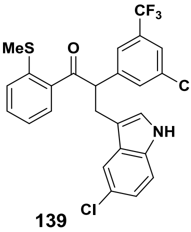


^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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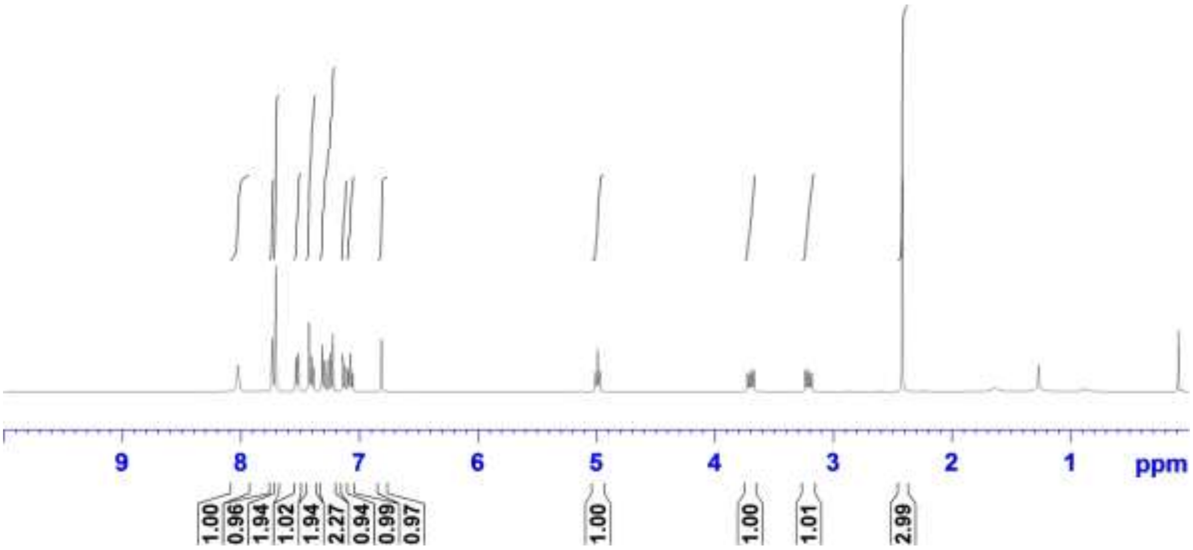
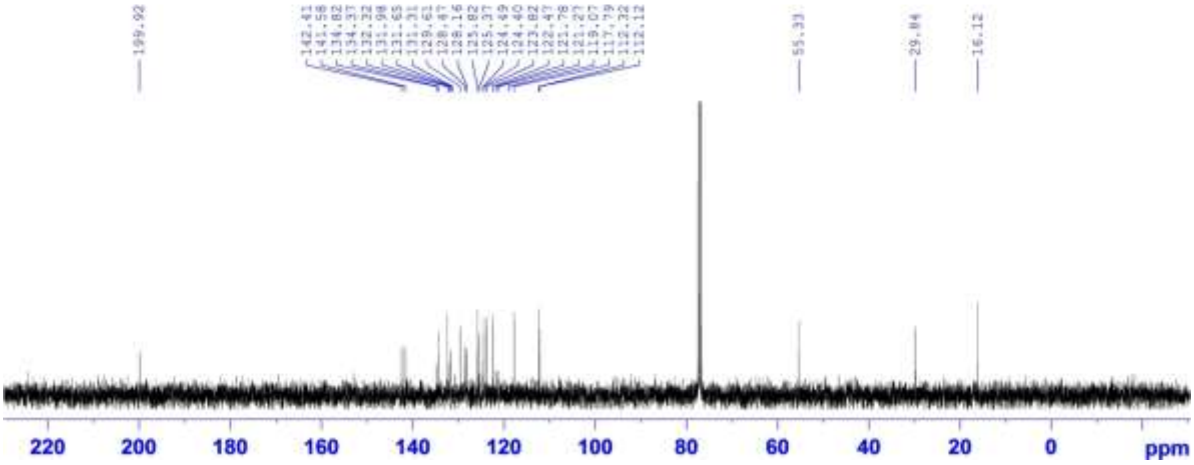


^{13}C NMR (101 MHz, CDCl$_3$)



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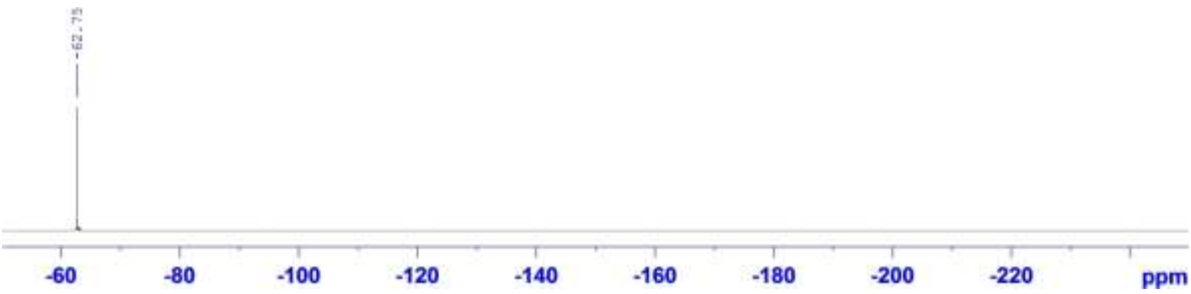

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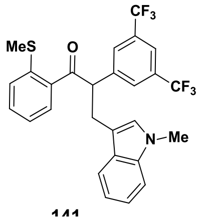

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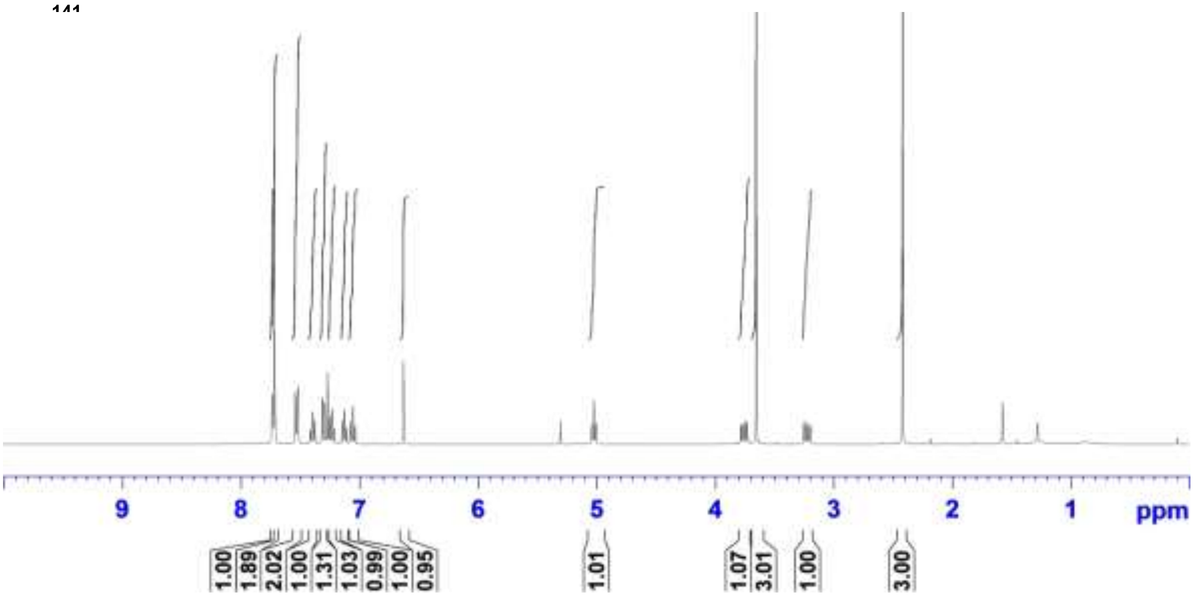

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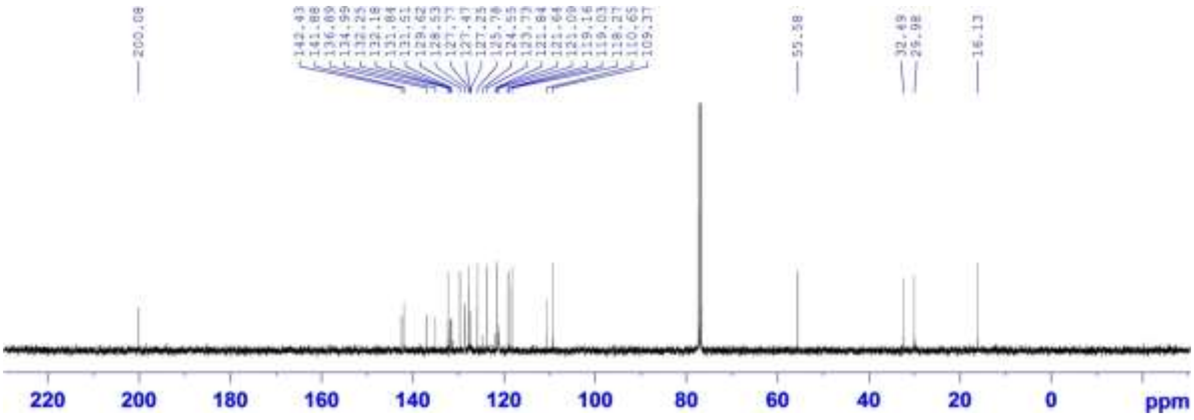

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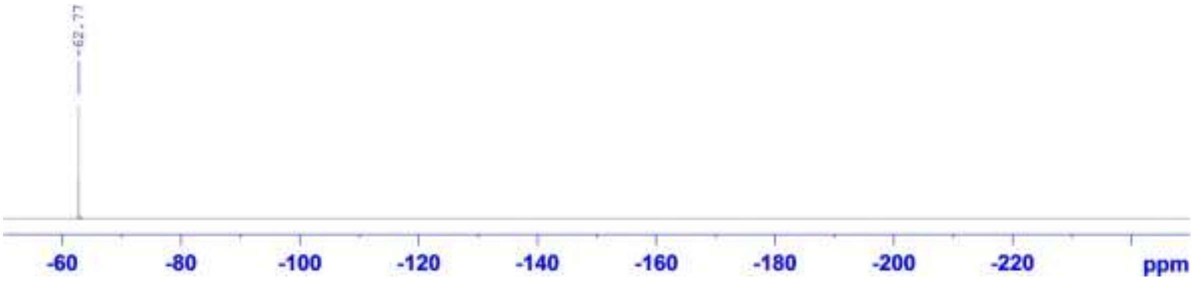

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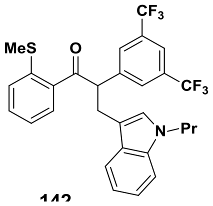

