Asymmetric Addition Reactions Using Chiral Diamine Derived Catalysts

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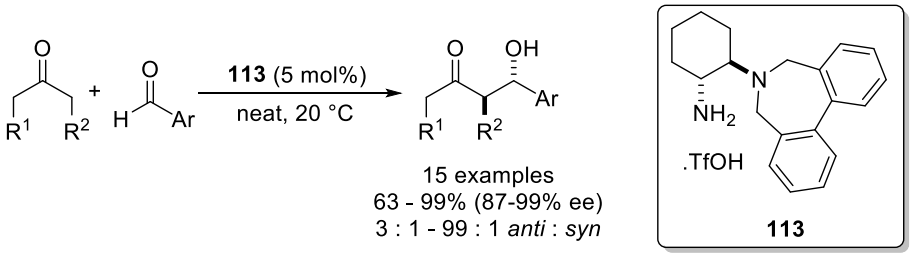
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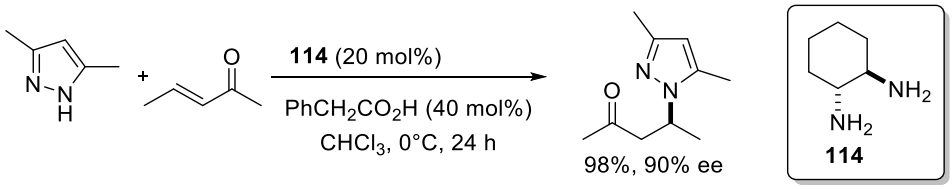
Abstract

This thesis details the use of chiral diamine derived catalysts in asymmetric addition reactions. Three separate projects are outlined within.

The first project involved the investigation of dibenz[c,e]azepinium salt **113** as a catalyst for the aldol reaction. The catalyst was synthesised in 4 steps from commercially available 1*R*,2*R*-diaminocyclohexane in 74% overall yield. It was found to be an efficient catalyst in the aldol reaction of cyclic ketones with a range of aromatic aldehydes, giving high yields, diastereo- and enantioselectivities. This catalyst was also found to be effective when acyclic ketones were used, in which case the major diastereoisomer produced was no longer an *anti*-aldol but a the *syn*-aldol. A catalytic cycle for these reactions is proposed, with the stereochemical outcome of these reactions being further investigated by computational calculations.

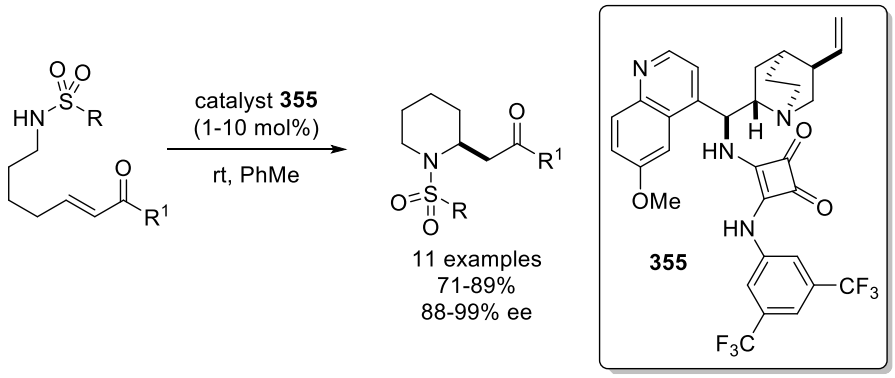


The second project investigated the use of chiral primary amine catalysts in the conjugate addition of *N*-heterocycles to α,β-unsaturated ketones. It was found that commercially available 1*R*,2*R*-diaminocyclohexane **114** was an efficient and enantioselective catalyst for the addition of pyrazoles to α,β-unsaturated ketones. Through comparison with the performance of related catalyst structures we propose a catalytic cycle in which **114** forms bonds with both the α,β-unsaturated ketone and the incoming pyrazole. Alternative chiral amines derived from camphor sulfonic acid were investigated as catalysts for the conjugate addition reaction; these proved to be relatively poor catalysts giving the product with a low enantiomeric excess.



Finally, an investigation into intramolecular *N*-conjugate additions was performed. We found that 9-*epi*-9-amino-9-deoxyquinine derived squaramide **355** was a

highly enantioselective catalyst for the intramolecular cyclisation of sulfonamides to α,β-unsaturated ketones. Best results were seen with α,β-unsaturated ketones conjugated to an aryl group, however squaramide **355** also proved to be an enantioselective catalyst for the cyclisation of methyl ketone and ester conjugated alkenes. In the latter two cases higher temperatures and catalyst loadings were required. In conjunction with molecular modelling studies we propose a catalytic cycle that accounts for the observed stereochemistry.



Acknowledgements

I wish to acknowledge the invaluable direction and supervision provided by Prof. Barry Lygo. I would also like to thank Dr. John Leonard and Dr. Ian Ashworth for their suggestions and advice, both during my placement at AstraZeneca, and during my time at the University of Nottingham. I would like to thank all the members of the Lygo group past and present. Anthony Ball, Lee Eccleshare, and Dr. Timothy Evans are deserved of special thanks as each has made a contribution (as detailed within) to work that appears in this thesis.

I would like to thank AstraZeneca for financial assistance, as well as the University of Nottingham. I would like to thank all the support staff at the Uniiversity of Nottingham chemistry department, particularly Kevin Butler and Shaz Aslam for NMR support.

Abbreviations

BBN	Borabicyclo[3.3.1]nonane
Boc	*tert*-Butyloxycarbonyl
Cbz	Carboxybenzyl
DAB	1,3-Dimethylbarbituric acid
DABOH	1,3-Dimethyl-5-acetyl-barbituric acid
DCE	Dichloroethane
DFT	Density Functional Theory
DHA	Dihydroxyacetone
DHAP	Dihydroxyacetone phosphate
DIAD	Diisopropylazodicarboxylate
DMAP	Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformaldehyde
DMP	2,6-Dimethylphenol
DMSO	Dimethylsulfoxide
EWG	Electron Withdrawing Group
c-Hex	Cyclohexane
HPLC	High Performance Liquid Chromatography
Ipc	isopinocamphenyl
LA	Lewis Acid
LDA	Lithium diisopropylamide
NMP	*N*-Methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance
Ns	4-Nitrophenylsulfonyl
Nu	Nucleophile
PTC	Phase Transfer Catalysed
Py	Pyridine
rt	Room Temperature

TBS	*tert*-Butyldimethylsilyl
TCA	Trichloroacetic acid
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
tol	Toluene
Ts	Toluenesulfonyl

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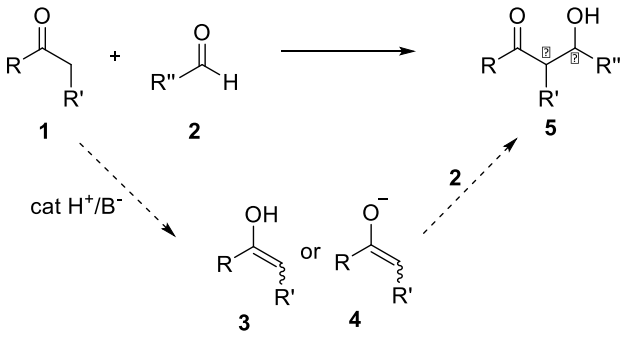
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Chapter 1: Enantioselective Aldol Reactions Using A *Tropos* Dibenz[*c,e*]azepine Catalyst

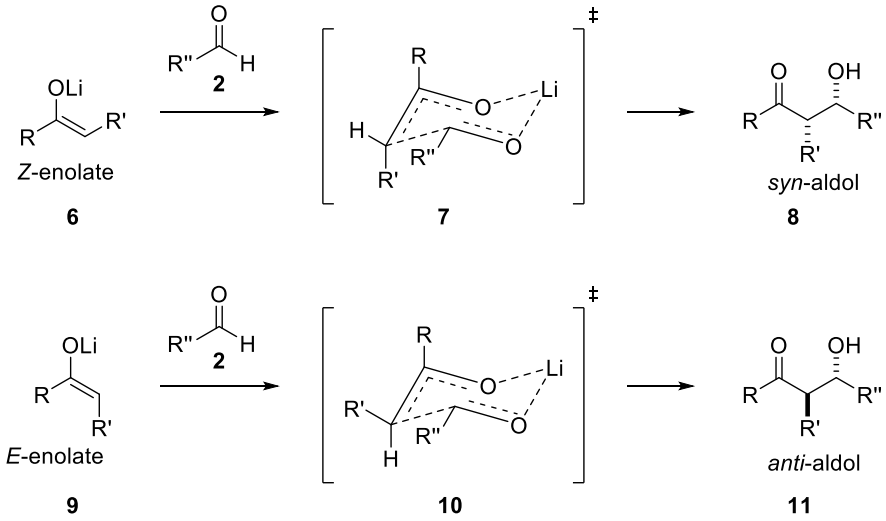
Intoduction

The aldol reaction, first reported by Wurtz in 1872[1], is an important tool for forming carbon-carbon bonds. The reaction proceeds through the formation of a nucleophilic enol **3** or enolate **4** species and unites two carbonyl compounds (**1** and **2**) to form a β-hydroxyl carbonyl **5** (Scheme 1).[2]



Scheme 1. The aldol reaction.

The newly formed carbon-carbon bond tethers two new (potentially) stereogenic centres, control of the regio- and stereoselectivity of the aldol reaction can present a significant challenge.

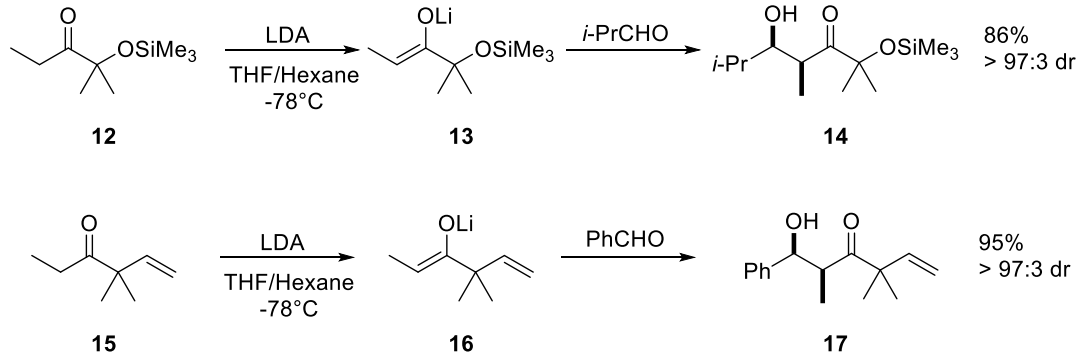


Scheme 2. Closed transition states for *cis* and *trans* enolates.

Control of the regio- and stereoselectivity of the aldol reaction has been the subject of a considerable amount of research.[3] Many methods for controlling diastereoselectivity make use of the observation that *cis*-enolates often give *syn*-aldols, while *trans*-enolates tend to give *anti*-aldols preferentially.[4] These observations can be rationalised by considering a 6 membered ring transition state in which a metal ion (or proton) bridges both the oxygen of the enolate and

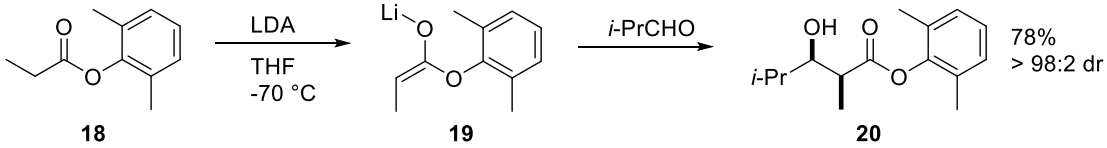
the oxygen of the electrophilic carbonyl species (Scheme 2). This type of transition state was initially proposed by Zimmerman and Traxler during their investigations into the related diastereoselective Ivanov reaction.[5] In transition states **7** and **10** the electrophilic carbonyl will preferentially orientate itself in such a way that the large substituent R'' is in a pseudoequatorial position to minimise steric interactions. The enolate partner of the reaction has no such choice and the orientation of the groups is set by the geometry of the enolate formed.

When *syn*-aldol adducts are desired, good to excellent diastereocontrol can usually be achieved if the R group attached to the oxygen bearing carbon atom of the enolate is bulky.[6] This ensures a *cis*-enolate is formed and hence the *syn*-aldol product. Examples that illustrate this are reactions involving α-trimethylsilyloxy ketone **12**[7], and the ketone **15**[8] (Scheme 3).



Scheme 3. Substrates for *syn*-selective aldol reactions.

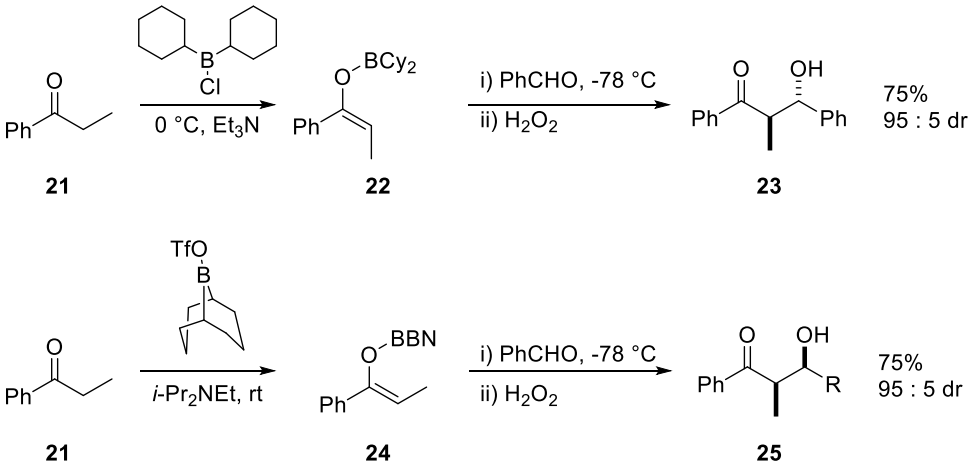
Substrates that favour *trans*-enolates are less common[9], but one example is the use of 2,6-dimethylphenol (DMP) esters **18**[10] (Scheme 4).



Scheme 4. Substrate for *anti* selective aldol reaction.

Stereoselective formation of either *cis*- or *trans*- enolates can be achieved *via* boron enolates. Simply by choosing the appropriate boron ligands it is usually possible to selectively produce the desired enolate geometry. Bulky groups on boron tend to favour a *trans*-enolate and smaller groups on boron favour a *cis*-enolate (Scheme 5).[11] Boron enolates are also often found to give better diastereoselectivity than alternative metal enolates. This is partly due to the

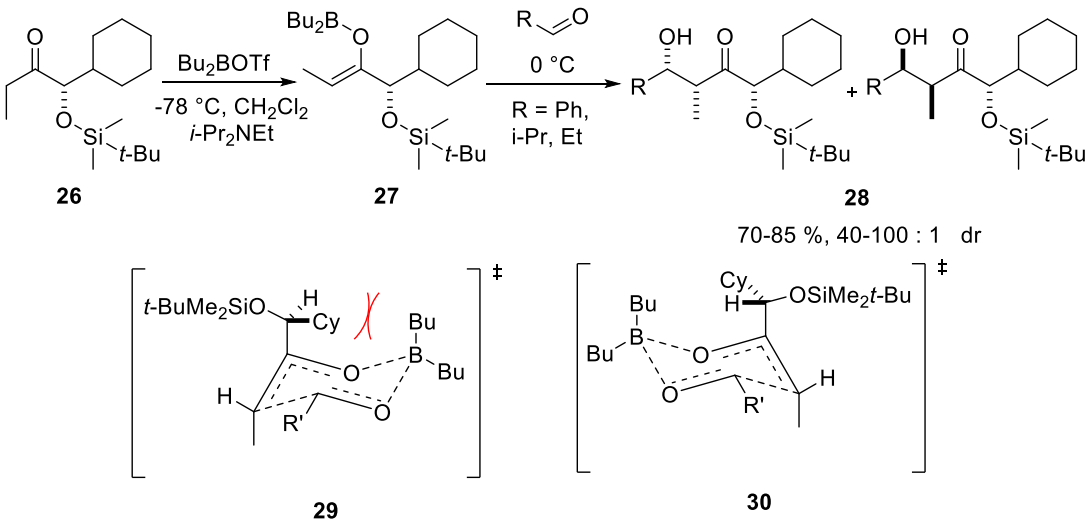
shorter boron-oxygen and boron-carbon bond lengths compared to other metal based systems.[12]



Scheme 5. Stereoselective formation of boron enolates.

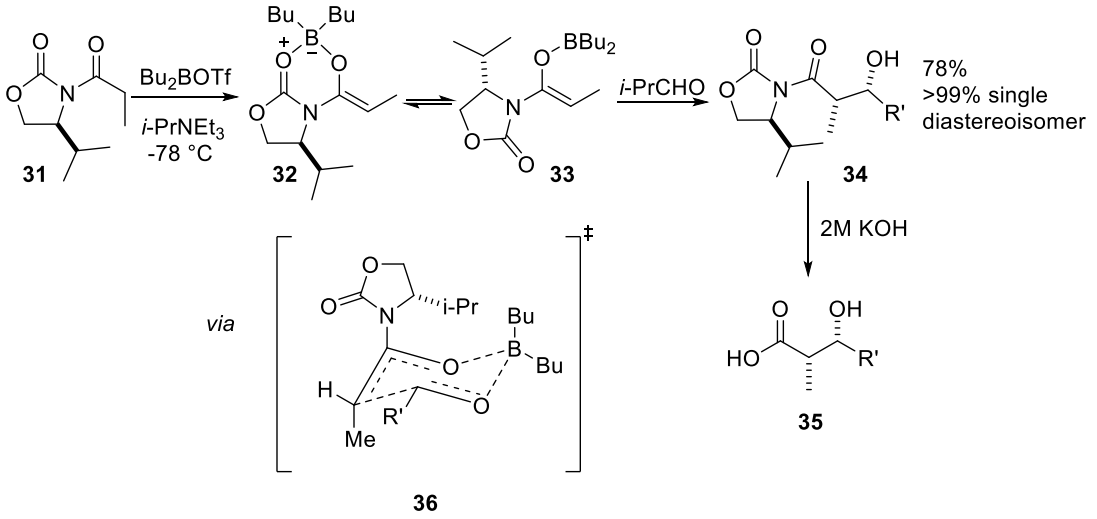
Substrate Control In Asymmetric Aldol Reactions[13]

As control of boron enolate geometry can determine the diasteroselectivity of an aldol reaction, it therefore follows that incorporation of a chiral element can provide an asymmetric variant of the aldol reaction. Masamune has demonstrated the utility of a class of chiral boron enolates.[14] He showed that α-oxygenated boron enolate **27** gives good selectivity for a single stereoisomer of product **28** (Scheme 6). The high stereoselectivity can be rationalised by considering the transition states **29** and **30**. In both cases the silyloxy group orientates itself to minimise dipolar interactions with the enolate. In **29** the bulky silyloxy substituent causes destabilising interactions with the substituents on boron resulting in **30** being the lower energy transition state.[12]



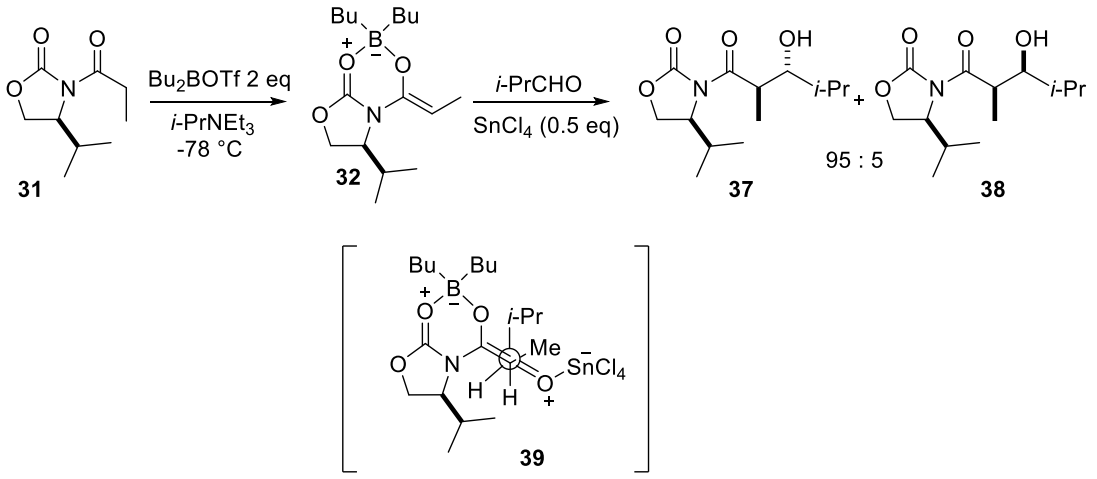
Scheme 6. Masamune's chiral boron enolate.

This concept has also been studied by the Evans group.[15] Using chiral oxazolidone **31** Evans showed that very high *syn*-diastereoselectivity could be achieved in the resulting β-hydroxyl imide **34** (Scheme 7).[16] On hydrolysis this then provides access to chiral carboxylic acid **35**. As before, a chair transition state **36**, in which the enolate is arranged to minimise dipolar and steric interactions, can account for the observed stereoselectivity.



Scheme 7. Evans oxazolidone auxiliary approach.

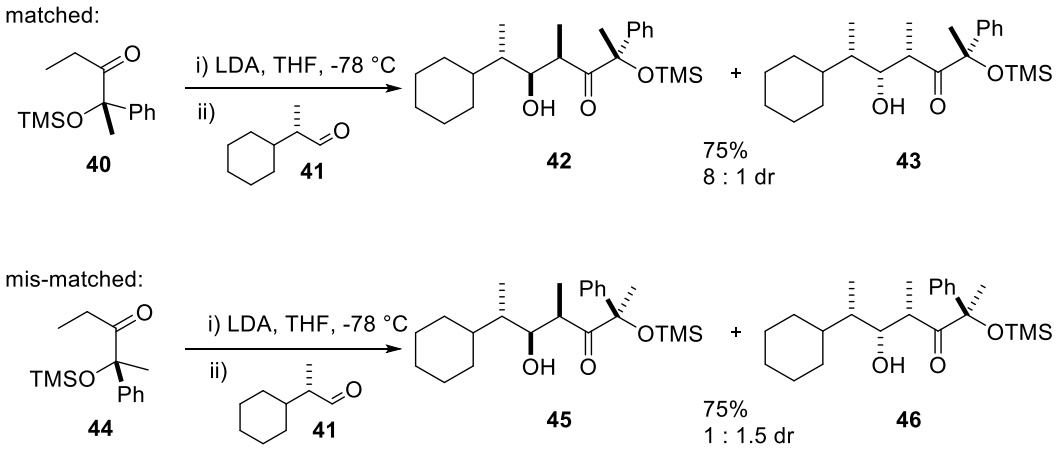
Further elaboration on Evans' work has shown that a second equivalent of dialkyl boron triflate (or an alternative Lewis acid) can produce an *anti*-aldol from the *cis*-enolate.[17] This is because the reaction can now proceed through an open transition state in which the intramolecular bidentate chelation of boron is preserved (Scheme 8).[6] In this case the *syn* aldol is the 'non Evans' diastereoisomer.



Scheme 8. Open aldol transition state.

Reaction of achiral enolates with chiral aldehydes present another means of achieving stereoselective aldol reactions. Nucleophilic addition to chiral aldehydes has been well described by Felkin and Anh, leading to their model for facial selectivity.[18] However, as discussed boron enolate aldol reactions often proceed through cyclic transition states in which other factors influence stereoselectivity. As a consequence most reports in the literature show that chiral aldehydes only impart moderate levels of stereoinduction. Some success has been achieved using a combination of silyl enol ether nucleophiles in conjunction with an achiral Lewis acid (the Mukiayama reaction) to activate the chiral electrophile and promote an open transition state.[12]

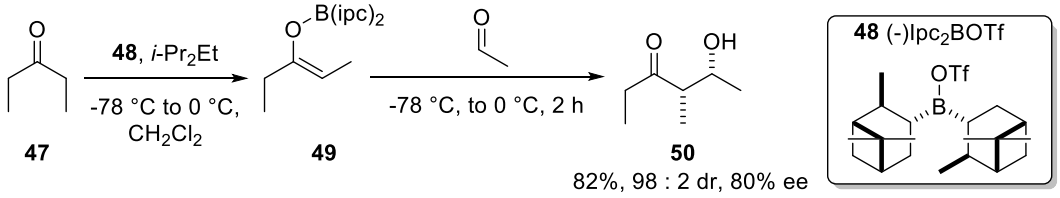
It is not a great leap to see that the two aforementioned methods of stereoinduction, a chiral enolate and a chiral aldehyde, can be combined in a 'matched' fashion to produce aldols with a raised level of stereoinduction. This technique is known as double asymmetric synthesis.[19] Masamune showed that chiral aldehyde **41** matched with (2*S*)-2-phenyl-2-trimethylsilylbutan-3-one **40** to give an aldol adduct with higher diastereoselectivity than when employing an achiral ketone, or indeed the mismatched chiral ketone **44**.[20] Although academically interesting, it has limited use due to its dependence on two enantiomerically pure chiral reaction partners with the 'matching' absolute stereochemistry.



Scheme 9. Double asymmetric synthesis.

It is also possible to achieve chirality transfer from chiral ligands on a boron enolate. This can be advantageous because it produces enantiomerically enriched aldol products from two prochiral starting materials. Paterson[21] showed that disopinocamphenylboron triflate (Ipc_2BOTf) **48** could be used to prepare chiral (*Z*) boron enolates. These boron enolates could then undergo aldol reactions with aldehydes giving access to *syn*-aldols in good enantiomeric excess. Scheme 10

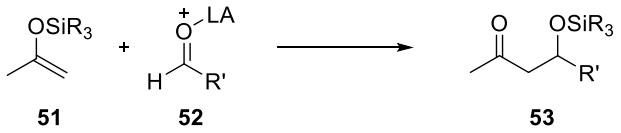
details this sequence. Boron enolate **49** is prepared from diethylketone **47** then reacted with acetaldehyde to give adduct **50** in good enantioselectivity.



Scheme 10. Boron ligand mediated stereochemical induction.

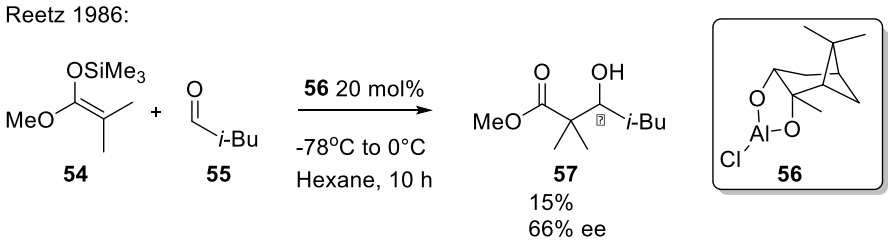
Asymmetric Catalysis In Aldol Reactions

In 1974 Mukaiyama[22] reported that silyl enol ethers could act as latent enolate equivalents, undergoing addition to aldehydes in the presence of Lewis acid activators. This process is now commonly referred to as the Mukaiyama aldol reaction (Scheme 11).[23] In contrast to most boron-mediated aldol reactions, the Lewis acid-catalysed reaction of silyl enol ethers with aldehydes usually proceeds through an open transition state. This means that the geometry of the enol ether is not necessarily reflected in the aldol product stereochemistry.



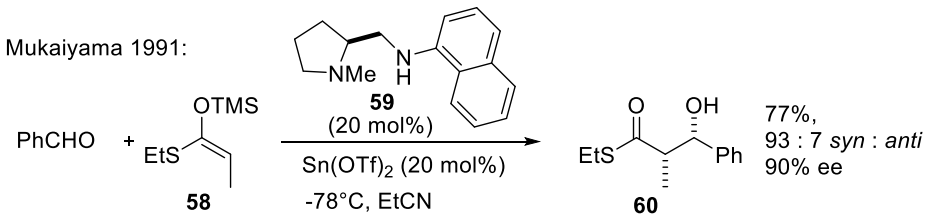
Scheme 11. Mukaiyama aldol reaction.

The requirement of a Lewis acid offers the potential to employ a substoichometric amount of chiral Lewis acid, the first report of such a reaction was in 1986 (Scheme 12).[24]



Scheme 12. First reported enantioselective Mukaiyama aldol reaction.

Since then this field has greatly expanded. There now exists a range of chiral Lewis acids capable of inducing high levels of stereoselectivity in aldol reactions. Catalysts based on tin(II), boron, titanium(IV) and copper(II), in combination with chiral amine or alcohol ligands are most prominent.[23] One illustrative example is shown in Scheme 13.[25]



Scheme 13. Enantioselective Mukaiyama aldol reaction.

Despite these advances there are still long-standing problems associated with substrate controlled and Lewis acid-mediated methodologies. Activation of the donor carbonyl component *via* metal enolate or silyl enol ether formation requires a previous synthetic operation. In each case stoichiometric quantities of reagents are required for the prior synthetic step. This gives the advantage to catalytic methods that allow the crossed aldol reaction of otherwise unmodified carbonyl donors (occasionally referred to as direct as opposed to directed aldol reactions).

One method that overcomes some of these problems involves the use of aldolases.[26] Aldolases are present in all organisms and their role is to take part in the metabolism of carbohydrates and proteins. Although their main function is degradative retro-aldol cleavage of metabolites, under the right conditions, such as an excess of one of the reactants, these equilibrating reactions can be reversed. Mechanistically, there are two distinct classes of aldolase (Figure 1).[26b] Type I aldolases form a nucleophilic enamine intermediate in the active site with the donor substrate **61**; this enamine subsequently adds to the acceptor. Type II aldolases use a Zn^{2+} cofactor which acts as a Lewis acid in the active site. In both cases the resulting stereochemistry is controlled by the chiral active site of the enzyme.

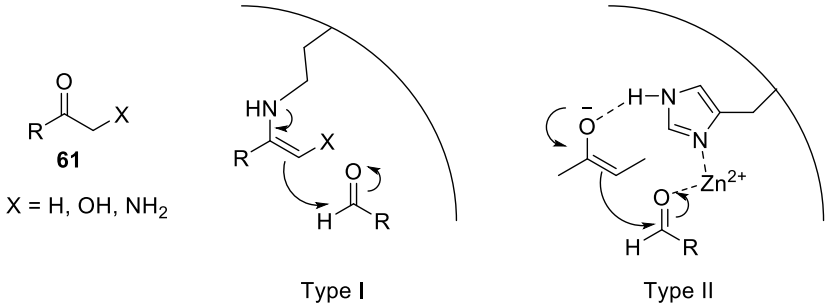
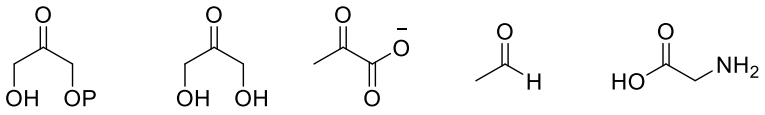


Figure 1. Type I and type II aldolases.

Type I aldolases are primarily found in animals and higher plants, type II aldolases are predominantly encountered in bacteria and fungi. In general, type II aldolases are more stable than type I aldolases.[26c] Both types of enzymes are rather specific for the donor substrate but can be more promiscuous with regards

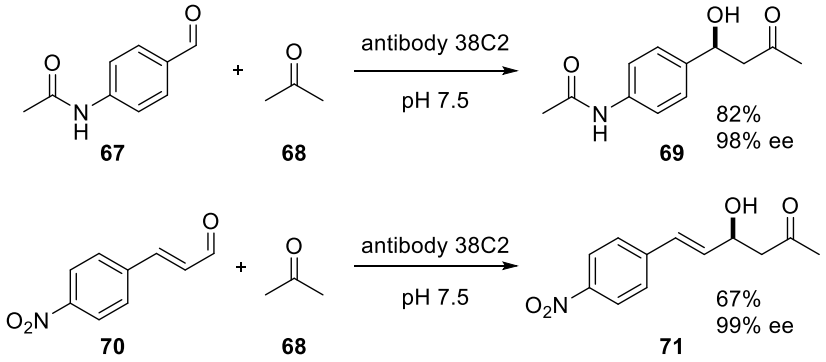
to the acceptor substrate. Aldolases that have been investigated can be further divided into 5 main groups on the basis of the donor substrate they work with[27]: dihydroxy acetone phosphate (DHAP) **62** donors, dihydroxy acetone (DHA) **63** donors, pyruvate **64** donors, acetaldehyde **65** donors and glycine **66** donors (Figure 2).



62 **63** **64** **65** **66**

Figure 2. Adolase donors.

Antibodies that can catalyse the aldol reaction have also been developed. These can be engineered to have substrate specificity different to that of aldolases. Barbas and Lerner showed that antibody 38C2 was an effective catalyst which showed reasonable substrate scope (Scheme 14).[28]

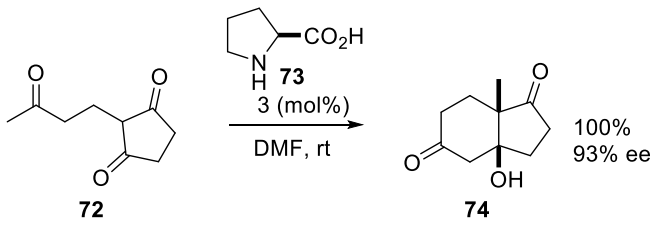


67 **68** **69** **70** **68** **71**

Scheme 14. Aldol reactions of acetone catalysed by Antibody 38C2.

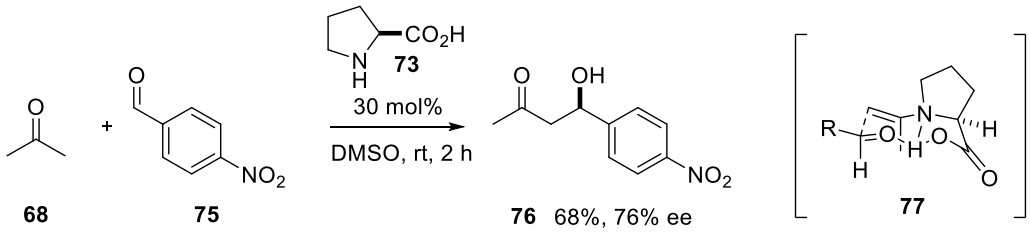
Amines can also catalyse the aldol reaction.[29] Although it has long been recognised[30], it was not until the early 1970s that the first use of a chiral amine to produce an enantioenriched product was reported. This involved the intramolecular aldol reaction of triketone **72** catalysed by L-proline **73** to produce the enantiomerically enriched β-hydroxy ketone **74** (Scheme 15).[31] Hajos and Parrish[31b] found that amines which readily form enamines, such as pyrrolidines, were important to achieve an appreciable rate of reaction. They also reported that the carboxylic acid functionality on proline is essential to obtain a product of high optical purity and that aprotic solvents give best results. They suggested that the reaction proceeds through an enamine intermediate and that hydrogen bonding between the catalyst and substrate was an important interaction in the transition state. Hajos and Parrish speculated that their results 'may be considered an example of a simplified model of a biological system in which (*S*)-proline plays the role of an enzyme'. Following on from this work attempts were made to

expand the substrate scope of the reaction,[29a] however investigations of proline as a catalyst for intermolecular aldol reaction went unreported for the next 26 years. In 2000 the intermolecular proline-catalysed aldol reaction using acetone and non-enolisable aldehydes was published by List, Lerner and Barbas (Scheme 16).[32]



Scheme 15. The proline-catalyzed intramolecular aldol reaction.

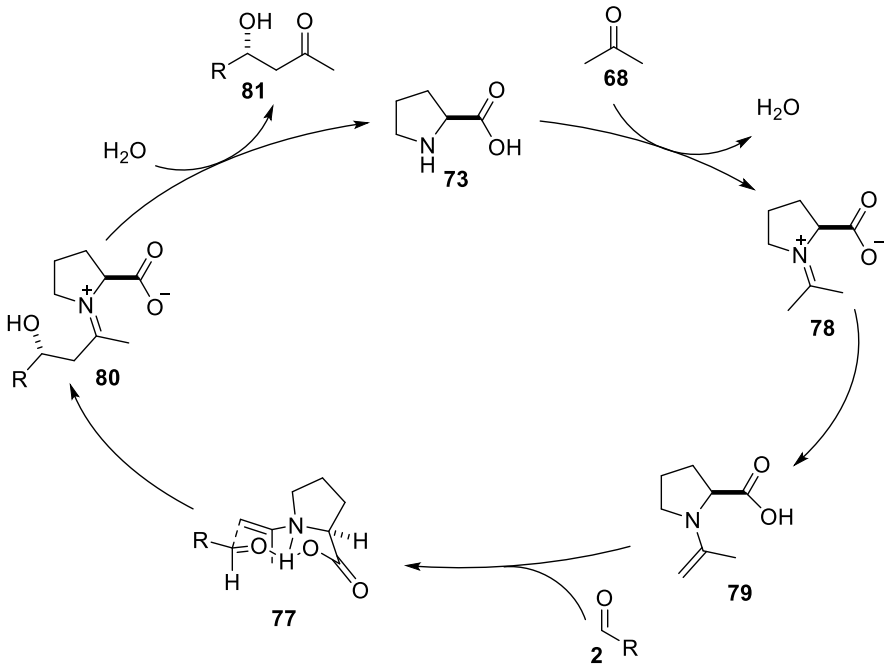
List, Lerner and Barbas proposed a six membered transition state **77** to account for the observed stereochemistry. Here proline is acting in a bifunctional manner forming the nucleophilic enamine intermediate and activating the aldehyde electrophile *via* a hydrogen bond.



Scheme 16. The proline-catalyzed intermolecular aldol reaction.

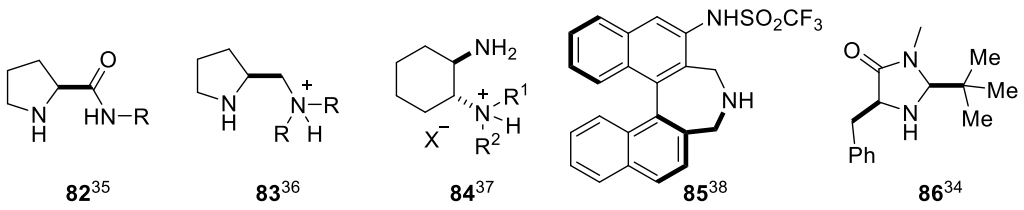
The proposed catalytic cycle for this process is presented in Scheme 17. Formation of the iminium ion **78** significantly lowers the *p*Ka of the α-proton(s) on the carbonyl compound allowing generation of the key enamine intermediate **79**. The aldehyde can then form a hydrogen bond with the proline carboxylate and be attacked by the enamine producing a new iminium ion **80**. Subsequent hydrolysis then affords the product **81** and regenerates the catalyst **73**.

Various other chiral amine structures have been reported to give good selectivity in aldol reactions, most mimic the bifunctional nature of proline using an acidic proton to hydrogen bond to the electrophile. Examples of such amines are **82**-**85** (Figure 3). Amines **82**-**85** influence the stereochemistry of the product by directing the aldehyde to attack from a single diastereotopic face of the enamine intermediate. It is also possible for chiral amines to achieve a similar result by blocking one diastereotopic face of the enamine with steric bulk.[33] One such example is imidazolidinone **86** which was utilised by MacMillan (Figure 3).[34]



Scheme 17. Proposed catalytic cycle of proline promoted aldol reaction.

For enamines to be nucleophilc, good delocalisation of the nitrogen lone pair with the carbon-carbon π orbital in the formed enamine is required. For this reason the amine catalyst has to have good sp^2 hybridisation at the nitrogen in the enamine thus allowing efficient orbital overlap to occur.[39] Although not always necessary, acid co-catalysts are often added to reactions of this type as they are thought to assist in enamine formation.



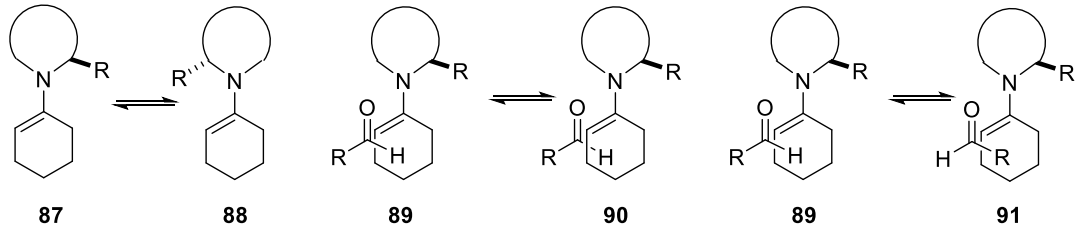
82[35] **83**[36] **84**[37] **85**[38] **86**[34]

prolinamide diamine diaminocyclohexane binaphthylazepine imidazolidinone

Figure 3. Chiral amines for the catalysis of the aldol reaction.

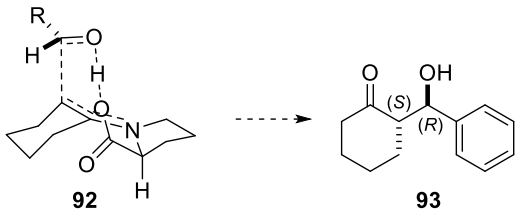
For a chiral amine to give good stereocontrol numerous variables must be controlled. This can be illustrated by considering the reaction of cyclohexanone with an aldehyde. Firstly, a single conformer about the carbon-nitrogen bond of the enamine must be formed (**87** vs **88**). Secondly, a single enamine carbon-carbon double bond isomer must be produced. There is no choice in the example described as a cyclic ketone must give an (*E*)-double bond geometry. Thirdly, the catalyst must be able to bias the approach of the aldehyde to a single face of this enamine, either by favourable interactions or by steric repulsion (**89** vs **90**).

Finally the aldehyde must present preferentially the *Re* or *Si* face (**89** vs **91**) (Scheme 18).



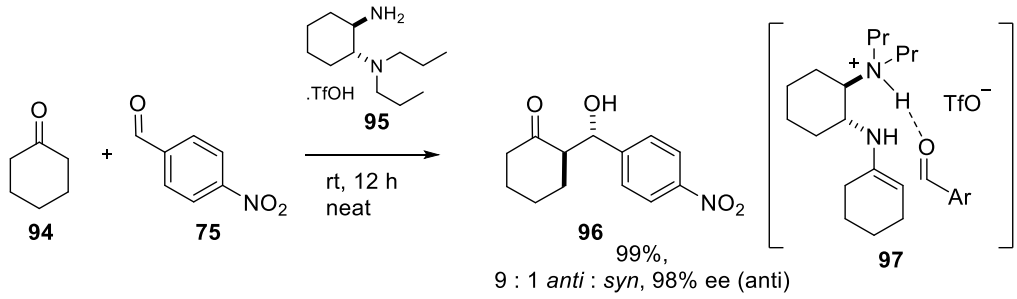
Scheme 18. The aldol reaction of cyclohexanone with an aldehyde.

In an effort to understand how proline is able to catalyse the aldol reaction stereoselectively proline-catalysed aldol reactions have been studied by a combination of computational and experimental methods.[40] Product selectivities of the proline catalysed reaction between cyclohexanone and benzaldehyde have been found to be extremely sensitive to water content.[40] The Houk-List model (Scheme 17) as well as variations including water playing a role in proton relays have been computationally modelled by Rzepa.[41] The lowest energy transition state found was a Houk-List like transition state **92** in which the aldehyde is hydrogen bonding with the carboxylic acid and has its *Re* face presented to an *anti* (relative to the acid) enamine (Scheme 19). Incorporation of water into the transition state was deemed to be unlikely as calculated transition states were higher in energy and computed kinetic isotope effects were incompatible with the experimental values.



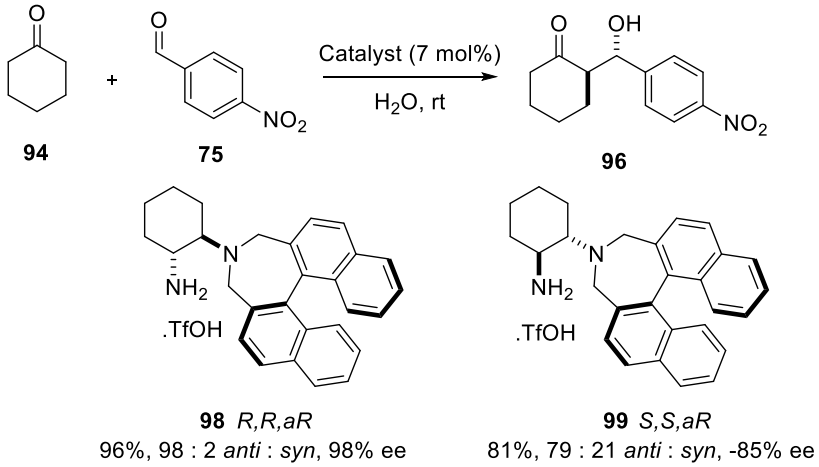
Scheme 19. Aldol transition state for cyclohexanone and benzaldehdye.[41]

An alternative chiral amine core is 1,2-diaminocyclohexane. Luo and Cheng showed that ammonium salt **95** could reliably give good diastereo- and enantioselectivity.[37] A proposed transition state for this reaction is shown in Scheme 20. In this case catalyst **95** manages to control the key stereochemical determining factors discussed above (Scheme 18). A 9 : 1 *anti* : *syn* preference is observed.



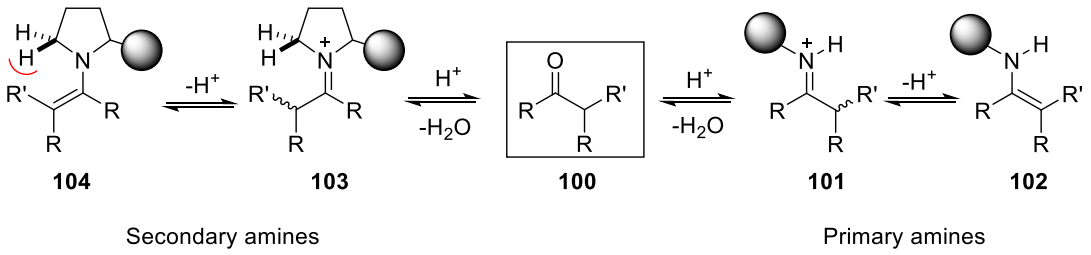
Scheme 20. 1,2-Diaminecyclohexane derivative as an aldol catalyst.

In 2008 Shao reported that a similar 1,2-diaminocyclohexane salt **98** gave high diastereoselectivity in aldol reactions of cyclic ketones with aromatic aldehydes (Scheme 21).[42] Ammonium salts **98** and **99** bear an extra chiral element: a conformationally locked biaryl axis. This can either match or mismatch with the chiral cyclohexane backbone. The central chiral element of the diaminocyclohexane determines the absolute configuration of the product **96** but the axial chirality significantly influences the diastereoselectivity and enantioselectivity of this reaction. The matched combination was found to be *R,R,aR* (amine salt **98**).



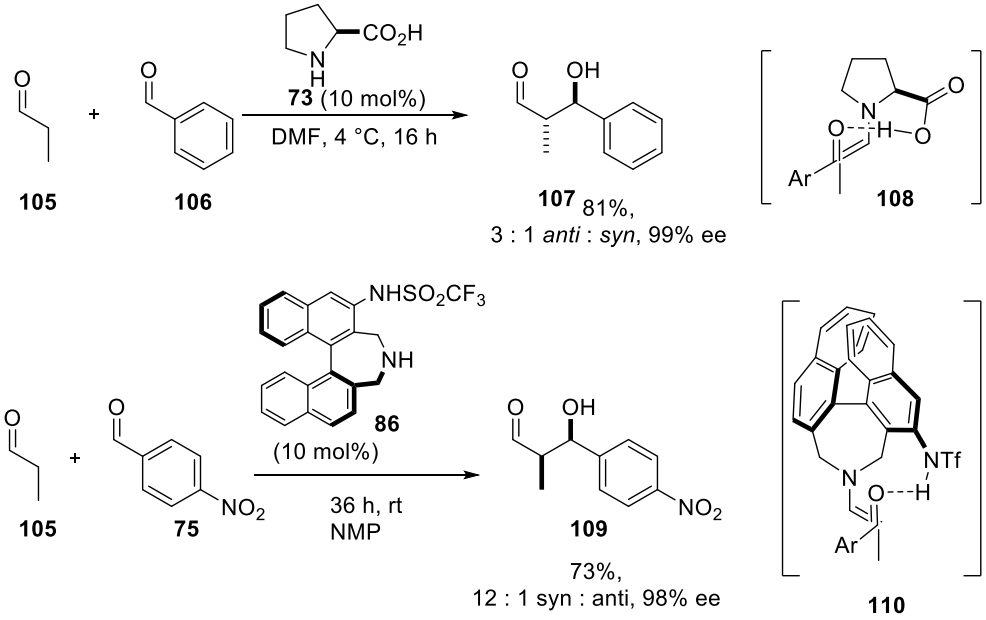
Scheme 21. Cyclohexyldiamines with an additional chiral element.

The two catalysts described above, **95** and **98**, are useful alternatives to proline-derived amines. In general primary amine catalysts have been shown to be more active catalysts for hindered aldehydes and ketones presumably because there is less steric hindrance around the nitrogen atom and enamine double bond (Scheme 22). This means that enamines from primary amines are quicker to form and allow more efficient overlap of the nitrogen lone-pair and the carbon-carbon double bond making them more nucleophilic.[43]



Scheme 22. Secondary vs primary amine catalysis.

Secondary amine catalysts generally form *E* enamines which tend to favour *anti*-aldol products. Recently Maruoka has reported that amine **86**[44] can give *syn*-aldol products in reactions where proline gives rise to the *anti*-aldol product (Scheme 23).[45] Maruoka has proposed that the *syn*-aldol arises from an *E* enamine *via* transition state **110**.[46]

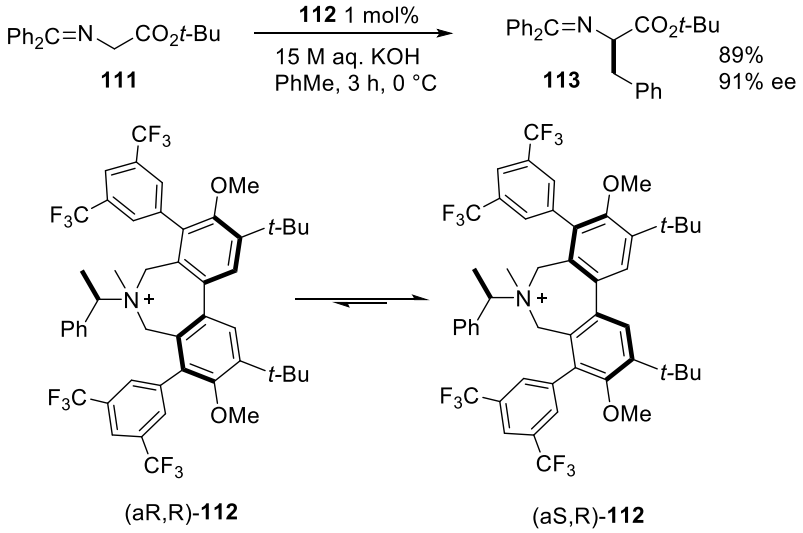


Scheme 23. Maruoka's *syn* selective azepine catalyst.

Results and Discussion

Project aims

Previous work within our group has demonstrated that the *tropos* dibenz[*c,*e]azepinium salt **112** derived from (*R*)-α -methylbenzylamine gives high enantioselectivity in the phase transfer catalysed (PTC) alkylation of glycine imines (Scheme 24).[47] The magnitude and sense of enantioselectivity obtained in these reactions is consistent with the active catalyst preferentially adopting an (a*S*)-conformation about the aryl-aryl bond.[48]



Scheme 24. Tropos dibenz[*c,e*]azepinium salt for PTC alkylations.

Accordingly we decided to investigate if it would be possible to replace the conformationally locked binaphthyl group of **98** with a *tropos* biphenyl group and still retain high stereoselectivity in aldol reactions. It was envisioned that the target dibenz[*c,*e]azepinium salt **113** should be significantly easier to synthesise than the corresponding binaphthyl[*c,e*]azepinium salt **98**. Consequently, if salt **113** could mimic **98**, we considered that it might be a better alternative, especially for use on a larger scale.

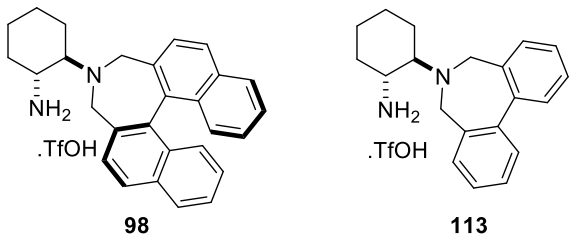
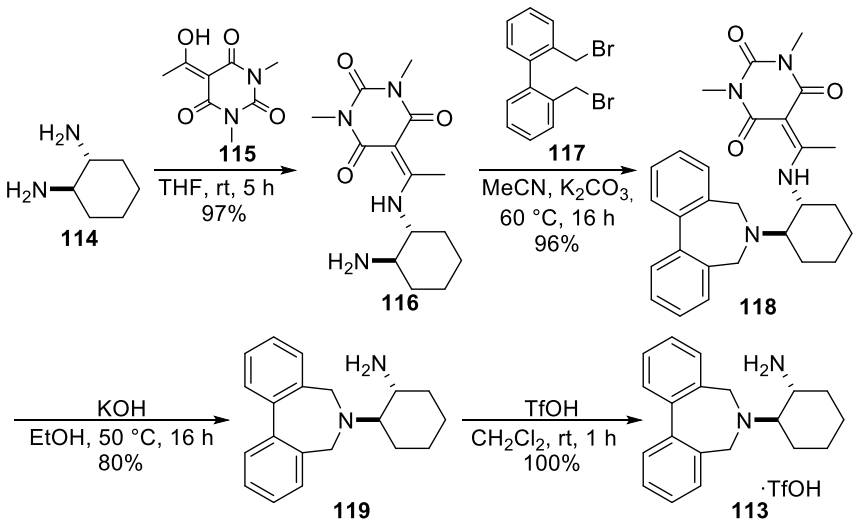


Figure 4

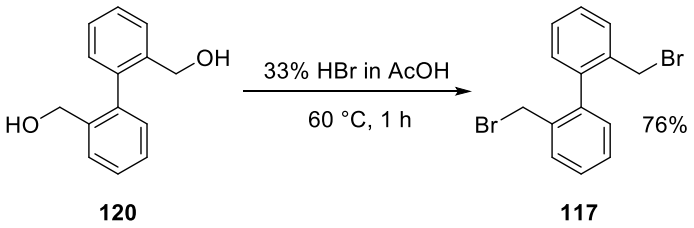
Synthesis and Evaluation of Dibenz[c,e]azepinium Salt 113 and Related Structures

For the synthesis of amine **119** we adapted a sequence previously reported for the synthesis of amine **122**.[49] This started with mono-protection of the commercially available (*R*,*R*)-diamine **114** with 1,3-dimethyl-5-acetyl-barbituric acid (DABOH) **115**. This gave **116** in good yield. Alkylation with dibromide **117**[50] then gave dibenz[*c*,*e*]azepine **118**. Hydroxide mediated cleavage of the DAB group gave primary amine **119** which was quantitatively transformed into salt **113** with triflic acid. This four step sequence gave the target salt **113** in 74% overall yield (Scheme 25).



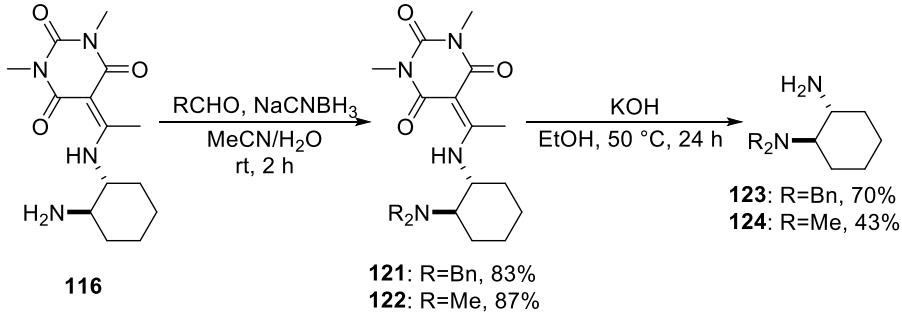
Scheme 25. Synthesis of ammonium salt **113.**

A key difference between the synthesis of **113** and **98** is that the biaryl precursor **117** is readily prepared in one step from commercially available 2,2'-biphenyldimethanol **120** (Scheme 26). This contrasts with the preparation of the corresponding binaphthyl derivative which requires a 3 step synthesis starting from resolved binaphthol.[51]



Scheme 26. Synthesis of **117**.

To aid evaluation of salt **113**, amines **123**[38] and **124**[52] were synthesised following known procedures (Scheme 27).

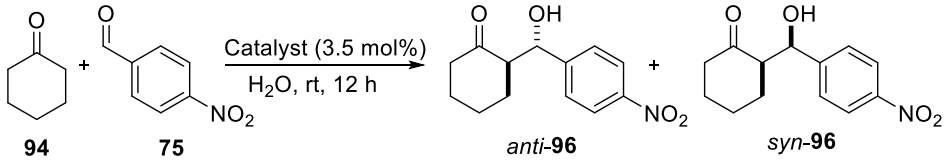


Scheme 27. Synthesis of amines **123** and **124**.

We chose to investigate the aldol reaction between cyclohexanone and nitrobenzaldehyde, repeating the conditions reported for the axially locked

dinaphthyl[*c*,e]azepinium salt **98**,[42] to evaluate the performance of the dibenz[*c*,e]azepinium salt **113**. The triflate salts derived from **123** and **124** were included to gain an insight into the role of the biaryl substituent. The results obtained are shown in Table 1.

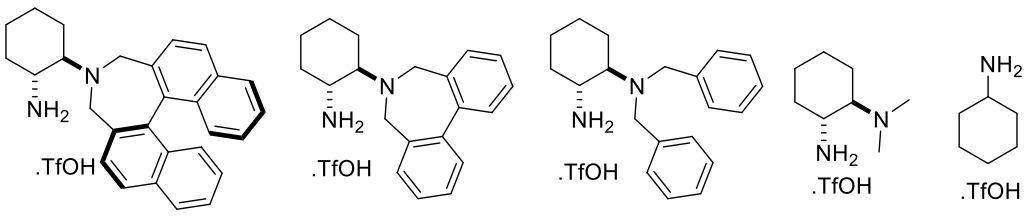
It was found that the *tropos*-diamine salt **113** generated the *anti* aldol product **96** with a high stereoselectivity (entry b).[53] The rate of reaction, diastereoselectivity and enantioselectivity observed were almost identical to those reported for the *atropos*-diamine salt **98**. In contrast *N*,*N*-dibenzyl analogue **125** generated the same aldol product but with significantly reduced diastereoselectivity (entry c). The lower diastereoselectivity obtained with this catalyst is in line with results previously reported by Luo and Cheng for other primary-tertiary *trans*-1,2-diaminocyclohexane salts possessing alkyl substituents on the tertiary amine group.[37] It was also found that the *N*,*N*-dimethyl analogue **126** was a poor catalyst for this process (entry d), a result that is also in agreement with previous observations.[38] It was found that cyclohexylamine salt **127** did not catalyse the reaction at all whereas a 1:1 mixture of cyclohexylamine and salt **127** did lead to ca. 2% conversion after 12 h, and gave a slight preference for the *syn*-aldol product (entry e).



94 **75** *anti*-**96** *syn*-**96**

Entry	Catalyst	Conversion (%)[a]	*anti* : *syn*[a]	ee (%)[b]
a	**98**	100	98 : 2 [42]	98 [42]
b	**113**	100	98 : 2	98
c	**125**	14	90 : 10	97
d	**126**	18	90 : 10	95
e	**127**[c]	2	36 : 64	-

[a] Determined by ^{1}H NMR spectroscopy. [b] ee of *anti*-diastereoisomer.
[c] 1 : 1 mixture of cyclohexylamine and salt **127.**



98 **113** **125** **126** **127**

Table 1

Taken together these results suggest that the reaction probably proceeds *via* an enamine and that the biphenyl group plays an important role in maximising the diastereoselectivity of the aldol reaction. The level of diastereoselectivity also

suggests that catalyst **113** may preferentially adopt an *aR*-axis during the carbon-carbon bond forming step.

Although highly stereoselective, this procedure was found to be problematic. As the organic substrates were not soluble in water they tended to stick to the sides of the reaction vessel and were not well dispersed. This led to difficulties monitoring the reaction and did not avoid the use of organic solvents as an extractive workup was still required. Consequently we decided to investigate the use of an organic solvent in which the reaction mixture was homogeneous. Initially we employed dichloromethane and found that the reaction was slower than that carried out in water. We next attempted to increase the rate of reaction by increasing the concentration of cyclohexanone (Figure 5). Using 5 mol% of catalyst **113**, it was found that varying ketone concentration between 0.5 M and 4.0 M had a dramatic effect on the rate of reaction. At concentrations below 0.5 M the reaction took ca. 58 h to reach completion, whereas at concentrations of 4.0 M and above it was complete within 3 h. In neat cyclohexanone (9.7 M) the reaction was complete within 2 h. The selectivity of the reaction was unchanged by variations in ketone concentration as in all cases the *anti*-aldol product **96** was obtained with ≥97:3 dr and 97±1 % ee.

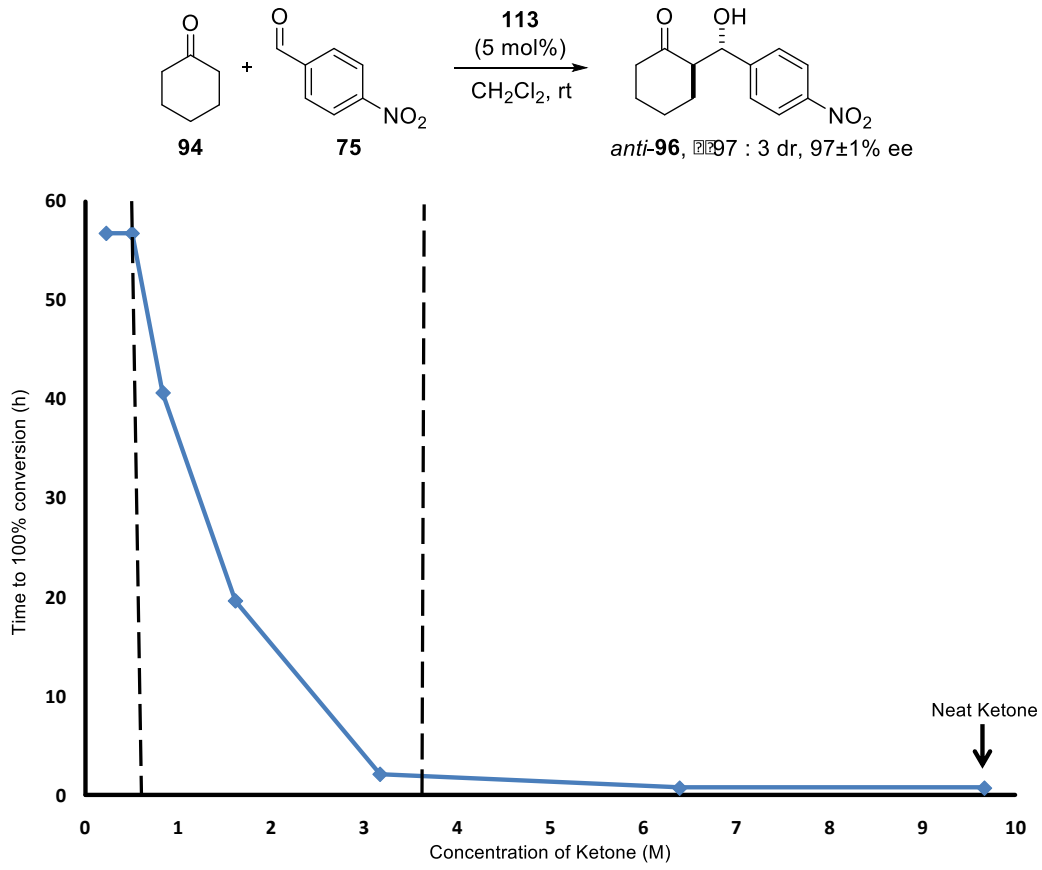
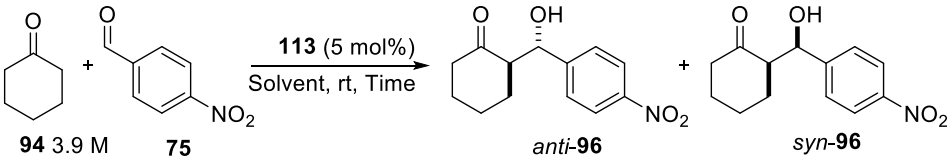


Figure 5. Effect of ketone concentration on rate of reaction.

Reaction conditions employing 5 mol% catalyst and a ketone concentration of 3.9 M were selected to probe the effect of changing the reaction solvent. Another member of the research group, Tim Evans, carried out this study and the results are presented in Table 2.[54] It was found that the process is tolerant of a wide range of solvents. In all cases the *anti*-aldol product **96** was obtained as the major product. Diastereoisomer ratios typically ranged from 95:5-98:2 and enantiomeric excesses for the *anti*-aldol **96** were typically 96-99%. It was found that the reactions were slower when more polar solvents were used (Entries j-n). This may be because these solvents (ε>20) are better able to stabilise polar intermediates, thus retarding the catalytic cycle.



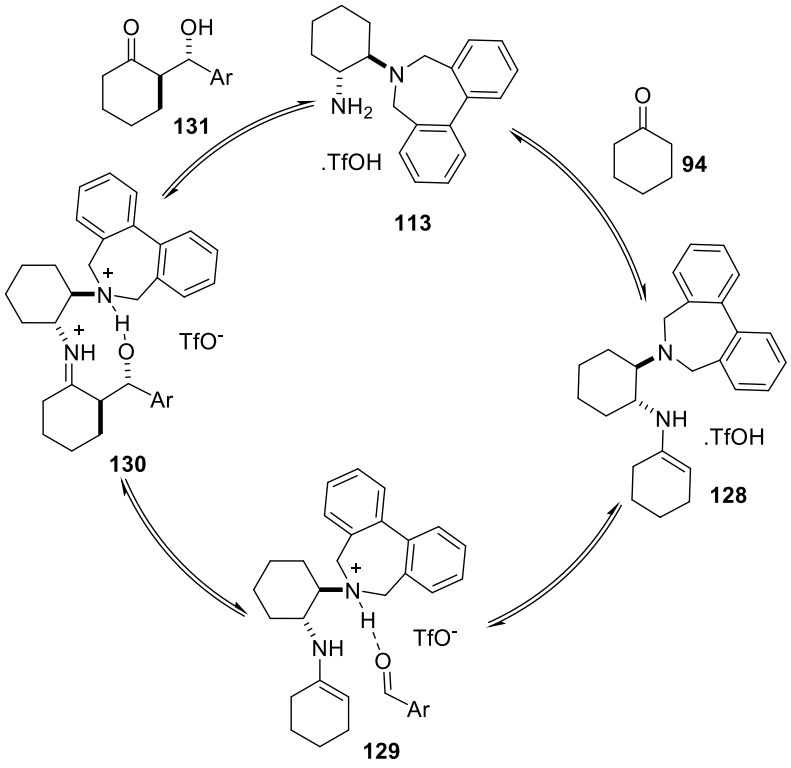
Entry	Solvent	Dielectric Constant (ε)	Time (h)[b]	*anti* : *syn*[c]	ee (%)[d]
a	PhMe	2.4	3	97 : 3	96
b	$(MeO)_2CO$	3.1	3	95 : 5	93
c	*t*-BuOMe	4.5	3	97 : 3	97
d	EtOAc	6.0	3	97 : 3	96
e	2-Me-THF	7.0	3	97 : 3	96
f	THF	7.6	3	97 : 3	96
g	CH_2Cl_2	8.9	3	96 : 4	96
h	Cyclohexanone[a]	16.1	3	98 ; 2	99
i	*i*-PrOH	19.9	3	97 : 3	98
j	EtOH	24.6	6	92 : 8	96
k	MeOH	32.7	15	95 : 5	98
l	CH_3CN	35.9	6	95 : 5	97
m	DMF	36.7	15	97 : 3	98
n	H_2O	78.3	8	97 : 3	98

[a] 9.7 M Ketone used. [b] Time required for ≥97% conversion.
[c] Determined by ^1H NMR spectroscopy. [d] ee of *anti*-diastereoisomer.

Table 2. Effect of solvent on reaction.

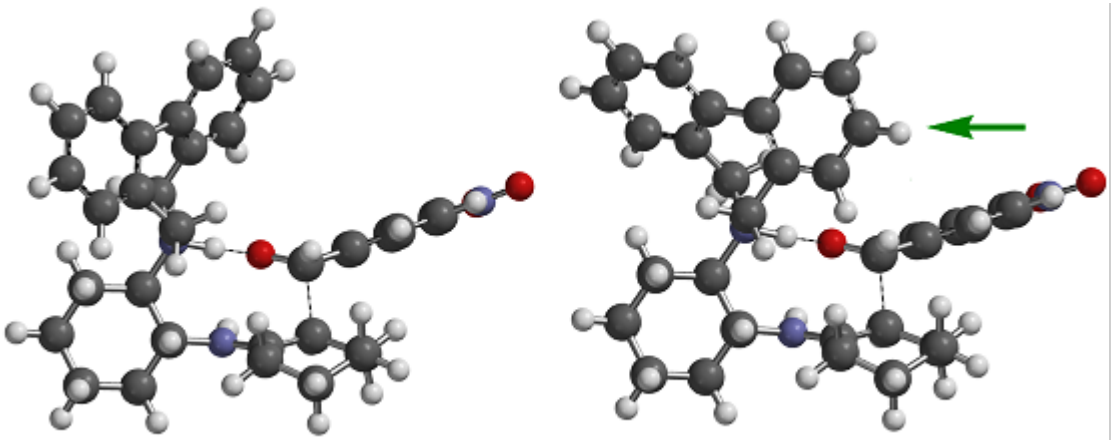
Proposed Catalytic Cycle

A catalytic cycle in which primary tertiary diamine salt **113** is acting in a bifunctional manner is proposed (Scheme 28). As stated above, the magnitude of stereoselectivity observed with **113** suggests that the reaction may preferentially proceed with the *tropos*-biaryl element adopting a (a*R*)-conformation during the carbon-carbon bond forming step. To investigate this further we examined potential transition states for the carbon-carbon bond forming step using DFT.[55] These suggested that **132** and **133** were the two most viable transition states that could lead to the *anti*-aldol precursor (Figure 6).



Scheme 28. Plausable catalytic cycle for aldol reaction mediated by **113**.

Both transition state structures have the aldehyde in the same orientation, the only difference between the two is the conformation of the azepinium ring, **132** having an (a*S*)-conformation about the biaryl axis, and **133** having an (a*R*)-conformation.



132 (a*S*) **133** (a*R*)

Figure 6. Predicted transition state structures (B3LYP/6-31G**) for conversion of **129** to **130**.[55]

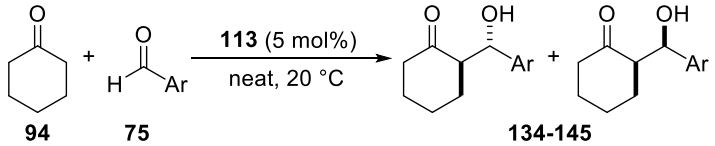
In the gas phase, **132** and **133** were predicted to be almost identical in energy, with **132** being favoured by 0.1 kcal/mol. Inspection of these two transition state structures shows that in **133**, one of the aryl rings in the dibenz[*c*,*e*]azepinium

fragment (indicated by the green arrow) projects over the reactive enamine moiety. This fragment blocks the aldehyde from approaching with an orientation that would lead to the (minor) *syn*-diastereoisomer. In **132**, this aryl ring is twisted away from the region above the enamine and this may allow the aldehyde to approach *via* orientations that would lead both *anti*- and *syn*-aldol products. The two transition state structures shown are consistent with the proposal that the high diastereo- and enantioselectivities reported are a consequence of the dibenz[*c*,*e*]azepinium salt **113** acting as a bifunctional catalyst. They are also consistent with earlier observations that the corresponding (*R*,*R*,a*R*)-*atropos* binaphthyl[*c*,*e*]azepinium salt **98** also delivers high diastereo- and enantioselectivity, whereas its (*S*,*S*,a*R*)-diastereoisomer **99** (which would necessarily lead to a transition state analogous to **132**) results in significantly lower levels of diastereoselectivity. However, as these two proposed transition states are predicted to be nearly identical in energy, it may be that the high diastereoselectivity obtained using **113** is not a consequence of induced atropisomerism. Instead, it may simply be that the dynamic nature of the *tropos* dibenz[*c*,*e*]azepinium ring results in an effective steric barrier preventing approach of the aldehyde in orientations that would lead to the minor *syn*-aldol product.

Reaction Scope

The results shown in Table 2 suggest that running the reaction in neat ketone is likely to give the best results, consequently these conditions were adopted for investigation into substrate scope. Results from variation of the aromatic aldehyde are presented in Table 3. Reactions involving electron-deficient aromatic aldehydes (Entries a-g) were complete within 4 h at room temperature. For these substrates the *anti*-aldol products were obtained as the major product and diastereoisomer ratios ranged from 95:5 to 99:1. The enantiomeric excesses of the *anti*-aldol products were also high in all cases (96-98% ee). Although some variation in diastereoisomeric ratio and enantiomeric excess was observed, this does not appear to correlate to the substitution pattern in the aromatic ring.

For electron-neutral and electron-rich aromatic aldehydes (Entries h-l) the outcome was more complicated. Apart from Entry j, furfural (see later), all give the *anti*-aldol products as the major isomer, and in all cases the ee of the product was high (94-98% ee). However, with these substrates the aldol process was found to be slower, and generally did not proceed to completion. The reaction times quoted in Table 3 refer to the point at which the ratio of starting material



94 75 134-145

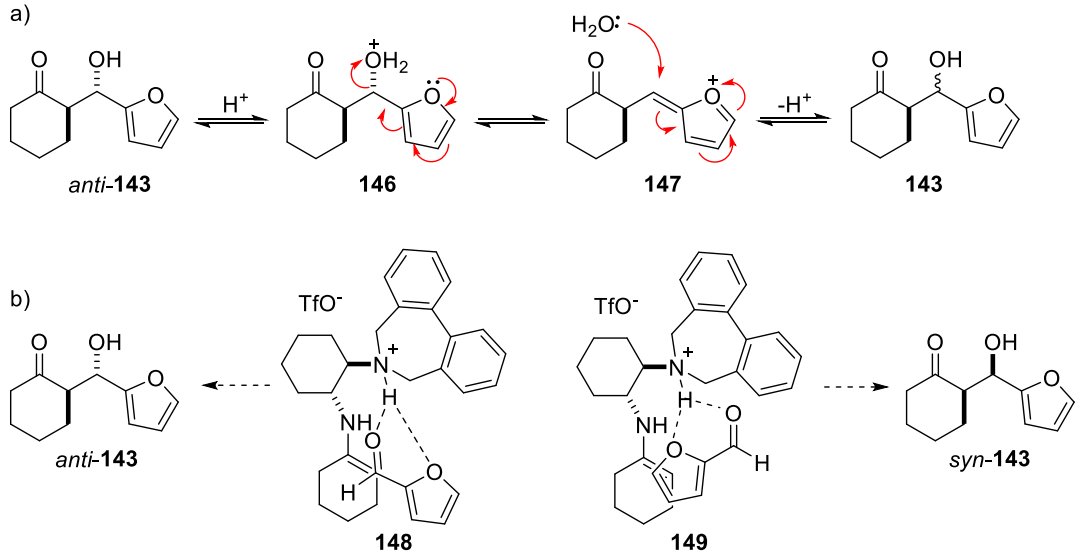
Entry	Product	Ar	Time (h)	Yield (%)[a]	*anti* : *syn*[b]	ee (%)[c]
a	**134**	3-NO_2-C_6H_4	3	88	97 : 3	96
b	**135**	2-NO_2-C_6H_4	3	89	99 : 1	96
c	**136**	4-Br-C_6H_4	3	90	98 : 2	98
d	**137**	3-Br-C_6H_4	3	92	95 : 5	98
e	**138**	2-Br-C_6H_4	3	87	97 : 3	96
f	**139**	4-CN-C_6H_4	3	91	98 : 2	97
g	**140**	4-Cl-C_6H_4	4	84	97 : 3	97
h	**141**	Ph	6	61 (75)[d]	96 : 4	95
i	**142**	2-Naphthyl	5	63 (86)[d]	98 : 2	98
j	**143**	2-Furyl	4	89	50 : 50	89 (95)
k	**144**	3-Furyl	15	65 (73)[d]	96 : 4	98
l	**145**	4-MeO-C_6H_4	30	25 (93)[d]	87 : 13	92

[a] Isolated yield after purification. [b] dr calculated from ^{1}H NMR of crude materials. [c] ee of *anti*-product. ee in parentheses is that of the *syn*-product. [d] Yield in parentheses is based on consumed aldehyde.

Table 3. Aldehyde substrate scope.

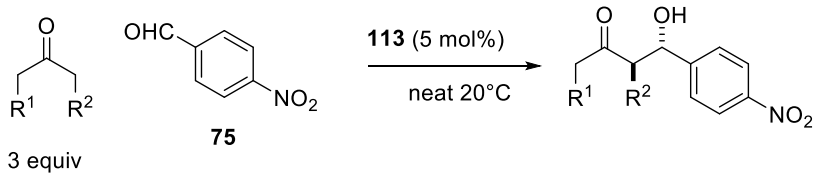
(aldehyde) to product remains constant. After this point, the proportion of product does not increase, but the dr starts to diminish. This is most pronounced for the electron-rich aromatic aldehyde anisaldehyde (Entry l), which after 6 h gave the *anti*-aldol product **145** in 93 : 7 dr, but after 30 h this deteriorated to 87 : 13. As the catalyst and starting materials do not appear to degrade under the reaction conditions, this is most likely a consequence of equilibration *via* a retro-aldol reaction. It is known that primary-tertiary *trans*-1,2-diaminocyclohexane salts are able to catalyse the retro-aldol reaction, and that electron rich aldehydes are suitable candidates as their equilibrium point lies closer to the ketone/aldehyde side.[56]

The results with furfural (Entry j) are anomalous in that the diastereomeric ratio is significantly lower than in other cases. We envisaged that this could be for one of two reasons: i) the product was able to epimerise the hydroxyl stereogenic centre assisted by the furan ring (a, Scheme 29), ii. The oxygen of the furan ring was interfering in the hydrogen bonding network and favouring and alternative approach of the aldehyde (b, Scheme 29). To test this we subjected *anti*-**143** to the reaction conditions but observed no change in the diastereomeric ratio by ^{1}H NMR. We also investigated the use of 3-furyl aldehyde (Entry k) which could not form the hydrogen bond indicated in pathway b. This gave high selectivity for the *anti*-diastereoisomer. Taken together these results suggest that epimerisation is not occurring and that pathway b might account for the poor diastereoselectivity observed with furfural.



Scheme 29. Possible explanations for low diastereoselectivity in adduct **143**.

We next investigated the scope of the reaction with respect to the ketone (Table 4). It was found that when the ketone was changed it was generally necessary to modify the reaction conditions in order to optimise stereoselectivity. Using cyclopentanone (Entry a) the reaction was found to proceed quickly but yielded a substantial amount of bis-aldol adduct. This could be suppressed by lowering the concentration of the aldehyde. The diastereoselectivity using cyclopentanone was lower than when cyclohexanone is employed as the ketone. With cycloheptanone (Entry b) the rate of reaction was slower but the yield and diastereoselectivity were good. The addition of 2 equivalents of H_2O was found to raise the enantioselectivity from 72% ee to 87% ee. Next we examined three acyclic ketones, in each case the reactions were found to be slower than cyclohexanone, but addition of *m*-nitrobenzoic acid (5 mol%) was found to increase their rate of reaction.[37] Using acetone (Entry c), increasing the ketone concentration and cooling to 10 °C helped to minimise the amount of bis-aldol by-product formed. Using 3-pentanone (Entry d) the *syn*-aldol **155** was obtained as the major product. This is presumably due to the formation of a *cis*-enamine as opposed to the *trans*-enamine that is formed with cyclic donors. This is in agreement with results reported for a related primary-tertiary diamine catalyst.[38] Next unsymmetrical donor, benzyloxyacetone **152** was investigated. Again the *syn*-aldol was favoured in high ee. In this case only the branched aldol product (*syn* and *anti* **156**) could be detected by ^{1}H NMR, indicating that the reaction proceeds with high regioselectivity.

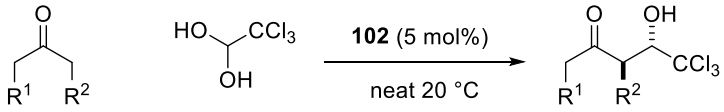


Entry	Ketone	Product	R^1	R^2	Time (h)	Yield (%)	*anti* : *syn*	ee (%)[a]
a[b,c]	**150**	**153**	—$(CH_2)_2$—		3.5	76	80:20	97
b[d]	**151**	**154**	—$(CH_2)_4$—		13	99	90:10	87
c[c,e,f]	**68**	**76**	H	H	22	86	-	88
d[c,e]	**47**	**155**	CH_3	CH_3	30	93	20:80	98
e[e]	**152**	**156**	H	OBn	10	92	17:83	98

[a] ee of major diastereoisomer. [b] Aldehyde added in 3 batches to minimise formation of bis-aldol adduct. [c] 10 eq of ketone. [d] Water (2 eq) was added. [e] *m*-nitrobenzoic acid (5 mol%) was added. [f] Reaction performed at 10 °C.

Table 4. Variation of ketone donor.

Finally the use of an aldehyde hydrate, chloral hydrate, as an aldehyde equivalent was examined. It was found that this reacted with both cyclopentanone and cyclohexanone giving the *anti*-diastereoisomer in good ee (Table 5).



Entry	Ketone	Product	R^1	R^2	Time (h)	Yield (%)	*anti* : *syn*	ee (%)[a]
a	**150**	**157**	—$(CH_2)_2$—		2	70	75 : 25	94
b	**94**	**158**	—$(CH_2)_3$—		2	91	98 : 2	>99

[a] ee of major diastereoisomer

Table 5 Aldol reactions using chloral hydrate

Conclusions

The results presented in this chapter detail our discovery of tropos dibenz[c,e]azepinium salt **113** as an efficient catalyst for the commercially important aldol reaction. These results were also presented in a publication by the group in 2011.[57] Azepinium salt **113** is derived from *trans*-1,2-diaminocyclohexane and can be prepared in four steps and 74% overall yield. This salt is able to promote stereoselective crossed-aldol reactions between ketones and aldehydes. When cyclic ketones are used, *anti*-aldol products are obtained with high diastereo- and enantioselectivity. In contrast acyclic ketones were found to favour *syn*-aldol products. These observations are consistent with cyclic ketones reacting *via* an (*E*)-enamine intermediate and acyclic ketones reacting preferentially *via* a (*Z*)-enamine intermediate. High conversions and isolated yields are obtained when electron deficient aromatic aldehydes or chloral

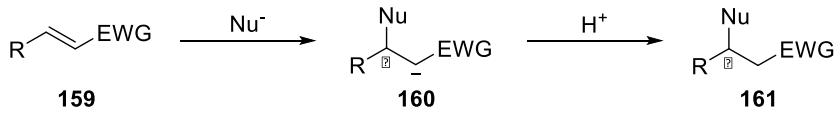
hydrate are used. With electron neutral and electron deficient aromatic aldehydes the reactions do not proceed to completion, but in most cases reasonable isolated yields (60-65%) of the aldol products can be obtained and the stereoselectivity is good.

The introduction of the biphenyl axis is particularly effective at delivering a product with a high diastereomeric ratio. The biphenyl system is able to mimic a highly diastereoselective axially locked binaphthyl system, but the biphenyl system holds the advantage of being significantly easier to synthesise and install than the binaphthyl equivalent.

Chapter 2: N-Conjugate Addition Reactions Using 1,2-Diaminocyclohexane Derived Catalysts

Introduction

Conjugate additions (1,4-additions) are the addition of a nucleophile to an alkene or alkyne attached to an electron withdrawing group. This nucleophilic addition is followed by the trapping of the anionic intermediate with an electrophile. In the simplest case this is a proton (Scheme 30). The field of research on conjugate addition reactions is large and has been summarised comprehensively elsewhere.[58]



159 160 161

Scheme 30. Conjugate addition reaction.

Akin to the aldol reaction discussed earlier, much research has been dedicated to the control of stereochemistry in conjugate addition reactions. Enantioselective conjugate addition of carbon centred nucleophiles is well developed. The use of organometallic reagents in combination with substoichiometric amounts of chiral ligands has emerged as the method of choice (Scheme 31).[59]

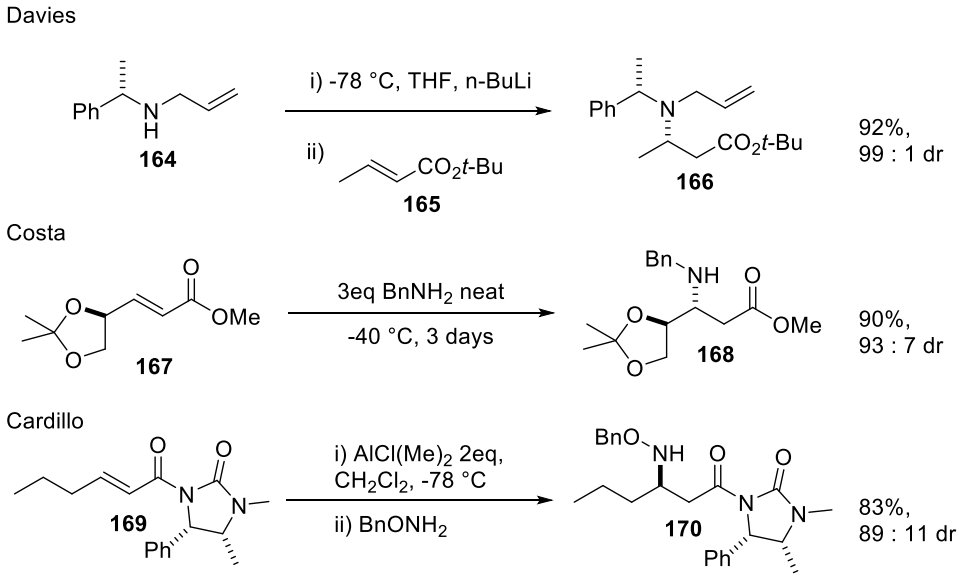


162 163

Scheme 31. Enantioselective conjugate addition reaction of carbon nucleophile.

In comparison to the carbon equivalent, enantioselective conjugate addition of nitrogen centred nucleophiles (enantioselective N-conjugate addition) is less well developed.[60] Stereoselectivity in the N-conjugate addition can be induced through the use of pre-existing chirality in a reaction partner. Some examples are shown in Scheme 32. Davies showed that chiral amine **164** could react with α,β-unsaturated ester **165** diastereoselectively.[61] Costa showed that benzylamine reacted diastereoselectively with ester **167**.[62] Cadillo showed that imide **169** is able to react diastereoselectively with O-benzylhydroxylamine.[63] In this case the use of a Lewis acid, dimethylaluminium chloride is required. These examples highlight that good stereoselectivity can be obtained *via* the use of pre-existing chirality in a reaction partner.

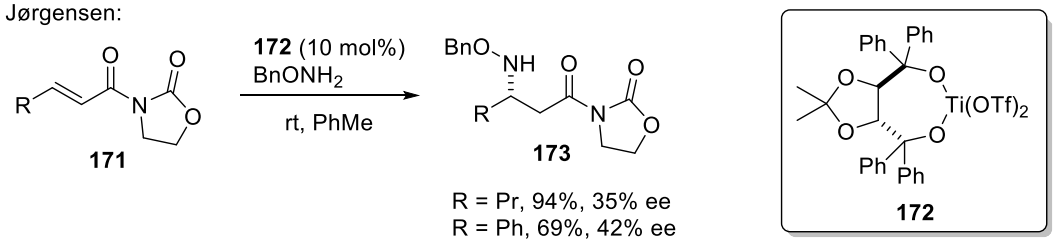
A major disadvantage of using a chiral reaction partner is that a full equivalent of enantiopure substrate is required. If the whole structure is not required in the final product, further steps to remove the chiral element (auxiliary) will be necessary.



Scheme 32. Substrate control in stereoselective *N*-conjugate addition reactions.

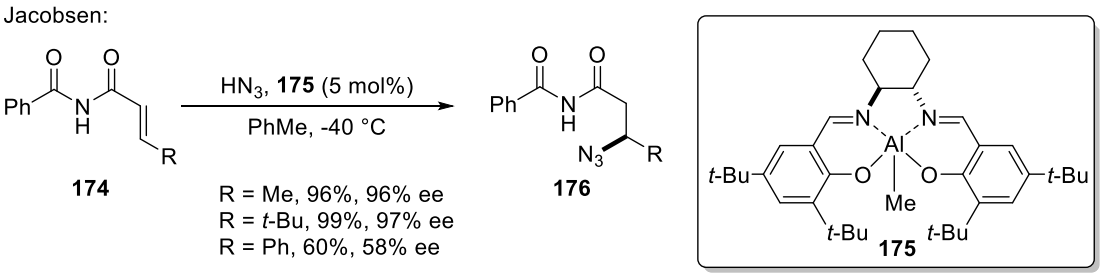
Lewis Acid Catalysed N-Conjugate Additions[64]

In 1996 Jørgensen reported the use of a chiral Lewis acid catalyst for N-conjugate addition reactions.[65] He showed that in the presence of 10 mol% of chiral titanium complex **172** O-benzylhydroxylamine could react with *N*-acylated oxazolidinones **171** to produce enantio-enriched products (Scheme 33). Enantioselectivity was modest (up to 42% ee), but this work did establish a suitable combination of substrates for a metal Lewis acid-promoted *N*-conjugate addition reaction. It was shown that all three components of the reaction mixture must be chosen carefully as i) the Lewis acid is required to preferentially bind with the electrophile, not exclusively the nucleophile, and ii) the nucleophile must be of appropriate nucleophilicity to perform the conjugate addition, but only in the presence of the catalyst.



Scheme 33. Catalytic enantioselective *N*-conjugate addition reaction.

Further studies into Lewis acid-catalysed N-conjugate addition reactions have led to higher levels of enantioselectivity.[64] Jacobsen showed that chiral (salen)Al(III) complex **175** promoted the addition of hydrazoic acid to α,β-unsaturated imides (Scheme 34).[66]

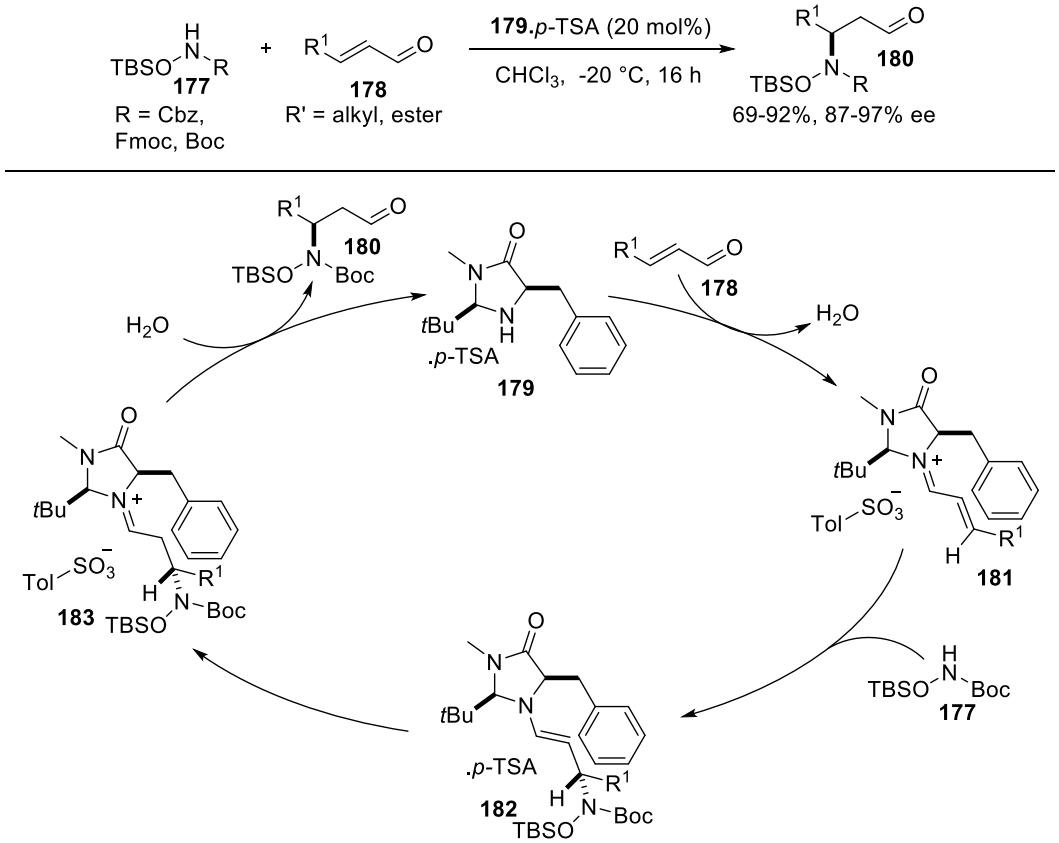


Scheme 34. Catalytic enantioselective *N*-conjugate addition reaction.

Asymmetric Organocatalysis

The relatively recent emergence of 'asymmetric organocatalysis', that is the use of organic molecules to carry out reactions in a catalytic and enantioselective way, is proving to be useful when performing many chemical transformations. Conjugate additions catalysed by organic molecules are a key application of asymmetric organocatalysis.[67] Publications in the smaller field of asymmetric organocatalytic *N*-conjugate additions have been reviewed.[68]

Asymmetric Organocatalysed N-Conjugate Additions to α,β-Unsaturated Aldehydes



Scheme 35. Catalytic *N*-conjugate addition reaction reported by MacMillan.

