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I. Studies on the Organocatalytic Formation of Quaternary Stereocenters. II. Studies on the Claisen Rearrangement as a Route to Quaternary Stereocenters. III. Asymmetric Synthesis of Aldehydes Bearing Quaternary Carbon Centers via the Decarboxylative Asymmetric Allylic Alkylation

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I. STUDIES ON THE ORGANOCATALYTIC FORMATION OF QUATERNARY STEREOCENTERS

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III. ASYMMETRIC SYNTHESIS OF ALDEHYDES BEARING QUATERNARY CARBON CENTERS VIA THE DECARBOXYLATIVE ASYMMETRIC ALLYLIC ALKYLATION

by

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ABSTRACT

I. STUDIES ON THE ORGANOCATALYTIC FORMATION OF QUATERNARY STEREOCENTERS. II. STUDIES ON THE CLAISEN REARRANGEMENT AS A ROUTE TO QUATERNARY STEREOCENTERS. III. ASYMMETRIC SYNTHESIS OF ALDEHYDES BEARING QUATERNARY CARBON CENTERS VIA THE DECARBOXYLATIVE ASYMMETRIC ALLYLIC ALKYLATION.

by

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The University of Wisconsin-Milwaukee, 2013
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The asymmetric synthesis of all carbon quaternary stereocenters poses a particular challenge due to the steric congestion inherent in the formation of such centers and has been the object of intense research these last 20-30 years. However, the amount of literature for the synthesis of *aldehydes* bearing quaternary stereocenters via enolate type chemistry is much more limited due to problems associated with the alkylation of such substrates including such types as Cannizzaro and Tischenko related reactions or self aldol condensations. The formation of aldehydes with quaternary stereocenters via use of enolate equivalents such as the DAAA (decarboxylative asymmetric allylic alkylation) of ally enol carbonates has also not been fully explored. Herein, we describe the creation of all carbon stereocenters starting from 3-hydroxy aryl acrylates via several routes. The first method employs organocatalysts; reactions that have been investigated using this route are phase transfer catalyzed alkylations and organocatalytic Michael additions catalyzed by Cinchona alkaloid catalysts. The phase transfer catalyzed alkylation is less

successful than the Michael addition due to competing C- vs. O-alkylation. The second method involves the well known Claisen rearrangement via the O-alkylation of 3-hydroxy aryl acrylates and the subsequent [3,3] sigmatropic rearrangement. The O-alkylated products are obtained in yields ranging from 65-84%, and the corresponding Claisen rearrangement products in yields ranging from 55-91%. Multiple attempts at achieving an asymmetric Claisen rearrangement employing Lewis acid metal catalysts failed either due to insufficient activation of the Claisen substrate or due to cleavage of the oxygen allyl bond. The last method involves the DAAA of allyl enol carbonates derived from 3-hydroxy aryl acrylates. A stereoselective synthesis of these carbonates was devised that can form the *Z*- or *E*- stereoisomer in very high *Z*/*E* ratios (50:1 and 1:99 respectively). The stereochemical outcome depends on the choice of base, addition of TMEDA and reaction temperature. The *Z*- and *E*- stereoisomers have different reactivities towards the DAAA reaction, with the *E*-stereoisomer displaying both greater reactivity and enantio-differentiation with chiral ligands. The DAAA of *E*- stereoisomer analogues takes place in excellent yields ranging from 96-99% and enatioselectivities ranging from 42-78% ee.

I dedicate this thesis to my family

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LIST OF ABBREVIATIONS

EDA	Ethyl diazoacetate
TBAI	Tetrabutylammonium iodide
PTC	Phase transfer catalyst
TLC	Thin layer chromatography
LiHMDS	Lithium bis(trimethylsilyl)amide
NaHMDS	Sodium bis(trimethylsilyl)amide
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
TFA	Trifluoroacetic acid
$(DHQ)_2AQN$	Hydroquinine anthraquinone-1,4-diyl diether
Eq.	Equivalents
EtOAc	Ethyl acetate
DCM	Dichloromethane
Tol.	Toluene
Hex.	Hexane
DME	1,2-dimethoxyethane
rt	Room temperature
sat.	Saturated
conc.	Concentrated
temp.	Temperature
ee	Enantiomeric excess

dr	Diastereomeric ratio
AVE	Allyl vinyl ether
AAA	Asymmetric allylic alkylation
DcA	Decarboxylative allylation
DAAA	Decarboxylative asymmetric allylic alkylation
AREA	Asymmetric ring expanding allylation

CHAPTER I: STUDIES ON THE ORGANOCATALYTIC FORMATION OF QUATERNARY STEREOCENTERS

1.1. Introduction

1.1.1. Importance of quaternary stereocenters and asymmetric catalysis

In 2006, Dr. Masakatsu Shibasaki claimed:

"*The construction of chiral tetrasubstituted carbon stereocenters, especially quaternary stereocenters, is one of the most important and difficult tasks in asymmetric catalysis*."[1]

All carbon quaternary stereocenters, i.e. carbon atoms bearing four different carbon substituents, pose a particular challenge in organic synthesis due to the inherent steric congestion present in the formation of these stereocenters. Owing to steric hindrance, relatively harsh reaction conditions are required and only limited combinations of nucleophile and electrophile can be combined. Most quaternary centers are also stereocenters with the further implication that once the stereocenter is formed it is almost impossible to invert the stereochemistry. Despite recent progress in this area, the number of methods available for the construction of all carbon quaternary stereocenters is still limited and the object of ongoing research. Recent reviews have highlighted important contributions in this area of research.[2,3,4,5,6] Moreover, there has been much interest in the development of routes for the *asymmetric* synthesis of quaternary stereocenters because of their ubiquitous presence in natural products as well as in some important pharmaceuticals (Figure 1).[6,7,8]

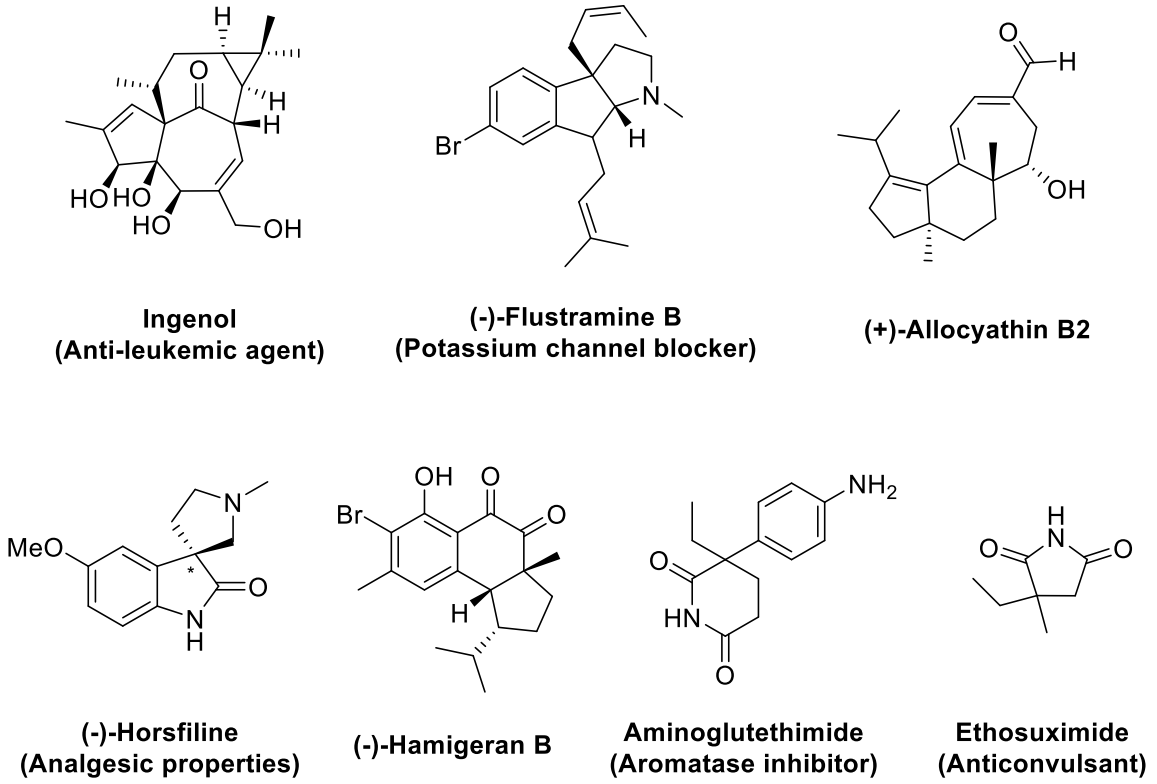


Figure 1. Natural products bearing chiral quaternary carbons.

In biological systems two enantiomers of a molecule can have drastically different biochemical effects, and in some cases it can even be the case that one enantiomer has therapeutic properties while the opposite enantiomer can be highly toxic. Therefore there is a pronounced interest in the synthesis of chiral molecules via an asymmetric route. Great progress has been achieved in the area of asymmetric catalysis, especially the last thirty years. Among the various techniques for creating quaternary stereocenters in an enantioselective fashion, catalytic asymmetric synthesis is the method of choice for several reasons: firstly, it avoids the use of chiral auxiliaries which need to be added and removed, adding to the overall cost of the synthesis; secondly, high amounts of enantioselectivity can often be achieved with small catalyst loadings; thirdly, the use of

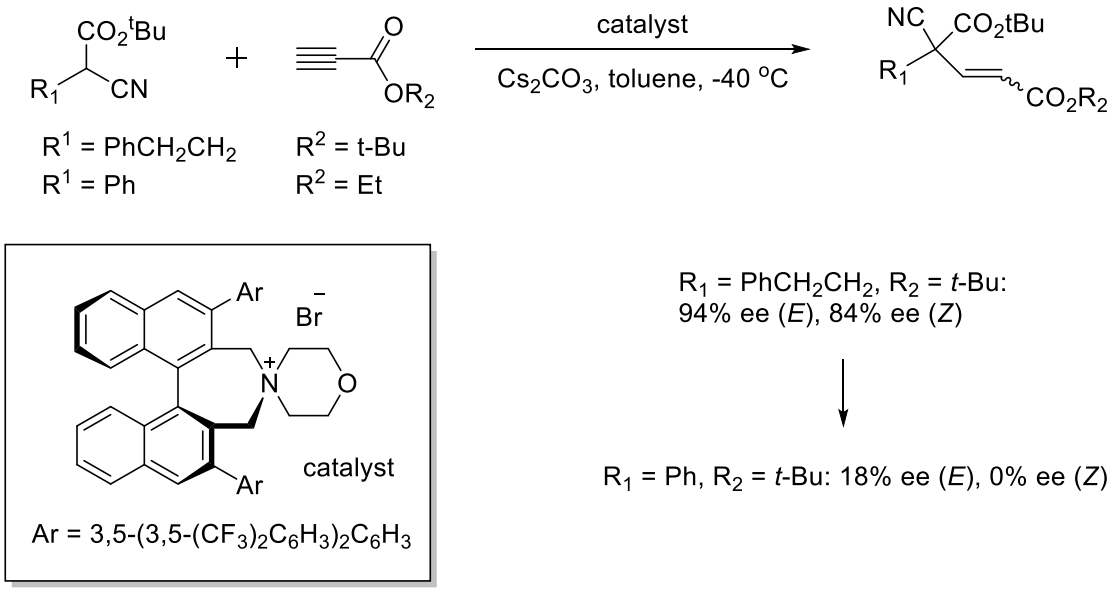
catalysts often allows for the reaction to proceed via much milder reaction conditions and in a chemoselective fashion; fourthly, compared to enzyme catalysis the substrate scope is often much greater, and both enantiomers of a molecule can be created merely by switching the chirality of the catalyst being employed.

1.1.2. General considerations in the formation of quaternary stereocenters via asymmetric catalysis

Without the aid of catalysts, reaction conditions to form quaternary stereocenters can be quite unusual and involve harsh conditions such as high temperatures and long reaction times. This fact would usually adversely affect the stereoselectivity of a reaction, but organocatalysis or metal catalysis allows for much milder reaction conditions to be employed, such as low temperature, which has the added benefit of often improving the stereoselectivity of a reaction.

All reactions have certain limitations in their substrate scope. As an example, an S_N2 reaction with a nucleophile bearing a tertiary carbon is possible with an electrophile that has a primary carbon at the electrophilic position, conversely, the same reaction could not take place with an electrophile having a tertiary carbon. In the case of asymmetric reactions the problem of substrate scope is particularly pertinent. Minor changes in the structure of substrates (“reaction partners”) can lead to profound changes in stereoselectivity, the worst case being where a change in substrate structure leads to loss of stereocontrol. These strong limitations on the “partner combinations” are common to

all asymmetrically catalyzed reactions. As an example[9] (Scheme 1) nearly complete loss of stereoselectivity in the α,β-unsaturated products is observed when small modifications are made in the structure of the Michael donor and acceptor. When the alkyl group of the Michael donor is changed from phenethyl to phenyl, the ee (enantiomeric excess) changes from 94% to 18% in the case of the (*E*) stereoisomer Michael adduct and from 84% to 0% in the case of the (*Z*)-stereoisomer. Changing the ester moiety of the Michael acceptor from *t*-butyl to ethyl also results in a moderate decrease in enantioselection. Unfortunately, it is often the case that authors fail to report on limitations of the substrate scope, although occasionally they will be mentioned in the supporting information. Pronounced and sometimes unexpected changes in stereoselectivity can also be observed by subtle changes in the structure of the catalyst. Commonly solvent choice and temperature also have an important effect on the stereoselectivity of a reaction. Taken together this means that extensive screening of reaction conditions often has to be carried out to optimize stereoselectivity and yield. Occasionally asymmetric catalysis will lead to satisfactory results for only a few analogues of the reaction partners, and specific reaction conditions may need to be found in other cases.



Scheme 1: Striking effect in stereocontrol with subtle changes in structure.