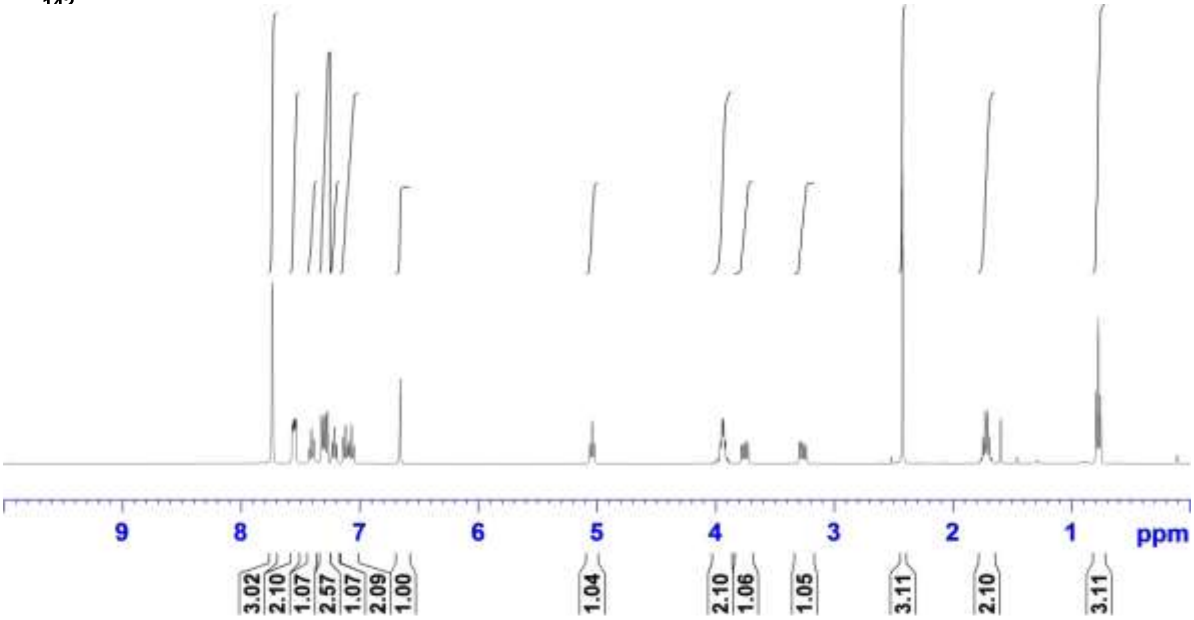

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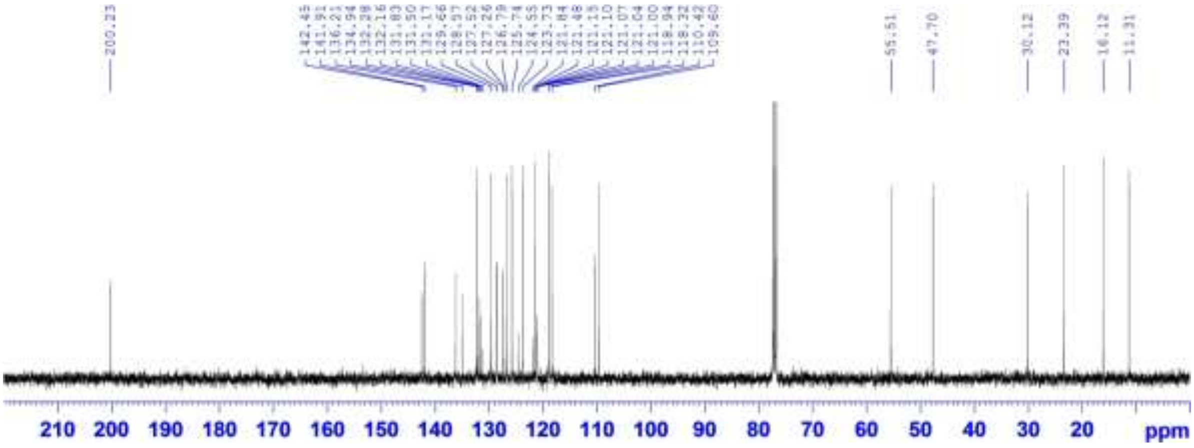

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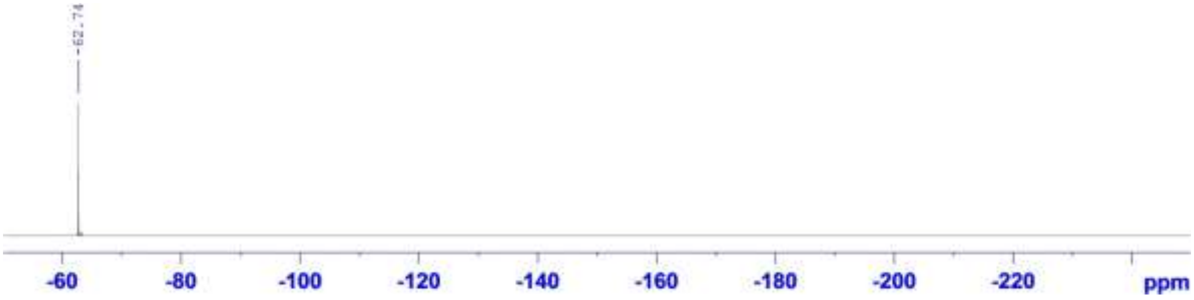

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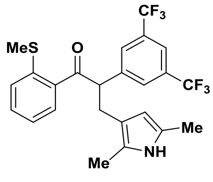

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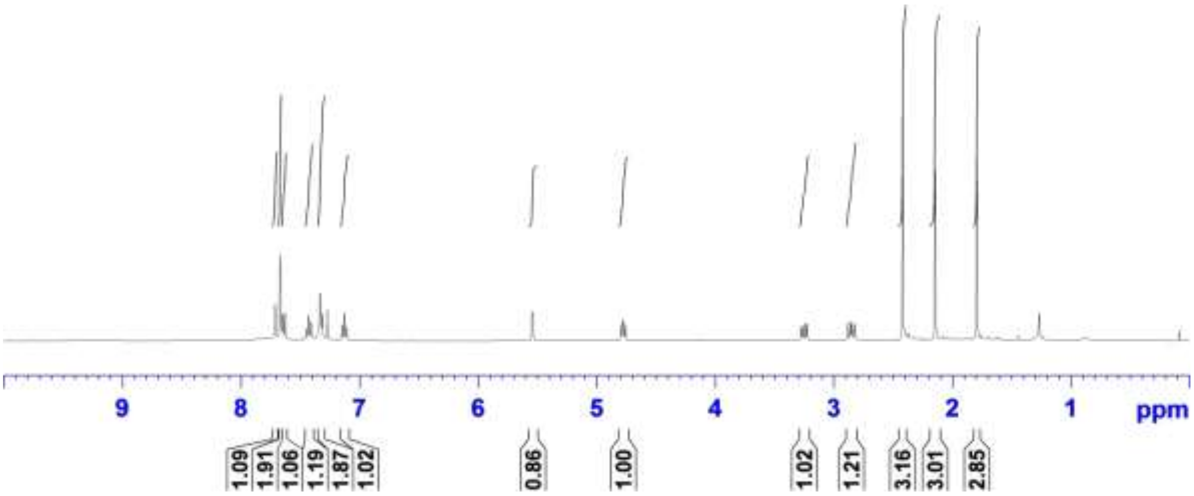
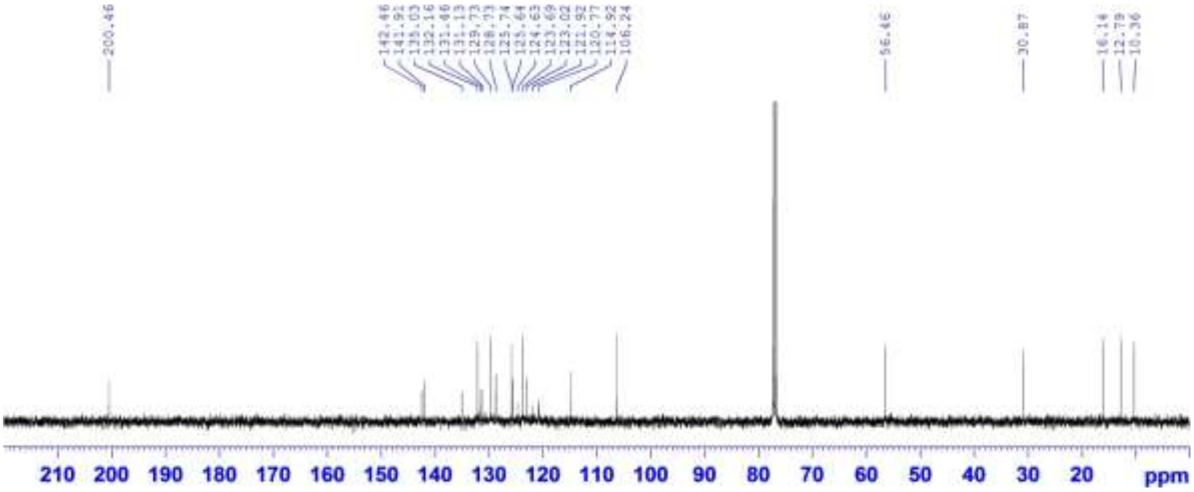


^{13}C NMR (101 MHz, CDCl$_3$)



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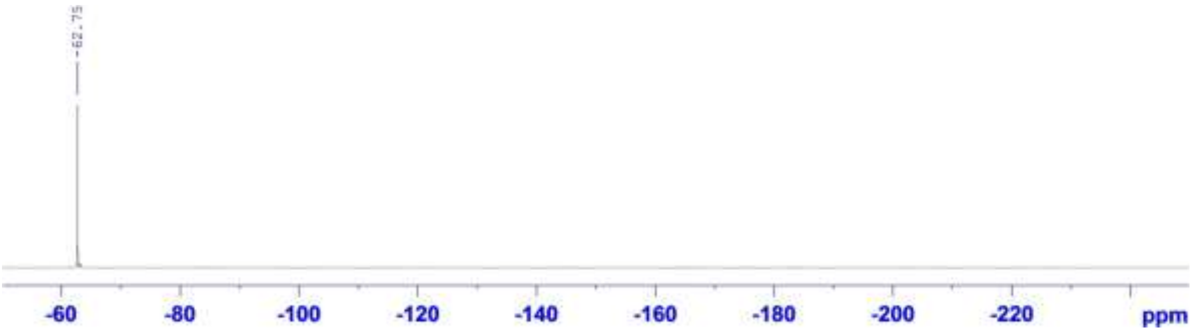
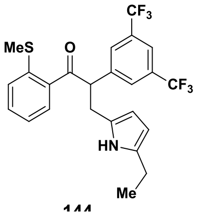


^{1}H NMR (400 MHz, $CDCl_3$)



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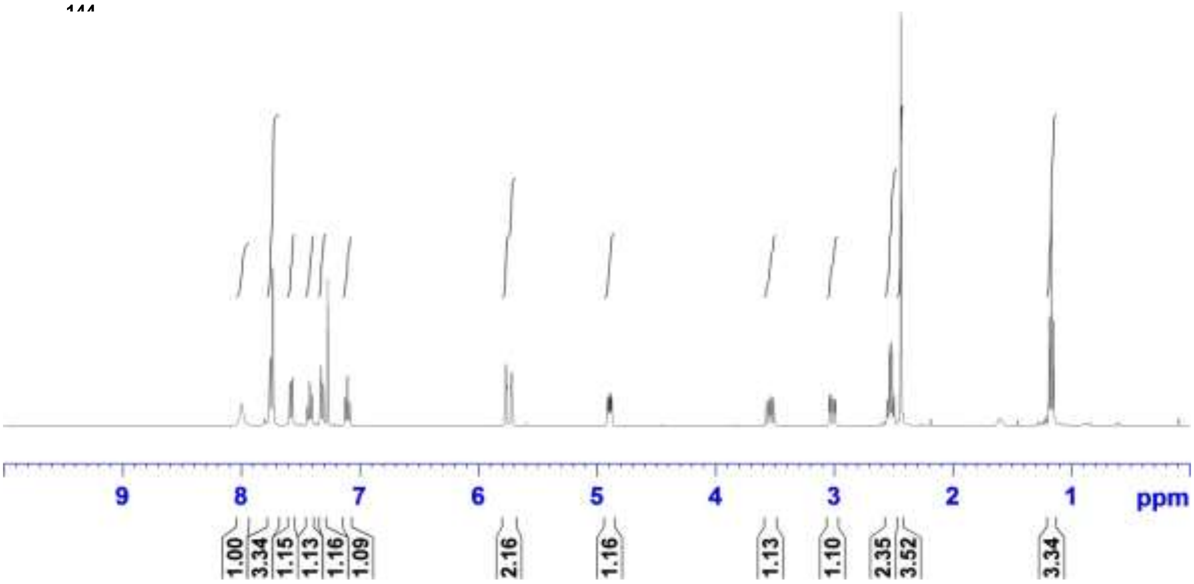

