Tandem catalytic processes involving Rhodium-catalysed intermolecular hydroacylation

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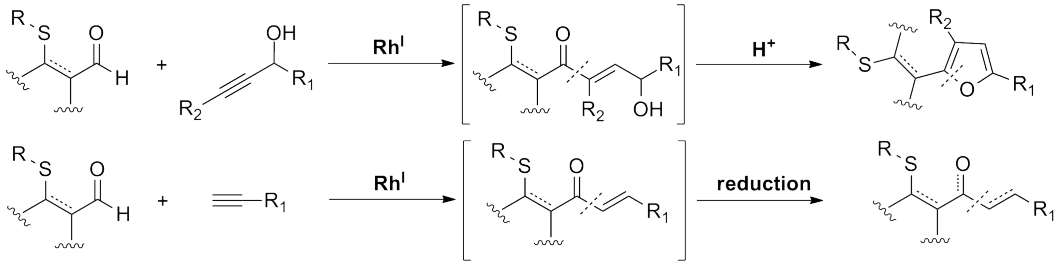
Abstract

This work describes the extension of rhodium-catalysed intermolecular hydroacylation to encompass some tandem catalytic processes, wherein a further catalytic process is enacted on the product of an intermolecular hydroacylation reaction in "one pot" (Scheme 1).



Scheme 1. Examples of tandem catalytic processes which involve rhodium-catalysed intermolecular hydroacylation

Chapter 1 entails an overview of the development of hydroacylation chemistry, with a focus on the different types of catalytic systems which have been used to facilitate this transformation. A brief description of some precedented examples of tandem catalytic processes which include a hydroacylation reaction is also included.

Chapter 2 describes the intermolecular hydroacylation of chelating aldehydes and propargylic alkynes to form γ-hydroxy-α,β-enones, and their subsequent acid-catalysed cyclisation to form substituted furans in a "one-pot" procedure. Additionally, a tandem intermolecular hydroacylation/double-bond isomerisation protocol for the synthesis of 1,4-dicarbonyl compounds is detailed, and the subsequent transformation of this class of compounds to heterocycles is included.

Chapter 3 focuses on the development of tandem catalytic hydroacylation/reductive processes, wherein a hydroacylation product undergoes a reduction which is catalysed by the hydroacylation catalyst.

Chapter 4 describes an attempt to utilise the rhodium-catalysed conjugate addition

of arylmetal species to enones to create a tandem alkyne hydroacylation/conjugate addition process.

Chapter 5 encompasses the use of a small range of different solvents in rhodium-cataylsed hydroacylation, in an attempt to find higher-boiling alternatices to acetone and a “green” alternative to the commonly used DCE.

Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated and does not include any collaborative research.

This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Philip Lenden

August 2011

Acknowledgements

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The NMR spectroscopy and mass spectrometry services at the University of Oxford have collectively done a huge amount of work in collecting experimental data for this thesis, so an appropriately huge thank you to them.

Finally, endless thanks and gratitude to Alex for putting up with my whinging. I know there has sometimes been a lot of it, so thank you for your bottomless patience.

Contents

List of Abbreviations

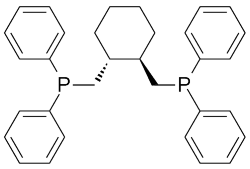
Å	Ångstrom
μW	microwave
Ac	acyl
acac	acetylacetonate
Ar	aryl
$[BAr_4^F]^-$	$[B(3,5\text{-}CF_{32}C_6H_3)_4]^-$
Bn	benzyl
Bu	butyl
cat	catalytic
cod	cyclooctadiene
coe	cyclooctene
Cy	cyclohexyl
dba	dibenzylideneacetone
DCE	dichloroethane
DCM	dichloromethane
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
E	entgegen

ee	enantiomeric excess
equiv.	equivalents
ESI	electrospary ionization
Et	ethyl
FI	field ionization
FT	fourier transform
HA	hydroacylation
h	hour(s)
HRMS	high resolution mass spectrometry
Hydrog.	hydrogenation
*i*Pr	*iso*-propyl
IR	infra-red
J	coupling constant J in Hz
M	molar, moles per litre
Me	methyl
min	minute(s)
mmol	millimole(s)
mol	mole(s)
MS	mass spectrometry
MS	molecular sieves
MTM	methylthiomethyl
MW	molecular weight
m/z	mass to charge ratio
nbd	norbornadiene
*n*Bu	*normal*-butyl
*n*Hex	*normal*-hexyl
NMP	*N*-methyl-2-pyrrolidinone

NMR	nuclear magnetic resonance
PC	propylene carbonate
Ph	phenyl
PPA	polyphosphoric acid
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
p-TSA	*para*-toluene sulfonic acid
quant.	quantitative
rt	room temperature
TBAB	tetrabutylammonium bromide
t-Bu	*tert*-butyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	trimethylsilyl
X	generic halide
Z	zusammen

Ligand list

DIPMC



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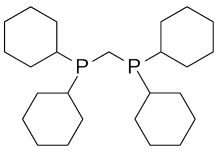

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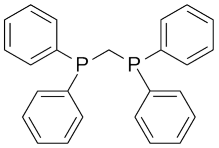

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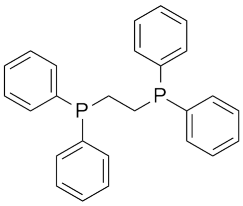

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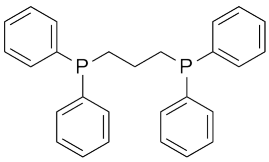

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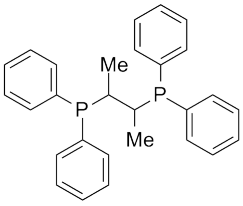

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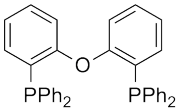

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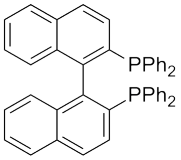

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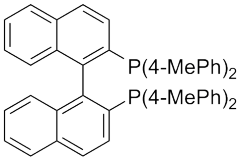

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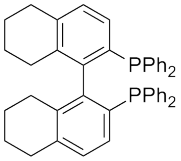

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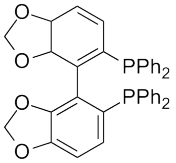

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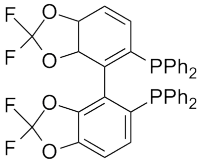

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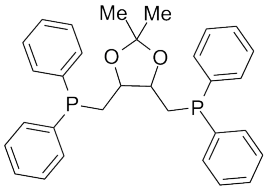

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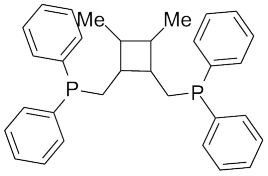

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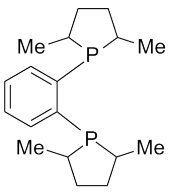

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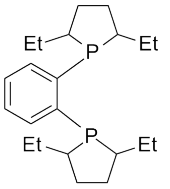

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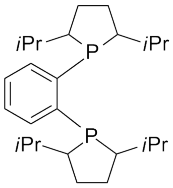

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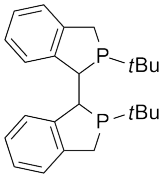

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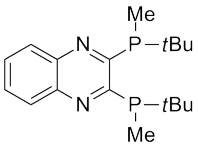

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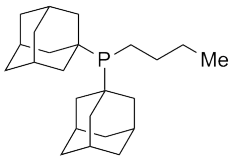

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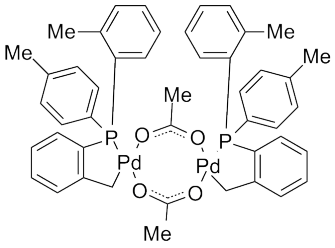

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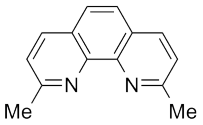
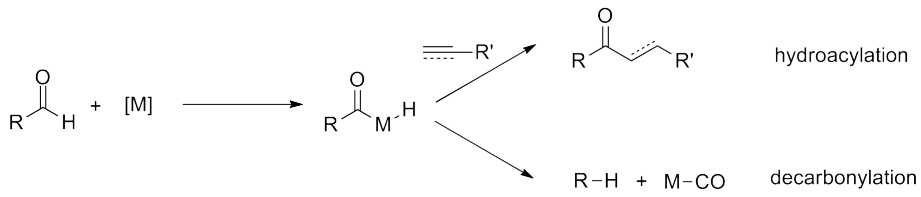


Chapter 1

Introduction

Hydroacylation reactions involve the addition of an acyl unit and a hydrogen atom across an unsaturated system - typically an alkene, an alkyne or a carbonyl group. Hydroacylation is conceptually similar to the hydroformylation of alkenes, but rather than the addition of carbon monoxide and hydrogen, an aldehyde unit is added across an unsaturated substrate in an atom-economic manner (Scheme 1.1)



Scheme 1.1. General outline of hydroacylation and decarbonylation processes

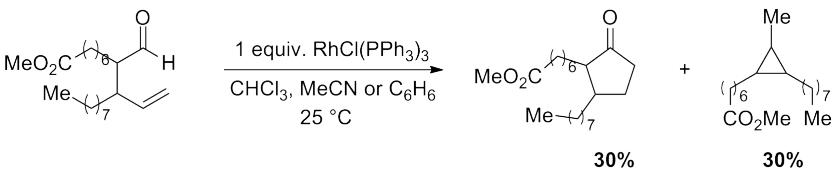
Metal-catalysed hydroacylation reactions have their origins in decarbonylation reactions, where initially stoichiometric[1] and, latterly, catalytic[2–6] amounts of a metal insert into an aldehyde C-H bond followed by reductive elimination to form decarbonylated product and a metal carbonyl. Competitive decarbonylation pathways remain an obstacle to all hydroacylation reactions, although various strategies have been developed to suppress or overcome this undesired side-reaction, which will be discussed in greater detail later. The goal of this chapter is to provide an overview of

the types of catalysts which have been employed in hydroacylation processes to date, rather than to provide an exhaustive list of all metal-catalysed hydroacylation systems which have thus far been published. A recent review of the area has been written by Willis which covers the field in detail.[7] Carbonyl hydroacylation processes will not be included. Additionally, selected relevant examples of tandem catalytic processes, wherein the same catalyst system facilitates two mechanistically distinct processes, will be discussed.

1.1 Hydroacylation catalysts

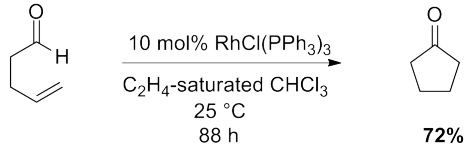
1.1.1 Wilkinson's catalyst

The first reports of hydroacylation reactions were reported with Wilkinson's catalyst (chlorotris(triphenylphosphine)rhodium(I), $RhCl(PPh_3)_3$)[8] and concerned the intramolecular cyclisation of pentenals. These intramolecular cyclisations represent a large proportion of (particularly early) precedented examples of hydroacylation, and Wilkinson's catalyst and modifications thereof feature extensively in these early examples. Sakai reported the hydroacylation of 4-enals with stoichiometric Wilkinson's catalyst,[9] resulting in approximately equimolar amounts of hydroacylation product and cyclopentane resulting from the decarbonylation pathway (Scheme 1.2). Sakai later applied similar methodology to the stereospecific synthesis of *cis* 3,4-disubstituted cyclopentanones from single stereoisomers of starting products. Using 30% of Wilkinson's catalyst, the desired products were isolated in 49-88% yield.[10]



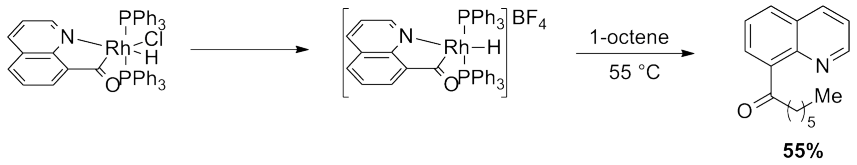
Scheme 1.2. The first reported example of rhodium-catalysed hydroacylation

The process was made sub-stoichiometric in Wilkinson's catalyst in the work of Miller, who employed ethylene-saturated chloroform to coordinatively saturate the metal center and thus suppress decarbonylation. In doing so, he demonstrated that 4-pentenal could be cyclised in 72% yield with 10 mol% of Wilkinson's catalyst (Scheme 1.3).[11] The first hints of the possibility of rhodium-catalysed intermolecular hydroacylation reactions were revealed, with the isolation of small amounts of the products of intermolecular hydroacylation between 4-pentenal and ethylene.



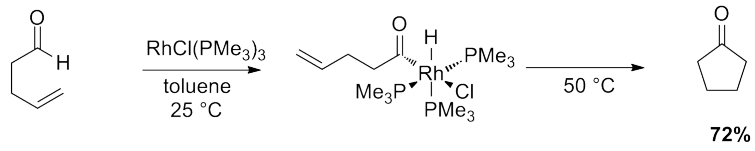
Scheme 1.3. The use by Miller of ethylene-saturated solvent to suppress decarbonylation and permit the use of catalytic amounts of Wilkinson's catalyst in hydroacylation

Suggs employed Wilkinson's catalyst in the first example of heteroatom chelation to stabilise acylrhodium intermediates,[12] a strategy which would later be used to greatly expand the scope of intermolecular rhodium-catalysed hydroacylation. The addition of Wilkinson's catalyst to one equivalent of 8-quinolinecarboxaldehyde gave a heteroatom-stabilised acylrhodium hydride in 95% isolated yield, which was transformed into a coordinatively unsaturated species by treatment with $AgBF_4$. This species reacted with excess octene in THF at 50 °C to furnish the intermolecular hydroacylation product in 55% yield Scheme 1.4. A related protocol was developed which used a *ortho*-diphenylphosphino group to stabilise the acylrhodium intermediate, again using Wilkinson's catalyst.[13]



Scheme 1.4. Suggs' use of quinolinecarboxaldehyde to faciliate a chelation-controlled intermolecular hydroacylation

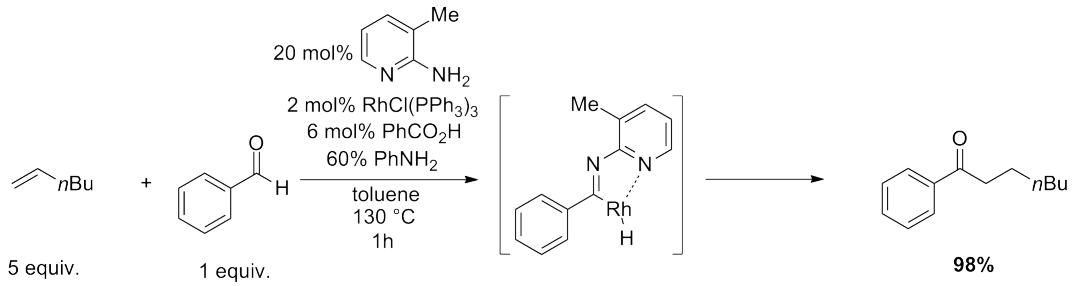
A modification of Wilkinson's catalyst whereby the PPh_3 groups were replaced with PMe_3 was used by Milstein to effect the first catalytic example of hydroacylation which was not dependent on an external source of chelation for stabilisation, albeit with only 3 turnovers.[14] The author stated that the catalysis was faciliated by the slow dissociation of the PMe_3 ligands from the rhodium center, resulting in a more stable catalytic intermediate which was less prone to decarbonylation.[15]



Scheme 1.5. Milstein's use of PMe_3-modified Wilkinson's catalyst to construct a stable hydroacylation intermediate

In an extension of an approach originally developed by Suggs as an expansion on his previously reported quinolinecarboxaldehyde work,[16] Jun has published extensively on the use of 2-amino-3-picoline as a removable *in situ* chelating group for intermolecular hydroacylation of aldehydes with alkenes and alkynes; almost all of these reactions were conducted with Wilkinson's catalyst.[17–26] The catalyst system utilises benzoic acid and aniline to promote the condensation of 2-amino-3-picoline with the aldehyde substrate, to create an imine intermediate with a chelating nitrogen atom to stabilise the required acylrhodium intermediate. This intermediate undergoes hydroiminoacylation followed by hydrolysis of the resultant imine to furnish the desired ketone product (one representative example is shown in Scheme 1.6). This method-

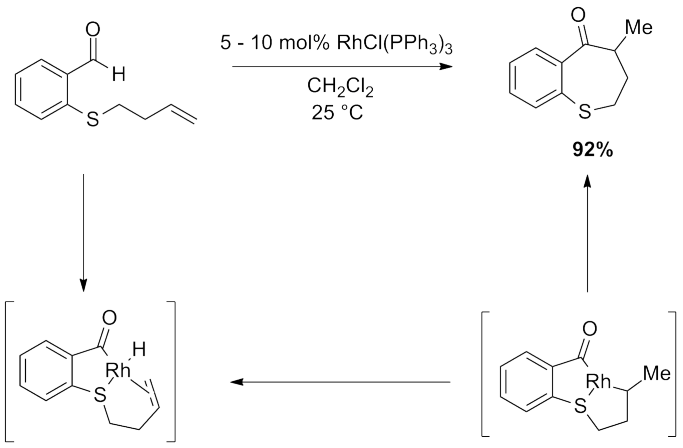
ology has been applied to the synthesis of 1,4-dicarbonyls by Willis,[27] and has been used in a number of other synthetic applications.[23,28–30] Several review articles which cover this area have been published.[31–35]



Scheme 1.6. An example of Jun's picolylamine chelation-assisted intermolecular hydroacylation chemistry

Jun's initial publications with this system were disclosed in 1995, at which point the Bosnich-type cationic *bis*-phosphine catalysts were well-established as generally more reactive in hydroacylation processes (see Section 1.1.3). Bo and Castillón conducted computational and ^{1}H and ^{31}P NMR spectroscopy studies to establish why the neutral Wilkinson's complex resulted in higher conversions in Jun's picolylamine systems than cationic species.[36] While the net reaction in this system is a hydroacylation, the rhodium-catalysed portion proceeds through oxidative addition of rhodium into the C-H bond of an *imine* rather than an aldehyde, and hence the metal-catalysed reaction is formally a hydroiminoacylation. Their investigations showed that the formation of the aminoacylrhodium intermediate *via* oxidative addition of rhodium into the imine C-H bond was endothermic and hence energetically disfavoured when a cationic rhodium species was employed, thus favouring the reverse reaction and resulting in low conversions to the desired product. In contrast, the oxidative addition was favoured when neutral Wilkinson's complex was employed, and hence it is this catalyst which produces the higher conversions for these reactions.

A further example of a chelation-assisted approach to hydroacylation which utilises Wilkinson's catalyst is provided by Bendorf, who exploited sulfur-chelation to achieve



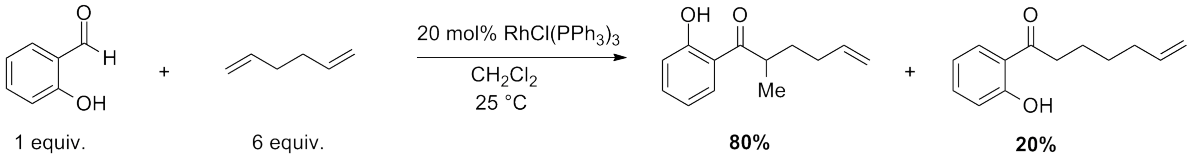
Scheme 1.7. Bendorf's use of sulfur-chelation to achieve the synthesis of medium-sized rings using intramolecular hydroacylation

a rare example of medium-ring synthesis by intramolecular hydroacylation.[37] Using 5-10 mol% of Wilkinson's catalyst, seven- and eight-membered rings were synthesised from alkene- or alkyne-containing starting materials, *via* a chelation-stabilised intermediate (Scheme 1.7). Control experiments showed that the sulfur chelation was necessary for the reaction to proceed, as analagous substrates which replaced sulfur with oxygen or carbon did not form products.

An earlier example of Wilkinson's catalyst in a six-membered ring formation (which is unusual due to the tendency for even hexenals to produce cyclopentanones if such a pathway is available)[38] was reported by Gable,[39] who employed carbohydrate-containing substrates. The authors postulated that the six-membered ring was formed in preference to a five-membered ring due to the resulting ring strain in what would be a 5,5,5-tricyclic product. Due to the types of substrate employed, this did not constitute a general approach to larger than 5-membered ring sizes.

In another example of a chelation-assisted approach to hydroacylation, Suemune used 20 mol% Wilkinson's catalyst to facilitate the reaction between salicaldehydes and 1,4- or 1,5-dienes in good yields under mild conditions.[40] The authors termed this a "double-chelation-assisted" approach, due to the presence of coordinating groups on

both the salicaldehydes and dienes employed. While good to excellent conversions were observed, the products were often obtained as a mixture of linear and branched isomers (Scheme 1.8). In a related process, Tanaka and Suemune used Wilkinson's catalyst in the intermolecular hydroacylation of salicaldehyde with norbornene and norbornadiene. They witnessed an *endo* to *exo* selectivity switch on changing substrate from norbornene to norbornadiene, which they attributed to the same "double-chelation" as described above.



Scheme 1.8. Suemune's "double-chelation-assisted" intemolecular hydroacylation of salicaldehydes

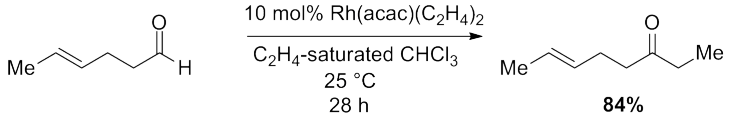
1.1.2 Neutral rhodium diene complexes

A few examples of the use of neutral rhodium diene complexes in hydroacylation have been published, although they are less commonly seen than either Wilkinson's catalyst or cationic rhodium diene species (see Section 1.1.3). The earliest published example of neutral rhodium diene complexes in hydroacylation is provided by Larock, who found that $[Rh(coe)Cl]_2$ with various monodentate triarylphosphine ligands was more effective than Wilkinson's catalyst for the synthesis of cyclopentanones from 4-enals.[41] These catalyst systems could not be applied to the synthesis of larger ring systems.

Sakai reported the first asymmetric cyclisation of 4-pentenals with 25 mol% of neutral $[Rh(DIPMC)_2]Cl$ (DIPMC = *trans*-1,2-bis[(diphenylphosphino)methyl]cyclohexane),[42,43] but this system was superceded by Bosnich's use of $[Rh(BINAP)]ClO_4$ for the same transformation (see Section 1.1.3).

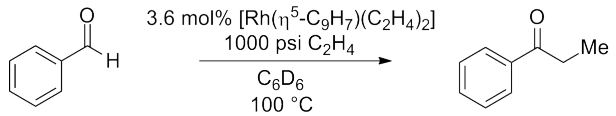
In Miller's work on the cyclisation of 4-pentenals using Wilkinson's complex,[11]

he found that changing the catalyst to [Rh(acac)(C_2H_4)$_2$] resulted in the formation of some intermolecular hydroacylation products, with the ethylene which the solvent had been saturated with to suppress decarbonylation acting as the unsaturated component in the hydroacylation reaction. While pentenal produced only 6% of the desired intermolecular hydroacylation product (plus 39% of the double-bond isomerised hydroacylation product), hexenal was a much better substrate under these conditions, with the intermolecular hydroacylation product being isolated in 84% yield after 28 hours at room temperature (Scheme 1.9). It is notable that unsaturated aldehydes were required as substrates for the reaction to proceed, which implies that intramolecular chelation from the aldehyde substrate is important.



Scheme 1.9. Miller's use of [Rh(acac)(C_2H_4)$_2$] in an early example of intermolecular hydroacylation

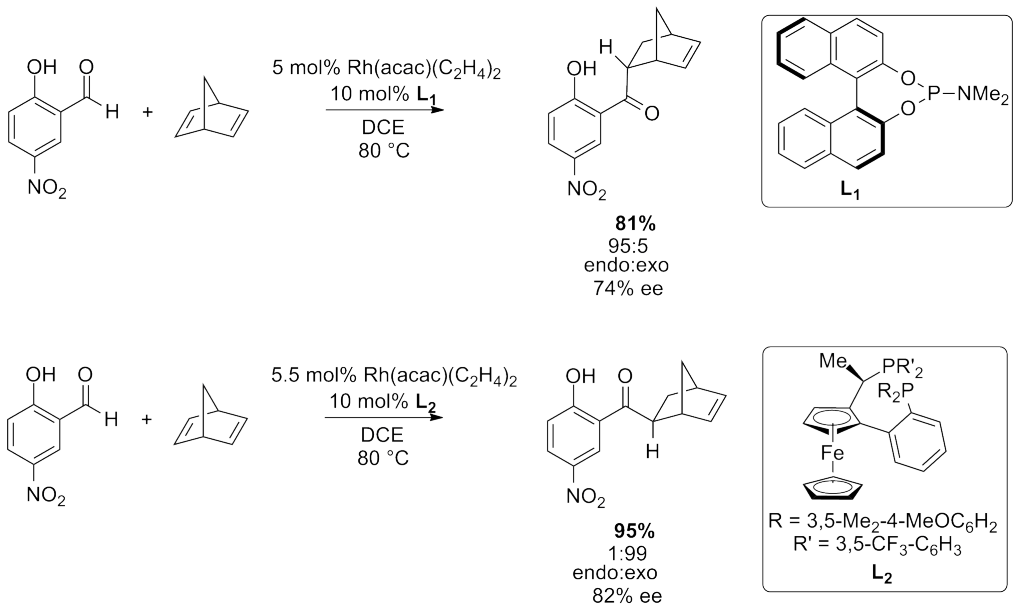
Milstein reported the intermolecular hydroacylation of benzaldehyde and ethylene using a neutral indenyl rhodium complex, [Rh(η^5-C_9H_7)(C_2H_4)$_2$], under 1000 psi of ethylene at 25 °C, with turnover frequencies of around 4 h^{-1} (Scheme 1.10).[44] However, the reaction was much slower when anything other than the model system was employed.



Scheme 1.10. Milstein's indenyl rhodium complex as used for intermolecular alkene hydroacylation

Bolm utilised [Rh(acac)(C_2H_4)$_2$] in combination with chiral mono- or bidentate phosphine ligands for the enantioselective intermolecular hydroacylation of salicalde-

hydes and norbornadiene.[45] He found that bidentate phosphines resulted in the selective formation of the *exo* product isomer, which he states is due to the bidentate ligand forcing norbornadiene to bind to rhodium in a monodentate fashion. Conversely, monodentate ligands were selective for the *endo* product (Scheme 1.11).

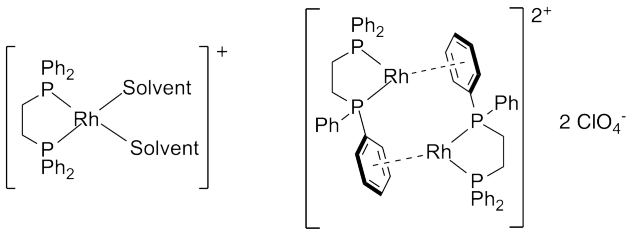


Scheme 1.11. Bolm's use of $[Rh(acac)(C_2H_4)_2]$ with mono- or bidentate phosphine ligands for the enantioselective intermolecular hydroacylation of salicaldehydes with norbornadiene

1.1.3 Cationic rhodium *bis*-phosphine complexes

The discovery by Bosnich of coordinatively unsaturated [Rh(*bis*-phosphine)]X (where X = ClO_4, BF_4, OTf or BAr^f) complexes as active hydroacylation catalysts (the complexes themselves had previously been described by Shrock and Osborn)[46] was a large step forward for hydroacylation, and ultimately led to the widespread use of these types of complexes in a variety of hydroacylation systems.[47,48] Through studying the $[Rh(dppe)]ClO_4$ example, Bosnich found that the precise catalytic species depended on the solvent in which the pre-catalyst was dissolved; in the solid state or in non-

coordinating solvents, the predominant species is an aryl-bridged dimer, whereas in coordinating solvents a solvated monomer predominates (Scheme 1.12). From a practical perspective, either of these [Rh(dppe)]ClO_4 complexes are accessible through hydrogenation of a solution of [Rh(dppe)(nbd)]ClO_4, which is easily prepared from $[Rh(cod)Cl]_2$, dppe and $AgClO_4$.



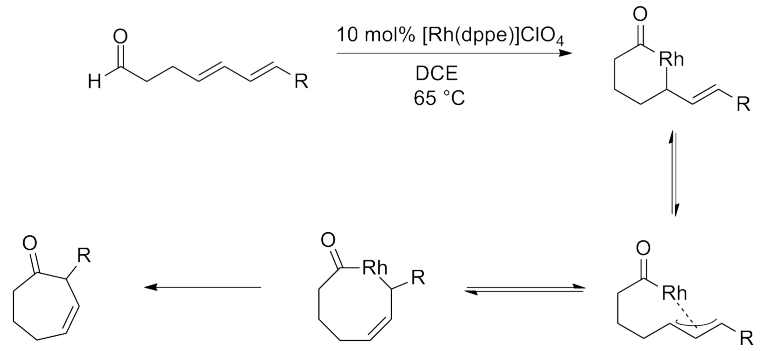
Scheme 1.12. Catalytically-relevant species when [Rh(dppe)]ClO_4 is used in hydroacylation

Bosnich also reported the use of isolated $[Rh(dppe)_2](ClO_4)_2$ dimer. The use of either method produced the same results in catalysis, indicating that the reaction pathway is not altered depending on the pre-catalyst used. Using this catalyst system, Bosnich demonstrated the intramolecular cyclisation of 1-, 2-, 3-, 4- and 5-substituted pentenals with as little as 1 mol% catalyst at 20 °C in CD_3NO_2. The reactions have sufficiently high TOF for hydroacylation that no significant amounts of decarbonylated products were observed, although with some substrates products resulting from double-bond isomerisation processes were detected.

Cationic rhodium *bis*-phosphine complexes for the synthesis of larger ring systems

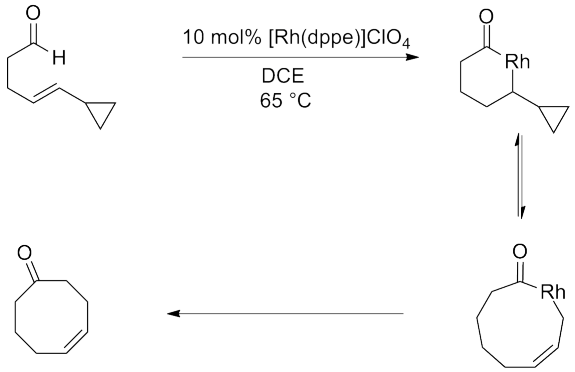
As well as cyclopentanone synthesis, the Bosnich-type catalysts were also used for the construction of 7- and 8-membered rings. Mori used 10 mol% of [Rh(dppe)]ClO_4 in dichloroethane at 65 °C to produce cycloheptenones from dienals in reasonable yields (around 45-70%, depending on the particular substrate employed) (Scheme 1.13). The

yields were diminished by competing formation of the relevant cyclopentanone and its double-bond isomerised product.[49]



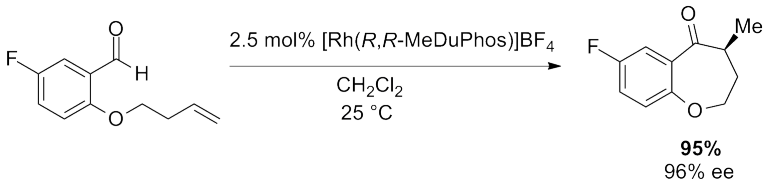
Scheme 1.13. Mori's cycloheptenone synthesis *via* the hydroacylation of dienals

Shair used the cationic complexes [Rh(dppe)]ClO_4 and [Rh(dppe)]OTf to transform cyclopropane-containing enals into cyclooctenones.[50] Using 20 mol% of catalyst and an ethylene atmosphere, the desired medium-ring products were obtained in reasonable yields (54-65%) (Scheme 1.14). Wilkinson's catalyst was ineffective with these substrates. Related procedures using a similar approach to 7- and 8- membered rings were later reported by Furstner and Aissa.[51,52] Notably, the latest of these described the use of substrates incorportating cyclobutane- and azetidine-containing substrates and did not require the use of ethylene-saturated solvents when a [Rh(BINAP)]BF_4 catalyst (formed *in situ* from [Rh(nbd)$_2$)]BF_4 and BINAP) was used.



Scheme 1.14. Shair's synthesis of cyclooctenones *via* the hydroacylation of cyclopropane-containing substrates

Dong reported the use of several [Rh(*bis*-phosphine*)]BF_4[†] catalysts in an asymmetric variation on Bendorf's[37] 7- and 8-membered ketone synthesis *via* intramolecular hydroacylation.[53] Thioethers and sulfoxides were used as the directing groups for this process and, in contrast to the Bendorf examples, ethers were also tolerated (Scheme 1.15). The stereocenter being formed could be either α- or β to the product ketone.



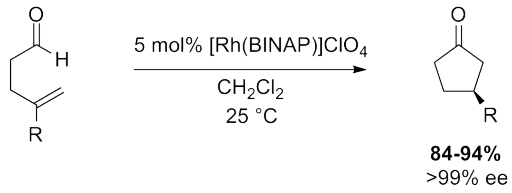
Scheme 1.15. Dong's asymmetric medium-ring ketone synthesis *via* intramolecular hydroacylation using chiral rhodium *bis*-phosphine complexes

Cationic rhodium *bis*-phosphine* complexes in asymmetric intramolecular processes

While some early reports of asymmetric cyclopentanone syntheses from racemic or achiral starting materials *via* rhodium-catalysed intramolecular hydroacylation using neutral rhodium species exist, they are generally low-yielding or poorly selective,[54,55] or require high catalyst loadings for the reactions to proceed.[43] The use of cationic rhodium complexes containing chiral *bis*-phosphine ligands, however, permitted the synthesis of asymmetric cyclopentanones in good yields, excellent enantioselectivity and using low catalyst loadings. For example, Sakai reported the use of [Rh(BINAP)]ClO_4 catalysts in 5 mol% loading at room temperature to furnish either enantiomer of enantioenriched cyclopentanones from 4-substituted pentenals in high yields and excellent enantioselectivities (Scheme 1.16).[56]

Separately, Bosnich reported the asymmetric synthesis of cyclopentanones using [Rh(BINAP)]ClO_4, as well as several other complexes containing different chiral *bis*-

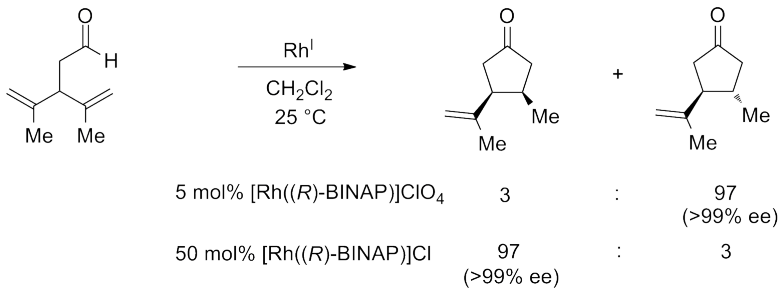
[†]where "*bis*-phosphine*" denotes a chiral phosphine ligand



Scheme 1.16. Sakai's use of $[Rh(BINAP)]ClO_4$ in the asymmetric synthesis of cyclopentanones from racemic starting materials

phosphine ligands; the optimum ligand depended on the type of substitutent present in the substrates, but examples which utilised BINAP, MeDuPhos and chiraphos were all described.[57–59] The work was notable for its excellent functional group tolerance, as well as >95% conversion and 94-99% ee for nearly all examples. Separately, a kinetic resolution process using the same cationic catalyst has been reported by Bosnich.[60]

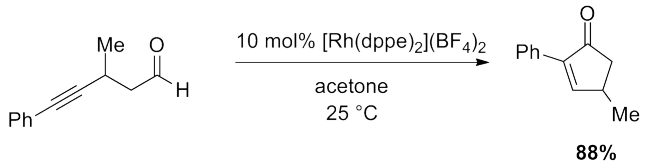
A particularly interesting example of this type of chemistry is provided by Sakai amd Suemune, who used $[Rh(BINAP)]ClO_4$ to effect an enantioselective desymmetrisation in substrates which would produce products with two stereocenters.[61,62] The cationic complex could be used in 5 mol% and was generally *trans* selective with 96:4 dr's or above and >95% ee's, with reaction times of 1 to 4 hours. In contrast, the analogous neutral complex [Rh(BINAP)]Cl required 50 mol% catalyst loading and reaction times of 72 hours to achieve good conversions - but to the *cis* products, in 97:3 dr and similarly excellent ee (Scheme 1.17). As such, all four stereoisomers of the products were accessible by using the appropriate catalyst. A related kinetic resolution protocol has been published by the same authors.[63]



Scheme 1.17. Sakai and Suemune's enantioselective desymmetrisation *via* an intramolecular hydroacylation

For a comprehensive overview of asymmetric alkene hydroacylation reactions and their applications, see the recent hydroacylation review by Willis.[7]

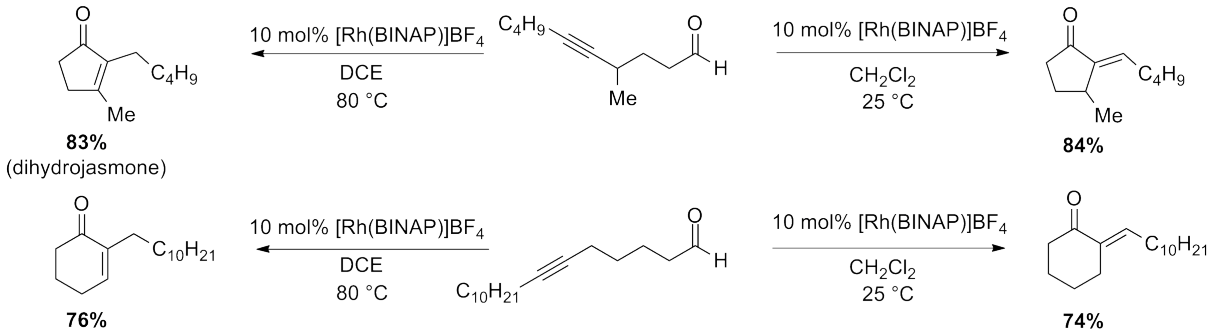
The Fu and Tanaka groups have published several accounts of the use of cationic rhodium *bis*-phosphine complexes in intramolecular alkyne hydroacylation processes. Fu disclosed the synthesis of cyclopentenones using 10 mol% $[Rh(dppe)_2](BF_4)_2$ in acetone at room temperature - a reaction which must proceed *via* the *trans* addition of the intermediate rhodium hydride across the alkyne (Scheme 1.18).[64,65]



Scheme 1.18. Fu's cyclopentenone synthesis *via* intramolecular alkyne hydroacylation

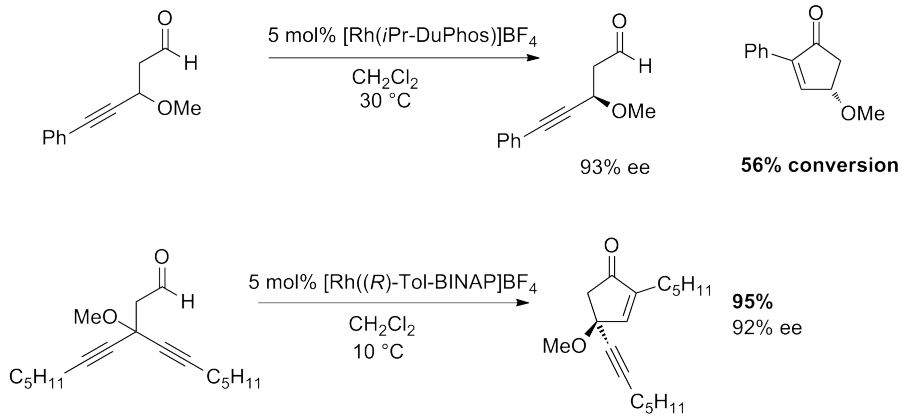
Complementary reactivity has been described by Tanaka, who used $[Rh(BINAP)]BF_4$ to access cyclopentenones and cyclohexenones containing exocyclic double bounds.[66] Cycloheptenones were inaccessible using this methodolgy, and the use of the Fu catalyst system ($[Rh(dppe)_2](BF_4)_2$ in acetone) resulted in a complex mixture. Running the reactions at 80 °C under otherwise identical conditions resulted in a rhodium-catalysed double-bond isomerisation to occur, producing the analagous endocyclic product isomers (Scheme 1.19). Interestingly, the methodology could not be extended

to the synthesis of nitrogen- or oxygen-containing heterocycles, as a reductive dimerisation/cyclisation process occurs preferentially in those substrates.[67]



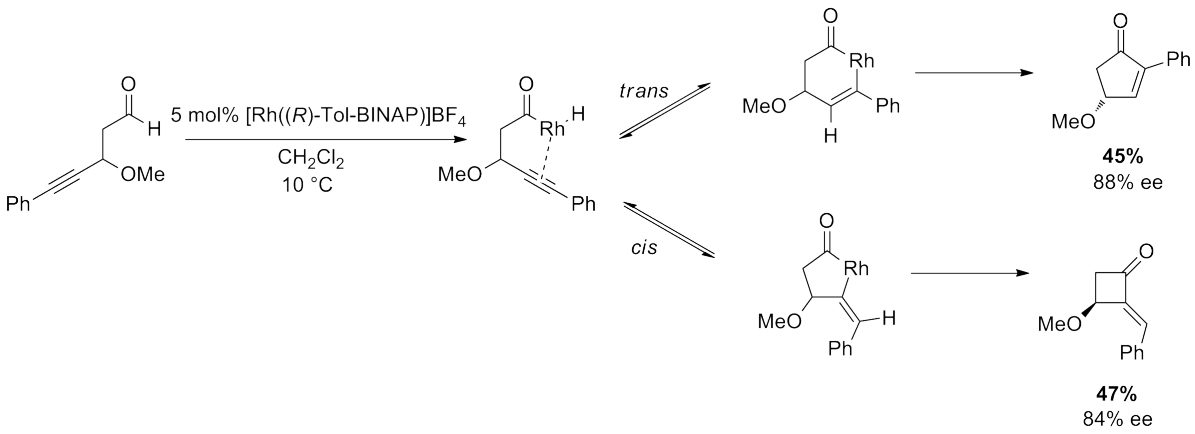
Scheme 1.19. Tanaka's intramolecular alkyne hydroacylation procedure to access exo- or endocyclic alkene-contaning cyclopentenones and cyclohexenones

As alkyne hydroacylation reactions do not innately produce an sp^3 center, the expansion of intramolecular alkyne hydroacylation reactions to encompass asymmetric processes must instead be desymmetrisations or kinetic resolutions revolving around existing stereocenters in the racemic starting materials employed. Fu has published a kinetic resolution to produce cyclopentenones containing tertiary and quaternary centers using cationic rhodium *bis*-phosphine complexes as intramolecular alkyne hydroacylation catalysts.[68] The optimum catalyst for the process depended on the substrate; those containing tertiary centers underwent the most selective reactions with [Rh(*i*PrDuPhos)]BF_4, whereas substrates containing a quaternary center were best cyclised with [Rh(*p*-Tol-BINAP)]BF_4 (Scheme 1.20). The presence of a methoxy group in the starting materials was crucial for high conversions to be attained (a 97% yield of the desired product was obtained in a methoxy-containing substrate, compared to 31% for the analagous methyl-containing compound), which the authors believe is due to the oxygen coordinating to the rhodium center and thus assisting the reaction. A desymmetrisation of prochiral 4-alkynals was also reported, which - similarly to the kinetic resolution of substrates containing quaternary stereocenters - utilised the [Rh(*p*-Tol-BINAP)]BF_4 catalyst.



Scheme 1.20. Fu's kinetic resolution and desymmetrisation reactions using [Rh(*bis*-phosphine*)]BF_4 catalysts

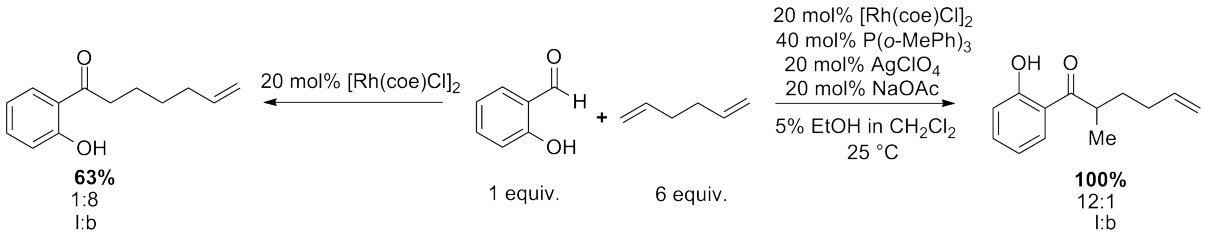
The same group disclosed a related parallel kinetic resolution, whereby a racemic methoxy-containing 4-alkynal underwent intramolecular hydroacylation catalysed by [Rh(*p*-Tol-BINAP)]BF_4 to produce an enantioenriched cyclobutanone and a cyclopentanone, both in good ee.[69] The two products result from *cis* and *trans* addition, respectively, of the intermediate rhodium hydride across the alkyne (Scheme 1.21)



Scheme 1.21. Fu's parallel kinetic resolution of methoxy-containing 4-alkynals, catalysed by [Rh(*p*-Tol-BINAP]BF_4

Cationic rhodium *bis*-phosphine complexes as catalysts for intermolecular hydroacylation reactions

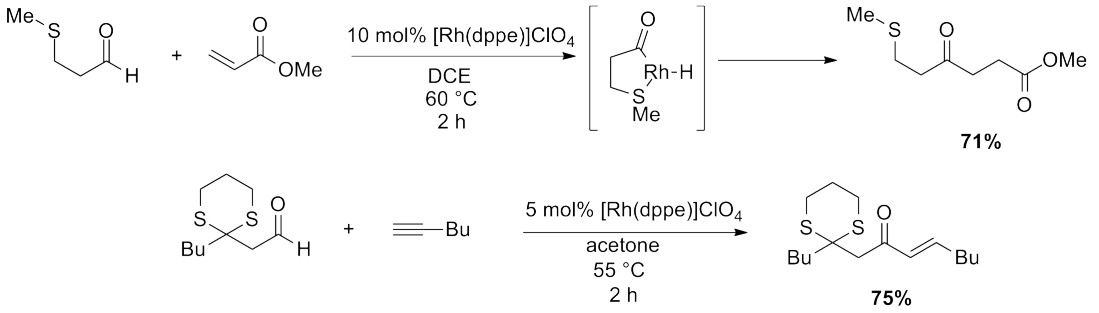
Suemune's "double-chelation" approach to intermolecular hydroacylation of salicaldehydes and dienes using Wilkinson's catalyst has been mentioned previously;[40] a modification of this procedure utilised cationic complexes (formed *in situ* by the addition of $AgClO_4$ to $[Rh(coe)Cl]_2$ and P(*o*-MePh)$_3$) for the branched-selective intermolecular hydroacylation of the above substrates.[70] The complementary linear-selective process was achieved by using neutral $[Rh(coe)Cl]_2$ (Scheme 1.22). Neutral complexes were also used by Miura to expand the methodology to encompass alkyne substrates.[71,72]



Scheme 1.22. Suemune's use of a cationic rhodium/phosphine complex to switch between linear and branched selective intermolecular hydroacylation processes

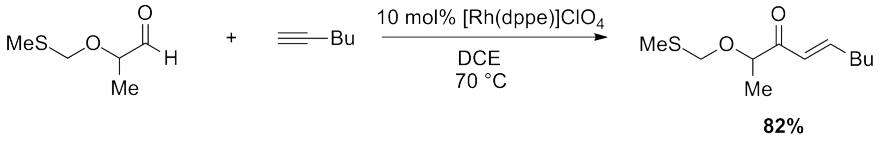
The Willis group has made extensive use of Bosnich-type cationic rhodium *bis*-phosphine complexes in the intermolecular hydroacylation of chelating β-sulfur-containing aldehydes with alkenes, alkynes and allenes. Using 10 mol% of the Bosnich catalyst, $[Rh(dppe)]ClO_4$, 3-(methylthio)propionaldehyde and electron-deficient alkenes gave the intermolecular hydroacylation products in good yields (Scheme 1.23).[73] The methodology was later extended to include dithiane-containing aldehydes as the requisite chelating substrate, significantly expanding the synthetic utility of a sulfur-chelation approach.[74,75] Terminal and internal alkynes could also be tolerated as the unsaturated component in the reaction, to form α,β-unsaturated enones, as could allenes,[76] leading to the synthesis of β,γ-enones.

Recently, the range of aldehydes which are competent in this intermolecular pro-



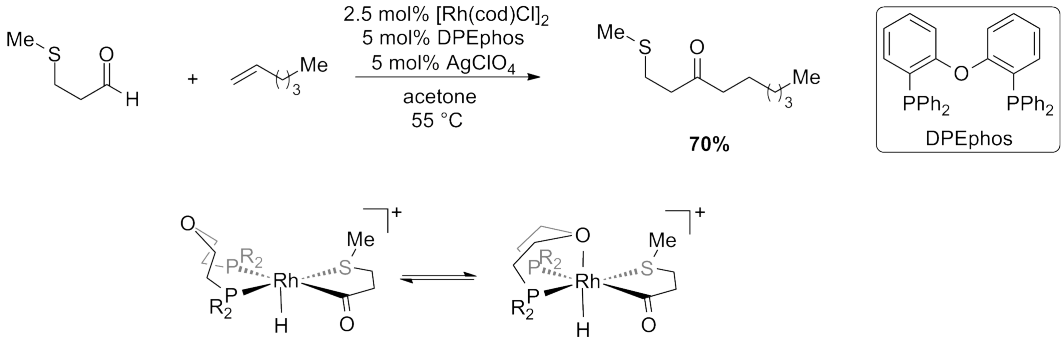
Scheme 1.23. Willis' use of [Rh(dppe)]ClO_4 to catalyse the intermolecular hydroacylation of β-sulfur-substituted aldehydes with alkynes and activated alkenes

cess was further expanded to contain methylthiomethyl (MTM) ethers as the chelating moiety, again using the [Rh(dppe)]ClO_4 catalyst (Scheme 1.24) If the sulfur in the MTM group was replaced with oxygen or carbon, the reaction did not proceed, and increasing the distance of the chelating atoms from the aldehyde had similarly deleterious effects.[77] The MTM group could be removed with water or $AgNO_3$ to furnish the free alcohol.



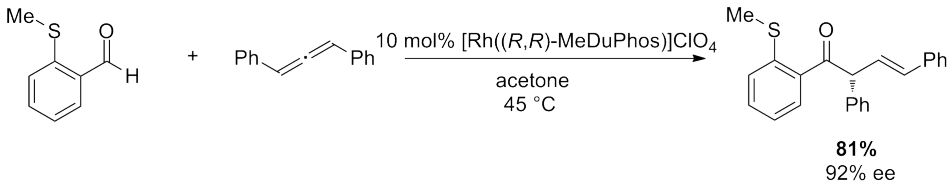
Scheme 1.24. Willis' use of MTM-protected alcohols as substrates in [Rh(dppe)]ClO_4-catalysed intermolecular alkyne hydroacylation

Willis and Weller have also described a "second-generation" catalyst of this type, which uses DPEphos as a ligand which incorporates a hemi-labile oxygen atom to stabilise the crucial acylrhodium hydride intermediate.[78] This catalyst system was reported to have increased activity and better stability, and permitted the use of unactivated alkenes in intermolecular hydroacylation reactions (Scheme 1.25). The active catalytic species could be formed *in situ* by mixing $[Rh(cod)Cl]_2$, DPEphos and $AgClO_4$, and crystal structures were obtained which demonstrated the various coordination modes of the DPEphos ligand.[79]



Scheme 1.25. The second generation DPEphos-containing catalyst system and its use in the hydroacylation of unactivated alkenes

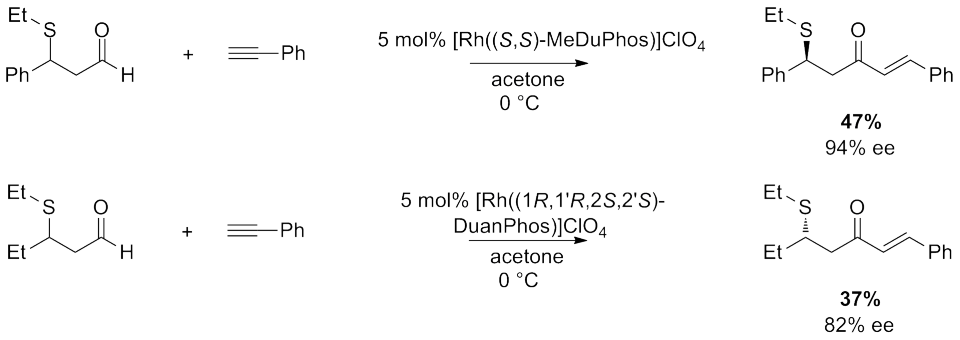
The Willis group has also reported asymmetric examples of their sulfur-chelation-controlled hydroacylation reactions. The first utilises [Rh(MeDuPhos)]ClO_4 to catalyse the hydroacylation of aromatic β-thioaldehydes and racemic 1,3-disubstituted allenes to produce enantioenriched β,γ-enones in high yields and ee's (Scheme 1.26). The authors showed that this process was not a kinetic resolution, but a dynamic kinetic asymmetric transformation in which the allene was racemised during the course of the reaction.[80]



Scheme 1.26. Willis' asymmetric intermolecular hydroacylation of racemic 1,3-disubstited allenes with [Rh(MeDuPhos)]ClO_4

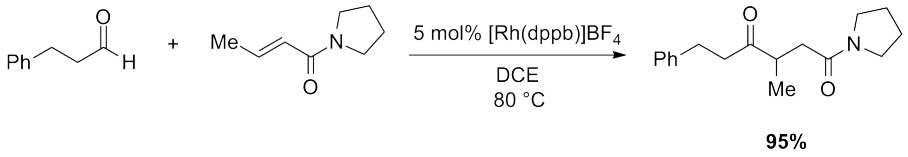
The second asymmetric process reported by the group was the synthesis of chiral α- and β-substited enones *via* the kinetic resolution of racemic aldehydes.[81,82] While [Rh(MeDuPhos)]ClO_4 proved to be the most selective catalyst for the majority of substrates explored, it was found that for β-alkyl aldehydes, greater selectivity was obtained when DuanPhos was used as the ligand (Scheme 1.27).

Tanaka used a modification of the typical Bosnich catalyst, [Rh(dppb)]BF_4, in the



Scheme 1.27. Willis' asymmetric synthesis of α- and β-substited enones *via* a kinetic resolution catalysed by [Rh(MeDuPhos)]ClO_4 and [Rh(DuanPhos)]ClO_4

intermolecular hydroacylation of non-chelating aldehydes and acrylamides, in which the acylrhodium hydride intermediate is presumed to be stabilised by coordination to the acrylamide oxygen and olefin (Scheme 1.28).[83] One example used methyl acrylate rather than an acrylamide, to produce the intermolecular hydroacylation product in 55% yield, but it was necessary to use the methyl acrylate as the solvent (c.f. 1.1 - 2.0 equiv. when acrylamides were employed). An asymmetric variation of the same process, using QuinoxP and DuPhos-type ligands, was also reported.[84]



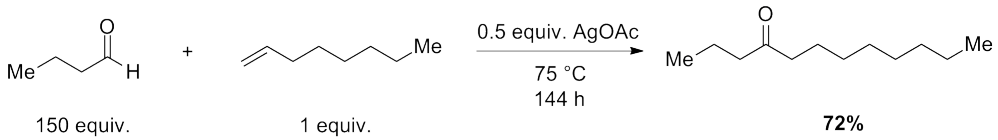
Scheme 1.28. Tanaka's use of [Rh(dppb)]BF_4 to catalyse the intermolecular hydroacylation of non-chelating aldehydes with *N,N*-dialkylacrylamides

1.1.4 Other metals

While the majority of hydroacylation reactions have been reported using rhodium catalysts, a relatively small number of examples exist in which another metal has been used.

In 1977, Sillion reported the silver acetate-promoted addition of an aldehyde across

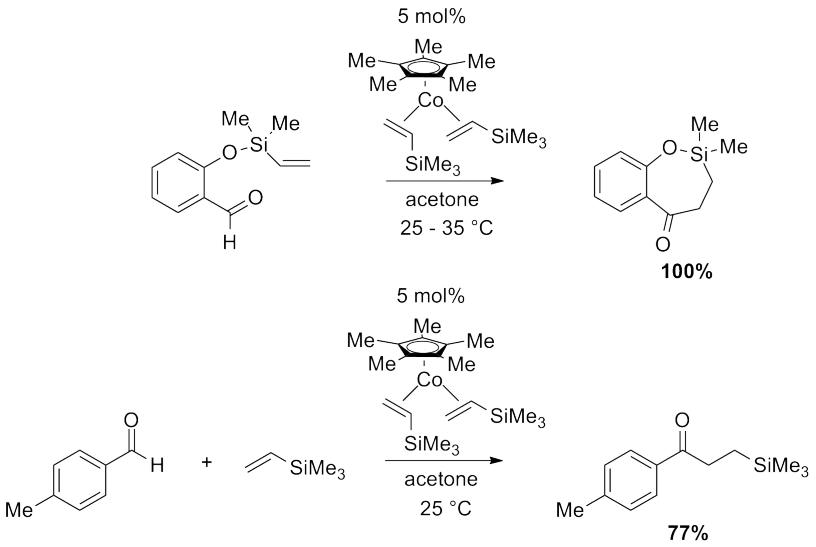
an alkene.[85] While a sub-stoichiometric amount of silver was employed, reaction times of over a week were required to achieve significant amounts of the addition product, as well as 150 equivalents of the aldehyde relative to the olefin. A number of radical or photo-catalyzed processes have been reported, which are synthetically equivalent to hydroacylation processes, albeit mechanistically distinct.[86–89]



Scheme 1.29. Silver-promoted addition of an aldehyde across an olefin

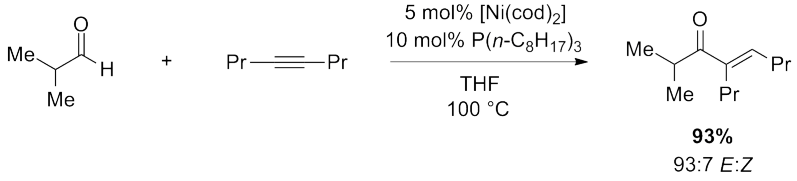
Vinogradov has reported a cobalt-catalysed system for the formation of cyclopentanones *via* intramolecular hydroacylation of 4-pentenal.[90] The authors utilised $Co_2(\mu\text{-}N_2)(PPh_3)_6$ and $Co(dppe)(PPh_3)_2$ complexes, and state that the most likely mechanism proceeds through oxidative addition of a Co(0) species into the aldehyde C-H bond to form an acylcobalt(II) intermediate, in analogy to the equivalent rhodium-catalysed reaction. They also isolated species resulting from solvent-dependent decarbonylation.

Brookhart has reported the use of a cobalt-cyclopentadienyl complex for intra- and limited intermolecular hydroacylations.[91,92] While the intermolecular examples were limited to vinyltrialkylsilanes as substrates, a reasonably broad range of aldehydes was tolerated, and the intramolecular reactions included a rare example of medium-ring formation in intramolecular hydroacylation (Scheme 1.30). Brookhart later published the use of an analogous rhodium complex, wherein one of the cyclopentadienyl methyl groups was replaced with a trifluoromethyl group, and applied this complex to the intermolecular hydroacylation of aromatic aldehydes and electron-rich alkenes.[93]



Scheme 1.30. Brookhart's cobalt catalysis of intra- and intermolecular hydroacylation

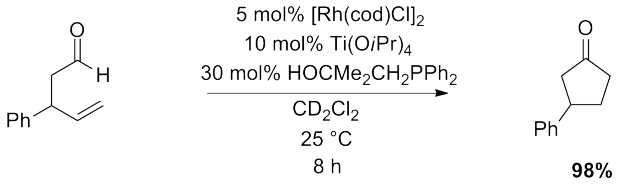
Tsuda and Saegusa reported the Ni(0)-catalysed intermolecular hydroacylation of alkyl aldehydes with symmetrical internal alkynes.[94] When trialkyl monophosphines were used in combination with [Ni(cod)$_2$], good *E*:*Z* selectivity was observed (Scheme 1.31), although the use of non-symmetrical alkynes resulted in poor regioselectivity.



Scheme 1.31. The Ni(0) catalysed intermolecular hydroacylation of alkyl aldehydes and symmetrical internal alkynes

Doyle described the use of a neutral, heterobimetallic system comprising both rhodium and titanium metal centers for the intramolecular hydroacylation of 3-substituted pentenals.[95] While perhaps more of a modification of known rhodium-catalysed processes rather than a discrete non-rhodium hydroacylation catalyst, it is included here as control experiments show that in the absence of titanium, or in an analogue of the postulated catalyst in which the titanium atoms are replaced with carbons, no reac-

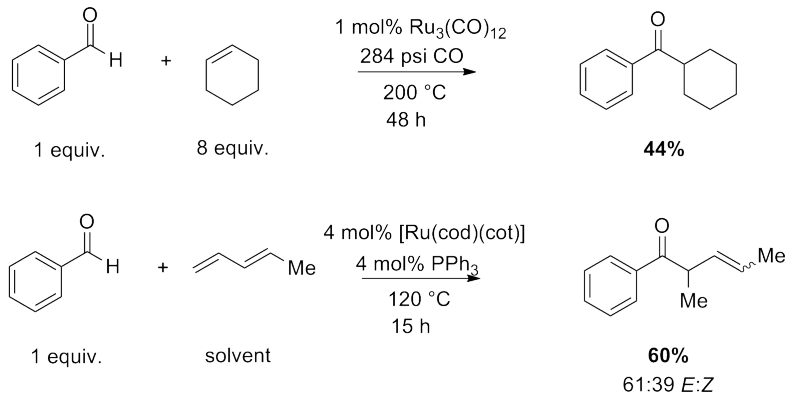
tion occurs. The active catalyst system comprises a 1:1:3 mixture of $[Rh(cod)Cl]_2$, $Ti(O\textit{i}Pr)_4$ and $HOCMe_2CH_2PPh_2$ which - on the basis of ^{31}P NMR spectroscopy evidence - the authors believe forms a monomeric complex *in situ*, although attempts at isolating such a species were unsuccessful. This catalyst was particularly selective in the intramolecular hydroacylation of 3-phenyl-4-pentenal, with no rearrangement or alkene migration products being observed (Scheme 1.32), although it should be noted that such comparisons were made to literature reactions in which 10-fold less catalyst was employed, rather than a direct comparison between the catalysts employed.



Scheme 1.32. Bimetallic Rh/Ti catalyst system for the intramolecular hydroacylation of 3-substituted pentenals

A ruthenium-catalysed intermolecular hydroacylation was reported in 1982,[96] although it was limited by low yields and multiple (mostly aldehyde-derived) byproducts. In 1987 Watanabe published an account of $Ru_3(CO)_{12}$ as an active catalyst for some intermolecular hydroacylations of benzaldehyde derivatives and alkenes in modest (ca. 40-54%) yields.[97,98] The reaction required heating at 200 °C for 48 h, and a high pressure (20 kg/cm^{-2}) of carbon monoxide, albeit with only 1 mol% of catalyst (Scheme 1.33). The authors suggest that the role of the carbon monoxide is to stabilise active $Ru(CO)_x$ species and thus suppress decarbonylation. The reaction did not proceed under similar pressures of argon, or when aliphatic rather than aromatic aldehydes were employed.

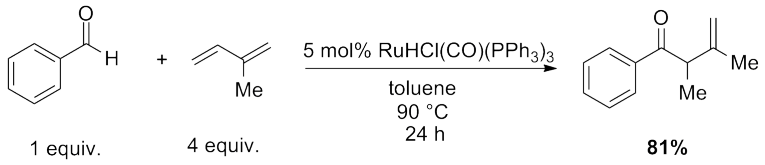
The same group later published a hydroacylation between aromatic or alphatic aldehydes and 1,3-dienes, using a catalyst system comprising an equimolar combination of [Ru(cod)(cot)] and PPh_3.[99] Notably, a carbon monoxide atmosphere was



Scheme 1.33. Watanabe's ruthenium-catalysed intermolecular hydroacylation system

no longer required to suppress decarbonylation, although the reactions were run at 100-120 °C for 15 h under an argon atmosphere, and with the diene substrates as the solvent. Yields were still modest, being in the range of 40-60% (Scheme 1.33). As *trans*-dienes were competent in the system but *cis*-dienes were completely unreactive, the authors suggested the intermediacy of a (η^3-allyl)ruthenium species as being crucial.

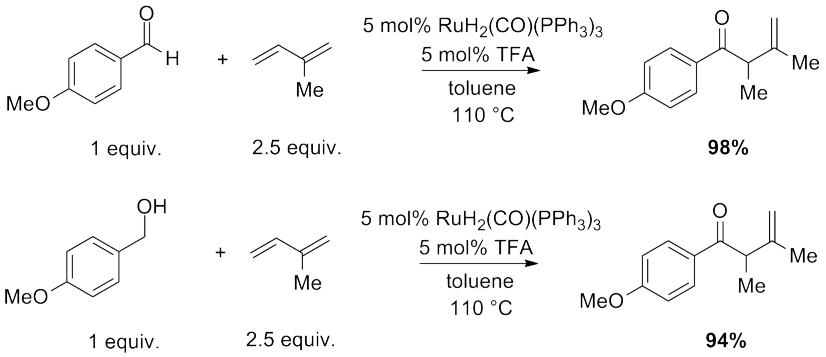
Ryu utilised the ruthenium hydride species $RuHCl(CO)(PPh_3)$ as a more effective catalyst for this transformation,[100] with a wider range of aldehydes (aryl, heteroaryl or alkyl) being tolerated and good yields of β,γ-unsaturated ketones being obtained under milder reaction conditions: 90 °C in toluene for 24 h (Scheme 1.34).



Scheme 1.34. Ryu's ruthenium hydride-catalysed intermolecular hydroacylation of aldehydes and 1,3-dienes

Krische has described a similar process which uses a $RuH_2(CO)(PPh_3)_3$-containing system for the hydroacylation of alkyl, aryl or heteroaryl aldehydes with 1,3-dienes to

give β,γ-unsaturated ketones in excellent yields.[101] In the presence of 5 mol% of this catalyst and the same amount of trifluoroacetic acid at 110 °C in toluene, the branched diene hydroacylation products were isolated in 62-98% yield. An important facet of this work is that either the requisite aldehyde or alcohol could be used under identical conditions to furnish the same formal hydroacylation product, due to the ability of the ruthenium catalyst employed to participate in transfer hydrogenation chemistry (Scheme 1.35).



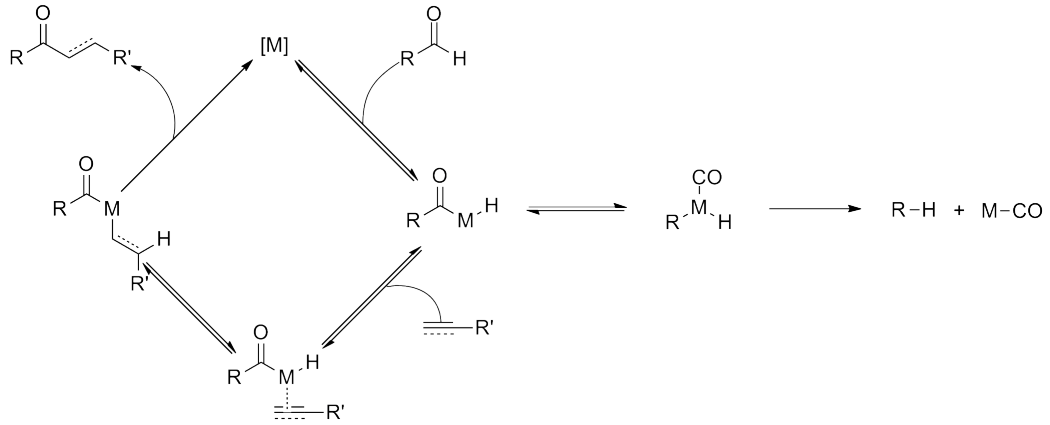
Scheme 1.35. Krische's ruthenium-catalysed coupling of aldehydes or alcohols to 1,3-dienes to product formal hydroacylation products

A notable feature of both the Ryu and Krische chemistry is that the proposed mechanisms for both processes no do not proceed through a ruthenium acyl intermediate, and hence are mechanistically distinct from rhodium-catalysed hydroacylation.

1.2 The mechanism of rhodium-catalysed hydroacylation

The mechanism of rhodium-catalysed hydroacylation has been extensively studied in both intra- and intermolecular systems. Miller used deuterium labelling studies to elucidate the mechanism of intramolecular hydroacylation,[38,102] which were followed up by extensive NMR spectroscopy work by Bosnich.[48] Morehead and Sargent,[103] among

others,[104–107] have conducted computational studies into hydroacylation mechanisms. Weller and Willis conducted mechanistic studies centering around their DPEphos-containing catalyst system,[78,79] and Brookhart undertook extensive mechanistic studies of both his Rh(I) and Co(I) hydroacylation catalysts.[91–93] Presented here is an overview of the generally accepted mechanism; for further detail or nuances of the individual systems, see the individual papers referenced above or the recent review by Willis.[7]



Scheme 1.36. A schematic overview of the generally accepted mechanism of metal-catalysed hydroacylation

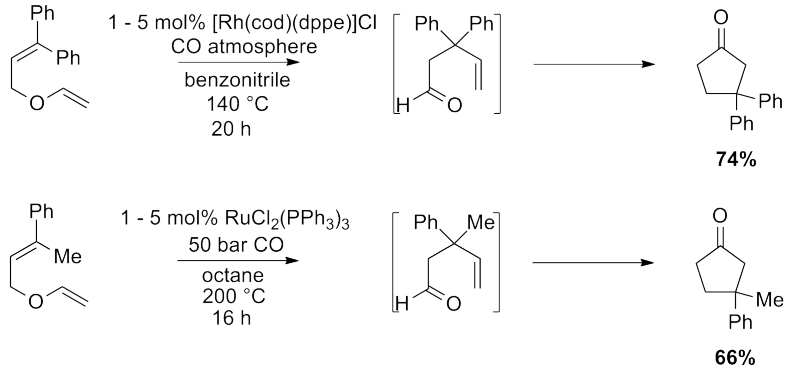
Oxidative addition of a metal into the aldehyde C-H bond results in an acylmetal hydride. Carbonyl deinsertion followed by reductive elimination at this point in the cycle results in the unproductive decarbonylation pathway. Coordination of the unsaturated species to the acylmetal hydride is followed by insertion of the unsaturated species into the metal hydride. Reductive elimination furnishes the hydroacylation product and regenerates the metal catalyst. All steps in the cycle, except for reductive elimination to form the product and the same process in the decarbonylation pathway have been shown to be reversible.

The unproductive decarbonylation pathway is the biggest challenge in the development of any hydroacylation system. Ethylene saturation of solvents and chelation approaches in general suppress decarbonylation by temporarily saturating the metal

center; with no vacant coordination site on the metal center, carbonyl deinsertion cannot occur. A vacant coordination site is required for several steps in the productive catalytic cycle (namely coordination of the unsaturated substrate and the productive reductive elimination required for product formation), and as such designing catalyst systems which favour product formation while suppressing decarbonylation remains non-trivial.

1.3 Tandem catalytic processes involving hydroacylation

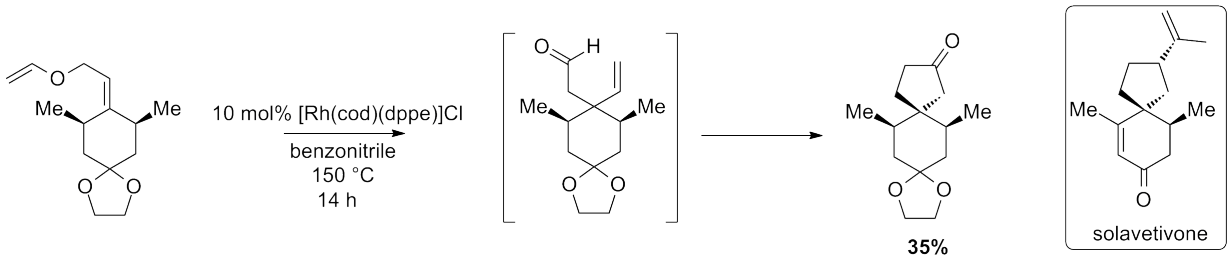
Several processes have been described which utilise hydroacylation catalysts to carry out another transformation, either prior to or following a hydroacylation process. Selected examples of these processes will be described here, along with examples of other methods which utilise the same metal catalyst to carry out two distinct processes.



Scheme 1.37. Eilbracht's tandem Claisen rearrangement/intramolecular hydroacylation procedure

Eilbracht described the use of rhodium or ruthenium catalysts to promote the Claisen rearrangement of allyl vinyl ethers to 4-pententals, followed by an intramolecular hydroacylation to form cyclopentanones.[108] [Rh(cod)(dppe)]Cl and $RuCl_2(PPh_3)_3$ were

both effective at catalysing this tandem process; the former at 140 - 190 °C, the latter at 200 °C and under 50 bar carbon monoxide pressure (Scheme 1.37). Wilkinson's catalyst and $[Rh(dppe)_2](ClO_4)_2$ were both ineffective, and complexes of several other metals - palladium, cobalt, iridium and nickel - proved to be ineffective at catalysing the tandem process, although some accelerated the initial Claisen rearrangement relative to purely thermal conditions.

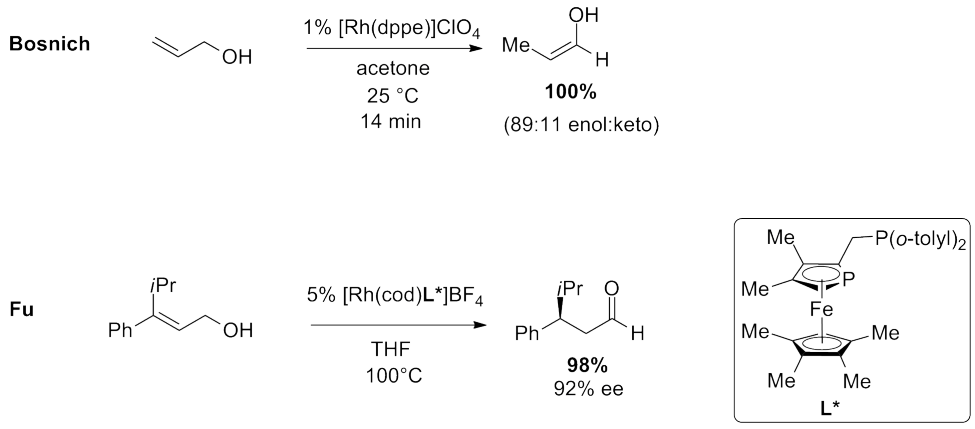


Scheme 1.38. The application of Eilbracht's tandem Claisen rearrangement/intramolecular hydroacylation procedure to a potential intermediate for the synthesis of solavetivone

The same authors applied this tandem Claisen rearrangement/intramolecular hydroacylation process to the synthesis of a potential intermediate to solavetivone,[109] and to a formal synthesis of erythrodiene and spirojatamol.[110] The latter examples did not conduct the protocol as a tandem sequence, however, due to the need to separate diastereoisomers of the aldehyde prior to intramolecular hydroacylation.

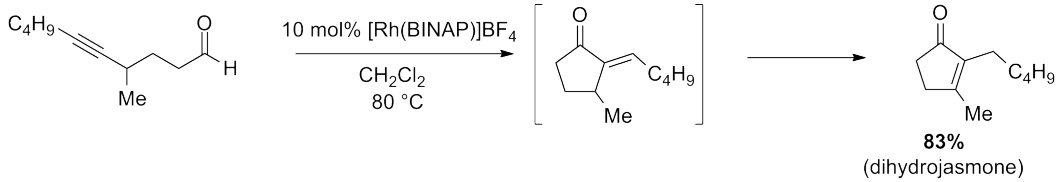
The ability of $[Rh(dppe)]ClO_4$ Bosnich-type catalysts to cause alkene migration processes was noted in the original publication of their use in hydroacylation by Bosnich.[47] Bosnich later exploited the ability of $[Rh(dppe)]ClO_4$ to catalyse alkene migrations in a catalytic synthesis of enols from allylic alchols,[111] and Fu developed an asymmetric variation of this process by utilising prochiral allyl alcohols and isomerising them to chiral aldehydes with a catalyst system comprising $[Rh(cod)_2]BF_4$ and a planar chiral ferrocene-containing *bis*-phosphine ligand (Scheme 1.39).[112]

Tanaka's tandem hydroacylation/double-bond isomerisation process has been dis-



Scheme 1.39. [Rh(*bis*-phosphine)]X complexes in alkene migration processes

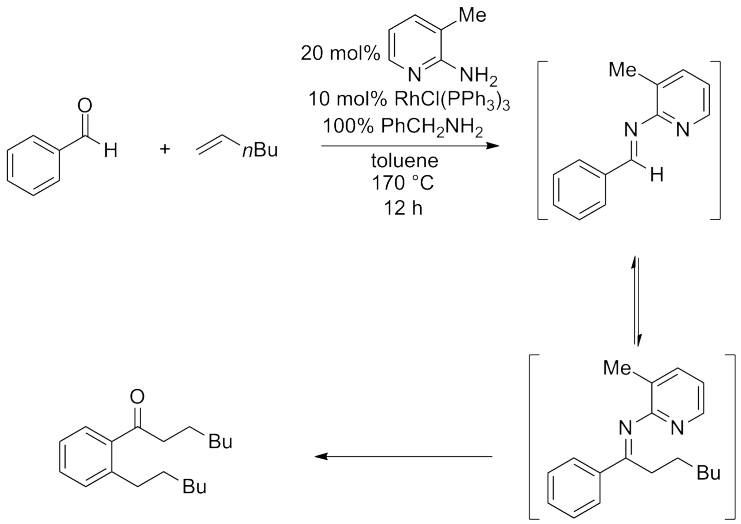
cussed before (Scheme 1.18), but merits a mention here as an example of a tandem hydroacylation process (Scheme 1.40).



Scheme 1.40. Tanaka's intramolecular alkyne hydroacylation procedure to access exo- or endocyclic alkene-contaning cyclopentenones and cyclohexenones

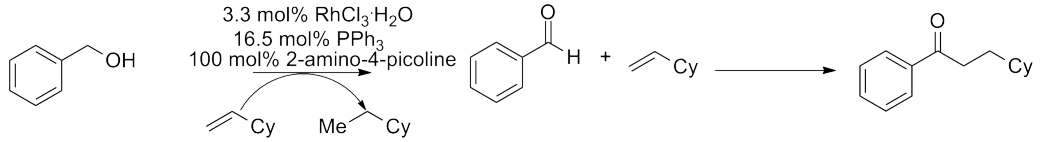
Jun has exploited the directing group ability of the picolylamines employed in his intermolecular hydroacylation methodology to facilitate further metal-catalysed derivitsations of his hydroacylation products. One such example is a tandem intermolecular hydroacylation/*ortho*-alkylation procedure (Scheme 1.41).[113] Other tandem catalytic processes involving picolyl imine intermediates have been reported.[114,115]

An interesting expansion of Jun's picolyl amine intermolecular hydroacylation system was described in which the ability of rhodium to participate in redox chemistry was incorporated into the system, allowing alcohols (and, following some modifications, primary amines)[116] to be used as aldehyde equivalents.[117] Using $RhCl_3 \cdot H_2O$, primary alcohols were oxidised to aldehydes using another equivalent of alkene as the



Scheme 1.41. Jun's tandem intermolecular hydroacylation/nitrogen-directed *ortho*-alkylation procedure

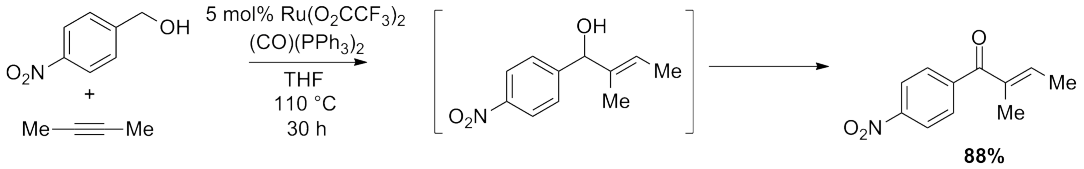
oxidising agent, before participating in intermolecular hydroacylation (Scheme 1.42).



Scheme 1.42. Jun's tandem oxidation/intermolecular hydroacylation system

A similar oxidation/hydroacylation approach in Krische's ruthenium-catalysed intermolecular hydroacylation of dienes has already been noted, whereby either the alcohol or aldehyde oxidation level of the starting material could be employed under identical reaction conditions, owing to the ability of the ruthenium catalyst employed to participate in transfer hydrogenation. Krische also disclosed a ruthenium-catalysed synthesis of α,β-enones from alcohols and symmetricral or non-symmetrical internal alkynes.[118] In contrast to the Jun system, however, this reaction proceeds by the reaction of the alcohol with the unsaturated component, followed by oxidation of the product (rather than oxidation of one starting material prior to the carbon-carbon bond forming process) (Scheme 1.43). As with the diene hydroacylation chemistry, the req-

uisite aldehyde could also be employed rather than the alcohol.



Scheme 1.43. Krische's tandem "hydroacylation"/oxidation procedure

1.4 Summary

The majority of hydroacylation reactions have been reported using rhodium catalysts, with Bosnich's [Rh(dppe)]ClO_4 catalyst (or variations thereof) featuring heavily. Although some exceptions do exist, the scope of rhodium-based catalysts which have been used in hydroacylation processes remains fairly narrow, and only a handful of non-rhodium systems have been decribed. Despite this, several groups have exploited the versatility of these catalysts to conduct additional transformations either to form the requisite hydroacylation substrate, or to further derivatise the product of a hydroacylation reaction. There would still appear to be a range of reactivity of rhodium(I) catalysis which has not been exploited in a tandem process, however, and this is an approach which may provide a demonstration of the potential synthetic utility of hydroacylation.

Chapter 2

Hydroacylation as a method to access highly substituted furans

2.1 Introduction

Heterocyclic compounds, such as the bioactive natural products pukalide and nakadomarin A, and the hugely successful drug molecules ranitidine (Zantac) and atorvastatin (Lipitor) - the top selling pharmaceutical compound in the US for most of the last decade - are of great importance in pharmaceutical, agrochemical and other fine chemical applications (Figure 2.1).

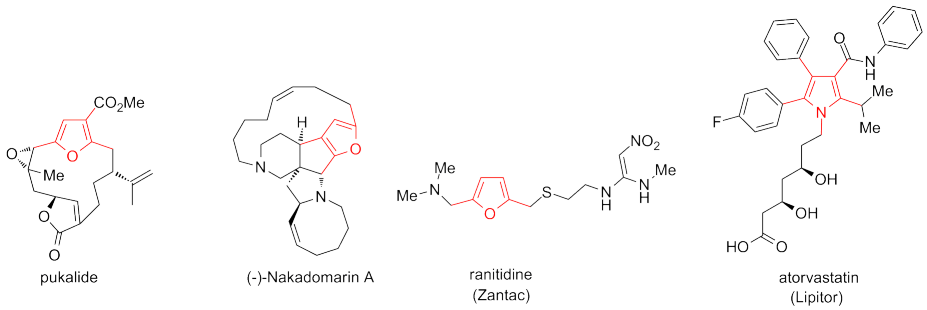


Figure 2.1. Examples of important 5-membered heterocyclic compounds

While there exists a range of methodologies for transforming relatively complex starting materials into substituted heterocycles,[119–123] and a variety of methods known for the functionalisation of existing heterocycles, there is less precedent for methodology which results in the direct, regiodefined synthesis of highly substituted heterocycles from simple starting materials.[124] As such, methods which allow the synthesis of substituted heterocycles (or their precursors) with high atom efficiency are potentially of significant value,[125–127] particularly if such methods do not suffer from the same drawbacks as the traditional syntheses of 1,4-dicarbonyl compounds, which are often either step- or atom-inefficient.

Intermolecular hydroacylation is now an ideal method to exploit for the synthesis of these molecules, as it uses commercially available catalyst systems, can employ a non-toxic, environmentally friendly solvent, and generates no by-products due to its 100% atom economy. A broad range of aldehydes can now be employed and, particularly in the case of alkyne hydroacylation, significant substitution of the unsaturated component can be tolerated, allowing for the regioselective production of highly substituted complex molecules in one catalytic intermolecular carbon-carbon bond forming step.