1.1.3. General reaction classes for formation of quaternary stereocenters

Stereoselective formation of quaternary stereocenters through catalytic methods can be classified in two main categories: through *organocatalysis* (the use of organic molecules as catalysts) or through metal and Lewis acid catalysis. Lewis acid catalyzed asymmetric construction of quaternary stereocenters has been successfully achieved for the following reaction classes: Diels-Alder reactions, 1,3-dipolar [3+2] cycloadditions, the synthesis of β-lactams via overall [2+2] cycloadditions, cyclopropanations, 1,4 conjugate additions (Michael additions), the alkylation of tributyl tin enolates, Michael additions with hard nucleophiles, copper catalyzed S_N2' allylation, reactions with carbonyl and imine electrophiles, metal catalyzed diene and enyne cyclizations, rhodium catalyzed C-H insertions[2] and Claisen rearrangements[74,75,76]. Organometallic reactions that take place via

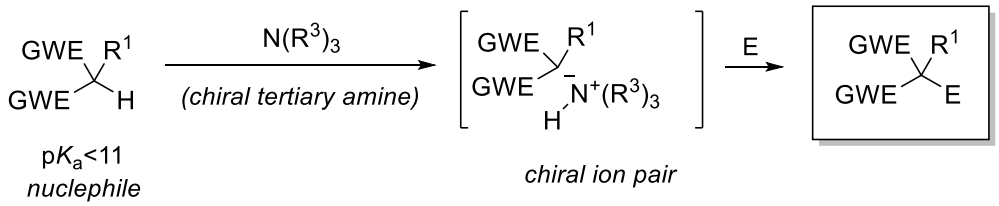
oxidative addition-reductive elimination processes include: α-arylation and vinylation reactions of ketones and lactones, intramolecular Heck reactions and most importantly allylation via palladium π-allyl intermediates.[2]

A survey of the literature reveals that the majority of reactions involving the construction of quaternary stereocenters involve *cyclic* systems. As an example, in the review by Marco Bella on the organocatalytic formation of quaternary stereocenters[3] out of a total of twenty-eight examples of Michael adducts bearing quaternary stereocenters, only six different acyclic substrates were used. For other reaction classes [10] (such as the asymmetric decarboxylative allylic alkylation), the use of acyclic substrates is much rarer, with most existing examples having been published only within the past 5-10 years, and for some reaction classes, non-existent. The reason for the prevalence of cyclic substrates in the literature is due to the challenge associated with an increase in the number of degrees of freedom associated with acyclic structures.[4]

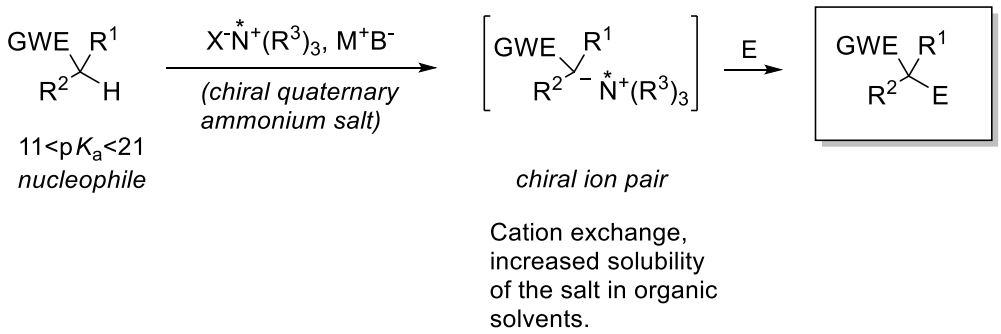
1.1.4. General mechanisms of activation for formation of quaternary stereocenters via organocatalysis

A general classification of the reaction classes used in organocatalysis shows that two general approaches are feasible: nucleophile (Scheme 2; i-iii)) or electrophile activation (Scheme 3; iv,v)).

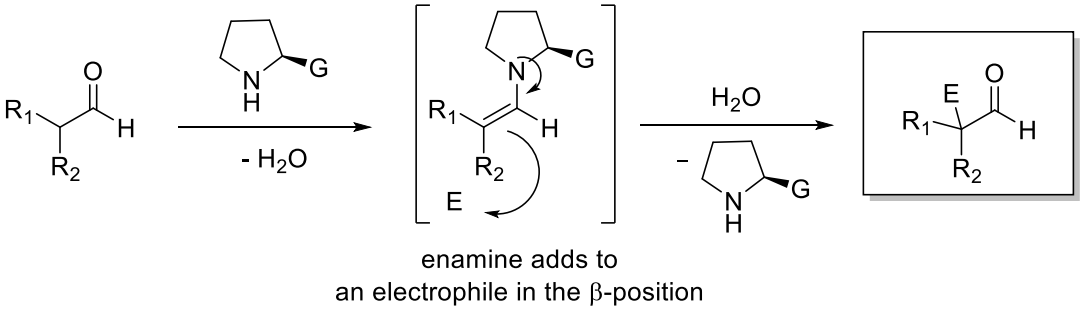
i) Via tertiary amine:



ii) Via inorganic base-quaternary ammonium salt:

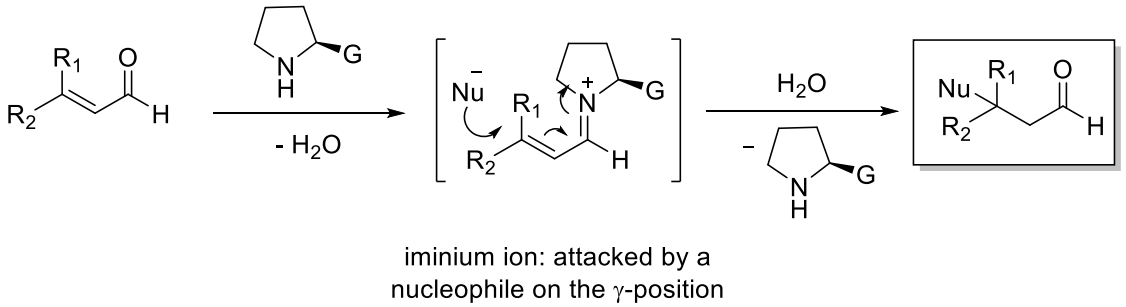


iii) Via enamine:



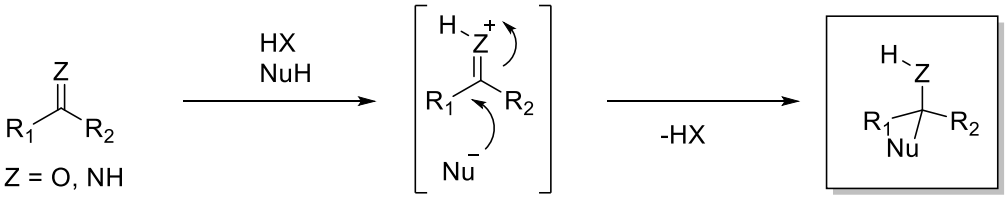
Scheme 2. Organocatalytic nucleophilic activation.

iv) Via iminium ion:



iminium ion: attacked by a nucleophile on the γ-position

v) Via Brønsted acid:



Scheme 3. Organocatalytic electrophilic activation.

Activation of the nucleophile can occur in various ways:

i) Tertiary amines: Nucleophiles with a pK_a < 10-11 are deprotonated to a significant extent by tertiary amines, upon deprotonation a tight ion pair is formed between the conjugate base of the acid (typically an enolate) and the quaternary ammonium ion. If a chiral tertiary amine is used, usually based from a cinchona based alkaloid scaffold[11], then the activated nucleophile can attack the electrophile from the less hindered face (Scheme 4[12,13,14]). Some catalysts that have been employed recently involve mostly transformation at C-9 or C-6' (Figure 2). The C-6' position is frequently demethylated in order to position and activate the electrophile via hydrogen bonding to a carbonyl group.

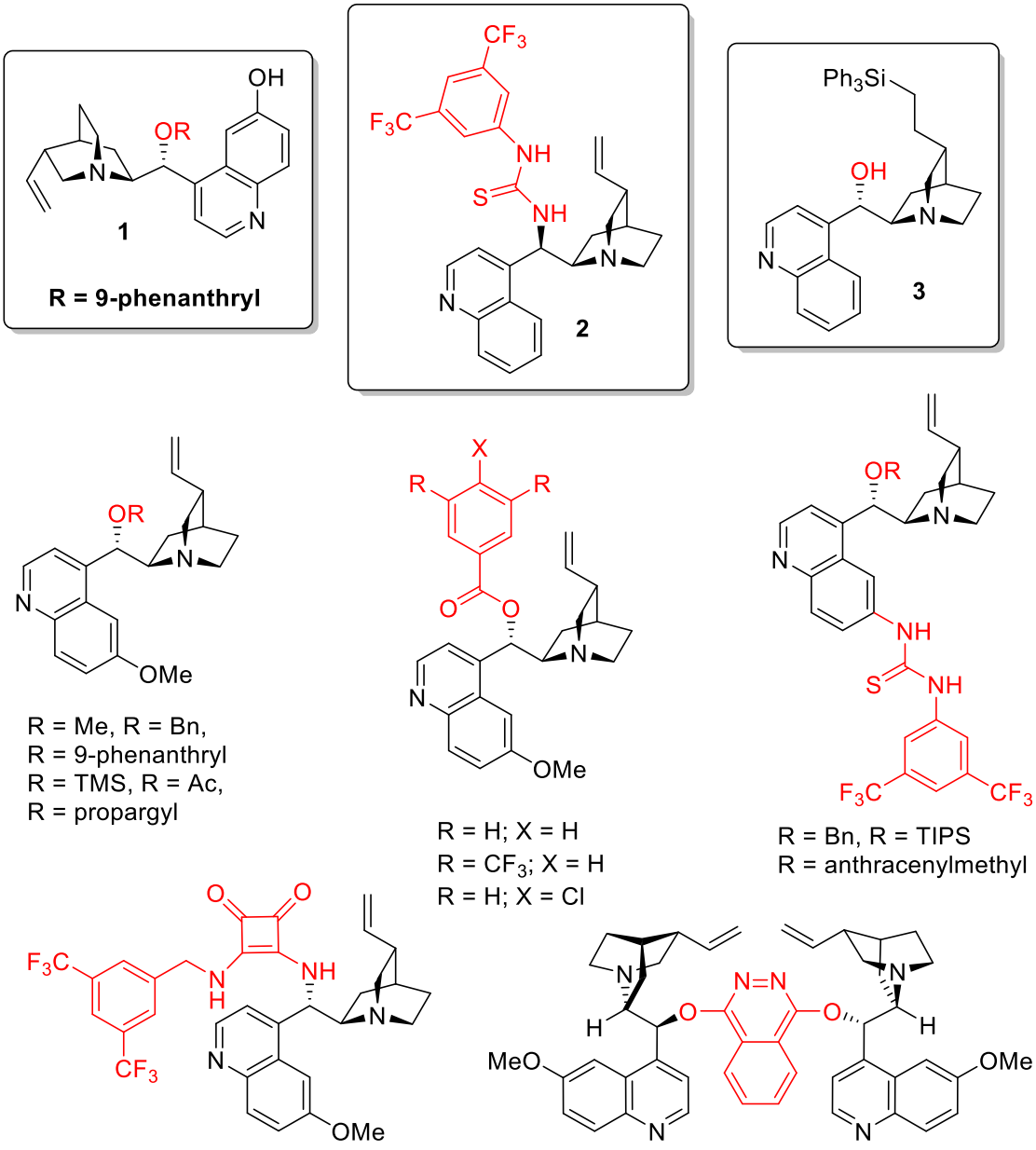
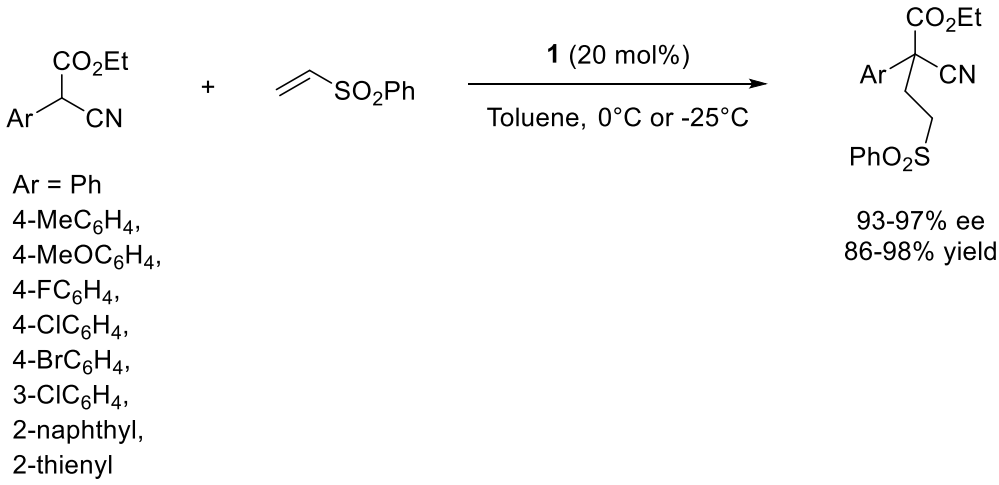
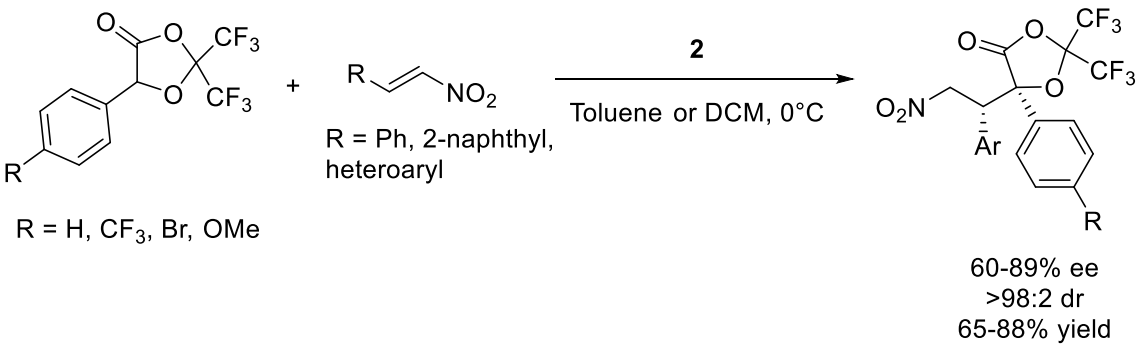


Figure 2. Cinchona alkaloid based catalysts.