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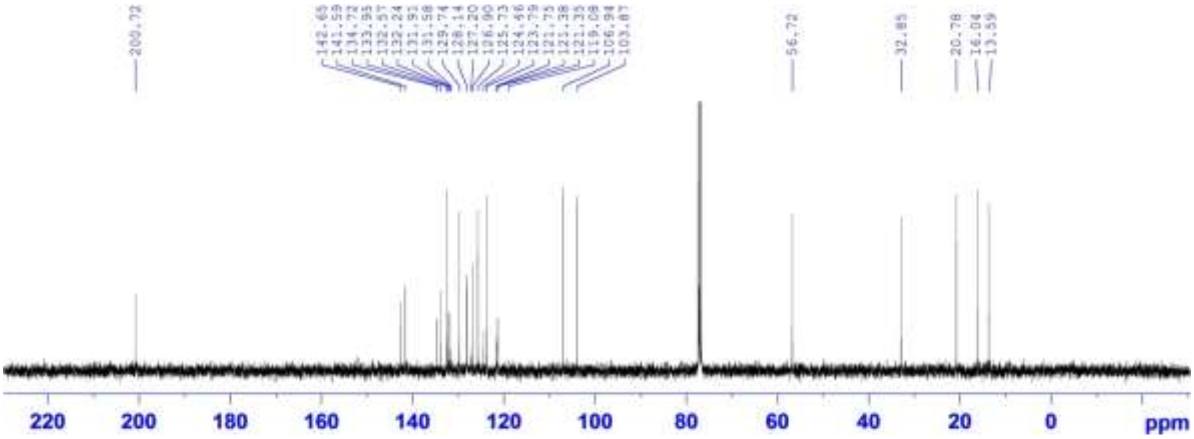
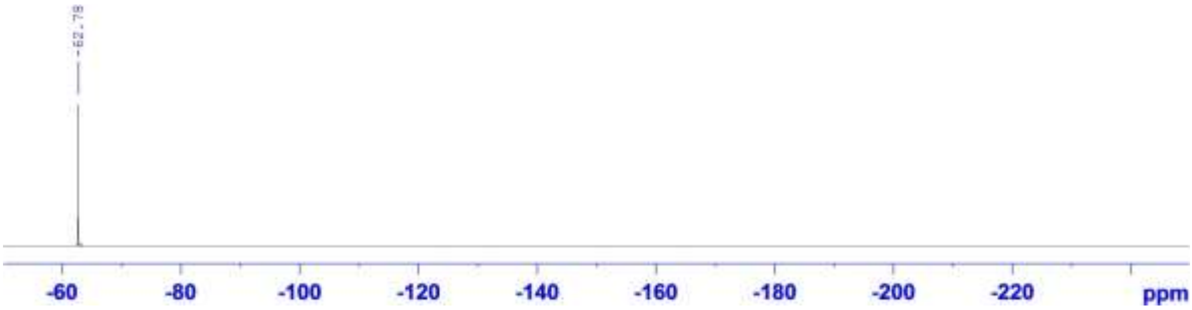


^{19}F NMR (376 MHz, $CDCl_3$)



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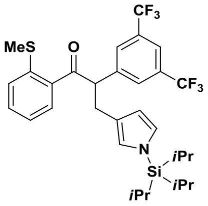

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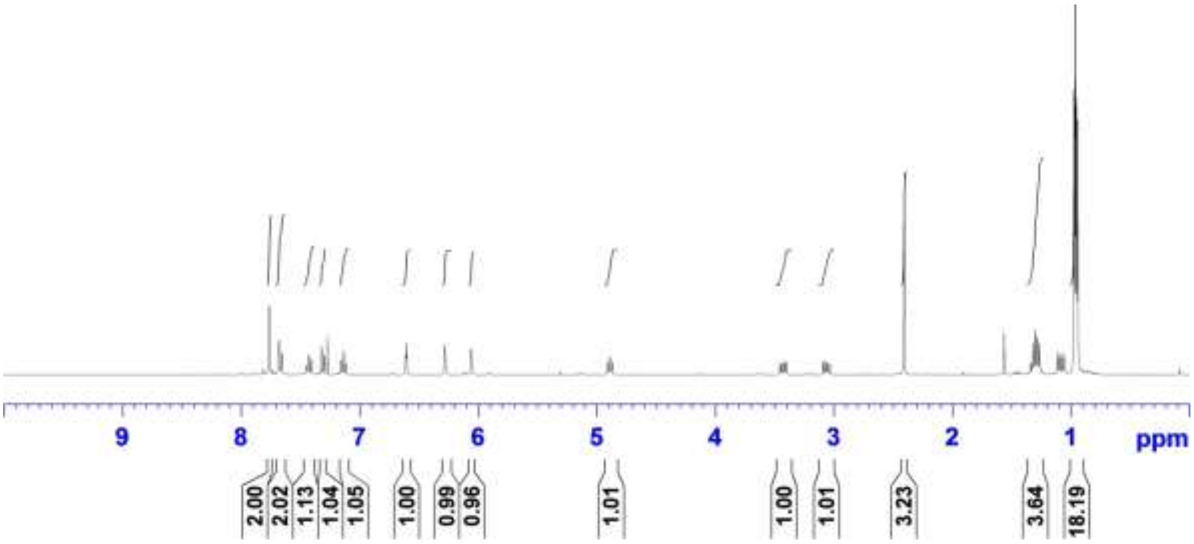
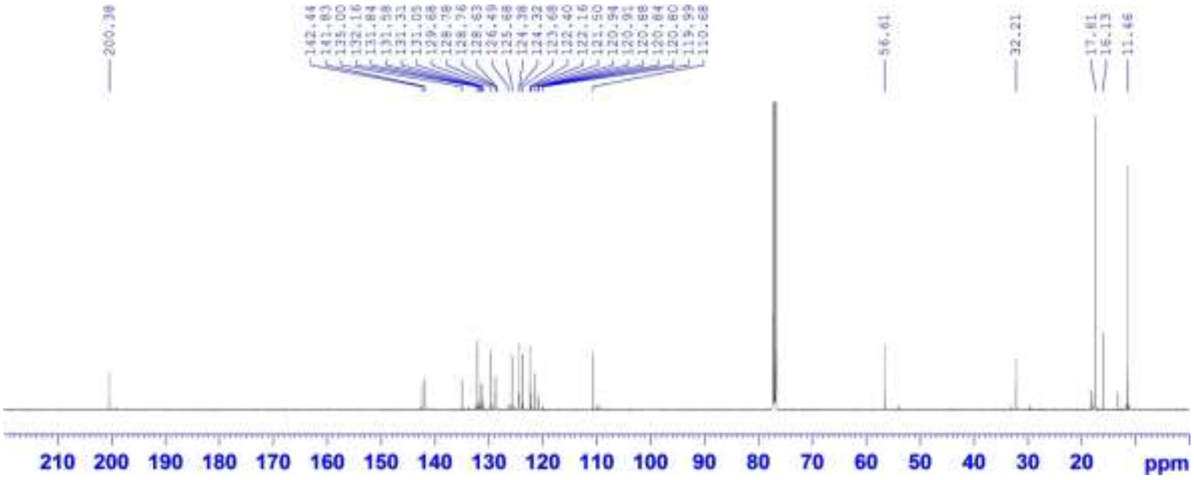
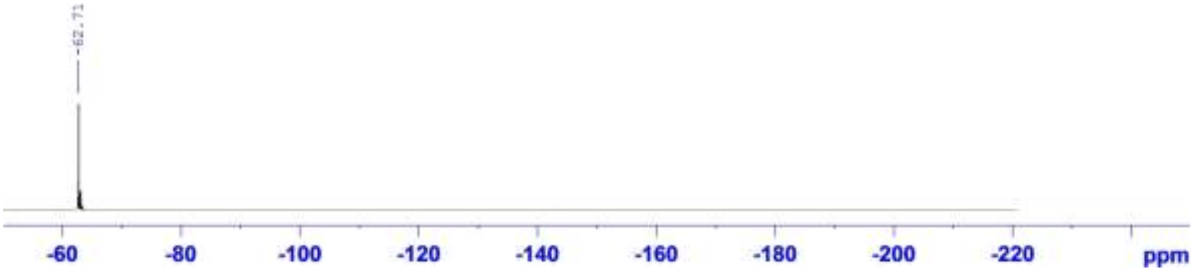


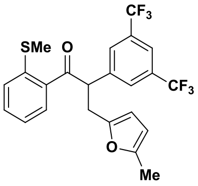
^{13}C NMR (126 MHz, CDCl$_3$)



^{19}F NMR (470 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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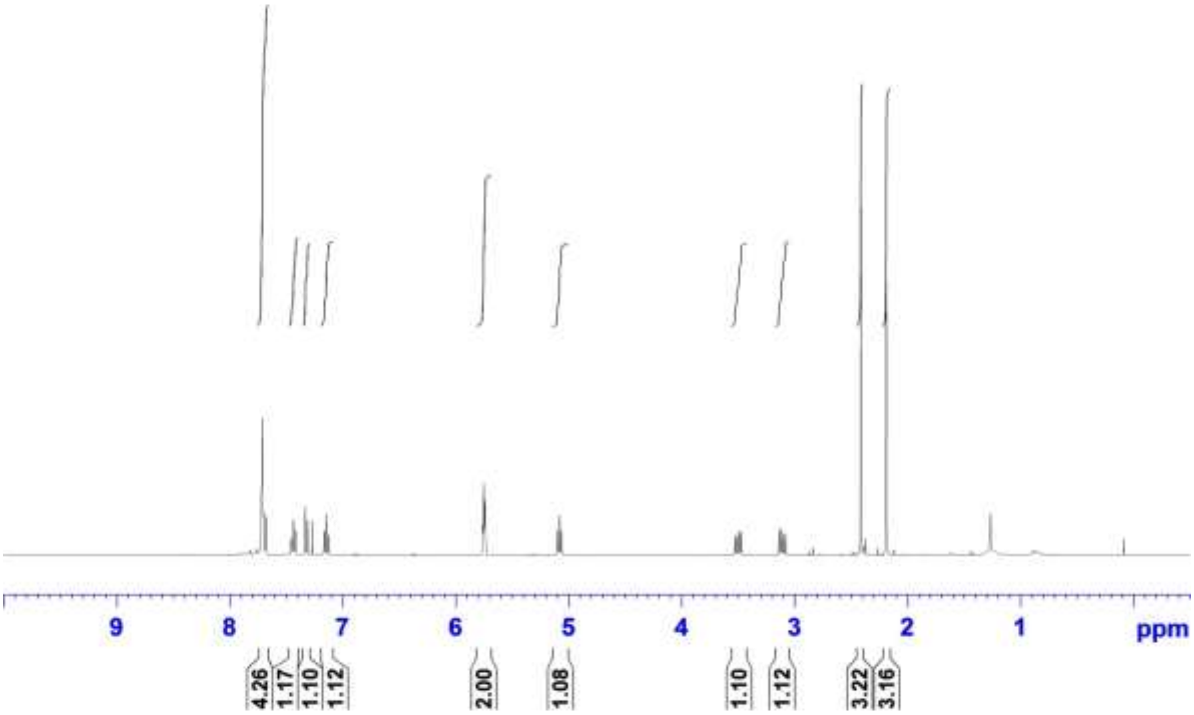
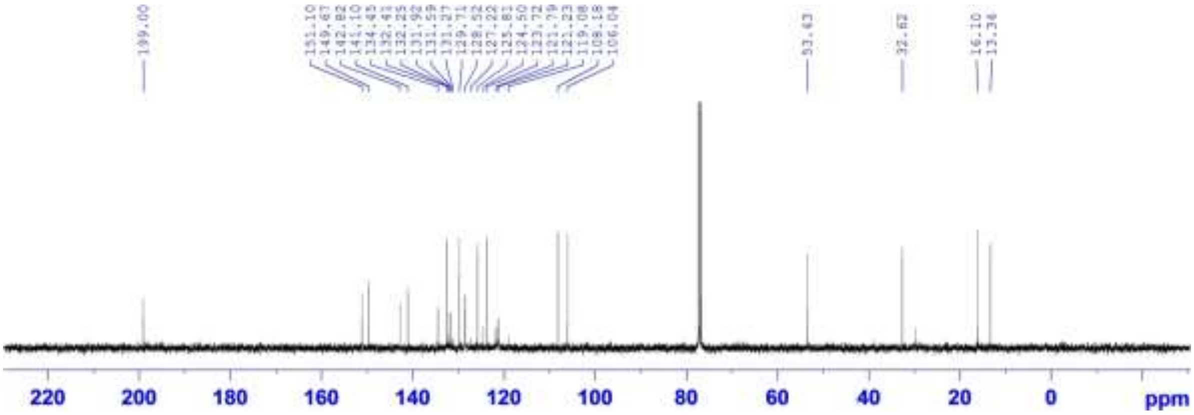
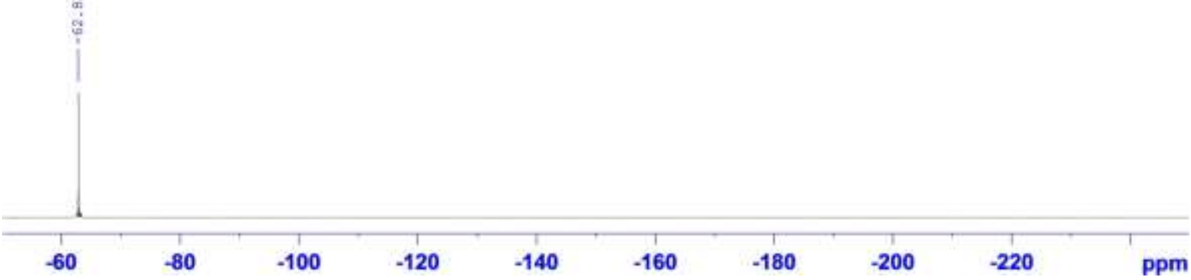