γ-Hydroxy-α,β-enones are known to undergo acid-catalysed dehydrative cyclisation to form furans, a transformation which has been exploited by several research groups,[128–132] most notably in the recent high-profile work by Donohoe.[133,134] The intermolecular hydroacylation of a chelating aldehyde with readily available propargylic alkynes would permit the synthesis of γ-hydroxy-α,β-enones with 100% atom efficiency; coupling this carbon-carbon bond formation with an acid-catalysed dehydrative cyclisation would allow for the entirely regioselective synthesis of di- or tri-substituted furans *via* a novel disconnection for this type of heterocycle (Figure 2.2).

Alternatively, the isomerisation of alkenes and alkynes by rhodium catalysts is well-precedented,[47,111,112,135] although not specifically for γ-hydroxy-α,β-enones. The identification of a suitable catalyst which is adept at catalysing an initial carbon-carbon

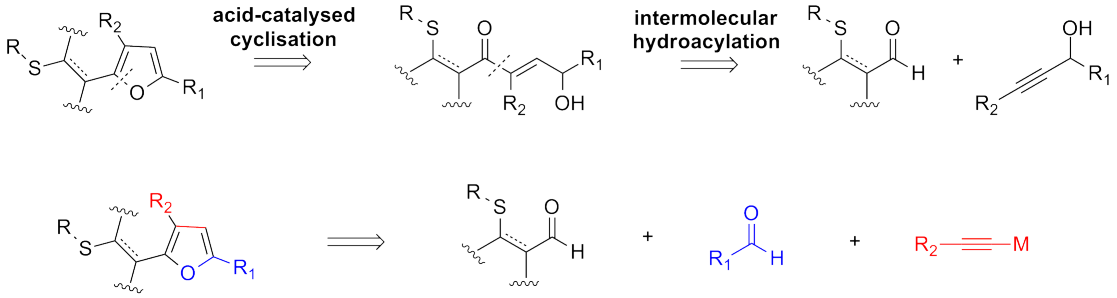


Figure 2.2. The novel disconnection afforded by a hydroacylation approach to substituted furans

bond forming hydroacylation step as well as a subsequent double-bond isomerisation could permit an atom-efficient synthesis of 1,4-dicarbonyl compounds from simple starting materials (Figure 2.3).

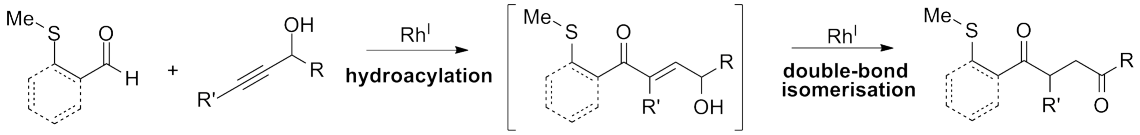


Figure 2.3. A potential tandem hydroacylation process for the atom-efficient synthesis of 1,4-dicarbonyl compounds

If successful, the 1,4-dicarbonyl compounds thus produced could be transformed into 5- or 6-membered heterocycles using traditional dehydrative cyclisation methodology (Scheme 2.1).[136–138]

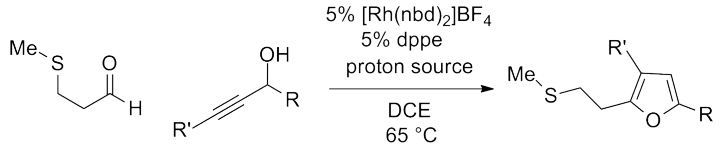
Scheme 2.1. Generic Paal-Knorr synthesis of 5-membered heterocycles

2.2 2,5-Disubstituted furans *via* the hydroacylation of propargylic alcohols

2.2.1 Initial reaction evaluation

Initial reactions employed propargyl alcohol **1** (Table 2.1, R = R' = H) as the substrate, but the $[Rh(nbd)_2]BF_4$/dppe-catalysed reaction between it and 3-(methylthiopropionaldehyde) **2** resulted in a complex mixture of products from which no furan was isolated. The use of 3-butyn-2-ol **3** (Table 2.1, R = Me; R' = H), however, resulted in the formation of the desired furan **4** in 13% isolated yield following column chromarography, after the addition of Amberlyst 15 to the hydroacylation reaction mixture (entry 4).

Table 2.1: Initial attempts at furan formation *via* the hydroacylation of propargylic alcohols



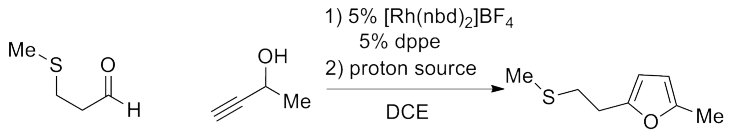
2

Entry	R	R'	Proton source	Yield (%)
1	H	H	none	0
2	H	H	Amberlyst 15	0
3	Me	H	none	trace
4	Me	H	Amberlyst 15	13
5	Me	Et	Amberlyst 15	7

Conditions: **2** (0.75 mmol), propargylic alcohol (1.1 equiv.), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.), DCE (5 mL), Amberlyst 15 (20 mg), 65 °C, 1 h; Amberlyst 15 added after 1 h.

While the intermolecular hydroacylation step appeared to be proceed smoothly, the yield of the desired furan was low. As such, attempts were undertaken to optimise the cyclisation conditions for this system (Table 2.2). The use of excess trifluoroacetic acid (Table 2.2, entries 1-4) produced the desired furan **4** in up to 50% isolated yield, but was less effective when used in stoichiometric or catalytic amounts (results not

Table 2.2: Optimizing the conditions for the *in situ* cyclisation of γ-hydroxy-α,β-unsaturated enone hydroacylation products to 2,5-disubstituted furans



2 3 4

Entry	Proton source	Reaction time	Temperature	Yield (%)
1	TFA (excess)	16 h	25 °C	trace
2	TFA (excess)	1 h	25 °C	29
3	TFA (excess)	10 min	25 °C	50
4	TFA (excess)	1 h	0 °C	38
5	*p*TSA (10 mol%)	16 h	25 °C	36
6	*p*TSA (10 mol%)	2 h	25 °C	66
7	*p*TSA (10 mol%)	30 min	25 °C	57
8	*p*TSA (10 mol%)	1 h	0 °C	21
9	PPTS (10 mol%)	16 h	25 °C	7
10	PPTS (10 mol%)	1 h	25 °C	0
11	anydrous HCl (10 mol%)	1 h	25 °C	8
12	PPA/P_2O_5 (excess)	1 h	25 °C	18
13	*p*TSA (10 mol%) + $MgSO_4$ (200 mol%)	1 h	25 °C	27

Conditions: **2** (0.75 mmol), **3** (1.1 equiv.), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.), DCE (5 mL), 65 °C, 1 h, followed by acid (equivalents as stated) at the given conditions.

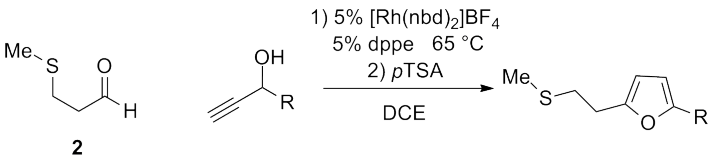
shown). For all acids screened, reaction times of longer than 2 hours resulted in reduced yields (entries 1, 5 and 9), presumably due to decomposition of the furan on prolonged exposure to acidic media (also note the reduced yield of entry 2 when compared to entry 3). Reactions conducted at 0 °C showed poor conversion (entries 4 and 8). *p*-Tolylsulfonic acid produced the best results, although the final yield was very dependent on the reaction time (entries 5-8). Attempts to use PPTS as a milder, buffered equivalent to *p*TSA were unsuccessful, with mostly starting materials recovered (entries 9 and 10). As furans are unstable to aqueous acidic media, and a stoichiometric amount of water is formed by the cyclisation, PPA was employed as both acidic cata-

lyst and dehydrating agent, but the yield was disappointing (entry 12). Similarly, the presence of oven-dried magnesium sulfate in the reaction medium did not lead to an increase in yield (entry 13).

2.2.2 Purification of 2,5-disubstituted furans obtained through a one-pot hydroacylation/acid-catalysed cyclisation sequence

Given the acid-sensitivity of the desired compounds, attempts were made to purify the furans by chromatography which avoided the use of acidic silica (Table 2.3).

Table 2.3: Varying the method of purifying 2,5-disubstituted furans by column chromatography

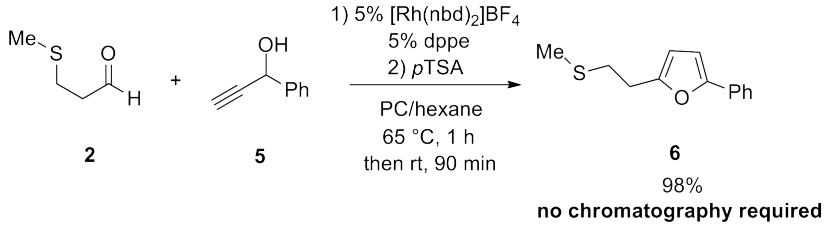


Entry	R	Purification	Yield (%)
1	Me	silica	66
2	Me	neutral alumina	26
3	Me	basic alumina	33
4	Me	Florisil®	75
5	Me	NEt_3-washed silica	85
6	Ph	silica	26
7	Ph	Florisil®	74
8	Ph	NEt_3-washed silica	60

Conditions: **2** (0.75 mmol), propargylic alcohol (1.1 equiv.), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.), DCE (5 mL), *p*TSA (10 mg), 65 °C, 1 h, then 25 °C, 2 h.

Neutral and basic alumina proved to be no improvement over silica (entries 2 and 3), but the use of Florisil® (magnesium silicate) furnished the products in 74-75% isolated yield (entries 4 and 7). Silica which had been repeatedly washed with column

eluant containing 1% triethylamine was also a significant improvement over untreated silica (entries 5 and 8). All attempts at purifying these compounds by column chromatography where carried out using as little column packing material as possible, due to the propensity for 2,5-disubstituted furans (particularly electron-rich examples) to degrade on exposure to silica. Similarly, all chromatography was conducted as quickly as possible to minimize the residence time of the sensitive furans on the column packing material. Purifaction of the furans in this manner was greatly aided by two factors: the reactions were generally extremely clean, with both steps in the tandem process proceeding in quantitative "spot to spot" conversion according to tlc analysis; and the extreme polarity difference between the desired furans and the compounds from which they were separated, i.e. the excess alkyne from the initial hydroacylation reaction, and the hydroacylation product itself, both of which contain alcohol functional groups and hence are considerably more polar than the desired furans.



Scheme 2.2. Biphasic propylene carbonate/hexane solvent system for the chromatography-free synythesis of 2,5-disubstituted furans

Finally, one alternative method of purification was employed. By carrying the reaction out in a biphasic propylene carbonate/hexane mixture, it was hoped that the immiscibility of these two solvents would result in a higher yield of the acid-sensitive furan (the use of propylene carbonate as a hydroacylation solvent is detailed elsewhere;[139] see Chapter 5). The furans themselves are highly non-polar, so should have reasonable solubility in hexane, whereas it was hoped that the acid used would reside mostly in the water-miscible propylene carbonate layer and thus decomposition of the

desired furan by the acidic media required to effect its formation should be minimised. The catalyst is also insoluble in hexane but very soluble in propylene carbonate, and this fact should further aid purification of the product furan. The reaction between 3-(methylthio)propionaldehyde **2** and alkyne **5** was conducted in a 2:1 mixture of hexane:propylene carbonate, with vigorous magnetic stirring (Scheme 2.2). After 1 hour, the reaction mixture was transferred to a separating funnel and the more dense propylene carbonate layer was removed and extracted into hexane. ^{1}H NMR spectoscopy analysis of the crude product obtained from the hexane extracts showed that the desired furan **6** was the sole product, albeit contamined with propylene carbonate. The contamination was deemed to be mechanical in origin, as hexane and propylene carbonate are completely immiscible. The reaction was repeated as described above, but with the hexane extracts being washed with water in an attempt to remove the propylene carbonate contaminant, and the desired furan **6** was produced in 98% isolated yield and in high (by ^{1}H NMR analysis) purity (Figure 2.4).

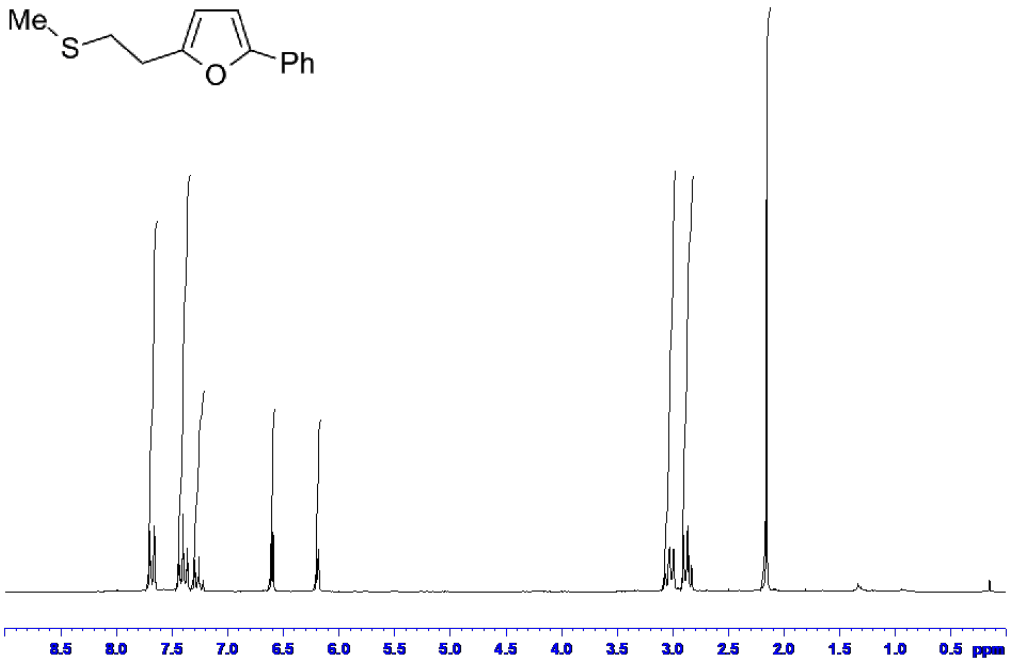


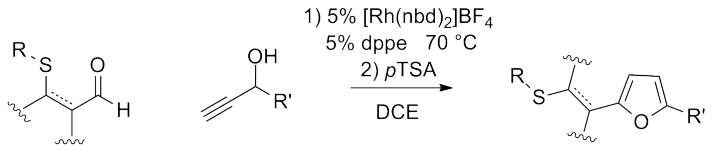
Figure 2.4. ^{1}H NMR spectrum of crude **6** from the biphasic propylene carbonate/hexane reaction

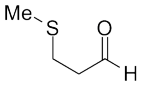
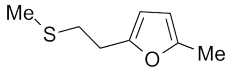
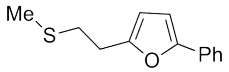
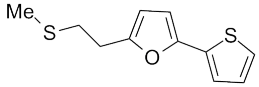
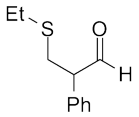
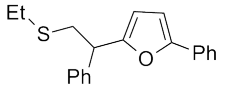
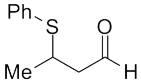
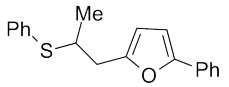
This purification method did not appear to be general, however, with systems which were already low-yielding after chromatography providing no increase in yield when subjected to the biphasic system.

2.2.3 Reaction scope of the synthesis 2,5-disubstituted furans *via* a hydroacylation disconnection

With *p*TSA identified as a suitable catalyst for the conversion of γ-hydroxyenones to 2,5-disubstituted furans, and the isolation and purification of these furans using NEt_3-washed silica established, a short series of 2,5-disubstituted furans were synthesised under these conditions (Table 2.4). The conditions tolerated the incorporation of alkyl, aryl and heteroaryl substituents (entries 1, 2 and 3 respectively), as well as α- and β-branched aldehydes. All samples were purified by column chromatography without issue, and furan **6** could be obtained in 98% isolated yield when using the biphasic propylene carbonate/hexane conditions mentioned above.

Table 2.4: Initial attempts at furan formation *via* the hydroacylation of propargylic alchohols



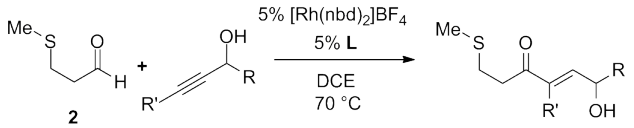
Entry	Aldehyde	R'	Product	Yield (%)
1	 **2**	Me	 **4**	85
2	**2**	Ph	 **6**	75
3	**2**	2-thiophene	 **7**	66
4	 **8**	Ph	 **9**	77
5	 **10**	Ph	 **11**	65

Conditions: (i) aldehyde (1 equiv.), alkyne (1.1. equiv), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.), DCE (0.15 M), 70 °C for 1 h; (ii) *p*TSA (0.10 equiv), room temperature, 1.5 h. Products isolated using column chromatography with NEt_3-washed silica.

2.3 Trisubstituted furans *via* the hydroacylation of internal propargylic alkynes

While the use of *p*TSA was suitable for the preparation of 2,5-disubstituted furans, these conditions could not be directly applied to the synthesis of trisubstituted furans. To synthesise trisubstituted furans by this methodology, the hydroacylation of an internal propargylic alkyne would need to be performed efficiently. While the hydroacylation of internal alkynes has been reported in our group, they are noticeably less reactive substrates than the terminal alkynes which are more usually employed. As such, it was necessary to conduct a brief screen of hydroacylation conditions and substrates to identify suitable conditions which would permit the efficient hydroacylation of an internal propargylic alkyne (Table 2.5).

Table 2.5: Identification of conditions which permit the hydroacylation of an internal propargylic alkyne

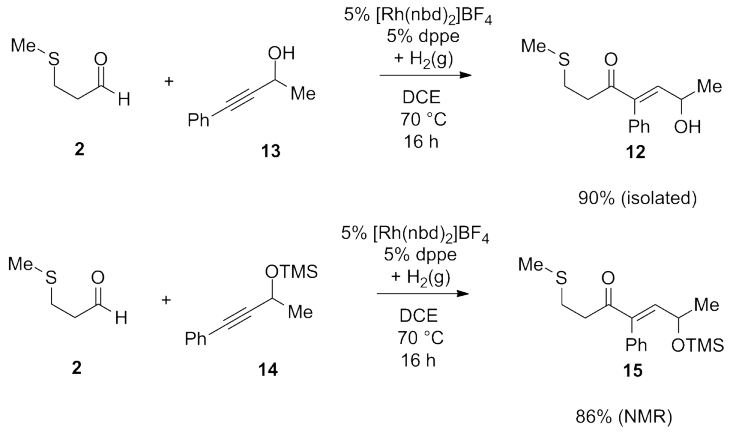


Entry	R	R'	Ligand	Yield (%)
1	Me	Et	dppe	trace
2	Me	Et	dppe	38[a]
3	Me	Et	DPEphos	0
4	Me	Et	DPEphos	52[a]
5	Me	Ph	dppe	57[b]
6	Me	Ph	dppm	trace
7	Me	Ph	dcpm	trace
8	Me	Ph	DPEphos	trace
9	Ph	Me	dppe	57[b]
10	Ph	Me	dppe	90[a,c]
11	Ph	Me	DPEphos	0

Conditions: **2** (0.75 mmol), alkyne (1.1. equiv), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), ligand (0.05 equiv.), DCE (0.15 M), 70 °C for 1 h. [a] pre-catalyst solution activated by hydrogenation; [b] reaction conducted for 2 h; [c] reaction conducted for 16 h

Of the ligands screened, only dppe and DPEphos produced significant amounts of hydroacylation products, although analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy revealed that the reactions which used DPEphos were also producing small amounts of multiple unidentified byproducts. To obtain the best results, it

was found that the pre-catalyst should be activated by hydrogenation, and the reaction required overnight heating to proceed to completion (Table 2.5, entry 10), which provided the desired product **12** in 90% isolated yield. To rule out the possibility that the free hydroxyl group on the alkyne substrates were causing a reduction in reaction rate or yield by coordination to the rhodium center, a TMS-protected variant of alkyne **13** (alkyne **14**) was prepared.[140] After 16 hours at 70 °C, ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed 86% conversion to hydroacylation product **15** (14% **2** remaining), which is comparable to the 90% isolated yield obtained with the propargylic alkyne **13** which contains a free alcohol (Scheme 2.3).



Scheme 2.3. Comparison of the reactivity between TMS-protected internal propargylic alcohols and the unprotected variant

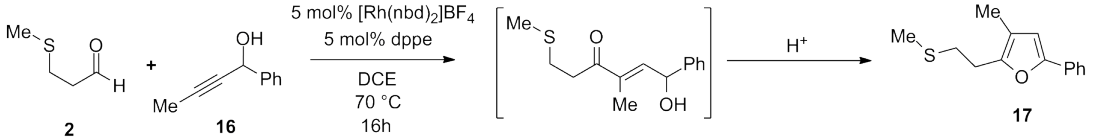
There therefore appears to be little benefit to protecting the alcohol, as the desired hydroacylation products (and hence furans) can be obtained after 16 hours when using the unprotected alcohol.

2.3.1 Optimisation of acid-catalysed dehydrative cyclisations of substituted γ-hydroxyenones to form trisubstituted furans

With hydroacylation conditions which were compatible with internal propargylic alkynes in hand, attempts were made to cyclise these hydroacylation products to the furan and

hence create a tandem, one-pot procedure for the synthesis of trisubstituted furans directly from aldehydes and propargylic alkynes. The conditions which proved to be optimal for the majority of the 2,5-disubstituted examples - 10 mol % *p*TSA - were unsuccessful in these trisubstituted substrates, with only partial conversion to the desired furan being observed. A screen of acidic conditions was thus undertaken, using aldehyde **2** and alkyne **16** (Table 2.6).

Table 2.6: Screening of suitable acidic conditions for the cyclisations to furnish trisubstituted furans



Entry	Proton source	Time	Temperature (°C)	Yield (%)
1	*p*TSA (10 mol%)	2 h	25	40
2	*p*TSA (10 mol%)	16 h	40	44
3	*p*TSA (10 mol%)	16 h	40	trace[a]
4	TFA (catalytic)	4 h	25	11
5	TFA (1 equiv.)	20 min	25	23
6	TFA (1 equiv.)	20 min	70	decomposition
7	TFA (0.5 equiv.)	45 min	25	decomposition
8	PPTS (10 mol%)	1 - 16 h	25 - 40	0
9	AcOH (0.5 - 2 equiv.)	1 - 72 h	25 - 70	0
10	TMSOTf (1 equiv.)	10 min	0 - 70	decomposition
11	HCl (4.0M in dioxane, 1 equiv.)	10 min	25	78

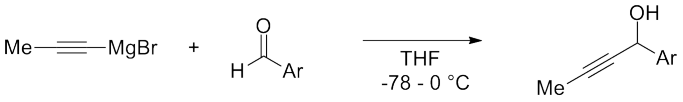
Conditions: (i) aldehyde (1 equiv.) **2**, alkyne **16** (1.1. equiv), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), ligand (0.05 equiv.), DCE (0.15 M), 70 °C for 16 h. (ii) as stated; [a] ethanol additive

Any of the screened conditions which utilised *p*TSA (entries 1 - 3), the acid which produced the best results for the synthesis of 2,5-disubstituted furans, resulted in incomplete reactions and recovery of unreacted hydroacylation product. The recent Dixon synthesis of (-)-nakadomarin A[141] included the formation of a relatively electron-

rich furan in ethanol in 69% yield; the use of ethanol as an additive to our system, however, had a deleterious effect on the yield of the desired furan (entry 3). TFA (entries 4 - 7) resulted in decomposition products only, whereas acetic acid (entry 9) produced no detectable amounts of furan under a variety of reaction conditions. PPTS (entry 8), as in the case of the 2,5-disubstituted furans, was similarly unreactive, and TMSOTf (entry 10) only gave decomposition products. Finally, anhydrous HCl (entry 11), which produced only traces of furan in the majority of 2,5-disubstituted examples due to product decomposition, rapidly and cleanly converted the hydroacylation product *in situ* to the desired 2,3,5-trisubstituted furan **17** in 78% isolated yield.

2.3.2 Scope of the synthesis of trisubstiuted furans *via* a hydroacylation disconnection

These conditions were applied to the synthesis of a variety of trisubstituted furans departing from alkyl aldehydes (Table 2.7). Non-commercially available alkynes were prepared by the addition of an alkynyl metal species to the requisite aldehyde (Scheme 2.4)

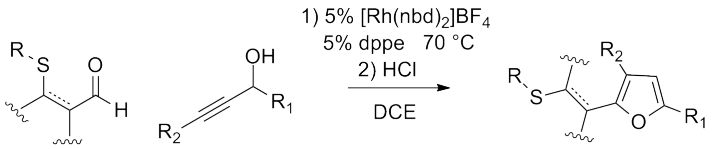


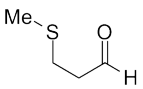
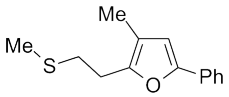
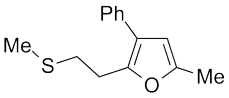
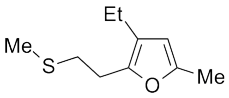
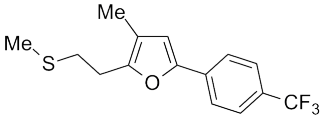
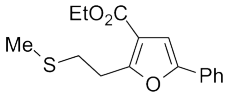
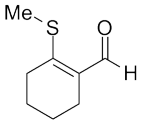
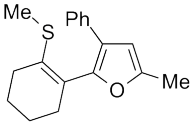
Scheme 2.4. Synthesis of non-commercially available internal propargylic alkynes

While these reactions were generally low-yielding when unoptimised, sufficient material was produced to include them in furan syntheses. Various methods exist for the higher-yielding syntheses of these starting materials,[142,143] but were not explored due to the inefficient methodology being sufficient for the preparation of small amounts of internal propargylic alkynes.

Two regioisomeric trisubstituted furans (Table 2.7, entries 1 and 2) were produced by simply altering the alkyne employed in the hydroacylation step. Pleasingly, on scaling up the reaction, furan **18** was obtained in an excellent 93% isolated yield (entry 2).

Table 2.7: Scope of trisubstituted furan formation from hydroacylation products of an alkyl aldehyde

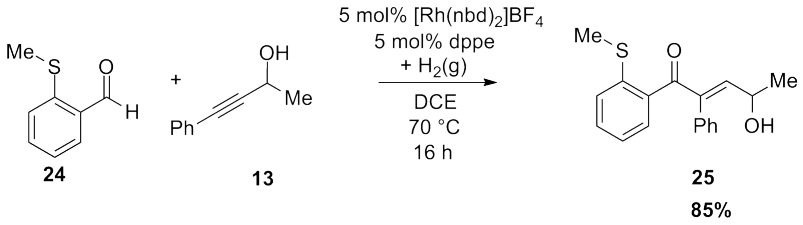


Entry	Aldehyde	R_1	R_2	Product	Yield (%)
1	 **2**	Ph	Me	 **17**	78
2	**2**	Me	Ph	 **18**	93[a]
3	**2**	Me	Et	 **19**	42
4	**2**	Me	*p*-CF_3Ph	 **20**	82
5	**2**	Ph	CO_2Et	 **21**	59[b]
6	 **22**	Me	Ph	 **23**	78

Conditions: (i) aldehyde (1 equiv.), alkyne (1.1. equiv), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.), DCE (0.15 M), 70 °C for 16 h; (ii) HCl (4.0 M in dioxane, 1 equiv.), room temperature for 10 min; [a] 3.0 mmol scale; [b] no acid added

A trialkyl variant **19** was synthesised, but isolated only in 42% yield (entry 3); while both the hydroacylation step and the acid-catalyzed dehydrative cyclisation appeared to proceed to completion (by tlc monitoring of the reaction) without the production

of any by-products, the product degraded when purified by column chromatography, despite the use of thoroughly base-washed silica as described for previous examples. It appears that three alkyl groups with no stabilising electron withdrawing groups on the furan may represent the limit for this methodology, insofar as product isolation by chromatography is concerned. An ester substitutent was also incorporated (entry 5, **21**), although the electron deficient alkyne employed was sluggish in the hydroacylation step and the reaction did not proceed to completion. Despite this, the furan formed *in situ* without requiring any acid to be added. Finally, cyclohexenyl aldehyde **22** was utilised to furnish **23** (entry 6), although multiple byproducts appeared to be present in the tlc following the addition of acid, presumably due to acid-catalysed decomposition of the vinyl sulfide moiety. With multiple examples of trisubstituted furans originating from the hydroacylation of alkyl aldehydes with internal propargylic alkynes demonstrated, it was decided to attempt to incorporate an aromatic thioether-containing aldehyde. A test reaction confirmed that the hydroacylation of aromatic aldehyde **24** with and internal propargylic alkyne proceeded to completion and furnished the requisite hydroacylation product **25** in good yield (Scheme 2.5).

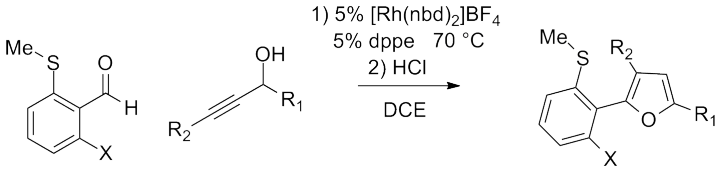


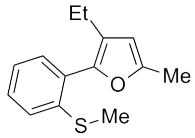
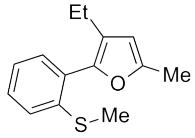
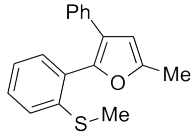
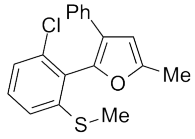
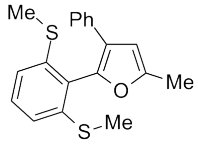
Scheme 2.5. The hydroacylation of aryl aldehyde **24** with an internal propargylic alkyne

A series of examples was prepared to demonstrate the incorporation of aromatic chelating aldehydes (Table 2.8). Aromatic analogues of two previously prepared furans **26** and **27** were synthesised in good yield (Table 2.8, entries 2 and 3). A chloride-containing example also proceeded in acceptable yield (entry 4, **28**), demonstrating the tolerance of this methodology towards incorporating halide substituents for poten-

tial derivatisation of the products, and a dithioether containing example **29** was also prepared (entry 5).

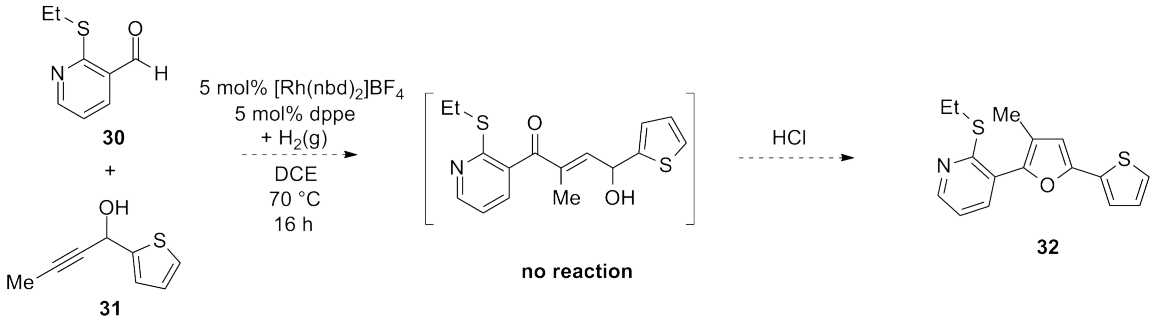
Table 2.8: Scope of trisubstituted furan formation from hydroacylation products of aryl aldehydes



Entry	X	R_1	R_2	Product	Yield (%)
1	H	Me	Et	 **26**	46[a]
2	H	Me	Et	 **26**	67
3	H	Me	Ph	 **27**	85
4	Cl	Me	Ph	 **28**	55
5	SMe	Me	Ph	 **29**	72

Conditions: (i) aldehyde (1 equiv.), alkyne (1.1. equiv), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.), DCE (0.15 M), 70 °C for 1 h; (ii) HCl (4.0 M in dioxane, 1 equiv.); [a] DPEphos as ligand

An attempt was made to incorporate pyridine aldehyde **30**, as its reaction with thiophene-containing alkyne **31** and subsequent acid-catalysed cyclisation would result in three separate heterocycles (a pyridine, a furan and a thiophene) linked together in compound **32** (Scheme 2.6). Unfortunately, the hydroacylation step to form intermediate **33** was unsuccessful.



Scheme 2.6. Failed hydroacylation employing pyridine-containing aldehyde **30**

2.4 Heck reactions of hydroacylation products for the synthesis of trisubstituted furans

Recent publications from the Donohoe group[133,134] disclosed the synthesis of di- and trisubstituted furans by means of the cross-metathesis of α, β-unsaturated ketones and vinyl alcohols under acidic conditions to produce 2,5-disubstituted furans. As this approach utilises an alkene metathesis for its carbon-carbon bond forming step, this particular approach is necessarily limited to the synthesis of 2,5-disubstituted furans, as any further substituents on the starting materials would be lost in the course of the metathesis reaction. To circumvent this limitation, the group carried out the same cross-metathesis under neutral conditions to access the γ-hydroxy-α, β-enone intermediates, which were isolated before being used as the substrates in a Heck reaction. The Heck reaction produced the trisubstituted furan products without the need to add

any acid, which the authors postulated was due to isomerisation of the arylated intermediate during the course of the reaction (Figure 2.5).

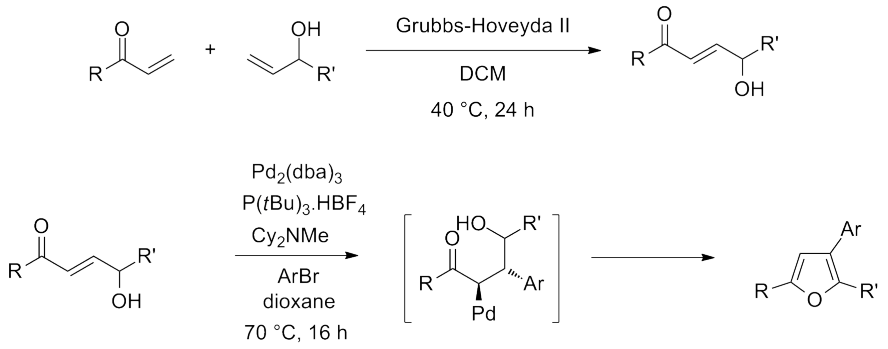


Figure 2.5. Donohoe group approach to trisubstituted furans

The application of this methodology to the hydroacylation products of terminal propargylic alcohols would produce trisubstituted Heck products, with complementary regiochemistry compared to the direct utilisation of internal propargylic alkynes. If the Heck conditions could also be applied to the hydroacylation products which have previously been used as the precursors to trisubstituted furans, this would permit the regioselective synthesis of tetrasubstituted furans. (Figure 2.6).

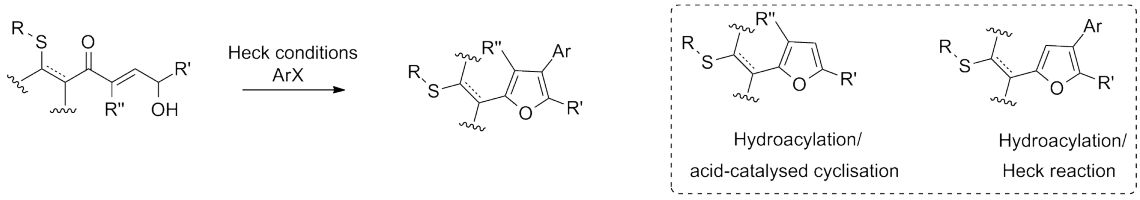
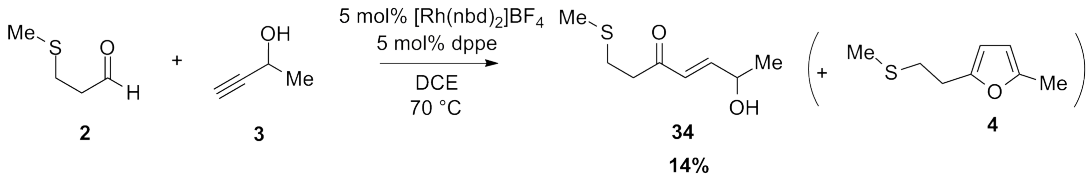


Figure 2.6. The potential application of Heck chemistry to hydroacylation products to produce tri- and tetrasubstituted furans

To test the applicability of this methodology to our system, it was decided to synthesise γ-hydroxy-α,β-enone **34** (Scheme 2.7). This substrate was chosen for two reasons: the lack of steric bulk caused by the presence of a methyl group; and because the furan derived from the Heck product of bromobenzene and this substrate would be a regioisomer of two of the trisubstituted furans which had already been prepared by

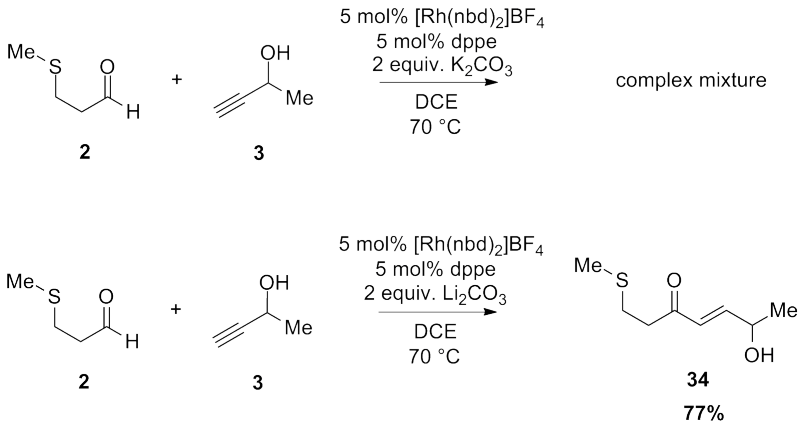
the hydroacylation of internal propargylic alkynes.



Scheme 2.7. Low-yielding preparation of the substrate for Heck reactions

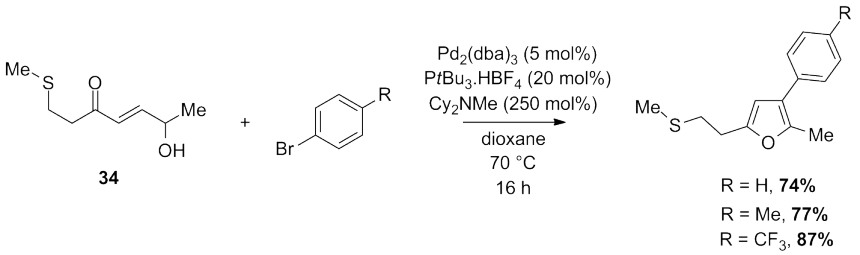
The preparation of this substrate did not prove to be entirely straightforward, however, due to its propensity to undergo spontaneous dehydrative cyclisation to the furan under the ostensibly neutral hydroacylation conditions - presumably due to either the Lewis acidity of the hydroacylation catalyst, the presence of trace amounts of moisture (and hence a proton source) being sufficient to cyclise this substrate, or because the dehydrative cyclisations to furans of particularly labile γ-hydroxy-α,β-enones are known to be accelerated by light. The cyclisation of γ-hydroxy-α,β-enones to the requisite furans has been noted as a spontaneous degradation process,[144] which has been postulated to proceed *via* a spontaneous stereoisomerisation of the double bond to the *cis* isomer followed by cyclisation to the cyclic hemiacetals followed by loss of water.[145] This isomerisation/cyclisation process was shown by Sammakia to be accelerated by light, but to still proceed in darkness if an acid was present.[130] To prevent undesired furan formation in this instance, the reaction was conducted in the presence of two equivalents of K_2CO_3; however, this resulted in a complex reaction mixture and incomplete consumption of the starting aldehyde. Previous work in the group which attempted to apply conditions used by Krische[146] to carry out tandem hydroacylation/reductive Aldol reactions had shown that our alkyne hydroacylation methodology was unaffected by the presence of Li_2CO_3. Conducting this hydroacylation in the presence of two equivalents of Li_2CO_3 permitted the formation and isolation of the desired γ-hydroxy-α,β-enone **34** in 77% yield, albeit with some loss of yield to the furan still being observed (Scheme 2.8). Conducting the reaction in the absence of base

but at the lower temperature of 40 °C merely resulted in poor (approximately 20% by ^{1}H NMR spectroscopic analysis) conversion to the hydroacylation product. Despite the previously mentioned instability of γ-hydroxy-α,β-enones and their tendencies to spontaneously form furans, it was found that a sealed, analytically pure sample of **34** which had been left on the bench for 4 months (with no precautions to shield the sample from light or adventitious moisture) contained less than 10% of the relevant furan.



Scheme 2.8. Improved preparation of the substrate for Heck reactions

With the desired test substrate **34** in hand, the Donohoe conditions were applied unmodified and were found to produce the desired trisubstituted furans in good to excellent yields (Scheme 2.9).



Scheme 2.9. Synthesis of trisubstituted furans by Heck reactions of hydroacylation products

The reaction tolerated the incorporation of an electron rich and an electron poor

aryl unit, as well as unsubstituted phenyl. The bromobenzene product **35** was shown to be a different regioisomer to the trisubstituted furans **18** and **17** by comparison of the ^{1}H NMR spectra, and the absolute regiochemistry of two of these structures was confirmed by nOe experiments (Figure 2.7).

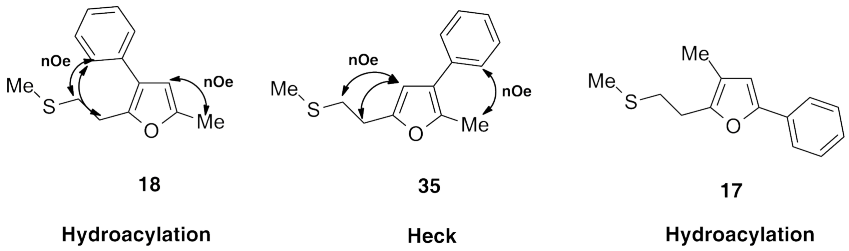


Figure 2.7. Application of Heck methodology and the production of regioisomeric trisubstituted furans

2.4.1 Tetrasubstituted furans *via* Heck reactions

It was hoped that the application of this methodology to the more highly substituted examples of our existing furan methodology would permit the synthesis of fully substituted furans, with complete regiocontrol (Figure 2.8). The Heck conditions which were successful for the synthesis of trisubstituted furans, however, did not prove to be applicable for the synthesis of a tetrasubstituted example.

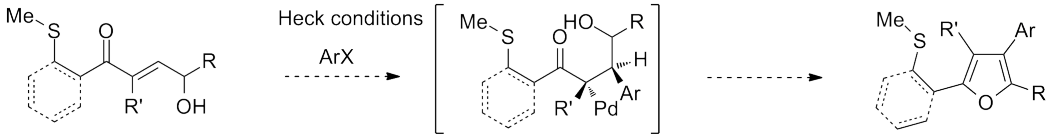
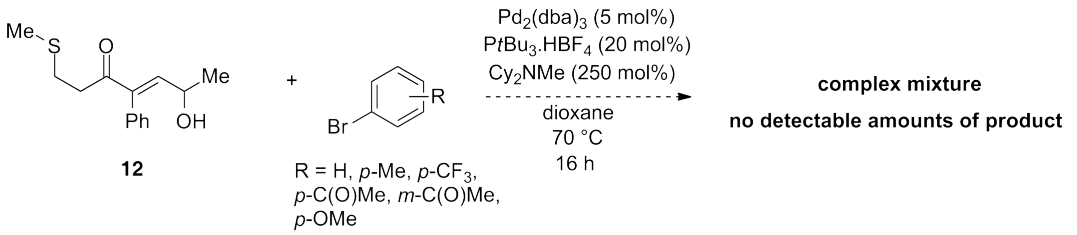


Figure 2.8. Planned application of Heck methodology to the production of regiodefined tetrasubstituted furans

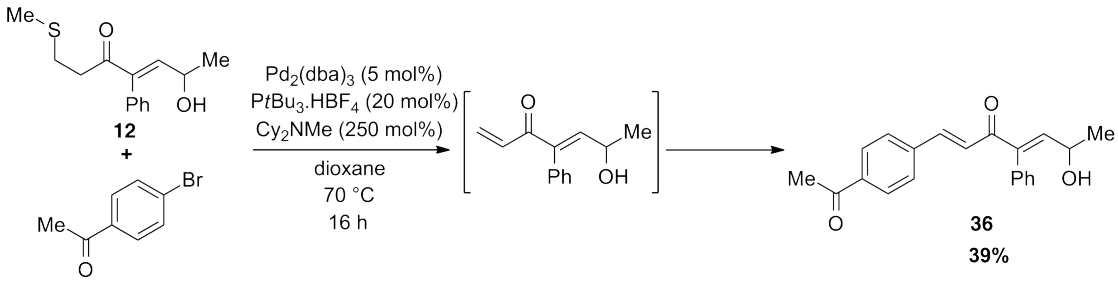
Applying the previously tested conditions to substrate **12** did not produce any detectable amounts of Heck product, nor did it result in the complete consumption of starting material (Scheme 2.10). Instead, multiple products were detected, but the

desired tetrasubstituted furan was not one of them. The product resulting from homo-coupling of the aryl halide was present in all cases, and its formation appeared to be faster in the case of electron-deficient aryl halides such as 3- or 4-bromoacetophenone.



Scheme 2.10. Failure of Heck reaction in the production of tetrasubstituted furans

In one reaction with electron-deficient aryl halide *p*-bromoacetophenone, product **36** was isolated in 39% yield (Scheme 2.11), and presumably originates from the elimination of methanethiol under the reaction conditions, followed by the Heck coupling of this terminal enone - a much more facile Heck substrate than the starting material (**12**). Evidence of the same elimination/Heck product from a similar reaction with less electron-rich *p*-methylbromobenzene was seen in the low resolution mass spectrum of the reaction, but the product was not isolated cleanly.



Scheme 2.11. Failure of Heck reaction in the production of tetrasubstituted furans

If elimination products of type **36** were accessed through the proposed eliminated intermediate, and such a process proved to be relatively general for alkyl thioether-containing hydroacylation products, then the potential would exist for the development

of a palladium-catalysed "deprotection" of the thioether moiety which is required for the hydroacylation reaction to proceed. Additionally, identifying which elements of the reaction conditions from which this product was isolated could perhaps lead to the development of conditions which avoided this presumed elimination process and hence potentially increase the chances of the desired Heck product being isolated.

Table 2.9: Attempt to identify the reaction conditions which resulted in the presumed elimination of methanethiol

37 38

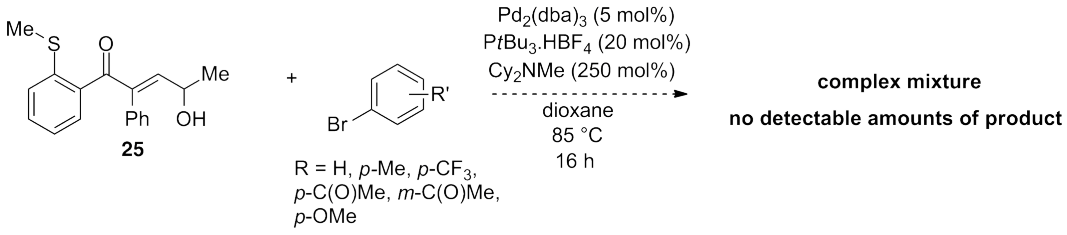
Entry	Palladium source	Ligand	Base	Yield (%)
1	none	none	Cy_2NMe	0
2	$Pd_2(dba)_3$	$P(tBu)_3 \cdot HBF_4$	Cy_2NMe	0
3	$Pd(OAc)_2$	none	Cy_2NMe	0
4	$Pd(OAc)_2$	$P(tBu)_3 \cdot HBF_4$	Cy_2NMe	0

Conditions: **37** (0.2 mmol), palladium source (0.05 equiv.), base (2.5 equiv.), DCE (2 mL), 100 °C, 16 h

Control experiments on simpler hydroacylation-derived substrate **37** (Table 2.9) indicated that this reaction did not proceed merely in the presence of Cy_2NMe (Table 2.9, entry 1), or the palladium source/ligand combination and base from the initial reaction (entry 2). From the hypothesis that perhaps a more Lewis acidic Pd(II) species - resulting from the oxidative addition of $Pd_2(dba)_3$ into the aryl halide utilised - was responsible for the elimination, $Pd(OAc)_2$ was tested, with and without the ligand employed in the original reaction (entries 4 and 3, respectively); none of these sets of conditions produced any detectable amounts of the elimination product **38**.

Further screening of Heck conditions was conducted using enone **25**, which could not undergo the methanethiol elimination which was observed when using non-aromatic substrate **12**. While the original Donohoe paper[133] from which this Heck approach was inspired conducted the Heck reactions at 70 °C, a further publication by the same

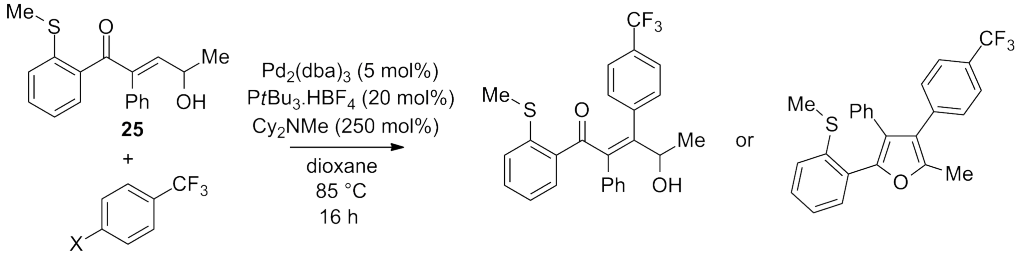
group[134] contained a detailed general procedure in which the same Heck reactions were conducted at 85 °C. In our system, no reaction was observed in any of the reaction conditions screened with either substrate, other than the predicted homocoupling of the range of aryl halides which were included in the screen (Scheme 2.12).



Scheme 2.12. Failure of Heck reaction in the production of tetrasubstituted furans from an aromatic thioether-containing starting material

To ensure that the failure of the Heck reactions screened so far were not a peculiarity of using aryl bromides, comparative reactions were run which involved the analogous aryl chloride and iodide for one example (Table 2.10).

Table 2.10: Aryl halide screening for the Heck reaction of aryl thioether-containing substrates



Entry	X	Yield (%)
1	Cl	0
2	Br	0
3	I	0

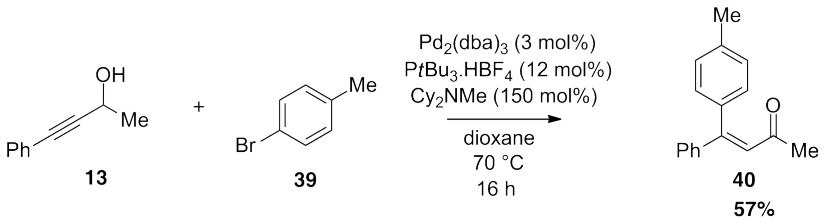
Conditions: **25** (0.2 mmol), aryl halide (2.5 equiv.) $Pd_2(dba)_3$ (0.05 equiv.), $P(tBu)_3 \cdot HBF_4$ (0.20 equiv.), Cy_2NMe (2.5 equiv.) DCE (2 mL), 85 °C, 24 h

No reaction occurred regardless of the aryl halide employed, although monitoring

the reaction by tlc indicated that homocoupling of the aryl halide was significantly faster when the aryl iodide was employed (Table 2.10, entry 3).

2.4.2 A "Heck-type" reaction of internal propargylic alcohols

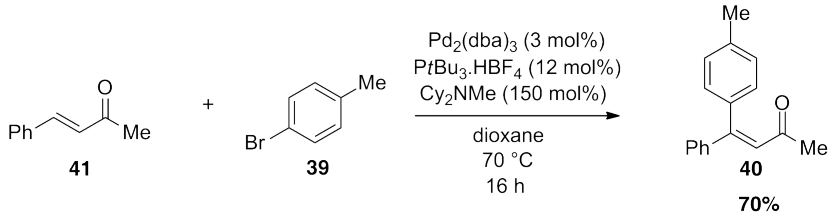
During the course of reaction screening of Heck reactions of trisubstituted substrates, a serendipitous discovery of a palladium-catalysed arylation of internal alkynes was discovered. Internal alkyne **13** was erroneously added to the Donohoe catalyst system ($Pd_2(dba)_3$, $P(tBu)_3 \cdot HBF_4$ and Cy_2NMe) with 4-bromotoluene **39**, rather than the intended enone substrate **12**. Surprisingly, the alkyne was consumed after 16 hours at 70 °C, and the product was found to have ^{1}H NMR and mass spectrometric data consistent with ketone **40** (Scheme 2.13).



Scheme 2.13. A "Heck-type" reaction of internal propargylic alkyne **13**

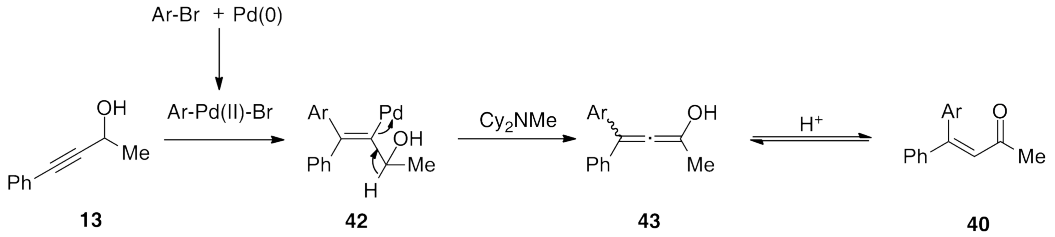
While the intramolecular rearrangement of secondary and tertiary propargylic alcohols to enones (the Meyer-Schuster rearrangement) is known,[147] and Larock[148] and Wu[149] have separately disclosed palladium-catalysed ring-expanding arylations of alkynylcyclobutanols to methylenecyclopentanones, this particular reaction does not appear to have been reported in the literature. The same product would however be accessible through a simple Heck reaction of the enone isomer of the propargylic alcohol which was employed; therefore unless the product of this reaction is the opposite double bond isomer to that which is obtained through a Heck reaction of the appropriate enone, it is perhaps of limited synthetic utility. A Heck reaction was conducted using the same catalyst system and aryl halide, but with enone **41** as the substrate, and the product of

this reaction produced identical, overlapping ^{1}H and ^{13}C NMR spectroscopy spectra to the product of the previous reaction (Scheme 2.14).



Scheme 2.14. Analogous Heck reaction of enone **41**

As the starting material for this comparison reaction was the *E* isomer and the Heck reaction is known to proceed through a *syn* addition of the intermediate Pd-aryl species,[150,151] the product of this reaction can be reasonably assumed to be the *Z* isomer (i.e. the addition of a higher-priority group to the *E* starting material with retention of stereochemistry). As the two products are NMR-identical, it is also reasonable to assume that the "Heck-type" reaction of alkyne **13** is similarly resulting in the *Z* isomer of enone **40**.



Scheme 2.15. A potential mechanism for the observed production of **40** from **13** under Heck conditions

The Pd(0)-catalysed isomerisation of propargylic alcohols to α,β-unsaturated enones is precedented,[152] and as such the reaction could conceivably proceed *via* such an isomerisation followed by Heck coupling of the resultant enone. Alternatively, a Pd-Ar species could undergo *syn* addition to propargylic alcohol **13** to give palladated intermediate **42**. Although this intermediate cannot undergo β-hydride elimination *via* the ordinary Heck mechanism, a β-hydrogen is available on the adjacent sp^3-hybridised

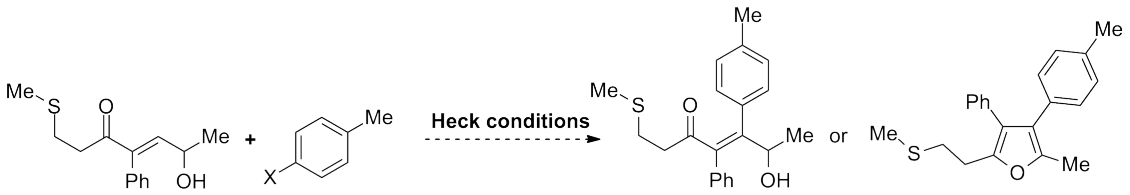
carbon. β-hydride elimination in this manner would produce allene **43**, which is the tautomer of the observed ketone product **40** (Scheme 2.15). No experimental evidence has been obtained to support or discredit this mechanism, and as such it is presented here merely as one possible mechanism for the observed process.

2.4.3 Alternative catalyst systems for the Heck reaction of trisubstituted substrates

The catalyst system which was used by the Donohoe group[133] (namely $Pd_2(dba)_3$, $P(tBu)_3 \cdot HBF_4$ and Cy_2NMe) and succesfully adopted for our analogous system was initially developed by Fu for the room temperature oxidative addition into aryl chlorides and bromides.[153] The challenging aspect of our intended Heck reaction to form a tetrasubstituted alkene and thence a tetrasubstituted furan is not this oxidative addition step, but the subsequent carbon-carbon bond forming step, and hence it seems entirely possible that this catalyst is not optimal for our substrates. As such, attempts were undertaken to identify Heck-type conditions which would be more succesful when applied to substrate **12**; avoiding the formation of the elimination/Heck product, and successfully achieving the arylation of the trisubstituted alkenes which would be required to synthesise tetrasubstituted furans (Table 2.11).

The previously attempted failed conditions (Table 2.11, entry 1) were repeated at 85 °C, in accordance with the previously mentioned updated protocol published by Donohoe[134] (entry 2), but still no reaction was observed. In case the reaction rate was being decreased by the requirement for the ligand required to equilibrate to its conjugate base before forming the active palladium complex, an alternative electron-rich monodentate phosphine (cataCXium® A) was used in the place of $P(tBu)_3 \cdot HBF_4$, but no improvement was observed (entry 3). While there is very little precedent for Heck reactions which result in tetrasubstituted alkenes in the literature, a rare example is

Table 2.11: Screen of various Heck conditions found in the literature

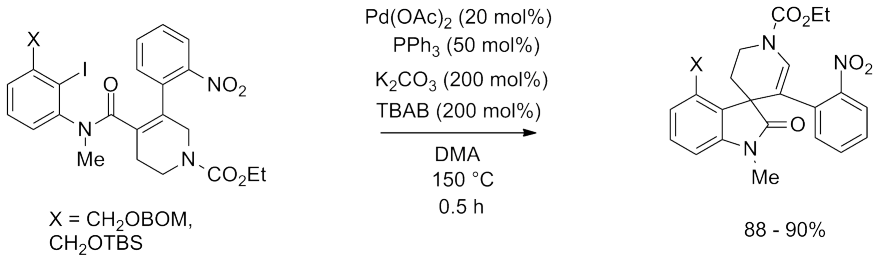


Entry	Palladium source	Ligand	Base	Additive	X	Yield (%)
1	$Pd_2(dba)_3$ (5 mol%)	$P(tBu)_3 \cdot HBF_4$ (20 mol%)	Cy_2NMe (250 mol%)	-	Br	0[a]
2	$Pd_2(dba)_3$ (5 mol%)	$P(tBu)_3 \cdot HBF_4$ (20 mol%)	Cy_2NMe (250 mol%)	-	Br	0[b]
3	$Pd_2(dba)_3$ (5 mol%)	cataCXium® A (20 mol%)	Cy_2NMe (250 mol%)	-	Br	0[a]
4	$Pd(OAc)_2$ (20 mol%)	PPh_3 (50 mol%)	K_2CO_3 (200 mol%)	TBAB (200 mol%)	Br	0[c]
5	$Pd(OAc)_2$ (4 mol%)	-	Cy_2NMe (150 mol%)	$nBuN^+Cl^-$ (150 mol%)	Br	0[d]
6	$Pd(OAc)_2$ (1 mol%)	dmphen (1.2 mol%)	-	-	$B(OH)_2$	0[e]
7	$Pd(OAc)_2$ (1 mol%)	dmphen (1.2 mol%)	-	*p*-benzoquinone (100 mol%)	$B(OH)_2$	0[f]

Conditions: **12** (0.2 mmol), palladium source (0.05 equiv.), base (2.5 equiv.), DCE (2 mL), 100 °C, 16 h; [a] dioxane, 70 °C; [b] dioxane, 85 °C; [c] DMA, 150 °C; [d] DMA, 100 °C; [e] acetonitrile, open to air, 25 °C; [f] acetonitrile, microwave for 80 min, 100 °C.

Weinreb's synthesis of communesin F,[154] in which a tetrasubstituted alkene undergoes an intramolecular Heck reaction with an aryl iodide (Scheme 2.16).

The difficulty of this transformation is reflected in the high palladium loading of 20% (with 50% ligand) and high temperature used. Like the work of Jeffery,[155,156] the reaction also utilised tetraalkylammonium salts. When applied to test substrate **12** (entry 4), all starting material was consumed but a complex mixture resulted which



Scheme 2.16. Weinreb's Heck reaction of a tetrasubstituted alkene in the synthesis of communesin F

containing nothing which was identifiable as either the Heck product or the tetrasubstituted furan. Buchwald published "*A new general procedure for the Heck arylation of disubstituted olefins*"[157] which used $Pd(OAc)_2$, tetraalkylammonium salts and no additional ligand; these conditions were also unsuccessful in our test system (entry 5). Larhed[158] disclosed a base-free oxidative Heck reaction which was catalysed by $Pd(OAc)_2$ and 2,9-dimethyl-1,10-phenanthtroline (dmphen) in acetonitrile, with either air or *p*-benzoquinone as the oxidant and arylboronic acids as the coupling partner. While the conditions employed in conjunction with this system were considerably milder than the previous unsuccessful reactions - and with the potential issue of thioether oxidation - it was hoped that these very different reaction conditions might prove successful where more traditional Heck reactions had failed. Additionally, the base-free nature of the reaction should prevent the formation of the elimination/Heck product which had previously been observed, if such a product was indeed originating from an elimination process. Unfortunately, both the reaction which was run open to air at room temperature for 16 hours (entry 6) and one which was heated to 100 °C under microwave conditions with *p*-benzoquinone as the oxidant (entry 7) returned only starting materials. It therefore seemed that tetrasubstited furans were inaccessible from the application of Heck methodology to γ-hydroxy-α,β-enones containing trisubstituted alkenes.

2.5 Brominations as a means to introduce further functionality

As Heck methodology was found to be unsuitable for the synthesis of tetrasubsituted olefins and hence tetrasubstituted furans, a different approach was undertaken. Precedent exists for the bromination of trisubstituted olefins to form tetrasubstituted bromoolefins,[159–161] and this would provide a handle for functionalisation in the same position that the Heck reactions proved unsuitable for. Alternatively, the direct cyclisation of this bromoolefin would itself produce a tetrasubstituted bromofuran (Figure 2.9). Brominated furans can be functionalised by lithium-halogen exchange[162] followed by trapping of the lithiated species with an electrophile,[163] or used as the substrate in palladium-catalysed cross-coupling reactions.[164,165]

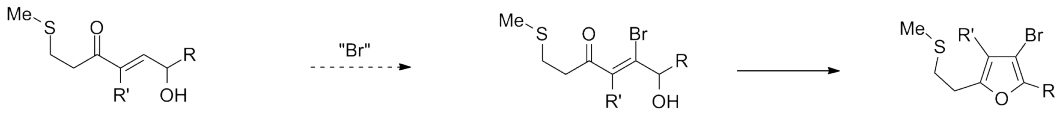


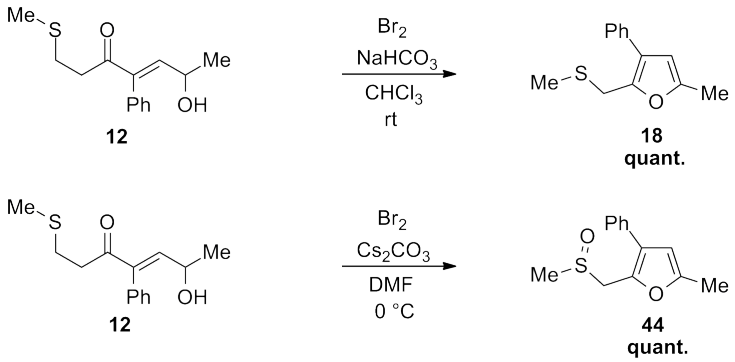
Figure 2.9. Bromination strategy for producing tetrasubstited furans

Several limitations immediately presented themselves on considering this approach: thioethers can be oxidized to sulfones or sulfoxides under some bromination conditions.[166,167] While thioether oxidation would not in itself present a problem, the potential exists for mixtures of inseparable products to be created (for example, oxidised starting material together with oxidised and unoxidised products). Secondly, any successful bromination would likely be limited to non-aromatic substrates, as the electron-donating nature of a thioether on an aromatic ring would most likely result in facile *ortho*- or *para*-bromination of the aromatic ring rather than the desired olefin bromination. Finally, it would be preferable to avoid acidic conditions for the olefin bromination, as the substrate would likely rapidly cyclise to non-brominated furan (unless the furan thus formed was itself amenable to bromination under acidic conditions);

this constraint rather limits the availability of applicable olefin bromination conditions.

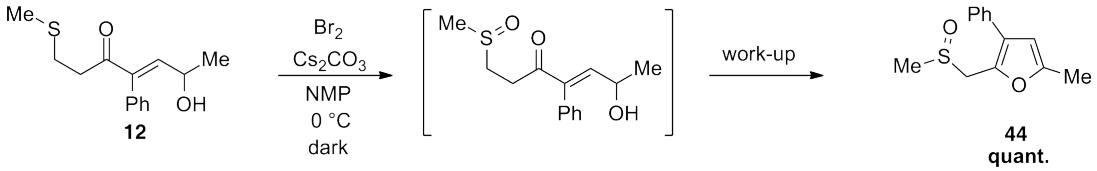
The first set of conditions which were employed were based on literature precedent for the bromination of a trisubstituted olefin (Scheme 2.17). The substrate in chloroform was treated with elemental bromine at room temperature, with the reaction being buffered by 10 equivalents of $NaHCO_3$. Surprisingly, quantitative conversion to the non-brominated furan was observed by ^1H NMR spectroscopic analysis of the crude reaction mixture. As the $NaHCO_3$ which was employed as a buffer is largely insoluble in chloroform at room temperature, it was supposed that this cyclisation was perhaps being promoted by trace amounts of HBr. Accordingly, the reaction was next attempted with an inorganic base which was soluble in the chosen solvent; Cs_2CO_3 in DMF was used, and the reaction was conducted at 0 °C as it had previously been shown that the cyclisation of these substrates to the requisite trisubstituted furan was sluggish at low temperatures. Under these conditions, crude NMR spectroscopic analysis showed quantitative conversion to a non-brominated furan product, which was confirmed by mass spectrometry to be the sulfoxide of the non-brominated furan (Scheme 2.17), **44**. It is possible that moisture was introduced to the system through either the base, which was not oven-dried and was present in large excess, or the solvent, and this allowed the oxidation of the thioether to occur. While this was not the desired outcome of the reaction, it is a potentially useful set of cyclisation conditions nonetheless; treatment of γ-hydroxyenones with HCl forms the thioether-containing furan, whereas these conditions would furnish the same furan but with a sulfoxide rather than the starting thioether.

As the cyclisation of these substrates is known to be accelerated by light,[130] the reaction was repeated in the dark, and with DMF replaced by NMP (as Cs_2CO_3 is more soluble in NMP than DMF), in an attempt to minimise unwanted cyclisation by either light- or acid-acceleration. Following the reaction by tlc indicated that the starting material was being consumed to a slightly more polar spot, which was confirmed by



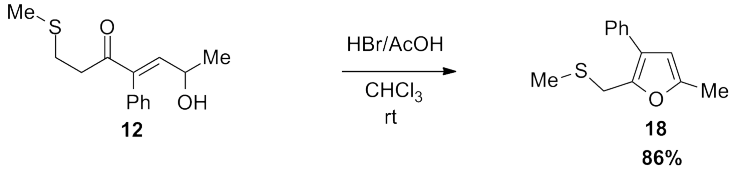
Scheme 2.17. Attempts at olefin bromination under basic conditions

mass spectrometry to be the sulfoxide of the starting material. On being exposed to light, this sulfoxide quantitatively cyclised to the appropriate furan (Scheme 2.18).



Scheme 2.18. Formation of the sulfoxide-containing furan

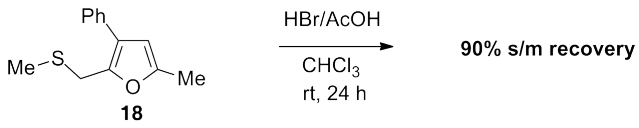
Given the propensity of these substrates to undergo cyclisation to non-brominated furans under even basic conditions, the need to avoid acidic bromination conditions seemed to be unnecessary. The γ-hydroxyenone test substrate **12** in chloroform was treated with HBr/AcOH, which resulted in rapid conversion to the non-brominated furan, in 86% isolated yield (Scheme 2.19).



Scheme 2.19. Attempts at olefin bromination under acidic conditions

In a separate reaction, the non-brominated furan was treated under these same conditions for 24 hours, but no trace of brominated furan was observed by tlc or mass

spectrometry; indeed, the starting non-brominated furan was recovered in 90% yield. It thus seems that conversion of γ-hydroxyenones was unlikely to occur, and the furan itself seemed to be similarly unreactive to acidic bromination conditions (Scheme 2.20).



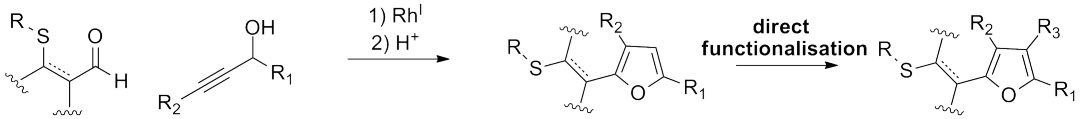
Scheme 2.20. Attempts at furan bromination under acidic conditions

2.6 Functionalisation of the final position

The functionalisation of trisubstituted furans to form tetrasubstituted furans is not particularly well precedented in the literature - particularly reactions which introduce functionality at the 3- or 4-position of a trisubstituted furan. The lithiation[163] and direct palladium-catalyzed oxidative Heck-type reaction of fluorinated trisubstituted furans with aryl bromides[168] and styrenes[169] (with the new functional group being introduced adjacent to the fluorine atom) is known; Cao reported the direct palladium-catalysed arylation of electron deficient furans with aryl halides, although at least two electron withdrawing groups were required for the reaction to proceed;[170] and Knochel described a magnesiation/transmetalation/copper-catalysed acylation protocol for producing a tetrasubstituted furan from a trisubstituted furan, but only one example was demonstrated (albeit in high yield);[171]

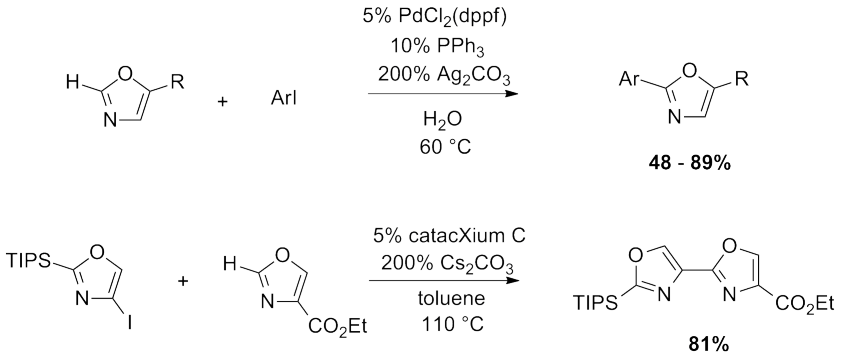
Given the failure of the direct bromination approach and the literature precedent for some limited direct arylation chemistry of trisubstituted furans, it was decided to apply some recent examples of direct heterocyclic C-H functionalisation conditions to a trisubstituted furan which had been synthesised according to our methodology. It was hoped that the successful application of such a functionalisation would permit the synthesis of regiodefined tetrasubstituted furans in just two steps from chelating

aldehydes and propargylic alkynes (Scheme 2.21).



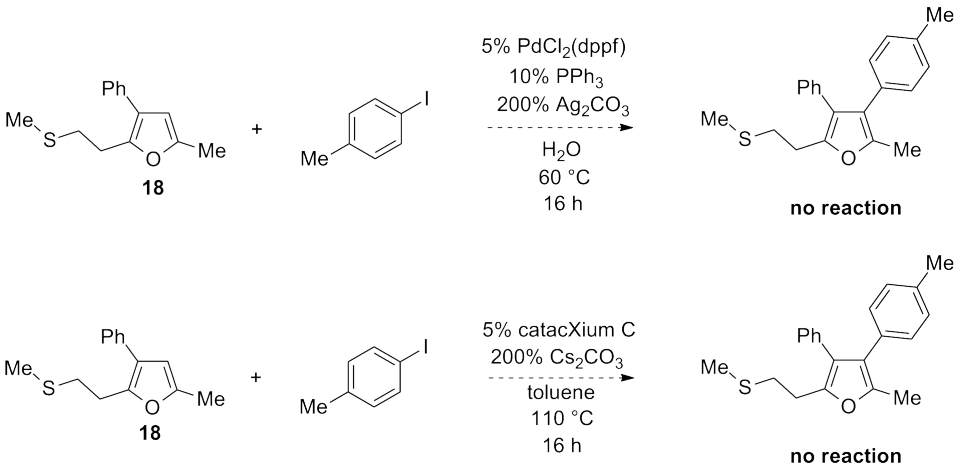
Scheme 2.21. Proposed route to tetrasubstituted furans *via* a catalytic functionalisation of trisubstituted furans from the one-pot approach

Greaney has described the direct palladium-catalysed C-H functionalisation of oxazoles with aryl iodides, both "on water" and in organic solvents (Scheme 2.22).[172]



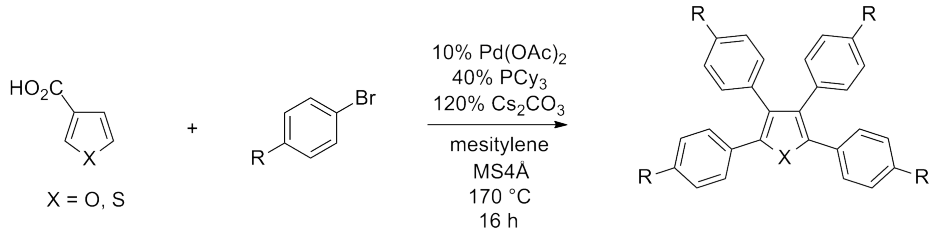
Scheme 2.22. Greaney's conditions for C-H functionalisation of oxazoles

The application of both of these types of conditions to test substrate **18** were unsuccessful, resulting in only starting materials being recovered from the reaction (Scheme 2.23).



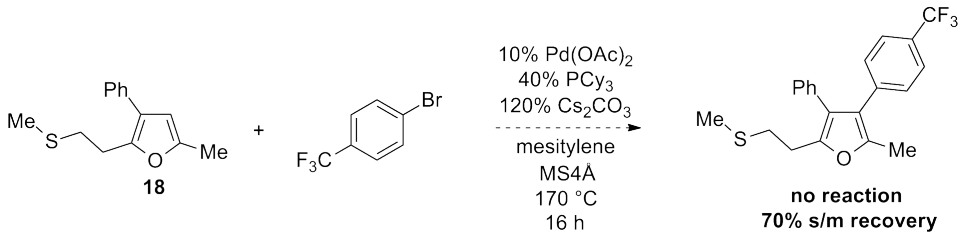
Scheme 2.23. Greaney's conditions for C-H functionalisation of oxazoles

Miura has published a perarylation of 3-thiophene and 3-furancarboxylic acids under palladium-catalysed conditions,[173] which is presumed to involve some combination of directed arylations on either side of the acid and a decarboxylative coupling (Scheme 2.24). While the order in which the sequential arylations occur is unclear and not experimentally proven, at some point in the pathway there is presumably the arylation of a trisubstituted furan to a tetrasubstited furan.



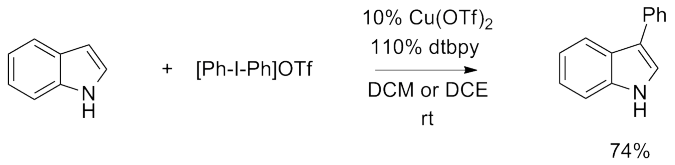
Scheme 2.24. Miura's synthesis of perarylated furans and thiophenes from 3-thiopene- and 3-furancarboxylic acid)

As such, these conditions were applied to test substrate **18** (Scheme 2.25), but no product was observed.



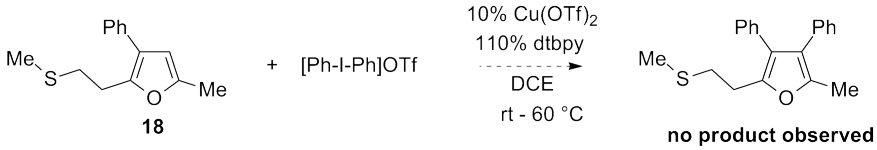
Scheme 2.25. The application of Miura's perarylation conditions to a trisubstituted furan

Recent high-profile work by Gaunt[174,175] has described the direct copper-catalysed arylation of a variety of arenes, including heterocycles, with diaryliodonium salts under mild reaction conditions (Scheme 2.26).



Scheme 2.26. An example of Gaunt's copper-catalysed direct arylation of heterocycles with diaryliodonium salts

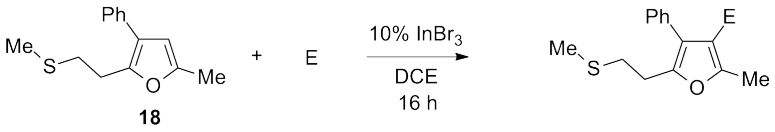
The application of these conditions to substrate **18** did not result in any observed formation of the desired product, but the outcome of the reaction was somewhat temperature dependent (Scheme 2.27). Reactions which were run at room temperature returned only starting materials, whereas reactions which were run at 40 or 60 °C consumed all of the starting material (by tlc analysis of the crude reaction mixture) but resulted in only a baseline spot in the tlc. Given how non-polar the starting furan and desired product are, it was thought to be unlikely that this baseline material was product-related.

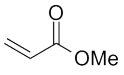
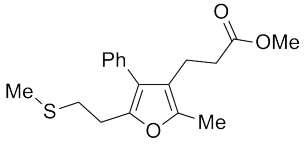
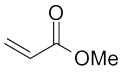
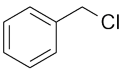
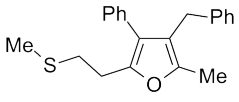
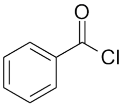
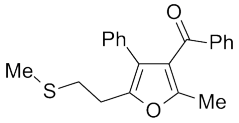
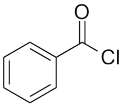
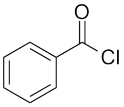


Scheme 2.27. The application of Gaunt's copper-catalysed direct arylation of heterocycles with diaryliodonium salts to a trisubstituted furan

Indium(III) reagents have been increasingly used as Lewis acid catalysts,[176] including Friedel-Crafts alkylations and acylations of heterocyclic systems.[177] A brief screen of mild Friedel-Crafts-type conditions for the functionalisation of trisubstituted furan **18** was undertaken (Table 2.12). Reactions with methyl acrylate (Table 2.12, entries 1 and 2) and $InBr_3$ returned only starting material on work-up (the unreacted methyl acrylate is presumably lost on work-up due to its volatility). Employing benzyl chloride (entry 3) resulted in the consumption of the benzyl chloride (by tlc analysis), but no product formation. The use of benzoyl chloride, however, resulted in a trace amount of product being formed at room temperature (entry 4). On raising the temperature to 40 °C, the desired product **47** was isolated in 65% yield (entry 5). A modest increase in yield was observed by further raising the temperature, increasing the catalyst loading to 20 mol% and using an excess of benzoyl chloride (entry 6). To the best of our knowledge, this reaction represents the first synthesis of a tetrasubstituted furan by indium catalysis, and the first functionalisation of a substituted furan at the 3- or 4-position by indium catalysis.

Table 2.12: Initial screen of indium catalysis as a means to introduce functionality at the final position of the trisubstituted furan



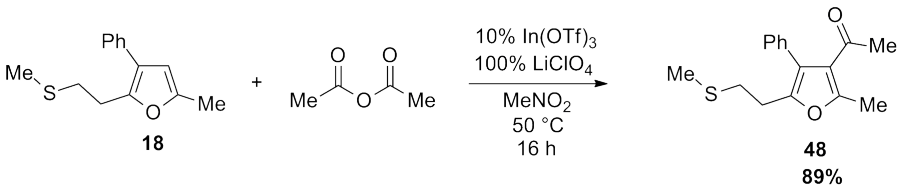
Entry	Temperature (°C)	E	Product	Yield (%)
1	25		 **45**	0
2	40		**45**	0
3	25		 **46**	0
4	25		 **47**	trace
5	40		**47**	65
6	60		**47**	71[a]

Conditions: **18** (0.2 mmol), electrophile (1 equiv.), DCE (2 mL); [a] $InBr_3$ (0.2 equiv.), BzCl (2 equiv.)

Frost has published an account of a catalyst system comprising catalytic $In(OTf)_3$ and stoichiometric $LiClO_4$ for the acylation of a variety of aryl units,[178] including one

example in which furan was transformed into 2-acetylfuran in quantitative yield. These conditions were applied unmodified to substrate **18** and, pleasingly, gave the desired product **48** in excellent yield (Scheme 2.28).

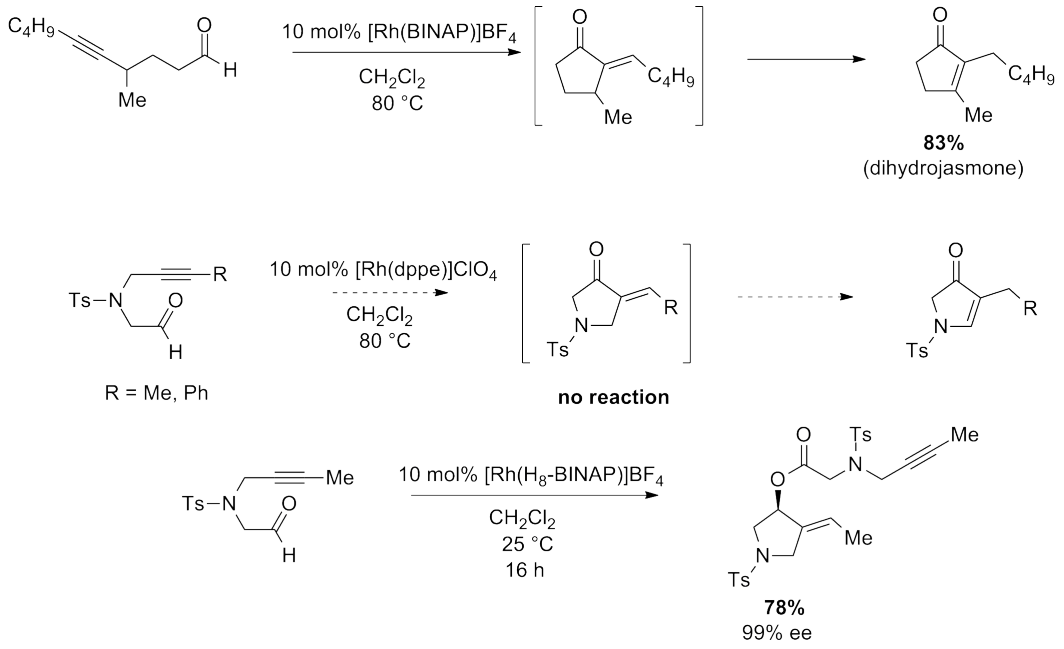
The discovery that convenient and relatively mild conditions can be used to functionalise the trisubstituted furans produced by hydroacylation-based methodology creates a fairly simple route to access regiodefined tetrasubstituted furans. While no attempts were made to consolidate the two separate sets of indium-catalysed acylations, it is possible that further optimisation would reveal a more general catalytic system for these transformations.