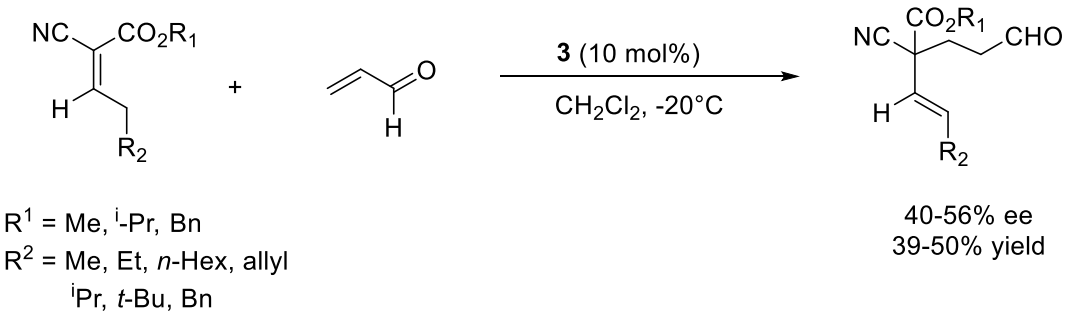
Michael addition to vinyl sulfones:



Michael addition to β-nitrostyrene:



Deconjugative Michael addition:

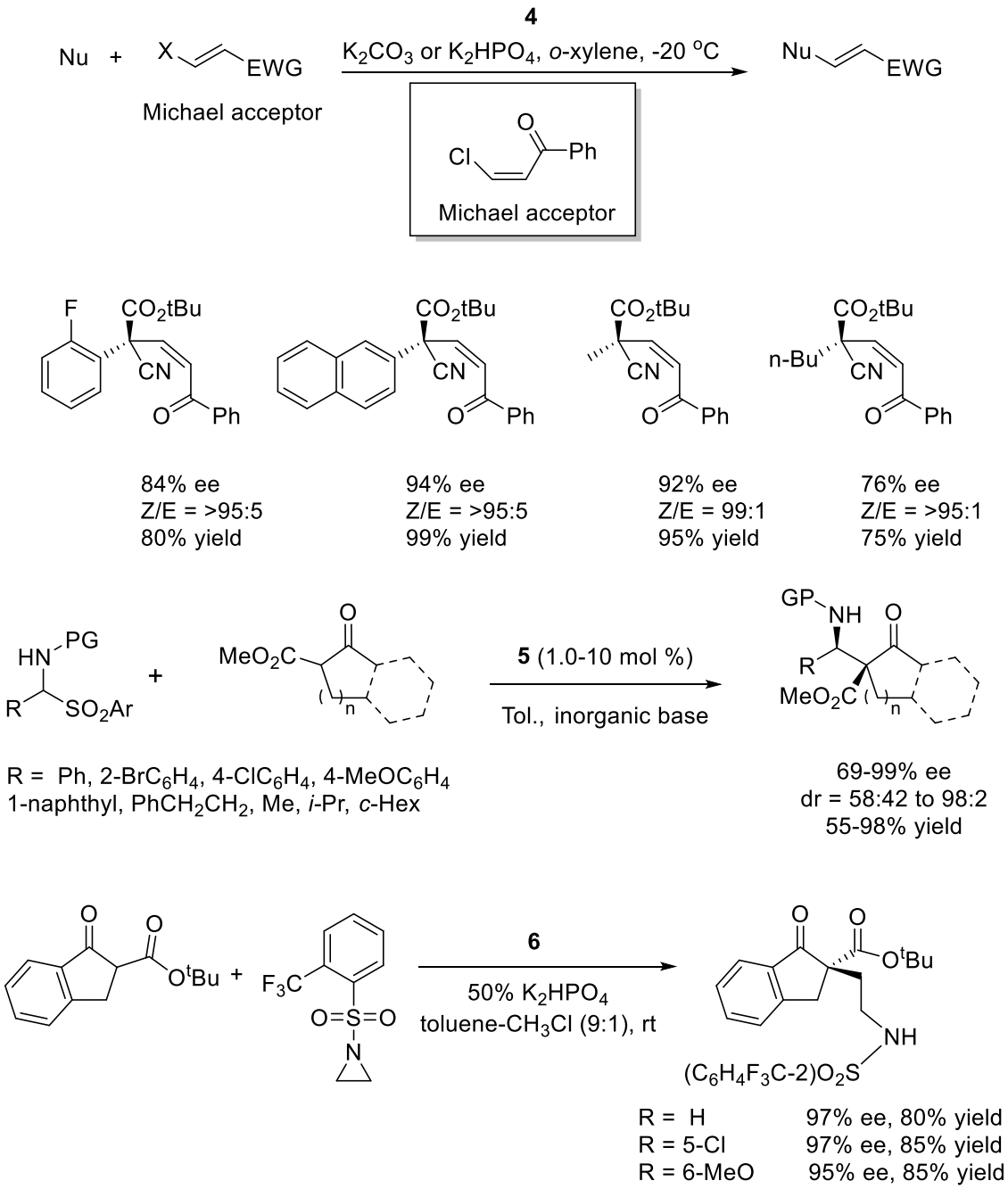


Scheme 4. Organocatalytic Michael additions using Cinchona alkaloid catalysts.

ii) Inorganic bases and quaternary ammonium salts[15]*:* Nucleophiles with pK_a values < 22 can be deprotonated by inorganic bases (either aqueous solutions or in solid form). Once

the base deprotonates the acid, an ion exchange then takes place between the counter ion of the inorganic base and the quaternary ammonium ion, leading to the nucleophile having much greater solubility in organic solvents and to much faster reaction times. As with i), the nucleophile forms a tight ion pair with the chiral counterion, thus allowing for one face of the nucleophile to be blocked from attack by the electrophile (Scheme 5).[16,17,18] The quaternary ammonium salts employed are usually derived from cinchona alkaloids or from axially chiral quaternary ammonium salts (Figure 3).[19] This approach has been used successfully for the asymmetric alkylation of cyclic ketones[20] (Scheme 6) and cyclic β-keto esters[21] (Scheme 7).

iii) Enamine activation of aldehydes with secondary or primary amines: Aldehydes can be activated for nucleophilic attack by the formation of enamines from pyrrolidine or proline derived catalysts or from primary amines (Scheme 8[22,23,24], Figure 4). Enamines derived from ketones are much weaker nucleophiles and have thus far not been used for the asymmetric formation of quaternary stereocenters. Aldehydes that are doubly substituted at the terminal position of the enamine are rather weak nucleophiles and very strong electrophiles must be employed.



Scheme 5. Organocatalytic reactions with chiral phase transfer catalysts.

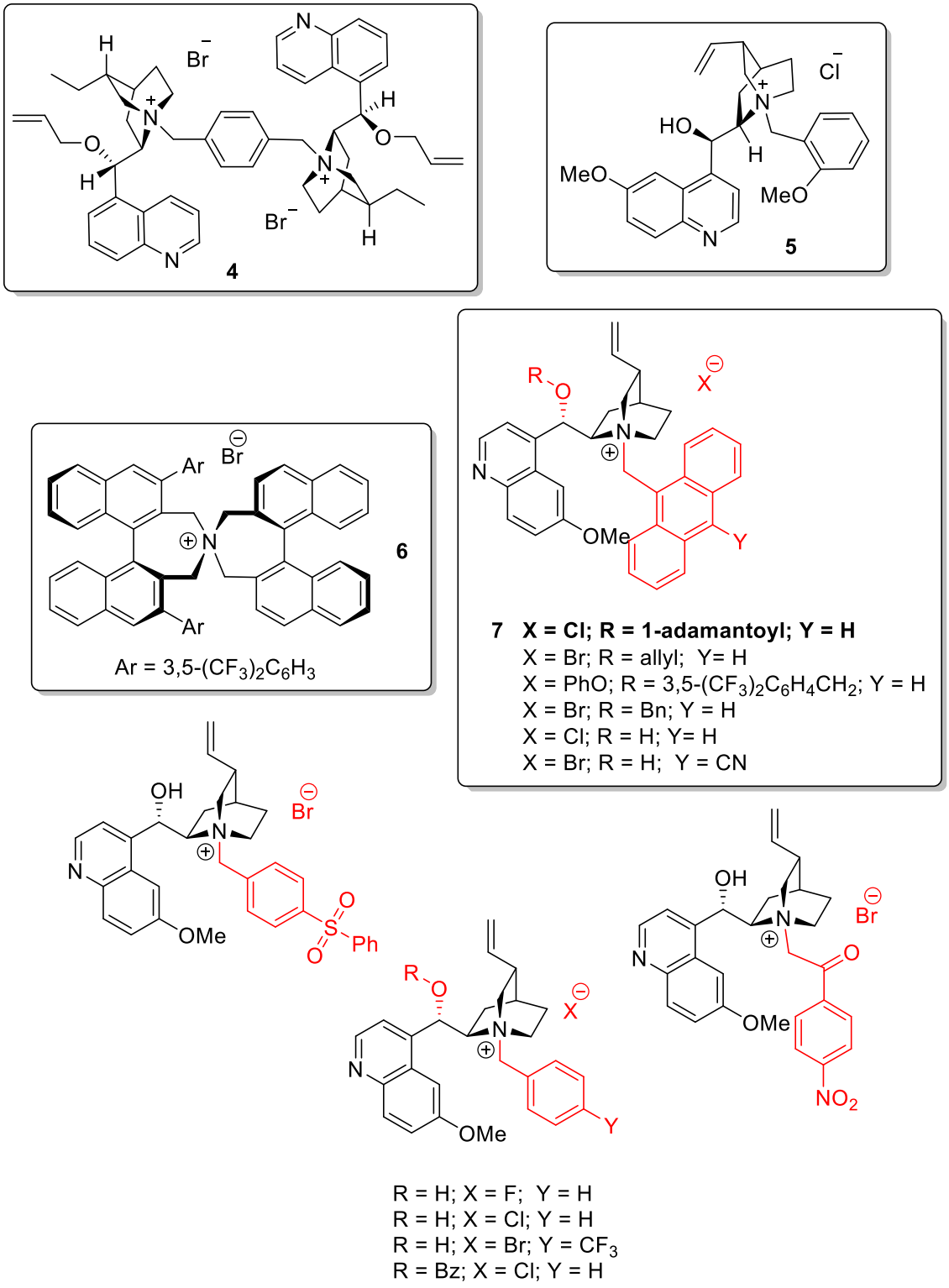
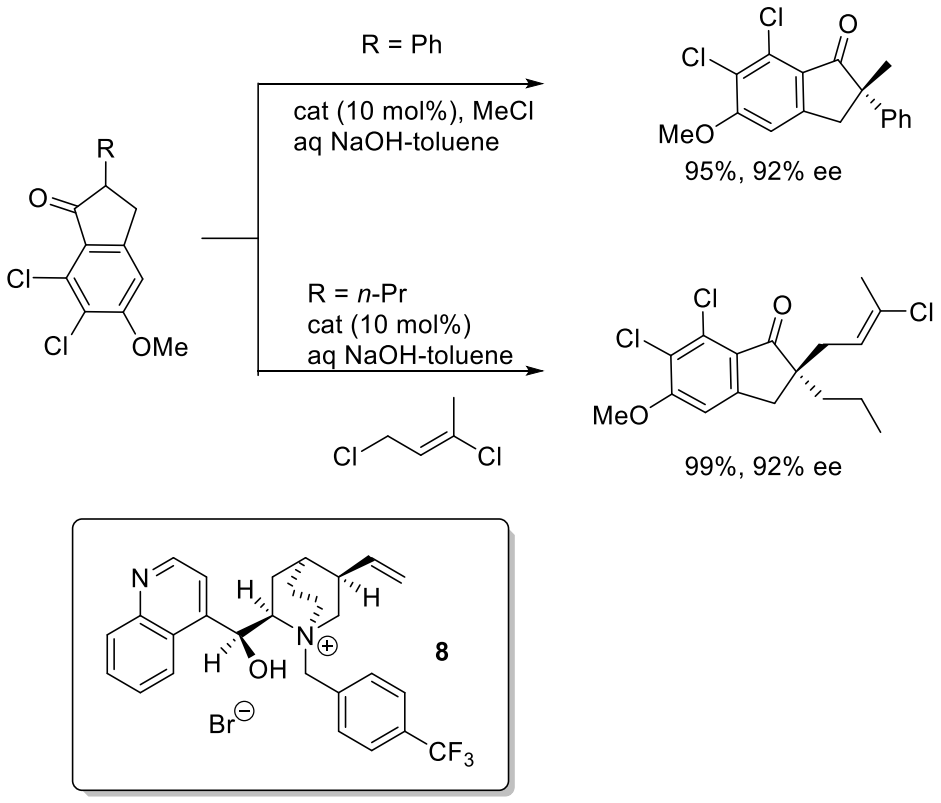
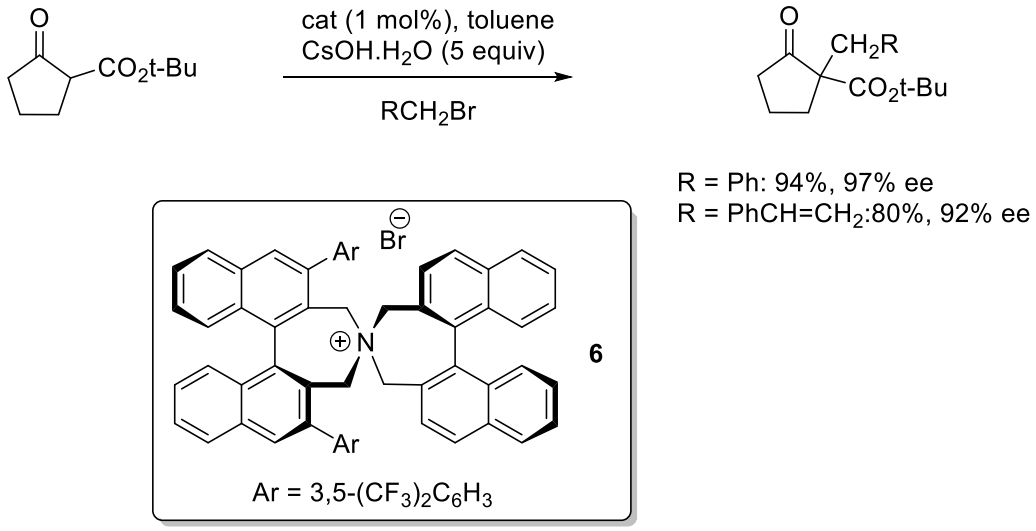