The first report of an asymmetric organocatalytic N-conjugate addition reaction was by MacMillan.[69] He utilised chiral imidazolidinone **179** as a catalyst for the reaction between *N*-silyloxycarbamates and α,β-unsaturated aldehydes. A proposed catalytic cycle is shown in Scheme 35. The oxazolidinone combines with the α,β-unsaturated aldehyde to form a conjugated iminium ion **181**. This iminium ion **181** has a lower energy LUMO than the parent α,β-unsaturated aldehyde, thus making it more reactive towards nucleophiles.[70]

Many further subtleties of this reaction contribute to its success. Roles for both the catalyst and nucleophile must be clearly established. The chiral amine catalyst must not undergo conjugate addition reaction, as this would eventually lead to catalyst consumption. The nucleophile must not participate in iminium ion formation as this would lead to a racemic product. The α-silyloxy group on the nucleophile increases its nucleophilicity, while the carbamate moiety renders the nucleophile non basic so it can permanently lose its proton upon conjugate addition, this prevents the reverse $E1_{CB}$ (retro conjugate addition) reaction.

The catalyst imparts stereoselectivity in the product by hindering access to one diastereotopic face of iminium intermediate **181**. For the catalyst to produce a product of high enantiomeric excess, effective steric shielding of one from two diastereotopic faces must be achieved. Of equal importance is the formation of a single iminium geometry as a mixture of *E*/*Z* isomers would result in reduced diastereoselectivity in the addition step. Catalyst **179** favours the (*E*) s-*cis* geometrical isomer upon condensation with an α,β-unsaturated aldehyde (Figure 7). The sterically demanding *tert*-butyl group dictates that the (*E*)-isomer dominates over the (*Z*)-isomer. An s-*trans* conformation is favoured over s-*cis* to minimise steric interaction.

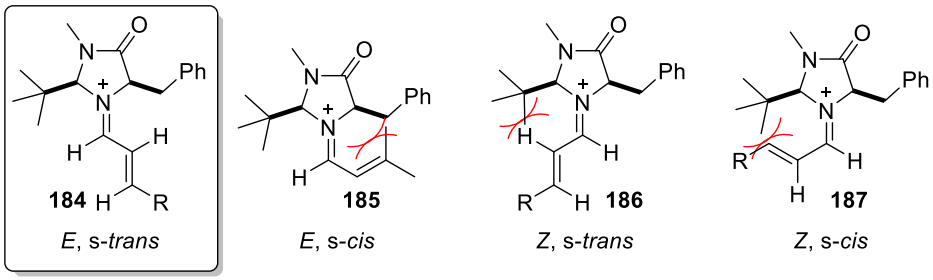
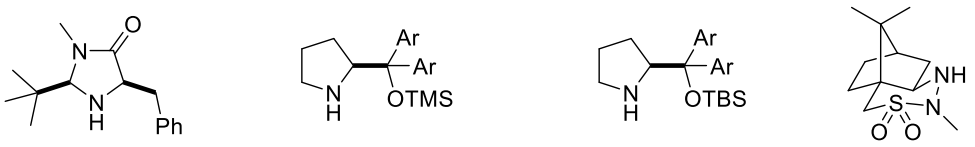


Figure 7. Potential iminium intermediates.

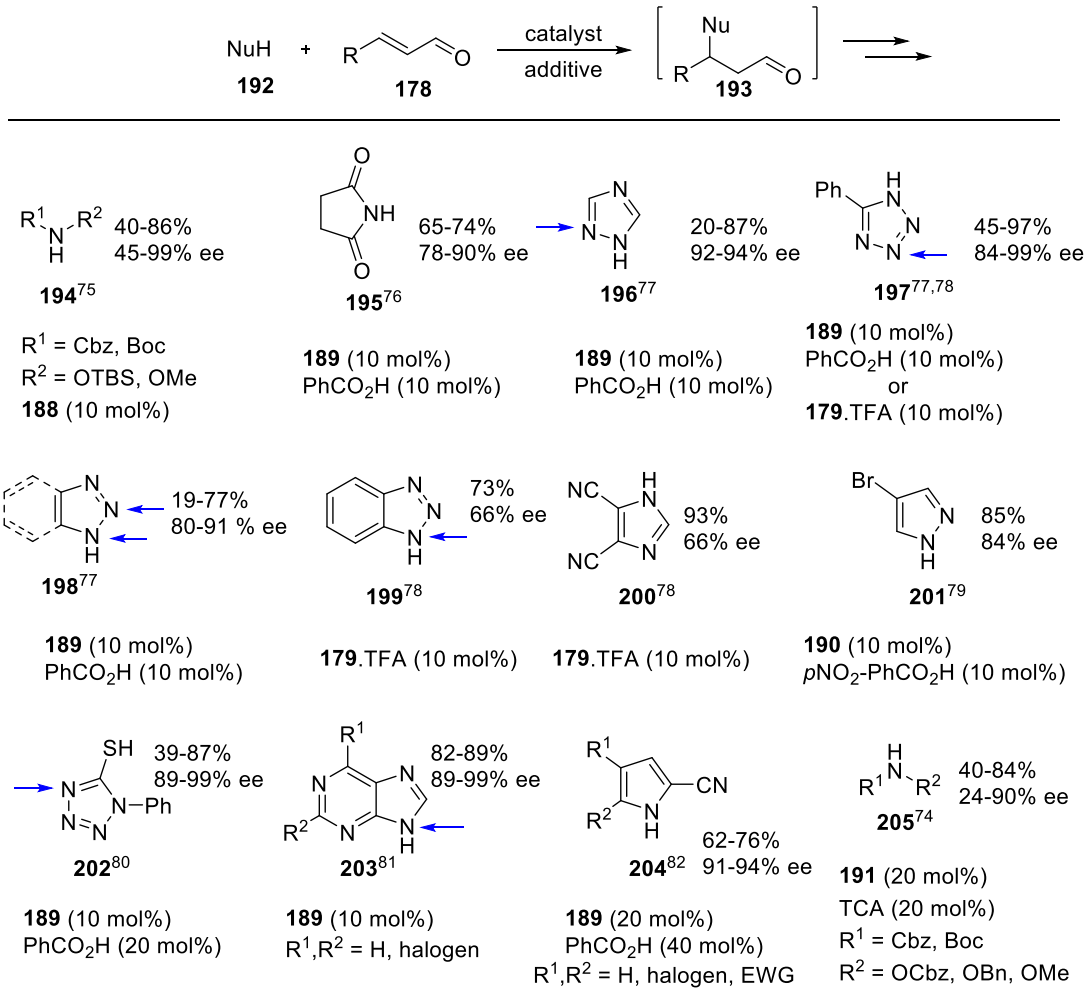
Alternative secondary amine catalysts **188**-**191** (Figure 8) have also found use in N-conjugate addition reactions of α,β-unsaturated aldehydes.



179[71] **188**[72] Ar = Ph; **189**[72] Ar = 3,5-$CF_3C_6H_3$; **190**[73] Ar = 3,5-$CF_3C_6H_3$; **191**[74]

Figure 8 Secondary amine organocatalysts

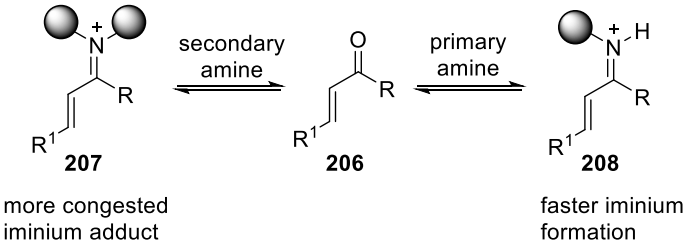
The range of nucleophiles shown to participate in the reaction is shown in Scheme 36. Some of the reactions incorporate a Brønsted acid additive in order to increase the rate of iminium ion formation and breakdown. Often the unstable aldehyde products are reduced to the corresponding alcohols or functionalised to facilitate isolation.



Scheme 36. N-Conjugate additions to enals with secondary amine catalysts. Yields are of the isolated major regioisomer, in cases of ambiguity the site of nucleophilic addition is indicated by a blue arrow.

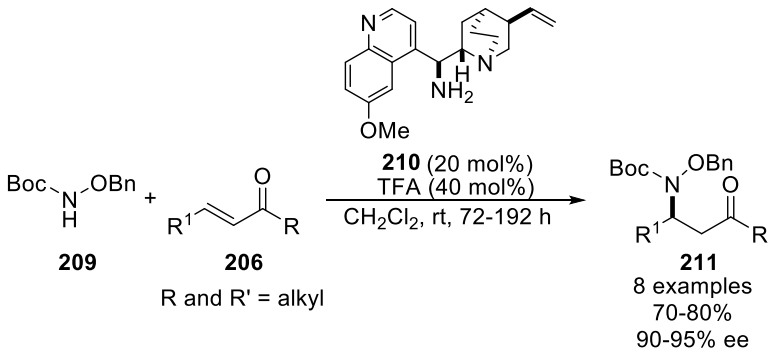
Asymmetric Organocatalysed N-Conjugate Additions to α,β-Unsaturated Ketones

Catalysts **179** and **188**-**191**, which are well established catalysts for conjugate addition to α,β-unsaturated aldehydes often give no reaction, or at best sluggish reaction rates, with α,β-unsaturated ketones.[83] This observation is assigned to the problems in forming congested iminium ions from secondary amines and ketones.[83b] The use of primary amine catalysts can offer a solution to sluggish reaction rates as the intermediate iminium ions formed are less congested (Scheme 37)



Scheme 37. Secondary vs primary amine catalysis.

The first report of a primary amine catalysing the conjugate addition of a nitrogen nucleophile to an α,β-unsaturated ketone was by Deng.[84] He used primary amine **210**,[85] derived from the cinchona alkaloid quinine, as the catalyst to add carbamate **209** to various α,β-unsaturated ketones. The resulting β-amidoketones were produced in good yield and high enantioselectivity (Scheme 38).



Scheme 38. Primary amine catalyzed *N*-conjugate addition.

Precisely how amine **210** induces selectivity in conjugate addition reactions has not been definitively proven. It seems likely that this differs depending on different nucleophilic substrates employed.[86] The authors Lu and Deng speculated that the primary amine of **210** is able to form an iminium ion that activates the enone. They also propose that the quinuclidine motif of **210**, as either the free base (Figure 9, mode a), or the protonated form (Figure 9, mode b), could bind

to the nitrogen nucleophile (**209**) through hydrogen-bonding interactions.[84] This brings the nucleophile into the proximity of the activated enone. In this sense the catalyst would be acting in a bifunctional manner, interacting with both reaction partners.

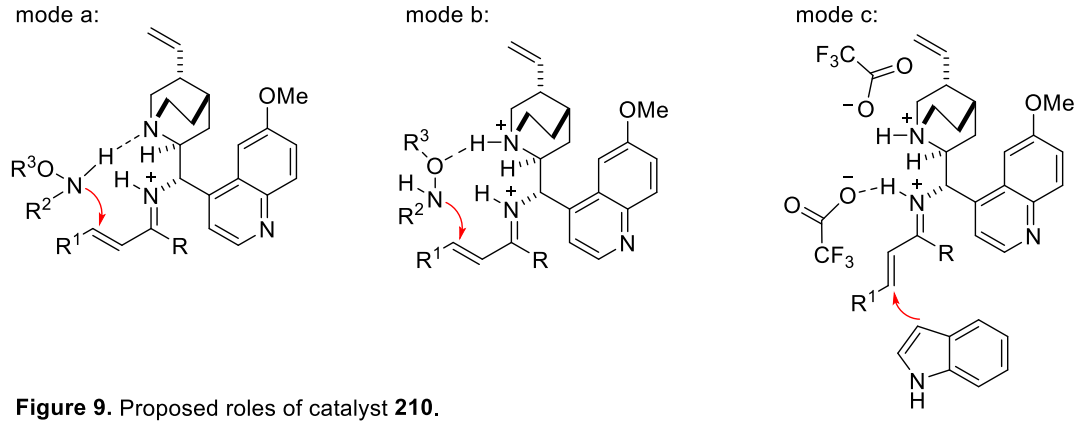
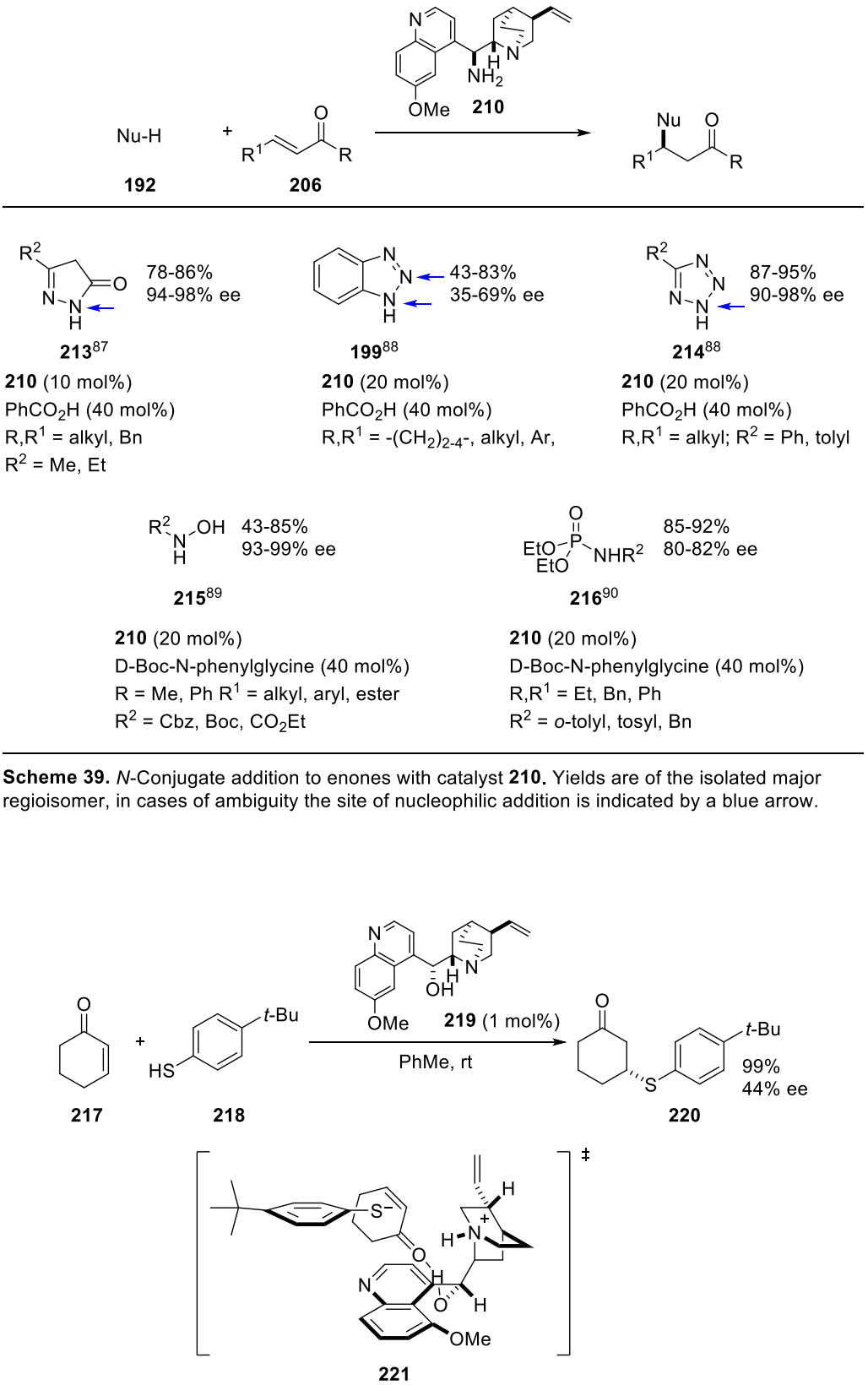


Figure 9. Proposed roles of catalyst **210**.

Interestingly the mechanism of catalysis proposed by Lu and Deng differs to that proposed by Melchiorre for the conjugate addition of indoles to enones using the same catalyst **210**.[86a] In the latter case the catalyst is proposed to impart stereoselectivity through a tightly bound ion pair of the iminium and additive counteranion (Figure 9, mode c). The achiral acid being the structural element responsible for the π-facial discrimination of the iminium ion intermediate.[86a]

Scheme 39 shows the range of N-nucleophiles that have been shown to undergo enantioselective conjugate addition to α,β-unsaturated ketones when catalysed by amine **210**.

Hydrogen bond donor organocatalysts are a second class of organocatalysts that have found use for the *N*-conjugate addition to α,β-unsaturated ketones. Organic Brønsted acids are able to hydrogen bond to, or protonate the carbonyl of the electrophile which results in a significant decrease in in the electrophiles LUMO.[67] During the 1970s and 1980s, Wynberg utilised this concept to perform asymmetric catalysed reactions.[91] He showed that cinchona alkaloids could promote various enantioselective 1,2 and 1,4 additions. Wynberg proposed that 'the amine portion of an alkaloid enhances the nucleophilicity of the the nucleophile, whereas the free hydroxyl group enhances the acceptor qualities of the electrophile' (Scheme 40).

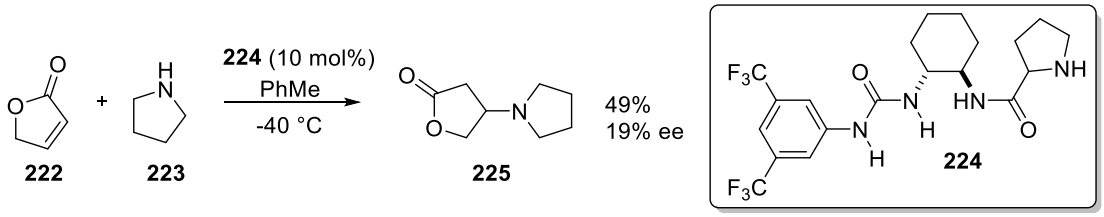


Scheme 39. *N*-Conjugate addition to enones with catalyst **210.** Yields are of the isolated major regioisomer, in cases of ambiguity the site of nucleophilic addition is indicated by a blue arrow.

Scheme 40. Wynberg's proposed mechanism of thiol conjugate addition.[91]

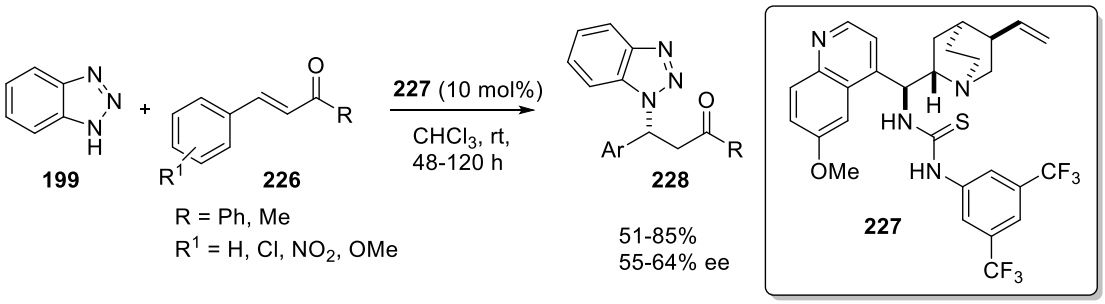
The first example of an enantioselective *N*-conjugate addition reaction *via* hydrogen bond activation was published by Nagasawa in 2004.[92] He found that the reaction of pyrrolidine **223** with γ-crotonolactone **222** could be promoted by

chiral hydrogen bond donors (Scheme 41). The product was obtained only in a modest yield with low enantioselectivity.



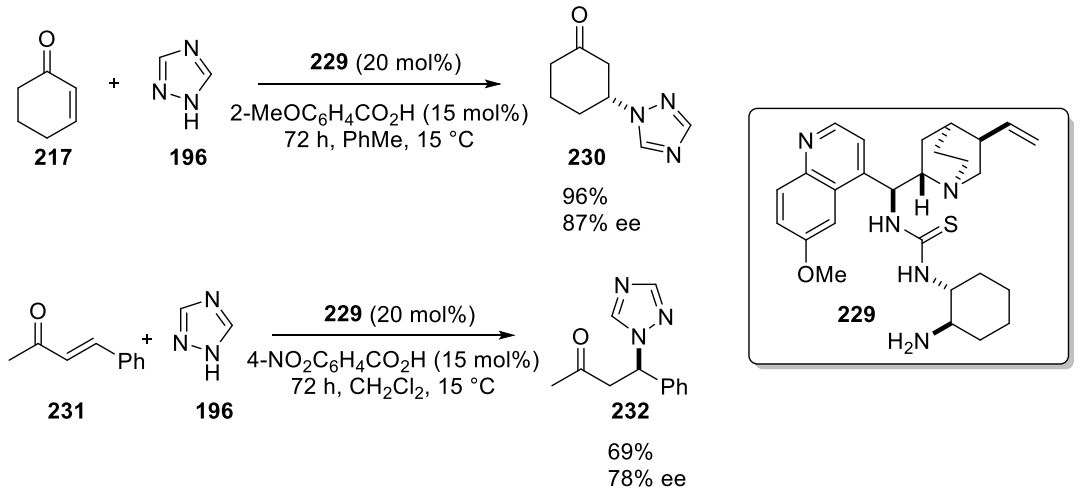
Scheme 41. Enantioselective *N*-conjugate addition of pyrrolidine.

The suitability of a catalyst is dependent on its ability to form a conformationally rigid hydrogen bonded structure with the electrophile. Alkaloid **219** does this through its hydroxyl group, whereas **224** uses a urea moiety. Thioureas have emerged as one of the most efficient classes of hydrogen-bond donors, often found to be superior to their urea equivalents.[67] Wang demonstrated that quinine derived thiourea **227** was able to catalyse the addition of 1*H*-benzotriazole to aryl and alkyl ketones (Scheme 42).[93] Selectivities obtained with thiourea catalyst **227** were still lower than can be obtained with primary amine catalysts,[88] but in contrast to amine organocatalysts the reaction proceeded with high regioselectivity at the benzotriazole.



Scheme 42. Addition of 1*H*-benzotriazoles to enones using thiourea **227**.

Liang and Ye were able to show that high enantioselectivities could be obtained using the related catalyst **229**.[94] 1,2,4-Triazole was reacted with cyclic and non-cyclic α,β-unsaturated ketones, giving ketones **230** and **232** respectively (Scheme 43).

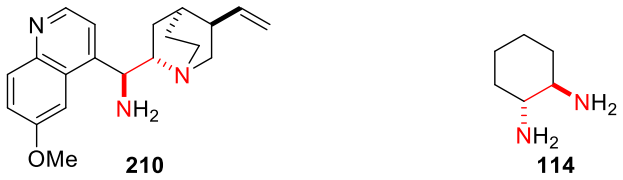


Scheme 43. Addition of 1,2,4-triazole to □□□-unsaturated ketones.

Results and Discussion

Project Aims

The use of primary amines as catalysts for the asymmetric *N*-conjugate addition of α,β-unsaturated ketones offers an efficient and stereoselective route to interesting β-aminoketones. The majority of publications on primary amine catalysed *N*-conjugate addition reactions with α,β-unsaturated ketones to date had identified quinine-derived amine **210** as the optimal catalyst. We recognised that catalysts based on (1*R*,2*R*)-*trans*-diaminocyclohexane **114**, which we have found to be highly stereoselective in aldol reactions, also had potential as catalysts for *N*-conjugate additions. Structures **210** and **114** both contain a chiral ethylene diamine fragment (Figure 10). If catalyst **210** is acting in a bifunctional manner the dihedral angle between the two nitrogen atoms likely impacts on the outcome of the reaction. Accordingly we were interested to assess amines derived from commercially available (1*R*,2*R*)-*trans*-diaminocyclohexane **114**.

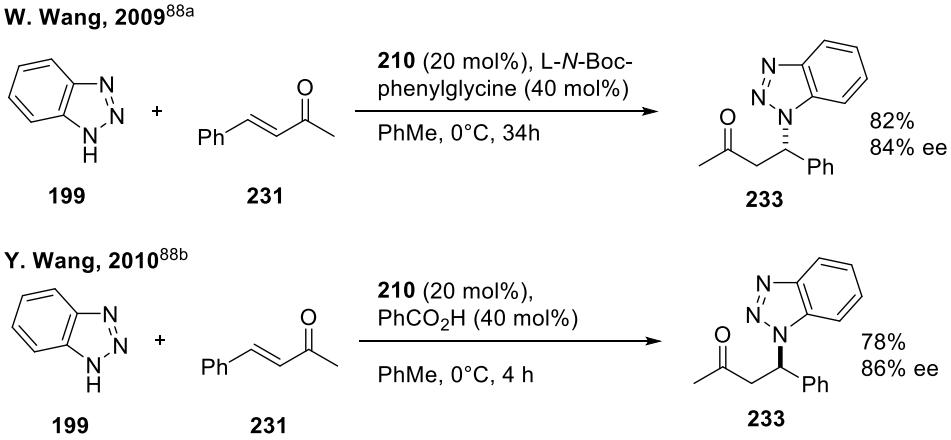


9-*epi*-9-amino-9-deoxyquinine (1*R*,2*R*)-diaminocyclohexane motif

Figure 10

We also hoped to investigate how primary amine catalyst structures are operating in the reaction. As discussed in the introduction there have been alternative proposals about how primary-tertiary diamine **210** is able to enantioselectively catalyse *N*-conjugate addition reactions. None of the proposed transition states

have been supported with molecular modelling studies, and preliminary calculations carried out within the group[55] suggest both proposals (mode a and mode b, figure 9) by Lu and Deng[84] as well as that put forward by Zhao[87] are unlikely based on, firstly the proposed iminium geometry and secondly the angle of approach of the nucleophile. Issues surrounding the identity of the major enantiomer produced have also arisen. Wei Wang[88a] reported that amine **210** catalyses the addition of benzotriazole to α,β-unsaturated ketones giving the (*S*)-enantiomer as the major product, yet Yongmei Wang[88b] reports that the same reaction with the same catalyst gives the (*R*)-enantiomer (Scheme 44).



Scheme 44. *N*-Conjugate addition of benzotriazoles with amine **210**.

In order to study the effectiveness of potential new catalyst structures based on **114** we first needed to identify a suitable nucleophile for the reaction with α,β-unsaturated ketones. We surveyed the nucleophiles known to participate in asymmetric organocatalytic *N*-conjugate addition reactions and listed them according to their approximate pK_a values (Figure 11).[95]

It appeared that only relatively acidic aromatic nucleophiles had so far been shown to undergo addition to α,β-unsaturated ketones using amine catalysis. Interestingly pyrazoles, which are non-acidic heterocycles, had been reported to undergo addition to α,β-unsaturated aldehydes.[79] We reasoned these would therefore be an interesting nucleophile to begin our studies with as the α,β-unsaturated aldehyde chemistry suggests the chemistry should be successful but the addition of a non-acidic nucleophile represent a significant expansion in nucleophile scope. Pyrazoles can be easily synthesised from the condensation of 1,3-dicarbonyl compounds and hydrazine[96] so this allows facile incorporation of substituents around the pyrazole ring which could be used to tune the basicity of the nucleophile.

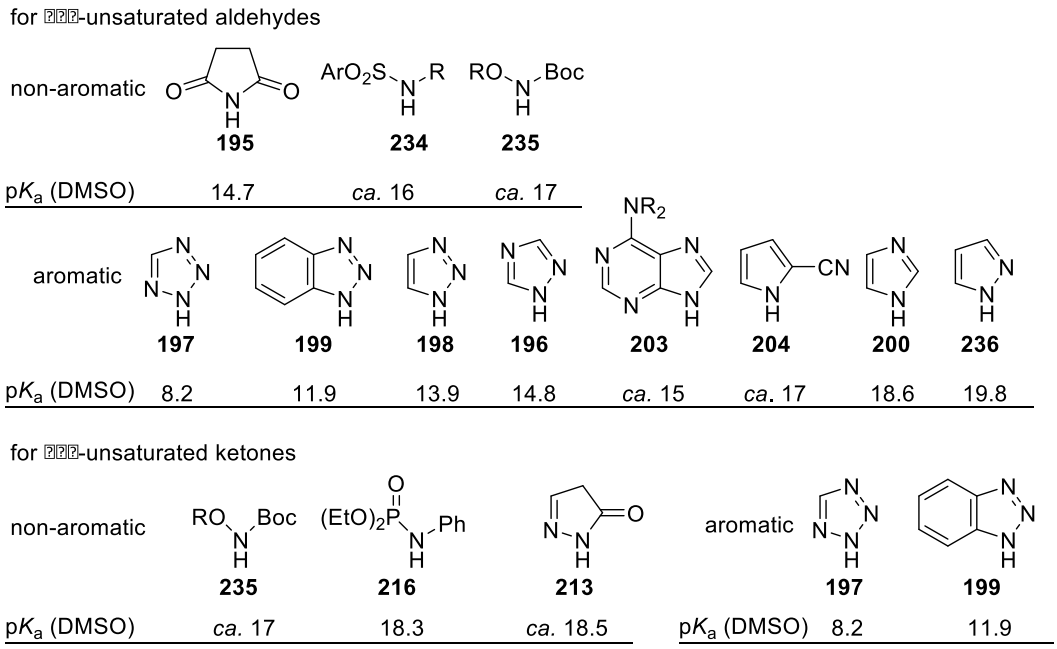
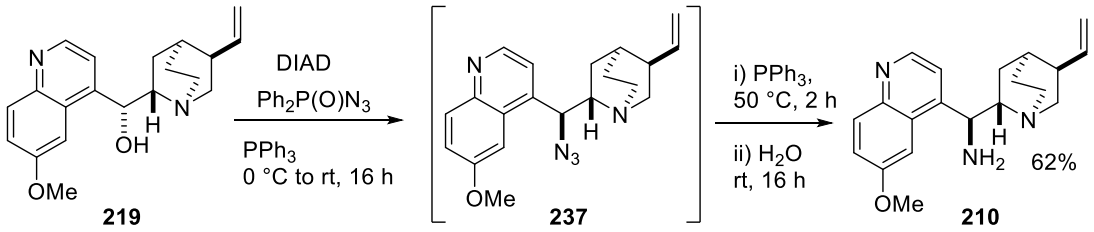


Figure 11. Nucleophiles known to participate in N-conjugate addition reactions.

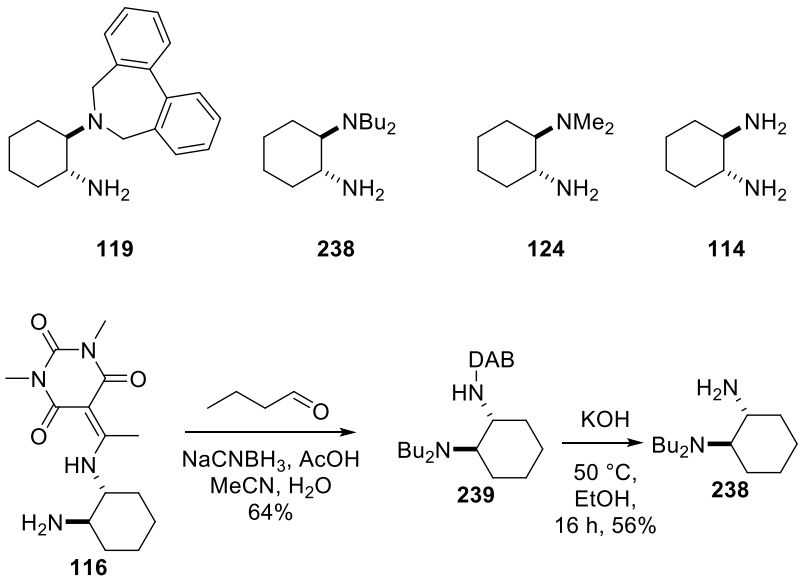
Synthesis and Evaluation of Primary Amine Catalysts

We started by preparing amine **210** using the reported procedure.[97] Quinine **219** was subjected to a Mitsunobu reaction and the resulting azide was reduced in a one-pot procedure yielding 9-*epi*-9-amino-9-deoxyquinine in 62% yield (Scheme 45).



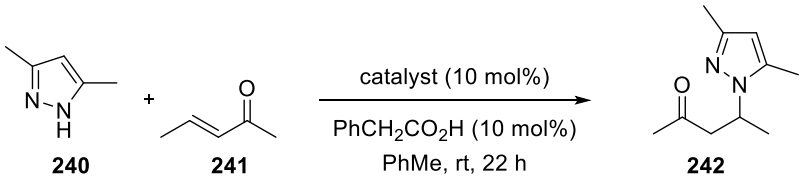
Scheme 45. Synthesis of 9-*epi*-9-amino-9-deoxyquinine **210**.

We next prepared a series of amine structures based on commercially available (1*R*,2*R*)-*trans*-diaminocyclohexane **114** (Scheme 46). Amines **119** and **124** were prepared from the DAB protected intermediate **116** as described in Chapter 1. Amine **238** was prepared in similar fashion. 1,3-Dimethylbarbituric acid (DAB) protected (1*R*,2*R*)-*trans*-diaminocyclohexane **116** was alkylated *via* reductive amination to give **239**. Hydroxide-mediated cleavage of the DAB group gave **238** in an overall yield of 35%.



Scheme 46. Synthesis of **238**.

We next evaluated the performance of amines **210**, **119**, **238**, **124** and **114** in the reaction between dimethyl pyrazole **240** and 3-penten-2-one **241** (Table 6). Reactions were run for 22 h at room temperature in toluene. We included phenylacetic acid as a co-catalyst.



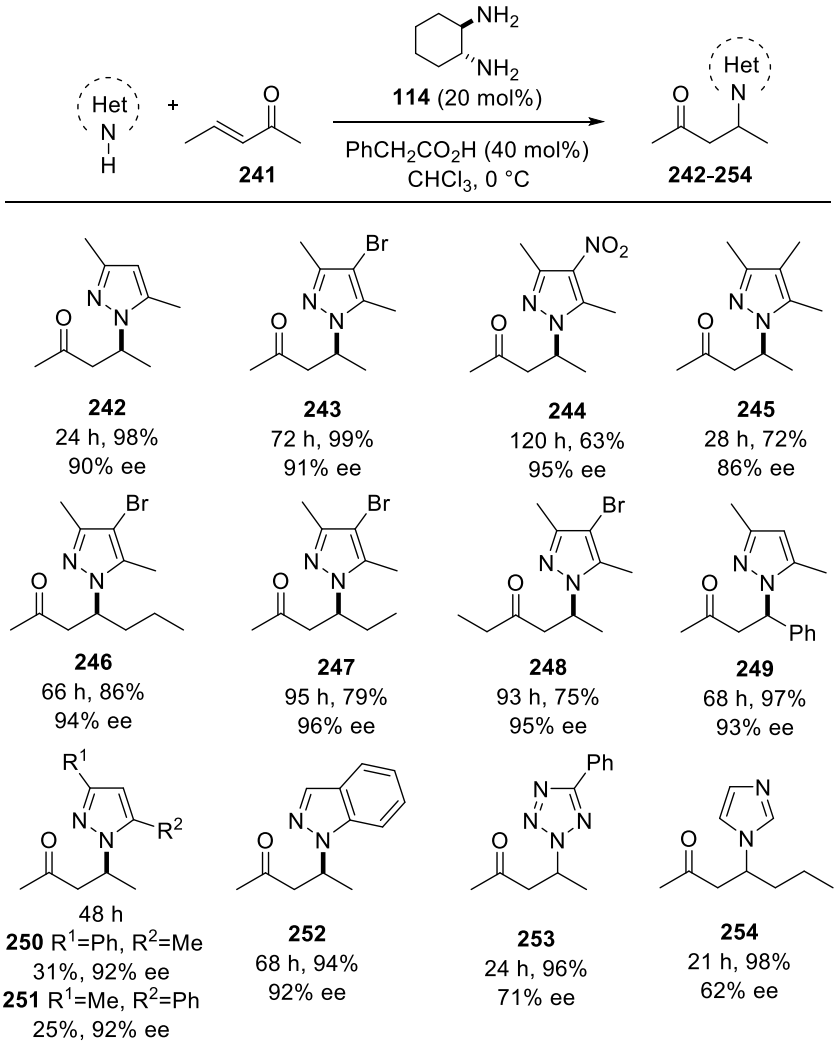
Entry	Catalyst	Conversion (%)	ee (%)[a]
a	**210**	80	96 (*R*)
b	**119**	43	6 (*S*)
c	**238**	20	22 (*S*)
d	**124**	35	38 (*S*)
e	**114**	>95	85 (*S*)

[a] Determined by chiral phase HPLC

Table 6. Catalyst screening.

It was found that all the amines investigated were able to catalyse the conjugate addition. The quinine derivative **210** (Entry a) gave product **242** in high yield and enantiomeric excess. Catalysts derived from (1*R*,2*R*)-*trans*-diaminocyclohexane (Entries b-e) also produced enantiomerically enriched products. The results appear to show a trend, as the size of tertiary amine substitutions decrease, the enantioselectivity of the reaction increases. Interestingly (1*R*,2*R*)-*trans*-diaminocyclohexane **114** itself (Entry e) gave the product **242** in good enantiomeric excess.

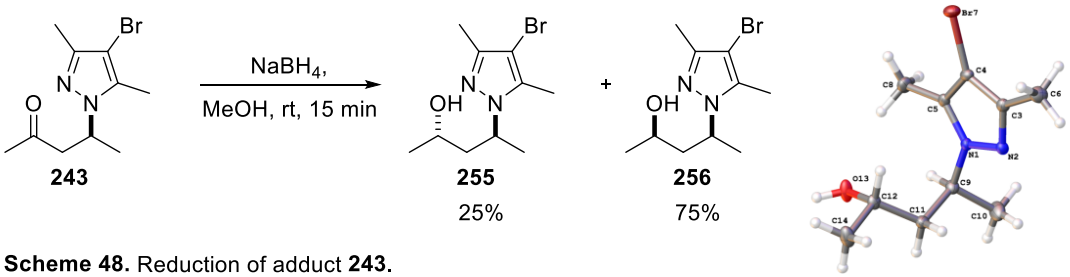
Encouraged by these results another member of the group, Dr. Tim Evans, investigated the optimisation of pyrazole conjugate additions using (1*R*,2*R*)-trans-diaminocyclohexane **114**. He found that performing the reactions in chloroform at 0 °C and increasing the catalyst and co-catalyst loading gave improvements in both yield and enantioselectivity. Using these conditions, the adduct **242** could be produced in 98% yield and 98% ee. Results for a selection of heterocycle nucleophiles and enones using these optimised conditions are shown in Scheme 47. Variation in the substitution of pyrazole, as well as enone structure was well tolerated. It is notable that **114** was also able to catalyse the regioselective conjugate addition of indazole yielding **252** with high enantioselectivity. Addition of 5-phenyl-1*H*-tetrazole and imidazole was also successful, but with reduced levels of enantioselectivity.



Scheme 47. (1*R*,2*R*)-*trans*-diaminocyclohexane as a catalyst for *N*-conjugate additions. Reactions performed by Dr. Tim Evans.

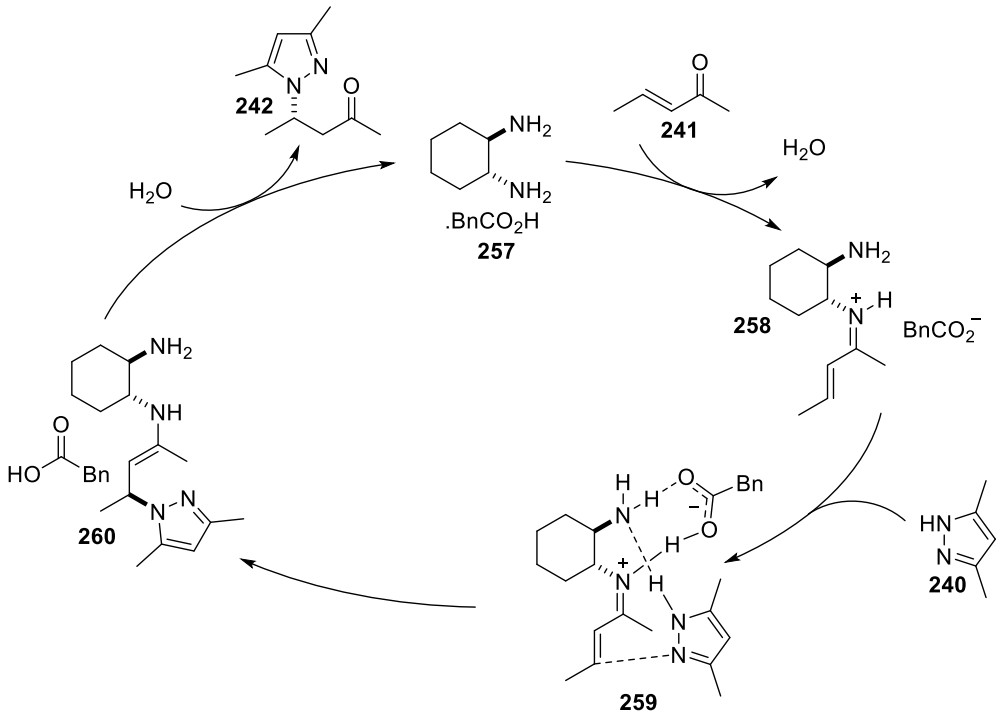
Dr. Evans was also able reduce adduct **243** and crystallise the minor diastereoisomer **255** (Scheme 48). X-ray crystallography of compound **255**

allowed us to determine that the pyrazole adducts produced by diamine **114** had the (*S*)-configuration.



Scheme 48. Reduction of adduct **243**.

It seems likely that *trans*-diaminocyclohexane is promoting the reactions *via* a bifunctional mode of catalysis (Scheme 49). One of the amine groups of catalyst **257** is able to form an iminium ion **258** assisted by the acid co-catalyst. The second amine then directs the pyrazole addition to a single diastereotopic face of the iminium ion *via* a hydrogen-bond (**259**). If the second amino group is disubstituted interactions between groups on the tertiary amine and the nucleophile may interfere with this directing effect and this could account for the lower enantioselectivities observed.



Scheme 49. Proposed catalytic cycle of 3,5-dimethylpyrazole with 3-penten-2-one.

To examine this hypothesis we prepared amines **261**, **262** and **263**. We reasoned that these amines would be unable to participate in hydrogen-bonding with the nucleophile as the lone pair of electrons on one nitrogen is delocalised

into an aromatic ring. So instead of directing in the nucleophile, the aromatic ring should now block one diastereotopic face of the iminium ion during the addition step (Figure 12).

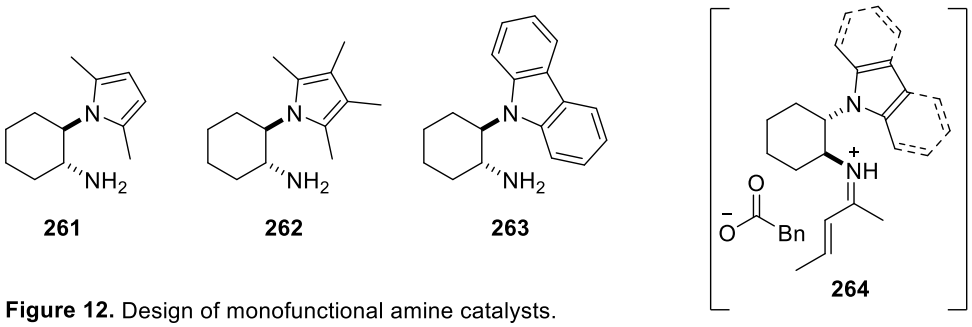
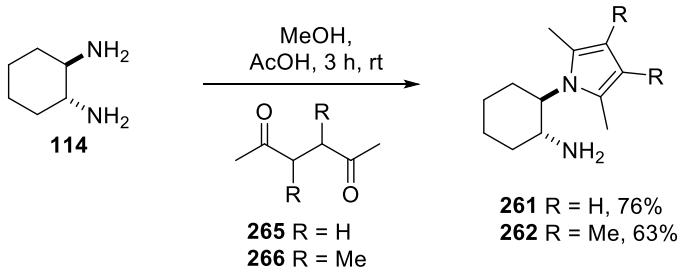


Figure 12. Design of monofunctional amine catalysts.

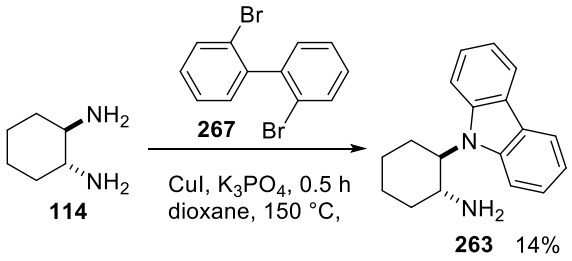
Using one amino-substituent as a shielding group would be expected to give the opposite enantiomer of **242**, compared to when the amino group is directing. Synthesis of this type of blocking monofunctional catalyst from trans-diaminocyclohexane has previously been reported by both Jacobsen[98] and Dixon.[99]

Pyrroles **261** and **262** were synthesised from the corresponding 1,4-dicarbonyl compounds by stirring with diamine **114** in the presence of acid (Scheme 50). Diketone **265** was commercially available, **266** was synthesised *via* lead oxide mediated coupling of butanone.[100]



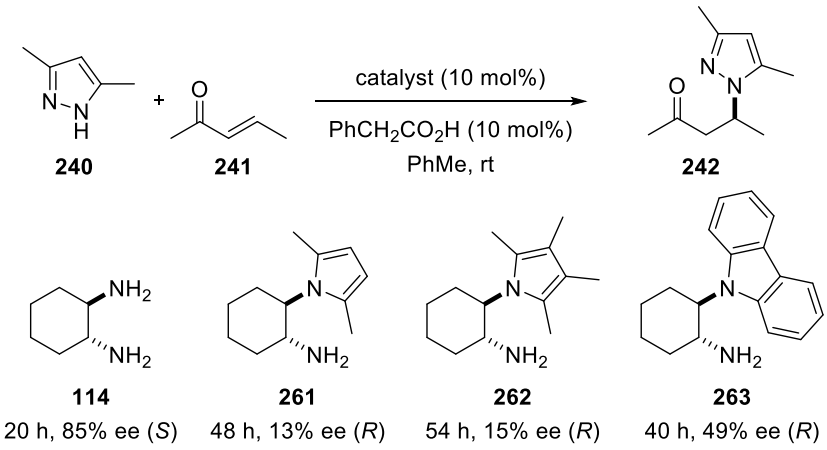
Scheme 50. Synthesis of monofunctional amines **261** and **262**.

Carbazole **263** was synthesised in one step 'Ullmann type' reaction following the procedure reported by Jacobsen (Scheme 51).[101]



Scheme 51. Synthesis of monofunctional amine **263**.

Amines **261**-**264** were then evaluated in the reaction between dimethyl pyrazole **240** and 3-penten-2-one **241** (Scheme 52).

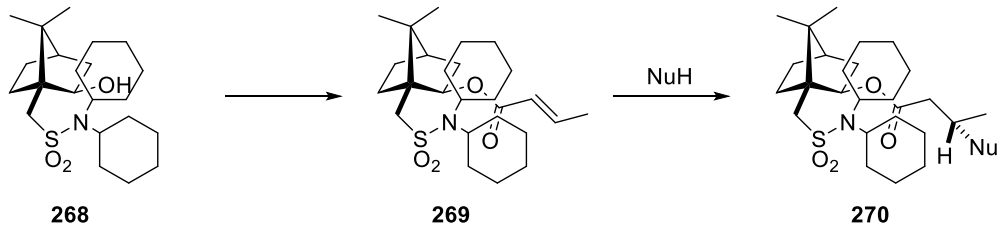


Scheme 52. Amines **261**-**263** as catalysts for the N-conjugate addition reaction.

Reactions were allowed to run until >95 % conversion of **240** to **242** as judged by ^{1}H NMR. All three monoamines **261**-**263** gave a slower rate of reaction and favoured the (*R*)-enantiomer of product **242**. As the size of the aromatic group incorporating the second nitrogen atom increased, the magnitude of enantioselectivity also increased. Carbazole **263** was able to produce the (*R*)-enantiomer of **242** in 49% ee. These results appear to support the hypothesis that diamine **114** is acting in a bifunctional manner with the second amino group directing in the nucleophile.

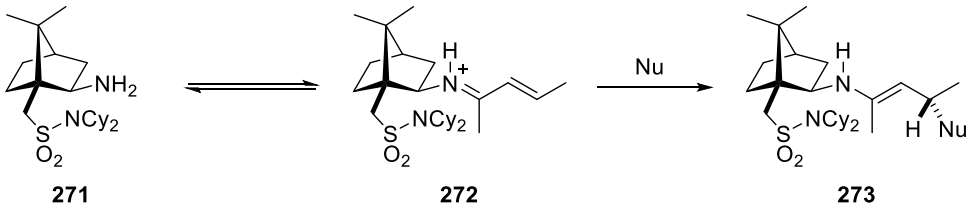
Encouraged by the level of enantioselectivity achieved using the carbazole catalyst **263** we decided to briefly investigate the potential of alternative monofunctional amine catalysts.

We considered that a primary amine adjacent to a large sterically hindering group might serve as a monofunctional catalyst for conjugate addition reactions. To this end, we considered the Oppolzer camphor derived sulfonamide **268** as a potential template. This system was extensively studied by Oppolzer who demonstrated that it could be used as an effective chiral auxiliary for conjugate addition reactions (Scheme 53).[102]



Scheme 53. Oppolzer's chiral auxiliary.[102]

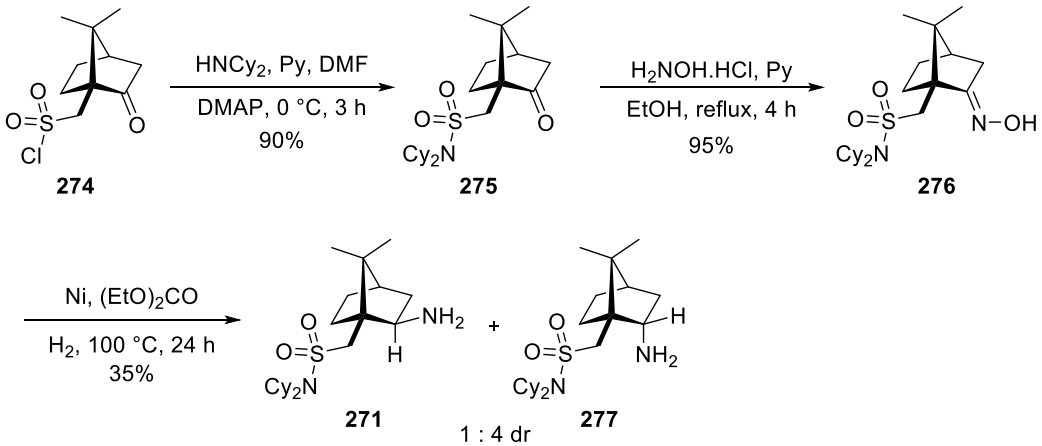
We imagined that if an α,β-unsaturated iminium salt **272** could be generated from the corresponding amine **271**, it might lead to highly diastereoselective conjugate addition reactions (Scheme 54).



271 **272** **273**

Scheme 54. Potential conjugate addition catalyst **271**.

We envisioned that the amine **271** could be prepared from camphor sulfonic acid *via* a similar route to that used by Oppolzer in the preparation of alcohol **268**.[103] Camphor sulfonyl chloride **274** was first reacted with dicyclohexylamine to yield sulfonamide **275**. This was then converted into the oxime **276** and reduced with Raney nickel. This resulted in a 1 : 4 mixture of diastereoisomers **271** : **277**, which could be separated by column chromatography on silica gel (Scheme 55).

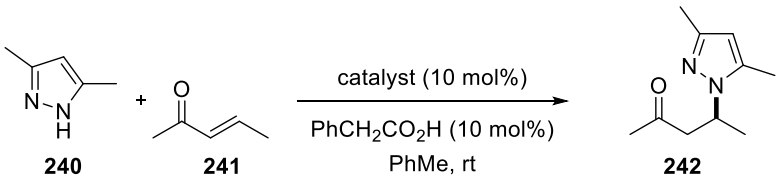


274 **275** **276** **271** **277**

Scheme 55. Synthesis of camphor derived amines **271** and **277**.

Given that we had produced both diastereoisomers of the primary amine we decided to test both as catalysts for the conjugate addition of dimethyl pyrazole **240** to 3-peten-2-one **241**. The results are shown in Table 7.

As can be seen, both amines were able to catalyse the addition, but the levels of enantioselectivity were low and relative reaction times were long. Given that *trans*-diaminocyclohexane was producing much better results, and was more readily available, we decided not to pursue the camphor sulfonic acid derived amines any further.



240 241 242

Entry	Catalyst	Time (h)	Yield (%)	ee (%)[a]
a	**271**	48	60	20 (*S*)
b	**277**	40	77	31(*R*)

[a] Determined by chiral phase HPLC

Table 7. Camphor-derived amines as N-conjugate addition catalysts.

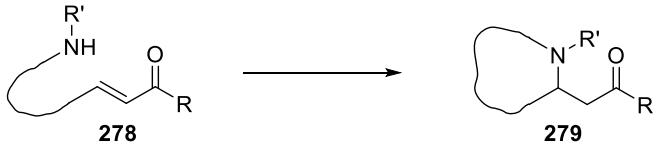
Conclusions

In conclusion we have been able to demonstrate that commercially available (1*R*,2*R*)-*trans*-diaminocyclohexane **114**, in combination with a an achiral acid co-catalyst, is able to catalyse the previously unreported conjugate addition reactions of pyrazoles to α,β-unsaturated ketones. The reaction is tolerant of substitution on the pyrazole ring as well as variation of the enone acceptor giving products in high yield and high enantioselectivity. We have also shown that modification of the diamine structure leads to results that are consistent with the parent diamine acting as a bifunctional catalyst.

Chapter 3: Intramolecular N-Conjugate Addition Reactions Using A Quinine Derived Squaramide

Introduction

A subset of nitrogen conjugate addition reactions that were not discussed in Chapter 2 are intramolecular nitrogen conjugate addition reactions (Scheme 56). This type of intramolecular reaction is of interest as it provides access to chiral nitrogen heterocycles, structures commonly found in molecules isolated from nature.[104]

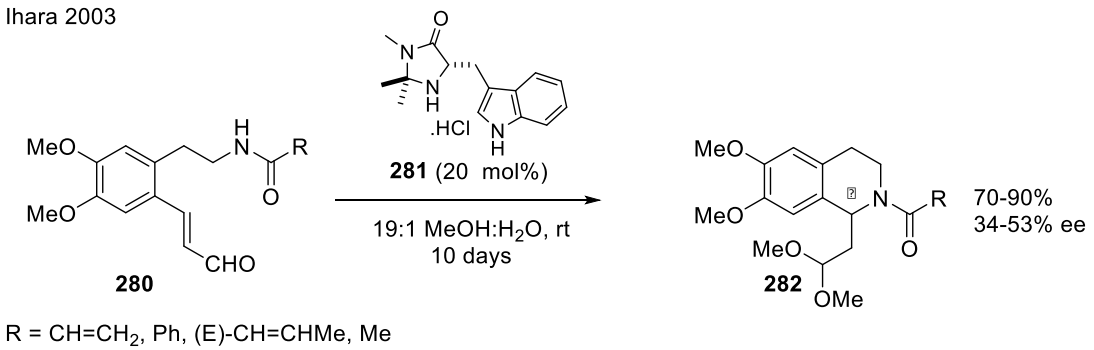


Scheme 56. Intramolecular nitrogen conjugate addition.

Organocatalysts can be used to promote asymmetric intramolecular N-conjugate addition reactions.[105-117] As is the case with the intermolecular reaction, different catalysts are employed depending on the type of α,β-unsaturated carbonyl substrate.

N-Conjugate Addition to α,β-Unsaturated Aldehydes

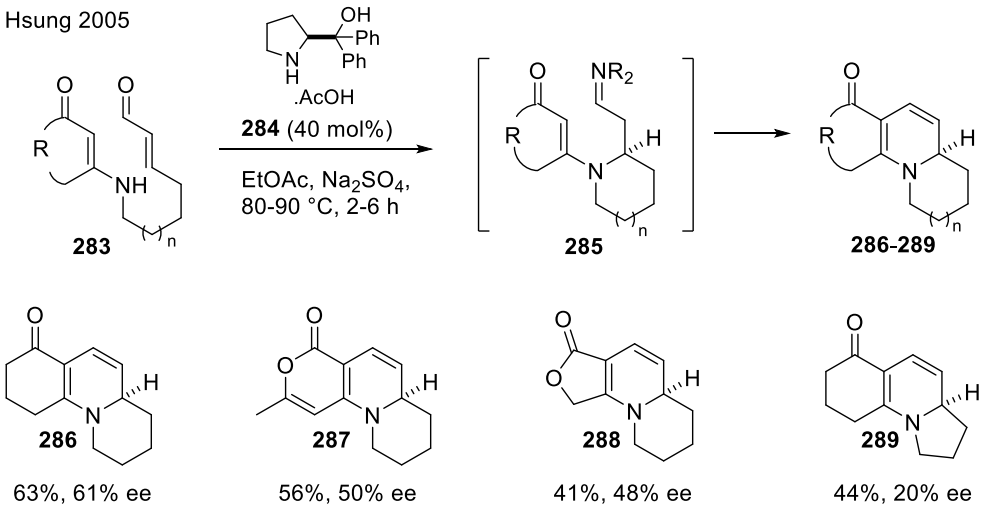
As with the corresponding intermolecular reactions, secondary amines appear to be the catalysts of choice for intramolecular N-conjugate additions to α,β-unsaturated aldehydes. As discussed in Chapter 2 secondary amines are able to form reactive iminium ions with α,β-unsaturated aldehydes. These iminium ions are susceptible to nucleophilic attack. Ihara was the first to publish an organocatalytic enantioselective intramolecular N-conjugate addition.[105] He showed that amides **280** could be cyclised to 1,2,3,4-tetrahydroisoquinolines **282** using a 'MacMillan-like' imidazolidinone catalyst **281** (Scheme 57). The products were produced in good yields, but enantioselectivity was only moderate, and reaction times were long.



R = $CH{=}CH_2$, Ph, (E)-CH=CHMe, Me

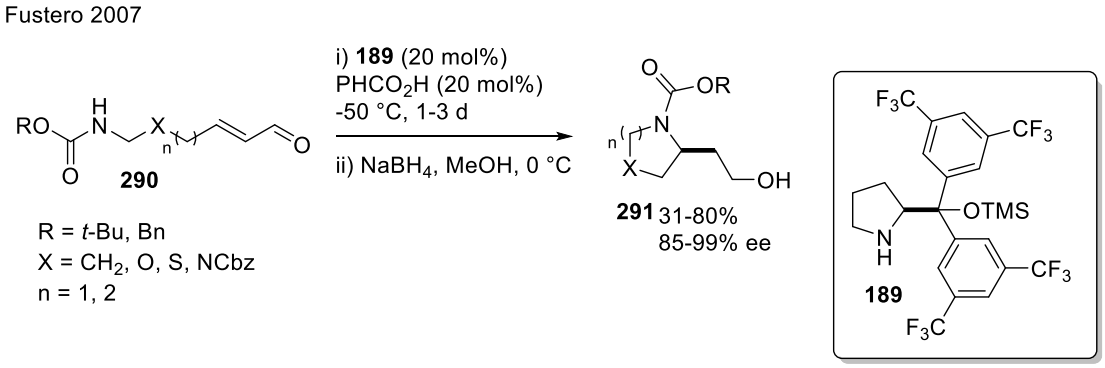
Scheme 57. Enantioselective formation of 1,2,3,4-tetrahydroisoquinolines **282.**[105]

Hsung made use of secondary amine **284** to catalyse the intramolecular conjugate addition of vinylogous amides to α,β-unsaturated aldehydes.[106] The conjugate addition step was followed by an intramolecular 1,2-addition and elimination to provide dihydropyridines **286**-**289** (Scheme 58). Proline-derived amine **284** was found to perform better than the MacMillan type imidazolidinones reported by Ihara.



Scheme 58. Conjugate addition of vinylogous amides. [106]

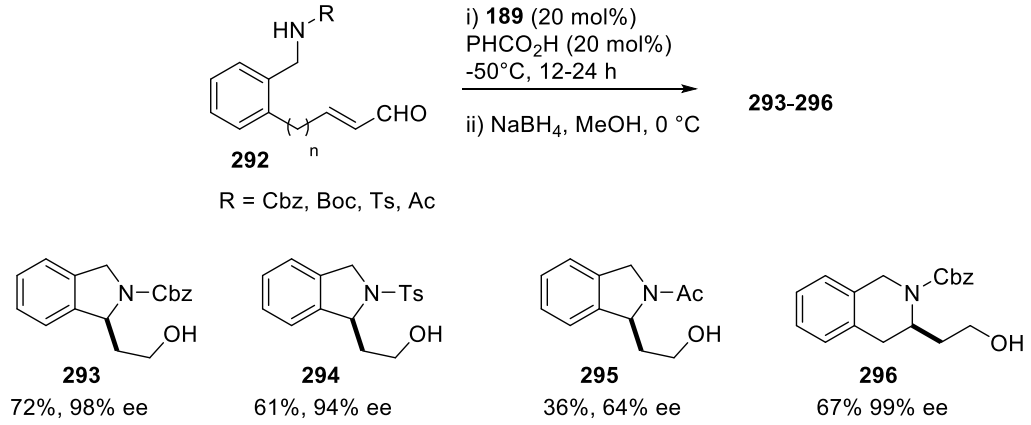
Subsequently the intramolecular N-conjugate addition into α,β-unsaturated aldehydes has been studied by the groups of Fustero[107] and Carter[108]. Fustero was first to publish the addition of carbamates to α,β-unsaturated aldehydes (Scheme 59).[107a] He identified prolinol **189** as an effective catalyst. Chiral pyrrolidines **291** could be produced in high enantiomeric excess.



Scheme 59. Intramolecular N-conjugate additions by the Fustero group.[107a]

In a separate communication Fustero demonstrated that his procedure was able to provide access to aryl fused heterocycles **293**-**296** (Scheme 60).[107b] The acetamide **295** was formed in significantly lower yield and enantioselectivity than when carbamates **293** and **296** or sulfonamide **294** was employed.

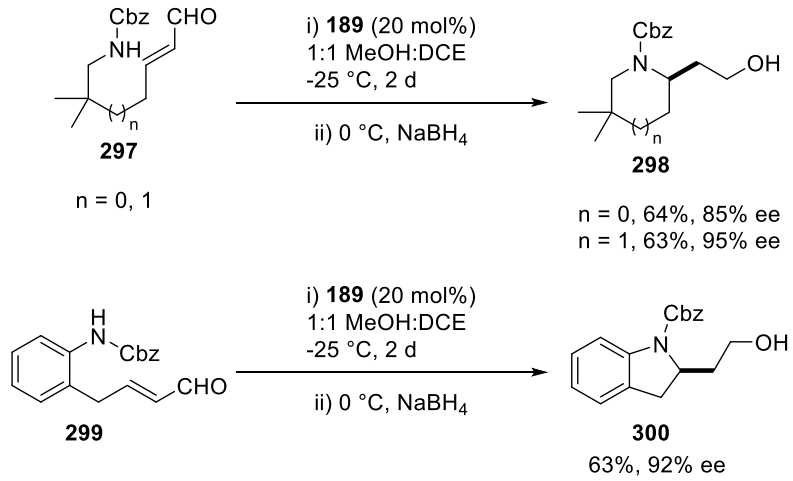
Fustero 2008



Scheme 60. Intramolecular N-conjugate additions by the Fustero group.[107b]

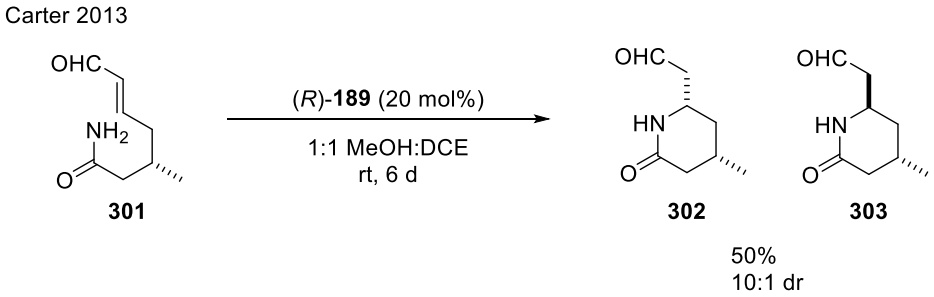
Carter also reported that carbamates could undergo intramolecular N-conjugate addition to α,β-unsaturated aldehydes (Scheme 61).[108a]

Carter 2008



Scheme 61. Intramolecular N-conjugate addition reactions by the Carter group.[108a]

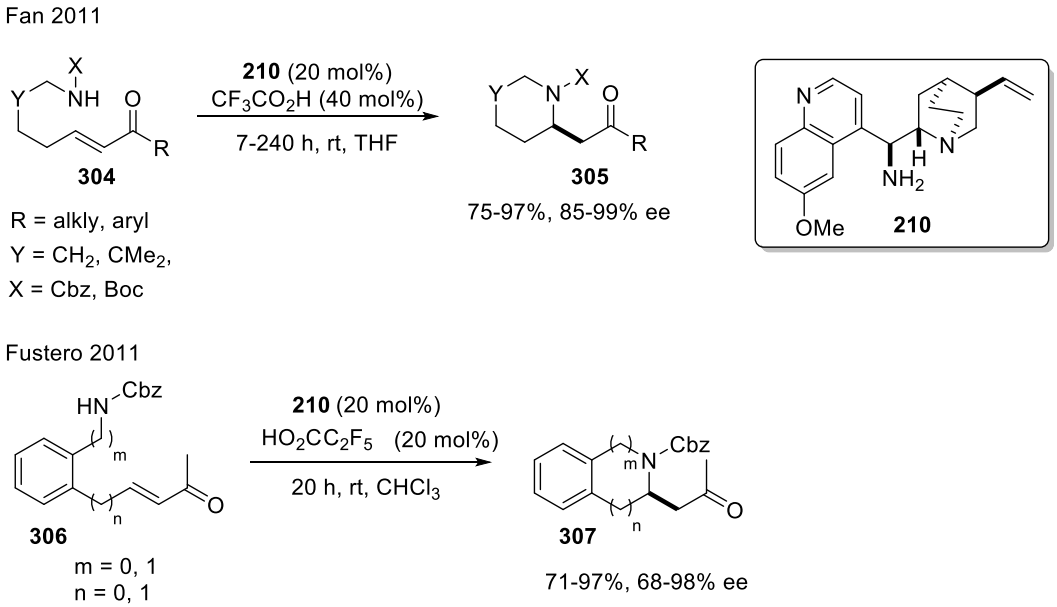
Subsequently Carter also reported that if a single enantiomer of primary amide **301** was cyclised using catalyst (*R*)-**189**[108b] diastereoisomers **302** and **303** were produced in a 10 : 1 ratio (Scheme 62). The cyclisation using achiral $BF_3.Et_2O$ gave a d.r. of 1:1.3. If (S)-**189** was used on the same substrate, **301,** a switch in the diastereoselectivity was not seen and a 1 : 1 ratio of diastereoisomers **302** and **303** was obtained. These findings suggest that the existing chiral centre in the connecting chain of substrate **301** has a significant influence on the stereochemistry of the forming centre.



Scheme 62 Intramolecular N-conjugate addition reactions with an existing chiral centre in the substrate.[108b]

N-Conjugate Addition to α,β-Unsaturated Ketones

There have been a number of reports of intramolecular N-conjugate addition to α,β-unsaturated ketones. As with intermolecular additions, these can be grouped according to the mode of catalysis used. Again it appears that primary amines are more suitable than secondary amines because the formed iminium ion intermediates are less congested.[83b] The quinine-derived amine **210** has been shown to be effective for reactions involving α,β-unsaturated ketones (Scheme 63).[109] Both Fustero[109a] and Fan[109b] reported that this catalyst could promote cyclisation of carbamates giving products with high enantioselectivity. Reaction times are typically 7-15 h at rt for alkyl ketones. Reaction times with aryl ketones are significantly longer, 12-240 h, presumably due to the slower rate of iminium ion formation for aryl ketones.



Scheme 63. N-Conjugate addition of carbamates to □□□-unsaturated ketones.

Chiral Brønsted acids have also been reported to catalyse intramolecular N-conjugate additions into α,β-unsaturated ketones. Brønsted acids protonate, or

partially protonate, the carbonyl of the enone (Figure 13). This protonation makes the enone more susceptible to nucleophilic attack. A chiral Brønsted acid catalyst can form a chiral environment around the enone and thus favour addition to a single enantiotopic face. This bias of the nucleophile's approach is achieved through either i) steric interactions or ii) directing the nucleophile with a second favourable interaction with the catalyst (bifunctional catalysis).

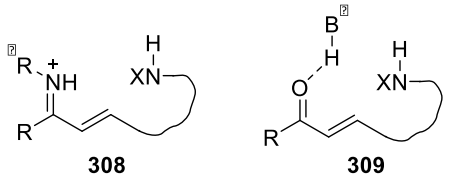
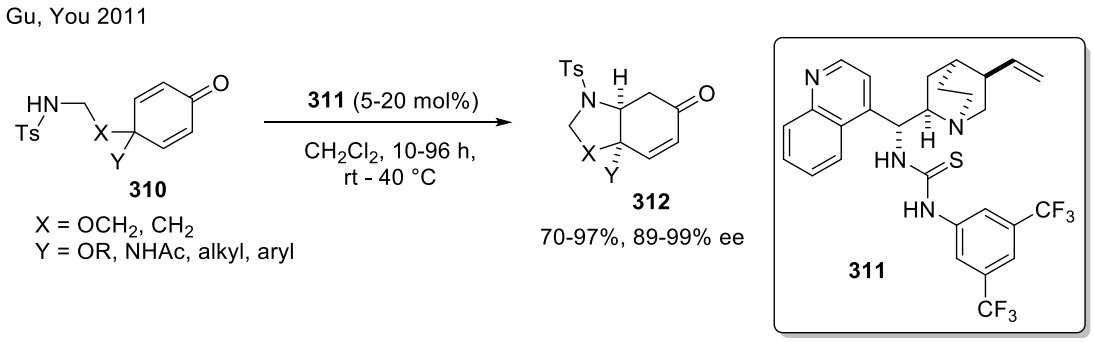


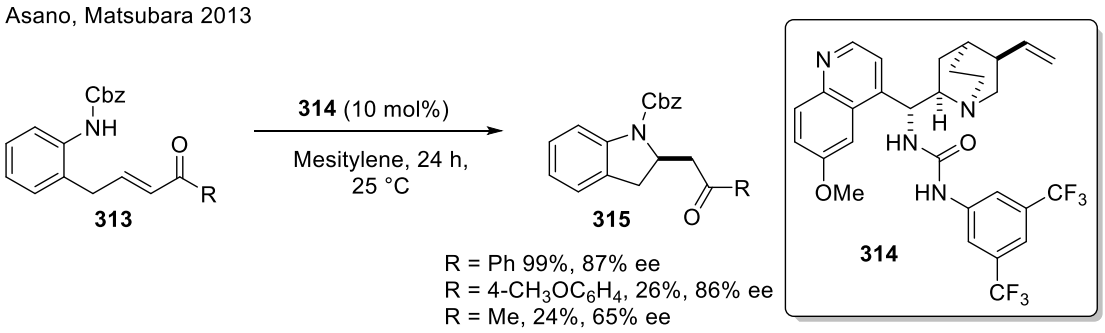
Figure 13. Amine and Brønsted acid activation of enones.

Cinchona alkaloid-derived thioureas have been reported to promote enantioselective intramolecular N-conjugate addition reactions. Gu and You showed that cyclohexadienones could be desymmetrised using **311** (Scheme 64).[110]



Scheme 64. Desymmetrisation of cyclohexadienones.[110]

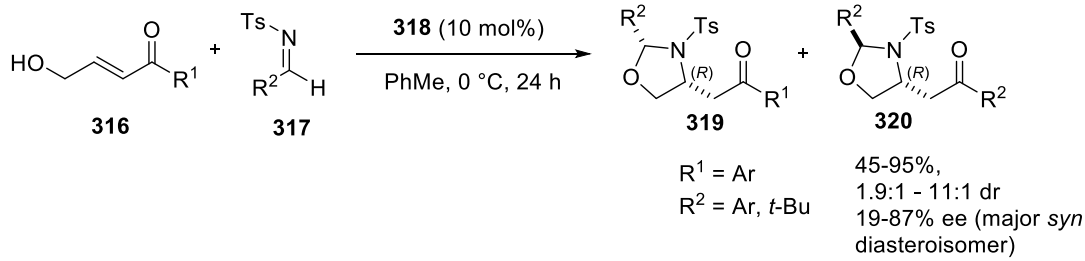
Asano and Matsubara showed that indolines **315** could be synthesised from anilines **313**.[111] The yields of **315** were dependent on the electronic properties on the enone. Enones conjugated to an electron donating group gave poorer results than those conjugated to an electron neutral phenyl ring (Scheme 65).



Scheme 65. Synthesis of indolines using cinchona alkaloid-derived urea.[111]

Asano and Matsubara also reported that sp^3 nitrogen centres formed *in-situ*, through the addition of an allylic alcohol to a carbon-nitrogen double bond, could participate in intramolecular N-conjugate addition.[112] When using imines **317** they found that the carbon-nitrogen bond forming step could be catalysed by thiourea **318** giving predominantly the (*R*)-configuration at the indicated stereocentre in both major and minor diastereoisomers (Scheme 66).[112a]

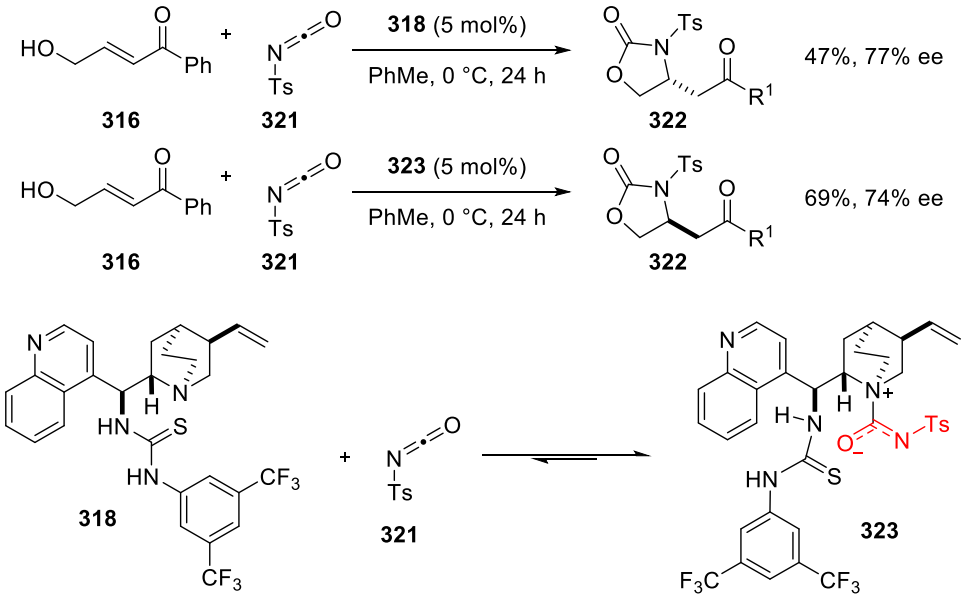
Asano, Matsubara 2013



Scheme 66. N-Conjugate addition of *in-situ* formed tosylamines to ???-unsaturated ketones.[112a]

Asano and Matsubara found that isocyanates were suitable substrates (Scheme 67). Interestingly it was found that enantioselectivity of the reaction can be switched by premixing isocyanate **321** with catalyst **318**.[112b] It was proposed that structure **323** is now the active catalyst which results in a switch in selectivity towards the opposite enantiomer.

Asano, Matsubara 2013



Scheme 67. N-Conjugate addition of *in-situ* formed tosylamines with ???-unsaturated ketones.[112b]

Chiral phosphoric acids have also found use in intramolecular N-conjugate additions. The proposed mode of action is through carbonyl protonation. It is also claimed that the phosphoric acid provides a Lewis basic site for an interaction with the nucleophile (Figure 14).[67]

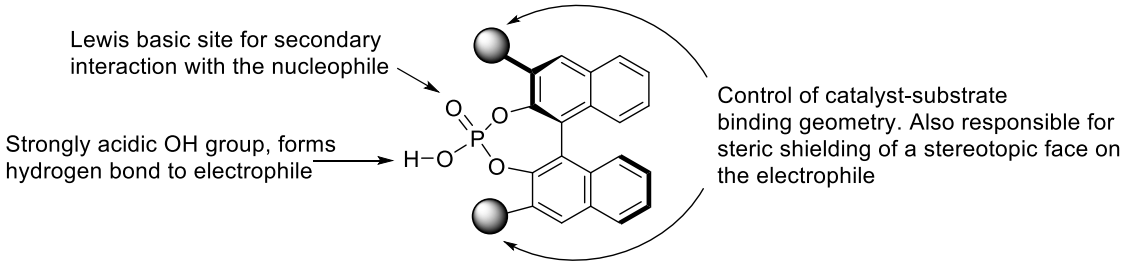
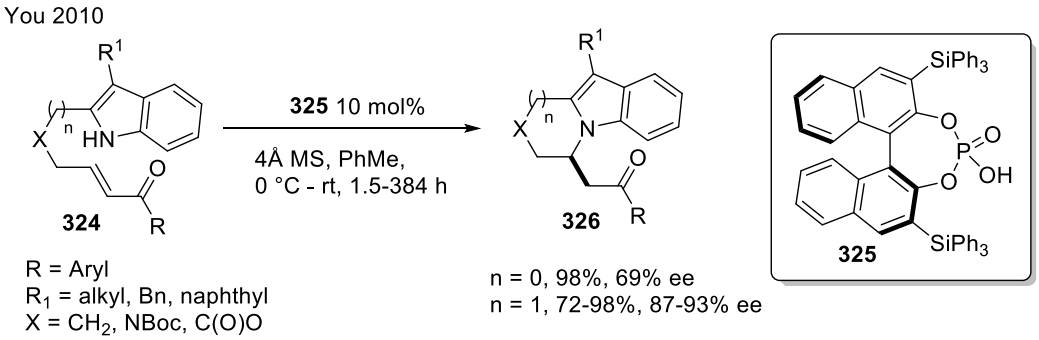


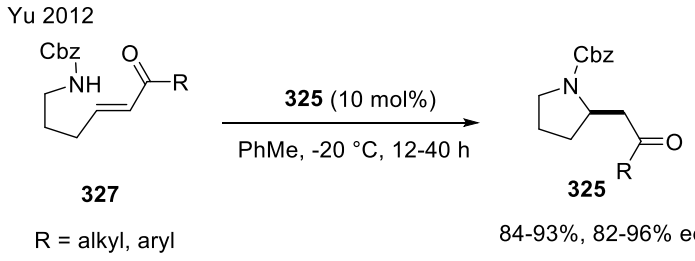
Figure 14. Phosphoric acids as Brønsted acid catalysts.

You reported that indoles **324** could be cyclised using phosphoric acid **325** (Scheme 68).[113] Products were produced in moderate to good enantioselectivity. The rate of reaction was highly dependent on the enone substrate.



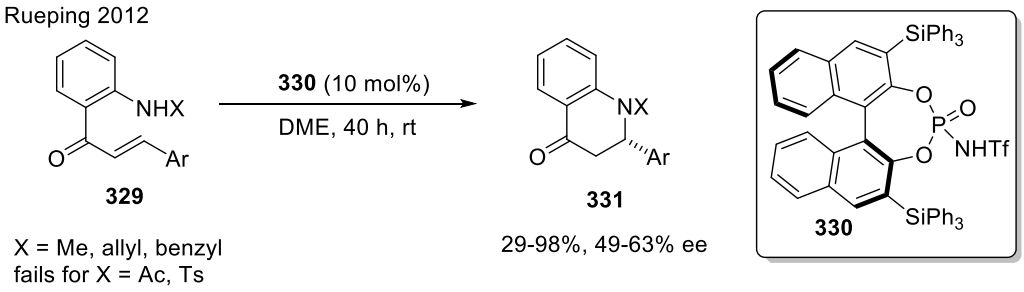
Scheme 68. Phosphoric acid promoted N-conjugate addition of indoles.[113]

Subsequently Yu demonstrated the utility of phosphoric acid **325** to cyclise carbamates **327** form chiral pyrrolidines **328** (Scheme 69).[114]



Scheme 69. Phosphoric acid promoted N-conjugate addition of carbamates.[114]

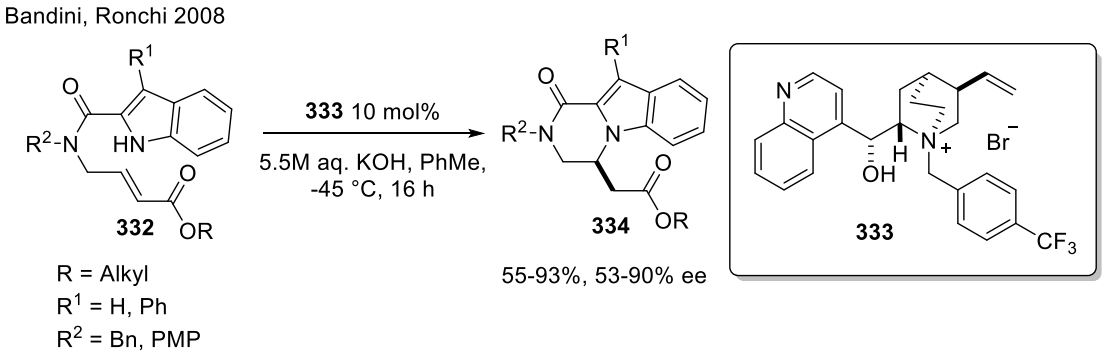
Rueping also reported that that phosphoramidate **330** was capable of cyclising anilines **329**, albeit in only moderate selectivity (Scheme 70).[115] The reaction failed for less nucleophilic amide and sulfonamide substrates.



Scheme 70. Phosphoramidate promoted N-conjugate addition of anilines.[115]

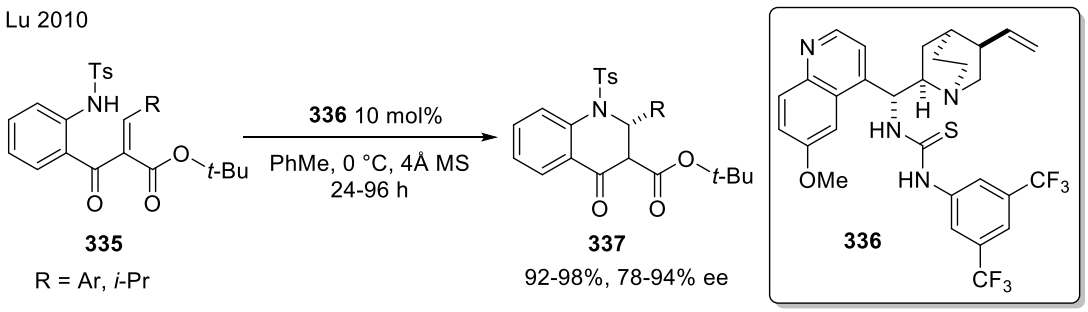
N-Conjugate Addition to Other Types of α,β-Unsaturated Carbonyl Compounds

Conjugate addition reactions to α,β-unsaturated esters and amides are less well studied than their aldehyde and ketone counterparts. This is probably because these are substantially less reactive and are not amenable to amine catalysis as they will not form iminium ions. Bandini and Ronchi have reported the use of phase transfer catalyst **333** to produce optically enriched esters **334** (Scheme 71).[116] In this case enantioselectivity is thought to arise from a tight ion pair formed prior to the conjugate addition step. This ion pair is formed between a deprotonated indole and the chiral quaternary ammonium salt catalyst.



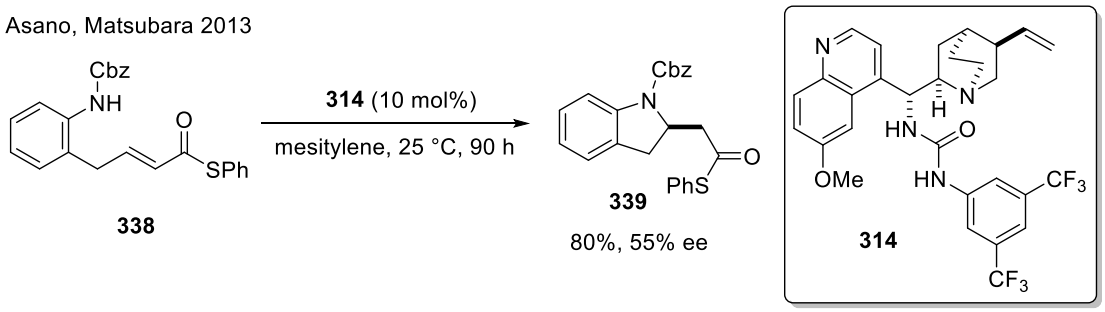
Scheme 71. Quaternary ammonium salt catalysed intramolecular N-conjugate addition.[116]

Lu demonstrated the addition of sulfonamides to alkylidene β-ketoesters in good yield and enantioselectivity (Scheme 72).[117]



Scheme 72. Intramolecular conjugate addition of sulfonamides to alkylidene β-ketoesters.[117]

Asano and Matsubara reported the N-conjugate addition to α,β-unsaturated thioesters using cinchona-derived urea **314** (Scheme 73).[111]



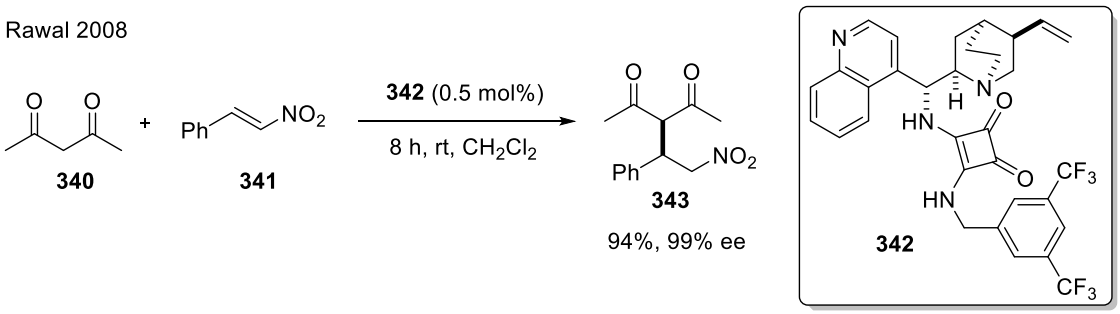
Scheme 73. Intramolecular N-conjugate addition of thioester **338**.[111]

Results and Discussion

Project Aims

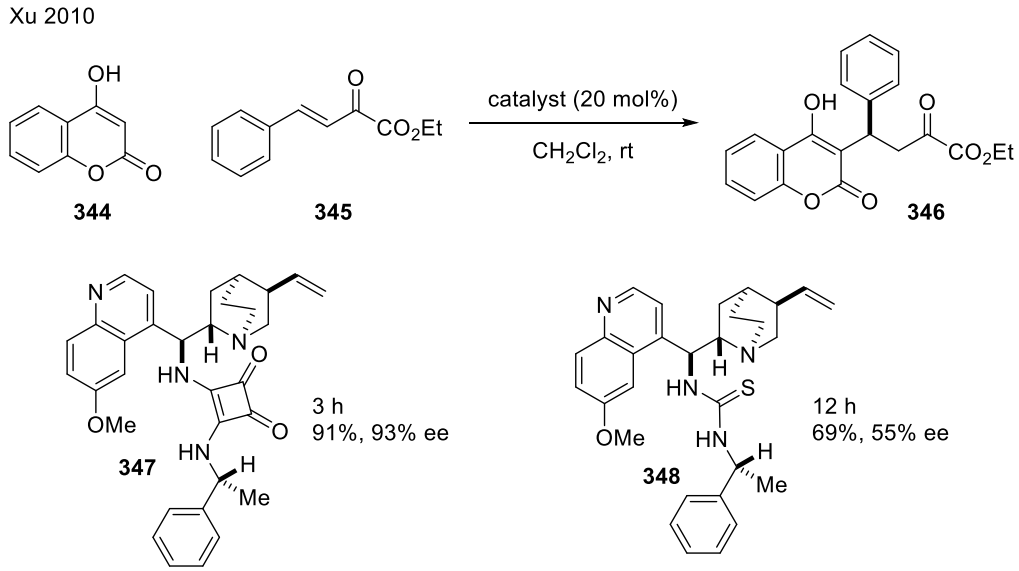
The aim of our study was to investigate new and existing Brønsted acid catalysts for intramolecular N-conjugate addition reactions. We were keen to explore the potential of intramolecular N-conjugate addition reactions using chiral amine catalysts that did not require iminium ion formation as their mode of activation. There were two reasons why we wished to avoid iminium ion formation: i) the formation and breakdown of the iminium species is often slow, leading to the requirement of long reaction times and high catalyst loading; ii) the need for iminium ion formation rules out the possibility of using α,β-unsaturated ester and amides as substrates.

It has been shown that squaramides are able to act as Brønsted acids.[118] Rawal demonstrated that a chiral amine containing a squaramide motif **342** was able to promote an asymmetric conjugate addition reaction.[118a] This catalyst was able to promote the conjugate addition of acetylacetone **340** to β-nitrostyrene **341** in 99% ee (Scheme 74).



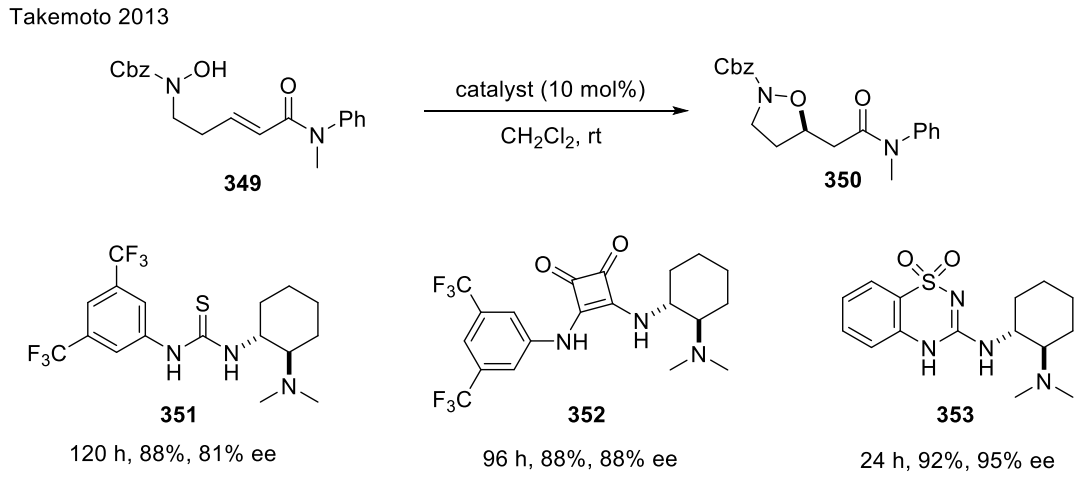
Scheme 74. Squaramide **342** for the conjugate addition of acetylacetone.[118a]

For some reactions, squaramide-containing catalysts have been shown to be superior to their structurally related thioureas.[118b] One example is the intermolecular Michael addition of 4-hydroxycoumarin **344** (Scheme 75).[119] Squaramide containing **347** is superior to structurally related thiourea **348** in terms of reaction rate and enantioselectivity.



Scheme 75. Intermolecular Michael addition of 4-hydroxycoumarin **344.**[119]

The use of squaramide-containing catalysts to promote N-conjugate addition reactions has not been reported, so we wanted to investigate their utility in the reaction.



Scheme 76. Screening of catalysts for intramolecular *O*-conjugate addition.[120]

The Takemoto group have recently shown that benzothiadiazine catalyst **353** is superior to thiourea **351** and squaramide **352** for the intramolecular O-conjugate addition of hydroxylamines and phenols to α,β-unsaturated carbonyl compounds (Scheme 76).[120] This was successful even with challenging substrates such as α,β-

unsaturated esters and amides. Because of this we were also eager to investigate how benzothiadiazine containing catalysts would perform in intramolecular N-conjugate additions.

Based on the literature discussed above, we concluded that catalysts bearing a tertiary amine and a weak Brønsted acid group might offer the best chance of success in our target reactions. Thus we selected a series of structurally related structures **354**-**357** to investigate intramolecular N-conjugate addition reactions with (Figure 15).

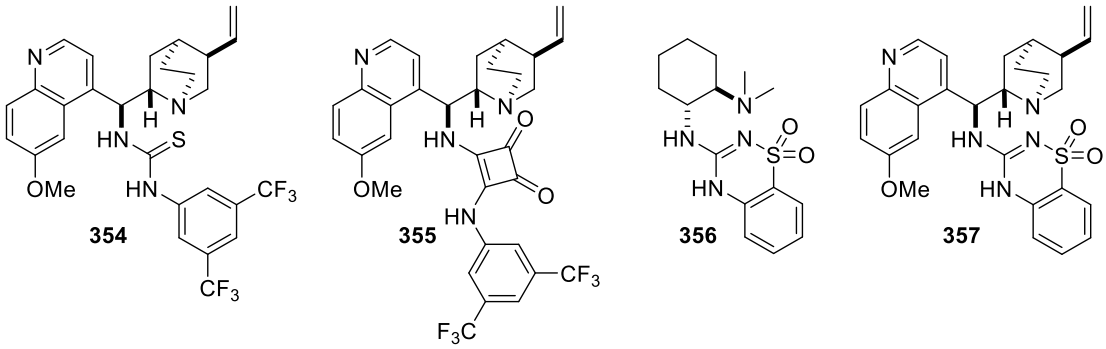
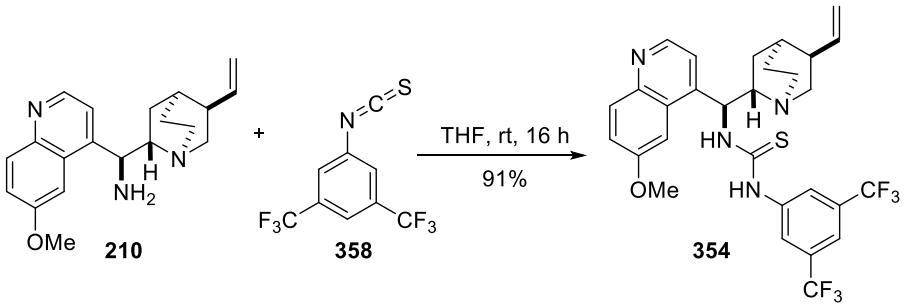


Figure 15

These structures are based on chiral amine templates known to give high enantioselectivity in other types of addition reactions. Structures **354**-**357** show variation in the nature of the Brønsted acid group.