Scheme 2.28. The application of Frost's $In(OTf)_3/LiClO_4$ catalyst system to the acylation of a trisubstituted furan

2.7 Tandem hydroacylation/double-bond isomerisation reactions for the atom-economic synthesis of 1,4-dicarbonyls

Tandem hydroacylation/double-bond isomerisation methodology has been described by Tanaka in intramolecular reactions of 4-alkynals.[66] Attempts within this group to expand this methodology to heterocycles by using heteroatom-containing analogues of the carbocycles used by Tanaka were unsuccesful; a later publication by the same group confirmed that these substrates instead undergo a reductive dimerisation/cyclisation process (Scheme 2.29).[67]

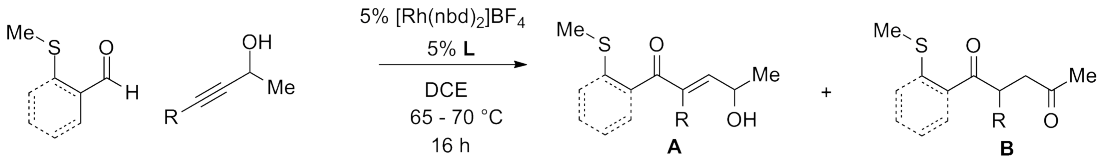


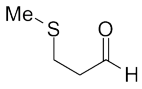
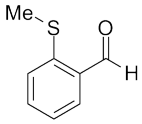
Scheme 2.29. Tanaka's intramolecular hydroacylation/double-bond isomerisation in carbocyclic substrates, and the failure of an analogous heterocyclic system

As a simple intramolecular tandem hydroacylation/double-bond isomerisation approach to heterocycle synthesis proved to be problematic, an alternative approach would need to be undertaken if a such an approach was to be applied to heterocycle synthesis. It was envisaged that a tandem intermolecular hydroacylation/double-bond isomerisation process with propargylic alcohol substrates might permit the atom-efficient synthesis of 1,4-dicarbonyl compounds *via* a hydroacylation disconnection, and that 1,4-dicarbonyl compounds thus formed could be transformed into heterocycles using traditional cyclisation methodology. As previous results indicated that the use of dppe-based catalyst system produced γ-hydroxyenones rather than 1,4-dicarbonyls, a ligand screen was undertaken in an attempt to identify a ligand which would enable the desired isomerisation in addition to intermolecular hydroacylation (Table 2.13).

As described previously, dppe is an excellent ligand for the hydroacylation of aldehyde **2** with both terminal (Table 2.13, entry 1) and internal propargylic alkynes (Ta-

Table 2.13: Screen to identify reaction conditions for a tandem hydroacylation/double-bond isomerisation process



Entry	Aldehyde	Ligand	R	Conversion (%)[a] A	B
1	 **2**	dppe	H	100	0
2	**2**	DPEphos	H	trace	trace
3	 **24**	dppe	H	24	15
4	**24**	dppm	H	trace	0
5	**24**	dcpm	H	30	20
6	**24**	DPEphos	H	0	100 (84)[b]
7	**24**	DPEphos	Et	0	0
8	**24**	DPEphos[c]	Et	57	0

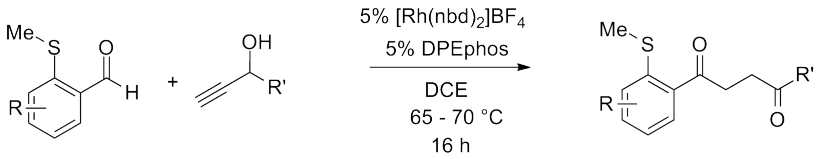
Conditions: aldehyde (0.75 mmol), propargylic alcohol (1.1 equiv.), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), ligand **L** (0.05 equiv.), DCE (5 mL), 65 - 70 °C, 16 h; [a] conversion determined by ^{1}H NMR; [b] isolated yield in brackets; [c] pre-catalyst activated by hydrogenation.

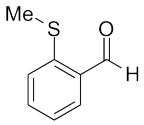
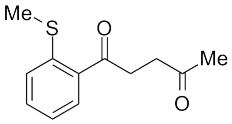
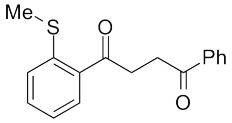
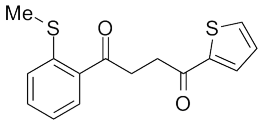
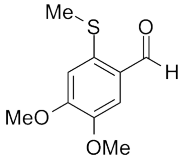
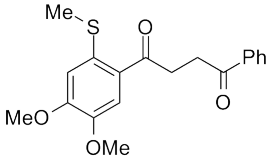
ble 2.5), with no double-bond isomerisation of the resulting γ-hydroxyenones to the requisite 1,4-dicarbonyl compounds being observed. When aromatic aldehyde **24** is employed, however, dppe proved to be ineffective at catalysing the hydroacylation of this aldehyde and terminal propargylic alkynes, resulting in a complex mixture which contained starting materials along with traces of isomerised and non-isomerised hydroacylation products (entry 2). Other structurally related ligands were similarly ineffective in this system; dppm produced only a trace of hydroacylation product (entry 4), and the electron-rich dcpm ligand gave incomplete conversion to a mixtures of

isomerised and non-isomerised hydroacylation products (entry 5). DPEphos, however, was completely selective for the production of 1,4-dicarbonyl compounds when aldehyde **24** was employed (entry 6), but not with alkyl aldehyde **2**, with which no consumption of starting material was observed (entry 2). The DPEphos catalyst system was incapable of tolerating internal propargylic alkynes (entry 7), producing neither hydroacylation product nor 1,4-dicarbonyl. Hydrogenation of the DPEphos precatalyst resulted in some conversion to the hydroacylation product, but still no isomerisation of the internal double bond was observed (entry 9).

The DPEphos catalyst system therefore appeared to be effective for the tandem hydroacylation/double-bond isomerisation reaction between aromatic aldehyde **24** and terminal propargylic alkynes, but not internal propargylic alkynes. This limitation is unsurprising given the relative rates of double bond isomerisation reactions and the limited precedent for rhodium-catalyzed double-bond isomerisation reactions of conjugated double-bonds.[179,180] With a working catalyst system for a tandem intermolecular hydroacylation/double-bond isomerisation in hand, a short series of 1,4-dicarbonyl compounds were prepared (Table 2.14). The reaction tolerated alkyl, aryl and heteroaryl terminal propargylic alkynes (Table 2.14, entries 1, 2 and 3 respectively) to deliver products **49**, **50** and **51** in reasonable to excellent yields. The thiophene example (entry 3) produced a more complex reaction mixture than the methyl or phenyl examples and hence a lower yield, although all starting material was consumed after 16 hours. An electron-rich aldehyde was also utilised (entry 4), although the lower yield in this case was a result of incomplete consumption of the starting material. All products were white crystalline solids which were readily recrystallised to analytical purity (the quoted yields in Table 2.14 are after recrystallisation).

Table 2.14: Scope of the tandem intermolecular hydroacylation/double-bond isomerisation of aromatic aldehydes and terminal propargylic alcohols

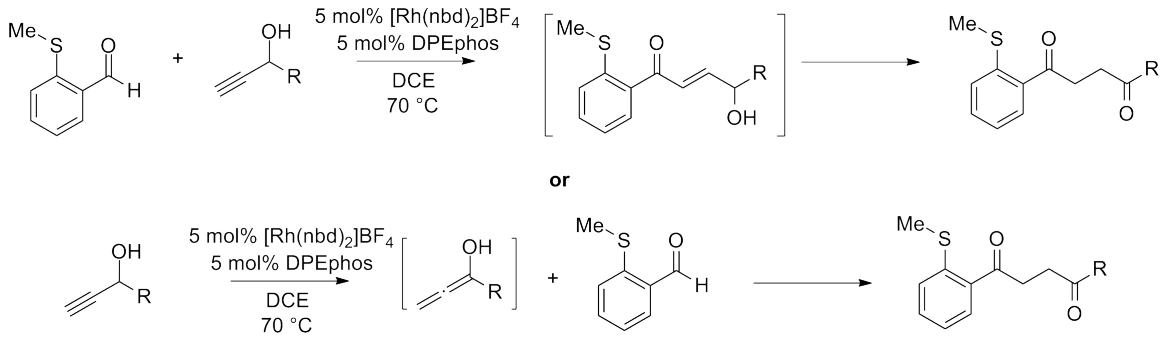


Entry	Aldehyde	R'	Product	Yield (%)
1	 **24**	Me	 **49**	84
2	**24**	Ph	 **50**	87
3	**24**	2-thiophene	 **51**	66
4	 **52**	Ph	 **53**	56

Conditions: aldehyde (0.75 mmol), propargylic alcohol (1.1 equiv.), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), DPEphos (0.05 equiv.), DCE (5 mL), 65 - 70 °C, 16 h

The reaction could conceivably proceed through two pathways: the described alkyne hydroacylation followed by a double-bond isomerisation of the product; or the initial isomerisation of the terminal alkyne to the corresponding allene, followed by the hy-

droacylation of this species (Scheme 2.30).



Scheme 2.30. The two potential reaction pathways which lead to observed 1,4-dicarbonyl product

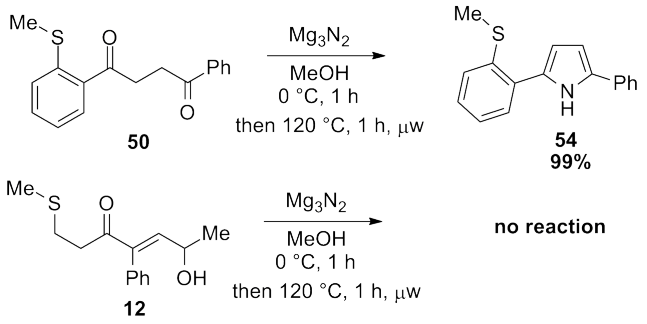
It was found that subjecting 1-phenyl-2-propyn-1-ol **5** to the $[Rh(nbd)_2]BF_4$/DPEphos catalyst system used in the tandem process did not produce any detectable amounts of the allene. While this does not rule out the possibility of small amounts of allene being produced and rapidly undergoing hydroacylation to the observed product, our previous experience within the group indicates that the hydroacylation of terminal alkynes is more facile than that of allenes, and hence the pathway which proceeds *via* the hydroacylation of the non-isomerised alkyne would appear to be more likely.

2.7.1 Heterocycles derived from the 1,4-dicarbonyl products of the tandem intermolecular hydroacylation/double-bond isomerisation reaction

As the primary motivation for the atom-efficient synthesis of 1,4-dicarbonyl compounds *via* a hydroacylation disconnection was their traditional use as heterocycle precursors, it was decided to demonstrate this utility by synthesising a small variety of heterocycles from the 1,4-dicarbonyl hydroacylation products.

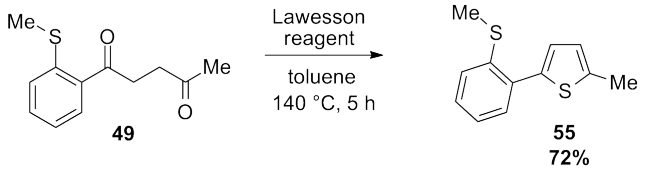
Ley has described the use of Mg_3N_2 in MeOH under microwave conditions as an effective means to produce pyrroles from 1,4-dicarbonyl compounds;[181] applying

these conditions unmodified to 1,4-dicarbonyl **50** produced the pyrrole **54** in an excellent 99% isolated yield (Scheme 2.31). The same conditions were ineffective when applied to γ-hydroxy-α,β-enones, i.e. the equivalent non-isomerised structures, as was a similar reaction in which the Mg_3N_2 was replaced with benzylamine.



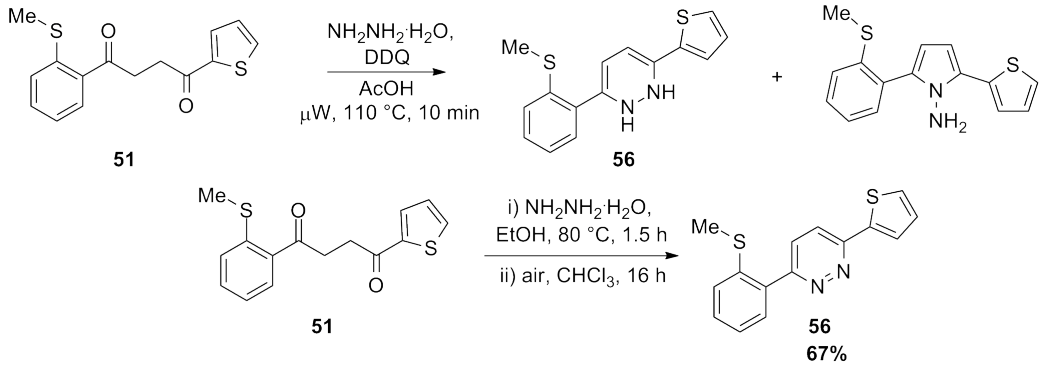
Scheme 2.31. The synthesis of pyrrole **54** from 1,4-dicarbonyl **50**

1,4-Dicarbonyl **49** was heated in the presence of Lawesson reagent to furnish the thiophene **55** in 72% yield (Scheme 2.32).



Scheme 2.32. The synthesis of thiophene **55** from 1,4-dicarbonyl **49**

An attempt was made to convert **51** to the requisite pyridazine **56** by treatment with hydrazine hydrate in acetic acid and in the presence of DDQ under microwave irradiation, as reported by Taddei,[182] but only the *N*-aminopyrrole and the dihydropyridazine appeared to be present by NMR and mass spectrometric analysis. The desired pyridazine was obtained, however, by heating **51** with $NH_2NH_2 \cdot H_2O$ in EtOH, followed by aerobic oxidation in $CHCl_3$, to produce the requisite pyridazine in 67% yield (Scheme 2.33). Pyridazines of this general structure, with thioether containing aromatics in the 2- or 5-position, have been patented as interleukin 1-βinhibitors.[183]



Scheme 2.33. The synthesis of pyridazine **56** from 1,4-dicarbonyl **51**

2.8 Conclusion

In summary, we have demonstrated the applicability of rhodium-catalysed intermolecular hydroacylation to the synthesis of di- and tri-substituted furans in a regiocontrolled fashion which proceeds through a 100% atom-economic carbon-carbon bond forming step followed by a simple dehydrative cyclisation. Pre-existing Heck methodology has been utilised to further increase the scope of regioisomeric trisubstituted furans which are accessible *via* this methodology. An unprecedented indium-catalysed acylation procedure for the synthesis of tetrasubstituted furans from the trisubstituted furans thus produced has also been described. In addition, we have a developed an atom-efficient synthesis of 1,4-dicarbonyl compounds, which is presumed to proceed through a tandem intermolecular hydroacylation/double-bond isomerisation process, and demonstrated the transformation of these products into 5- and 6-membered heterocycles using previously described methodology.

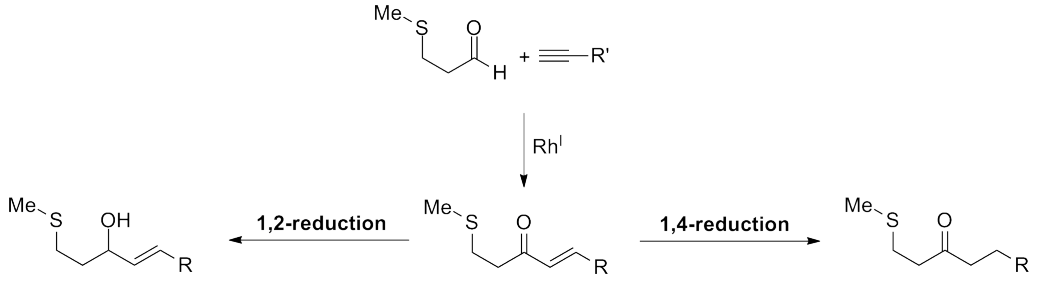
Chapter 3

Tandem rhodium-catalysed hydroacylation/reductive processes

3.1 Introduction

A wide range of rhodium catalysts are known to catalyse reductive processes, particularly hydrogenations, transfer hydrogenations[184,185] and hydrosilylations;[186] several examples of hydroacylation-like methodology which utilise a redox step are also known.[116–118] The hydroacylation methodology which has been developed by the Willis group encompasses a range of activated and non-activated alkenes as well as allenes, but alkynes remain the most facile class of substrate for this methodology.[73–75,81,82] A tandem hydroacylation/reduction procedure would therefore enable alkyne substrates to be utilised to provide the equivalent products to an alkene hydroacylation, broadening the scope of saturated ketones which are accessible through intermolecular hydroacylation methodology. Additionally, if a suitable reductive process was identified which could regioselectively reduce the carbonyl group of the α,β-unsaturated enones which are produced in an intermolecular alkyne hydroacylation (i.e. a 1,2-reduction of an enone) in a tandem catalytic manner, then this would permit the one-pot synthesis

of allylic alcohols *via* hydroacylation methodology (Scheme 3.1).



Scheme 3.1. The potential for a tandem hydroacylation/reduction protocol to access allylic alcohols or aliphatic ketones from chelating aldehydes and alkynes

3.2 Hydrogenations

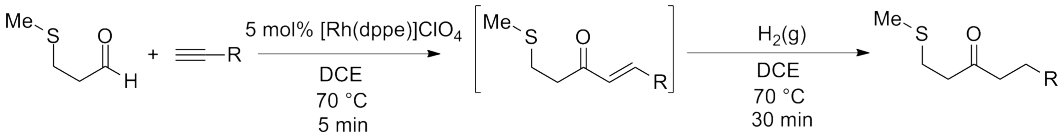
Previous work in the Willis group† has demonstrated that a tandem hydroacylation/hydrogenation protocol was possible simply by bubbling hydrogen gas through the reaction solution once the hydroacylation had proceeded to completion (Table 3.1).[187]

This procedure worked excellently when unbranched aliphatic alkynes were employed (Table 3.1, entries 1-3), with quantitative conversion to the reduced hydroacylation product. The use of 3-methyl-1-hexyne, however, required a 10 mol% catalyst loading to proceed to completion (entries 4 and 5), and the presence of a tertiary butyl substituent resulted in no reduction whatsoever being observed (entry 6). The reaction would therefore appear to be quite sensitive to steric bulk on the olefin which is to be reduced. Additionally, an aromatic substrate was unreactive towards hydrogenation (entry 6), even when 10 mol% of catalyst was employed (entry 8). No reduction of the carbonyl group was observed in any reaction.

These reductions provided solid proof of principle for a tandem hydroacylation/reduction process, but were subject to several limitations; while straight chain aliphatic substrates

†reactions originally conducted by a co-worker[187]

Table 3.1: Previous work in the Willis group demonstrating the viability of a tandem hydroacylation/hydrogenation procedure



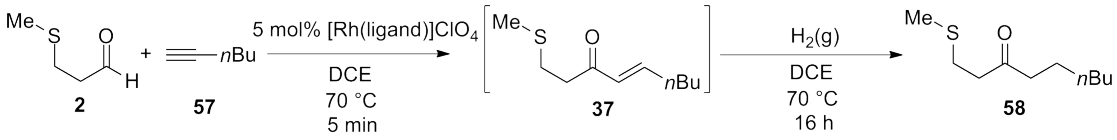
Entry	R	Hydroacylation conversion (%)	Reduction conversion (%)
1	*n*Bu	100	100
2	CH_2CH_2Ph	100	100
3	$CH_2CH_2CH_2OH$	100	100
4	$CH(CH_3)CH_2CH_2CH_3$	100	63
5	$CH(CH_3)CH_2CH_2CH_3$	100	98[a]
6	*t*Bu	100	0[a]
7	Ph	100	0
8	Ph	100	0[a]

Conditions: **2** (0.3 mmol), alkyne (2 equiv.), $[Rh(dppe)(nbd)]ClO_4$ (0.05 equiv.), DCE (3.0 mL), 70 °C, 5 min, then H_2(g) bubbled through the solution for 30 min; conversions determined by ^{1}H NMR spectroscopy; [a] 10 mol% catalyst loading. All reactions originally conducted by co-worker Lewis Vidler.[187]

were tolerated, branched chain substrates required either an increase in catalyst loading or simply did not proceed, and an aromatic substrate was similarly unreactive. The conditions also used relatively forcing conditions for the hydrogenation, with a constant stream of hydrogen gas flowing through the reaction rather than a balloon atmosphere. Comparison reactions were run to determine if this flow of hydrogen was required to achieve the observed conversions (Table 3.2).

It was found that conversion to the reduced product **58** drastically decreased when a balloon pressure of hydrogen was used, rather than a constant stream of gas through the reaction solution. This effect was observed when either dppe (Table 3.2, entries 1 and 2) or MeDuPhos (entries 3 and 4) were used as the ligand. This apparent requirement for a constant flow of hydrogen to facilitate the reduction of the most facile class of

Table 3.2: Examination of the effect of the physical supply of hydrogen on the tandem hydrogenation/hydroacylation protocol



Entry	Ligand	Hydrogen source	Hydroacylation conversion (%)	Reduction conversion (%)
1	dppe	Bubbled	100	100
2	dppe	Balloon	100	29
3	MeDuPhos	Bubbled	100	100
4	MeDuPhos	Balloon	100	31

Conditions: **2** (0.3 mmol), 1-hexyne **57** (2 equiv.), [Rh(ligand)(nbd)]ClO_4 (0.05 equiv.), DCE (3.0 mL), 70 °C, 5 min, then H_2(g) delivered to the reaction mixture by the stated method, 16 h; conversions determined by ^{1}H NMR spectroscopy

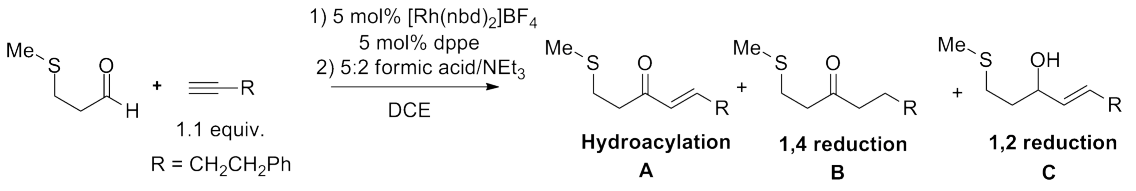
substrates further limits the usefulness of this procedure.

3.2.1 Transfer hydrogenations

A brief screen of transfer hydrogenation conditions was conducted, to determine if the *in situ* generation of hydrogen could be used to obviate the need for a flow of hydrogen gas through the reaction mixture and hence increase the ease of use of this methodology.[188] A tandem reaction was conducted in which the [Rh(nbd)$_2$]BF_4/dppe-catalysed hydroacylation of aldehyde **2** and 4-phenyl-1-butyne was heated at 70 °C for 1 hour, followed by the room temperature addition of a 5:2 mixture of formic acid:triethylamine.[189] Following column chromatography, hydroacylation product, 1,4-reduction product and 1,2-reduction product were all isolated. Increasing the equivalents of formic acid:triethylamine and raising the reaction temperature to 40 °C did not push the reduction to completion, and again resulted in a mixture of regioisomeric reduction products (Table 3.3). The use of sodium formate rather than formic acid:triethylamine resulted in no reduction being observed, which is to be expected in

an aprotic solvent.

Table 3.3: Selectivity of a tandem rhodium catalysed intermolecular alkyne hydroacylation/transfer hydrogenation procedure



Entry	Formic acid equiv.	Triethylamine equiv.	Temperature (°C)	A (%)	B (%)	C (%)
1	10	4	25 °C	56	32	12
2	50	20	40 °C	19	42	38

Conditions: **2** (0.75 mmol), 4-phenyl-1-butyne (1.1 equiv.), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.), DCE (5.0 mL), 70 °C, 1 h, then formic acid/triethylamine (stated equiv.), 16 h

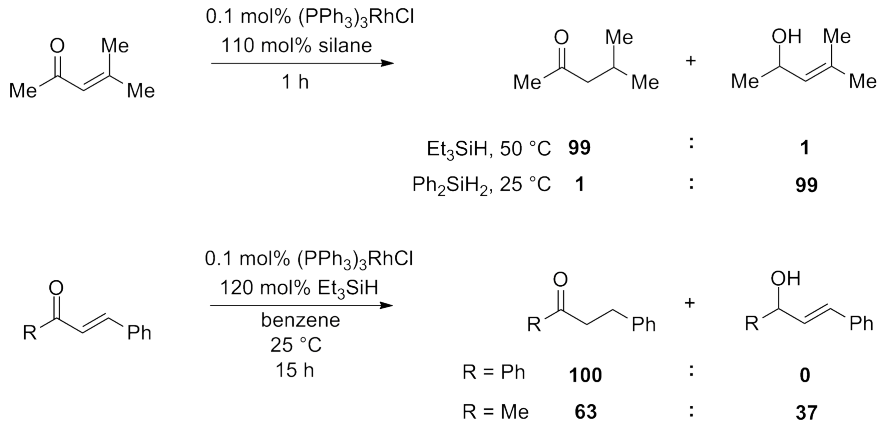
No further investigations were conducted due to the poor reactivity and lack of regioselectivity observed in these initial reactions.

3.3 Silanes as alternative reducing agents

3.3.1 Tandem hydroacylation/1,4-reduction

As an alternative to hydrogenation conditions, the possibility of a tandem hydroacylation/1,4-hydrosilylation (followed by protonolysis of the resultant silyl enol ether) was investigated. Ojima extensively studied the rhodium-catalysed hydrosilylation of ketones and enones,[190] and concluded that the regioselectivity of enone hydrosilylation was primarily controlled by the silane employed; monosilanes such as triethylsilane or triethoxysilane gave predominantly the 1,4-reduction product (*via* the silyl enol ether), whereas higher silanes (notably phenylsilane and diphenylsilane) have greater selectivity towards the 1,2-reduction product. While this general rule proved to be applicable

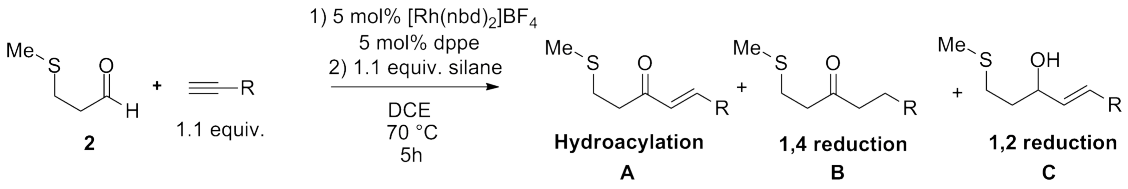
to a variety of substrates, other factors were demonstrated to influence the regioselectivity of the hydrosilylation, such as temperature, silane concentration and particularly substrate choice (Scheme 3.2).



Scheme 3.2. General trends in the regioselectivity of rhodium-catalysed hydrosilylation of enones as determined by Ojima, and the sensitivity of this regioselectivity to changes in substrate

Initial results in our laboratory were in line with Ojimas conclusions, and a tandem hydroacylation/1,4-hydrosilylation process was devised based on this precedent (Table 3.4).

Table 3.4: Investigation into the silane-dependent regioselctivity of a tandem hydroacylation/hydrosilylation reaction



Entry	R	Silane	A (%)	B (%)	C (%)
1	*n*Bu	Et_3SiH	0	100	0
2	Ph	Et_3SiH	100	0	0
3	*n*Bu	$(EtO)_3SiH$	0	100	0
4	Ph	$(EtO)_3SiH$	0	100	0
5	$CH(CH_3)CH_2CH_2CH_3$	$(EtO)_3SiH$	100	0	0
6	*t*Bu	$(EtO)_3SiH$	100	0	0
7	*n*Bu	PMHS	100	0	0
8	Ph	PMHS	100	0	0
9	Ph	Ph_2SiH_2	18	27	55

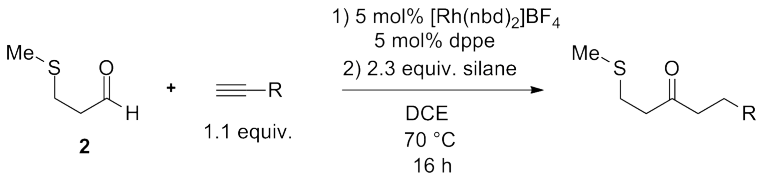
Conditions: **2** (0.5 mmol), alkyne (1.1 equiv.), $[Rh(dppe)]ClO_4$ (0.05 equiv.), DCE (3.0 mL), 70 °C, 5 h; hydrolysis by addition of HCl (aq.); conversions determined by ^1H NMR spectroscopy

While triethylsilane was usable for the reduction of straight chain aliphatic hydroacylation products (entry 1), it suffered from the same substrate limitation as the hydrogenation method, in that an aromatic substituent on the enone double bond prevented any reduction from procceding (entry 2). Pleasingly, triethoxysilane was capable of facilitating the desired tandem hydroacylation/1,4-reduction process for both aliphatic (entry 3) and aromatic (entry 4) substrates, although branched alkyl (entry 5) and tertiary butyl (entry 6) substituents were not tolerated. The very economical

silane polymer polymethylhydrosiloxane (PMHS) unfortunately did not produce any reduction products in the examples which were screened (entries 7 and 8). Finally, diphenylsilane (Ph_2SiH_2), which according to the work of Ojima should be selective for the 1,2-reduction of α,β-unsaturated enones, produced a mixture of 1,4- and 1,2-reduction products, and did not completely consume the hydroacylation product within 5 hours.

A small range of saturated ketones were prepared using this triethoxysilane-mediated tandem hydroacylation/1,4-reduction methodology (Table 3.5). It was found that replacing pre-formed catalyst [Rh(dppe)(nbd)]ClO_4 with a catalyst formed *in situ* from [Rh(nbd)$_2$]BF_4 and dppe produced identical yields, and as such this catalyst system was used in all further reactions (as it removes the requirement to synthesise the desired catalyst prior to the reaction).

Table 3.5: The scope of the tandem intermolecular alkyne hydroacylation/1,4-reduction with $(EtO)_3SiH$

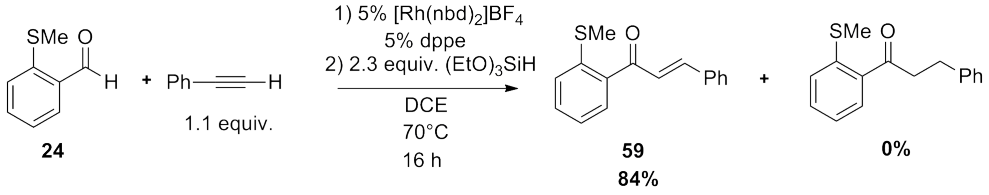


Entry	R	Yield (%)
1	*n*Bu	88
2	Ph	97
3	C_2H_4Ph	79
4	*p*-tolyl	82
5	*p*-NO_2Ph	0
6	*p*-CO_2MePh	0
7	3-thiophene	60

Conditions: **2** (0.3 mmol), alkyne (1.1 equiv.), [Rh(nbd)$_2$]BF_4 (0.05 equiv.), dppe (0.05 equiv.) DCE (3.0 mL), 70 °C, 1 h, then $(EtO)_3SiH$ (2.3 equiv.), 16 h; work-up by addition of TBAF (1.0M in THF) and H_2O or K_2CO_3/MeOH

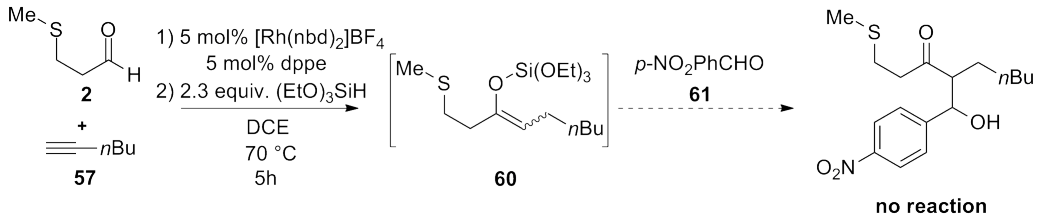
Alkyl (entries 1 and 3), aryl (entries 2 and 4) and heteroaryl (entry 7) examples

were successfully employed, but electron deficient enones proved to be either resistant to reduction (entry 6) or to simply not undergo the initial hydroacylation step to produce the requisite enone (entry 5). Additionally, replacing alkyl aldehyde **2** with aromatic aldehyde **24** produced only the non-reduced hydroacylation product **59** in 84% isolated yield, potentially due to the highly conjugated nature of the double bond in **59** (Scheme 3.3).



Scheme 3.3. The poor reactivity of enone **59** to rhodium-catalysed reduction by $(EtO)_3SiH$

Attempts to trap out the intermediate silyl enol ether **60** resulting from the hydrosilylation of **37** (formed *in situ* from the hydroacylation of aldehyde **2** and 1-hexyne **57**) by $(EtO)_3SiH$ with *p*-nitrobenzaldehyde **61** were unsuccessful, with no consumption of **61** observed (Scheme 3.4).

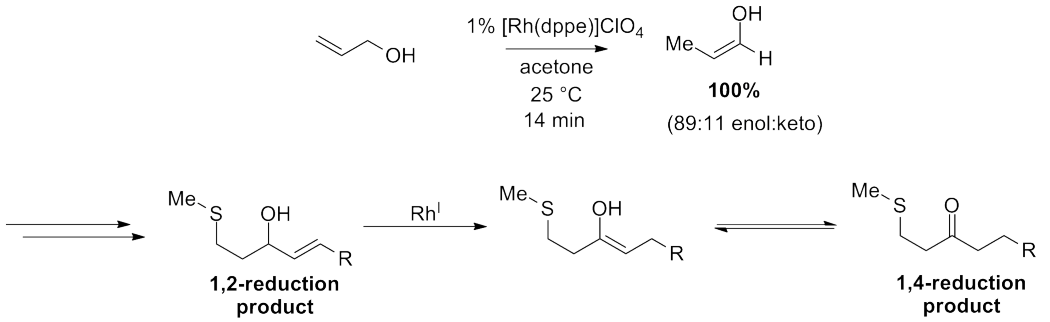


Scheme 3.4. The failed attempt to trap out an intermediate silyl enol either with an electrophilic aldehyde

^{1}H NMR spectroscopic analysis of the crude reaction mixture of the above reaction (Scheme 3.4) following the completion of the hydrosilylation step but prior to the addition of *p*-nitrobenzaldehyde **61** showed that the intermediate silyl enol ether was a 3:2 mixture of geometrical isomers. The geometry of each isomer was not determined.

3.3.2 Tandem hydroacylation/1,2-reduction

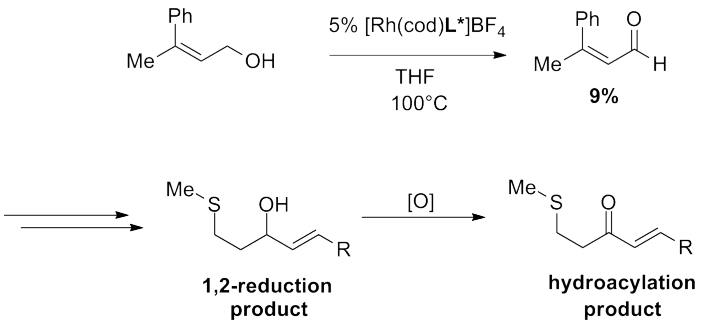
With a tandem intermolecular alkyne hydroacylation/1,4-hydrosilylation developed - albeit with a somewhat limited scope - the potential for a similar process which incorporated a 1,2-reduction to form an allylic alchohol was investigated. A promising lead result had been obtained in the initial investigation into the reactivity of various silanes (Table 3.4, entry 9), with Ph_2SiH_2 producing a mixture of 1,4- and 1,2- reduced products. It was thought that the development of a regioselective 1,2-reduction in this system might prove to be significantly more challenging than the 1,4-selective process, due to the potential of the rhodium catalyst to degrade the desired 1,2-reduction product. Catalysts such as $[Rh(dppe)]ClO_4$ have been reported as being active in the isomerisation of allylic alcohols to enol ethers (and hence, following tautomerisation, ketones),[111] which - entirely separately from the issue of an initial regioselective hydrosilylation event - could result in the isomerisation of the desired 1,2-reduction product to the undesired 1,4-reduction product (Scheme 3.5).



Scheme 3.5. The potential for the rhodium catalyst to isomerise a 1,2-reduction product to its 1,4-reduction regioisomer

In attempts to develop an asymmetric variant of the above allylic alcohol isomerisation process, Fu reported oxidised allylic alcohol as a byproduct of this reaction;[112] in a tandem hydroacylation/hydrosilylation reaction, this would result in the desired 1,2-reduction product being converted back to the hydroacylation product (Scheme 3.6). While this oxidised byproduct was only observed by Fu in small quantities, the amount

observed was more than could be accounted for by a stoichiometric reaction involving the rhodium catalyst used. The author did not postulate whether the byproduct resulted from a catalytic oxidation or the presence of adventitious oxygen.



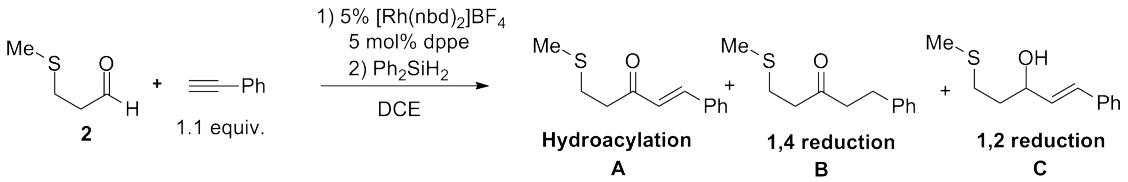
Scheme 3.6. The potential for the rhodium catalyst to oxidise a 1,2-reduction product to the appropriate hydroacylation product

Nevertheless, optimisation of the promising lead result (Table 3.4, entry 9) was undertaken in an attempt to improve the conversion and regioselectivity (Table 3.6).

The initial promising result (Table 3.6, entry 1) was repeated with the hydrosilylation step conducted at 0 °C (entry 2); while lower conversion in terms of consumption of the hydroacylation product was observed, the reaction did appear to be selective for 1,2-reduction over 1,4-reduction when conducted at this temperature. Cooling the reaction mixture to 0 °C for the silane addition, followed by warming to room temperature on completion of the addition resulted in greater conversion, but poorer selectivity (entry 3). Carrying out the entirety of the hydrosilylation step at room temperature was a further improvement (entry 4), and in combination with halving the solvent volume (to double the effective concentration of silane) resulted in effectively completely selective 1,2-reduction (entry 5). If the reaction was carried out in the absence of solvent, however, decomposition of the starting materials was the outcome (entry 6). Repeating the optimised reaction conditions on 1.5 mmol scale resulted in the production of the 1,2-reduction product in 93% isolated yield.

Unfortunately, the reaction appeared to be extremely sensitive to variations in the

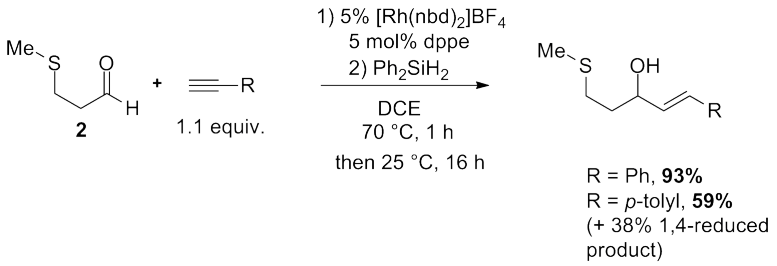
Table 3.6: Optimisation of the tandem intermolecular hydroacylation/1,2-hydrosilylation with Ph_2SiH_2



Entry	Temperature (°C)	Silane concentration (mM)	A (%)	B (%)	C (%)
1	70	0.15	18	27	55
2	0	0.15	72	0	28
3	0 - 25 overnight	0.15	23	22	55
4	25	0.15	0	29	71
5	25	0.30	0	trace	>99
6	25	neat	-	-	-

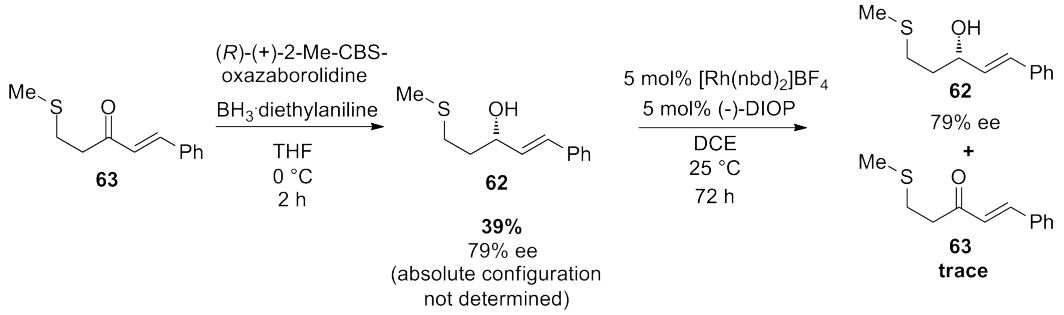
Conditions: **2** (0.50 mmol), phenylacetylene (1.1 equiv.), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.) DCE (5 - 10 mL), 70 °C, 1 h, then Ph_2SiH_2 (1.5 equiv.), 16 h; work-up by addition of TBAF (1.0M in THF) and H_2O; conversions determined by ^1H NMR spectroscopy

structure of the substrate. Simply altering the alkyne initially employed from phenyl- to *p*-tolyl acetylene resulted in a decrease from 93% to 59% isolated yield, with the remainder of the mass being 1,4-reduction product (Scheme 3.7). Heteroaromatic and alkyl substituents resulted in poor conversions and poor selectivities, with incomplete conversions, poor regioselectivity and even over-reduction to the fully saturated alcohol being observed depending on the substrate employed. Efforts to improve reactions with these substrates were unsuccessful, with the outcome of the reaction seemingly being more dependent on the substrate to be reduced rather than any alterations in the reaction conditions employed. The use of $PhSiH_3$ or $PhMeSiH_2$ in place of Ph_2SiH_2 provided no improvement in any substrate. Similarly to the tandem 1,4-reduction process (Scheme 3.3), use of aromatic aldehyde **24** rather than aldehyde **2** was unsuccessful, with only the unreduced hydroacylation product being isolated.



Scheme 3.7. Examples of a successful tandem intermolecular alkyne hydroacylation/1,2-hydrosilylation procedure

As this tandem hydroacylation/1,2-hydrosilylation methodolody produces a stereocenter, attempts were made to develop an asymmetric process through the use of a chiral *bis*-phosphine ligand in place of dppe. While the use of (-)-DIOP resulted in a mere 8% ee in the standard system, the remainder of the ligands screened (BINAP, *p*-Tol-BINAP, Chiraphos, C4-DIOP, MeDuphos, EtDuphos, iPrDUPHOS, DuanPhos) did not produce any improvement on this lead result - mostly through poor conversion to the hydroacylation product. An enantioenriched sample of the 1,2-reduction product **62** was prepared by CBS reduction of the hydroacylation product **63**, resulting in a product with 79% ee (absolute configuration not determined). To determine if the 1,2-reduction product was being formed in high ee and racemising under the reaction conditions, the enantioenriched product thus obtained was heated at 70 °C in the presence of $[Rh(nbd)_2]BF_4$ and (-)-DIOP for 72 hours. Analysis of the reaction mixture indicated that, while no racemisation was occurring, the allylic alcohol was being partially oxidised to the hydroacylation product (Scheme 3.8).



Scheme 3.8. The synthesis of enantioenriched 1,2-reduction product and an investigation into poor ee's obtained when using chiral phosphines in rhodium-catalysed hydrosilylation

3.4 Conclusion

In summary, several tandem hydroacylation/reduction processes have been described. A tandem intermolecular alkyne hydroacylation/hydrogenation protocol is effective for the production of saturated aliphatic ketones, which are synthetically equivalent to the hydroacylation of the appropriate (generally less reactive) alkene. The same transformation can be conducted on aromatic substrates by replacing the hydrogenation with a 1,4-selective hydrosilylation using $(EtO)_3SiH$; this procedure also tolerates alkyl substrates. A tandem intermolecular alkyne hydroacylation/1,2-hydrosilyilation to produce allylic alcohols was also achieved, by exchanging $(EtO)_3SiH$ for Ph_2SiH_2, although this process appears to suffer from strong substrate dependence and hence a lack of general applicability. Attempts to extend this protocol to an asymmetric variant were unsuccessful.

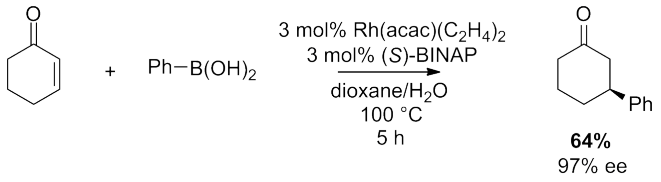
Chapter 4

Tandem rhodium-catalysed intermolecular alkyne hydroacylation/conjugate addition of organometallic reagents

4.1 Introduction

Rhodium(I) complexes are capable of catalysing a number of carbon-carbon bond-forming reactions,[191] as well as multiple other transformations, and as such the potential exists for a "tandem two-step process to be developed in which a hydroacylation catalyst then facilitates a further functionalisation of the hydroacylation product. A very well-established example of such a carbon-carbon bond forming reaction is the conjugate addition of aryl-metal species to electron deficient alkenes. The rhodium-catalysed 1,4-addition of aryl- and alkenylboronic acids to α,β-unsaturated enones was first reported by Miyaura in 1997,[192] and utilised a catalyst formed *in situ* from Rh(acac)$(CO)_2$ and dppb in aqueous solvents. An asymmetric variant of this reaction

was published by Miyaura and Hiyashi in 1998,[193] in which a modification of the originally reported conditions (with BINAP used as the ligand and $Rh(acac)(C_2H_4)_2$ used as the rhodium source) allowed the addition of phenylboronic acid to 2-cyclohexenone in 97% ee (Scheme 4.1).

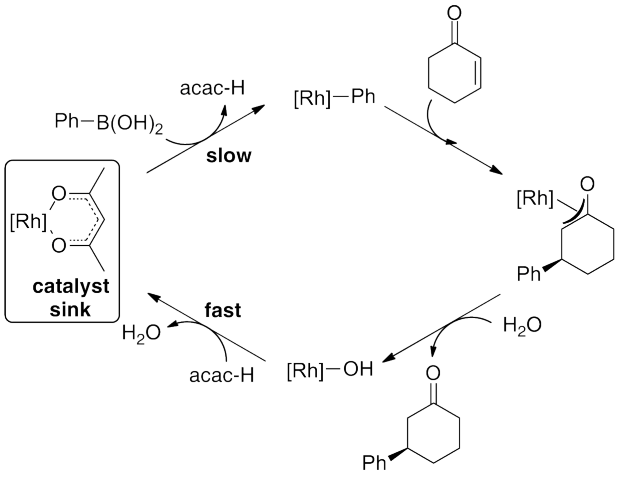


Scheme 4.1. Miyaura's asymmetric addition of phenylboronic acid to 2-cyclohexenone catalysed by $Rh(acac)(C_2H_4)_2$ and BINAP

Since these pioneering reports were published, the breadth of Rh^I catalysts which facilitate this transformation has been widely expanded,[194] and now encompasses a reasonable variety of catalyst systems.

Mechanistic studies by Hayashi found that the initially used $Rh(acac)CO_2$ or $Rh(acac)(C_2H_4)_2$ complexes were sub-optimal for this transformation due to Rh(acac) species effectively being a catalyst sink.[195] These ^1H and ^{31}P NMR spectroscopy studies found that transmetallation of phenylboronic acid to Rh(acac) species was extremely slow, and that trapping of the crucial Rh-OH catalytic intermediate (formed by protodeboronation of the intermediate Rh oxa-π-allyl intermediate) by the acac-H formed in this slow transmetallation step was extremely fast (Scheme 4.2). As a result, relatively high temperatures (around 65 - 100 °C) were required in reactions which employ acac-containing Rh sources, whereas the authors demonstrated that directly employing either $[Rh(BINAP)OH]_2$ or $[Rh(BINAP)Cl_2]$ and KOH permitted the reaction to proceed at 35 °C.

Following the publication of this mechanistic insight, acac-containing rhodium sources were generally disfavoured for rhodium-catalysed conjugate addition chemistry, with the use of Rh(*bis*-phosphine) complexes becoming more prevalent.[194] The



Scheme 4.2. Miyaura's proposed mechanism for rhodium-catalysed conjugate additions and the slowing effect of acac

use of monodentate phosphine ligands was also precedented,[196] although less commonly adopted. It was also noted the addition of BINAP to $Rh(acac)(C_2H_4)_2$ resulted in immediate quantitative conversion to $Rh(BINAP)(C_2H_4)_2$, which indicated that the aforementioned Rh(*bis*-phosphine) catalysts could be conveniently formed *in situ* from the ligand and an appropriate Rh(diene) precursor (the pre-formed $[Rh(BINAP)Cl]_2$ utilised by Hayashi and Miyaura in their mechanistic studies required the use of a glovebox to prepare).[195,197] In a later publication investigating the effects of ligands and bases on the rate of rhodium-catalysed conjugate addition reactions, Miyaura disclosed that $[Rh(cod)Cl]_2$ - or other neutral or cationic rhodium-diene species in the presence of additional cod - were effective catalysts for this transformation in the absence of any phosphine ligands whatsoever.[198] Hayashi and Carreira have independently published chiral dienes[199,200] as effective ligands for the asymmetric conjugate addition of arylmetal species - the former based on a norbornadiene scaffold,[201,202] the latter on a [2.2.2]-bicyclooctadiene scaffold.[203,204] Chiral hybrid phosphine/diene ligands have also been synthesised[205] and used in this chemistry, and examples of the use of both chiral *bis*-phosphine ligands and chiral diene ligands for these asymmetric transformations continue to be published.[206–208]

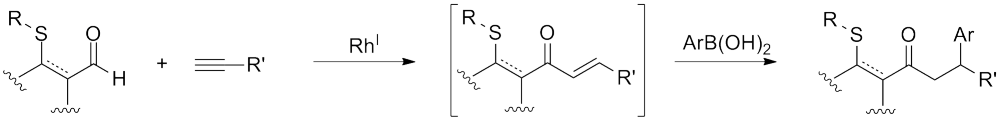
The rhodium-catalysed conjugate addition of aryl- and vinyl-metal species is now a well-established facet of rhodium catalysis, and as such several applications of this methodology have been disclosed and covered in a recent review article.[209]

4.2 Exploring the possibility of a tandem hydroacylation/conjugate addition procedure

Several examples exist of rhodium(I)-catalysed conjugate addition reactions which have employed cationic Rh/*bis*-phosphine catalysts: Miyaura's previously mentioned work on the acclerating effects of various ligands and bases on this reaction describes the use of [Rh(BINAP)(nbd)]BF_4 for the asymmetric addition of arylboronic acids to cyclic and acyclic substrates;[198] Tedrow has published the use of [Rh(DuanPhos)(nbd)]BF_4 to catalyse the asymmetric addition of arylboronic acids to 4-oxobutenamides;[210] and Itoh disclosed the use of a catalyst comprising [Rh$(nbd)_2$]BF_4 and chiraphos - essentially a chiral analog of the dppe ligand commonly used by our group in intermoleular hydroacylation reactions - to facilitate the reaction of arylboronic acids and β-aryl-α,β-unsaturated ketones and esters.[211] These selected examples are not exhaustive, and further systems can be found in relevant review articles.[194,209]

Based on the literature precedent of the types of catalyst which are known to function in rhodium-catalysed conjugate addition, and the seemingly signficant amount of overlap between some of these precedented catalyst systems and those which have been shown to catalyse chelation-controlled intermolecular hydroacylation reactions, it was envisioned that a catalyst might exist which could catalyse both a chelation-controlled intermolecular hydroacylation and the conjugate addition of an arylboronic acid (or similar) to the resulting hydroacylation product. This would allow a tandem hydroacylation/conjugate addition process to be developed, using the same catalyst

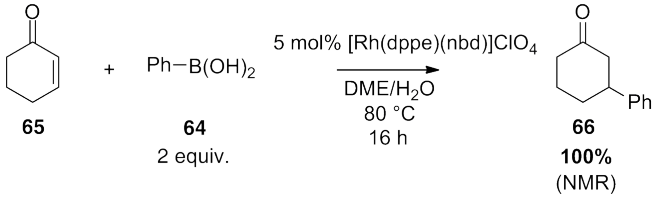
and without isolation of the intermediate α,β-unsaturated enone (Scheme 4.3).



Scheme 4.3. The possibility for a tandem hydroacylation/conjugate addition protocol to permit two carbon-carbon bond forming processes enabled by the same catalyst

4.3 Initial exploration of the activity of known hydroacylation catalysts in rhodium-catalysed conjugate addition reactions

A test reaction was run in which the ability of the preformed catalyst [Rh(dppe)(nbd)ClO_4] to catalyse the addition of phenylboronic acid **64** to 2-cyclohexenone **65** was examined. This catalyst has been used extensively within the Willis group for conducting intermolecular hydroacylation reactions, and is moderately similar to the cationic conjugate addition catalysts with were described in the previous section. This catalyst was found to be capable of facilitating this test reaction to produce 3-phenylcyclohexanone **66** under a variety of conditions; one representative example is shown here in which the reaction proceeded to completion (by ^{1}H NMR spectroscopy) (Scheme 4.4).

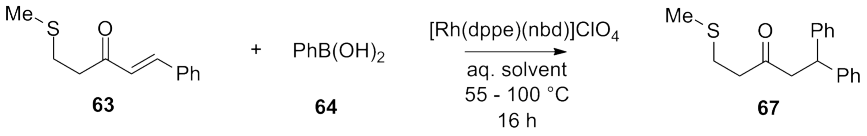


Scheme 4.4. The formation of 3-phenylcyclohexanone **66**, catalysed by known hydroacylation catalyst [Rh(dppe)(nbd)ClO_4]

With the encouraging result of a hydroacylation catalyst effectively catalysing the conjugate addition of phenylboronic acid to an enone, the conditions were then applied

to an isolated hydroacylation product. The reaction between enone **63** and excess phenylboronic acid **64** in the presence of 5 mol% [Rh(dppe)(nbd)ClO_4] in a variety of aqueous solvent systems at 55-100 °C did not, however, produce any detectable amounts of conjugate addition product **67** (Table 4.1).

Table 4.1: Attempted conjugate addition of $PhB(OH)_2$ to **63** catalysed by [Rh(dppe)(nbd)ClO_4]

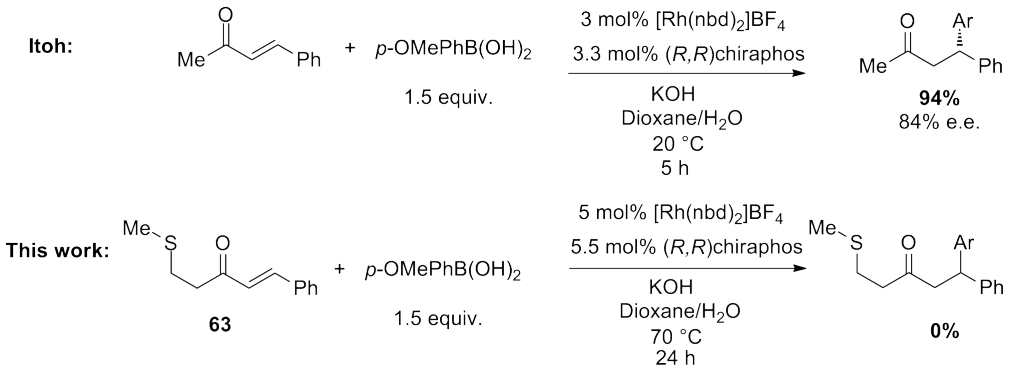


Entry	Catalyst loading (mol %)	Solvent	Temperature (°C)	Base	Yield (%)
1	2	19:1 DME/H_2O	65	NEt_3	0
2	5	19:1 DME/H_2O	65	NEt_3	0
3	5	19:1 DME/H_2O	65	K_2CO_3	0
4	5	19:1 DME/H_2O	65	KOH	0
5	5	19:1 DME/H_2O	100	KOH	0
6	5	6:1 DME/H_2O	65	none	0
7	5	19:1 acetone/H_2O	55	NEt_3	0
8	5	6:1 acetone/H_2O	55	NEt_3	0
9	5	1:1 DME/H_2O	80	none	0

Conditions: **63** (0.75 mmol), $PhB(OH)_2$ **64** (2.0 equiv.), [Rh(dppe)(nbd)ClO_4] (2-5 mol%), 16 h.

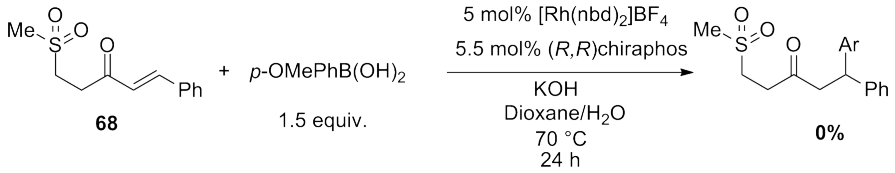
Conditions which were analagous to an example published by Itoh[211] were similarly ineffective with this substrate, with only starting materials returned even after 24 hours at 70 °C (c.f. complete conversion after 5 hours at 20 °C in the literature

example) (Scheme 4.5).



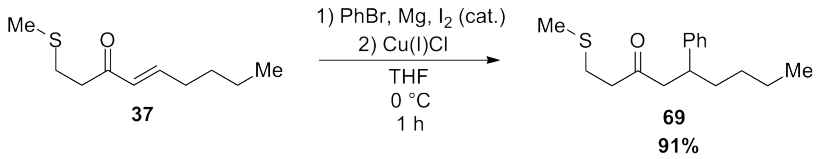
Scheme 4.5. The application of the Itoh conditions to hydroacylation product **63**

Sulfone **68** was prepared by *m*CPBA oxidation of thioether-containing enone **63**, but this substrate was also unreactive when subjected to the Itoh conditions (Scheme 4.6).



Scheme 4.6. The application of the Itoh conditions to sulfone **68**

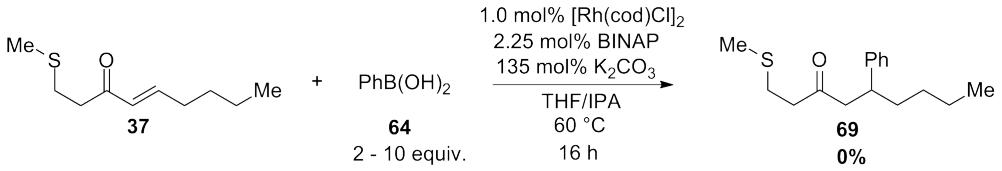
With the failure of these initial screens, it was decided to conduct all further test reactions with the less sterically hindered hydroacylation product **37**. A marker sample of a desired conjugate addition product **69** departing from enone **37** was easily prepared in good yield by the addition of phenylmagnesium bromide to **37** in the presence of a stoichiometric amount of Cu(I)Cl (Scheme 4.7).



Scheme 4.7. Synthesis of conjugate addition product **69** from enone **37** using a Grignard reagent and stoichiometric copper

Several sets of conditions from the initial screen on substrate **63** from Table 4.1 were applied to substrate **37** but were similarly unsuccessful; no trace of the desired conjugate addition product was isolated or detected by mass spectrometry or ^{1}H NMR spectroscopy of the crude reaction mixtures.

The AstraZeneca process group published the first kilogram-scale asymmetric rhodium-catalysed conjugate addition, which is also unique in using IPA as the proton source for the reaction rather than water (to reduce protodeboronation of the electron-deficient arylboronic acid employed).[212] The conditions from this paper were tested on substrate **37**, but did not produce any product (Scheme 4.8). These same conditions were employed using 10 equivalents of phenylboronic acid, and still no product formation was seen.



Scheme 4.8. Unsuccessful application of the water-free AstraZeneca conditions to substrate **37**

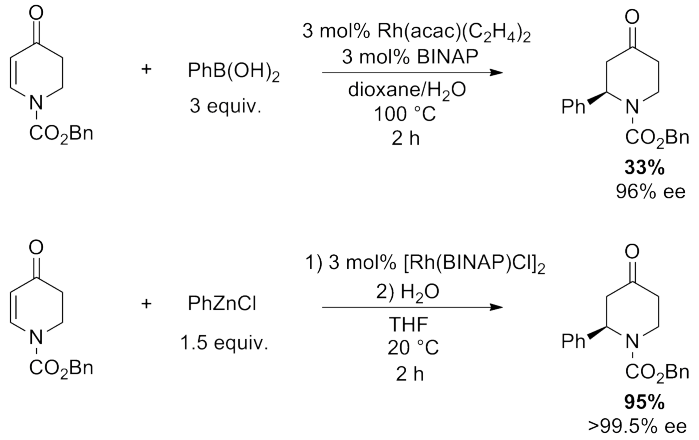
4.4 Alternative nucleophiles

Organotrifluoroborate salts, of general formula $KArBF_3$, have been used as pre-activated boronic acid equivalents in rhodium-catalysed conjugate addition chemistry,[213–215] although recent research suggests they may act as a slow-release source of arylboronic acids.[216] They have the additional benefits over boronic acids of consisting of one defined species,[212] increased stability to air and moisture, and some reports suggest that they may be more reactive than the equivalent boronic acid in certain systems. Enone **37** was subjected to several previously utilised catalytic systems but with potassium organotrifluoroborate salt $KPhBF_3$ **70** rather than phenylboronic acid **64**: the

[Rh(dppe)(nbd)]BF_4-catalysed, base-free conditions which were used to synthesise 3-phenylcyclohexanone **66** (Scheme 4.4); the Itoh conditions which utilised [Rh(nbd)$_2$]BF_4 and chiraphos (Scheme 4.5); and the water-free AstraZeneca conditions with a catalyst system comprising [Rh(cod)Cl]$_2$ and BINAP (Scheme 4.8). None of these sets of conditions produced any detectable amounts of conjugate addition product **69**.

Rhodium(I)-catalysed conjugate additions are not restricted to the use of aryl- or vinylboronic acids or esters as the nucleophile. Hayashi, in particular, has expanded the scope of this process to include aryl-9-BBN,[217] aryltitanium,[218] organosilanes[219] and arylzinc[220] reagents, among others. Of these, the use of arylzinc halides is particularly attractive for this project. The product of the addition of arylzinc halides to α,β-unsaturated carbonyl compounds is a zinc enolate, and as such anhydrous reaction conditions are employed, which are more compatible with the existing hydroacylation methodology and hence a tandem process. While the zinc enolate which is formed is typically hydrolysed on work-up, it is possible to trap out the enolate with an electrophile other than water, to effect a further transformation in one pot.

The use of arylzinc nuclophiles in rhodium-catalysed conjugate addition chemistry was first reported by Hayashi, who found that attempts to conduct the catalytic conjugate addition of phenylboronic acid to 2,3-dihydro-4-pyridones for the synthesis of medicinally relevant 2-aryl-4-piperidones were generally low-yielding.[220] A brief screen of alternative nucleophiles identified PhZnCl as a more effective alternative to the arylboron reagents screened (Scheme 4.9).

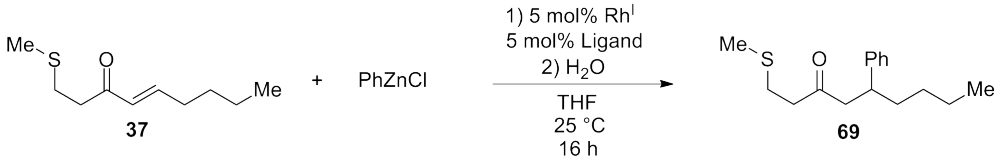


Scheme 4.9. Hayashi's discovery of arylzinc reagents as effective nucleophiles for the rhodium-catalysed conjugate addition of dihydropyridones

An investigation into discovering a suitable catalyst system for the conjugate addition of PhZnCl to enone **37** was conducted (Table 4.2).

The first attempt at the rhodium-catalysed conjugate addition of PhZnCl into **37** utilised $[Rh(cod)Cl]_2$ under phosphine-free conditions and consumed the starting material overnight, albeit in insufficient yield to isolate the desired product (Table 4.2, entry 1). A number of *bis*-phosphine ligands were tested in an attempt to produce isolatable amounts of conjugate addition product **69**; dppe and dppp were no improvement over phosphine-free conditions (entries 2 and 3), whereas the use of DPEphos returned only starting materials (entry 4). BINAP, as used by Hayashi in the original publication, consumed the starting material and produced enough product to be isolated, although the product was contaminated with multiple unidentified by-products which were present in the crude reaction mixture (entry 5). Making the Rh(BINAP) system cationic, through the addition of $AgBF_4$ or the use of $[Rh(nbd)_2]BF_4$ as the pre-catalyst, had a deleterious effect in all cases, with incomplete consumption of starting material, the production of multiple unidentified by-products and only trace amounts of the desired product being observed (entries 6, 7 and 9). The use of a neutral Rh(BINAP) catalyst system in combination with chlorotrimethylsilane as an

Table 4.2: Screen of conditions for the rhodium-catalysed conjugate addition of PhZnCl to enone **37**



Entry	Rhodium source	Ligand	Additive	Yield (%)
1	$[Rh(cod]Cl]_2$	-	-	trace
2	$[Rh(cod]Cl]_2$	dppe	-	trace
3	$[Rh(cod]Cl]_2$	dppp	-	trace
4	$[Rh(cod]Cl]_2$	DPEPhos	-	0
5	$[Rh(cod]Cl]_2$	BINAP	-	33
6	$[Rh(cod]Cl]_2$	BINAP	$AgBF_4$	trace[a]
7	$[Rh(nbd)_2]BF_4$	BINAP	-	trace
8	$[Rh(cod]Cl]_2$	BINAP	TMSCl	65[b]
9	$[Rh(cod]Cl]_2$	BINAP	$AgBF_4$, TMSCl	trace[a], [b]
10	-	-	TMSCl	0[b]
11	-	BINAP	TMSCl	0[b]

Conditions: **37** (0.54 mmol), PhZnCl (1.5 equiv.), rhodium source (0.05 equiv.), ligand (0.05 equiv.), THF (0.5 mL), 25 °C, 16 h, then quenched with H_2O (0.2 mL); [a] 1 equiv. relative to rhodium; [b] 1.3 equiv. relative to enone **37**

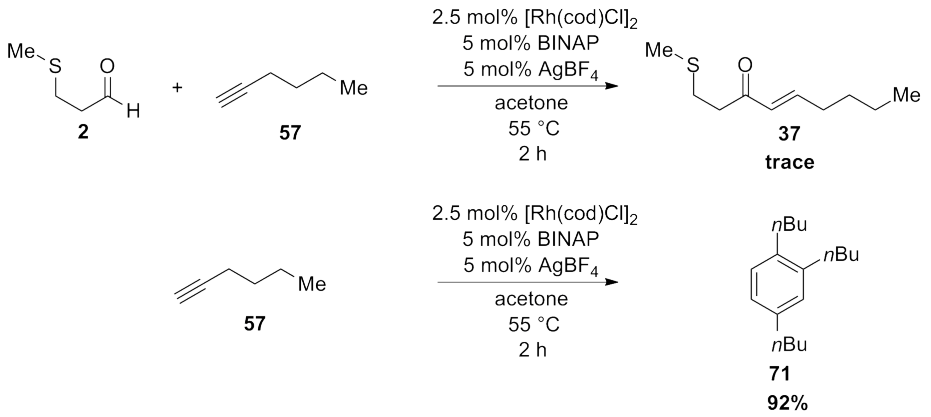
additive (as reported in a later protocol by Hayashi[221] and adopted by Frost)[222] produced a respectable yield of conjugate addition product **69**, albeit not in analytical purity (entry 8). Control reactions which omitted a rhodium source (entry 11) or both rhodium source and ligand (entry 10) confirmed that the observed reaction was not mediated by chlorotrimethylsilane alone.

4.5 Towards a tandem hydroacylation/conjugate addition protocol

While the success of the $[Rh(cod)Cl]_2$/BINAP/TMSCl system in producing a moderate amount of conjugate addition product **69** was encouraging, several barriers still existed for the development of a tandem hydroacylation/conjugate addition protocol. Firstly, the greater performance of neutral systems when compared to cationic rhodium in the conjugate reaction is problematic, as the intermolecular hydroacylation methodology developed in the Willis group requires cationic complexes. However, hydroacylation methodology with neutral rhodium species is not unprecedented (see Chapter 1), so this problem is not necessarily insurmountable. The use of THF as a solvent is broadly incompatible with known hydroacylation reactions in the Willis group, and while a solvent screen for this conjugate addition system was not undertaken, it would be difficult to remove THF from the system entirely. Whether or not THF would be required as a reaction solvent was not determined, but commercial PhZnCl is generally provided as a solution in THF, and to make PhZnCl "in house" generally requires the preparation of a THF solution of $ZnCl_2$, as it is largely insoluble in most other organic solvents. Furthermore, the ligands which are commonly used in chelation-controlled intermolecular hydroacylation reactions (dppe and DPEphos) were ineffective at catalysing the conjugate addition process. The most successful conjugate addition ligand - BINAP - had not previously been extensively tested within the group as a hydroacylation catalyst.

To remedy this last point, a hydroacylation reaction between 3-(methylthiopropionaldehyde) **2** and 1-hexyne **57** with a catalyst system comprising $[Rh(cod)Cl]_2$, $AgBF_4$ and BINAP was run. The reaction resulted in incomplete consumption of aldehyde **2** and only trace amounts of the desired hydroacylation product **37** (Scheme 4.10). A control experiment which omitted the aldehyde consumed 1-hexyne **57** within 2 hours, to produce a compound with ^{1}H NMR spectroscopy data consistent with that of the

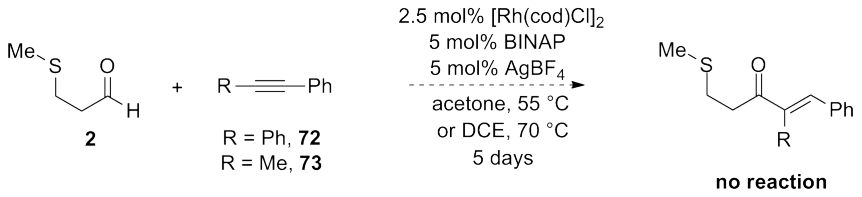
alkyne cyclotrimerisation product 1,2,4-tributylbenzene **71**;[223] this reaction is known to be catalysed by rhodium.[224] In an attempt to reduce this undesirable side-reaction, a reaction was attempted in which 1-hexyne **57** was added over 1 hour, but the previously seen alkyne cyclotrimer was accompanied by the formation of several other additional unidentified products. The use of 10 equivalents of alkyne **57** merely resulted in appropriately large amounts of cyclotrimerisation product, with still only a trace of hydroacylation product **37** being observed.



Scheme 4.10. Cyclotrimerisation of 1-hexyne **57** by a $[Rh(cod)Cl]_2$/BINAP/$AgBF_4$ catalyst system in preference to intermolecular alkyne hydroacylation

Given the lack of reactivity of DPEphos as a ligand in the rhodium-catalysed conjugate addition reaction (Table 4.2, entry 4), it was hoped that a mixed ligand system might be developed which would use a common rhodium source to effect both an intermolecular hydroacylation and the conjugate addition of PhZnCl in one pot. However, it was found that when using 5 mol% of $[Rh(cod)Cl]_2$ and 5 mol% each of DPEphos and BINAP, the alkyne trimerisation reaction proceeded at a competitive rate to the desired hydroacylation, and as such the aldehyde starting material **2** was not consumed.

While the alkyne cyclotrimerisation side-reaction was detrimental to the production of a tandem process using the BINAP catalyst system, this reaction could be effectively suppressed by using internal alkynes rather than terminal ones. The intermolec-



Scheme 4.11. The inability of a BINAP-containing catalyst system to catalyse the intermolecular hydroacylation of 3-(methylthio)propionaldehyde **2** and internal alkynes

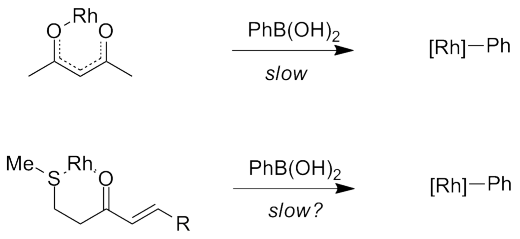
ular hydroacylation of internal alkynes has been performed within the group, using the standard hydroacylation catalysts, although they are considerably slower than the comparable reaction with a terminal alkyne. The intermolecular hydroacylation of 3-(methylthio)propionaldehyde **2** and diphenylacetylene **72** or 1-phenyl-1-propyne **73** with a catalyst system comprising $[Rh(cod)Cl]_2$, $AgBF_4$ and BINAP returned unreacted alkyne after heating at 55 or 70 °C for 5 days (Scheme 4.11).

A screen of other BINAP-type ligands for this process - including DuanPhos, MeDuPhos, DiFluorPhos, SegPhos and H_8-BINAP - did not succeed in identifying a catalyst system which was effective for the hydroacylation of terminal alkynes and the conjugate addition of PhZnCl to enone **37**. Depending on the ligand screened, the catalysts formed were incapable of catalysing either or both steps in the desired tandem process.

4.6 Discussion of the rhodium-catalysed conjugate addition of arylmetal species to thioether-containing hydoacylation products

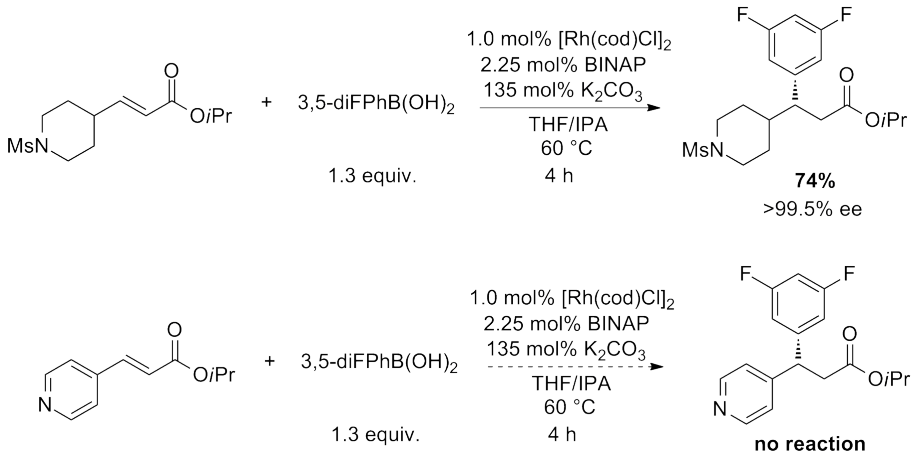
It seems likely that the difficulty in finding a suitable catalyst system for the rhodium-catalysed conjugate addition of arylmetal species - particularly boronic acids - to conjugate addition products such as **63** and **37** is the presence of the thioether chelat-

ing group which is necessary for the synthesis of these substrates *via* hydroacylation methodology. A comparison of these hydroacylation products to substrates successfully used by, for example, Itoh[211] shows that enones which are sterically and electronically very similar to hydroacylation products **63** and **37** are compatible with rhodium-catalysed conjugate addition methodology. The thioether motif in our hydroacylation products is demonstrably adept at chelating to rhodium catalysts (as its presence facilitates intermolecular hydroacylation reactions with these substrates), and a loose structural analogy can be drawn between this thioether/carbonyl motif and acac (Scheme 4.12). As previously discussed, Rh(acac) species are generally disfavoured as rhodium sources for conjugate addition reactions due to the slow transmetallation of arylboronic acids to Rh(acac) species (Scheme 4.2) and hence the presence of a catalyst sink. While acac has a significantly lower pK_a than the chelating motif in hydroacylation products, and hence is much more likely to strongly bind in an anionic manner to a metal center (when compared to the much less acidic thioether/carbonyl chelating system), in these conjugate addition reactions the hydroacylation products are present in a 10- to 20-fold excess to the rhodium catalyst (c.f. the 1:1 stoichiometry of acac:Rh when Rh(acac) sources are employed). It would therefore seem that the chelating motif which is required to be present in substrates which undergo rhodium-catalysed intermolecular hydroacylation may be inhibiting (or at lease decreasing the rate of) rhodium-catalysed conjugate addition reactions of substrates which contain this same chelating motif.



Scheme 4.12. A comparison of the potential similarities in metal binding of a known catalyst sink and the chelating motif in hydroacylation products

The intolerance of rhodium-catalysed conjugate addition methodology to chelating heteroatoms has been noted elsewhere. In the kilogram-scale conjugate addition disclosed by researchers at AstraZeneca which has been previously mentioned,[212] the authors noted that in an alternative route to their desired substrate which required a rhodium-catalysed conjugate addition to a pyridine (rather than the previously used protected piperidine), the reaction failed to produce any product whatsoever (Scheme 4.13). The authors state that they believe the reaction of the pyridine substrate fails due to coordinating of the pyridine nitrogen to the rhodium center, removing the metal from the catalytic cycle and preventing any appreciable amount of product from being made. As further evidence to support this hypothesis, they also mention that care had to be taken to minimise the amount of residual piperidine present in the successful substrate (piperidine is used as the base in the previous step of the synthesis of this substrate), as high levels of piperidine resulted in catalyst poisoning at the conjugate addition stage.



Scheme 4.13. The presence of a free heteroatom preventing a rhodium-catalysed conjugate addition from proceeding

It therefore seems probable that the presence of a chelating thioether group in a conjugate addition substrate has a significant deleterious effect on the reactivity of such a molecule as the substrate for a rhodium-catalysed conjugate addition.

4.7 Conclusion

In summary, the envisaged tandem rhodium-catalysed hydroacylation/conjugate addition of arylmetal species was not fully realised. While known hydroacylation catalasyts were found to be effective catalysts for the conjugate addition of phenylboronic acid to cyclohexenone, they were ineffective at catalysing the same transformation on hydroacylation products. These products appear to be challenging substrates for the rhodium-catalysed conjugate addition of arylmetal species. A separate catalyst system was identified which was competent for catalysing the conjugate addition of phenylzinc chloride to a hydroacylation product, but the conditions and catalyst system required were incompatible with existing hydroacylation methodology. As such, the overlap between the two halves of the tandem process were not reconciled, although it remains possible that a suitable ligand exists for the creation of a catalyst system which is capable of catalysing both of these reactions, as only a relatively small selection of *bis*-phosphine ligands has been examined.

Chapter 5

Alternative solvents for Rhodium-catalyzed hydroacylation reactions

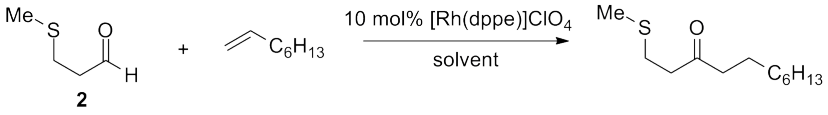
5.1 Introduction

The current solvents of choice for the Willis group's chelation-controlled intermolecular hydroacylation reactions as described in the published examples of this work are acetone and 1,2-dichloroethane (DCE).[73–76,78–80,225–227] DCE was identified as a suitable solvent for the reaction in an early solvent screen (Table 5.1), and acetone was later adopted for use in hydroacylation studies due to literature precedent of its use in intramolecular systems.[†]

Further research within the Willis group uncovered some nuances of the consequences of using each of these two solvents (briefly: the coordinating nature of acetone results in generally higher turnover number at the cost of decreased turnover frequency,

[†]the literature suggested that the [Rh(dppe)]ClO_4 catalyst used forms aryl-bridged dimeric species in non-coordinating solvents such as DCM and DCE, but forms solvated monomers in acetone; hence, these two solvents could potentially behave significantly differently in catalysis[47]

Table 5.1: Early solvent screen[228]



Entry	Solvent	Temperature (°C)	Yield (%)
1	DCE	60	33
2	THF	60	0
3	Benzene	60	0
4	DCM	25	13

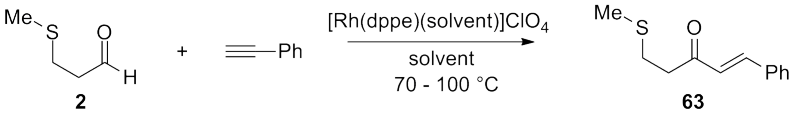
whereas DCE generally has the opposite effect).[187] However, neither of these solvents are without their drawbacks. The use of acetone confers an upper reaction temperature of 56 °C (760 mmHg), which can increase reaction times, reduce yields or prevent reactions from occurring at all in the case of more challenging reaction systems. DCE, while higher boiling, has significant toxicity issues and - like other halogenated solvents - has environmental hazards associated with its use and disposal. While these issues are of limited consequence on a laboratory scale, they present a significant impediment to the use of this hydroacylation methodology on an industrial scale or within process groups.

There therefore exists a need for the identification of alternative solvents for rhodium-catalyzed intermolecular hydroacylation if this methodology is to be adopted by the wider synthetic community. To be a viable substitute to acetone and DCE, an alternative solvent must necessarily solubilize hydroacylation catalysts, not prove to be deleterious to reaction rates or yields, have a reasonably large liquid range (preferably from 0 °C - >80 °C) and preferably have better "green solvent" credentials than DCE.

5.2 3-Pentanone

3-Pentanone was briefly investigated simply as a higher-boiling alternative to acetone, and the results are summarized in Table 5.2.

Table 5.2: Brief investigation of 3-pentanone as a higher-boiling alternative to acetone



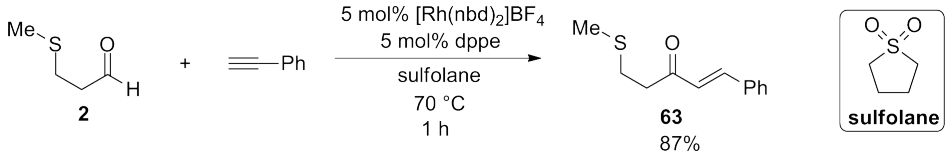
Entry	Solvent	Catalyst loading (mol%)	Temperature (°C)	Time (h)	Conversion (%)
1	acetone	5	55	0.5	88
2	3-pentanone	5	55	0.5	>99
3	acetone	1	100	1	81[a]
4	3-pentanone	1	100	1	>99

Conditions: 3-methylthiopropionaldehyde **2** (1.0 equiv.), phenylacetylene (2.0 equiv.), [Rh(dppe)(nbd)]ClO_4 (stated equivalents); catalyst pre-activated by hydrogenation; [a] reaction carried out in a sealed tube under microwave irradiation.

The small number of reactions done indicate that, at least in this straightforward reaction system, 3-pentanone is a viable alternative to acetone should a higher boiling solvent be required. In facile examples such as these, however, the minor increase in yields seen in the 1 mol% example (Table 5.2, entries 3 and 4) are perhaps insufficient to outweigh the convenient work-up which the use of acetone permits.

5.3 Sulfolane

Sulfolane is a water-miscible solvent which is used by the petrochemical industry for tasks such as the separation of specific hydrocarbons. An intermolecular hydroacylation reaction was conducted with sulfolane as the solvent (Scheme 5.1).



Scheme 5.1. The use of sulfolane as a solvent for rhodium-catalysed intermolecular hydroacylation

The hydroacylation product **63** was obtained in 87% yield. While sulfolane does not have any specific advantages over the solvents which are currently used for this reaction, it is interesting that the reaction proceeds at all in a sulfur-containing solvent.

5.4 Propylene Carbonate

While DCE has been successfully used as a solvent for intermolecular hydroacylation reactions on the laboratory scale, it is largely unsuitable for use on scale due to its significant toxicity issues and - like other halogenated solvents - it is undesirable for use on scale due to the environmental hazards associated with its use and disposal. Propylene carbonate, on the other hand, is gaining prominence as a useful solvent in organic synthesis due to its many desirable properties. Organic carbonates are used in a variety of industrial applications, such as degreasing, paint stripping, and as electrolytes in lithium ion batteries.[229] Propylene carbonate itself is a polar aprotic solvent which is non-toxic (to the extent that it has been used as a carrier solvent in cosmetics and topically applied medicines),[230] non-corrosive and biodegradable.[231] In addition to excellent solvency of metal ions[232] and organic compounds, its physical properties are also desirable: it has low viscosity, low vapour pressure and is miscible with water. A recent paper by Jessop[233] urged scientists to assess the green-ness of solvents for a given application based on the environmental effects of solvents, including their synthesis, use and disposal. Propylene carbonate can be synthesised in an atom-efficient manner from propylene oxide and carbon dioxide,[234,235] resulting in a short synthesis

tree with none of the downsides which would prevent it from being considered as a green solvent. More importantly, the use of propylene carbonate as a direct replacement solvent for DCE avoids the production of any chlorinated waste. These factors show propylene carbonate as being clearly advantageous to DCE in a like-for-like comparison.[236]

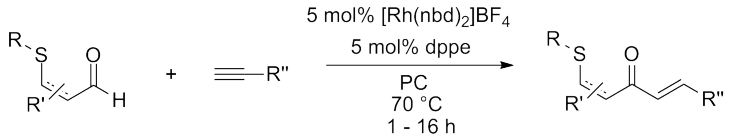
Despite the existing commercial uses, propylene carbonate has not seen extensive use as a solvent for transition metal catalysis. Several examples of its use are known: Börner has published a number of accounts of the use of propylene carbonate as a solvent for catalytic asymmetric hydrogenations with rhodium and iridium catalysts;[232,237] Behr has described examples of catalysis with propylene carbonate as a solvent,[238–242] including platinum-catalysed hydrosilylation and rhodium-catalysed hydroformylation reactions; and Reetz described its use in stabilising palladium clusters and their use in catalysing Heck reactions.[243] A review on the use of organic carbonates as solvents and in catalysis has recently been published,[244] and contains further examples of catalysis which use propylene carbonate as a solvent.