^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)



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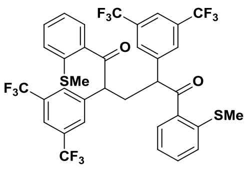

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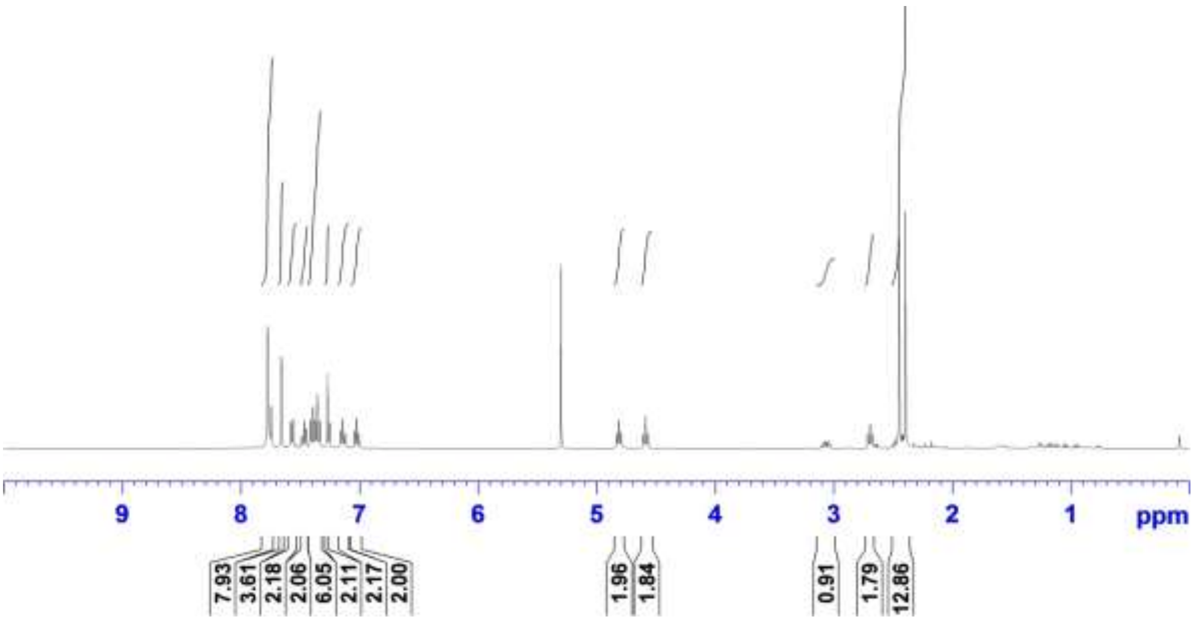

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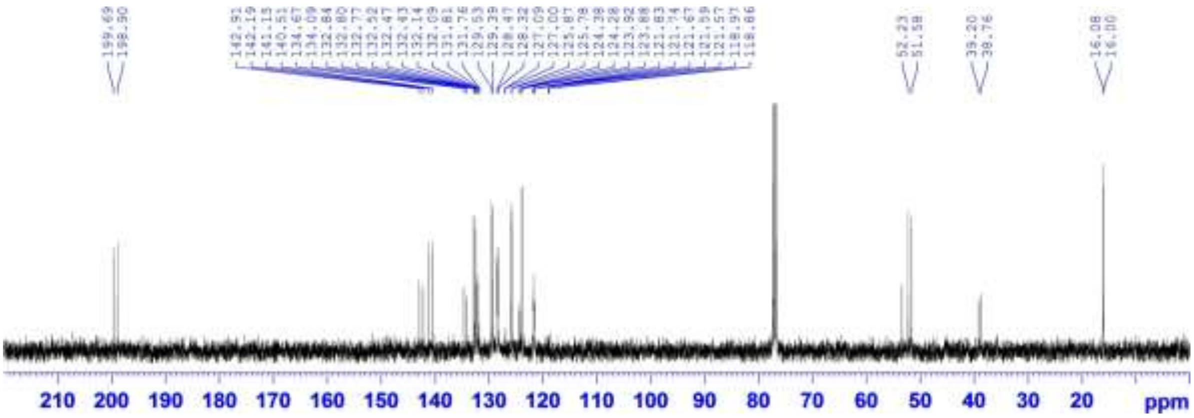
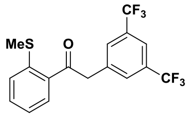


^{1}H NMR (400 MHz, CDCl$_3$)



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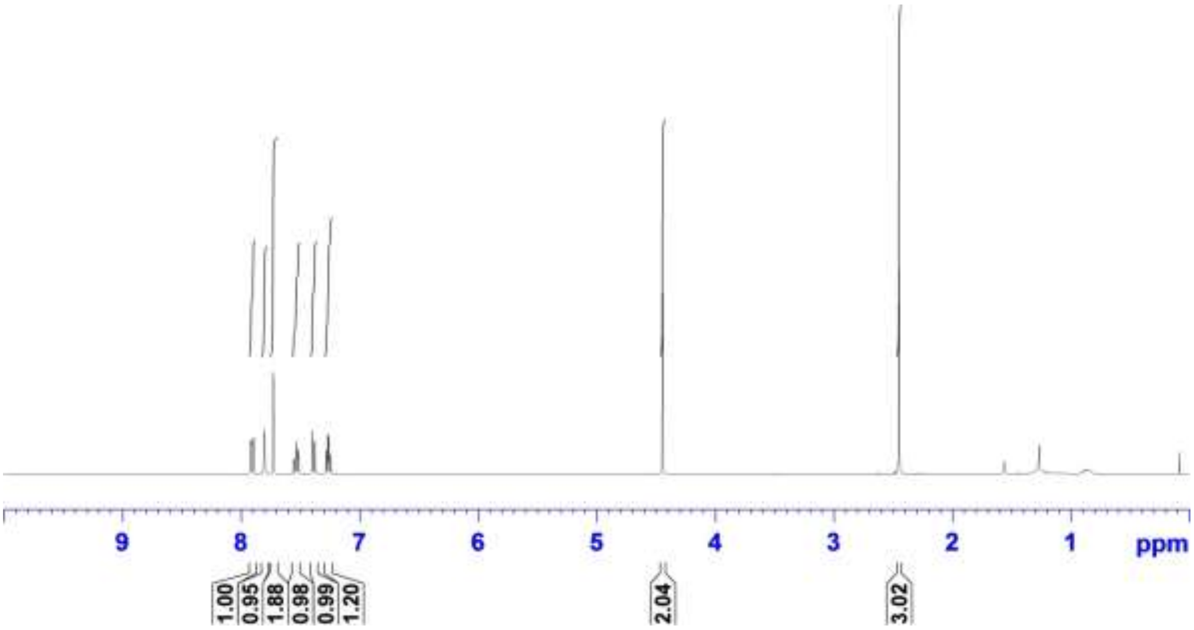
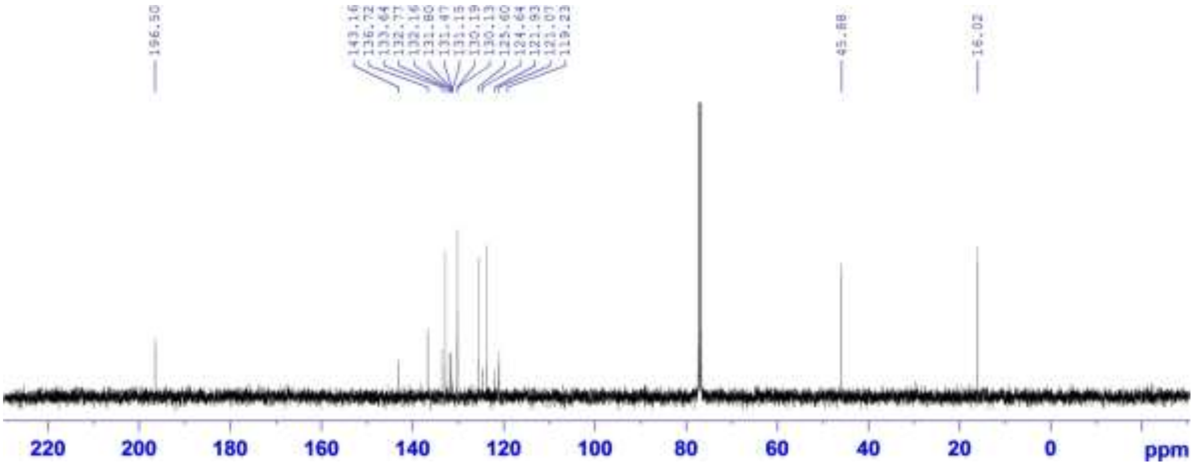
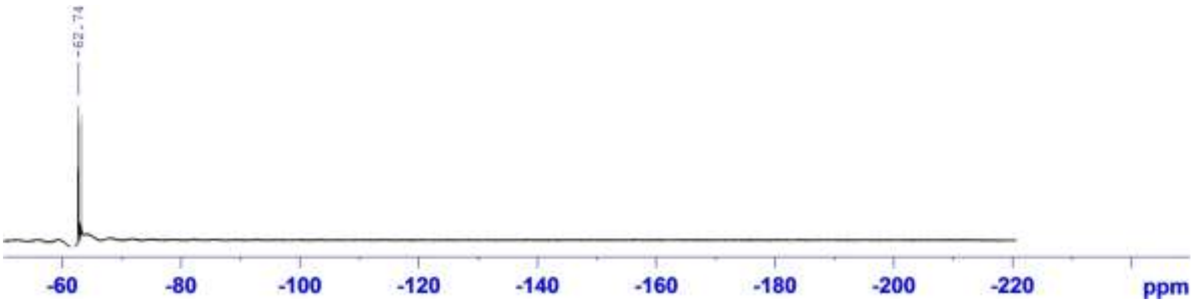