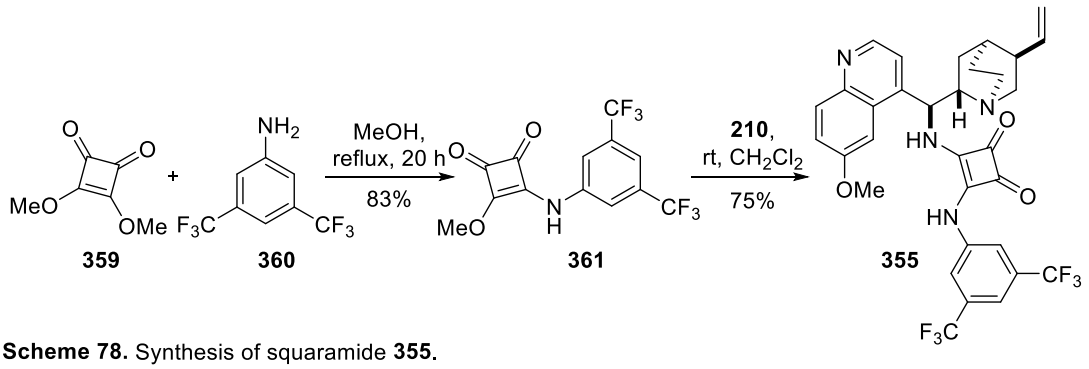
Synthesis and Evaluation of Catalysts for Intramolecular N-Conjugate Additions

Thiourea **354**[121] was prepared following the reported procedure; 9-*epi*-9-amino-9-deoxyquinine was reacted with isothiocyanate **358** to give the thiourea in 91% yield (Scheme 77).



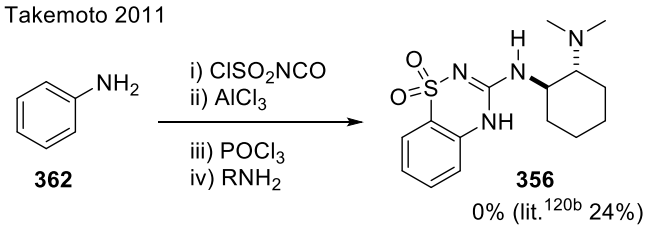
Scheme 77. Synthesis of thiourea **354**.

Squaramide **355**[122] was prepared by first reacting dimethylsquarate with 3,5-bistrifluoromethylaniline to give **361** in 83% yield. **361** was then mixed with **210** to give squaramide **355** in 75% yield (Scheme 78).



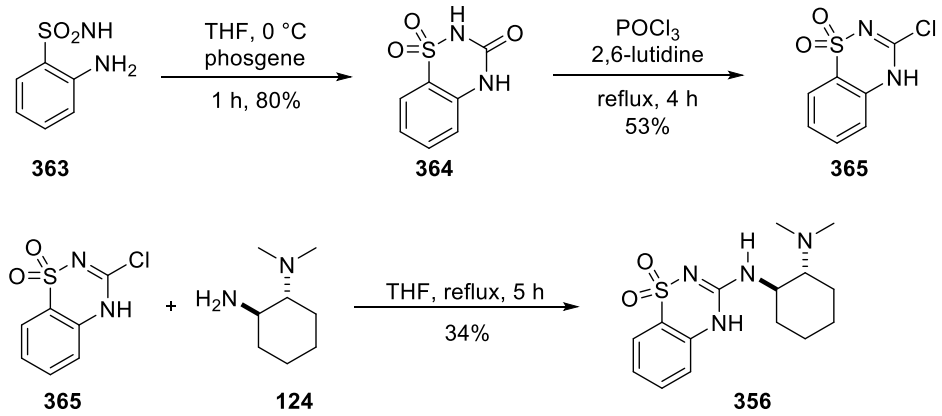
Scheme 78. Synthesis of squaramide **355**.

We attempted to prepare benzothiadiazine **356** using Takemoto's reported procedure (Scheme 79).[120b] Unfortunately this was unsuccessful so we modified the route.



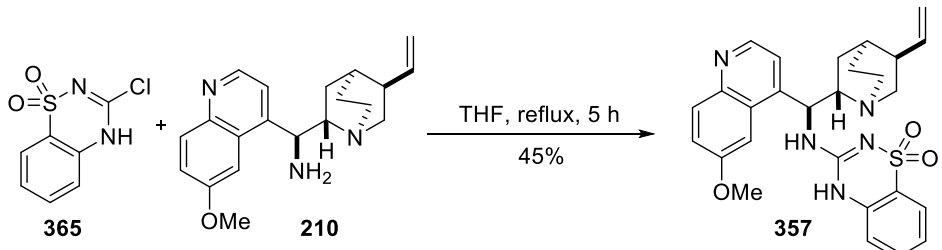
Scheme 79. Failed synthesis of benzothiadiazines **356**.

Starting aniline **363** was treated with phosgene yielding **364** in 80%. Arene **364** was then treated with phosphorus oxychloride giving **365** in 53% yield after recrystallisation.[123] Arene **365** and diamine **124**[37] were heated at reflux in tetrahydrofuran to give **356** in a 14% overall yield (Scheme 80).



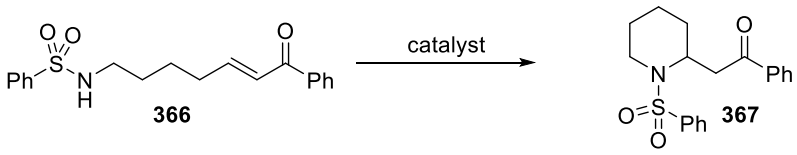
Scheme 80. Synthesis of benzothiadiazine **356**.

The previously unreported benzothiadiazine **357**, derived from 9-*epi*-9-amino-9-deoxyquinine **210**, was prepared in a 19% overall yield using the same approach (Scheme 81).



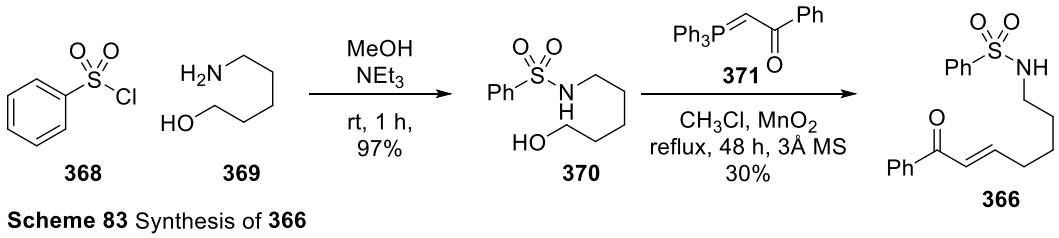
Scheme 81. Synthesis of benzothiadiazine **357**.

The literature on intramolecular conjugate additions to α,β-unsaturated carbonyl compounds suggests that Brønsted acid catalysts give higher rates of reaction with aryl ketones compared to alkyl ketones or esters. Consequently we initially directed our studies towards the cyclisation of substrates containing an α,β-unsaturated phenyl ketone. To this end we selected cyclisation of sulfonamide **366** as an appropriate reaction to test our selection of Brønsted acids catalysts in (Scheme 82). The cyclisation of simple keto sulfonamides has not previously been reported, so if successful this would expand the scope of this chemistry.



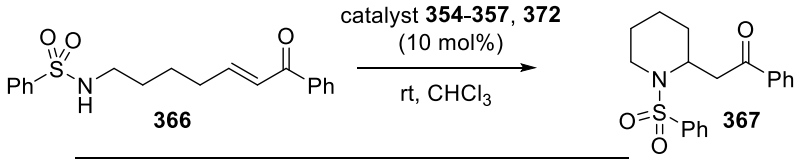
Scheme 82. cyclisation of keto sulfonamide **366**.

Sulfonamide **366** was synthesised in two steps from 5-aminopentanol (Scheme 83). Amine **369** was reacted with benzenesulfonyl chloride to give **370**. This was then subjected to a tandem oxidative Wittig reaction employing methodology developed by Taylor[124] to give target enone **366** in 29% overall yield.



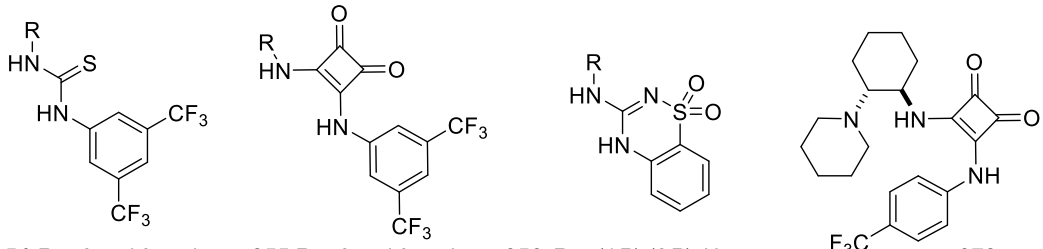
Scheme 83 Synthesis of **366**

Table 8 shows the results of our initial investigations into the performance of synthesised catalysts **354**-**357**. We included the commercially available squaramide **372**[125] in the study as we had it available in the lab. Reactions were performed in chloroform at room temperature.



Catalyst	Time (h)	Conversion (%)[a]	ee (%)[b]
354	70	90	82 (*S*)
355	3.5	100	98 (*S*)
356	70	72	81 (*R*)
357	70	100	87 (*S*)
372	70	52	87 (*R*)

[a] Determined by 1H NMR spectroscopy. [b] Determined by chiral phase HLPC



354 R = 9-*epi*-9-amino-9-deoxyquinine

355 R = 9-*epi*-9-amino-9-deoxyquinine

356 R = (1*R*),(2*R*)-*N*-dimethyldiaminocyclohexane

357 R = 9-*epi*-9-amino-9-deoxyquinine

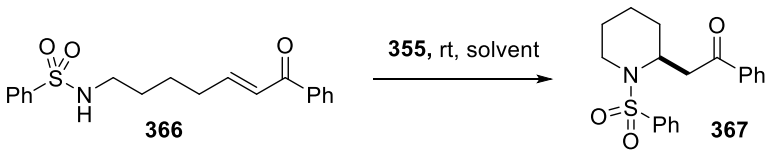
372

Table 8. Initial investigation into intramolecular N-conjugate addition using sulfonamide **366.**

Benzothiadiazines **356** and **357** were found to promote the cyclisation of **366**. The quinine derivative **357** gave a better conversion over the 70 h reaction period (72% Vs 100%). Both **356** and **357** gave the product with good enantioselectivity, but this was slightly higher using **357** (81% vs 87%). Comparison of these two results suggests that the cinchona alkaloid chiral backbone is marginally better than the *trans*-diaminocyclohexane backbone. Thiourea **354** gave 90% conversion after 70 h, the product had an ee of 82%. This is worse in both rate of reaction and enantioselectivity than its benzothiadiazine analogue **357**. Squaramide **355** was found to be the best catalyst. In this case the reaction was complete in 3.5 hours and the enantioselectivity was high (98% ee). Commercially available squaramide **372** gave the poorest conversion of all the catalysts investigated, although again enantioselectivity was good.

Having established that squaramide **355** was an effective catalyst, we next examined the effect of varying the reaction conditions (Table 9). It was found that toluene gave optimum results. It was also found that polar solvents resulted in greatly increased reaction times. Although reactions ran slowly in the more polar solvents, the enantiomeric excess of the product was still high. This suggests that the solvent is not interfering with a well defined transition state. It was also found that the catalyst loading could be reduced to 1 mol% while still

maintaining high levels of enantioselectivity and reasonable reaction times when toluene was used as a solvent.



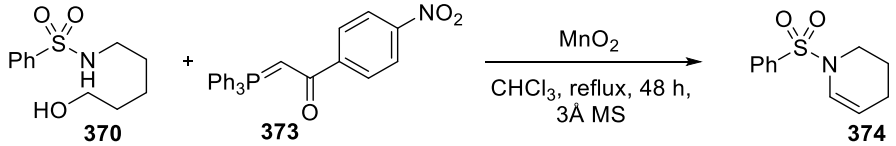
Entry	Solvent[a]	Dielectric constant (ε)	355 (mol %)	Time (h)	Conversion (%)[b]	ee (%)[c]
a	PhMe	2.4	10	4	100	99
b	$(EtO)_2CO$	2.8	10	23	100	98
c	EtOAc	3.0	10	48	100	99
d	$CHCl_3$	4.8	10	3.5	100	98
e	2-MeTHF	7.0	10	104	100	98
f	CH_2Cl_2	8.9	10	5	100	98
g	MeOH	32.7	10	168	39	90
h	MeCN	35.9	10	168	85	96
i	PhMe	2.4	5	4	100	99
j	PhMe	2.4	2	6	100	99
k	PhMe	2.4	1	12	100	99

[a] Reactions run at 0.1M. [b] Determined by ^1H NMR. [c] Determined by chiral phase HPLC.

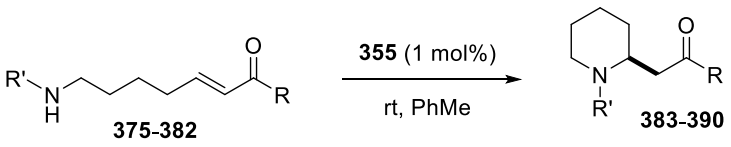
Table 9. Variation of reaction conditions.

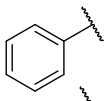
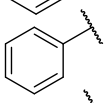
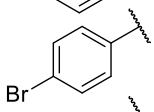
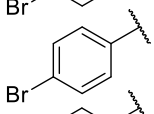
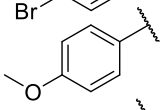
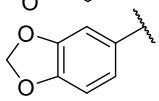
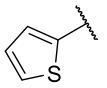
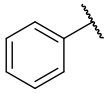
Next we investigated the effect of altering the structure of the aryl ketone and sulfonamide (Table 10). Changing from a phenylsulfonyl to 4-nitrophenylsulfonyl group on the nitogen resulted in shorter reaction times (Entries a vs b and c vs d). It was found that the aromatic ketone could be varied while still maintaining excellent levels of enantiomeric excess. Entry h shows that when the substitution on nitrogen was changed from a sulfonamide to a carbamate the reaction did not proceed at an appreciable rate.

No strongly electron deficient aryl ketones were included in the study as the oxidation/Wittig reaction failed when we attempted to prepare such substrates (Scheme 84). In these cases enamine **374** was obtained as the major product rather than the desired α,β-unsaturated ketone. Presumably the oxidation is successful but then an intramolecular condensation takes place in preference to the desired Wittig reaction.



Scheme 84. Failed oxidative Wittig reaction.



Entry	Substrate	R	R'	Product	Time (h)	Yield (%)	ee (%)[a]
a	**375**		SO_2Ph	**383**	12	84	99
b	**376**		Ns	**384**	3	77	99
c	**377**		SO_2Ph	**385**	7	83	98
d	**378**		Ns	**386**	0.5	89	98
e	**379**		SO_2Ph	**387**	24	84	99
f	**380**		SO_2Ph	**388**	48	81	99
g	**381**		SO_2Ph	**389**	6	73	99
h	**382**		Cbz	**390**	24	<5	-

[a] Determined by chiral phase HPLC

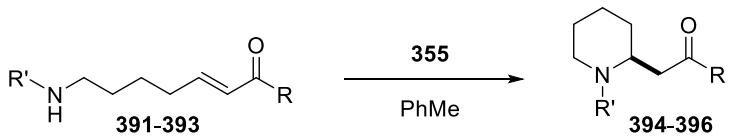
Table 10. Reaction scope.

We also examined substrates containing an α,β-unsaturated alkyl ketone and an α,β-unsaturated ester (Table 11).

Using the conditions employed for the cyclisation of aryl ketones the reaction did not proceed at an appreciable rate (Entry a). By increasing the catalyst loading, and temperature of the reaction, we were able to achieve cyclisations of both α,β-unsaturated alkyl ketones and α,β-unsaturated ester substrates. Employing 5 mol% of **355** allowed full conversion of enone **391** to ketone **394** at 80 °C in 4 h (Entry f). Product **394** was produced in 90% ee. The cyclisation of α,β-unsaturated esters was considerably slower, but by using 10 mol% catalyst and heating the reaction mixture to 80 °C, full conversion of ester **392** could be achieved (Entry g). The enantiomeric excess of the product **395** was 92% ee.

With α,β-unsaturated aryl ketones, increasing the acidity of the N-H bond by the use of a *p*-nitrophenyl sulfonamide increased the rate of reaction (Table 10). However the same modification did not appear to increase the rate of reaction for α,β-unsaturated esters; only a reduction in reaction enantioselectivity was

observed (Entry g vs h). It was also found that benzothiadiazine catalyst **357** failed to catalyse the intramolecular conjugate addition of ester **392** (Entry i).

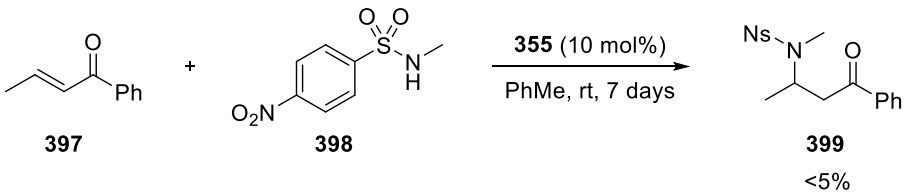


Entry	Substrate	R	R'	Product	Catalyst Loading (%)	Time	Temp	Conversion (%)[a]	E.e (%)[b]
a	**391**	Me	SO_2Ph	**394**	1	48 h	rt	<5	-
b	**391**	Me	SO_2Ph	**394**	10	168 h	rt	83	94
c[c]	**391**	Me	SO_2Ph	**394**	10	168 h	rt	82	82
d	**391**	Me	SO_2Ph	**394**	10	16 h	50 °C	100	92
e	**391**	Me	SO_2Ph	**394**	5	24 h	50 °C	100	91
f	**391**	Me	SO_2Ph	**394**	5	4 h	80 °C	100	90
g	**392**	OMe	SO_2Ph	**395**	10	7 d	80 °C	>95	92
h	**393**	OMe	Ns	**396**	10	7 d	80 °C	>95	88
i[d]	**392**	OMe	SO_2Ph	**395**	10	7 d	80 °C	<5	-

[a] Determined using ^1H NMR. [b] Determined using chiral phase HPLC. [c] Reaction run at 1M concentration.
[d] Using catalyst **357** instead of **355**.
Table 11. □□□-unsaturated alkyl ketones and □□□-unsaturated ester substrates.

Bar Bandini and Ronchi's PTC cyclisation of indoles[116] (Scheme 71), the cyclisation of **392** and **393** (entry g and h) are the first reports of an organocatalytic *N*-conjugate addition to alkenes conjugated to an ester. The reaction proceeds relatively slowly and requires heating but the enantioselectivity of the process is still very high.

We briefly investigated the intermolecular N-conjugate addition of sulfonamide **117** to enone **116** using catalysts **79**. Unfortunately no reaction was observed suggesting that this chemistry may be limited to intramolecular additions (Scheme 85).



Scheme 85. Intermolecular N-conjugate addition reaction.

Proposed Catalytic Cycle

We were able to obtain an X-ray crystal structure of piperidine **386**. This established that the configuration of the stereocentre in **386** was (*S*) (Figure 16).

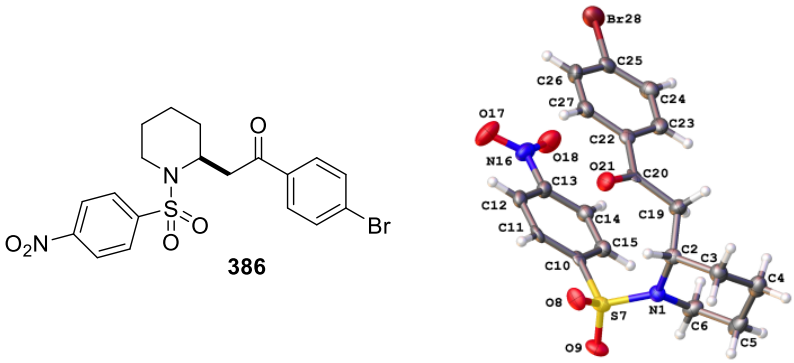
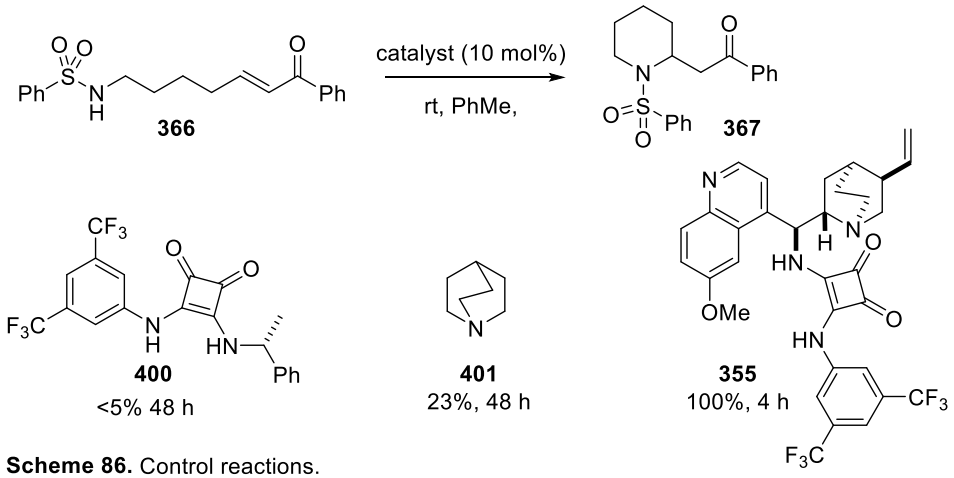


Figure 16. X-ray crystal structure of **386**.

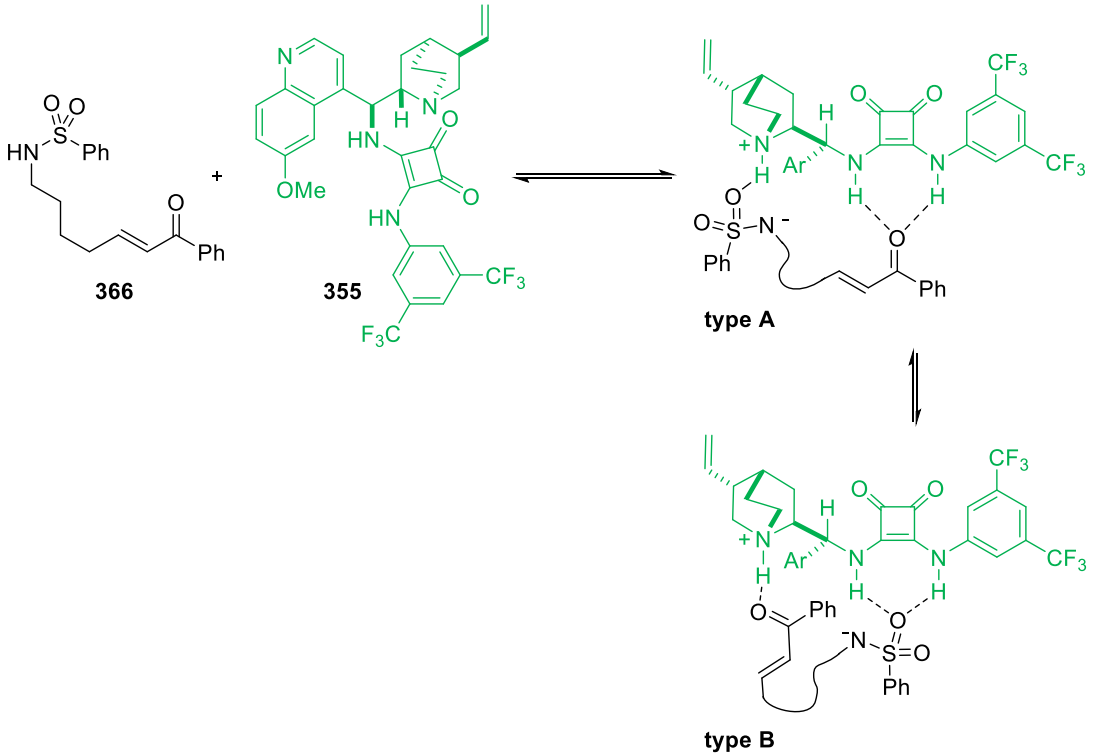
We propose that catalyst **355** is able to interact with the substrate through both the squaramide and quinuclidine functionality. Evidence in support of this comes from the fact that squaramide **400**, which does not possess a basic tertiary nitrogen centre, fails to catalyse the reaction. Also, although quinuclidine **401** does catalyse the reaction the rate is significantly slower than that observed with bifunctional **355** (Scheme 86).



Scheme 86. Control reactions.

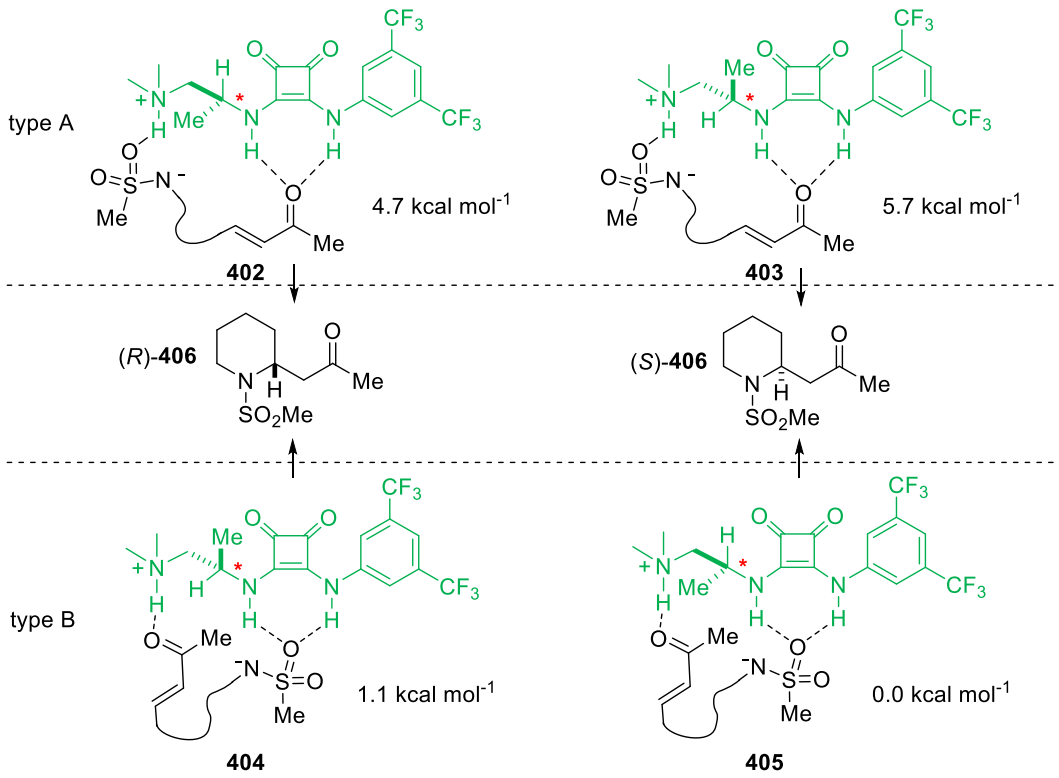
Based on these observations, we proposed that the first step of the catalytic cycle involves deprotonation of the substrate. At this point there are two possible modes of cyclisation that could occur, type A and type B (Scheme 87). In type A the enone is H-bonding with the squaramide while the sulfonamide is H-bonding with the protonated quinuclidine. In type B these bonding interactions have been switched. The greatest level of activation is expected to be *via* the bonding arrangement in type B. This is because the most acidic hydrogen, the protonated quinuclidine, is activating the electrophile and the less acidic squaramide is 'deactivating' the nucleophile. In arrangement A, the electrophile would be less activated, and the nucleophile more deactivated. However for the reaction to

proceed *via* arrangement B, the catalyst must first form an ion pair which can reorganise prior to cyclisation.



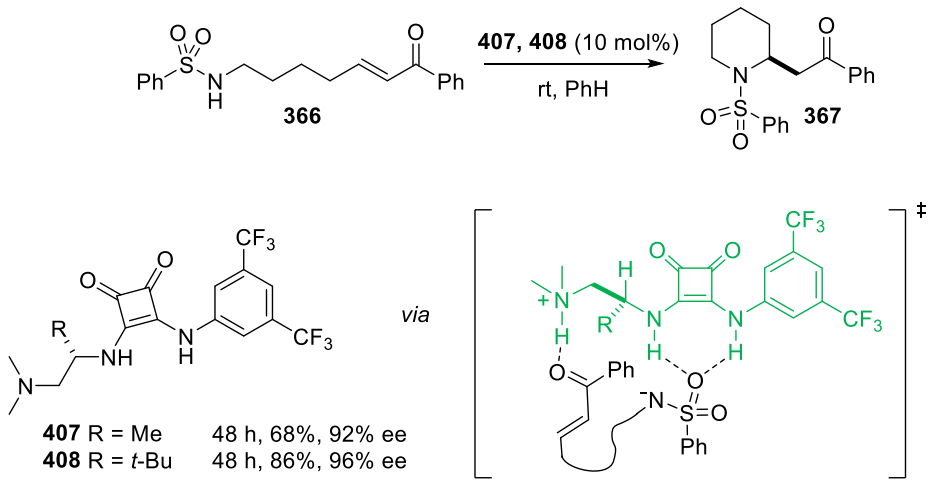
Scheme 87. Two potential modes of catalysis.

We have investigated these two modes of catalysis using molecular modelling.[55] A simplified model of the catalyst structure was used to reduce the computational cost. The model catalyst has a methyl group in place of the isoquinoline group, and a dimethyl tertiary amine instead of the quinuclidine. Two transition states for both type A and type B cyclisations were identified, **402**-**405** (Scheme 88). The pairs of transition states differ in the conformation around the starred carbon-nitrogen bond. In transition states **402** and **405**, this has the two H-atoms *anti*-periplanar, whereas in **403** and **404** they are *syn*-periplanar. In the free catalyst, the *anti*-periplanar arrangement is predicted to be more stable by ~1 kcal mol^{-1}. The reported X-ray structures of related squaramides have this bond in the *anti*-periplanar conformation.[118a,129] Consequently it is not surprising that the transition states corresponding to the cyclisation *via* arrangements **402** and **405** are predicted to be more favourable than than those proceeding *via* **403** and **404**. As previously discussed, the H-bonding arrangement in **405** would be expected to be more activating than that in **404**. This is supported by calculations which suggest that cyclisation *via* **405** offers the lowest energy pathway. Finally it should be noted that cyclisation *via* **405** would lead to the (*S*)-enantiomer of product **406**, and this is the enantiomer observed.



Scheme 88. Possible transition state energies predicted using B3LYPD3(BJ)/def2-TZVPP//B3LYP/6-316.

Based on these conclusions, a colleague in the lab, Lee Eccleshare has initiated studies on potential catalysts that are similar to the structures used for the calculations. As part of this investigation he has prepared two related structures **407** and **408**. Squaramide **407** is the model structure used in the calculations.



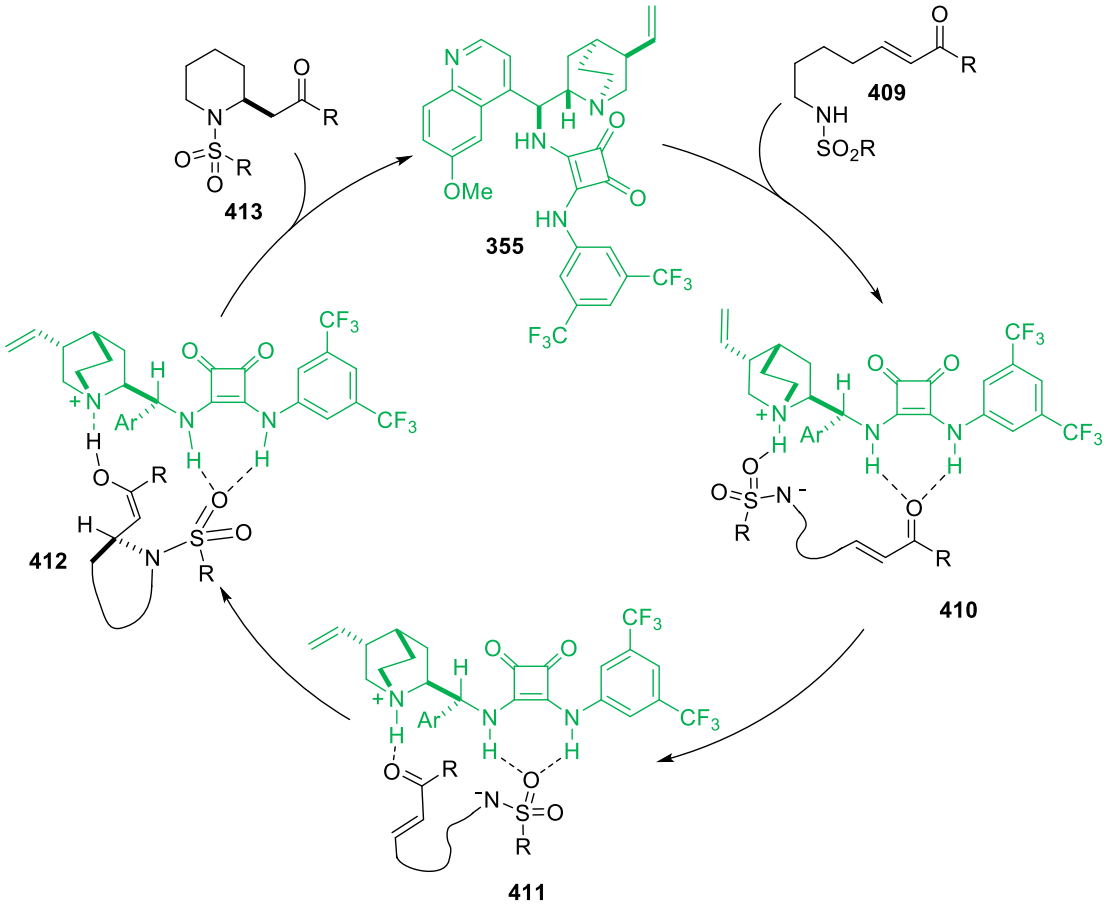
Scheme 89. Model catalyst **407** and rationally designed catalyst **408**.

To date he has only investigated application of these compounds in the cyclisation of ketone **366** (Scheme 89). Here it was found that both catalysts gave the predicted (*S*)-enantiomer of product, and both delivered the product with high levels of enantiomeric excess. The cyclisations were slower than those with

squaramide **355**, but this may be in part due to the very low solubility of **407** and **408** in the reaction solvent.

It is interesting to note that **407** and **408** have just a single stereocentre. This demonstrates that the additional stereocentres in catalyst **355** are not necessary for high enantioselectivity to be achieved. These results are consistent with those predicted by the calculations and so provide support for the idea that cyclisations may proceed *via* the H-bonding arrangement shown in **405**.

Based on this we propose the catalytic cycle shown in Scheme 90. This starts with deprotonation of the substrate **409** to give ion pair **410**. Reorganisation of the ion-pair to arrangement **411** then leads to cyclisation to give **412**. Finally tautomerism to the ketone gives the observed product **413** and regenerates the catalyst.



Scheme 90. Proposed catalytic cycle for **355.**

Conclusions

In conclusion we have shown that squaramide catalyst **355** can be employed as a highly enantioselective catalyst for the intramolecular N-conjugate addition

reaction of sulfonamides and α,β-unsaturated ketones. The catalyst is effective at 1 mol% loading and reaction times for phenyl ketone substrates varies from 0.5-48 h. **355** is also able to catalyse the intramolecular N-conjugate addition reaction of sulfonamides and α,β-unsaturated esters at elevated temperatures. In which case a high level of enantioselectivity is also realised.

Based on our computational and laboratory investigations we have put forward a mechanistic rationale for the studied reaction. We proposed that an initial deprotonation step is followed by ion pair rearrangement and cyclisation. Key to the observed stereochemistry is the *anti*-periplanar arrangement of the two hydrogen atoms α and β to the planar squarate ring. Prompted by our computational studies we have synthesised chiral squaramide containing catalysts **407** and **408**; these structures contain just a single stereocentre. The high enantioselectivity observed with catalysts **407** and **408** lend support to our proposed mechanistic rationale.

Conclusions and Further Work

This thesis has detailed investigations into asymmetric addition reactions using diamine derived catalysts. Firstly novel amine **113** was identified as a highly enantio- and diastereoselective catalyst for the aldol reaction of aromatic aldehydes with cyclic and acyclic ketones. Of note is the high diastereoselectivity achieved by incorporating a *tropos*-biphenyl axis into the catalyst structure. The biphenyl unit effectively mimics a single enantiomer of the locked binaphthyl unit, thus resulting in improved enantiofacial selection of the aldehyde. The *tropos*-biphenyl unit bears the advantage of being significantly cheaper and easier to synthesise than the locked binaphthyl element.

The thesis then moves on to detail an investigation utilising catalysts based on the 1,2-*trans*-diaminocyclohexane unit we found to be effective for the aldol reaction. We discovered that the parent 1,2-*trans*-diaminocyclohexane **114** was able to catalyse intermolecular *N*-conjugate addition reaction of pyrazoles with high enantioselectivity. Functionalisation of 1,2-*trans*-diaminocyclohexane's nitrogen atoms resulted in reduced catalyst activity and selectivity. When the H-bonding capabilities of a single nitrogen on **114** was removed, a switch in enantioselectivity was observed. The fact that **114** is a readily available and effective enantioselective-catalyst for *N*-conjugate addition reactions makes it an appealing catalyst choice for this type of chemistry.

Although not detailed within this thesis, within our group further work has been carried out, both experimentally and computationally, to assess the regioselectivity of unsymmetrical pyrazoles.[54] Questions arising about the geometry of the iminium ion formed and the role of the acid co-catalyst have also been addressed. Further work into expansion of the electrophile substrate scope could be undertaken. Constraints on the iminium ion formed by the electrophile may also prove useful in determining a transition state model of the reaction.

Thirdly an investigation into the intramolecular *N*-conjugate addition reaction was presented. The potential of catalysts possessing hydrogen bonding capabilities was noted and we prepared catalysts of this type to promote the intramolecular conjugate addition of *N*-nucleophiles to alkenes conjugated to phenyl ketones and esters. These reactions were targeted as primary amine catalysts had been shown to be ineffective in these cases.

Catalyst **355** possessing a tertiary amine and squaramide was found to be the best catalyst studied. It was able to enantioselectively cyclise phenyl ketone and ester substrates. Computational studies into the addition step suggests that an arrangement where the catalyst and substrate have rearranged following an initial deprotonation step could account for the observed stereochemical outcome. Synthesis of new effective catalyst structures based on this model have added support to the proposed catalyst-substrate arrangement.

Variations in the acidity of the nucleophile, along with the basicity of the catalyst could be examined further. This could then give an indication of substrate scope. Evidence for the ability and likelihood of catalyst-substrate reorganisation, after a formal deprotonation step could be examined. Addition of a base followed by the catalyst at low temperatures may be able to reveal more information on this process.

Experimental

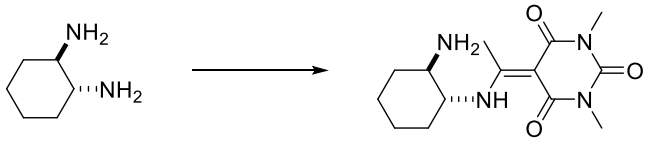
General Experimental

All solvents and reagents were used as supplied from commercial sources or if appropriate purified by standard techniques.[127] Melting points (mp) were determined using a Stuart SMP3 electrothermal apparatus and are uncorrected. Optical rotations were measured on a Bellingham and Stanley ADP440 polarimeter at wavelength 589 nm and are given in units of 10^{-1} deg cm^2 g^{-1}. Samples for the measurement of their optical rotation were prepared in the indicated solvent (concentration g/100 ml) and measurements taken until 3 values in close agreement were obtained. Infrared (IR) spectra were recorded using a Perkin-Elmer 1600 FT-IR or a Nicolet Avatar 360 FT-IR spectrometer. Spectra were recorded as neat samples or as chloroform solutions as indicated. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker (AV400, AV(III)400, DPX400, AV(III)500) spectrometer at ambient temperature. All chemical shifts (δ) are reported in parts per million (ppm). All multiplicities are designated by the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad; app = apparent. All coupling constants *J* are reported in Hertz. All ^{13}C NMR spectra were acquired using broadband decoupled mode and assignments were determined using DEPT sequences. Assignments of peaks was assisted by COSY, HMQC and/or HMBC experiments. Mass spectra were obtained on a Bruker microTOF (electrospray ionisation ESI) machine. High performance liquid chromatography (HPLC) was performed using a Varian ProStar 210 chromatograph with analytical 4.6 x 250 mm columns with a guard column attached using conditions outlined in the relevant experimental procedures. Flash chromatography was carried out using Kieselgel 60 (230-400 mesh) using solvent specified. Analytical thin layer chromatography (TLC) was performed using pre-coated glass backed plates (Kieselgel 60 with F254). Plates were visualised using short-wave UV followed by staining with an appropriate reagent. Petroleum ether refers to light petroleum ether 40-60 °C. Degassed solvents were prepared by cooling the specified solvent, under vacuum, to its freezing point. The solvent was then allowed to warm under vacuum and the process repeated twice more before placing it under an atmosphere of argon.

Compounds **115**[128], **117**[129], **122**, **124**[130], **126**, **127, 238**, **239** and **243**-**254** were prepared by Dr. Tim Evans. Compounds **354**[121] and **382**[109a] were prepared by Anthony Ball. Compounds **407** and **408** were prepared by Lee Eccleshare.

Experimental Data

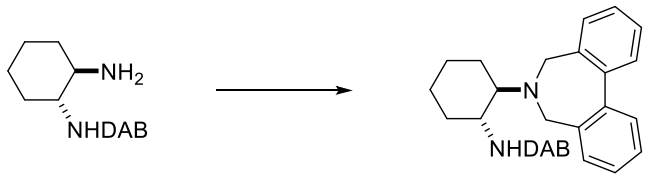
(1*R,*2*R*)-*N*-(1',3'-Dimethyl-5'-acetylbarbituric acid)-1,2-diaminocyclohexane **116**[49]



114 **116**

A solution of (1*R*,2*R*)-1,2-diaminocyclohexane (0.68 g, 6.00 mmol) in dry tetrahydrofuran (116 ml) was placed under an argon atmosphere. 1,3-Dimethyl-5-acetylbarbituric acid (1.19 g, 6.00 mmol) was added and the mixture was stirred at rt for 5 h. The product **116** (1.71 g, 97%) was collected by filtration as a colourless solid. mp 231-233 ^{o}C; $[\alpha]_D^{24}$ -63.0 (*c* 0.9 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3695, 3011, 2942, 2863, 1701, 1638, 1594, 1479, 1382; δ_H (400 MHz, $CDCl_3$) 12.76 (1H, d, *J* 6.0, NH), 3.43-3.40 (1H, m, NHC*H*), 3.33 (3H, s, NCH_3), 3.32 (3H, s, NCH_3), 2.85-2.79 (1H, m, NH_2CH), 2.75 (3H, s, CCH_3), 2.00-1.95 (2H, m, CH_2), 1.83-1.78 (2H, m, CH_2), 1.43-1.33 (6H, m, CH_2 and NH_2); δ_C (100 MHz, $CDCl_3$) 173.9 (C), 166.6 (C), 163.0 (C), 151.4 (C), 90.2 (C), 60.6 (CH), 54.9 (CH), 34.7 (CH_2), 32.4 (CH_2), 27.8 (CH_3), 27.6 (CH_3), 24.6 (CH_2), 24.4 (CH_2), 18.3 (CH_3); m/z (ES) 295 ($M+H^+$, 100%); m/z (ES) found $[M+H]^+$ 295.1769. $C_{14}H_{23}N_4O_3^+$ requires 295.1765. The compound has previously been synthesised but no analytical data is reported.[49]

(1'*R*,2'*R*)-6-(2'-*N*-(1'',3''-Dimethyl-5''-acetylbarbituric acid)aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine **118**

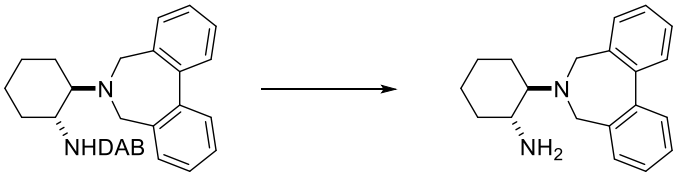


116 **118**

A solution of (1*R,*2*R*)-*N*-(1',3'-dimethyl-5'-acetylbarbituric acid)-1,2-diaminocyclohexane **116** (1.73 g, 5.88 mmol) and 2,2'-bis-bromomethylbiphenyl **117**[129] (2.00 g, 5.88 mmol) in acetonitrile (150 ml) was placed under an argon atmosphere. Anhydrous potassium carbonate (5.36 g, 38.8 mmol) was added and the mixture stirred at 60 ^{o}C for 24 h. The mixture was allowed to cool to rt then filtered and washed through with dichloromethane (100 ml). The filtrand was concentrated under reduced pressure and the residue purified by chromatography

on silica gel (69 : 30 : 1, petroleum ether : ethyl acetate : triethylamine) to give the product **118** (2.67 g, 96%) as a colourless solid. mp 106-108 °C; $[\alpha]_D^{22}$ -177.6 (*c* 0.8, $CHCl_3$); R_f 0.1 (69 : 30 : 1, petroleum ether : ethyl acetate : triethylamine); $\nu_{max}(CHCl_3)/cm^{-1}$ 3675, 3378, 3009, 2941, 2861, 1702, 1699, 1636, 1593; δ_H (400 MHz, $CDCl_3$) 12.90 (1H, br d, *J* 7.0, NH), 7.48-7.44 (2H, m, ArH), 7.44-7.38 (2H, m, ArH), 7.38-7.31 (4H, m, ArH), 3.81-3.71 (1H, m, CHN), 3.60 (2H, d, *J* 12.5, NC$H_a$$H_b$), 3.48 (2H, d, *J* 12.5, NC$H_a$$H_b$), 3.37 (3H, s, NCH_3), 3.31 (3H, s, NCH_3), 2.81-2.90 (1H, m, CHN), 2.73 (3H, s, CCH_3), 2.22-2.14 (1H, m, CH_2), 2.01-1.93 (1H, m, CH_2), 1.89-1.78 (2H, m, CH_2), 1.60-1.23 (4H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 172.8 (C), 166.4 (C), 163.2 (C), 151.6 (C), 140.8 (C), 135.9 (C), 129.6 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 90.0 (C), 68.5 (CH), 55.6 (CH), 52.4 (CH_2), 33.6 (CH_2), 27.8 (CH_3), 27.8 (CH_2), 27.6 (CH_3), 25.4 (CH_2), 24.6 (CH_2), 18.6 (CH_3); m/z (ES) 473 ($M+H^+$, 100%); m/z (ES) found $[M+H]^+$ 473.2552. $C_{28}H_{33}N_4O_3^+$ requires 473.2547.

(1'*R*,2'*R*)-6-(2'-Aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine **119**[130]

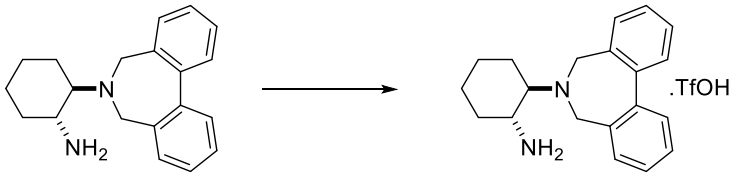


118 **119**

A solution of amine **118** (2.67 g, 5.64 mmol) in ethanol (100 ml) was placed under an argon atmosphere. Powdered potassium hydroxide (1.90 g, 33.9 mmol) was added and the mixture was stirred at 50 °C for 24 h. The resulting solution was allowed to cool to rt, then diluted with water (150 ml) and dichloromethane (150 ml). The aqueous layer was extracted with dichloromethane (2 x 150 ml), and the combined organics were then dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (97 : 2 : 1, dichloromethane : methanol : triethylamine) to give the product **119** (1.32 g, 80%) as a colourless oil. $[\alpha]_D^{25}$ -39.8 (*c* 0.8, $CHCl_3$); R_f 0.1 (97 : 2 : 1, dichloromethane : methanol : triethylamine); $\nu_{max}(CHCl_3)/cm^{-1}$ 3374, 2933, 2859, 1602, 1450, 1080; δ_H (400 MHz, $CDCl_3$) 7.49-7.36 (8H, m, ArH), 3.61 (2H, d, J 12.5, NC$H_a$$H_b$), 3.54 (2H, d, J 12.5, NC$H_a$$H_b$), 2.83 (1H, ddd, *J* 10.5, 10.5, 4.0, CHN), 2.47-2.38 (1H, m, C*H*NH_2), 2.07-2.00 (3H, m, C$H_a$$H_b$ and NH_2), 1.82-1.68 (3H, m, C$H_a$$H_b$ and CH_2), 1.39-1.14 (4H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 140.9 (C), 136.7 (C), 129.8 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 72.1 (CH), 52.1 (CH_2), 52.0 (CH), 35.2 (CH_2), 26.7 (CH_2), 26.3 (CH_2), 25.1 (CH_2); m/z (ES) 293 ($M+H^+$, 100%); m/z

(ES) found $[M+H]^+$ 293.2006. $C_{20}H_{25}N_2^+$ requires 293.2012. The compound has previously been synthesised by an alternative route but no analytical data is reported.[130]

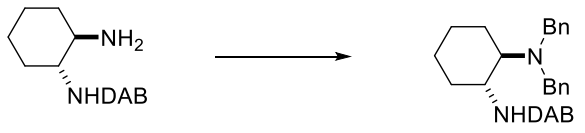
(1'*R*,2'*R*)-6-(2'-Aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepinium triflate **113**



119 **113**

A solution of triflic acid (765 mg, 5.09 mmol) in dichloromethane (40 ml) was added to a solution of (1'*R*,2'*R*)-6-(2'-aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine **119** (1.49 g, 5.09 mmol) in dichloromethane (40 ml). The solution was stirred at rt for 1 h, then concentrated under reduced pressure to afford the product **113** (2.25 g, 100%) as an off-white solid. mp 74-76 ^oC; $[\alpha]_D^{25}$ -6.0 (*c* 1.2, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 3250, 3075, 3011, 2948, 1602, 1452, 1288, 1240, 1028; δ_H (400 MHz, $CDCl_3$) 7.49-7.35 (8H, m, ArH), 5.47 (3H, br.s, NH_3), 3.63 (2H, d, J 12.5, NCH_aH_b), 3.55 (2H, d, J 12.5, NCH_aH_b), 3.19 (1H, ddd, J 11.5, 11.5, 4.0, CHN), 2.87 (1H, ddd, J 11.5, 11.5, 3.5, CHN), 2.34-2.31 (1H, m, CH_2), 1.92-1.80 (3H, m, CH_2), 1.68-1.58 (1H, m, CH_2), 1.48-1.27 (3H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 140.8 (C), 135.0 (C), 129.9 (CH), 128.2 (CH), 127.7 (CH), 120.2 (q, J 318, CF_3), 66.9 (CH), 52.4 (CH), 51.8 (CH_2), 52.2 (CH_2), 30.0 (CH_2), 26.6 (CH_2), 25.1 (CH_2), 24.2 (CH_2); m/z (ES) 293 ($M\text{-}OTf^+$, 100%), (54); m/z (ES) found $[M\text{-}OTf]^+$ 293.2000. $C_{20}H_{25}N_2^+$ requires 293.2012.

(1*R*,2*R*)-*N*-(5'-acetyl-1',3'-dimethylbarbituric acid)-*N*-dibenzyl-1,2-diaminocyclohexane **121**[49]

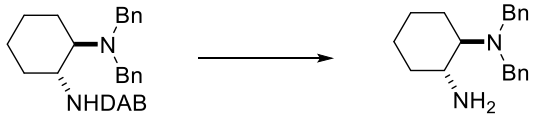


116 **121**

A solution of benzaldehyde (309 mg, 2.91 mmol) and (1*R*,2*R*)-*N*-(1',3'-dimethyl-5'-acetylbarbituric acid)-1,2-diaminocyclohexane **116** (171 mg, 0.58 mmol) in water : acetonitrile (1 : 20, 4.20 ml) was stirred for 45 mins. Sodium cyanoborohydride (76.8 mg, 1.22 mmol) was added and the mixture stirred for a further 30 mins. Acetic acid (0.2 ml) was added then added and the mixture was

concentrated under reduced pressure. The residue was dissolved in chloroform (10 ml), washed with 1M aq. sodium hydroxide (2 x 5 ml), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (dichloromethane to 1 : 99 methanol : dichloromethane) to give the product **121** (185 mg, 83%) as a colourless glassy solid. $[\alpha]_D^{24}$ -9.9 (*c* 1.0, $CHCl_3$); R_f 0.3 (1 : 99 methanol : dichloromethane); $\nu_{max}(CHCl_3)/cm^{-1}$ 3013, 2943, 1639, 1478, 1384; δ_H (400 MHz, $CDCl_3$) 12.81 (1H, d, J 7.0 Hz, NH), 7.37-7.35 (4H, m, ArH), 7.23-7.30 (6H, m, ArH), 3.79 (2H, d, J 14.0 Hz, NCH_aH$_b$), 3.58 (2H, d, J 14.0 Hz, NCH$_a$$H_b$), 3.51-3.56 (1H, m, CHN) 3.47 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 2.84 (1H, ddd, J 11.0, 11.0, 3.5 Hz, CHN), 2.40 (3H, s, CCH_3) 2.17-2.20 (1H, m, CH_2), 1.95-1-98 (1H, m, CH_2) 1.87-1.91 (1H, m, CH_2), 1.72-1.76 (1H, m, CH_2), 1.42-1.52 (1H, m, CH_2), 1.16-1.34 (3H, m, CH_2); δc (100 MHz, $CHCl_3$) 172.7 (C), 165.0 (C), 163.0 (C), 151.6 (C), 139.2 (C), 128.7 (CH), 128.3 (CH), 127.1 (CH), 89.8 (C), 63.0 (CH), 55.1 (CH), 54.5 (CH_2), 34.1 (CH_2), 27.8 (CH_3), 27.5 (CH_3), 25.0 (CH_2), 24.7 (CH_2), 23.6 (CH_2), 18.0 (CH_3); m/z (ES) 497 ($M+Na^+$, 100), 304 (60%); m/z (ES) found $[M+Na]^+$ 497.2524. $C_{28}H_{34}N_4O_3Na^+$ requires 497.2523. The compound has previously been synthesised but no analytical data was reported.[49]

(1*R*,2*R*)-*N*-Dibenzyl-1,2-diaminocyclohexane **123**[52]

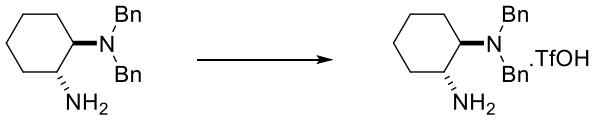


121 **123**

A solution of (1*R,*2*R*)-*N*-(5'-acetyl-1',3'-dimethylbarbituric acid)-*N*-dibenzyl-1,2-diaminocyclohexane **121** (132 mg, 0.26 mmol) in ethanol (4.0 ml) was placed under an argon atmosphere. Finely ground potassium hydroxide (0.07 g, 1.30 mmol) was added and the mixture heated to 50 °C for 25 h. The mixture was cooled to rt, diluted with dichloromethane (15 ml) and water (15 ml) then the layers separated. The aqueous was extracted with dichloromethane (2x10 ml) and the combined organics were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2 : 97 : 1, methanol : dichloromethane : triethylamine) to give the product **123** (53.0 mg, 70%) as an orange oil. $[\alpha]_D^{25}$ -61.3 (*c* 1.0, $CHCl_3$) [lit.,[52] $[\alpha]_D^{20}$ –42.5 (*c* 0.36 $CHCl_3$)]; R_f 0.1 (2 : 97 : 1, methanol : dichloromethane : triethylamine); $\nu_{max}(CHCl_3)/cm^{-1}$ 3373, 3352, 3011, 2933, 2859, 1602, 1494, 1452; δ_H (400 MHz, $CDCl_3$) 7.37-7.24 (10H, m ArH), 3.87 (2H, d, J 13.5 Hz, NCH_aH$_b$), 3.43 (2H, d, J 13.5 Hz, NCH$_a$$H_b$), 2.73 (1H, ddd, J 10.5, 10.5, 4.0 Hz,

CHN) 2.20 (1H, ddd, J 11.5, 10.5, 3.5 Hz, CHN) 2.04-2.00 (4H, m, NH_2 and CH_2) 1.87-1.82 (1H, m, CH_2), 1.69-1.65 (1H, m, CH_2) 1.33-1.09 (3H, m, CH_2) 1.03-0.92 (1H, m, CH_2); δc (100 MHz, $CHCl_3$) 140.1 (C), 128.8 (CH), 128.3 (CH), 126.8 (CH), 64.6 (CH), 53.7 (CH_2), 51.1 (CH), 34.7 (CH_2), 25.7 (CH_2), 25.1 (CH_2), 22.5 (CH_2); m/z (ES) 295 ($M+H^+$, 100%); m/z (ES) found $[M+H]^+$ 295.2172. $C_{20}H_{27}N_2^+$ requires 295.2169. ^1H NMR data is in agreement with that previously reported.[52]

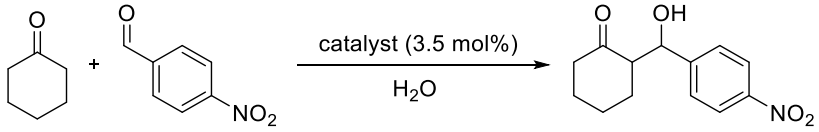
(1'*R,2'R*)-*N*-Dibenzyl-N-(2'aminocyclohexane) ammonium Triflate **125**



123 **125**

Triflic acid (18.9 mg, 0.13 mmol) was stirred in dichloromethane (1.0 ml). A solution of (1*R*,2*R*)-*N*-dibenzyl-1,2-diaminocyclohexane **123** (37.0 mg, 0.13 mmol) in dichloromethane (1.0 ml) was added and the mixture left to stir at rt for 1 h. The solution was then concentrated under reduced pressure and the residue re-dissolved in diethyl ether (0.5 ml). A small amount of petroleum ether was added to crystallise out an impurity then the remaining solution was concentrated under reduced pressure to give the product **125** (46 mg, 83%) as a colourless solid. mp 48-50 °C $[\alpha]_D^{22}$ -34.3 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2941, 1603, 1454, 1240, 1028; δ_H (400 MHz, $CDCl_3$) 7.37-7.24 (10H, m, ArH), 5.12 (3H, br. s, NH_3), 3.79 (2H, d, J 13.5 Hz, NCH_aH_b), 3.47 (2H, d, J 13.5 Hz, NCH_aH_b) 2.89 (1H, ddd, J 11.0, 11.0, 4.0 Hz, CHN), 2.49 (1H, ddd, J 11.5, 11.0, 3.5 Hz, CHN), 2.16-2.13 (1H, m, CH_2), 2.04-2.00 (1H, m, CH_2), 1.86-1.84 (1H, m, CH_2), 1.74-1.71 (1H, m, CH_2), 1.41-1.18 (4H, m, CH_2); δc (100 MHz, $CHCl_3$) 138.6 (C), 128.9 (CH), 128.7 (CH), 127.5 (C), 120.1 (C, q, J_{CF} 319, CF_3), 61.8 (CH), 53.9 (CH_2), 51.3 (CH), 30.6 (CH_2), 24.8 (CH_2), 24.1 (CH_2), 23.1 (CH_2); m/z 295 ($M\text{-}TfO^+$, 100%); m/z (ES) found $[M\text{-}OTf]^+$ 295.2164. $C_{20}H_{27}N_2^+$ requires 295.2169.

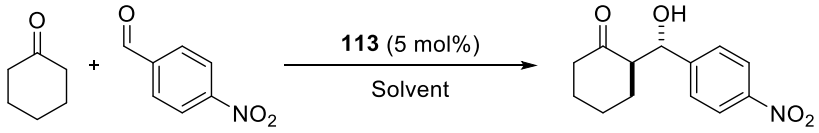
General procedure for catalyst screening in H_2O



Following the procedure reported by Shao[42] a mixture of cyclohexanone (118 mg, 1.2 mmol), *p*-nitrobenzaldehyde (60 mg, 0.40 mmol) and water (0.5 ml) were stirred at rt. A solution of the catalyst salt (14.0 μmol) in water (0.5 ml) was

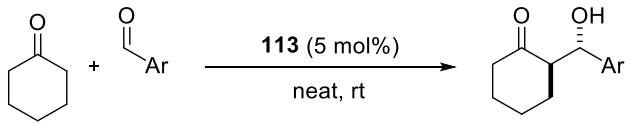
then. The mixture was stirred vigorously for 12 h. Saturated aqueous ammonium chloride (1.0 ml) was added and the organics extracted with ethyl acetate (3 x 5 ml). The combined organics were dried over sodium sulfate and concentrated under reduced pressure to give 2-(1'hydroxy-1'-(4-nitrophenyl)methyl)cyclohexan-1-one which was analysed by ^{1}H NMR and chiral HPLC (Chiralcel AD-H; mobile phase, hexane : 2-propanol (85 : 15 v/v); flow rate, 0.8 ml/min; 22.6 min (2*R*,1'*S*), 29.7 min (2*S*,1'*R*)) to determine its diastereo- and enantioselectivity.

General procedure for screening of reaction solvents



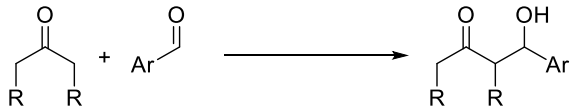
Cyclohexanone (0.80 ml, 7.7 mmol) was added to a solution of diamine salt **113** (9 mg, 0.02 mmol) in the specified solvent (0.6 ml). A solution of 4-nitrobenzaldehyde (60 mg, 0.40 mmol) in the same solvent (0.6 ml) was then added and the mixture stirred at 20 °C. Aliquots (0.1 ml) were taken after 1 h, 2 h, 3 h, 4 h, 8 h and 15 h. The catalyst was removed by passing the aliquots through a short plug of silica, using ethyl acetate (5 ml) to elute. They were then concentrated under reduced pressure and immediately assayed by ^{1}H NMR and chiral HPLC (Chiralcel AD-H; mobile phase, hexane : 2-propanol (85 : 15 v/v); flow rate, 0.8 ml/min; 22.6 min (2*R*,1'*S*), 29.7 min (2*S*,1'*R*)). Reactions were stopped after >97% consumption of 4-nitrobenzaldehyde.

General procedure A: Investigations into the effect of aldehyde structure



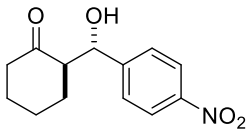
Aldehyde (0.40 mmol) in cyclohexanone (118 mg, 1.20 mmol) was added to a reaction tube containing diamine salt **113** (9 mg, 0.02 mmol). The mixture was stirred for between 3-30 h at 20 °C, then purified by chromatography on silica gel to give the aldol products which were analysed by chiral HPLC to determine enantiomeric excesses. Diastereoselectivities were determined my ^{1}H NMR on unpurified samples.

Racemic aldol adducts were prepared using the following procedure



Aldehyde (1.32 mmol) was dissolved in ketone (11.3 mmol) and sodium hydroxide (1 M aqueous solution, 1 ml) was added. The reaction was stirred at rt for 0.5-48 h. Ethyl acetate (5 ml) and water (1 ml) were added and the layers separated. The aqueous layer was extracted with dichloromethane (15 ml) and the combined organics were dried over magnesium sulfate then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether : ethyl acetate) to yield the products.

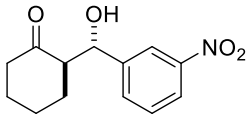
(2*R,*1'*S*)-2-(1'Hydroxy-1'-(4-nitrophenyl)methyl)cyclohexan-1-one **96**[132]



96

Following general procedure A product **96** (92.0 mg, 92%) was obtained as a colourless crystalline solid. mp 129-131 °C (lit.,[131] 129-130 °C); $[\alpha]_D^{24}$ -8.0 (*c* 0.7, $CHCl_3$, 99% ee) [lit.,[131] $[\alpha]_D^{20}$ –9.6 (*c* 1.0 $CHCl_3$, 98% ee)]; Rf 0.3 (2 : 5 ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3528, 3011, 2947, 2867, 1697, 1606, 1525, 1349, 856; δ_H (400 MHz, $CDCl_3$) 8.22 (2H, d, *J* 8.5, ArH), 7.52 (2H, d, *J* 8.5, ArH), 4.91 (1H, dd, *J* 8.5, 3.0, C*H*OH), 4.07 (1H, d, *J* 3.0, OH) 2.63-2.57 (1H, m, CHCO), 2.54-2.48 (1H, m, CH_2), 2.38 (1H, ddd, *J* 13.5, 13.5, 6.0, CH_2), 2.16-2.09 (1H, m, CH_2), 1.87-1.81 (1H, m, CH_2), 1.71-1.51 (3H, m, CH_2), 1.45-1.35 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 214.8 (C), 148.4 (C), 147.5 (C), 127.9 (CH), 123.6 (CH), 74.0 (CH), 57.2 (CH), 42.7 (CH_2), 30.8 (CH_2), 27.6 (CH_2), 24.7 (CH_2); *m/z* (ESI) 272 ($M+Na^+$, 100%); *m/z* (ESI) Found 272.0894. $C_{13}H_{15}NO_4Na^+$ requires 272.0893; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (85 : 15 v/v); flow rate, 0.8 ml/min; 22.6 min 99.4% (2*R*,1'*S*), 29.7 min 0.6% (2*S*, 1'*S*). The ^1H and ^{13}C NMR data is in agreement with those previously reported.[132]

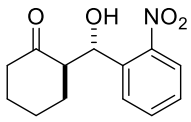
(2*R*,1'*S*)-2-(1'Hydroxy-1'-(3-nitrophenyl)methyl)cyclohexan-1-one **134**[132]



134

Following general procedure A product **134** (88.0 mg, 88%) was obtained as a colourless crystalline solid. mp 85-87 °C (lit.,[131] 69-71 °C); $[\alpha]_D^{26}$ -17.0 (*c* 0.7 $CHCl_3$, 96% ee) [lit.,[132] $[\alpha]_D^{20}$ +26.9 (*c* 0.5 $CHCl_3$, -98% ee); R_f 0.3 (1 : 2 ethyl acetate: petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3534, 3008, 2946, 2868, 1697, 1533, 1449, 1352, 1130; δ_H (400 MHz, $CDCl_3$) 8.22 (1H, dd, *J* 1.5, 1.5, ArH), 8.16 (1H, ddd, *J* 8.0, 1.5, 1.5, ArH), 7.68 (1H, ddd, *J* 8.0, 1.5, 1.5, ArH), 7.53 (1H, dd, *J* 8.0, 8.0, ArH), 4.90 (1H, dd, *J* 8.5, 3.0, C*H*OH), 4.12 (1H, d, *J* 3.0, OH), 2.66-2.59 (1H, m, CHCO), 2.54-2.48 (1H, m, CH_2), 3.42-2.34 (1H, m, CH_2) 2.09-2.15 (1H, m, CH_2), 1.86-1.81 (1H, m, CH_2), 1.52-1.74 (3H, m, CH_2), 1.34-1.45 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 214.9 (C), 148.3 (C), 143.3 (C), 133.2 (CH), 129.3 (CH), 122.9 (CH), 122.0 (CH), 74.1 (CH), 57.2 (CH), 42.7 (CH_2), 30.8 (CH_2), 27.7 (CH_2), 24.7 (CH_2); *m/z* (ESI) 272 ($M+Na^+$, 100%); *m/z* (ESI) Found 272.0895. $C_{13}H_{15}NO_4Na^+$ requires 272.0893; HPLC: Chiralpak AD-H; mobile phase; hexane : 2-propanol (90 : 10 v/v); flow rate, 1 ml/min; retention times, 19.0 min 1.8% (2*S*,1'*R*), 23.9 min 98.2% (2*R*,1'*S*). The ^1H and ^{13}C NMR data is in agreement with those previously reported.[132]

(2*R*,1'*S*)-2-(1'Hydroxy-1'-(2-nitrophenyl)methyl)cyclohexan-1-one **135**[132]

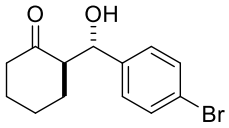


135

Following general procedure A product **135** (89.0 mg, 89%) was obtained as an orange oil. $[\alpha]_D^{24}$ -8.6 (*c* 0.7, $CHCl_3$, 96% ee) [lit.,[133] $[\alpha]_D^{22}$ +9.0 (*c* 1.6, $CHCl_3$, -99% ee)]; R_f 0.2 (1 : 4 ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3526, 3011, 2946, 2868, 1697, 1527, 1349, 1130;; δ_H (400 MHz, $CDCl_3$) 7.85 (1H, dd, *J* 8.0, 1.0, ArH), 7.78 (1H, dd, *J* 8.0, 1.5, ArH), 7.65 (1H, ddd, *J* 8.0, 7.5, 1.0, ArH), 7.44 (1H, ddd, *J*, 8.0, 7.5, 1.5, ArH), 5.46 (1H, d, *J* 7.0, C*H*OH), 4.04 (1H, br s, OH), 2.78-2.72 (1H, m, CHCO), 2.47-2.41 (1H, m, CH_2), 2.37-2.29 (1H, m, CH_2), 2.13-2.06 (1H, m, CH_2) 1.87-1.81 (1H, m, CH_2), 1.55-1.89 (4H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 214.5 (C), 148.7 (C), 136.6 (C), 133.1 (CH), 129.0 (CH), 128.4 (CH), 124.1 (CH) 69.7 (CH), 57.3 (CH), 42.8 (CH_2), 31.1 (CH_2), 27.8

(CH_2), 25.0 (CH_2); *m/z* (ESI) 272 (M+Na^+, 100%); *m/z* (ESI) Found 272.0900. $C_{13}H_{15}NO_4Na^+$ requires 272.0893; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (80 : 20 v/v); flow rate 1 ml/min; retention times, 12.2 min 2.0% (2*S*,1'*R*), 13.2 min 98.0% (2*R*,1'*S*). The ^{1}H NMR and ^{13}C NMR data are in agreement with those previously reported.[132]

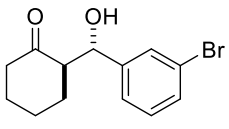
(2*R*,1'*S*)-2-(1'Hydroxy-1'-(4-bromophenyl)methyl)cyclohexan-1-one **136**[132]



136

Following general procedure A product **136** (102 mg, 90%) was obtained as an colourless solid. mp 128-130 °C; $[\alpha]_D^{24}$ -16.0 (*c* 0.7, $CHCl_3$, 98% ee) [lit.,[134] $[\alpha]_D^{22}$ -22.7 (*c* 0.79, $CHCl_3$, 98% ee)]; R_f 0.4 (1 : 2 ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3447, 3011, 2946, 2868, 1696, 1486, 1393, 1193, 1130, 1070, 828; δ_H (400 MHz, $CDCl_3$) 7.50-7.47 (2H, m, ArH), 7.23-7.20 (2H, m, ArH), 4.76 (1H, dd, *J* 8.5, 3.0, C*H*OH), 4.01 (1H, d, *J* 3.0, OH), 2.59-2.45 (2H, m, CHCO&CH_2), 2.40-2.32 (1H, m, CH_2), 2.12-2.06 (1H, m, CH_2), 1.84-1.78 (1H, m, CH_2), 1.73-1.50 (3H, m, CH_2), 1.36-1.25 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 215.2 (C), 140.1 (C), 131.5 (CH), 128.8 (CH), 121.7 (C), 74.2 (CH), 57.3 (CH), 42.7 (CH_2), 30.7 (CH_2), 27.7 (CH_2), 24.7 (CH_2); *m/z* (ESI) 305 (M (^{79}Br)+Na^+, 100%), 307 (M (^{81}Br)+Na^+, 99%); *m/z* (ESI) found 305.0148. $C_{13}H_{15}O_2{}^{79}BrNa^+$ requires 305.0148; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (85 : 15 v/v); flow rate, 1 ml/min; retention times, 10.6 min 98.9% (2*R*,1'*S*), 12.0 min 1.1% (2*S*,1'*R*). The ^{1}H NMR and ^{13}C NMR data are in agreement with those previously reported.[132]

(2*R*,1'*S*)-2-(1'Hydroxy-1'-(3-bromophenyl)methyl)cyclohexan-1-one **137**[135]

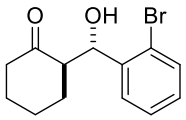


137

Following general procedure A product **137** (104 mg, 92%) was obtained as a colourless solid. mp 115-117 °C; $[\alpha]_D^{25}$ -24.8 (*c* 0.7, $CHCl_3$, 98% ee); R_f 0.4 (1 : 2 ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3447, 3001, 2946, 1697, 1533, 1352, 1130, 1043, 839; δ_H (400 MHz, $CDCl_3$) 7.51 (1H, dd, *J* 1.5, 1.5, ArH), 7.44 (1H, ddd, *J* 7.0, 1.5, 1.5, ArH), 7.28-7.18 (2H, m, ArH), 4.76 (1H, dd, *J* 9.0,

3.0, C*H*OH), 4.04 (1H, d, *J* 3.0, OH), 2.61-2.54 (1H, m, CHCO), 2.50-2.45 (1H, m, CH_2) 2.41-2.33 (1H, m, CH_2), 2.13-2.04 (1H, m, CH_2), 1.91-1.52 (4H, m, CH_2), 1.38-1.27 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 215.2 (C), 143.4 (C), 131.0 (CH), 130.1 (CH), 129.9 (CH), 122.6 (C), 74.2 (CH), 57.3 (CH), 42.7 (CH_2), 30.8 (CH_2), 27.8 (CH_2), 24.7 (CH_2); *m/z* (ESI) 305 (M (^{79}Br)+Na^+, 100%), 307 (M (^{81}Br)+Na^+, 97%); *m/z* (ESI) found 305.0147. $C_{13}H_{15}O_2{}^{79}BrNa^+$ requires 305.0148; HPLC: Chiralpak OD-H; mobile phase, hexane : 2-propanol (95 : 5 v/v); flow rate, 1 ml/min; retention times, 10.1 min 1.0% (2*S*,1'*R*), 12.7 min 99.0% (2*R*,1'*S*). The ^{1}H NMR and ^{13}C NMR data are in agreement with those previously reported.[135]

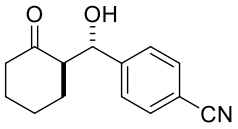
(2*R*,1'*S*)-2-(1'Hydroxy-1'-(2-bromophenyl)methyl)cyclohexan-1-one **138**[136]



138

Following general procedure A product **138** (99.0 mg, 87%) was obtained as a colourless solid. mp 61-63 °C; $[\alpha]_D{}^{23}$ -27.5 (*c* 0.7, $CHCl_3$, 96% ee) [lit.,[136] $[\alpha]_D{}^{rt}$ +20.1 (*c* 0.5, $CHCl_3$, -97% ee); R_f 0.3 (1 : 4 ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3463, 3011, 2945, 2868, 1696, 1130, 845; δ_H (400 MHz, $CDCl_3$) 7.56-7.51 (2H, m, ArH), 7.36 (1H, dd, *J* 7.0, 7.0, ArH), 7.15 (1H, ddd, *J*, 7.0, 7.0, 1.0, ArH), 5.32 (1H, dd, *J* 8.0, 4.0, C*H*OH), 4.08 (1H, d, *J* 4.0, OH), 2.70 (1H, dddd, *J* 12.5, 8.0, 6.0, 1.5, CHCO), 2.45-2.51 (1H, m, CH_2), 2.35 (1H, dddd, *J* 13.5, 13.5, 6.0, 1.0 CH_2), 2.13-2.07 (1H, m, CH_2), 1.86-1.54 (5H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 215.2 (C), 140.8 (C), 132.5 (CH), 129.1 (CH), 128.5 (CH), 127.9 (CH), 123.4 (C), 72.8 (CH), 57.7 (CH), 42.7 (CH_2), 30.6 (CH_2), 27.8 (CH_2), 25.0 (CH_2); *m/z* (ESI) 305 (M (^{79}Br)+Na^+, 100%), 307 (M (^{81}Br)+Na^+, 99%); *m/z* (ESI) found 305.0148. $C_{13}H_{15}O_2{}^{79}BrNa^+$ requires 305.0148; HPLC: Chiralpak OD-H; mobile phase, hexane : 2-propanol (95 : 5 v/v); flow rate, 1 ml/min; retention times, 9.8 min 1.9% (2*S*,1'*R*), 12.1 min 98.1% (2*R*,1'*S*). The ^{1}H NMR and ^{13}C NMR data are in agreement with that previously reported.[136]

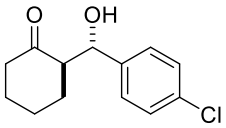
(2*R*,1'*S*)-2-(1'Hydroxy-1'-(4-cyanophenyl)methyl)cyclohexan-1-one **139**[132]



139

Following general procedure A product **139** (83.0 mg, 91%) was obtained as a colourless solid. mp 74-76 °C, (lit.,[137] 41-42 °C) $[\alpha]_D^{22}$ -14.9 (*c* 0.7, $CHCl_3$, 97% ee) [lit.,[134] $[\alpha]_D^{23}$ –19.6 (*c* 0.8 $CHCl_3$, 86% ee)]; R_f 0.3 (1 : 1 ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3534, 3010, 2947, 2868, 2232, 1698, 1449, 1395, 1130, 840; δ_H (400 MHz, $CDCl_3$) 7.66 (2H, d, *J* 8.0, ArH), 7.47 (2H, d, *J* 8.0, ArH), 4.86 (1H, dd, *J* 8.5, 2.5, C*H*OH), 4.07 (1H, d, *J* 2.5, OH), 2.59 (1H, dddd, *J* 13.0, 8.5, 5.5, 1.0, CHCO), 2.53-2.49 (1H, m, CH_2), 2.38 (1H, ddd, *J* 13.0, 13.0, 6.0, CH_2), 2.16-2.10 (1H, m, CH_2), 1.88-1.80 (1H, m, CH_2), 1.74-1.52 (3H, m, CH_2), 1.43-1.32 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 214.8 (C), 146.4 (C), 132.2 (CH) 127.8 (CH), 118.7 (C), 111.7 (C), 74.2 (CH), 57.1 (CH), 42.6 (CH_2), 30.7 (CH_2), 27.6 (CH), 24.7 (CH_2); *m/z* (ESI) 252 ($M+Na^+$, 100%); *m/z* (ESI) Found 252.0996. $C_{14}H_{15}NO_2Na^+$ requires 252.0995; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (90 : 10 v/v); flow rate, 0.8 ml/min; retention times, 27.9 min 98.6% (2*R*,1'*S*), 35.3 min 1.4% (2*S*,1'*R*). The ^1H NMR and ^{13}C NMR data are in agreement with those previously reported.[132]

(*2R, 1'S*)-2-(1'Hydroxy-1'-(4-chlorophenyl)methyl)cyclohexan-1-one **140**[135]

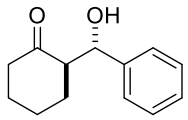


140

Following general procedure A product **140** (83.0 mg, 91%) was obtained as a colourless solid. 103-105 °C, (lit.,[138] 97-98 °C); $[\alpha]_D^{25}$ -24.8 (*c* 0.8, $CHCl_3$, 97% ee) [lit.,[134] $[\alpha]_D^{20}$ –26.0 (*c* 1.1 $CHCl_3$, 93% ee)]; R_f 0.4 (1 : 2 ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3537, 3011, 2946, 2868, 1696, 1489, 1130, 1089, 831; δ_H (400 MHz, $CDCl_3$) 7.36-7.32 (2H, m, ArH), 7.30-7.25 (2H, m, ArH), 4.79 (1H, dd, *J* 9.0, 3.0, C*H*OH), 4.01 (1H, d, *J* 3.0, OH), 2.59-38 (2H, m, CHCO & CH_2), 2.38 (1H, dddd, *J* 13.5, 13.5, 6.0, 1.0, CH_2), 2.16-2.08 (1H, m, CH_2), 1.89-1.79 (1H, m, CH_2), 1.76-1.51 (3H, m, CH_2), 1.37-1.26 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 215.3 (C), 139.5 (C), 133.6 (C), 128.5 (CH), 128.4 (CH), 74.1 (CH), 57.4 (CH), 42.7 (CH_2), 30.7 (CH_2), 27.7 (CH_2), 24.7 (CH_2); *m/z* (ESI) 261 ($M(^{35}Cl)$ $+Na^+$, 100%), 263 ($M(^{37}Cl)+Na^+$, 31%); *m/z* (ESI) Found 261.0654.

$C_{13}H_{15}{}^{35}ClO_2Na^+$ requires 261.0653; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (90 : 10 v/v); flow rate, 0.8 ml/min; retention times, 16.0 min 98.7% (2*R*,1'*S*), 18.2 min 1.3% (2*S*,1'*R*). The ^{1}H NMR and ^{13}C NMR data are in agreement with those previously reported.[135]

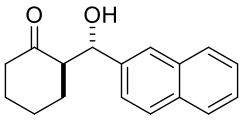
(2*R*,1'*S*)-2-(1'Hydroxy-1'-phenylmethyl)cyclohexan-1-one **141**[132]



141

Following general procedure A product **141** (50.0 mg, 61%) was obtained as a colourless solid. mp 38-40 °C, (lit.,[139] 41-42 °C); $[\alpha]_D^{22}$ -20.9 (*c* 0.6, $CHCl_3$, 95% ee) [lit.,[139] $[\alpha]_D^{24}$ -24.2 (*c* 1.03, $CHCl_3$, 93% ee)]; R_f 0.3 (1 : 4 ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3538, 3066, 3009, 2945, 2867, 1696, 1450, 1130; ; δ_H (400 MHz, $CDCl_3$) 7.39-7.32 (5H, m, ArH), 4.82 (1H, dd, *J* 9.0, 3.0, C*H*OH), 4.00 (1H, d, *J* 3.0, OH), 2.65 (1H, dddd, *J* 13.5, 9.0, 5.0, 1.0, C*H*CO), 2.51 (1H, dddd, *J* 13.5, 5.0, 3.0, 2.0, CH_2), 2.31 (1H, dddd, *J* 13.0, 13.0, 6.5, 2.0, CH_2), 2.15-2.07 (1H, m, CH_2), 1.85-1.51 (4H, m, CH_2), 1.38-1.27 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 215.6 (C), 141.0 (C), 128.4 (CH), 127.9 (CH), 127.0 (CH), 74.8 (CH), 57.5 (CH), 42.7 (CH_2), 30.9 (CH_2), 27.8 (CH_2), 24.8 (CH_2); *m/z* (ESI) 227 (M+Na$^+$, 100%)l; *m/z* (ESI) Found 227.1043. $C_{13}H_{16}O_2Na^+$ requires 227.1043; HPLC: Chiralpak OD-H; mobile phase, hexane : 2-propanol (97 : 3 v/v); flow rate, 0.8 ml/min; retention times, 24.3 min 2.7% (2*S*,1'*R*), 31.4 min 97.3% (2*R*,1'*S*). The ^{1}H NMR and ^{13}C NMR data are in agreement with those previously reported.[132]

(2*R*,1'*S*)-2-(1'Hydroxy-1'-(naphth-2-yl)methyl)cyclohexan-1-one **142**[140]

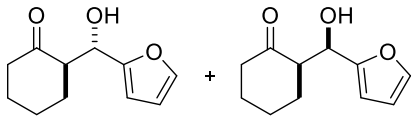


142

Following general procedure A product **142** (64.0 mg, 63%) was obtained as a colourless solid. mp 146-148 °C; $[\alpha]_D^{25}$ -19.5 (*c* 0.7, $CHCl_3$, 98% ee) (lit.,[140] $[\alpha]_D^{23}$ +17.3 (*c* 0.8, $CHCl_3$, -99% ee); R_f 0.3 (1 : 2 ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3536, 3010, 2945, 2867, 1697, 1129, 821; δ_H (400 MHz, $CDCl_3$) 7.87-7.83 (3H, m, ArH), 7.77 (1H, s, ArH), 7.51-7.46 (3H, m, ArH), 4.98 (1H, dd, *J* 9.0, 2.5, C*H*OH), 4.08 (1H, d, *J* 2.5, OH), 2.73 (1H, dddd, *J* 13.0,

9.0, 6.0, 1.0, CHCO), 2.49-2.54 (1H, m, CH_2), 2.39 (1H, dddd, *J* 13.0, 13.0, 6.0, 1.0, CH_2), 2.12-2.06 (1H, m, CH_2), 1.78-1.31 (5H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 215.5 (C), 138.4 (C), 133.2 (C), 133.1 (C), 128.3 (CH), 128.0 (CH), 127.7 (CH), 126.3 (CH), 126.2 (CH), 126.0 (CH), 124.7 (CH), 74.9 (CH), 57.4 (CH), 42.7 (CH_2), 31.0 (CH_2), 27.8 (CH_2), 24.7 (CH_2); *m/z* (ESI) 277 ($M+Na^+$, 100%); *m/z* (ESI) Found 277.1196. $C_{17}H_{18}O_2Na^+$ requires 277.1199; HPLC: Chiralpak OD-H; mobile phase, hexane : 2-propanol (80 : 20 v/v); flow rate, 0.25 ml/min; retention times, 34.5 min 0.7% (2*S*,1'*R*), 43.3 min 99.3% (2*R*,1'*S*). The ^{1}H NMR and ^{13}C NMR data are in agreement with those previously reported.[140]

(2*R*,1'*S*)-2-(1'Hydroxy-1'-(fur-2-yl)methyl)cyclohexan-1-one[141] and (2*R*,1'*R*)-2-(1'Hydroxy-1'-(fur-2-yl)methyl)cyclohexan-1-one[142] **143**



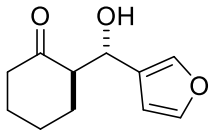
anti-**143** *syn*-**143**

Following general procedure A, product **143** (69.0 mg, 89%) was obtained in a 1 : 1 ratio of diastereoisomers. The diastereoisomers were separated by column chromatography on silica gel (1 : 4, ethyl acetate : petroleum ether). Anti diastereoisomer (30.0 mg, 38%), colourless oil. $[\alpha]_D^{25}$ 0.1 (*c* 0.6, $CHCl_3$, 89% ee); R_f 0.3 (1 : 4, ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3505, 2945, 1698, 1450, 1262; δ_H (400 MHz, $CDCl_3$) 7.40 (1H, dd, *J* 2.0, 1.0, ArH), 6.35 (1H, dd, *J* 3.0, 2.0, ArH), 6.30 (1H, dd, *J* 3.0, 1.0, ArH), 4.85 (1H, dd, *J* 8.5, 4.0, C*H*OH), 3.90 (1H, d, *J* 4.0, OH), 2.94 (1H, dddd, *J* 13.0, 8.5, 5.5, 1.0, CHCO), 2.49 (1H, dddd, *J* 13.0, 4.5, 3.0, 2.0, CH_2), 2.39 (1H, dddd, *J* 13.0, 13.0, 6.0, 1.0, CH_2), 2.17-2.09 (1H, m, CH_2), 1.89-1.81 (1H, m, CH_2), 1.74-1.64 (3H, m, CH_2), 1.41-1.31 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 215.0 (C), 153.6 (C), 142.3 (CH), 110.1 (CH), 108.0 (CH), 68.7 (CH), 54.9 (CH), 42.7 (CH_2), 30.6 (CH_2), 27.8 (CH_2), 24.7 (CH_2); *m/z* (ESI) 217 ($M+Na^+$, 100%); *m/z* (ESI) Found 217.0839. $C_{11}H_{14}O_3Na^+$ requires 217.0835; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (90 : 10 v/v); flow rate, 0.5 ml/min; retention times, 22.0 min 5.3% (2*S*,1'*R*), 23.7 min 94.7% (2*R*,1'*S*). The ^{1}H NMR and ^{13}C NMR data are in agreement with those previously reported.[141]

Syn diastereoisomer (25.0 mg, 32%), colourless oil. $[\alpha]_D^{29}$ 91.8 (*c* 0.9, $CHCl_3$, 95% ee); R_f 0.4 (1 : 4, ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3598, 3011, 2945, 1709, 1364, 1145, 1007; δ_H (400 MHz, $CDCl_3$) 7.36 (1H, dd, *J* 2.0, 1.0, ArH), 6.35 (1H, dd, *J* 3.0, 2.0, ArH), 6.29 (1H, ddd, *J* 3.0, 1.0, 1.0, ArH),

5.29 (1H, ddd, *J* 4.5, 4.5, 1.0, C*H*OH), 3.08 (1H, d, *J* 4.5, OH), 2.81-2.86 (1H, m, CHCO), 2.49 (2H, m, CH_2), 2.15-2.08 (1H, m, CH_2), 2.00-1.90 (2H, m, CH_2), 1.79-1.63 (3H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 213.7 (C), 154.6 (C), 141.5 (CH), 110.3 (CH), 106.5 (CH), 66.7 (CH), 54.5 (CH), 42.5 (CH_2), 27.6 (CH_2), 27.3 (CH_2), 24.8 (CH_2); *m/z* (ESI) 217 ($M+Na^+$, 100%); *m/z* (ESI) Found 217.0839. $C_{11}H_{14}O_3Na^+$ requires 217.0835; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (90 : 10 v/v); flow rate, 0.5 ml/min; retention times, 17.2 min 97.6% (2*R*,1'*R*), 18.2 min 2.4% (2*S*,1'*S*). The ^1H NMR and ^{13}C NMR data are in agreement with those previously reported.[142]

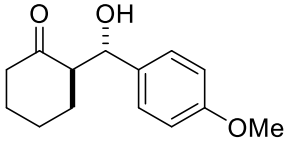
(2*R*,1'*S*)-2-(1'Hydroxy-1'-(fur-3-yl)methyl)cyclohexan-1-one **144**



144

Following general procedure A product **144** (50.0 mg, 65%) was obtained as a clear oil. $[\alpha]_D^{29}$ -11.4 (*c* 1.0, $CHCl_3$, 98% ee) ; R_f 0.3 (1 : 4, ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3528, 3009, 2944, 1697, 1504, 1450, 1239, 1023, 874; δ_H (400 MHz, $CDCl_3$) 7.42-7.41 (2H, m, ArH), 6.45-6.42 (1H, m, ArH), 4.83 (1H, dd, *J* 8.0, 3.0, C*H*OH), 3.86 (1H, d, *J* 3.0, OH), 2.63 (1H, dddd, *J* 13.0, 8.0, 5.0, 1.0, CHCO), 2.52-2.47 (1H, m, CH_2), 2.43-2.34 (1H, m, CH_2), 2.17-2.10 (1H, m, CH_2), 1.90-1.83 (2H, m, CH_2), 1.74-1.60 (2H, m, CH_2), 1.41-1.30 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 215.3 (C), 143.4 (CH), 140.1 (CH), 125.6 (C), 108.7 (CH), 67.1 (CH), 56.5 (CH), 42.7 (CH_2), 30.8 (CH_2), 27.8 (CH_2), 24.8 (CH_2); *m/z* (ESI) 217 ($M+Na^+$, 100%); *m/z* (ESI) Found 217.0839. $C_{11}H_{14}O_3Na^+$ requires 217.0835; HPLC: Chiralpak OD-H; mobile phase, hexane : 2-propanol (90 : 10 v/v); flow rate, 0.8 ml/min; retention times, 10.3 min 1.0% (2*S*,1'*R*), 13.6 min 99.0% (2*R*,1'*S*).