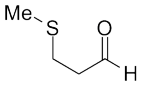
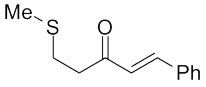
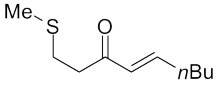
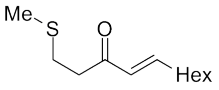
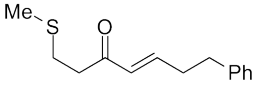
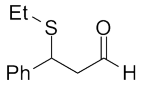
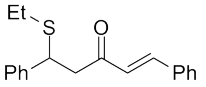
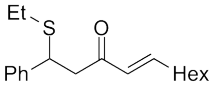
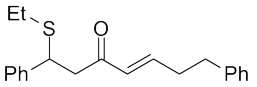
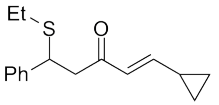
5.4.1 Investigating the viability of propylene carbonate for use in intermolecular hydroacylation

Thioether-containing aldehydes

The viability of using propylene carbonate as a solvent for our intermolecular hydroacylation methodology was investigated by carrying out reactions between representative thioether-containing aldehydes and alkynes selected from classes which had previously been described using either DCE or acetone as the reaction solvent. It was found that these reactions could be carried out in propylene carbonate with a catalyst system comprising commercially available rhodium complex $[Rh(nbd)_2]BF_4$ in combination with dppe as the ligand. The catalysts did not require pre-activation by

Table 5.3: Propylene carbonate as solvent in intermolecular rhodium-catalysed alkyne hydroacylation reactions of β-thioether-containing aldehydes.



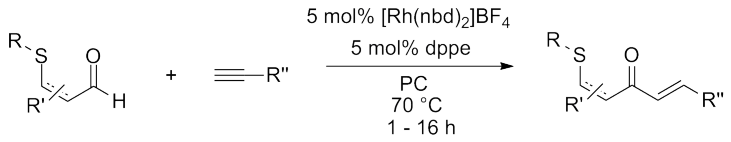
Entry	Aldehyde	Alkyne (R")	Product	Yield (%)
1	 **2**	Ph	 **63**	90
2	**2**	Bu	 **37**	91
3	**2**	Hex	 **74**	91
4	**2**	C_2H_4Ph	 **75**	83
5*	 **10**	Ph	 **76**	86
6*	**10**	Hex	 **77**	92
7*	**10**	C_2H_4Ph	 **78**	87
8*	**10**	cyclopropyl	 **79**	90

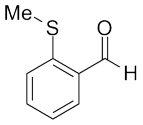
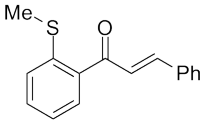
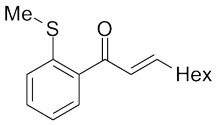
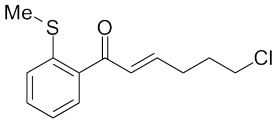
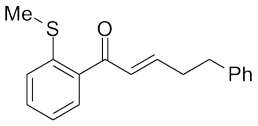
Conditions: aldehyde (0.75 mmol), alkyne (1.1 equiv.), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.), propylene carbonate (2.5 mL), 70 °C, 2 h. * Reaction conducted by co-worker Carlos González-Rodríguez

hydrogenation. Table 5.3 summarises the results, which are grouped by aldehyde class: β-methylthiopropanal **2** is the simplest aldehyde that fulfils the requirement of a chelating β-S-substituent, and this was combined with four alkynes, in all cases delivering the expected hydroacylation adducts in excellent yields (entries 1-4). Although the reactions were routinely performed using a 5 mol% catalyst loading it was also possible to reduce this loading and retain good activity. For example, performing the reaction shown in entry 2, but employing a 1 mol% catalyst loading, the enone product was still obtained in 91% yield. Further examples of alkyl aldehydes in this series were conducted by co-workers. Entries 5-8 document the succesful use of a more hindered alkyl aldehyde **10** with four representative alkynes (entries 6-9).

A co-worker demonstrated that the aromatic aldehyde, 2-(methylthio)benzaldehyde **24**, could also be employed without issue (Table 5.4).

Table 5.4: Propylene carbonate as solvent in intermolecular rhodium-catalysed alkyne hydroacylation reactions of β-thioether-containing aldehydes.



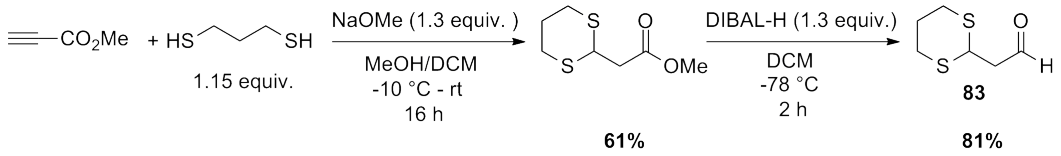
Entry	Aldehyde	Alkyne (R")	Product	Yield (%)
1*	 **24**	Ph	 **59**	84
2*	**24**	Hex	 **80**	86
3*	**24**	C_3H_6Cl	 **81**	66
4*	**24**	C_2H_4Ph	 **82**	70

Conditions: aldehyde **24** (0.75 mmol), alkyne (1.1 equiv.), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.), propylene carbonate (2.5 mL), 70 °C, 2 h. * Reaction conducted by co-worker Paul Ylioja

Dithiane containing aldehydes

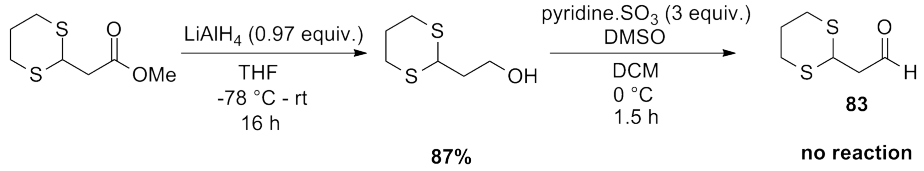
The Willis group has previously described the use of β-dithiane aldehydes in the intermolecular hydroacylation of alkynes. β-Dithiane aldehyde **83** was described in previously published work as being synthesised by double conjugate addition of 1,3-

propanedithiol into methyl propiolate,[245] followed by the selective DIBAL-H mediated reduction of the resulting dithiane ester to the required aldehyde.[246] While the double conjugate addition proceeded as described, the previously described conditions for the DIBAL-H reduction proved to be both unreliable and very sensitive to reaction time, temperature and equivalents of reductant used, producing the desired aldehyde in a mere 12 - 27% yield (Scheme 5.2).



Scheme 5.2. Synthesis of the unsubstituted dithiane aldehyde **83**

An alternative synthetic route which negated the need for the capricious DIBAL-H reduction was investigated. Reduction of the dithiane ester with $LiAlH_4$ furnished the alcohol in 87% yield, but the Parikh-Doering oxidation employed did not consume the starting material (Scheme 5.3), despite using conditions from the literature involving a very similar compound.[247]

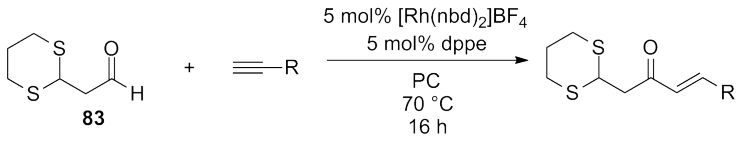


Scheme 5.3. Potential oxidative route to the unsubstituted dithiane aldehyde **83**

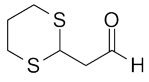
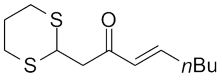
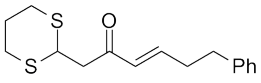
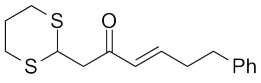
As the dithiane functional group can be deprotected under oxidative conditions, it was decided to optimise the capricious DIBAL-H reduction of the ester rather than pursue an oxidiative route. Optimisation of the DIBAL-H reduction resulted in the desired aldehyde ultimately being produced in 87% yield.

With the desired aldehyde **83** in hand, reaction screening which mirrored that of the thioether series was undertaken, but the results were slightly disappointing when compared with the previous series (Table 5.5).

Table 5.5: Propylene carbonate as solvent in intermolecular rhodium-catalysed alkyne hydroacylation reactions of dithiane-containing aldehydes.



83

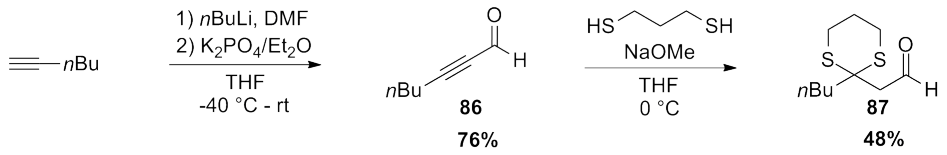
Entry	Aldehyde	R	Product	Yield (%)
1	 **83**	Bu	 **84**	59
2	**83**	C_2H_4Ph	 **85**	60
3	**83**	$C_2H_4Ph^a$	 **85**	63

Conditions: aldehyde **83** (0.75 mmol), alkyne (1.1 equiv.), $[Rh(nbd)_2]BF_4$ (0.05 equiv.), dppe (0.05 equiv.), propylene carbonate (2.5 mL), 70 °C, 2 h; [a] 1.5 equivalents of alkyne used

The reaction between dithiane aldehyde **83** and 1-hexyne produced the desired product **84** in 59% yield (Table 5.5). A similar yield was obtained with 4-phenyl-1-butyne (entry 2), and very little improvement was observed when increasing the equivalents of alkyne from 1.1 to 1.5 (entry 3). Raising the reaction temperature in an attempt to increase conversion was not possible due to the volatility of the alkynes employed.

A second, higher molecular weight dithiane-containing aldehyde was synthesised. This aldehyde had previously been used within the group,[246] and a known route was used for its synthesis: 1-heptynal **86** was synthesised by lithiation then formylation of 1-hexyne, and the resulting alkynal aldehyde **86** underwent double conjugate of addition of 1,3-propanedithiol to furnish the desired dithiane aldehyde **87**.

However, this route also required some optimisation from the previously employed methods. The described formylation conditions produced a mixture of products, a



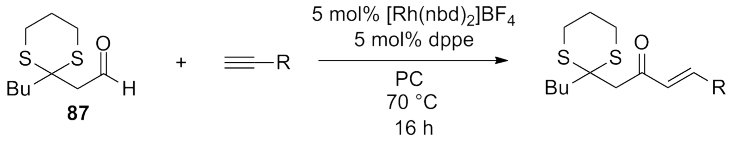
Scheme 5.4. Synthesis of the *n*-butyl dithiane aldehyde **87**

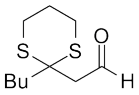
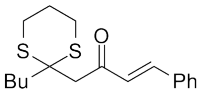
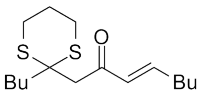
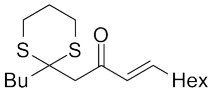
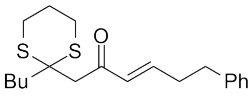
result which is explained by a paper published by the Merck Process Group.[†] The modified procedure in this paper for the formylation of terminal alkynes proved to be considerably more reproducible than the previous method, and permitted the synthesis of 1-heptynal **86** in 76% yield. The double conjugate addition of 1,3-propanedithiol to 1-heptynal proceeded smoothly, but difficulties arose in attempting to separate the product **87** from residual 1,3-propanedithiol (a contaminant which could very well inhibit the hydroacylation catalyst). Sufficiently pure dithiane aldehyde **87** was obtained after repeated column chromatography and washing of the material with aqueous copper(II) sulfate.

The final group of reactions all employ β-dithiane aldehyde **87** (Table 5.6). This sterically demanding aldehyde proved to be a more challenging substrate for the $[Rh(nbd)_2]BF_4$/dppe catalyst system used thus far, and several modifications were required to drive these reactions to completion: a larger excess of alkyne (1.5 equivalents, compared to 1.1 equivalents in the previously described examples), a prolonged reaction time, and changing the ligand from dppe to the second generation DPEphos catalyst system.[78] These modifications enabled the desired hydroacylation products to be synthesised in good yields, as illustrated in Table 5.4.1.

[†]The mixtures of products observed comprise various Michael adducts and condensation products. Their synthesis can be avoided by carrying out an inverse quench of the reaction, as described in the paper

Table 5.6: Propylene carbonate as solvent in intermolecular rhodium-catalysed alkyne hydroacylation reactions of dithiane aldehyde **87**.



Entry	Aldehyde	Alkyne (R)	Product	Yield (%)
1	 **87**	Ph	 **88**	73
2	**87**	Bu	 **89**	73
3	**87**	Hex	 **90**	83
4	**87**	C_2H_4Ph	 **91**	75

5.5 Conclusion

3-Pentanone was identified as a potentially higher-boiling replacement for acetone in rhodium-catalysed intermolecular reactions. Propylene carbonate was utilised as an environmentally benign replacement for DCE, and proved to be effective for intermolecular hydroacylations involving alkyl, aryl and dithiane-containing aldehydes. The results of this investigation have been communicated.[139]

Chapter 6

Experimental

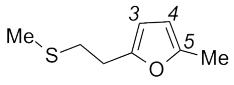
6.1 General considerations

Reactions were performed under an inert atmosphere of nitrogen with technical grade solvent unless otherwise stated. All glassware was oven dried at $>$100 °C and allowed to cool to room temperature under a positive nitrogen pressure. Cooling of reactions to 0 °C was achieved using an ice-water bath and cooling to -40 °C was achieved using a dry ice-acetone bath. Reactions were monitored by TLC until deemed complete using aluminium backed silica plates. Plates were visualised under ultraviolet light and/or by staining with $KMnO_4$, ceric ammoniun nitrate (CAN) or vanillin. Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd., Lancaster Synthesis Ltd, or Strem Chemicals Inc. and were used as supplied unless otherwise stated. Dry tetrahydrofuran was obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. DCE was distilled over CaH_2 prior to use. Dioxane was distilled under reduced pressure and stored over molecular sieves. 3-(methylthio)propionaldehyde and 2-(methylthio)benzaldehyde were distilled under reduced pressure prior to use. Petroleum ether refers to the fraction obtained between 30 and 40 °C or 40 and 60 °C.

Flash chromatography was carried out using matrix 60 silica, and pressure was applied at the column head via hand bellows or a positive pressure of nitrogen gas. Melting points were determined using a Leica Galen III hot-stage microscope. Infra-red spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. ^{1}H NMR spectra were obtained on a Bruker DPX-200 (200 MHz), Bruker DQX-400 (400 MHz) or Bruker AVC-500 (500 MHz) spectrometer using the residual solvent as an internal standard. ^{13}C NMR spectra were obtained on a Bruker DQX-400 (100 MHz) or Bruker AVC-500 (125 MHz) spectrometer using the residual solvent as an internal standard. Chemical shifts were reported in parts per million (ppm) with the multiplicities of the spectra reported as following: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectrometry measurements were recorded by the internal service at the Department of Organic Chemistry, University of Oxford.

Aldehyde **52** generously provided by Sarah-Jane Poingdestre. Aldehyde **30** generously provided by Paul Yljioja. Aldehyde **22** generously provided by Joel Hooper. Aldehydes **8** and **10** generously provided by Carlos González-Rodríguez.

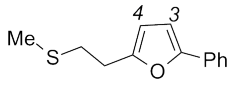
General procedure A, as exemplified by the preparation of2-methyl-5-(2-(methylthio)ethyl)furan, 4



[Rh(nbd$_2$)]BF$_4$ (14 mg, 0.0375 mmol) and dppe (15 mg, 0.0375 mmol) were dissolved in DCE (5 mL) and stirred at room temperature for 10 minutes. 3-(methylthio)-propionaldehyde (75 μL, 0.75 mmol) then 3-hexyn-2-ol (90 μL, 0.83 mmol) were added and the reaction mixture was heated at 65 °C for 1 hour. The reaction mixture was allowed to cool to room temperature, then *p*TSA (14 mg, 0.075 mmol) was added and the reaction mixture stirred at room temperature for 2 h. The crude reaction solution was loaded onto a short plug of triethylamine-washed silica and the prod-

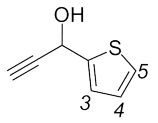
uct eluted (10% Et_2O/petrol + 1% NEt_3) to furnish a pale yellow oil (99 mg, 85%). ν_{max} (film)/cm^{-1} 2948, 1218, 1021; ^1H NMR (400 MHz, $CDCl_3$) δ_H 5.94 (s, 1H, H-*4*), 5.87 (s, 1H, H-*3*), 2.90-2.86 (m, 2H, -C(O)-CH_2-$C\underline{H}_2$-), 2.79-2.75 (m, 2H, -C(O)-$C\underline{H}_2$-CH_2-), 2.26 (s, 3H, -S-$C\underline{H}_3$), 2.12 (s, 3H, C*5*-$C\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.2, 150.7, 106.4, 106.0, 32.7, 28.5, 15.6, 13.5; HRMS (FI) found *m/z* 156.0609 $[M]^+$, $C_8H_{12}OS$ requires 156.0609.

2-(2-(methylthio)ethyl)-5-phenylfuran, 6



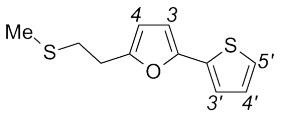
Prepared according to general procedure A (purified using Florisil), to furnish the product furan as a red-brown oil (122 mg, 74%). Alternatively, the reaction was conducted in a 2:1 mixture of hexane and propylene carbonate, and the layers separated upon completion of the reaction. The propylene carbonate fractions were extracted into hexane, and the combined hexane fractions were washed with water then concentrated *in vacuo* to furnish pure product (160 mg, 98%). ν_{max} (film)/cm^{-1} 2915, 1227, 1021; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (d, J = 7.3 Hz, 2H, ArH), 7.38 (t, J = 7.38 Hz, 2H, ArH), 7.25 (d, J = 7.3 Hz, 1H, ArH), 6.58 (d, J = 3.3 Hz, 1H, H-*3*), 6.18 (d, J = 3.3 Hz, 1H, H-*4*), 3.02 (t, J = 7.6 Hz, 2H, -C(O)-CH_2-$C\underline{H}_2$-), 2.86 (t, J = 7.6 Hz, 2H, -C(O)-$C\underline{H}_2$-CH_2-), 2.15 (s, 3H, -S-$C\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 153.9, 152.7, 131.0, 128.6, 127.0, 123.4, 108.0, 105.7, 32.6, 28.7, 15.6; HRMS (FI) found *m/z* 218.0764 $[M]^+$, $C_{13}H_{14}OS$ requires 218.0765.

1-(thiophen-2-yl)but-2-yn-1-ol



2-Thiophenecarboxaldehyde (1.12 g, 0.75 mmol) in THF (20 mL) was cooled to 0 °C (ice/water bath), followed by the slow addition of ethynylmagnesium bromide (22 mL of a 0.5 M solution in THF, 0.83 mmol). The reaction was allowed to warm to room temperature, then quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted into Et_2O, then the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purified by column chromatography (30% Et_2O/petrol) to furnish the product as a yellow oil (1.28 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.29 (dd, J = 5.1, 1.3 Hz, 1H, H-*5*), 7.17 (d, J = 3.5 Hz, 1H, H-*4*), 6.97 (dd, J = 5.1, 3.5 Hz, H-*3*), 5.62 (d, J = 1.8 Hz, 1H, -C<u>H</u>-OH), 3.87 (bs, 1H, -O<u>H</u>), 2.69 (d, J = 2.3 Hz, 1H, -C≡C<u>H</u>; ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.0, 126.9, 126.3, 125.9, 83.1, 74.5, 59.8; HRMS (FI) found *m/z* 138.0142 $[M]^+$, C_7H_6OS requires 138.0139. Data in accordance with the literature.[248]

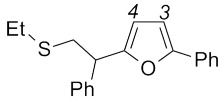
2-(2-(methylthio)ethyl)-5-(thiophen-2-yl)furan, 7



Prepared according to general procedure A, to furnish the product furan as a yellow oil (111 mg, 66%). ν_{max} (film)/cm^{-1} 2915, 1612, 1412; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.20 (m 2H, H-*4'*, H-*5'*), 7.02 (dd, J = 5.1, 3.5 Hz, 1H, H-*3'*), 6.42 (d, J = 3.3 Hz, 1H, H-*3*), 6.13 (d, J = 3.3 Hz, 1H, H-*4*, 2.98 (t, J = 7.8 Hz, 2H, -C(O)-CH_2-C<u>H</u>$_2$-), 2.83 (t, J = 7.8Hz, 2H, -C(O)-C<u>H</u>$_2$-CH_2-), 2.14 (s, 3H, -S-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 153.5, 148.2, 134.0, 127.6, 123.6, 122.0, 108.0, 105.8, 32.6, 28.5, 15.6;

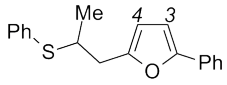
HRMS (FI) found 224.0331 $[M]^+$, $C_{11}H_{12}OS_2$ requires 224.0330.

2-(2-(ethylthio)-1-phenylethyl)-5-phenylfuran, 9



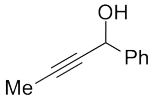
Prepared according to general procedure A to furnish the product furan as a yellow oil (115 mg, 77%). ν_{max} (film)/cm^{-1} 2966, 2925, 1485, 1451; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.70-7.67 (m, 2H, ArH), 7.43-7.37 (m, 6H, ArH), 7.34-7.25 (m, 2H, ArH), 6.64 (d, J = 3.3 Hz, 1H, H-*3*), 6.25 (d, J = 3.3 Hz, 1H, H-*4*), 4.31 (t, J = 7.8 Hz, 1H, Ph-C<u>H</u>-), 3.39 (dd, J = 13.1, 7.8 Hz, 1H, Et-S-C<u>H</u>$_2$-), 3.15 (dd, J = 13.1, 7.8 Hz, 1H, Et-S-C<u>H</u>$_2$-), 2.53 (q, J = 7.3 Hz, 2H, -S-C<u>H</u>$_2$-CH_3), 1.29 (t, J = 7.3 Hz, 3H, -S-CH_2-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 155.8, 153.0, 141.3, 131.0, 128.7 (2 x CH), 128.0, 127.1 (2 x CH), 123.6, 108.6, 105.8, 46.5, 36.8, 26.7, 14.8; HRMS (FI) found *m/z* 308.1231 $[M]^+$, $C_{20}H_{20}OS$ requires 308.1235.

2-phenyl-5-(2-(phenylthio)propyl)furan, 11



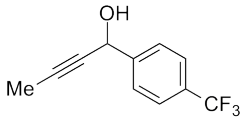
Prepared according to general procedure A, to furnish the product furan as a yellow oil (96 mg, 65%). ν_{max} (film)/cm^{-1} 2961, 2924, 1021; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.67-7.64 (m, 2H, ArH), 7.49-7.47 (m, 2H, ArH), 7.41-7.24 (m, 6H, ArH), 6.58 (d, J = 3.2 Hz, 1H, H-*3*), 6.19 (d, J = 3.2 Hz, 1H, H-*4*), 3.66-3.58 (m, 1H, H_3C-C<u>H</u>-SPh), 3.10 (dd, J = 15.0, 5.3 Hz, 1H, PhS-CH-C<u>H</u>$_2$-), 2.84 (dd, J = 15.0, 8.6 Hz, 1H, PhS-CH-C<u>H</u>$_2$-), 1.34 (d, J = 6.8 Hz, 3H, PhS-CH-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.9, 152.8, 134.7, 132.2, 131.0, 128.9, 128.6, 127.0 (2 x CH), 123.5, 109.2, 105.7, 42.1, 35.7, 20.6; HRMS (FI) found *m/z* 294.1077 $[M]^+$, $C_{19}H_{18}OS$ requires 294.1078.

1-phenylbut-2-yn-1-ol, 16



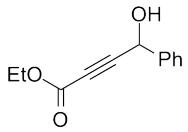
Prepared according to the procedure of Sigman[249] to give the propargylic alchol as a yellow oil (1.24 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56-7.54 (m, 2H, ArH), 7.41-7.37 (m, 2H, ArH), 7.35-7.31 (m, 1H, ArH), 5.44 (bs, 1H, -OH), 2.17 (d, J = 5.6 Hz, 1H, -CH-OH), 1.92 (d, J = 2.2 Hz, 3H, -CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 141.2, 128.6, 128.2, 126.6, 83.1, 79.1, 64.8, 3.7; HRMS (FI) found *m/z* 146.0739 $[M]^+$, $C_{10}H_{10}O$ requires 146.0732. Data in accordance with the literature.[250]

1-(4-(trifluoromethyl)phenyl)but-2-yn-1-ol



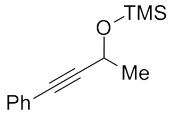
4-(Trifluoromethyl)benzaldehyde (1.37 mL, 10 mmol) in THF (20 mL) was cooled to 0 °C, followed by the slow addition of propynylmagnesium bromide (22 mL of a 0.5 M solution in THF, 11 mmol). The reaction mixture was allowed to warm to room temperature overnight, then quenched with saturated aqeous NH_4Cl. The reaction mixture was extracted into Et_2O, then the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to a red oil. The product was purified by column chromatography (30% Et_2O/petrol) to furnish the pure propargylic alcohol as a red oil (0.53 g, 25%). ν_{max} (film)/cm^{-1} 3338, 2924, 1414, 1323; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67-7.62 (m, 4H, ArH), 5.48 (d, J = 1.8 Hz, 1H, -CH(OH)-Ar), 1.92 (d, J = 2.2 Hz, 3H, -C≡C-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.9, 130.4, 126.8, 125.4, 122.7, 83.9, 78.5, 64.1, 3.6; HRMS (FI) found *m/z* 214.0602 $[M+H]^+$, $C_{11}H_{19}F_3O$ requires 214.0605.

Ethyl 4-hydroxy-4-phenylbut-2-ynoate



Ethyl propiolate (1.01 mL, 10 mmol) in THF (15 mL) was cooled to -78 °C, followed by the dropwise addition of *n*BuLi (6.7 mL of a 1.5 M solution in hexanes, 10 mmol). The reaction mixture was stirred at -78 °C for 10 minutes, then benzaldehyde (1.02 mL, 10 mmol) was added. After 20 minutes, the reaction was quenched with saturated aqueous NH_4Cl and allowed to warm to room temperature, until the reaction mixture was homogeneous. The reaction mixture was extracted into Et_2O, and the combined organic extracts were washed with water then brine, dried over $MgSO_4$ and concentrated *in vacuo* to an orange-red oil. Purified by column chromatography (30% Et_2O/petrol) to furnish the pure product as an orange-red oil (0.41 g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.54 (d, J = 7.2 Hz, 2H, ArH), 7.43-7.36 (m, 3H, ArH), 5.59 (s, 1H, Ph-C<u>H</u>(OH)-), 4.26 (q, J = 7.2 Hz, 2H, -O-C<u>H</u>$_2$-CH$_3$), 2.38 (bs, 1H, -O<u>H</u>), 1.33 (t, J = 7.2 Hz, 3H, -O-CH$_2$-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 153.5, 138.6, 128.9, 128.8, 126.7, 86.4, 77.8, 64.2, 62.3, 14.0; *m/z* (ESI) 227 (100%, $[M+Na]^+$). Data in accordance with the literature.[142]

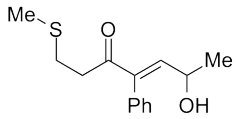
trimethyl((4-phenylbut-3-yn-2-yl)oxy)silane, 14



Prepared according to a modified procedure reported by Fürstner.[251] 4-Phenyl-3-butyn-2-ol (0.73 g, 5.0 mmol) dissolved in DMF/$CHCl_3$ (25 mL and 5 mL respectively), then freshly distilled trimethylsilylchloride (0.76 mL, 6.0 mmol), DMAP (22 mg, 0.9 mmol) and imidazole (0.41 g, 6.0 mmol) added. The reaction mixture was

stirred at room temperature for 48 hours, then quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted into petrol, and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo* to a colourless oil. The crude product was purified by column chromatography (10% Et_2O/petrol) to give the pure TMS-protected alcohol as a colourless oil (0.99 g, 93%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.45-7.24 (m, 2H, ArH), 7.32-7.30 (m, 3H, ArH), 4.77 (q, J = 6.7 Hz, 1H, -C<u>H</u>(OTMS)-CH_3), 1.57 (d, J = 6.7 Hz, 3H, -CH(OTMS)-C<u>H</u>$_3$), 0.08 (s, 9H, -Si(C<u>H</u>$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 131.7, 128.4, 128.3, 122.6, 90.9, 84.0, 58.8, 24.4, 1.9; HRMS (FI) found *m/z* 218.1121 $[M]^+$, $C_{13}H_{18}OSi$ requires 218.1127. Data in accordance with the literature.[140]

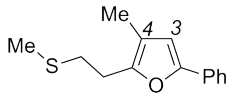
(E)-6-hydroxy-1-(methylthio)-4-phenylhept-4-en-3-one, 12



$[Rh(nbd)_2)]BF_4$ (37 mg, 0.10 mmol) and dppe (39 mg, 0.10 mmol) were dissolved in DCE (10 mL) and stirred at room temperature for 10 minutes. H_2(g) was bubbled through the pre-catalyst solution for 2 minutes, then the solution purged with N_2(g). 3-(methylthio)propionaldehyde (75 μL, 0.75 mmol) then 4-phenyl-3-butyn-2-ol (123 mg, 0.83 mmol) were added and the reaction mixture was heated at 70 °C for 16 h. The reaction mixture was diluted with Et_2O and filtered through a short silica plug, and the filtrate concentrated *in vacuo* followed by purification by column chromatography (10% Et_2O/petrol + 1% NEt_3) to furnish the product as a yellow oil (169 mg, 90%). ν_{max} (film)/cm^{-1} 3410, 2973, 2918, 1676, 1115, 1057, 909; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.31-7.24 (m, 3H, ArH), 7.03 (dd, J = 8.0, 1.0 Hz, 2H, ArH), 6.66 (d, J = 8.8 Hz, Me-CH(OH)-C<u>H</u>=), 4.16 (dq, J = 6.4, 2.3 Hz, 1H, Me-C<u>H</u>(OH)-CH=), 3.33 (bs, 1H, -O<u>H</u>), 2.79 (t, J = 7.1 Hz, 2H, -C(O)-C<u>H</u>$_2$-CH_2-), 2.64 (t, J = 7.1 Hz, 2H,

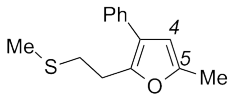
-C(O)-CH_2-C$\underline{H}_2$-), 1.97 (s, 3H, -S-C$\underline{H}_3$), 1.14 (d, J = 6.4 Hz, 3H-CH(OH)-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 199.8, 144.7, 140.7, 134.9, 129.3, 128.4, 127.9, 64.9, 39.4, 28.5, 22.9, 15.7; LRMS (ESI) *m/z* 249 (100%, $[M-H]^-$); HRMS (ESI) found *m/z* 273.0914 $[M+Na]^+$, $C_{14}H_{18}NaO_2S$ requires 273.0920.

General procedure B, as exemplified by the preparation of 3-methyl-2-(2-(methylthio)ethyl)-5-phenylfuran, 17



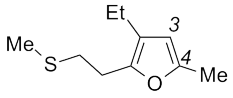
$[Rh(nbd)_2)]BF_4$ (14 mg, 0.0375 mmol) and dppe (15 mg, 0.0375 mmol) were dissolved in DCE (5 mL) and stirred at room temperature for 10 minutes. H_2(g) was bubbled through the pre-catalyst solution for 2 minutes, then the solution purged with N_2(g). 3-(methylthio)propionaldehyde (75 μL, 0.75 mmol) then 1-phenylbut-2-yn-1-ol (123 mg, 0.83 mmol) were added and the reaction mixture was heated at 70 °C for 16 h. The reaction mixture was allowed to cool to room temperature, then HCl (125 μL of a 4.0M solution in dioxane, 0.75 mmol) was added and the reaction mixture stirred at room temperature for 10 min. The crude reaction solution was loaded onto a short plug of base-washed silica and the product eluted (10% Et_2O/petrol + 1% NEt_3) to furnish a yellow oil (91 mg, 78%). ν_{max} (film)/cm^{-1} 2921, 2854, 1452, 1026, 909; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.62 (dd, J = 8.3, 1.8 Hz, 2H, ArH), 7.36 (t, J = 7.3 Hz, 2H, ArH), 7.23 (tt, J = 7.6, 1.3 Hz, 1H, ArH), 6.47 (s, 1H, H-*3*), 2.96-2.92 (m, 2H, -C(O)-C$\underline{H}_2$-CH_2-), 2.85-2.81 (m, 2H, -C(O)-CH_2-C$\underline{H}_2$-), 2.14 (s, 3H, -S-C$\underline{H}_3$) and 2.04 (s, 3H, C*4*-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 151.4, 149.1, 131.1, 128.6, 126.8, 123.3, 117.2, 108.4, 33.1, 26.6, 15.6 and 10.0; HRMS (FI) found *m/z* 232.0926 $[M]^+$, $C_{14}H_{16}OS$ requires 232.0922.

5-methyl-2-(2-(methylthio)ethyl)-3-phenylfuran, 18



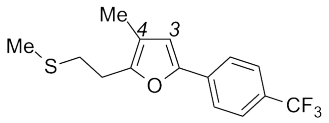
Prepared according to general procedure B on 3.0 mmol scale to furnish the product furan as a yellow oil (645 mg, 93%). ν_{max} (film)/cm^{-1} 2963, 1602, 1578, 1444, 1262, 1218, 1009; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42-7.38 (m, 4H, ArH), 7.29-7.25 (m, 1H, ArH), 6.12 (s, 1H, H-*4*), 3.06 (t, J = 7.7 Hz, 2H, -C(O)-C$\underline{H}_2$-CH$_2$-), 2.85 (t, J = 7.7 Hz, 2H, -C(O)-CH$_2$-C$\underline{H}_2$-), 2.32 (s, 3H, -S-C$\underline{H}_3$), 2.11 (s, 3H, C*5*-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 150.3, 147.6, 134.2, 128.6, 127.6, 126.4, 122.6, 107.3, 32.8, 27.4, 15.5, 13.5; HRMS (FI) found *m/z* 232.0931 [M]$^+$, $C_{14}H_{16}OS$ requires 232.0922.

3-ethyl-5-methyl-2-(2-(methylthio)ethyl)furan, 19



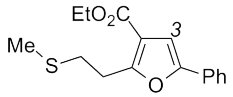
Prepared according to general procedure B to furnish the pure product as a yellow oil (58 mg, 42%). ν_{max} (film)/cm^{-1} 2964, 2918, 1579, 1435, 1255, 1221, 953, 798; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 (s, 1H, H-*3*), 2.84-2.79 (m, 2H, -C(O)-C$\underline{H}_2$-CH$_2$-), 2.75-2.71 (m, 2H, -C(O)-CH$_2$-C$\underline{H}_2$-), 2.32 (q, J = 7.6 Hz, 2H, -C$\underline{H}_2$-CH$_3$), 2.23 (s, 3H, -S-C$\underline{H}_3$), 2.11 (s, 3H, C*4*-C$\underline{H}_3$), 1.12 (t, J = 7.6 Hz, 3H, -CH$_2$-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 149.7, 146.5, 122.4, 107.1, 33.3, 26.4, 18.0, 15.5, 15.2, 13.5; HRMS (FI) found *m/z* 184.0928 [M]$^+$, $C_{10}H_{16}OS$ requires 184.0922.

3-methyl-2-(2-(methylthio)ethyl)-5-(4-(trifluoromethyl)phenyl)furan, 20



Prepared according to general procedure B to furnish the product furan as a yellow oil (123 mg, 82%). ν_{max} (film)/cm^{-1} 2922, 1228, 1069; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (d, J = 8.4 Hz, 2H, ArH), 7.59 (d, J = 8.4 Hz, 2H, ArH), 6.58 (s, 1H, H-*3*), 2.95 (t, J = 7.3 Hz, 2H, -C(O)-C$\underline{H}_2$-CH$_2$-), 2.83 (t, J = 7.3 Hz, 2H, -C(O)-CH$_2$-C$\underline{H}_2$-), 2.14 (s, 3H, -S-C$\underline{H}_3$), 2.05 (s, 3H, C*4*-C$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 150.5, 150.0, 134.2, 128.5, 128.2, 125.7, 123.3, 117.7, 110.5, 30.0, 26.6, 15.7, 10.0; HRMS (FI) found *m/z* 300.0801 [M]$^+$, $C_{15}H_{15}F_3OS$ requires 300.0796.

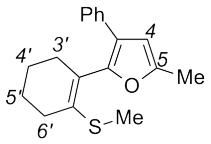
Ethyl 2-(2-(methylthio)ethyl)-5-phenylfuran-3-carboxylate, 21



[Rh(nbd$_2$)]BF$_4$ (14 mg, 0.0375 mmol) and dppe (15 mg, 0.0375 mmol) were dissolved in DCE (5 mL) and stirred at room temperature for 10 minutes. H_2(g) was bubbled through the pre-catalyst solution for 2 minutes, then the solution purged with N_2(g). 3-(methylthio)propionaldehyde (75 μL, 0.75 mmol) then ethyl 4-hydroxy-4-phenylbut-2-ynoate (230 mg, 1.13 mmol) were added and the reaction mixture was heated at 70 °C for 16 h. The crude reaction solution was loaded onto a short plug of base-washed silica and the product eluted (10% Et_2O/petrol + 1% NEt_3) to furnish a yellow oil (86 mg, 59%). ν_{max} (film)/cm^{-1} 2980, 2918, 1712, 1225, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (d, J = 8.2 Hz, 2H, ArH), 7.39 (t, J = 7.7 Hz, 2H, ArH), 7.29 (t, J = 7.7 Hz, 1H, ArH), 6.91 (s, 1H, H-*3*), 4.33 (q, J = 7.1 Hz, 2H, -O-C$\underline{H}_2$-CH$_3$), 3.37 (t, J = 7.5 Hz, 2H, -C(O)-CH$_2$-C$\underline{H}_2$-), 2.89 (t, J = 7.5 Hz, 2H, -C(O)-CH$_2$-C$\underline{H}_2$-), 2.17 (s, 3H, -S-C$\underline{H}_3$), 1.38 (t, J = 7.1 Hz, 3H, -O-CH$_2$-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

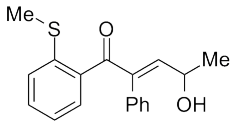
δ_C 163.7, 159.8, 152.2, 129.9, 128.7, 127.8, 123.7, 116.0, 105.6, 60.3, 32.2, 28.0, 15.4, 14.4; HRMS (ESI) found 313.0862 $[M+Na]^+$, $C_{16}H_{18}NaO_3S$ requires 313.0869.

5-methyl-2-(2-(methylthio)cyclohex-1-en-1-yl)-3-phenylfuran, 23



Prepared according to general procedure B to furnish the product furan as a yellow oil (166 mg, 78%). ν_{max} (film)/cm^{-1} 2930, 2861, 1261, 1261; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42-7.40 (m, 2H, ArH), 7.35-7.32 (m, 2H, ArH), 7.24-7.20 (m, 1H, ArH), 6.25 (s, 1H, H-*4*), 2.41-2.31 (m, 7H [incl. 2.35 (s, 3H, -S-C$\underline{H}_3$)], -C*3'*$\underline{H}_2$, -C*6'*$\underline{H}_2$), 2.06 (s, 3H, C*5*-C$\underline{H}_3$), 1.82-1.69 (m, 4H, -C*4'*$\underline{H}_2$, -C*5'*$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 150.9, 147.9, 135.7, 134.2, 128.4, 126.7, 126.2, 126.1, 122.5, 106.8, 30.5, 29.5, 23.2, 22.6, 14.1, 13.6; HRMS (FI) found *m/z* 284.1235 $[M]^+$, $C_{18}H_{20}OS$ requires 284.1235.

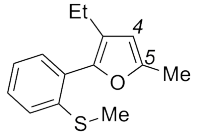
(E)-4-hydroxy-1-(2-(methylthio)phenyl)-2-phenylpent-2-en-1-one, 25



$[Rh(nbd)_2)]BF_4$ (37 mg, 0.10 mmol) and dppe (39 mg, 0.10 mmol) were dissolved in DCE (10 mL) and stirred at room temperature for 10 minutes. H_2(g) was bubbled through the pre-catalyst solution for 2 minutes, then the solution purged with N_2(g). 2-(methylthio)benzaldehyde (0.30 g, 2.0 mmol) then 4-phenyl-3-butyn-2-ol (0.32 mL, 2.2 mmol) were added and the reaction mixture was heated at 70 °C for 16 h. The reaction mixture was diluted with Et_2O and filtered through a short silica plug, and the filtrate concentrated *in vacuo*. Purified by column chromatography (30% EtOAc/petrol) to furnish the product enone as a yellow oil (505 mg, 85%). ν_{max} (film)/cm^{-1} 3484,

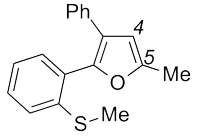
2974, 2923, 1633, 1445, 1240; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49-7.33 (m, 8H, ArH), 7.24 (dd, J = 7.4, 1.0 Hz, 1H, ArH), 7.06 (s, 1H, Ph-C=C<u>H</u>-) 5.02 (dq, J = 11.0, 6.6 Hz, 1H, H_3C-C<u>H</u>(OH)-), 3.98 (d, J = 11.0 Hz, 1H, -O<u>H</u>), 2.47 (s, 3H, -S-C<u>H_3</u>), 1.66 (d, J = 6.6 Hz, 3H, -CH(OH)-C<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 201.4, 144.5, 142.6, 138.6, 138.2, 134.4, 131.1, 129.4, 129.3, 129.2, 128.6, 127.2, 124.8, 66.0, 22.9, 16.9; LRMS (ESI) *m/z* 619 $[2M+Na]^+$, 100%, 299 $[M+H]^+$, 10%; HRMS (ESI) found 321.0913, $C_{18}H_{18}NaO_2S$ requires 321.0920.

3-ethyl-5-methyl-2-(2-(methylthio)phenyl)furan, 26



Prepared according to general procedure B to furnish the product furan as a yellow oil (79 mg, 67%). ν_{max} (film)/cm^{-1} 2965, 2921, 1373, 1319, 1253; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36-7.32 (m, 1H, ArH), 7.29-7.25 (m, 2H, ArH), 7.19-7.15 (m, 1H, ArH), 6.04 (s, 1H, H-*4*), 2.42 (s, 3H, -S-C<u>H_3</u>), 2.38 (q, J = 7.6 Hz, 2H, -C<u>H_2</u>-CH_3), 2.34 (s, 3H, C5-C<u>H_3</u>), 1.14 (t, J = 7.6 Hz, 3H, -CH_2-C<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 151.4, 145.6, 139.7, 130.7, 130.1, 128.7, 125.4, 125.0, 124.2, 107.7, 18.6, 15.8, 14.7, 13.7; HRMS (FI) found *m/z* 232.0924 $[M]^+$, $C_{14}H_{16}OS$ requires 232.0922.

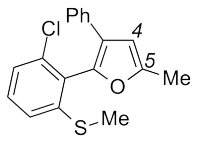
5-methyl-2-(2-(methylthio)phenyl)-3-phenylfuran, 27



Prepared according to general procedure B to furnish the product furan as a yellow oil (119 mg, 85%). ν_{max} (film)/cm^{-1} 2921, 1381, 1184, 1162, 909; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40-7.14 (m, 9H, ArH), 6.39 (s, 1H, H-*4*), 2.43 (s, 3H, -S-C<u>H_3</u>), 2.40 (s,

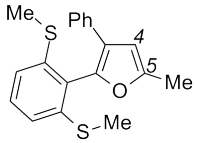
3H, C*5*-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.0, 146.0, 140.0, 133.7, 131.3, 130.6, 129.3, 128.4, 127.1, 126.5, 125.5, 124.6, 124.3, 107.4, 15.9, 13.7; HRMS (FI) found *m/z* 280.0924 $[M]^+$, $C_{18}H_{16}OS$ requires 280.0922.

2-(2-chloro-6-(methylthio)phenyl)-5-methyl-3-phenylfuran, 28



Prepared according to general procedure B to furnish the product furan as a yellow solid (69 mg, 55%). m.p. 89-90 °C (recrystallised from IPA); ν_{max} (film)/cm^{-1} 2921, 1556, 1271; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 (t, J = 8.0 Hz, 1H, ArH), 7.27-7.24 (m, 5H, ArH), 7.22-7.20 (m, 1H, ArH), 7.12 (dd, J = 7.9, 1.0 Hz, 1H, ArH), 6.45 (d, J = 1.0 Hz, 1H, H-*4*), 2.44 (d, J = 1.0 Hz, 3H, C*5*-C$\underline{H}_3$), 2.35 (s, 3H, -S-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.8, 144.4, 142.3, 136.8, 133.1, 130.6, 128.9, 128.4, 126.7, 126.4, 125.8, 125.4, 122.6, 106.7, 15.6, 13.8; LRMS (ESI) *m/z* 369 (100%, $[M+Na+CH_3OH]^+$, 315 (10%, $[M+H]^+$); HRMS (ESI) found *m/z* 315.0598 $[M+H]^+$, $C_{18}H_{16}{}^{35}ClOS$ requires 315.0605.

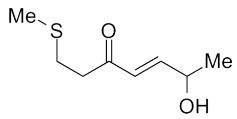
2-(2,6-bis(methylthio)phenyl)-5-methyl-3-phenylfuran, 29



Prepared according to general procedure B to furnish the product furan as a pale yellow solid (59 mg, 72%). m.p. 137-138 °C (recrystallised from IPA); ν_{max} (film)/cm^{-1} 2921, 1556, 1498; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (t, J = 8.0 Hz, 2H, ArH), 7.28-7.15 (m, 4H, ArH), 7.01 (d, 1H, 8.0 Hz, ArH), 6.46 (s, 1H, H-*4*), 2.43 (s, 3H, C*5*-C$\underline{H}_3$), 2.34 (s, 6H, -S-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.9, 143.1, 142.7, 133.1,

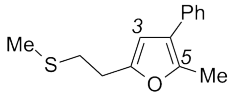
130.2, 128.4, 127.6, 126.5, 126.2, 125.8, 120.5, 106.5, 15.4, 13.8; HRMS (FI) found *m/z* 326.0794 $[M]^+$, $C_{19}H_{18}OS_2$ requires 326.0799.

(E)-6-hydroxy-1-(methylthio)hept-4-en-3-one, 34



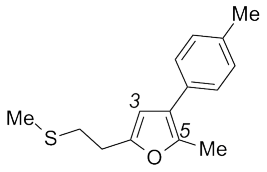
$[Rh(nbd)_2]BF_4$ (56 mg, 0.15 mmol), dppe (60 mg, 0.15 mmol) and Li_2CO_3 (222 mg, 3.0 mmol) in DCE (20 mL) were stirred at room temperature for 10 minutes, followed by the addition of 3-(methylthio)propionaldehyde (0.30 mL, 3.0 mmol) then 3-butyn-2-ol (0.26 mL, 3.3 mmol). The reaction was stirred at 70 °C for 5 hours, then allowed to cool to room temperature before being diluted with Et_2O and filtered through a short silica plug. The filtrate was concentrated *in vacuo* to an orange-brown oil, then purified by column chromatography (40% EtOAc/petrol + 1% NEt_3; the silica must be thoroughly washed with basic column eluant to prevent the formation of furan during purification) to furnish the product enone as a light yellow oil (400 mg, 77%). ν_{max} (film)/cm^{-1} 3422, 2974, 2918, 1669, 1632, 978; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.71 (dd, J = 15.9, 4.6 Hz, 1H, -C(O)-CH=C<u>H</u>-), 6.15 (dd, J = 15.9, 1.6 Hz, 1H, -C(O)-C<u>H</u>=CH-), 4.39-4.34 (m, 1H, -C<u>H</u>-OH), 3.54 (d, J = 4.4 Hz, 1H, -O<u>H</u>), 2.75 (t, J = 7.3 Hz, 2H, -C(O)-C<u>H</u>$_2$-CH$_2$-), 2.60 (t, J = 7.3 Hz, 2H, -C(O)-CH$_2$-C<u>H</u>$_2$-), 1.97 (s, 3H, -S-C<u>H</u>$_3$), 1.19 (d, J = 6.6 Hz, 3H, -CH(OH)-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 199.1, 150.1, 127.0, 66.8, 40.0, 28.0, 22.6, 15.6; HRMS (FI) found *m/z* 197.0612 $[M]^+$; $C_8H_{14}NaO_2S$ requires 197.0607.

General Procedure C, as exemplified by the preparation of 2-methyl-5-(2-(methylthio)ethyl)-3-phenylfuran, 35



Based on a procedure by Donohoe.[134] $Pd_2(dba)_3$ (20 mg, 0.0215 mmol), $P(tBu)_3 \cdot HBF_4$ (25 mg, 0.086 mmol) and bromobenzene (114 μL, 1.08 mmol) were dissolved in anhydrous dioxane (5.0 mL). A solution of (E)-6-hydroxy-1-(methylthio)hept-4-en-3-one (75 mg, 0.43 mmol) in anhydrous dioxane (2.5 mL) was added to the catalyst solution, followed by dicyclohexylmethylamine (0.23 mL, 1.08 mmol). The reaction mixture was heated at 70 °C for 16 h, then filtered through a short silica plug, eluting with EtOAc, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (10% Et_2O/petrol) to furnish the product furan as a yellow oil (74 mg, 74%). ν_{max} (film)/cm^{-1} 2917, 1602, 1576, 1219; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43-7.41 (m, 3H, ArH), 7.32-7.26 (m, 2H, ArH), 6.26 (s, 1H, H-*3*), 2.98-2.94 (m, 2H, -C(O)-C$\underline{H}_2$-CH$_2$-), 2.87-2.83 (m, 2H, -C(O)-CH$_2$-C$\underline{H}_2$-), 2.46 (s, 3H, -S-C$\underline{H}_3$), 2.18 (s, 3H, C*5*-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 151.8, 146.3, 134.4, 130.1, 128.5, 127.4, 126.2, 107.3, 32.6, 28.5, 15.6, 13.1; HRMS (FI) found *m/z* 232.0923 $[M]^+$, $C_{14}H_{16}OS$ requires 232.0922.

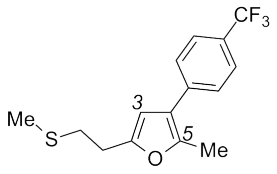
2-methyl-5-(2-(methylthio)ethyl)-3-(p-tolyl)furan



Prepared according to general procedure C to furnish the product furan as a yellow oil (82 mg, 77%). ν_{max} (film)/cm^{-1} 2922, 2856, 1216; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H

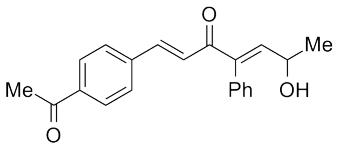
7.31 (d, J = 8.2 Hz, 2H, ArH), 7.23 (d, J = 8.2 Hz, 2H, ArH), 6.23 (s, 1H, H-*3*), 2.97-2.94 (m, 2H, -C(O)-C<u>H</u>$_2$-CH$_2$-), 2.86-2.82 (m, 2H, -C(O)-CH$_2$-C<u>H</u>$_2$-), 2.45 (s, 3H, -S-C<u>H</u>$_3$), 2.41 (s, 3H, Ar-C<u>H</u>$_3$), 2.18 (s, 3H, C*5*-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 151.7, 145.9, 135.8, 131.8, 129.7, 127.7, 121.7, 107.7, 33.1, 28.9, 21.5, 16.0, 13.4; HRMS (FI) found *m/z* 246.0924 $[M]^+$, $C_{15}H_{18}OS$ requires 246.1078.

2-methyl-5-(2-(methylthio)ethyl)-3-(4-(trifluoromethyl)phenyl)furan



Prepared according to general procedure C to furnish the product furan as a yellow oil (130 mg, 87%). ν_{max} (film)/cm^{-1} 2922, 1617, 1322, 1163, 1118, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63 (d, J = 8.1 Hz, 2H, ArH), 7.48 (d, J = 8.1 Hz, 2H, ArH), 6.24 (s, 1H, H-*3*), 2.94 (t, J = 7.4 Hz, 2H, -C(O)-C<u>H</u>$_2$-CH$_2$-), 2.84-2.78 (m, 2H, -C(O)-CH$_2$-C<u>H</u>$_2$-), 2.44 (s, 3H, -S-C<u>H</u>$_3$), 2.15 (s, 3H, C*5*-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 152.3, 147.3, 138.0, 128.7, 127.37, 127.34, 126.3, 125.4, 106.9, 32.5, 28.3, 15.6, 13.1; HRMS (FI) found *m/z* 300.0785 $[M]^+$, $C_{15}H_{15}F_3OS$ requires 300.0796.

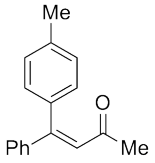
(1E,4E)-1-(4-acetylphenyl)-6-hydroxy-4-phenylhepta-1,4-dien-3-one, 36



Isolated as a by-product from a procedure analgous to general procedure C, utilising (E)-6-hydroxy-1-(methylthio)-4-phenylhept-4-en-3-one and 4-bromoacetophenone. Isolated as a yellow oil (62 mg, 39%). ν_{max} (film)/cm^{-1} 3432, 2974, 2927, 1681, 1603, 1265; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93 (d, J = 8.4 Hz, 2H, ArH), 7.68 (d, J = 15.7

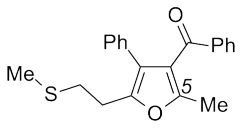
Hz, 1H, -C(O)-CH=CH-), 7.55 (d, J = 8.4 Hz, 2H, ArH), 7.42-7.36 (m, 3H, ArH), 7.21 (dd, J = 8.0, 1.4 Hz, 2H, ArH), 7.05 (d, J = 15.7 Hz, 1H, -C(O)-CH=CH-), 6.83 (d, J = 8.8 Hz, 1H, -C(O)-C(Ph)=CH-), 4.43 (qd, J = 8.8, 6.4 Hz, 1H, -CH(OH)-CH_3), 2.60 (s, 3H, -C(O)-CH_3), 1.90 (bs, 1H, -OH), 1.34 (d, J = 6.4 Hz, 3H, -CH(OH)-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 197.4, 190.3, 144.2, 142.4, 141.9, 139.1, 138.0, 135.0, 129.4, 128.8, 128.6, 128.4, 128.2, 124.9, 65.3, 26.7, 23.1; LRMS (ESI) *m/z* 663.32 ([2M+Na]$^+$, 100%); HRMS found *m/z* (ESI) 343.1293 [M+Na]$^+$; $C_{21}H_{20}NaO_3$ requires 343.1305.

(Z)-4-phenyl-4-(p-tolyl)but-3-en-2-one, 40



Prepared according to general procedure C to furnish the product as a yellow oil (from 4-phenyl-3-buten-2-one: 82 mg, 70%; from 4-phenyl-3-butyn-2-ol: 67 mg, 57%). ν_{max} (film)/cm^{-1} 3025, 2921, 1654, 1588, 1351, 1256, ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43-7.39 (m, 4H, ArH), 7.24-7.20 (m, 3H, ArH), 7.16-7.14 (m, 2H, ArH), 6.60 (s, 1H, -CH=), 2.37 (s, 3H, Ar-CH_3), 1.88 (s, 3H, -C(O)-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 200.2, 154.1, 139.8, 139.1, 137.9, 129.6, 129.2, 128.7, 128.40, 128.37, 126.9, 30.3, 21.3; Data in accordance with the literature.[252]

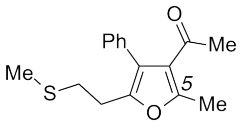
(2-methyl-5-(2-(methylthio)ethyl)-4-phenylfuran-3-yl)(phenyl)methanone, 47



Benzoyl chloride (23 μL, 0.2 mmol) was added to a solution of 5-methyl-2-(2-(methylthio)ethyl)-3-phenylfuran (46.5 mg, 0.2 mmol) and $InBr_3$ (7.1 mg, 0.02 mmol)

in DCE (1.0 mL) andthe reaction mixture heated at 40 °C for 16 hours. The reaction mixture was allowed to cool to room temperature then diluted with DCM and washed with saturated aqueous $NaHCO_3$. The aqeuous washes were reextracted with DCM and the combined organic extracts dried over $MgSO_4$. The product was purified by column chromatography (25% Et_2O/petrol) to furnish the product as a dark yellow oil, contaminated with 22% residual benzoyl chloride (56 mg, 65% product). ν_{max} (film)/cm^{-1} 3063, 2919, 1787, 1692, 1653, 1600, 1582, 1450, 1213; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.68-7.65 (m, 2H, ArH), 7.25-7.20 (m, 2H, ArH), 7.18-7.09 (m, 6H, ArH), 2.97 (t, J = 7.5 Hz, 2H, -C<u>H</u>$_2$-CH_2-S-CH_3), 2.82 (t, J = 7.5 Hz, 2H, -CH_2-C<u>H</u>$_2$-S-CH_3), 2.37 (s, 3H, C*5*-C<u>H</u>$_3$), 2.07 (s, 3H, -S-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 192.4, 162.3, 155.3, 148.6, 138.3, 130.6, 129.4, 129.3, 128.1, 127.9, 126.7, 122.8, 121.9, 32.7, 26.4, 15.4, 13.7; HRMS (ESI) found 359.1073 $[M+Na]^+$, $C_{21}H_{20}NaO_2S$ requires 359.1076.

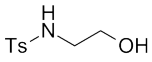
1-(2-methyl-5-((methylthio)methyl)-4-phenylfuran-3-yl)ethanone, 48



Based on a procedure by Frost.[178] $In(OTf)_3$ (11.2 mg, 0.02 mmol) and $LiClO_4$ (21.3 mg, 0.2 mmol) were dissolved in $MeNO_2$ (0.4 mL) and heated at 50 °C, followed by the addition of a solution of 5-methyl-2-(2-(methylthio)ethyl)-3-phenylfuran (46.5 mg, 0.2 mmol) in $MeNO_2$ (0.1 mL) then acetic anhydride (28 μL, 0.3 mmol). The reaction mixture was heated at 50 °C for 16 hours, then quenched with water and extracted into DCM. The organic fraction was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purified by column chromatography (25% EtOAc/petrol) to furnish the product as a light yellow oil (49 mg, 89%). ν_{max} (film)/cm^{-1} 2919, 1754, 1706, 1684, 1601, 1573, 1361, 1179; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.43-7.33 (m,

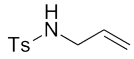
3H, ArH), 7.29-7.26 (m, 2H, ArH), 2.79-2.69 (m, 4H, -C(O)-C$\underline{H}_2$-C$\underline{H}_2$-), 2.55 (s, 3H, -C(O)C$\underline{H}_3$), 1.99 (s, 3H, C5-C$\underline{H}_3$), 1.91 (s, 3H, -S-C$\underline{H}_3$; LRMS (ESI) found *m/z* 297 ([M+Na]$^+$, 100%), 571 ([2M+Na]$^+$, 45%); HRMS (ESI) found *m/z* 297.0917 [M+Na]$^+$, $C_{16}H_{18}NaO_2S$ requires 297.0920.

N-(2-hydroxyethyl)-4-methylbenzenesulfonamide



A solution of ethanolamine (5.05g, 82.8 mmol) and triethylamine (14.5 g, 144 mmol) in DCM (150 mL) was cooled to 0 °C, followed by the addition of tosyl chloride (14.5 g, 74.5 mmol). The reaction mixture was allowed to warm to room temperature overnight, then diluted with water and extracted into DCM. The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude product was purified by column chromatography (10% MeOH in DCM) to give the final product as a white crystalline solid (14.74g, 92%). m.p. 52-54 °C (recrystallised from DCM/petrol); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 7.75 (d, J = 8.2 Hz, 2H, ArH), 7.31 (d, J = 8.2 Hz, 2H, ArH), 3.69 (t, J = 4.8 Hz, 2H, -C$\underline{H}_2$CH$_2$-NHTs), 3.08 (t, J = 4.8 Hz, 2H, -CH$_2$C$\underline{H}_2$-NHTs), 2.43 (s, 3H, -C$\underline{H}_3$); *m/z* (ESI) 214 (100%, [M-H]-). Data in accordance with the literature.[253]

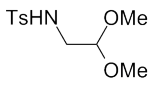
N-allyl-4-methylbenzenesulfonamide



A solution of allylamine (1.00 g, 17.5 mmol) and triethylamine (3.01 g, 29.8 mmol) in DCM (30 mL) was cooled to 0 °C, followed by the addition of tosyl chloride (3.00 g, 15.8 mmol). The reaction mixture was allowed to warm to room temperature overnight, then diluted with water and extracted into DCM. The combined organic

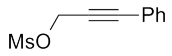
fractions were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude product was purified by column chromatography (10% MeOH in DCM) to give the final product as a white crystalline solid (2.96 g, 89%). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 7.76 (d, J = 8.2 Hz, 2H, ArH), 7.32 (d, J = 8.2 Hz, 2H, ArH), 5.83-5.64 (m, 1H, -CH_2C<u>H</u>=CH_2), 5.22-5.08 (m, 2H, -CH_2CH=C<u>H_2</u>) 4.54 (br s, 1H, -NH-), 3.59 (t, 2H, J = 6.0 Hz, -C<u>H_2</u>CH=CH_2), 2.44 (s, 3H, ArC<u>H_3</u>). Data in accordance with the literature.[254]

N-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide



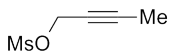
A solution of aminoacetaldehyde dimethyl acetal (4.00 g, 38.1 mmol) and tosyl chloride (7.27 g, 38.1 mmol) in DCM was cooled to 0 °C, and triethylamine (15.9 mL, 114.3 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature over 3 hours, then diluted with DCM and washed with water. The aqueous washes were re-extracted into DCM, and the combined organic fractions washed with brine and concentrated *in vacuo* to a yellow oil. The crude product was purified by column chromatography (30% EtOAc in petroleum ether) to produce the final product as a a colourless solid (8.48 g, 86%). m.p. 44-46 °C (recrystallised from DCM/petrol); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 7.74 (d, J = 8.3 Hz, 2H, ArH), 7.30 (d, J = 8.3 Hz, 2H, ArH), 4.80 (t, J = 6.2 Hz, 1H, N<u>H</u>Ts), 4.33 (t, J = 6.0 Hz, 1H, -C<u>H</u>$(OMe)_2$), 3.31 (s, 6H, OC<u>H_3</u>), 3.03 (t, J = 6.0 Hz, 2H, -C<u>H_2</u>NHTs, 2.42 (s, 3H, Ar-C<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.5, 136.8, 129.7, 127.1, 102.3, 54.6, 44.5, 21.5; *m/z* (ESI) 258 (100%, $[M-H]^-$). Data in accordance with the literature.[255]

3-Phenylprop-2-ynyl methanesulfonate



3-Phenyl-2-propyn-1-ol (2.00 g, 15.1 mmol) and triethylamine (2.52 mL, 18.1 mmol) in DCM (40 mL) cooled to -20 °C, followed by the slow addition of methanesulfonyl chloride (1.29 mL, 16.6 mmol). The reaction mixture was stirred at -20 °C for 1 hour, then allowed to warm to room temperature over 1 further hour, after which point all starting material had been consumed by tlc. The reaction mixture was diluted with DCM, washed with water, and the organic fractions dried over $MgSO_4$. The combined organic extracts were concentrated *in vacuo* to a yellow oil, which was purified by column chromatography (40% EtOAc in pentane) to give the product as a colourless oil (2.79 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50-7.30 (m, 5H, ArH), 5.10 (s, 2H, -C$\underline{H}_2$-), 3.17 (s, 3H, -C$\underline{H}_3$), ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 131.9, 129.5, 128.5, 121.2, 89.4, 80.9, 58.5, 39.0; *m/z* (ESI) 209 (45%, $[M-H]^-$). Data in accordance with the literature.[256]

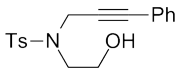
But-2-ynyl methanesulfonate



2-Butyn-1-ol (1.00 g, 14.29 mmol) and triethylamine (2.38 mL, 17.14 mmol) in DCM (20 mL) cooled to -20 °C, followed by the slow addition of methanesulfonyl chloride (1.22 mL, 15.71 mmol). The reaction mixture was stirred at -20 °C for 1 hour, then allowed to warm to room temperature over 1 further hour, after which all starting material had been consumed by tlc. The reaction mixture was diluted with DCM, washed with water, and the organic fractions dried over $MgSO_4$. The combined organic extracts were concentrated *in vacuo* to a yellow oil, which was purified by column chromatography (40% EtOAc in pentane) to give the product as a colourless oil

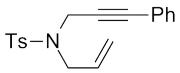
(1.92 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.82 (q, J = 2.4 Hz, 2H, -C$\underline{H}_2$-), 3.11 (s, 3H, -Ar-C$\underline{H}_3$), 1.90 (t, J = 2.4 Hz, 3H, -C≡C-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 86.6, 71.5, 58.5, 39.0, 3.7; *m/z* (ESI) 138 (100%, $[M+H]^+$). Data in accordance with the literature.[257]

N-(2-hydroxyethyl)-4-methyl-N-(3-phenylprop-2-ynyl)benzenesulfonamide



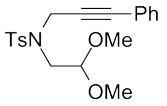
A suspension of NaH (60% w/w suspension in mineral oil, 0.21g, 5.29 mmol) in anhydrous DMF (10 mL) was cooled to 0 °C, followed by the addition of a solution of N-(2-hydroxyethyl)-4-methylbenzenesulfonamide (0.95 g, 4.41 mmol) in anhydrous DMF (10 mL). The suspension was allowed to warm to room temperature over 30 minutes, then 3-phenylprop-2-ynyl methanesulfonate (0.93 g, 4.41 mmol) was added. The reaction was stirred at room temperature for 3 hours, then diluted with EtOAc and washed with saturated aqueous NH_4Cl. The aqueous fractions were re-extracted into EtOAc, then the combined organic fractions repeatedly washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude product was purified by column chromatography (25% EtOAc in petroleum ether) to give the final product as a white powdery solid (0.94 g, 68%). m.p. 81-83 °C (recrystallised from DCM/petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (d, J = 8.6 Hz, 2H, ArH), 7.31-7.23 (m, 5H, ArH), 7.11 (d, J = 8.6 Hz, 2H, ArH), 4.43 (s, 2H, TsN-C$\underline{H}_2$-C≡C−Ph), 3.85 (t, J = 5.2 Hz, 2H, TsN-C$\underline{H}_2$-CH_2-OH), 3.43 (t, J = 5.2 Hz, 2H, TsN-CH_2-C$\underline{H}_2$-OH), 2.37 (s, 3H, Ar-C$\underline{H}_3$) 1.75 (bs, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.8, 135.5, 131.5, 129.6, 128.6, 128.2, 127.9, 122.0, 85.8, 82.0, 60.6, 49.1, 38.8,21.5; *m/z* (ESI) 388 (100%, $[M+NH_4+MeCN]^+$). Data in accordance with the literature.[258]

N-allyl-4-methyl-N-(3-phenyl-prop-2-ynyl)-benzenesulfonamide



A solution of N-allyl-4-methylbenzenesulfonamide (2.32 g, 11 mmol) in THF (20 mL) was added to a suspension of NaH (60% w/w, 0.44 g, 13.2 mmol) in THF (10 mL) at 0 °C, and stirred for 30 minutes. A solution of 3-phenylprop-2-ynyl methanesulfonate (2.31 g, 11 mmol) in THF (5 mL) was added dropwise, and the reaction mixture was heated at reflux for 90 minutes. The reaction mixture was diluted with water and the aqueous fractions re-extracted into Et_2O. The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude product was purified by column chromatography (25% EtOAc in petroleum ether) to give the final product as a white crystalline solid (2.33 g, 65%). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 7.78 (d, J = 8.5 Hz, 2H, ArH), 7.31-7.21 (m, 5H, ArH), 7.09-7.04 (m, 2H, ArH), 5.81 (tt, J = 9.9, 6.5 Hz, 1H, -NTs-CH_2-C<u>H</u>=CH_2), 5.38-5.25 (m, 2H, -NTs-CH_2-CH=C<u>H_2</u>), 4.32 (s, 2H, -NTs-C<u>H_2</u>-C≡C-Ph), 3.90 (d, J = 6.5 Hz, 2H, -NTs-C<u>H_2</u>CH=CH_2), 2.35 (s, 3H, ArC<u>H_3</u>). Data in accordance with the literature.[259]

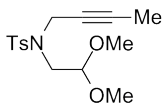
N-(2,2-dimethoxyethyl)-4-methyl-N-(3-phenylprop-2-ynyl)benzenesulfonamide



A suspension of NaH (60% w/w in mineral oil, 0.36 g, 9.24 mmol) in anhydrous DMF (40 mL) was cooled to 0 °C, followed by the dropwise addition of N-(2,2-dimethoxyethyl)-4-methyl-benzenesulfonamide (2.00 g, 7.70 mmol). The reaction mixture was stirred at 0 °C for 20 minutes, then 3-phenylprop-2-ynyl methanesulfonate (1.62 g, 7.70 mmol) added. The reaction mixture was allowed to warm to room temperature over 3 hours, then diluted with EtOAc and washed with saturated aqueous

NH_4Cl. The aqueous phases was re-extracted into EtOAc, and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude product was purified by column chromatography (15% EtOAc in petrol) to give the product as a pale yellow oil (2.32 g, 81%). ν_{max} (film)/cm^{-1} 2936, 2836, 1349, 1163; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.78 (d, J = 8.5 Hz, 2H, ArH), 7.29-7.16 (m, 5H, ArH), 7.08-7.00 (m, 2H, ArH), 4.61 (t, J = 5.5 Hz, 1H, TsN-CH_2-C<u>H</u>-$C(OMe)_2$), 4.47 (s, 2H, TsN-C<u>H</u>$_2$-C≡C-Ph), 3.44 (s, 6H, TsN-CH_2-CH-C(OC<u>H</u>$_3$)$_2$), 3.33 (d, J = 5.5 Hz, 2H, TsN-C<u>H</u>$_2$-CH-$C(OMe)_2$), 2.33 (s, 3H, ArCH3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.6, 136.0, 131.5, 129.6, 128.4, 128.1, 127.8, 104.4, 85.5, 82.3, 54.7, 47.7, 39.1, 21.4; *m/z* (ESI) 396 (100%, $[M+Na]^+$). Data in accordance with the literature.[67]

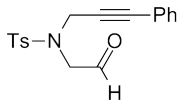
N-(but-2-ynyl)-N-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide



A suspension of NaH (60% w/w in mineral oil, 0.36 g, 9.24 mmol) in anhydrous DMF (40 mL) was cooled to 0 °C, followed by the dropwise addition of N-(2,2-dimethoxyethyl)-4-methyl-benzenesulfonamide (2.00 g, 7.70 mmol). The reaction mixture was stirred at 0 °C for 20 minutes, then 1-methanesulfonyloxy-2-butyne (1.06 g, 7.70 mmol) was added. The reaction mixture was allowed to warm to room temperature over 3 hours then diluted with EtOAc and washed with saturated aqueous NH_4Cl. The aqueous phase was re-extracted into EtOAc, and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude product was purified by column chromatography (15-30% EtOAc in petrol) to give the product as a colourless solid (1.71 g, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (d, J = 8.3 Hz, 2H, ArH), 7.27 (d, J = 8.3 Hz, 2H, ArH), 4.45 (t, J

= 5.5 Hz, -CH_2-C<u>H</u>-), 4.18 (q, J = 2.3 Hz, 2H, -NTs-C<u>H_2</u>-C≡C-CH_3), 3.41 (s, 6H, -NTs-CH_2-CH(OC<u>H_3</u>)$_2$), 3.24 (d, J = 5.5 Hz, 2H, -NTs-C<u>H_2</u>-CH(OCH_3)$_2$), 2.42 (s, 3H, ArC<u>H_3</u>), 1.52 (t, J = 2.3 Hz, 3H, -NTs-CH_2-C≡C-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.3, 136.1, 129.8, 127.9, 104.2, 81.5, 72.1, 54.7, 47.5, 38.7, 21.5, 3.3; *m/z* (ESI) 258 (100%, $[M-H]^-$). Data in accordance with the literature.[258]

4-methyl-N-(2-oxoethyl)-N-(3-phenylprop-2-ynyl)benzenesulfonamide



Procedure A

A solution of pyridine.SO_3 complex (159 mg, 1.00 mmol) in DMSO (5 mL) was added to a solution of N-(2-hydroxyethyl)-4-methyl-N-(3-phenylprop-2-ynyl)benzenesulfonamide (100 mg, 0.32 mmol) and triethylamine (225 mg, 2.22 mmol) in DMSO (5 mL), and the reaction mixture stirred at room temperature for 1 hour, after which the solution had changed from colourless to dark orange. The solution was acidified to pH 4 using 1N HCl, and extracted into EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to a brown oil. The product was purified by column chromatography (25% EtOAc in petroleum ether) to afford the pure product as a yellow oil (83 mg, 80%).

Procedure B

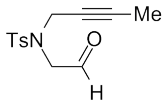
A solution of N-(2-hydroxyethyl)-4-methyl-N-(3-phenylprop-2-ynyl)benzenesulfonamide (0.57 g, 1.70 mmol) in DCM (15 mL) was added to a suspension of Dess-Martin periodinane (1.12 g, 3.06 mmol) in DCM (15 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 30 minutes, then quenched with saturated aqueous $NaHCO_3$ followed by a 10% aqueous solution of NaS_2O_3. The aqueous phase was extracted into Et_2O and the combined organic extracts dried over

$MgSO_4$ and concentrated in vacuo to a colourless oil. The product was purified by column chromatography (25% EtOAc in petroleum ether) to afford the pure product as a colourless oil (0.33 g, 60%).

Procedure C

A solution of N-allyl-4-methyl-N-(3-phenyl-prop-2-ynyl)-benzenesulfonamide (1.37 g, 4.21 mmol) in DCM (30 mL) was cooled to -78 °C, then purged with O_3 for 10 minutes until a blue colour appeared. The reaction mixture was purged with O_2 then N_2, followed by the addition of triphenylphosphine (1.10 g, 4.21 mmol), and was allowed to warm to room temperature overnight. The reaction mixture was concentrated *in vacuo*, and the residue purified by column chromatography (25% EtOAc in petrol) to give the pure product as a pale yellow solid (1.21 g, 88%). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 9.66 (s, 1H, C<u>H</u>O), 7.70 (d, J = 8.2 Hz, 2H, ArH), 7.28-6.96 (m, 7H, ArH), 4.34 (s, 2H, TsN-C<u>H</u>$_2$-CHO), 3.95 (s, 2H, TsN-C<u>H</u>$_2$-C≡C-Ph), 2.32 (s, 3H, Ar-C<u>H</u>$_3$); *m/z* (ESI) 316 (100%, $[M-H]^-$). Data in accordance with the literature.[258]

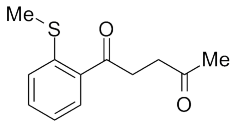
N-(but-2-ynyl)-4-methyl-N-(2-oxoethyl)benzenesulfonamide



N-(but-2-ynyl)-N-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (5.54 g, 14.8 mmol) was dissolved in THF (40 mL), and 3N HCl (30 mL) added. The reaction mixture was heated at reflux for 3.5 hours, then cooled to room temperature and extracted into EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The product was purified by column chromatography (25% EtOAc in petrol) to afford the pure product as a yellow oil (3.80 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.65 (t, J = 1.5 Hz, 1H, C<u>H</u>O), 7.68 (d, J = 8.5 Hz, 2H, ArH), 7.32 (d, J = 8.5 Hz, 2H, ArH), 4.07 (q, J = 2.4 Hz, 2H,

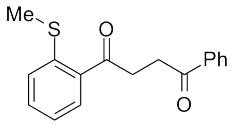
TsN-C$\underline{H}_2$-C≡C-C$\underline{H}_3$), 3.88 (d, J = 1.5 Hz, 2H, TsN-C$\underline{H}_2$-CHO), 2.43 (s, 3H, ArC$\underline{H}_3$), 1.61 (t, J = 2.4 Hz, 3H, -C≡C-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 198.0, 144.2, 134.8, 129.7, 127.7, 83.1, 71.3, 56.0, 39.4, 21.5, 3.3; *m/z* (ESI) 264 (100%, $[M-H]^-$). Data in accordance with the literature.[258]

General Procedure D, as exemplified by the preparation of 1-(2-(methylthio)-phenyl)pentane-1,4-dione, 49



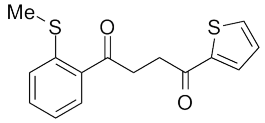
$[Rh(nbd)_2]BF_4$ (14 mg, 0.0375 mmol) and DPEphos (20 mg, 0.0375 mmol) were dissolved in DCE (5 mL) and stirred at room temperature, followed by the addition of 2-(methylthio)benzaldehyde (96 μL, 0.75 mmol) then 1-phenyl-2-propyn-1-ol (101 μL, 0.83 mmol). The reaction mixture was heated at 70 °C for 16 h, then allowed to cool to room temperature before being diluted with Et_2O and filtered through a short silica plug. The filtrate was concentrated *in vacuo* then purified by column chromatography (30% Et_2O/petrol). The product was recrystallised from DCM/petrol to afford the pure product as a white crystalline solid (140 mg, 84%). m.p. 60-63 °C (recrystallised from DCM/petrol); ν_{max} (film)/cm^{-1} 2952, 2917, 1709, 1670; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93 (dd, J = 7.8, 1.4 Hz, 1H, ArH), 7.45 (dd, J = 6.8, 1.4 Hz, 1H, ArH), 7.32 (d, J = 8.3 Hz, 1H, ArH), 7.20 (d, J = 7.8, 1.8 Hz, 1H, ArH), 3.26 (t, J = 6.3 Hz, 2H, -C(O)-C$\underline{H}_2$-CH$_2$-), 2.89 (t, J = 6.3 Hz, 2H, -C(O)-CH$_2$-C$\underline{H}_2$-), 2.43 (s, 3H, -S-C$\underline{H}_3$), 2.26 (s, 3H, -C(O)-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 207.3, 199.3, 142.4, 133.9, 132.3, 130.4, 125.0, 123.5, 37.2, 33.7, 30.1, 15.9; LRMS *m/z* (ESI) 245 (100%, $[M+Na]^+$); HRMS (ESI) found 245.0608 $[M+Na]^+$, $C_{12}H_{14}NaO_2S$ requires 245.0607.

1-(2-(methylthio)phenyl)-4-phenylbutane-1,4-dione, 50



Prepared according to general procedure D to furnish the pure product as a white solid (185 mg, 87%). m.p. 128-130 °C (recrystallised from DCM/petrol); ν_{max} (film)/cm^{-1} 2916, 1679, 1667, 1177; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.04-8.01 (m, 3H, ArH), 7.57 (t, J = 7.4 Hz, 1H, ArH), 7.48 (q, J = 7.4 Hz, 1H, ArH), 7.33 (d, J = 8.1 Hz, 1H, ArH), 7.23 (d, J = 7.5 Hz, 1H, ArH), 3.50-3.42 (m, 4H, -C(O)-C$\underline{H}_2$-C$\underline{H}_2$-), 2.43 (s, 3H, -S-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 199.5, 198.6, 142.5, 136.7, 134.1, 133.1, 132.3, 130.4, 128.6, 128.1, 125.0, 123.5, 33.8, 32.7, 15.9; LRMS (ESI) *m/z* 591 ([2M+Na]$^+$, 100%), 307 ([M+Na]$^+$, 50%), 285 ([M+H]$^+$, 10%); HRMS (ESI) found *m/z* 307.0757 [M+Na]$^+$, $C_{17}H_{16}NaO_2S$ requires 307.0763.

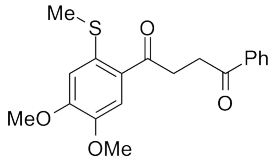
1-(2-(methylthio)phenyl)-4-(thiophen-2-yl)butane-1,4-dione, 51



Prepared according to general procedure D to furnish the product as a tan solid (144 mg, 66%). m.p. 122-124 °C (recrystallised from DCM/petrol); ν_{max} (film)/cm^{-1} 3094, 2915, 1656, 1226; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.97 (dd, J = 7.8, 1.1 Hz, 1H, ArH), 7.80 (dd, J = 3.8, 0.9 Hz, 1H, ArH), 7.62 (dd, J = 5.0, 0.9 Hz, 1H, ArH), 7.47 (t, J = 8.3 Hz, 1H, ArH), 7.32 (d, J = 8.0 Hz, 1H, ArH), 7.21 (t, J = 7.5 Hz, 1H, ArH), 7.13 (t, J = 4.4 Hz, 1H, ArH), 3.44-3.38 (m, 4H, -C(O)-C$\underline{H}_2$-C$\underline{H}_2$-C(O)-), 2.41 (s, 3H, -S-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 199.3, 191.2, 143.9, 142.5, 133.9, 133.5, 132.3, 132.1, 130.4, 128.1, 125.0, 123.5, 33.8, 33.3, 15.9; LRMS (ESI) *m/z* 603 (100%, [2M+Na]$^+$), 313 (50%, [M+Na]$^+$); HRMS (ESI) found *m/z* 313.0316

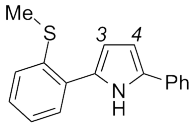
$[M+Na]^+$, $C_{15}H_{14}NaO_2S_2$ requires 313.0327.

1-(4,5-dimethoxy-2-(methylthio)phenyl)-4-phenylbutane-1,4-dione, 53



Prepared according to general procedure D to furnish the product as a white solid (145 mg, 56%). m.p. 110-114 °C (recrystallised from DM/petrol); ν_{max} (film)/cm^{-1} 3061, 2977, 2915, 2843, 1683, 1662, 1598, 1554, 1503, 1268, 1167; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44 (d, J = 7.4 Hz, 2H, ArH), 7.56 (d, J = 7.2 Hz, 1H, ArH), 7.49-7.45 (m, 3H, ArH), 6.80 (s, 1H, ArH), 3.96 (s, 3H, -O-C$\underline{H}_3$), 3.94 (s, 3H, -O-C$\underline{H}_3$), 3.49-3.39 (m, 4H, -C(O)-C$\underline{H}_2$-C$\underline{H}_2$-), 2.43 (s, 3H, -S-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 198.9, 197.8, 152.5, 145.5, 136.8, 136.2, 133.1, 128.6, 128.1, 127.0, 113.4, 108.3, 56.3, 56.0, 33.7, 32.9, 16.5; LRMS (ESI) *m/z* 711 (100%, $[2M+Na]^+$), 367 (35%, $[M+Na]^+$), 345 (15%, $[M+H]^+$); HRMS (ESI) found *m/z* 367.0964, $C_{19}H_{20}NaO_4S$ requires 367.0975.

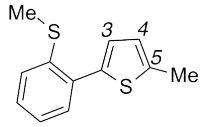
2-(2-(methylthio)phenyl)-5-phenyl-1H-pyrrole, 54



Based on a procedure by Ley.[181] 1-(2-(methylthio)phenyl)-4-phenylbutane-1,4-dione (57 mg, 0.20 mmol) dissolved in methanol (3 mL), then cooled to 0 °C prior to the addition of magnesium nitride (51 mg, 0.50 mmol). The reaction vessel was sealed and allower to slowly warm to room temperature over 1 hour (**CAUTION**: removal of the reaction vessel from the ice/water bath may result in an explosion!). The reaction mixture was heated to 120 °C in a microwave reactor for 1 hour, then diluted with DCM.

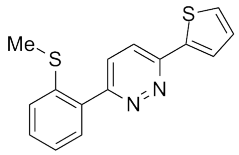
Water was added, the phases separated and the aqueous phase acidified to pH7 with saturated aqueous NH_4Cl, then extracted into DCM. The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude product was purified by column chromatography (10% EtOAc/petrol) to furnish the pure pyrrole as a yellow oil (52 mg, 99%). ν_{max} (film)/cm^{-1} 3353, 3055, 2920, 1604, 1513, 1284, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.10 (bs, 1H, -NH), 7.60-7.55 (m, 3H, ArH), 7.44-7.39 (m, 3H, ArH), 7.29-7.20 (m, 3H, ArH), 6.63-6.61 (m, 2H, H-*3*, H-*4*), 2.45 (s, 3H, -S-CH$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 133.4, 133.2, 133.0, 132.9, 132.0, 130.1, 129.4, 128.9, 127.3, 127.2, 126.7, 124.1, 111.1, 107.2, 18.0; LRMS (ESI) *m/z* 264 (100%, [M-H]$^-$); HRMS (ESI) found *m/z* 264.0850 [M-H]$^-$, $C_{17}H_{14}NS$ requires 264.0852.