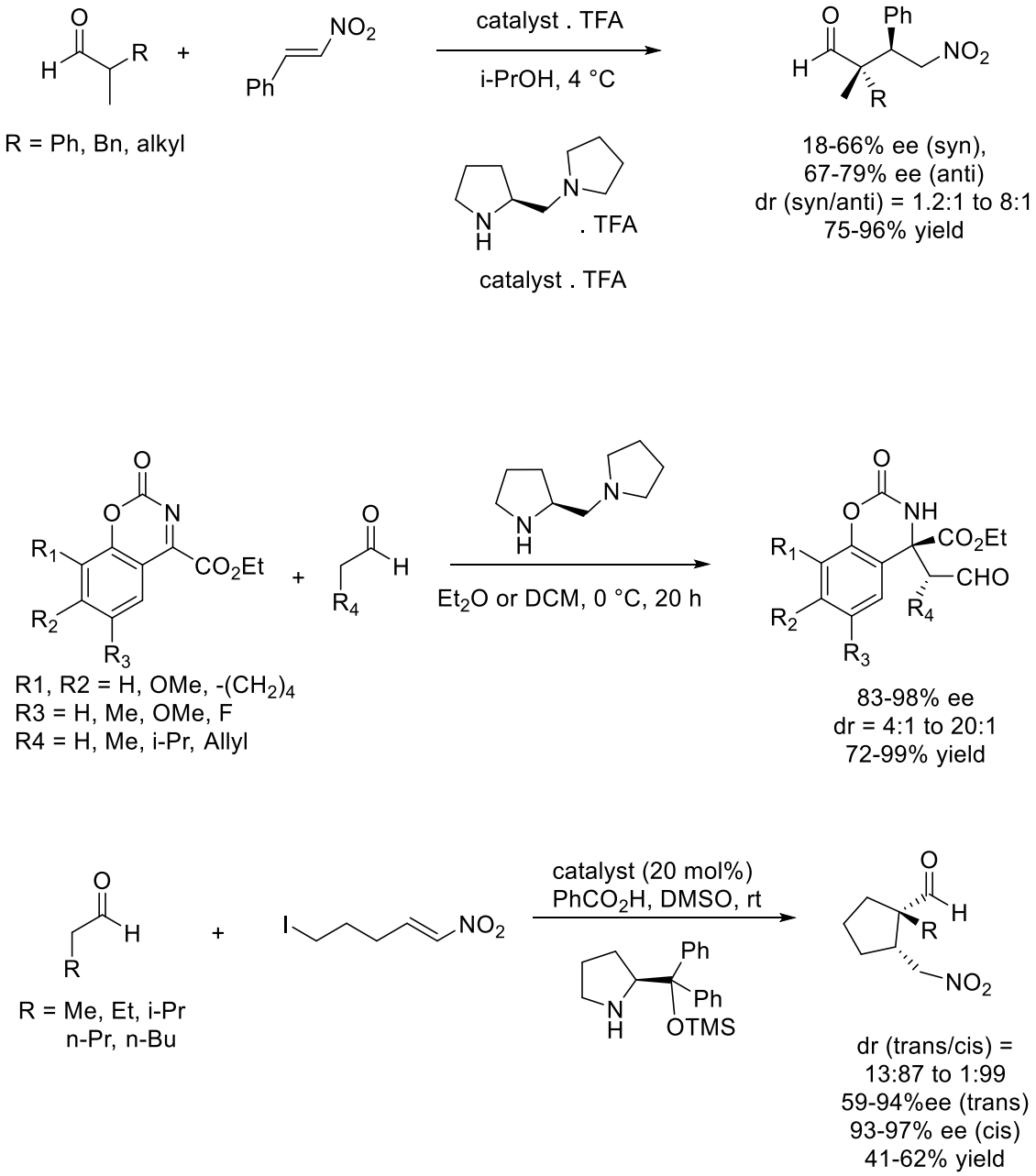
Figure 3. Chiral phase transfer catalysts.



Scheme 6. Alkylation of indanones catalyzed by chiral phase transfer catalysts.



Scheme 7. Alkylation of β-keto esters by C_2 symmetric chiral phase transfer catalyst.



Scheme 8. Organocatalytic Michael addition of aldehydes via enamine catalysis.

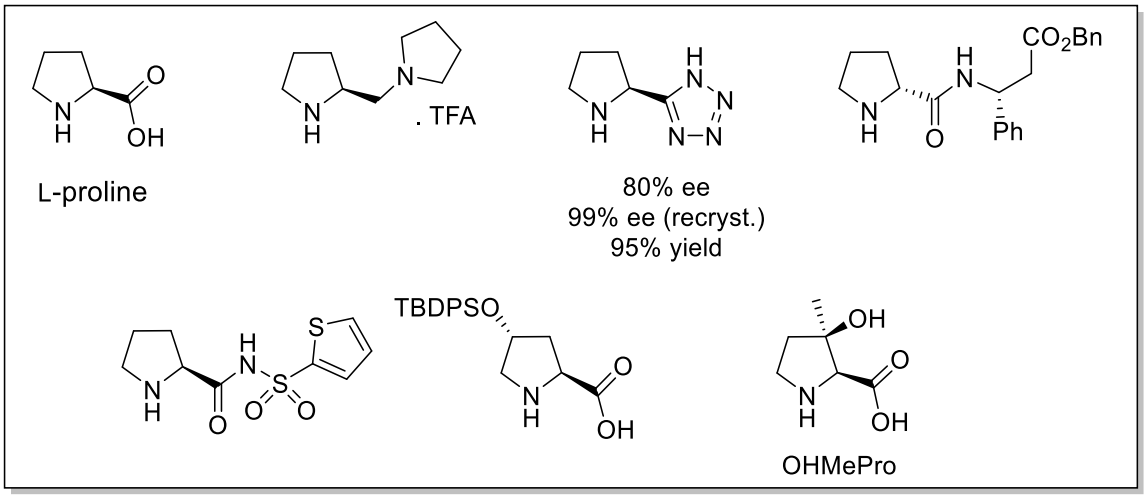


Figure 4. Proline based catalysts.

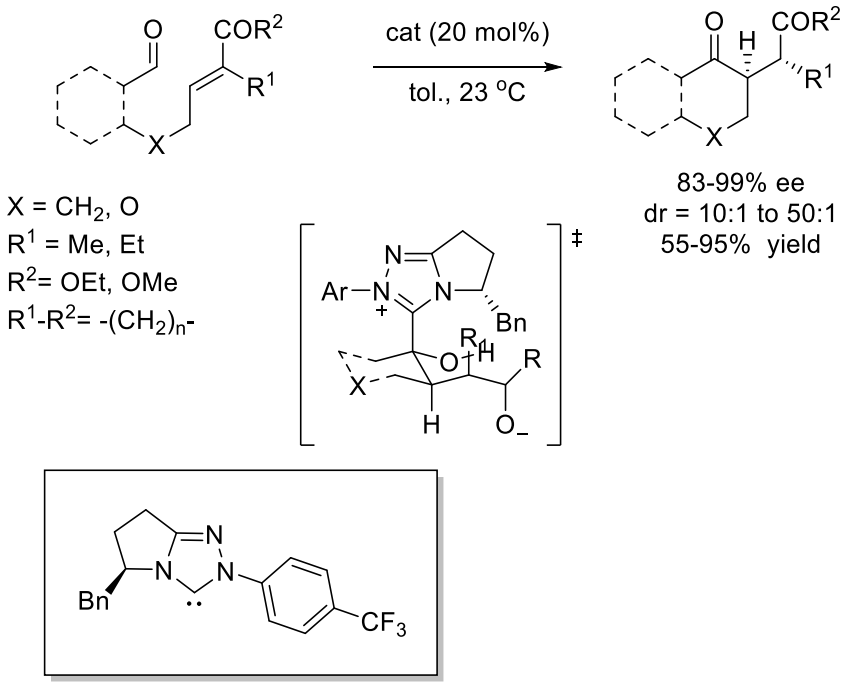
The most common methods for *electrophilic* activation are discussed below (Scheme 3):

iv) Formation of iminium ions of α,β-unsaturated carbonyl compounds: An α,β-unsaturated carbonyl compound can be activated for nucleophilc attack by formation of an iminium ion with a secondary amine (occasionally primary amines are also used), thus making the β-position more electron deficient and therefore more susceptible to nucleophilic attack. So far, no examples have been reported in the literature for this approach. The secondary amine catalyst can also be used to activate a dienophile towards a diene for the Diels-Alder reaction, and this approach has been used successfully in various examples.[25]

v) Activation by Brønsted acids: In this case a ketone or an imine will be activated for nucleophilic attack by, more commonly, a synthetic axially chiral phosphoric acid catalyst. This approach is somewhat less reported in the literature than approaches i)-iv) due to the somewhat limited scope of substrates that have been proven to be successful

thus far giving high yields and satisfactory enantiomeric excesses. The quaternary center is formed on the electrophile ketone or imine[26].

vi)_Activation via heterocyclic carbenes: A carbene reacts with a ketone or aldehyde, inverting the reactivity at the carbonyl group (umpolung chemistry). The Stetter reaction has often been used in this approach[27] (Scheme 9):

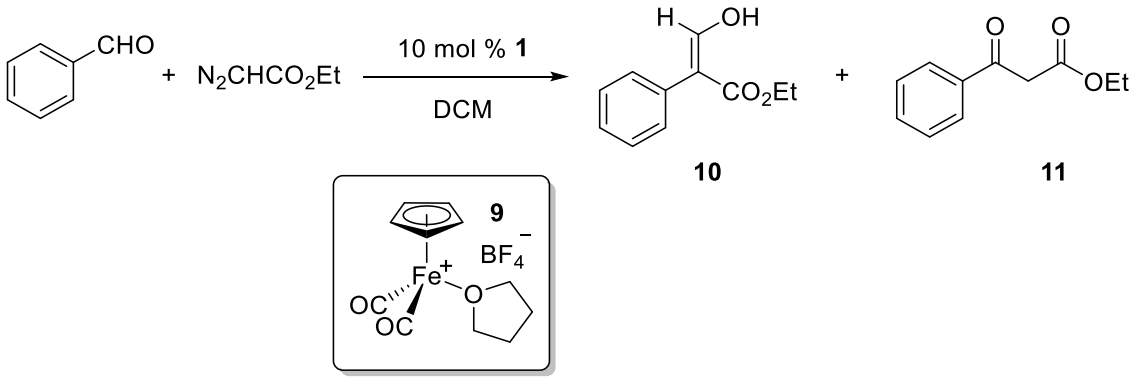


Scheme 9. Catalytic intramolecular Stetter reaction.

vii) Mixed activation: Recently a combination of organocatalysts have been used successfully to counter reduced reactivity in some substrates, such as the reaction of di-substituted α-aryl aldehydes to enones. It was found that the proline catalyzed reaction was unreactive, but the reactivity was dramatically enhanced by deprotonation of the carboxylic acid proton in proline by quinine based catalysts.[28]

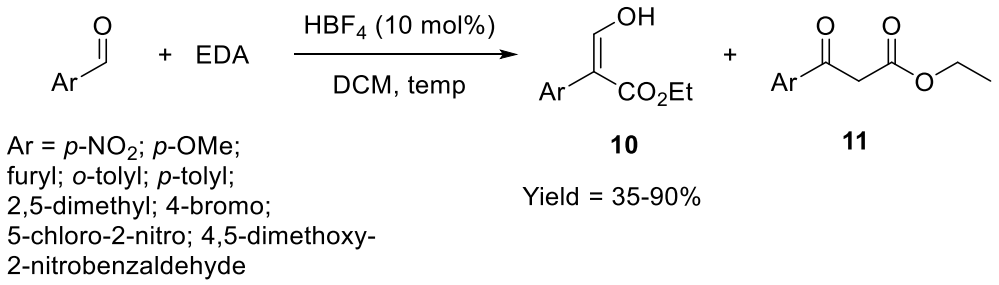
1.2. Aryl acrylates as prochiral nucleophiles for asymmetric synthesis of quaternary stereocenters.

In 1998 the Hossain group reported on an unprecedented reaction between aromatic aldehydes and EDA (ethyl diazoacetate) to afford 3-hydroxy aryl acrylates via a [1,2]-aryl shift **10** with concomitant formation of β-keto esters via a [1,2]-hydride shift **11**, catalyzed by an iron Lewis acid, [η^5-(C_5H_5)Fe(CO)$_2$(THF)]BF_4 **9**.[29] The yield of 3-hydroxy acrylate diminished with a resultant increase in the undesired β-keto ester with electron poor aldehydes due to the increased difficulty of achieving the necessary [1,2]-aryl shift.



Scheme 10. Reaction of benzaldehyde with EDA in the presence of catalyst **9**.

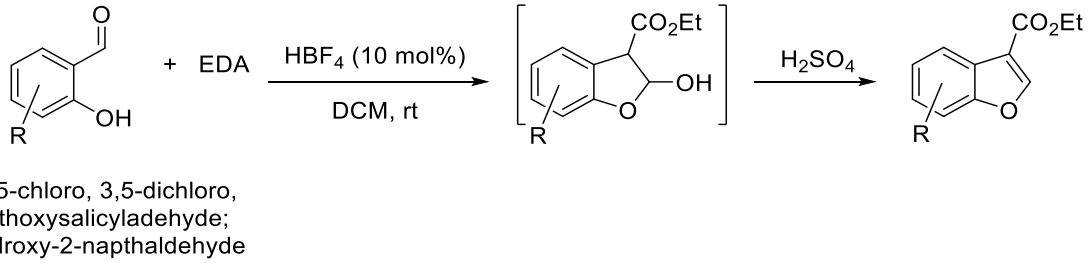
In 2004, in an extension of the previous work with the [η^5-(C_5H_5)Fe(CO)$_2$(THF)]BF_4 Lewis acid catalyzed reaction between aromatic aldehydes and EDA, the same group reported that Brønsted acids such as $HBF_4 \cdot OEt_2$ are also able to effectively catalyze the same reaction (Scheme 11).[30] Again, use of electron deficient aromatic aldehydes has a detrimental effect on the yield of the desired 3-hydroxy aryl acrylates.



Scheme 11. HBF_4 catalyzed reaction between aromatic aldehydes and EDA.

In a subsequent publication, Hossain et al. reported on a convenient one pot synthesis of 3-ethoxycarbonylbenzofuran analogs from 2-hydroxybenzaldehyde derivatives and ethyl diazoacetate.[31] The final benzofuran product is made from the dehydration of the hemiacetal intermediate formed in situ (

Scheme **12**).



Scheme 12. Formation of benzofurans via an in situ formed hemiacetal.