(2*R*,1'*S*)-2-(1'Hydroxy-1'-(4-methoxyphenyl)methyl)cyclohexan-1-one **145**[132]

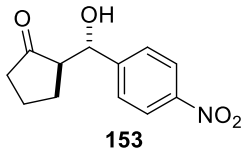


145

Following general procedure A product **145** (23.0 mg, 25%) was obtained as a colourless solid. m.p. 56-57 °C (lit.,[131] 74-76 °C); $[\alpha]_D^{26}$ -37.1 (*c* 0.7, $CHCl_3$,

92% ee) [lit.,[143] $[\alpha]_D^{25}$ +30.5 (*c* 1.7, $CHCl_3$, -91% ee)]; R_f 0.3 (1 : 2 ethyl acetate : petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3534, 3008, 2942, 1696, 1613, 1515, 1250, 1035, 834; δ_H (400 MHz, $CDCl_3$) 7.25-7.23 (2H, m, ArH), 6.89-6.86 (2H, m, ArH), 4.75 (1H, dd, *J* 9.0, 2.5, C*H*OH), 3.92 (1H, d, *J* 2.5, OH), 3.80 (3H, s, OCH_3), 2.61-2.56 (1H, m, CHCO), 2.45-2.51 (1H, m, CH_2), 2.36 (1H, dddd, *J* 13.5, 13.5, 5.5, 1.0, CH_2), 2.12-2.05 (1H, m, CH_2), 1.81-1.49 (4H, m, CH_2), 1.32-1.21 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$), 215.7 (C), 159.3 (C), 131.2 (C), 128.2 (CH), 113.8 (CH), 74.3 (CH), 57.5 (CH), 55.3 (CH_2), 42.7 (CH_2), 30.8 (CH_2), 27.8 (CH_2), 24.7 (CH_2); *m/z* (ESI) 257 ($M+Na^+$, 100%); *m/z* (ESI) Found 257.1147. $C_{14}H_{18}O_3Na^+$ requires 257.1148; HPLC: Chiralpak OD-H; mobile phase, hexane : 2-propanol (97 : 3 v/v); flow rate, 0.8 ml/min; retention times, 27.6 min 4.0% (2*S*,1'*R*), 36.6 min 96.0% (2*R*,1'*S*). The ^1H NMR and ^{13}C NMR data are in agreement with those previously reported.[132]

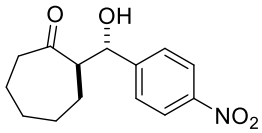
(2*R*,1'*S*)-2-(1'-Hydroxy-1'-(4-nitrophenyl)methyl)cyclopentan-1-one **153**[140]



153

Cyclopentanone (0.34 g, 4.0 mmol) was added to a reaction tube containing diamine salt **113** (9 mg, 0.02 mmol). 4-Nitrobenzaldehyde (60 mg, 0.40 mmol) was then added to the reaction mixture in 3 batches at 1 h intervals. After addition of the final batch of aldehyde the reaction was stirred at rt for 75 mins. The mixture was then concentrated under reduced pressure and purified by chromatography on silica gel (1 : 9 ethyl acetate : toluene) to give the product **153** (72 mg, 76%) as a colourless solid. m.p. 64-66 °C; $[\alpha]_D^{22}$ 104.5 (c 0.7, $CHCl_3$, 97% ee) [lit.,[140] $[\alpha]_D^{23}$ -77 (c 0.5, $CHCl_3$, -92% ee)]: R_f 0.2 (1 : 9 ethyl acetate : toluene); ν_{max} ($CHCl_3$)/cm^{-1} 3481, 2975, 2884, 1723, 1606, 1525, 1348, 1109, 858; δ_H (400 MHz, $CDCl_3$) 8.28-8.21 (2H, m, ArH), 7.60-7.54 (2H, m, ArH), 4.87 (1H, dd, *J* 9.0, 1.0, C*H*OH), 4.77 (1H, d, J 1.0, OH), 2.56-2.26 (3H, m, COCH & CH_2), 2.11-1.99 (1H, m, CH_2), 1.85-1.71 (2H, m, CH_2), 1.62-1.53 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 222.4 (C), 148.7 (C), 147.6 (C), 127.4 (CH), 123.7 (CH), 74.4 (CH), 55.1 (CH), 38.6 (CH_2), 26.8 (CH_2), 20.4 (CH_2); m/z (ES) 258 (M+Na+, 100%); m/z (ES) Found 258.0733. $C_{12}H_{13}NO_4Na^+$ requires 258.0737; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (95 : 5 v/v); flow rate, 1 ml/min; retention times, 37.7 min 98.5% (2*R*,1'*S*), 40.7 min 1.5% (2*S*,1'*R*). The ^1H NMR and ^{13}C NMR data are in agreement with those previously reported.[140]

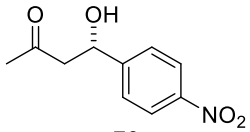
(2*R*,1'*S*)-2-(1'-Hydroxy-1'-(4-nitrophenyl)methyl)cycloheptan-1-one **154**[141]



154

4-Nitrobenzaldehye (60 mg, 0.40 mmol) in cycloheptanone (118 mg, 1.20 mmol) was added to a reaction tube containing diamine salt **113** (9 mg, 0.02 mmol) and water (14 mg, 0.80 mmol). The mixture was stirred for 13 h at rt, then purified by chromatography on silica gel (2 : 1, petroleum ether : ethyl acetate) to give the product **154** (104 mg, 99%) as a colourless crystalline solid. m.p. 29-31 °C; $[\alpha]_D^{25}$ 22.9 (*c* 0.9, $CHCl_3$, 87% ee) [lit.[151] $[\alpha]_D^{26}$ 10.7 (*c* 1.08, $CHCl_3$, 73% ee)]; R_f 0.3 (2 : 1, petroleum ether : ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3593, 3430, 3009, 2976, 2885, 1724, 1403, 1155; δ_H (400 MHz, $CDCl_3$) 8.27-8.19 (2H, m, ArH), 7.56-7.50 (2H, m, ArH), 4.93 (1H, dd, *J* 7.5, 5.0, C*H*OH), 3.72 (1H, d, *J* 5.0, OH), 2.99 (1H, ddd, J 10.0, 7.5, 3.5, COCH), 2.60-2.43 (2H, m, CH_2), 1.95-1.58 (5H, m, CH_2), 1.47-1.22 (3H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 216.8 (C), 149.3 (C), 147.5 (C), 127.8 (CH), 123.6 (CH), 74.7 (CH), 57.9 (CH), 44.1 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 28.2 (CH_2), 23.5 (CH_2); m/z (ES) 286 ($M+Na^+$, 100%); m/z (ES) Found 286.1038. $C_{14}H_{17}NO_4Na^+$ requires 286.1050; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (85 : 15 v/v); flow rate, 1 ml/min; retention times, 14.1 min 93.3% (2*R*,1'*S*), 30.6 min 6.7% (2*S*,1'*R*). ^{1}H NMR data in agreement with that previously reported.[141]

(4*S*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one **76**[140]

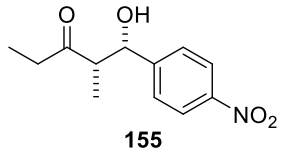


76

Acetone (0.32 g, 4.0 mmol) was added to a reaction tube containing diamine salt **113** (9 mg, 0.02 mmol) and *m*-nitrobenzoic acid (3 mg, 0.02 mmol) that had been cooled to 10 °C. 4-Nitrobenzaldehyde (60 mg, 0.40 mmol) was added to the mixture and the temperature maintained at 10 °C for 22 h. The mixture was then concentrated under reduced pressure and the residue purified by chromatography on silica gel (1 : 1 petroleum ether : ethyl acetate) to give the product **76** (72.0 mg, 86%), as a colourless solid. m.p. 65 °C (lit.,[131] 59-61 °C); $[\alpha]_D^{23}$ -61.6 (*c* 1.0, $CHCl_3$, 88%) [lit.,[140] $[\alpha]_D^{23}$ 54 (*c* 0.55, $CHCl_3$, -87% ee); Rf 0.2 (1 : 1 petroleum ether : ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3600, 3042, 1710, 1522,

1349; δ_H (400 MHz, $CDCl_3$) 8.21 (2H, d, *J* 9.0, ArH), 7.56 (2H, d, *J* 9.0, ArH), 5.27 (1H, td, *J* 7.5, 3.5, C*H*OH), 3.59 (1H, d, *J* 3.5, OH), 2.93-2.79 (2H, m, $COCH_2$), 2.23 (3H, s, CH_3); δ_c (100 MHz, $CDCl_3$) 208.5 (C), 150.0 (C), 147.4 (C), 126.4 (CH), 123.8 (CH), 68.9 (CH), 51.5 (CH_2), 30.7 (CH_3); m/z (ES) 232 ($M+Na^+$, 100%); m/z (ES) Found 232.0587. $C_{10}H_{11}NO_4Na^+$ requires 232.0577; HPLC: Chiralpak AS; mobile phase, hexane : 2-propanol (3 : 1 v/v); flow rate, 0.8 ml/min; retention times, 17.7 min 5.9% (4*R*), 24.0 min 94.1% (4*S*). The ^1H NMR and ^{13}C NMR data are in agreement with those previously reported.[140]

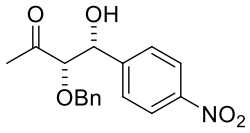
(2*S*,1'*S*)-2-(1'-Hydroxy-1'-(4-nitrophenyl)methyl)pentan-3-one **155**[52]



155

3-Pentanone (0.32 g, 4.0 mmol) was added to a reaction tube containing diamine salt **155** (9 mg, 0.02 mmol) and *m*-nitrobenzoic acid (3 mg, 0.02 mmol). 4-Nitrobenzaldehyde (60 mg, 0.40 mmol) was added and the mixture was stirred at rt for 30 h. The mixture was then concentrated under reduced pressure and the residue purified by chromatography on silica gel (3 : 17, ethyl acetate : toluene) to give the product **155** (88 mg, 93%) as a colourless solid. m.p 52-53 °C; $[\alpha]_D^{21}$ -28.5 (*c* 0.8, $CHCl_3$, 98% ee) [lit.,[37] $[\alpha]_D^{20}$ -19.4 (*c* 1.0, $CHCl_3$, >95% ee); R_f 0.2 (3 : 17, ethyl acetate : toluene); ν_{max} ($CHCl_3$)/cm^{-1} 3521, 2983, 1699, 1522, 1349; δ_H (400 MHz, $CDCl_3$) 8.23-8.14 (2H, m, ArH), 7.54-7.47 (2H, m, ArH), 5.22 (1H, dd, *J* 3.0, 2.5, C*H*OH), 3.62 (1H, d, *J* 2.5, OH), 2.84 (1H, qd, *J* 7.5, 3.0, CH_3CH), 2.60 (1H, dq, *J* 18.0, 7.5, $CH_3CH_aH_b$), 2.45 (1H, dq, *J* 18.0, 7.5, $CH_3CH_aH_b$), 1.05 (3H, dd, *J* 7.5, 7.5, CH_3CH_2), 1.03 (3H, d, *J* 7.5, CH_3); δ_c (100 MHz, $CDCl_3$) 216.1 (C), 149.2 (C), 147.2 (C), 126.8 (CH), 123.5 (CH), 72.0 (CH), 51.4 (CH), 35.1 (CH_2), 9.9 (CH_3), 7.5 (CH_3); m/z (ES) 260 ($M+Na^+$, 100%); m/z (ES) Found 260.0894. $C_{12}H_{15}NO_4Na^+$ requires 260.0893; HPLC: Chiralpak OJ-H; mobile phase, hexane : 2-propanol (91 : 9 v/v); flow rate, 0.8 ml/min; retention times, 16.5 min 1.0% (2*R*,1'*R*), 20.6 min 99.0% (2*S*,1'*S*). The ^1H NMR and ^{13}C NMR data are in agreement with those previously reported.[52]

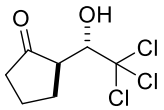
(1*R*,2*S*)-1-hydroxy-2-benzyloxy-1-(4-nitrophenyl)butan-3-one **156**[52]



156

Benzyloxyacetone (0.20 g, 1.2 mmol) was added to a reaction tube containing diamine salt **113** (9 mg, 0.02 mmol) and *m*-nitrobenzoic acid (3 mg, 0.02 mmol). 4-Nitrobenzaldehyde (60 mg, 0.40 mmol) was added and the mixture was stirred at rt for 10 h. The mixture was then purified by chromatography on silica gel (2 : 1, petroleum ether : ethyl acetate) to give the product **156** (72.0 mg, 86%), as a colourless solid (116 mg, 92%). m.p. 115-116 °C; $[\alpha]_D^{25}$ -74.6 (*c* 0.6, $CHCl_3$, 98% ee) [lit.,[52] $[\alpha]_D^{20}$ -72.4 (*c* 0.3, $CHCl_3$, 97% ee)]; R_f 0.3 (2 : 1, petroleum ether : ethyl acetate); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3607, 3561, 3009, 2871, 1716, 1603, 1524, 1348, 1064; δ_H (400 MHz, $CDCl_3$) 8.21-8.16 (2H, m, ArH), 7.53-7.47 (2H, m, ArH), 7.37-7.25 (3H, m, ArH), 7.15-7.08 (2H, m, ArH), 5.09 (1H, dd, *J* 7.5, 3.5, C*H*OH), 4.60 (1H, d, *J* 11.5, PhC$H_a$$H_b$), 4.36 (1H, d, *J* 11.5, PhC$H_a$$H_b$), 3.98 (1H, d, *J* 3.5, OH), 3.04 (1H, d, *J* 7.5, COCH), 2.22 (3H, s, CH_3); δ_c (100 MHz, $CDCl_3$) 209.9 (C), 147.6 (C), 147.5 (C), 135.9 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.1 (CH), 123.5 (2 x CH), 87.0 (CH), 73.8 (CH_2), 73.6 (CH), 27.9 (CH_3); m/z (ES) 338 ($M+Na^+$, 100%); m/z (ES) Found 338.1000. $C_{17}H_{17}NO_5Na^+$ requires 338.0999; HPLC: Chiralpak AS; mobile phase, hexane : 2-propanol (70 : 30 v/v); flow rate, 0.8 ml/min; retention times, 10.1 min 1.2% (1*S*,2*R*), 15.9 min 98.8% (1*R*,2*S*). The ^1H NMR and ^{13}C NMR data are in agreement with those previously reported.[52]

(2*R*,1'*S*)-2-(1'-Hydroxy-2', 2', 2'-trichloroethyl)cyclopentan-1-one **157**[145]

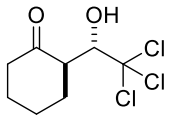


157

Following general procedure A product **157** (65.0 mg, 70%) was obtained as a colourless solid. m.p. 128-130 °C; (lit.,[144] 126-127 °C) $[\alpha]_D^{25}$ 89.4 (*c* 0.5, $CHCl_3$, 94% ee); R_f 0.2 (1 : 19 ethyl acetate : toluene); ν_{max} ($CHCl_3$)/cm^{-1} 3426, 2976, 2885, 1723, 1403, 1156; δ_H (400 MHz, $CDCl_3$) 5.55 (1H, d, *J* 5.5, OH), 4.26 (1H, dd, *J* 6.0, 5.5, C*H*OH), 2.45-2.65 (3H, m, COCH *and* CH_2), 2.24-2.37 (1H, m, CH_2), 2.11-2.21 (1H, m, CH_2), 1.79-2.08 (2H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 220.9 (C), 102.3 (C), 83.2 (CH), 50.6 (CH), 38.2 (CH_2), 30.4 (CH_2), 20.7 (CH_2);

m/z (ES) 255 (M (2 x ^{35}Cl + 1 x ^{37}Cl)+Na^+, 97%), 253 (M (3 x ^{35}Cl)+Na^+, 100%); *m/z* (ES) Found 252.9561. $C_7H_9O_2{}^{35}Cl_3Na^+$ requires 252.9560; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (98 : 2 v/v); flow rate, 1 ml/min; retention times, 23.5 min 2.9% (2*S*,1'*R*), 30.6 min 97.1% (2*R*,1'*S*). ^1H NMR data is in agreement with those previously reported.[145]

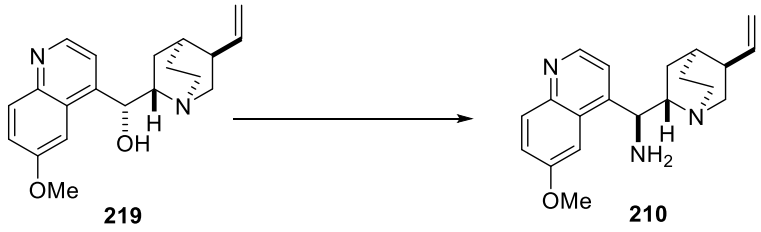
(2*R*,1'*S*)-2-(1'-Hydroxy-2', 2', 2'-trichloroethyl)cyclohexan-1-one **158**[145]



158

Following general procedure A product **158** (89.0 mg, 91%) was obtained as a colourless solid. m.p. 73-75 °C; $[\alpha]_D{}^{23}$ 53.8 (*c* 0.9, $CHCl_3$, 99% ee) [lit.,[145] $[\alpha]_D{}^{20}$ -26.2 (*c* 0.7, $CHCl_3$ -97% ee)]; ν_{max} ($CHCl_3$)/cm^{-1} 3358, 2945, 2867, 1698, 1449, 1128; R_f 0.2 (1:4 diethyl ether:petroleum ether); δ_H (400 MHz, $CDCl_3$) 6.52 (1H, d, *J* 9.5, OH), 4.01 (1H, dd, *J* 9.5, 5.5, C*H*OH), 3.11 (1H, dd, *J* 13.0, 5.5, CHCO), 2.44-2.48 (2H, m, CH_2), 1.69-2.37 (6H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 215.7 (C), 103.5 (C), 87.4 (CH), 48.8 (CH), 43.9 (CH_2), 35.6 (CH_2), 28.3 (CH_2), 25.0 (CH_2); *m/z* (ES) 269 (M (2 x ^{35}Cl + 1 x ^{37}Cl)+Na^+, 96%), 267 (M (3 x ^{35}Cl)+Na^+, 100%); *m/z* (ES) Found 266.9717. $C_8H_{11}O_2{}^{35}Cl_3Na^+$ requires 266.9717; HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (98 : 2 v/v); flow rate, 1 ml/min; retention times, 14.2 min 99.8% (2*R*,1'*S*), 18.5 min 0.2% (2*S*,1'*R*). The HPLC retention times and ^1H NMR data are in agreement with those previously reported.[145]

9-*epi*-9-Amino-9-deoxyquinine **210**[97]



219 **210**

Quinine (6.0 g, 18.5 mmol) and triphenylphosphine (5.82 g, 22.2 mmol) were dissolved in dry tetrahydrofuran (100 ml). The solution was then cooled in an ice bath and diisopropyl diazodicarboxylate (4.49 g, 22.2 mmol) was added in one portion. A solution of diphenyl phosphoryl azide (6.11 g, 22.2 mmol) in dry tetrahydrofuran (50 ml) was then added dropwise to the cooled reaction solution. After complete addition the reaction was allowed to warm to rt and stirred for 16 h. The reaction was then heated to 50 °C for 2 h. Triphenylphosphine (6.31 g,

24.1 mmol) was added and the reaction held at 50 °C for a further 2 h. The mixture was then cooled to rt and water (2.0 ml) added before stirring for 16 h at rt. The reaction was then diluted with dichloromethane (100 ml) and 10% aqueous hydrogen chloride (100 ml). The aqueous layer was washed with dichloromethane (2 x 50 ml) then adjusted to pH 9 with 18 M aqueous ammonia (ca. 19ml). The aqueous was then extracted with dichloromethane (3 x 50 ml) and the combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to yield a crude product which was purified by column chromatography on silica gel (50 : 39 : 10 : 1, petroleum ether : ethyl acetate : ethanol : 18M aqueous ammonia to 39 : 10 : 1, ethyl acetate : ethanol : 18M aqueous ammonia) to give the product **210** (3.71 g, 62%) as a pale yellow oil. $[\alpha]_D^{23}$ +78.0 (*c* 0.7, $CHCl_3$), [lit,.[146] $[\alpha]_D^{25}$ +80 (*c* 1.1, $CHCl_3$)]; R_f 0.1 (39 : 10 : 1, ethyl acetate : ethanol : 18M aqueous ammonia); $\nu_{max}(CHCl_3)/cm^{-1}$ 3365, 2939, 1621, 1589, 1508, 1474, 1358, 1231, 1029; δ_H (400 MHz, $CDCl_3$) 8.76 (1H, d, *J* 4.5, ArH), 8.05 (1H, d, *J* 9.5, ArH), 7.67 (1H, br s, ArH), 7.47 (1H, br d, *J* 4.0, ArH), 7.40 (1H, dd, *J* 9.0, 3.0, ArH), 5.82 (1H, ddd, *J* 17.0, 10.5, 7.5, CH), 5.03-4.97 (2H, m, CH_2), 4.61 (1H, br d, *J* 9.5, C*H*NH_2), 3.98 (3H, s, CH_3), 3.33-3.07 (3H, m, CH and CH_2), 2.87-2.79 (2H, m, CH_2), 2.34-2.28 (1H, m, CH), 1.98 (2H, br s, NH_2), 1.66-1.64 (1H, m, CH), 1.60-1.55 (2H, m, *C*H_2), 1.48-1.42 (1H, m, CH_2), 0.82-0.76 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 157.5 (C), 147.7 (CH), 147.0 (C), 144.7 (C), 141.7 (CH), 131.6 (CH), 128.7 (C), 121.1 (CH), 119.9 (CH), 114.2 (CH_2), 102.0 (CH), 61.7 (CH), 56.2 (CH_2), 55.4 (CH_3), 52.7 (CH), 40.8 (CH_2), 39.7 (CH), 28.1 (CH_2), 27.5 (CH), 25.9 (CH_2); *m/z* (ESI) 324 ($M+H^+$, 100%); *m/z* (ESI) Found 324.2058. $C_{20}H_{26}N_3O^+$ requires 324.2070. The ^1H and ^{13}C NMR data are in agreement with those previously reported.[97]

General procedure for the screening of catalysts

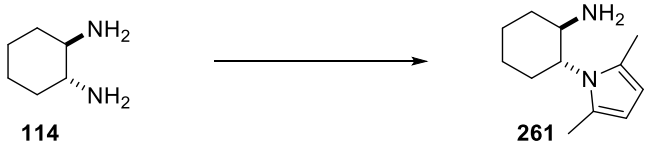


240 **241** **242**

To a solution of the catalyst (0.03 mmol) in toluene (0.3 ml) was added phenylacetic acid (4 mg, 0.03 mmol) and 3-penten-2-one (28 mg, 0.33 mmol). Dimethyl pyrazole (29 mg, 0.30 mmol) was then added and the mixture left to stir at rt for 22 h. The mixture was then concentrated under reduced pressure and the conversion was assessed by ^1H NMR. The product was purified by column chromatography on silica gel (2 : 1 ethyl acetate : peteroleum ether) to give 4-(2,4-dimethylpyrazole)pentan-2-one **242** as a colourless oil; R_f 0.3 (2 : 1 ethyl

acetate : peteroleum ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 2977, 1717, 1553, 1454, 1423, 1367; δ_H (400 MHz, $CDCl_3$) 5.71 (1H, s, ArH), 4.72-4.64 (1H, m, CHN), 3.33 (1H, dd, *J* 17.5, 8.0, C*H*$_a$H$_b$), 2.80 (1H, dd, *J* 17.5, 5.5, CH$_a$*H*$_b$), 2.26 (3H, s, CH_3), 2.20 (3H, s, CH_3), 2.07 (3H, s, C(O)CH_3), 1.40 (3H, d, *J* 6.5, CH_3); δ_c (100 MHz, $CDCl_3$) 206.7 (C), 147.4 (C), 138.5 (C), 104.4 (CH), 49.3 (CH_2), 48.7 (CH), 30.7 (CH_3), 21.4 (CH_3), 13.6 (CH_3), 10.9 (CH_3); *m/z* (ESI) 181 ($M+H^+$, 100%); *m/z* (ESI) Found 181.1347. $C_{10}H_{17}N_2O^+$ requires 181.1335. HPLC: Chiralpak AD-H; mobile phase, hexane : 2-propanol (98:2 v/v); flow rate, 0.8 ml/min; retention times, 6.2 min, 7.2 min

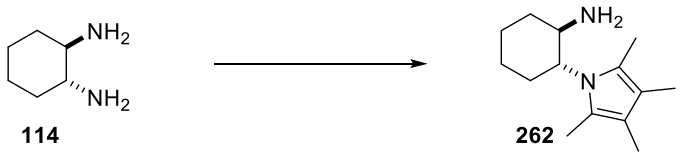
2-(2,5-Dimethyl-pyrrol-1-yl)-cyclohexylamine **261**[98]



114 **261**

To a solution of (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane (114 mg, 1.00 mmol) and acetic acid (57 µl, 1.00 mmol) in degassed methanol (2 ml) was added a solution of 2,5-hexanedione (114 mg, 1.00 mmol) in degassed methanol (3 ml). The mixture was left to stir in the dark for 3 h, then concentrated under reduced pressure. The residue was dissolved in dichloromethane (20 ml) and washed with 4M aqueous sodium hydroxide (10 ml). The aqueous was extracted with dichloromethane (2 x 5 ml), the combined organics were dried over sodium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (1 : 19 methanol : dichloromethane) to give the product **261** (146 mg, 76%) as a light yellow oil. $[\alpha]_D^{23}$ -29.6 (c 0.86, $CHCl_3$), [lit.,[147] $[\alpha]_D^{25}$ -24.6 (*c* 1.0, $CHCl_3$)]; R_f 0.2 (1 : 19 methanol : dichloromethane); $\nu_{max}(CHCl_3)/cm^{-1}$ 3370, 2940, 2860, 1449, 1394, 1291; δ_H (400 MHz, $CDCl_3$) 5.79 (1H, s, ArH), 5.76 (1H, s, ArH), 3.61 (1H, ddd, *J* 10.5, 10.5, 5.0, CHN), 3.27 (1H, ddd, *J* 10.5, 10.5, 4.0, CHN), 2.37 (3H, s, CH_3), 2.24 (3H, s, CH_3), 2.09-2.02 (1H, m, CH_2), 1.95-1.77 (4H, m, CH_2), 1.42-1.34 (2H, m, CH_2), 1.27-1.16 (3H, m, CH_2 and NH_2); δ_c (100 MHz, $CDCl_3$) 129.8 (C), 126.8 (C), 107.9 (CH), 105.3 (CH), 63.7 (CH), 53.0 (CH), 35.5 (CH_2), 31.4 (CH_2), 26.3 (CH_2), 25.1 (CH_2), 15.3 (CH_3), 13.8 (CH_3); *m/z* (ESI) 193 ($M+H^+$, 100%); *m/z* (ESI) Found 193.1710. $C_{12}H_{21}N_2^+$ requires 193.1699. The ^1H and ^{13}C data are in agreement with those previously reported.[98]

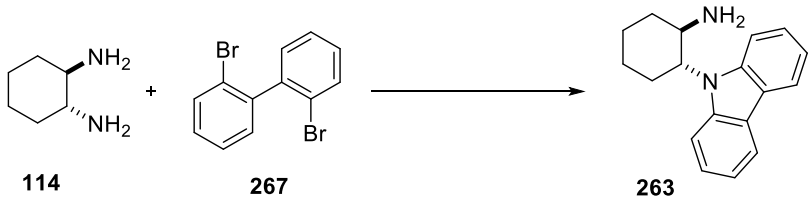
(1*R*,2*R*)-2-(2,3,4,5-Tetramethyl-pyrrol-1-yl)-cyclohexylamine **262**



114 **262**

To a solution of (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane (114 mg, 1.00 mmol) and acetic acid (57 µl, 1.00 mmol) in degassed methanol (2.5 ml) was added a solution of 3,4-dimethyl-2,5-hexanedione **262** (142 mg, 1.00 mmol) in degassed methanol (2.5 ml). The mixture was left to stir in the dark for 3 h, then concentrated under reduced pressure. The residue was dissolved in dichloromethane (20 ml) and washed with 4M aqueous sodium hydroxide (10 ml). The aqueous was extracted with dichloromethane (2 x 5 ml), the combined organics were dried over sodium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (1 : 19 methanol : dichloromethane) to give the product **262** (140 mg, 63%) as a light yellow oil. $[\alpha]_D^{24}$ -21.5 (*c* 0.67, $CHCl_3$); R_f 0.2 (1 : 19 methanol : dichloromethane); $\nu_{max}(CHCl_3)/cm^{-1}$ 3365, 2938, 2863, 1452, 1342, 910; δ_H (400 MHz, $CDCl_3$) 3.62-3.58 (1H, m, CHN), 3.24 (1H, ddd, *J* 10.5, 10.5, 4.0, CHN), 2.27 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.09-2.02 (1H, m, CH_2), 1.95 (3H, s, CH_3), 1.92 (3H, s, CH_3), 1.90-1.77 (4H, m, CH_2), 1.42-1.14 (5H, m, CH_2 and NH_2); δ_c (100 MHz, $CDCl_3$) 124.2 (C), 121.4 (C), 115.0 (C), 112.6 (C), 63.5 (CH), 53.0 (CH), 35.5 (CH_2), 31.7 (CH_2), 26.3 (CH_2), 25.1 (CH_2), 12.3 (CH_3), 10.8 (CH_3), 9.7 (CH_3), 9.3 (CH_3); *m/z* (ESI) 221 ($M+H^+$, 100%); *m/z* (ESI) Found 221.2017. $C_{14}H_{25}N_2^+$ requires 221.2012.

(1*R*,2*R*)-2-(9H-Carbazol-9-yl)cyclohexanamine **263**[101]

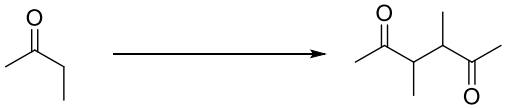


114 **267** **263**

A flame dried microwave tube was filled with 2,2'dibromophenyl (250 mg, 0.80 mmol), (1*R*,2*R*)-*trans*-diaminocyclohexane (110 mg, 0.96 mmol), copper (I) iodide (76 mg, 0.40 mmol) and potassium phosphate (374 mg, 1.76 mmol). The mixture was placed under an atmosphere of Ar and 1,4-dioxane (1.6 ml) was added. The mixture was then heated in a microwave to 150 °C for 30 mins. The resulting mixture was cooled to rt then filtered through Celite and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 : 19 methanol : dichloromethane) to give the product **263** (29 mg,

14%) as an off white solid; mp 134 °C; $[\alpha]_D^{23}$ +67.4 (*c* 0.6, $CHCl_3$), [lit.,[101] $[\alpha]_D^{25}$ +66.8 (*c* 0.9, $CHCl_3$); R_f 0.1 (1 : 19 methanol : dichloromethane); $\nu_{max}(CHCl_3)/cm^{-1}$ 2941, 2861, 1594, 1482, 1453, 1328; δ_H (400 MHz, $CDCl_3$) 8.15 (1H, d, *J* 8.0, ArH), 8.11 (1H, d, *J* 8.0, ArH), 7.66 (1H, d, *J* 8.5, ArH), 7.54-7.40 (3H, m, ArH), 7.25 (2H, dd, *J* 7.5, 7.5, ArH), 4.22 (1H, ddd, *J* 12.5, 9.0, 4.0, CHN), 3.77 (1H, ddd, *J* 10.5, 10.5, 4.0, CHN), 2.48-2.37 (1H, m, CH_2), 2.21-2.17 (1H, m, CH_2), 2.00-1.93 (3H, m, CH_2), 1.63-1.50 (2H, m, CH_2), 1.48-1.38 (1H, m, CH_2), 1.23 (2H, br s, NH_2); δ_c (100 MHz, $CDCl_3$) 141.7 (C), 138.6 (C), 125.8 (CH), 125.3 (CH), 124.1 (C), 122.7 (C), 120.5 (CH), 120.1 (CH), 118.9 (2 x CH), 111.6 (CH), 109.0 (CH), 62.2 (CH), 52.0 (CH), 35.4 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 25.2 (CH_2); *m/z* (ESI) 265 ($M+H^+$, 100%); *m/z* (ESI) Found 265.1692. $C_{18}H_{21}N_2^+$ requires 265.1699. The ^1H and ^{13}C NMR data are in agreement with those previously reported.[101]

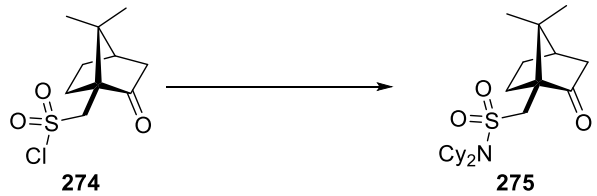
3,4-Dimethylhexan-2,5-dione **266**[100]



266

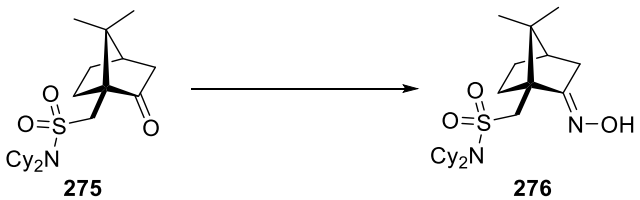
A 25 x 90 mm Soxhlet thimble was filled with a mixture of sand (20 g) and PbO_2 (23.9 g, 100 mmol). Butanone (127 ml, 1.50 mol) was placed in a 500 ml flask. The flask, fitted with the Soxhlet and reflux condenser, was put under an Ar atmosphere and heated to reflux. After 21 h the apparatus was allowed to cool, excess butanone was removed under reduced pressure to give a light yellow oil which was purified by distillation under reduced pressure to give the product **266** (mixture of diastereoisomers, 1 : 1, 4.41 g, 31%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 2.90-2.81 (2H, m, CH), 2.20 (6H, s, 2 x CH_3 diastereoisomer A) 2.19 (6H, s, 2 x C*H*$_3$ diastereoisomer B), 1.13-1.07 (6H, m, 2 x C*H*$_3$); δ_c (100 MHz, $CDCl_3$) 212.4 (C), 211.3 (C), 48.8 (CH), 48.5 (CH), 29.5 (CH_3), 28.8 (CH_3), 15.0 (CH_3), 13.8 (CH_3); *m/z* (ESI) 165 ($M+Na^+$, 100%); *m/z* (ESI) Found 165.0888. $C_8H_{14}O_2Na^+$ requires 165.0886. The ^1H and ^{13}C data are in agreement with those previously reported.[100]

N,*N*-Dicyclohexyl-(+)-camphor-10-sulfonamide **275**[103]



To a solution of *N*-dimethyl-4-aminopyridine (0.48 g, 4.00 mmol), pyridine (3.16 g, 40.0 mmol) and dicyclohexylamine (7.25 g, 40.0 mmol) in dimethylformamide (20 ml) at 0 °C was added a stirred solution of (1*S*)-(+)-10-camphorsulfonyl chloride **274** (5.01 g, 20.0 mmol) in dimethylformamide (10 ml) over a period of 1 h. The mixture was then allowed to warm to rt and stirred for a further 2 h. The mixture was then diluted with ethyl acetate (50 ml) and 0.5 M aqueous citric acid (50 ml). The mixture was filtered and the organic phase washed with 0.5 M aqueous citric acid (3 x 50 ml). The combined aqueous was extracted with dichloromethane (30 ml) and the combined organics were dried over $MgSO_4$ then concentrated under reduced pressure. The residue was recrystallised from petroleum ether to yield the product **275** (7.14 g, 90%) as an off white solid; mp 138 °C (lit.,[103] 134-135 °C); $[\alpha]_D^{21}$ +25.5 (*c* 0.7, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2937, 2858, 1743, 1324, 1143, 1046, 1165; δ_H (400 MHz, $CDCl_3$) 3.35-3.27 (3H, m, CHN and $CH_aH_bSO_2N$) 2.80 (1H, d, *J* 14.5, $CH_aH_bSO_2N$), 2.65-2.57 (1H, m, CH_2) 2.37 (1H, ddd, *J* 18.5, 3.5, 3.5, CH_2), 2.09-2.00 (2H, m, CH_2 and CH), 1.92 (1H, d, *J* 18.5, CH_2), 1.84-1.71 (12 H, m, CH_2), 1.65-1.58 (3H, m, CH_2), 1.43-1.25 (5H, m, CH_2), 1.18 (3H, s, CH_3), 1.17-1.07 (2H, m, CH_2), 0.90 (3H, s, CH_3); δ_c (100 MHz, $CDCl_3$) 215.7 (C), 59.1 (C), 57.7 (CH), 52.3 (CH_2), 47.5 (C), 42.6 (CH_2), 33.0 (CH_2), 32.6 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 26.5 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 20.4 (CH_3), 19.9 (CH_3); *m/z* (ESI) 418 ($M+Na^+$, 100%; $M+H^+$, 71%); *m/z* (ESI) Found 418.2381. $C_{22}H_{37}NO_3SNa^+$ requires 418.2386.

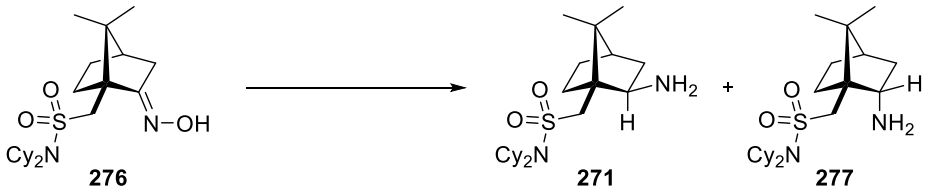
(1*S*,4*S*)-*N*,*N*-Dicyclohexyl-2-hydroxyimino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide **276**



Hydroxylamine hydrochloride (0.21 g, 3.03 mmol) and pyridine (0.75 ml) were dissolved in ethanol (3.0 ml) and stirred at rt for 15 mins. *N*,*N*-Dicyclohexyl-(+)-camphor-10-sulfonamide **275** (1.00 g, 2.53 mmol) was added to the solution and

the mixture heated at reflux for 4 h. The mixture was then cooled to rt and concentrated under reduced pressure. The residue was dissolved in 1 : 1 petroleum ether : ethyl acetate (10 ml), and washed sequentially with 1M hydrochloric acid (3 x 10 ml), water (10 ml) and brine (10 ml). The organic phase was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (3 : 1, petroleum ether : ethyl acetate) to give the product **276** (0.99 g, 95%) as a colourless solid. mp 168-170 °C; $[\alpha]_D^{23}$ +101.7 (*c* 0.85, $CHCl_3$); R_f 0.2 (3 : 1 petroleum ether : ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3585, 2937, 2858, 1454, 1325, 1166, 1144; δ_H (400 MHz, $CDCl_3$) 7.71 (1H, s, OH), 3.38 (1H, d, *J* 14.5, C*H*$_a$H$_b$SO$_2$N), 3.35-3.26 (2H, m, CHN), 2.90 (1H, d, *J* 14.5, CH$_a$*H*$_b$SO$_2$N), 2.62-2.51 (2H, m, CH and C*H*$_a$H$_b$CNOH), 2.08 (1H, d, *J* 18.0, CH$_a$*H*$_b$CNOH), 1.97-1.89 (2H, m, CH_2), 1.83-1.70 (13H, m, CH_2), 1.64-1.59 (2H, m, CH_2), 1.38-1.25 (5H, m, CH_2), 1.18-1.07 (5H, m, CH_2 and CH_3), 0.86 (3H, s, CH_3); δ_c (100 MHz, $CDCl_3$) 168.3 (C), 57.7 (C), 57.5 (CH), 54.0 (CH_2), 49.4 (C), 43.7 (CH), 33.1 (CH_2), 32.8 (CH_2), 32.5 (CH_2), 28.2 (CH_2), 27.2 (CH_2), 26.5 (CH_2), 26.5 (CH_2), 25.3 (CH_2), 19.5 (CH_3), 19.4 (CH_3); *m/z* (ESI) 433 ($M+Na^+$), 100%, 411 ($M+H^+$, 70%); *m/z* (ESI) Found 433.2497. $C_{22}H_{38}N_2O_3SNa^+$ requires 433.2495.

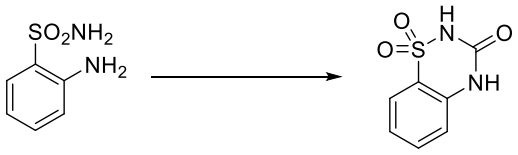
(1*S*,2*R*,4*S*)-*N*,*N*-Dicyclohexyl-2-amino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide **271** and (1*S*,2*S*,4*S*)-*N*,*N*-Dicyclohexyl-2-amino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide **277**



Raney nickel (2.00 g, 50% w/w in H_2O) was washed with acetonitrile and then diethyl carbonate before being added to a suspension of oxime **276** (2.00 g, 4.87 mmol) in diethyl carbonate (40 ml). The mixture was placed under an atmosphere of hydrogen and heated to 100 °C for 24 h. The mixture was allowed to cool to rt and then filtered. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (0.5 : 4.5 : 95 18 M aqueous ammonia : methanol : dichloromethane) to give amine **271** (97 mg, 5%) as a colourless oil. $[\alpha]_D^{25}$ -20.7 (*c* 0.65, $CHCl_3$); R_f 0.1 (0.5 : 4.5 : 95 18 M aqueous ammonia : methanol : dichloromethane); ν_{max} $(CHCl_3)/cm^{-1}$ 3300, 2938, 2859, 1454, 1319, 1140; δ_H (400 MHz, $CDCl_3$) 3.36 (1H, d, *J* 13.5, C*H*$_a$H$_b$), 3.31-3.23 (3H, m, CHN), 2.64 (1H, d, *J,* 13.5, CH$_a$*H*$_b$),

1.85-1.50 (21H, m, CH_2 and CH and NH_2), 1.37-1.08 (8H, m, CH_2), 1.05 (3H, s, CH_3), 0.82 (3H, s, CH_3); δ_c (100 MHz, $CDCl_3$) 57.7 (CH), 57.1 (CH), 54.6 (CH_2), 49.8 (C), 48.9 (C), 44.7 (CH), 39.9 (CH_2), 33.1 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 27.4 (CH_2), 26.5 (CH_2), 25.2 (CH_2), 21.2 (CH_3), 20.2 (CH_3); *m/z* (ES) 397 ($M+H^+$, 100%); *m/z* (ES) Found 397.2884. $C_{22}H_{41}N_2O_2S^+$ requires 397.2883. Followed by **277** (0.39 g, 20%) as a colourless solid. m.p. 163-165 °C; $[\alpha]_D^{25}$ +20.8 (*c* 1.0, $CHCl_3$); R_f 0.05 (0.5 : 4.5 : 95 18 M aqueous ammonia : methanol : dichloromethane); ν_{max} ($CHCl_3$)/cm^{-1} 3390, 3010, 2938, 2859, 1319, 1143; δ_H (400 MHz, $CDCl_3$) 3.47-3.42 (1H, m, C*H*N), 3.31-3.23 (2H, m, CHN), 2.87 (1H, d, *J* 13.5, C$H_a$$H_b$), 2.81 (1H, d, *J* 13.5, C$H_a$$H_b$), 2.40-2.32 (1H, m, CH_2), 2.28-2.21 (1H, m, CH_2), 1.85-1.60 (20H, m, CH and CH_2 and NH_2), 1.37-1.25 (5H, m, CH_2), 1.18-1.07 (2H, m, CH_2), 0.92 (3H, s, CH_3), 0.90 (3H, s, CH_3); δ_c (100 MHz, $CDCl_3$) 63.7 (CH_2), 59.1 (CH), 57.6 (CH), 51.3 (C) 51.3 (C), 44.0 (CH), 39.9 (CH_2), 32.8 (CH_2), 32.7 (CH_2), 28.4 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 25.1 (CH_2), 24.5 (CH_2), 20.7 (CH_3),18.8 (CH_3); *m/z* (ES) Found 397.2884. $C_{22}H_{41}N_2O_2S^+$ requires 397.2883.

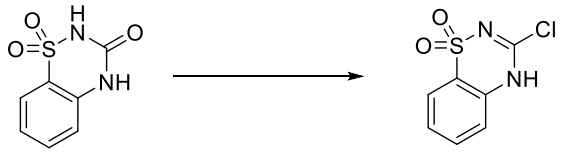
3-Oxo-2*H*-4*H*-1,2,4-benzothiadiazine-1,1-dioxide **364**[148]



363 **364**

A solution of 2-aminobenzenesulfonamide (4.36 g, 25.3 mmol) in tetrahydrofuran (20 ml) was cooled to 0 °C. Phosgene (38 mmol, 20% w/w in toluene) was added, immediately resulting in a white precipitate. The mixture was allowed to warm to 25 °C and stirred for 1 h. Toluene (20 ml) was added and the mixture filtered to give the product **364** (4.02 g, 80%) as a white solid. m.p. 295 °C (lit.,[148] 296-298 °C); δ_H (400 MHz, DMSO) 11.23 (1H, s, NH), 7.78 (1H, dd, *J* 8.0. 1.0, ArH), 7.65 (1H, ddd, *J* 8.5, 7.5, 1.5, ArH), 7.29 (1H, ddd, *J* 8.5,7.5, 1.5, ArH), 7.25 (1H, d, *J* 8.5, ArH); δ_c (100 MHz, DMSO) 151.1 (C),135.5 (C), 134.5 (CH), 123.9 (CH), 123.0 (C), 122.5 (CH), 117.5 (CH); *m/z* (ESI) 197 ($M-H^+$, 100%); *m/z* (ESI) Found 197.0024. $C_7H_6N_2O_3S^-$ requires 197.0026. The ^1H and ^{13}C NMR data are in agreement with those previously reported.[148]

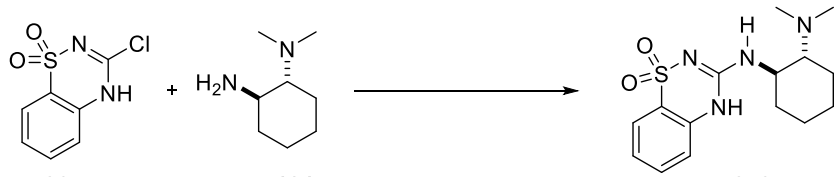
3-Chloro-4*H*-1,2,4-benzothiadiazine-1,1-dioxide **365**[123]



364 **365**

A stirred solution of urea **364** (2.00 g, 10.1 mmol) in phosphorusoxychloride (12 ml) was cooled to 0 °C. 2,6-Lutidine (1.87 ml, 16.1 mmol) was added dropwise, then the solution was heated at reflux for 4 h. The solution was then cooled to rt and concentrated under reduced pressure. The residue was recrystallised from water to give the product **365** (1.16 g, 53%) as a white solid. mp 237°C (lit.,[123] 238-239°C); δ_H (400 MHz, DMSO) 13.36 (1H, br s, NH), 7.87 (1H, d, *J* 8.0, ArH), 7.74 (1H, dd, *J* 8.0, 2.0, ArH), 7.51 (1H, dd, *J* 8.0, 2.0, ArH), 7.38 (1H, d, *J* 8.0, ArH); δ_c (100 MHz, DMSO) 145.8 (C), 135.1 (C), 134.3 (CH), 127.7 (CH), 124.1 (CH), 121.7 (C), 118.4 (CH); *m/z* (ESI) 215 ($M\text{-}H^+$ 100%); *m/z* (ESI) Found 214.9686. $C_7H_4Cl^{35}N_2O_2S^-$ requires 214.9687.

3-(((1R,2R)-2-(Dimethylamino)cyclohexyl)amino)-4H-benzo-1,2,4-thiadiazine-1,1-dioxide **356**[120b]

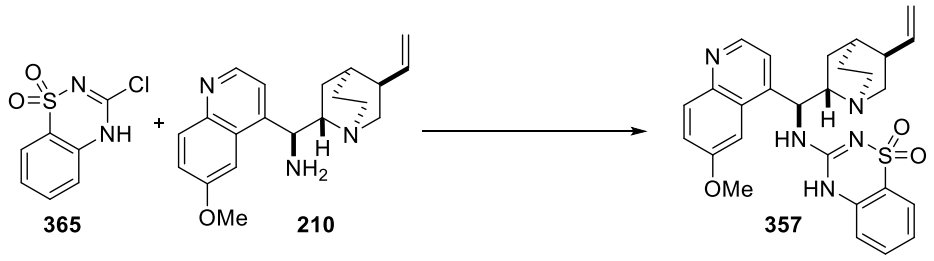


365 **124** **356**

Chloride **365** (0.31 g, 1.45 mmol) and (1*R*,2R)-N,N-dimethyldiaminocyclohexane (0.21 g, 1.45 mmol) were dissolved in tetrahydrofuran (5 ml) and heated at reflux for 5 h. The mixture was then cooled to rt and concentrated under reduced pressure. The residue was dissolved in chloroform (10 ml) and washed with saturated aqueous sodium hydrogen carbonate (3 x 10 ml). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to yield the product **365** (0.16 g, 34%) as an off white glassy solid. $[\alpha]_D^{24}$ +46.1 (*c* 0.91, $CHCl_3$) [lit.,[120b] $[\alpha]_D$ +32.6 (c 0.97, $CHCl_3$); mp 220 °C (lit.,[120b] 222-223 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 3406, 3299, 3006, 2943, 2865, 1624, 1588, 1482, 1290, 1168, 1160; δ_H (400 MHz, $CDCl_3$) 7.87 (1H, dd, *J* 8.0, 1.0, ArH), 7.42 (1H, ddd, *J* 8.0, 7.0, 1.0, ArH), 7.22 (1H, ddd, *J* 8.0, 7.0, 1.0, ArH), 6.94 (1H, br d, *J* 8.0, ArH), 5.72 (2H, br s, NH), 3.61 (1H, br s, CHN), 2.52 (1H, ddd, *J* 11.5, 11.5, 3.5, CHN), 2.43 (6H, s, CH_3), 2.28-2.24 (1H, m, CH_2), 1.94-1.70 (3H, m, CH_2), 1.33-1.13 (4H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 151.6 (C), 136.1 (C), 132.6 (CH), 124.0

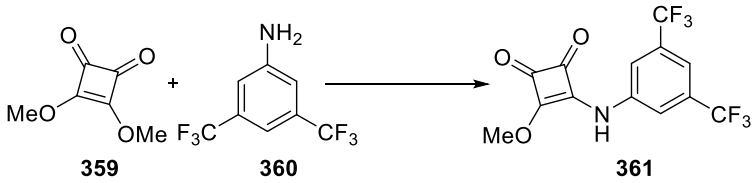
(CH), 123.5 (CH), 121.9 (C), 116.7 (CH), 67.0 (CH), 52.2 (CH), 40.2 (CH_3), 32.8 (CH_2), 24.7 (CH_2), 24.5 (CH_2), 22.2 (CH_2); *m/z* (ESI) 323 ($M+H^+$, 100%); *m/z* (ESI) Found 323.1535. $C_{15}H_{23}N_4O_2S^+$ requires 323.1536. The ^1H and ^{13}C NMR data are in agreement with those previously reported.[120b]

(9-epi-9-Amino-9-deoxyquinine)-4H-benzo-1,2,4-thiadiazine-1,1-dioxide **357**



9-*epi*-9-Amino-9-deoxyquinine (0.53 g, 1.65 mmol) and chloride **365** (0.33 g, 1.5 mmol) were dissolved in tetrahydrofuran (5 ml) and heated at reflux for 18 h. The mixture was then cooled to rt and concentrated under reduced pressure. The residue was precipitated from chloroform / ethyl acetate (25 ml : 5 ml). The resulting solid was dissolved in chloroform (10 ml) and washed with saturated aqueous sodium hydrogen carbonate (3 x 10 ml). The organic layer was dried over magnesium sulfate then concentrated under reduced pressure. The residue was recrystallised from ethanol / diethyl ether to give the product **357** (0.34 g, 45%) as a white solid. $[\alpha]_D^{24}$ -45.9 (*c* 0.6, $(CH_3)_2SO$); mp. 229 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3608, 3583, 3320, 2925, 1622, 1580, 1471, 1430, 1264, 1157; δ_H (400 MHz, DMSO) 8.76 (1H, d, *J* 4.5, ArH), 7.96 (1H, d, *J* 9.0, ArH), 7.84 (1H, br s, ArH), 7.63-7.60 (2H, m, ArH), 7.50 (1H, dd, *J* 7.5, 2.0, ArH), 7.43 (1H, dd, *J* 9.0, 2.0, ArH), 7.20 (1H, dd, *J* 7.5, 2.0, ArH), 7.09 (1H, d, *J* 8.0, ArH), 5.87 (1H, ddd, *J* 17.5.0, 9.0, 9.0, CH), 5.51 (1H, br s, CHN), 5.00 (1H, d, *J* 17.5, CH_2), 4.94 (1H, d, *J* 10.0, CH_2), 3.99 (3H, s, CH_3), 3.36-3.16 (3H, m, CH and CH_2), 2.73-2.63 (2H, m, CH_2), 2.28-2.22 (1H, m, CH), 1.65-1.31 (4H, m, CH_2 and CH), 0.77-0.72 (1H, m, CH_2); δ_C (100 MHz, DMSO) 157.8 (C), 150.9 (C), 148.1 (CH), 144.7 (C), 144.5 (C), 142.5 (CH), 135.9 (C), 132.9 (CH), 131.8 (CH), 128.3 (C), 124.2 (CH), 123.3 (CH), 122.9 (C), 122.0 (CH), 120.9 (CH), 116.9 (CH), 114.8 (CH_2), 102.8 (CH), 59.0 (CH), 56.2 (CH_3), 55.8 (CH_2), 51.9 (CH), 41.2 (CH_2), 39.7 (CH), 27.7 (CH_2), 27.6 (CH), 26.4 (CH_2); *m/z* (ESI) 504 ($M+H^+$, 100%); *m/z* (ESI) Found 504.2063. $C_{27}H_{30}N_5O_3S^+$ requires 504.2064.

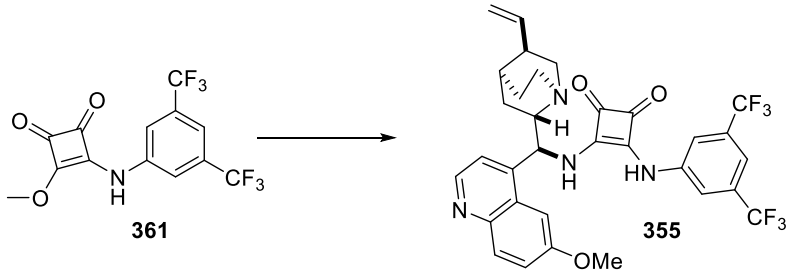
3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione **361**[122]



359 **360** **361**

Dimethyl squarate (1.42 g, 10.0 mmol) and 3,5-bis(trifluoromethyl)aniline (2.29 g, 10mmol) were dissolved in MeOH (20 ml) and placed under an Ar atmosphere. The solution was then heated at reflux for 20 h, then cooled in an ice bath. The resulting precipitate was collected by filtration to yield the product **361** (1.80 g, 53%). Additional product (1.01 g, 30%) was obtained by concentrating the filtrand under reduced pressure and recrystallising the residue from ethyl acetate / petroleum ether. mp 196 °C (lit.,[122] 179-181 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 3373, 1810, 1734, 1607, 1458, 1380, 1357; δ_H (400 MHz, DMSO) 11.18 (1H, br s, NH) 8.04 (2H, s, ArH), 7.78 (1H, s, Ar*H*), 4.41 (3H, s, CH_3); δ_c (100 MHz, DMSO) 187.9 (C), 185.0 (C), 180.4 (C), 169.6 (C), 140.7 (C), 131.7 (C, q, J_{CF} 33), 123.6 (C, q, J_{CF} 273), 119.8 (CH), 116.7 (CH), 61.4 (CH_3); *m/z* (ESI) 362 ($M+Na^+$, 100%; $M+H^+$, 90%); *m/z* (ESI) Found 362.0218. $C_{13}H_7F_6NO_3Na^+$ requires 362.0222. ^1H and ^{13}C NMR data is in agreement with those previously reported.[122]

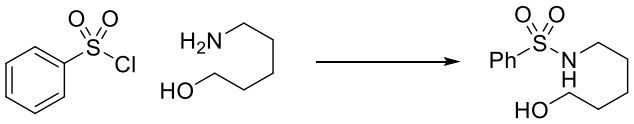
3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(9'-*epi*-9'-amino-9'-deoxyquinine)cyclobut-3-ene-1,2-dione **355**[122]



To a solution of 9-*epi*-9-amino-9-deoxyquinine (288 mg, 0.89 mmol) in dichloromethane (5 ml) was added 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (302 mg, 0.89 mmol). The resulting mixture was stirred at rt for 72 h, then filtered to yield the product **83** (419 mg, 75%) as a colourless solid. $[\alpha]_D^{24}$ -61.4 (*c* 0.85, $(CH_3)_2SO$), [lit.,[122] $[\alpha]_D^{25}$ -52.8 (*c* 0.5, $(CH_3)_2SO$)]; mp. 215 °C (lit.,[122] 227-228 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 3215, 2930; 1793, 1684, 1601, 1557, 1437, 1380, 1278, 1181, 1134; δ_H (400 MHz, DMSO) 10.19 (1H, br s, NH), 8.82 (1H, d, *J* 4.5, ArH), 8.32 (1H, br s, NH), 8.00-7.96

(3H, m, ArH), 7.75 (1H, br s, ArH), 7.67 (1H, d, *J* 4.5, ArH), 7.65 (1H, s, ArH), 7.45 (1H, dd, *J* 9.5, 2.5, ArH), 6.03-5.94 (2H, m, CHN and C*H*CH_2), 5.04 (1H, d, *J* 17.5, CH_2), 4.99 (1H, d, *J* 10.5, CH_2), 3.95 (3H, s, CH_3), 3.50-3.44 (1H, m, CH), 3.30-3.25 (1H, m, CH_2), 3.23-3.17 (1H, m, CH_2), 2.73-2.61 (2H, m, CH_2), 2.33-2.25 (1H, m, CH), 1.60-1.45 (4H, m, CH_2 and CH), 0.72-0.67 (1H, m, CH_2); δ_C (100 MHz, DMSO) 185.2 (C), 180.6 (C), 169.1 (C), 163.2 (C), 158.4 (C), 148.2 (CH), 144.8 (C), 143.5 (C), 142.6 (CH), 141.3 (C), 132.0 (CH), 131.7 (C, q, J_{CF} 33), 127.9 (C), 123.6 (C, q, J_{CF} 273), 122.4 (CH), 120.0 (CH), 118.8 (C), 115.3 (CH), 114.8 (CH_2), 101.9 (CH), 59.4 (CH), 56.1 (CH_3), 56.1 (CH_2), 53.8 (CH), 40.6 (CH_2), 39.9 (CH), 27.7 (CH_2), 27.8 (CH), 26.5 (CH_2); *m/z* (ESI) 631 ($M+H^+$, 100%); *m/z* (ESI) Found 631.2137. $C_{32}H_{29}F_6N_4O_3^+$ requires 631.2138. ^1H and ^{13}C NMR data is in agreement with those previously reported.[122]

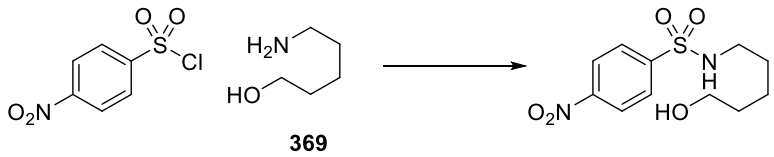
N-(5-Hydroxypentyl)benzenesulfonamide **370**



368 **369** **370**

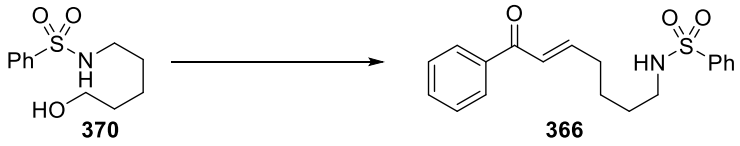
5-Aminopentanol (2.56 g, 24.8 mmol) and triethylamine (6.05 g, 59.9 mmol) were dissolved in methanol (20 ml). To the stirred solution was added benzenesulfonylchloride (6.05 g, 34.3 mmol) drop-wise. The resulting mixture was stirred at rt for 1 h, then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (50 ml) and washed with 1M hydrochloric acid (3 x 30 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give the product **370** (5.84 g, 97%) as a colourless oil. ν_{max}(neat)/cm^{-1} 3282, 2938, 2866, 2360, 2342, 1447, 1322, 1157, 1093; δ_H (400 MHz, CD_3Cl) 7.89-7.86 (2H, m, ArH), 7.60-7.50 (3H, m, ArH), 4.97 (1H, br t, *J* 6.0, NH), 3.59 (2H, t, *J* 6.0, C*H*$_2$OH) 2.96 (2H, dt, *J* 6.5, 6.0, C*H*$_2$NH), 1.74 (1H, br s, OH), 1.54-1.47 (m, 4H, CH_2), 1.40-1.32 (2H, m, CH_2); δ_C (100 MHz, CD_3Cl) 140.0 (C), 132.6 (CH), 129.1 (CH), 127.0 (CH), 62.5 (CH_2), 43.1 (CH_2), 31.9 (CH_2), 29.2 (CH_2), 22.7 (CH_2); *m/z* (ESI) 266 [($M+Na^+$, 100%), 244 ($M+H^+$, 44%) (M_2+Na^+, 23%)]; *m/z* (ESI) Found 266.0811. $C_{11}H_{17}NO_3SNa^+$ requires 266.0821.

N-(5-Hydroxypentyl)-4-nitrobenzenesulfonamide



5-Aminopentanol (0.50 g, 4.80 mmol) and triethylamine (1.18 g, 11.7 mmol) were dissolved in methanol (4 ml). The solution was cooled to 0 °C and a solution of nosylchloride (1.29 g, 5.82 mmol) in dichloromethane (4 ml) was added drop-wise. The resulting mixture was stirred at rt for 1 h, then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and washed with 1M hydrochloric acid (3 x 10 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2 : 1 petroleum ether : ethyl acetate) and subsequently recrystallised (ethyl acetate/petroleum ether) to give the product (1.15 g, 83%) as a colourless solid. m.p 90 °C; R_f 0.2 (2 : 1 petroleum ether : ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3626, 3391, 3043, 2941, 2868, 1608, 1537, 1350, 1165; δ_H (400 MHz, $CDCl_3$) 8.37 (2H, d, *J* 9.0, ArH), 8.06 (2H, d, *J* 9.0, ArH), 5.19 (1H, t, *J* 6.0, NH), 3.62 (2H, t, *J* 6.0, C*H*$_2$OH), 3.03 (2H, dt, *J* = 6.0, 6.0, CH_2N), 1.77 (1H, brs, OH), 1.54 (4H, m, CH_2), 1.40 (2H, m, CH_2); δ_C (100 MHz, CD_3Cl) 150.1 (C), 146.0 (C), 128.3 (CH), 124.4 (CH), 62.4 (CH_2), 43.2 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 22.7 (CH_2); *m/z* (ESI) 311 ($M+Na^+$ 100%), 599 (M_2+Na^+ 18%); *m/z* (ESI) Found 311.0643. $C_{11}H_{16}N_2O_5SNa^+$ requires 311.0672.

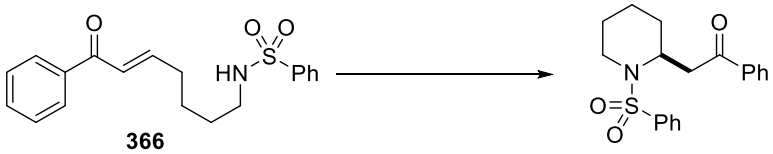
(*E*)-N-(7-Oxo-7-phenylhept-5-en-1-yl)benzenesulfonamide **366**



N-(5-Hydroxypentyl)benzenesulfonamide (5.84 g, 24.0 mmol) and benzoylmethylene(triphenylphosphorane) (14.6 g, 38.0 mmol) were dissolved in chloroform (100 ml). 3 Å powdered molecular sieves (10 g) were added, followed by manganese dioxide (12.5 g, 144 mmol). The mixture was heated at reflux for 48 h, then allowed to cool to rt, diluted with diethyl ether (50 ml), and filtered through celite. The resulting solution was concentrated under reduced pressure and the residue dissolved in minimum amount hot ethyl acetate (20 ml). After cooling to rt the precipitated phosphine oxide was removed by filtration. The

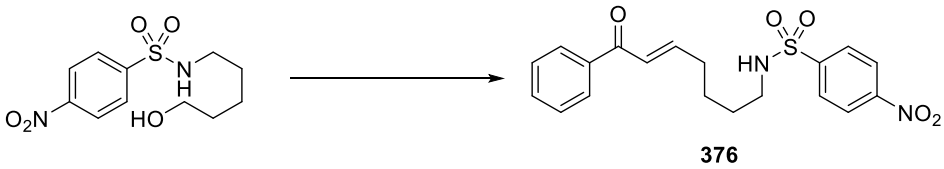
filtrand was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (2 : 1 petroleum ether : ethyl acetate). The resulting product was further purified by recrystallisation from ethyl acetate / petroleum ether to give the product **366** (2.47 g, 30%) as a colourless solid. m.p 85 °C; R_f 0.2 (2 : 1 petroleum ether : ethyl acetate); ν_{max}(neat)/cm^{-1} 3274, 2938, 1666, 1618, 1447, 1327, 1158; δ_H (400 MHz, $CDCl_3$) 7.93-7.86 (4H, m, ArH), 7.60-7.46 (6H, m, ArH), 6.97 (1H, dt, *J* 15.5, 7.0, CH), 6.87-6.83 (1H, m, CH), 4.51 (1H, t, *J* 6.0, NH), 3.03-2.98 (2H, m, CH_2N), 2.31-2.27 (2H, m, CH_2), 1.56-1.52 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 190.7 (C), 148.7 (CH), 139.9 (C), 137.8 (C), 132.8 (CH), 132.7 (CH), 129.2 (CH), 128.6 (CH), 128.6 (CH), 127.0 (CH), 126.3 (CH), 43.0 (CH_2), 32.1 (CH_2), 29.2 (CH_2), 25.1 (CH_2); *m/z* (ESI) 344 (M+H$^+$ 100%), 366 (M+Na$^+$ 21%); *m/z* (ESI) Found 344.1310. $C_{19}H_{22}NO_3S^+$ requires 344.1315.

(*S*)-1-Phenyl-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one **367**



Enone **366** (68.6 mg, 0.20 mmol) and squaramide catalyst **355** (1.3 mg, 0.002 mmol) were dissolved in toluene (1.0 ml) and stirred at rt for 12 h. The solution was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (3 : 7 ethyl acetate : petroleum ether) to give the product **367** (67 mg, 84%) as a colourless solid. m.p. 132 °C; $[\alpha]_D^{23}$ -37.0 (*c* 0.84, $CHCl_3$, 99% ee); R_f 0.2 (3 : 7 ethyl acetate : petroleum ether); ν_{max}(neat)/cm^{-1} 2939, 1681, 1447, 1328, 1288, 1155; δ_H (400 MHz, $CDCl_3$) 7.93-7.91 (2H, m, ArH), 7.85-7.83 (2H, m, ArH), 7.60-7.52 (2H, m, ArH), 7.49-7.46 (4H, m, ArH), 4.72-4.69 (1H, m, CHN), 3.91-3.87 (1H, m, CH_cH$_d$), 3.37 (1H, dd, *J* 16.0, 11.0, CH_aH$_b$), 3.16 (1H, dd, *J* 16.0, 3.5, CH$_a$$H_b$), 3.08 (1H, ddd, *J* 13.0, 13.0, 2.5, CH$_c$$H_d$), 1.64-1.52 (5H, m, CH_2), 1.42-1.31 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 197.6 (C), 141.1 (C), 136.5 (C), 133.4 (CH), 132.4 (CH), 129.1 (CH), 128.7 (CH), 128.2 (CH), 127.0 (CH), 49.5 (CH), 41.5 (CH_2), 39.0 (CH_2), 27.5 (CH_2), 24.8 (CH_2), 18.4 (CH_2); *m/z* (ESI) 366 (M+Na$^+$ 100%); *m/z* (ESI) Found 366.1131. $C_{19}H_{21}NO_3SNa^+$ requires 366.1134; R_t HPLC (Chiralpak AD-H; 80 : 20, hexane : isopropyl alcohol, 240 nm, 1.0 ml/m) 12.0 min 99.3% (*S*)-isomer, 35.5 min 0.7% (*R*)-isomer, 99% e.e.

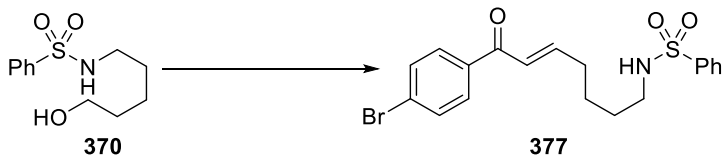
(*E*)-N-(7-Oxo-7-phenylhept-5-en-1-yl)-4-nitrobenzenesulfonamide **376**



376

N-(5-Hydroxypentyl)-4-nitrobenzenesulfonamide (1.00 g, 3.47 mmol) and benzoylmethylene(triphenylphosphorane) (2.11 g, 5.55 mmol) were suspended in toluene (20 ml). 3 Å powdered molecular sieves (2 g) were added followed by manganese dioxide (1.81 g, 20.8 mmol). The mixture was heated at 70 °C for 24 h, cooled to rt, and filtered through celite. The resulting solution was then concentrated under reduced pressure and the residue dissolved in minimum amount hot ethyl acetate (10 ml). After cooling to rt the precipitated phosphine oxide was removed by filtration. The filtrand was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (1 : 2 ethyl acetate : petroleum ether). The resulting product was further purified by recrystallisation from ethyl acetate / petroleum ether to give the product **376** (0.11 g, 8%) as a light yellow solid. mp. 110 °C; R_f 0.2 (1 : 2 ethyl acetate : petroleum ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 3278, 2938, 2865, 1666, 1616, 1529, 1349, 1163; δ_H (400 MHz, $CDCl_3$) 8.39-8.36 (2H, m, ArH), 8.07-8.04 (2H, m, ArH), 7.93-7.91 (2H, m, ArH), 7.58 (1H, dddd, *J* 7.5, 7.5, 2.0, 2.0 ArH), 7.50-7.47 (2H, m, ArH), 6.99 (1H, dt, *J* 15.5, 6.5, CH), 6.88 (1H, dt, *J* 15.5, 1.0, CH), 4.65 (1H, t, *J* 6.5, NH), 3.09-3.04 (2H, m, CH_2), 2.35-2.31 (2H, m, CH_2), 1.60-1.56 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 190.7 (C), 150.1 (C), 148.5 (CH), 146.0 (C), 137.7 (C), 132.9 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 126.4 (CH), 124.5 (CH), 43.2 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 25.0 (CH_2); *m/z* (ESI) 411 ($M+Na^+$ 100%); *m/z* (ESI) Found 411.0990. $C_{19}H_{20}N_2O_5SNa^+$ requires 411.0985.

(*E*)-N-(7-(4-Bromophenyl)-7-oxohept-5-en-1-yl)benzenesulfonamide **377**

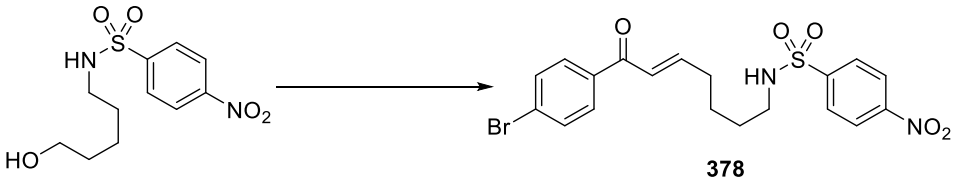


370 **377**

N-(5-Hydroxypentyl)benzenesulfonamide (1.21 g, 5.00 mmol) and (1-(4-bromophenyl)-2-(triphenylphosphoranylidene)ethanone (3.67 g, 8.00 mmol) were dissolved in chloroform (20 ml). 3 Å powdered molecular sieves (2 g) were added, followed by manganese dioxide (2.61 g, 30.0 mmol). The mixture was then heated at reflux for 48 h, cooled to rt, diluted with diethyl ether (10 ml), and

filtered through Celite. The resultind solution was then concentrated under reduced pressure and the residue dissolved in minimum amount hot ethyl acetate (10 ml). After cooling to rt the precipitated phosphine oxide was removed by filtration. The filtrand was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (1 : 9 ethyl acetate : toluene). The resulting product was further purified by recrystallisation from ethyl acetate / petroleum ether to give the product **377** (0.08 g, 4%) as a colourless solid. mp. 95 °C; R_f 0.2 (1 : 9 ethyl acetate : toluene); $\nu_{max}(CHCl_3)/cm^{-1}$ 3393, 3010, 2924, 2867, 1731, 1669, 1619, 1586, 1331, 1162; δ_H (400 MHz, $CDCl_3$) 7.88-7.86 (2H, m, ArH), 7.81-7.78 (2H, m, ArH), 7.63-7.51 (5H, m, ArH), 6.99 (1H, dt, *J* 15.5, 7.0, CH), 6.82 (1H, dt, *J* 15.5, 1.0, CH), 4.34 (1H, t, *J* 6.0, NH), 3.04-2.99 (2H, m, CH_2), 2.32-2.28 (2H, m, CH_2), 1.57-1.53 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 189.5 (C), 149.3 (CH), 136.5 (C), 132.7 (CH), 131.9 (CH), 130.1 (C), 129.2 (CH), 127.9 (C), 127.0 (CH), 125.8 (CH), 42.9 (CH_2), 32.1 (CH_2), 29.2 (CH_2), 25.0 (CH_2); *m/z* (ESI) 446 ($M+Na^+$ (^{81}Br) 100%), 444 ($M+Na^+$ (^{79}Br) 95%); *m/z* (ESI) Found 446.0232. $C_{19}H_{20}{}^{81}BrNO_3SNa^+$ requires 446.0219.

(*E*)-N-(7-(4-Bromophenyl)-7-oxohept-5-en-1-yl)-4-nitrobenzenesulfonamide **378**

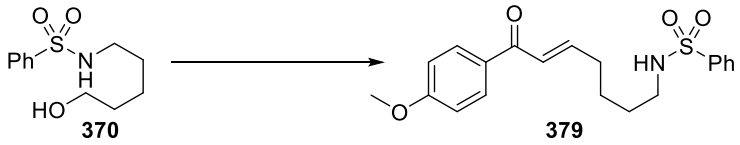


378

N-(5-Hydroxypentyl)-4-nitrobenzenesulfonamide (0.94 g, 3.26 mmol) and (1-(4-bromophenyl)-2-(triphenylphosphoranylidene)ethanone (2.40 g, 5.22 mmol) were suspended in a solution of toluene (20 ml). The suspension was heated to 70 °C then 3 Å powdered molecular sieves (2 g) followed by manganese dioxide (1.70 g, 19.6 mmol) were added to the mixture. The mixture was heated to 70 °C for 48 h, cooled to rt, and filtered through Celite. The resulting solution was then concentrated under reduced pressure and the residue dissolved in minimum amount hot ethyl acetate. After cooling to rt the precipitated phosphine oxide was removed by filtration. The filtrand was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (1 : 2 ethyl acetate : petroleum ether). The resulting product was further purified by recrystallisation from ethyl acetate / petroleum ether to give the product **378** (0.18 g, 12%) as a light brown solid. mp. 95 °C; R_f 0.2 (1 : 2 ethyl acetate : petroleum ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3011, 2942, 2867, 1670, 1619, 1586, 1534, 1350, 1166; δ_H (400 MHz, $CDCl_3$) 8.39-8.35 (2H, m, ArH), 8.08-8.03 (2H, m, ArH), 7.79-7.76

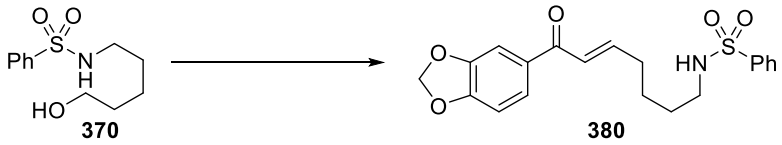
(2H, m, ArH), 7.63-7.60 (2H, m, ArH), 6.99 (1H, dt, *J* 15.5, 7.0 CH), 6.83 (1H, dt, *J* 15.5, 1.0, CH), 4.82 (1H, t, *J* 6.0, NH), 3.08-3.03 (2H, m, CH_2), 2.34-2.30 (2H, m, CH_2), 1.61-1.53 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 189.4 (C), 150.1 (C), 149.0 (CH), 145.9 (C), 136.4 (C), 131.9 (CH), 130.1 (CH), 128.3 (CH), 128.0 (C), 125.9 (CH), 124.5 (CH), 43.1 (CH_2), 32.1 (CH_2), 29.3 (CH_2), 25.0 (CH_2); *m/z* (ESI) 491 ($M+Na^+$ (^{81}Br) 100%), 489 ($M+Na^+$ (^{79}Br) 94%); *m/z* (ESI) Found 491.0062. $C_{19}H_{19}{}^{81}BrN_2O_5SNa^+$ requires 491.0070.

(*E*)-N-(7-(4-Methoxyphenyl)-7-oxohept-5-en-1-yl)benzenesulfonamide **379**



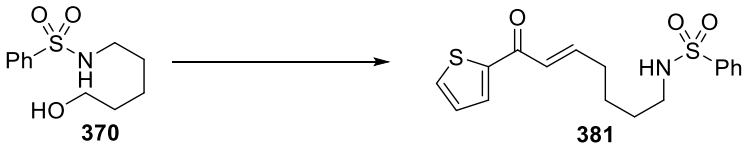
N-(5-Hydroxypentyl)benzenesulfonamide (1.21 g, 5.00 mmol) and (1-(4-methoxyphenyl)-2-(triphenylphosphoranylidene)ethanone (3.28 g, 8.00 mmol) were dissolved in chloroform (20 ml). 3 Å powdered molecular sieves (2 g) and manganese dioxide (2.61 g, 30.0 mmol) were added to the solution. The mixture was heated at reflux for 48 h, cooled to rt, diluted with diethyl ether (10 ml), and filtered through Celite. The resulting solution was concentrated under reduced pressure and the residue dissolved in minimum amount hot ethyl acetate (10 ml). After cooling to rt the precipitated phosphine oxide was removed by filtration. The filtrand was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (1 : 1 petroleum ether : ethyl acetate). The resulting product was further purified by recrystallisation from ethyl acetate / petroleum ether to give the product **379** (0.37 g, 20%) as a pale yellow solid. mp. 84 °C; R_f 0.2 (1 : 1 petroleum ether : ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3011, 2939, 1666, 1618, 1599, 1332, 1260, 1168; δ_H (400 MHz, $CDCl_3$) 7.96-7.92 (2H, m, ArH), 7.88-7.86 (2H, m, ArH), 7.59-7.49 (3H, m, ArH), 6.98-6.91 (3H, m, ArH), 6.86 (1H, dt, *J* 15.5, 1.0, CH), 4.63 (1H, t, *J* 6.0, NH), 3.88 (3H, s, CH_3), 3.02-2.97 (2H, m, CH_2), 2.29-2.24 (2H, m, CH_2), 1.54-1.52 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 188.9 (C), 171.2 (C), 147.6 (CH), 140.0 (C), 132.7 (CH), 130.9 (CH), 130.7 (C), 129.2 (CH), 127.0 (CH), 126.0 (CH), 113.8 (CH), 55.5 (CH_3), 43.0 (CH_2), 32.0 (CH_2), 29.2 (CH_2), 25.1 (CH_2); *m/z* (ESI) 396 ($M+Na^+$ 100%); *m/z* (ESI) Found 396.1240. $C_{20}H_{23}NO_4SNa^+$ requires 396.1240.

(*E*)-N-(7-(Benzo[*d*][1,3]dioxol-5-yl)-7-oxohept-5-en-1-yl)benzenesulfonamide **380**



N-(5-Hydroxypentyl)benzenesulfonamide (1.21 g, 5.00 mmol) and (1-(benzo[*d*][1,3]dioxol-5-yl)-2-(triphenylphosphoranylidene)ethanone (3.40 g, 8.00 mmol) were suspended in a solution of 9 : 1 toluene : chloroform (20 ml) then heated to 70 °C. 3 Å powdered molecular sieves (2 g) followed by manganese dioxide (2.61 g, 30.0 mmol) were added. The mixture was stirred at 70 °C for 48 h, cooled to rt, diluted with diethyl ether (10 ml), and filtered through Celite. The resulting solution was then concentrated under reduced pressure and the residue dissolved in minimum amount hot ethyl acetate. After cooling to rt the precipitated phosphine oxide was removed by filtration. The filtrand was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (3 : 7 ethyl acetate : petroleum ether The resulting product was further purified by recrystallisation from ethyl acetate / petroleum ether to give the product **380** (0.18 g, 9%) as a colourless solid. mp. 101 °C; R_f 0.2 (3 : 7 ethyl acetate : petroleum ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 3393, 3011, 2929, 2858, 1664, 1621, 1602, 1444, 1358, 1251, 1162; δ_H (400 MHz, $CDCl_3$) 7.89-7.86 (2H, m, ArH), 7.60-7.50 (4H, m, ArH), 7.44 (1H, d, *J* 1.5, ArH), 6.95 (1H, dt, *J* 15.5, 7.0, CH), 6.87 (1H, d, *J* 8.0, ArH), 6.81 (1H, dt, *J* 15.5, 1.5, CH), 6.05 (2H, s, CH_2), 4.59 (1H, t, *J* 6.0, NH), 3.02-2.99 (2H, m, CH_2), 2.29-2.24 (2H, m, CH_2), 1.54-1.52 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 188.4 (C), 151.7 (C), 148.3 (C), 147.9 (CH), 140.0 (C), 132.7 (CH), 132.6 (C), 129.2 (CH), 127.0 (CH), 125.9 (C), 124.8 (CH), 108.4 (CH), 107.9 (CH), 101.9 (CH_2), 43.0 (CH_2), 32.0 (CH_2), 29.2 (CH_2), 25.1 (CH_2); *m/z* (ESI) 410 ($M+Na^+$ 100%); *m/z* (ESI) Found 410.1032. $C_{20}H_{21}NO_5SNa^+$ requires 410.1033.

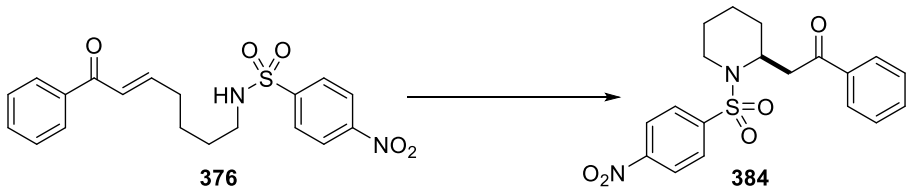
(*E*)-N-(7-Oxo-7-(thiophen-2-yl)hept-5-en-1-yl)benzenesulfonamide **381**



N-(5-Hydroxypentyl)benzenesulfonamide (1.56 g, 6.41 mmol) and (1-(thiphen-2-yl)-2-(triphenylphosphoranylidene)ethanone (3.96 g, 10.3 mmol) were dissolved

in 2 : 1 toluene : chloroform (30 ml). 3 Å powdered molecular sieves (2 g) and manganese dioxide (3.34 g, 38.5 mmol) were added. The mixture was then heated at reflux for 48 h, cooled to rt, diluted with diethyl ether (20 ml), and filtered through Celite. The resulting solution was then concentrated under reduced pressure and the residue dissolved in minimum amount hot ethyl acetate (10 ml). After cooling to rt the precipitated phosphine oxide was removed by filtration. The filtrand was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (2 : 1 Petroleum ether : ethyl acetate). The resulting product was further purified by recrystallisation from ethyl acetate / petroleum ether to give the product **381** (0.17 g, 8%) as a pale yellow solid. mp. 90 °C; R_f 0.2 (2 : 1 Petroleum ether : ethyl acetate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3393, 3011, 2942, 1659, 1614, 1416, 1332, 1162; δ_H (400 MHz, $CDCl_3$) 7.89-7.86 (2H, m, ArH), 7.76 (1H, dd, *J* 4.0, 1.0, ArH), 7.66 (1H, dd, *J* 5.0, 1.0, ArH), 7.60-7.50 (3H, m, ArH), 7.16 (1H, dd, *J* 5.0, 4.0, ArH), 7.02 (1H, dt, *J* 15.5, 7.0, CH), 6.77 (1H, dt, *J* 15.5, 1.5, CH), 4.65 (1H, t, *J* 6.0, NH), 2.97 (2H, m, CH_2), 2.30-2.25 (2H, m, CH_2), 1.55-1.52 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 182.2 (C), 147.9 (CH), 145.0 (C), 139.9 (C), 133.9 (CH), 132.7 (CH), 132.0 (CH), 129.2 (CH), 128.2 (CH), 127.0 (CH), 125.8 (CH), 42.9 (CH_2), 31.9 (CH_2), 29.1 (CH_2), 25.0 (CH_2); *m/z* (ESI) 350 ($M+H^+$ 100%), 372 ($M+Na^+$ 94%); *m/z* (ESI) Found 350.0875. $C_{20}H_{23}NO_4SNa^+$ requires 350.0879.

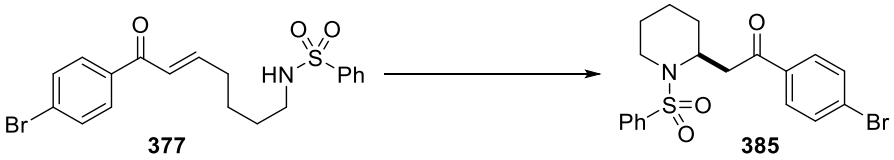
(*S*)-2-(1-((4-Nitrophenyl)sulfonyl)piperidin-2-yl)-1-phenylethan-1-one **384**



Enone **376** (77.7 mg, 0.20 mmol) and squaramide catalyst **355** (1.3 mg, 0.002 mmol) were dissolved in toluene (1.0 ml) and stirred at room temperature for 3 h. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (3 : 7 ethyl acetate : petroleum ether) to give the product **384** (60 mg, 77%) as a colourless solid. mp. 150 °C; $[\alpha]_D^{23}$ -63.5 (*c* 0.84, $CHCl_3$, 99% ee); R_f 0.3 (3 : 7 ethyl acetate : petroleum ether); ν_{max}(neat)/cm^{-1} 2948, 2870, 1684, 1532, 1350, 1159; δ_H (400 MHz, $CDCl_3$) 8.29-8.26 (2H, m, ArH), 8.00-7.97 (2H, m, ArH), 7.90-7.87 (2H, m, ArH), 7.61-7.58 (1H, m, ArH), 7.49-7.45 (2H, m, ArH), 4.77-4.74 (1H, m, CH), 3.95-3.90 (1H, m, CH_2), 3.35 (1H, dd, *J* 16.0, 9.0, CH_2), 3.23-3.12 (2H, m, CH_2), 1.69-1.54 (5H, m, CH_2), 1.42-1.33 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 197.0 (C),

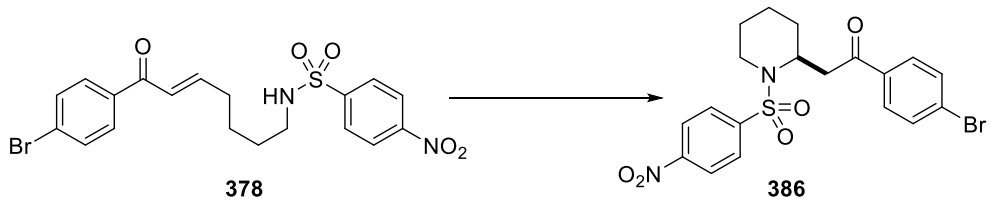
149.8 (C), 147.0 (C), 136.3 (C), 133.6 (CH), 128.8 (CH), 128.1 (CH), 124.3 (CH), 50.0 (CH), 41.8 (CH_2), 39.1 (CH_2), 28.1 (CH_2), 25.0 (CH_2), 18.4 (CH_2); *m/z* (ESI) 411 ($M+Na^+$ 100%); *m/z* (ESI) Found 411.0984. $C_{19}H_{20}N_2O_5SNa^+$ requires 411.0985; R_t HPLC (Chiralpak AD-H; 1 : 1 hexane : isopropyl alcohol, 242 nm, 1.0 ml/m) 10.7 min 99.3% (*S*)-isomer, 32.8 min 0.7% (*R*)-isomer.

(*S*)-1-(4-Bromophenyl)-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one **385**



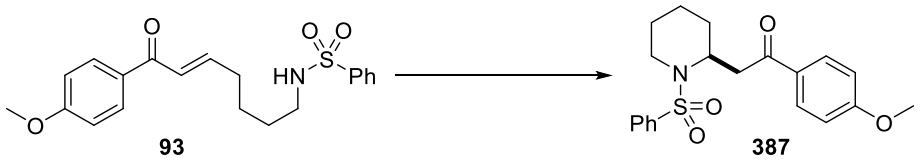
Enone **377** (82.4 mg, 0.20 mmol) and squaramide catalyst **355** (1.3 mg, 0.002 mmol) were dissolved in toluene (1.0 ml) and stirred at room temperature for 7 h. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (3 : 7 ethyl acetate : petroleum ether) to give the product **385** (70 mg, 83%) as a colourless oil. $[\alpha]_D^{23}$ -42.9 (*c* 0.9, $CHCl_3$, 98% ee); R_f 0.3 (3 : 7 ethyl acetate : petroleum ether); ν_{max}(neat)/cm^{-1} 3012, 2947, 2868, 1684, 1586, 1156, 909; δ_H (400 MHz, $CDCl_3$) 7.86-7.80 (4H, m, ArH), 7.65-7.63 (2H, m, ArH), 7.59-7.55 (1H, m, ArH), 7.52-7.48 (2H, m, ArH), 4.86-4.70 (1H, m, CH), 3.91-3.87 (1H, m, C$H_a$$H_b$), 3.33 (1H, dd, *J* 10.0, 16.0, C$H_c$$H_d$), 3.17 (1H, dd, *J* 16.0, 4.0, C$H_c$$H_d$), 3.09 (1H, ddd, *J* 13.5, 13.5, 2.5, C$H_a$$H_b$), 1.65-1.53 (5H, m, CH_2), 1.42-1.33 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 196.6 (C), 141.0 (C), 135.2 (C), 132.5 (CH), 132.0 (CH), 129.7 (CH), 129.1 (CH), 128.6 (C), 126.9 (CH), 49.5 (CH), 41.4 (CH_2), 39.1 (CH_2), 27.5 (CH_2), 24.7 (CH_2), 18.4 (CH_2); *m/z* (ESI) 446 ($M+Na^+$ (^{81}Br) 100%), 444 ($M+Na^+$ (^{79}Br) 99%); *m/z* (ESI) Found 446.0219. $C_{19}H_{20}{}^{81}BrNO_3SNa^+$ requires 446.0219; R_t HPLC (Chiralpak AD-H; 1 : 1 hexane : isopropyl alcohol, 256 nm, 1.0 ml/m) 8.9 min 99.1% (*S*)-isomer, 19.5 min 0.9% (*R*)-isomer.

(*S*)-1-(4-Bromophenyl)-2-(1-((4-nitrophenyl)sulfonyl)piperidin-2-yl)ethan-1-one **386**



Enone **378** (93.5 mg, 0.20 mmol) and squaramide catalyst **355** (1.3 mg, 0.002 mmol) were dissolved in toluene (1.0 ml) and stirred at room temperature for 0.5 h. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (3 : 7 ethyl acetate : petroleum ether) to give the product **386** (83 mg, 77%) as a colourless solid. mp. 157 °C; $[\alpha]_D^{23}$ -76.5 (*c* 0.75, $CHCl_3$, 98% ee); R_f 0.3 (3 : 7 ethyl acetate : petroleum ether); ν_{max}(neat)/cm^{-1} 3045, 2948, 2871, 1685, 1533, 1349, 1158; δ_H (400 MHz, $CDCl_3$) 8.32-8.29 (2H, m, CH_2), 8.01-7.98 (2H, m, CH_2), 7.80-7.76 (2H, m, CH_2), 7.64-7.60 (2H, m, CH_2), 4.72-4.69 (1H, m, CH), 3.92-3.88 (1H, m, CH_2), 3.33 (1H, dd, *J* 16.0, 9.0, CH_2), 3.23-3.11 (2H, m, CH_2), 1.68-1.51 (5H, m, CH_2), 1.38-1.29 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 196.1 (C), 149.9 (C), 147.0 (C), 135.0 (C), 132.1 (CH), 129.6 (CH), 128.9 (C), 128.1 (CH), 124.4 (CH), 49.9 (CH), 41.8 (CH_2), 39.3 (CH_2), 27.9 (CH_2), 24.9 (CH_2), 18.4 (CH_2); *m/z* (ESI) 491 ($M+Na^+$ (^{81}Br) 100%), 489 ($M+Na^+$ (^{79}Br) 94%); *m/z* (ESI) Found 491.0067. $C_{19}H_{19}{}^{81}BrN_2O_5SNa^+$ requires 491.0070; R_t HPLC (Chiralpak AD-H; 1 : 1 hexane : isopropyl alcohol, 260 nm, 1.0 ml/m) 13.0 min 99.0% (*S*)-isomer, 29.1 min 1.0% (*R*)-isomer.

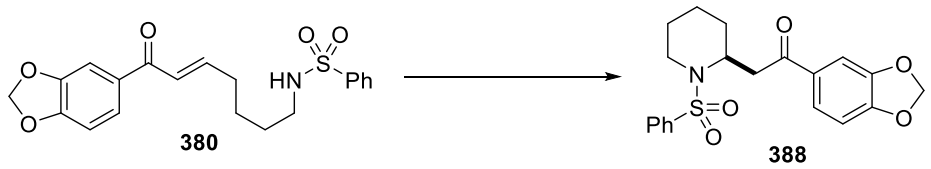
(*S*)-1-(4-Methoxyphenyl)-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one **387**



Enone **379** (74.7 mg, 0.20 mmol) and squaramide catalyst **355** (1.3 mg, 0.002 mmol) were dissolved in toluene (1.0 ml) and stirred at room temperature for 24 h. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (3 : 7 ethyl acetate : petroleum ether) to give the product **387** (62 mg, 84%) as a white solid. m.p. 96 °C; $[\alpha]_D^{23}$ -42.4 (*c* 1.0, $CHCl_3$, 99% ee); R_f 0.3 (3 : 7 ethyl acetate : petroleum ether); ν_{max}(neat)/cm^{-1} 3009, 2945, 2867, 1672, 1600, 1262, 1171, 1156; δ_H (400 MHz,

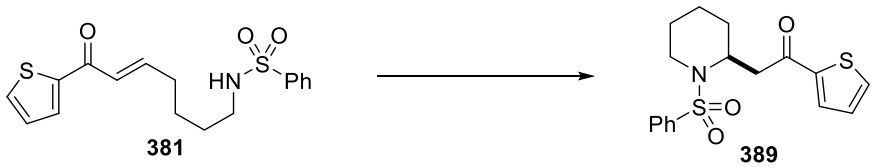
$CDCl_3$) 7.92-7.90 (2H, m, ArH), 7.85-7.83 (2H, m, ArH), 7.55-7.52 (1H, m, ArH), 7.49-7.45 (2H, m, ArH), 6.95-6.93 (2H, m, ArH), 4.69-4.66 (1H, m, CH), 3.88-3.85 (4H, m, CH_2 and CH_3), 3.29 (1H, dd, *J* 15.5, 10.5, CH_aH$_b$), 3.13-3.04 (2H, m, CH$_a$$H_b$ and CH_2), 1.63-1.48 (5H, m, CH_2), 1.40-1.30 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 196.2 (C), 163.7 (C), 141.1 (C), 132.4 (CH), 130.6 (CH), 129.6 (C) 129.1 (CH), 127.0 (CH), 113.9 (CH), 55.5 (CH_3), 49.7 (CH), 41.4 (CH_2), 38.8 (CH_2), 27.4 (CH_2), 24.8 (CH_2), 18.4 (CH_2); *m/z* (ESI) 396 (M+Na^+ 100%); *m/z* (ESI) Found 410.1030. $C_{20}H_{21}NO_5SNa^+$ requires 410.1033; R_t HPLC (Chiralpak AD-H; 1 : 1 hexane : isopropyl alcohol, 256 nm, 1.0 ml/m) 9.4 min 99.6% (*S*)-isomer, 16.9 min 0.4% (*R*)-isomer.