2-methyl-5-(2-(methylthio)phenyl)thiophene, 55



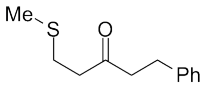
Prepared according to a method described by Handa.[260] 1-(2-(methylthio)phenyl)-pentane-1,4-dione (90 mg, 0.40 mmol) and Lawesson reagent (194 mg, 0.48 mmol) were dissolved in toluene (2 mL) and heated at 140 °C for 5 h. The reaction mixture was allowed to cool to room temperature then loaded directly onto a silica column. Purified by column chromatography (10% Et_2O/petrol) to furnish the pure thiophene as a pale yellow oil (63 mg, 72%). ν_{max} (film)/cm^{-1} 2917, 1584, 1433; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 (dd, J = 7.4, 1.0 Hz, 1H, ArH), 7.35-7.27 (m, 2H, ArH), 7.21-7.17 (m, 1H, ArH), 7.09 (d, J = 3.5 Hz, 1H, H-*3*), 6.80 (dd, J = 3.5 Hz, 1.0 Hz, 1H, H-*4*), 2.57 (d, J = 1.0 Hz, 3H, C*5*-CH$_3$), 2.46 (s, 3H, -S-CH$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 140.5, 138.9, 137.8, 133.6, 130.7, 128.1, 127.5, 125.7, 125.3, 124.7, 16.2, 15.3; HRMS (FI) found *m/z* 220.0379 [M]$^+$, $C_{12}H_{12}S_2$ requires 220.0380.

3-(2-(methylthio)phenyl)-6-(thiophen-2-yl)pyridazine, 56



1-(2-(methylthio)phenyl)-4-(thiophen-2-yl)butane-1,4-dione (30 mg, 0.10 mmol) was dissolved in EtOH (2 mL), and hydrazine hydrate (10 μL, excess, approx. 0.21 mmol) added. The reaction mixture was heated at reflux for 2 h, quenched with water and extracted into EtOAc. The combined organic extracts were washed with water then brine, then concentrated *in vacuo* to a yellow oil. The crude oil was redissolved in $CHCl_3$ (5 mL), and stirred at room temperature open to the atmosphere overnight before being concentrated *in vacuo* to a yellow oil. Purified by column chromatography (40% Et_2O/petrol) to furnish the pure product as a yellow oil (19 mg, 67%). ν_{max} (film)/cm^{-1} 3065, 2920, 1579, 1543, 1434, 1407; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.82 (s, 2H, ArH), 7.73 (dd, J = 3.7, 1.0 Hz, 1H, ArH), 7.61 (d, J = 7.7 Hz, 1H, ArH), 7.51 (dd, J = 5.0, 1.0 Hz, 1H, ArH), 7.45-7.43 (m, 2H, ArH), 7.35-7.29 (m, 1H, ArH), 7.18 (dd, J = 5.0, 3.7 Hz, 1H, ArH), 2.41 (s, 3H, -S-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.8, 153.4, 140.7, 137.5, 136.8, 130.4, 129.8, 129.3, 128.1, 128.0, 127.4, 126.3, 125.6, 121.5, 17.0; LRMS (ESI) *m/z* 591 ([2M+Na]$^+$, 100%), 307 ([M+Na]$^+$, 10%); HRMS (ESI) found *m/z* 285.0514 [M+H]$^+$, $C_{15}H_{13}N_2S_2$ requires 285.0515.

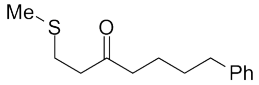
General procedure E, as exemplified by the preparation of 1-(methylthio)-5-phenylpentan-3-one



$[Rh(nbd)_2]BF_4$ (14 mg, 0.0375 mmol) and dppe (15 mg, 0.0375 mmol) were dissolved in DCE (10 mL) and stirred at room temperature for 10 minutes, before the

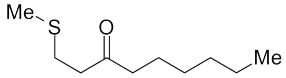
addition of 3-(methylthio)propionaldehyde (75 μL, 0.75 mmol) then phenylacetylene (90 μL, 0.83 mmol). The reaction mixture was heated at 70 °C for 1 hour, followed by the addition of $(EtO)_3SiH$ (0.32 mL, 1.73 mmol). The reaction was geated at 70 °C for 5 hours, then TBAF (2.0 mL of a 1M solution in THF) added, followed by water (5.0 mL). The resulting suspension was vigorously stirred for 1 hour, the phases separated, and the aqueous phase extracted into EtOAc. The combined organic extracts were washed with water then brine, drived over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The product was purified by column chromatography (20% EtOAc/petrol to furnish the product as a yellow oil (151 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31-7.27 (m, 2H, ArH), 7.22-7.18 (m, 3H, ArH), 2.92 (t, J = 7.6 Hz, 2H, -C(O)-C$\underline{H}_2$-CH_2-Ph), 2.79-2.69 (m, 6H, MeS-C$\underline{H}_2$-C$\underline{H}_2$-, -C(O)-CH_2-C$\underline{H}_2$-Ph), 2.10 (s, 3H, -S-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 208.2, 140.9, 128.6, 128.3, 126.2, 44.6, 42.6, 29.7, 27.9 and 15.8; *m/z* (ESI) 231 (100%, $[M+Na]^+$). Data in accordance with the literature.[73]

1-(methylthio)-7-phenylheptan-3-one



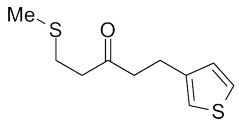
Prepared according to general procedure E to furnish the product ketone as a colourless oil (109 mg, 77%). ν_{max} (film)/cm^{-1} 2917, 2855, 1715, 1600, 1494; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30-7.26 (m, 2H, ArH), 7.20-7.17 (m, 3H, ArH), 2.75-2.66 (m, 4H, MeS-C$\underline{H}_2$-C$\underline{H}_2$-), 2.65-2.61 (m, 2H, -C(O)-C$\underline{H}_2$-CH_2-CH_2-), 2.47-2.43 (m, 2H, Ph-C$\underline{H}_2$), 2.11 (s, 3H, -S-C$\underline{H}_3$), 1.66-1.62 (m, 4H, Ph-CH_2-C$\underline{H}_2$-C$\underline{H}_2$-); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 209.0, 142.1, 128.4, 128.3, 125.8, 42.9, 42.3, 35.7, 30.9, 28.0, 23.3, 15.8; HRMS (FI) found *m/z* 236.1234 $[M]^+$, $C_{14}H_{20}OS$ requires 236.1235.

1-(methylthio)nonan-3-one



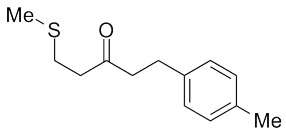
Prepared according to general procedure E to furnish the product ketone as a pale yellow oil (125 mg, 88%). ν_{max} (film)/cm^{-1} 2956, 2926, 2858, 1712, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.70-2.67 (m, 4H, -C(O)-C<u>H</u>$_2$-C<u>H</u>$_2$-S-CH$_3$), 2.39 (t, J = 7.4 Hz, 2H, -C(O)-C<u>H</u>$_2$-C$_5$H$_9$), 2.07 (s, 3H, -S-C<u>H</u>$_3$), 1.56-1.50 (m, 2H), 1.26-1.23 (m, 6H), 0.86-0.82 (m, 3H, -CH$_2$-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 209.3, 43.0, 42.3, 31.5, 28.8, 27.9, 23.6, 22.4, 15.7, 14.0; HRMS (FI) found *m/z* 188.1239 [M]$^+$, $C_{10}H_{20}OS$ requires 188.1235.

1-(methylthio)-5-(thiophen-3-yl)pentan-3-one



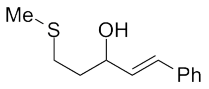
Prepared according to general procedure E to furnish the product ketone as a pale yellow oil (97 mg, 60%). ν_{max} (film)/cm^{-1} 2916, 1710, 1409, 1363, 1087, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.24-7.22 (m, 1H, C1), 6.95-6.92 (m, 2H, C3, C4), 2.93 (t, J = 7.4 Hz, 2H, -C(O)-C<u>H</u>$_2$-CH$_2$-S-CH$_3$), 2.75 (t, J = 7.4 Hz, 2H, -C(O)-CH$_2$-C<u>H</u>$_2$-S-CH$_3$), 2.71-2.68 (m, 4H, -C(O)-C<u>H</u>$_2$-C<u>H</u>$_2$-heteroaryl), 2.08 (s, 3H, -S-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 208.1, 141.1, 128.0, 125.6, 120.5, 43.7, 42.6, 27.9, 24.1, 15.8; HRMS (FI) found *m/z* 214.0486 [M]$^+$, $C_{10}H_{14}OS_2$ requires 214.0486.

1-(methylthio)-5-*p*-tolylpentan-3-one



Prepared according to general procedure E to furnish the product as a pale yellow oil (55 mg, 82%). ν_{max} (film)/cm^{-1} 2919, 1712, 1515, 1087, 910, 807, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.09 (dd, J = 8.6, 2.3 Hz, 4H, ArH), 2.88 (t, J = 7.3 Hz, 2H, -C(O)-C$\underline{H}_2$-), 2.75-2.69 (m, 6H, -CH_2-), 2.32 (s, 3H, Ar-C$\underline{H}_3$), 2.10 (s, 3H, -S-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 208.3, 137.8, 135.7, 129.2, 128.2, 44.7, 42.6, 29.3, 27.9, 21.0, 15.8; HRMS (FI) found 222.1071 $[M]^+$, $C_{13}H_{18}OS$ requires 222.1078.

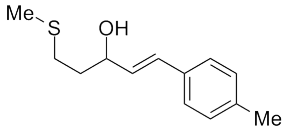
(E)-5-(methylthio)-1-phenylpent-1-en-3-ol, 62



$[Rh(nbd)_2]BF_4$ (28 mg, 0.075 mmol) and dppe (30 mg, 0.075 mmol) were dissolved in DCE (7.5 mL) and stirred at room temperature for 10 minutes, before the addition of 3-(methylthio)propionaldehyde (0.15 mL, 1.5 mmol) then phenylacetylene (0.18 mL, 1.65 mmol). The reaction mixture was heated at 70 °C for 1 hour, then allowed to cool to room temperature before the slow addition of Ph_2SiH_2 (0.42 mL, 2.25 mmol). The reaction was stirred at room temperature for 16 hours, then TBAF (2.5 mL of a 1M solution in THF) added, followed by water (5 mL). The resulting suspension was vigorously stirred for 1 hour, the phases separated, and the aqueous phase extracted into Et_2O. The combined organic extracts were washed with water then brine, drived over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The product was purified by column chromatography (40% EtOAc/petrol) to furnish a pale yellow oil (290 mg, 93%). ν_{max} (film)/cm^{-1} 3379, 2917, 1429, 1126, 908, 729, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 (d, J = 7.2 Hz, 1H, ArH), 7.33 (t, J = 7.3 Hz, 2H,

ArH), 7.26-7.20 (m, 1H, ArH), 6.62 (d, J = 15.9 Hz, 1H, -CH=C<u>H</u>-Ar), 6.24 (dd, J = 15.9, 6.6 Hz, 1H, -C<u>H</u>=CH-Ar), 4.50-4.44 (m, 1H, -C<u>H</u>(OH)-), 2.68-2.64 (m, 2H, -CH_2-C<u>H_2</u>-S-CH_3), 2.14 (s, 3H, -S-C<u>H_3</u>), 2.04 (d, J = 3.8 Hz, -O<u>H</u>), 1.97-1.90 (m, 2H, -C<u>H_2</u>-CH_2-S-CH_3); 136.5, 131.7, 130.6, 128.6, 127.8, 126.5, 72.0, 36.0, 30.4, 15.5; HRMS (FI) found *m/z* 208.0918 $[M]^+$, $C_{12}H_{16}OS$ requires 208.0922.

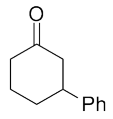
(E)-5-(methylthio)-1-*p*-tolylpent-1-en-3-ol



$[Rh(nbd)_2]BF_4$ (14 mg, 0.0375 mmol) and dppe (15 mg, 0.0375 mmol) were dissolved in DCE (3.75 mL) and stirred at room temperature for 10 minutes, before the addition of 3-(methylthio)propionaldehyde (75 μL, 0.75 mmol) then *p*-tolylacetylene (105 μL, 0.83 mmol). The reaction mixture was heated at 70 °C for 1 hour, then allowed to cool to room temperature before the slow addition of Ph_2SiH_2 (0.21 mL, 1.13 mmol). The reaction was stirred at room temperature for 16 hours, then TBAF (1.25 mL of a 1M solution in THF) added, followed by water (2.5 mL). The resulting suspension was vigorously stirred for 1 hour, the phases separated, and the aqueous phase extracted into Et_2O. The combined organic extracts were washed with water then brine, drived over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The product was purified by column chromatography (40% EtOAc/petrol) to furnish a pale yellow oil (98 mg, 59%). ν_{max} (film)/cm^{-1} 3383, 2918, 2859, 1514, 1428, 968, 908, 855, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.29 (d, J = 7.8 Hz, 2H, ArH), 7.14 (d, J = 8.0 Hz, 2H, ArH), 6.58 (d, J = 15.9 Hz, 1H, -CH=C<u>H</u>-Ar), 6.17 (dd, J = 15.9, 6.8 Hz, 1H, -C<u>H</u>=CH-Ar), 4.43 (q, J = 6.6 Hz, 1H, -C<u>H</u>(OH)-), 2.61 (t, J = 7.1 Hz, 2H, -CH_2-C<u>H_2</u>-S-CH_3), 2.35 (s, 3H, Ar-C<u>H_3</u>), 2.13 (s, 3H, -S-C<u>H_3</u>), 1.97-1.87 (m, 2H, -C<u>H_2</u>-CH_2-S-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 137.6, 130.7, 130.6, 129.3, 128.3, 126.4, 72.0, 36.2, 30.4,

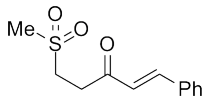
21.3 and 15.5; HRMS (FI) found *m/z* 222.1081 $[M]^+$, $C_{13}H_{18}OS$ requires 222.1078.

3-phenylcyclohexanone, 66



[Rh(dppe)(nbd)]ClO_4 was suspended in a 1:1 DME/H_2O mixture (3 mL), followed by the addition of 2-cyclohexen-1-one (48 μL, 0.5 mmol) then phenylboronic acid (122 mg, 1.0 mmol). The suspension was heated to 80 °C for 16 hours, after which the reaction was cooled to room temperature, diluted with Et_2O, and filtered through silica. The filtrate was concentrated *in vacuo* to an orange-brown oil. Crude ^{1}H NMR spectroscopy identified the substance as the conjugate addition product, with Data in accordance with the literature.[261] ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 7.45-7.14 (m, 5H, ArH), 3.14-2.88 (m, 1H, Ph-C<u>H</u>-), 2.74-2.24 (m, 4H -CH_2-), 2.23-1.64 (m, 4H, -CH_2-).

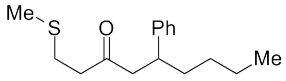
(E)-5-(methysulfonyl)-1-phenylpent-1-en-3-one, 68



(E)-5-(methylthio)-1-phenylpent-1-en-3-one (100 mg, 0.49 mmol) was dissolved in dry DCM (5 mL) and cooled to 0 °C. mCPBA (176 mg, 1.02 mmol) was added in one portion, and the reaction mixture allowed to warm to room temperature over 2 hours. The reaction mixture was diluted with DCM then washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvent removed *in vacuo* to give the crude product as an off-white solid. The product was recrystallised from DCM/petroleum ether to afford the pure product as a white solid (83 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (d, J = 16.3 Hz, 1H, -C(O)C<u>H</u>=CH), 7.60-7.53 (m, 2H, ArH) 7.50-7.35

(m, 3H, ArH), 6.78 (d, J = 16.3 Hz, 1H, -C(O)CH=C<u>H</u>-), 3.56-3.38 (m, 2H, -CH_2-C<u>H_2</u>-C(O)-), 3.38-3.24 (m, 2H, -C<u>H_2</u>-CH_2-C(O)-), 3.00 (s, 3H, -SO_2-C<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 195.4, 144.5, 133.9, 131.1, 129.1, 128.5, 125.0, 49.2, 41.7, 32.8; LRMS *m/z* (ESI) 239 (100%, $[M+H]^+$). Data in accordance with the literature.[262]

1-(methylthio)-5-phenylnonan-3-one, 69



Procedure A

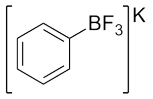
Bromobenzene (74 μL, 0.70 mmol) added dropwise to a pre-stirred solution of magnesium turnings (19 mg, 0.81 mmol) in THF (3 mL). An iodine crystal was added, and the magnesium spot-heated until the reaction mixture reached reflux. The rate of addition of bromobenzene was controlled to maintain reflux. The phenylmagnesium bromide solution thus obtained was slowly added by cannula to a solution of (E)-1-(methylthio)non-4-en-3-one (100 mg, 0.54 mmol) and Cu(I)Cl (69 mg, 0.70 mmol) in THF (3 mL) at 0 °C. After 1 hour, saturated aqueous NH_4Cl (15 mL) was added, and the reaction mixture stirred vigorously until a deep blue colour appeared. The reaction mixture was extracted into Et_2O, and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to a dark yellow oil. Purified by column chromatoraphy (25% Et_2O in petroleum ether) to give the product as light yellow oil (130 mg, 91%).

Procedure B

Based on a procedure by Hayashi *et al.*[221] $[Rh(cod)Cl]_2$ (12.9 mg, 0.027 mmol) was dissolved in THF (0.5 mL), followed by the addition of BINAP (33.6 mg, 0.054 mmol), and the solution stirred at room temperature for 30 min before (E)-1-(methylthio)non-4-en-3-one (100 mg, 0.54 mmol) was added to the catalyst solution. PhZnBr (1.62 mL

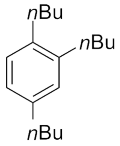
of a 0.5 M solution in THF, 0.81 mmol) and freshly distilled TMSCl (89 μl, 0.70 mmol) were added simultaneously. The reaction mixture was stirred at room temperature for 16 hours, then quenched with water (0.2 mL) and stirred at room temperature for 1 hour. The biphasic mixture was loaded onto a silica plug and eluted with Et_2O, and the filtrate concentrated *in vacuo* to a yellow oil. The crude product was purified by column chromatography (10% Et_2Oin petroleum ether) to give the product (contaminated with unidentified impurities) as a light yellow oil (115 mg, 65%). ν_{max} (film)/cm^{-1} 3028, 2956, 1714; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 7.37-7.11 (m, 5H, ArH), 3.13 (quin., J = 7.2 Hz, 1H, Ph-C<u>H</u>-), 2.79-2.41 (m, 6H, -CH_2-), 2.02 (s, 3H, -S-C<u>H</u>$_3$), 1.71-1.48 (m, 2H, -CH_2-) 1.39-1.01 (m, 4H, -CH_2-), 0.81 (t, J = 7.3 Hz, 3H, -CH_2-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 208.2, 144.5, 128.5, 127.5, 126.4, 50.3, 43.3, 41.3, 36.1, 29.6, 27.7, 22.6, 15.7 and 14.0; *m/z* (ESI) 265 (100%, [M+H]$^+$); HRMS (ESI) found *m/z* 287.1436 [M+Na]$^+$, $C_{16}H_{24}NaOS$ requires 287.1440.

Potassium phenyltrifluoroborate



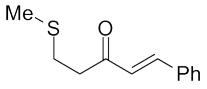
A saturated aqueous solution of KHF_2 (2.24 g in 6 mL water) was added to a stirring solution of phenylboronic acid (1.00 g, 8.20 mmol) in methanol (2.5 mL). The clear solution immediately became a white slurry, and the precipitate was isolated by by filtration and washed with cold methanol. The crude product was recrystallised from acetonitrile, to afford the final product as a white crystalline solid (1.30 g, 86%). m.p. 292-293 °C (recrystallised from acetonitrile); ^{1}H NMR (400 MHz,CD_3CN) δ_H 7.45 (d, J = 7.1 Hz, 2H, ArH), 7.18 (t, J = 7.8 Hz, 2H, ArH), 7.14-7.10 (m, 1H, ArH). Data in accordance with the literature.[263]

1,2,4-tributylbenzene, 71



$[Rh(cod)Cl]_2$ (6.5 mg, 0.0135 mmol) dissolved in acetone (1 mL), followed by the addition of $AgBF_4$ (5.3 mg, 0.027 mmol). The suspension was stirred for 10 min, followed by the addition of BINAP (16.8 mg, 0.027 mmol). The catalyst solution was stirred at room temperature for 30 min, then 1-hexyne (0.13 mL, 1.08 mmol) added and the reaction heated to 55 °C for 2 hours. The reaction mixture was loaded onto a silica plug and eluted with Et_2O, then concentrated *in vacuo* to a yellow oil (82 mg, 92%). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 7.13-6.80 (m, 3H, ArH), 2.76-2.42 (m, 6H, Ph-C$\underline{H}_2$-), 1.77-1.17 (m, 12H, -CH_2-), 1.08-0.86 (m, 9H, -CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 142.7, 140.3, 140.1, 137.7, 129.2, 125.8, 35.7, 35.3, 33.8, 33.6, 32.5, 32.0, 22.94, 22.91, 22.6, 22.5, 14.1, 14.0; *m/z* (ESI) 265 (100%, $[M+Na]^-$). Data in accordance with the literature.[223]

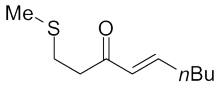
General procedure F, as exemplified by the preparation of (E)-5-(methylthio)-1-phenylpent-1-en-3-one, 63



$[Rh(nbd)_2]BF_4$ (14 mg, 0.0375 mmol) and dppe (15 mg, 0.0375 mmol) were dissolved in propylene carbonate (2.5 mL) and stirred at room temperature for 10 minutes. 3-(methylthio)propionaldehyde (75 μL, 0.75 mmol) then phenylacetylene (90 μL, 0.83 mmol) were added and the reaction heated at 70 °C for 1 hour. The reaction mixture was loaded directly onto silica and eluted with 30% Et_2O/petrol to furnish the pure product as a yellow oil (139 mg, 90%). ν_{max} (film)/cm^{-1} 2917, 1688, 1661, 1612; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69-7.49 (m, 3H [including d, J =

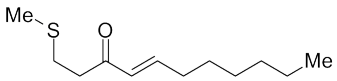
16.3 Hz, 1H, -C(O)C<u>H</u>=CH-], ArH), 7.47-7.35 (m, 3H, ArH) 6.75 (d, J = 16.3 Hz, 1H, -C(O)CH=C<u>H</u>-), 3.05-2.92 (m, 2H, -C(O)-C<u>H</u>$_2$-CH$_2$-S-CH$_3$), 2.91-2.77 (m, 2H, -C(O)-CH$_2$-C<u>H</u>$_2$-S-CH$_3$), 2.15 (s, 3H, -S-C<u>H</u>$_3$);^{13}C NMR (101 MHz, CDCl$_3$) δ_C 198.4, 143.1, 134.3, 130.7, 129.0, 128.4, 125.9, 40.6, 28.4 and 15.9; HRMS (ESI) found *m/z* 229.0658 [M+Na]$^+$, $C_{12}H_{14}NaOS$ requires 229.0660.

(E)-1-(methylthio)non-4-en-3-one, 37



Prepared according to general procedure F to furnish the product as a yellow oil (127 mg, 91%). ^{1}H NMR (200 MHz, CDCl$_3$) δ_H 6.85 (dt, J = 15.9, 6.9 Hz, 1H, -C(O)CH=C<u>H</u>-), 6.08 (dt, J = 15.9, 1.5 Hz, 1H, -C(O)C<u>H</u>=CH-), 2.92-2.66 (m, 4H, -C(O)-C<u>H</u>$_2$-C<u>H</u>$_2$-S-CH$_3$), 2.29-2.13 (m, 2H, -CH=CH-C<u>H</u>$_2$-CH$_2$-CH$_2$-CH$_3$), 2.10 (s, 3H, -S-C<u>H</u>$_3$), 1.56-1.19 (m, 4H, -CH=CH-CH$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-CH$_3$), 0.91 (t, J = 6.9 Hz, 3H, -CH=CH-CH$_2$-CH$_2$-CH$_2$-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ_C 198.6, 148.2, 130.1, 39.7, 32.2, 30.1, 28.3, 22.2, 15.8, 13.8; *m/z* (ESI) 187 (100%, [M+H]$^+$). Data in accordance with the literature.[75]

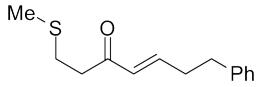
(E)-1-(methylthio)undec-4-en-3-one, 74



Prepared according to general procedure F to furnish the product as a yellow oil (146 mg, 91%) as a mixture of linear and branched isomers (84:16 l:b). ν_{max} (film)/cm^{-1} 2956, 2927, 2857, 1696, 1673, 1629; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 6.81 (dt, J = 15.9, 6.9 Hz, 1H, -C(O)CH=C<u>H</u>-), 6.05 (d, J = 15.9 Hz, 1H, -C(O)C<u>H</u>=CH-), 2.82-2.78 (m, 2H, -C(O)-C<u>H</u>$_2$-CH$_2$-S-CH$_3$), 2.73-2.69 (m, 2H, -C(O)-CH$_2$-C<u>H</u>$_2$-S-CH$_3$), 2.21-2.14 (m, 2H, -CH=CH-C<u>H</u>$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 2.07 (s, 3H, -

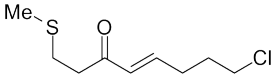
S-C$\underline{H}_3$), 1.45-1.38 (m, 2H, -CH=CH-CH$_2$-C$\underline{H}_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 1.31-1.28 (m, 6H, -CH=CH-CH$_2$-CH$_2$-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH$_3$), 0.85-0.81 (m, 3H, -CH=CH-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 198.5, 148.2, 130.0, 124.0, 39.7, 32.5, 31.6, 28.3, 28.0, 22.5, 15.8, 14.0; HRMS (ESI) found *m/z* 237.1281 $[M+Na]^+$, $C_{12}H_{22}NaOS$ requires 237.1284.

(E)-1-(methylthio)-7-phenylhept-4-en-3-one, 75



Prepared according to general procedure F to furnish the product as a pale yellow oil (146 mg, 83%) as a mixture of linear and branched isomers (80:20 l:b). ν_{max} (film)/cm^{-1} 2917, 1671, 1628; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32-7.17 (m, 5H, ArH), 6.88 (dt, J = 15.9, 6.8 Hz, 1H, -C(O)CH=C$\underline{H}$-), 6.13 (d, J = 15.9 Hz, 1H, -C(O)C$\underline{H}$=CH-), 2.85-2.72 (m, 6H, -C(O)-C$\underline{H}_2$-C$\underline{H}_2$-S-CH$_3$ and -CH=CH-C$\underline{H}_2$-CH$_2$-Ph), 2.55 (q, J = 7.4 Hz, 2H, -CH=CH-CH$_2$-C$\underline{H}_2$-Ph), 2.11 (s, 3H, -S-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 198.4, 146.7, 140.6, 130.6, 128.6, 128.4, 126.3, 39.9, 34.4, 34.2, 28.3, 15.8; HRMS (ESI) found *m/z* 257.0972 $[M+Na]^+$, $C_{14}H_{18}NaOS$ requires 257.0971.

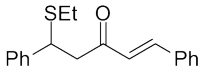
(E)-8-chloro-1-(methylthio)oct-4-en-3-one



Prepared according to general procedure F to furnish the product as a pale yellow oil (85 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.80 (dt, J = 15.8, 6.9 Hz, 1H, -C(O)CH=C$\underline{H}$-), 6.13 (d, J = 15.8 Hz, 1H, -C(O)C$\underline{H}$=CH-), 3.52 (t, J = 6.4 Hz, 2H, -CH=CH-CH$_2$-CH$_2$-C$\underline{H}_2$-Cl), 2.83-2.80 (m, 2H, -C(O)-C$\underline{H}_2$-CH$_2$-S-CH$_3$), 2.74-2.71 (m, 2H, -C(O)-CH$_2$-C$\underline{H}_2$-S-CH$_3$), 2.40-2.34 (m, 2H, -CH=CH-C$\underline{H}_2$-CH$_2$-CH$_2$-

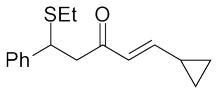
Cl), 2.08 (s, 3H, -S-C<u>H</u>$_3$) , 1.91 (quin, J = 7.1 Hz, 2H, -CH=CH-CH$_2$-C<u>H</u>$_2$-CH$_2$-Cl); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 198.2, 145.6, 130.8, 44.0, 40.0, 30.7, 29.5, 28.2 and 15.8; *m/z* (FI) 206 (100%, $[M]^+$). Data in accordance with the literature.[75]

(E)-5-(ethylthio)-1,5-diphenylpent-1-en-3-one, 76



Prepared according to general procedure F to furnish the product as a white solid (196 mg, 86%). m.p. 100-102 °C (recrystallised from IPA); ν_{max} (film)/cm^{-1} 2970, 1648, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.54-7.50 (m, 3H, ArH), 7.43-7.39 (m, 5H, ArH), 7.34-7.30 (m, 2H, ArH), 7.25-7.21 (m, 1H, -C(O)CH=C<u>H</u>-), 6.68 (d, J = 16.1 Hz, 1H, -C(O)C<u>H</u>=CH-), 4.50 (t, J = 7.2 Hz, 1H, Ph-C<u>H</u>-SEt), 3.23 (d, J = 7.2 Hz, 2H, Ph-CH-C<u>H</u>$_2$-C(O)-), 2.43-2.29 (m, 2H, -S-C<u>H</u>$_2$-CH$_3$), 1.18 (t, J = 7.6 Hz, 3H, -S-CH$_2$-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 196.9, 143.2, 142.1, 134.3, 130.6 (2CH), 128.9 (2CH), 128.5, 128.3 (2CH), 127.8 (2CH), 127.2, 126.1, 47.4, 44.2, 25.4 and 14.3. HRMS (FI) found *m/z* 296.1231 $[M]^+$, $C_{21}H_{25}O_2$ requires 296.1235. Data in accordance with the literature.[82]

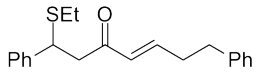
(E)-1-Cyclopropyl-5-(ethylthio)-5-phenylpent-1-en-3-one, 79



Prepared according to general procedure F to furnish the product as a colourless oil (174 mg, 90%). ν_{max} (film)/cm^{-1} 3027, 3006, 2926, 2870, 1949, 1876, 1805, 1713, 1667, 1616, 950, 937, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36-7.09 (m, 10H, ArH), 6.19 (dd, J = 15.6, 9.6 Hz, 1H, -C(O)CH=C<u>H</u>-), 6.08 (d, J = 15.6 Hz, 1H, -C(O)C<u>H</u>=CH-), 4.34 (t, J = 7.2 Hz, 1H, Ph-C<u>H</u>-SEt) , 2.96 (d, J = 7.2 Hz, 2H, Ph-CH-C<u>H</u>$_2$-C(O)-), 2.33-2.17 (m, 2H, -S-C<u>H</u>$_2$-CH$_3$), 1.51-1.39 (m, 1H, -C(O)-CH=CH-C<u>H</u>-

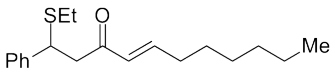
), 1.08 (t, J = 7.4 Hz, 3H, -S-CH_2-C$\underline{H}_3$), 0.95-0.84 (m, 2H, -C$\underline{H}_2$-CH_2-), 0.59-0.51 (m, 2H, -CH_2-C$\underline{H}_2$-); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 196.1, 153.5, 142.2, 128.4 (2CH2), 127.7 (2CH2), 127.2, 127.1, 46.8, 44.1, 25.4, 14.8, 14.3, 9.1 (2CH2). HRMS (FI) found *m/z* 260.1242 $[M]^+$, $C_{16}H_{20}OS$ requires 260.1235. Data in accordance with the literature.[82]

(E)-1-(Ethylthio)-1,7-diphenylhept-4-en-3-one, 78



Prepared according to general procedure F to furnish the product as a colourless oil (210 mg, 87%). ν_{max} (film)/cm^{-1} 3061, 3027, 2967, 2926, 2869, 1693, 1677, 1453, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37-6.96 (m, 10H, ArH), 6.74 (dt, J = 15.8, 6.8 Hz, 1H, -C(O)CH=C$\underline{H}$-), 5.98 (d, J = 15.8Hz, 1H, -C(O)C$\underline{H}$=CH-), 4.33 (t, J = 7.2, 1H, Ph-C$\underline{H}$-SEt), 2.99 (d, J = 7.2 Hz, 2H, Ph-CH-C$\underline{H}_2$-C(O)-), 2.67 (t, J = 7.7 Hz, 2H, -CH=CH-CH_2-C$\underline{H}_2$-Ph), 2.42 (q, J = 7.4 Hz, 2H, -S-C$\underline{H}_2$-CH_3), 2.30-2.18 (m, 2H, -CH=CH-C$\underline{H}_2$-CH_2-Ph), 1.08 (t, J = 7.4 Hz, 3H, -S-CH_2-C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 196.9, 146.89, 142.1, 140.6, 130.8, 128.5 (2CH), 128.4 (2CH), 128.3 (2CH), 127.7 (2CH), 127.1, 126.2, 46.6, 44.1, 34.3, 34.1, 25.4, 14.3; HRMS (ESI) found *m/z* 325.1621 $[M+H]^+$, $C_{21}H_{25}OS$ requires 325.1621. Data in accordance with the literature.[139]

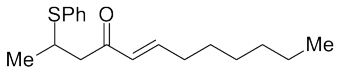
(E)-1-(ethylthio)-1-phenylundec-4-en-3-one



Prepared according to general procedure F to furnish the product as a colourless oil (207 mg, 95%). ν_{max} (film)/cm^{-1} 2928, 2870, 1674, 1627, 1409, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40-7.35 (m, 2H, ArH), 7.30 (t, J = 7.7, 2H, ArH), 7.25-7.19 (m,

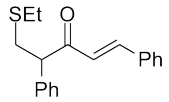
1H, ArH), 6.80 (dt, J = 15.8, 6.9 Hz, 1H, -C(O)CH=C<u>H</u>-), 6.04 (d, J = 15.8 Hz, 1H, -C(O)C<u>H</u>=CH-), 4.43 (t, J = 7.2 Hz, 1H, Ph-C<u>H</u>-SEt), 3.09 (d, J = 7.2 Hz, 2H, Ph-CH-C<u>H</u>$_2$-C(O)-), 2.33 (t, J = 7.3, 2H, -C<u>H</u>$_2$-), 2.24-2.11 (m, 4H, -C<u>H</u>$_2$-), 1.48-1.36 (m, 4H, -C<u>H</u>$_2$-), 1.34-1.22 (m, 6H, -C<u>H</u>$_2$-), 1.16 (t, J = 7.3 Hz, 3H, -S-CH$_2$-C<u>H</u>$_3$), 0.95-0.82 (m, 3H, -CH$_2$-CH$_2$-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 197.1, 148.5, 142.2, 130.3, 128.43 (2CH), 127.7 (2CH), 127.1, 46.5, 44.1, 32.5, 31.5, 28.8, 27.9, 25.4, 22.5, 14.3, 14.0; *m/z* (ESI) 327 (100%, $[M+Na]^+$), 305 (45%, $[M+H]^+$); HRMS (ESI) found *m/z* 305.1934 $[M+H]^+$, $C_{19}H_{29}OS$ requires 305.1934. Data in accordance with the literature.[139]

(E)-2-(phenylthio)dodec-5-en-4-one



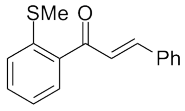
Prepared according to general procedure F to furnish the product as a colourless oil (215 mg, 92%). ν_{max} (film)/cm^{-1} 2928, 2870, 1671, 1627, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36-7.30 (m, 2H, ArH), 7.25-7.10 (m, 3H, ArH), 6.70 (dt, J = 15.8, 6.9 Hz, 1H, -C(O)CH=C<u>H</u>-), 5.98 (d, J = 15.8 Hz, 1H, -C(O)C<u>H</u>=CH-), 3.74-3.60 (m, 1H, PhS-C<u>H</u>-), 2.78 (dd, J = 16.3, 4.8 Hz, 1H, -C(O)-C<u>H</u>$_a$-CH$_b$-), 2.59 (dd, J = 16.3, 8.9 Hz, 1H, -C(O)-CH$_a$-C<u>H</u>$_b$-), 2.16-2.05 (m, 2H, -CH$_2$-), 1.41-1.29 (m, 2H, -CH$_2$-), 1.27-1.13 (m, 9H, incl. -CH(SPh)-CH$_3$), 0.80 (t, J = 6.7 Hz, 3H, -CH$_2$-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 198.1, 148.3, 134.4, 132.2 (2CH), 130.4, 128.9 (2CH), 127.1, 46.6, 38.6, 32.5, 31.5, 28.8, 27.9, 22.5, 20.9, 14.0; HRMS (ESI) found *m/z* 291.1779 $[M+H]^+$, $C_{18}H_{27}OS$ requires 291.1777. Data in accordance with the literature.[139]

(E)-5-(ethylthio)-1,4-diphenylpent-1-en-3-one



Prepared according to general procedure F to furnish the product as a colourless oil (210 mg, 95%). ν_{max} (film)/cm^{-1} 3261, 2927, 1687, 1660, 1612; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (d, J = 16.0 Hz, 1H, -C(O)CH=C<u>H</u>-), 7.49-7.47 (m, 2H, ArH), 7.38-7.27 (m, 8H, ArH), 6.73 (d, J = 16.0 Hz, 1H, -C(O)C<u>H</u>=CH-), 4.09 (t, J = 7.3, 1H, -C(O)-C<u>H</u>(Ph)-CH_2-), 3.38 (dd, J = 13.2, 7.8 Hz, 1H, EtS-C<u>H</u>$_a$-CH_b-), 2.90 (dd, J = 13.2, 6.7 Hz, 1H, EtS-CH_a-C<u>H</u>$_b$-), 2.55-2.49 (m, 2H, -S-C<u>H</u>$_2$-CH_3), 1.24 (t, J = 7.2 Hz, 3H, -S-CH_2-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 197.6, 143.2, 138.0, 134.3, 130.5 (2CH), 129.0 (2CH), 128.8 (2CH), 128.34, 128.31 (2CH), 127.6, 124.9, 58.1, 34.9, 26.8, 14.7; HRMS (FI) found *m/z* 296.1240 [M]$^+$, $C_{19}H_{20}OS$ requires 296.1235. Data in accordance with the literature.[82]

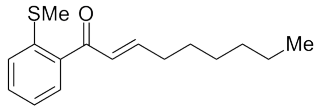
(E)-1-(2-(methylthio)phenyl)-3-phenylprop-2-en-1-one, 59



Prepared according to general procedure F to furnish the product as a yellow oil (160 mg, 84%) as mixture of linear and branched isomers (11:1, l:b). ν_{max} (film)/cm^{-1} 3059, 2912, 1655, 1598, 1208, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (dd, J = 7.7 and 1.3 Hz, 1H, ArH), 7.64 (d, J = 15.9, 1H, -C(O)CH=C<u>H</u>-), 7.60-7.58 (m, 2H, ArH), 7.49-7.45 (m, 1H, ArH), 7.40-7.37 (m, 4H, ArH), 7.32 (d, J = 15.9, 1H, -C(O)C<u>H</u>=CH-), 7.26-7.22 (m, 1H, ArH), 2.45 (s, 3H, -S-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 192.9, 145.2, 140.5, 137.2, 134.8, 131.6, 130.6, 129.5, 129.0, 128.5, 126.3, 124.8, 124.2, 16.5; HRMS (ESI) found *m/z* 277.0657 [M+Na]$^+$, $C_{16}H_{14}NaOS$ requires

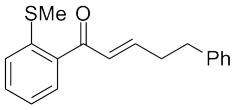
277.0658. Data in accordance with the literature.[139]

(E)-1-(2-(methylthio)phenyl)non-2-en-1-one, 80



Prepared according to general procedure F to furnish the product as a yellow oil (169 mg, 86%). ν_{max} (film)/cm^{-1} 2955, 2926, 2856, 1661, 1615; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56 (d, J = 7.7 Hz, 1H, ArH), 7.43-7.39 (m, 1H, ArH), 7.32 (d, J = 8.0 Hz, 1H, ArH), 7.19-7.15 (m, 1H, ArH), 6.90-6.83 (m, 1H, -C(O)CH=C<u>H</u>-), 6.63 (d, J = 15.6 Hz, 1H, -C(O)C<u>H</u>=CH-), 2.41 (s, 3H, -S-C<u>H</u>$_3$), 2.26 (app. q, J = 7.2 Hz, 2H, -CH=CH-C<u>H</u>$_2$-)), 1.51-1.44 (m, 2H, -CH=CH-CH$_2$-C<u>H</u>$_2$-), 1.36-1.28 (m, 6H, -C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-CH$_3$), 0.87 (t, J = 6.6 Hz, 3H, -CH$_2$-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 193.4, 151.1, 140.2, 137.1, 131.2, 129.3, 128.5, 126.1, 124.0, 32.8, 31.6, 28.9, 28.0, 22.5, 16.4, 14.1; HRMS (ESI) found *m/z* 285.1280 $[M+Na]^+$, $C_{16}H_{22}NaOS$ requires 285.1284. Data in accordance with the literature.[139]

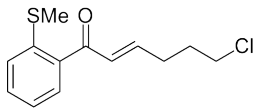
(E)-1-(2-(methylthio)phenyl)-5-phenylpent-2-en-1-one, 82



Prepared according to general procedure F to furnish the product as a yellow oil (149 mg, 70%). ν_{max} (film)/cm^{-1} 3060, 3026, 2920, 2856, 1661, 1615, 1300, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.52 (d, J = 7.7 Hz, 1H, ArH), 7.46-7.41 (m, 1H, ArH), 7.36-7.29 (m, 3H, ArH), 7.24-7.16 (m, 4H, ArH), 6.91 (dt, J = 15.5 and 6.8 Hz, 1H, -C(O)CH=C<u>H</u>-), 6.67 (dd, J = 15.5 and 1.0 Hz, 1H, -C(O)C<u>H</u>=CH-), 2.83 (t, J = 7.7 Hz, 2H, -CH$_2$-C<u>H</u>$_2$-Ph), 2.61 (m, 2H, -C<u>H</u>$_2$-CH$_2$-Ph), 3.45 (s, 3H, -S-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 193.2, 149.4, 140.8, 140.5, 136.8, 131.4, 129.5, 129.2, 128.5, 128.4,

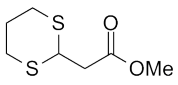
126.2, 126.1, 124.0, 34.5, 34.4 and 16.4; HRMS (ESI) found *m/z* 305.0972 $[M+Na]^+$, $C_{18}H_{18}NaOS$ requires 305.0971. Data in accordance with the literature.[139]

(E)-6-chloro-1-(2-(methylthio)phenyl)hex-2-en-1-one, 81



Prepared according to general procedure F to furnish the product as a yellow oil (126 mg, 66%). ν_{max} (film)/cm^{-1} 3059, 2957, 2020, 1662, 1616, 1298, 755, 740; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.60 (d, J = 7.7 Hz, 1H, ArH), 7.46-7.43 (m, 1H, ArH), 7.34 (d, J = 8.0 Hz, 1H. ArH), 7.22-7.18 (m, 1H, ArH), 6.85 (dt, J = 15.5 and 6.8 Hz, 1H, -C(O)CH=C<u>H</u>-), 6.72 (d, J = 15.6 Hz, 1H, -C(O)C<u>H</u>=CH-), 3.57 (t, J = 6.4 Hz, 2H, -C<u>H</u>$_2$-Cl), 2.50-2.44 (m, 2H, -CH=CH-C<u>H</u>$_2$-), 2.44 (s, 3H, -S-C<u>H</u>$_3$), 2.01-1.94 (m, 2H, -C<u>H</u>$_2$-CH_2-Cl); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 192.8, 148.1, 140.6, 136.7, 131.5, 129.5, 129.4, 126.1, 124.0, 44.1, 30.7, 29.7 and 16.4; HRMS (ESI) found *m/z* 277.0424 $[M+Na]^+$, $C_{13}H_{15}ClNaOS$ requires 277.0424. Data in accordance with the literature.[139]

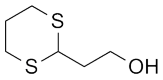
methyl 2-(1,3-dithian-2-yl)acetate



Methyl propiolate (2.00 mL, 20.1 mmol) was dissolved in MeOH/DCM (60 mL/15 mL) and cooled to -10 °C, followed by the addition of 1,3-propanedithiol (2.32 mL, 23.2 mmol) then NaOMe (1.40 g, 26.0 mmol). The solution was stirred at -10 °C for 5 hours then allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted into Et_2O. The combined organic extracts were washed with water then brine, dried over $MgSO_4$ and concentrated

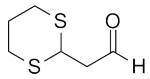
in vacuo. Purified by column chromatography (20% Et_2O in petrol) to give the final product as a pale yellow oil (2.35 g, 61%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 4.78 (t, J = 7.4 Hz, 1H, -C<u>H</u>-CH_2-CO_2Me), 3.65 (s, 3H, -CO_2-C<u>H</u>$_3$), 3.22-3.16 (m, 4H, -S-C<u>H</u>$_2$-CH_2-C<u>H</u>$_2$-S-) , 2.80 (d, J = 7.4 Hz, 2H, -CH_2-CO_2Me), 2.29-1.70 (m, 2H, -S-CH_2-C<u>H</u>$_2$-CH_2-S-); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.4, 51.3, 47.2, 44.2 and 38.0; LRMS (ESI) 439 ([2M+Na+MeOH]$^+$), 100%. Data in accordance with the literature.[264]

2-(1,3-dithian-2-yl)ethanol



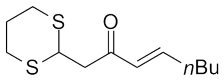
Based on a procedure by Ley.[265] THF (20 mL) was added dropwise to $LiAlH_4$ (0.39 g, 10.1 mmol) cooled to -78 °C. The suspension was stirred at -78 °C for 15 minutes, followed by the dropwise addition of a solution of methyl 2-(1,3-dithian-2-yl)acetate (2.00 g, 10.4 mmol) in THF (10 mL). The reaction mixture was stirred at -78 °C for 3 hours then allowed to warm to room temperature overnight. The reaction mixture was cooled to 0 °C before being quenched with water (5 mL) followed by a saturated aqueous solution of Rochelle salt (30 mL). The mixture was stirred at room temperature overnight, the aqueous layer separated and extracted into Et_2O, the combined organic extracts washed with water then brine, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil (1.48 g, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 4.22 (t, J = 7.1 Hz, 1H, -C<u>H</u>-CH_2-CH_2-OH), 3.80 (t, J = 6.0 Hz, 2H, -C<u>H</u>$_2$-OH), 2.91-2.79 (m, 4H, -S-C<u>H</u>$_2$-), 2.14-2.07 (m, 1H, -S-CH_2-C<u>H</u>$_a$H$_b$-CH_2-S-), 1.99 (q, J = 6.0 Hz, 2H, -C<u>H</u>$_2$-CH_2-OH), 1.92-1.81 (m, 1H, -S-CH_2-CH_a<u>H</u>$_b$-CH_2-S-); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 59.5, 44.2, 37.9, 30.2, 25.9. Data in accordance with the literature.[266]

2-(1,3-dithian-2-yl)acetaldehyde, 83



Methyl 2-(1,3-dithian-2-yl)acetate (2.00 g, 10.4 mmol) was dissolved in DCM (70 mL) and cooled to -78 °C, followed by the dropwise addition of DIBAL-H (1M in DCM, 13.5 mL, 13.5 mmol) over 10 minutes. The reaction mixture was stirred at -78 °C for 2 hours, quenched with ethyl acetate (5 mL) then diluted with DCM. The organic phase was separated and washed with saturated aqueous Rochelle salt, water then brine, dried over $MgSO_4$ then concentrated *in vacuo*. Purified by column chromatography (40% Et_2O in petrol) to a pale yellow oil (1.36 g, 81%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.72 (t, J = 1.8 Hz, 1H, -C$\underline{H}$O), 4.49 (t, J = 6.9 Hz, 1H, -C$\underline{H}$-CH_2-CH_2-CHO), 2.98-2.78 (m, 4H, -S-C$\underline{H}_2$-CH_2-C$\underline{H}_2$-S-), 2.16-2.06 (m, 2H, -C$\underline{H}_2$-CHO), 1.94-1.79 (m, 2H, -S-CH_2-C$\underline{H}_2$-CH_2-S-); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 199.0, 52.3, 45.3, 39.5 and 38.4. Data in accordance with the literature.[267]

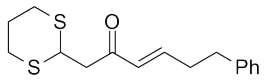
(E)-1-(1,3-dithian-2-yl)oct-3-en-2-one, 84



Prepared according to general procedure F to furnish the product as a yellow oil (108 mg, 59%). ν_{max} (film)/cm^{-1} 2955, 2930, 1671, 1625, 908; ^1H NMR (200 MHz, $CDCl_3$) δ_H 6.86 (dt, J = 15.9, 6.9 Hz, 1H, -CH=C$\underline{H}$-CH_2-), 6.10 (dt, J = 15.9, 1.5 Hz, 1H, -C$\underline{H}$= CH-CH_2-), 4.53 (t, J = 6.9 Hz, 1H, -C(O)-CH_2-C$\underline{H}$-), 2.96-2.74 (m, 6H, incl. -S-C$\underline{H}_2$-CH_2-C$\underline{H}_2$-), 2.23-2.02 (m, 3H, incl. m, 1H, -S-CH_2-C$\underline{H}_a$$H_b$-$CH_2$-S-), 1.94-1.73 (m,1H, -S-CH_2-$CH_a$$\underline{H}_b$-$CH_2$-S-), 1.52-1.23 (m, 4H, -CH_2-C$\underline{H}_2$-C$\underline{H}_2$-CH_3), 0.89 (t, J = 6.9 Hz, 3H, -C$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 195.6, 149.2, 130.2, 44.9, 41.7, 32.2, 30.3, 30.1, 25.3, 22.2, 13.8; HRMS (FI) found *m/z* 244.0949 $[M]^+$,

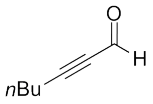
$C_{12}H_{20}OS_2$ requires 244.0956

(E)-1-(1,3-dithian-2-yl)-6-phenylhex-3-en-2-one, 85



Prepared according to general procedure F to furnish the product as a yellow oil (131 mg, 60%). ν_{max} (film)/cm^{-1} 3026, 2932, 2900, 1671, 1603, 909; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32-7.24 (m, 2H, ArH), 7.23-7.17 (m, 3H, ArH), 6.90 (dt, J = 15.9, 6.9 Hz, 1H, -CH=C<u>H</u>-CH_2-), 6.15 (dt, J = 15.9, 1.5 Hz, 1H, -C<u>H</u>= CH-CH_2-), 4.54 (t, J = 6.9 Hz, 1H, -C(O)-CH_2-C<u>H</u>-), 2.95-2.78 (m, 8H, -CH_2-), 2.59-2.54 (m, 2H, -CH_2-), 2.15-2.09 (m, 1H, -S-CH_2-C<u>H</u>$_a$H$_b$-CH_2-S-), 1.93-1.82 (m, 1H, -S-CH_2-CH$_a$<u>H</u>$_b$-CH_2-S-); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 195.4, 147.6, 140.5, 130.6, 128.5, 128.3, 126.2, 45.0, 41.6, 34.3, 34.2, 30.3, 25.3; HRMS (FI) found *m/z* 292.0954 $[M]^+$, $C_{16}H_{20}OS_2$ requires 292.0956.

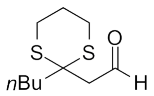
Hept-2-ynal, 86



Prepared according to a procedure described by Journet.[268] *n*BuLi (2.5M in hexanes, 8.0 mL, 20 mmol) added over 2 minutes to a solution of 1-hexyne (3.3 mL, 20 mmol) in dry THF (50 mL) at -40 °C. DMF (3.1 mL, 40 mmol) added in one portion and the reaction mixture was allowed to warm to room temperature over 30 minutes, before being added to a rapidly stirred mixture of Et_2O (140 mL) and NaH_2PO_4 (14.2 g, 80 mmol) in water (140 mL) at 0 °C. The organic phase was separated and washed with water (2 x 40 mL), and the combined aqueous washes back-extracted into Et_2O. The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and

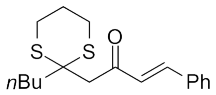
purified by column chromatography (20% Et_2O in petrol) to furnish the aldehyde as a light yellow oil (1.68 g, 76%). ν_{max} (film)/cm^{-1} 2961, 2937, 2873, 2281, 2203, 1671; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.17 (s, 1H, -C<u>H</u>O), 2.41 (t, J = 7.1 Hz, 2H, -C≡C-C<u>H</u>$_2$-CH$_2$-CH$_2$-CH$_3$), 1.58 (tt, J = 7.6, 6.8 Hz, 2H, -C≡C-CH$_2$-C<u>H</u>$_2$-CH$_2$-CH$_3$), 1.44 (sxt, J = 7.58 Hz, 2H, -C≡C-CH$_2$-CH$_2$-C<u>H</u>$_2$-CH$_3$), 0.93 (t, J = 7.3 Hz, 3H, -C≡C-CH$_2$-CH$_2$-CH$_2$-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 177.2, 99.3, 81.7, 29.5, 21.9, 18.8 and 13.4; HRMS (FI) found *m/z* 111.0810 [M+H]$^+$, $C_7H_{11}O$ requires 111.0810.

2-(2-butyl-1,3-dithian-2-yl)acetaldehyde, 87



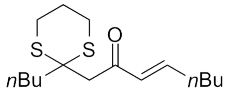
A solution of hept-2-ynal (3.10 g, 28 mmol) in THF (280 mL) was cooled to 0 °C, followed by the addition of 1,3-propanedithiol (3.11 mL, 31 mmol) then NaOMe (1.97 g, 36 mmol). The reaction mixture was allowed to warm to room temperature overnight, then quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase extracted into Et_2O (2 x 100 mL). The combined organic extracts were washed with water then brine, dried over $MgSO_4$and concentrated *in vacuo*. The crude product was washed with saturated aqueous $CuSO_4$ then purified by column chromatography (20% Et_2O in petrol) to provide the aldehyde as a bright yellow oil (2.92 g, 48%). ν_{max} (film)/cm^{-1} 2955, 2934, 1718; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.78 (t, J = 2.7 Hz, 1H, -C<u>H</u>O), 2.94-2.80 (m, 6H, -S-C<u>H</u>$_2$-CH$_2$-C<u>H</u>$_2$-S- and -C<u>H</u>$_2$-CHO), 2.09-1.88 (m, 4H, -C≡C-C<u>H</u>$_2$-C<u>H</u>$_2$-CH$_2$-CH$_3$), 1.55-1.46 (m, 2H, -C≡C-CH$_2$-CH$_2$-C<u>H</u>$_2$-CH$_3$), 1.40-1.30 (m, 2H, -S-CH$_2$-C<u>H</u>$_2$-CH$_2$-S-), 0.93 (t, J = 7.3 Hz, 3H, -C≡C-CH$_2$-CH$_2$-CH$_2$-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 199.8, 50.1, 49.2, 40.2, 26.2, 26.1, 24.7, 22.8, 13.9; HRMS (ESI) found *m/z* 273.0953 [M+Na]$^+$, $C_{11}H_{22}NaO_2S_2$ requires 273.0953.

(E)-1-(2-butyl-1,3-dithian-2-yl)-4-phenylbut-3-en-2-one, 88



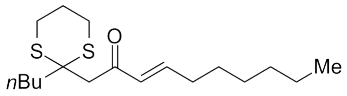
Prepared according to general procedure F to furnish the product as a bright yellow oil (175 mg, 73%). ν_{max} (film)/cm^{-1} 2954, 1717, 1605; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59-7.54 (m, 3H [incl. 7.57, d, J = 15.9 Hz, 1H, -C(O)CH=C<u>H</u>-], ArH), 7.39-7.38 (m, 3H, ArH), 6.85 (d, J = 15.9 Hz, 1H, -C(O)C<u>H</u>=CH-), 3.25 (s, 2H, -C(O)-C<u>H</u>$_2$-), 2.95-2.82 (m, 2H, -CH_2-), 2.16-2.09 (m, 2H, -CH_2-)), 2.08-1.90 (m, 2H, -CH_2-)), 1.57-1.50 (m, 2H, -CH_2-)), 1.41-1.31 (m, 2H, -CH_2-)), 0.94 (t, J = 7.3 Hz, 3H, -C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 195.8, 142.6, 134.5, 130.5, 129.0, 128.4, 126.7, 51.1, 48.6, 38.6, 26.5, 26.4, 25.0, 22.8, 14.0; HRMS (ESI) found *m/z* 343.1159 [M+Na]$^+$, $C_{18}H_{24}NaOS_2$ requires 343.1161.

(E)-1-(2-butyl-1,3-dithian-2-yl)oct-3-en-2-one, 89



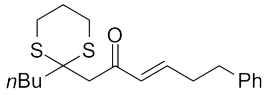
Prepared according to general procedure F to furnish the product as a bright yellow oil (175 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (1H, dt, J = 15.6, 6.9 Hz, -C(O)CH=C<u>H</u>-), 6.12 (1H, dt, J = 15.6, 1.5 Hz, -C(O)C<u>H</u>=CH-), 3.06 (2H, s, -C(O)-C<u>H</u>$_2$-), 2.82-2.77 (4H, m, -CH_2-), 2.15 (2H, tdd, J = 7.0, 6.9, 1.4 Hz, -CH_2-), 2.05-1.85 (4H, m, -CH_2-), 1.47-1.19 (8H, m, -CH_2-), 0.86 (3H, t, J = 7.2 Hz, -C<u>H</u>$_3$), 0.84 (3H, t, J = 7.1 Hz, -C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 196.4, 148.3, 131.4, 51.6, 47.8, 38.9, 32.6, 30.6, 26.9 (2 x CH2), 26.8, 25.5, 23.3, 22.7, 14.4, 14.2; HRMS (EI) found *m/z* 301.1654 [M+H]$^+$, $C_{16}H_{29}OS_2$ requires 301.1651. Data in accordance with the literature.[74]

(E)-1-(2-butyl-1,3-dithian-2-yl)dec-3-en-2-one, 90

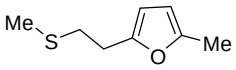


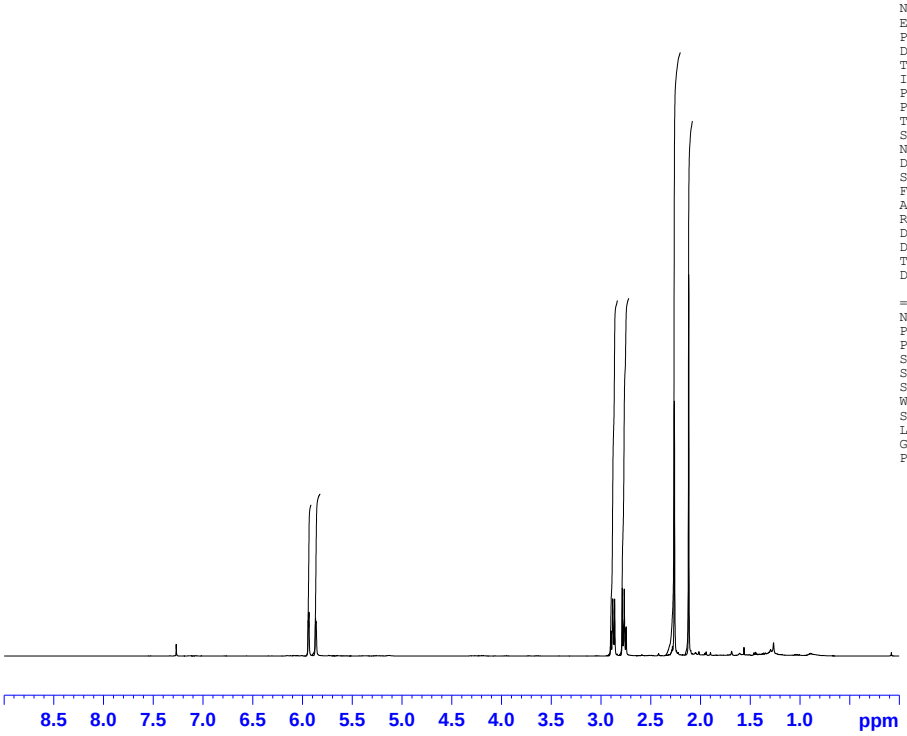
Prepared according to general procedure F to furnish the product as a yellow oil (204 mg, 83%). ν_{max} (film)/cm^{-1} 2956, 2929, 2858, 1618, 1555; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.87 (dt, J = 15.7, 6.9 Hz, 1H, -C(O)CH=C<u>H</u>-), 6.20 (d, J = 15.7 Hz, 1H, -C(O)C<u>H</u>=CH-), 3.14 (s, 2H, -C(O)-C<u>H</u>$_2$-), 2.89-2.85 (m, 4H, -CH$_2$-), 2.25-2.20 (m, 2H, -CH$_2$-), 2.11-2.07 (m, 2H, -CH$_2$-), 2.01-1.95 (m, 2H, -CH$_2$-), 1.52-1.46 (m, 4H, -CH$_2$-), 1.38-1.26 (m, 8H, -CH$_2$-), 0.96-0.87 (m, 6H, 2 x -C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 196.0, 148.0, 130.9, 50.9, 47.3, 38.4, 32.4, 31.6, 28.8, 28.0, 26.5, 26.4, 25.0, 22.8, 22.5, 14.02, 13.97; HRMS (ESI) found *m/z* 351.1785 [M+Na]$^+$, $C_{18}H_{32}NaOS_2$ requires 351.1787.

(E)-1-(2-butyl-1,3-dithian-2-yl)-6-phenylhex-3-en-2-one, 91



Prepared according to general procedure F to furnish the product as a yellow oil (196 mg, 75%). ν_{max} (film)/cm^{-1} 2954, 2931, 2870, 1686, 1663, 1622; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32-7.28 (m, 2H, ArH), 7.23-7.18 (m, 3H, ArH), 6.89 (dt, J = 15.7, 7.1 Hz, 1H, -C(O)CH=C<u>H</u>-), 6.21 (d, J = 15.7 Hz, 1H, -C(O)C<u>H</u>=CH-), 3.12 (s, 2H, -C(O)-C<u>H</u>$_2$-), 2.87-2.78 (m, 6H, -CH$_2$-), 2.59-2.52 (m, 2H, -CH$_2$-), 2.09-2.05 (m, 2H, -CH$_2$-), 2.01-1.92 (m, 2H, -CH$_2$-), 1.52-1.45 (m, 2H, -CH$_2$-), 1.38-1.29 (m, 2H, -CH$_2$-), 0.93 (t, J = 7.6 Hz, 3H, -C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 195.8, 146.3, 140.7, 131.4, 128.5, 128.4, 126.2, 50.9, 47.4, 38.5, 34.3, 34.1, 26.4, 26.1, 25.0, 22.8, 14.0; HRMS (ESI) found *m/z* 371.1469 [M+Na]$^+$, $C_{20}H_{28}NaOS_2$ requires 371.1474.



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FIDRES           0.126314 Hz
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RG                    128
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TE                 300.0 K
D1              1.00000000 sec

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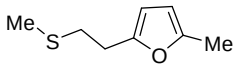

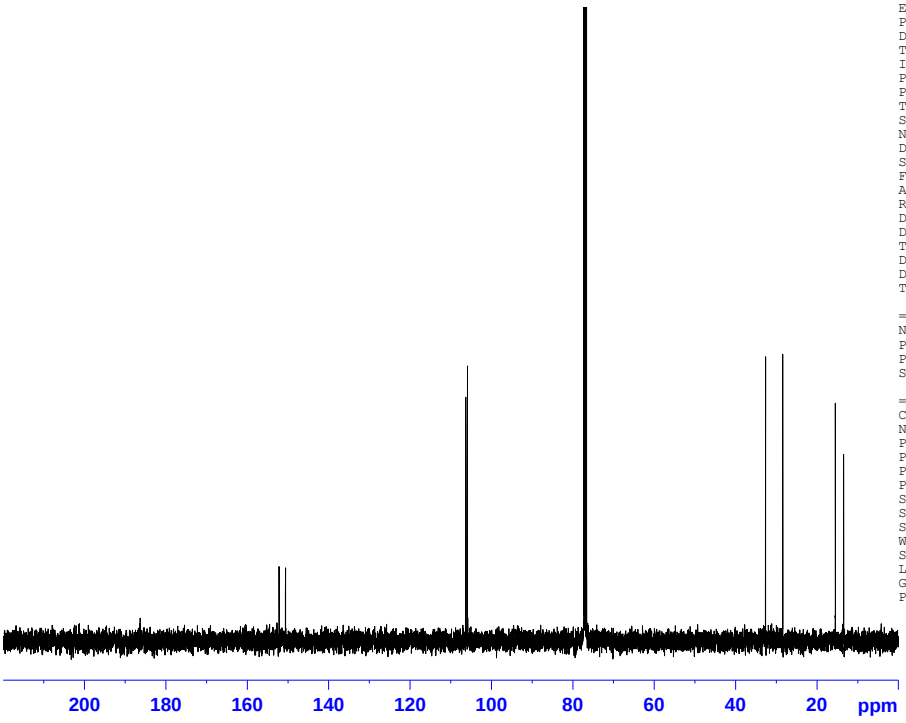


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D11             0.03000000 sec
TD0                     1

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PL1                 0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
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PL13               25.00 dB
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GB                      0
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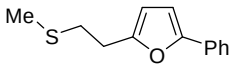

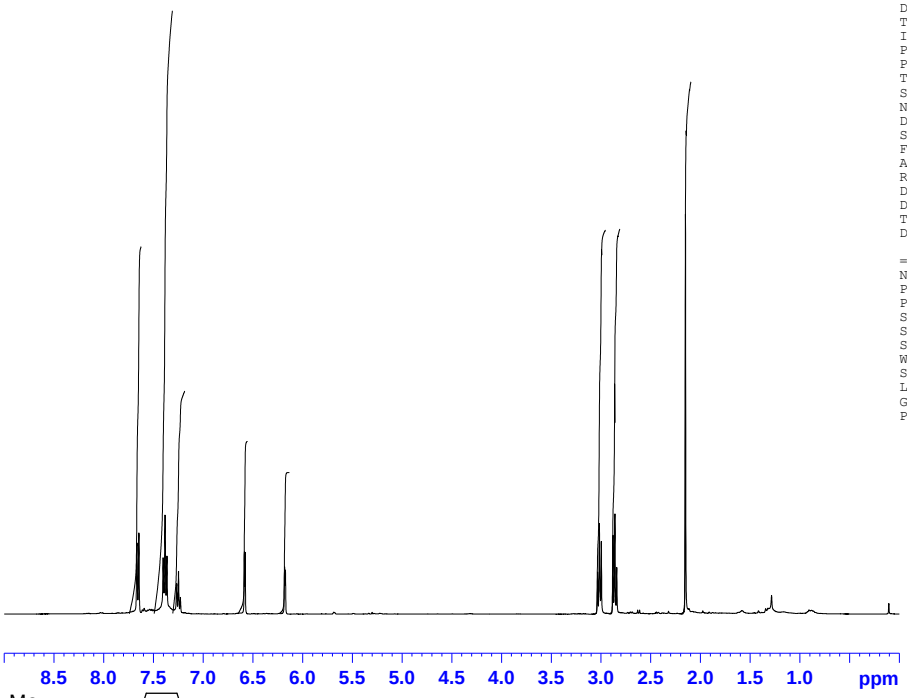

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TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
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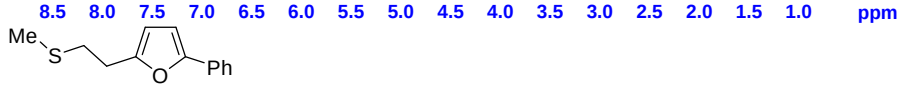
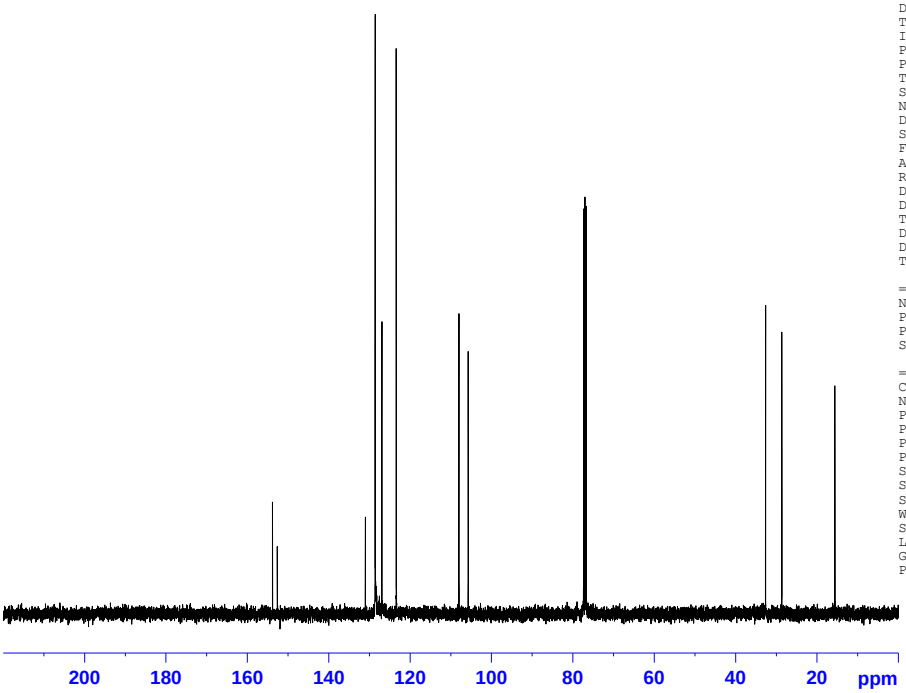
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz
SI                 32768
SF          400.2000028 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
```

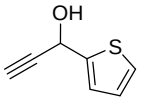


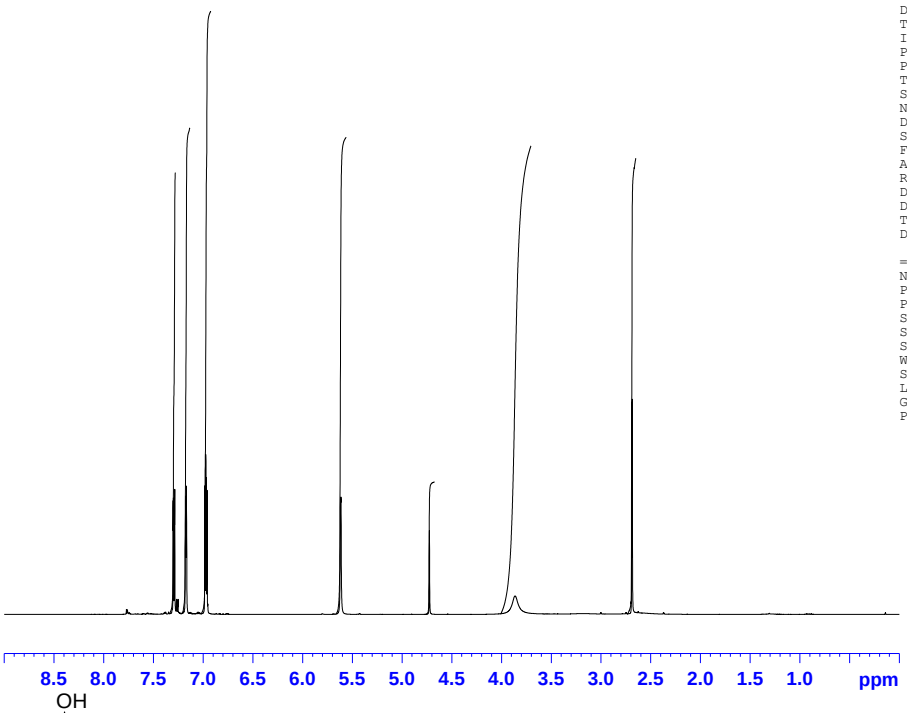


```
NAME       May24-2010-12
EXPNO                  2
PROCNO                 1
Date_           20100525
Time                7.50
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ              0.6259188 sec
RG                 32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                    1

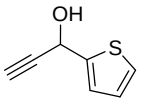
======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1        100.6403931 MHz

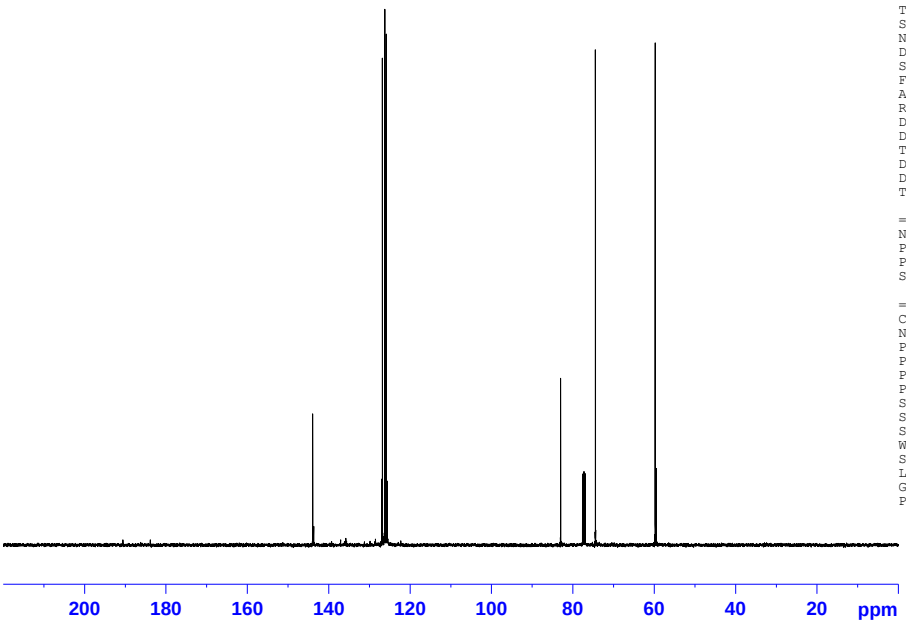
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz
SI                 32768
SF          100.6303718 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```



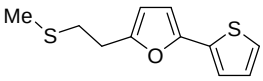


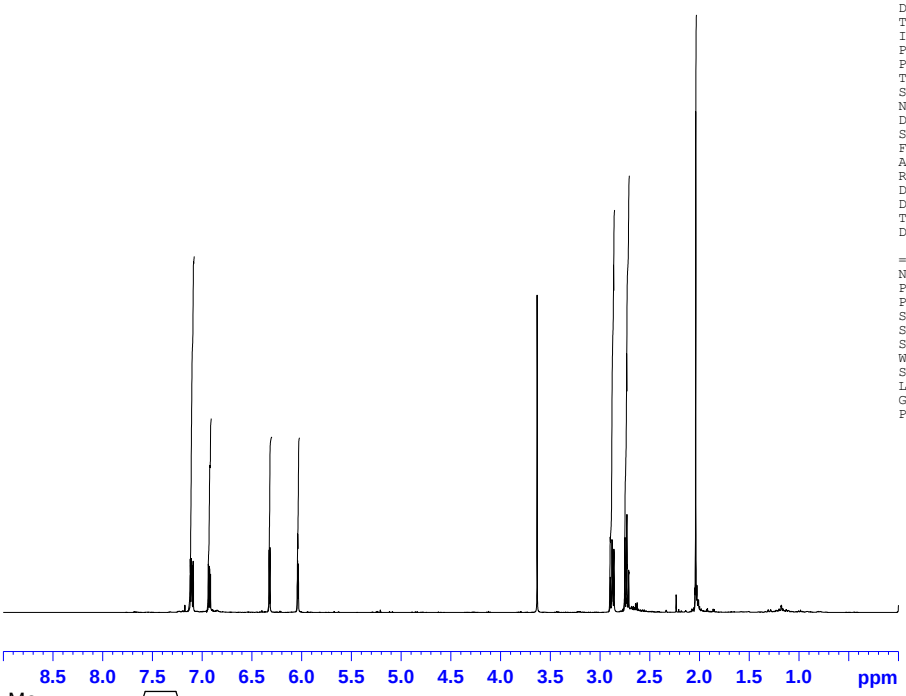
NAME	Sep15-2010-34
EXPNO	1
PROCNO	1
Date_	20100915
Time	14.31
INSTRUM	av400
PROBHD	5 mm QNP 1H/13
PULPROG	zg60
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	22.6
DW	60.400 usec
DE	7.50 usec
TE	300.0 K
D1	1.00000000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	9.00 usec
PL1	0.00 dB
SFO1	400.2024714 MHz
SI	32768
SF	400.2000028 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00





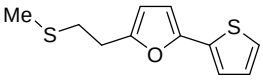
NAME	Sep15-2010-34
EXPNO	2
PROCNO	1
Date_	20100915
Time	14.39
INSTRUM	av400
PROBHD	5 mm QNP 1H/13
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	256
DS	4
SWH	26178.010 Hz
FIDRES	0.798889 Hz
AQ	0.6259188 sec
RG	32768
DW	19.100 usec
DE	7.50 usec
TE	300.0 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.50 usec
PL1	0.00 dB
SFO1	100.6403931 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	19.00 dB
PL13	25.00 dB
SFO2	400.2016008 MHz
SI	32768
SF	100.6303718 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

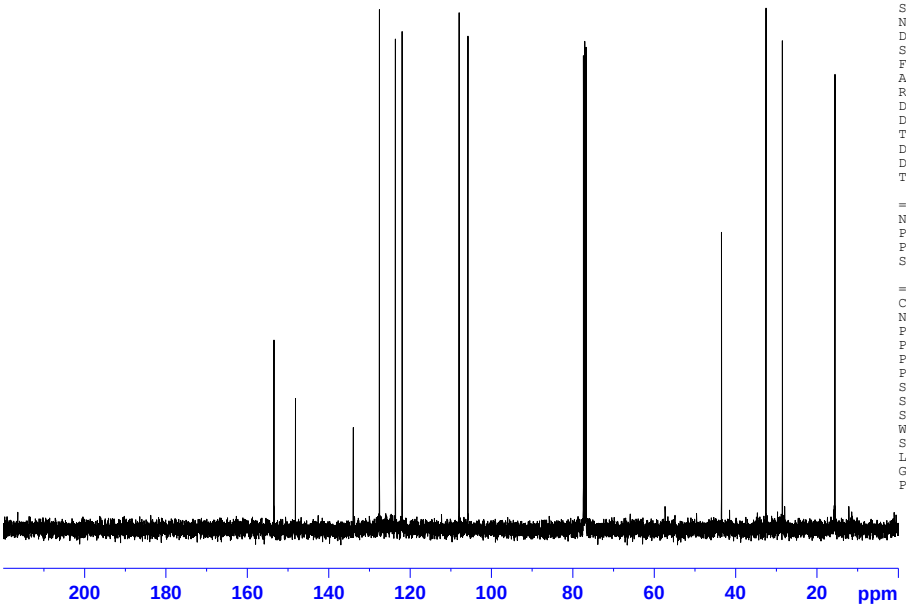




```
NAME       Sep17-2010-10
EXPNO                 1
PROCNO                1
Date_          20100917
Time              12.09
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 35.9
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1          1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000416 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

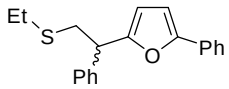



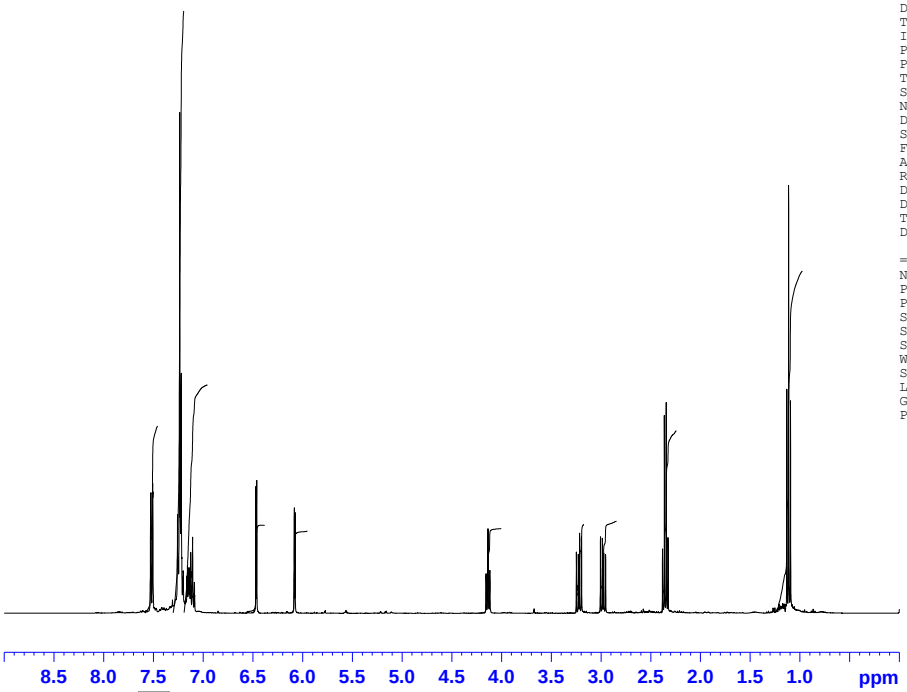


```
NAME       Sep17-2010-10
EXPNO                 2
PROCNO                1
Date_          20100917
Time              12.17
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1          1.00000000 sec
D11         0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                0.00 dB
SFO1       100.6403931 MHz

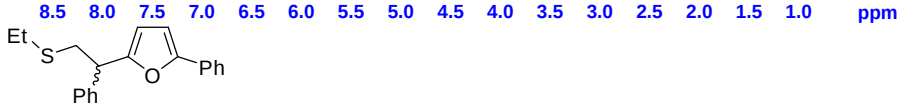
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

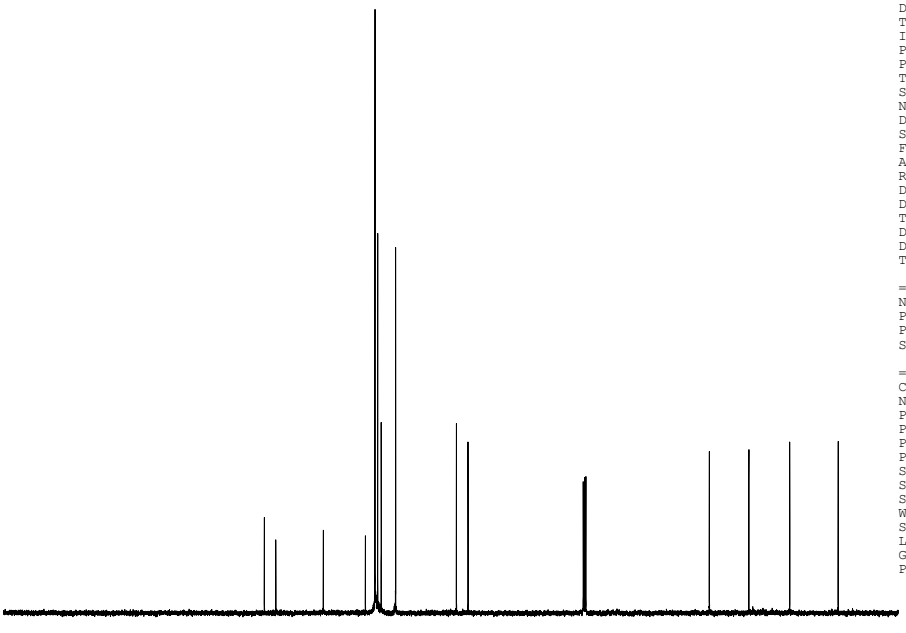




```
NAME          Sep20-2010-9
EXPNO                    1
PROCNO                   1
Date_             20100920
Time                 10.51
INSTRUM              av400
PROBHD    5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                   28.5
DW                 60.400 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000714 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

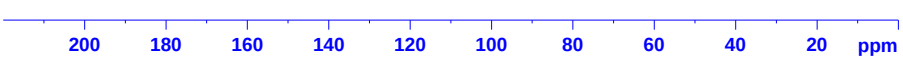


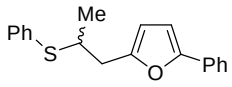


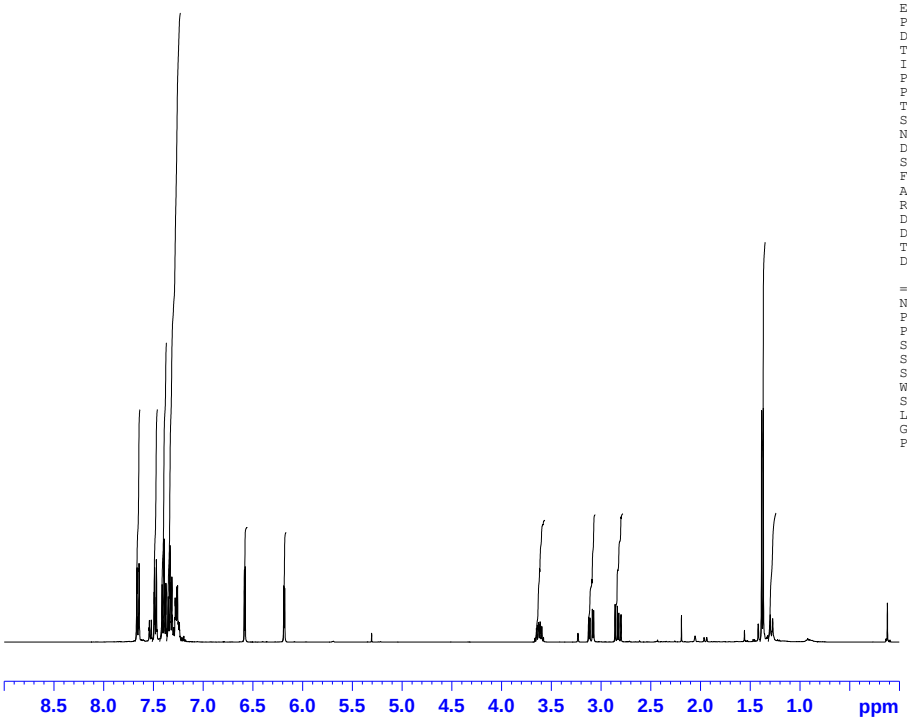
```
NAME          Sep20-2010-9
EXPNO                    2
PROCNO                   1
Date_             20100920
Time                 10.59
INSTRUM              av400
PROBHD    5 mm QNP 1H/13
PULPROG           zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                 19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2          400.2016008 MHz
SI                   32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