The versatility of the 3-hydroxyaryl acrylates to make heterocyclic aromatic compounds was further demonstrated by the Hossain group in the synthesis of indoles via the synthesis of ethyl-3-hydroxy-2-(2-nitrophenyl)acrylates and their subsequent reduction followed by concomitant cyclisation to form the desired indole products (Figure 5).[32]

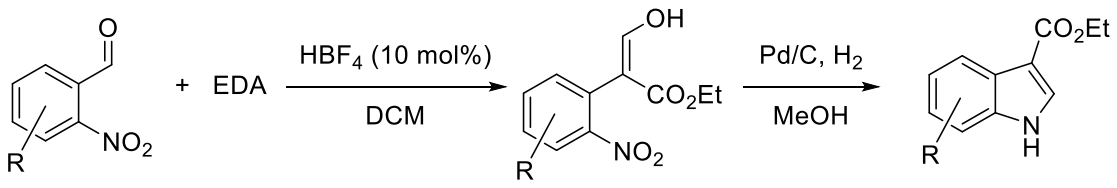


Figure 5. Formation of indoles via a one pot reductive ring closing.

It becomes readily apparent that the usefulness of 3-hydroxyaryl acrylates for synthesizing versatile reaction intermediates can be extended further due to the prochiral nature of the doubly substituted vinylic carbon in order to form *all carbon quaternary stereocenters*. Due to the previously mentioned importance of quaternary stereocenters in various natural products and pharmaceuticals, and the enormous current interest in their synthesis via asymmetric catalytic routes, 3-hydroxyaryl acrylates became an obvious choice to pursue this goal. The reaction of 3-hydroxyaryl acrylates with an appropriate electrophile will yield either of two possible stereoisomers with all carbon quaternary stereocenters, depending on whether the electrophile is attacked from the *Re* or *Si* faces. With the aid of a chiral catalyst, the reaction should be more favorable from either of the two prochiral faces, the unreacting face being blocked from attack by the presence of the chiral catalyst (Figure 6).

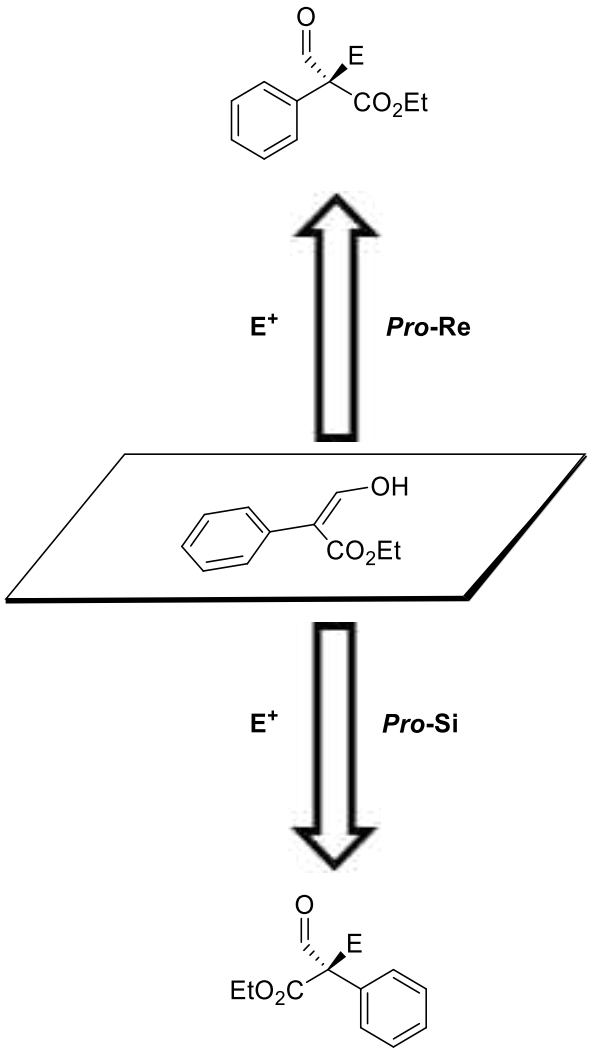
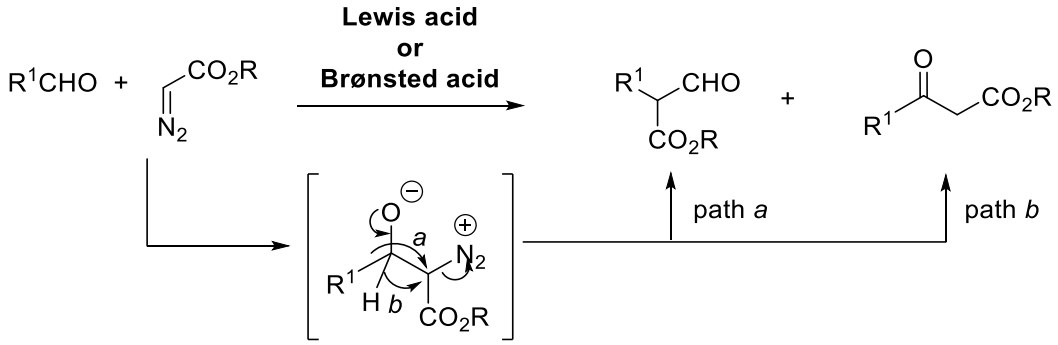


Figure 6. Formation of quaternary stereocenters via 3-hydroxy aryl acrylates.

The product yielded from the reaction of the 3-hydroxyaryl acrylate with an electrophile is an *aldehyde* bearing a quaternary carbon center, much less common than the formation of ketones bearing α-quaternary carbon centers, for reasons explained in further detail below.

1.2.1. Synthesis of 3-hydroxy aryl acrylates

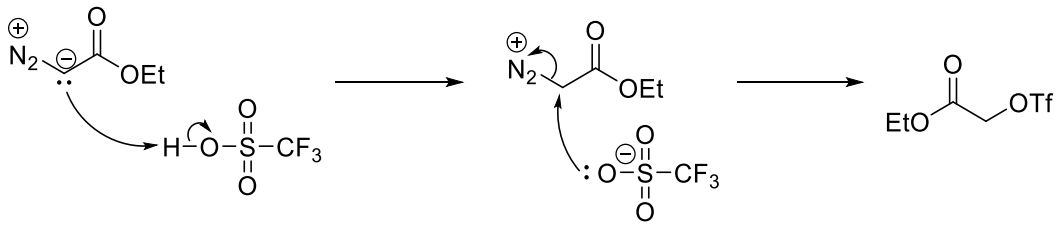
In our efforts to further the scope and usefulness of the reaction of aromatic aldehydes with EDA into 3-hydroxy aryl acrylates, we decided to investigate the use of other acids as catalysts for the reaction. Despite the usefulness of HBF_4 as a Brønsted acid catalyst for the formation of 3-hydroxy aryl acrylates[30], its use suffers from formation of a considerable amount of undesired β-keto ester product. If one considers the mechanism for the formation of these 3-hydroxy aryl acrylates (Scheme 13), it is apparent that a careful choice of acid, solvent, and temperature will affect the propensity of either the aryl or hydride to shift and displace the diazonium ion, the former process being the desired one.



Scheme 13. Mechanism for reaction of aromatic aldehydes with EDA.

With these considerations in mind, both triflic acid and $BF_3{\cdot}OEt_2$ were tested as possible alternatives for acids that could efficiently catalyze the formation of 3-hydroxy aryl acrylates. Triflic acid (pK_a = -15) potentially offered the advantage of greatly speeding up the rate of formation of 3-hydroxyaryl acrylates, but because of the extremely low pK_a

could cause protonation of the methine proton in EDA, and hence lower the yield of the desired product. $BF_3 \cdot OEt_2$ could potentially have the same disadvantage, by acting as a Lewis acid to the lone pair present in the methine carbon of ethyl diazoacetate (bearing a negative charge in one of the possible resonance forms), thus effectively deactivating the reactant. After screening possible reaction conditions, it was ascertained that the optimal conditions were the use of TfOH (20 mol%) with DCM as solvent at -78 ºC (Table 1). At this temperature, it was gratifying to find that no undesired β-keto ester was formed. Furthermore, with TfOH the reaction is conveniently very fast, with reaction completion being achieved in 30 minutes. A singlet around δ 4.9 ppm was usually present in the crude NMR, although no attempt was made to ascertain the identity of the compound representing this peak, it is probable that it is due to protonation of EDA, with concomitant expulsion of diazonium by the conjugate base of TfOH (Scheme 14). Carrying out the reaction with TfOH in toluene at the same temperature also proved satisfactory, but resulted in a small amount of β-keto ester being formed.



Scheme 14. Proposed mechanism for formation of product with singlet at δ 4.9 ppm.

Using TfOH as catalyst, the reaction of 3-methoxy-2-nitrobenzaldehyde as well as of 5-chloro-2-nitrobenzaldehyde with EDA yielded no product, probably because the EDA

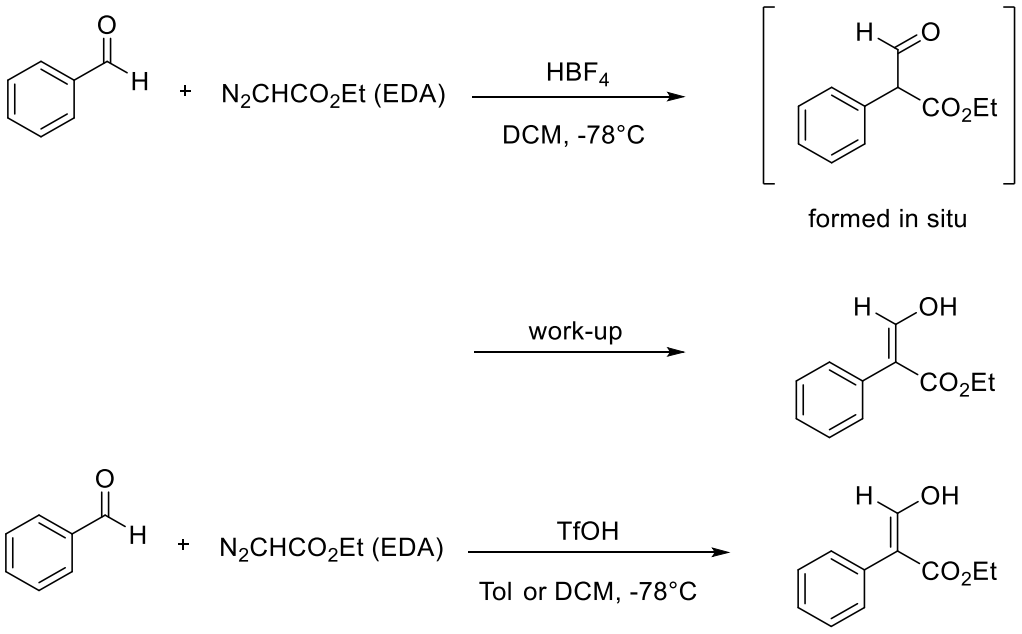
was protonated faster than the rate at which the electron poor aromatic ring could undergo the required [1,2] aryl shift with concomitant expulsion of nitrogen gas. Hence an investigation was undertaken on the use of $BF_3 \cdot OEt_2$ as a catalyst for the reaction of 3-methoxy-2-nitrophenyl acrylate with EDA (Table 1). Unfortunately, this catalyst resulted in very little amount of product being formed. Interestingly, a substantial amount of β-keto ester product was formed. It is possible that the low yield of desired 3-hydroxy acrylate might be a combination of two factors: a) the Lewis acid might have a strong affinity for binding with EDA, hence deactivating the nucleophilic carbon of the reactant for attack; b) there might be product inhibition of the catalyst, where the Lewis acid is irreversibly bound to the two carbonyl oxygens of the β-keto ester. In conclusion it would appear that TfOH is an excellent catalyst for the reaction with electron rich aromatic aldehydes, but is a poor choice for electron poor aromatic aldehydes.

Table 1. Reaction of aryl aldehydes with EDA under different reaction conditions.

Acid	Aromatic aldehyde	Solvent	Temp. (ºC)	Yield acrylate (%)	Yield β-keto ester (%)
TfOH (20 mol%)	Phenyl	DCM	-78	75	0
TfOH (20 mol%)	Phenyl	Toluene	-78	71	4
TfOH (20 mol%)	3-methoxy-2-nitro	DCM	-78	0	0
TfOH (20 mol%)	5-chloro-2-nitro	DCM	-78	0	0
$BF_3 \cdot OEt_2$ (20 mol%)	3-methoxy-2-nitro	DCM	-78 to 0	3	36

It is interesting that under strictly anhydrous conditions, the reaction with TfOH results in the more conjugated enol tautomer being formed, whereas the reaction with HBF_4 results

in the aldehyde tautomer being formed (Scheme 15**;** Figure 7**;** Figure 8). It is clear from the crude NMR spectra (Figure 7; Figure 8) that the reaction aliquot taken from the reaction carried out with TfOH is much cleaner, simplifying the purification process via column chromatography. After work-up, the reaction with HBF_4 yields the enol tautomer.



Scheme 15. Reaction of benzaldehyde with EDA in the presence of HBF_4 or TfOH.

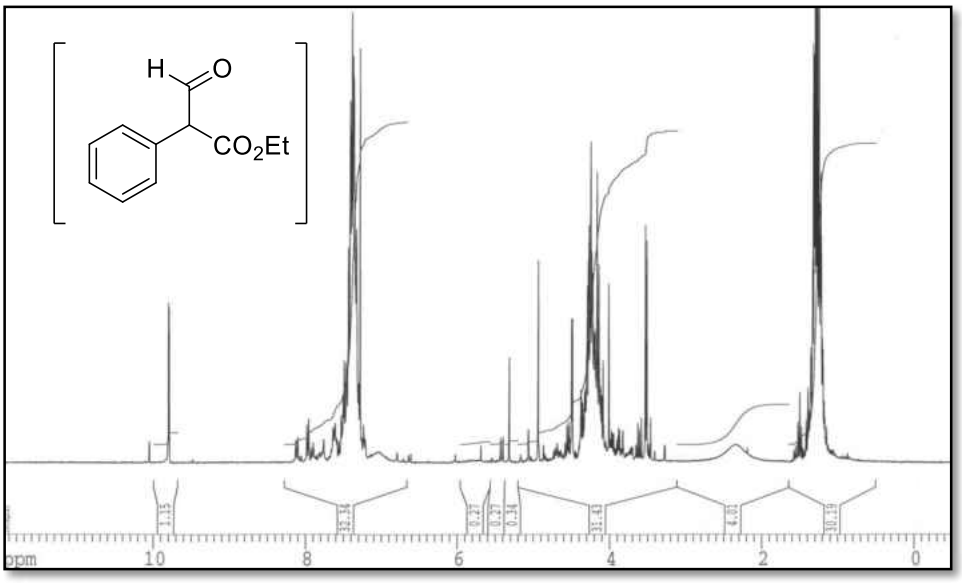


Figure 7. Crude NMR of aliquot taken from reaction with HBF_4 catalyst.