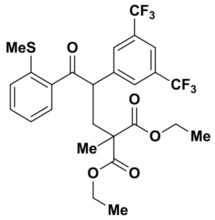
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (470 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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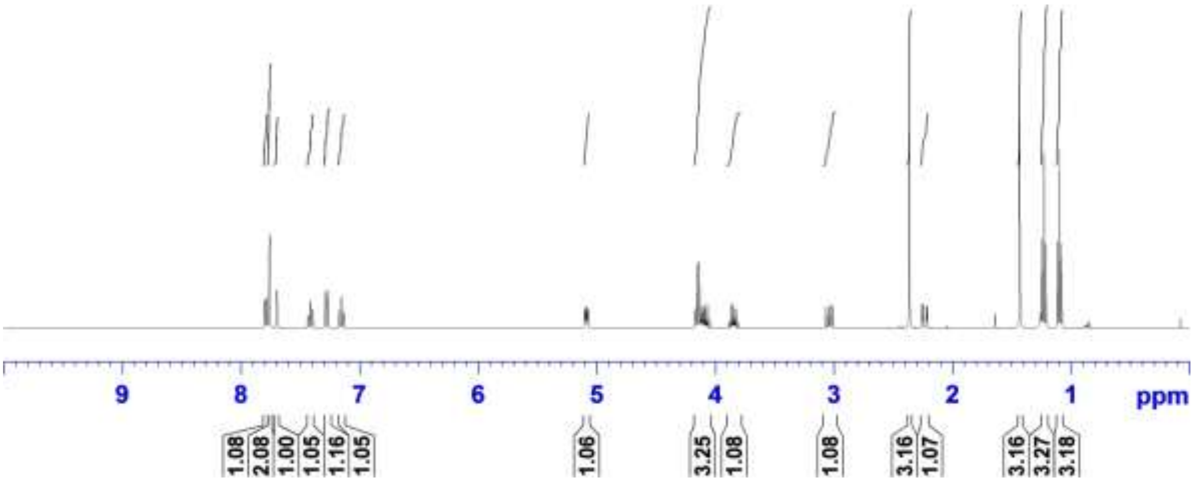
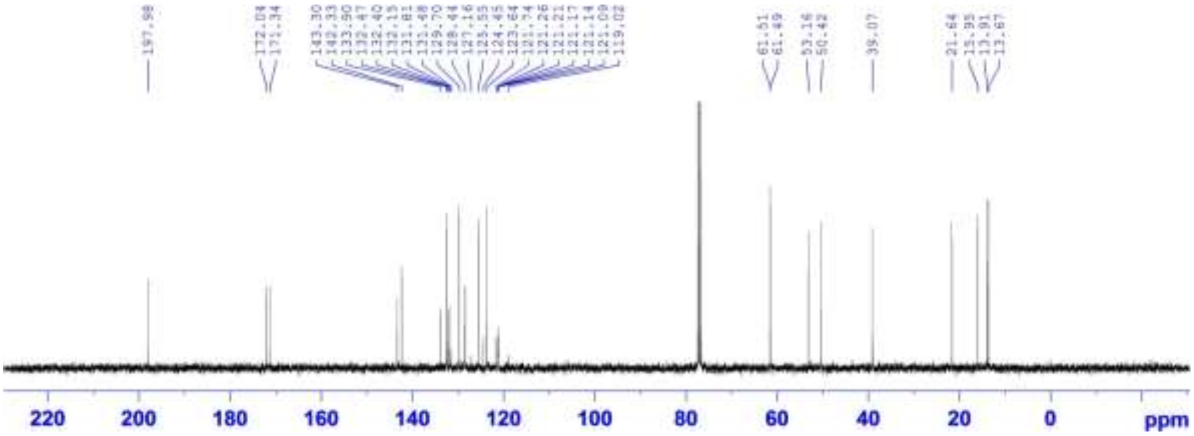


^{13}C NMR (101 MHz, CDCl$_3$)



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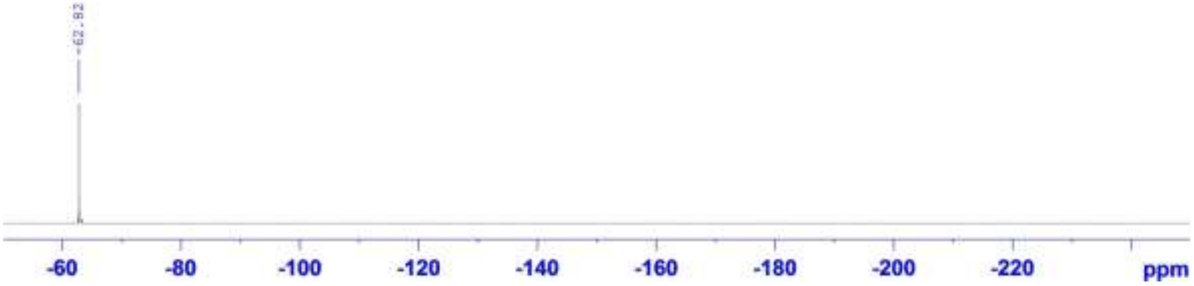

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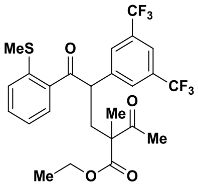

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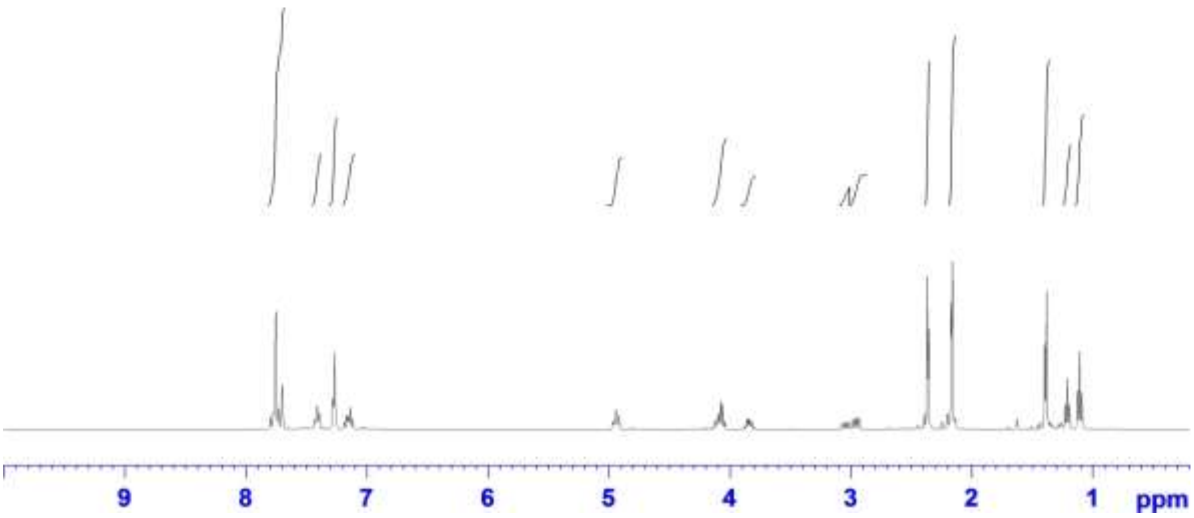
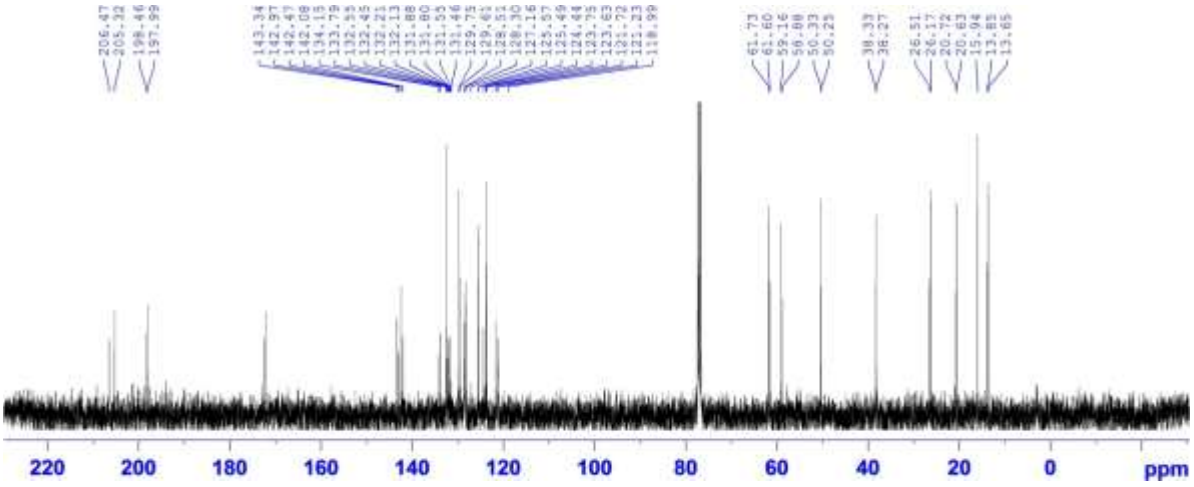
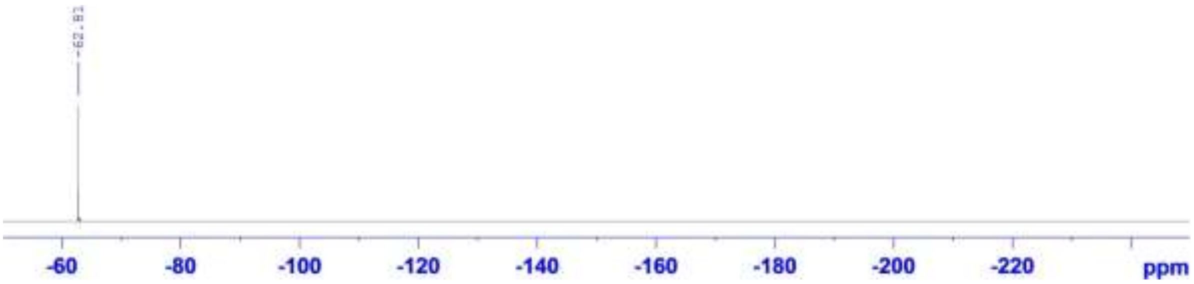


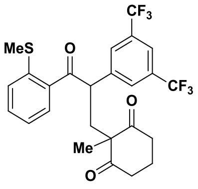
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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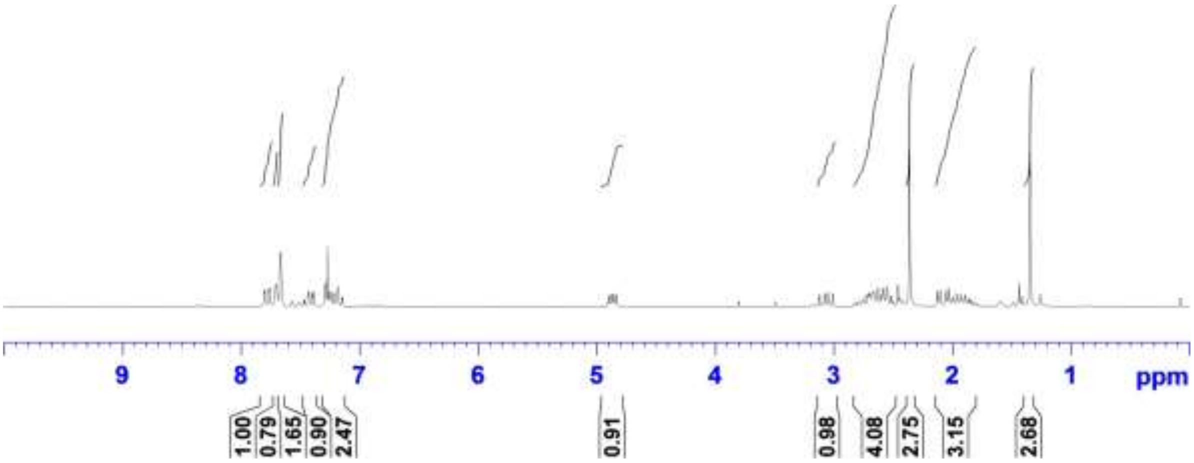
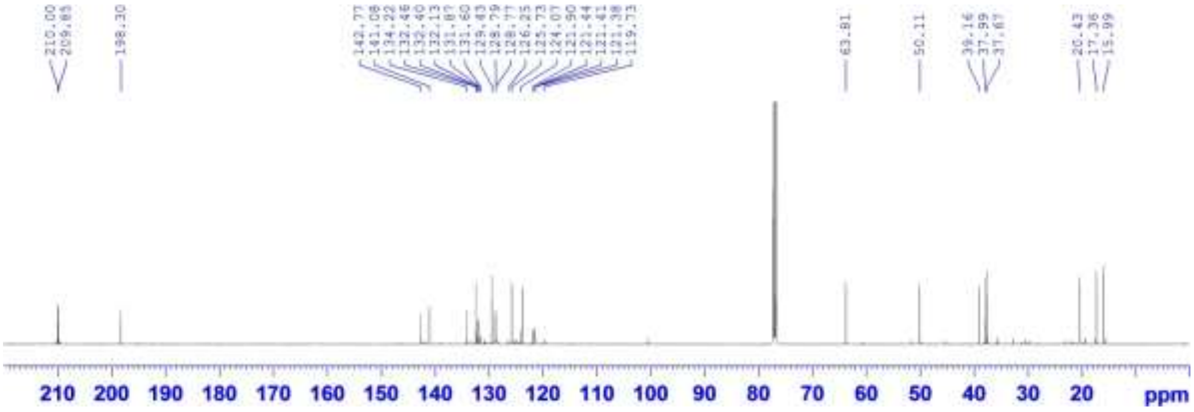
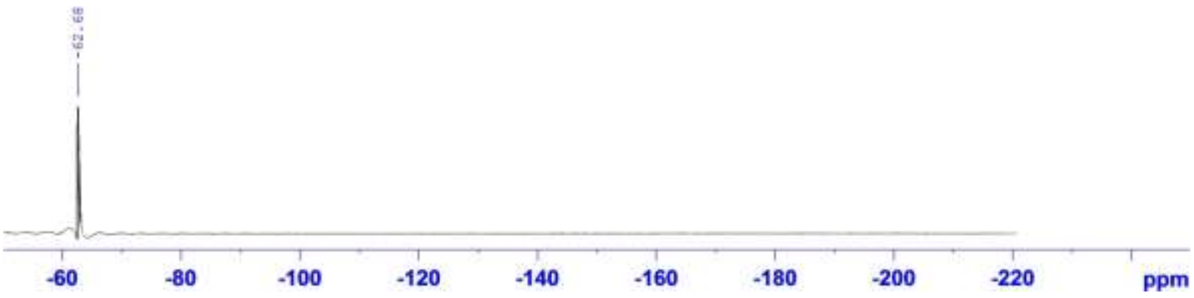