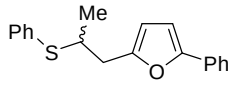


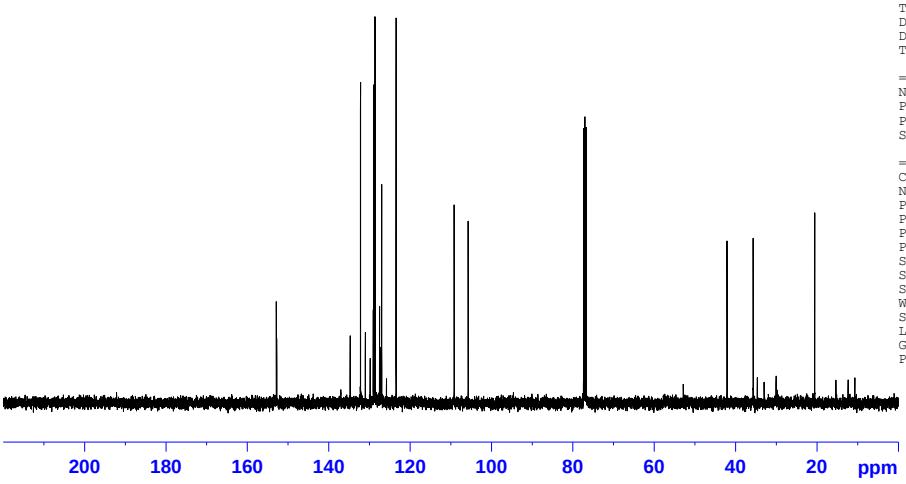





```
NAME          May11-2011-56
EXPNO                    1
PROCNO                   1
Date_             20110512
Time                 4.46
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH           8278.146 Hz
FIDRES         0.126314 Hz
AQ            3.9584243 sec
RG                   90.5
DW                60.400 usec
DE                 7.50 usec
TE                 300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1        400.2024714 MHz
SI                  32768
SF          400.2000028 MHz
WDW                    EM
SSB                     0
LB                  0.30 Hz
GB                      0
PC                   1.00
```

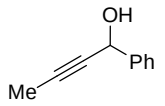


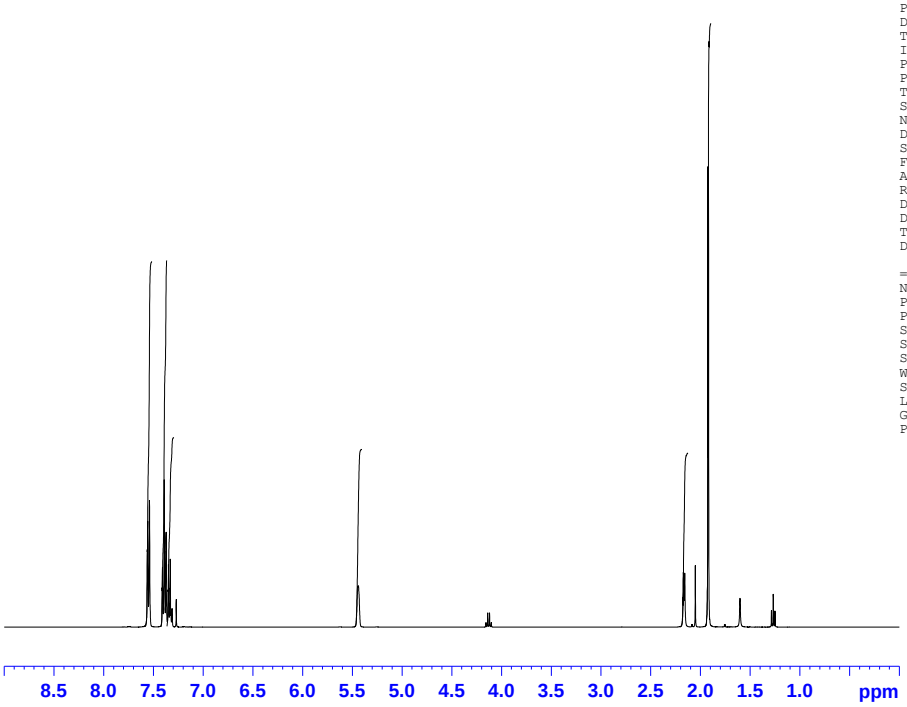



```
NAME          May11-2011-56
EXPNO                    2
PROCNO                   1
Date_             20110512
Time                 4.54
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH          26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                  32768
DW                19.100 usec
DE                 7.50 usec
TE                 300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1        100.6403931 MHz

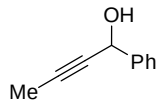
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2        400.2016008 MHz
SI                  32768
SF          100.6303718 MHz
WDW                    EM
SSB                     0
LB                  1.00 Hz
GB                      0
PC                   1.40
```

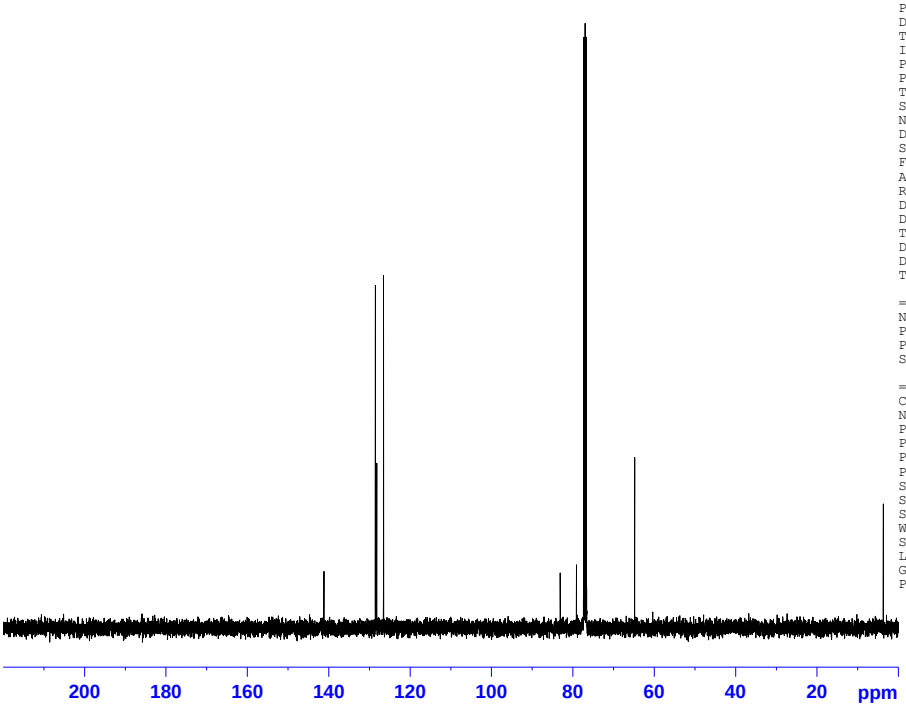





```
NAME       Aug19-2010-46
EXPNO                 1
PROCNO                1
Date_          20100819
Time              21.09
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                  181
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

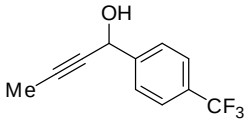


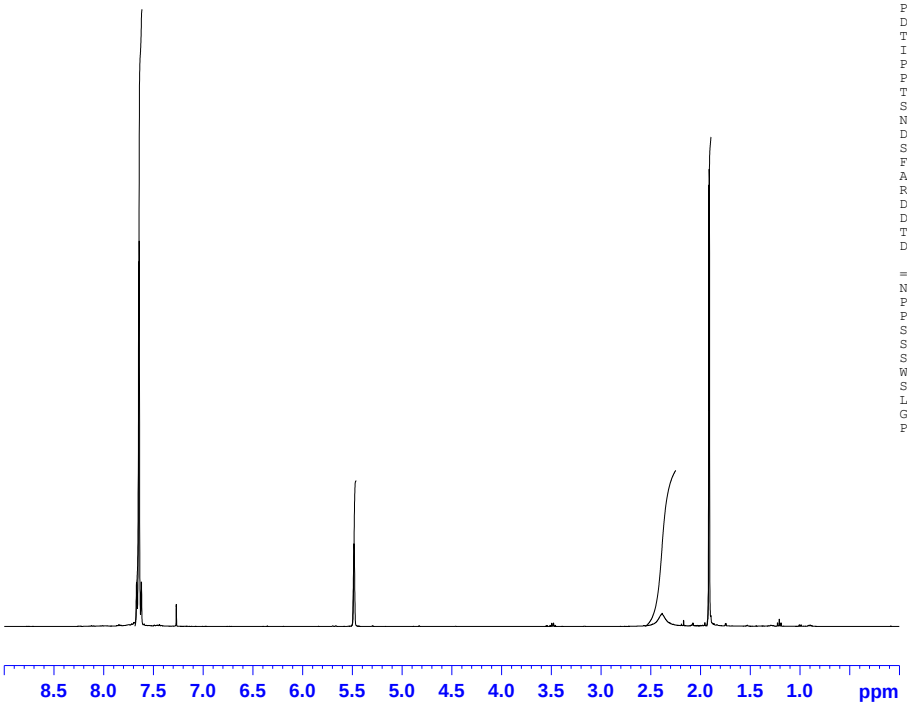



```
NAME       Aug19-2010-46
EXPNO                 2
PROCNO                1
Date_          20100819
Time              21.17
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                0.00 dB
SFO1        100.6403931 MHz

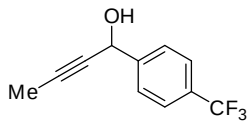
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

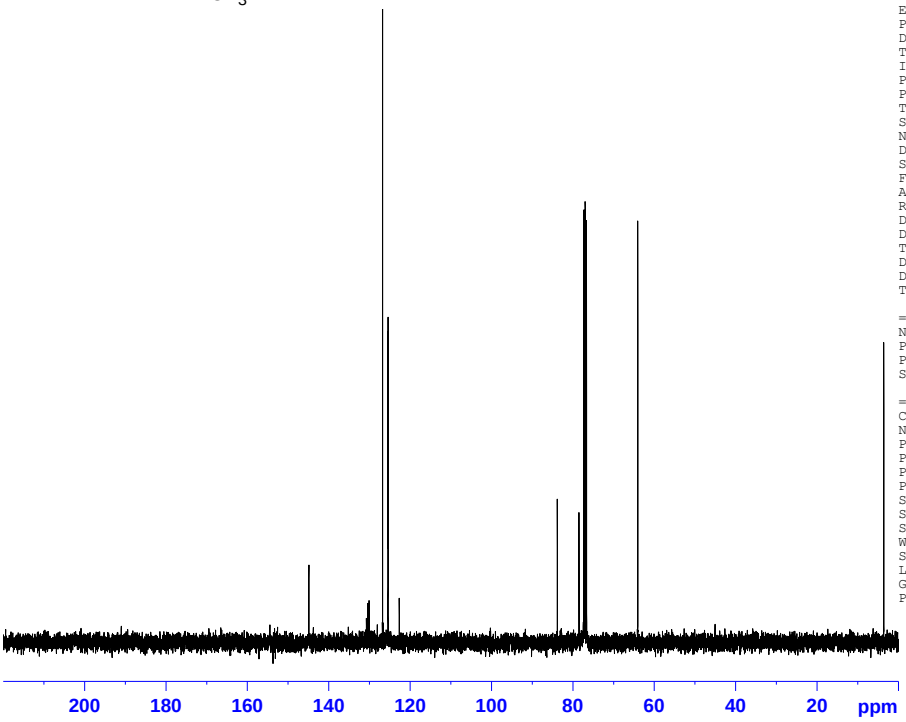





```
NAME          Mar01-2011-11
EXPNO                     1
PROCNO                    1
Date_              20110302
Time                  1.31
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH            8278.146 Hz
FIDRES         0.126314 Hz
AQ             3.9584243 sec
RG                  90.5
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1         400.2024714 MHz
SI                  32768
SF           400.2000028 MHz
WDW                    EM
SSB                     0
LB                 0.30 Hz
GB                      0
PC                 1.00
```

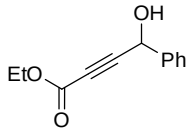


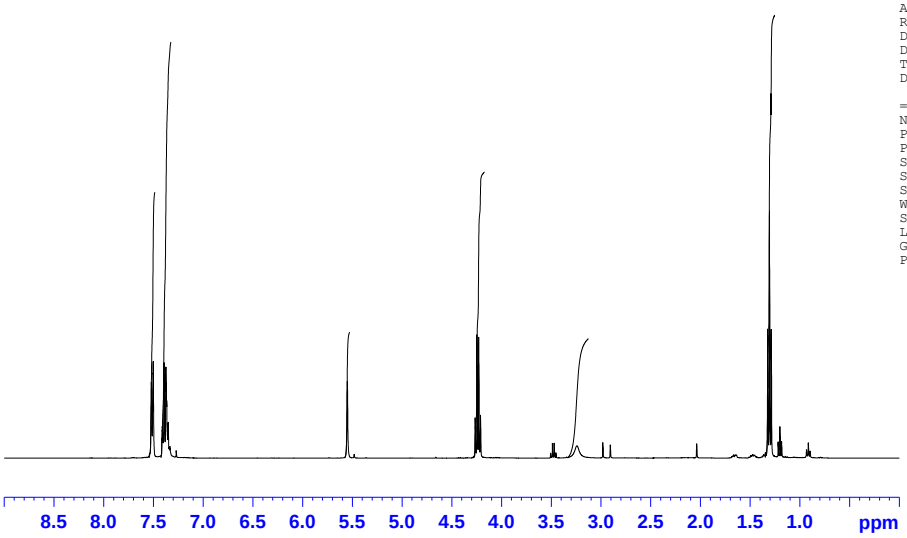



```
NAME          Mar01-2011-11
EXPNO                     2
PROCNO                    1
Date_              20110302
Time                  1.39
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG           zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ             0.6259188 sec
RG                  32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1         100.6403931 MHz

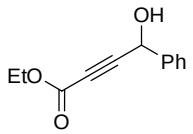
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz
SI                  32768
SF           100.6303718 MHz
WDW                    EM
SSB                     0
LB                 1.00 Hz
GB                      0
PC                 1.40
```

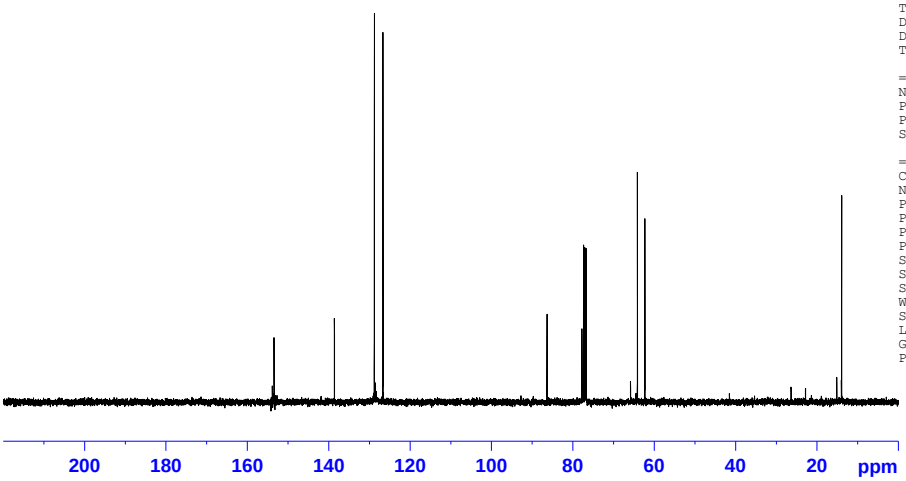





```
NAME       Apr13-2011-53
EXPNO                 1
PROCNO                1
Date_          20110414
Time               6.54
INSTRUM          av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 40.3
DW               60.400 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1       400.2024714 MHz
SI               32768
SF         400.2000028 MHz
WDW                 EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.00
```

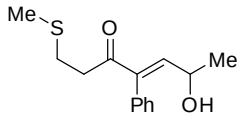


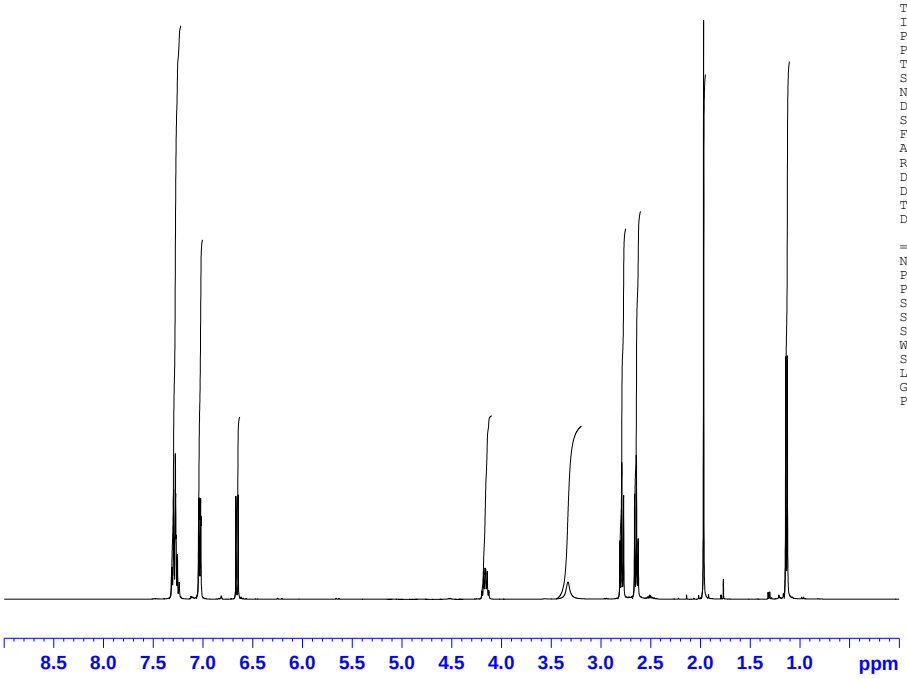



```
NAME       Apr13-2011-53
EXPNO                 2
PROCNO                1
Date_          20110414
Time               7.03
INSTRUM          av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                0.00 dB
SFO1       100.6403931 MHz

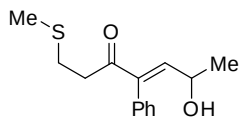
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI               32768
SF         100.6303718 MHz
WDW                 EM
SSB                  0
LB                1.00 Hz
GB                   0
PC                1.40
```

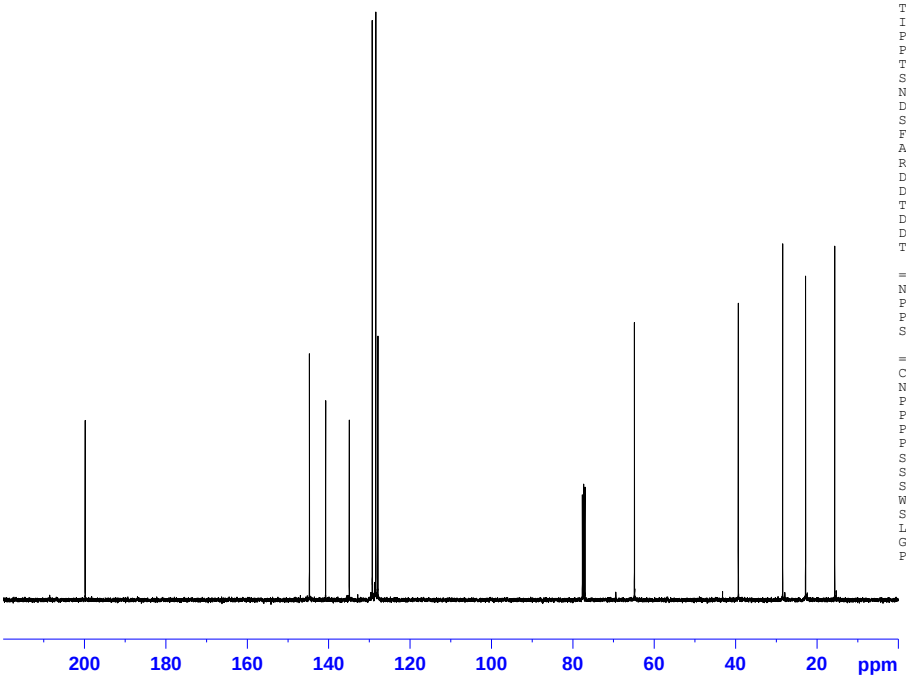





```
NAME       Jan14-2011-17
EXPNO                 1
PROCNO                1
Date_          20110115
Time               8.52
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 11.3
DW               60.400 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                1H
P1               9.00 usec
PL1              0.00 dB
SFO1       400.2024714 MHz
SI               32768
SF         400.2000028 MHz
WDW                 EM
SSB                  0
LB               0.30 Hz
GB                   0
PC                1.00
```

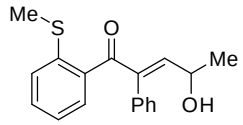


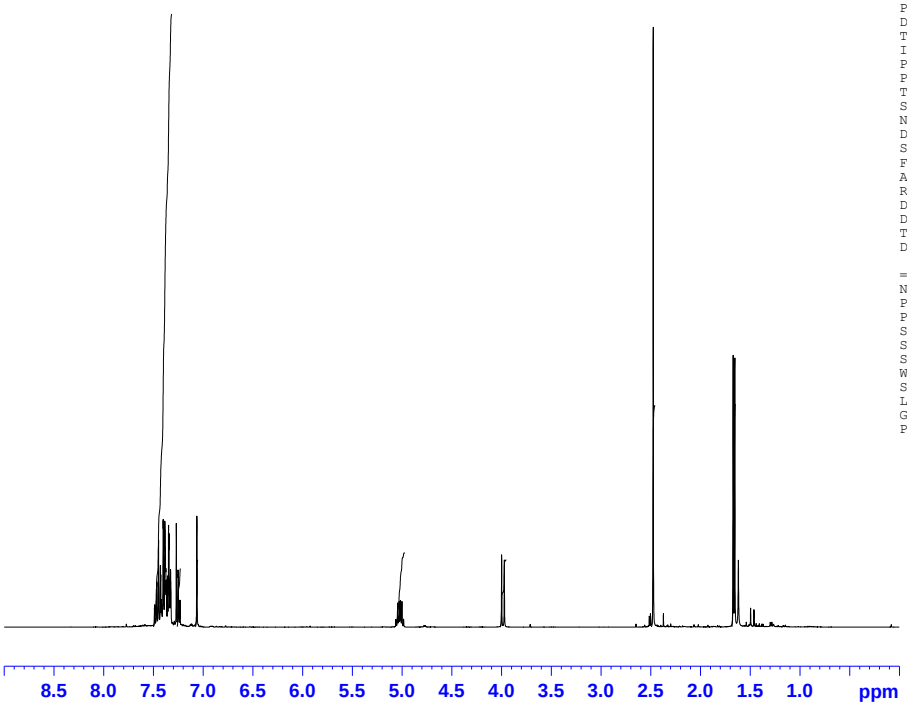



```
NAME       Jan14-2011-17
EXPNO                 2
PROCNO                1
Date_          20110115
Time               9.00
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1               13C
P1               9.50 usec
PL1              0.00 dB
SFO1       100.6403931 MHz

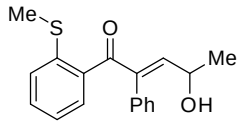
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2            80.00 usec
PL2              0.00 dB
PL12             19.00 dB
PL13             25.00 dB
SFO2       400.2016008 MHz
SI               32768
SF         100.6303718 MHz
WDW                 EM
SSB                  0
LB               1.00 Hz
GB                   0
PC                1.40
```

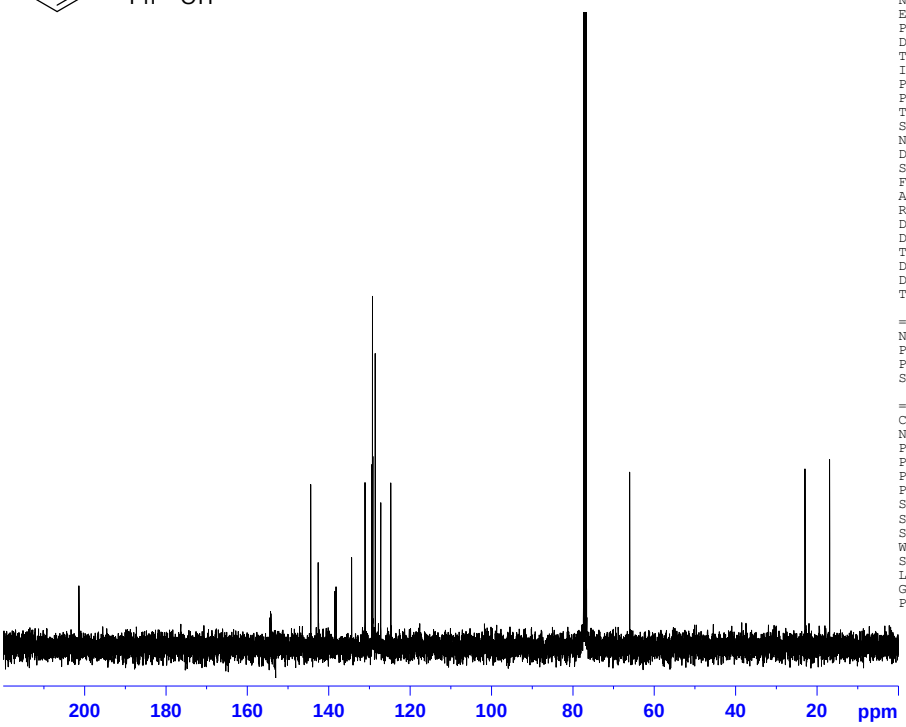





```
NAME          Feb27-2011-3
EXPNO                    1
PROCNO                   1
Date_             20110227
Time                 13.28
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                     181
DW                  60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000028 MHz
WDW                     EM
SSB                      0
LB                   0.30 Hz
GB                       0
PC                    1.00
```

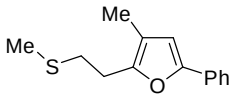


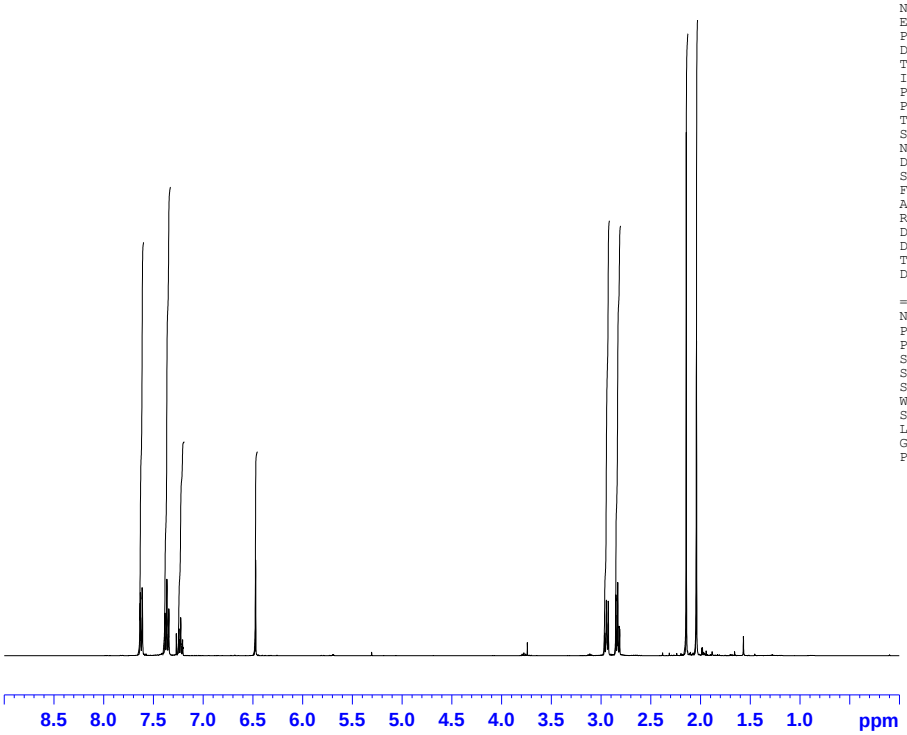



```
NAME          Feb27-2011-3
EXPNO                    2
PROCNO                   1
Date_             20110227
Time                 13.36
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES           0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

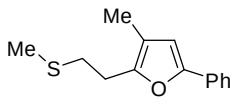
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                    1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz
SI                   32768
SF            100.6303718 MHz
WDW                     EM
SSB                      0
LB                   1.00 Hz
GB                       0
PC                    1.40
```

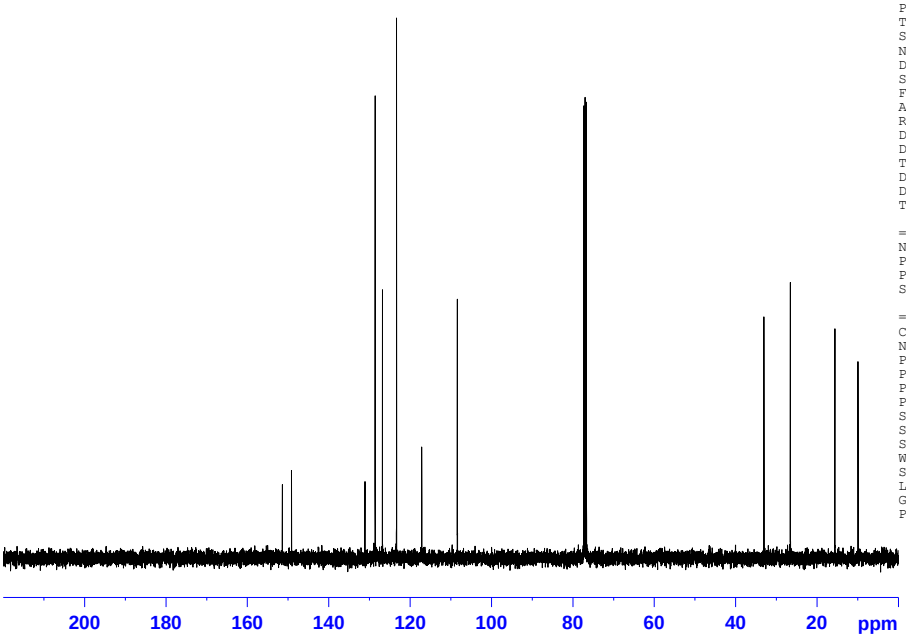





```
NAME          Jul10-2011-53
EXPNO                     1
PROCNO                    1
Date_              20110710
Time                  15.12
INSTRUM               av400
PROBHD     5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                     90.5
DW                   60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

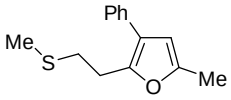


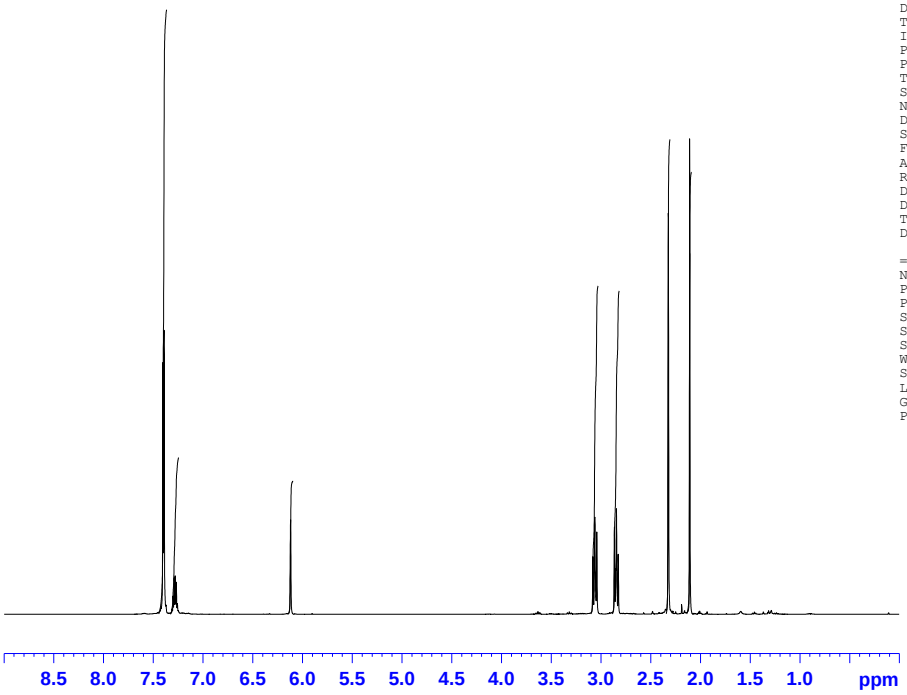



```
NAME          Jul10-2011-53
EXPNO                     2
PROCNO                    1
Date_              20110710
Time                  15.21
INSTRUM               av400
PROBHD     5 mm QNP 1H/13
PULPROG           zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ                0.6259188 sec
RG                     32768
DW                   19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1          100.6403931 MHz

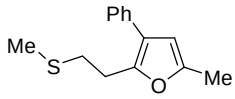
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2          400.2016008 MHz
SI                   32768
SF            100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

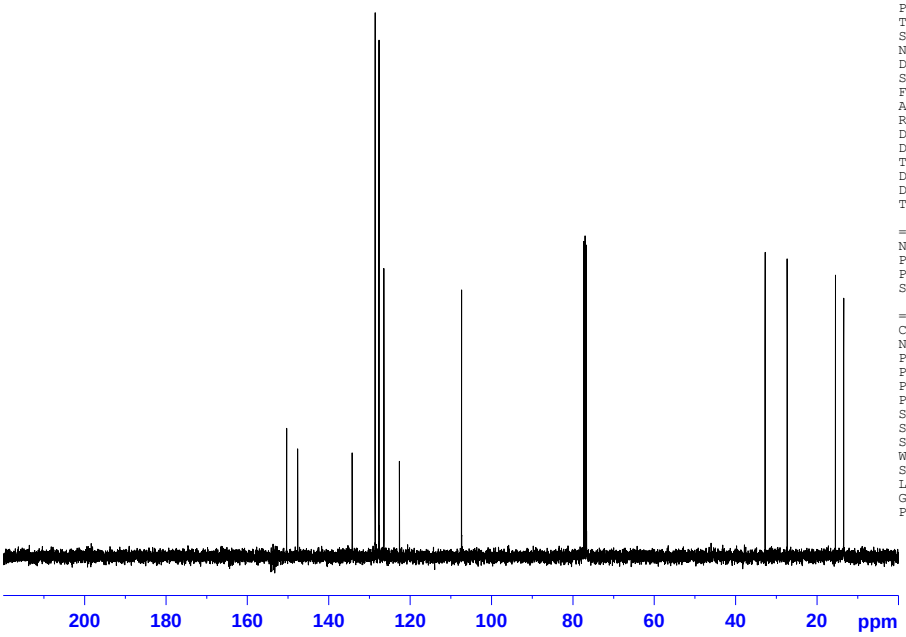





```
NAME       Apr08-2011-28
EXPNO                 1
PROCNO                1
Date_          20110409
Time               7.11
INSTRUM          av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 90.5
DW               60.400 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                9.00 usec
PL1               0.00 dB
SFO1        400.2024714 MHz
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.00
```

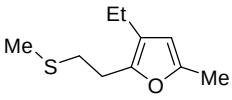





```
NAME       Apr08-2011-28
EXPNO                 2
PROCNO                1
Date_          20110409
Time               7.19
INSTRUM          av400
PROBHD   5 mm QNP 1H/13
PULPROG         zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH          26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

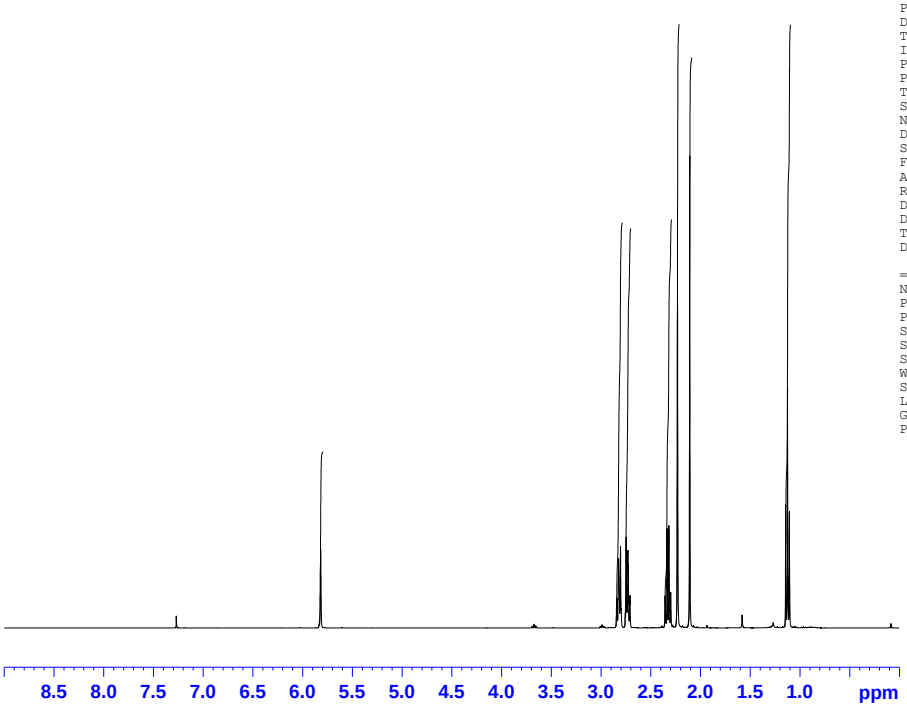
======== CHANNEL f1 ========
NUC1                13C
P1                9.50 usec
PL1               0.00 dB
SFO1        100.6403931 MHz

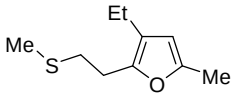
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            80.00 usec
PL2               0.00 dB
PL12             19.00 dB
PL13             25.00 dB
SFO2        400.2016008 MHz
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                1.00 Hz
GB                    0
PC                1.40
```




```
NAME       Jul07-2011-43
EXPNO                  1
PROCNO                 1
Date_           20110708
Time                6.31
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                  90.5
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz
SI                 32768
SF          400.2000028 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
```

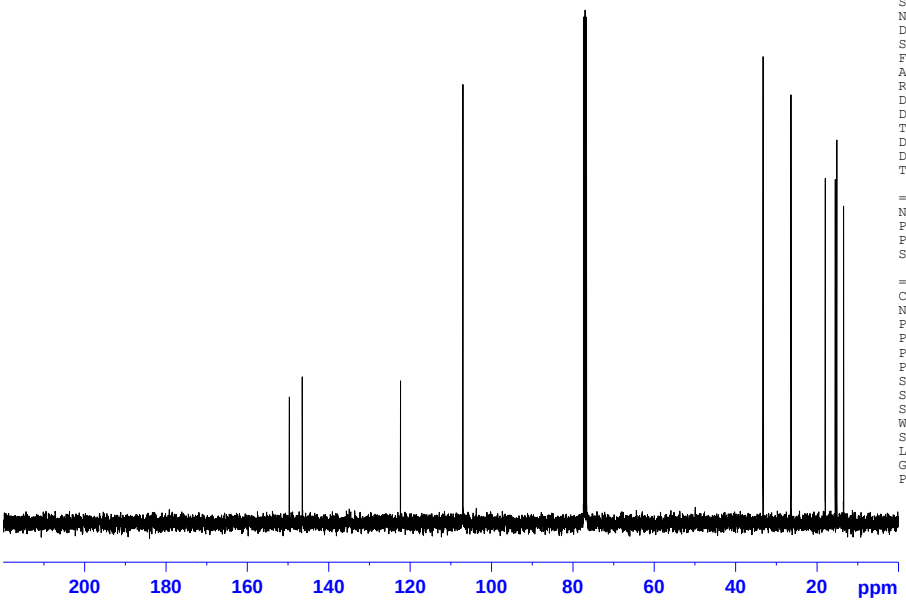


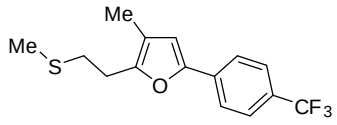


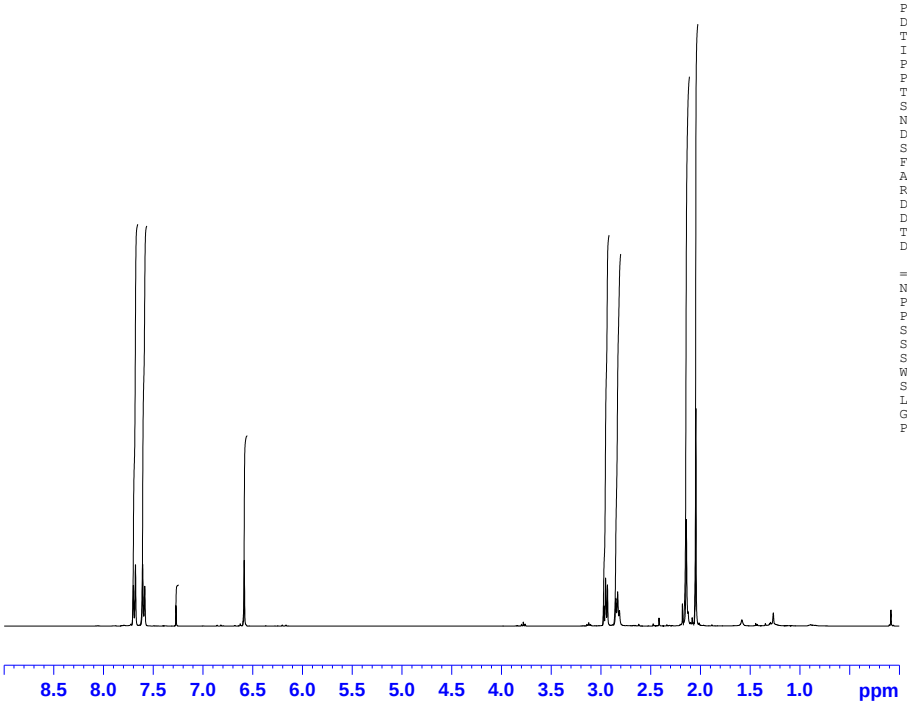

```
NAME       Jul07-2011-43
EXPNO                  2
PROCNO                 1
Date_           20110708
Time                6.39
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ              0.6259188 sec
RG                 32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1        100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz
SI                 32768
SF          100.6303718 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```

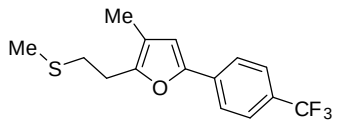


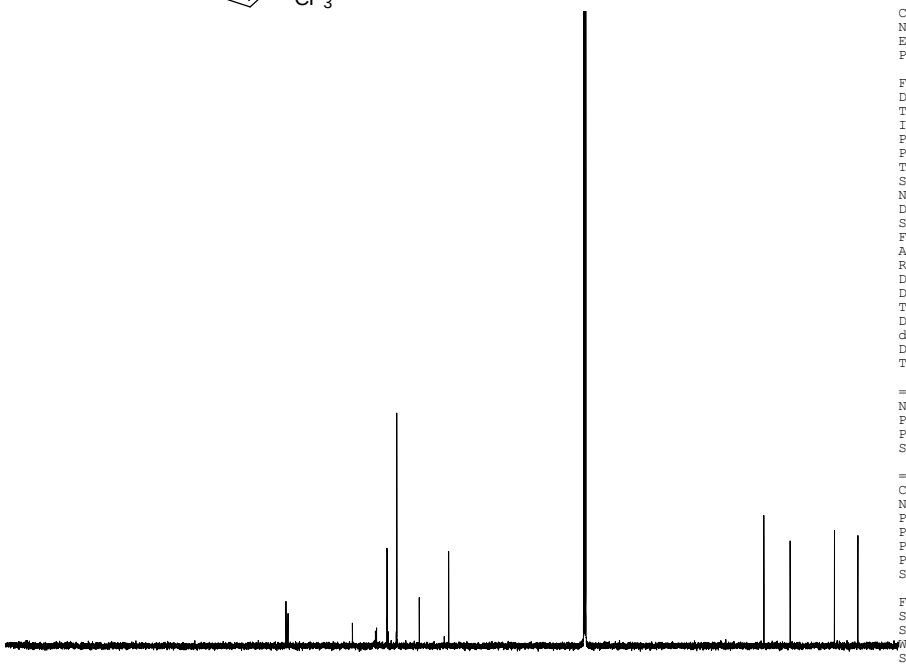


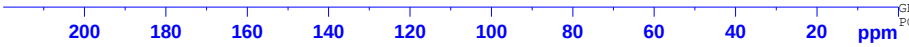



```
NAME       Apr19-2011-18
EXPNO                  1
PROCNO                 1
Date_           20110420
Time                7.15
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                   181
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz
SI                 32768
SF          400.2000028 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
```







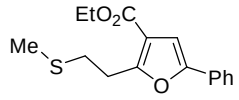

```
Current Data Parameters
NAME          pl38112704
EXPNO                  2
PROCNO                 1

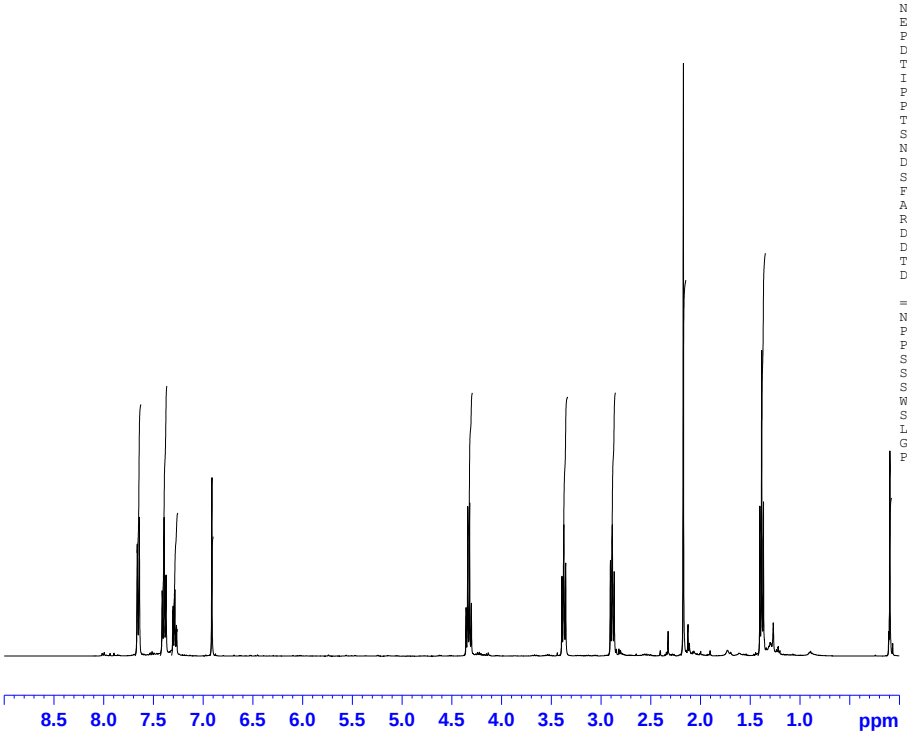
F2 - Acquisition Parameters
Date_           20110428
Time                8.45
INSTRUM          drx500
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     4
SWH            30030.029 Hz
FIDRES          0.458222 Hz
AQ             1.0912410 sec
RG                  6502
DW                16.650 usec
DE                 6.00 usec
TE                298.0 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                5.00 dB
SFO1        125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                0.00 dB
PL12              19.50 dB
PL13              22.50 dB
SFO2        500.1320005 MHz

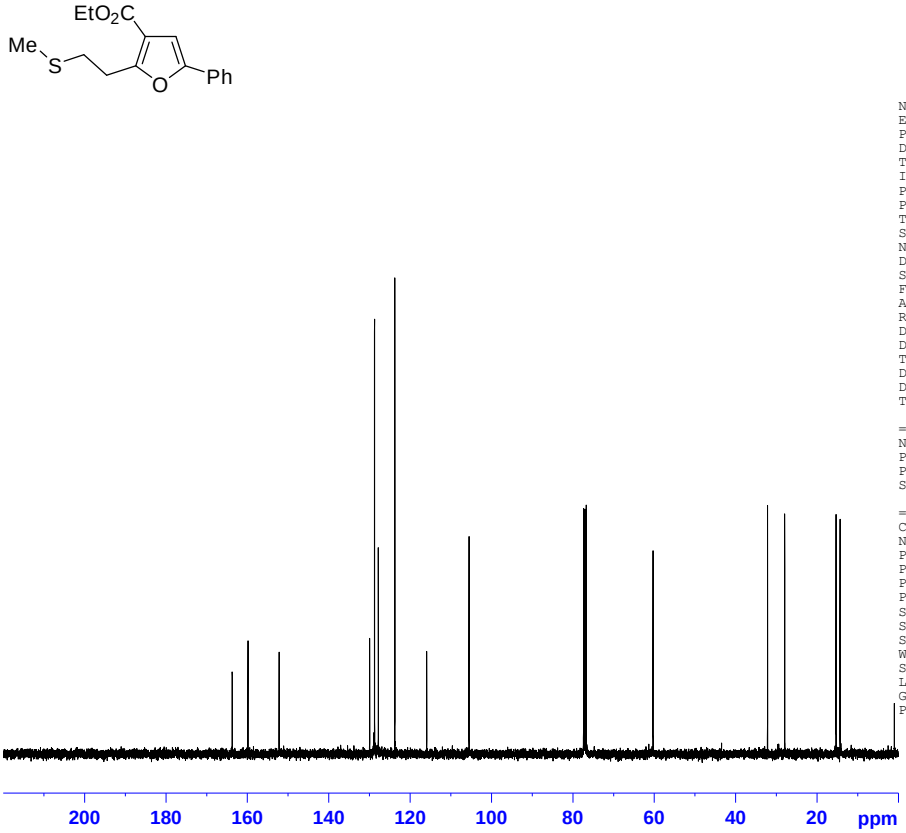
F2 - Processing parameters
SI                 32768
SF          125.7577890 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```





```
NAME       Apr29-2011-18
EXPNO                 1
PROCNO                1
Date_          20110429
Time               19.54
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES             0.126314 Hz
AQ              3.9584243 sec
RG                  35.9
DW                 60.400 usec
DE                  7.50 usec
TE                300.0 K
D1             1.00000000 sec

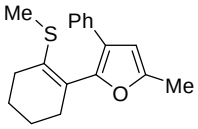
======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                0.00 dB
SFO1         400.2024714 MHz
SI                 32768
SF           400.2000028 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
```

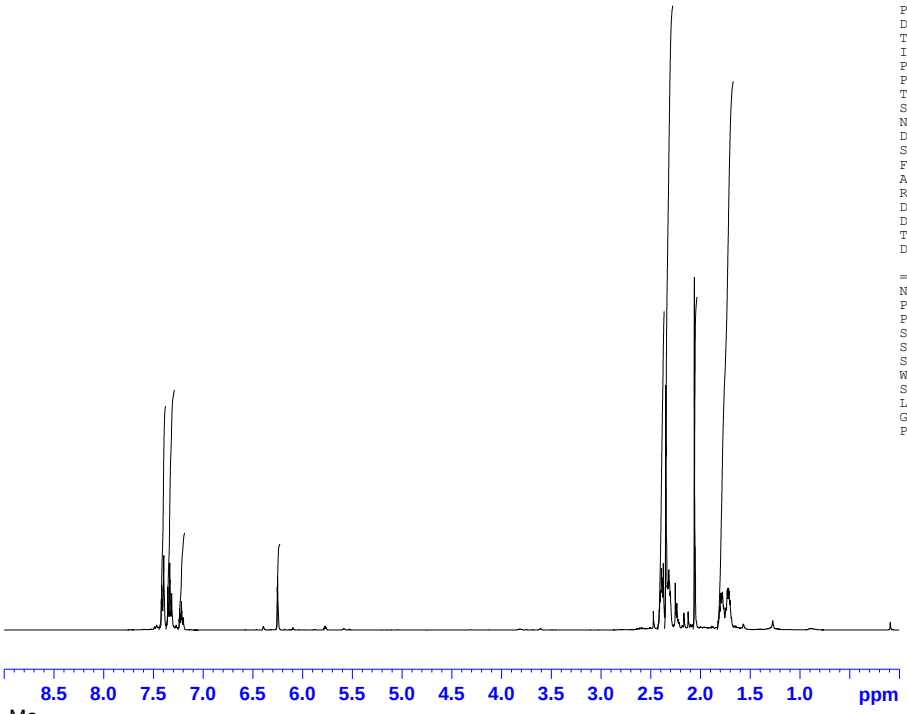



```
NAME       Apr29-2011-18
EXPNO                 2
PROCNO                1
Date_          20110429
Time               20.02
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES             0.798889 Hz
AQ              0.6259188 sec
RG                 32768
DW                 19.100 usec
DE                  7.50 usec
TE                300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1         100.6403931 MHz

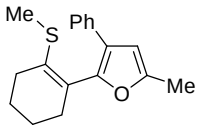
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz
SI                 32768
SF           100.6303718 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```

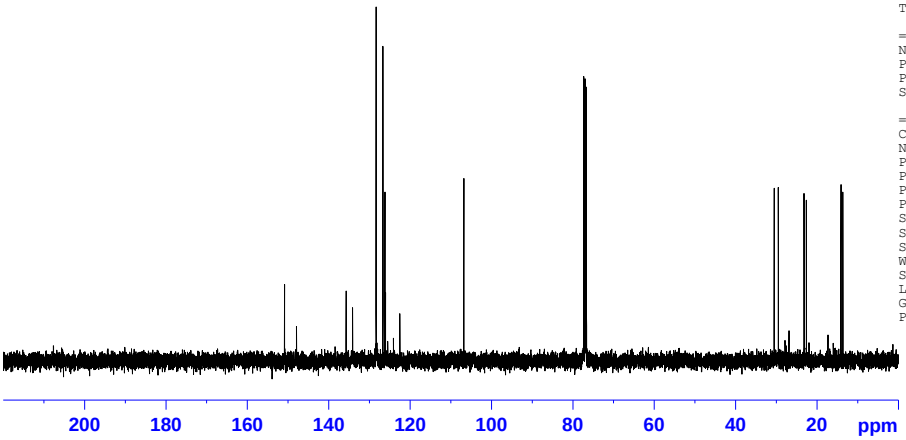





```
NAME       Jun29-2011-29
EXPNO                 1
PROCNO                1
Date_          20110630
Time               1.03
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 90.5
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1          1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                9.00 usec
PL1               0.00 dB
SFO1        400.2024714 MHz
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.00
```

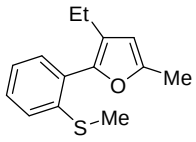


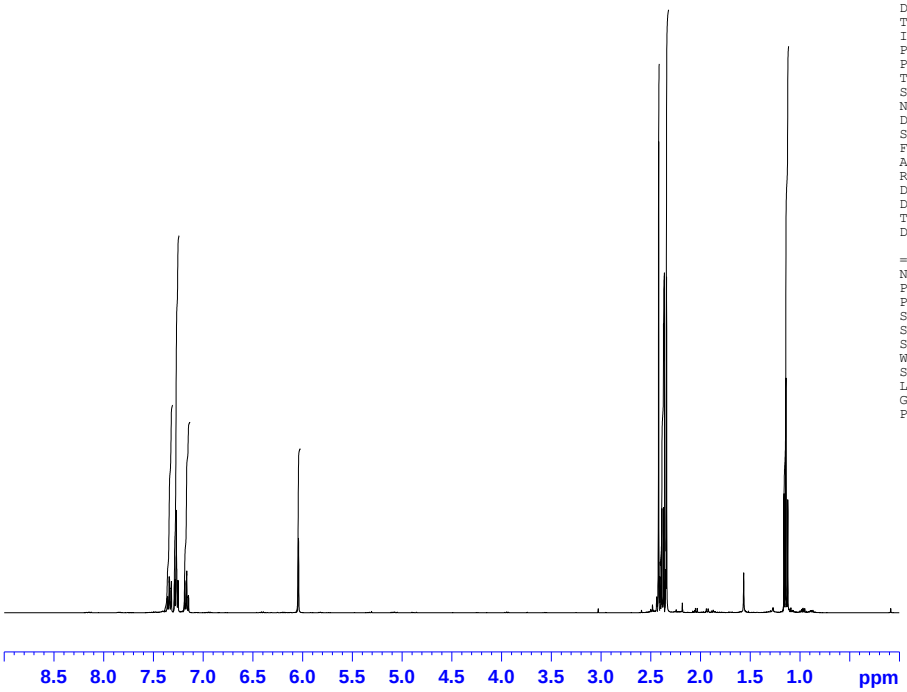



```
NAME       Jun29-2011-29
EXPNO                 2
PROCNO                1
Date_          20110630
Time               1.11
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1          1.00000000 sec
D11         0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                9.50 usec
PL1               0.00 dB
SFO1        100.6403931 MHz

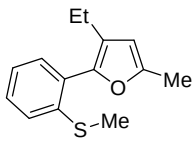
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2               0.00 dB
PL12             19.00 dB
PL13             25.00 dB
SFO2        400.2016008 MHz
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                1.00 Hz
GB                    0
PC                1.40
```

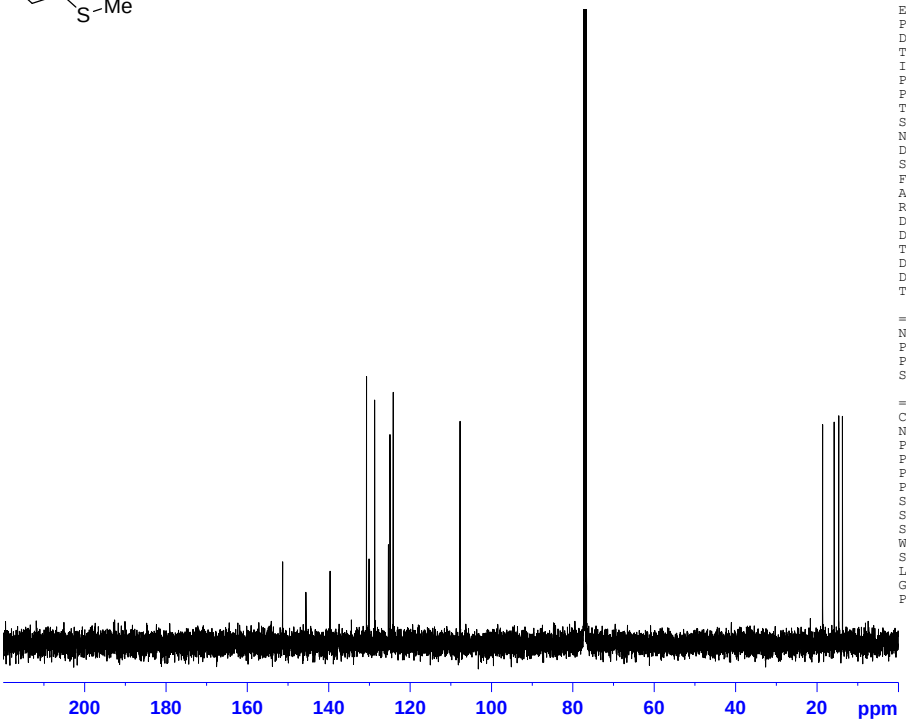





```
NAME       Nov09-2010-56
EXPNO                 1
PROCNO                1
Date_          20101110
Time               4.23
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                161.3
DW               60.400 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz
SI                 32768
SF          400.2000028 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
```

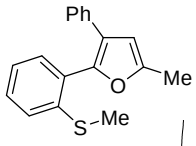


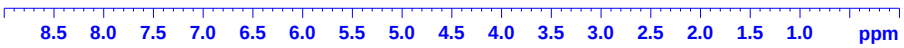



```
NAME       Nov09-2010-56
EXPNO                 2
PROCNO                1
Date_          20101110
Time               4.31
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1        100.6403931 MHz

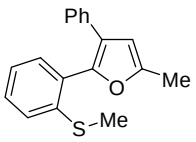
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz
SI                 32768
SF          100.6303718 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```

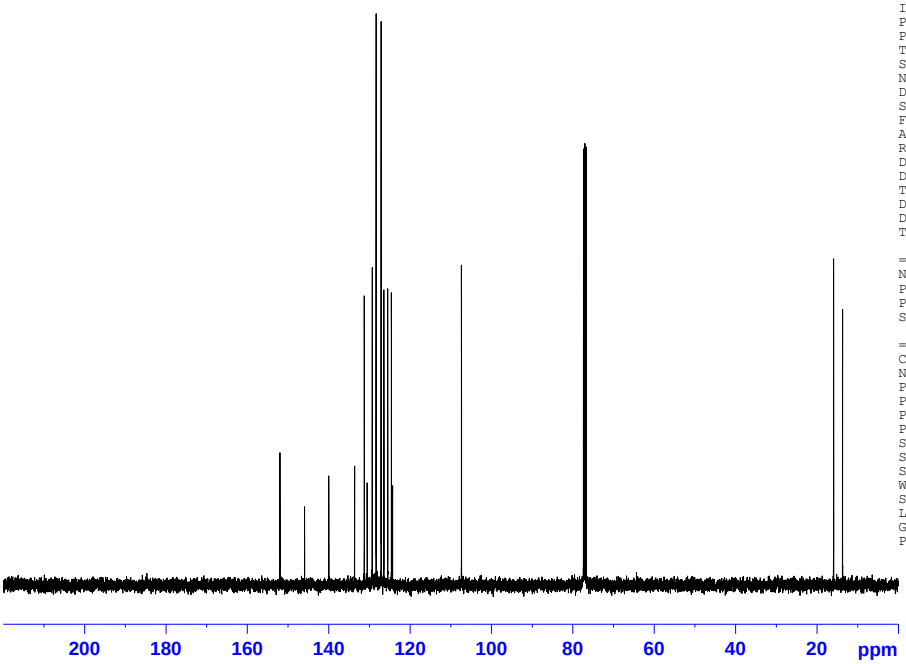





```
NAME          Jul05-2011-25
EXPNO                     1
PROCNO                    1
Date_              20110705
Time                  17.22
INSTRUM               av400
PROBHD    5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH           8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                    45.3
DW                  60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

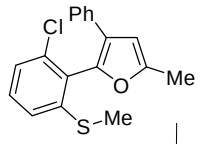


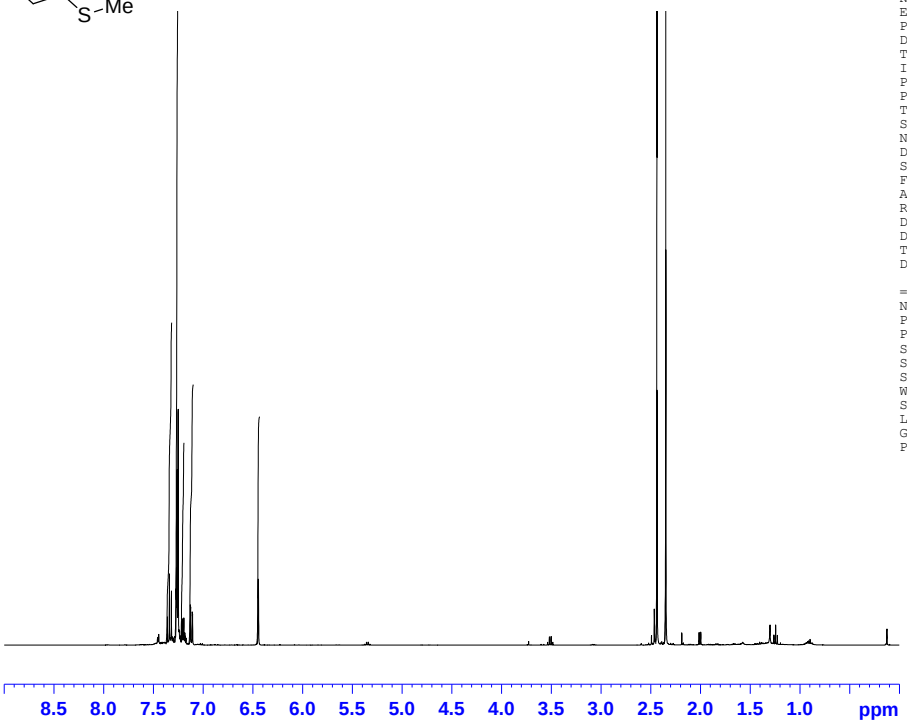



```
NAME          Jul05-2011-25
EXPNO                     2
PROCNO                    1
Date_              20110705
Time                  17.31
INSTRUM               av400
PROBHD    5 mm QNP 1H/13
PULPROG           zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH          26178.010 Hz
FIDRES           0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

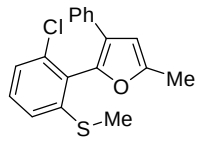
======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz
SI                   32768
SF            100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

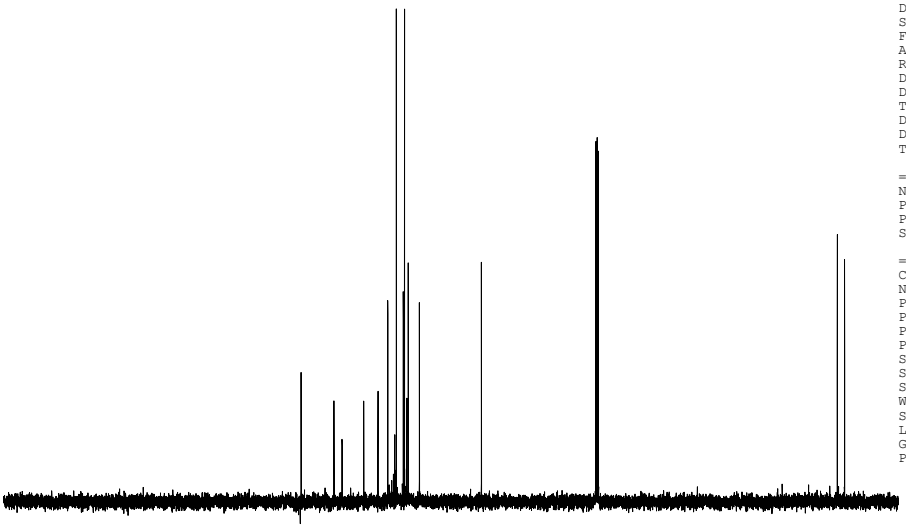


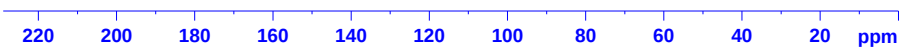



```
NAME          Jan12-2011-59
EXPNO                    1
PROCNO                   1
Date_             20110113
Time                 2.48
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                   40.3
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1         400.2024714 MHz
SI                   32768
SF           400.2000028 MHz
WDW                    EM
SSB                     0
LB                  0.30 Hz
GB                      0
PC                   1.00
```



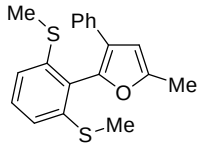





```
NAME          Jan12-2011-59
EXPNO                    2
PROCNO                   1
Date_             20110113
Time                 2.56
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ              0.6259188 sec
RG                   32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                     1

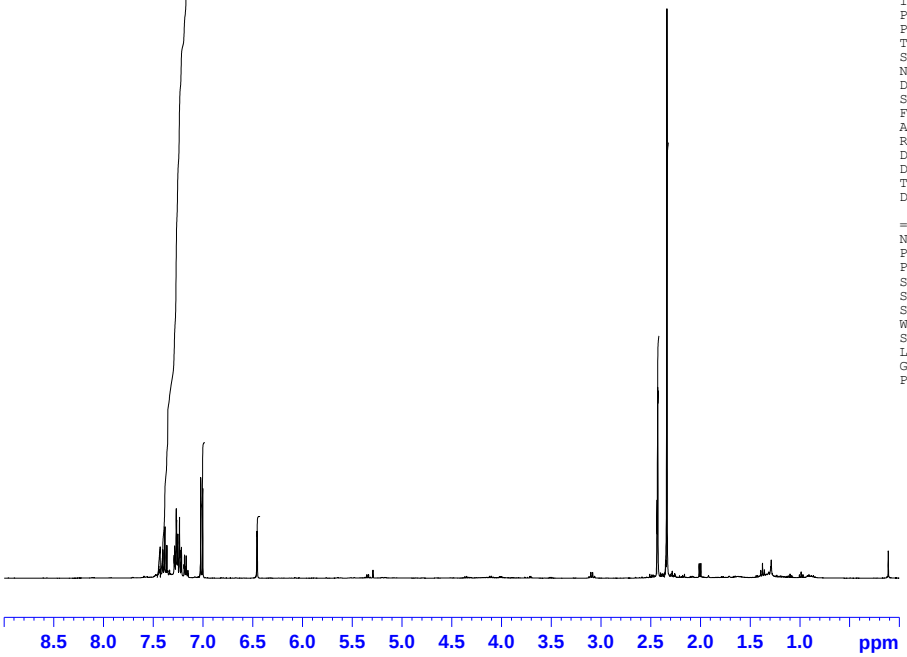
======== CHANNEL f1 ========
NUC1                   13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1        100.6403931 MHz

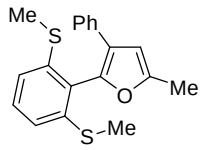
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz
SI                   32768
SF           100.6303718 MHz
WDW                    EM
SSB                     0
LB                  1.00 Hz
GB                      0
PC                   1.40
```




```
NAME        Jan14-2011-19
EXPNO                   1
PROCNO                  1
Date_            20110115
Time                 9.31
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH           8278.146 Hz
FIDRES         0.126314 Hz
AQ            3.9584243 sec
RG                 35.9
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1        400.2024714 MHz
SI                  32768
SF          400.2000028 MHz
WDW                    EM
SSB                     0
LB                  0.30 Hz
GB                      0
PC                   1.00
```

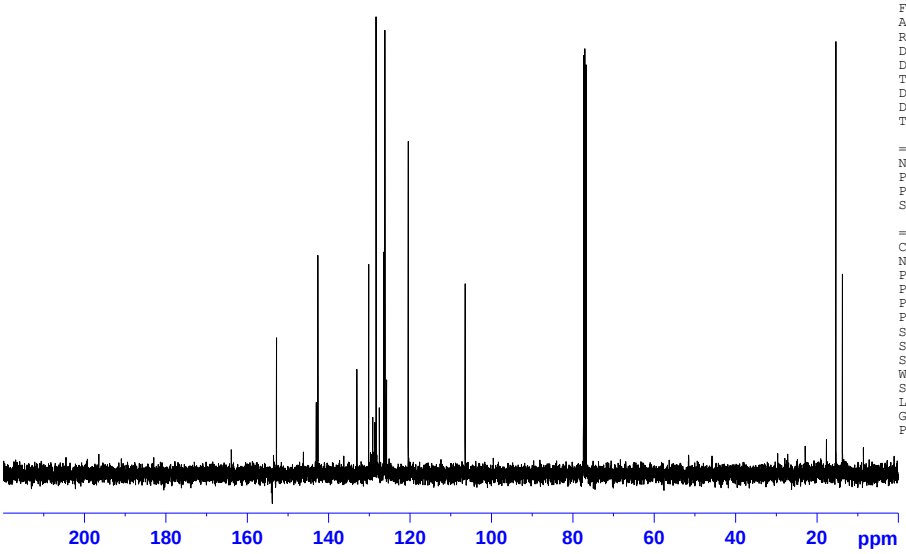


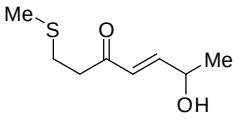



```
NAME        Jan14-2011-19
EXPNO                   2
PROCNO                  1
Date_            20110115
Time                 9.39
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG           zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH          26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                  32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1        100.6403931 MHz

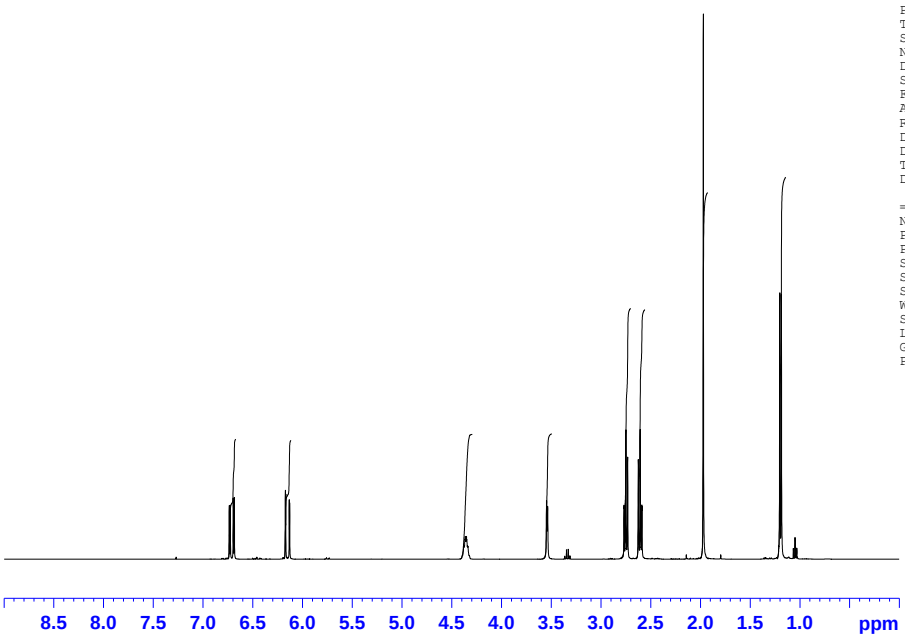
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2        400.2016008 MHz
SI                  32768
SF          100.6303718 MHz
WDW                    EM
SSB                     0
LB                  1.00 Hz
GB                      0
PC                   1.40
```

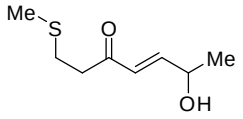





```
NAME       Apr30-2011-50
EXPNO                 1
PROCNO                1
Date_          20110430
Time              15.54
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 14.3
DW               60.400 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

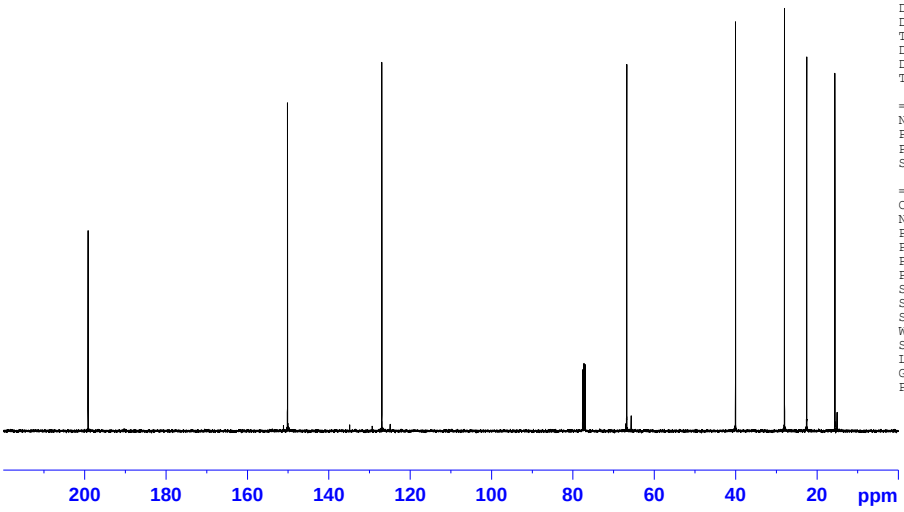


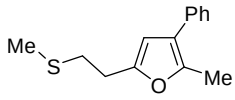



```
NAME       Apr30-2011-50
EXPNO                 2
PROCNO                1
Date_          20110430
Time              16.02
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1       100.6403931 MHz

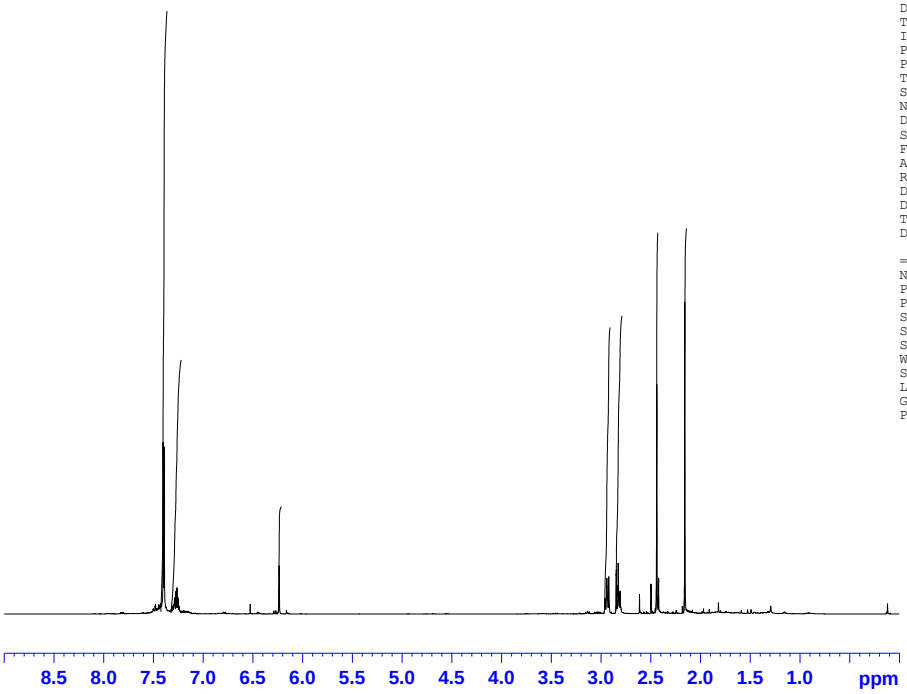
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

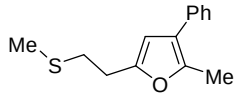





```
NAME       Jul27-2011-58
EXPNO                 1
PROCNO                1
Date_          20110727
Time              21.32
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 35.9
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1          1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

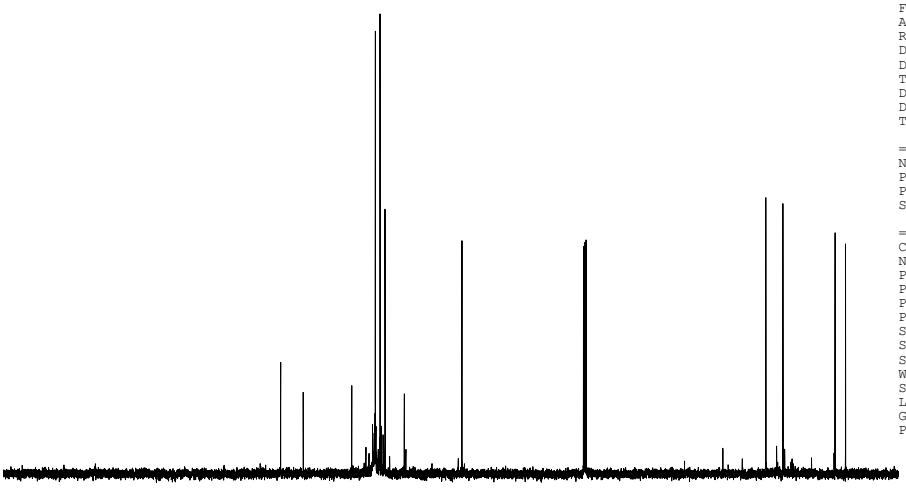


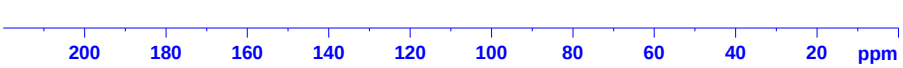


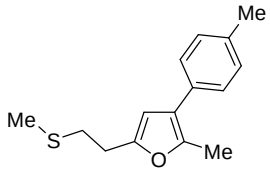

```
NAME       Jul27-2011-58
EXPNO                 2
PROCNO                1
Date_          20110727
Time              21.40
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ             0.6259188 sec
RG                 32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1          1.00000000 sec
D11         0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                0.00 dB
SFO1       100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

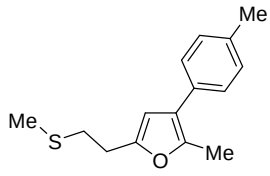







```
NAME       Oct29-2010-12
EXPNO                 1
PROCNO                1
Date_          20101030
Time               1.50
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                 35.9
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

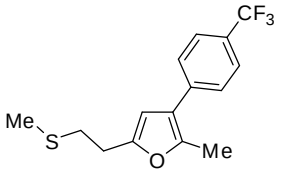
======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz
SI                 32768
SF          400.2000000 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
```

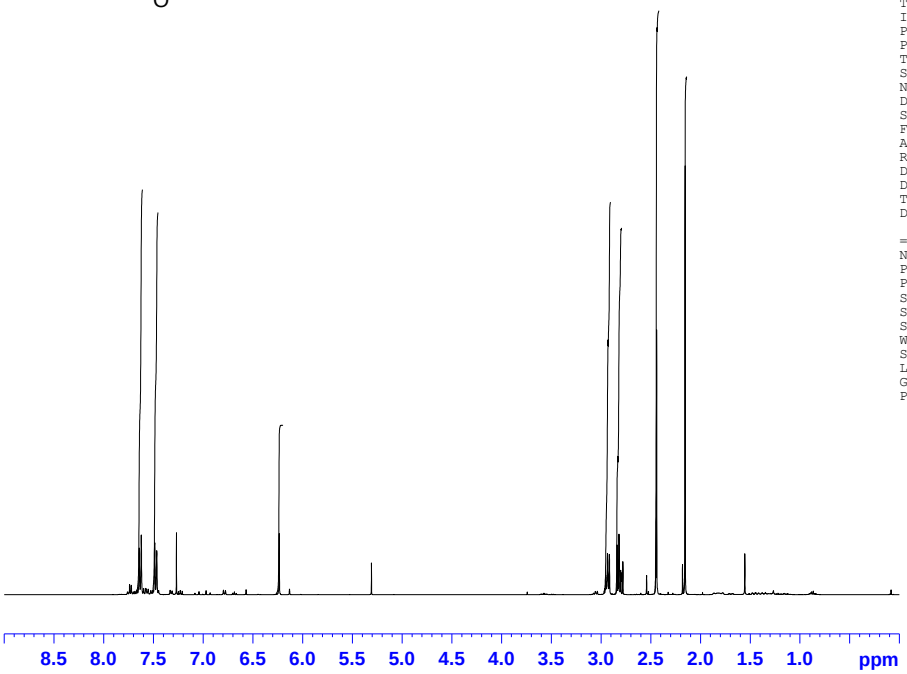



```
NAME       Oct29-2010-12
EXPNO                 3
PROCNO                1
Date_          20101030
Time               2.02
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ              0.6259188 sec
RG                 32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1        100.6403931 MHz

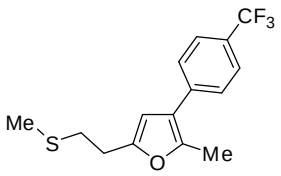
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz
SI                 32768
SF          100.6303300 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```

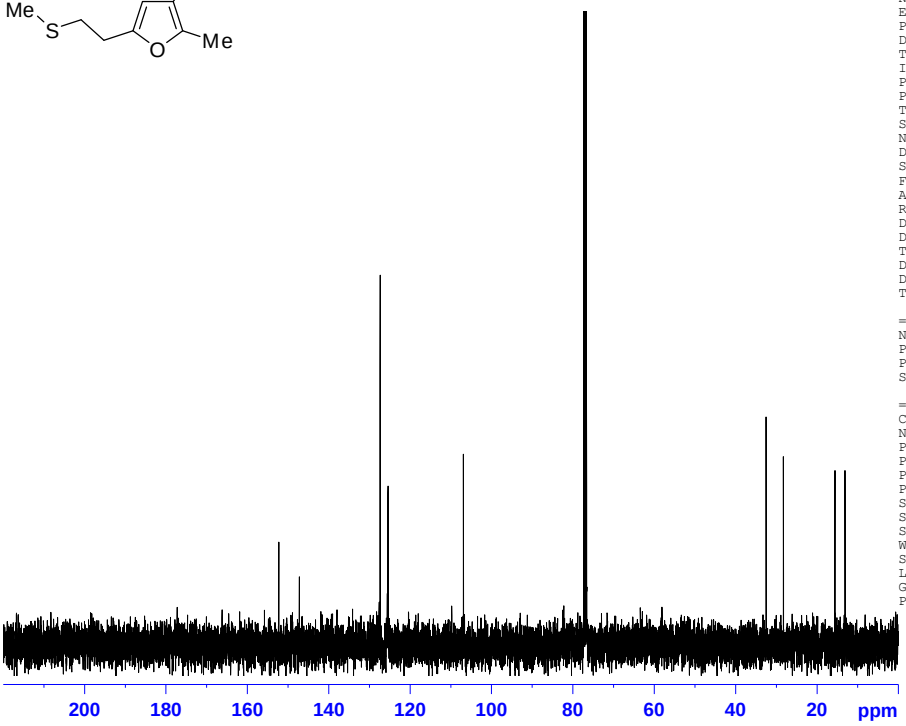