(*S*)-1-(Benzo[d][1,3]dioxol-5-yl)-2-(1-(phenylsulfonyl)piperidin-2-yl)ethan-1-one **388**



Enone **380** (77.5 mg, 0.20 mmol) and squaramide catalyst **355** (1.3 mg, 0.002 mmol) were dissolved in toluene (1.0 ml) and stirred at room temperature for 48 h. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (3 : 7 ethyl acetate : petroleum ether) to give the product **388** (63 mg, 81%) as a white solid. mp. 138 °C; $[\alpha]_D^{23}$ -42.9 (*c* 0.9, $CHCl_3$, 99% ee); R_f 0.4 (3 : 7 ethyl acetate : petroleum ether); ν_{max}(neat)/cm^{-1} 3011, 2946, 2870, 1674, 1445, 1252, 1158; δ_H (400 MHz, $CDCl_3$) 7.85-7.83 (2H, m, ArH), 7.56-7.46 (4H, m, ArH), 7.39 (1H, d, *J* 1.0, ArH), 6.86 (1H, d, *J* 8.0, ArH), 6.06 (2H, s, CH_2), 4.67-4.62 (1H, m, CH), 3.89-3.85 (1H, m, CH_aH$_b$), 2.31-3.24 (1H, dd, *J* 15.5, 10.5, CH_2), 3.11-3.03 (2H, m, CH_2), 1.62-1.50 (5H, m, CH_2), 1.40-1.32 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 195.6 (C), 152.0 (CH), 148.3 (C), 141.1 (C), 132.4 (CH), 131.5 (C), 129.1 (CH), 127.0 (CH), 124.6 (CH), 107.9 (CH), 101.9 (CH_2), 49.8 (CH), 41.4 (CH_2), 38.8 (CH_2), 27.4 (CH_2), 24.8 (CH_2), 18.4 (CH_2); *m/z* (ESI) 410 (M+Na^+ 100%); *m/z* (ESI) Found 410.1030. $C_{20}H_{21}NO_5SNa^+$ requires 410.1033; R_t HPLC (Chiralpak AD-H; 1 : 1 hexane : isopropyl alcohol, 256 nm, 1.0 ml/m) 9.4 min 99.8% (*S*)-isomer, 16.9 min 0.2% (*R*)-isomer.

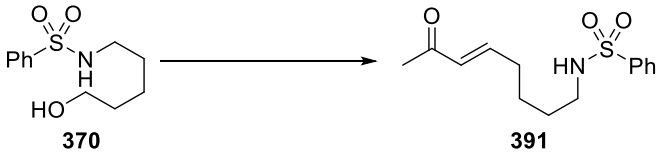
(*S*)-2-(1-(Phenylsulfonyl)piperidin-2-yl)-1-(thiophen-2-yl)ethan-1-one **389**



381 389

Enone **381** (69.9 mg, 0.20 mmol) and squaramide catalyst **355** (1.3 mg, 0.002 mmol) were dissolved in toluene (1.0 ml) and stirred at room temperature for 6 h. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (3 : 7 ethyl acetate : petroleum ether) to give the product **389** (46 mg, 73%) as a white solid. mp. 73 °C; $[\alpha]_D^{23}$ -16.5 (*c* 0.9, $CHCl_3$, 99% ee); R_f 0.3 (3 : 7 ethyl acetate : petroleum ether); ν_{max}(neat)/cm^{-1} 2947, 2867, 1659, 1416, 1156; δ_H (400 MHz, $CDCl_3$) 7.86-7.83 (2H, m, ArH), 7.75 (1H, *J* 4.0, 1.0, dd, ArH), 7.65 (1H, dd, *J* 5.0, 1.0, ArH), 7.56-7.52 (1H, m, ArH), 7.50-7.46 (2H, m, ArH), 7.14 (1H, dd, *J* 5.0, 4.0, ArH), 4.69-4.66 (1H, m, CH), 3.88-3.84 (1H, m, CH_aH$_b$), 3.27 (1H, dd, J 15.0, 10.5, CH_cH$_d$), 3.13-3.03 (2H, m, CH$_a$$H_b$ and CH$_c$$H_d$), 1.67-1.52 (5H, m, CH_2), 1.42-1.32 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 190.4 (C), 144.1 (C), 141.0 (C), 134.2 (CH), 132.5 (CH), 129.1 (CH), 128.3 (CH), 127.0 (CH), 49.9 (CH), 41.4 (CH_2), 39.9 (CH_2), 27.5 (CH_2), 24.8 (CH_2), 18.3 (CH_2); *m/z* (ESI) 372 (M+Na^+ 100%) 350 (M+H^+ 68%); *m/z* (ESI) Found 372.0691. $C_{17}H_{19}NO_3S_2Na^+$ requires 372.0699; R_t HPLC (Chiralpak AD-H; 1 : 1 hexane : isopropyl alcohol, 261 nm, 1.0 ml/m) 6.6 min 99.5% (*S*)-isomer, 27.5 min 0.5% (*R*)-isomer.

(*E*)-N-(7-Oxooct-5-en-1-yl)benzenesulfonamide **391**

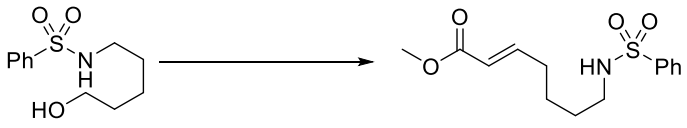


370 391

N-(5-Hydroxypentyl)benzenesulfonamide (0.49 g, 2.01 mmol) and methyl(triphenylphosphorane)methyl ketone (1.28 g, 4.03 mmol) were dissolved in chloroform (20 ml). 3 Å powdered molecular sieves (2 g) followed by manganese dioxide (0.87 g, 10.1 mmol) were added. The mixture was then heated at reflux for 48 h, cooled to rt, diluted with diethyl ether (10 ml), and filtered through Celite. The resulting solution was then concentrated under reduced pressure and the residue dissolved in minimum amount hot ethyl acetate. After cooling to rt the precipitated phosphine oxide was removed by filtration. The filtrand was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (2 : 1 petroleum ether : ethyl

acetate). The resulting product was further purified by recrystallisation from ethyl acetate / petroleum ether to give the product **391** (0.15 g, 26%) as a colourless solid. mp 62 °C; R_f 0.2 (2 : 1 petroleum ether : ethyl acetate); ν_{max}(neat)/cm^{-1} 3276, 2938, 2865, 1670, 1625, 1447, 1363, 1159; δ_H (400 MHz, $CDCl_3$) 7.89-7.86 (2H, m, ArH), 7.61-7.57 (1H, m, ArH), 7.54-7.50 (2H, m, ArH), 6.72 (1H, dt, *J* 16.0, 7.0, CH), 6.03 (1H, dt, *J* 16.0, 1.5, CH), 4.79 (1H, t, *J* 6.0, NH), 2.97 (2H, td, *J* 6.5, 6.0, CH_2), 2.23 (3H, s, CH_3), 2.18 (2H, dtd, *J* 7.0, 7.0, 1.5 Hz, CH_2), 1.53-1.45 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 198.6 (C), 147.3 (CH), 140.0 (C), 132.7 (CH), 131.6 (CH), 129.2 (CH), 127.0 (CH), 42.9 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 27.0 (CH_3), 24.9 (CH_2); *m/z* (ESI) 304 (M+Na$^+$ 100%), 282 (M+H$^+$ 17%); *m/z* (ESI) Found 304.0961. $C_{14}H_{19}NO_3SNa^+$ requires 304.0978.

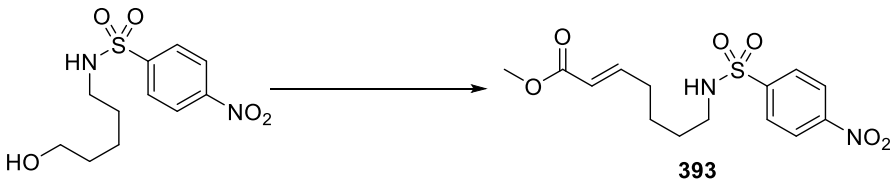
Methyl (*E*)-7-(phenylsulfonamide)hept-2-enoate **392**



370 **392**

N-(5-Hydroxypentyl)benzenesulfonamide (0.50 g, 2.10 mmol) and methyl(triphenylphosphoranylidene)acetate (1.10 g, 3.40 mmol) were dissolved in chloroform (20 ml). 3 Å powdered molecular sieves (2 g) followed by manganese dioxide (0.89 g, 10.3 mmol) were added. The mixture was then heated at reflux for 48 h, cooled to rt, diluted with diethyl ether (10 ml), and filtered through Celite. The resulting solution was then concentrated under reduced pressure and the residue dissolved in minimum amount hot ethyl acetate. After cooling to rt the precipitated phosphine oxide was removed by filtration. The filtrand was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (2 : 1 petroleum ether : ethyl acetate) to give product **392** (0.28 g, 46%) as a low melting clear solid. R_f 0.2 (2 : 1 petroleum ether : ethyl acetate); ν_{max}(neat)/cm^{-1} 3284, 2948, 1720, 1655, 1447, 1326, 1159; δ_H (400 MHz, $CDCl_3$) 7.89-7.86 (2H, m, ArH), 7.62-7.58 (1H, m, ArH), 7.56-7.51 (2H, m, ArH), 6.88 (1H, dt, *J* 15.5, 7.0, CH), 5.78 (1H, dt, *J* 15.5, 1.5, CH), 4.43 (1H, br s, NH), 3.20 (3H, s, CH_3), 2.98 (2H, dt, *J* 7.0, 7.0, CH_2N), 2.19-2.14 (2H, m, CH_2), 1.54-1.42 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 166.9 (C), 148.4 (CH), 140.0 (C), 132.7 (CH), 129.2 (CH), 127.0 (CH), 121.5 (CH), 51.5 (CH_3), 42.9 (CH_2), 31.5 (CH_2), 29.1 (CH_2) 24.9 (CH_2); *m/z* (ESI) 320 (M+Na$^+$ 100%); *m/z* (ESI) Found 320.0913. $C_{14}H_{19}NO_4SNa^+$ requires 320.0927.

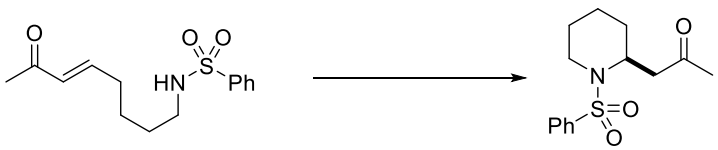
Methyl (*E*)-7-(4-nitrophenylsulfonamide)hept-2-enoate **393**



393

N-(5-Hydroxypentyl)-4-nitrobenzenesulfonamide (1.22 g, 4.23 mmol) and methyl(triphenylphosphoranylidene)acetate (2.67 g, 8.00 mmol) were suspended in a solution of toluene (20 ml). 3 Å powdered molecular sieves (2 g) followed by manganese dioxide (2.61 g, 30 mmol) were added. The mixture was heated at 70 °C for 48 h, cooled to rt and filtered through Celite. The resulting solution was then concentrated under reduced pressure and the residue dissolved in minimum amount hot ethyl acetate (10 ml). After cooling to rt the precipitated phosphine oxide was removed by filtration. The filtrand was concentrated under reduced pressure and the residue purified by column chromatography on silica gel (1 : 2 ethyl acetate : petroleum ether). The resulting product was further purified by recrystallisation from ethyl acetate / petroleum ether to give the product **393** (0.38 g, 26%) as a colourless solid. mp. 100 °C; R_f 0.2 (1 : 2 ethyl acetate : petroleum ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 3392, 3045, 2950, 2867, 1718, 1534, 1350, 1166; δ_H (400 MHz, $CDCl_3$) 8.40-8.37 (2H, m, ArH), 8.08-8.05 (2H, m, ArH), 6.88 (1H, dt, *J* 15.5, 7.0, CH), 5.79 (1H, dt, *J* 15.5, 1.0, CH), 4.74 (1H, t, *J* 6.0, NH), 3.73 (3H, s, CH_3), 3.06-3.01 (2H, m, CH_2), 2.22-2.17 (2H, m, CH_2), 1.57-1.43 (4H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 166.9 (C), 150.1 (C), 148.2 (CH), 146.0 (C), 128.3 (CH), 124.5 (CH), 121.6 (CH), 51.5 (CH_3), 43.1 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 24.9 (CH_2); *m/z* (ESI) 365 ($M+Na^+$ 100%); *m/z* (ESI) Found 365.0765. $C_{14}H_{18}N_2O_6SNa^+$ requires 365.0778.

1-(1-(Benzenesulfonyl)piperidin-2-yl)-2-propanone **394**

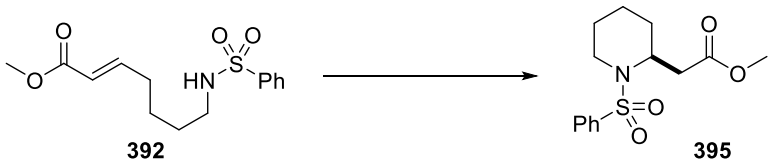


391 **394**

Enone **391** (28.1 mg, 0.1 mmol) and squaramide catalyst **355** (3.2 mg, 0.005 mmol) were dissolved in toluene (0.5 ml) then heated to 80 °C for 4 h. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (1 : 2 ethyl acetate : petroleum ether) to give the product **394** (23 mg, 82%) as a colourless solid. mp. 75 °C; $[\alpha]_D^{25}$ -22.1

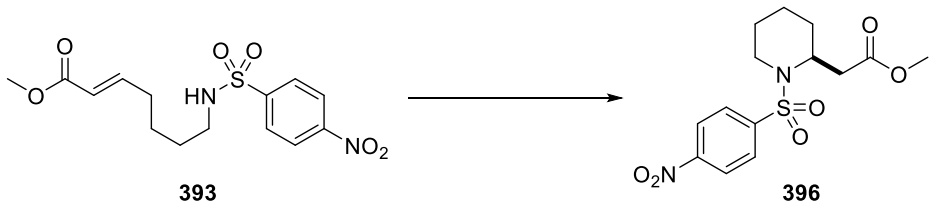
(*c* 0.74, $CHCl_3$, 90% ee); R_f 0.3 (1 : 2 ethyl acetate : petroleum ether); ν_{max}(neat)/cm^{-1} 2940, 2863, 1712, 1446; δ_H (400 MHz, $CDCl_3$) 7.85-7.82 (2H, m, ArH), 7.59-7.55 (1H, m, ArH), 7.53-7.49 (2H, m, ArH), 4.56-4.52 (1H, m, CH), 3.84-3.79 (1H, m, CH_2), 2.96 (1H, ddd, *J* 14.0, 13.0, 2.5, CH_2), 2.80 (1H, dd, *J* 16.5, 9.5, CH_2), 2.59 (1H, dd, *J* 16.5, 4.5 CH_2), 2.12 (3H, s, CH_3), 1.57-1.26 (6H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 205.9 (C), 141.1 (C), 132.4 (CH), 129.1 (CH), 127.0 (CH), 48.8 (CH), 44.0 (CH_2), 41.3 (CH_2), 30.3 (CH_3), 27.8 (CH_2), 24.6 (CH_2), 18.4 (CH_2); *m/z* (ESI) 304 (M+Na^+ 100%), 282 (M+H^+ 47%); *m/z* (ESI) Found 304.0962. $C_{14}H_{19}NO_3SNa^+$ requires 304.0978; R_t HPLC (Chiralpak AD-H; 9 : 1 hexane : isopropyl alcohol, 235 nm, 1.0 ml/m) 15.3 min 95.0% (*S*)-isomer, 20.0 min 5.0% (*R*)-isomer.

Methyl 2-(1-(phenylsulfonyl)piperidin-2-yl)acetate **395**



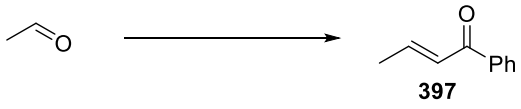
Ester **392** (30 mg, 0.10 mmol) and squaramide catalyst **355** (6.3 mg, 0.01 mmol) were dissolved in toluene (0.5 ml) then heated to 80 °C for 7 days. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (1 : 2 ethyl acetate : petroleum ether) to give the product **395** (21 mg, 71%) as a colourless oil. $[\alpha]_D^{25}$ -11.1 (*c* 0.45, $CHCl_3$, 92% ee); R_f 0.3 (1 : 2 ethyl acetate : petroleum ether); ν_{max}(neat)/cm^{-1} 2926, 2854, 1735, 1446; δ_H (400 MHz, $CDCl_3$) 7.86-7.84 (2H, m, ArH), 7.58-7.49 (3H, m, ArH), 4.57-4.54 (1H, m, CHN), 3.83 (1H, dd, *J* 13.5, 3.5, C$H_a$$H_b$), 3.64 (3H, s, CH_3), 3.01-2.94 (1H, m, $CH_a$$H_b$), 2.64 (1H, dd, *J* 15.0, 9.0, CH_2), 2.52 (1H, dd, *J* 15.0, 6.0, CH_2), 1.59-1.29 (6H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 171.2 (C), 141.2 (C), 132.4 (CH), 129.1 (CH), 127.0 (CH), 51.8 (CH_3), 49.8 (CH), 41.0 (CH_2), 35.0 (CH_2), 27.2 (CH_2), 24.6 (CH_2), 18.3 (CH_2); *m/z* (ESI) 320 [(M+Na^+ 100%), 298 (M+H^+ 81%), (M_2+Na^+ 29%)]; *m/z* (ESI) Found 320.0905. $C_{14}H_{19}NO_4SNa^+$ requires 320.0927; R_t HPLC (Chiralpak AD-H; 9 : 1 hexane : isopropyl alcohol, 245 nm, 1.0 ml/m) 14.2 min 96.0% (*S*)-isomer, 18.0 min 4.0% (*R*)-isomer.

Methyl 2-(1-(4-nitrophenylsulfonyl)piperidin-2-yl)acetate **396**



Ester **393** (34.2 mg, 0.10 mmol) and squaramide catalyst **355** (6.3 mg, 0.01 mmol) were dissolved in toluene (0.5 ml) then heated to 80 °C for 7 days. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (3 : 7 ethyl acetate : petroleum ether) to give the product **396** (25 mg, 73%) as a colourless solid; mp. 80 °C; $[\alpha]_D^{23}$ -25.1 (*c* 0.75, $CHCl_3$, 88%ee); R_f 0.3 (3 : 7 ethyl acetate : petroleum ether); ν_{max}(neat)/cm^{-1} 2951, 2872, 1735, 1533, 1349, 1160, 909; δ_H (400 MHz, $CDCl_3$) 8.37-8.34 (2H, m, ArH), 8.05-8.02 (2H, m, ArH), 4.60-4.56 (1H, m, CH), 3.88-3.83 (1H, m, CH_2), 3.65 (3H, s, CH_3), 3.04 (1H, ddd, *J* 14.0, 14.0, 2.0, CH_2), 2.65 (1H, dd, *J* 15.0, 6.5, CH_2), 2.56 (1H, dd, *J* 15.0, 6.5, CH_2), 1.63-1.52 (5H, m, CH_2), 1.37-1.27 (1H, m, CH_2); δ_c (100 MHz, $CDCl_3$) 170.9 (C), 147.2 (C), 128.2 (CH), 124.4 (CH), 52.0 (CH_3), 50.2 (CH), 41.3 (CH_2), 35.3 (CH_2), 28.0 (CH_2), 24.8 (CH_2), 18.2 (CH_2); *m/z* (ESI) 365 ($M+Na^+$ 100%), 343 ($M+H^+$ 94%); *m/z* (ESI) Found 365.0774. $C_{14}H_{18}N_2O_6SNa^+$ requires 365.0778; R_t HPLC (Chiralpak AD-H; 1 : 1 hexane : isopropyl alcohol, 273 nm, 1.0 ml/m) 8.8 min 93.8% (*S*)-isomer, 11.0 min 6.2% (*R*)-isomer.

(*E*)-1-Phenylbut-2-en-1-one **397**[149]



Benzoylmethylenetriphenylphosphorane (1.0 g, 2.6 mmol) was dissolved in dichloromethane (10 ml) under an Ar atmosphere. The solution was cooled to 4 °C and acetaldehyde (0.3 ml, 5.3 mmol) was added. The solution was stirred for 2 h then concentrated under reduced pressure. The residue was diluted with diethyl ether (20 ml) and filtered. The solution was then concentrated under reduced pressure and the residue purified by column chromatography (1 : 9 diethyl ether : petroleum ether) to give the product **397** (0.07 g, 18%) as a low melting solid. ν_{max}(neat)/cm^{-1} 3010, 1668, 1625, 1298, 909; δ_H (400 MHz, $CDCl_3$) 7.94-7.92 (2H, m, ArH), 7.58-7.54 (1H, m, ArH), 7.49-7.46 (2H, m, ArH), 7.08 (1H, dq, *J* 15.0, 7.0, CH), 6.92 (1H, dq, *J* 15.0, 1.5, CH), 2.01 (3H, dd, *J* 7.0, 1.5,

CH_3); δ_c (100 MHz, $CDCl_3$) 190.8 (C), 145.1 (CH), 137.9 (C), 132.6 (CH), 128.5 (CH), 127.6 (CH), 18.6 (CH_3); *m/z* (ESI) 147 ($M+Na^+$ 100%); *m/z* (ESI) Found 147.0796. $C_{10}H_{11}O^+$ requires 147.0804. The ^1H and ^{13}C NMR data are in agreement with those previously reported.[149]

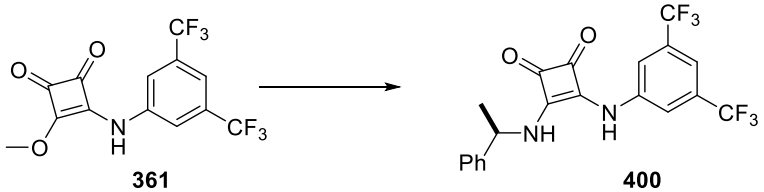
Methyl 4-nitrophenylsulfonamide **398**[150]



398

4-Nitrobenzenesulfonyl chloride (0.50 g, 2.26 mmol) and Methylamine solution 30% wt. in H_2O (5.0 ml) were shaken in a vial for 10 mins. The mixture was then extracted with dichloromethane (2 x 10 ml), the combined organics were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by recrystallisation from ethyl acetate / petroleum ether giving the product **398** (0.39 g, 80%) as a colourless solid. m.p. 108 °C (lit.,[150] m.p. 105 °C); ν_{max}(neat)/cm^{-1} 3394, 3012, 1534, 1350, 1168; δ_H (400 MHz, $CDCl_3$) 8.41-8.37 (2H, m, ArH), 8.09-8.05 (2H, m, ArH), 4.62 (1H, br s, NH), 2.75 (3H, d, *J* 4.5, CH_3); δ_c (100 MHz, $CDCl_3$) 150.2 (C), 144.9 (C), 128.5 (CH), 124.5 (CH), 29.3 (CH_3); *m/z* (ESI) 239 ($M+Na^+$ 100%); *m/z* (ESI) Found 239.0101. $C_7H_8N_2O_4SNa^+$ requires 239.0097. The ^1H and ^{13}C NMR data are in agreement with those previously reported.[150]

3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-((2R)-2-phenylethylamine)cyclobut-3-ene-1,2-dione **400**



361 **400**

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (50.0 mg, 0.15 mmol) and (*R*)-α-methylbenzylamine (21.4 mg, 0.18 mmol) in ethanol (2 ml) were heated at reflux for 30 mins. The mixture was then allowed to cool to rt and the product **400** (44 mg, 70%) was collected by filtration as a colourless solid. m.p. 279 °C; $[\alpha]_D^{24}$ -4.8 (*c* 0.80, $(CH_3)_2SO$); δ_H (400 MHz, DMSO) 10.09 (1H, br s, NH), 8.17 (1H, br s, NH), 8.01 (2H, s, ArH), 7.67 (1H, s, ArH), 7.44-7.30 (5H, m, ArH), 5.27-5.35 (1H, m, CH), 1.61 (3H, d, *J* 7.0, CH_3); δ_C (125 MHz, DMSO) 184.9 (C), 181.1 (C), 169.3 (C), 163.1 (C), 143.4 (C),

141.5 (C), 131.8 (C, q, *J* 32.5), 129.2 (CH), 128.1 (CH), 126.6 (CH), 123.6 (C, q, *J* 271.0), 118.6 (CH), 115.3 (CH), 53.9 (CH), 23.3 (CH_3); *m/z* (ESI) 451 [($M+Na^+$, 100%) 429 ($M+H^+$, 75%) *m/z* (ESI) Found 451.0860. $C_{20}H_{14}F_6N_2O_2Na^+$ requires 451.0852.

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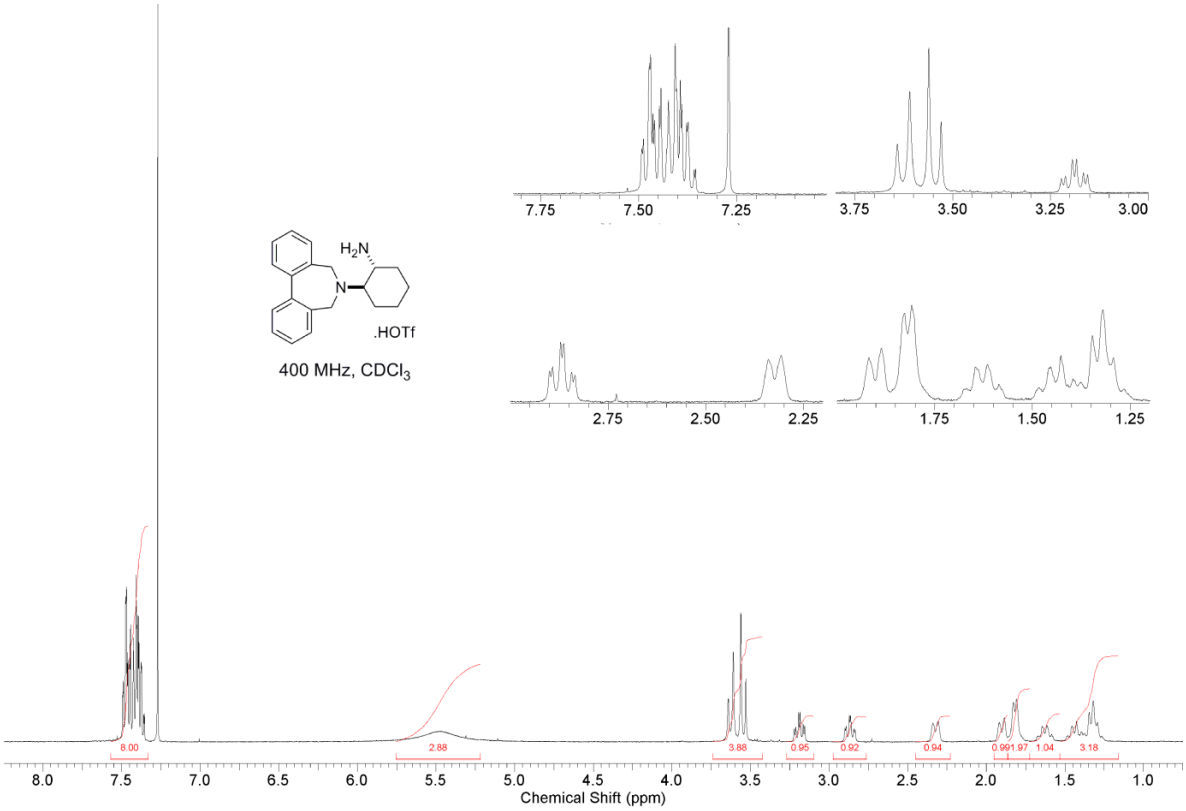
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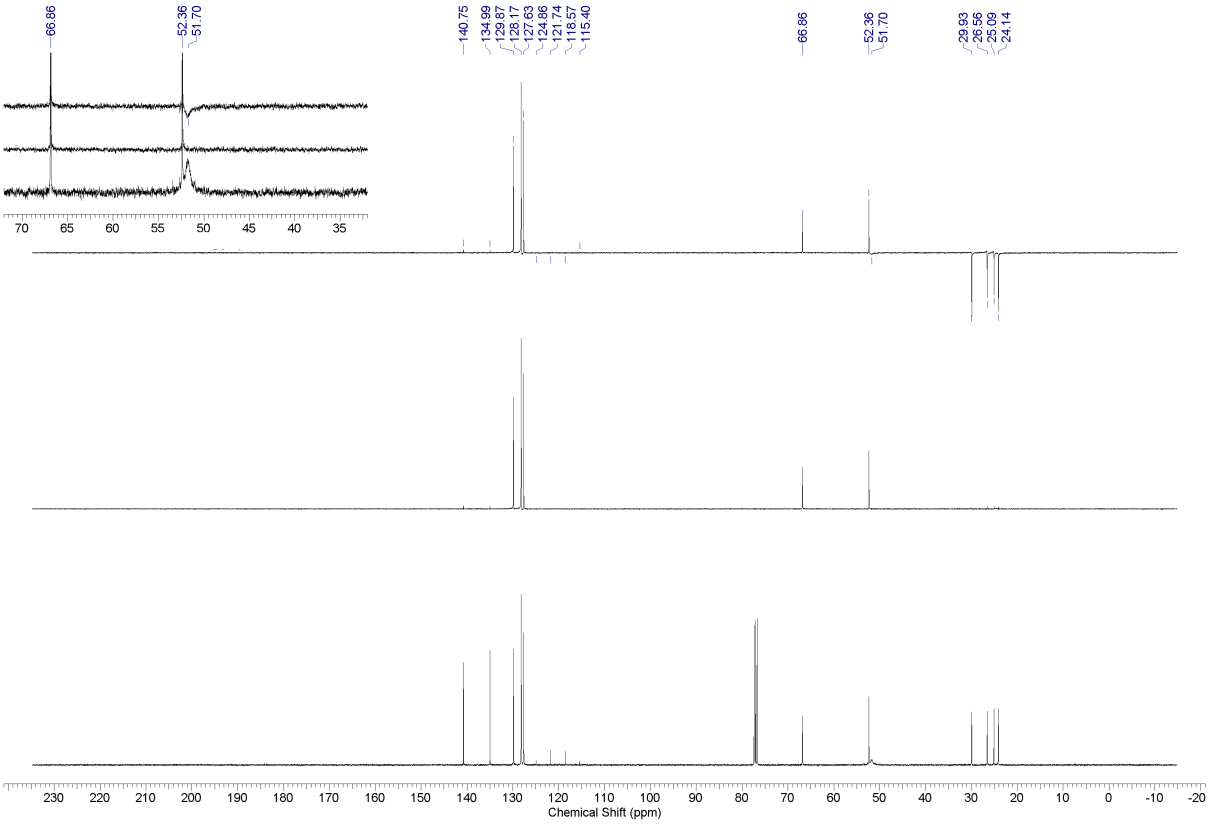
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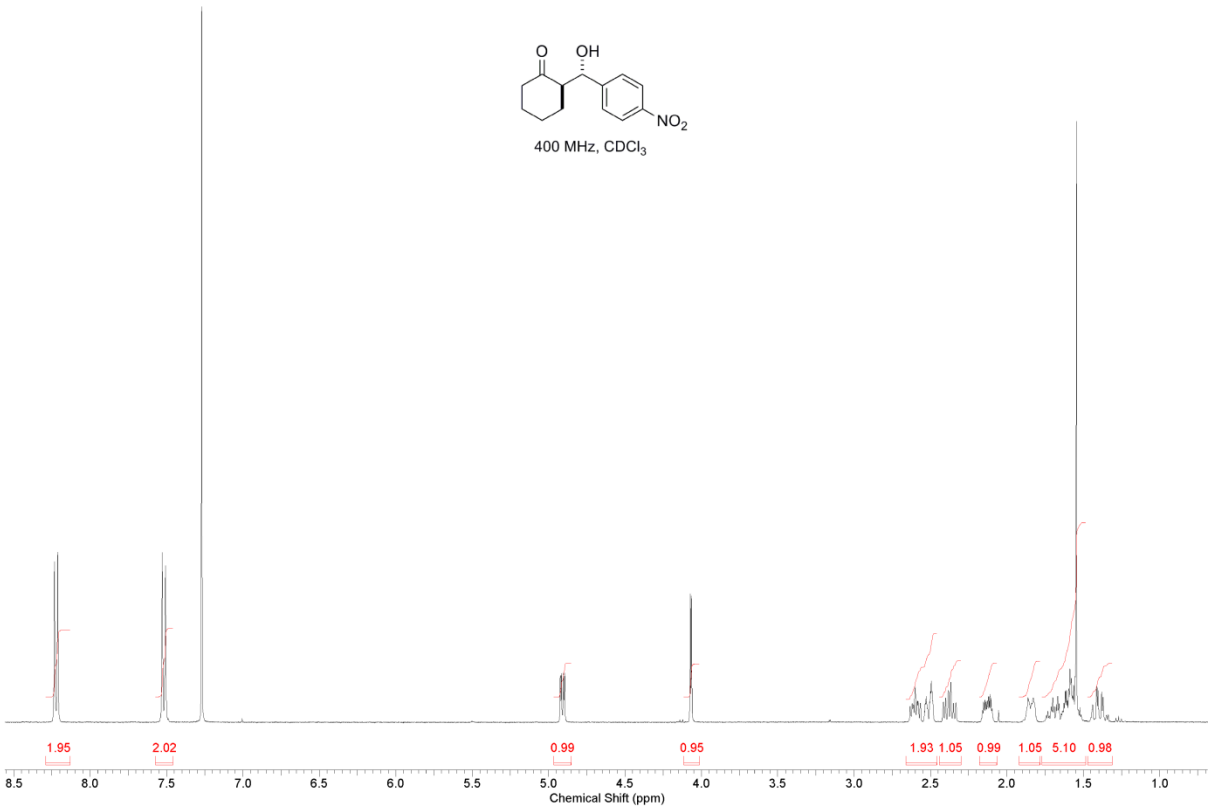
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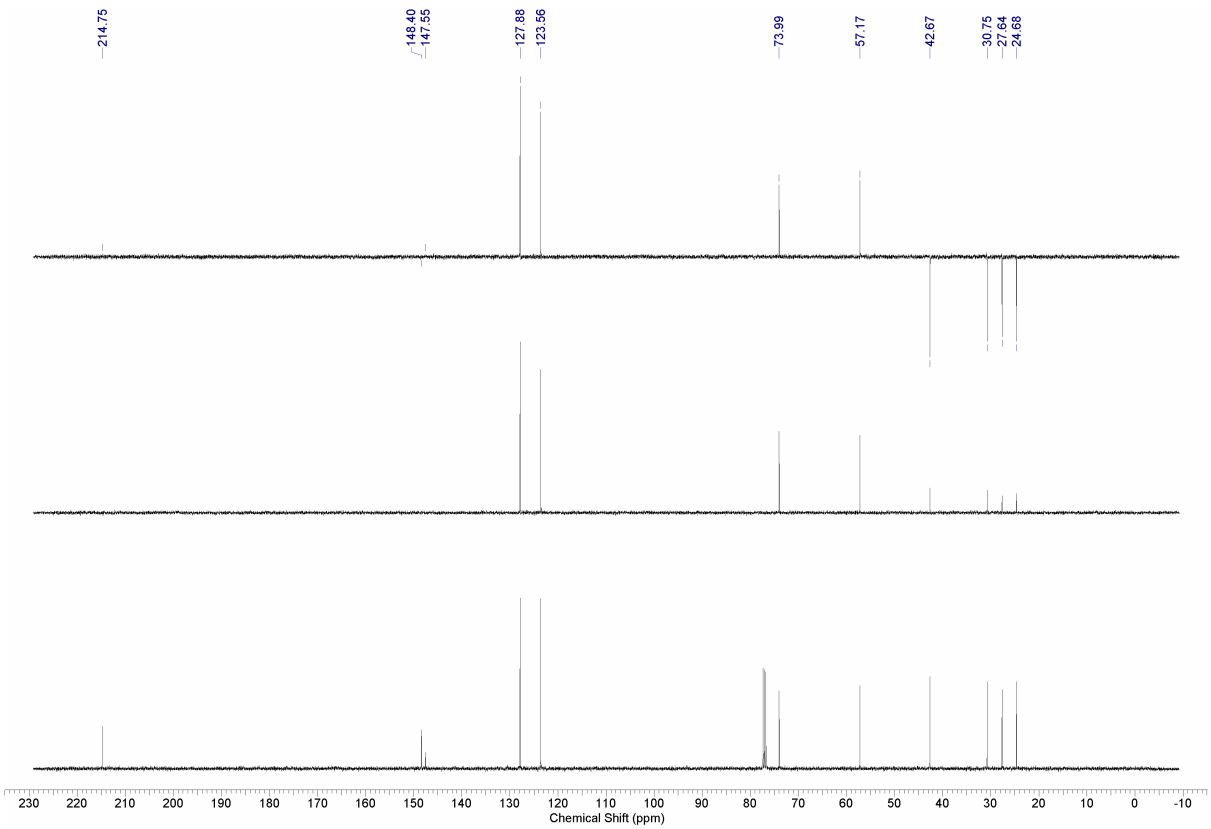
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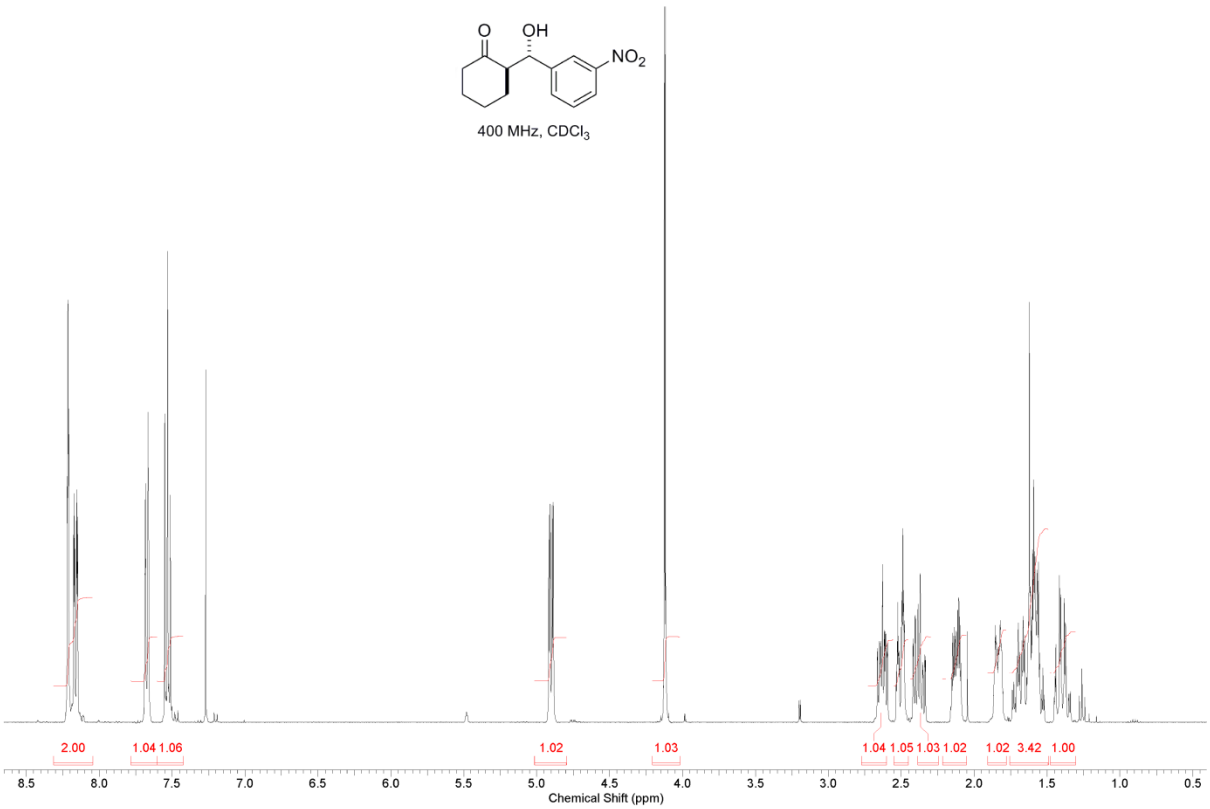
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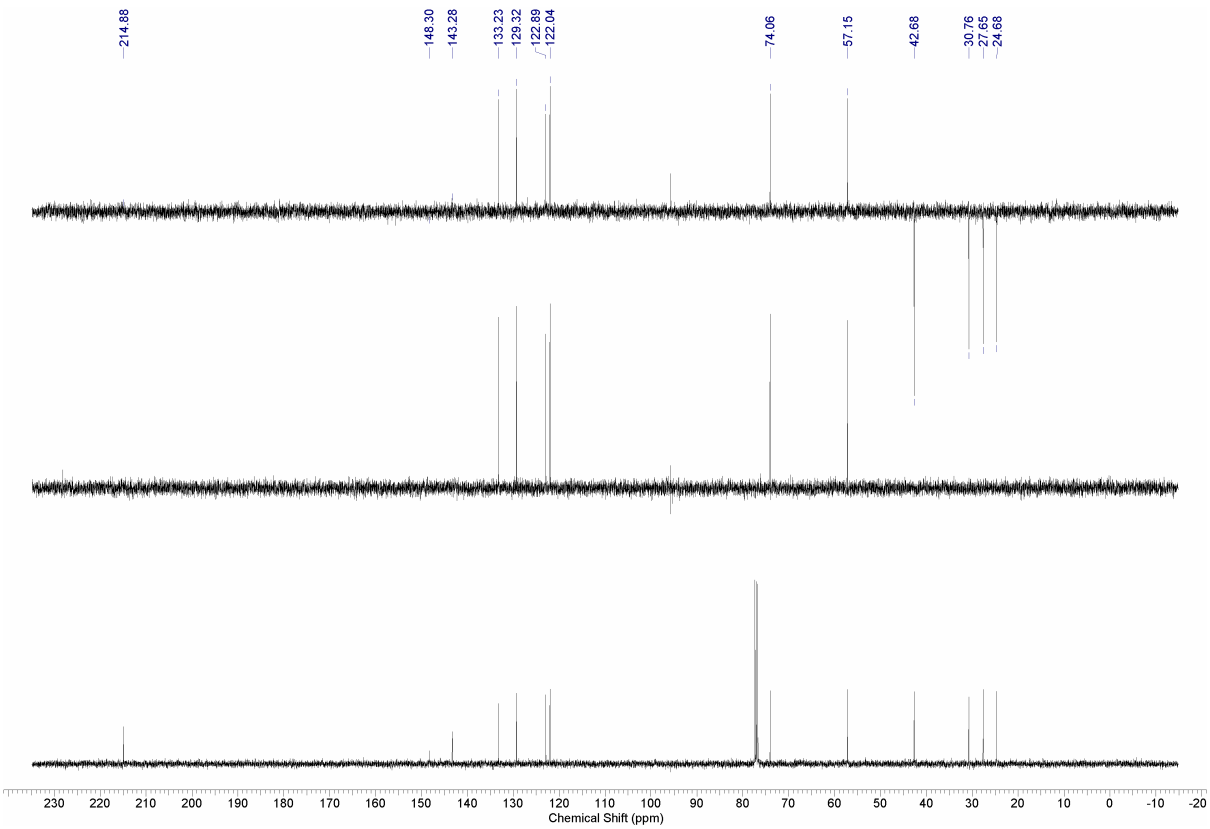


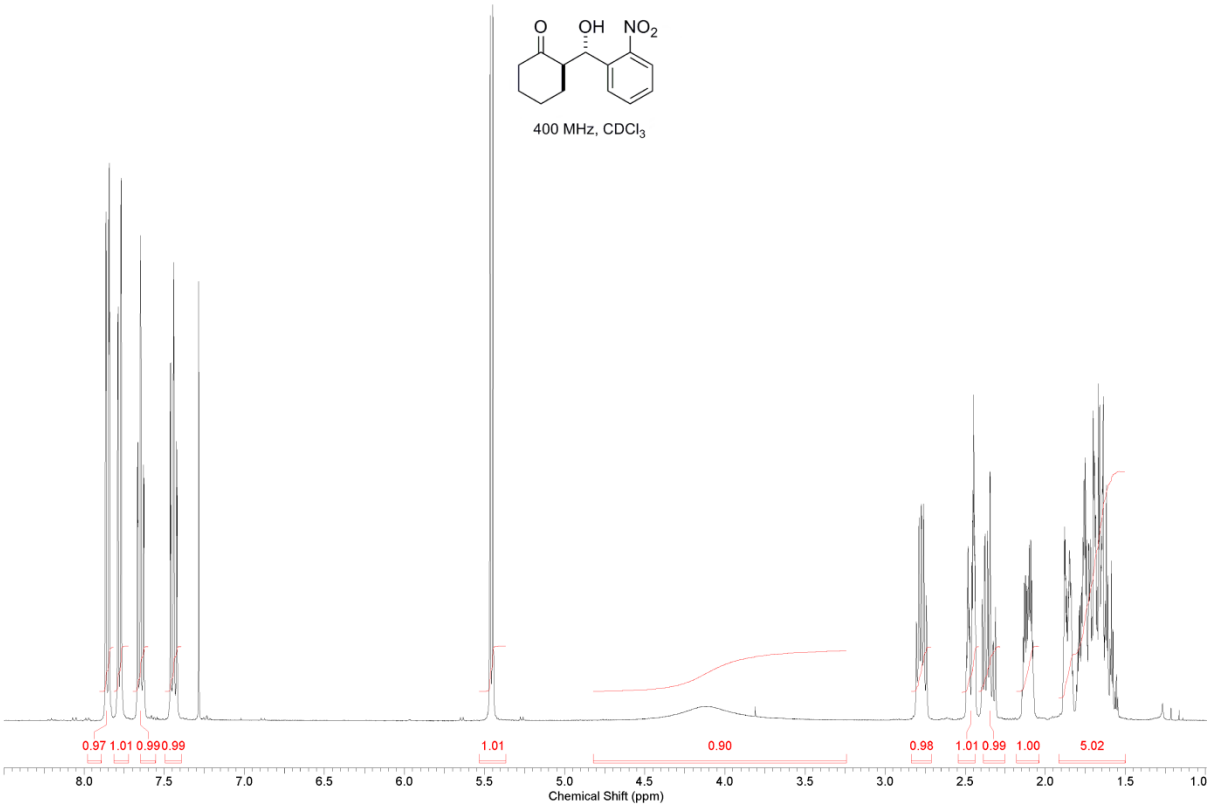


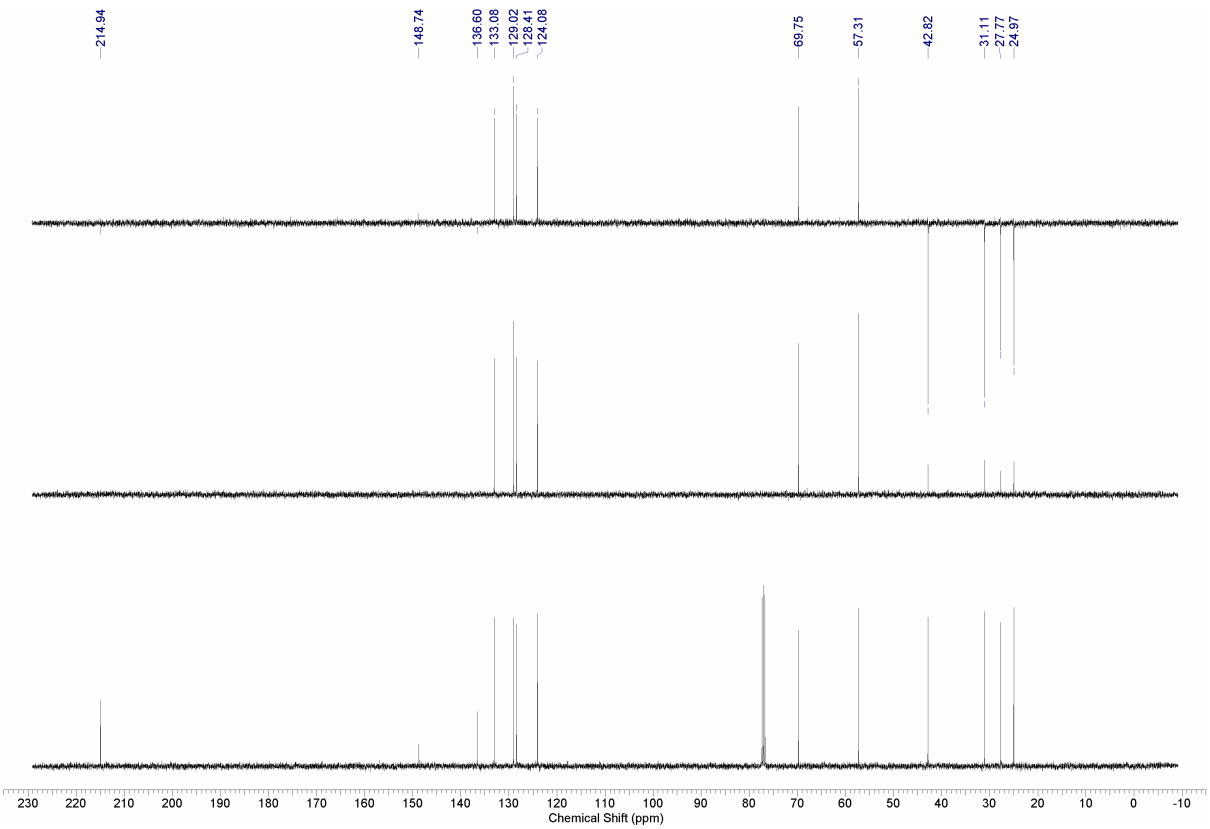

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1.05
5.10
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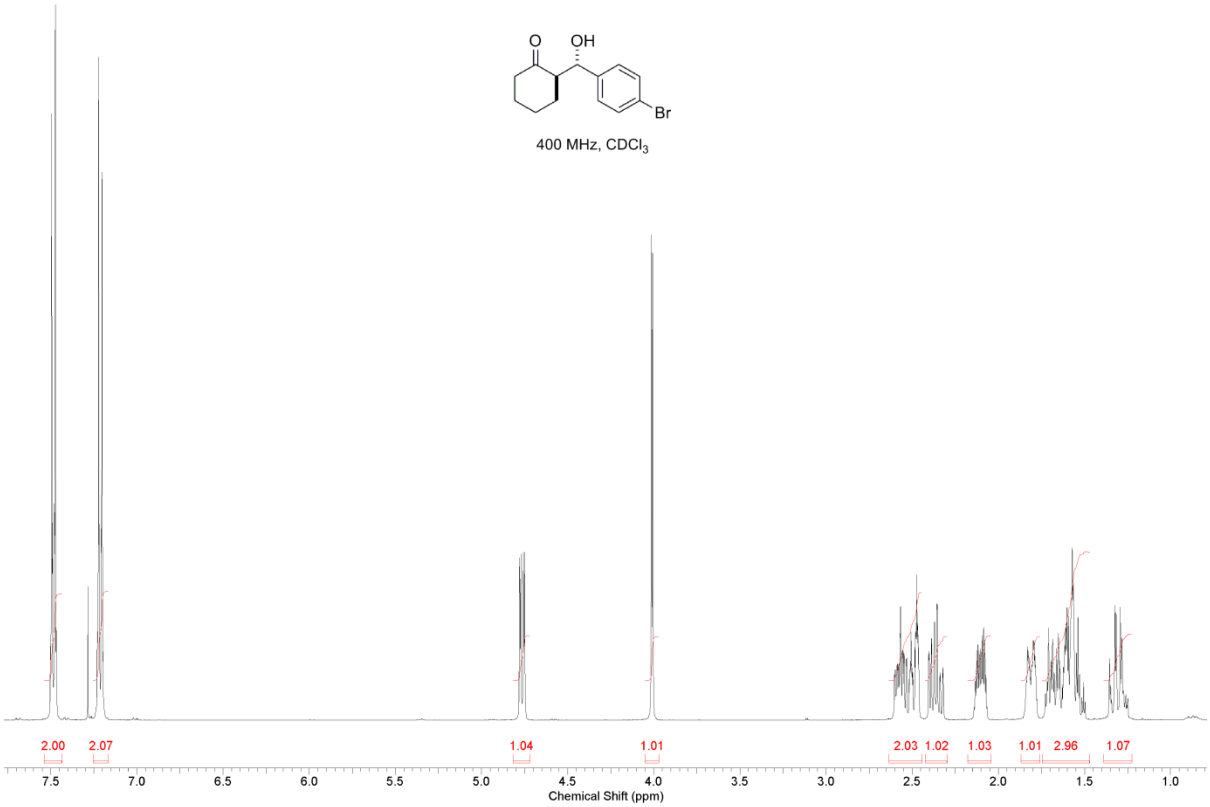

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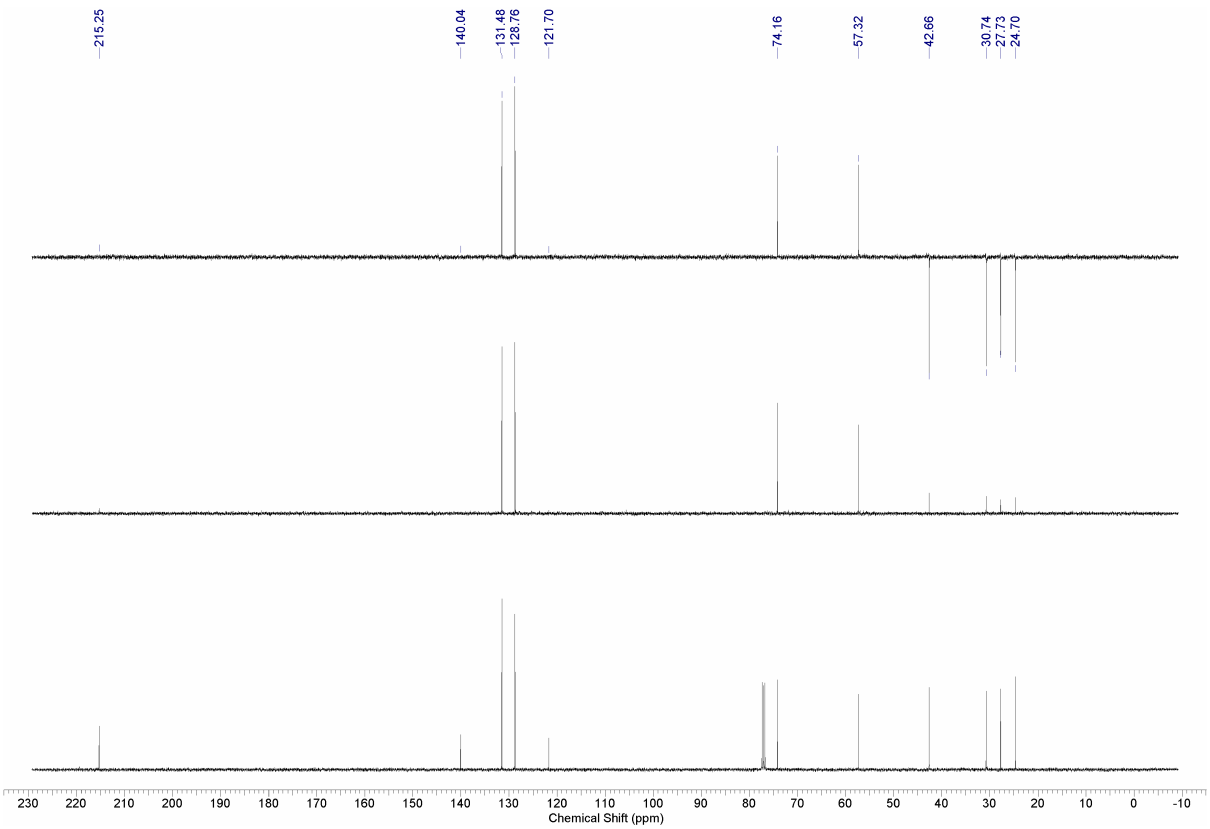

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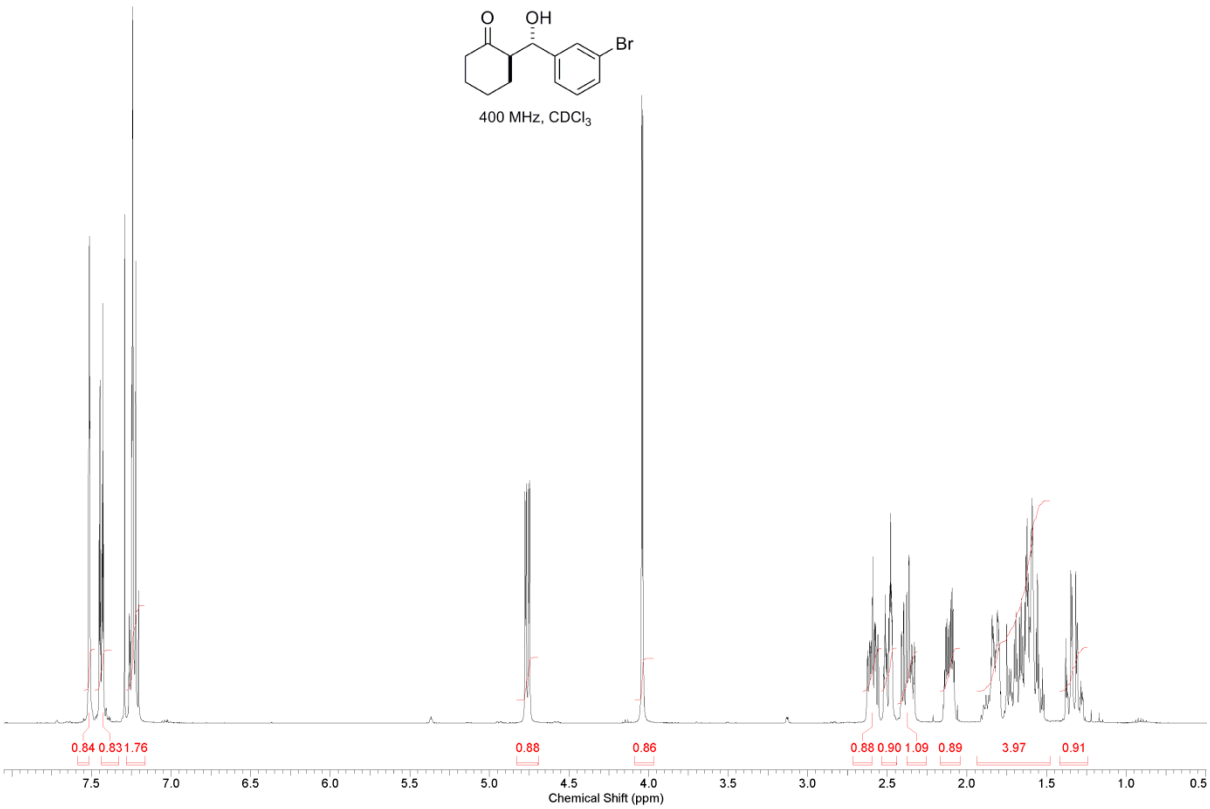

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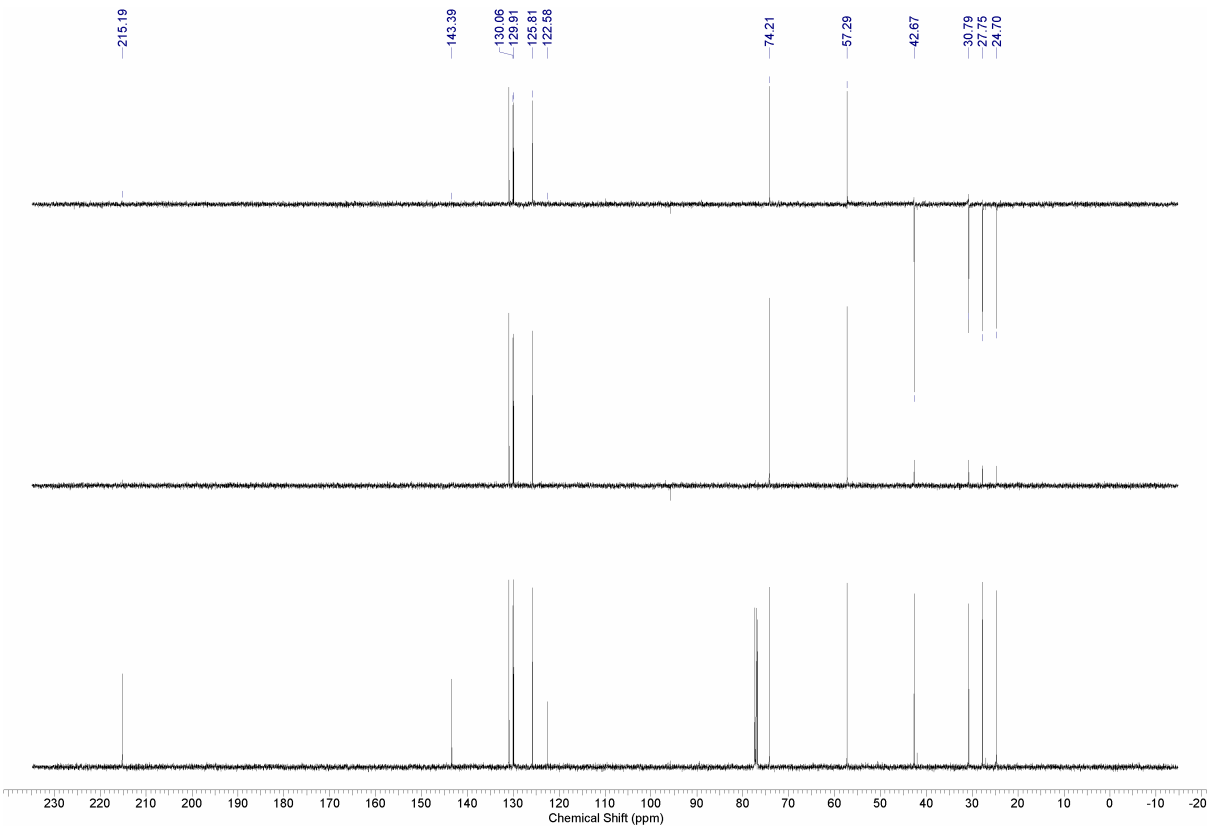

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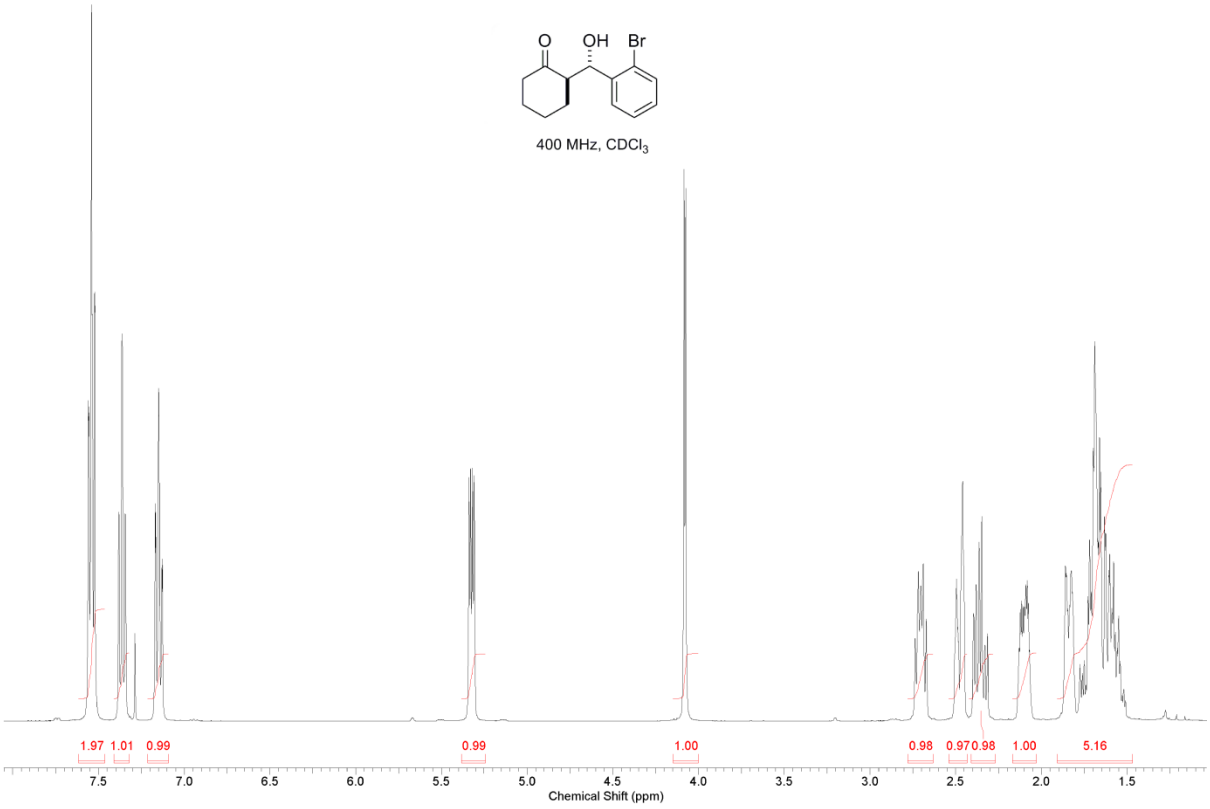

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27.77
24.97
Chemical Shift (ppm)

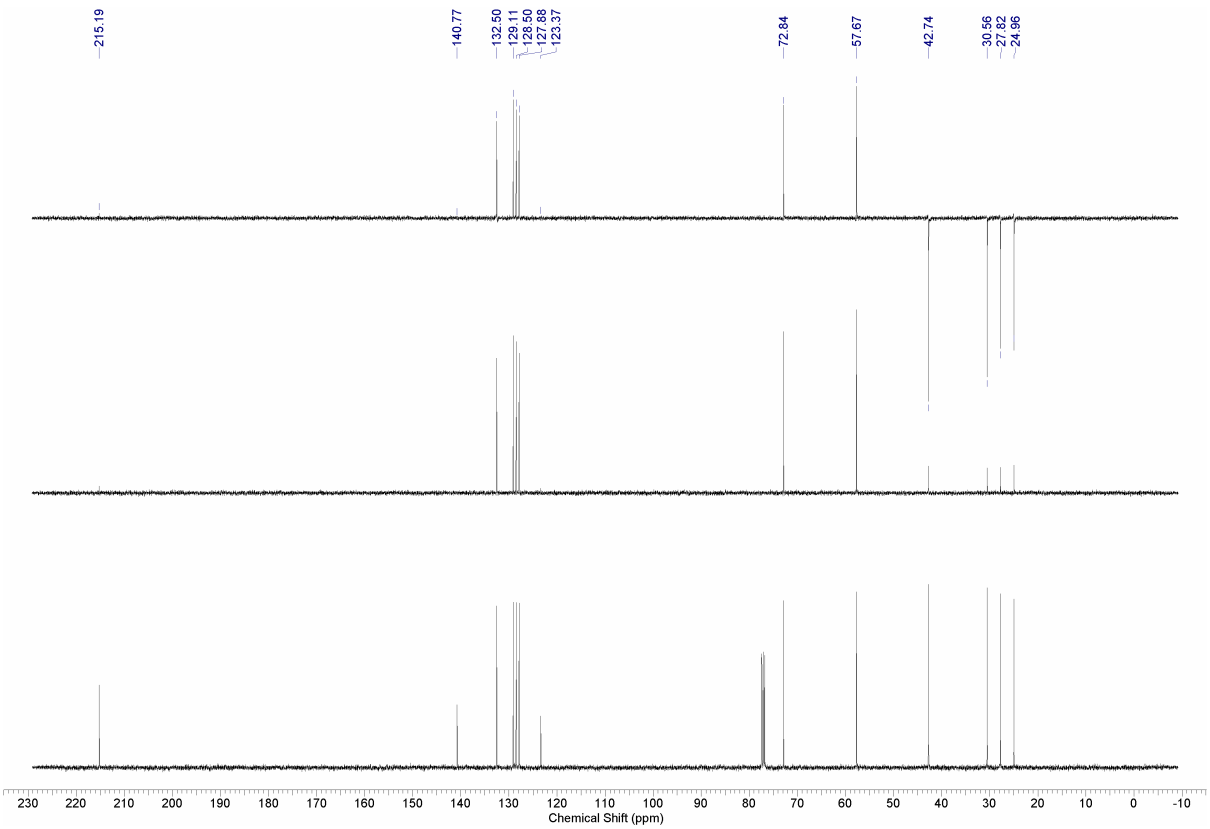

O
OH
Br
400 MHz, CDCl3
2.00
2.07
1.04
1.01
2.03
1.02
1.03
1.01
2.96
1.07
Chemical Shift (ppm)

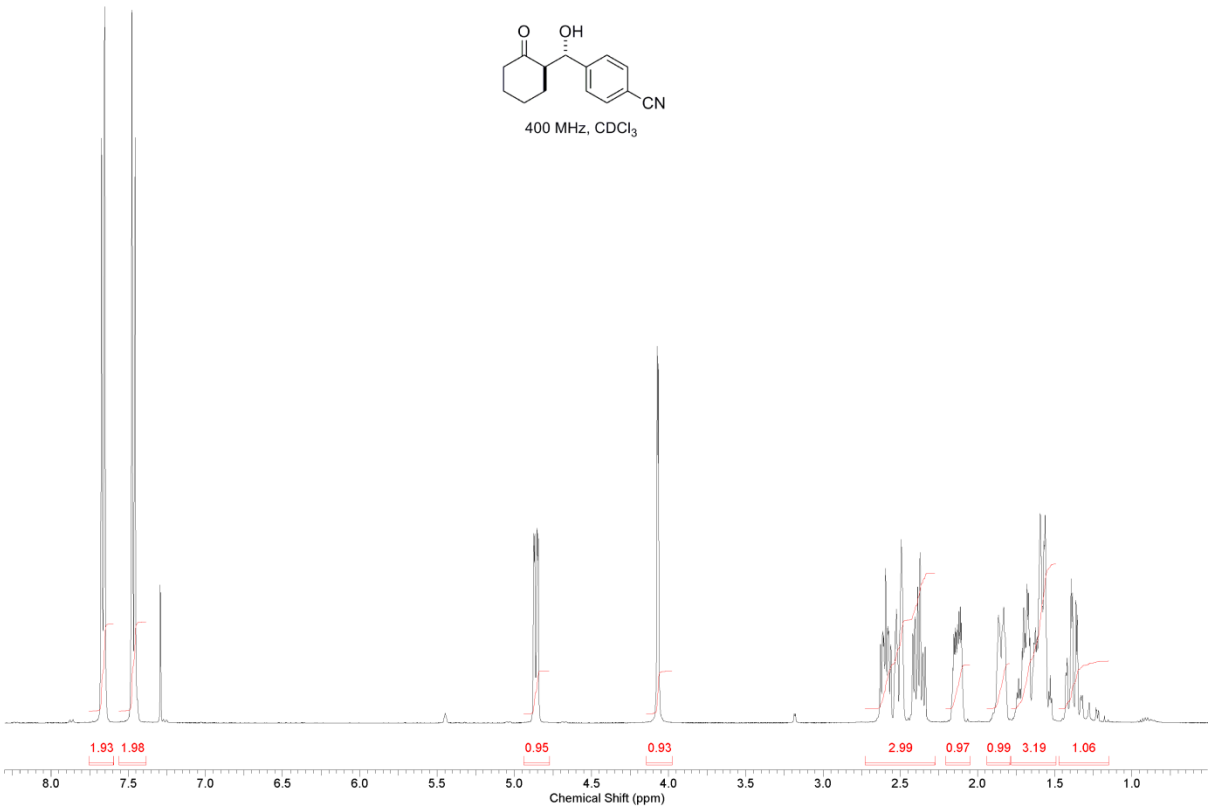

215.25
140.04
131.48
128.76
121.70
74.16
57.32
42.66
30.74
27.73
24.70
Chemical Shift (ppm)

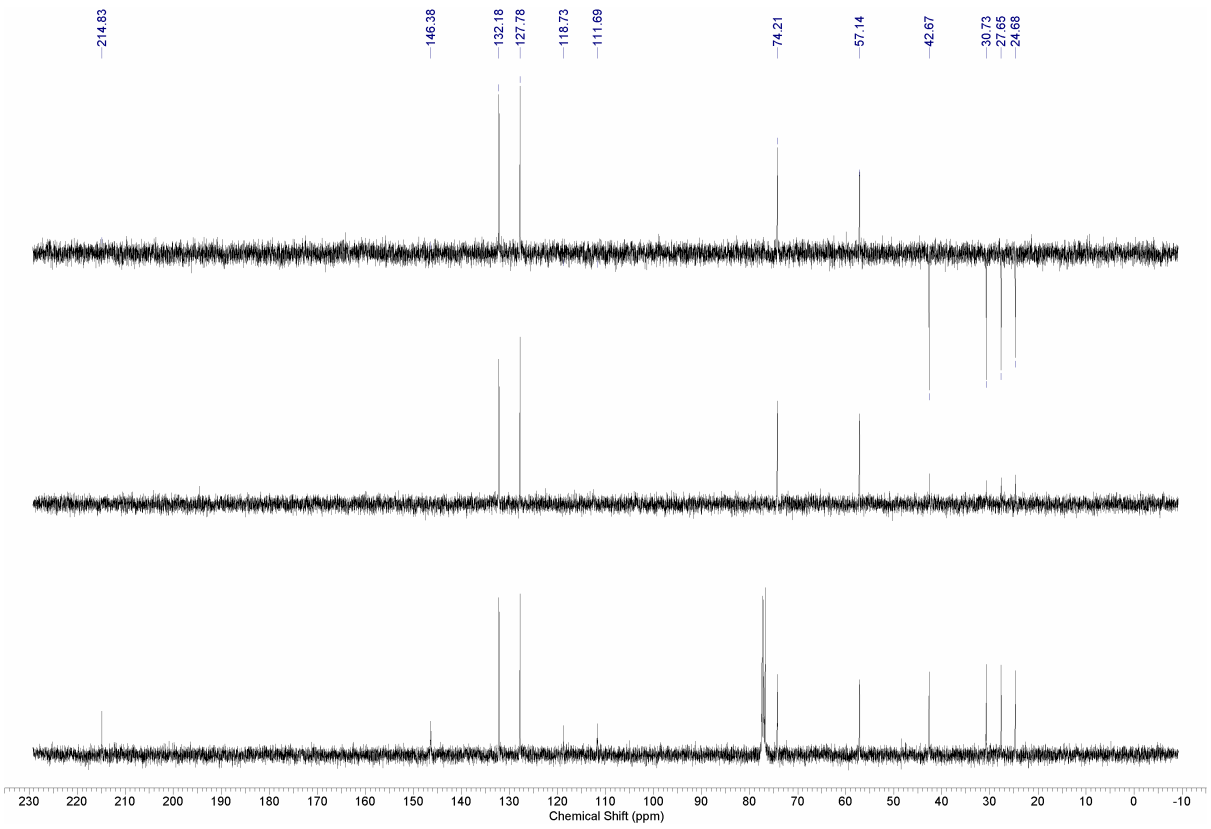

O
OH
Br
400 MHz, CDCl3
0.84 0.83 1.76
0.88
0.86
0.88 0.90 1.09 0.89
3.97
0.91
Chemical Shift (ppm)

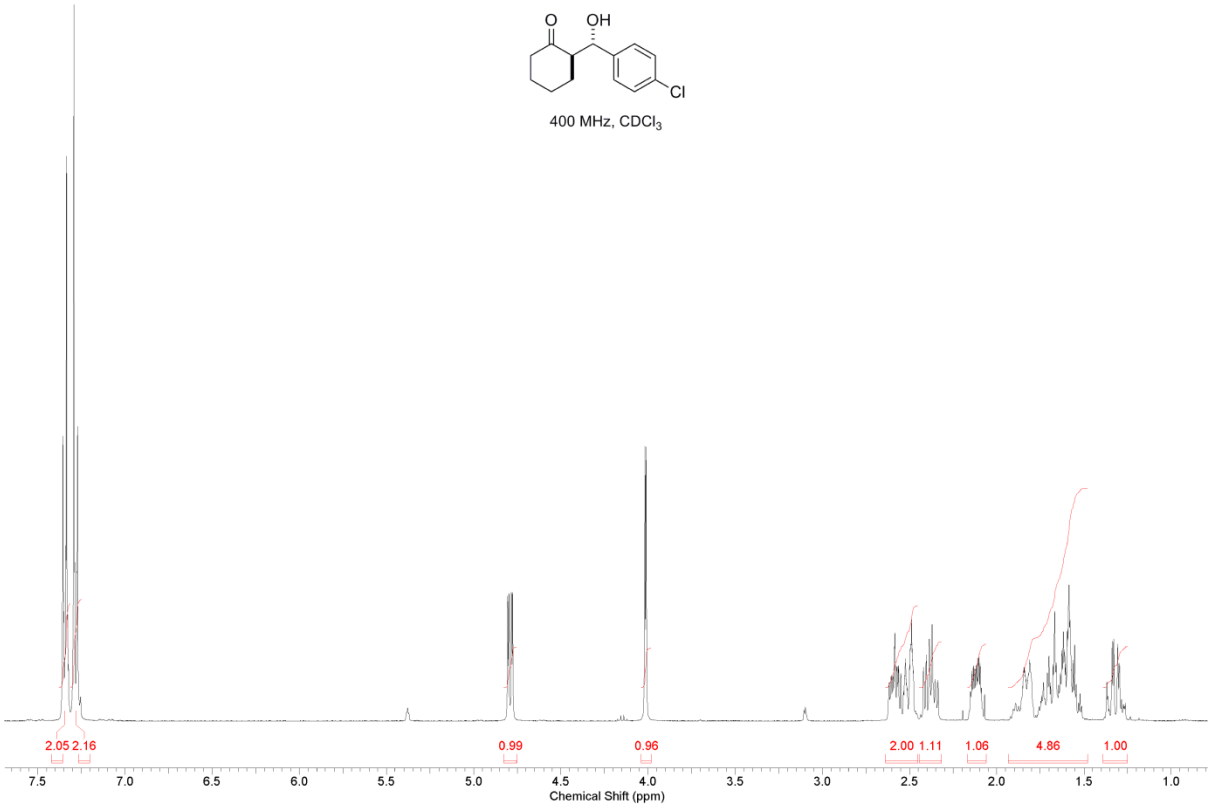

215.19
143.39
130.06
129.91
125.81
122.58
74.21
57.29
42.67
30.79
27.75
24.70
Chemical Shift (ppm)

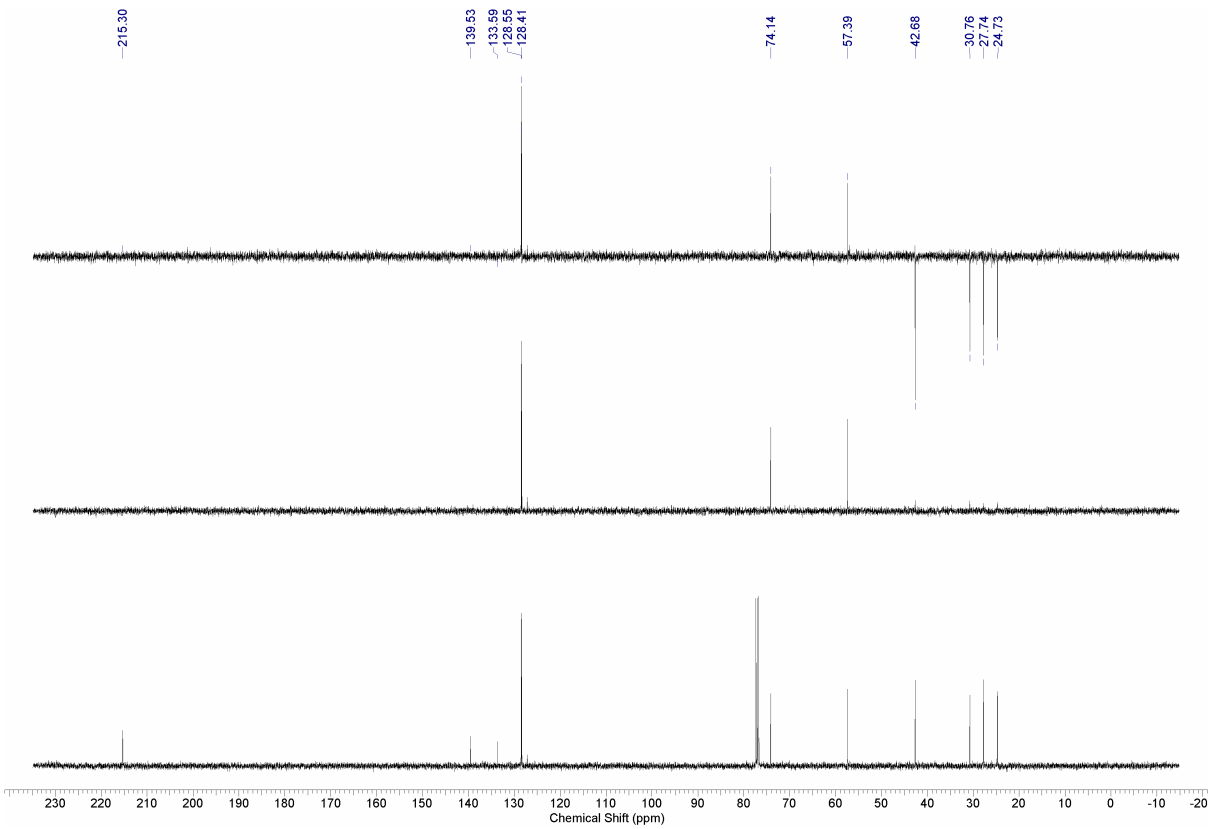

O
OH
Br
400 MHz, CDCl3
1.97
1.01
0.99
0.99
1.00
0.98
0.97
0.98
1.00
5.16
Chemical Shift (ppm)

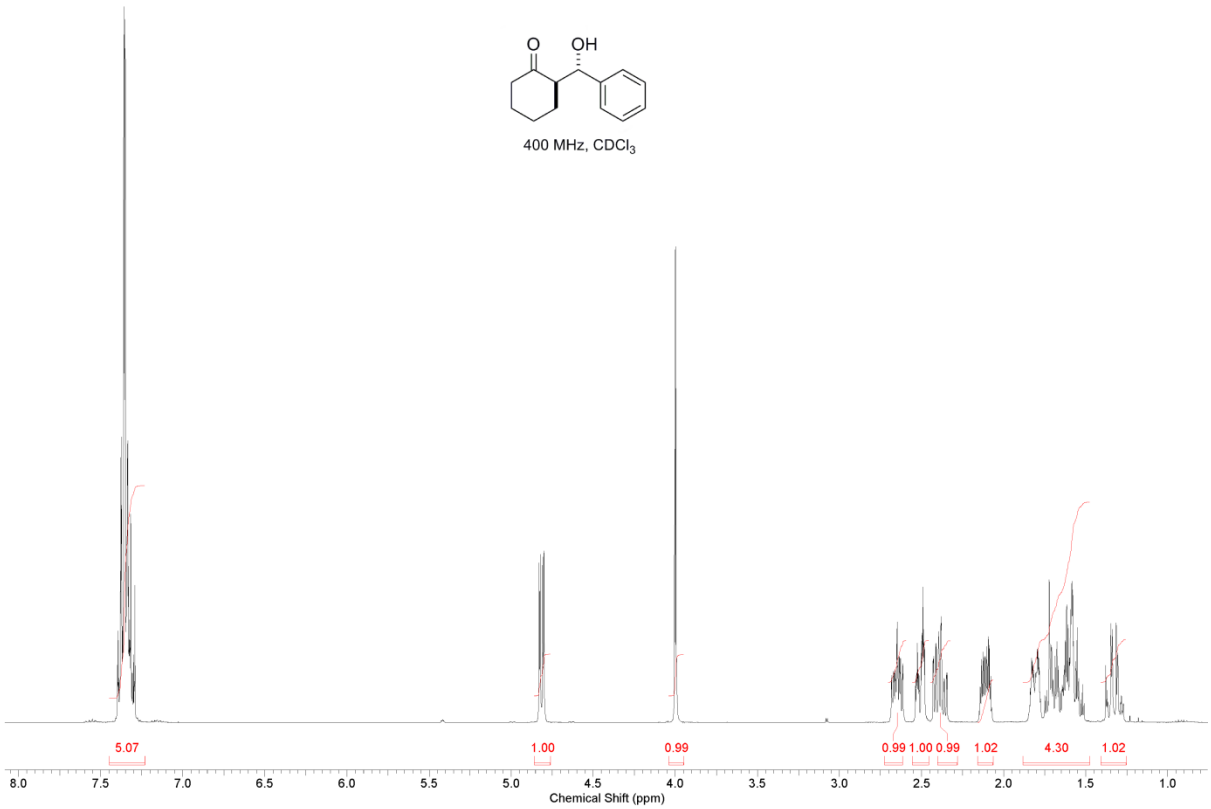

215.19
140.77
132.50
129.11
128.50
127.88
123.37
72.84
57.67
42.74
30.56
27.82
24.96
Chemical Shift (ppm)

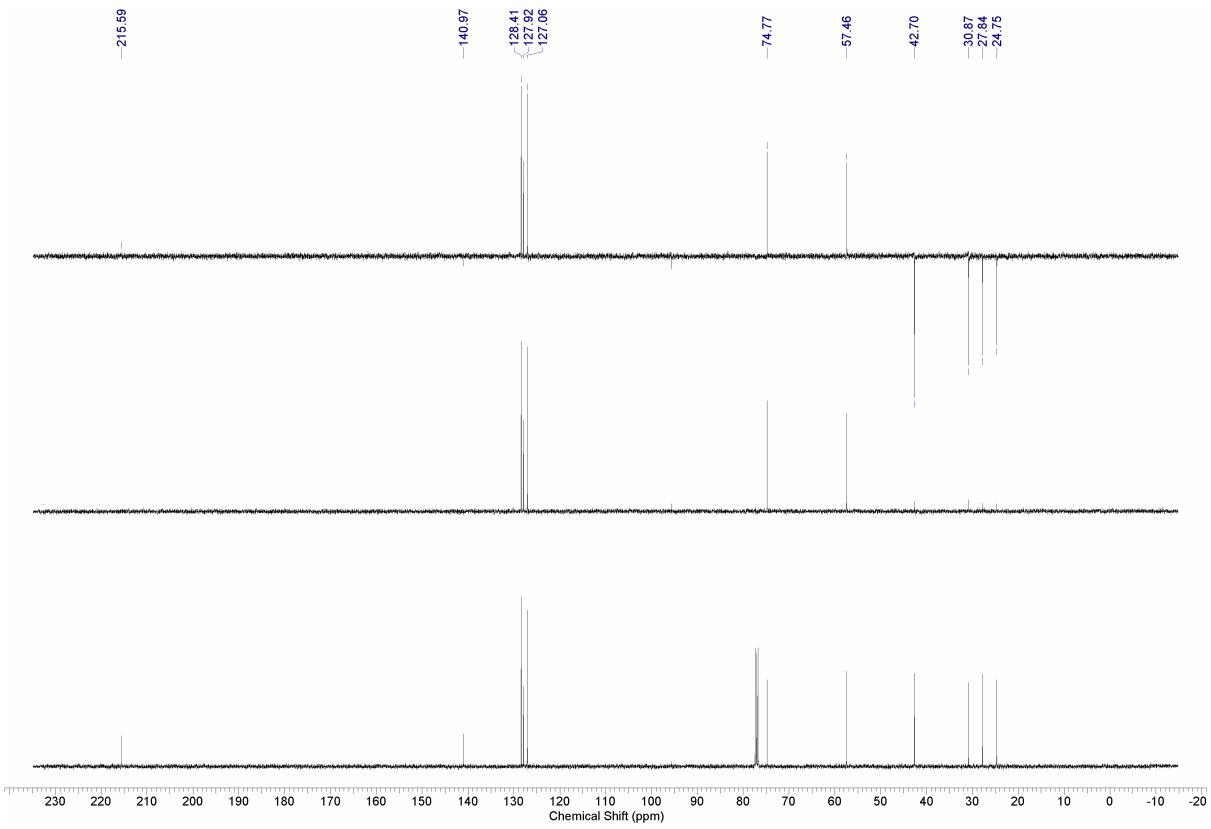

O
OH
CN
400 MHz, CDCl3
1.93
1.98
0.95
0.93
2.99
0.97
0.99
3.19
1.06
Chemical Shift (ppm)

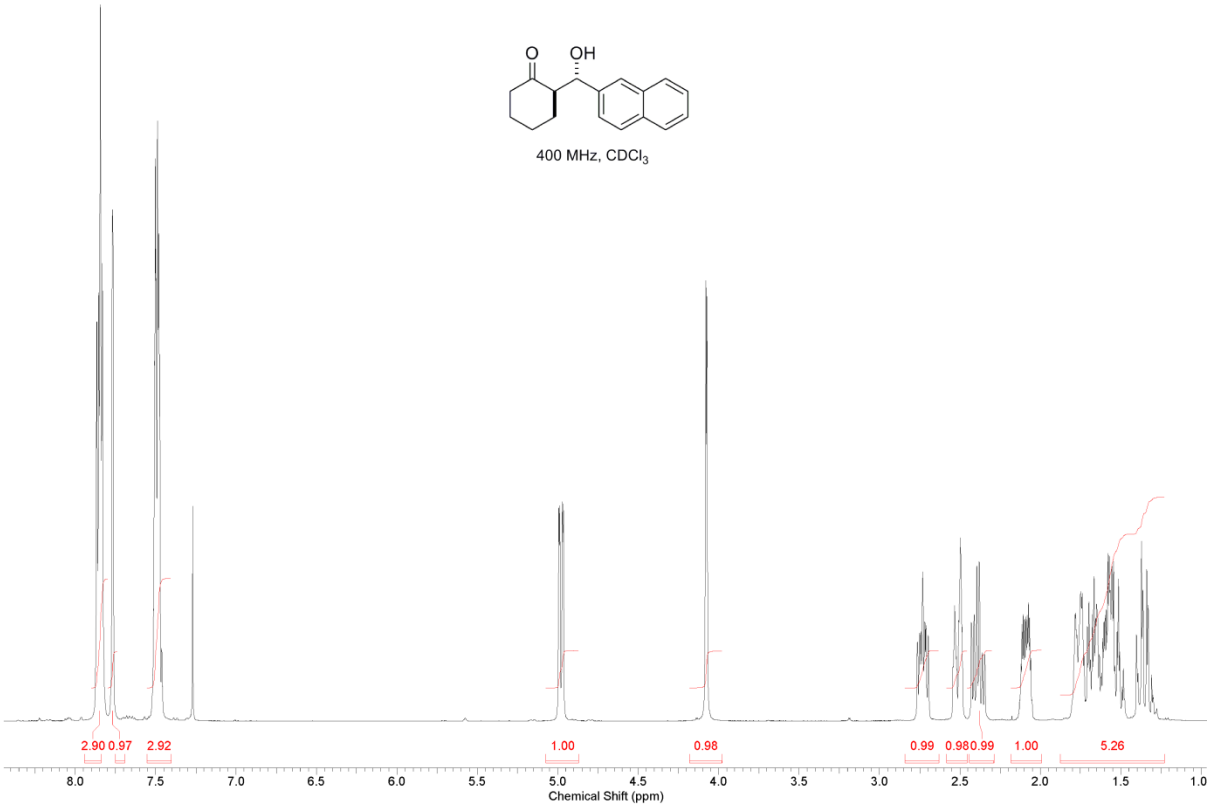

214.83
146.38
132.18
127.78
118.73
111.69
74.21
57.14
42.67
30.73
27.65
24.68
Chemical Shift (ppm)

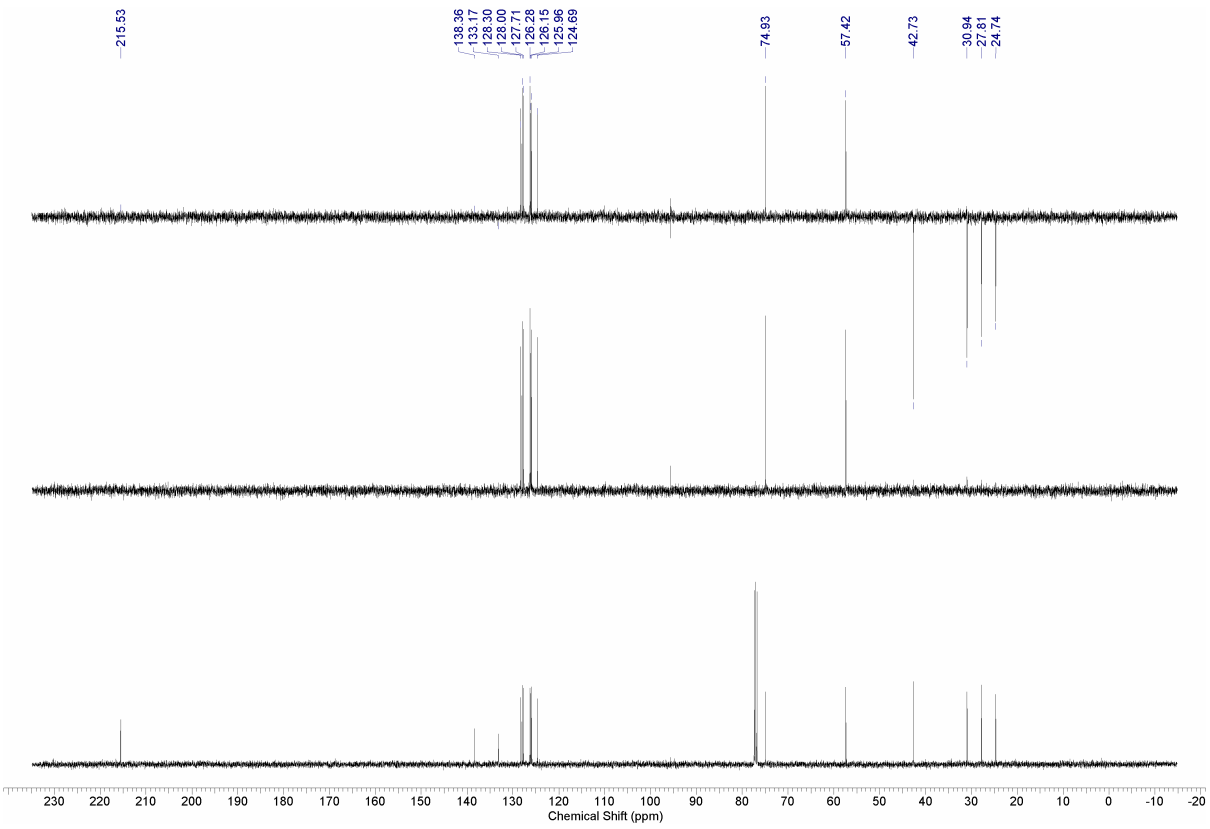

O
OH
Cl
400 MHz, CDCl3
2.05 2.16
0.99
0.96
2.00 1.11
1.06
4.86
1.00
Chemical Shift (ppm)