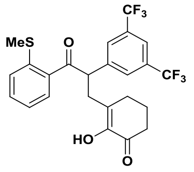
^{13}C NMR (126 MHz, CDCl$_3$)



^{19}F NMR (470 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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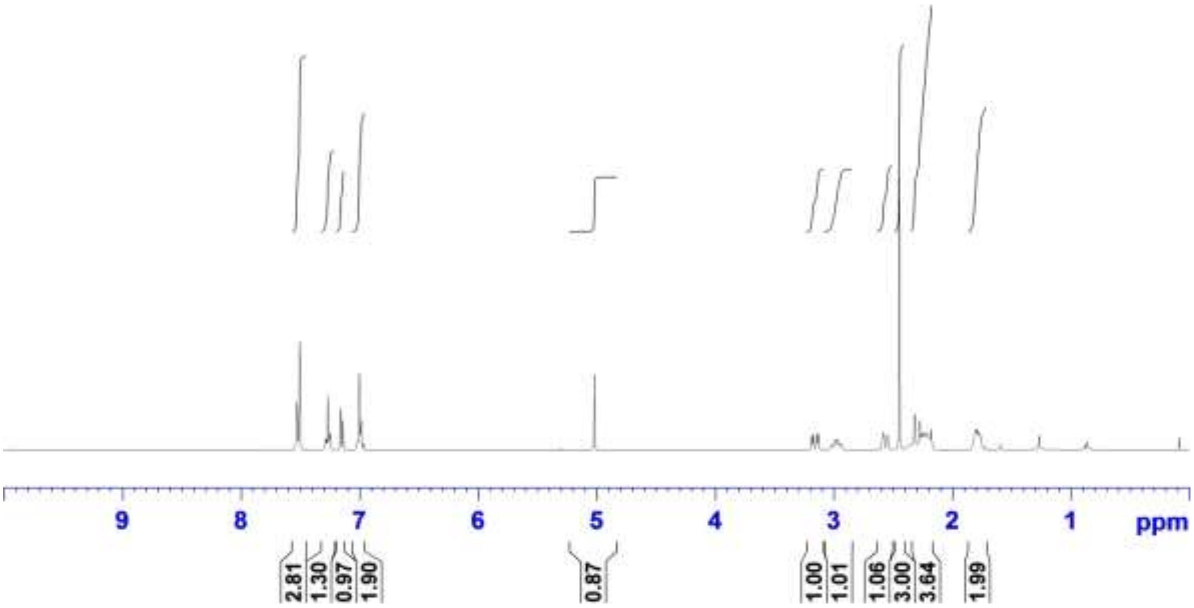
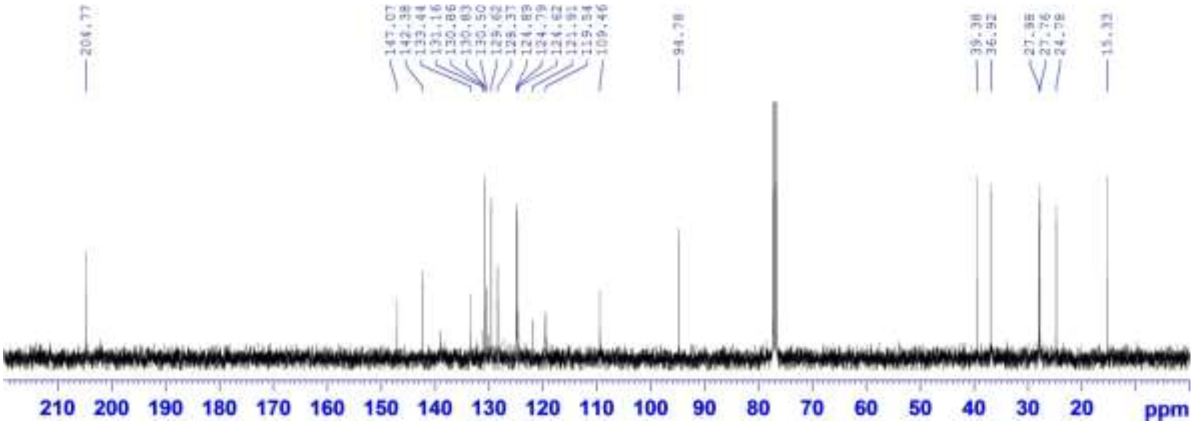
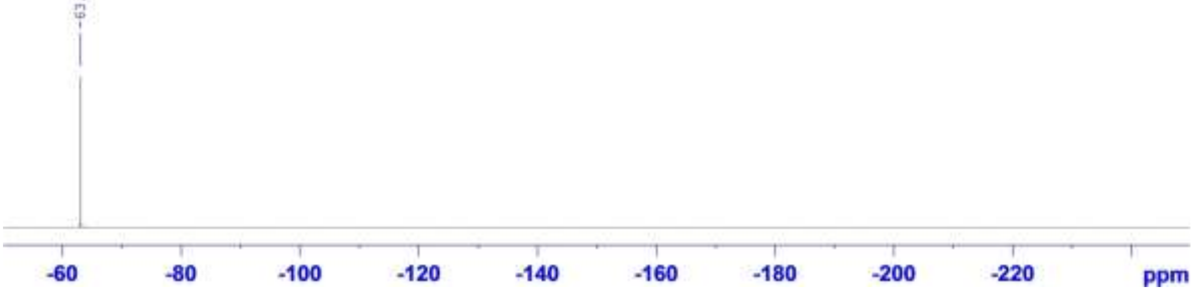


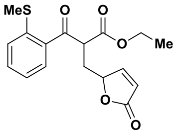
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (376 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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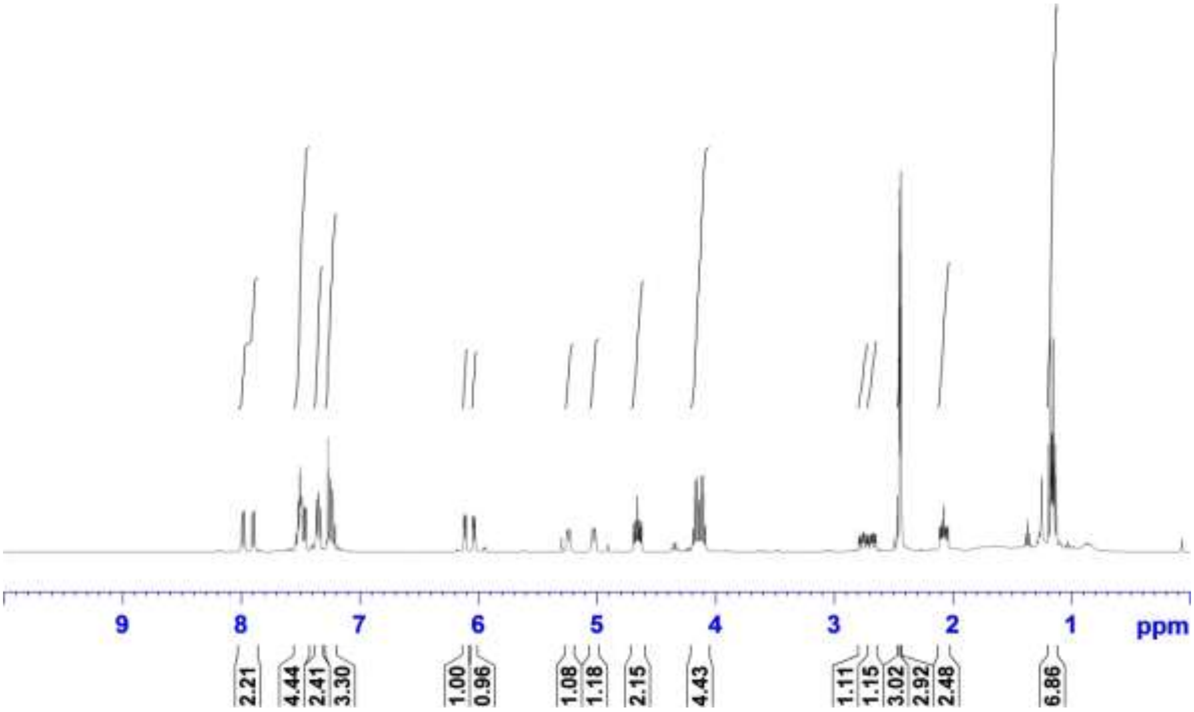
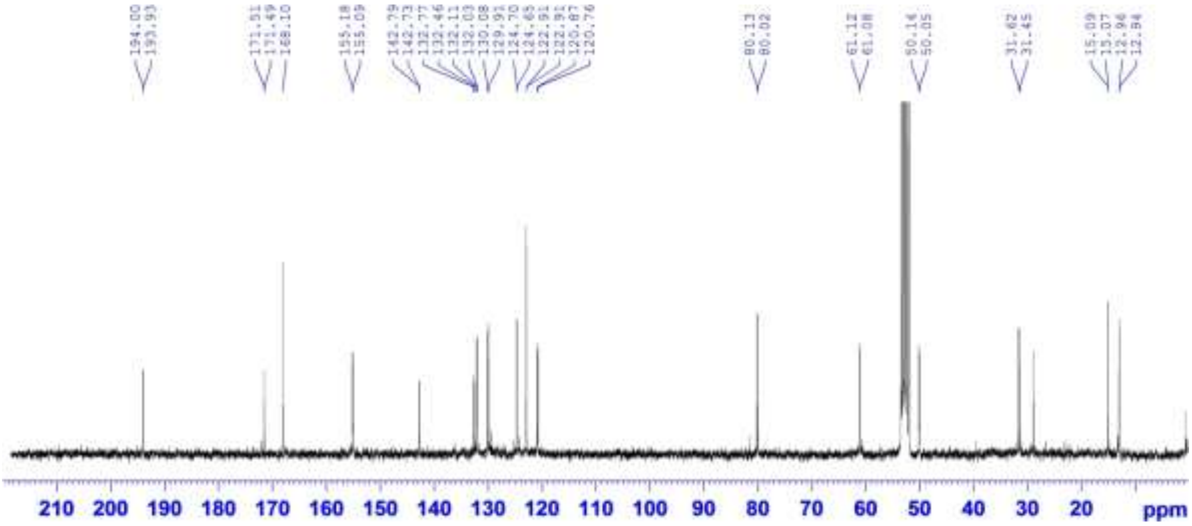
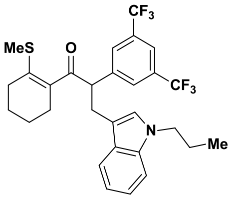