```
NAME          Jun29-2011-17
EXPNO                    1
PROCNO                   1
Date_             20110629
Time                 19.11
INSTRUM              av400
PROBHD    5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                    256
DW                 60.400 usec
DE                  7.50 usec
TE                 300.0 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000028 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

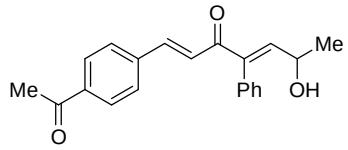


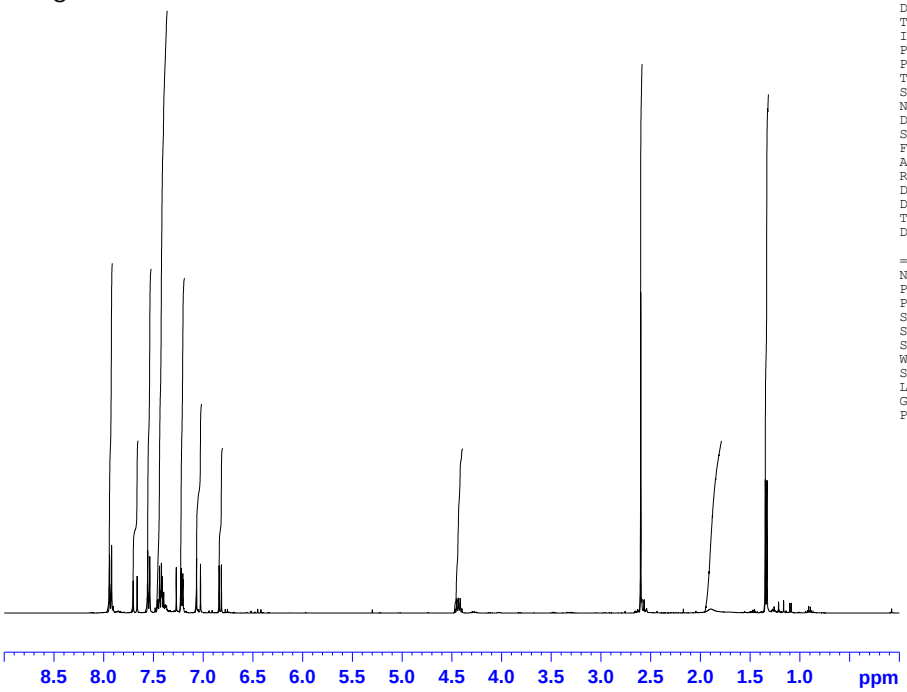



```
NAME          Jun29-2011-17
EXPNO                    2
PROCNO                   1
Date_             20110629
Time                 19.19
INSTRUM              av400
PROBHD    5 mm QNP 1H/13
PULPROG          zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ               0.6259188 sec
RG                    32768
DW                 19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1            1.00000000 sec
D11           0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

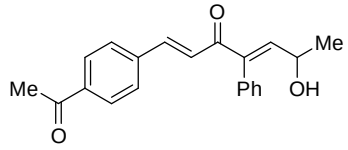
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2          400.2016008 MHz
SI                   32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

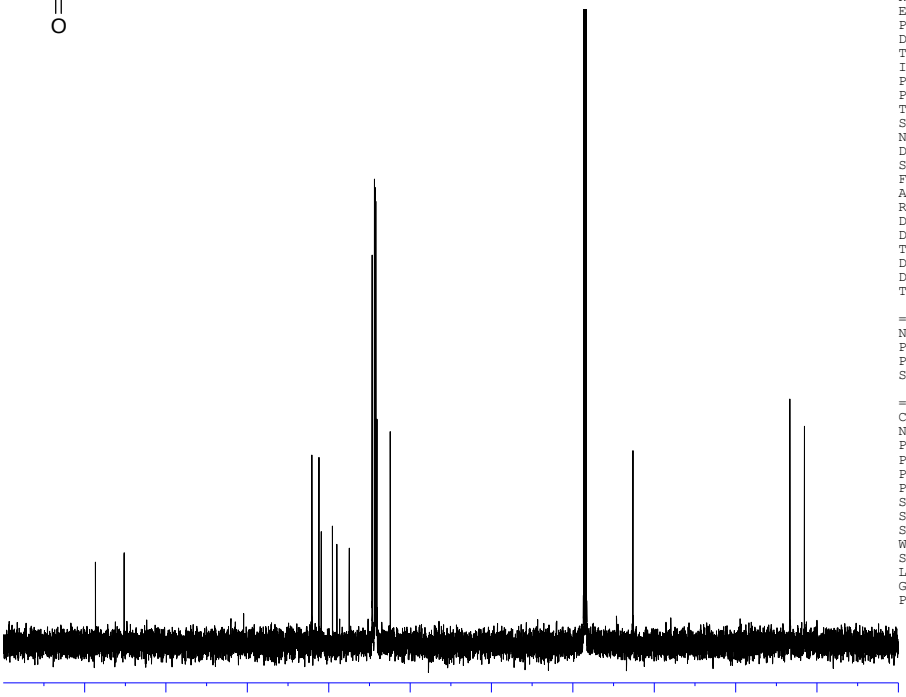


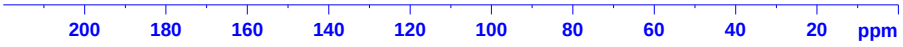



```
NAME          Jan20-2011-24
EXPNO                    1
PROCNO                   1
Date_             20110120
Time                 18.56
INSTRUM              av400
PROBHD    5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                   90.5
DW                 60.400 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000028 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



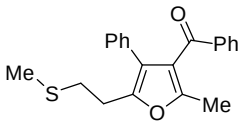


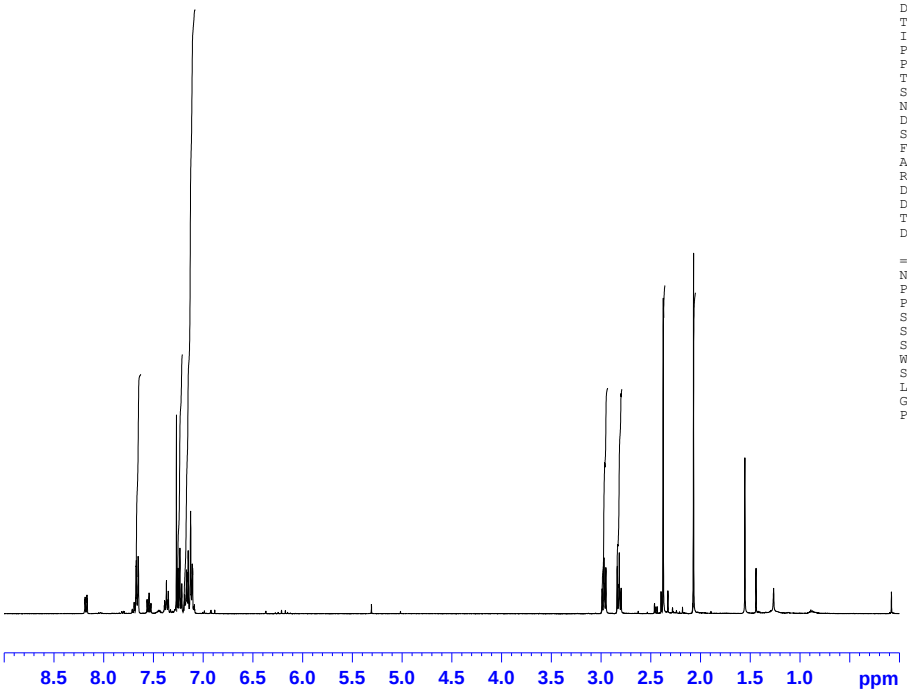



```
NAME          Jan20-2011-24
EXPNO                    2
PROCNO                   1
Date_             20110120
Time                 19.04
INSTRUM              av400
PROBHD    5 mm QNP 1H/13
PULPROG           zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                 19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

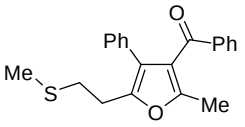
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2          400.2016008 MHz
SI                   32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

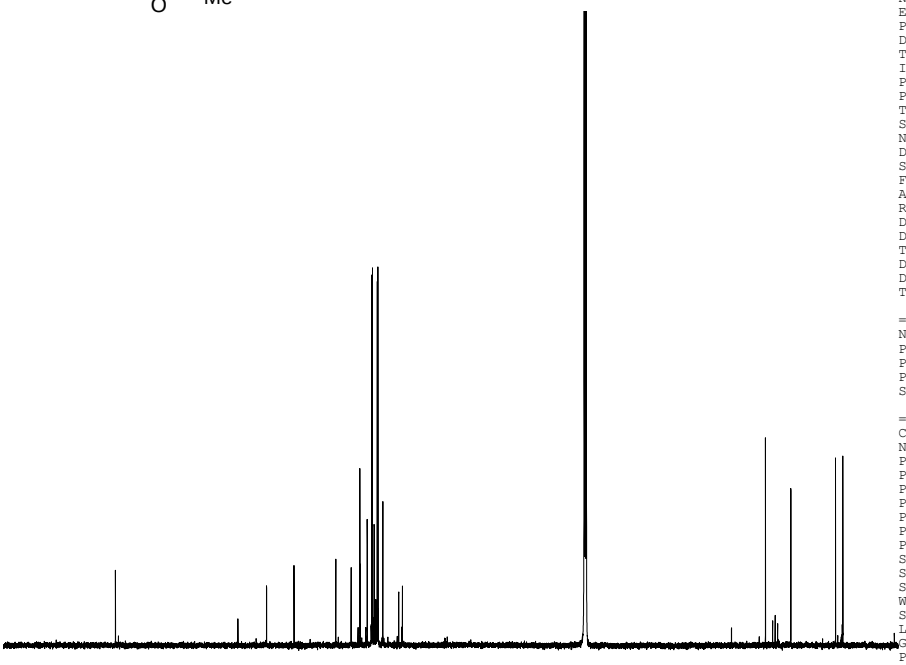


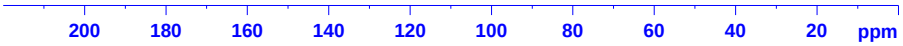



```
NAME          Jul29-2011-7
EXPNO                    1
PROCNO                   1
Date_             20110729
Time                 19.21
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                   574.7
DW                  60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



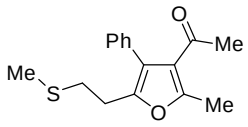


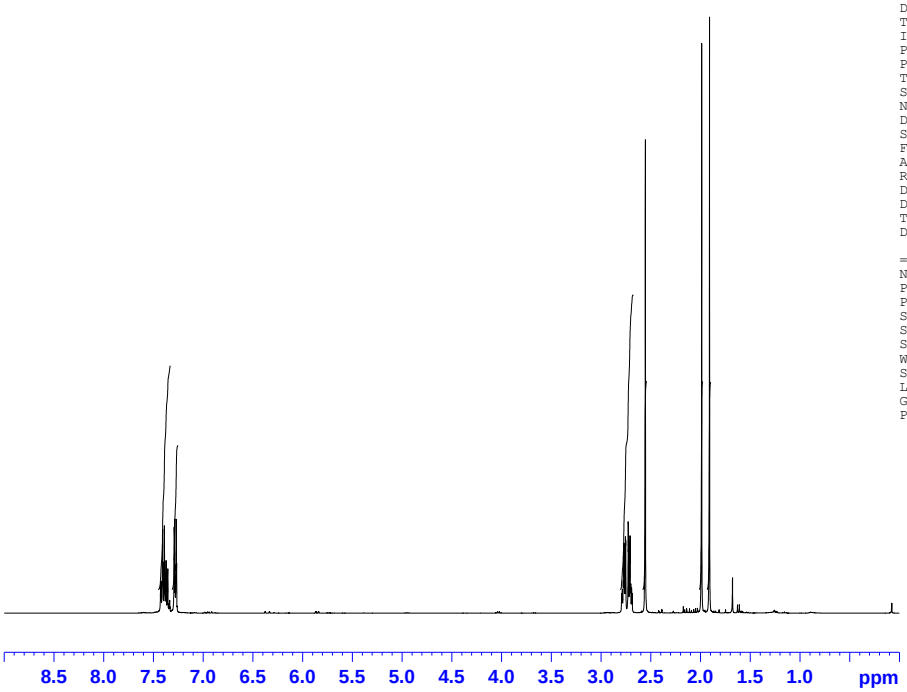



```
NAME          pl53530208
EXPNO                    2
PROCNO                   1
Date_             20110805
Time                 1.12
INSTRUM             avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    2048
DS                       2
SWH              31250.000 Hz
FIDRES           0.476837 Hz
AQ               1.0486259 sec
RG                    1820
DW                  16.000 usec
DE                   20.00 usec
TE                  298.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                   9.10 usec
PL1                 -4.40 dB
PL1W          28.15752029 W
SFO1          125.8131151 MHz

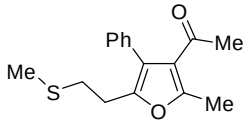
======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -6.00 dB
PL12                 12.42 dB
PL13                 18.42 dB
PL2W          15.19999981 W
PL12W          0.21869738 W
PL13W          0.05493430 W
SFO2          500.3020012 MHz
SI                   32768
SF            125.8005438 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

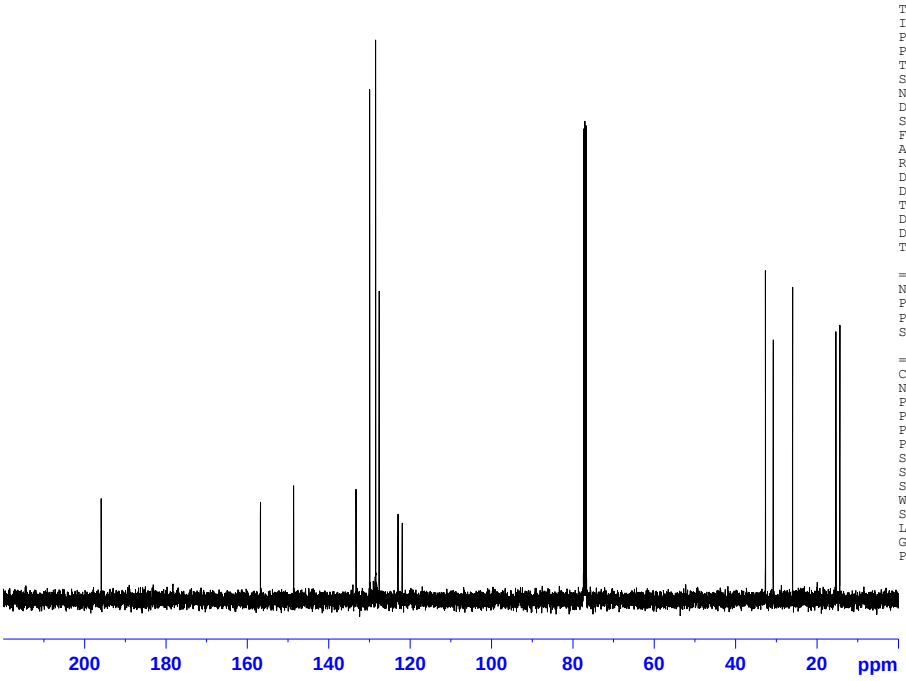




```
NAME       May27-2011-44
EXPNO                 1
PROCNO                1
Date_          20110528
Time              12.55
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 90.5
DW               60.400 usec
DE                7.50 usec
TE                300.0 K
D1          1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

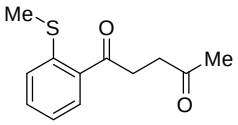





```
NAME       May27-2011-44
EXPNO                 2
PROCNO                1
Date_          20110528
Time              13.03
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG         zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE                300.0 K
D1          1.00000000 sec
D11         0.03000000 sec
TD0                   1

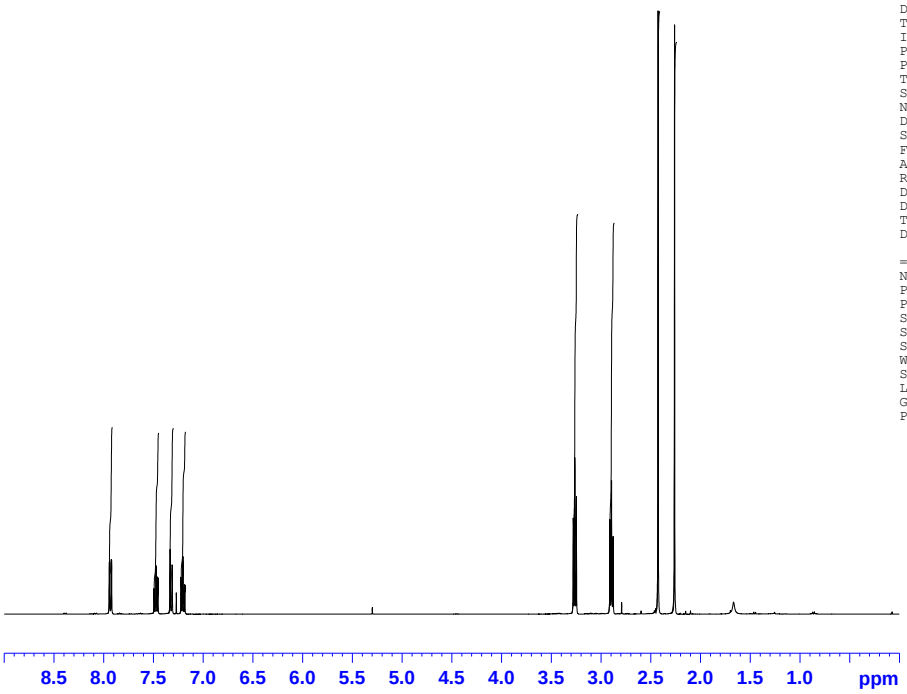
======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1       100.6403931 MHz

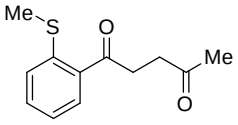
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```




```
NAME       Aug26-2010-24
EXPNO                 1
PROCNO                1
Date_          20100827
Time              15.09
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                  128
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                9.00 usec
PL1               0.00 dB
SFO1        400.2024714 MHz
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

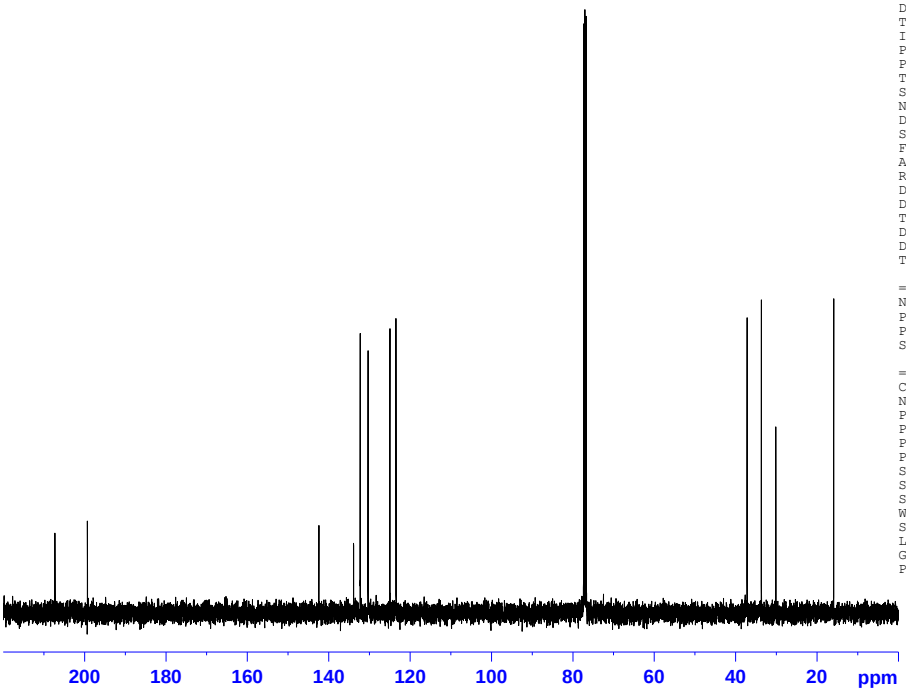


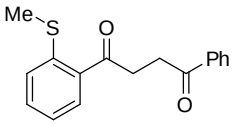


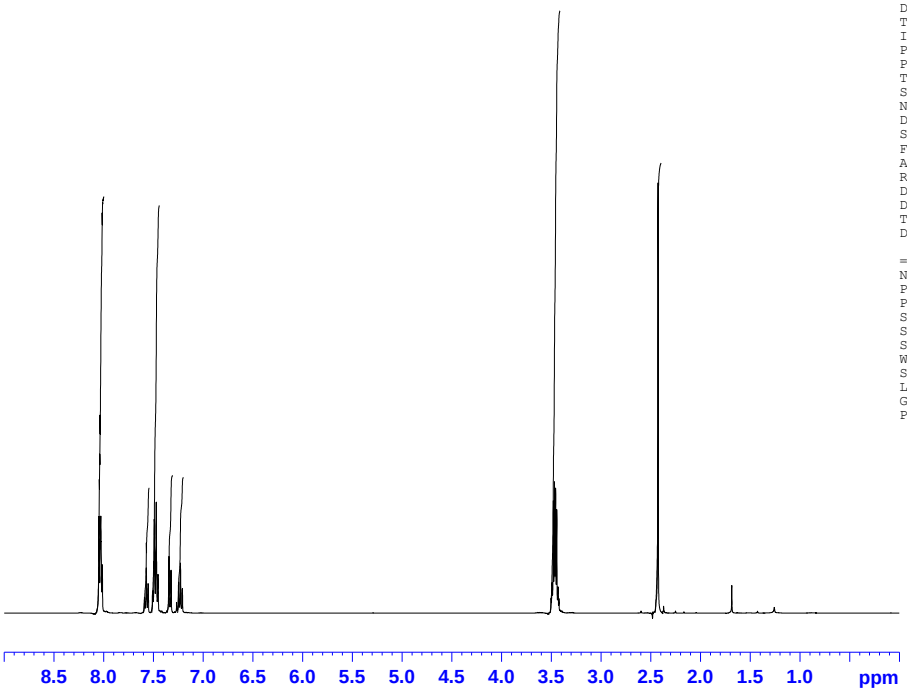

```
NAME       Aug26-2010-24
EXPNO                 2
PROCNO                1
Date_          20100827
Time              15.17
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                9.50 usec
PL1               0.00 dB
SFO1        100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

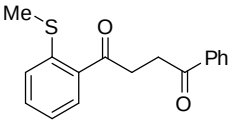


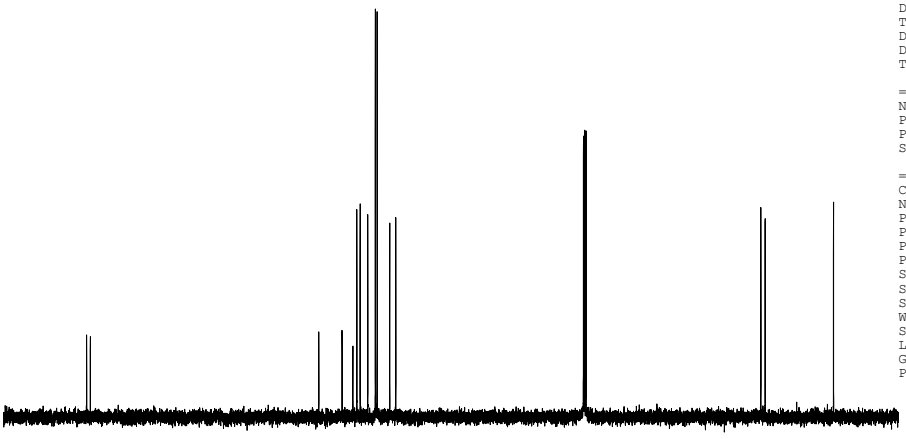


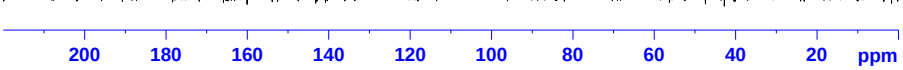



```
NAME       Nov23-2010-28
EXPNO                 1
PROCNO                1
Date_          20101123
Time               9.20
INSTRUM          dpx400
PROBHD   5 mm Dual 1H/1
PULPROG             zg60
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             5592.841 Hz
FIDRES             0.170680 Hz
AQ              2.9295092 sec
RG                  45.3
DW                 89.400 usec
DE                 17.00 usec
TE                 300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                  7.30 usec
PL1                 0.00 dB
SFO1         400.1320007 MHz
SI                 32768
SF           400.1300182 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  0.60
```



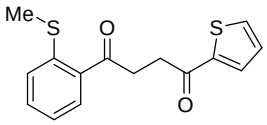





```
NAME       Nov22-2010-44
EXPNO                 2
PROCNO                1
Date_          20101122
Time              18.31
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES             0.798889 Hz
AQ              0.6259188 sec
RG                 32768
DW                 19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                    1

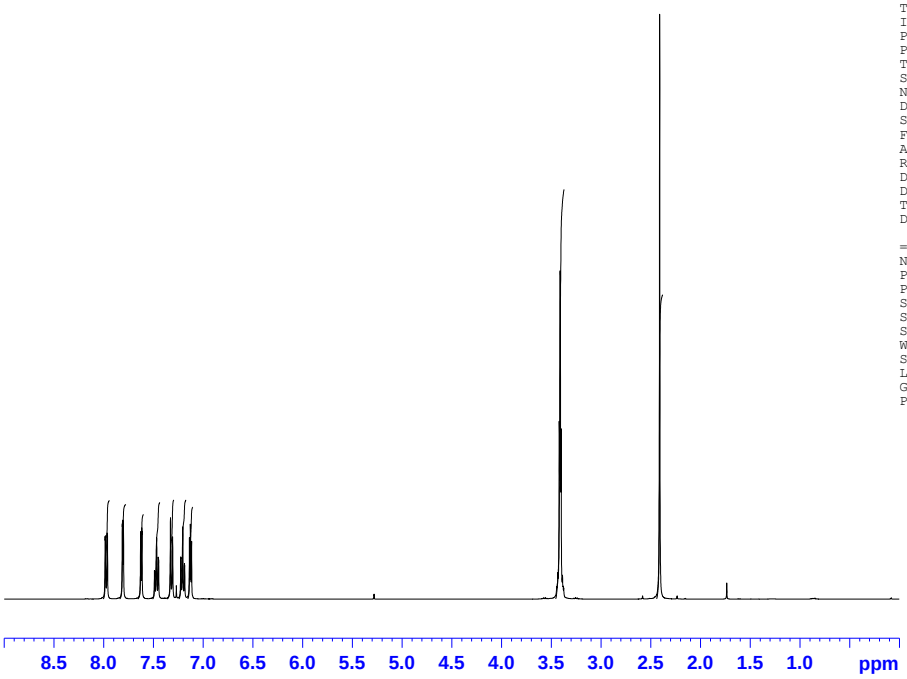
======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1         100.6403931 MHz

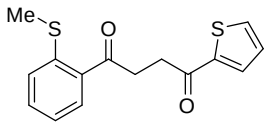
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz
SI                 32768
SF           100.6303718 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```




```
NAME       May10-2011-54
EXPNO                 1
PROCNO                1
Date_          20110511
Time               1.41
INSTRUM          av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 40.3
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

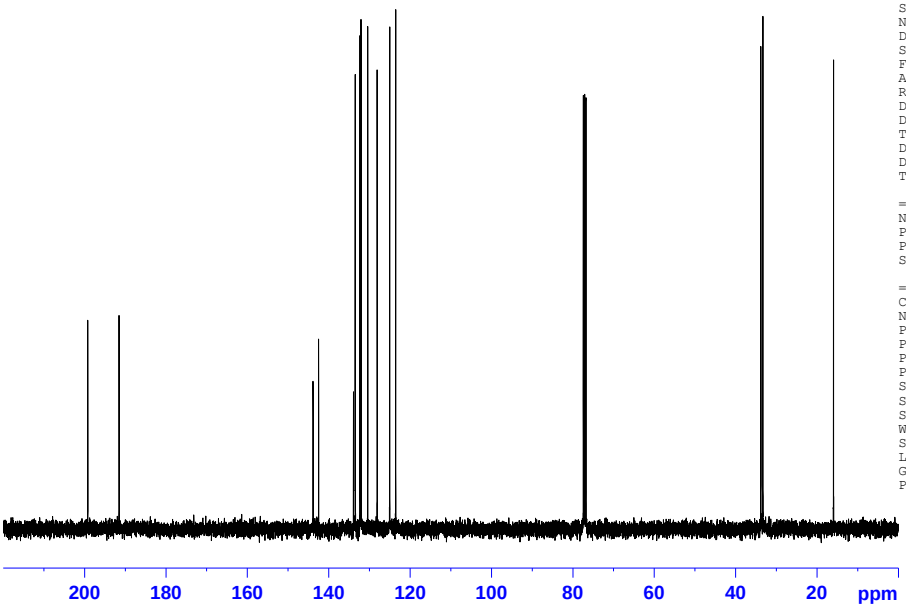


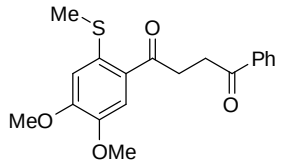


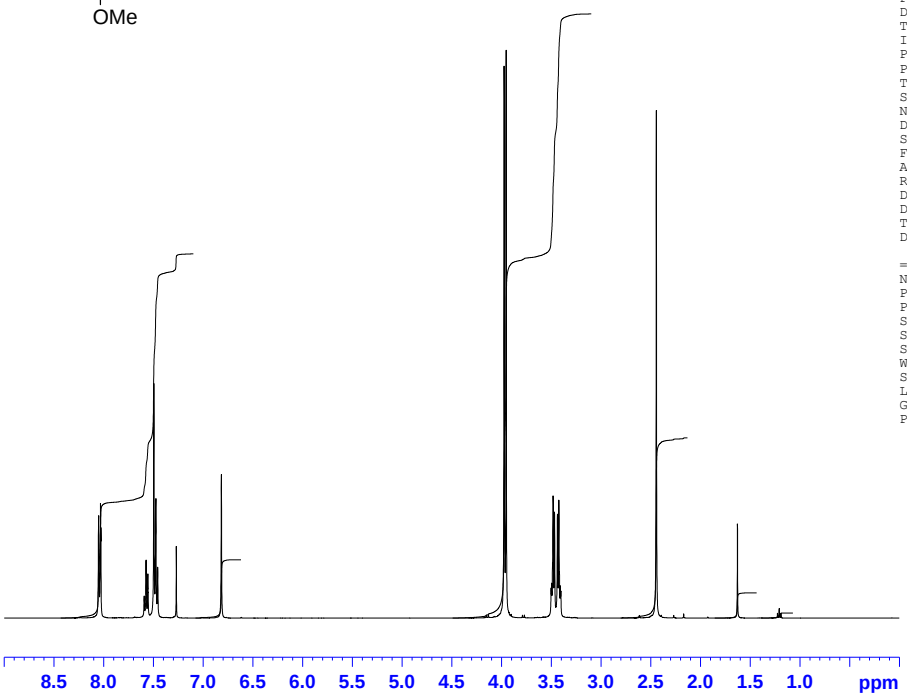

```
NAME       May10-2011-54
EXPNO                 2
PROCNO                1
Date_          20110511
Time               1.49
INSTRUM          av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1       100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

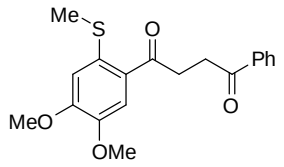


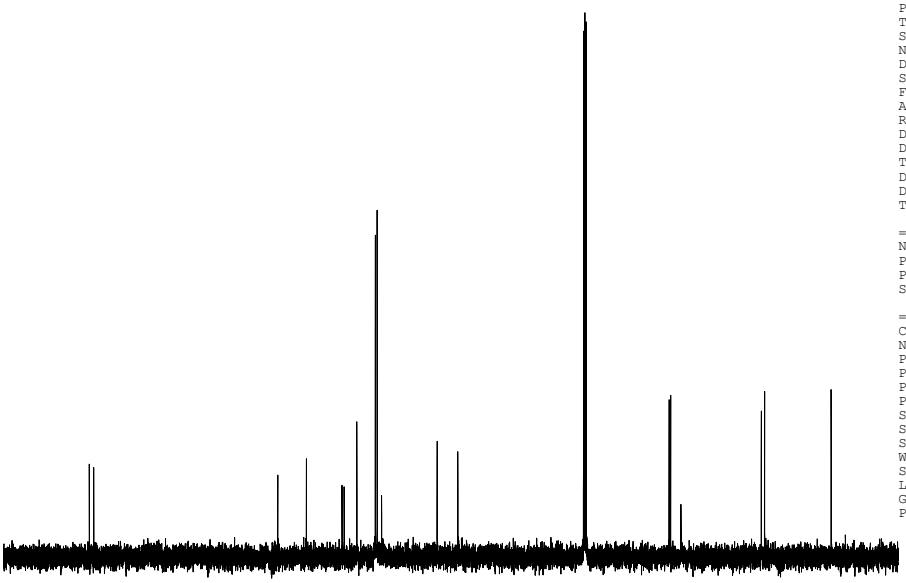


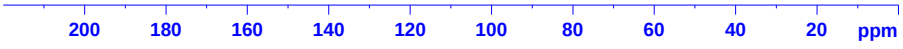



```
NAME       Jan14-2011-18
EXPNO                 1
PROCNO                1
Date_          20110115
Time               9.11
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                  128
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                9.00 usec
PL1               0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000028 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.00
```



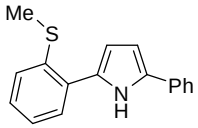


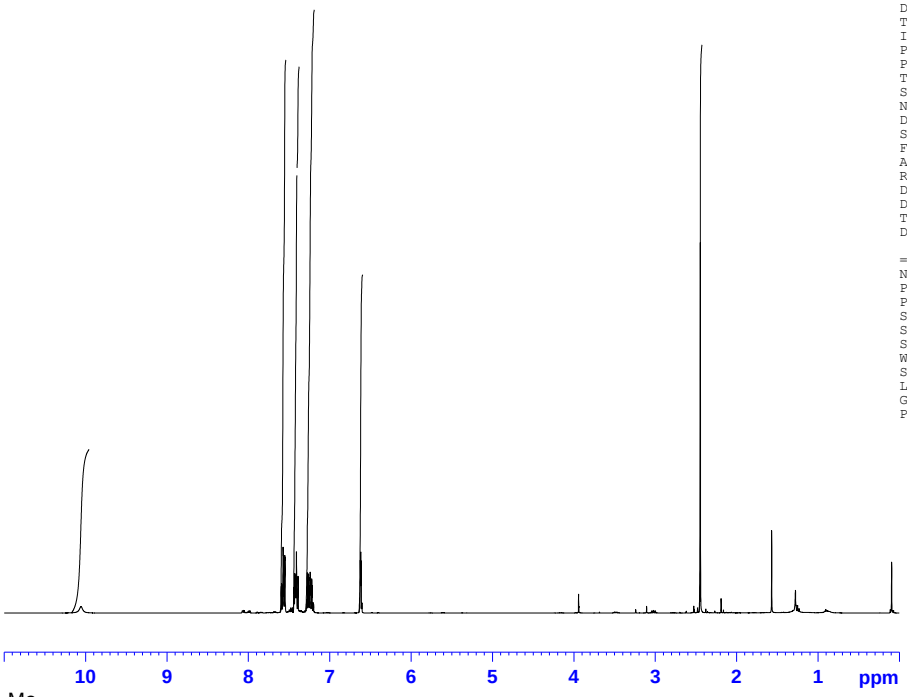



```
NAME       Jan10-2011-11
EXPNO                 2
PROCNO                1
Date_          20110111
Time               6.57
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG         zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                9.50 usec
PL1               0.00 dB
SFO1       100.6403931 MHz

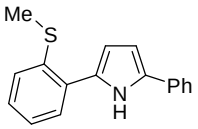
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB                1.00 Hz
GB                    0
PC                1.40
```

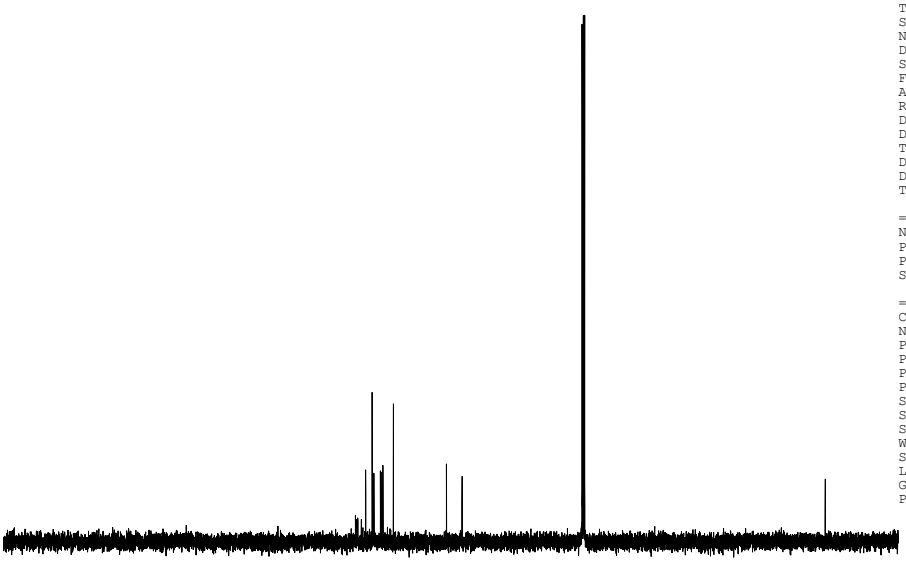




```
NAME       Oct01-2010-59
EXPNO                 1
PROCNO                1
Date_          20101001
Time              22.17
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                  256
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1       400.2024714 MHz
SI               32768
SF         400.2000000 MHz
WDW                 EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.00
```

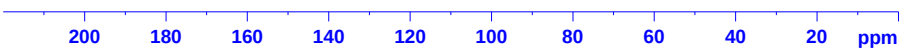


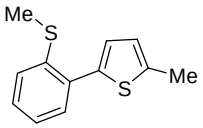


```
NAME       Oct01-2010-59
EXPNO                 2
PROCNO                1
Date_          20101001
Time              22.25
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                0.00 dB
SFO1       100.6403931 MHz

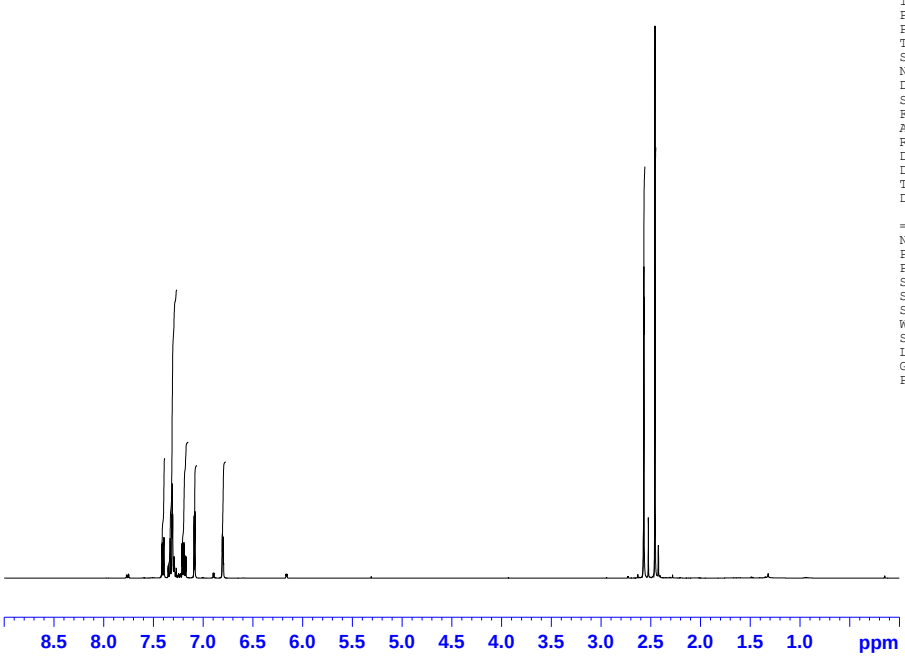
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI               32768
SF         100.6303300 MHz
WDW                 EM
SSB                  0
LB                1.00 Hz
GB                   0
PC                1.40
```

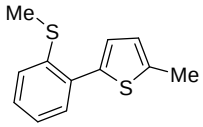





```
NAME       May10-2011-30
EXPNO                 1
PROCNO                1
Date_          20110510
Time              18.42
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 35.9
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

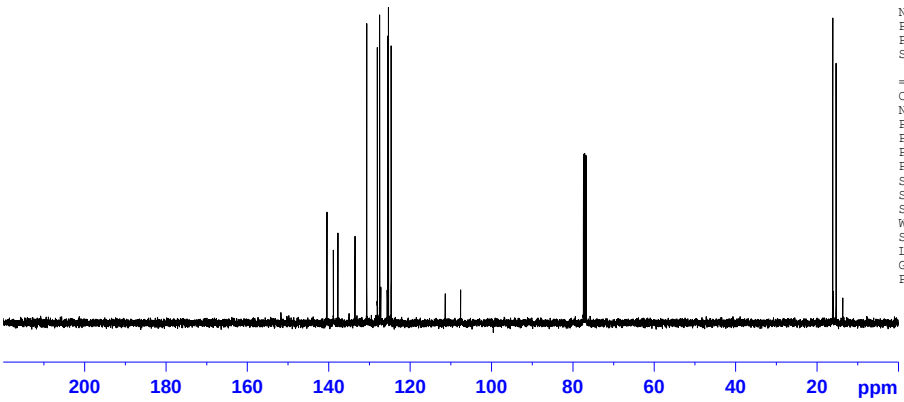


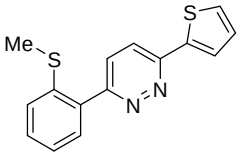


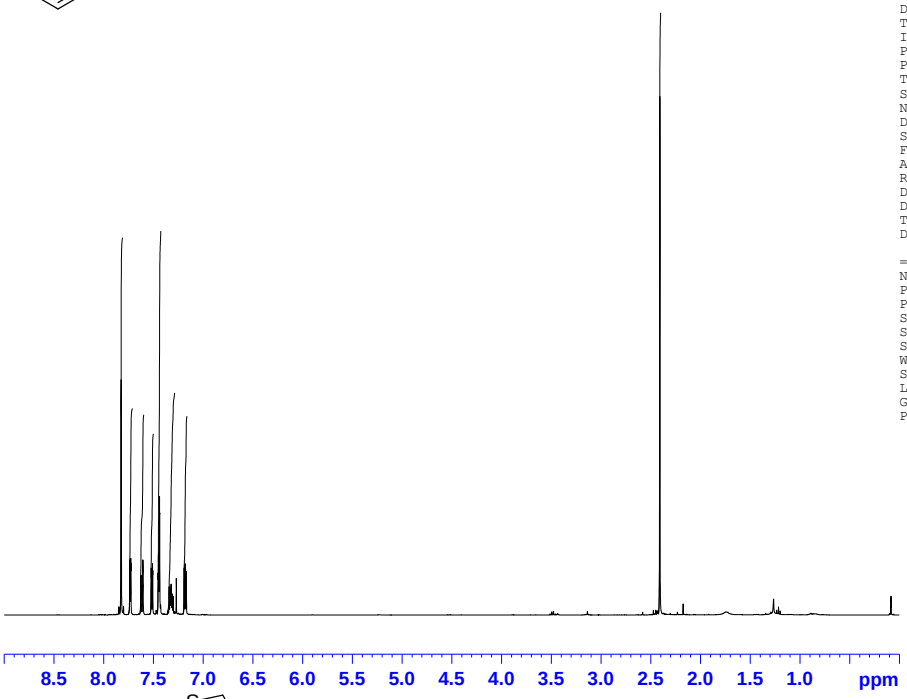

```
NAME       May10-2011-30
EXPNO                 2
PROCNO                1
Date_          20110510
Time              18.50
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                0.00 dB
SFO1       100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

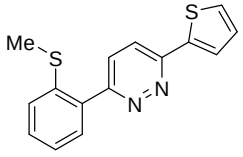


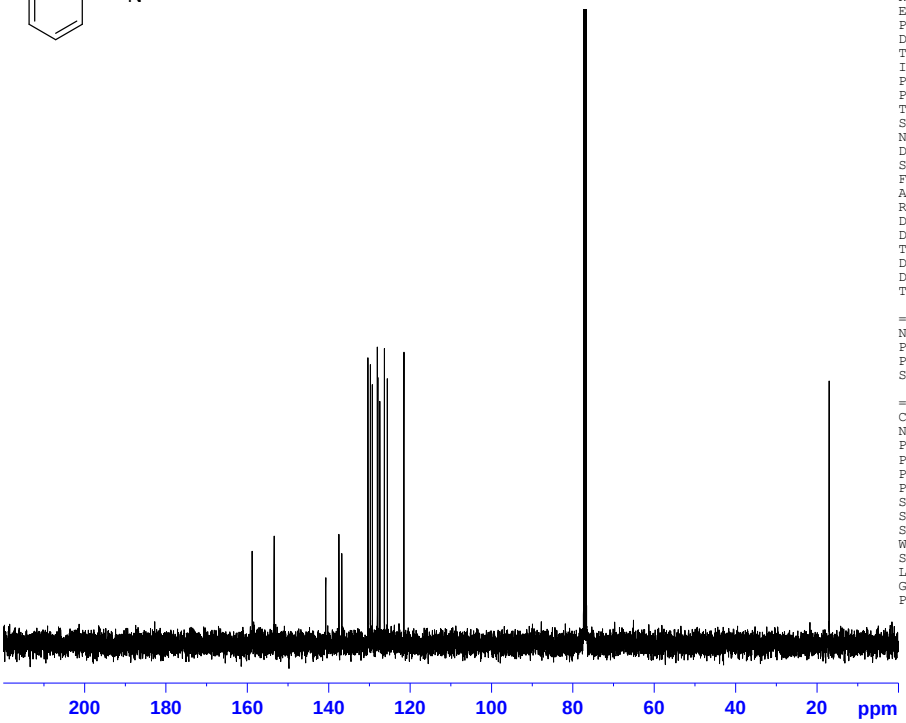





```
NAME         May20-2011-9
EXPNO                   1
PROCNO                  1
Date_            20110520
Time                23.29
INSTRUM           av400
PROBHD    5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                   181
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1         400.2024714 MHz
SI                   32768
SF           400.2000028 MHz
WDW                    EM
SSB                     0
LB                 0.30 Hz
GB                      0
PC                   1.00
```

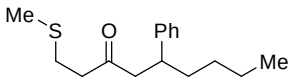


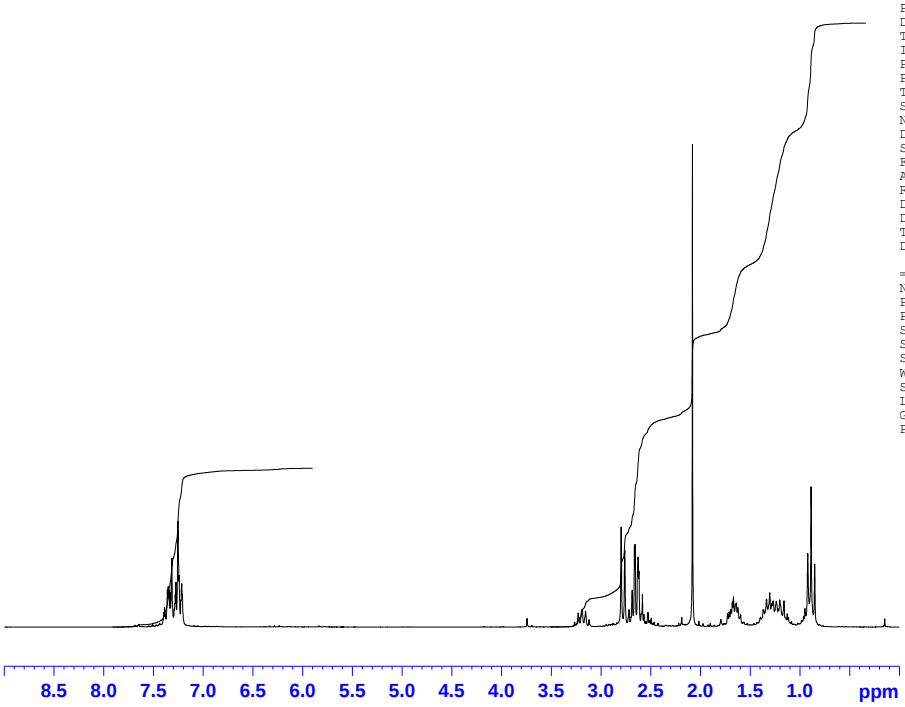



```
NAME         May20-2011-9
EXPNO                   2
PROCNO                  1
Date_            20110520
Time                23.37
INSTRUM           av400
PROBHD    5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ              0.6259188 sec
RG                   32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1         100.6403931 MHz

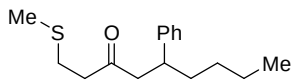
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz
SI                   32768
SF           100.6303718 MHz
WDW                    EM
SSB                     0
LB                 1.00 Hz
GB                      0
PC                   1.40
```

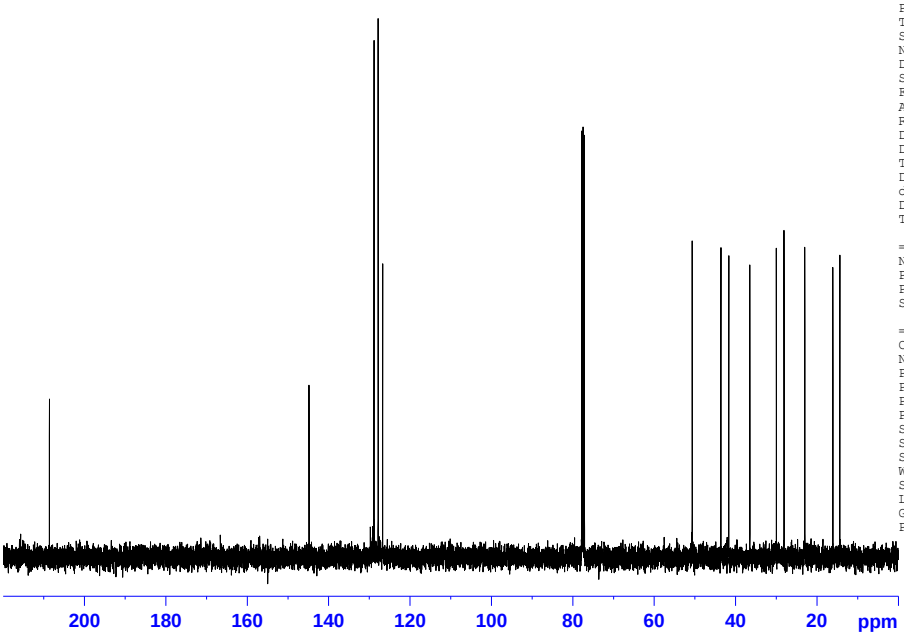





```
NAME       Feb13-2008-18
EXPNO                  1
PROCNO                 1
Date_           20080213
Time               19.24
INSTRUM           dpx200
PROBHD   5 mm Dual 13C/
PULPROG             zg60
TD                 16384
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             2796.421 Hz
FIDRES          0.170680 Hz
AQ              2.9295092 sec
RG                    64
DW               178.800 usec
DE                 6.00 usec
TE                 300.0 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 7.80 usec
PL1                -3.00 dB
SFO1         200.1310007 MHz
SI                 32768
SF           200.1300000 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
```

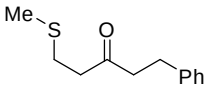


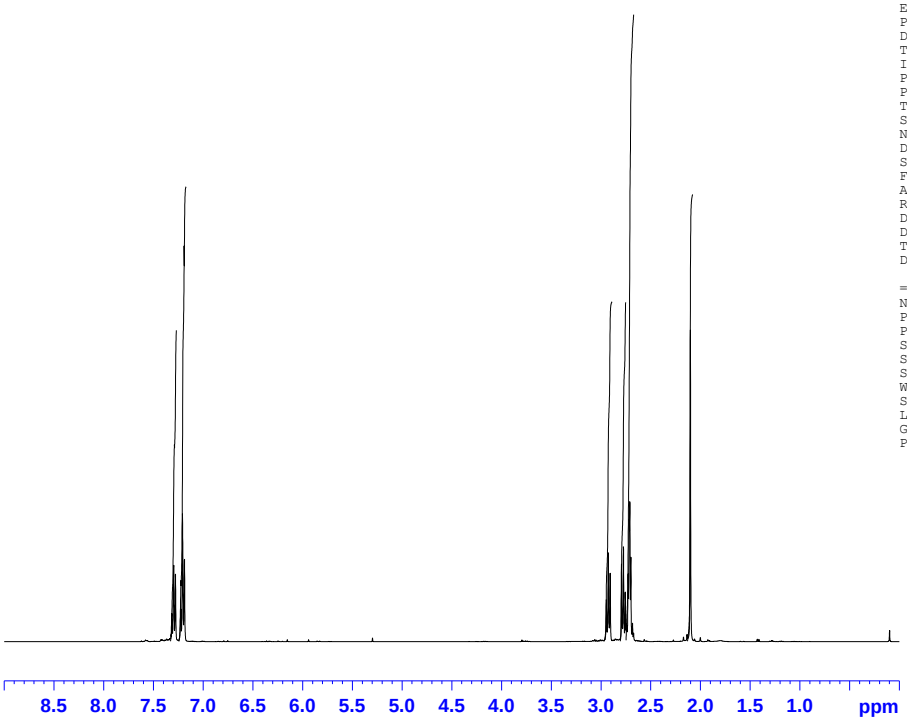



```
NAME       Feb14-2008-48
EXPNO                  1
PROCNO                 1
Date_           20080214
Time               10.58
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ              0.6259188 sec
RG                 32768
DW                19.100 usec
DE                 7.50 usec
TE                 295.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1         100.6403931 MHz

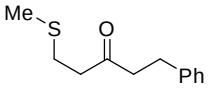
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL12               19.00 dB
PL13               25.00 dB
PL2                 0.00 dB
SFO2         400.2016008 MHz
SI                 32768
SF           100.6303300 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```

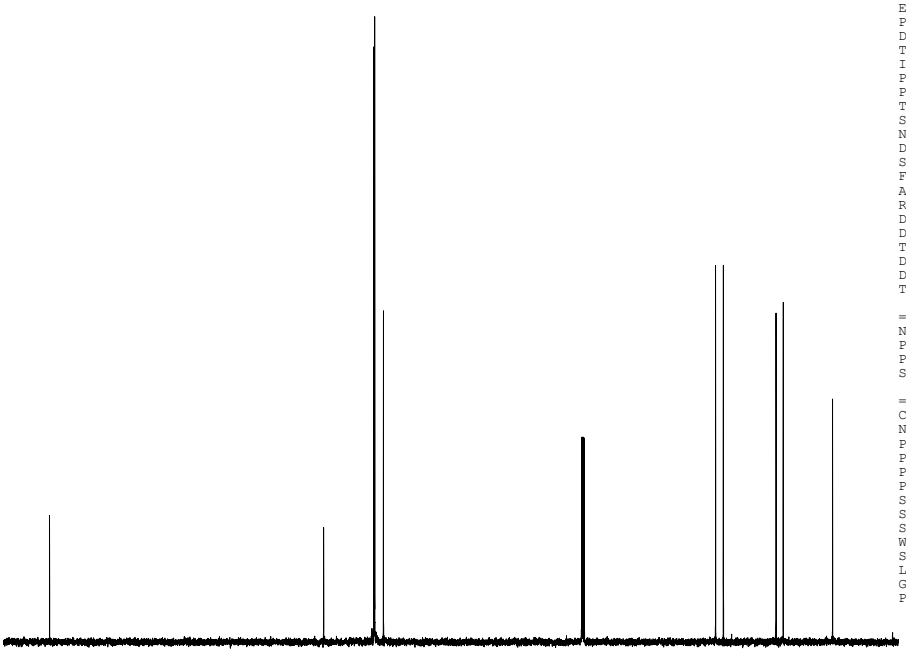


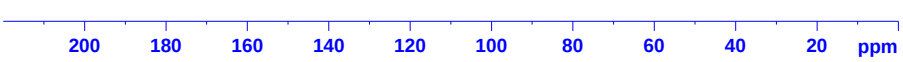



```
NAME          Jul06-2009-37
EXPNO                    1
PROCNO                   1
Date_             20090706
Time                 20.48
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                     35.9
DW                   60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



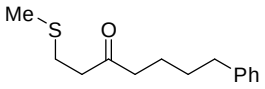





```
NAME          Jul06-2009-37
EXPNO                    2
PROCNO                   1
Date_             20090706
Time                 20.56
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ                0.6259188 sec
RG                   32768
DW                   19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                      1

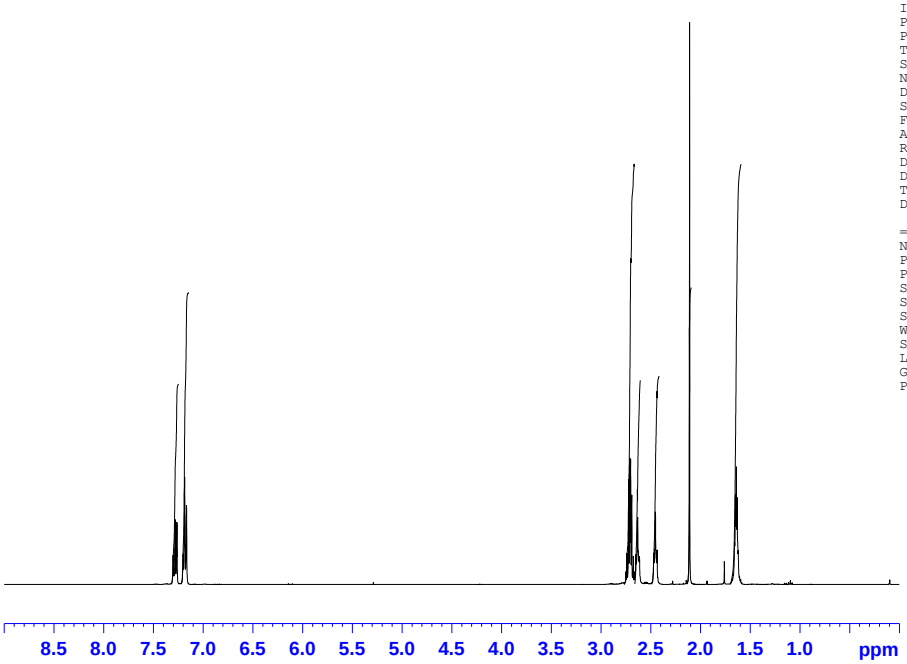
======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1          100.6403931 MHz

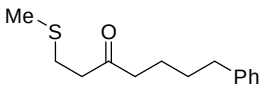
======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2          400.2016008 MHz
SI                   32768
SF            100.6303300 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```




```
NAME       May30-2011-54
EXPNO                 1
PROCNO                1
Date_          20110531
Time               0.49
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 28.5
DW               60.400 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

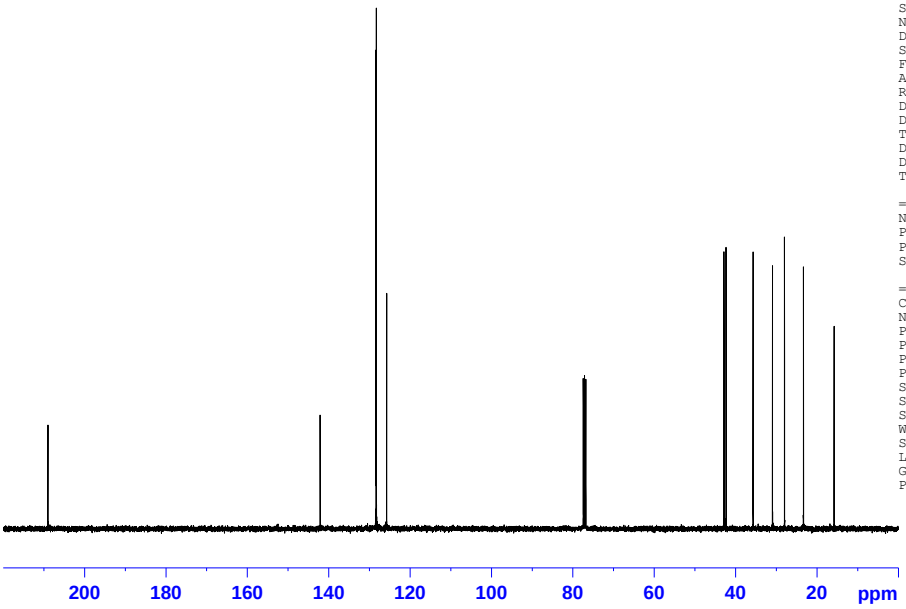


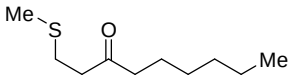


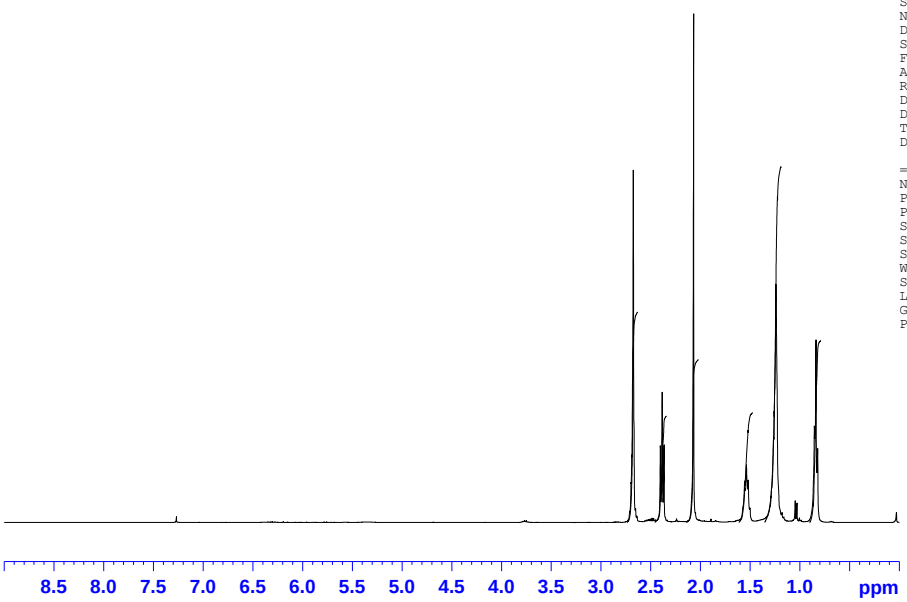

```
NAME       May30-2011-54
EXPNO                 2
PROCNO                1
Date_          20110531
Time               0.58
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1       100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

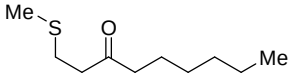


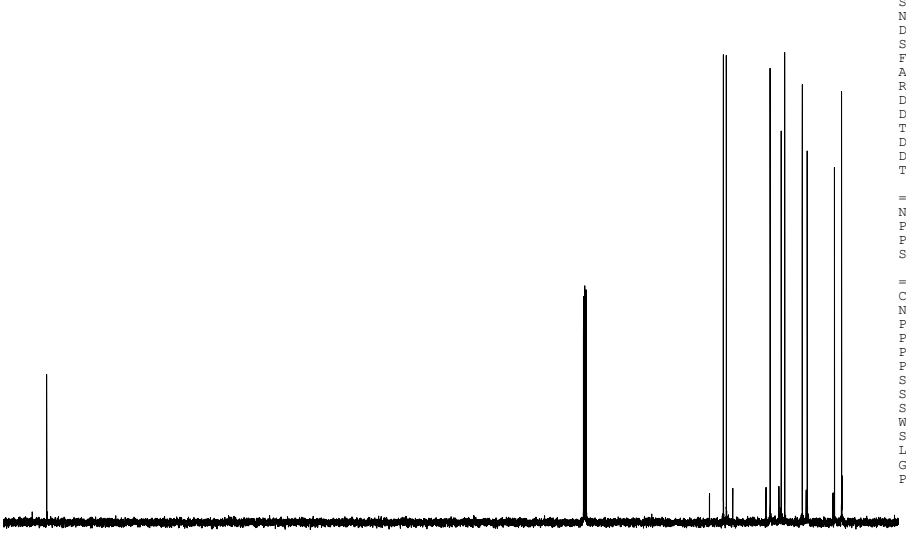




```
NAME          May31-2011-3
EXPNO                    1
PROCNO                   1
Date_             20110601
Time                 5.04
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                   22.6
DW                 60.400 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000028 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

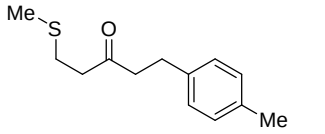





```
NAME          May31-2011-3
EXPNO                    2
PROCNO                   1
Date_             20110601
Time                 5.14
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG          zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                 19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                     1

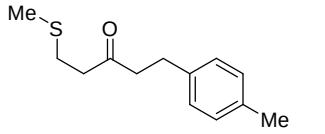
======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz
SI                   32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```




```
NAME       Jul26-2011-13
EXPNO                 1
PROCNO                1
Date_          20110726
Time              19.53
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 90.5
DW               60.400 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec

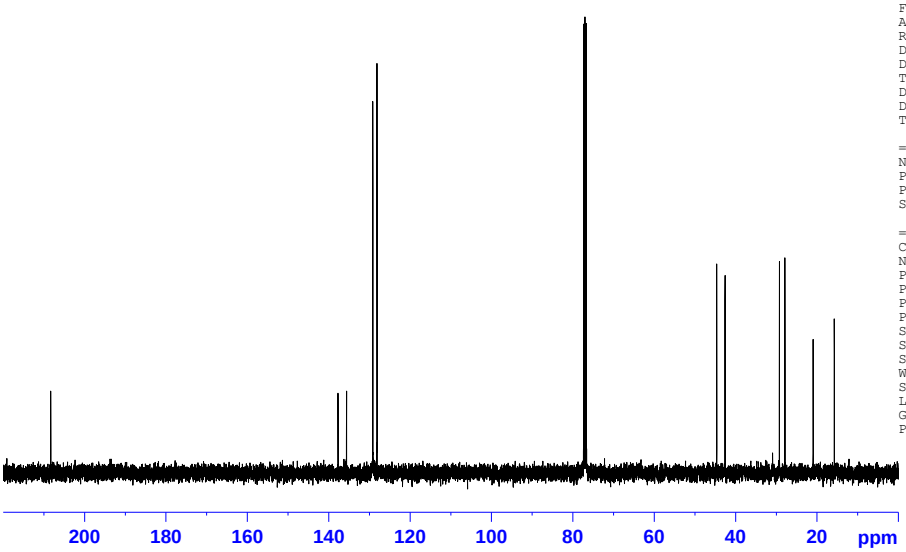
======== CHANNEL f1 ========
NUC1                1H
P1                9.00 usec
PL1               0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000028 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.00
```

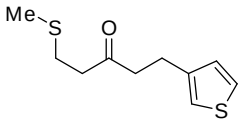


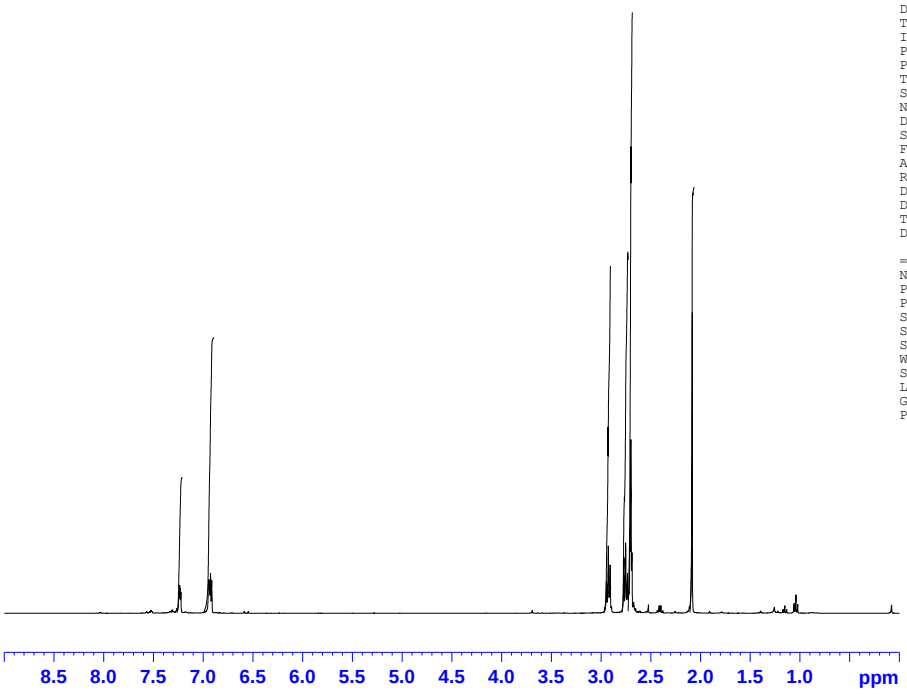

```
NAME       Jul26-2011-13
EXPNO                 2
PROCNO                1
Date_          20110726
Time              20.01
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1               13C
P1                9.50 usec
PL1               0.00 dB
SFO1       100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2            80.00 usec
PL2               0.00 dB
PL12             19.00 dB
PL13             25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB                1.00 Hz
GB                    0
PC                1.40
```

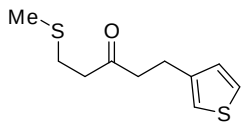


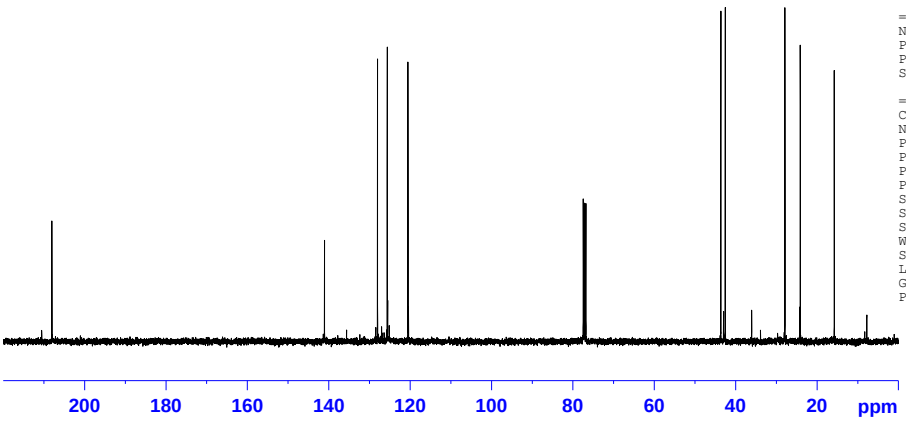





```
NAME          Jun01-2011-5
EXPNO                    1
PROCNO                   1
Date_             20110602
Time                 7.25
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                     32
DW                 60.400 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1          400.2024714 MHz
SI                  32768
SF            400.2000028 MHz
WDW                    EM
SSB                     0
LB                  0.30 Hz
GB                      0
PC                   1.00
```

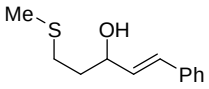


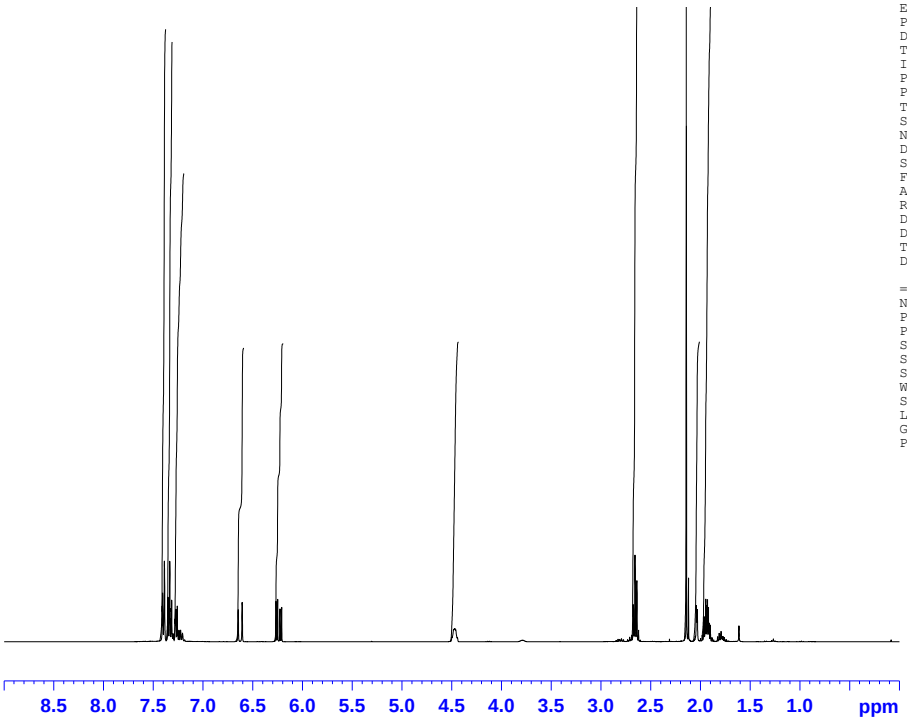



```
NAME          Jun01-2011-5
EXPNO                    2
PROCNO                   1
Date_             20110602
Time                 7.34
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG           zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ               0.6259188 sec
RG                  32768
DW                 19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1          100.6403931 MHz

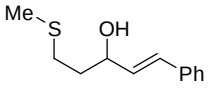
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz
SI                  32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

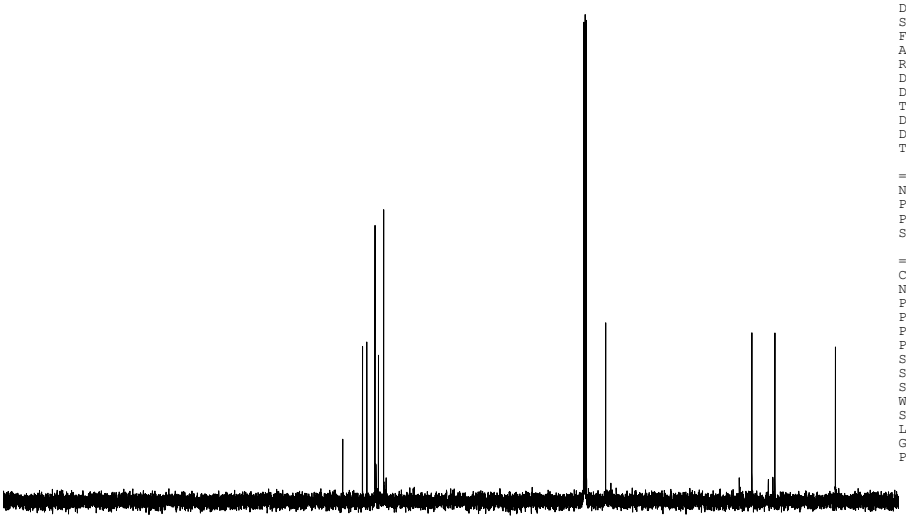


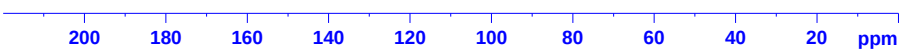



```
NAME       Jul29-2011-59
EXPNO                 1
PROCNO                1
Date_          20110729
Time              15.56
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                  128
DW               60.400 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                1H
P1               9.00 usec
PL1              0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000028 MHz
WDW                  EM
SSB                   0
LB               0.30 Hz
GB                    0
PC                 1.00
```



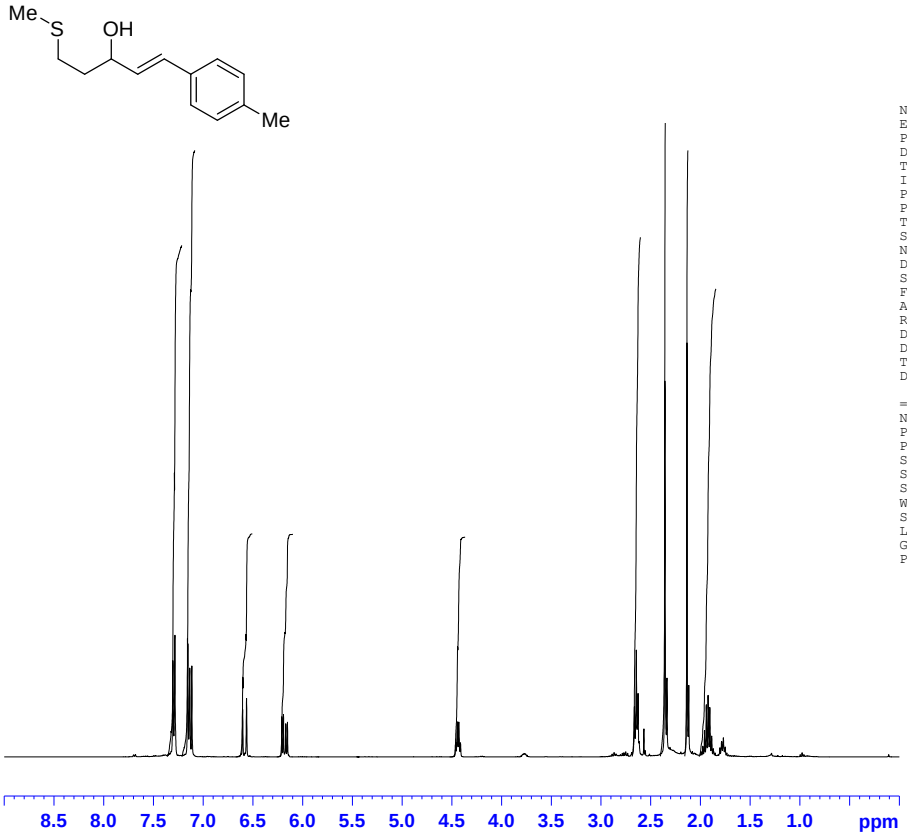





```
NAME       Jul29-2011-59
EXPNO                 2
PROCNO                1
Date_          20110729
Time              16.05
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

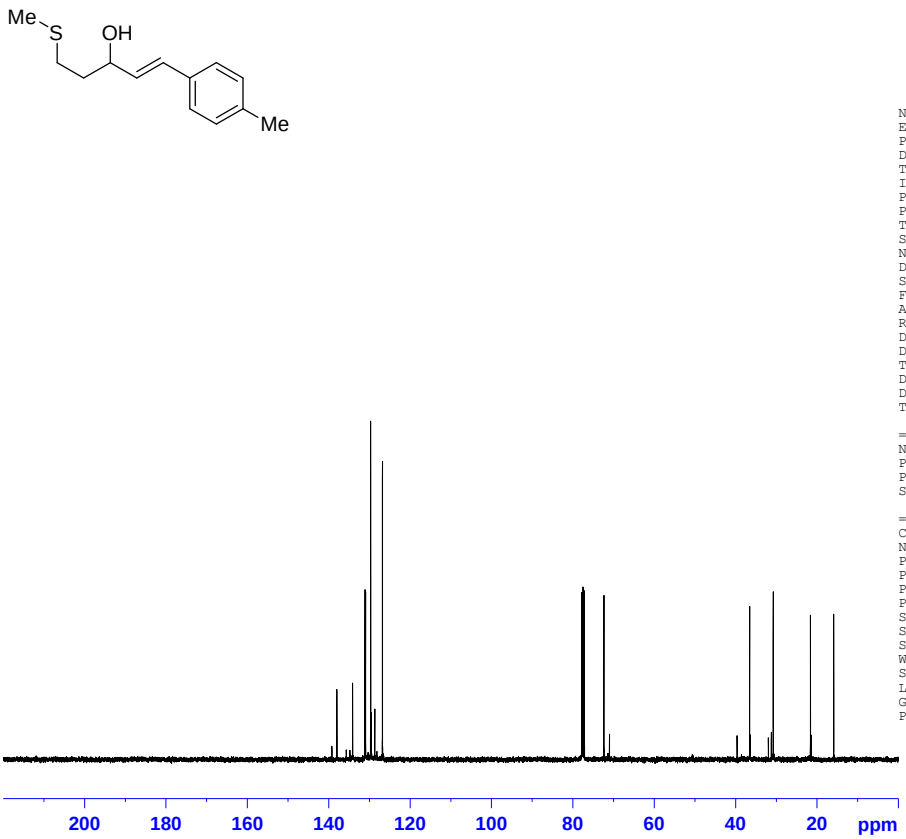
======== CHANNEL f1 ========
NUC1                13C
P1               9.50 usec
PL1              0.00 dB
SFO1       100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2            80.00 usec
PL2               0.00 dB
PL12             19.00 dB
PL13             25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB               1.00 Hz
GB                    0
PC                 1.40
```




```
NAME       Dec16-2009-31
EXPNO                 1
PROCNO                1
Date_          20091216
Time              17.38
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES         0.126314 Hz
AQ             3.9584243 sec
RG                 35.9
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

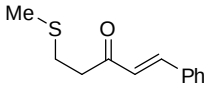
======== CHANNEL f1 ========
NUC1                1H
P1                9.00 usec
PL1               0.00 dB
SFO1        400.2024714 MHz
SI                32768
SF          400.2000000 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.00
```

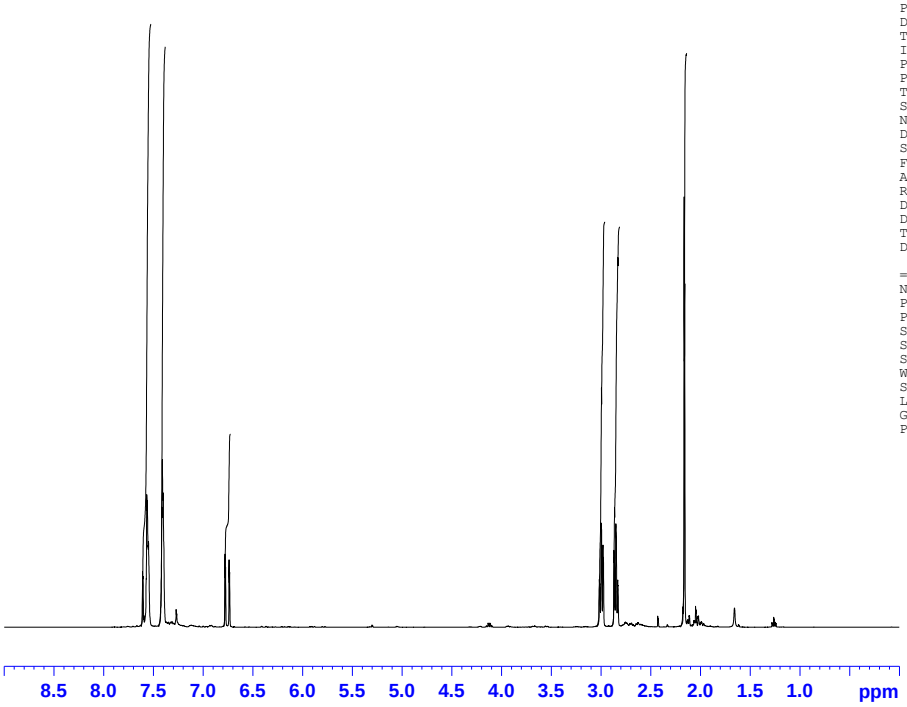



```
NAME       Dec16-2009-31
EXPNO                 2
PROCNO                1
Date_          20091216
Time              17.45
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH            26178.010 Hz
FIDRES         0.798889 Hz
AQ             0.6259188 sec
RG                32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                9.50 usec
PL1               0.00 dB
SFO1        100.6403931 MHz

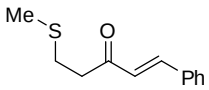
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2             80.00 usec
PL2               0.00 dB
PL12             19.00 dB
PL13             25.00 dB
SFO2        400.2016008 MHz
SI                32768
SF          100.6303300 MHz
WDW                  EM
SSB                   0
LB                1.00 Hz
GB                    0
PC                1.40
```