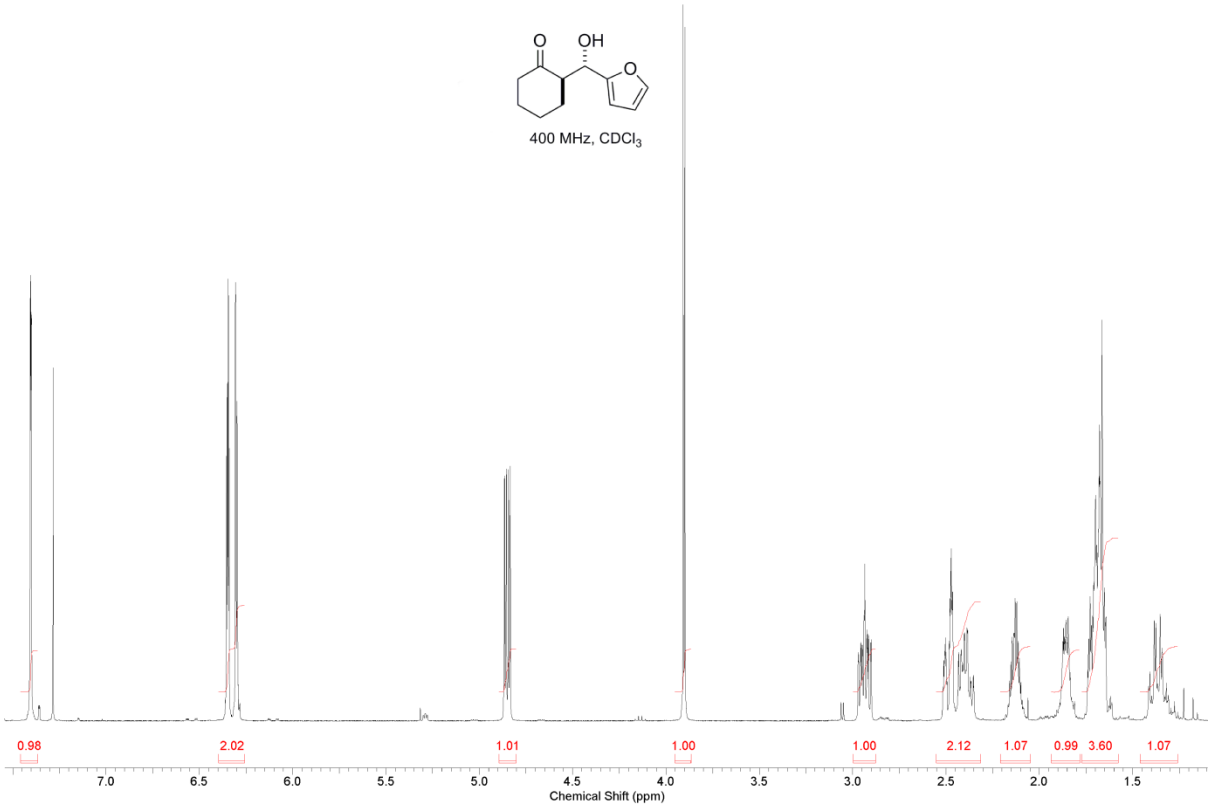

215.30
139.53
133.59
128.55
128.41
74.14
57.39
42.68
30.76
27.74
24.73
Chemical Shift (ppm)

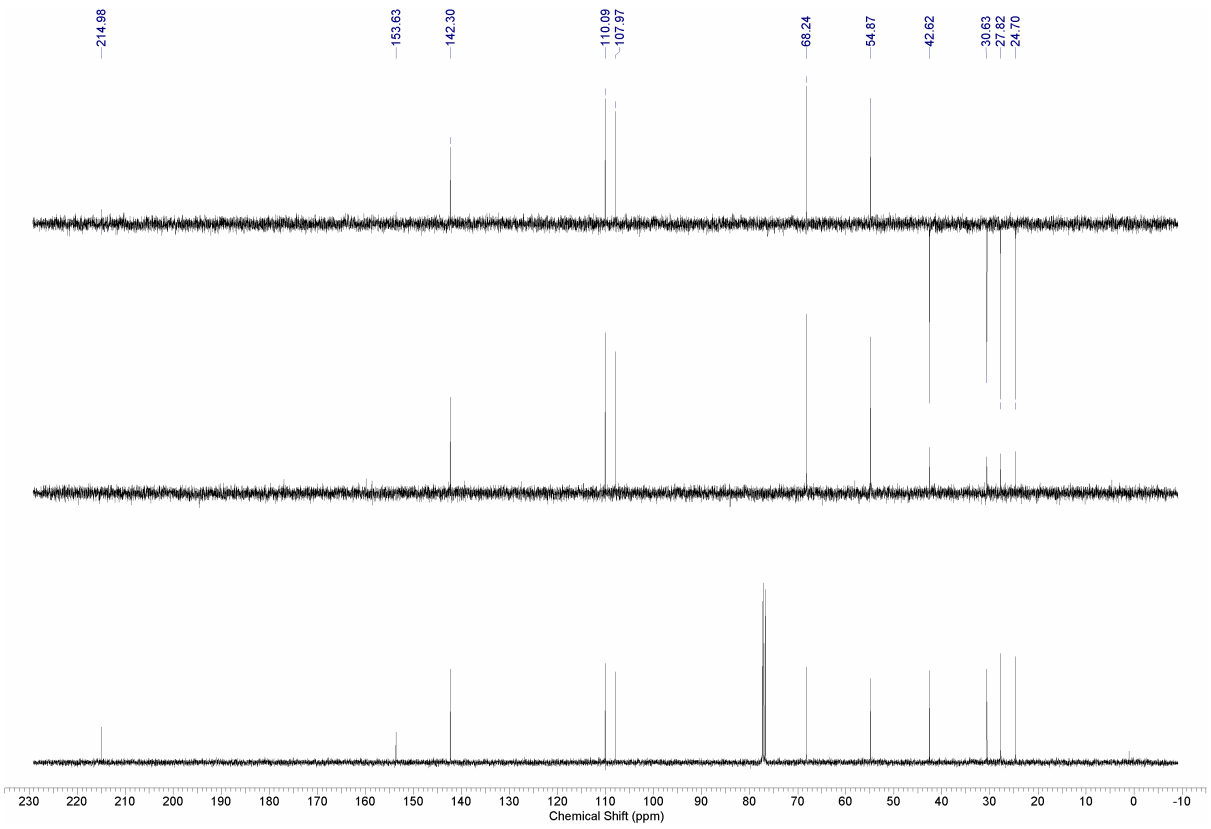

O
OH
400 MHz, CDCl3
5.07
1.00
0.99
0.99
1.00
0.99
1.02
4.30
1.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

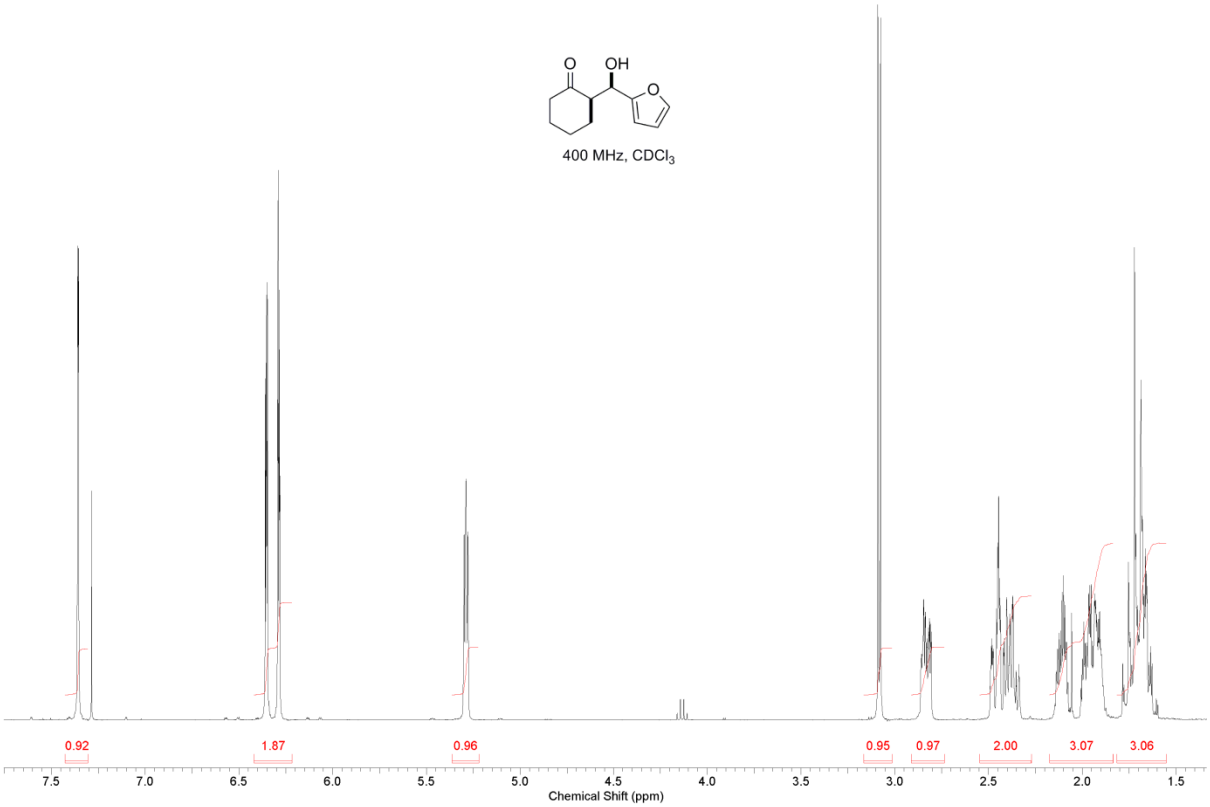

215.59
140.97
128.41
127.92
127.06
74.77
57.46
42.70
30.87
27.84
24.75
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
Chemical Shift (ppm)

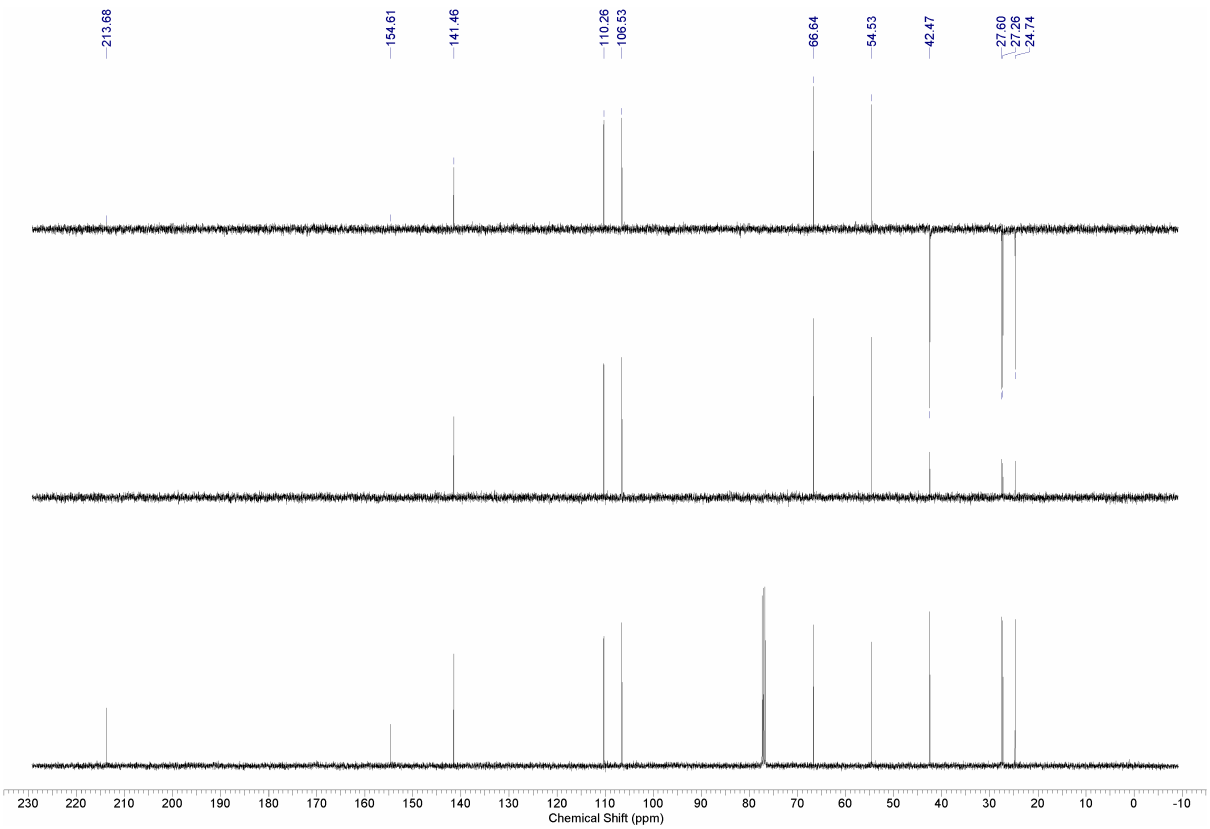

O
OH
400 MHz, CDCl3
2.90
0.97
2.92
1.00
0.98
0.99
0.98
0.99
1.00
5.26
Chemical Shift (ppm)

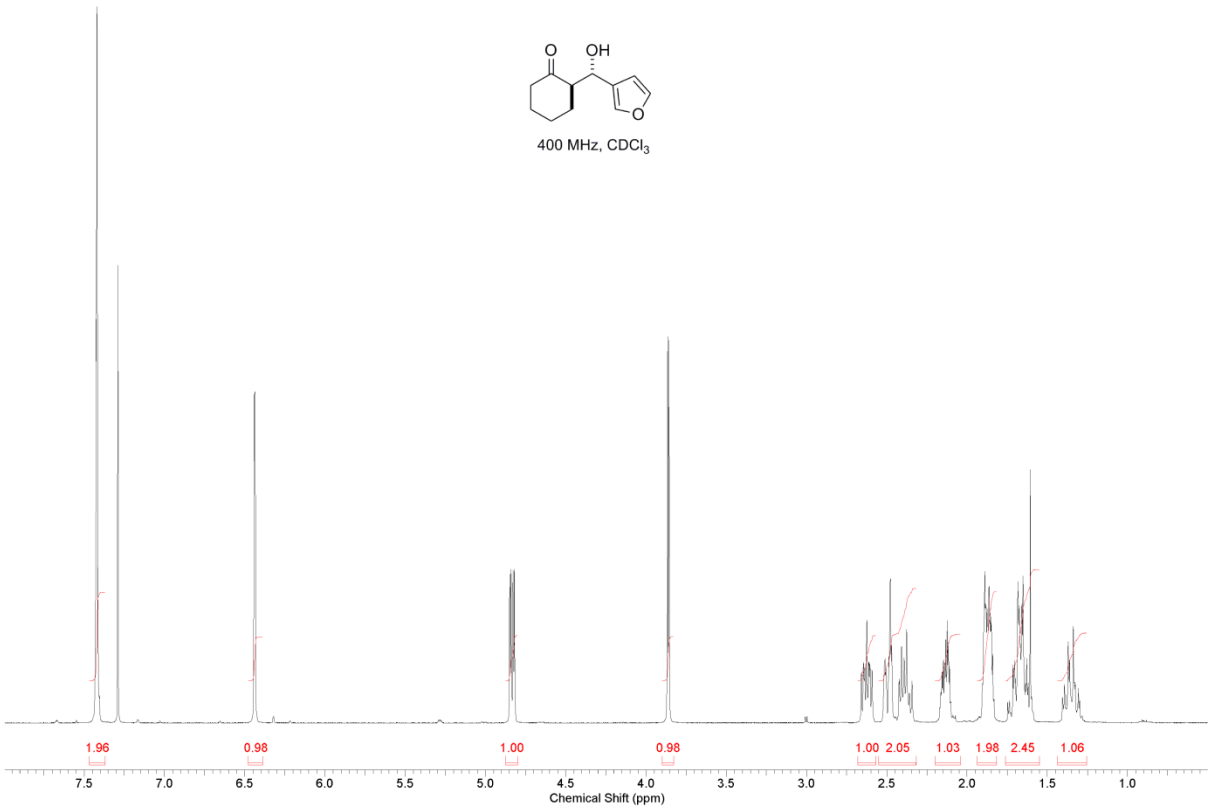

215.53
138.36
133.17
128.30
128.00
127.71
126.28
126.15
125.96
124.69
74.93
57.42
42.73
30.94
27.81
24.74
Chemical Shift (ppm)

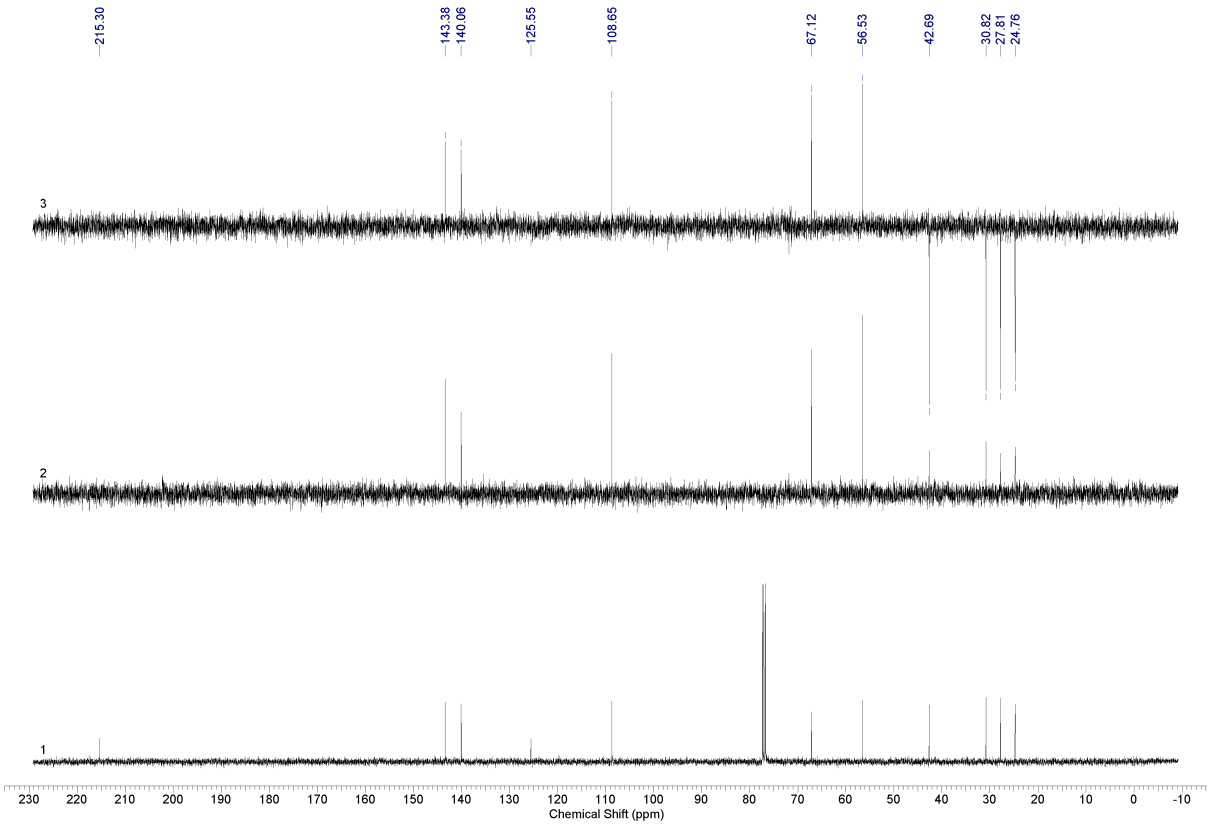

O
OH
O
400 MHz, CDCl3
0.98
2.02
1.01
1.00
1.00
2.12
1.07
0.99
3.60
1.07
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

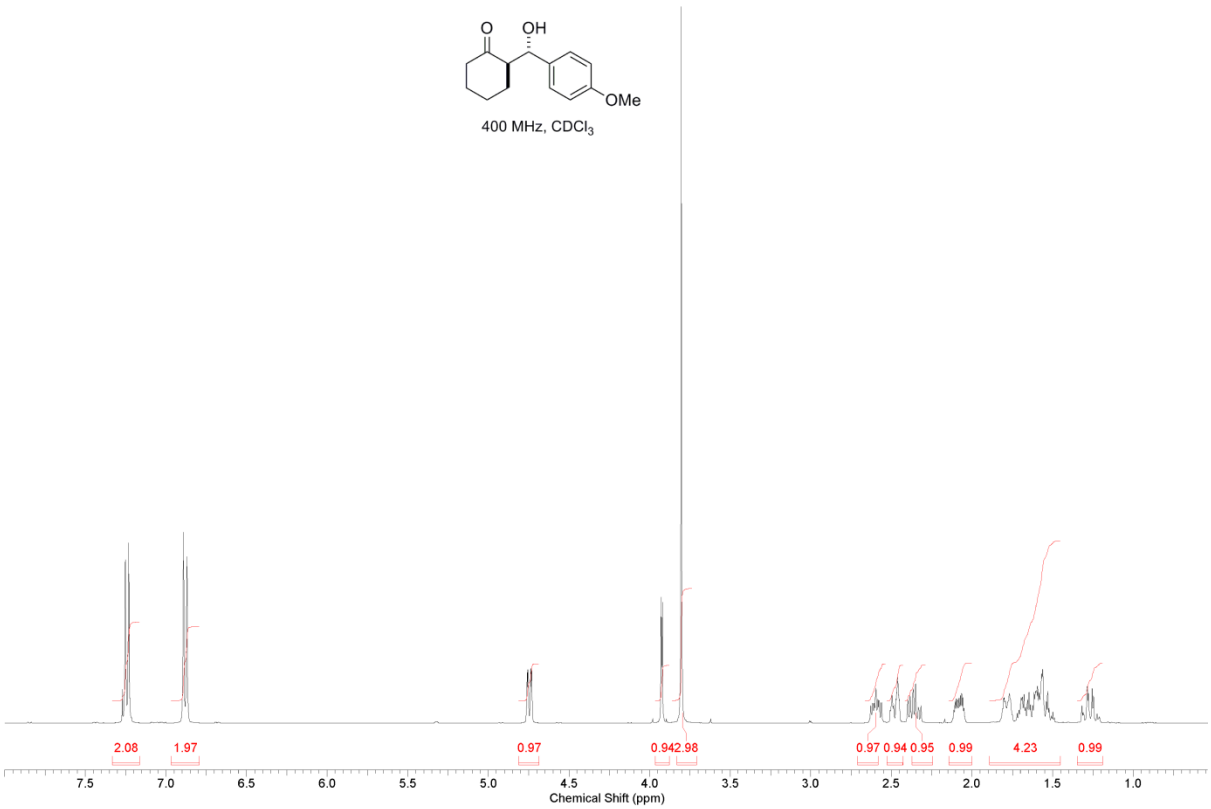

214.98
153.63
142.30
110.09
107.97
68.24
54.87
42.62
30.63
27.82
24.70
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

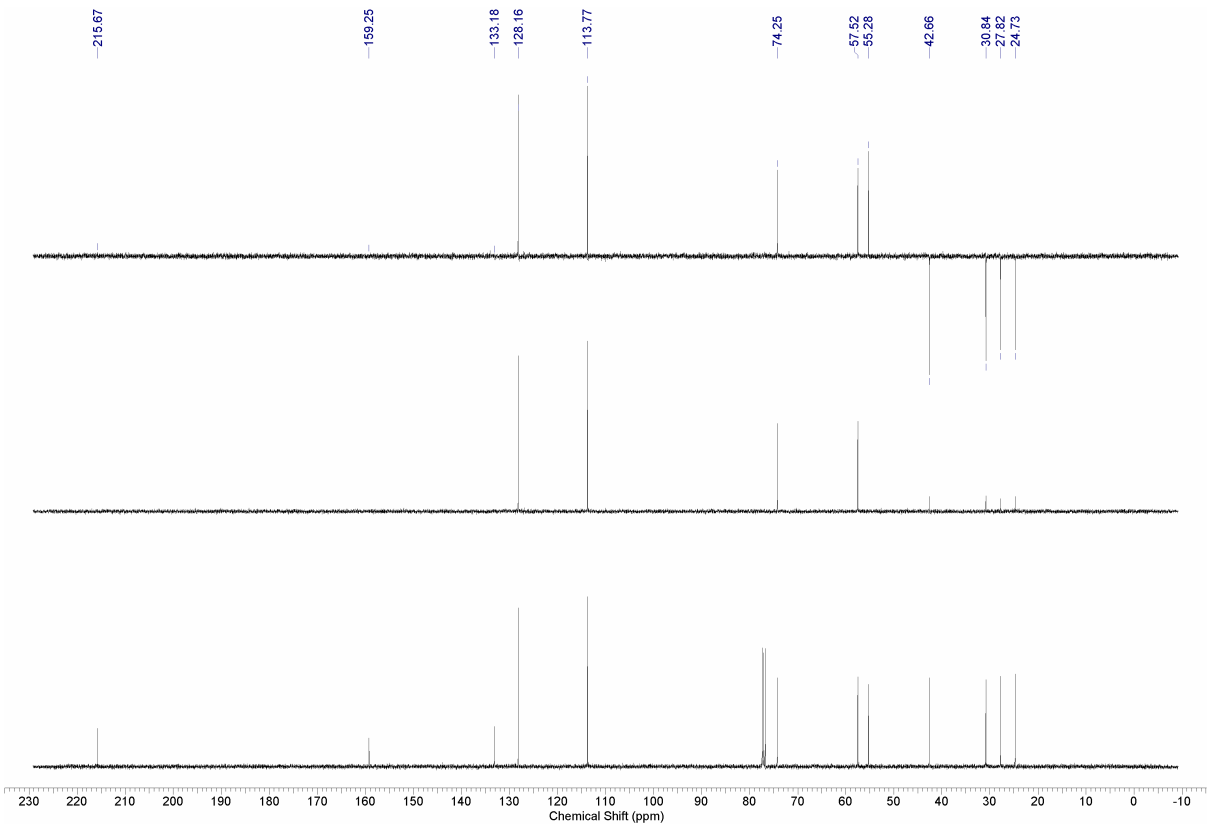

O
OH
O
400 MHz, CDCl3
0.92
1.87
0.96
0.95
0.97
2.00
3.07
3.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

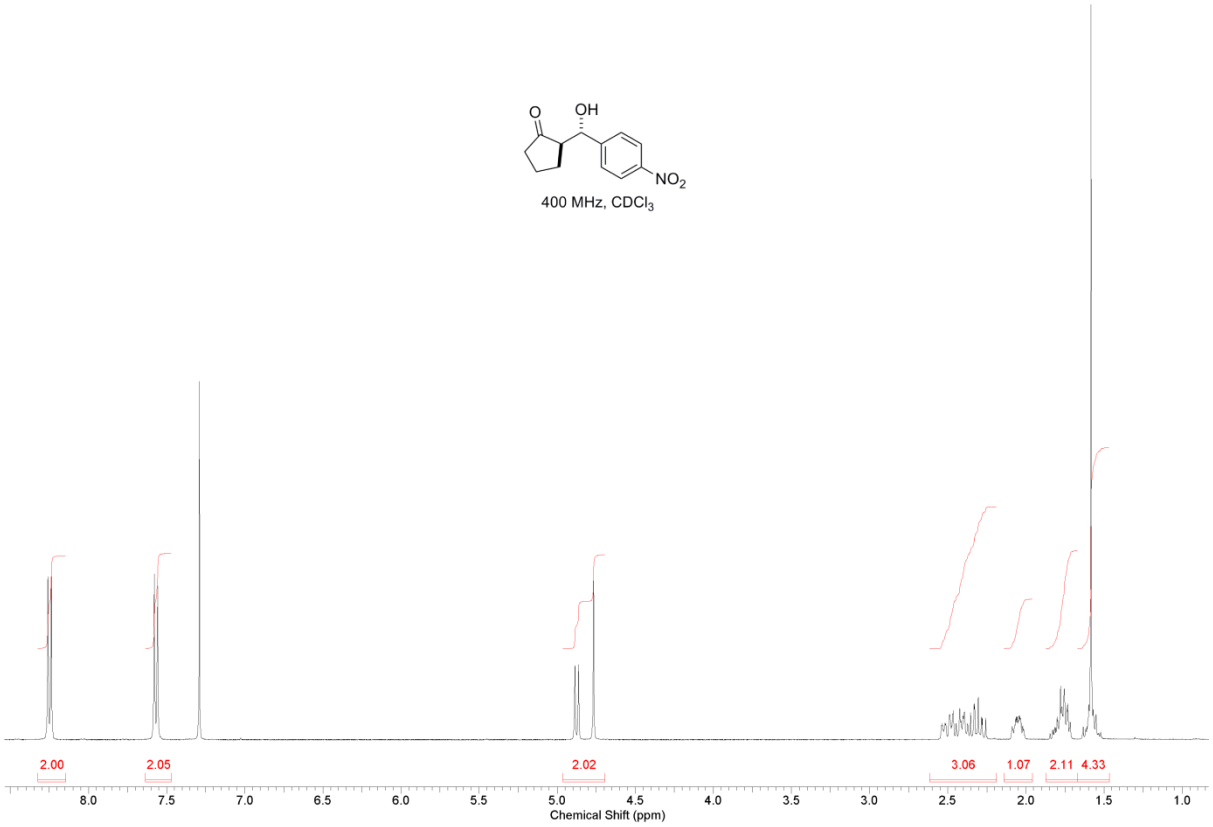

213.68
154.61
141.46
110.26
106.53
66.64
54.53
42.47
27.60
27.26
24.74
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

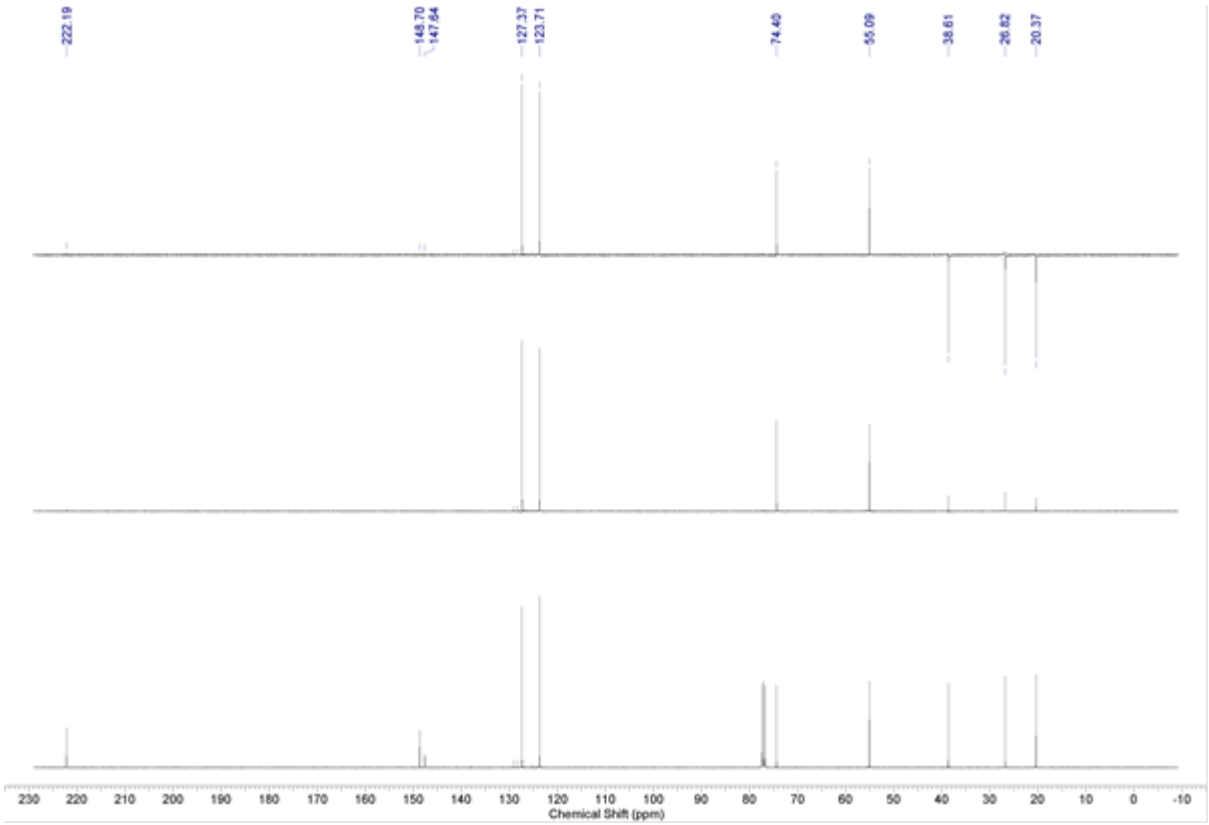

O
OH
O
400 MHz, CDCl3
1.96
0.98
1.00
0.98
1.00
2.05
1.03
1.98
2.45
1.06
Chemical Shift (ppm)

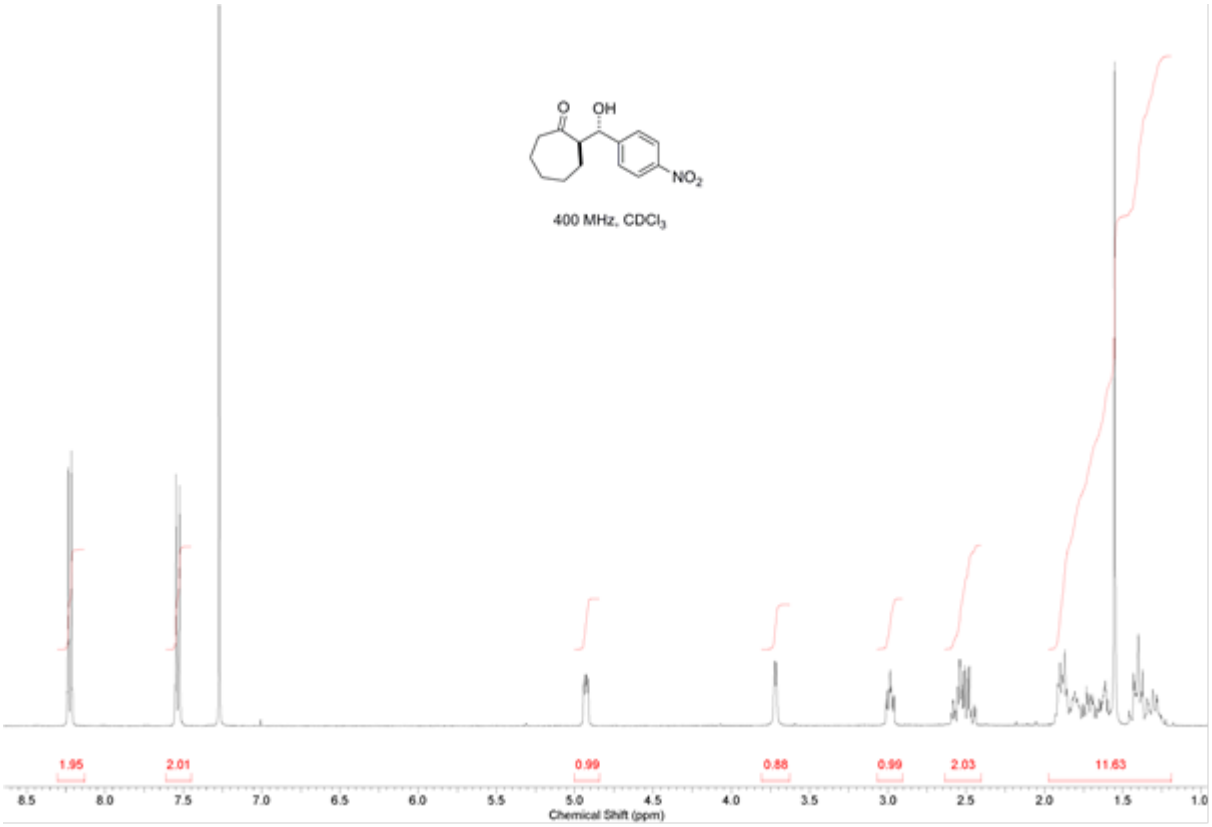

215.30
143.38
140.06
125.55
108.65
67.12
56.53
42.69
30.82
27.81
24.76
3
2
1
Chemical Shift (ppm)

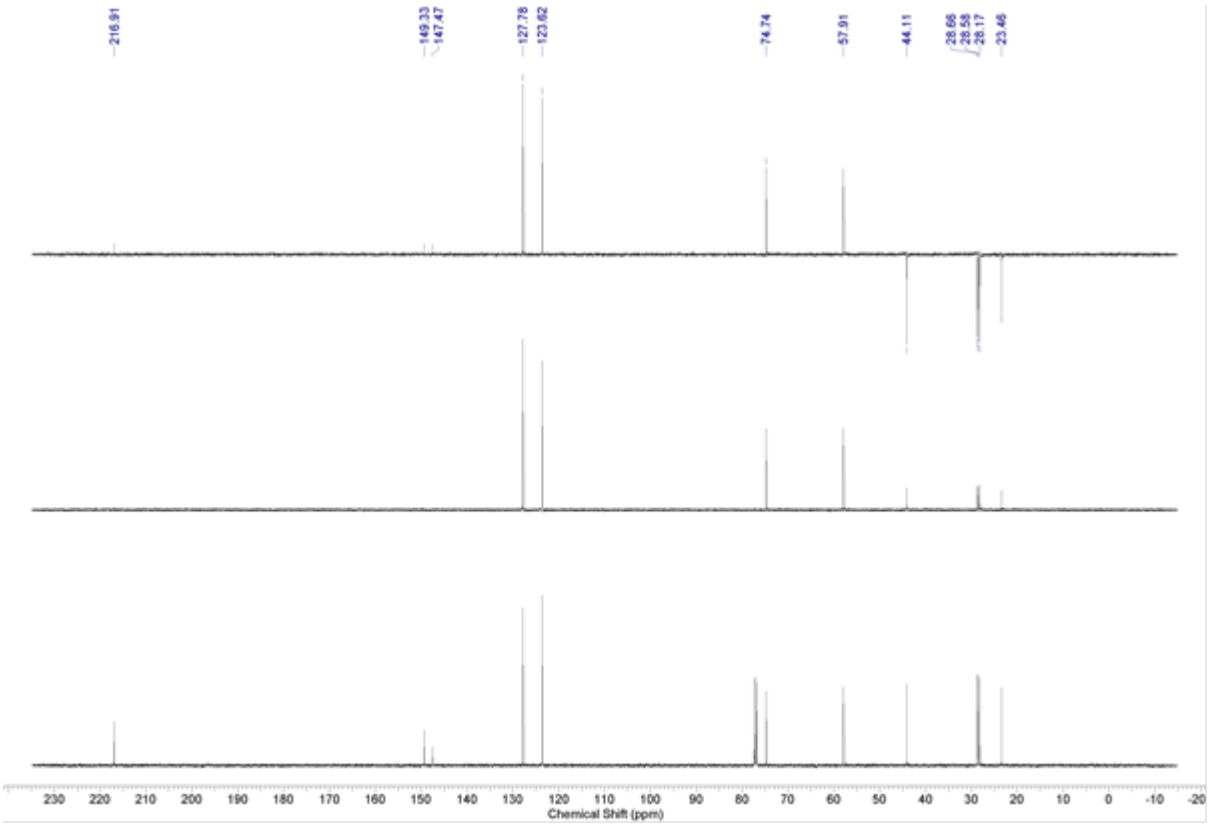

O
OH
OMe
400 MHz, CDCl3
2.08
1.97
0.97
0.94
2.98
0.97
0.94
0.95
0.99
4.23
0.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

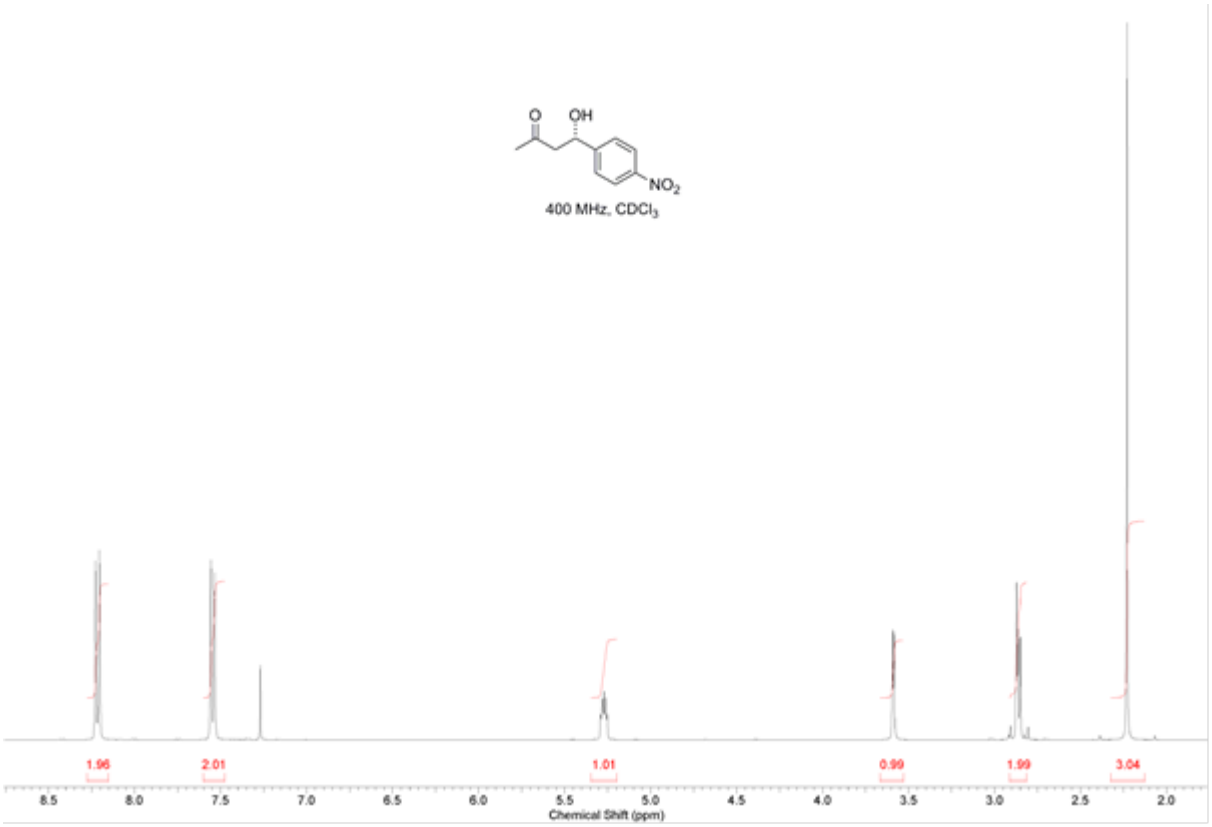

215.67
159.25
133.18
128.16
113.77
74.25
57.52
55.28
42.66
30.84
27.82
24.73
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

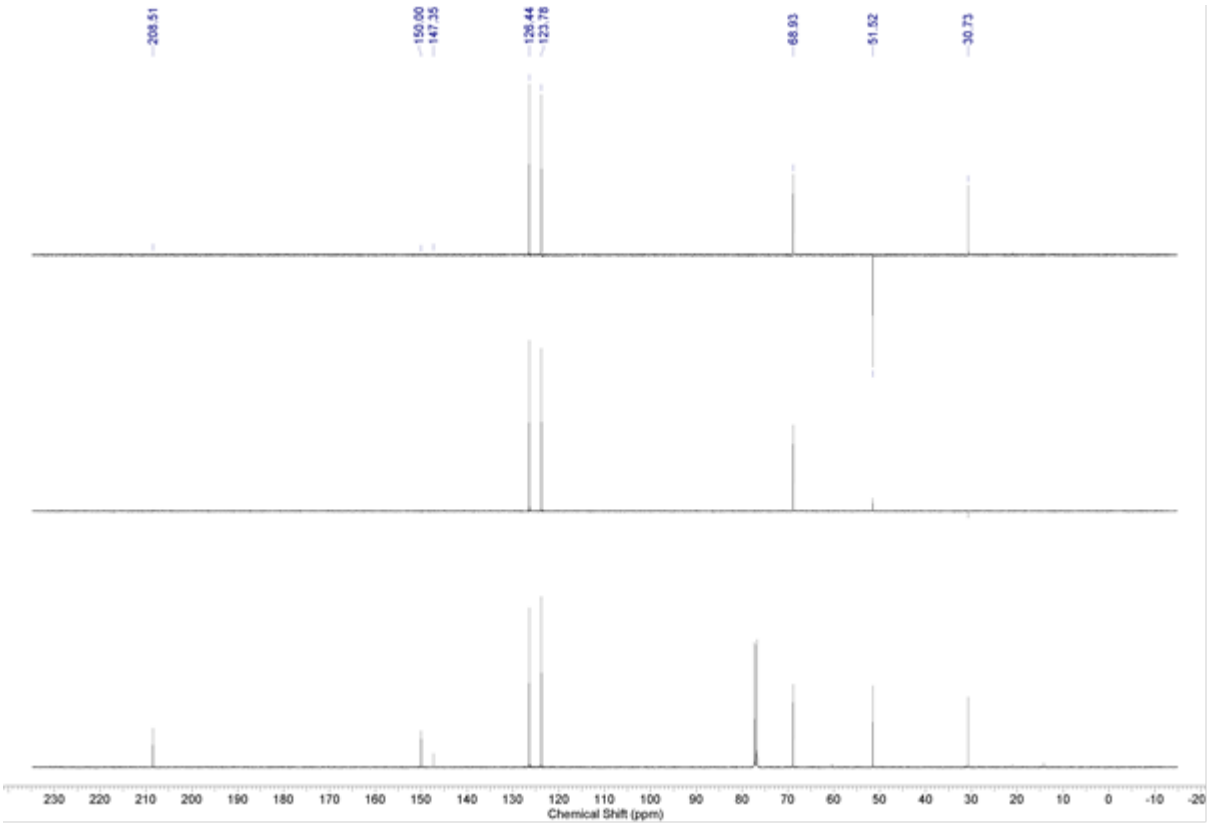

O
OH
NO2
400 MHz, CDCl3
2.00
2.05
2.02
3.06
1.07
2.11
4.33
Chemical Shift (ppm)

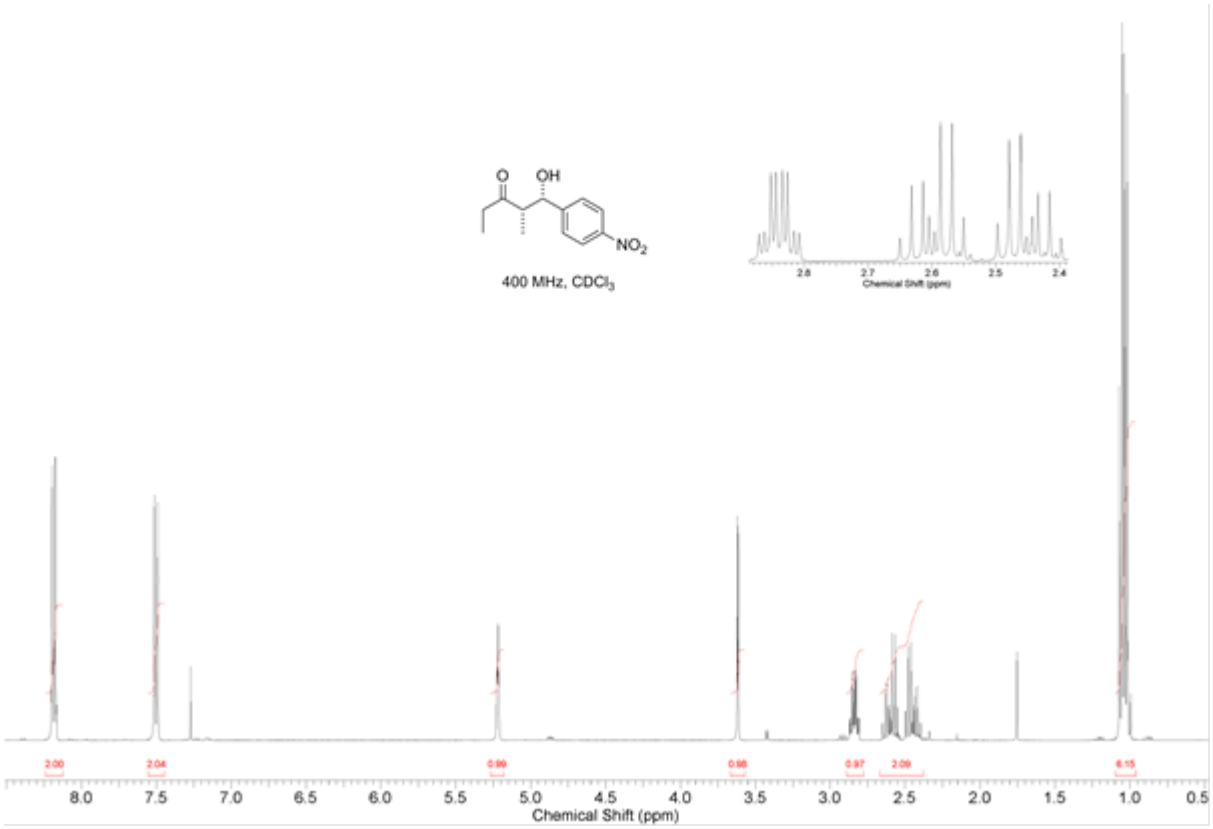

222.19
148.70
147.64
127.37
123.71
74.40
55.09
38.61
26.82
20.37
Chemical Shift (ppm)

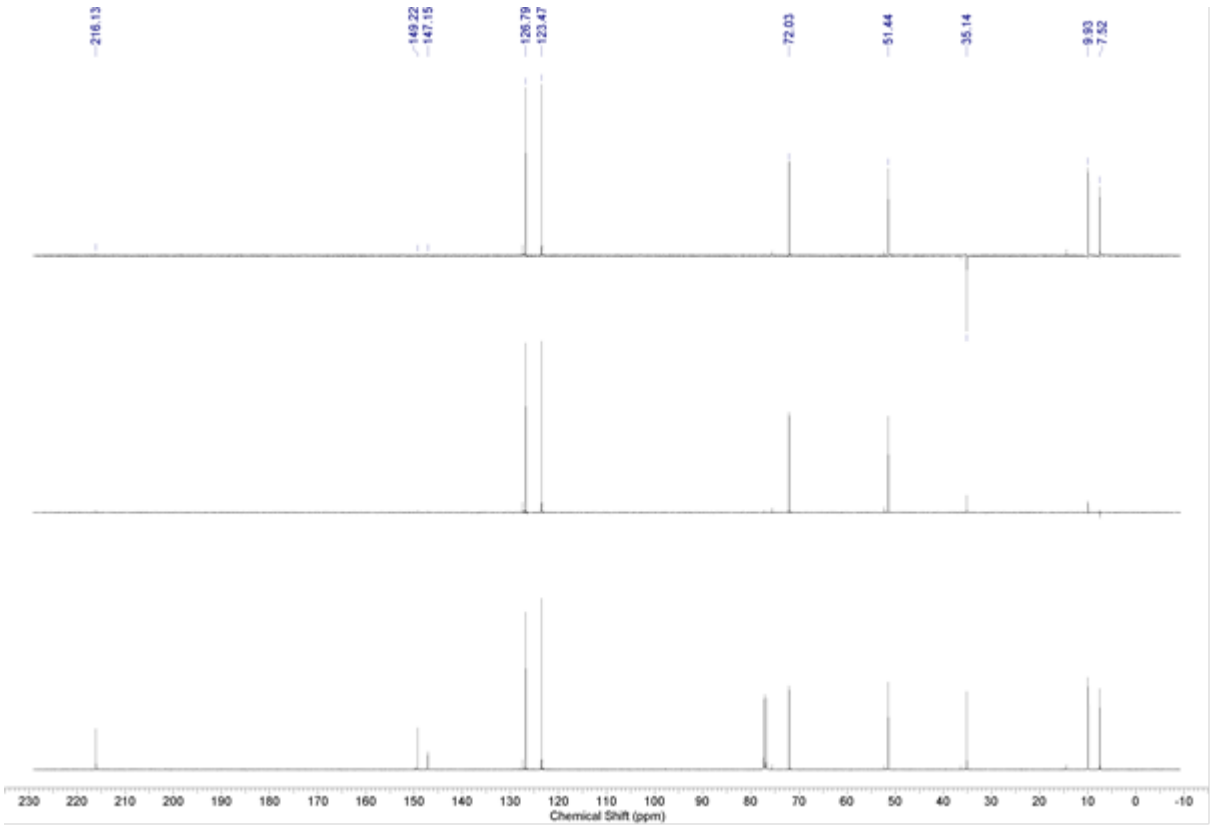

O
OH
NO2
400 MHz, CDCl3
1.95
2.01
0.99
0.88
0.99
2.03
11.63
Chemical Shift (ppm)

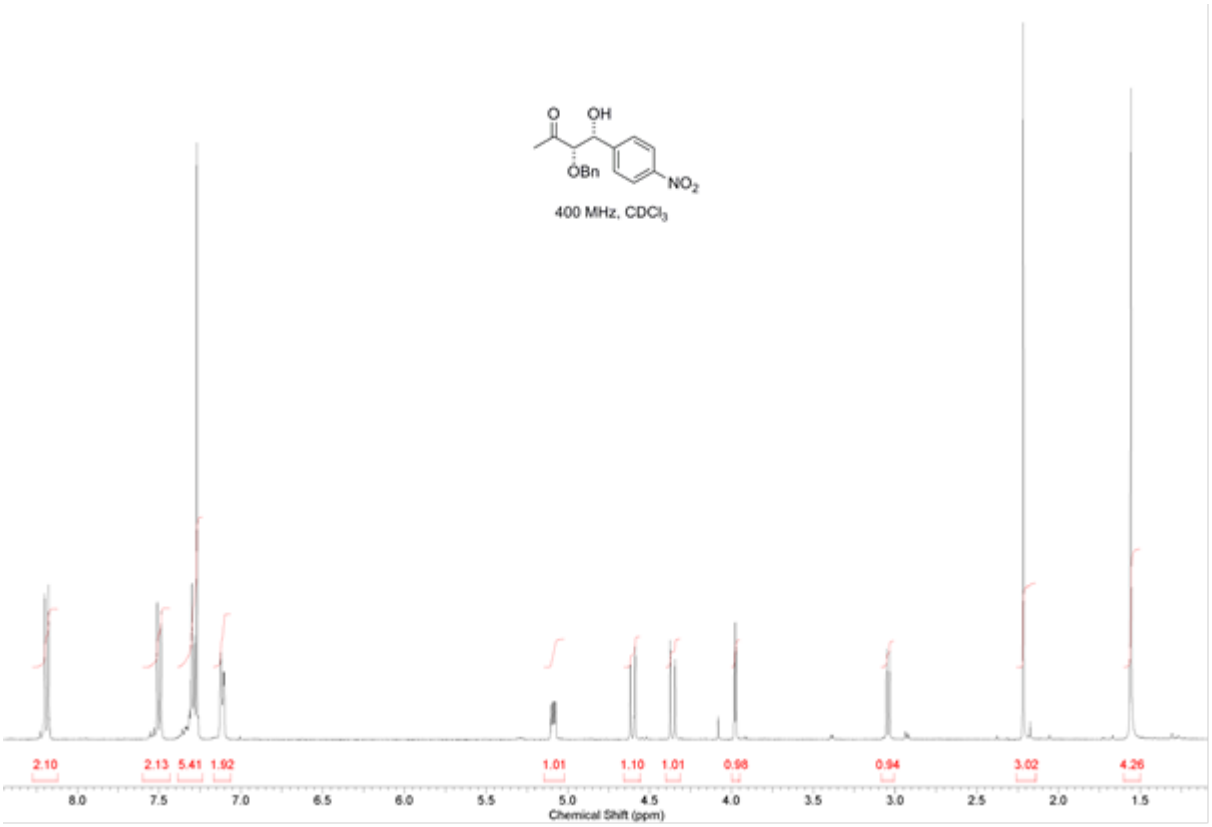

216.91
149.33
147.47
127.78
123.62
74.74
57.91
44.11
28.66
28.58
28.17
23.46
Chemical Shift (ppm)

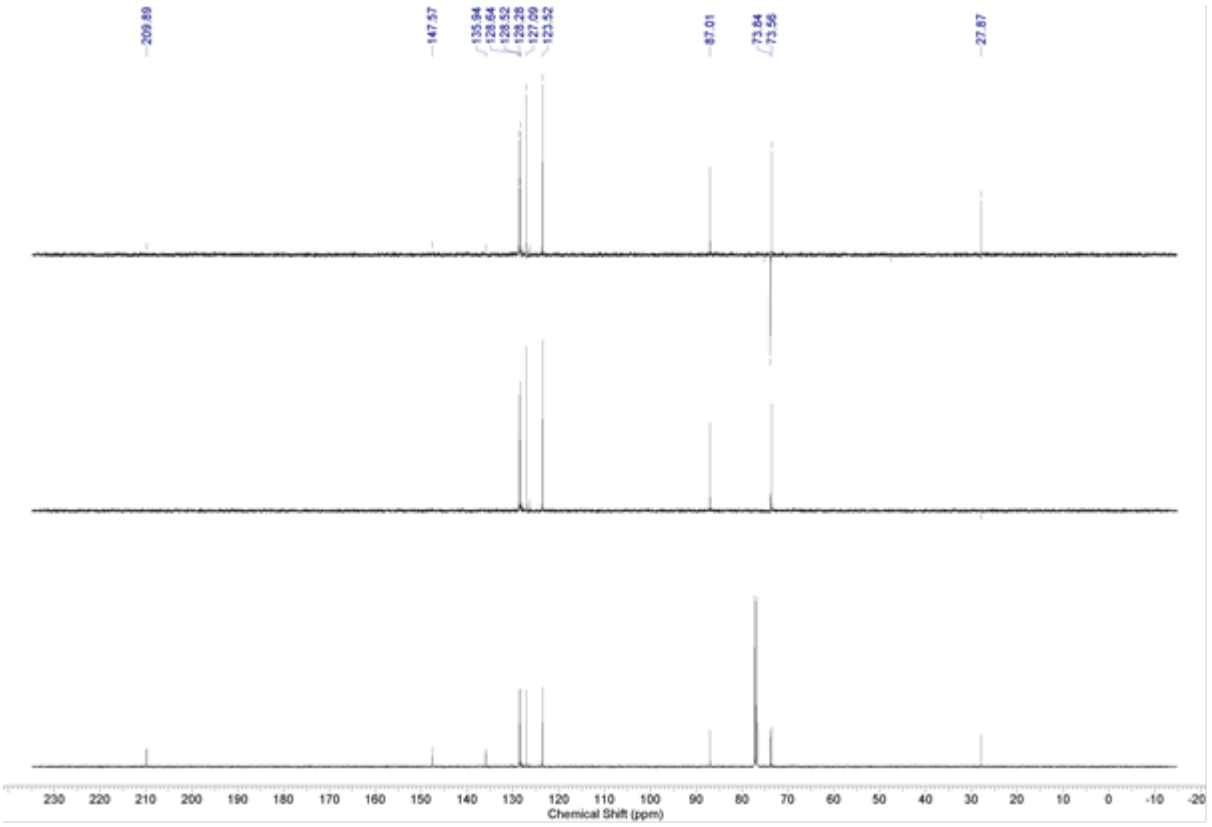

O
OH
NO2
400 MHz, CDCl3
1.96
2.01
1.01
0.99
1.99
3.04
Chemical Shift (ppm)

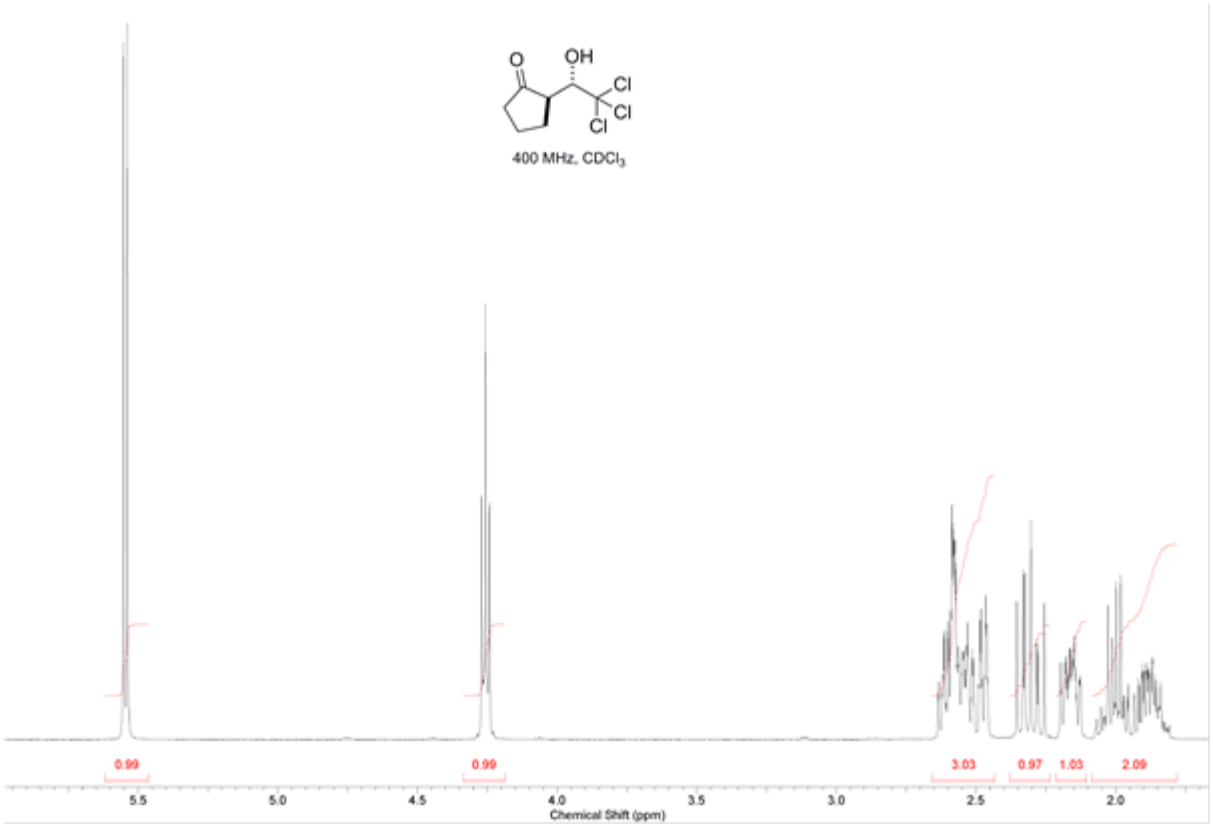

208.51
150.00
147.35
128.44
123.78
68.93
51.52
30.73
Chemical Shift (ppm)

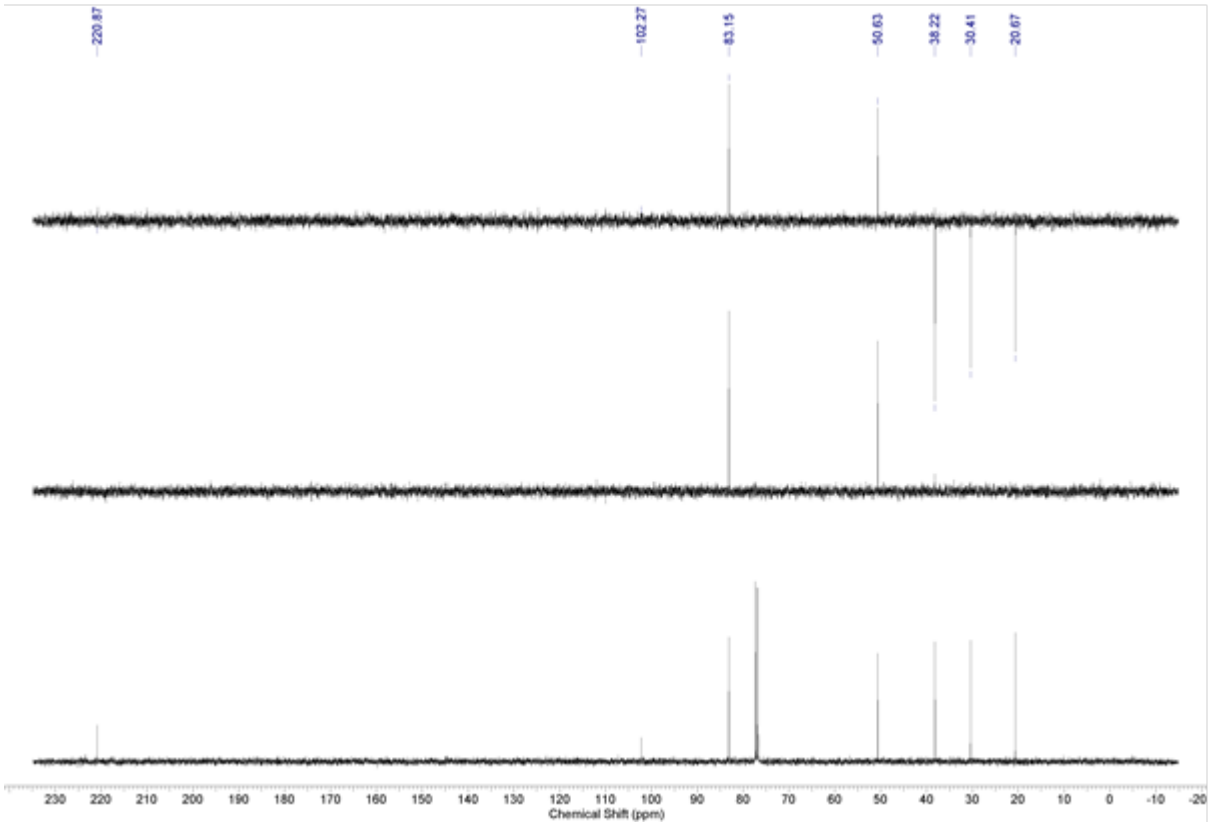

O
OH
NO2
400 MHz, CDCl3
Chemical Shift (ppm)

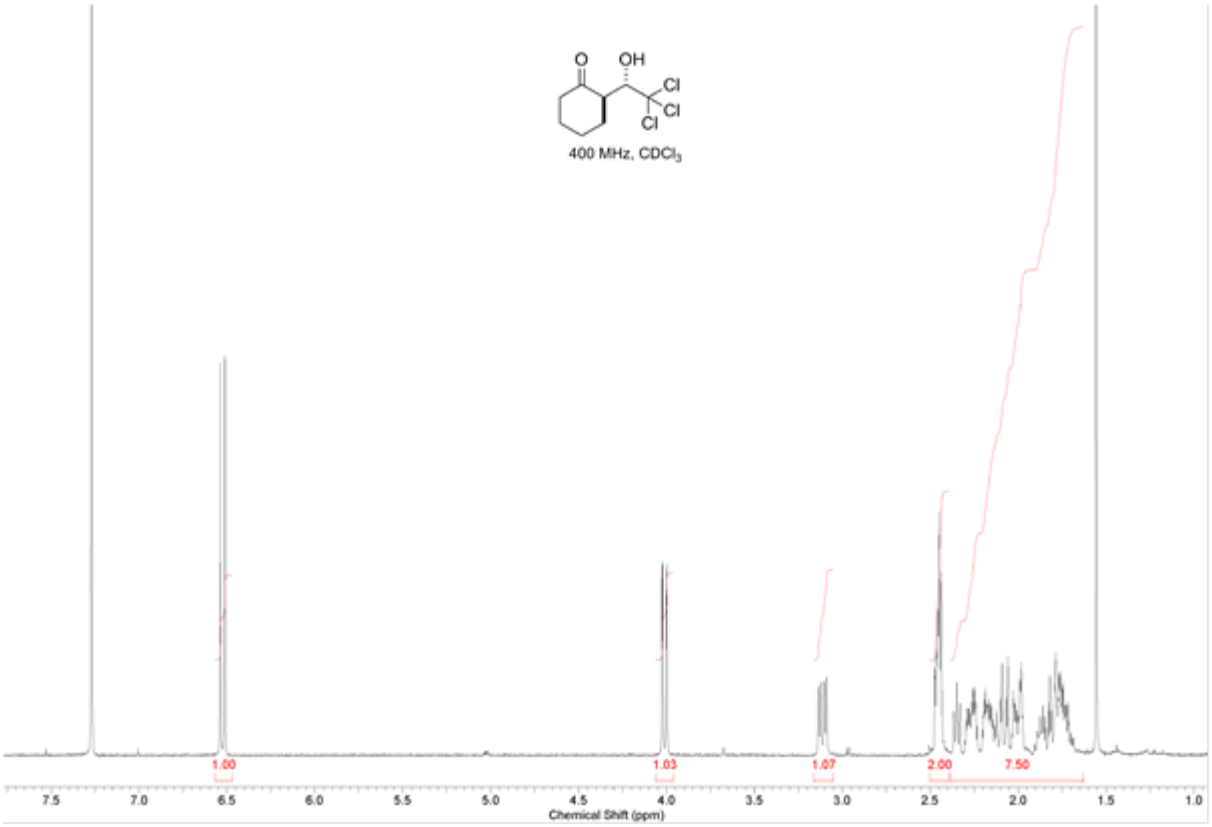

216.13
149.22
147.15
126.79
123.47
72.03
51.44
35.14
8.93
7.52
Chemical Shift (ppm)

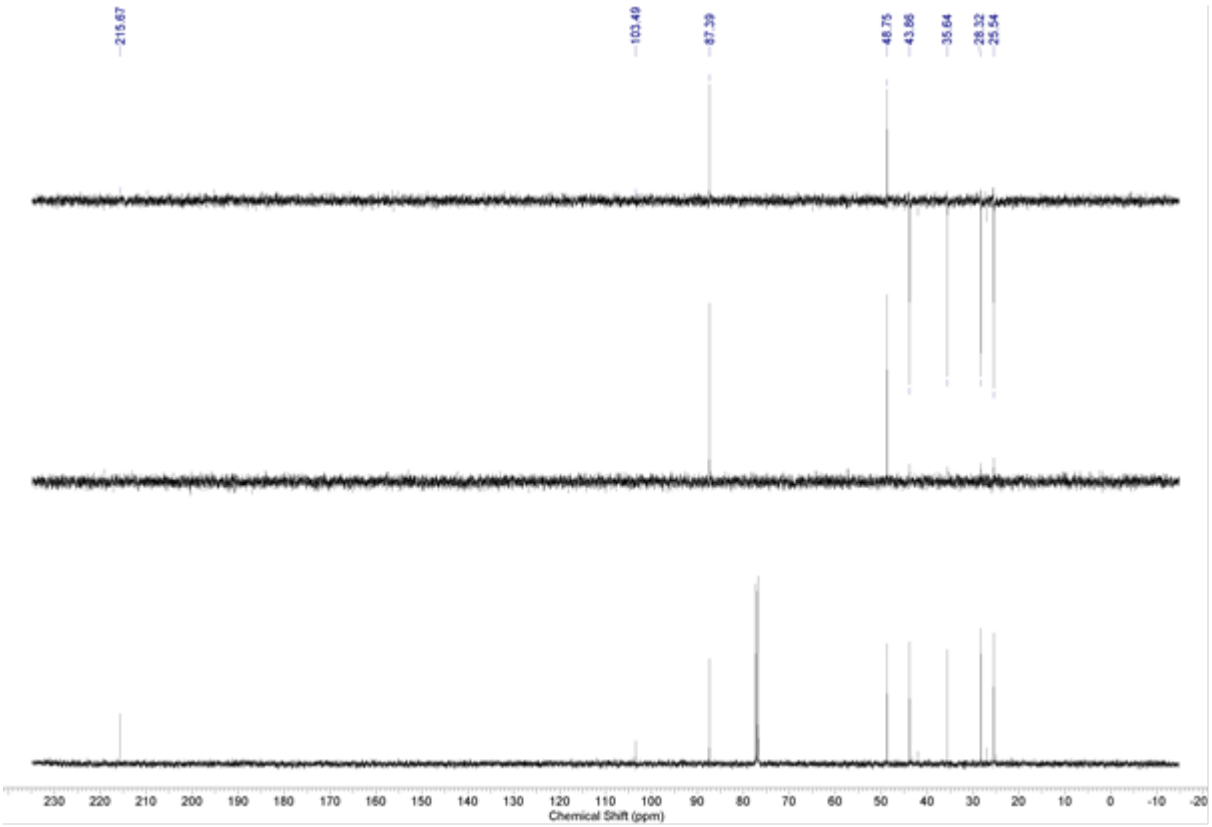

O
OH
OBn
NO2
400 MHz, CDCl3
2.10
2.13
5.41
1.92
1.01
1.10
1.01
0.98
0.94
3.02
4.26
Chemical Shift (ppm)

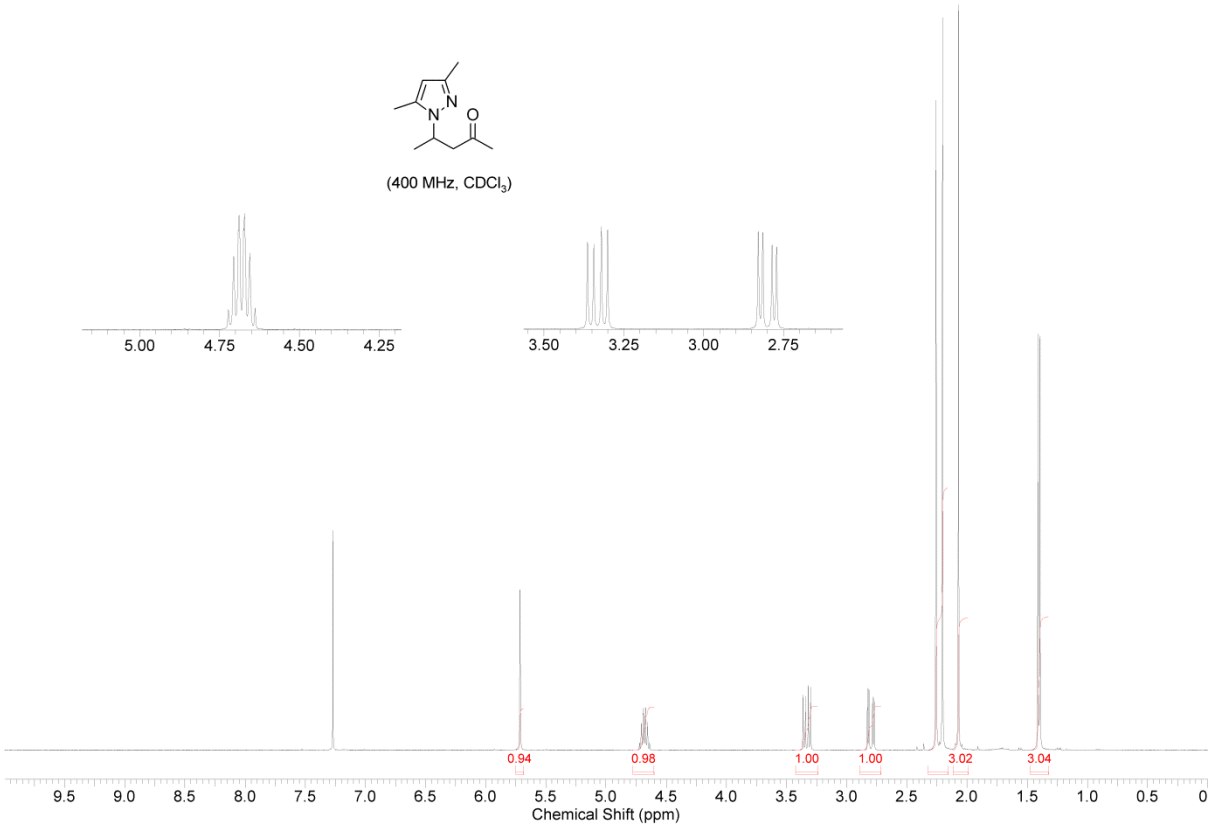

209.89
147.57
135.94
128.64
128.52
128.28
127.09
123.52
87.01
73.84
73.56
27.87
Chemical Shift (ppm)

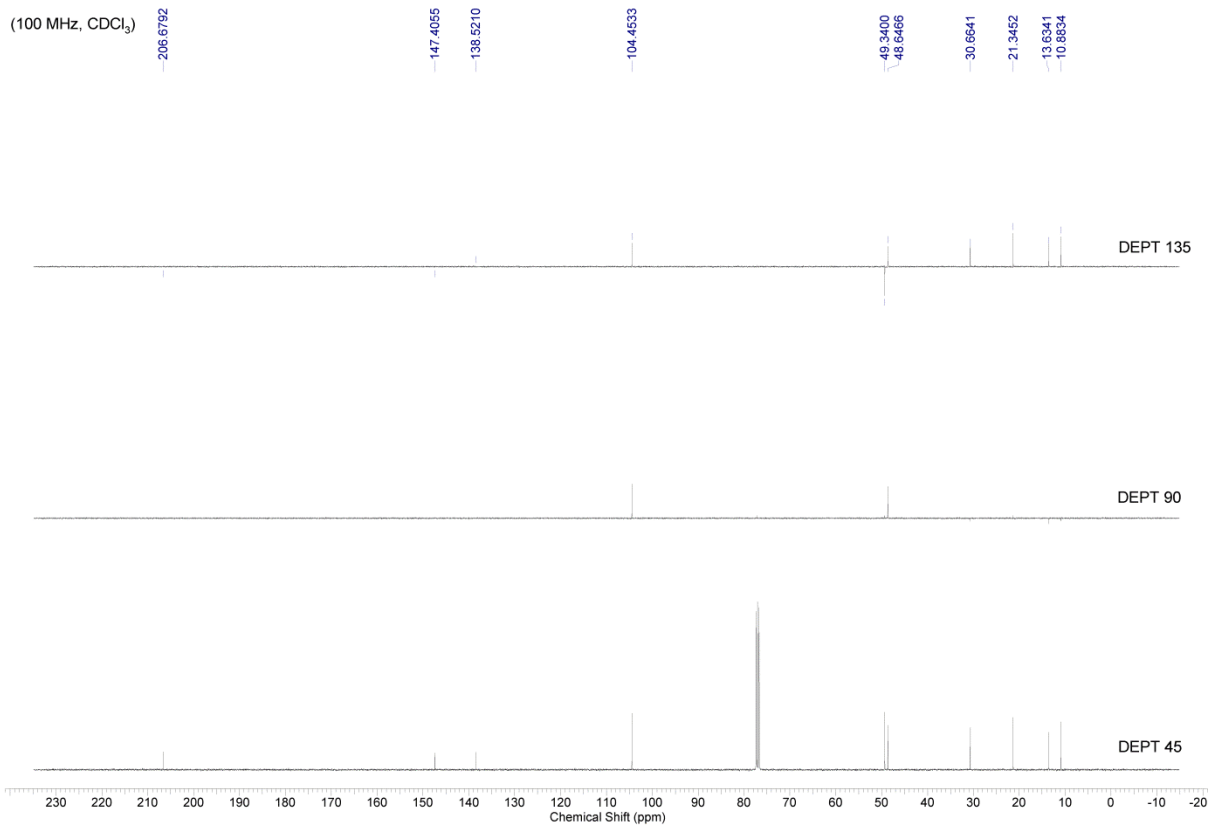

O
OH
Cl
Cl
Cl
400 MHz, CDCl3
0.99
0.99
3.03
0.97
1.03
2.09
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Chemical Shift (ppm)


220.87
102.27
83.15
50.63
38.22
30.41
20.67
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
Chemical Shift (ppm)

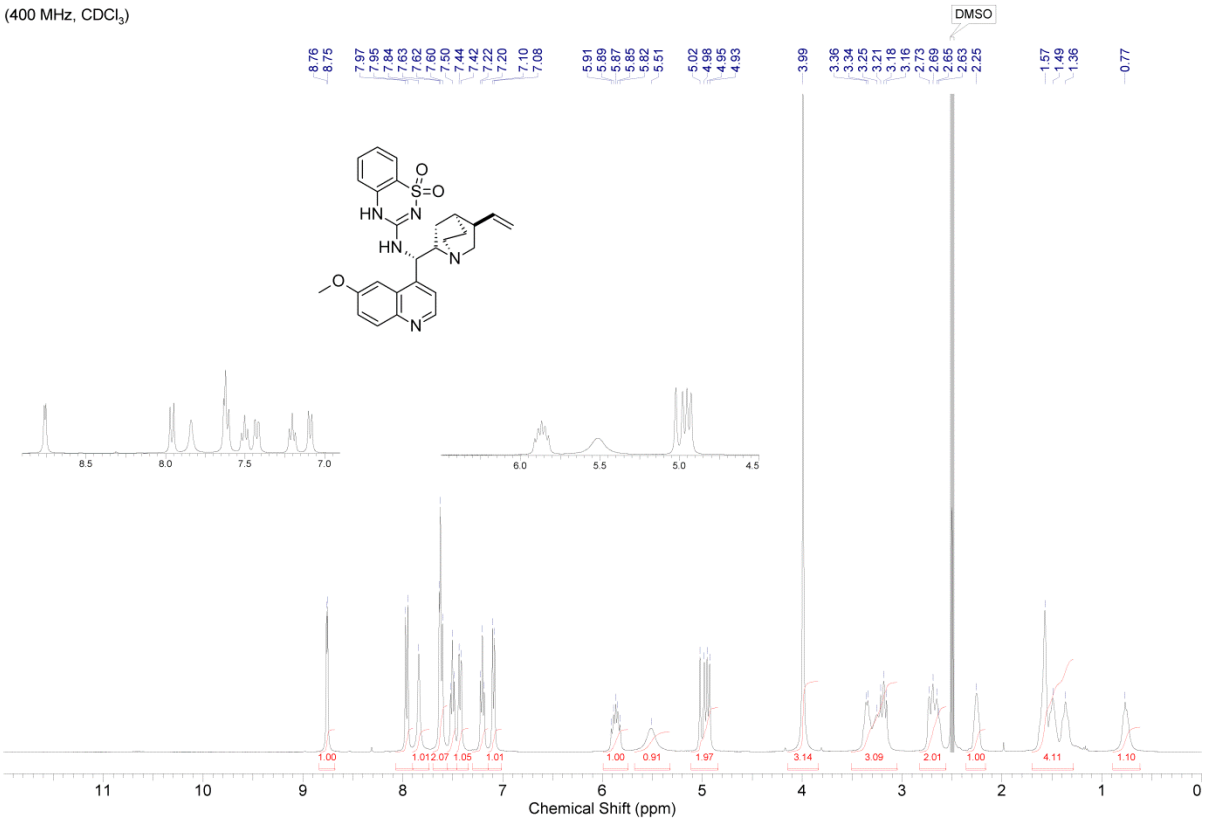

O
OH
Cl
Cl
Cl
400 MHz, CDCl3
1.00
1.03
1.07
2.00
7.50
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)


215.67
103.49
87.39
48.75
43.86
35.64
28.32
25.54
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
Chemical Shift (ppm)

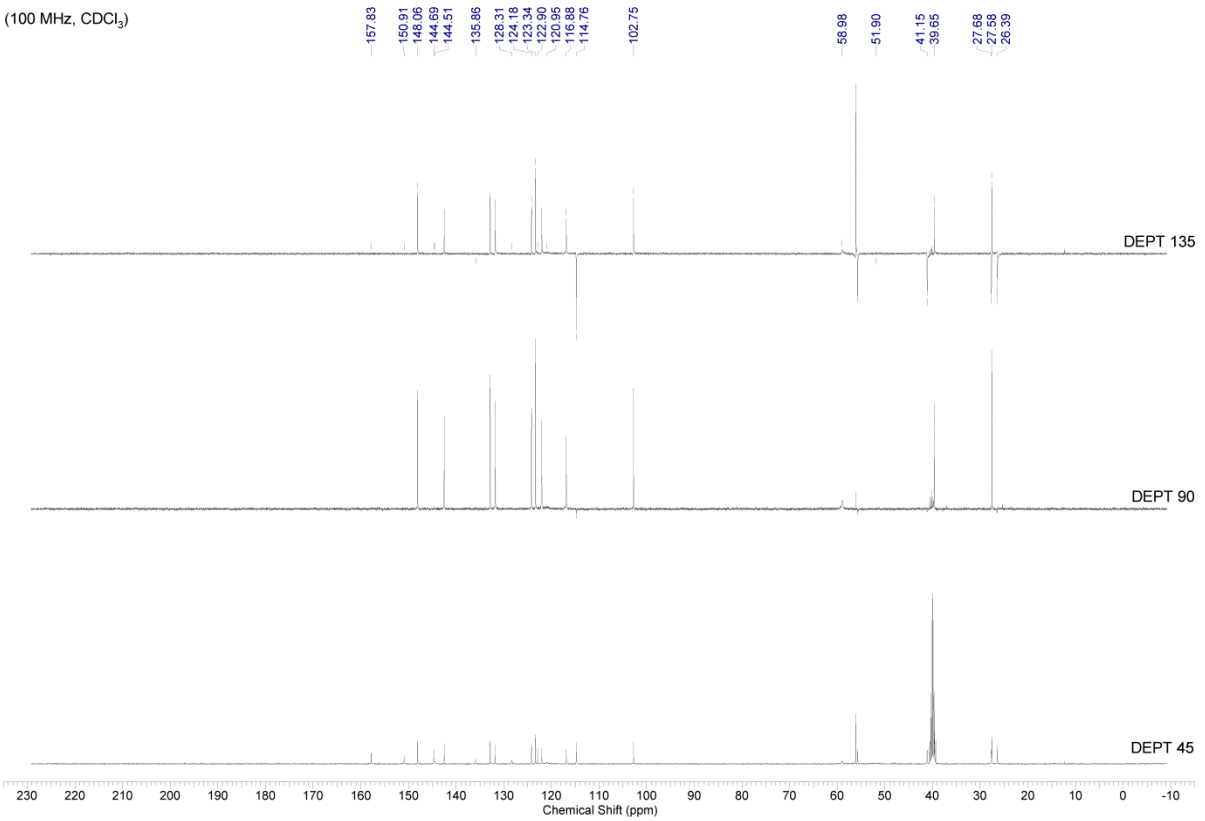

(400 MHz, CDCl3)
5.00
4.75
4.50
4.25
3.50
3.25
3.00
2.75
0.94
0.98
1.00
1.00
3.02
3.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

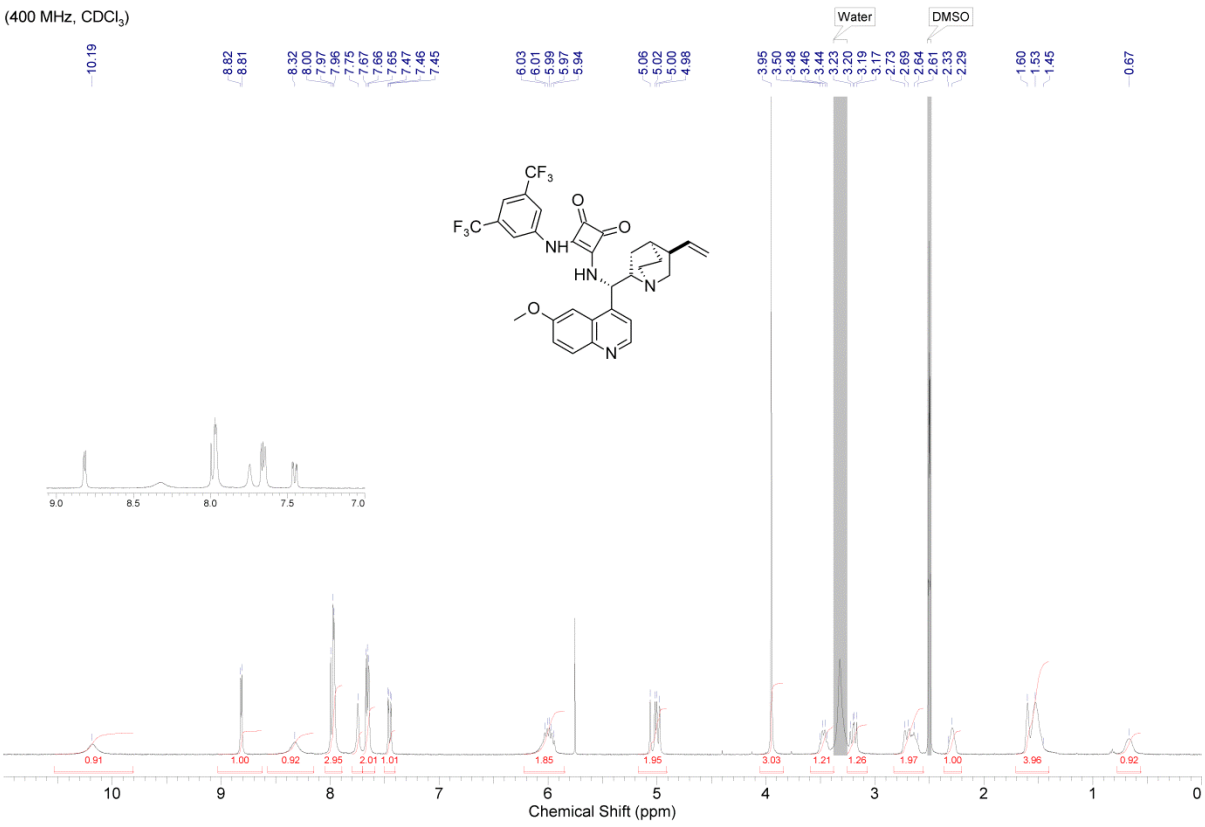

(100 MHz, CDCl3)
206.6792
147.4055
138.5210
104.4533
49.3400
48.6466
30.6641
21.3452
13.6341
10.8834
DEPT 135
DEPT 90
DEPT 45
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
Chemical Shift (ppm)

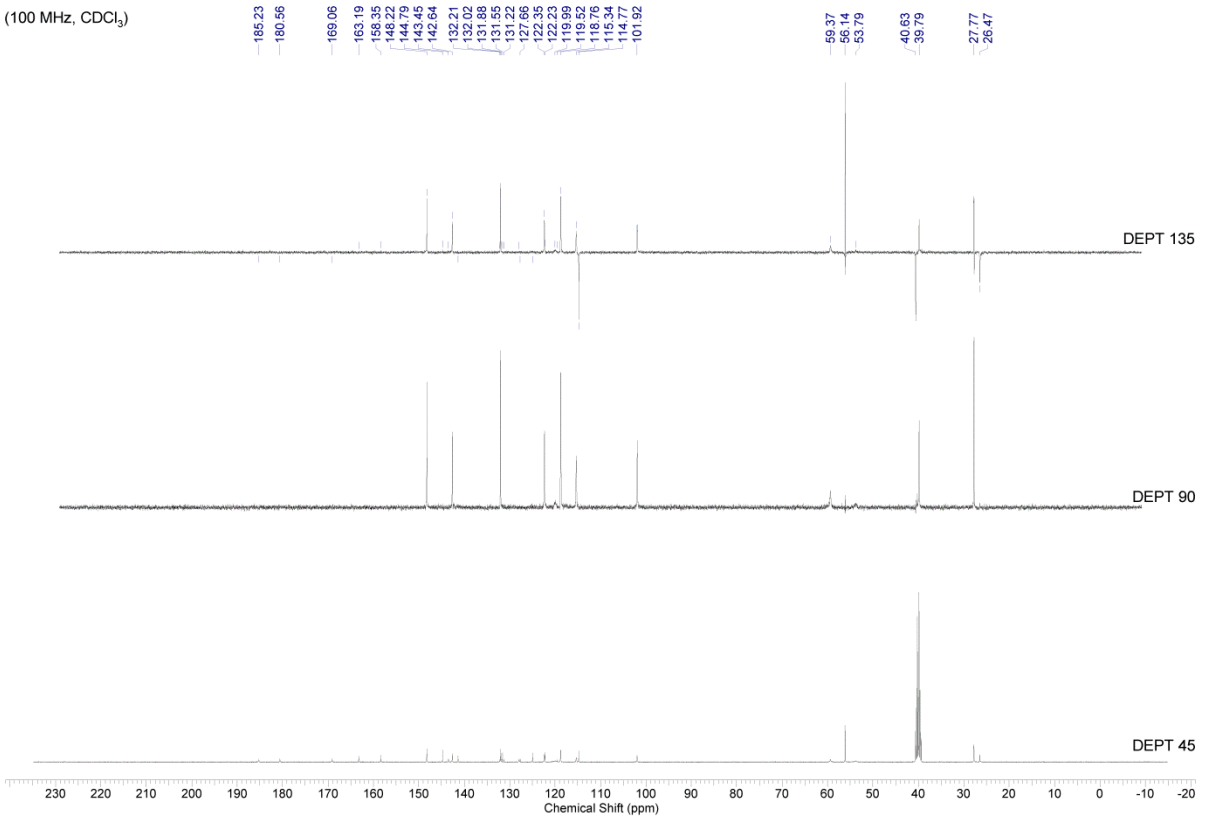
(400 MHz, $CDCl_3$)