^{13}C NMR (101 MHz, CDC$_2$Cl$_2$)



^{1}H NMR (400 MHz, CDCl$_3$)



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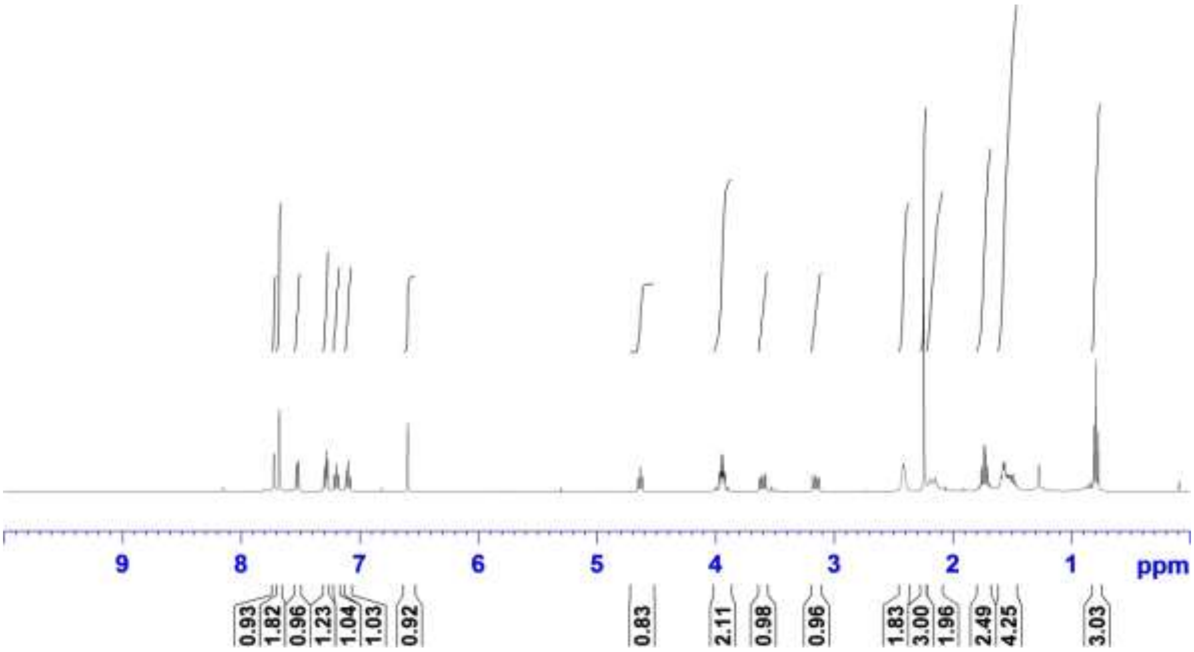
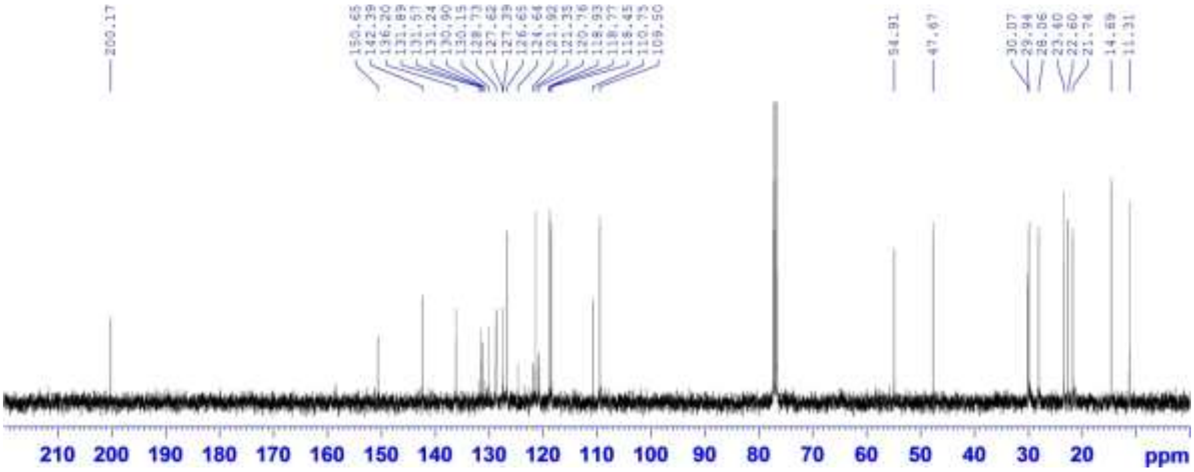
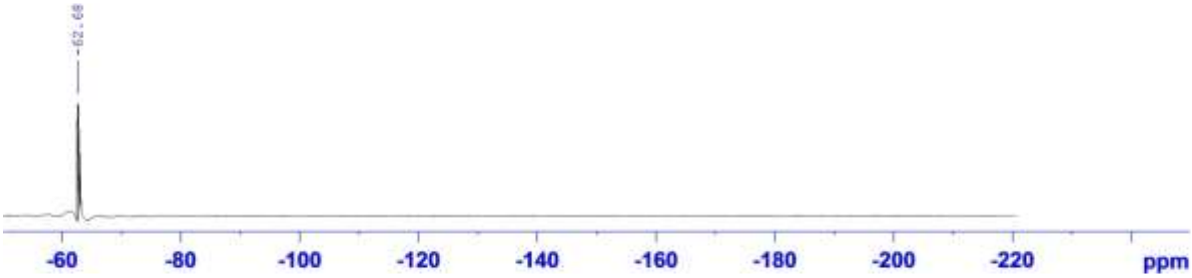


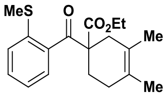
^{13}C NMR (101 MHz, CDCl$_3$)



^{19}F NMR (470 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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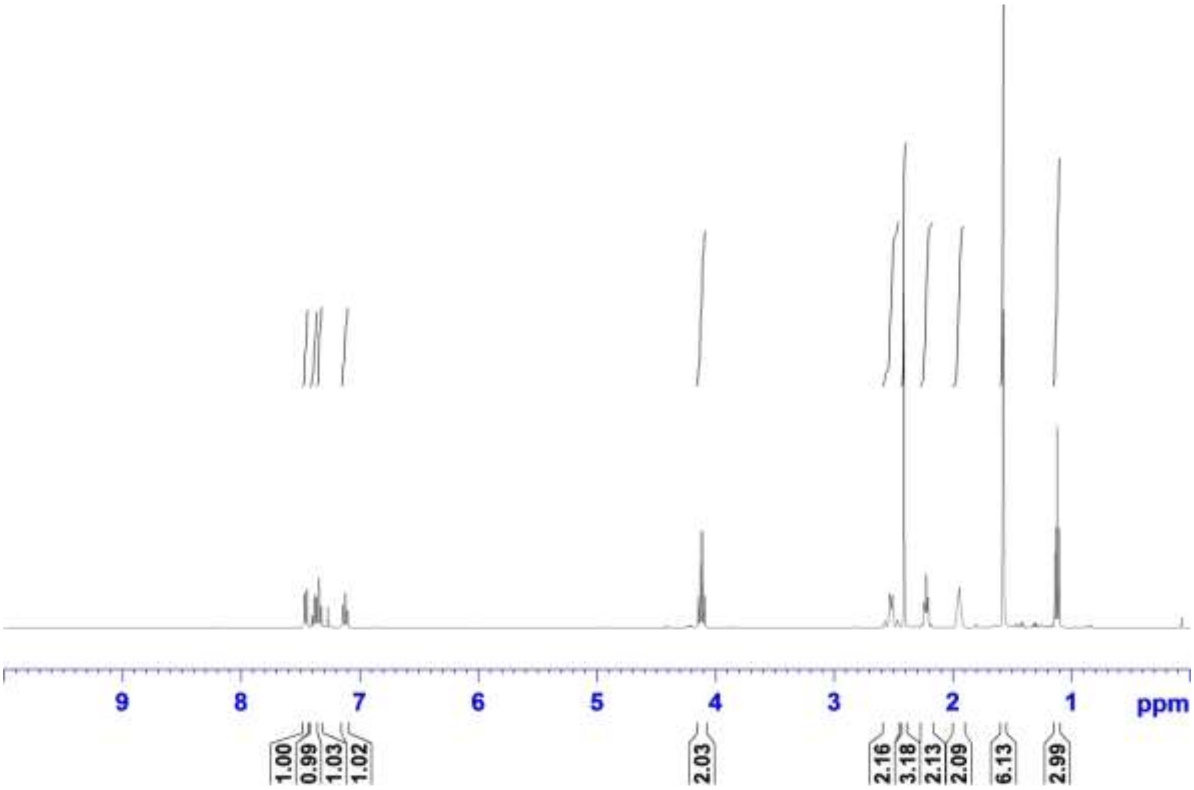
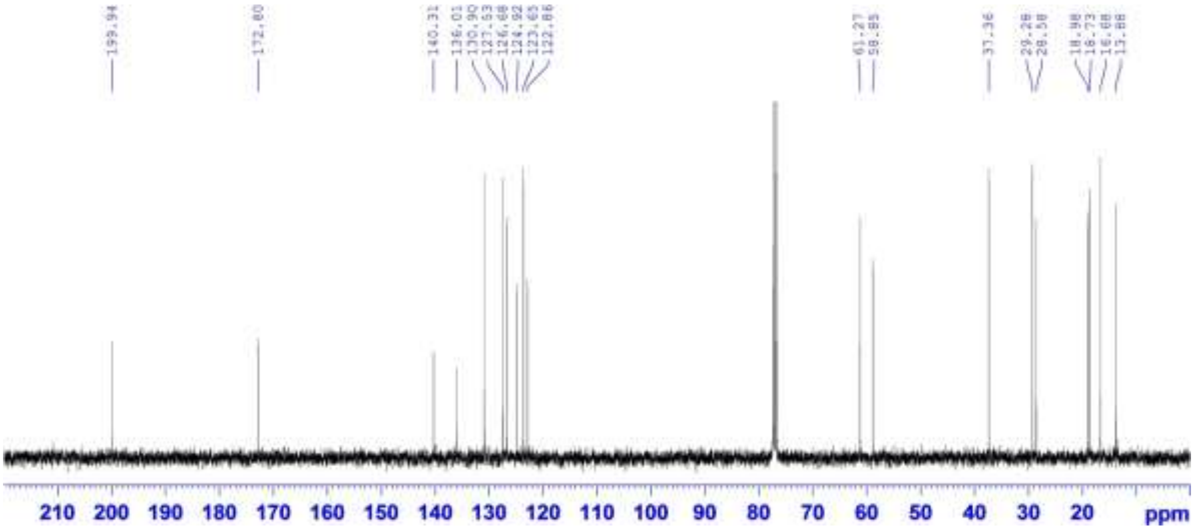
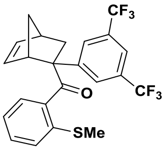