NMR from reaction aliquot of reaction between benzaldehyde and EDA in the presence of HBF_4, with aldehyde tautomer present in the crude reaction mixture.

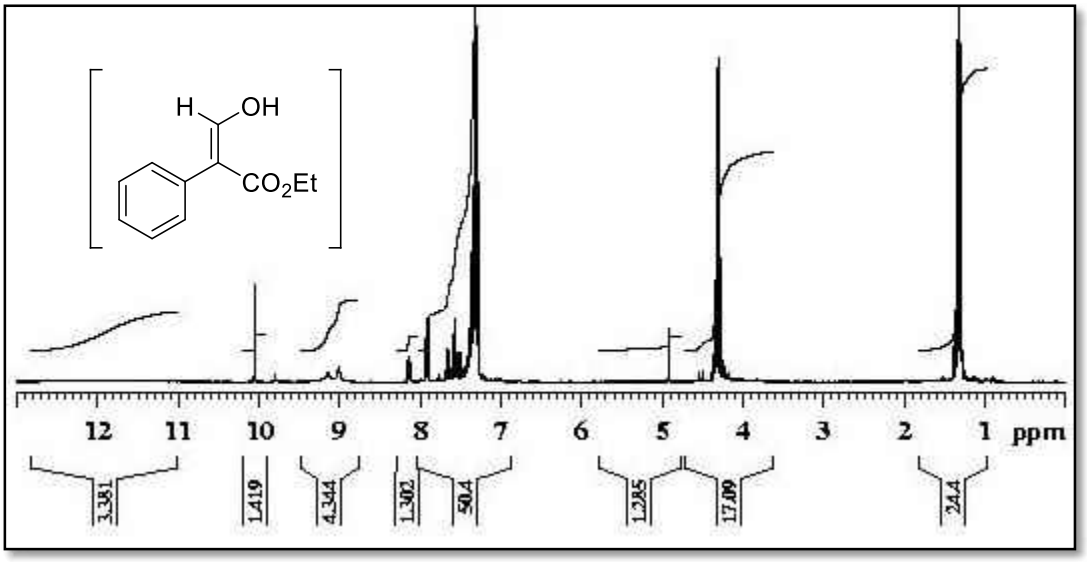
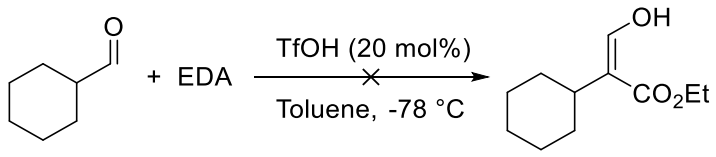


Figure 8. Crude NMR of aliquot taken from reaction with HBF_4 catalyst.

It is known that the BF_4^- counter ion present in HBF_4 is non-nucleophilic due to the strong electron withdrawing effect of the fluorine atoms. Hence, even though boron has a formal negative charge, this is spread over the four fluorine atoms, leading to a very weakly Lewis basic boron atom. Therefore, the tautomerisation of the aldehyde into the enol form is greatly hindered. However, when efforts are not made to keep strictly anhydrous conditions (such as not drying glassware, etc) this will cause a significant amount of the enol tautomer to be formed. Perhaps surprisingly, despite the extremely low pK_a of TfOH, the conjugate base is able to aid in the formation of the enol tautomer via the acid catalyzed tautomerisation process.

A brief investigation was carried out on whether aliphatic aldehydes are possible candidates as substrates that can undergo the required [1,2] shift yielding the desired aldehyde-enol product preferentially over undesired β-keto ester. Unfortunately, no aldehyde or enol protons were observed in the crude NMR, either of the aldehyde starting material or of the desired product (Scheme 16). From this result, it is clear that only a strongly electron rich aromatic ring will undergo a facile [1,2] shift to form the desired prochiral nucleophiles, in this case 3-hydroxy aryl acrylates.

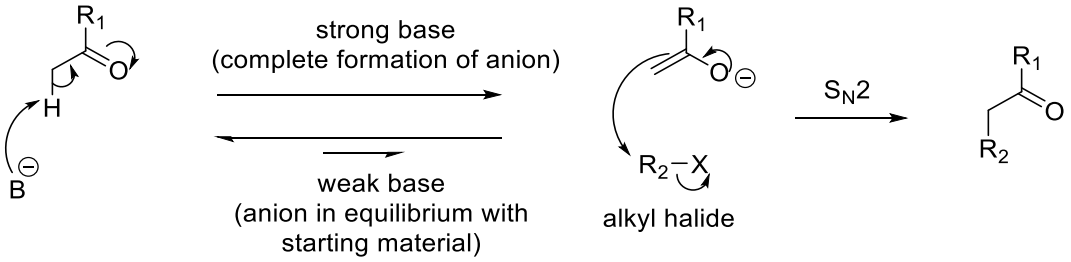


Scheme 16. Attempted reaction between aliphatic aldehyde and EDA.

1.3. 3-Hydroxy aryl acrylates as prochiral nucleophiles for organocatalytic asymmetric alkylation

1.3.1. General considerations in the alkylation of carbonyl compounds

Generally speaking, alkylation reactions consist of two main steps. In the first a stabilized anion is formed by deprotonation with base (Scheme 17). The second is a substitution reaction with an electrophilic alkyl halide. All the factors controlling S_N1 and S_N2 reactions are applicable.[33]



Scheme 17. Reaction mechanism of alkylation of carbonyl compounds.

When choosing a base for the deprotonation step of the carbonyl compound, various factors are taken into consideration:

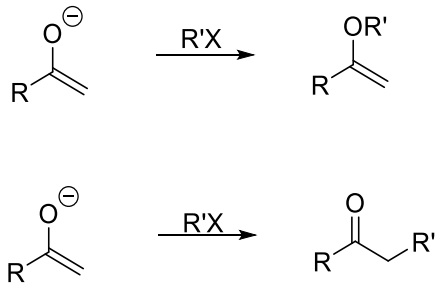
a) If a strong base is employed, there will be complete conversion to the corresponding enolate. In a subsequent step, the electrophile is added and reacts with the enolate.

b) Alternatively, a weaker base can be used in the presence of the electrophile. In this case, there will not be quantitative conversion of the carbonyl to its enolate,

but more of the enolate will be formed during the course of the reaction as it is consumed by reaction with the electrophile.

The first approach requires separate addition of base and nucleophile, usually more tedious than approach b), but offers the advantage of not having to worry about compatibility issues between the base and electrophile. The second approach is easier in a practical sense (just mix carbonyl compound, base and electrophile and allow to react) but for this approach to work the base and electrophile must be compatible, or at least not react to any significant extent. Excess of base and electrophile can be used to overcome to some extent this problem.

The alkylation of carbonyl compounds requires consideration of another factor: enolates are ambident nucleophiles, hence there is the question of whether alkylation will take place at the carbon nucleophile or the oxygen nucleophile (Scheme 18).



Scheme 18. O vs C alkylation of enolates.

There are various factors that determine whether C- or O-alkylation will take place:

a) In the case that an inorganic base is used, whether the metal counter-ion will be dissociated or clustered (depends on the metal and solvent). Furthermore, O-alkylation is favored when the enolate is dissociated and a "naked" enolate is present i.e. the oxygen is unhindered for nucleophilic attack. In polar aprotic solvents the metal counter-ion will tend to be solvated by a lone pair of electrons from the solvent leading to an exposed enolate oxygen atom. In addition, metal chelators such TMEDA can be added to the mixture to efficaciously promote O-alkylation, hence forming a "naked enolate".

   In contrast, C-alkylation is favored when harder, smaller counter-ions are present, due to a tighter coordination with the oxygen, hence effectively blocking the oxygen from electrophilic attack. Protic solvents will generally also favor C-alkylation, probably due to H-bonding between the solvent and the enolate oxygen, an effect similar to that of using harder counterions. Apolar solvents also generally tend to favor C-alkylation.[54] Examples of ion clustering using lithium, sodium and potassium enolates of pinacolone were described by Williard et al.[34] and Seeback et al.[35] Using lithium and sodium enolates, tetrameric clusters were obtained, while the use of potassium enolates resulted in the formation of hexameric clusters (Figure 9).

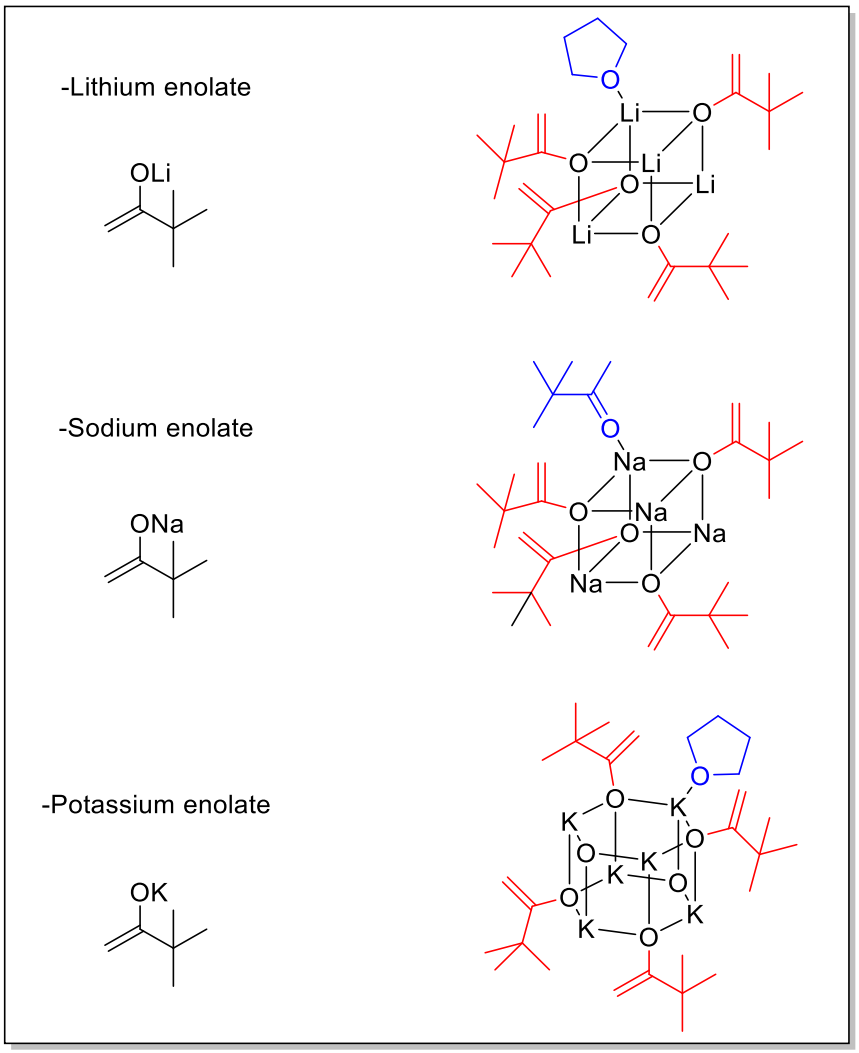
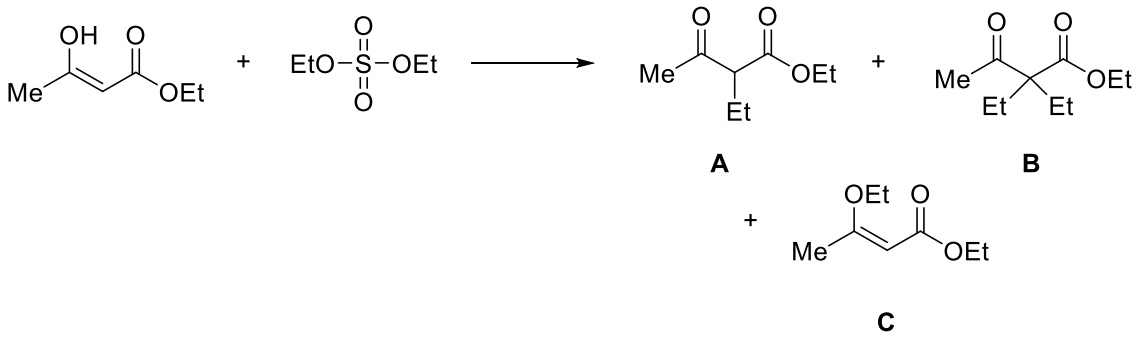


Figure 9. Clustering of enolates with different metal ions and THF.

From the following example (Scheme 19; Table 2), it becomes evident that as dissociation of metal clusters is favored, the percentage of product that become O-alkylated dramatically increases. THF promotes ion clustering of the potassium enolate, leading to an increased amount of C-alkylation, while *t*-BuOH is able to hydrogen bond with the enolate anion, hence favoring C-alkylation.[36]



Scheme 19. Reaction of enol with electrophiles leading to O- and/or C-alkylation.

Table 2. Ratios of O- vs C-alkyltion with different solvents.