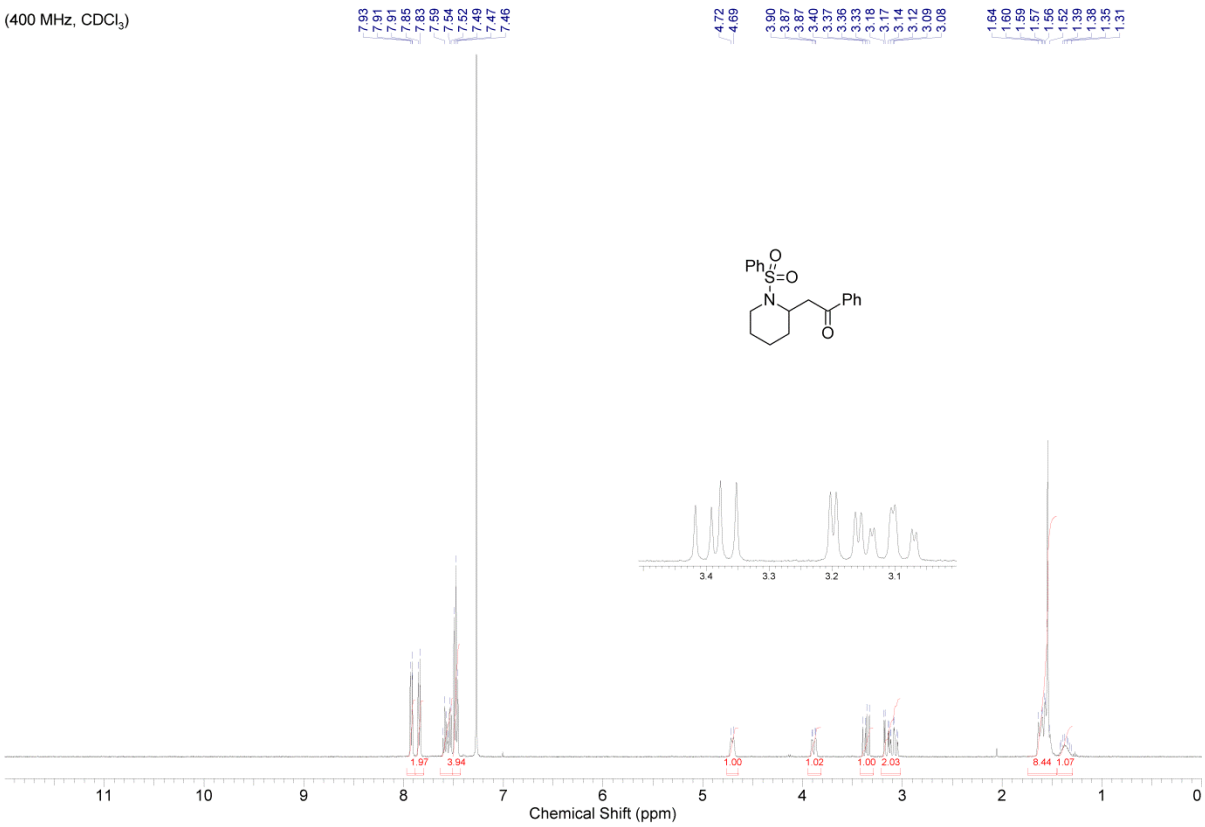


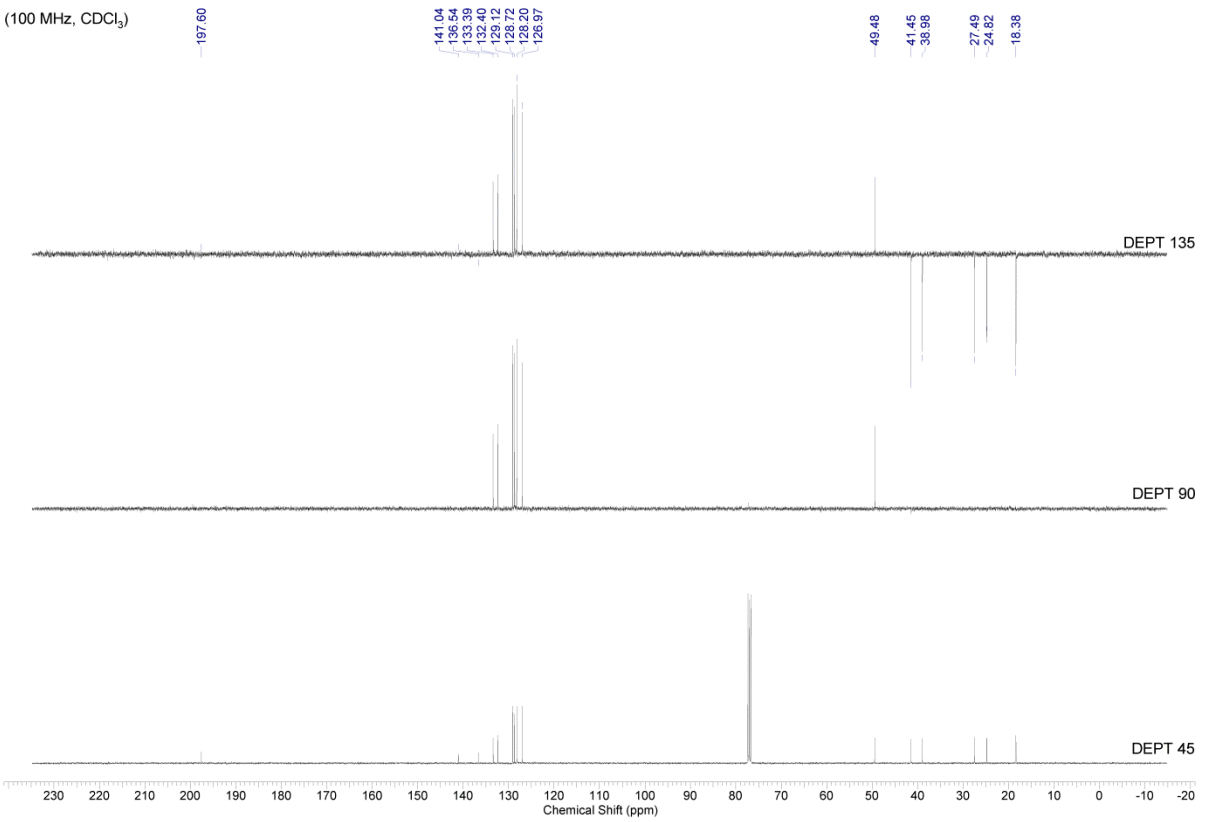
(100 MHz, $CDCl_3$)

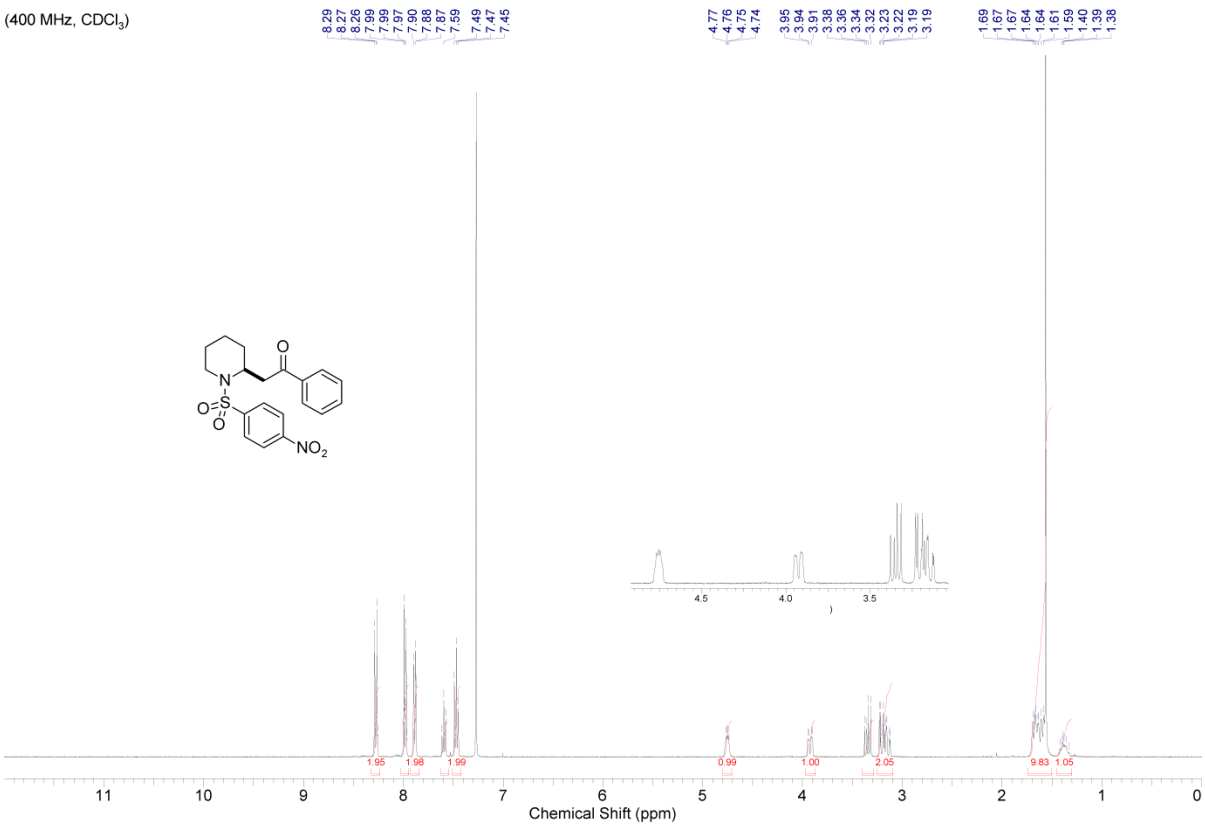


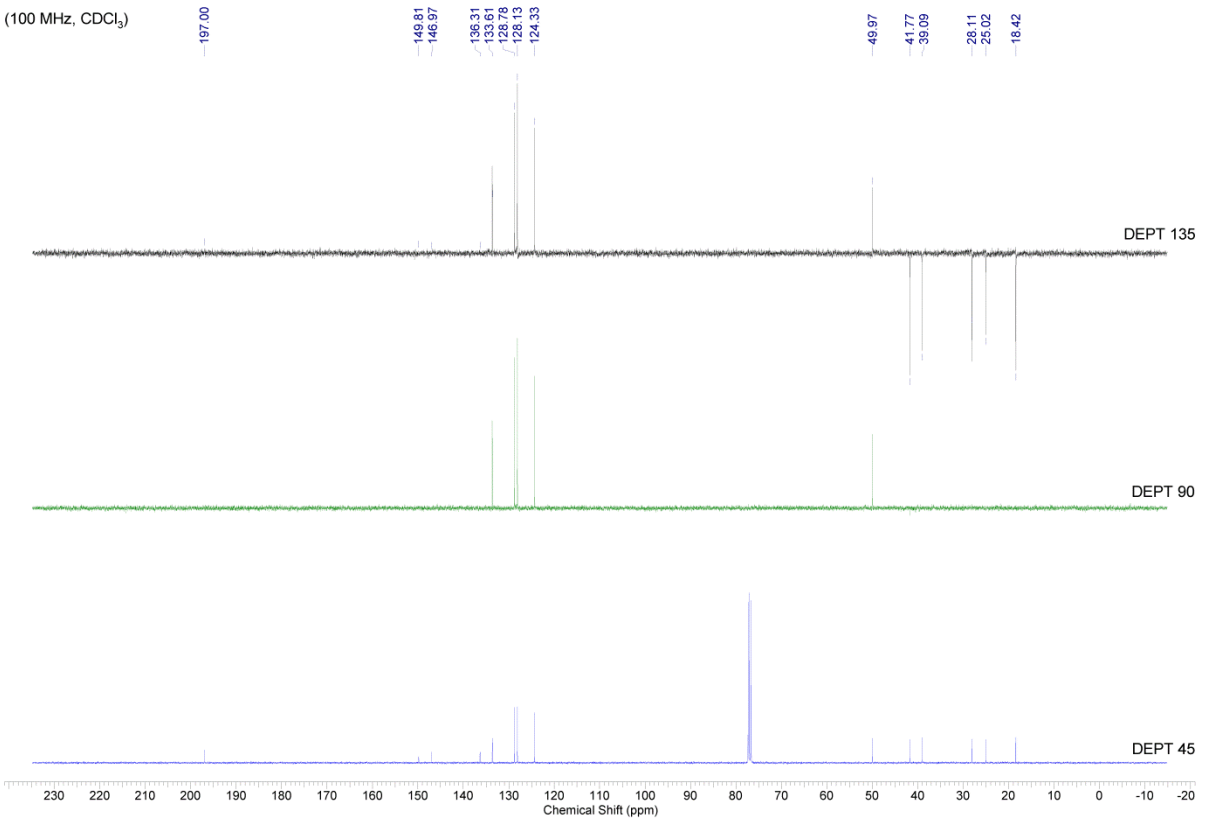

(400 MHz, CDCl3)
Water
DMSO
Chemical Shift (ppm)


(100 MHz, CDCl3)
DEPT 135
DEPT 90
DEPT 45
Chemical Shift (ppm)

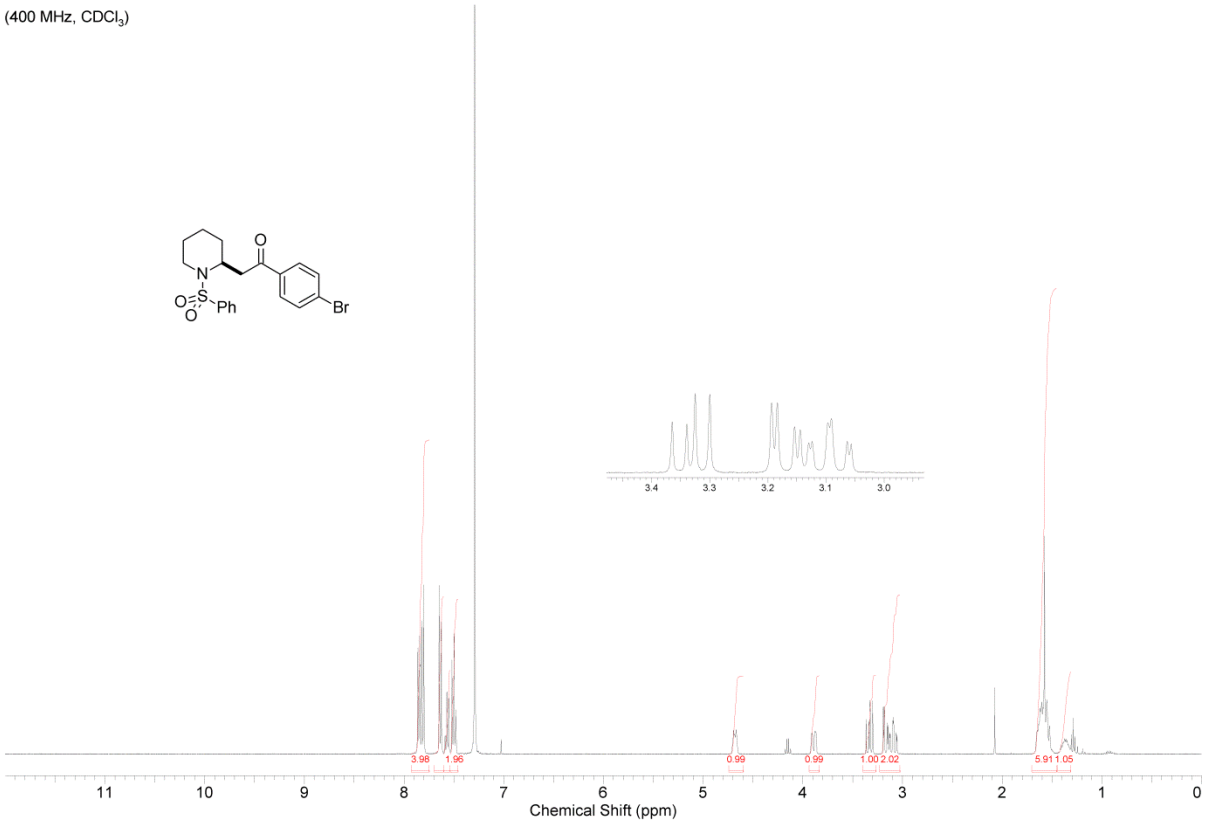

(400 MHz, CDCl3)
7.93
7.91
7.91
7.85
7.83
7.59
7.54
7.52
7.49
7.47
7.46
4.72
4.69
3.90
3.87
3.87
3.40
3.37
3.36
3.33
3.18
3.17
3.14
3.12
3.09
3.08
1.64
1.60
1.59
1.57
1.56
1.52
1.39
1.38
1.35
1.31
Ph
O
S=O
N
Ph
O
3.4
3.3
3.2
3.1
1.97
3.94
1.00
1.02
1.00
2.03
8.44
1.07
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


(100 MHz, CDCl3)
197.60
141.04
136.54
133.39
132.40
129.12
128.72
128.20
126.97
49.48
41.45
38.98
27.49
24.82
18.38
DEPT 135
DEPT 90
DEPT 45
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
Chemical Shift (ppm)

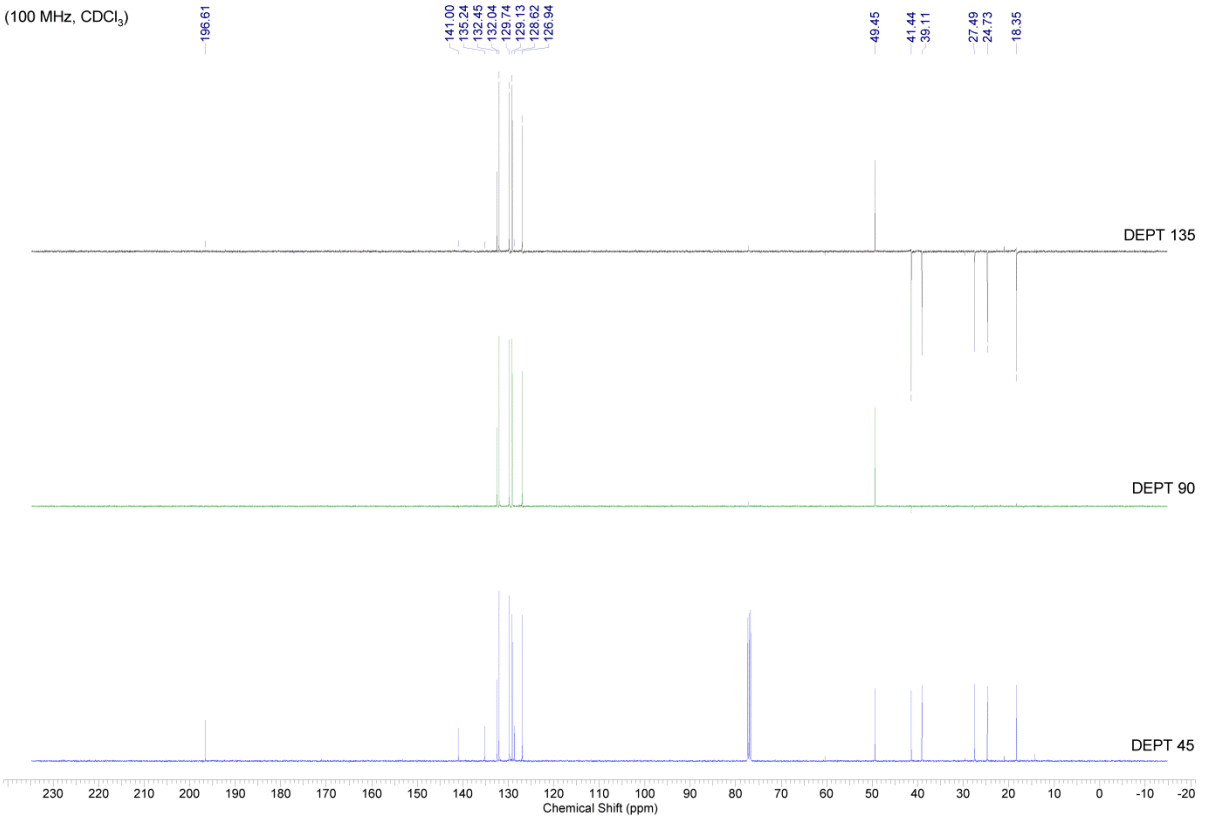

(400 MHz, $CDCl_3$)
8.29
8.27
8.26
7.99
7.99
7.97
7.90
7.88
7.87
7.59
7.49
7.47
7.45
4.77
4.76
4.75
4.74
3.95
3.94
3.91
3.38
3.36
3.34
3.32
3.23
3.22
3.19
3.19
1.69
1.67
1.67
1.64
1.64
1.61
1.59
1.40
1.39
1.38
O
N
O=S
O
NO_2
1.95
1.98
1.99
0.99
1.00
2.05
9.83
1.05
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

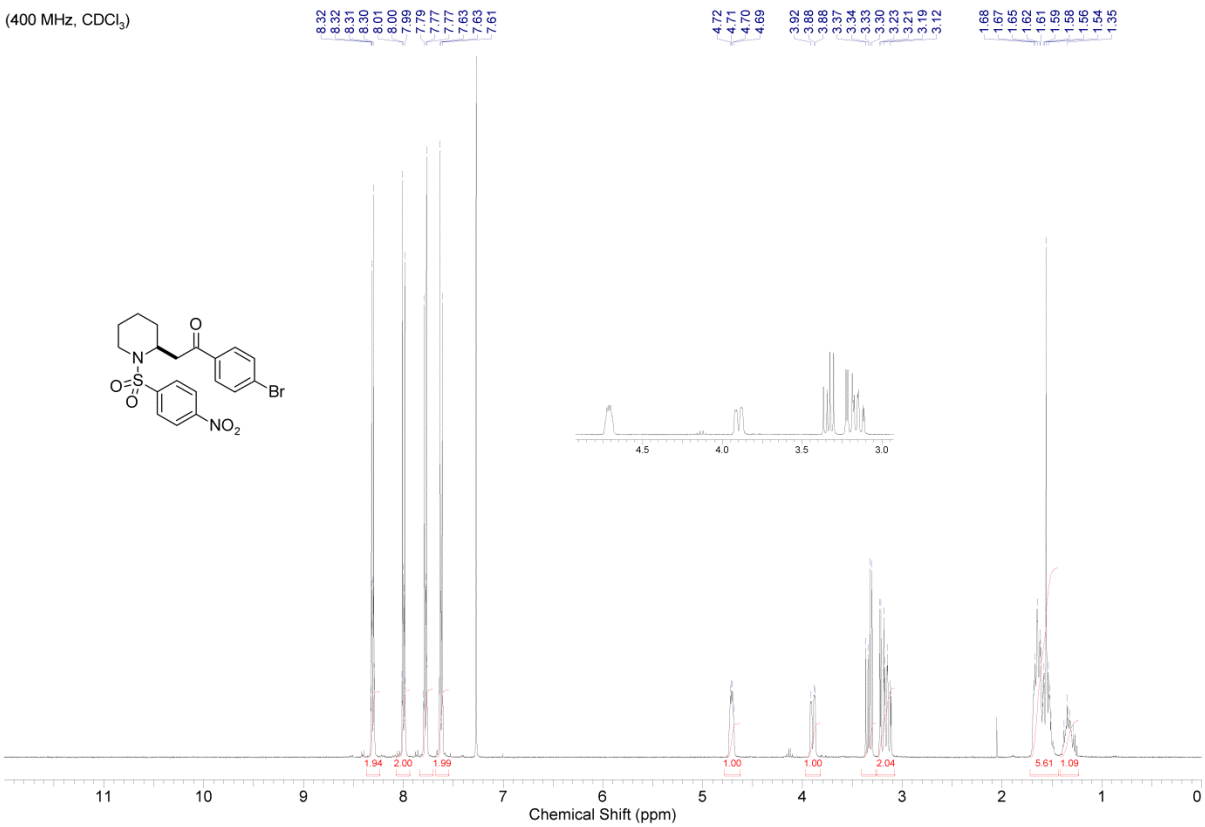

(100 MHz, $CDCl_3$)
197.00
149.81
146.97
136.31
133.61
128.78
128.13
124.33
49.97
41.77
39.09
28.11
25.02
18.42
DEPT 135
DEPT 90
DEPT 45
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
Chemical Shift (ppm)

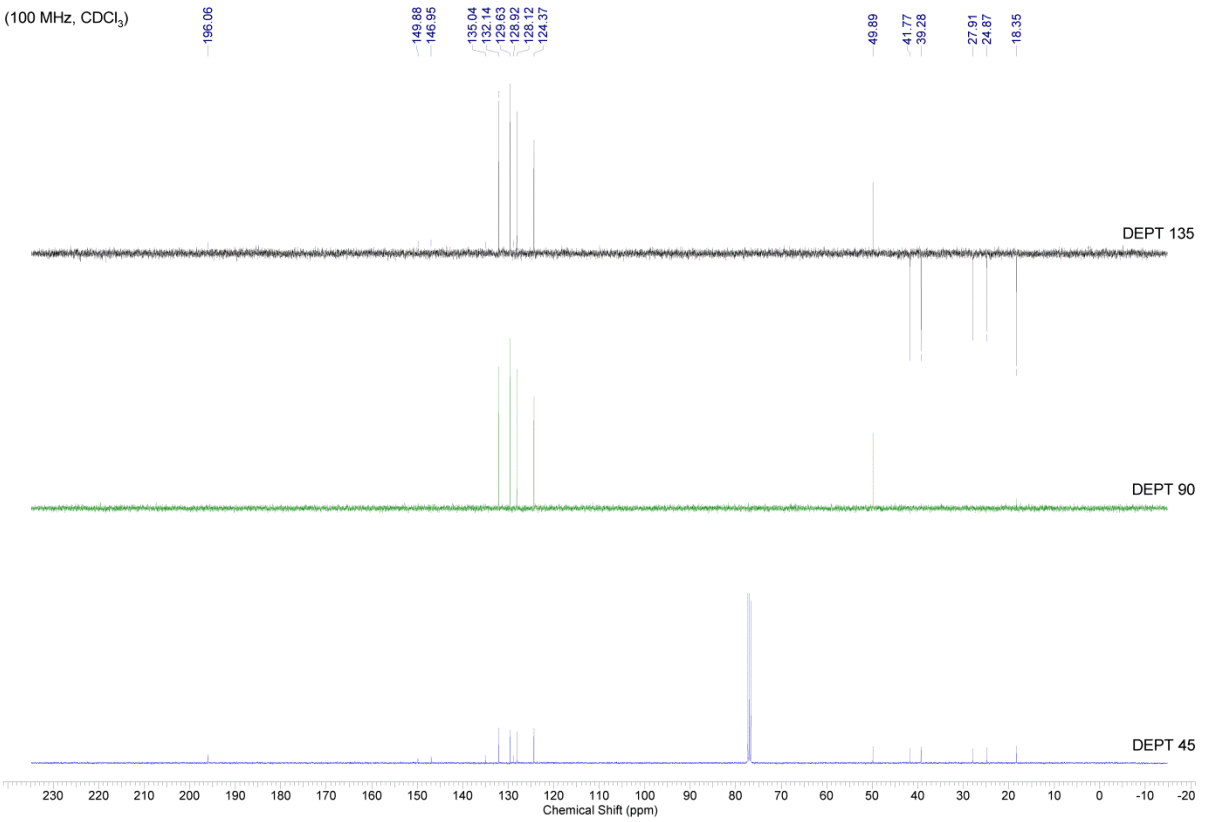
(400 MHz, $CDCl_3$)



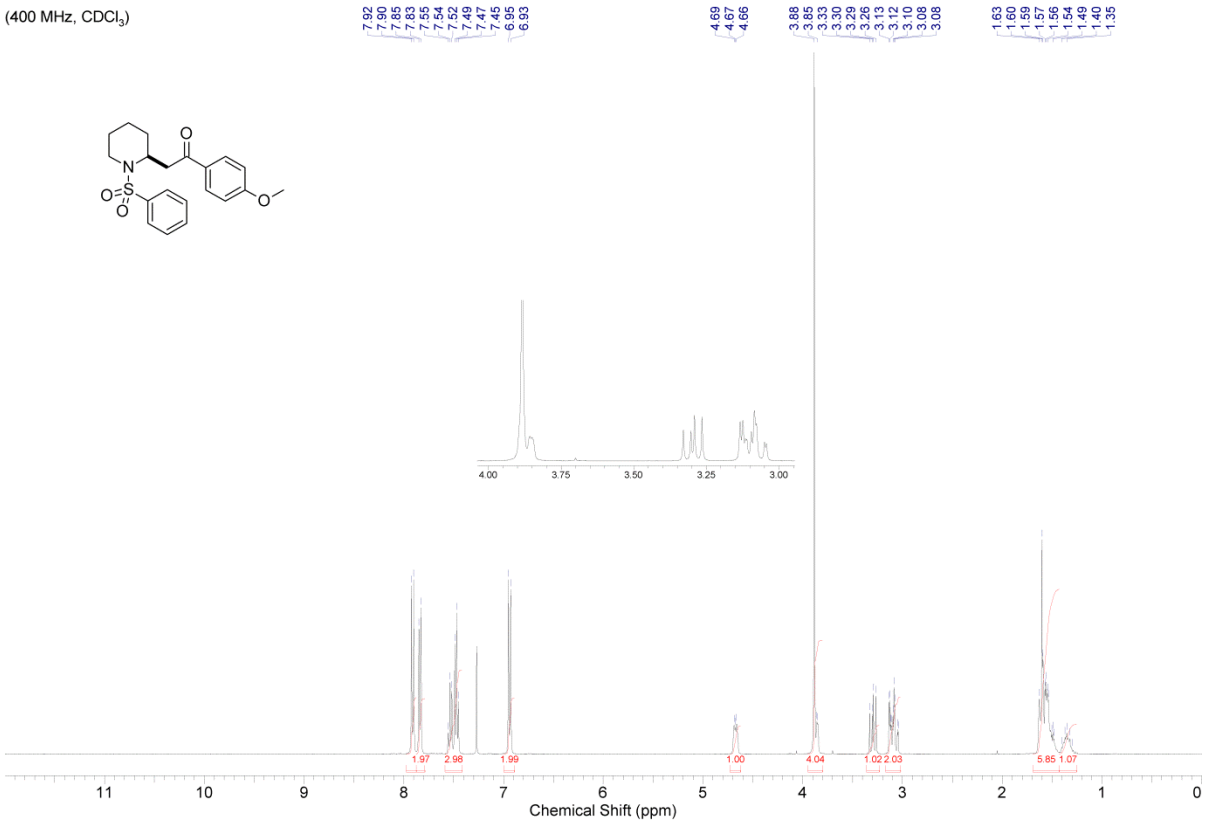
(100 MHz, $CDCl_3$)



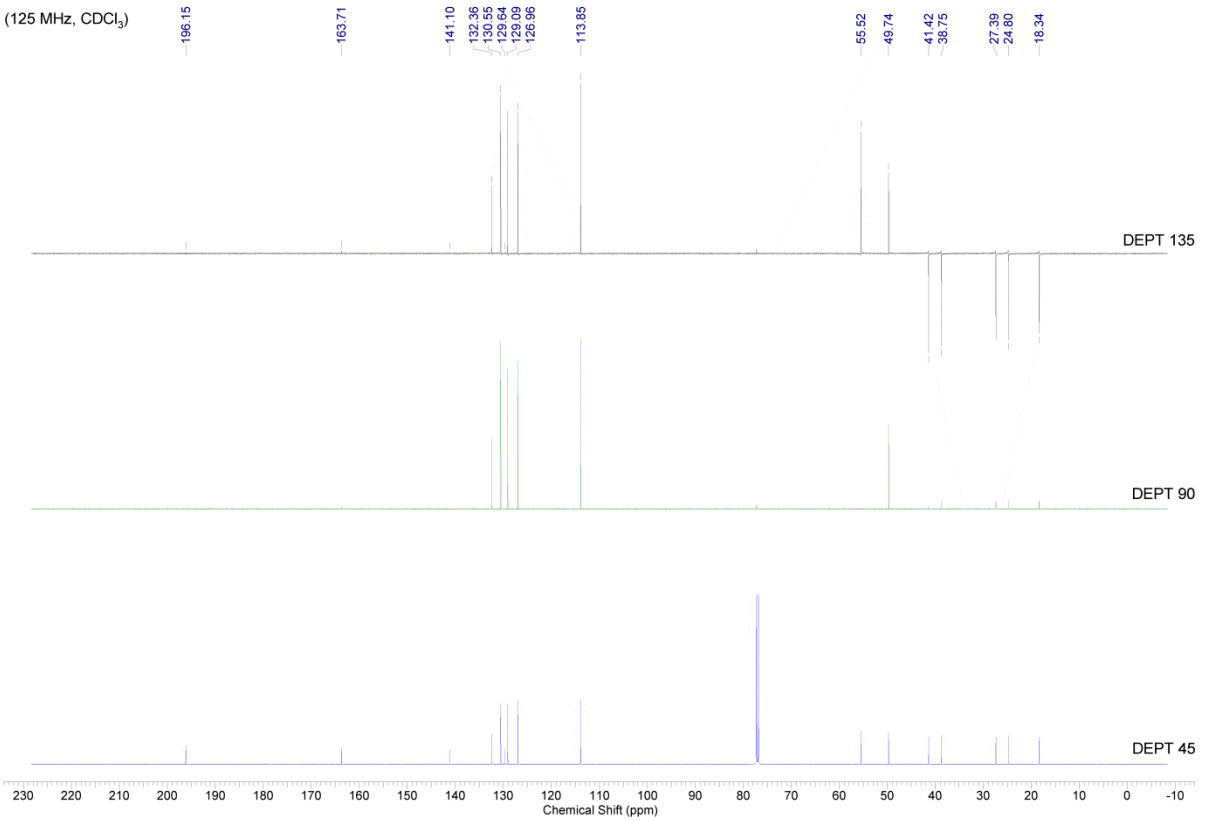

(400 MHz, CDCl3)
8.32
8.32
8.31
8.30
8.01
8.00
7.99
7.79
7.77
7.77
7.63
7.63
7.61
4.72
4.71
4.70
4.69
3.92
3.88
3.88
3.37
3.34
3.33
3.30
3.23
3.21
3.19
3.12
1.68
1.67
1.65
1.62
1.61
1.59
1.58
1.56
1.54
1.35
O
N
O=S=O
Br
NO2
1.94
2.00
1.99
1.00
1.00
2.04
5.61
1.09
Chemical Shift (ppm)


(100 MHz, CDCl3)
196.06
149.88
146.95
135.04
132.14
129.63
128.92
128.12
124.37
49.89
41.77
39.28
27.91
24.87
18.35
DEPT 135
DEPT 90
DEPT 45
Chemical Shift (ppm)

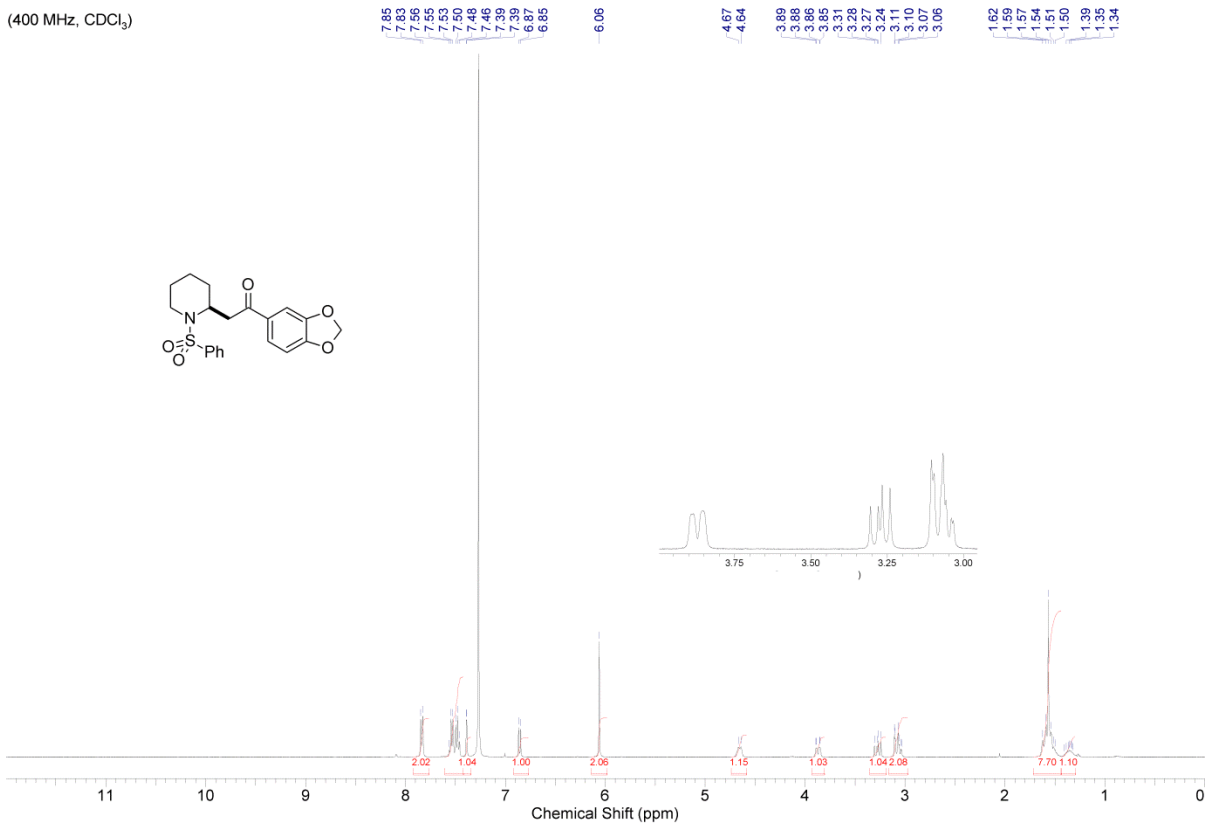
(400 MHz, $CDCl_3$)



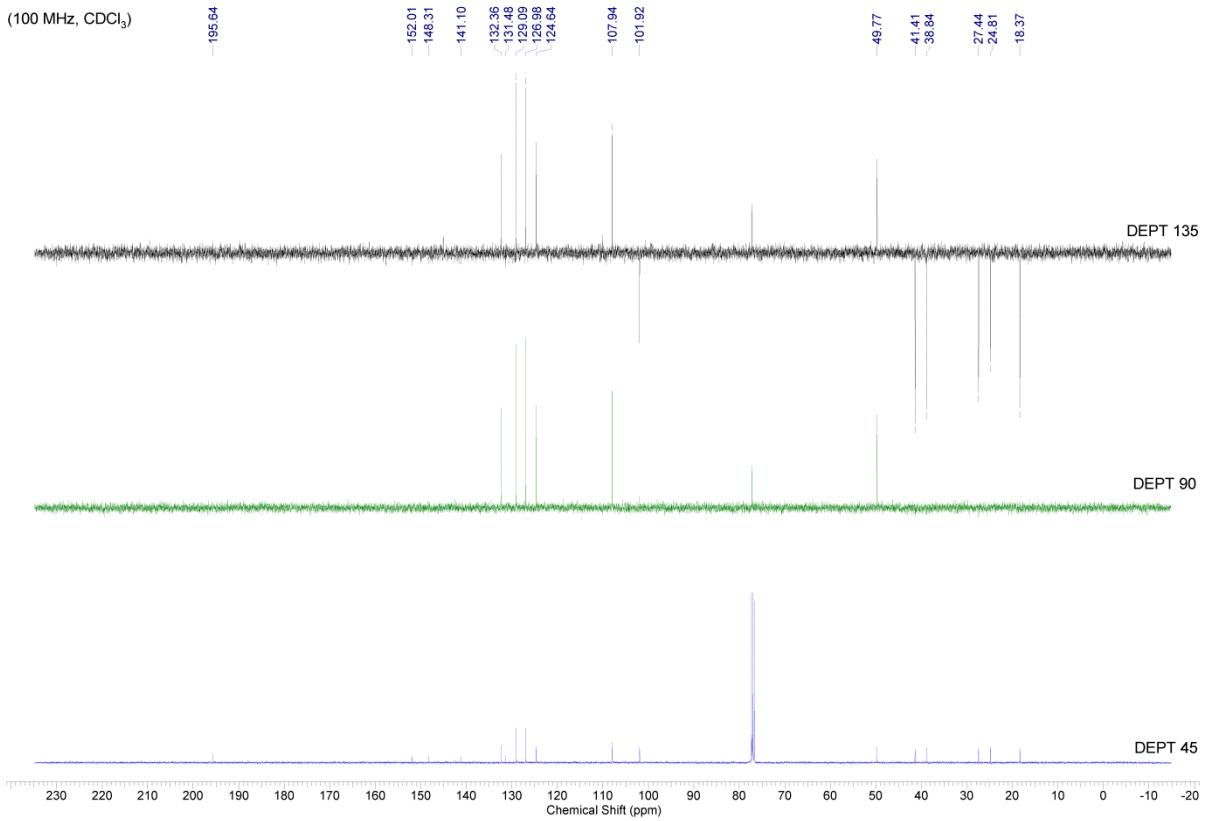
(125 MHz, $CDCl_3$)



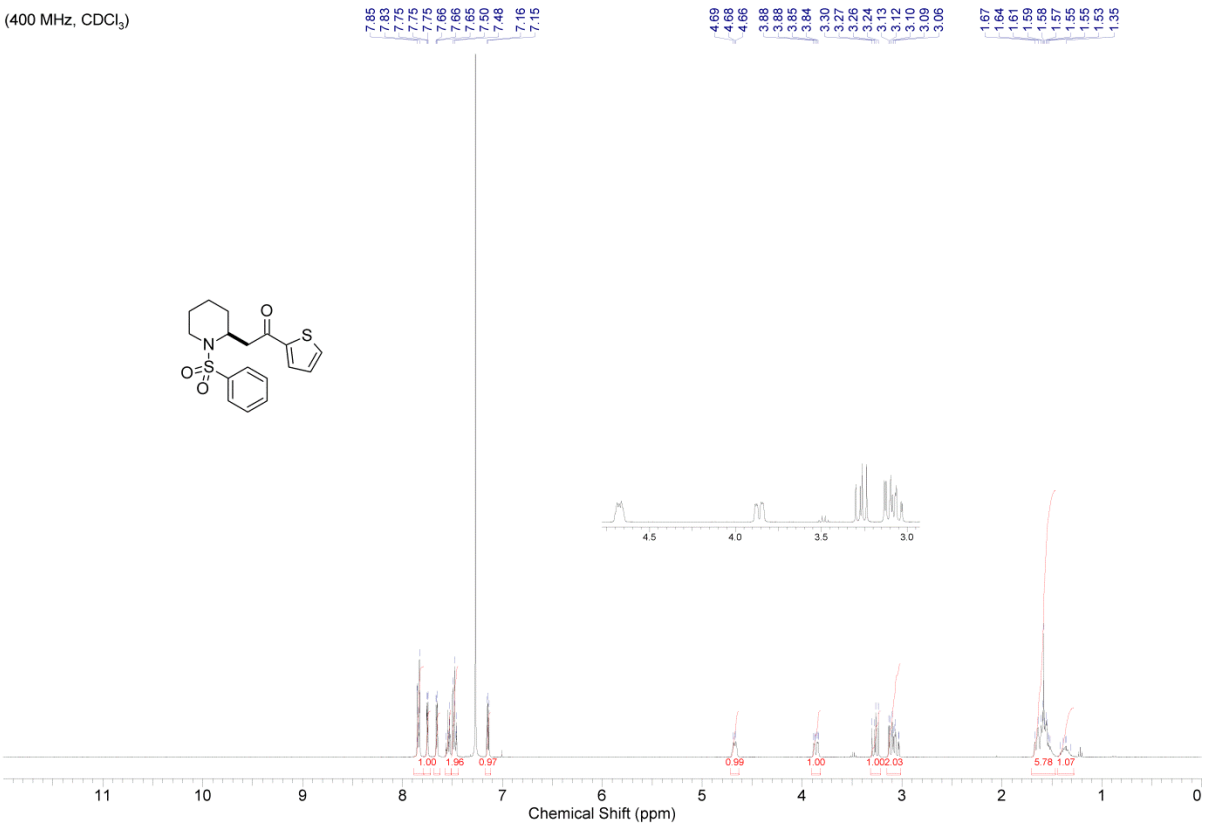
(400 MHz, $CDCl_3$)



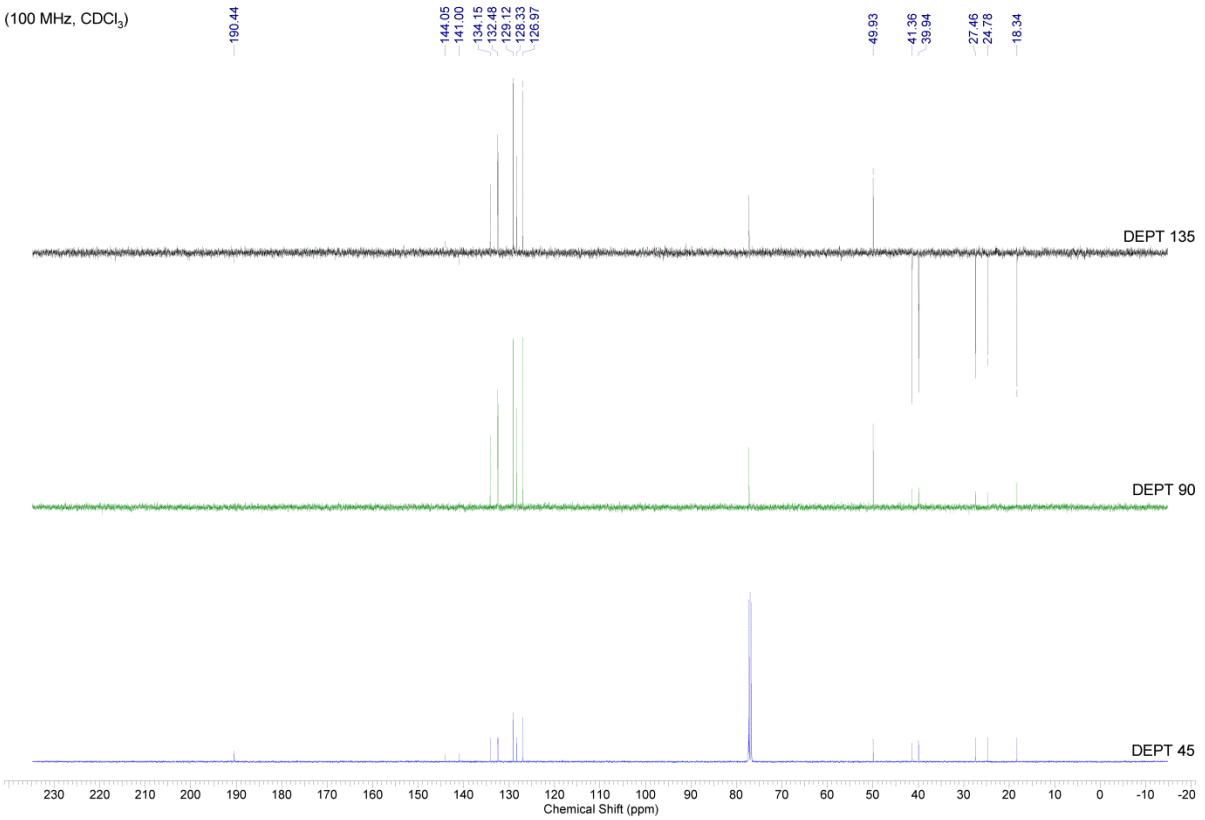
(100 MHz, $CDCl_3$)

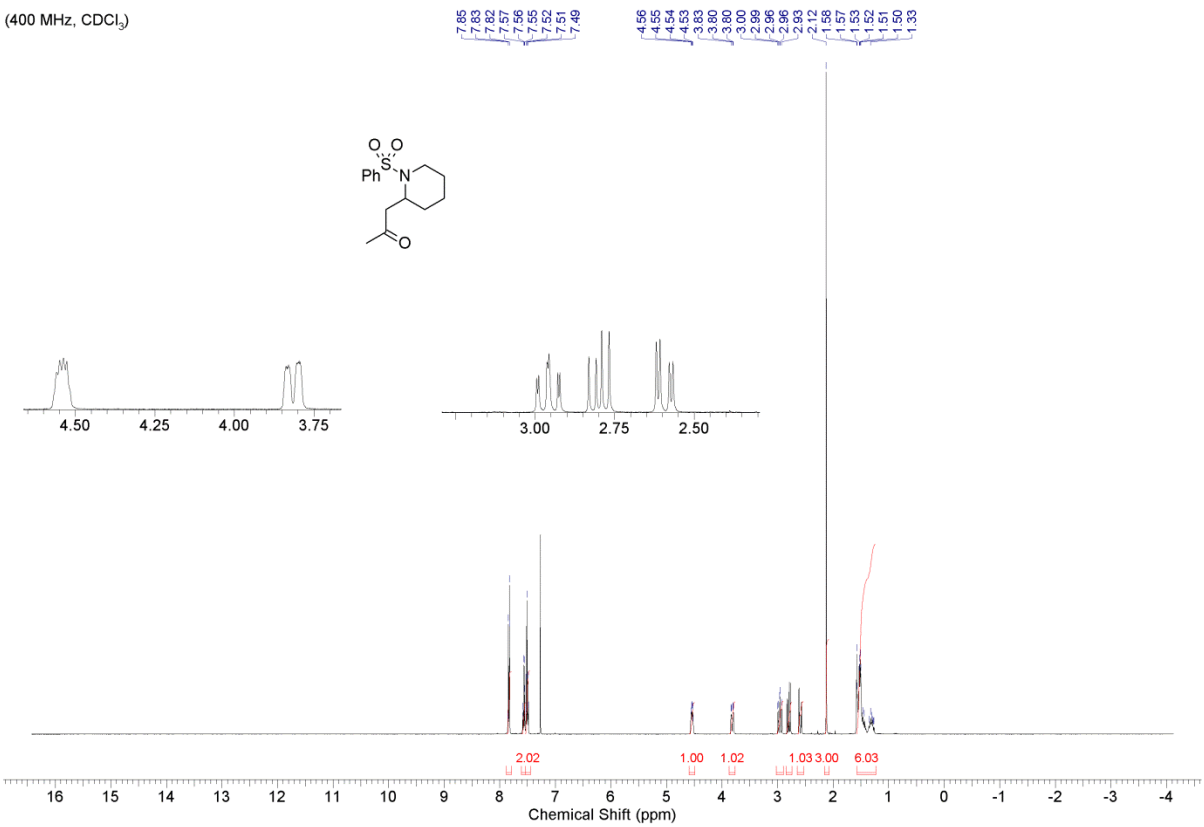


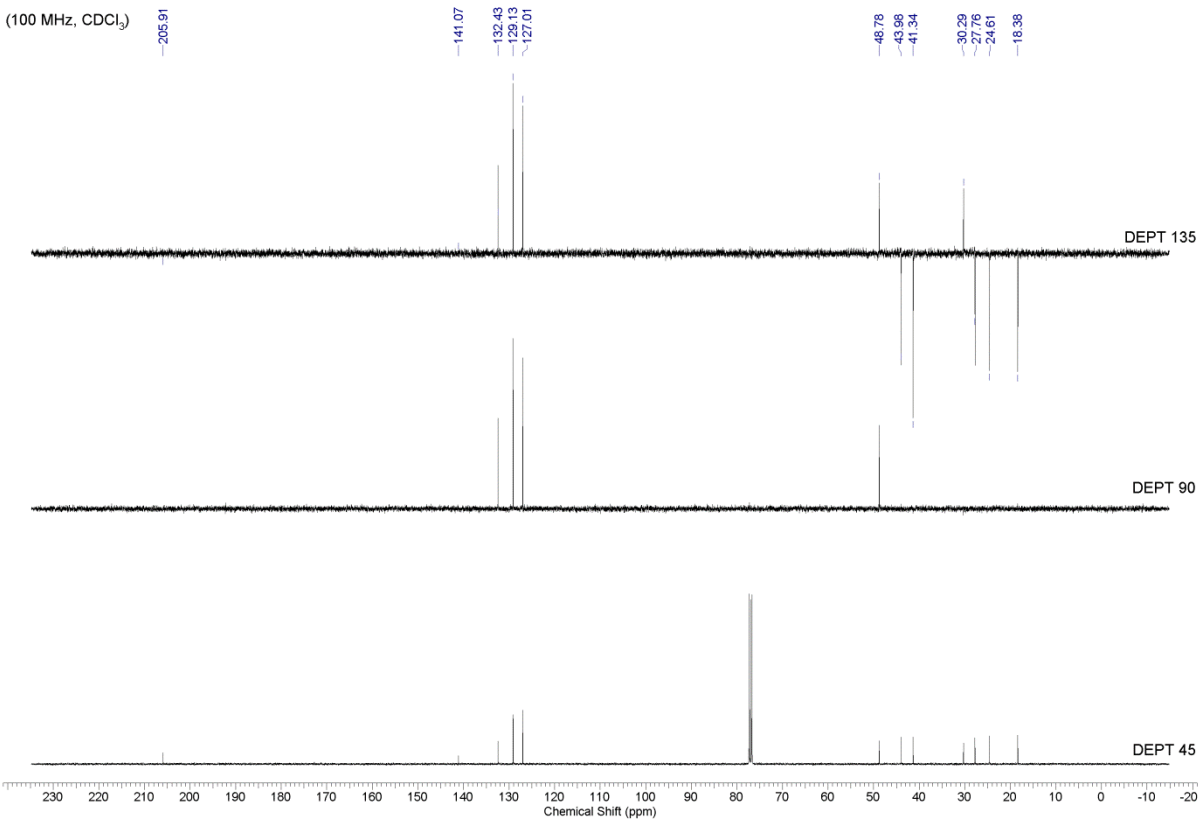
(400 MHz, $CDCl_3$)



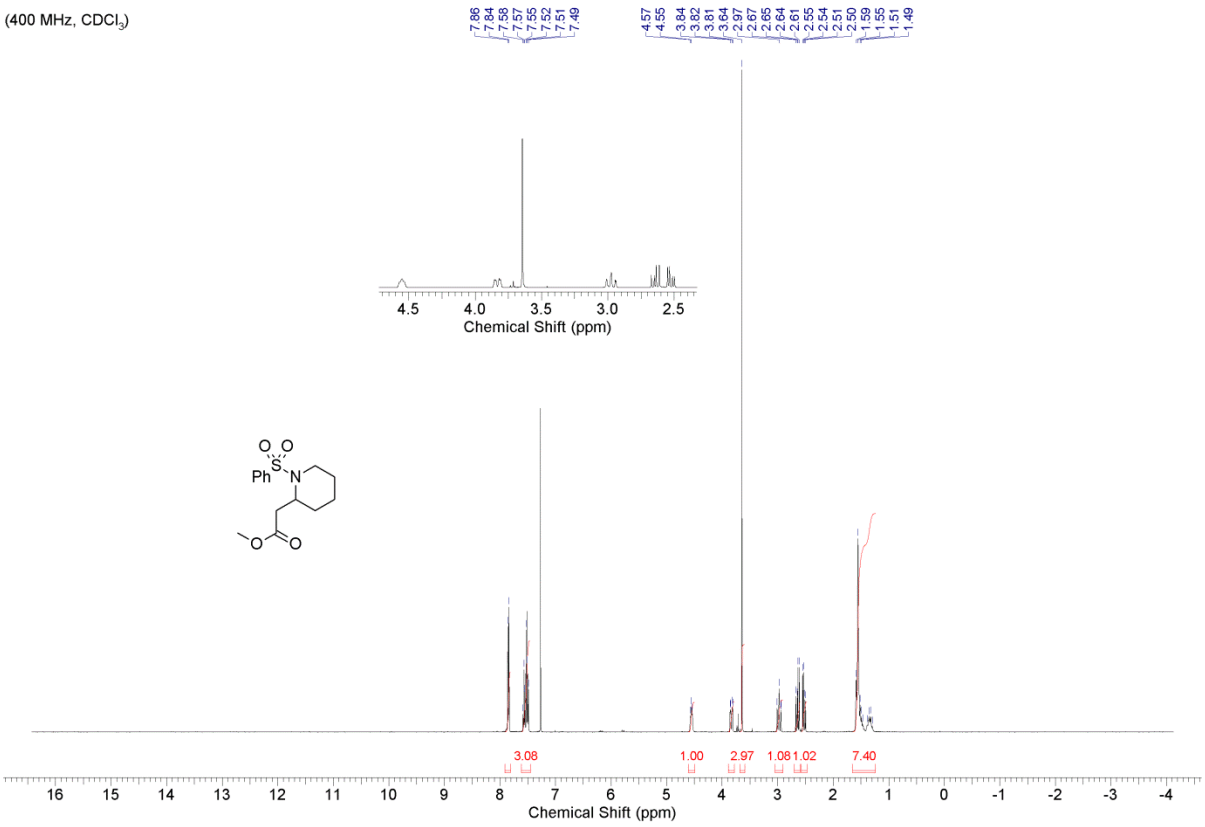
(100 MHz, $CDCl_3$)



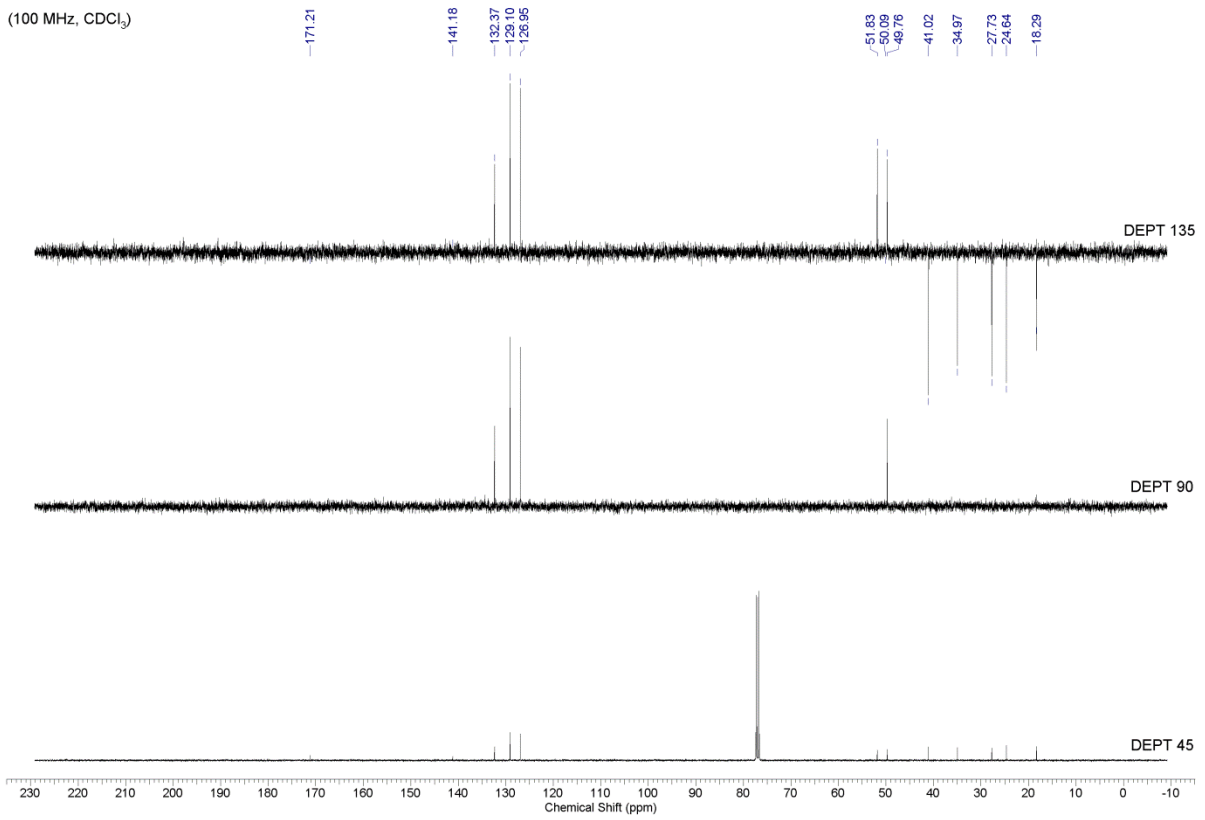

(400 MHz, CDCl3)
7.85
7.83
7.82
7.57
7.56
7.55
7.52
7.51
7.49
4.56
4.55
4.54
4.53
3.83
3.80
3.80
3.00
2.99
2.96
2.96
2.93
2.12
1.58
1.57
1.53
1.52
1.51
1.50
1.33
Ph
S
N
O
O
O
4.50
4.25
4.00
3.75
3.00
2.75
2.50
2.02
1.00
1.02
1.03
3.00
6.03
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
Chemical Shift (ppm)


(100 MHz, CDCl3)
205.91
141.07
132.43
129.13
127.01
48.78
43.98
41.34
30.29
27.76
24.61
18.38
DEPT 135
DEPT 90
DEPT 45
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
Chemical Shift (ppm)

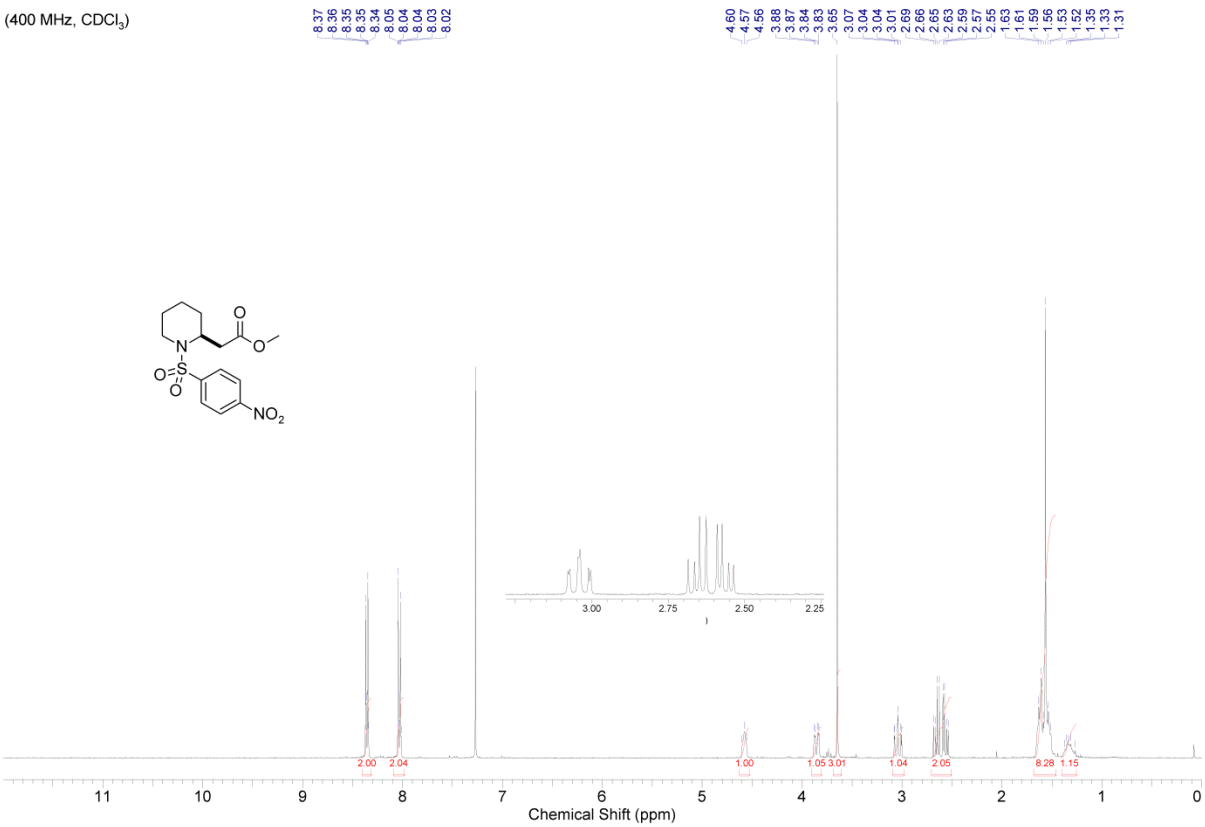
(400 MHz, $CDCl_3$)



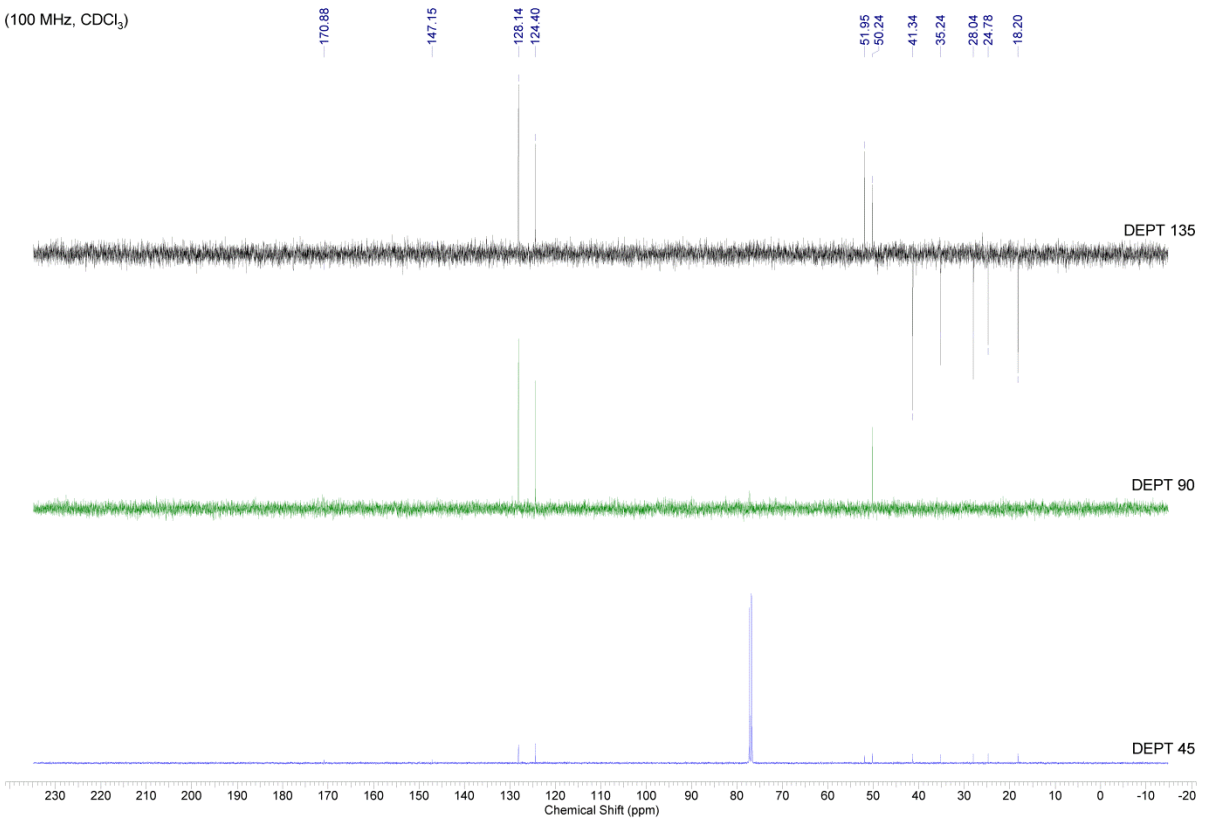
(100 MHz, $CDCl_3$)



(400 MHz, $CDCl_3$)

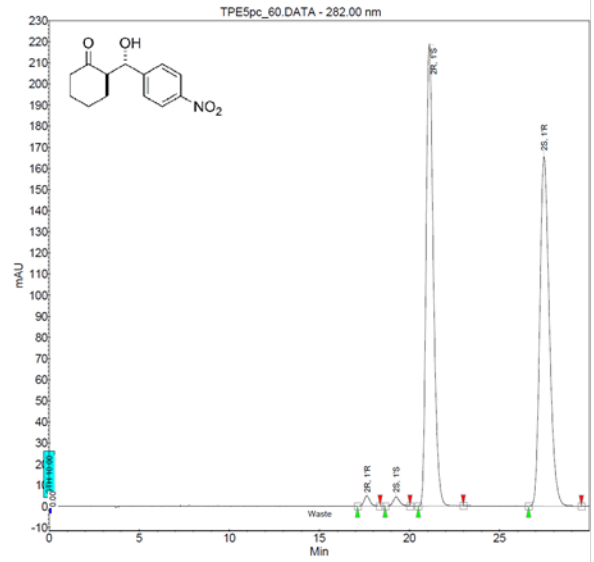


(100 MHz, $CDCl_3$)



Sample HPLC data

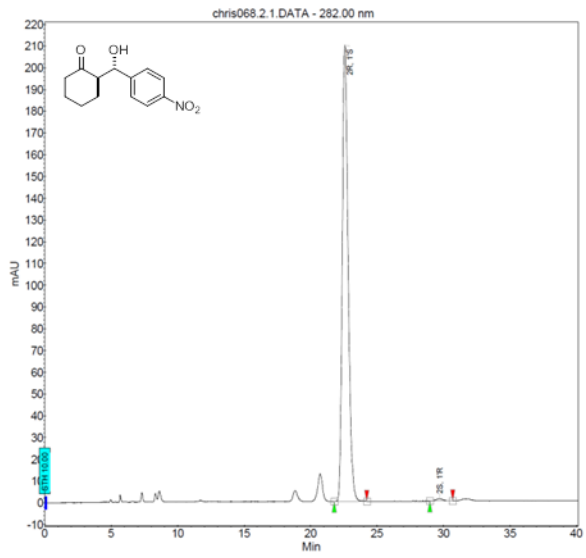
column:=ADH P=460 Flow=0.8 Solvent=15%ipa Acquired : 17/05/2011 17:54:18
Processed : 04/06/2011 17:10:45
Printed : 04/06/2011 17:10:51



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	2R, 1'R	17.64	0.86	4.8	1.8	0.864
2	2S, 1'S	19.25	0.91	4.3	1.9	0.906
3	2R, 1'S	21.09	49.28	219.0	102.4	49.278
4	2S, 1'R	27.46	48.95	165.6	101.8	48.953
Total			100.00	393.7	207.9	100.000

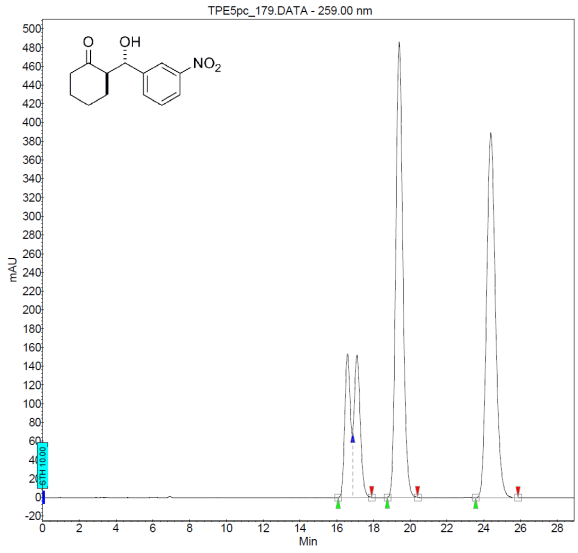
column:=ADH P=460 Flow=0.8 Solvent=15%ipa Acquired : 21/02/2011 15:59:48
Processed : 24/05/2011 12:27:26
Printed : 24/05/2011 12:27:36



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	2R, 1'S	22.57	99.44	210.1	106.7	99.438
2	2S, 1'R	29.69	0.56	1.0	0.6	0.562
Total			100.00	211.0	107.3	100.000

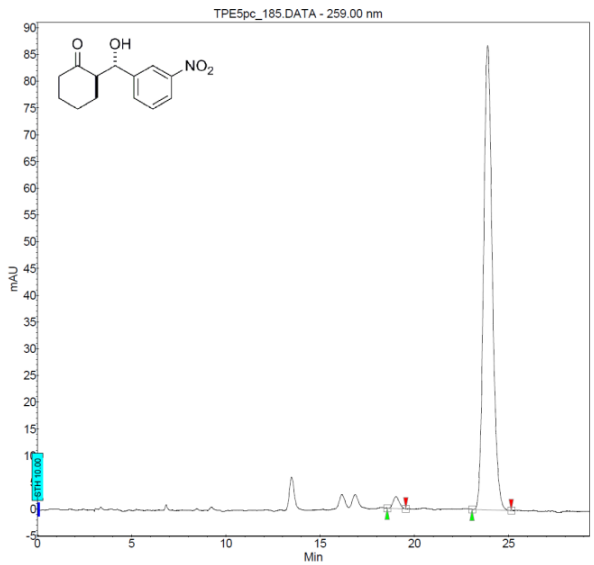
TPE306rc 10% IPA AD-H 1ml/min 565.6psi Acquired : 23/05/2011 16:52:02
Processed : 23/05/2011 17:27:32
Printed : 23/05/2011 17:27:56



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	16.59	10.20	153.5	55.9	10.202
4	UNKNOWN	17.11	10.62	152.1	58.2	10.620
2	UNKNOWN	19.40	39.46	486.1	216.1	39.456
3	UNKNOWN	24.38	39.72	389.5	217.6	39.722
Total			100.00	1181.3	547.8	100.000

TPE320 10% IPA AD-H 1ml/min 536.6psi Acquired : 25/05/2011 17:31:23
Processed : 26/05/2011 12:56:32
Printed : 26/05/2011 12:57:11

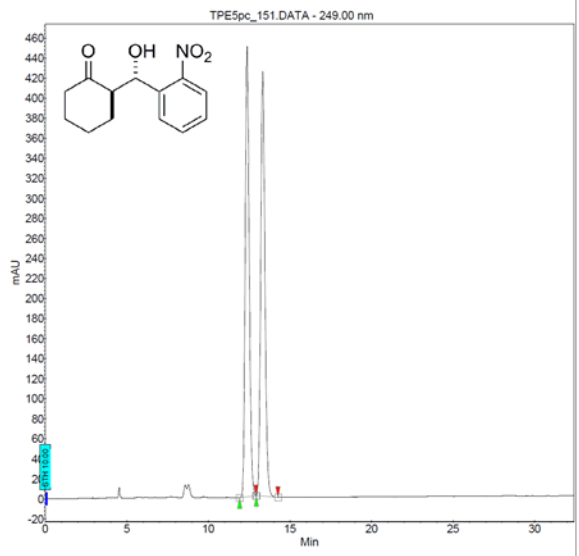


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	19.03	1.78	2.2	0.8	1.778
2	UNKNOWN	23.89	98.22	86.9	46.4	98.222
Total			100.00	89.1	47.3	100.000

TPE290anti 20% IPA AD-H 1ml/min 594.7psi

Acquired : 07/05/2011 11:20:47
Processed : 07/05/2011 12:37:53
Printed : 07/05/2011 12:38:18

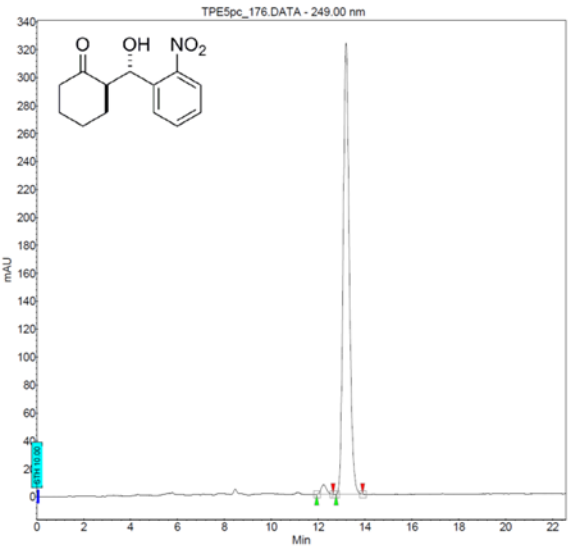


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12.39	49.91	449.6	127.6	49.915
2	UNKNOWN	13.33	50.09	424.0	128.0	50.085
Total			100.00	873.6	255.6	100.000

TPE318 20% IPA AD-H 1ml/min 609.2psi

Acquired : 22/05/2011 13:49:01
Processed : 22/05/2011 14:53:58
Printed : 22/05/2011 14:54:14

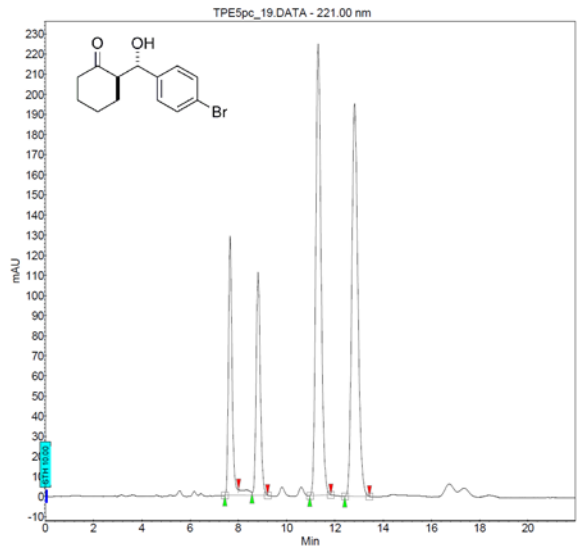


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12.23	1.91	7.0	1.9	1.914
2	UNKNOWN	13.19	98.09	323.2	97.8	98.086
Total			100.00	330.1	99.7	100.000

TPE174f3 15%IPA AD-H 1ml/min

Acquired : 10/10/2010 12:40:05
Processed : 10/10/2010 13:21:18
Printed : 10/10/2010 13:21:57

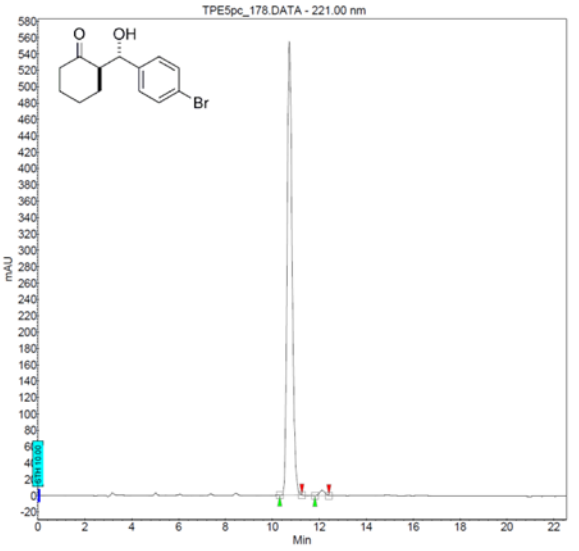


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	7.65	13.94	128.9	22.1	13.941
4	UNKNOWN	8.81	13.83	111.0	21.9	13.829
2	UNKNOWN	11.31	35.99	224.6	57.0	35.995
3	UNKNOWN	12.81	36.23	195.4	57.4	36.235
Total			100.00	659.9	158.4	100.000

TPE318 15% IPA AD-H 1ml/min 580.2psi

Acquired : 22/05/2011 14:56:55
Processed : 22/05/2011 15:21:30
Printed : 22/05/2011 15:21:47

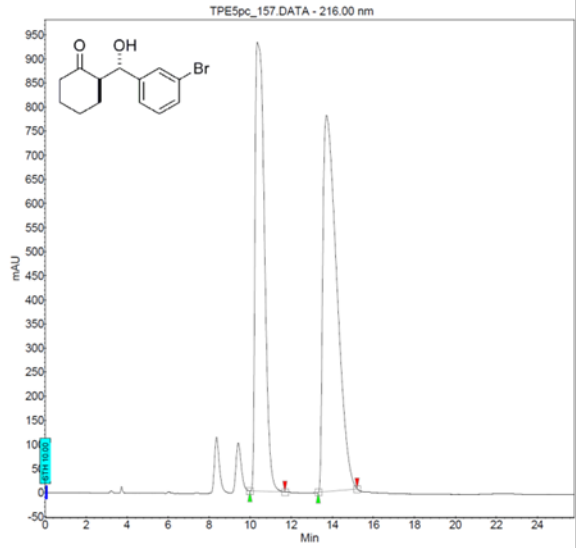


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.72	98.85	554.7	137.3	98.849
2	UNKNOWN	12.12	1.15	6.3	1.6	1.151
Total			100.00	561.1	138.9	100.000

TPE294 5% IPA OD-H 1ml/min 609.2psi

Acquired : 14/05/2011 10:29:25
Processed : 14/05/2011 14:22:38
Printed : 14/05/2011 14:23:38

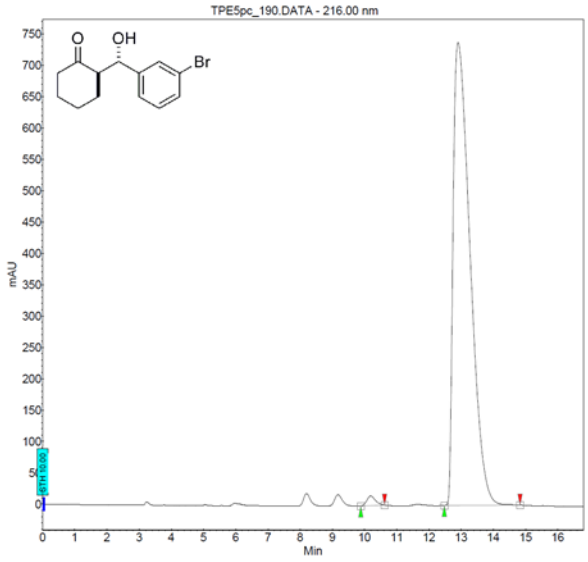


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.35	44.36	931.9	492.3	44.364
2	UNKNOWN	13.72	55.64	780.0	617.4	55.636
Total			100.00	1711.8	1109.7	100.000

TPE319a 5% IPA OD-H 1ml/min 565.6psi

Acquired : 27/05/2011 09:56:38
Processed : 27/05/2011 10:32:32
Printed : 27/05/2011 10:33:06

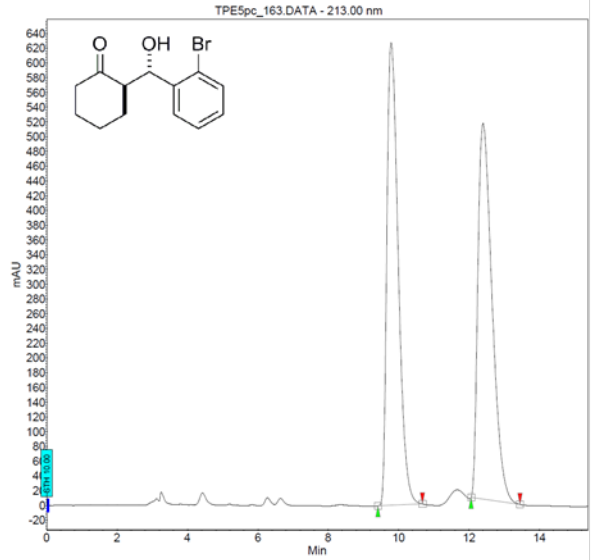


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.19	1.04	15.3	4.7	1.043
2	UNKNOWN	12.91	98.96	738.9	449.2	98.957
Total			100.00	754.2	454.0	100.000

TPE291 5% IPA OD-H 1ml/min 565.6psi

Acquired : 14/05/2011 14:19:49
Processed : 14/05/2011 14:37:35
Printed : 14/05/2011 14:37:56

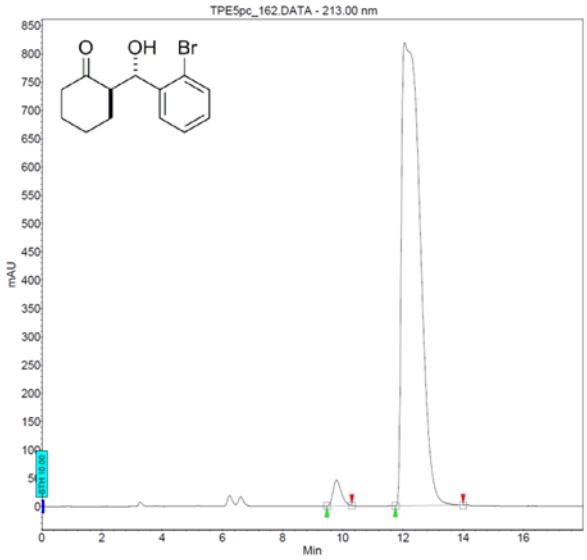


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	9.79	49.64	627.7	233.9	49.640
2	UNKNOWN	12.40	50.36	509.4	237.3	50.360
Total			100.00	1137.1	471.2	100.000

TPE298 5% IPA OD-H 1ml/min 580.2psi

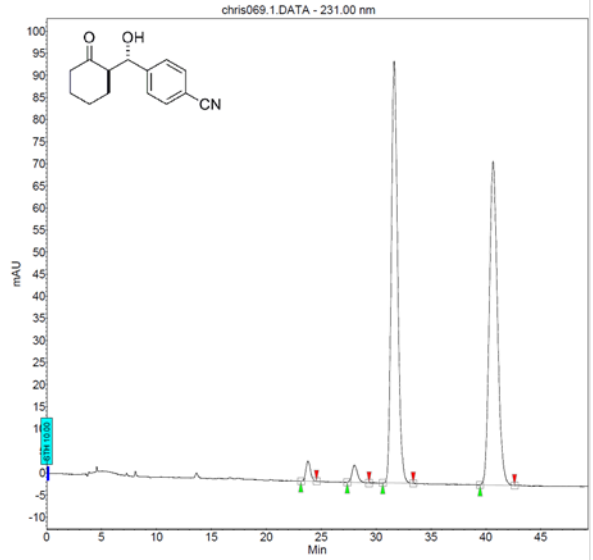
Acquired : 14/05/2011 13:57:31
Processed : 14/05/2011 14:26:34
Printed : 14/05/2011 14:26:52



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	9.80	2.43	45.6	14.5	2.434
2	UNKNOWN	12.05	97.57	819.0	581.6	97.566
Total			100.00	864.6	596.1	100.000

column:= ADH P= 450 Flow= 0.8 ml/m Solvent= 10% ipa in hexane from stock solution
Acquired : 16/02/2011 11:15:29

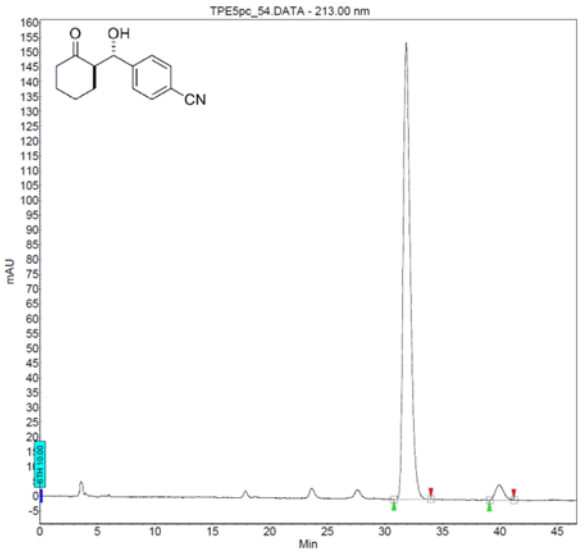


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23.80	1.66	4.5	2.2	1.664
2	UNKNOWN	28.02	1.76	3.9	2.3	1.756
3	UNKNOWN	31.64	48.52	95.5	63.6	48.518
4	UNKNOWN	40.65	48.06	73.3	63.0	48.063
Total			100.00	177.3	131.1	100.000

TPE297 10% IPA AD-H 0.8ml/min 435.1psi

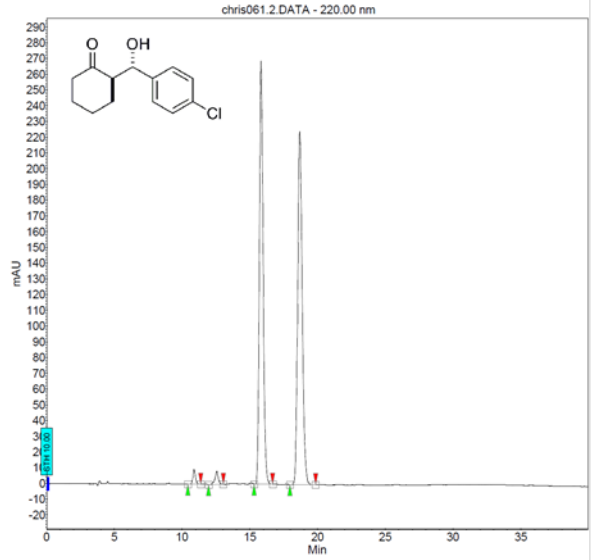
Acquired : 14/05/2011 16:15:32
Processed : 14/05/2011 17:05:29
Printed : 14/05/2011 17:05:44



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	31.85	96.18	154.4	109.4	96.183
2	UNKNOWN	39.94	3.82	5.1	4.3	3.817
Total			100.00	159.5	113.8	100.000

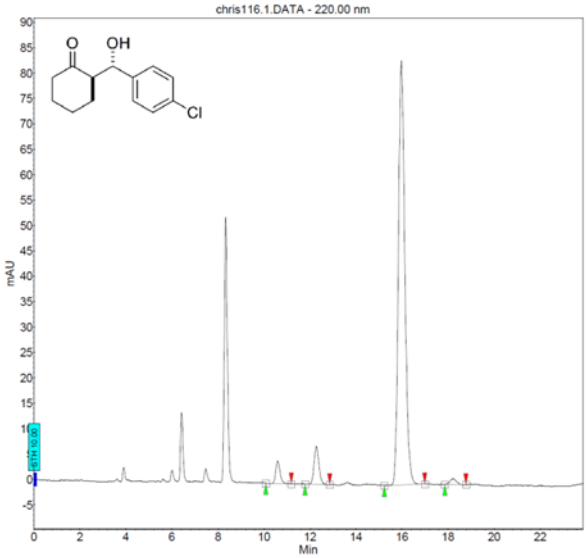
column:=ADH P=430 Flow=0.8 Solvent=10% ipa in hexane
Acquired : 11/02/2011 11:43:07



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.88	1.16	9.5	2.1	1.159
2	UNKNOWN	12.56	1.28	8.1	2.3	1.285
3	UNKNOWN	15.83	48.71	269.0	86.9	48.706
4	UNKNOWN	18.68	48.85	224.4	87.2	48.851
Total			100.00	511.0	178.5	100.000

column:= ADH P=430 Flow= 0.8 ml/m Solvent= 10% ipa in hexane from stock solution
Acquired : 06/06/2011 17:09:47

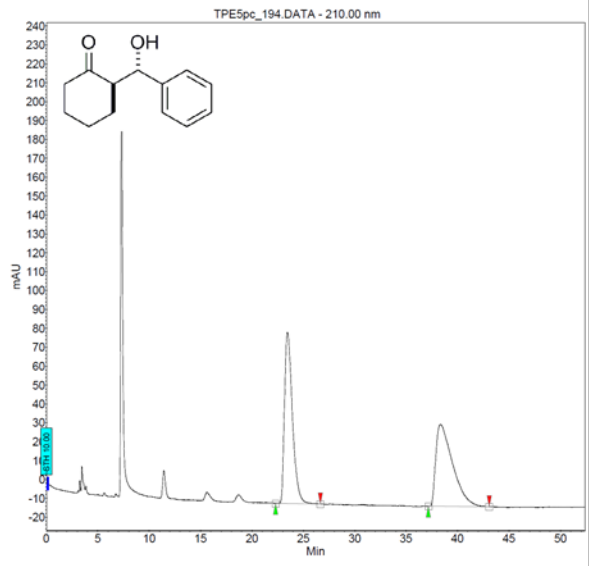


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.59	3.13	4.5	0.9	3.127
2	UNKNOWN	12.27	6.02	7.5	1.8	6.019
3	UNKNOWN	15.97	89.66	83.5	26.9	89.659
4	UNKNOWN	18.21	1.19	1.1	0.4	1.195
Total			100.00	96.6	30.0	100.000

PhCHO racemate 1% IPA OD-H 1ml/min 565.6psi

Acquired : 01/06/2011 10:45:16
Processed : 02/06/2011 17:03:15
Printed : 02/06/2011 17:03:33

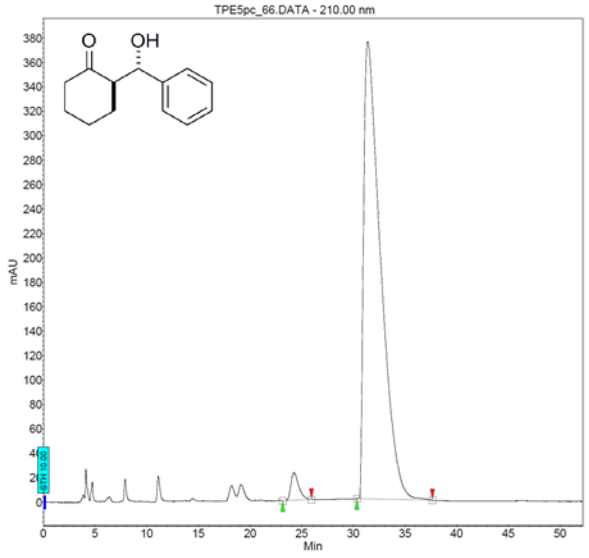


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23.45	49.71	90.6	80.8	49.708
2	UNKNOWN	38.33	50.29	43.3	81.8	50.292
Total			100.00	133.9	162.6	100.000

cd112 3% IPA OD-H 0.8ml/min 420.6psi

Acquired : 02/06/2011 14:09:51
Processed : 02/06/2011 17:04:25
Printed : 02/06/2011 17:04:45

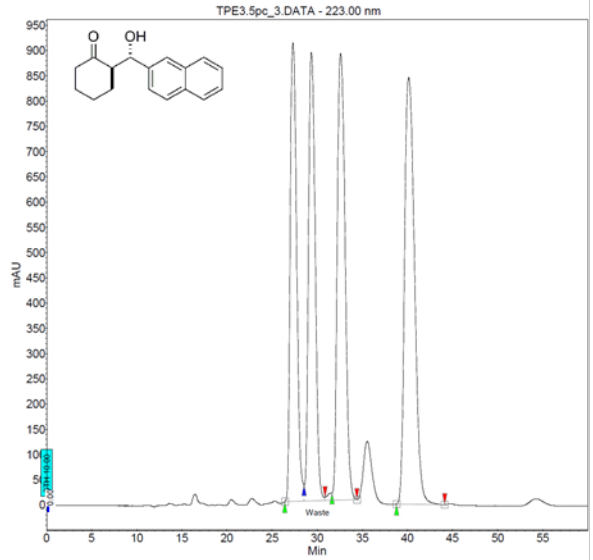


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24.25	2.69	22.6	19.7	2.695
2	UNKNOWN	31.40	97.31	374.6	711.0	97.305
Total			100.00	397.2	730.7	100.000

TPE178 20% IPA OD-H 0.25ml/min

Acquired : 11/10/2010 09:33:47
Processed : 11/10/2010 13:15:49
Printed : 11/10/2010 13:16:49