^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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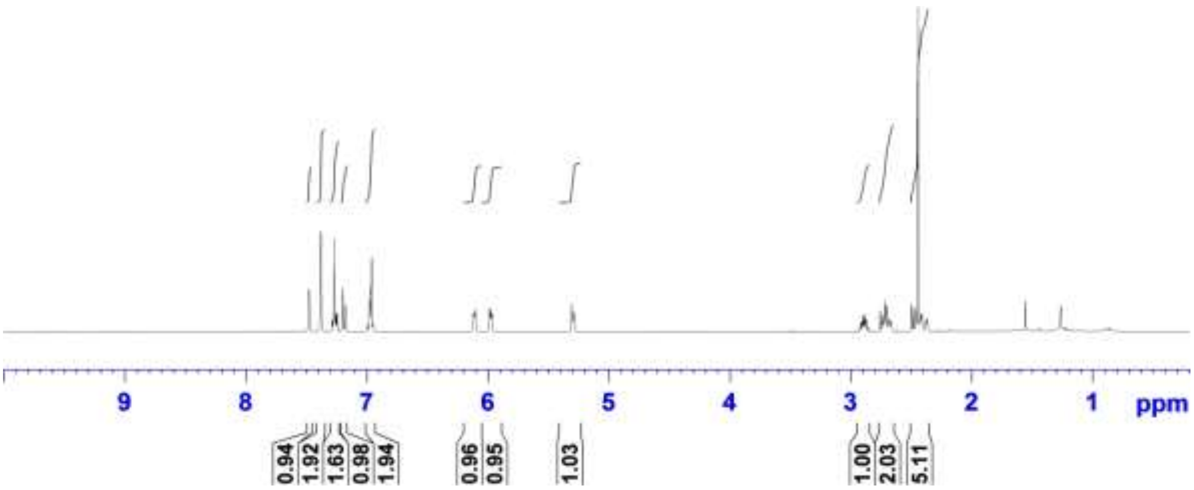
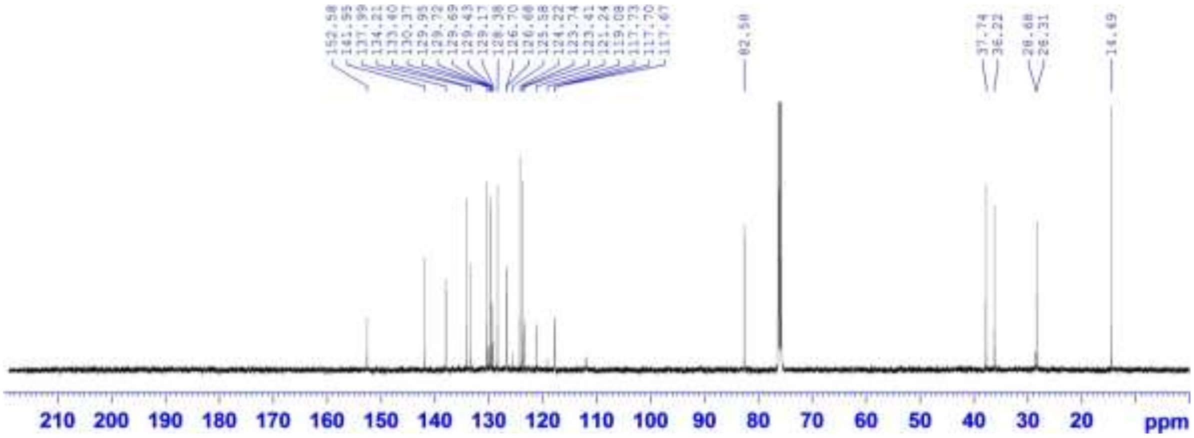
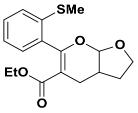


^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (400 MHz, CDCl$_3$)



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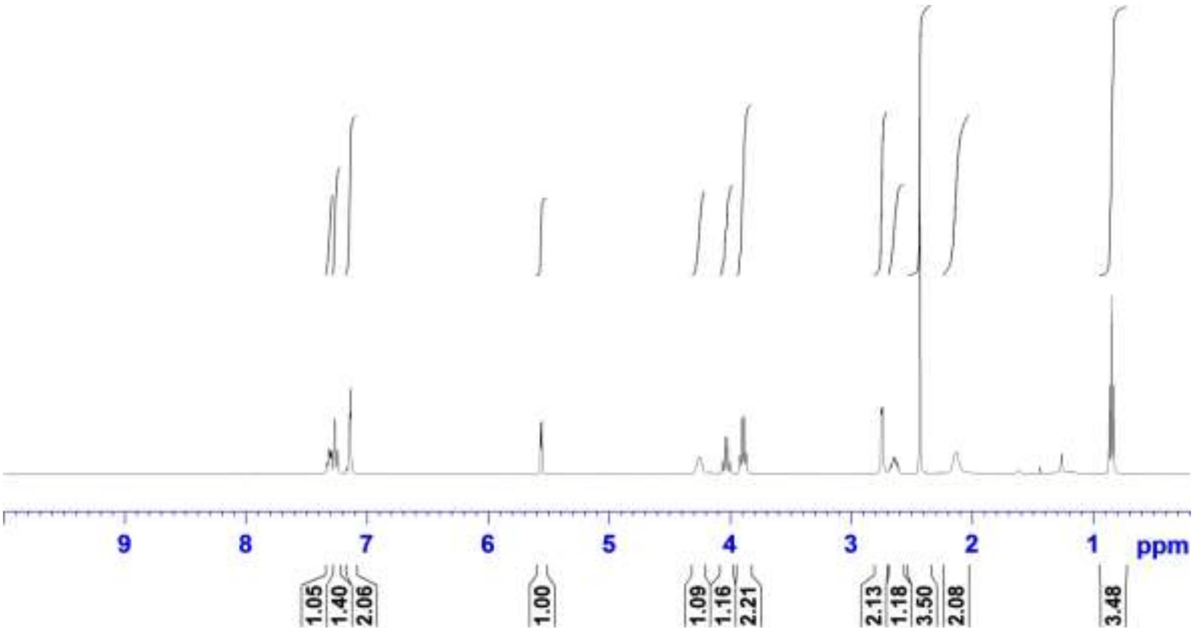
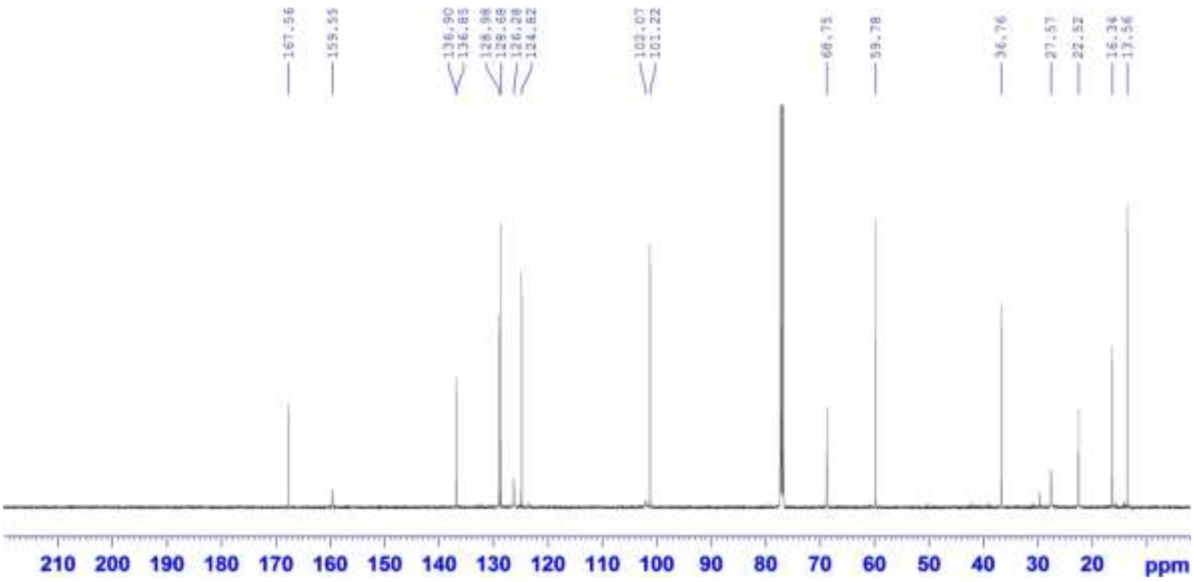
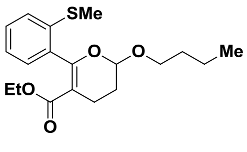


^{13}C NMR (101 MHz, CDCl$_3$)



^{1}H NMR (500 MHz, CDCl$_3$)



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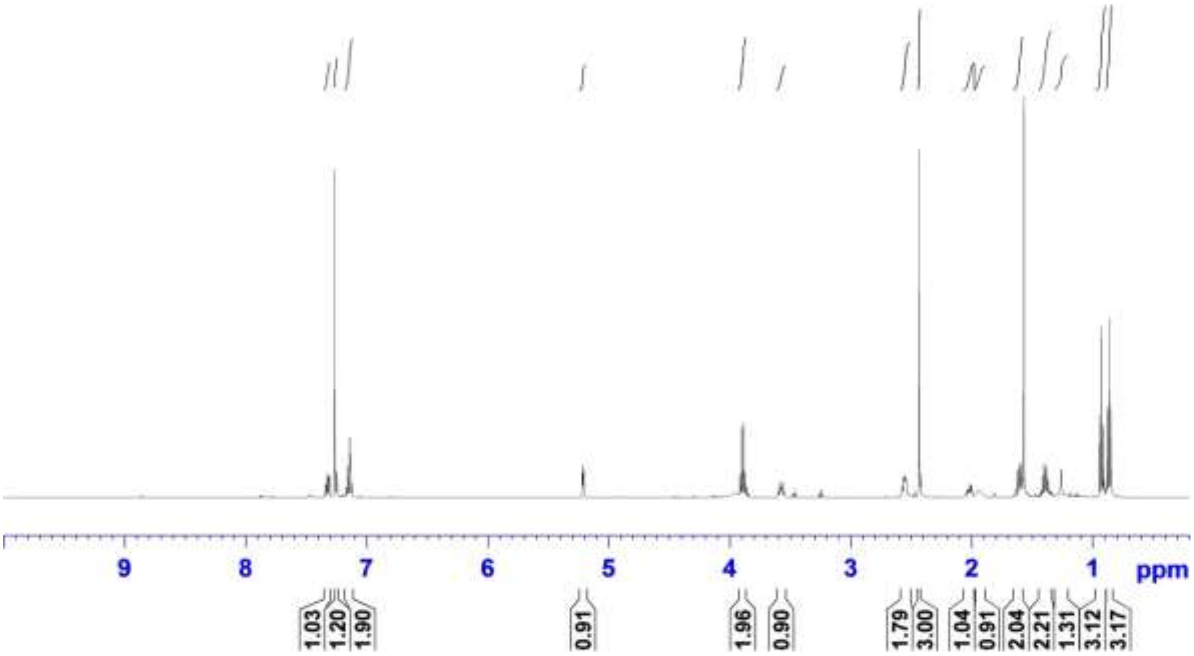
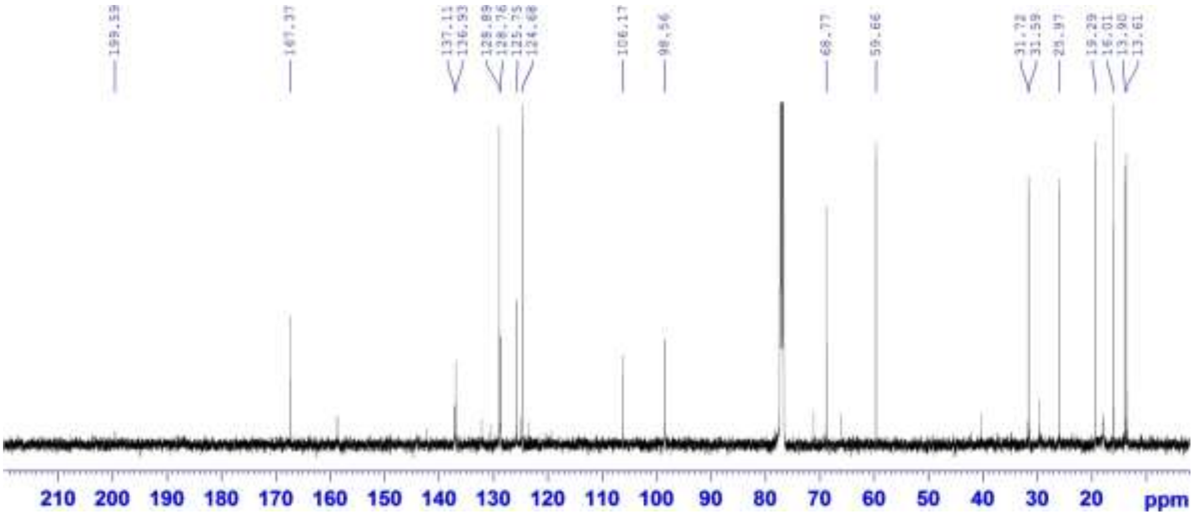


^{13}C NMR (126 MHz, CDCl$_3$)



nOe Difference Experiments for Compound 145