Solvent	A	B	C
HMPA	15%	2%	83%
t-BuOH	94%	6%	0%
THF	94%	6%	0%

b) Charge vs. orbital control (Figure 10). In charge control, reaction occurs at the atom carrying the highest total electron density.[37] This takes place predominantly in reactions with electrophiles with hard leaving groups, or with charged electrophiles (e.g. H^+). Charge control is favored by an early transition state, where charge distribution is the most important factor, as well as by conditions that favor dissociated enolate clusters. In orbital control, reaction takes place at the atom that has the highest frontier electron density, and is favored by neutral electrophiles with soft leaving groups. In this case a later transition state will cause partial bond formation to be the dominant factor. The C-alkylated product is the thermodynamic product, since the total bond energies for the C-alkylated product (C=O: 745 kJ mol^{-1} + C-C bond: 347 kJ mol^{-1} = 1097 kJ mol^{-1}) are

greater than the total bond energies for the O-alkylated product (C=C: 614 kJ mol^{-1} + C-O: 358 kJ mol^{-1} = 972 kJ mol^{-1}).[38]

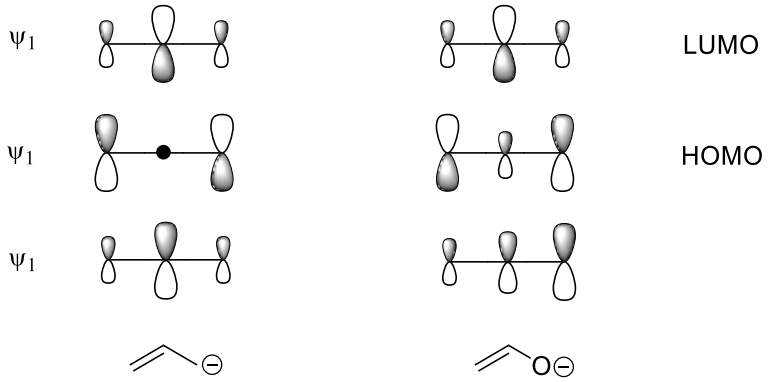
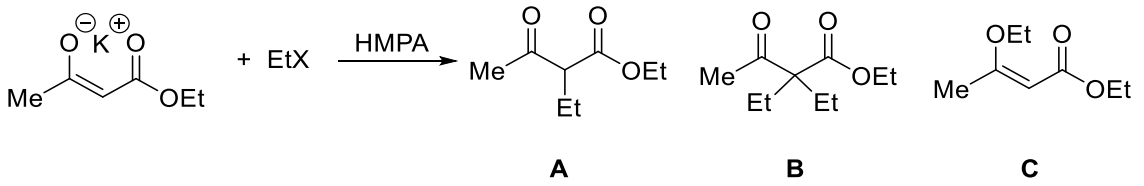


Figure 10. Molecular orbital theory to illustrate charge vs orbital control.

c) Hard-soft compatibility. According to the hard-soft theory of acid and bases, hard acids will combine with hard bases, and likewise with soft acids and bases. The hardness of the leaving group on the electrophile will be the determining factor on whether attack takes places at oxygen (hard) or carbon (soft). The reaction between the potassium enolate of ethyl 3-oxobutanoate and electrophiles with leaving groups of varying hardness will serve to illustrate the remarkable difference that can be achieved in O- vs C- alkylation by vaying the hardness of the leaving group (Scheme 20; Table 3).[39] From the results, it becomes evident that harder leaving groups will favor O-alkylation while softer leaving groups favor C-alkylation.

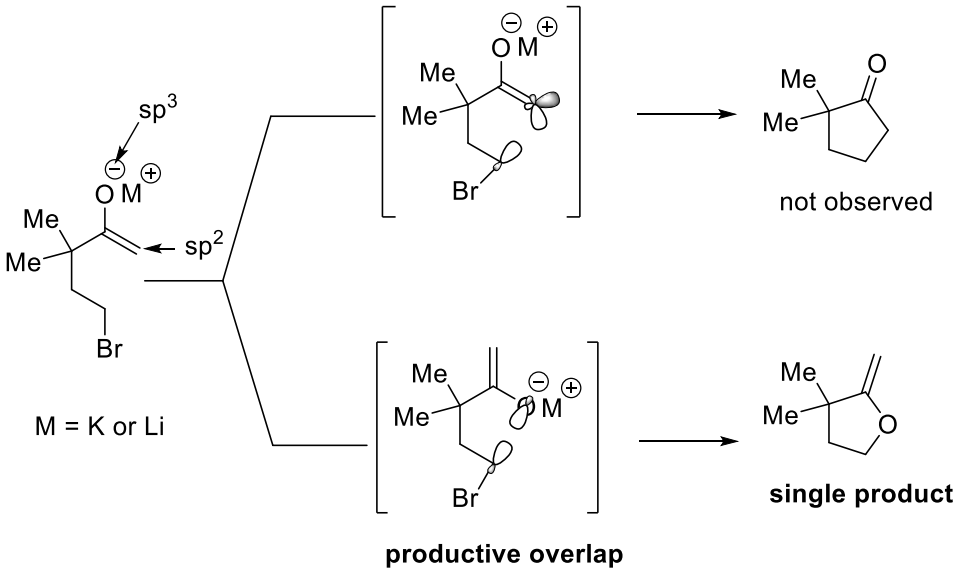


Scheme 20. Reaction of enolate with electrophile leading to O- and/or C-alkylation.

Table 3. Ratios of O- vs C-alkyltion with different solvents.

X	A	B	C
OTs	11%	1%	88%
Cl	32%	8%	60%
Br	38%	23%	39%
I	71%	16%	13%

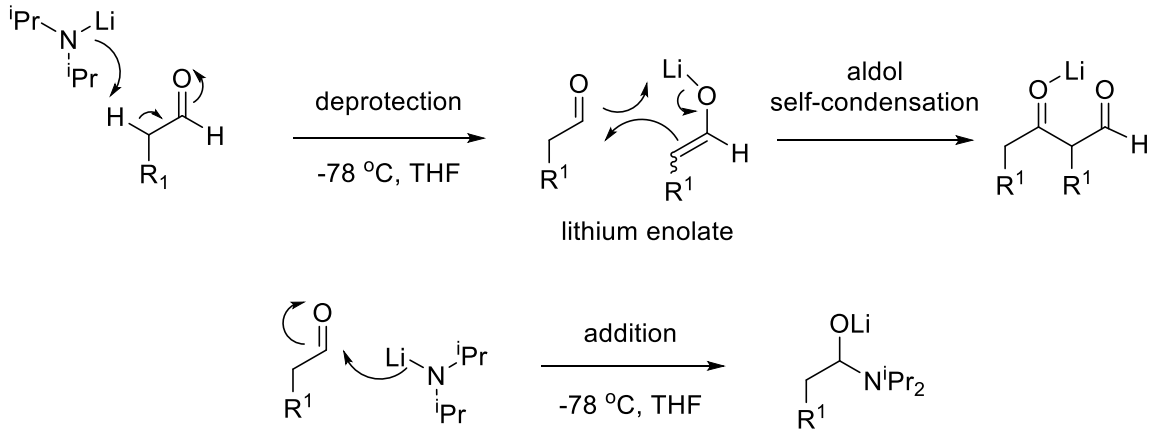
d) Stereoelectronics. Alkylation will take place at the nucleophilic site that provides maximal orbital overlap (Scheme 21).[40] Orbital overlap is key for a successful cyclization to be able to take place. Since oxygen and carbon have different hybridizations in an enolate (sp^3 and sp^2 respectively), and hence their orbitals point in different directions, their orbitals will have varying degrees of overlap with the C-X σ^* orbital. The orbital of the atom that is able to achieve maximum overlap will be the one to react with the leaving group via an S_N2 displacement.



Scheme 21. Effect of stereoelectronics in C- vs O-alkylation.

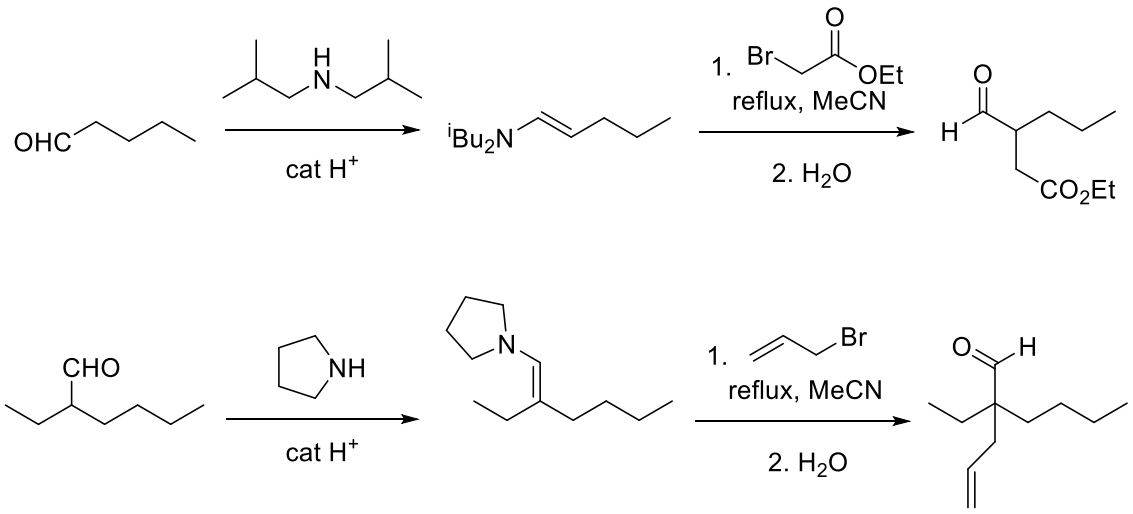
1.3.2. General considerations in the alkylation of aldehydes

The problem of self-condensation of carbonyl compounds (that is, enolate reacting with unenolized carbonyl) under basic conditions does not exist in most cases if there is absolutely no unenolized carbonyl compound present. However, *aldehydes* are so electrophilic that even at -78 °C, the rate at which deprotonation occurs is not as fast as the rate at which the enolate will react with an unenolized aldehyde still remaining in the mixture. Furthermore, strong bases can also directly react with the highly electrophilic carbonyl group of an aldehyde and this can pose a problem (Scheme 22).



Scheme 22. Rapid self-aldol condensation with lithium enolates.

The problems encountered with alkylation of aldehydes (mostly self-aldol condensation) means that they are not generally useful as reactive intermediates. However, aldehydes are useful intermediates for alkylation in masked form, through which the aldehyde is converted to a less reactive form; after the alkylation step, the original aldehyde is then reformed. One of the most important specific enol equivalent if the use of *enamines*, formed when aldehydes or ketones react with secondary amines. The choice of secondary amine is not arbitrary, although simple dialkyl amines can be employed, much more often cyclic secondary amines such as pyrrolidine, piperidine, and morpholine are used because of the greater nucleophilicity of the ensuing enamine (the alkyl groups do not have as many rotational degrees of freedom as the dialkyl amines). Strong electrophiles are usually required in the reaction with enamine enol equivalents due to their rather weak nucleophilicity (Scheme 23).

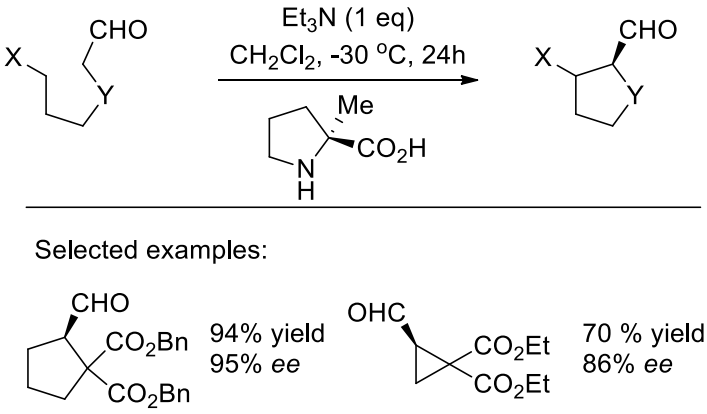


Scheme 23. Achiral alkylation of aldehydes via enol equivalents.

1.3.3. Organocatalytic alkylation of aldehydes via enamine catalysis

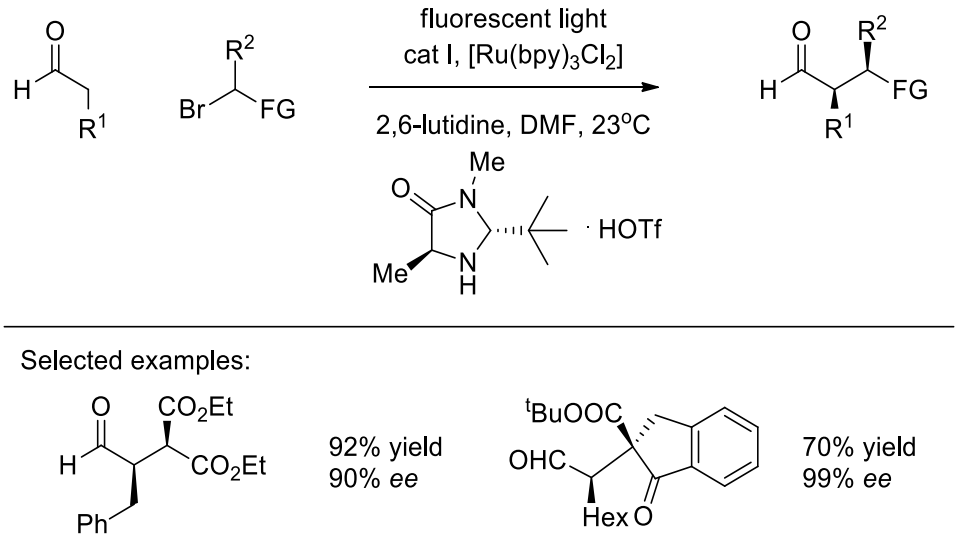
Even though the *achiral* version of aldehyde alkylation via enamines has been achieved (Scheme 23) the *asymmetric* alkylation of aldehydes still remains very much the "holy grail" of asymmetric catalysis.[41] After the advent of asymmetric catalysis via enamines,[42] it was easy to assume that the concept could be easily extended to the asymmetric alkylation of aldehydes. This has proven to be such a formidable challenge (versus the wide applicability of asymmetric Michael additions via enamine catalysis) because of deactivation of the catalyst via N- or O- alkylation. With preformed aldehyde enolates using stoichiometric amounts of electrophile, thus far no asymmetric version of the reaction has emerged because of their tendency to form self-aldol condensation products, or to carry out Canizzaro or Tischenko type reactions.

However, despite enormous effort by various research groups, the first catalytic asymmetric alkylation of aldehydes did not appear as recently as 2004, with the *intramolecular* alkylation of aldehydes to form five-membered aliphatic or heterocyclic ring systems with proline derived catalysts (Scheme 24).[43]



Scheme 24. Intramolecular α-alkylation by Vignola and List.

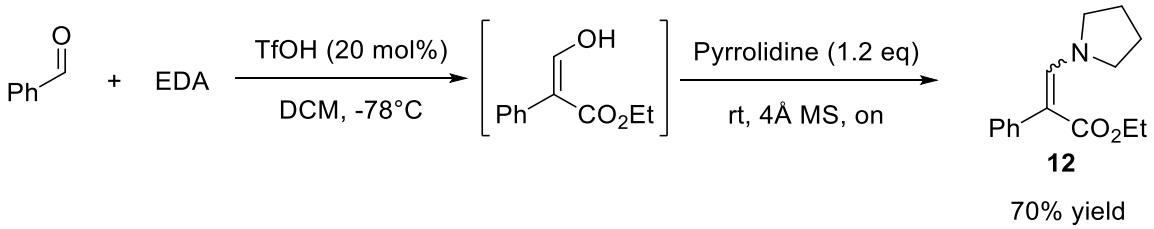
After the initial report by List[43], in 2006 Ibrahem and Córdova reported on the first non-asymmetric catalytic intermolecular α-allylic alkylation of aldehydes by combination of transition-metal and enamine catalysis.[44] This was followed soon after by the novel amino-catalytic concept exploited by MacMillan et al. based on radical intermediates, using a combination of photoredox catalysis and amine catalysis, to effect the first catalytic asymmetric α-allylation of aldehydes (Scheme 25).[45] However, this methodology cannot be regarded as purely organocatalytic, moreover it still suffers from a lack of general applicability to other substrate classes.