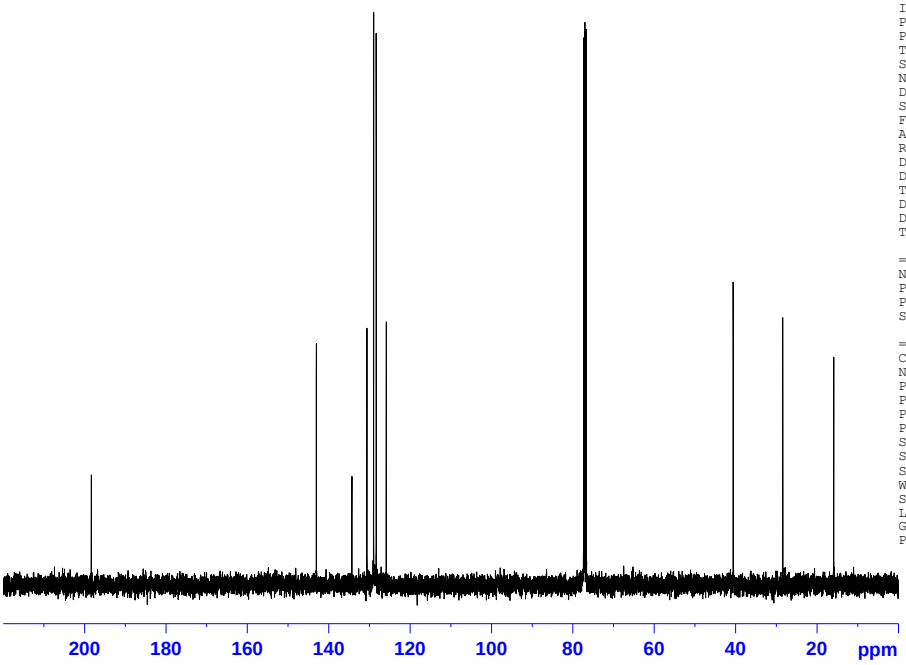





```
NAME       Nov08-2010-26
EXPNO                 1
PROCNO                1
Date_          20101108
Time              17.30
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 90.5
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1       400.2024714 MHz
SI               32768
SF         400.2000028 MHz
WDW                 EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.00
```

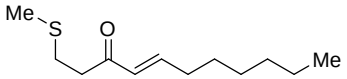


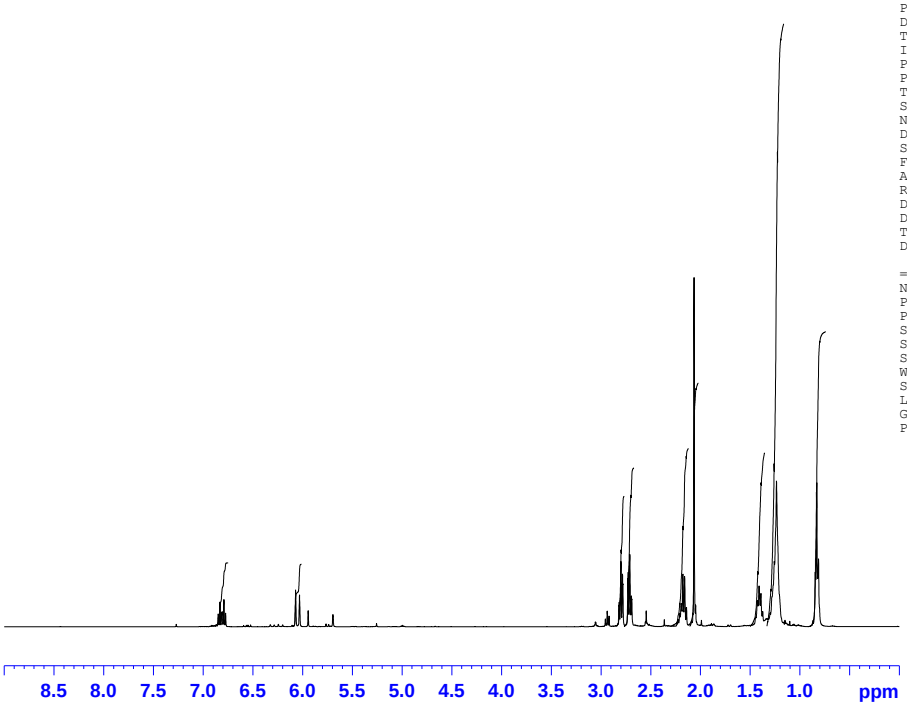



```
NAME       Nov08-2010-26
EXPNO                 2
PROCNO                1
Date_          20101108
Time              17.38
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG         zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                0.00 dB
SFO1       100.6403931 MHz

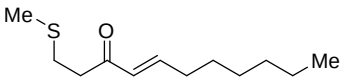
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2       400.2016008 MHz
SI               32768
SF         100.6303718 MHz
WDW                 EM
SSB                  0
LB                1.00 Hz
GB                   0
PC                1.40
```

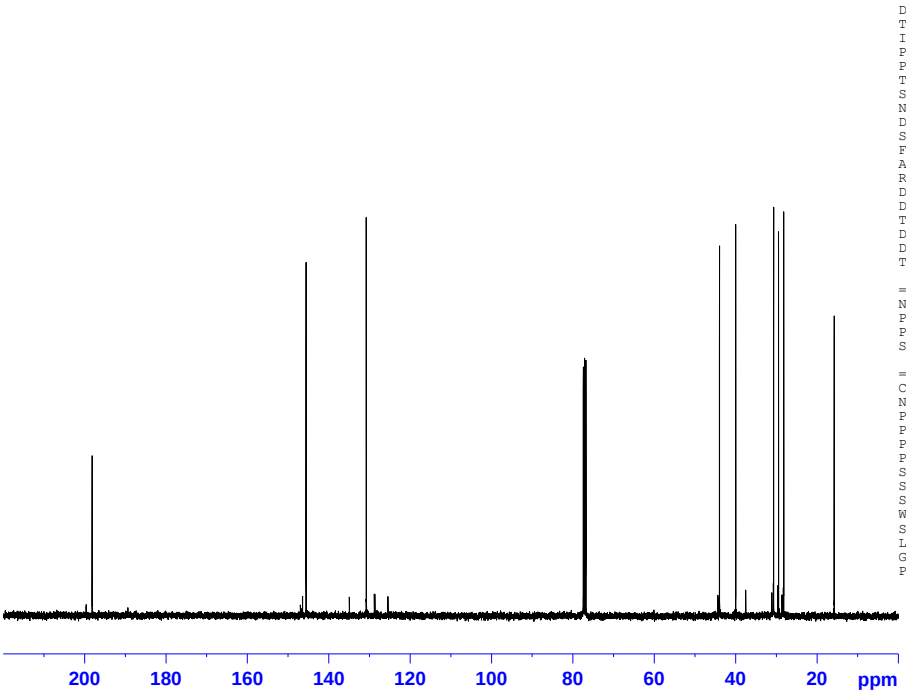





```
NAME       Dec14-2009-34
EXPNO                 1
PROCNO                1
Date_          20091214
Time              16.02
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                   18
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                9.00 usec
PL1               0.00 dB
SFO1        400.2024714 MHz
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.00
```

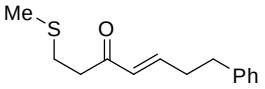


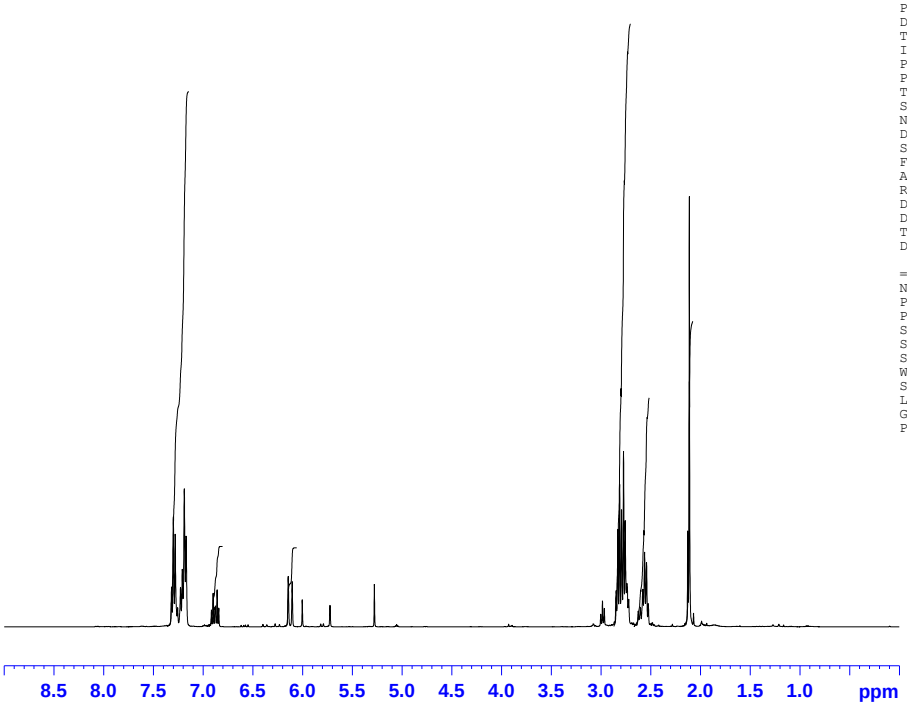



```
NAME       Dec14-2009-33
EXPNO                 3
PROCNO                1
Date_          20091214
Time              15.52
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                9.50 usec
PL1               0.00 dB
SFO1        100.6403931 MHz

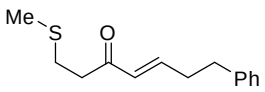
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2               0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                1.00 Hz
GB                    0
PC                1.40
```

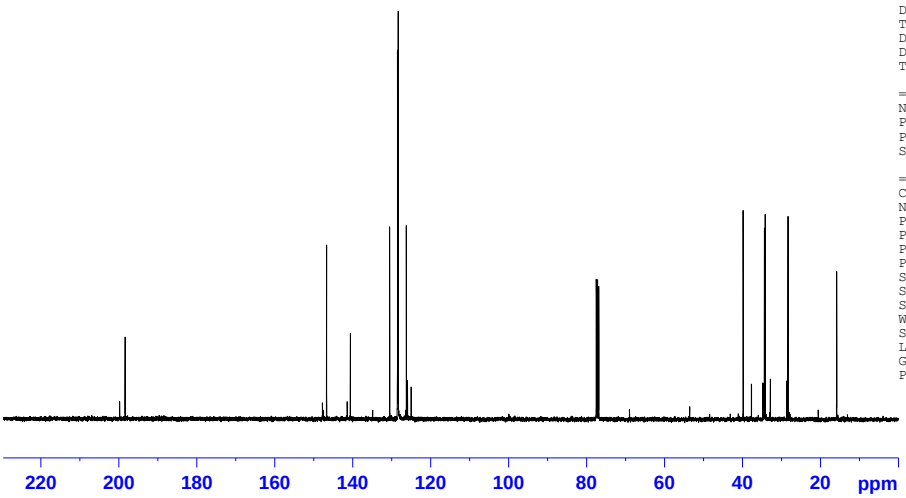





```
NAME          Dec14-2009-52
EXPNO                    1
PROCNO                   1
Date_             20091214
Time                 23.13
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH           8278.146 Hz
FIDRES         0.126314 Hz
AQ            3.9584243 sec
RG                   25.4
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1         400.2024714 MHz
SI                   32768
SF           400.2000028 MHz
WDW                    EM
SSB                     0
LB                 0.30 Hz
GB                      0
PC                   1.00
```

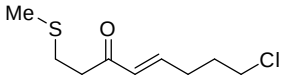


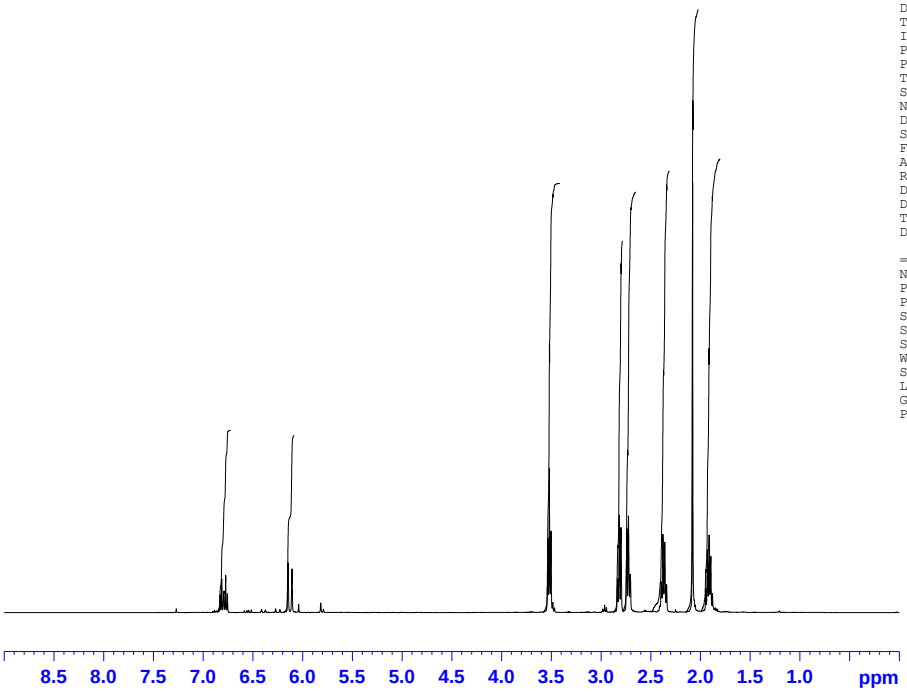



```
NAME          Dec14-2009-52
EXPNO                    2
PROCNO                   1
Date_             20091214
Time                 23.21
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH          26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                   32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1         100.6403931 MHz

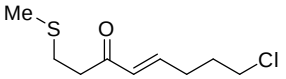
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz
SI                   32768
SF           100.6303718 MHz
WDW                    EM
SSB                     0
LB                 1.00 Hz
GB                      0
PC                   1.40
```

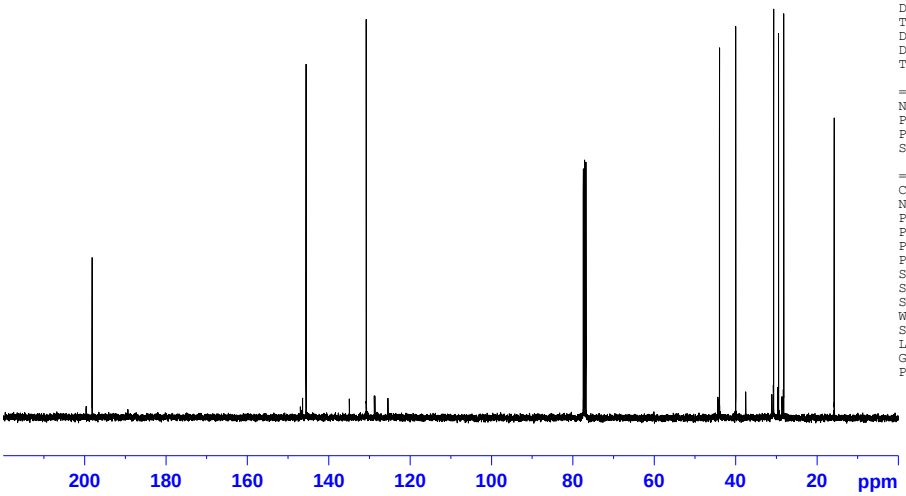





```
NAME       Dec14-2009-33
EXPNO                 1
PROCNO                1
Date_          20091214
Time              15.44
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES         0.126314 Hz
AQ             3.9584243 sec
RG                   32
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

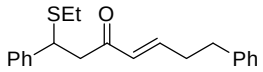


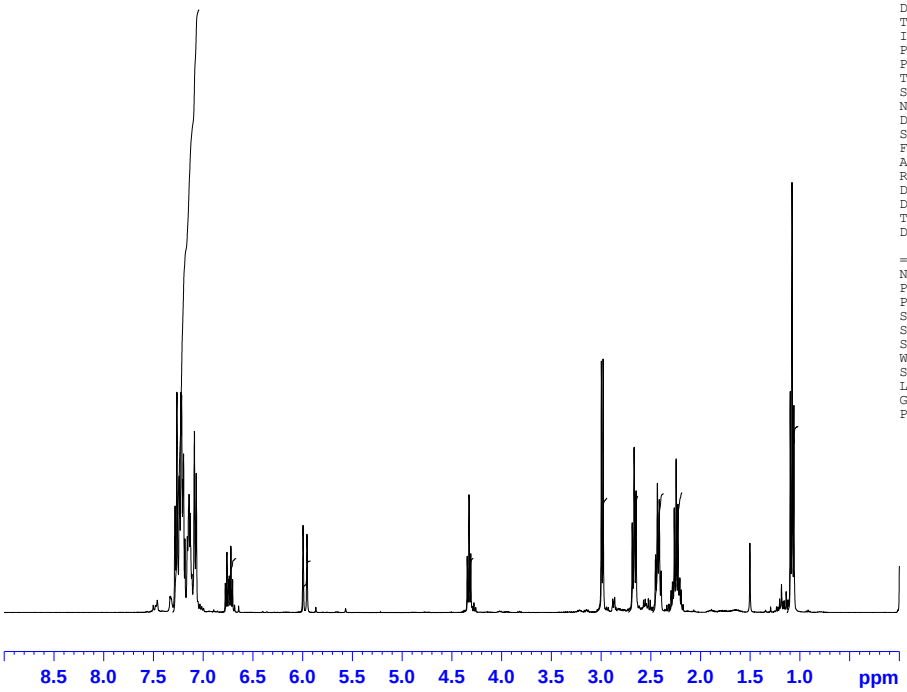



```
NAME       Dec14-2009-33
EXPNO                 3
PROCNO                1
Date_          20091214
Time              15.52
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG         zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ             0.6259188 sec
RG                32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                0.00 dB
SFO1        100.6403931 MHz

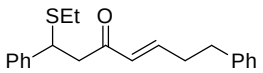
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2        400.2016008 MHz
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

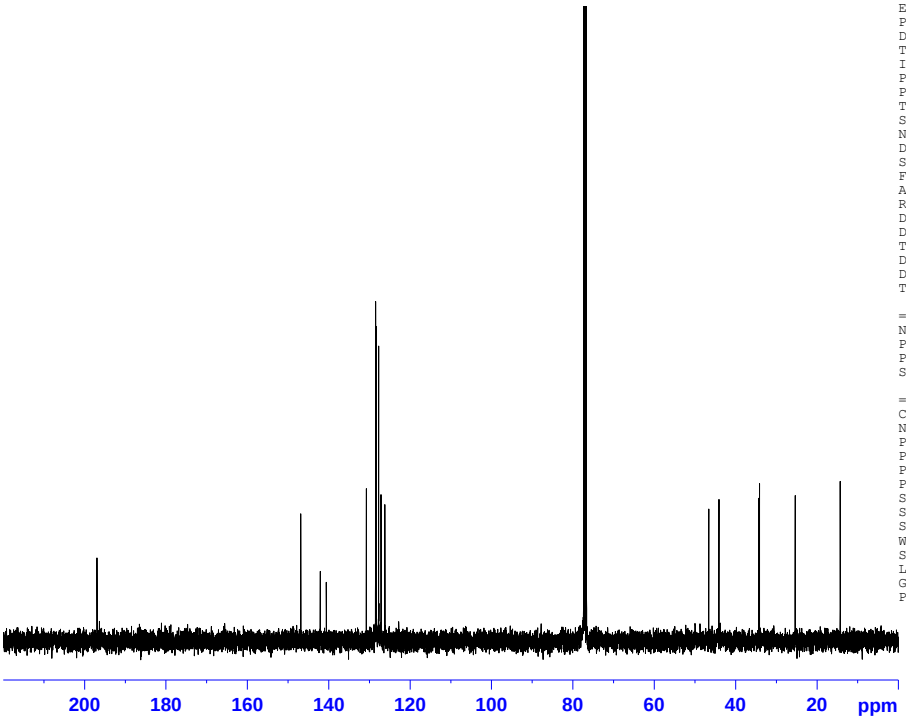




```
NAME                 1c
EXPNO                 1
PROCNO                1
Date_          20100417
Time               9.16
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                  128
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1          1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                9.00 usec
PL1               0.00 dB
SFO1       400.2024714 MHz
SI                32768
SF         400.2000378 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.00
```

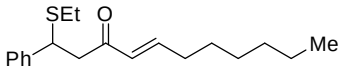



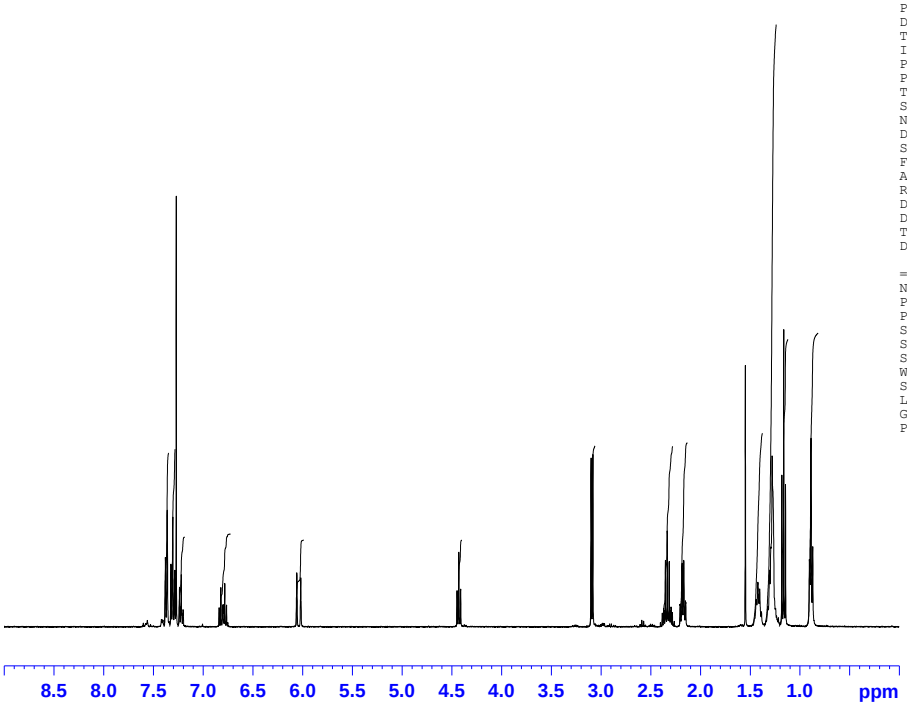


```
NAME                 1c
EXPNO                 2
PROCNO                1
Date_          20100417
Time               9.24
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG         zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1          1.00000000 sec
D11         0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                9.50 usec
PL1               0.00 dB
SFO1       100.6403931 MHz

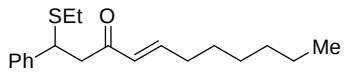
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2               0.00 dB
PL12             19.00 dB
PL13             25.00 dB
SFO2       400.2016008 MHz
SI                32768
SF         100.6303718 MHz
WDW                  EM
SSB                   0
LB                1.00 Hz
GB                    0
PC                1.40
```

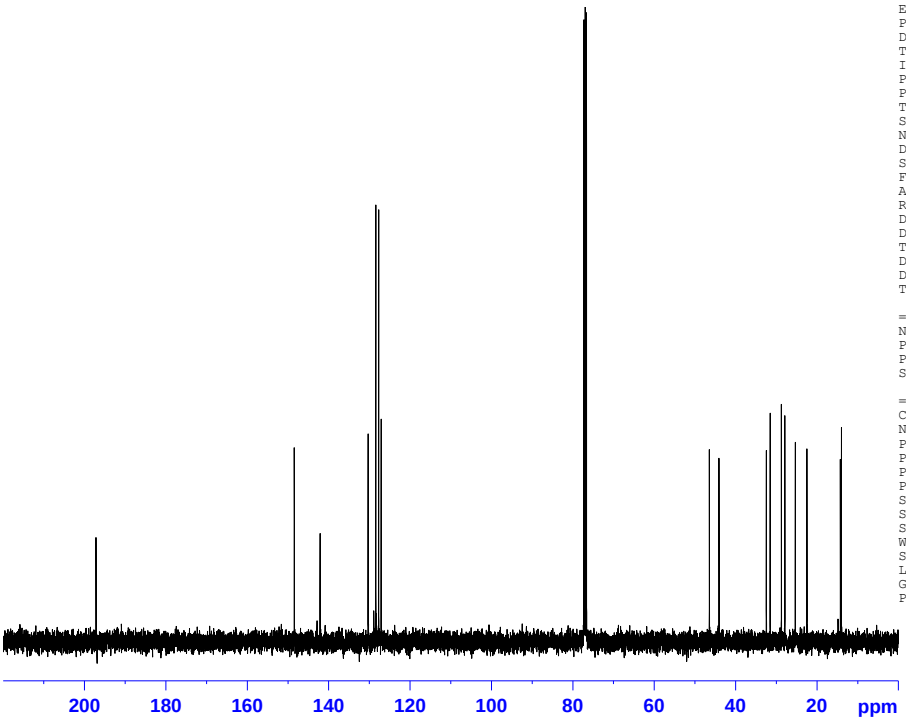





```
NAME          Sep18-2010-5
EXPNO                    1
PROCNO                   1
Date_             20100918
Time                 19.03
INSTRUM              av400
PROBHD    5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                   812.7
DW                  60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

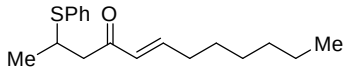


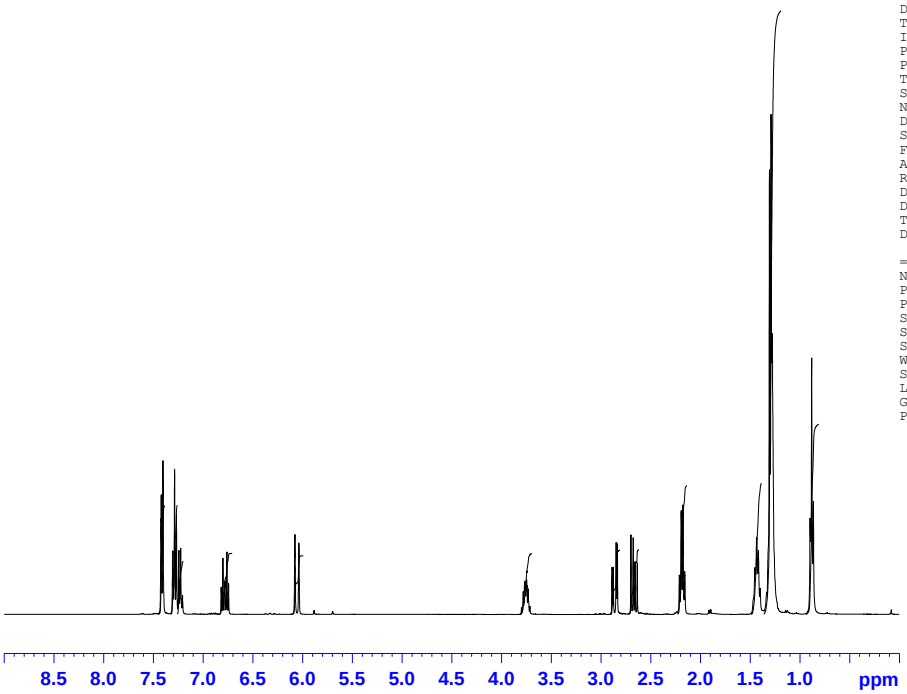



```
NAME                    1d
EXPNO                    2
PROCNO                   1
Date_             20100918
Time                 19.18
INSTRUM              av400
PROBHD    5 mm QNP 1H/13
PULPROG          zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

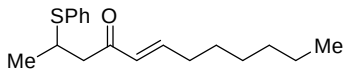
======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2          400.2016008 MHz
SI                   32768
SF            100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

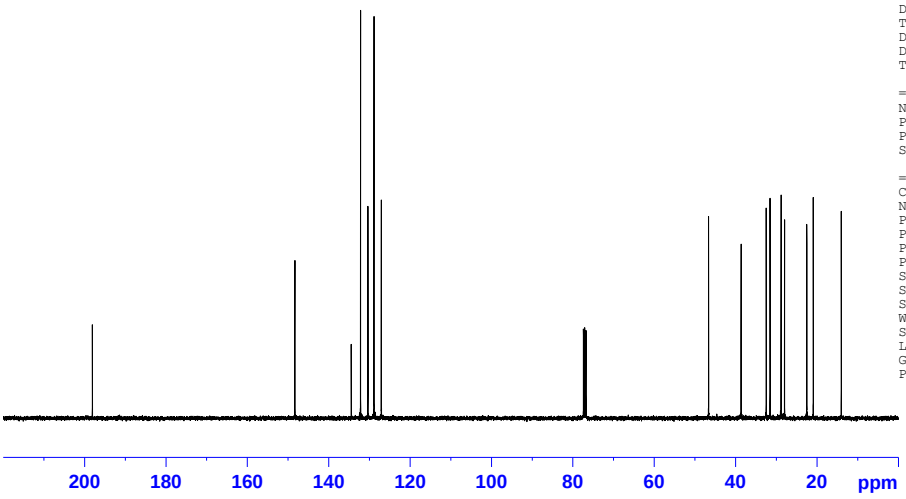





```
NAME                 1e
EXPNO                 1
PROCNO                1
Date_          20100728
Time               8.27
INSTRUM          av400
PROBHD   5 mm QNP 1H/13
PULPROG           zg60
TD               65536
SOLVENT          CDCl3
NS                   16
DS                    2
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 20.2
DW               60.400 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                9.00 usec
PL1               0.00 dB
SFO1        400.2024714 MHz
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.00
```

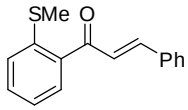


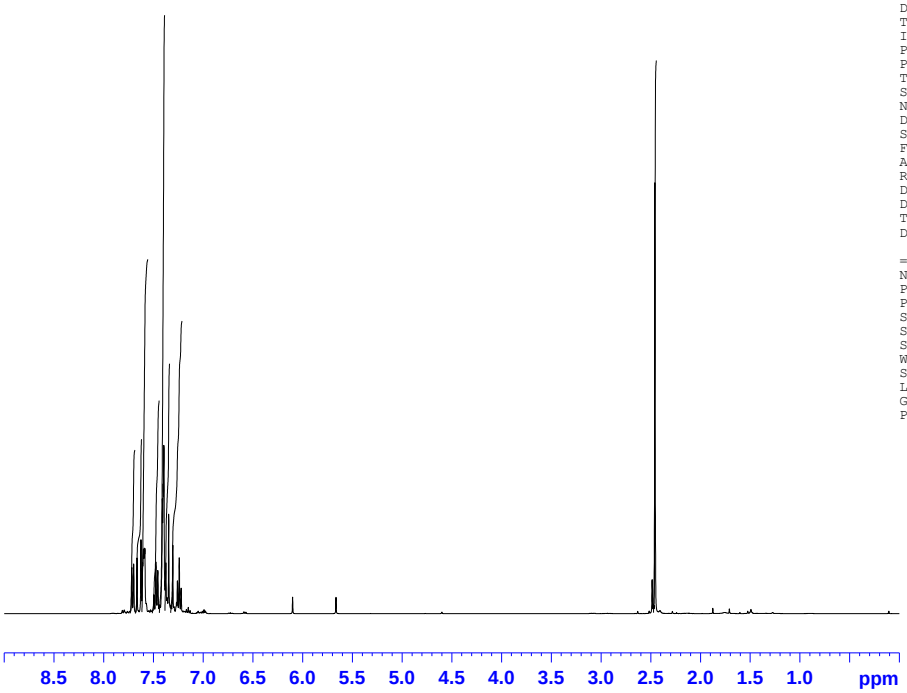



```
NAME                 1e
EXPNO                 2
PROCNO                1
Date_          20100728
Time               8.34
INSTRUM          av400
PROBHD   5 mm QNP 1H/13
PULPROG         zgpg30
TD               32768
SOLVENT          CDCl3
NS                  256
DS                    4
SWH          26178.010 Hz
FIDRES        0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                7.50 usec
TE               300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                9.50 usec
PL1               0.00 dB
SFO1        100.6403931 MHz

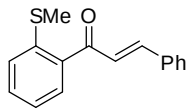
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2               0.00 dB
PL12             19.00 dB
PL13             25.00 dB
SFO2        400.2016008 MHz
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                1.00 Hz
GB                    0
PC                1.40
```

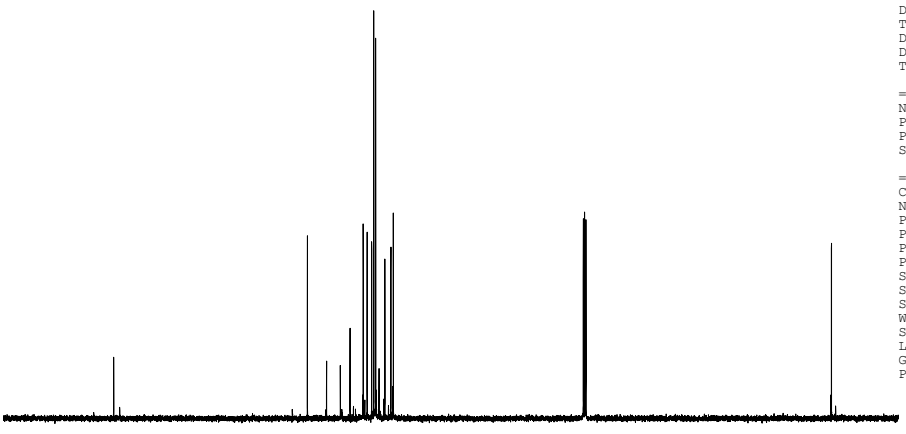


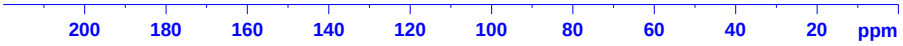



```
NAME      PY063021 DQX400
EXPNO               1
PROCNO              1
Date_        20100104
Time           21.03
INSTRUM        av400
PROBHD   5 mm QNP 1H/13
PULPROG         zg60
TD             65536
SOLVENT        CDCl3
NS                16
DS                 2
SWH         8278.146 Hz
FIDRES         0.126314 Hz
AQ          3.9584243 sec
RG              40.3
DW             60.400 usec
DE              7.50 usec
TE             300.0 K
D1          1.00000000 sec

======== CHANNEL f1 ========
NUC1               1H
P1              9.00 usec
PL1             0.00 dB
SFO1       400.2024714 MHz
SI             32768
SF         400.2000028 MHz
WDW               EM
SSB                0
LB              0.30 Hz
GB                 0
PC              1.00
```



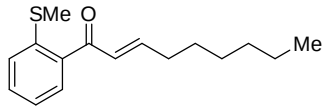


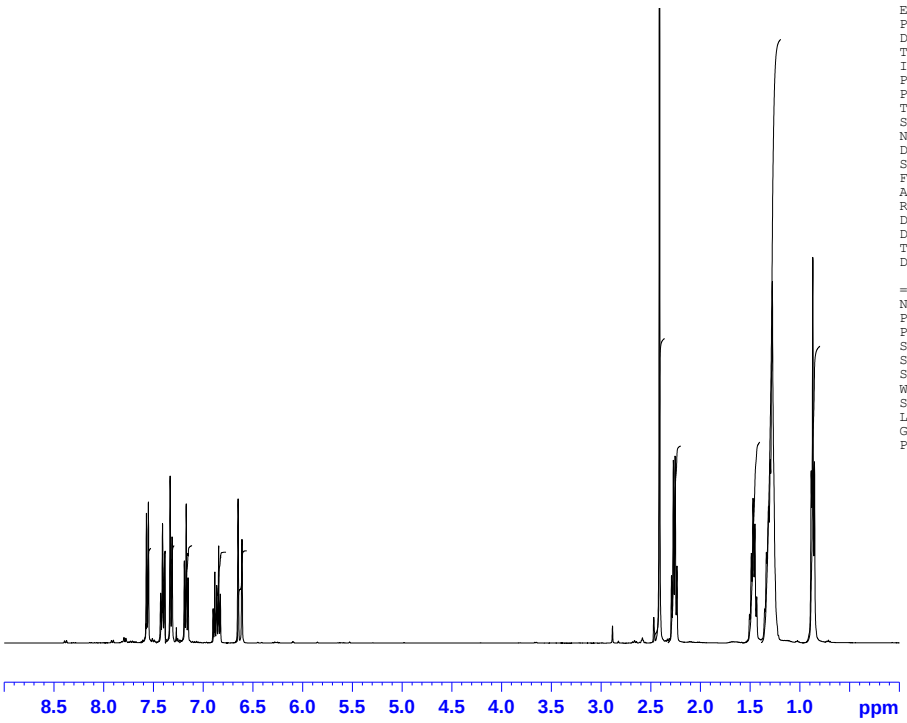



```
NAME      PY063021 DQX400
EXPNO               2
PROCNO              1
Date_        20100104
Time           21.11
INSTRUM        av400
PROBHD   5 mm QNP 1H/13
PULPROG        zgpg30
TD             32768
SOLVENT        CDCl3
NS               256
DS                 4
SWH        26178.010 Hz
FIDRES         0.798889 Hz
AQ          0.6259188 sec
RG             32768
DW             19.100 usec
DE              7.50 usec
TE             300.0 K
D1          1.00000000 sec
D11         0.03000000 sec
TD0                1

======== CHANNEL f1 ========
NUC1              13C
P1              9.50 usec
PL1             0.00 dB
SFO1       100.6403931 MHz

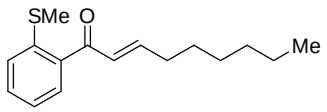
======== CHANNEL f2 ========
CPDPRG2        waltz16
NUC2               1H
PCPD2           80.00 usec
PL2              0.00 dB
PL12            19.00 dB
PL13            25.00 dB
SFO2       400.2016008 MHz
SI             32768
SF         100.6303718 MHz
WDW               EM
SSB                0
LB              1.00 Hz
GB                 0
PC              1.40
```

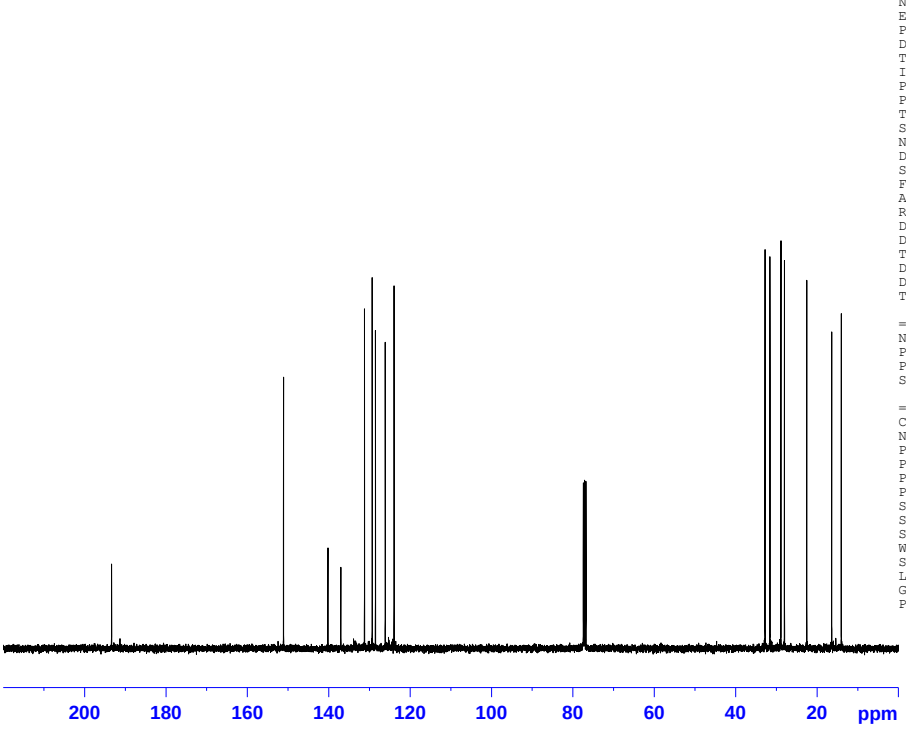





```
NAME                 Hex
EXPNO                  1
PROCNO                 1
Date_           20100104
Time                21.16
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                  28.5
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                1H
P1                9.00 usec
PL1               0.00 dB
SFO1        400.2024714 MHz
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.00
```

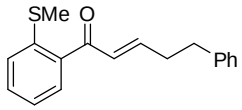


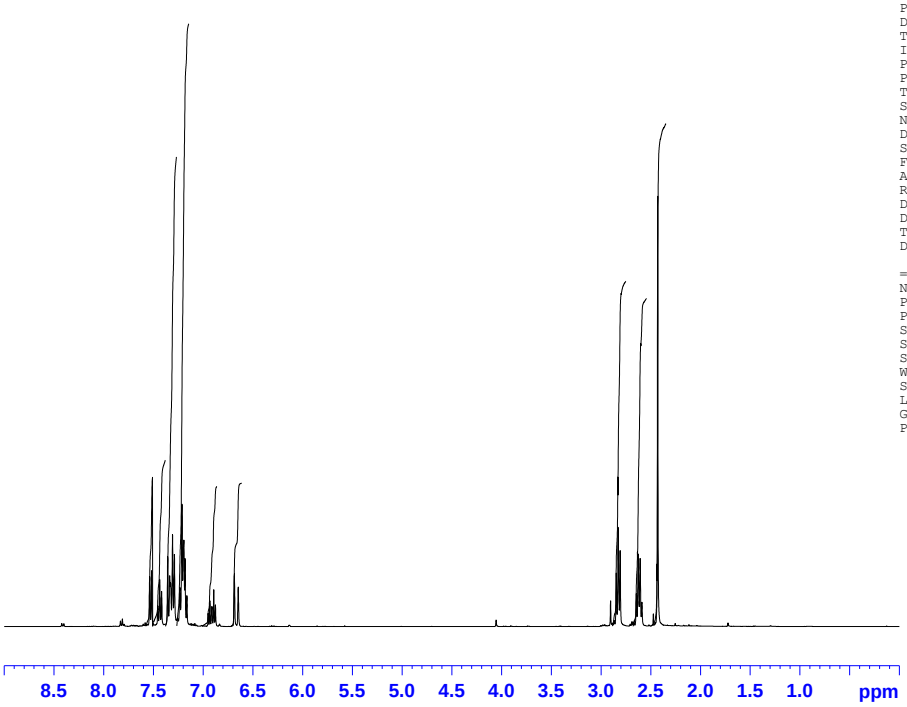



```
NAME                 Hex
EXPNO                  2
PROCNO                 1
Date_           20100104
Time                21.24
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ              0.6259188 sec
RG                 32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                13C
P1                9.50 usec
PL1               0.00 dB
SFO1        100.6403931 MHz

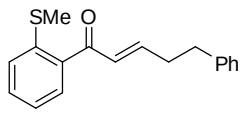
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2             80.00 usec
PL2               0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                1.00 Hz
GB                    0
PC                1.40
```

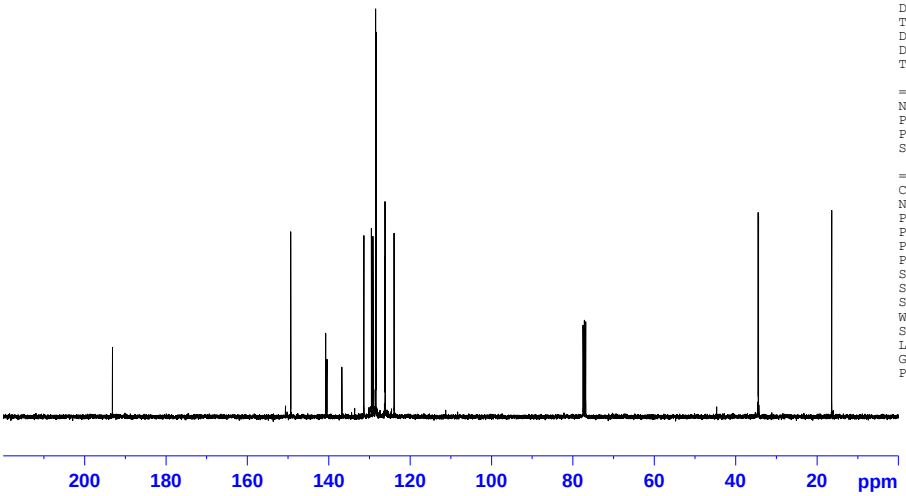





```
NAME            CH2CH2Ph
EXPNO                  1
PROCNO                 1
Date_           20100812
Time               12.15
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                  28.5
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz
SI                 32768
SF          400.2000028 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
```

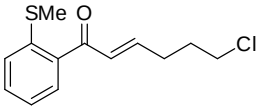


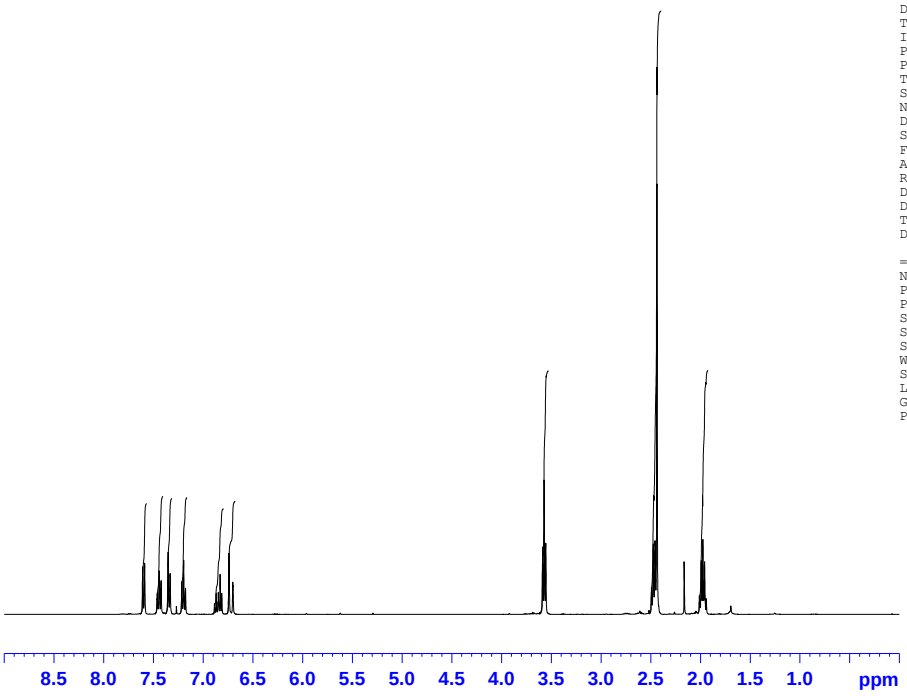



```
NAME            CH2CH2Ph
EXPNO                  2
PROCNO                 1
Date_           20100812
Time               12.23
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ              0.6259188 sec
RG                 32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
SFO1        100.6403931 MHz

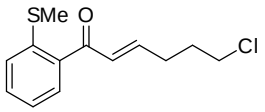
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz
SI                 32768
SF          100.6303718 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```

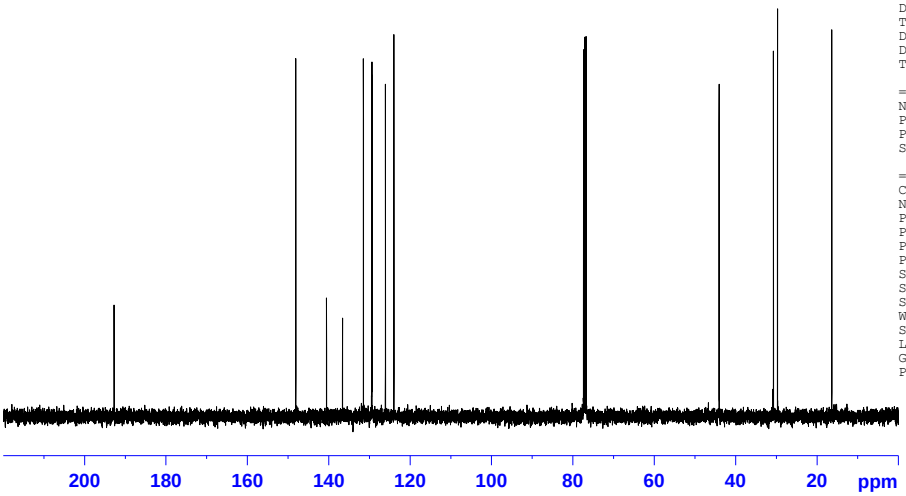





```
NAME                 C12
EXPNO                  1
PROCNO                 1
Date_           20091110
Time                10.49
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES             0.126314 Hz
AQ              3.9584243 sec
RG                  90.5
DW                 60.400 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1         400.2024714 MHz
SI                 32768
SF           400.2000028 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

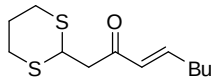


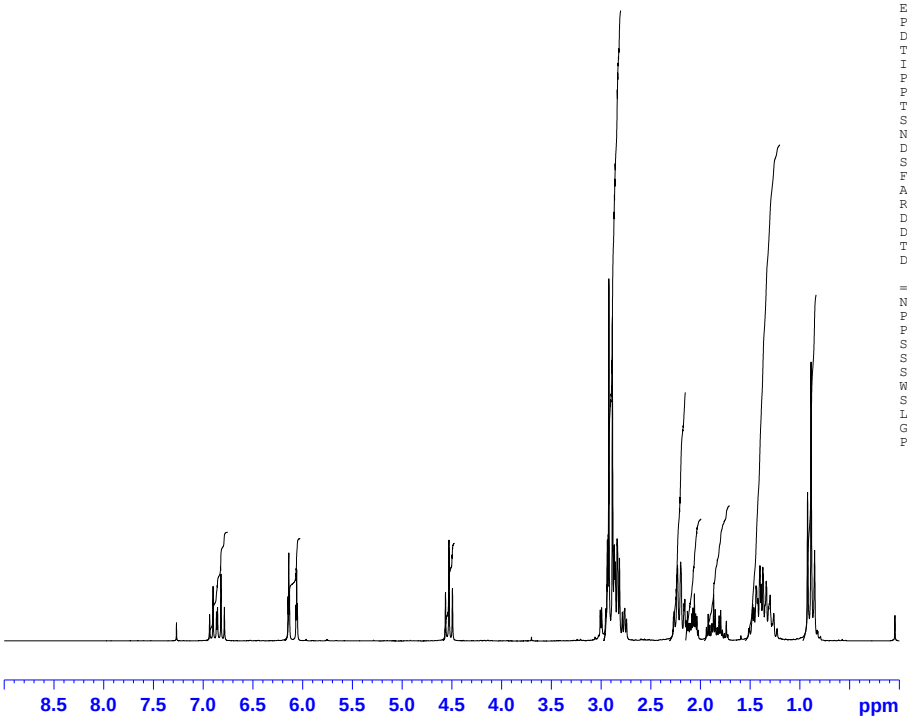



```
NAME                 C12
EXPNO                  3
PROCNO                 1
Date_           20091110
Time                11.01
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES             0.798889 Hz
AQ              0.6259188 sec
RG                 32768
DW                 19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1         100.6403931 MHz

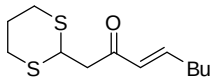
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz
SI                 32768
SF           100.6303718 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

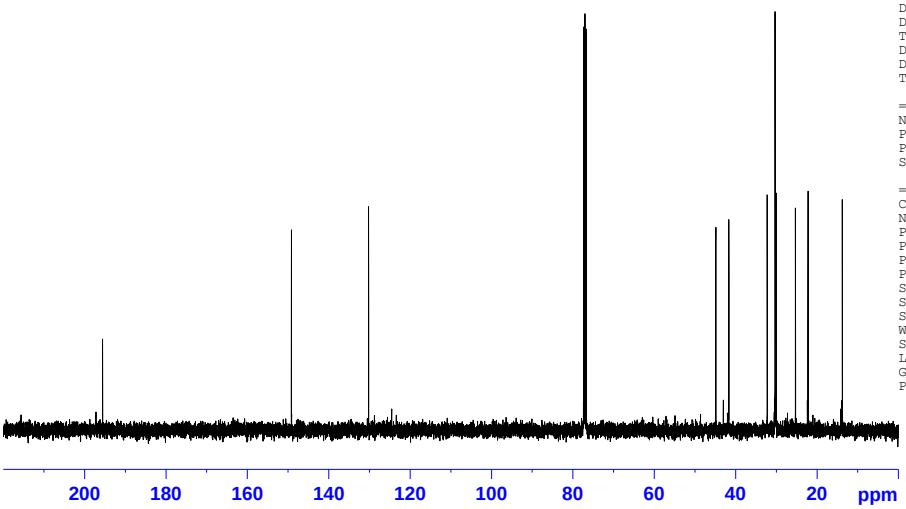





```
NAME       Feb19-2010-30
EXPNO                 2
PROCNO                1
Date_          20100219
Time              17.17
INSTRUM          dpx200
PROBHD   5 mm Dual 13C/
PULPROG            zg60
TD                16384
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            2796.421 Hz
FIDRES         0.170680 Hz
AQ             2.9295092 sec
RG                  128
DW              178.800 usec
DE                6.00 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                7.80 usec
PL1               -3.00 dB
SFO1        200.1310007 MHz
SI                32768
SF          200.1300125 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

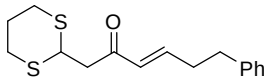


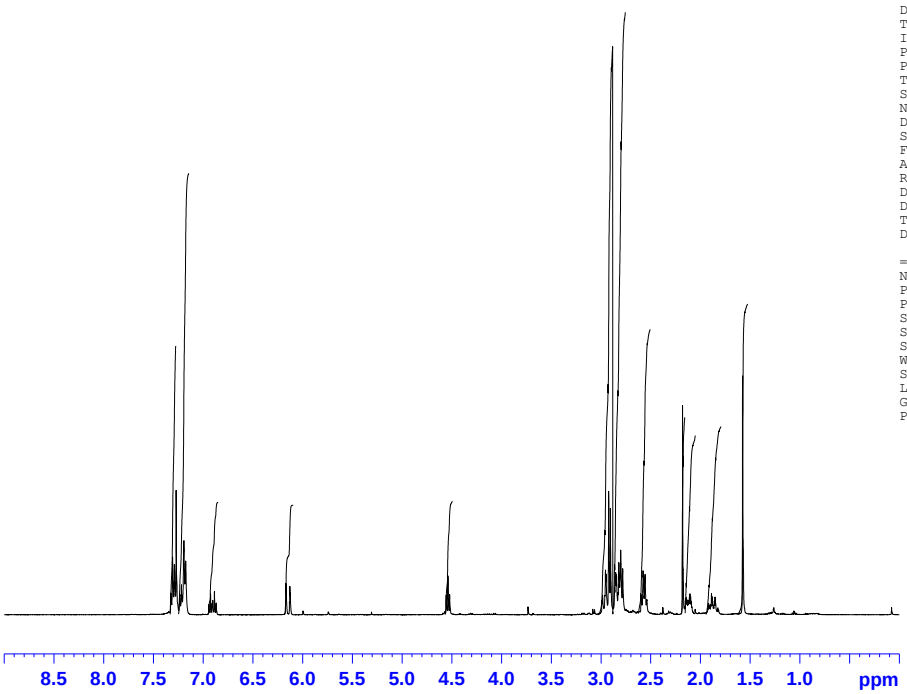



```
NAME        Jul26-2011-5
EXPNO                 2
PROCNO                1
Date_          20110726
Time              16.29
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ             0.6259188 sec
RG                32768
DW              19.100 usec
DE                7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                9.50 usec
PL1               0.00 dB
SFO1        100.6403931 MHz

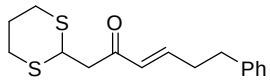
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2            80.00 usec
PL2               0.00 dB
PL12             19.00 dB
PL13             25.00 dB
SFO2        400.2016008 MHz
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

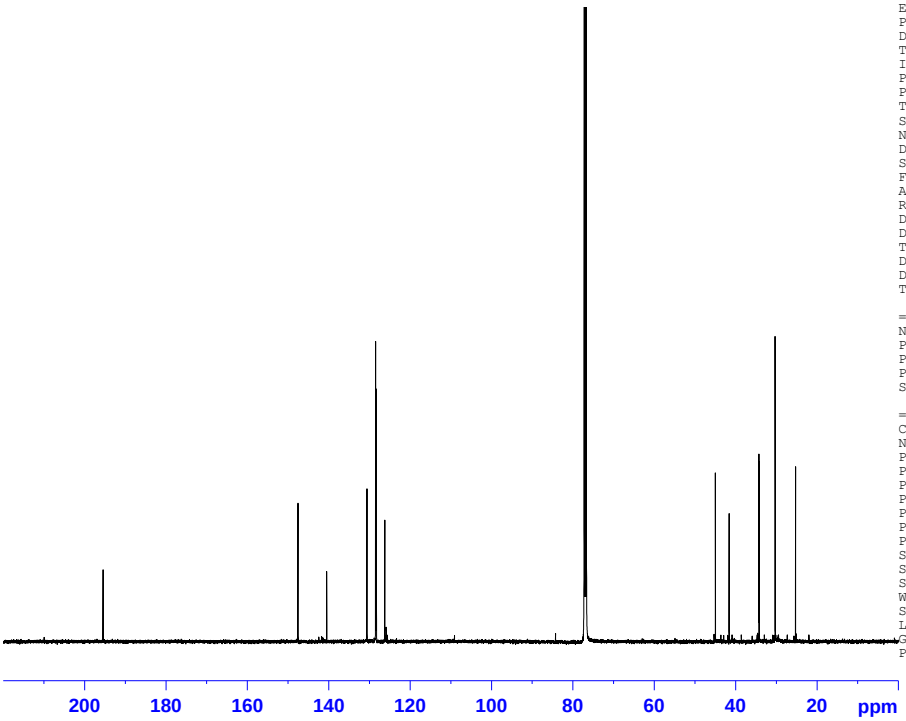





```
NAME          Jul26-2011-12
EXPNO                     1
PROCNO                    1
Date_              20110726
Time                  19.26
INSTRUM               av400
PROBHD    5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                     362
DW                  60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000028 MHz
WDW                     EM
SSB                      0
LB                   0.30 Hz
GB                       0
PC                    1.00
```

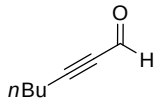


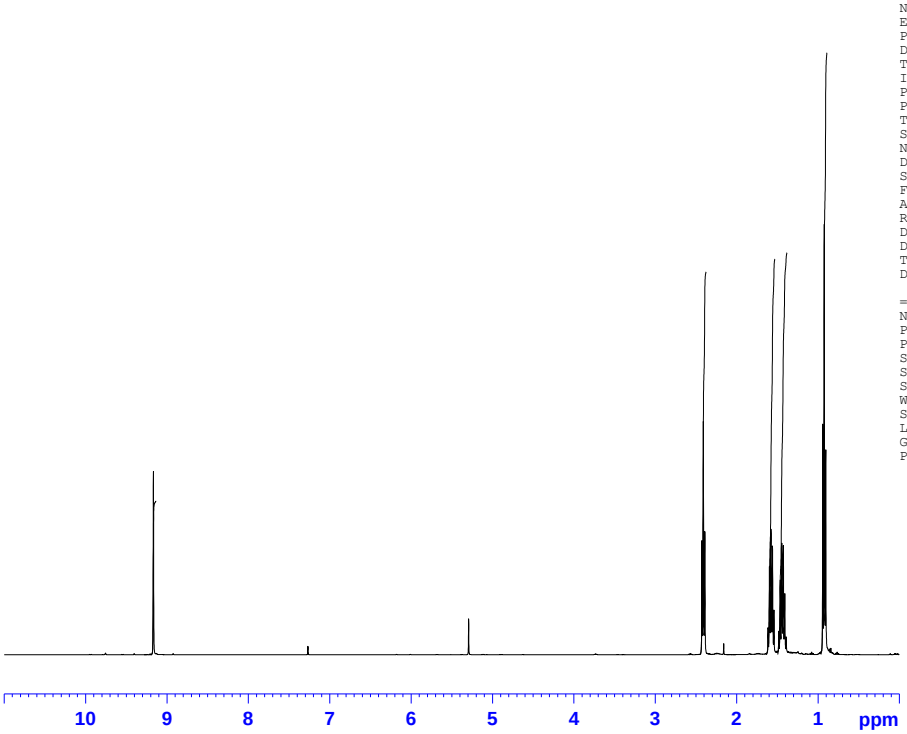



```
NAME           pl52752807
EXPNO                   2
PROCNO                  1
Date_            20110729
Time                 8.59
INSTRUM           avc500
PROBHD    5 mm CPDUL 13C
PULPROG          zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    1536
DS                       2
SWH              31250.000 Hz
FIDRES           0.476837 Hz
AQ               1.0486259 sec
RG                    1820
DW                  16.000 usec
DE                   20.00 usec
TE                  298.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                   9.10 usec
PL1                 -4.40 dB
PL1W          28.15752029 W
SFO1         125.8131151 MHz

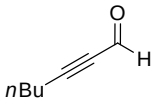
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                 -6.00 dB
PL12                12.42 dB
PL13                18.42 dB
PL2W          15.19999981 W
PL12W          0.21869738 W
PL13W          0.05493430 W
SFO2         500.3020012 MHz
SI                   32768
SF            125.8005438 MHz
WDW                     EM
SSB                      0
LB                   1.00 Hz
GB                       0
PC                    1.40
```

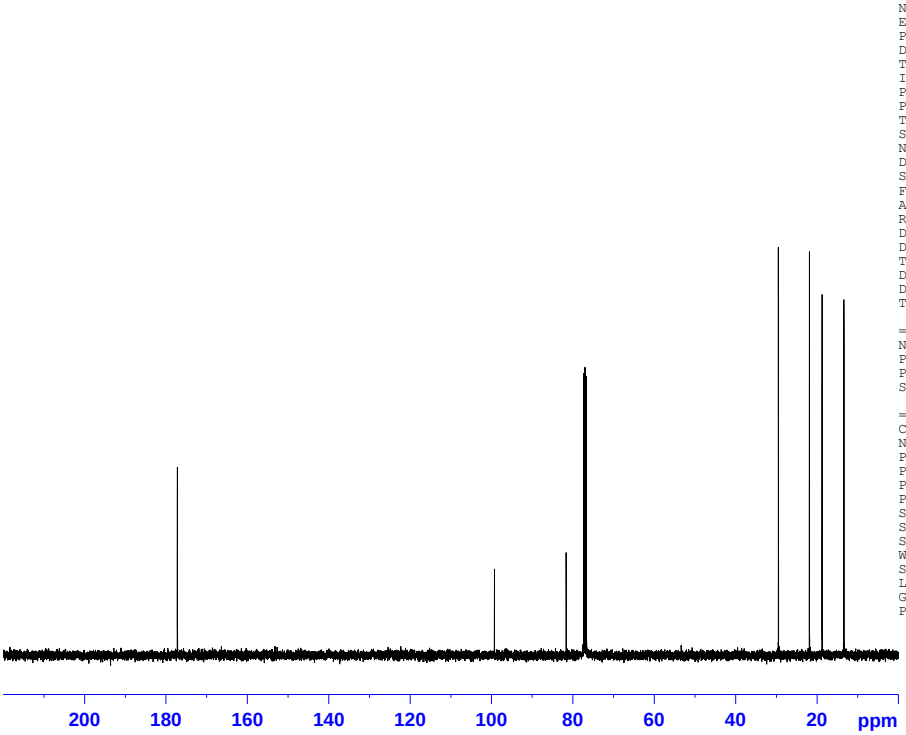





```
NAME          Aug06-2010-40
EXPNO                    1
PROCNO                   1
Date_             20100806
Time                 12.51
INSTRUM              av400
PROBHD    5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                   40.3
DW                 60.400 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

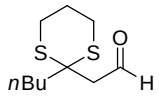


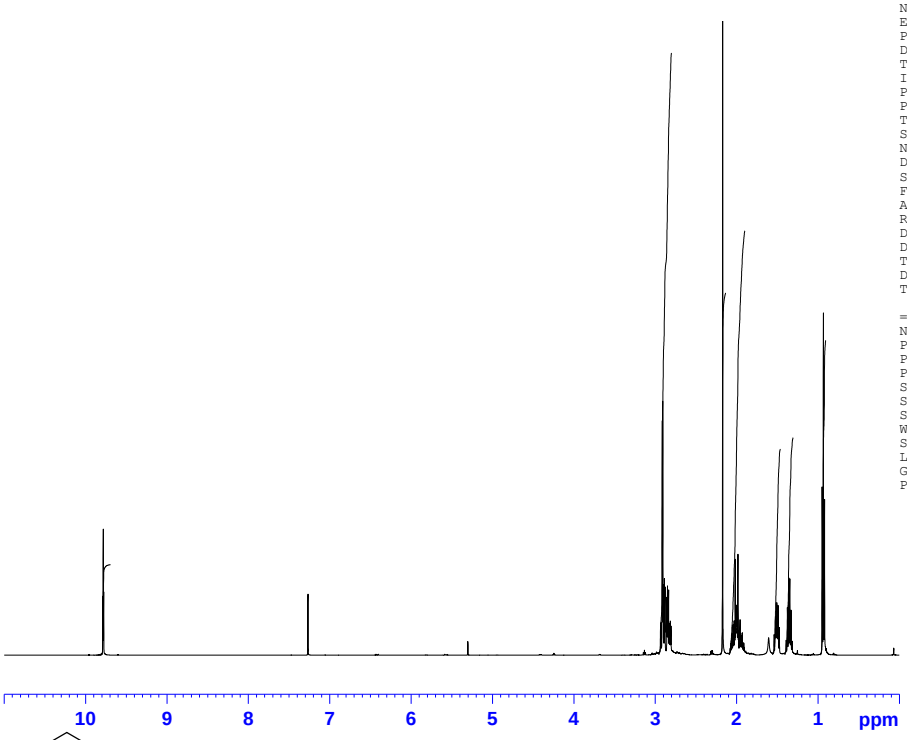



```
NAME          Aug06-2010-40
EXPNO                    2
PROCNO                   1
Date_             20100806
Time                 12.58
INSTRUM              av400
PROBHD    5 mm QNP 1H/13
PULPROG          zgpg30
TD                  32768
SOLVENT             CDCl3
NS                     256
DS                       4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ              0.6259188 sec
RG                   32768
DW                 19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

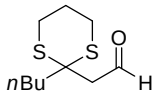
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz
SI                   32768
SF            100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

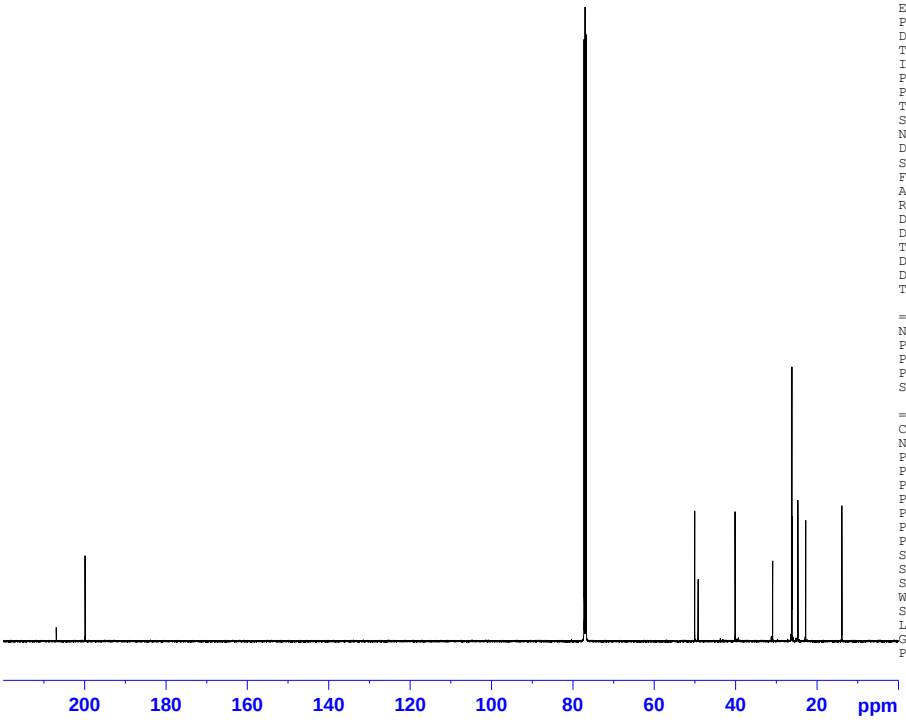





```
NAME          pl12460811
EXPNO                  1
PROCNO                 1
Date_           20101109
Time                7.46
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719923 sec
RG                     4
DW               48.400 usec
DE                6.00 usec
TE                298.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.60 usec
PL1               -6.00 dB
PL1W        15.19999981 W
SFO1        500.3030896 MHz
SI                 32768
SF          500.3000240 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                1.00
```

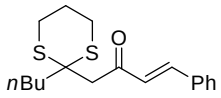


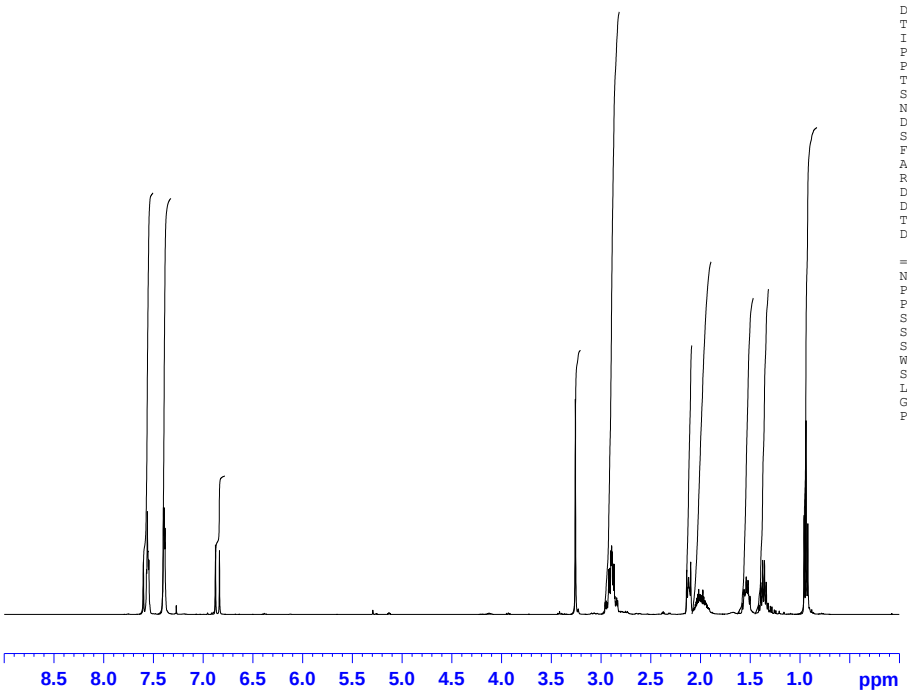



```
NAME          pl12460811
EXPNO                  2
PROCNO                 1
Date_           20101109
Time                8.00
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     2
SWH           31250.000 Hz
FIDRES         0.476837 Hz
AQ            1.0486259 sec
RG                  1820
DW               16.000 usec
DE                20.00 usec
TE                298.1 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1               -4.40 dB
PL1W        28.15752029 W
SFO1        125.8131151 MHz

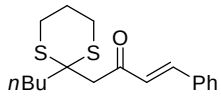
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2               -6.00 dB
PL12               12.42 dB
PL13               18.42 dB
PL2W        15.19999981 W
PL12W        0.21869738 W
PL13W        0.05493430 W
SFO2        500.3020012 MHz
SI                 32768
SF          125.8005438 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                1.40
```

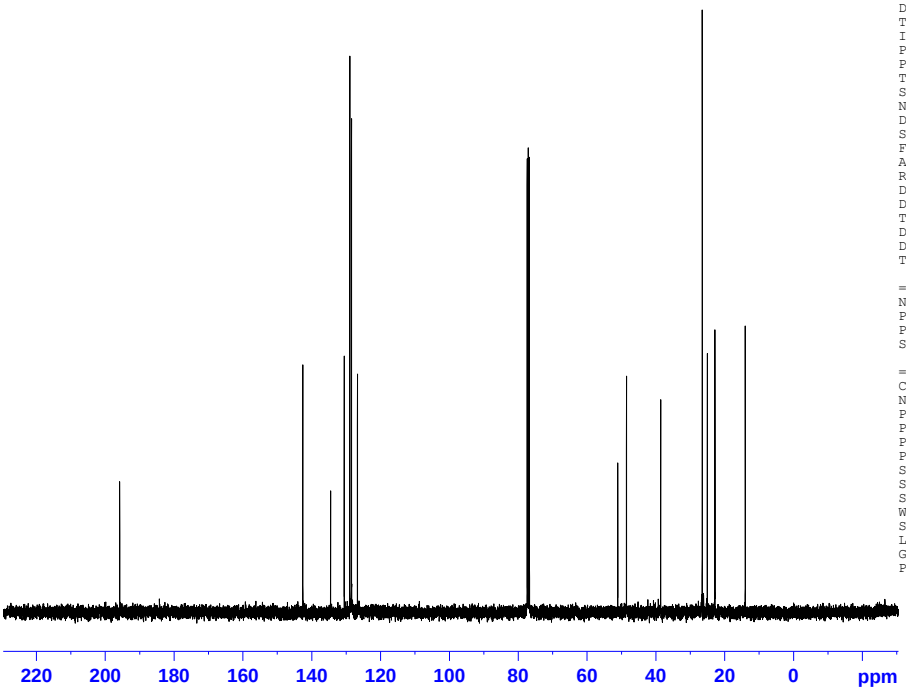




```
NAME        Aug09-2010-11
EXPNO                   1
PROCNO                  1
Date_            20100809
Time                13.19
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                  35.9
DW                60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1         400.2024714 MHz
SI                 32768
SF           400.2000028 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

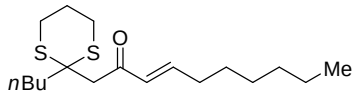


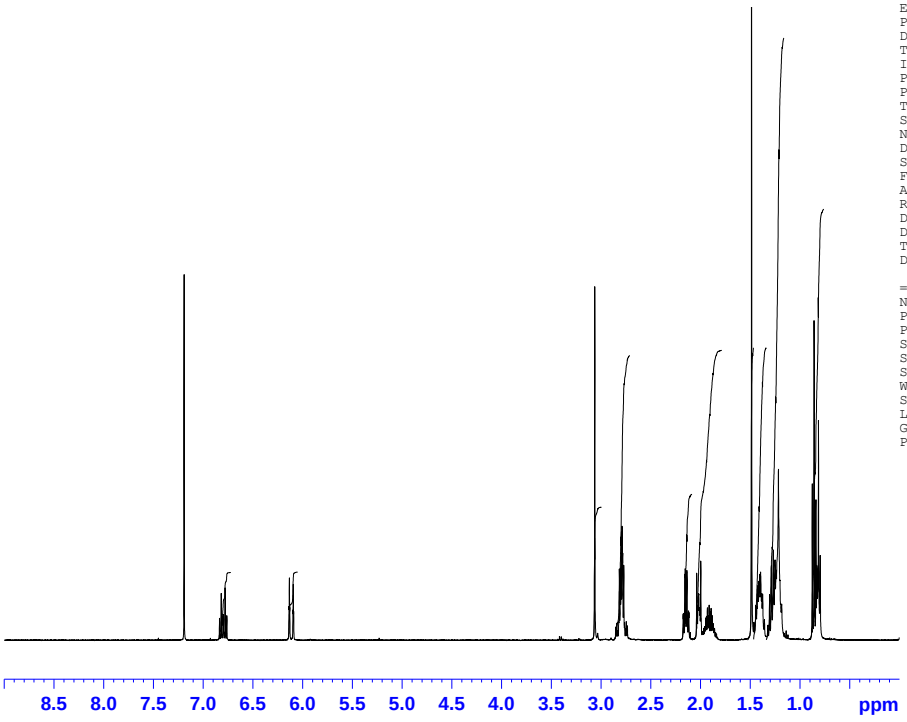


```
NAME        Aug09-2010-11
EXPNO                   2
PROCNO                  1
Date_            20100809
Time                13.26
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ              0.6259188 sec
RG                  32768
DW                19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1        100.6403931 MHz

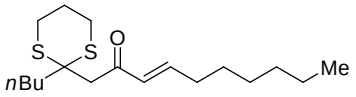
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz
SI                 32768
SF           100.6303718 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

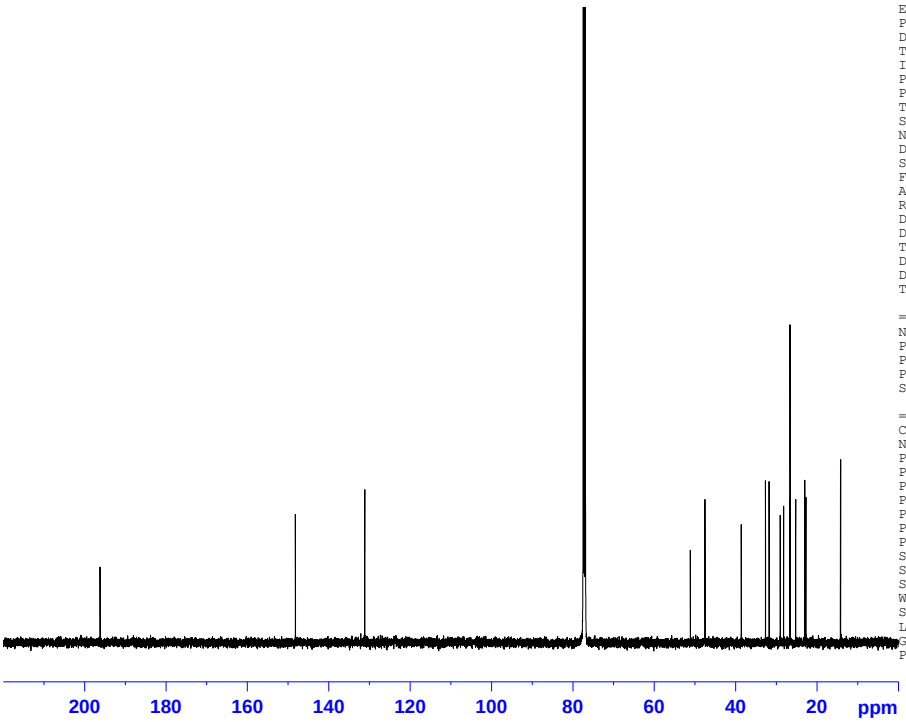





```
NAME          Oct12-2010-55
EXPNO                    5
PROCNO                   1
Date_             20101012
Time                 21.21
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                   574.7
DW                  60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz
SI                   32768
SF            400.2000337 MHz
WDW                     EM
SSB                      0
LB                   0.30 Hz
GB                       0
PC                   1.00
```

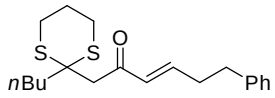


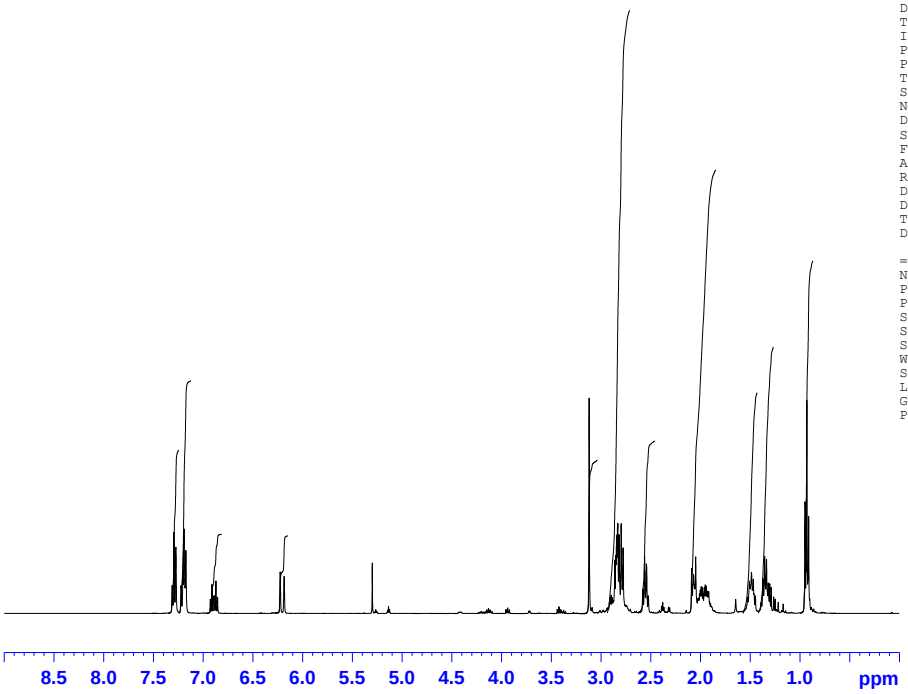



```
NAME          pl11840311
EXPNO                  1
PROCNO                 1
Date_           20101104
Time               3.54
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    2
SWH          31250.000 Hz
FIDRES        0.476837 Hz
AQ            1.0486259 sec
RG                 1820
DW               16.000 usec
DE               20.00 usec
TE               298.0 K
D1          2.00000000 sec
D11         0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                 9.50 usec
PL1                -4.40 dB
PL1W       28.15752029 W
SFO1       125.8131151 MHz

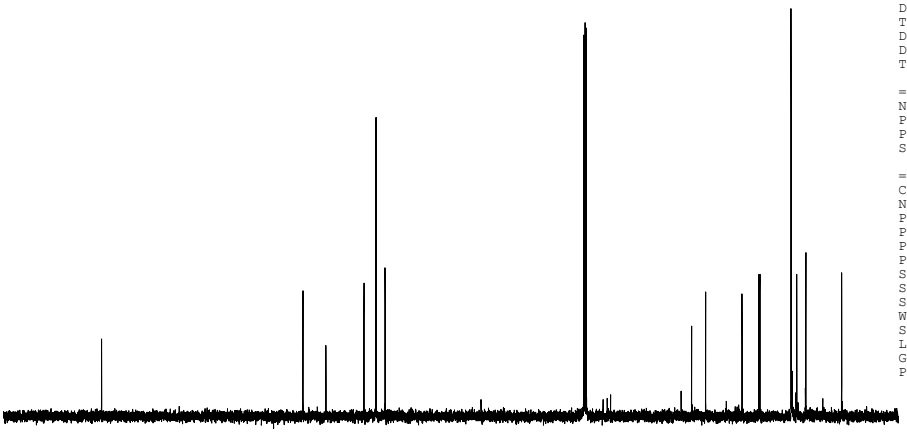
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                -6.00 dB
PL12               12.42 dB
PL13               18.42 dB
PL2W       15.19999981 W
PL12W       0.21869738 W
PL13W       0.05493430 W
SFO2       500.3020012 MHz
SI                 32768
SF         125.8005176 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```





```
NAME        Aug04-2010-38
EXPNO                   1
PROCNO                  1
Date_            20100804
Time                15.59
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH           8278.146 Hz
FIDRES          0.126314 Hz
AQ            3.9584243 sec
RG                   35.9
DW                60.400 usec
DE                 7.50 usec
TE                 300.0 K
D1           1.00000000 sec

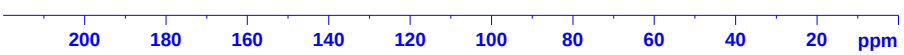
======== CHANNEL f1 ========
NUC1                   1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1         400.2024714 MHz
SI                  32768
SF           400.2000028 MHz
WDW                    EM
SSB                     0
LB                  0.30 Hz
GB                      0
PC                   1.00
```



```
NAME        Aug09-2010-33
EXPNO                   2
PROCNO                  1
Date_            20100809
Time                20.57
INSTRUM             av400
PROBHD    5 mm QNP 1H/13
PULPROG          zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH          26178.010 Hz
FIDRES           0.798889 Hz
AQ            0.6259188 sec
RG                  32768
DW                19.100 usec
DE                 7.50 usec
TE                 300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1         100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz
SI                  32768
SF           100.6303718 MHz
WDW                    EM
SSB                     0
LB                  1.00 Hz
GB                      0
PC                   1.40
```



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