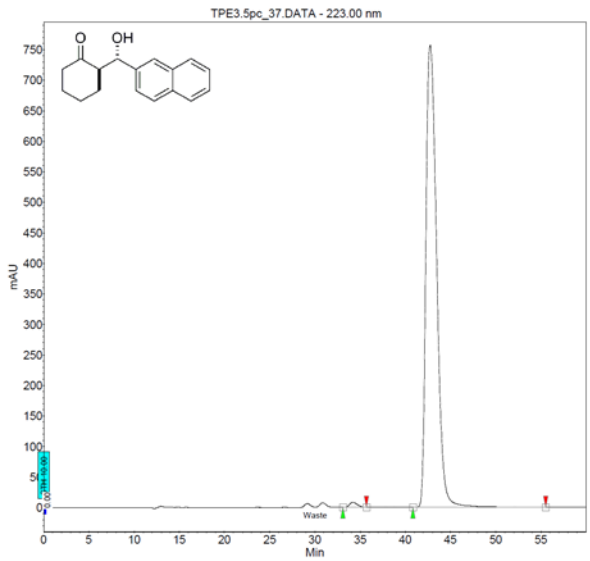


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	27.29	21.73	908.4	758.9	21.725
3	UNKNOWN	29.33	22.05	888.7	770.1	22.046
4	UNKNOWN	32.58	25.44	884.4	888.6	25.439
2	UNKNOWN	40.13	30.79	844.8	1075.5	30.790
Total			100.00	3526.2	3493.1	100.000

cd110 20% IPA OD-H 0.25ml/min 174psi

Acquired : 25/05/2011 13:23:18
Processed : 25/05/2011 14:47:00
Printed : 25/05/2011 14:48:25

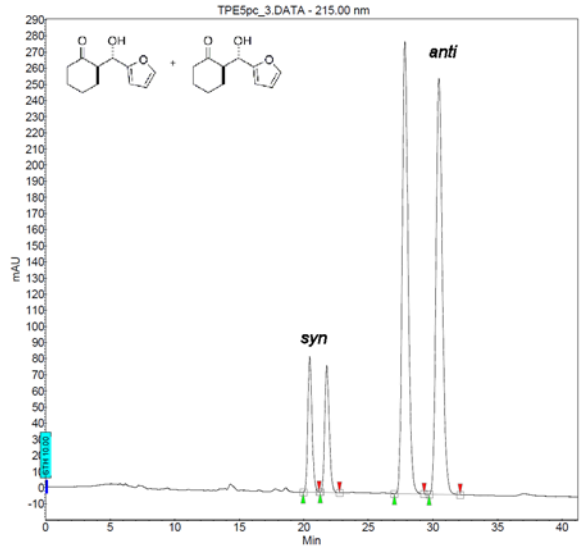


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	34.20	0.75	8.1	7.8	0.749
2	UNKNOWN	42.74	99.25	756.6	1038.1	99.251
Total			100.00	764.7	1045.9	100.000

TPE180f3 10% IPA AD-H 0.5ml/min

Acquired : 10/10/2010 13:18:57
Processed : 10/10/2010 15:15:06
Printed : 10/10/2010 15:16:20

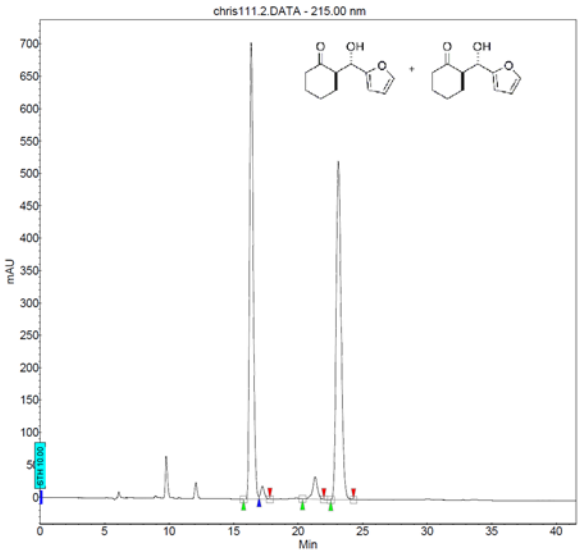


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20.45	8.92	84.2	32.0	8.921
2	UNKNOWN	21.77	8.89	78.6	31.9	8.893
3	UNKNOWN	27.82	41.13	280.4	147.6	41.134
4	UNKNOWN	30.46	41.05	257.9	147.3	41.052
Total			100.00	701.1	358.7	100.000

column:= ADH P=300 Flow= 0.5 ml/m Solvent= 10%ipa in hexane from stock solution

Acquired : 02/06/2011 15:28:28
Processed : 02/06/2011 15:28:57
Printed : 02/06/2011 15:29:28

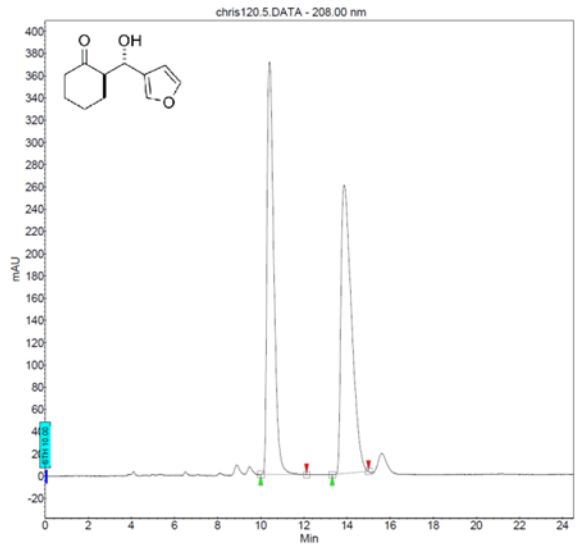


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
3	UNKNOWN	16.36	47.81	705.4	234.5	47.813
4	UNKNOWN	17.23	1.32	19.7	6.5	1.323
1	UNKNOWN	21.32	3.07	34.4	15.1	3.072
2	UNKNOWN	23.12	47.79	522.5	234.4	47.793
Total			100.00	1282.1	490.5	100.000

column:=ODH P=460 Flow= 0.8 ml/m Solvent= 10% ipa in hexane from stock solution

Acquired : 13/06/2011 13:06:15

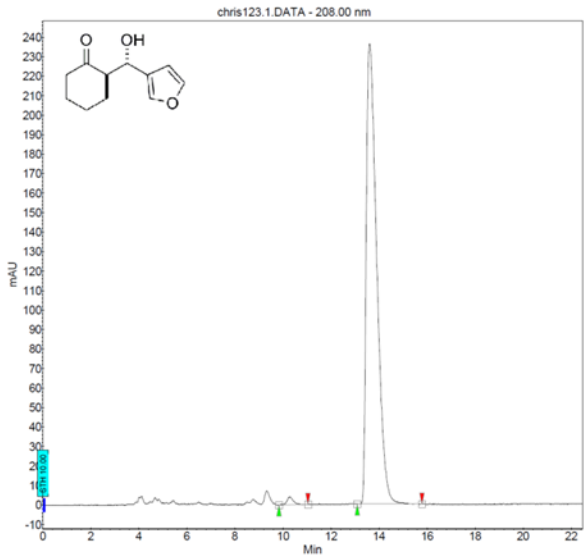


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.40	48.01	370.9	135.8	48.013
2	UNKNOWN	13.87	51.99	259.5	147.0	51.987
Total			100.00	630.4	282.8	100.000

column:=ODH P=460 Flow= 0.8 ml/m Solvent= 10% ipa in hexane from stock solution

Acquired : 15/06/2011 16:07:52
Processed : 17/06/2011 09:00:39
Printed : 17/06/2011 09:01:58

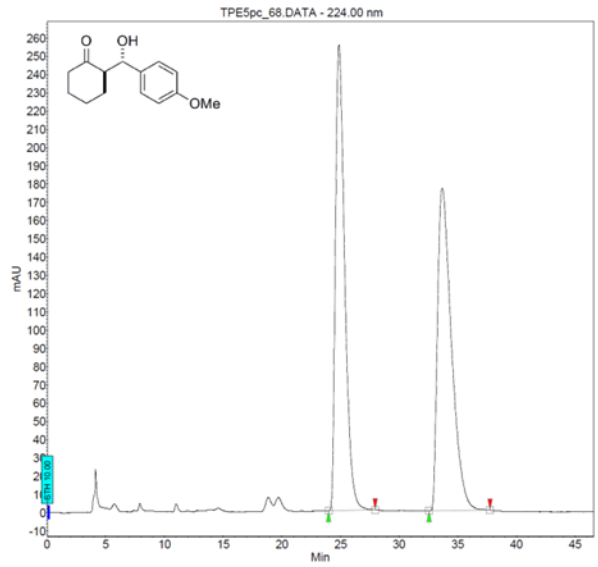


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.25	1.04	3.9	1.2	1.039
2	UNKNOWN	13.60	98.96	236.2	118.9	98.961
Total			100.00	240.1	120.1	100.000

OMe race 3% IPA OD-H 0.8ml/min

Acquired : 02/06/2011 16:08:31
Processed : 02/06/2011 17:07:14
Printed : 02/06/2011 17:07:31

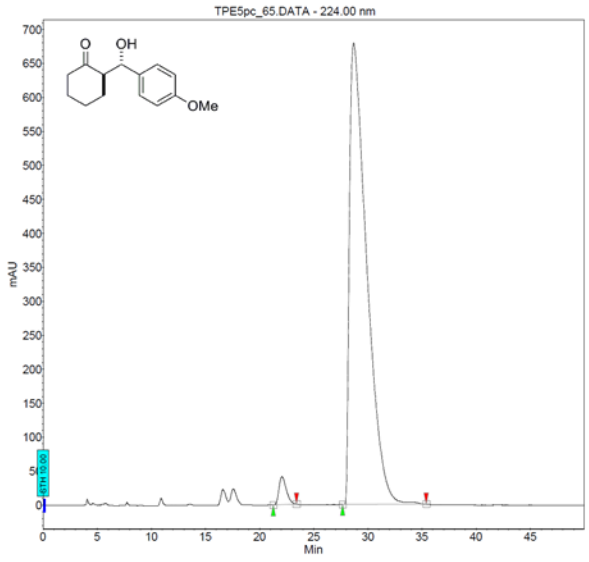


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24.86	49.02	255.2	233.8	49.019
2	UNKNOWN	33.66	50.98	176.7	243.2	50.981
Total			100.00	431.9	477.0	100.000

cd112 3% IPA OD-H 0.8ml/min 435.1psi

Acquired : 02/06/2011 13:08:28
Processed : 02/06/2011 17:06:14
Printed : 02/06/2011 17:06:43

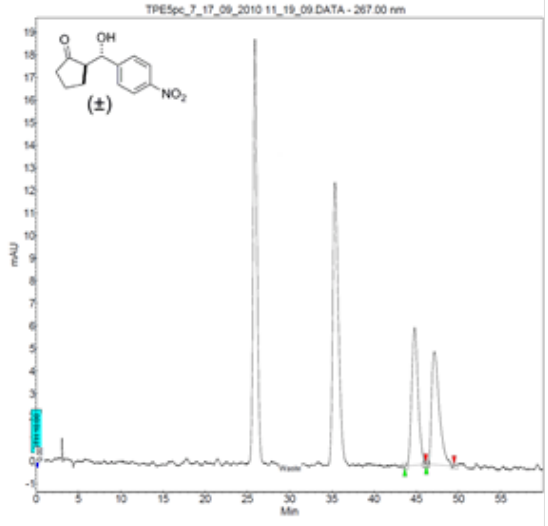


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	22.07	2.54	41.0	32.5	2.535
2	UNKNOWN	28.69	97.46	678.9	1250.7	97.465
Total			100.00	720.0	1283.2	100.000

TPE131-Racemate AD-H 5% IPA 1ml/min

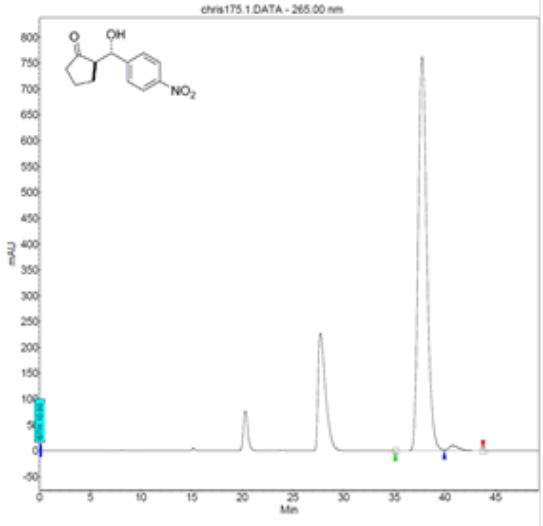
Acquired : 17/09/2010 11:20:14
Processed : 17/09/2010 13:23:01
Printed : 13/09/2011 09:59:23



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	44.77	50.39	6.1	5.3	50.395
2	UNKNOWN	47.13	49.61	5.0	5.3	49.605
Total			100.00	11.1	10.6	100.000

column:=AD-H P=536 Flow=1.0 ml/m Solvent= 5% ipa in hexane
Acquired : 06/09/2011 15:59:44

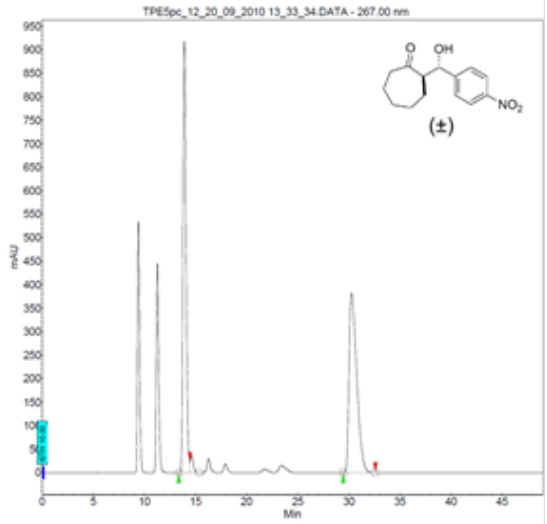


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	37.74	98.53	762.3	752.2	98.535
2	UNKNOWN	40.77	1.47	9.8	11.2	1.465
Total			100.00	772.2	763.4	100.000

TPE172f2 Racemate 15% IPA AD-H 1ml/min

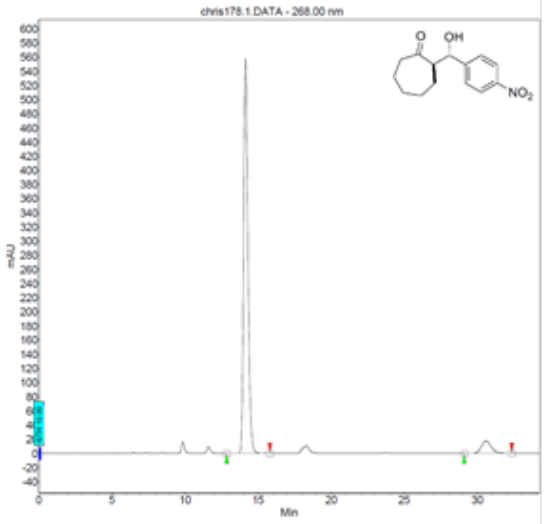
Acquired : 20/09/2010 13:34:25
Processed : 20/09/2010 15:03:17
Printed : 13/09/2011 09:57:31



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	13.91	49.09	918.4	323.5	49.093
2	UNKNOWN	30.26	50.91	382.4	335.5	50.907
Total			100.00	1300.8	659.0	100.000

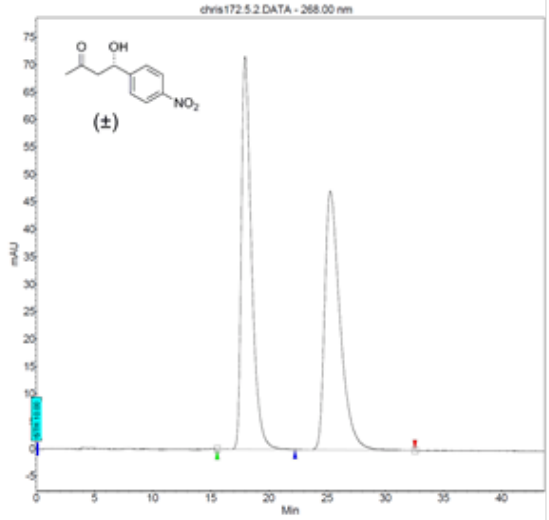
column:= AD-H P=478PSI Flow=0.8ml/m Solvent= 15% ipa in hexane
Acquired : 08/09/2011 19:54:57



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	14.13	93.31	557.6	188.3	93.308
2	UNKNOWN	30.58	6.69	17.6	13.5	6.692
Total			100.00	575.2	201.8	100.000

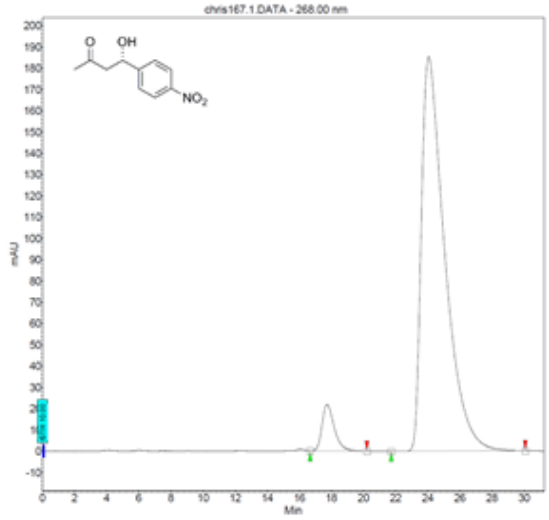
column:= AS P=300PSI Flow=0.8ml/m Solvent= 25% ipa in hexane
Acquired : 05/09/2011 15:17:37



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	17.95	49.85	71.5	71.9	49.851
2	UNKNOWN	25.28	50.15	47.2	72.3	50.149
Total			100.00	118.8	144.3	100.000

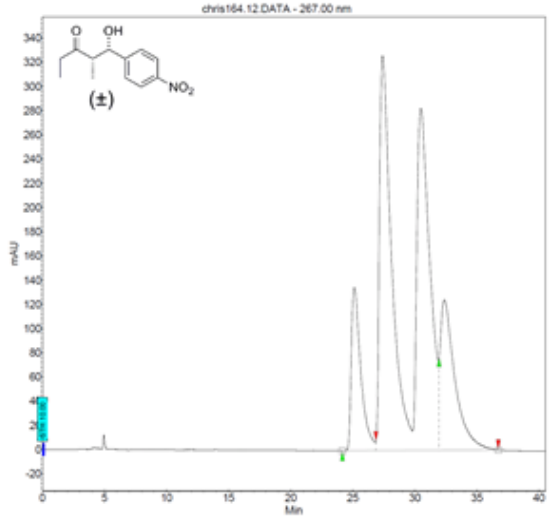
column:= AS P=290PSI Flow=0.8 ml/m Solvent= 25% ipa in hexane
Acquired : 05/09/2011 16:14:00



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	17.72	5.85	21.9	19.4	5.854
2	UNKNOWN	24.04	94.15	185.4	311.4	94.146
Total			100.00	207.3	330.8	100.000

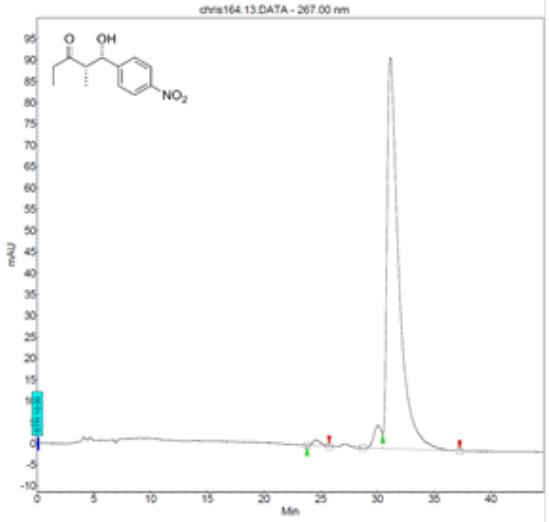
column:=OJ-H P= 478PSI Flow=0.8ml/m Solvent= 9% ipa in hexane
Acquired : 15/09/2011 16:27:42



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	25.10	41.50	134.5	120.4	41.499
2	UNKNOWN	32.36	58.50	124.2	169.7	58.501
Total			100.00	258.7	290.1	100.000

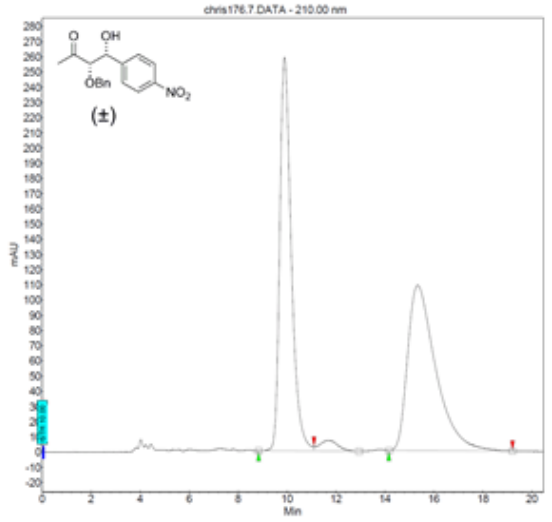
column:= OJ-H P=478PSI Flow=0.8ml/m Solvent= 9% ipa in heaxne
Acquired : 15/09/2011 17:17:56



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	24.56	0.92	1.4	1.0	0.922
2	UNKNOWN	31.14	99.08	91.9	110.7	99.078
Total			100.00	93.3	111.7	100.000

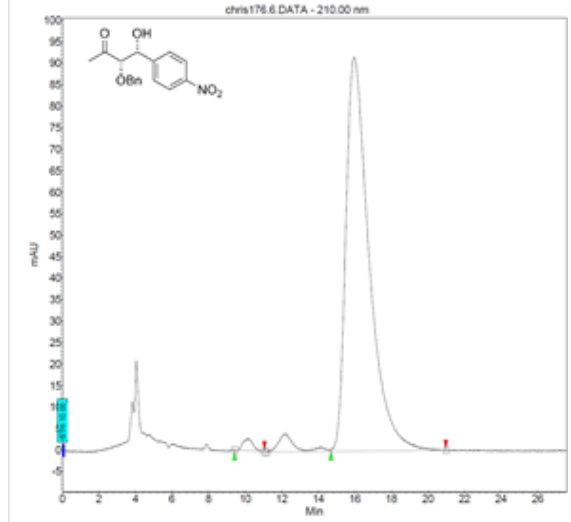
column:= AS P= 333 Flow=0.8ml/m Solvent= 30% ipa in hexane
Acquired : 15/09/2011 12:41:30



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	9.89	49.30	259.1	141.0	49.300
2	UNKNOWN	15.33	50.70	108.9	145.0	50.700
Total			100.00	368.0	286.0	100.000

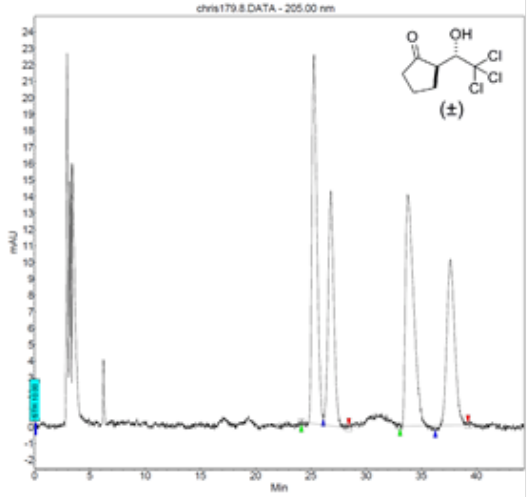
column:= AS P=348 Flow=0.8ml/m Solvent= 30% ipa in hexane
Acquired : 15/09/2011 11:55:41



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	10.20	1.25	2.6	1.7	1.246
2	UNKNOWN	15.96	98.75	91.7	135.2	98.754
Total			100.00	94.4	136.9	100.000

column:= AD-H P= 536 Flow=1.0 ml/m Solvent= 2% ipa in hexane
Acquired : 16/09/2011 00:27:41



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	25.29	29.28	22.4	11.8	29.283
4	UNKNOWN	26.81	21.04	14.2	8.5	21.039
2	UNKNOWN	33.77	29.35	14.1	11.9	29.348
3	UNKNOWN	37.62	20.33	10.1	8.2	20.329
Total			100.00	60.7	40.4	100.000

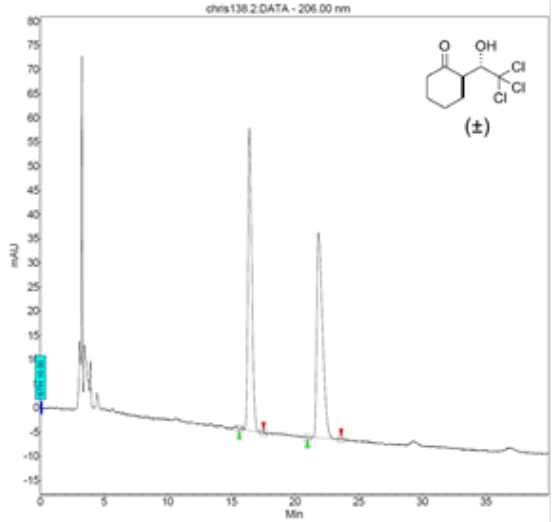
column:=AD-H P= 493 Flow=1.0 ml/m Solvent= 2% ipa in hexane
Acquired : 09/09/2011 18:43:24



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	23.52	2.89	2.0	0.8	2.892
2	UNKNOWN	30.58	97.11	27.6	27.1	97.108
Total			100.00	29.6	27.9	100.000

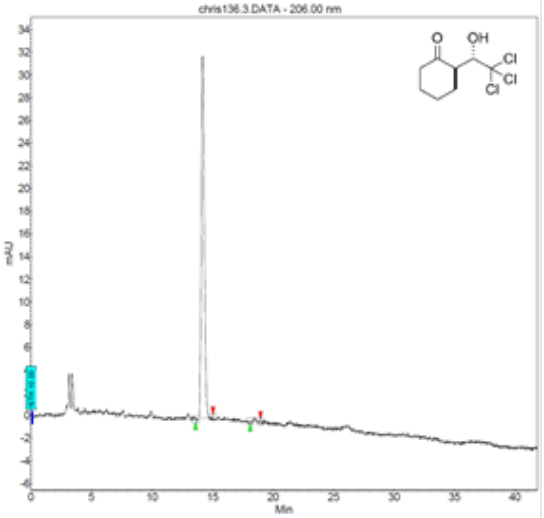
column:=ADH P=493 Flow=1.0 ml/m Solvent= 2% ipa in hexane
Acquired : 25/07/2011 16:40:28



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
2	UNKNOWN	16.41	49.76	62.5	22.4	49.765
1	UNKNOWN	21.84	50.24	42.5	22.6	50.235
Total			100.00	105.0	45.0	100.000

column:= AD-H P=493 Flow=1.0 ml/m Solvent= 2% ipa in hexane
Acquired : 25/07/2011 15:42:44

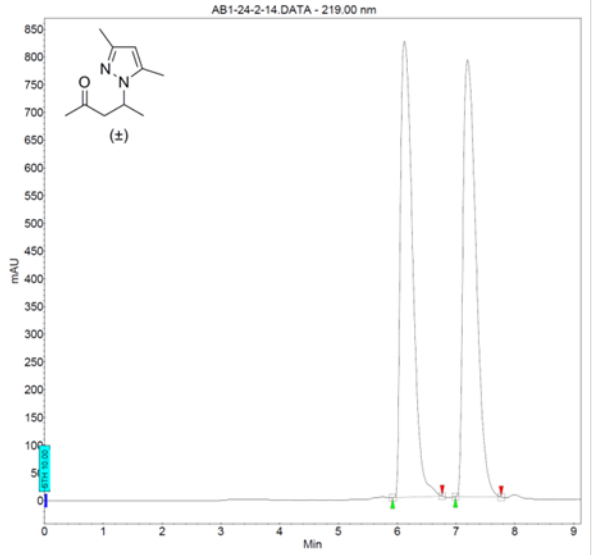


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU Min]	Area % [%]
1	UNKNOWN	14.17	99.80	31.9	9.1	99.802
2	UNKNOWN	18.47	0.20	0.3	0.0	0.198
Total			100.00	32.2	9.2	100.000

AB1-24-2 2%IPA AD-H 1.0mL/min 507.6PSI

Acquired : 26/11/2012 18:37:37
Processed : 26/11/2012 18:47:49
Printed : 26/11/2012 18:48:14

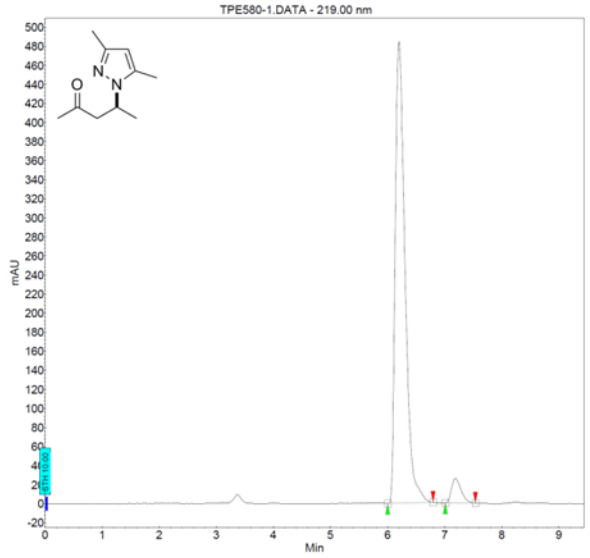


Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6.12	49.39	822.4	198.6	49.389
2	UNKNOWN	7.20	50.61	787.6	203.5	50.611
Total			100.00	1610.0	402.1	100.000

TPE580 2%IPA AD-H 1.0mL/min 493.1PSI

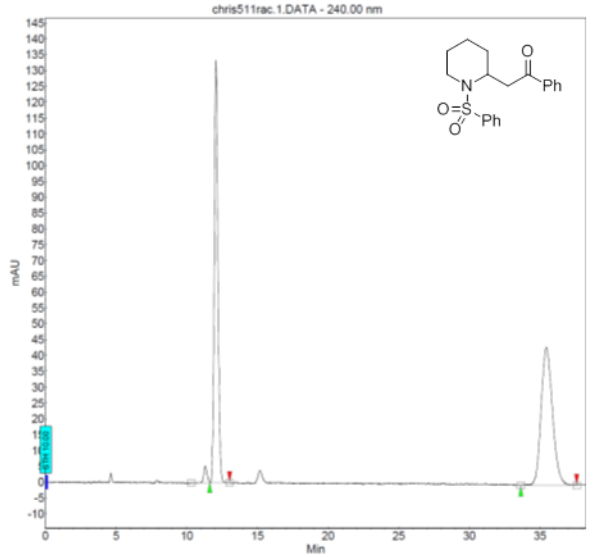
Acquired : 19/07/2012 16:10:10
Processed : 19/07/2012 16:27:36
Printed : 19/07/2012 16:27:56



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6.20	95.02	484.5	96.2	95.022
2	UNKNOWN	7.19	4.98	25.8	5.0	4.978
Total			100.00	510.4	101.3	100.000

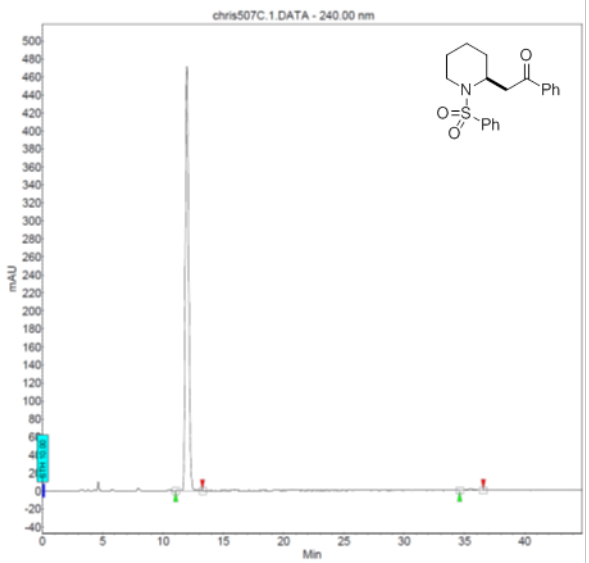
column:= AD-H P= 590 Flow=1.0 ml/m Solvent= 20% ipa in hexane
Acquired : 24/04/2014 12:07:35



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
2	UNKNOWN	12.05	49.42	133.4	39.6	49.424
1	UNKNOWN	35.45	50.58	43.5	40.5	50.576
Total			100.00	176.9	80.0	100.000

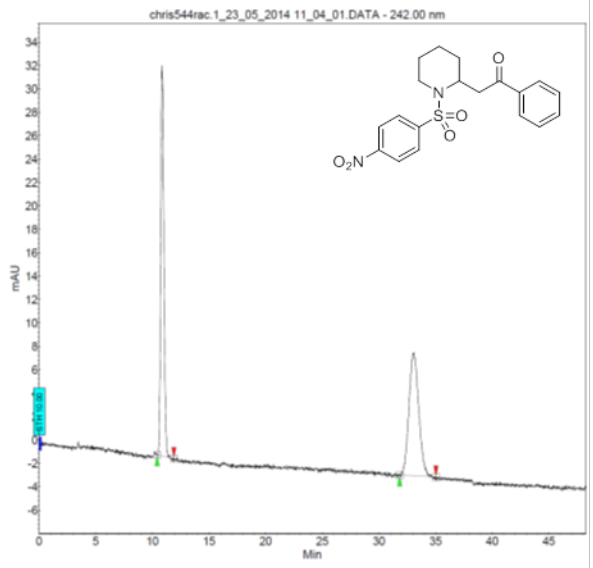
column:=ADH P= 740 Flow=1.0 ml/m Solvent= 20% ipa in hexane
Acquired : 15/02/2014 20:07:36



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	11.97	99.33	471.2	149.3	99.326
2	UNKNOWN	35.50	0.67	1.2	1.0	0.674
Total			100.00	472.4	150.3	100.000

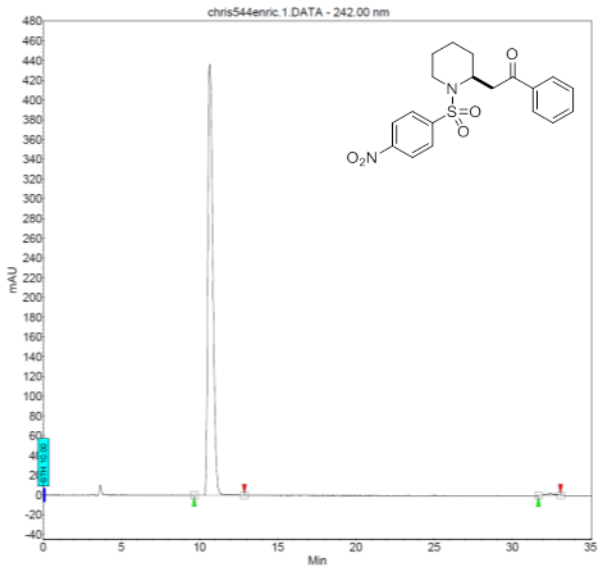
column:= ADH P=1040 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 23/05/2014 11:05:30



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.87	50.38	33.3	10.7	50.384
2	UNKNOWN	33.08	49.62	10.5	10.5	49.616
Total			100.00	43.9	21.2	100.000

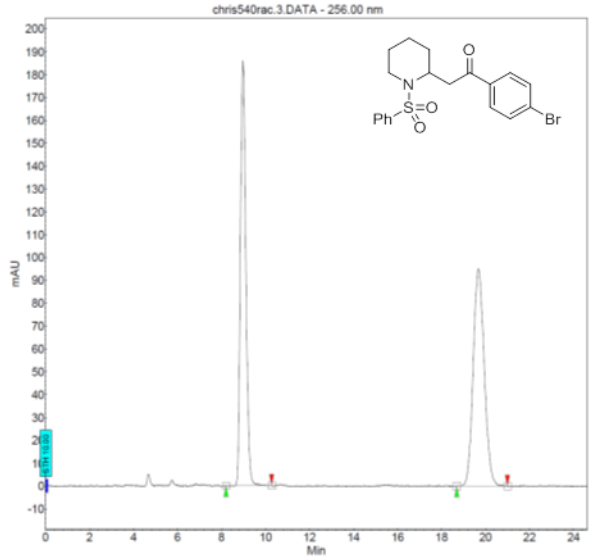
column:=ADH P= 1058 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 23/05/2014 12:05:44



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.65	99.28	436.7	163.7	99.276
2	UNKNOWN	32.42	0.72	1.6	1.2	0.724
Total			100.00	438.3	164.8	100.000

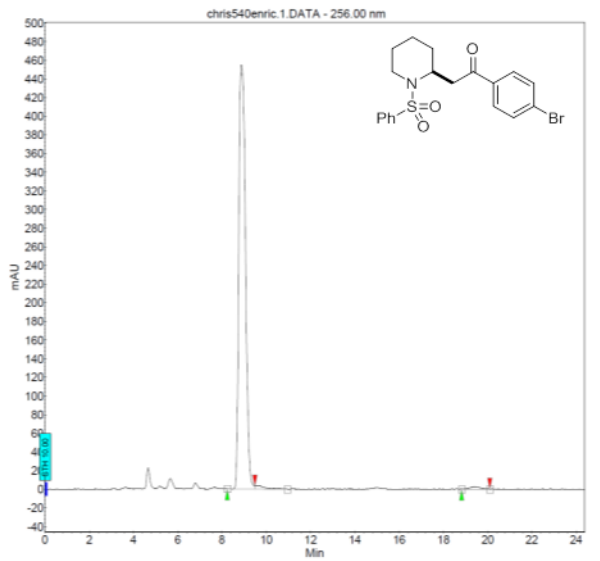
column:= ADH P=1060 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 23/05/2014 12:47:40



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.96	49.05	185.9	53.4	49.055
2	UNKNOWN	19.68	50.95	95.1	55.4	50.945
Total			100.00	281.0	108.8	100.000

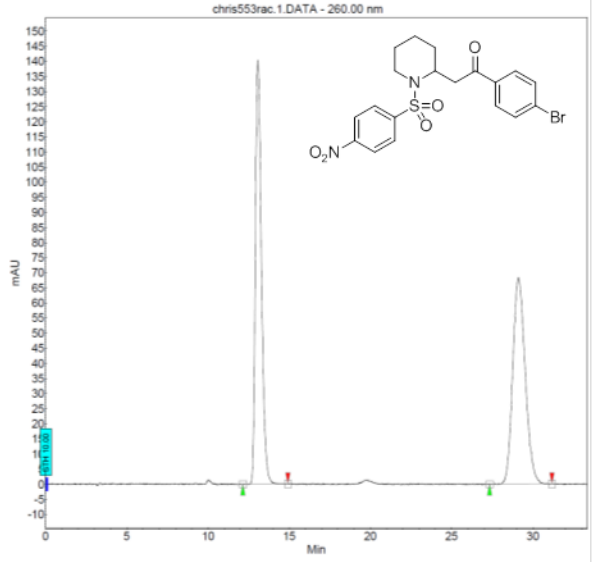
column:=540 P= 1050 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 23/05/2014 13:24:06



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.88	99.10	454.8	159.1	99.100
2	UNKNOWN	19.41	0.90	2.6	1.4	0.900
Total			100.00	457.5	160.6	100.000

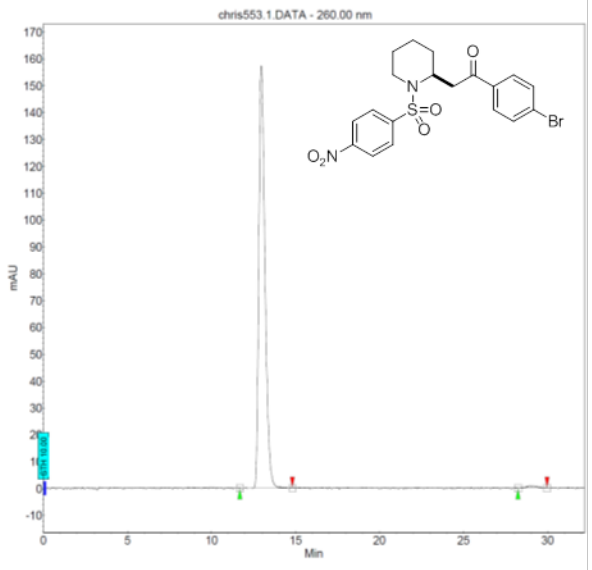
column:= ADH P= 1000 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 02/06/2014 17:23:33



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	13.07	49.63	140.3	60.0	49.632
2	UNKNOWN	29.10	50.37	68.2	60.9	50.368
Total			100.00	208.5	121.0	100.000

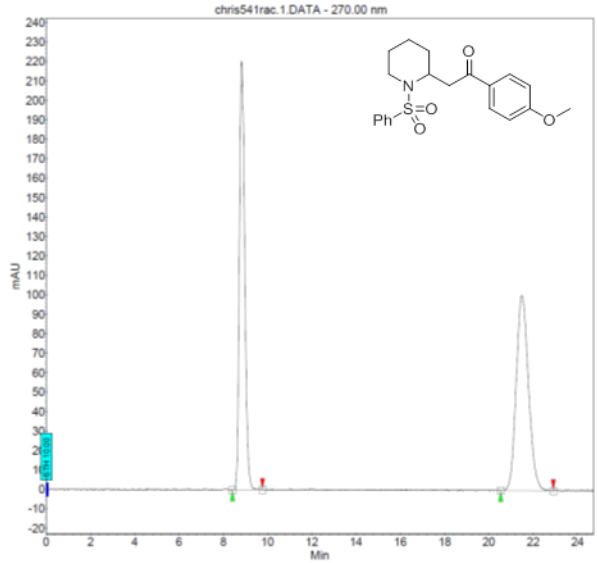
column:= ADH P= 1000 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 02/06/2014 18:02:59



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12.96	99.04	157.3	67.1	99.045
2	UNKNOWN	29.14	0.96	0.9	0.6	0.955
Total			100.00	158.1	67.7	100.000

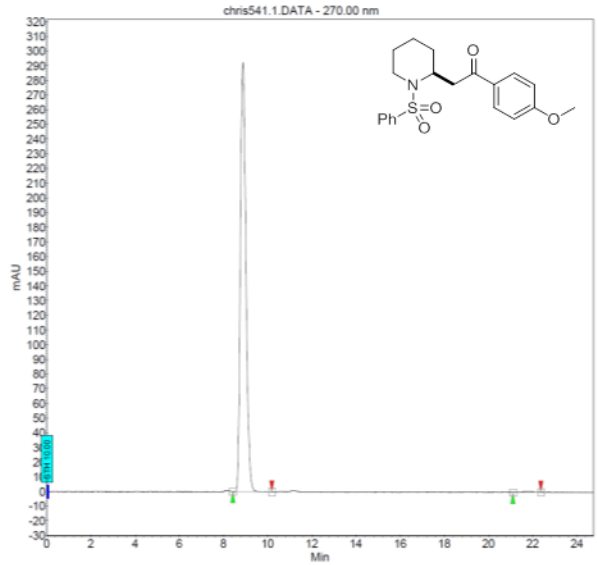
column:= ADH P= 1015 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 01/06/2014 15:32:25



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.83	48.99	220.3	62.0	48.993
2	UNKNOWN	21.49	51.01	100.2	64.5	51.007
Total			100.00	320.5	126.5	100.000

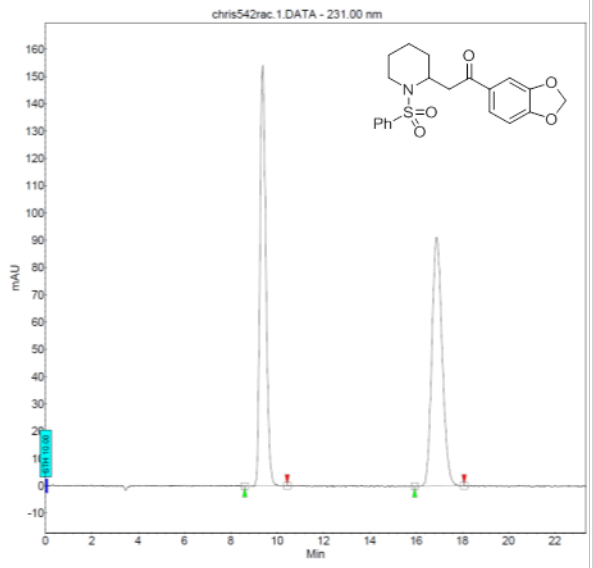
column:= ADH P= 1015 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 01/06/2014 16:03:03



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.88	99.62	292.5	84.6	99.619
2	UNKNOWN	21.67	0.38	0.7	0.3	0.381
Total			100.00	293.2	84.9	100.000

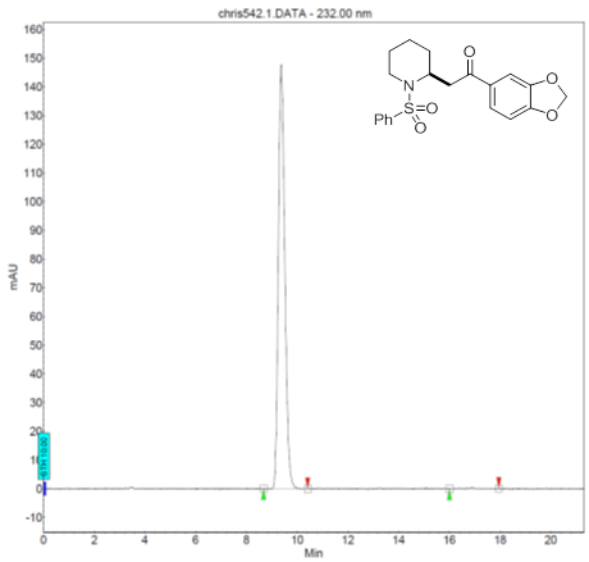
column:= ADH P= 1015 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 01/06/2014 16:32:41



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	9.37	49.28	154.0	45.5	49.285
2	UNKNOWN	16.89	50.72	91.1	46.8	50.715
Total			100.00	245.1	92.4	100.000

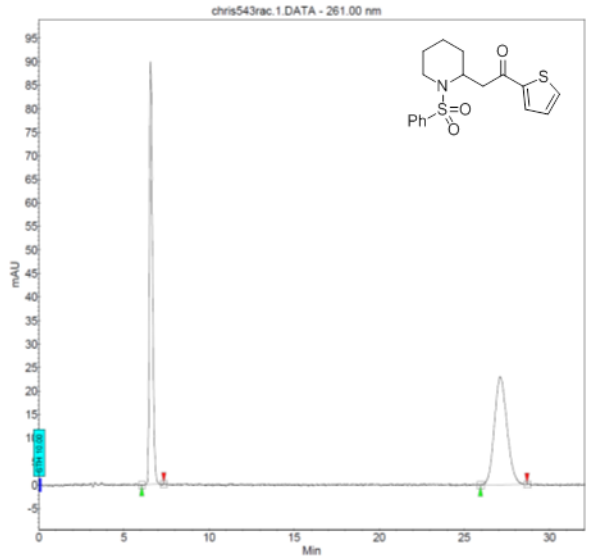
column:= ADH P= 1015 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 01/06/2014 17:01:09



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	9.37	99.79	147.8	43.5	99.787
2	UNKNOWN	16.71	0.21	0.3	0.1	0.213
Total			100.00	148.1	43.6	100.000

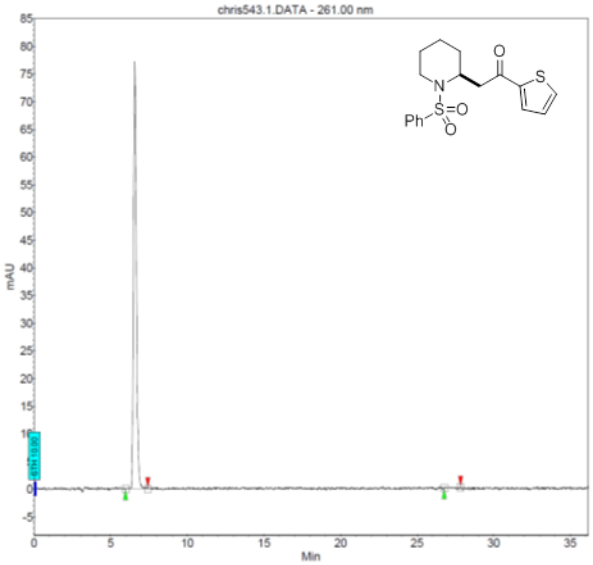
column:= ADH P=1015 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 01/06/2014 17:26:56



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6.56	49.34	89.8	19.4	49.343
2	UNKNOWN	27.10	50.66	22.9	19.9	50.657
Total			100.00	112.7	39.3	100.000

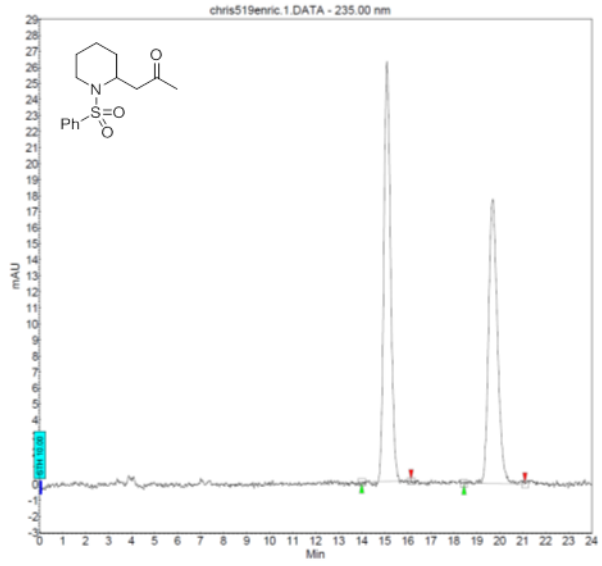
column:= ADH P= 1015 Flow=1.0 ml/m Solvent= 50% ipa in hexane
Acquired : 01/06/2014 18:05:02



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6.56	99.50	77.1	16.9	99.497
2	UNKNOWN	27.69	0.50	0.2	0.1	0.503
Total			100.00	77.3	17.0	100.000

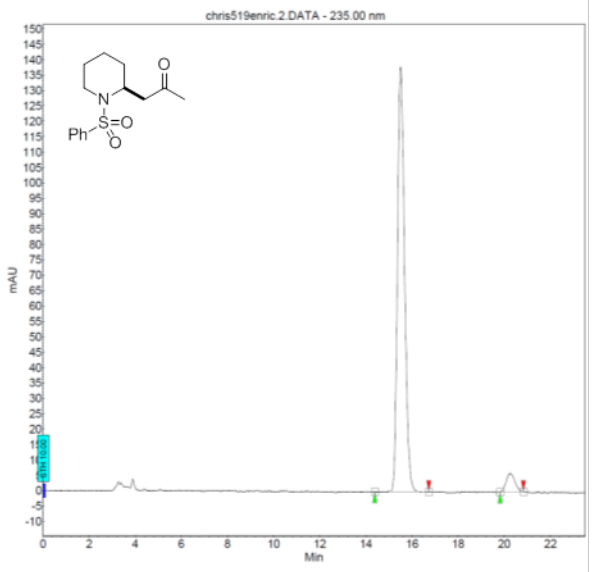
column:= ADH P=565 Flow=1.0 ml/m Solvent= 10% ipa in hexane
Acquired : 22/05/2014 18:46:26



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	15.09	52.17	26.2	8.7	52.174
2	UNKNOWN	19.69	47.83	17.7	8.0	47.826
Total			100.00	43.9	16.8	100.000

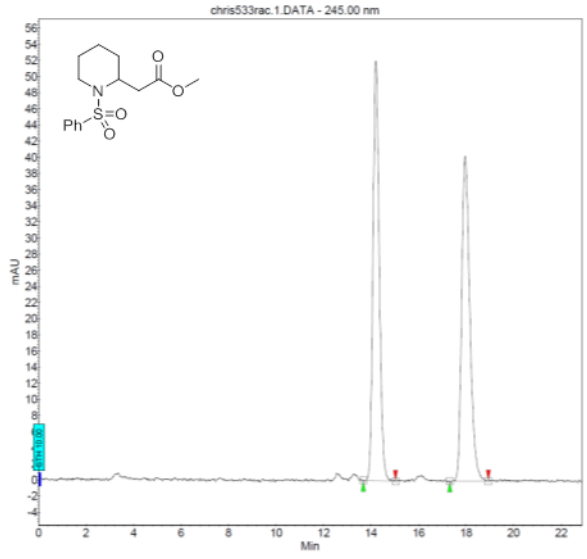
column:= ADH P=565 Flow=1.0 ml/m Solvent= 10% ipa in hexane
Acquired : 22/05/2014 19:20:58



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	15.51	94.96	138.0	48.8	94.962
2	UNKNOWN	20.25	5.04	6.1	2.6	5.038
Total			100.00	144.0	51.4	100.000

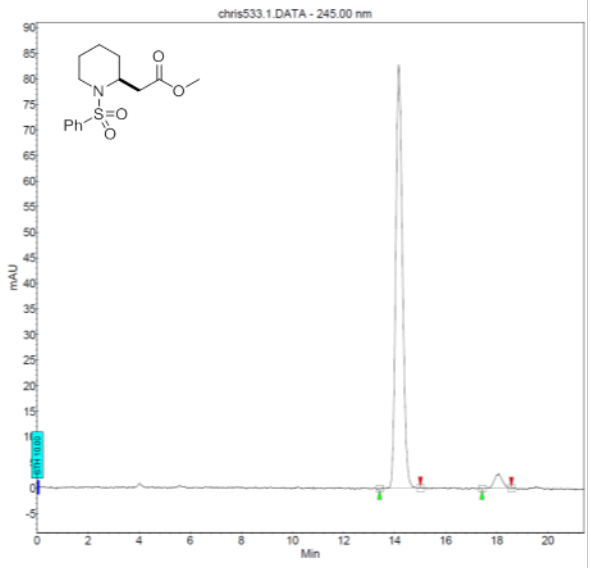
column:= ADH P= 493 Flow=1.0 ml/m Solvent= 10% ipa in hexane
Acquired : 18/05/2014 17:00:36



Peak results :

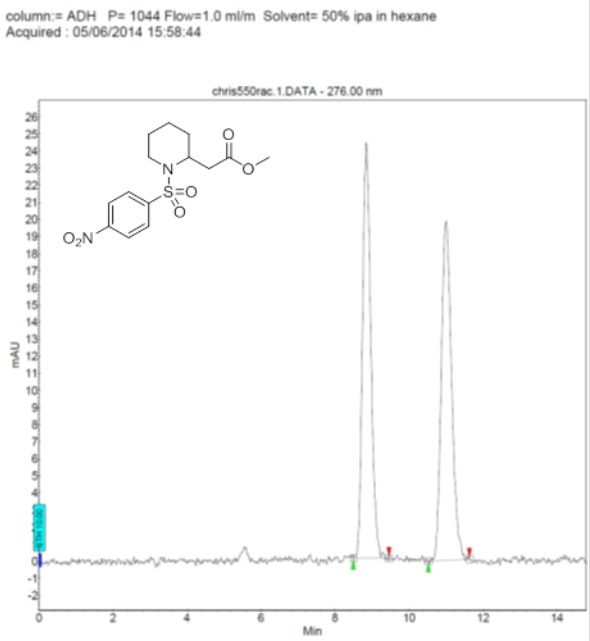
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14.20	49.74	52.0	15.9	49.738
2	UNKNOWN	17.96	50.26	40.2	16.1	50.262
Total			100.00	92.2	32.0	100.000

column:=ADH P= 493 Flow=1.0 ml/m Solvent= 10% ipa in hexane
Acquired : 18/05/2014 16:32:08



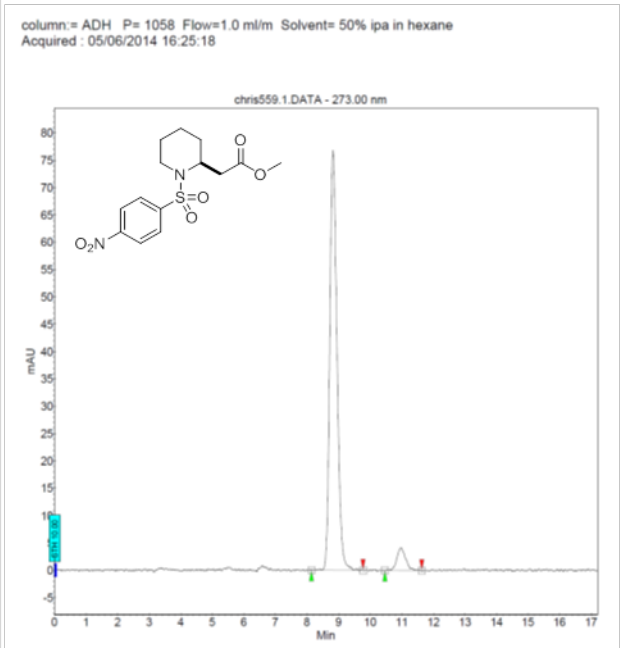
Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14.16	96.04	82.8	25.2	96.036
2	UNKNOWN	18.08	3.96	2.9	1.0	3.964
Total			100.00	85.7	26.3	100.000



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.84	49.74	24.3	6.3	49.742
2	UNKNOWN	11.00	50.26	19.8	6.4	50.258
Total			100.00	44.2	12.7	100.000



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.83	93.83	76.8	20.4	93.828
2	UNKNOWN	10.97	6.17	4.2	1.3	6.172
Total			100.00	81.0	21.7	100.000

Molecuar modelling information

For **132** and **133** Calculations were performed using B3LYP/6-31G** as implemented in Spartan '10 v1.1.0.[152] Relative energies quoted are based on total energies (gas phase) at 298 K and have zpe corrections applied. XYZ Co-ordinates for Aldol Transition States **132** and **133**

(**132**):

C	1.57758080	0.56629710	-0.25684707
C	2.66111419	2.91970941	-1.52739730
O	0.75014523	0.31105658	0.73085757
C	4.84238996	-0.35028118	1.47045720
C	0.34053533	2.79903549	-0.51454177
C	1.72409350	2.44009185	-0.42055224
N	-0.40240776	2.62286350	0.57503461
C	5.60393152	-0.75532449	0.37419081
C	3.54100866	0.08772692	1.25375798

C	3.00674222	0.12901779	-0.04251606
C	-0.30267723	3.16103206	-1.83153206
C	1.98484806	2.97263426	-2.90256399
C	3.79428294	-0.29116869	-1.12260572
C	5.09944589	-0.73676335	-0.92287128
C	0.69050403	3.78582925	-2.82741292
H	5.72126363	-1.07254676	-1.74382442
H	3.38144017	-0.28903561	-2.12824431
H	5.27401862	-0.39184754	2.46324916
H	2.91606826	0.37971369	2.09137761
H	-0.72551843	2.24127154	-2.26825441
H	-1.14741596	3.83826834	-1.66565105
H	0.20776106	3.85826116	-3.80744054
H	1.76240598	1.95659328	-3.25922104
H	2.66771060	3.41749147	-3.63409508
H	0.92088960	4.81134018	-2.51094516
H	3.02480086	3.92357103	-1.26729546
H	3.54754578	2.27922666	-1.55655307
C	-1.86335105	2.59909758	0.72069374
C	-3.85373073	1.26839781	1.56004869
C	-3.83348943	3.78135153	1.84439551
C	-4.28696479	2.44756387	2.44622309
C	-2.32013110	3.78705106	1.59633177
C	-2.33110640	1.26247518	1.35635218
H	-4.35991023	1.34339845	0.59094644
H	-4.36239135	3.95690140	0.89693586
H	-3.86361582	2.32911576	3.45328809
H	-1.78363176	3.73866292	2.55407325
H	-1.85003545	1.18977421	2.34116712

H	-2.30678112	2.70307930	-0.27268365
H	-4.17626912	0.32401208	2.00795956
H	-4.09714976	4.61344999	2.50566553
H	-5.37559965	2.42865188	2.56248660
H	2.13550981	2.59445021	0.57850155
H	1.23675835	0.29850007	-1.27310197
H	0.11466521	2.25193238	1.37091073
N	-1.79893071	0.04590984	0.61620677
C	-2.35875427	-0.21768018	-0.77423889
C	-1.85432499	-1.20278473	1.47800289
H	-0.70023309	0.20182825	0.51479325
H	-2.00431984	4.71591444	1.10870801
H	-4.88878955	0.39168163	-1.53244361
C	-4.77912463	-0.66707435	-1.30797872
H	-6.81280988	-1.12584490	-1.84670486
C	-5.86382870	-1.52130631	-1.49758042
C	-3.38757122	-2.53742497	-0.61691896
C	-5.71698412	-2.88522813	-1.24182244
C	-3.54477428	-1.15240271	-0.85994936
C	-4.49014571	-3.38420704	-0.80996044
C	-1.29672937	-2.41275507	0.77383177
C	-2.07646963	-3.08648942	-0.19212532
C	0.44531071	-4.08548149	0.55505387
C	-1.57625189	-4.26952413	-0.75748579
C	-0.03887787	-2.91072449	1.12820941
C	-0.32987589	-4.76831201	-0.38379555
H	0.56359832	-2.36924725	1.85106319
H	1.42142687	-4.46584592	0.84042569
H	-1.27115947	-0.97271847	2.37225808

H	-2.89566884	-1.36564696	1.76355462
H	-2.60483683	0.74979445	-1.21495722
H	-1.51672010	-0.63426162	-1.33423894
H	0.04062115	-5.68432917	-0.83459933
H	-2.16130116	-4.78652437	-1.51248081
H	-4.38118905	-4.44473773	-0.60373990
H	-6.55620675	-3.56041339	-1.37996128
N	6.98282943	-1.22922647	0.59736736
O	7.62482225	-1.58756663	-0.38759078
O	7.39939315	-1.23411291	1.75394509

(**133**):

C	-1.81158612	0.02472648	-0.96230714
C	-2.21479199	1.64775623	-3.35374142
O	-0.91534127	-0.83890225	-0.55621920
C	-4.61665711	-2.40947414	-1.76009999
C	0.06563458	0.97968695	-2.46932356
C	-1.28670580	0.61103563	-2.73081190
N	0.92570572	0.00147925	-2.19281217
C	-5.72576066	-1.58247634	-1.58484447
C	-3.34938425	-1.87450464	-1.56452226
C	-3.19030977	-0.52727600	-1.20734417
C	0.47828548	2.42384703	-2.31473964
C	-1.89142220	3.08024833	-2.91387148
C	-4.32497721	0.27550703	-1.02757607
C	-5.60304387	-0.24645141	-1.21605389
C	-0.40745748	3.38180717	-3.12972749
H	-6.49446202	0.35239799	-1.07765695

H	-4.21261779	1.31165435	-0.72048455
H	-4.76597349	-3.44652207	-2.03390144
H	-2.46904645	-2.50031733	-1.66032288
H	0.40874579	2.68819312	-1.24785093
H	1.52897318	2.54551205	-2.59466812
H	-0.16456061	4.41131985	-2.85008322
H	-2.14692250	3.21906367	-1.85437034
H	-2.50697312	3.78836103	-3.47698951
H	-0.16465631	3.27812627	-4.19441795
H	-2.13215856	1.58004061	-4.44677289
H	-3.25244584	1.39493197	-3.11888870
C	2.26452778	0.07134316	-1.59581529
C	3.77257052	-0.77721178	0.25558056
C	4.73911729	-0.38450717	-2.05022401
C	4.81190877	-1.23730838	-0.77938852
C	3.31964700	-0.38129108	-2.62855149
C	2.34921109	-0.82133936	-0.32656435
H	4.01433072	0.24708963	0.56344685
H	5.04585528	0.64497828	-1.82129260
H	4.64186576	-2.29282189	-1.03009620
H	3.05479264	-1.39008842	-2.97347398
H	2.13680265	-1.84943063	-0.64645299
H	2.46312550	1.10960947	-1.31938136
H	3.82582995	-1.39779621	1.15337441
H	5.43931814	-0.75518083	-2.80509802
H	5.81066243	-1.18074330	-0.33587050
H	-1.38868206	-0.38138933	-3.17094716
H	-1.84731512	0.99487203	-0.44121534
H	0.52889129	-0.93228079	-2.24632371

N	1.24986133	-0.51472178	0.67655413
C	1.43488668	0.78339629	1.41754113
C	0.95954953	-1.66577148	1.64173622
H	0.26036742	-0.49311921	0.09340523
H	3.25140566	0.27506576	-3.50213565
H	-0.56866947	2.61402972	1.21742026
C	-0.61225482	2.06196223	2.15305398
H	-2.30988710	3.16802139	2.88382571
C	-1.58730894	2.38639451	3.09510466
C	0.30481824	0.37438211	3.64357572
C	-1.62097792	1.70576793	4.31230832
C	0.33138781	1.06189705	2.40869907
C	-0.68254625	0.71193888	4.58157300
C	1.67068638	-1.63415944	2.97095786
C	1.30887126	-0.67671790	3.94667620
C	3.19470487	-2.67897281	4.55196494
C	1.91334879	-0.74091480	5.21165395
C	2.60343377	-2.62802957	3.29066770
C	2.84789760	-1.72901369	5.51323585
H	2.85098442	-3.38561823	2.55097221
H	3.91405192	-3.45762946	4.78391206
H	-0.12211371	-1.62198935	1.78686887
H	1.17708669	-2.58835037	1.10177563
H	2.39471426	0.73455764	1.93556926
H	1.48871271	1.58001213	0.67261772
H	3.30490588	-1.75649733	6.49734174
H	1.65748018	0.00398335	5.95860656
H	-0.72122816	0.17390244	5.52332192
H	-2.37791613	1.94703651	5.05175089

N	-7.07489383	-2.14529796	-1.78552010
O	-7.15160052	-3.32933703	-2.10629107
O	-8.03230846	-1.39248176	-1.62004791

XYZ Co-ordinates for Transition States **402**-**405** (calculated using B3LYP-D3(BJ)/def2-TZVPP//B3LYP/6-31G* as implemented in Gaussian 09[153]).

(**402**)

N	1.54109300	-3.34588000	-0.57461400
C	2.37270900	-3.90422400	0.53990100
H	1.71264900	-4.43489200	1.22764000
H	2.83266800	-3.07298400	1.07806300
C	0.73876500	-4.42011800	-1.23635600
H	0.13044000	-4.00953600	-2.04391200
H	0.09243400	-4.87042200	-0.48098900
C	2.38909400	-2.54520100	-1.52267100
C	1.61086900	-1.76088900	-2.59990200
H	3.09042400	-3.23677700	-2.00173000
N	0.54697600	-0.93696900	-2.03032800
C	-0.73713500	-1.08996200	-2.39432300
C	-1.92189600	-0.36897900	-2.15483800
C	-1.43946400	-2.11977500	-3.17661600
C	-2.73454500	-1.33929400	-2.95493700
O	-3.89923200	-1.46664700	-3.27678400
O	-1.09454800	-3.16596200	-3.71443700
N	-2.10272300	0.76749000	-1.44855800
H	-1.24717800	1.17350100	-1.04188100
H	0.89376900	-2.65366900	-0.08309900
H	0.77180700	-0.15071200	-1.40764400
O	0.44564000	1.50501300	-0.44223000

C	2.78298100	0.61595100	0.95820100
C	4.24187000	0.34409400	1.26564800
C	2.58274900	-0.46880400	3.70726600
N	2.09581100	-0.81788800	2.36412000
C	4.11201700	-0.41775200	3.70427400
C	4.68094300	0.60590400	2.71588700
H	4.48161900	-0.69531300	1.00939600
H	4.83159200	0.98098600	0.58965200
H	4.38390300	1.61915100	3.01851300
H	5.77728900	0.58262800	2.75914900
H	4.45878700	-0.18163800	4.71880400
H	4.49664000	-1.41725200	3.45884800
H	2.19758500	0.51598000	4.02909800
H	2.24492500	-1.20708600	4.44666900
S	0.56954800	-1.33021700	2.31528500
O	0.22736500	-1.55342100	0.86736600
O	0.32070200	-2.47607000	3.21635300
C	-0.56496800	-0.01613700	2.82146500
H	-1.57948700	-0.41382500	2.75397200
H	-0.43370600	0.82862700	2.14488400
H	-0.34320000	0.26908100	3.85208600
C	2.23303000	1.88936700	1.07164200
H	2.70879300	2.63556500	1.70117700
C	1.08487600	2.27758100	0.33053200
H	2.34475000	-0.00193000	0.18411200
C	0.60183300	3.71501000	0.45532600
H	1.33927700	4.36590200	0.93330400
H	-0.31950400	3.76060100	1.05060200
H	0.36305400	4.10830600	-0.53822500

H	2.96398000	-1.85676300	-0.89733800
H	1.42286400	-5.17473500	-1.63448900
H	3.12409500	-4.58126300	0.12658000
C	2.60585900	-0.90669700	-3.40206100
H	3.40286900	-1.52348900	-3.83316300
H	3.06748600	-0.14102300	-2.76777700
H	2.08360700	-0.40135800	-4.21871700
H	1.12583400	-2.46575400	-3.27972900
C	-3.28780200	1.45261400	-1.15397600
C	-5.55920400	2.95406600	-0.44448800
C	-3.16883400	2.58729400	-0.33617800
C	-4.55423000	1.06821900	-1.61901200
C	-5.66903700	1.82702700	-1.25904600
C	-4.29441900	3.32379100	0.01492800
H	-2.18994100	2.88709800	0.01914500
H	-4.66925800	0.18985300	-2.24827000
H	-6.43655700	3.52819300	-0.17337000
C	-7.01771400	1.45218500	-1.82185700
C	-4.15351000	4.48736600	0.95929100
F	-8.02667100	1.87459100	-1.02544000
F	-7.21623000	2.01288500	-3.03713400
F	-4.35920000	4.11340400	2.24396900
F	-2.91579700	5.03557100	0.90714700
F	-5.04220000	5.46635700	0.68868300
F	-7.14967800	0.12005600	-1.97285700

(**403**)

N	-1.94017600	3.18170900	0.63119100
C	-2.76489400	3.15385800	1.87673300

H	-2.09667900	3.29064800	2.72901600
H	-3.26305100	2.18585600	1.94401500
C	-1.16609800	4.45767400	0.52786900
H	-0.56227200	4.43011100	-0.38013500
H	-0.50231700	4.52790500	1.39168900
C	-2.74564400	2.88654900	-0.61244900
C	-1.97880000	2.02627400	-1.63739400
H	-3.02657300	3.84663200	-1.05549000
N	-1.65588100	0.69599100	-1.11744300
H	-0.66678700	0.42021000	-1.06619800
O	0.85938100	-0.74149500	-1.01391100
C	2.10982000	-0.68723000	-1.20588400
C	2.85972100	0.51251800	-1.31545300
H	3.92681700	0.42329700	-1.49775300
C	2.26638200	1.77537900	-1.27839800
C	2.89543000	2.96999700	-1.97015300
C	3.58323100	3.11544400	1.00723200
N	2.24108900	2.69633800	0.58074200
H	1.18271200	1.77194500	-1.26552700
H	2.98687900	2.70669800	-3.03398700
H	2.20880700	3.82303100	-1.91185100
H	-1.19385500	2.42996300	0.75802800
S	1.30613100	2.08841000	1.72711200
O	1.01230200	3.04683800	2.82293700
O	0.08643800	1.52707200	1.04977200
C	2.08223700	0.64710100	2.49673100
H	3.00471900	0.95804900	2.99165900
H	2.28983400	-0.08373600	1.71307900
H	1.38184000	0.24296900	3.23008100

C	-2.56777900	-0.22156200	-0.75071500
C	-2.45531300	-1.57001500	-0.35032300
C	-4.03119300	-0.21960400	-0.54539100
C	-3.92961200	-1.68664700	-0.13825800
O	-4.71258600	-2.54646500	0.21651300
O	-4.91829100	0.62090700	-0.63047500
C	4.26972300	3.40670200	-1.43588900
H	4.70820700	4.12487500	-2.14027800
H	4.95241900	2.54665400	-1.40933900
C	4.18663000	4.04732900	-0.04601700
H	5.18901300	4.34962500	0.28430900
H	3.57658900	4.95912200	-0.09965400
H	3.54001600	3.63883400	1.97250900
H	4.25062400	2.24439700	1.13533400
N	-1.35078800	-2.33899300	-0.24243700
H	-0.46287400	-1.88581000	-0.51260200
C	2.85826000	-2.00484100	-1.35780100
H	2.92832600	-2.51843500	-0.39030500
H	3.87443400	-1.87094100	-1.73889600
H	2.30678100	-2.66559300	-2.03497500
H	-3.50942400	3.95253700	1.83874700
H	-1.86375600	5.29797100	0.49615600
H	-3.66052700	2.36195500	-0.32602200
C	-2.78389700	1.96905300	-2.94661800
H	-3.78348200	1.56317600	-2.76402400
H	-2.26952000	1.33073100	-3.67034700
H	-2.89007600	2.96922700	-3.38207600
H	-1.00860600	2.49262800	-1.84378600
C	-1.23233400	-3.65963800	0.21124100

C	-0.79615800	-6.29832500	1.08450500
C	0.06938100	-4.17719100	0.30156100
C	-2.32204300	-4.46974200	0.56385200
C	-2.08637100	-5.77597100	0.99524300
C	0.27970000	-5.48172900	0.73390500
H	0.91035700	-3.55284700	0.02521900
H	-3.33792100	-4.09016000	0.49725200
H	-0.63404600	-7.31950700	1.40681700
C	-3.25517400	-6.62523000	1.42940400
C	1.68598800	-5.99736100	0.88389900
F	-3.54558500	-6.43088300	2.73681000
F	-2.99572200	-7.94458400	1.27820500
F	-4.37215300	-6.34780700	0.72916100
F	2.14223500	-5.83969800	2.14863900
F	2.55446900	-5.34809600	0.07285900
F	1.77133400	-7.31405700	0.59822600

(**404**)

N	-2.36296000	3.10353700	-0.64035000
C	-1.79954100	4.20172500	-1.48434600
H	-1.68307800	3.83058000	-2.50297200
H	-0.82173300	4.47110000	-1.08635600
C	-3.63878100	2.57872800	-1.21278700
H	-3.93402600	1.68383600	-0.66841100
H	-3.45997400	2.30745600	-2.25462200
C	-2.50729100	3.56890700	0.78677700
C	-2.62795700	2.43911500	1.82309500
H	-3.39230800	4.21338900	0.82109000
N	-1.45280500	1.57149100	1.82186800

C	-0.18676500	1.96417800	2.03889900
C	1.02720500	1.25606800	2.03917400
C	0.49096500	3.24860600	2.31116300
C	1.81421800	2.48005900	2.35742500
O	2.98341000	2.75775000	2.54436700
O	0.13105700	4.41512500	2.39405500
N	1.23461400	-0.05507700	1.78008600
H	0.39928900	-0.58245800	1.50679200
H	-1.63115700	2.32917500	-0.70947000
H	-1.60346900	0.59801800	1.56453700
H	-4.40252900	3.35885200	-1.15745500
H	-2.47619500	5.05971900	-1.46446000
H	-1.62992900	4.17385300	1.03077500
O	-0.21316600	1.71598500	-1.11794800
C	-1.09960800	-0.61379100	-2.70133300
C	-1.43560200	-1.53627700	-3.86242500
C	-0.66323500	-3.04386600	-1.36472600
N	-1.65633700	-1.96529300	-1.33038900
C	-0.79431400	-3.75603500	-2.71717200
C	-0.58536400	-2.81976600	-3.91884000
H	-2.49707600	-1.80134900	-3.81736200
H	-1.28233600	-0.96589000	-4.79072900
H	0.47667100	-2.55481800	-3.99519600
H	-0.82725600	-3.36193500	-4.84186500
H	-0.07024000	-4.57986400	-2.76396400
H	-1.79666300	-4.20148300	-2.77098700
H	0.35213300	-2.63615300	-1.24222300
H	-0.81035100	-3.76914000	-0.55225600
S	-2.24768100	-1.50054400	0.07086200

O	-1.25770600	-1.37736100	1.20088600
O	-3.08403900	-0.28868300	-0.12829000
C	-3.37309700	-2.80726900	0.62987600
H	-3.78861400	-2.49933200	1.59191100
H	-2.81659700	-3.73942600	0.74760500
H	-4.16054400	-2.91991900	-0.11668800
C	0.21643500	-0.15506800	-2.53924500
H	1.02331100	-0.68989900	-3.02944700
C	0.57598300	0.98825000	-1.79252200
H	-1.89007200	0.06703800	-2.40186500
C	2.03724800	1.41416600	-1.79437600
H	2.65635600	0.81687900	-2.46917900
H	2.44836500	1.33432400	-0.78130400
H	2.10906100	2.46953500	-2.08092900
C	2.42630900	-0.78713300	1.74369800
C	4.71796800	-2.40932000	1.59249900
C	3.68610900	-0.24546700	2.03869500
C	2.31963000	-2.14075600	1.38574300
C	3.45748500	-2.93617800	1.30710600
C	4.81230000	-1.06615700	1.95853000
H	3.78495000	0.79900100	2.32296800
H	1.34340600	-2.55964400	1.16491400
H	5.60380500	-3.02899400	1.53125700
C	6.17095800	-0.46120700	2.20984600
C	3.30680300	-4.39414000	0.96464900
F	7.06785100	-1.39225700	2.60880300
F	6.12940400	0.49523100	3.15805900
F	4.41380700	-4.89183000	0.37370000
F	3.07401500	-5.14708900	2.06448500

F	2.26674700	-4.60674300	0.12151700
F	6.67129500	0.11081000	1.09000900
H	-3.45807600	1.77874100	1.55810900
C	-2.90071300	3.05909700	3.20419900
H	-2.95672400	2.26911000	3.95841400
H	-3.85182400	3.60401800	3.20521400
H	-2.10143100	3.75416100	3.47883100

(**405**)

N	-2.84121700	2.71417100	0.49607500
C	-2.51843300	3.76437000	1.51291900
H	-2.49021300	3.27907000	2.48785000
H	-1.53857100	4.19775300	1.30864000
C	-4.14787000	2.05634100	0.80100900
H	-4.29228700	1.24563600	0.08704100
H	-4.09114500	1.65210200	1.81228600
C	-2.81890800	3.22015300	-0.91759800
C	-1.43544200	3.68540200	-1.40167600
H	-3.16143200	2.38954200	-1.53708500
N	-0.45138000	2.61728500	-1.24739300
H	-1.08215300	4.52565900	-0.79900900
C	-1.53808000	4.13638600	-2.86643000
H	-0.56731500	4.50347500	-3.21041100
H	-1.83914600	3.30462600	-3.51404100
H	-2.27094800	4.94319600	-2.98112100
C	0.63173200	2.73316200	-0.46558700
C	1.71434500	1.89060500	-0.17190200
C	1.11550000	3.78872100	0.44172700
C	2.32480000	2.89750900	0.74580700

O	3.31550500	2.96729500	1.44727600
O	0.66757400	4.86471000	0.81295900
N	1.94382500	0.62882800	-0.60631100
H	1.18097400	0.21738200	-1.15270000
H	-2.12197400	1.94693200	0.64235900
H	-0.60137900	1.72991200	-1.73341300
H	-4.95166300	2.79362500	0.72992600
H	-3.29289600	4.53570900	1.48329900
H	-3.54014500	4.04244800	-0.97939100
O	-1.21530900	1.07028800	1.67229900
C	-2.08266600	-1.69512800	1.16402200
C	-2.66560500	-3.08513000	1.37513100
C	-0.58319500	-2.99766100	-0.79326200
N	-1.66863000	-2.01311300	-0.73044600
C	-1.11986500	-4.33238700	-0.26230700
C	-1.65745200	-4.23249200	1.17415400
H	-3.51840900	-3.22492000	0.70200300
H	-3.05424300	-3.12496800	2.40314500
H	-0.81825300	-4.11073800	1.87045100
H	-2.14024700	-5.17999700	1.44506000
H	-0.31905800	-5.08176500	-0.30772400
H	-1.92175500	-4.67131400	-0.93185000
H	0.26738100	-2.66154300	-0.18172400
H	-0.20575900	-3.13202500	-1.81621700
S	-1.71713500	-0.83082500	-1.79116600
O	-0.39289100	-0.18922900	-2.13116000
O	-2.77967900	0.13168400	-1.40159600
C	-2.24916800	-1.55823700	-3.36412700
H	-2.28392300	-0.76080100	-4.10982700

H	-1.53079100	-2.32157600	-3.67040800
H	-3.23714000	-1.99662700	-3.21632200
C	-0.97362600	-1.28930100	1.92916700
H	-0.35947500	-2.04506100	2.40798600
C	-0.64082500	0.05845200	2.17808300
H	-2.80780500	-0.92164500	0.93180500
C	0.47493900	0.34887600	3.17276200
H	0.92373800	-0.55660100	3.59023300
H	1.26140400	0.94485800	2.69639800
H	0.07620800	0.95693600	3.99364500
C	3.00618400	-0.23685400	-0.32613000
C	5.03508700	-2.12436600	0.15696900
C	4.09783300	0.10279900	0.48662300
C	2.94695100	-1.51375100	-0.90635100
C	3.94768300	-2.44653700	-0.65580900
C	5.09558100	-0.84613900	0.71363600
H	4.16237600	1.08830600	0.94035700
H	2.10868500	-1.77162600	-1.54456500
H	5.81466500	-2.84971700	0.35251400
C	6.23050900	-0.49434800	1.64301200
C	3.86848300	-3.79605100	-1.31766700
F	7.32311800	-1.25805500	1.41200500
F	6.60193500	0.79503500	1.51642800
F	4.53797400	-4.74007900	-0.62407900
F	4.39023600	-3.77655600	-2.56559100
F	2.58481300	-4.21870600	-1.44207800
F	5.88546500	-0.68337200	2.93741200

X-ray crystallography data

X-ray crystallography was performed by Dr William Lewis. Single crystals of $C_{19}H_{19}BrN_2O_5S$ **386** were crystallised from isopropanol. A suitable crystal was selected and placed in fomblin film on a micromount on aDual Cu SuperNova Atlas diffractometer. The crystal was kept at 120(2) K during data collection. Using Olex2[153], the structure was solved with the olex2.solve[154] structure solution program using Charge Flipping and refined with the ShelXL[155] refinement package using Least Squares minimisation.

*Crystal data and structure refinement for **386**.*

Identification code	**386**
Empirical formula	$C_{19}H_{19}BrN_2O_5S$
Formula weight	467.33
Temperature/K	120(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.9640(2)
b/Å	13.5921(5)
c/Å	23.4651(11)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1902.16(14)
Z	4
ρ_{calc}g/cm^3	1.632
μ/mm^{-1}	4.281
F(000)	952.0
Crystal size/mm^3	0.4765 × 0.1066 × 0.015
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.516 to 148.766

Index ranges	$-4 \le h \le 7, -16 \le k \le 16, -28 \le l \le 28$
Reflections collected	7263
Independent reflections	3754 [R_{int} = 0.0277, R_{sigma} = 0.0346]
Data/restraints/parameters	3754/0/253
Goodness-of-fit on F^2	1.031
Final R indexes [I>=2σ (I)]	R_1 = 0.0350, wR_2 = 0.0901
Final R indexes [all data]	R_1 = 0.0370, wR_2 = 0.0921
Largest diff. peak/hole / e $Å^{-3}$	0.54/-0.35
Flack parameter	-0.014(12)

Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$×10^3) for ***386****. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.*

Atom	*x*	*y*	*z*	U(eq)
Br1	-73.1(8)	6523.6(3)	5684.5(2)	38.28(15)
S2	2614.9(13)	3383.0(6)	2493.9(4)	21.60(19)
O3	5001(5)	3300.7(18)	2480.2(12)	28.6(5)
O4	5790(4)	5372(2)	3279.2(14)	29.5(6)
O5	1344(6)	3399(3)	5311.0(14)	46.5(8)
N6	-20(6)	3670(2)	4951.9(14)	32.1(7)
C	1830(6)	3473(3)	3224.9(16)	21.3(7)
C1	-443(6)	4554(3)	2005.8(17)	28.1(8)
O9	1282(5)	2609(2)	2256.6(14)	32.8(7)
O10	-1883(6)	3987(3)	5064.5(15)	42.8(8)
C2	3912(6)	5716(3)	3306.3(18)	22.0(7)
C3	2799(6)	3309(3)	4214.4(18)	28.2(8)

N13	1904(5)	4396(2)	2186.5(14)	20.7(6)
C4	639(6)	3599(3)	4348.5(16)	24.3(7)
C5	2909(6)	5962(3)	3871.1(18)	22.0(7)
C6	3392(6)	3252(3)	3643.7(18)	25.5(8)
C7	-336(6)	3756(3)	3368.9(17)	25.1(7)
C8	-75(7)	6573(3)	4472.2(18)	29.4(7)
C9	2571(7)	5918(3)	2770.5(18)	26.0(8)
C10	791(6)	6397(3)	3936.3(18)	27.4(8)
C11	-482(7)	5123(4)	1451.5(18)	34.4(9)
C12	-922(6)	3831(3)	3935.7(18)	25.3(8)
C13	4112(7)	5719(3)	4361.7(19)	28.3(8)
C14	3250(8)	5888(3)	4899(2)	31.4(9)
C15	1150(7)	6306(3)	4945.3(19)	29.2(8)
C16	3212(7)	5864(3)	1696(2)	29.8(9)
C17	806(7)	6083(3)	1508.2(19)	33.5(9)
C18	3300(6)	5297(3)	2255.5(17)	22.1(7)

*Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **386**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.*

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1	49.9(3)	31.3(2)	33.6(2)	2.32(17)	10.7(2)	1.8(2)
S2	19.6(4)	16.6(4)	28.6(4)	-3.2(3)	4.4(3)	-1.4(3)
O3	22.6(12)	23.5(11)	39.9(14)	2.5(11)	7.7(12)	6.4(11)
O4	19.9(12)	33.1(14)	35.4(15)	-1.8(13)	-3.2(11)	5.7(11)
O5	46.1(18)	67(2)	26.7(15)	8.4(17)	-7.8(13)	-12.1(19)
N6	36.6(17)	32.2(16)	27.5(16)	2.1(13)	-3.1(16)	-10.3(17)

C	19.3(15)	15.1(15)	29.4(18)	-1.5(14)	1.3(13)	-2.7(14)
C1	16.6(17)	38(2)	29.8(19)	-3.3(16)	1.3(14)	-1.0(15)
O9	36.5(16)	23.4(13)	38.4(16)	-8.2(12)	6.1(13)	-11.7(12)
O10	47.0(19)	53(2)	28.7(16)	-0.2(15)	7.3(15)	4.3(16)
C2	18.8(17)	15.6(15)	32(2)	1.2(15)	-5.3(15)	-2.1(13)
C3	27.6(18)	24.3(18)	33(2)	5.1(15)	-7.6(15)	-1.5(15)
N13	14.7(13)	22.6(15)	24.8(16)	-2.9(13)	-0.1(11)	-4.0(11)
C4	29.0(17)	19.1(15)	24.8(17)	2.7(15)	-0.9(14)	-4.8(13)
C5	21.2(18)	15.7(16)	29.2(19)	-2.7(13)	-2.9(15)	-1.4(13)
C6	16.8(15)	19.6(17)	40(2)	2.0(15)	-2.5(15)	2.0(13)
C7	19.1(17)	27.0(17)	29.2(18)	-0.5(14)	-2.9(15)	2.4(14)
C8	24.4(16)	26.3(17)	37.6(19)	-4.6(15)	-0.9(15)	4(2)
C9	27.5(18)	20.3(17)	30.1(19)	-4.8(14)	-7.6(17)	8.5(15)
C10	22.4(16)	23.7(18)	36(2)	-1.6(16)	-7.8(15)	3.5(15)
C11	22.8(19)	54(3)	25.9(19)	-1.5(18)	-2.6(15)	6.8(18)
C12	21.4(16)	25.5(18)	29(2)	-0.7(15)	0.0(15)	0.9(15)
C13	28.0(18)	22.2(16)	35(2)	-2.1(16)	-7.4(17)	3.4(15)
C14	36(2)	24.3(19)	34(2)	3.8(16)	-7.5(19)	5.4(16)
C15	37(2)	21.0(17)	30(2)	-2.1(15)	4.1(17)	-2.9(16)
C16	31(2)	26(2)	33(2)	3.8(16)	3.2(18)	0.5(15)
C17	35(2)	37(2)	28(2)	6.8(17)	4.6(17)	12.6(18)
C18	18.7(15)	17.7(16)	29.9(19)	-1.9(15)	-1.5(13)	-0.9(13)

*Bond Lengths for **386**.*

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Br1	C15	1.905(4)	C3	C4	1.384(5)

S2	O3	1.428(3)	C3	C6	1.387(6)
S2	C	1.782(4)	N13	C18	1.489(5)
S2	O9	1.432(3)	C4	C12	1.380(5)
S2	N13	1.611(3)	C5	C10	1.402(5)
O4	C2	1.216(5)	C5	C13	1.396(6)
O5	N6	1.228(5)	C7	C12	1.379(6)
N6	O10	1.220(5)	C8	C10	1.380(6)
N6	C4	1.473(5)	C8	C15	1.378(6)
C	C6	1.387(5)	C9	C18	1.537(5)
C	C7	1.390(5)	C11	C17	1.520(7)
C1	N13	1.478(5)	C13	C14	1.382(7)
C1	C11	1.514(6)	C14	C15	1.379(6)
C2	C5	1.492(6)	C16	C17	1.530(6)
C2	C9	1.515(5)	C16	C18	1.525(6)

*Bond Angles for **386**.*

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
O3	S2	C	106.78(17)	C12	C4	C3	122.3(4)
O3	S2	O9	119.16(17)	C10	C5	C2	123.5(4)
O3	S2	N13	108.61(16)	C13	C5	C2	118.2(3)
O9	S2	C	106.19(18)	C13	C5	C10	118.2(4)
O9	S2	N13	107.93(17)	C	C6	C3	120.0(4)
N13	S2	C	107.64(17)	C12	C7	C	119.4(4)
O5	N6	C4	117.6(4)	C15	C8	C10	119.3(4)
O10	N6	O5	124.1(4)	C2	C9	C18	113.8(3)

O10	N6	C4	118.3(3)	C8	C10	C5	120.6(4)
C6	C	S2	119.4(3)	C1	C11	C17	110.8(4)
C6	C	C7	120.8(4)	C7	C12	C4	119.3(4)
C7	C	S2	119.8(3)	C14	C13	C5	121.5(4)
N13	C1	C11	109.6(3)	C15	C14	C13	118.5(4)
O4	C2	C5	120.2(4)	C8	C15	Br1	119.3(3)
O4	C2	C9	120.8(4)	C8	C15	C14	121.8(4)
C5	C2	C9	119.0(3)	C14	C15	Br1	118.9(3)
C4	C3	C6	118.2(4)	C18	C16	C17	112.2(3)
C1	N13	S2	120.1(3)	C11	C17	C16	109.4(3)
C1	N13	C18	116.2(3)	N13	C18	C9	112.3(3)
C18	N13	S2	120.4(2)	N13	C18	C16	107.6(3)
C3	C4	N6	119.1(3)	C16	C18	C9	112.9(3)
C12	C4	N6	118.7(3)				

*Torsion Angles for **386**.*

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
S2	C	C6	C3	-179.4(3)	C2	C9	C18	N13	95.7(4)
S2	C	C7	C12	-179.5(3)	C2	C9	C18	C16	-142.4(3)
S2	N13	C18	C9	-90.0(3)	C3	C4	C12	C7	1.1(6)
S2	N13	C18	C16	145.1(3)	N13	S2	C	C6	-129.7(3)
O3	S2	C	C6	-13.2(3)	N13	S2	C	C7	50.7(3)
O3	S2	C	C7	167.2(3)	N13	C1	C11	C17	-55.5(4)
O3	S2	N13	C1	164.1(3)	C4	C3	C6	C	-0.7(6)
O3	S2	N13	C18	-37.0(3)	C5	C2	C9	C18	-157.5(3)

O4	C2	C5	C10	177.4(4)	C5	C13	C14	C15	0.1(6)
O4	C2	C5	C13	-4.7(5)	C6	C	C7	C12	0.9(5)
O4	C2	C9	C18	23.5(5)	C6	C3	C4	N6	-179.7(3)
O5	N6	C4	C3	-5.0(5)	C6	C3	C4	C12	0.0(6)
O5	N6	C4	C12	175.3(4)	C7	C	C6	C3	0.2(6)
N6	C4	C12	C7	-179.2(3)	C9	C2	C5	C10	-1.6(5)
C	S2	N13	C1	-80.6(3)	C9	C2	C5	C13	176.3(3)
C	S2	N13	C18	78.2(3)	C10	C5	C13	C14	0.7(6)
C	C7	C12	C4	-1.6(6)	C10	C8	C15	Br1	-178.7(3)
C1	N13	C18	C9	69.6(4)	C10	C8	C15	C14	1.6(6)
C1	N13	C18	C16	-55.3(4)	C11	C1	N13	S2	-143.8(3)
C1	C11	C17	C16	57.1(5)	C11	C1	N13	C18	56.5(4)
O9	S2	C	C6	114.9(3)	C13	C5	C10	C8	-0.3(6)
O9	S2	C	C7	-64.7(3)	C13	C14	C15	Br1	179.1(3)
O9	S2	N13	C1	33.6(3)	C13	C14	C15	C8	-1.2(6)
O9	S2	N13	C18	-167.5(3)	C15	C8	C10	C5	-0.8(6)
O10	N6	C4	C3	175.4(4)	C17	C16	C18	N13	54.6(4)
O10	N6	C4	C12	-4.3(5)	C17	C16	C18	C9	-69.9(4)
C2	C5	C10	C8	177.6(4)	C18	C16	C17	C11	-57.6(5)
C2	C5	C13	C14	-177.3(4)					

Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for ***386****.*

Atom	*x*	*y*	*z*	U(eq)
H1A	-1261	4925	2303	34

H1B	-1198	3911	1954	34
H3	3848	3153	4505	34
H6	4869	3061	3540	31
H7	-1403	3897	3080	30
H8	-1501	6875	4514	35
H9A	2720	6623	2672	31
H9B	968	5787	2849	31
H10	-55	6571	3609	33
H11A	-2054	5265	1344	41
H11B	195	4719	1146	41
H12	-2385	4039	4041	30
H13	5556	5431	4325	34
H14	4084	5720	5230	38
H16A	3972	5477	1395	36
H16B	4035	6492	1740	36
H17A	66	6511	1793	40
H17B	819	6432	1138	40
H18	4885	5084	2319	27