Scheme 25. Amino-catalytic concept exploited by MacMillan et al.

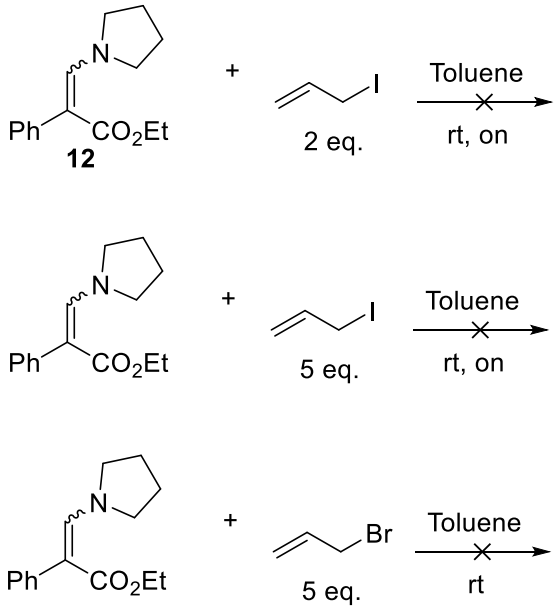
1.3.3.1. Attempted C-alkylation of 3-hydroxy aryl acrylates via alkylation of enamines

In our attempt to access C-alkylated products through the enamine catalyzed reaction between 3-hydroxy aryl acrylates and electrophiles, we set out first to synthesize the enamine formed from the reaction of 3-hydroxy aryl acrylate and pyrrolidine. We managed to devise a one-pot synthesis for the creation of these enamines whereby the 3-hydroxy aryl acrylate is formed in situ, followed by addition of pyrrolidine to furnish the corresponding enamine **12** in good yield (Scheme 26).



Scheme 26. One-pot synthesis of enamine 12 starting from benzaldehyde and EDA.

However, when the alkylation reaction with enamine **12** was attempted, no reaction took place (Scheme 27).



Scheme 27. Attempted reaction between enamine 12 and electrophiles.

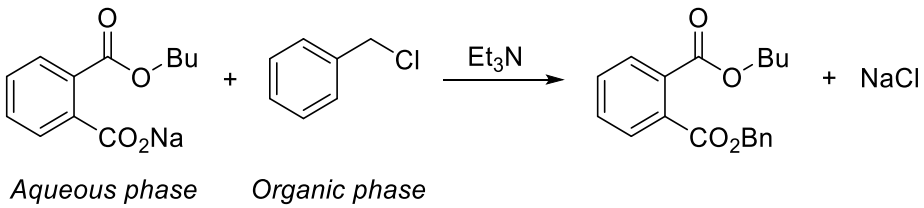
There are two major reasons for the failure of the enamine to react with electrophiles. Firstly, N-alkylation of the enamine is certainly possible, especially with allyl iodide because of the softer leaving group, thereby deactivating the nucleophile for attack. Secondly, it is evident that enamine **12** is a poor nucleophile because of the extensive

conjugation present in the system, which would have to disrupted in order for nucleophilic attack to take place. According to the nucleophilicity scale for enamines devised by Mayr et al.[46] the presence of a single ester on the same position as the nucleophilic carbon will have a dramatic effect on lowering the reactivity of the enamine. The increased conjugation due to the presence of a phenyl group in **12** will have an even more pronounced effect in hindering the reactivity of the enamine.

1.3.4. Phase transfer catalysis: general concepts and mechanisms of action

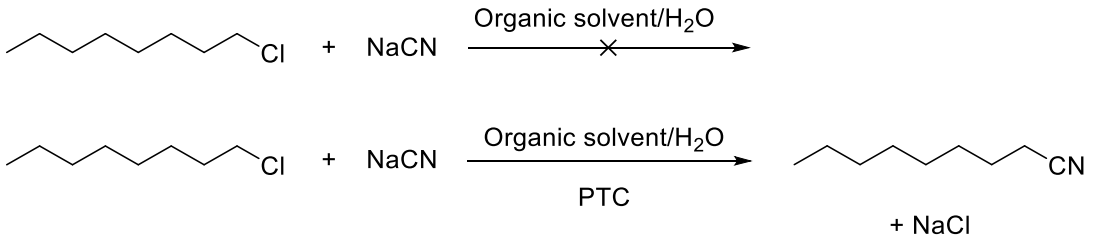
As can be seen from the previous section, the organocatalytic α-alkylation of aldehydes has still not been achieved with a methodology that would be broadly applicable to a wide range of electrophiles. Currently the main methodologies are: the amino-catalytic concept exploited by MacMillan et al. based on radical intermediates, using a combination of photoredox catalysis and amine catalysis[45] and the use of electrophiles with highly stabilized carbenium ions such as: 3-substituted indoles employed by Melchiorre[45] or the use of benzylic carbocations,[49] stabilized isolable carbenium ions,[50] and a benzodithiolylium carbocation developed by Cozzi and coworkers.[51] It is clear from these examples that a methodology with a much broader substrate scope is highly desirable. Hence, we were interested to see whether the *phase-transfer catalyzed alkylation* could be achieved for such a purpose. In theory, such a methodology would allow a much broader scope of electrophiles to be employed, and hence would allow for the discovery of a truly versatile methodology for the α-alkylation of aldehydes.

In order to promote the successful alkylation of 3-hydroxyaryl acrylates, some understanding of the basic processes underlying the phase transfer catalyzed reaction is required.[15] In 1946 the first clear-cut example of a phase transfer catalyzed reaction was reported on the alkylation of a sodium carboxylate salt. The phase transfer catalyst, benzyltriethylammonium chloride, is formed in situ by attack of triethylamine to benzyl chloride (Scheme 28).[47]



Scheme 28. First report in 1946 of a true example of phase transfer catalysis.

The first report on the use of the term *phase transfer catalysis* was made by Starks in 1971 [48] where he described the dramatic increase in the rate of reaction for the tetralkyammonium or tetralkylphosphonium catalyzed reaction between an organic solution of an alkyl halide and an inorganic solution of sodium cyanide (Scheme 29).



Scheme 29. Examples reported by Starks of phase transfer catalyzed reactions.

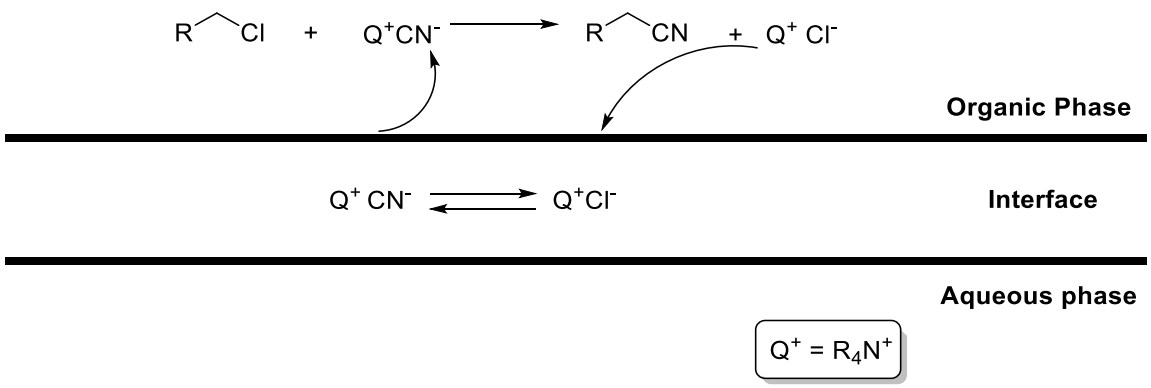


Figure 11. Mechanism for halide displacement by cyanide ion catalyzed by PTC.

The reaction is unable to proceed without the aid of a phase transfer catalyst because of the insolubility of NaCN in the organic phase. Hence, nucleophile and electrophile are unable to meet and react. The role of the phase transfer catalyst is therefore to "shuttle" the cyanide ion into the organic phase through ion exchange with the phase transfer catalyst at the interface. From there, the new ion pair (Q^+CN^-) travels to the organic phase where it is allowed to readily react with the electrophile (Figure 11). If the organic phase reaction is rate determining (in the above example the reaction between cyanide and octyl bromide), the mechanism is known as the *extraction mechanism*. If the transfer of the aqueous soluble ion into the organic phase via the aid of the phase transfer catalyst (the transfer step) is rate determining, the mechanism is known as the *interfacial mechanism*. Factors affecting the rate at which the transfer of ions into the organic phase takes place include:

a) Interfacial tension. An increase in the interfacial tension will result in a decrease of the interfacial area, with a resulting lowering of the rate at which ions can be

shuttled from the aqueous into the organic phases. Highly concentrated solutions and non-polar solvents result in a decrease of the interfacial area due to an increased interfacial tension.

b) Stirring. With high stirring speeds, the formation of tiny droplets present in emulsions can greatly increase the interfacial area leading to enhanced reaction rates

c) Nature of the anion in the phase transfer catalyst. Large anions that are weakly hydrated such as perchlorate and iodide permit easier access to the interface from the organic phase. The contrary holds true for small anions that are hydrated with much greater ease, such as fluoride or hydroxide.

d) The bulkiness of the cation in the PTC. Bulkier alkyl groups cause a diminishment in the transfer step by a decrease of the effective concentration of the cation at the interface, unsymmetrical cations allow closer approach of the cation to the interface, enhancing the transfer step.

Overall the phase transfer catalyzed reaction will be subject to the following variables:

a) Quantity of water (concentration): Even though the use of more concentrated solutions leads to an increased interfacial tension and a decreased transfer rate, as long as this is not the limiting factor, the transfer of anions into the organic phase will be promoted by using more concentrated solutions, promoting formation of the catalyst substrate complex.

b) Catalyst (most important variable): The shape and size of the catalyst may influence such factors as: the surfactant property of the catalyst, its ability to promote the transfer of the substrate anion into the organic phase, transfer rates (as seen above bulkier cations lead to decreased rates), moreover the catalyst could also be a factor in the activation of the anion for reaction towards reactant in the organic phase. Many phase transfer catalysts are able to undergo a Hoffmann elimination under the commonly used basic conditions, therefore a catalyst should be chosen that will be reasonably stable under the reaction conditions employed.

c) Solvent. Dichloromethane is frequently used as a solvent due to its ability to dissolve most phase transfer catalysts readily. Choice of solvent is important as it can affect both the rate of the reaction taking place in the organic solvent and the interfacial tension, which can affect the rate of transfer.

d) Temperature. A temperature should be chosen for optimal rate of reaction while avoiding decomposition of the phase transfer catalyst under high temperatures in the presence of base.

Among other reactions that were also described[48] were the dichlorocyclopropanation of alkenes with chloroform and aqueous NaOH, oxidation of alkenes with aqueous $KMnO_4$ and hydrolysis of esters and alkanesulfonyl chlorides with aqueous NaOH. The use of phase transfer catalysis presents various practical advantages:

1) Inexpensive inorganic bases (such as NaOH, KOH, K_2CO_3) can often be substituted from more expensive and difficult to handle stronger, organic soluble bases such as MHMDS bases, NaH, *t*-BuOK etc. This also usually leads to a simplified work-up and the reaction being able to be conducted in the absence of special conditions such as an inert atmosphere.
2) High yields and purity are often reported for many reactions.
3) The reactions are often amenable to scale-up, advantageous for industrial processes requiring large scale-ups from much smaller scales usually carried out in the laboratory.
4) The reactions are frequently low-cost and tend to minimize industrial waste.

Just a few of the reactions that have successfully found application in asymmetric catalysis via phase transfer catalysis include: alkylations, Michael additions, aldol reactions, Darzens reactions, cyclopropanations, epoxidations, aziridinations and oxidations.[15a] The asymmetric alkylation of t-butyl glycinate esters will serve to illustrate the mechanism of the asymmetric phase transfer catalyzed reaction (Figure 12).

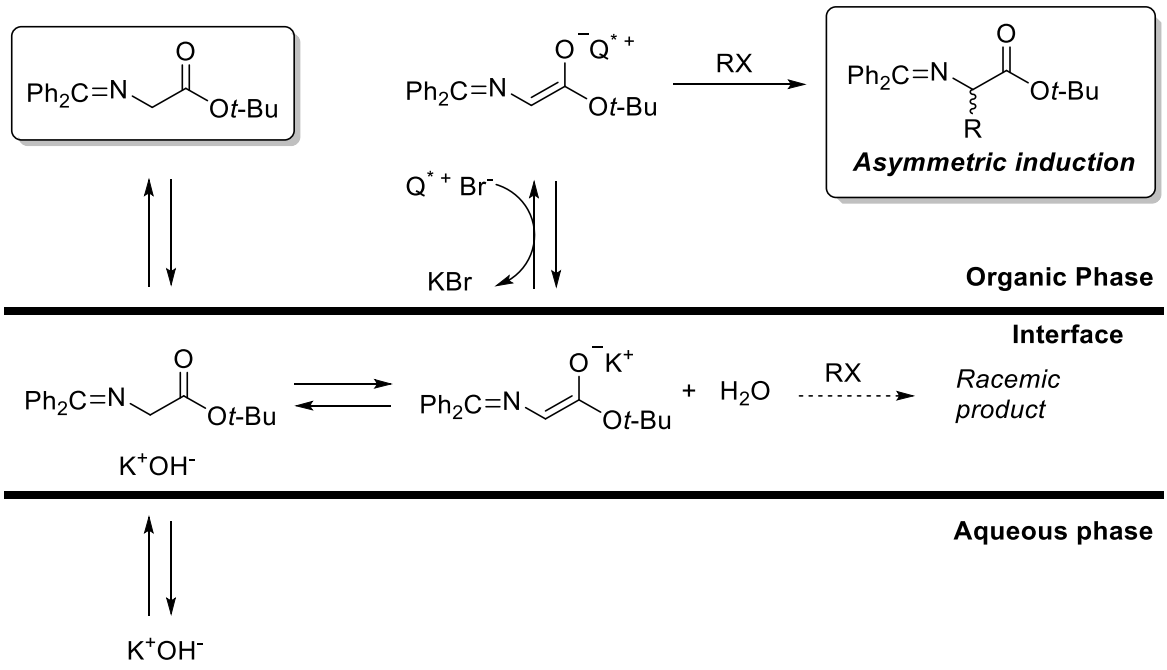


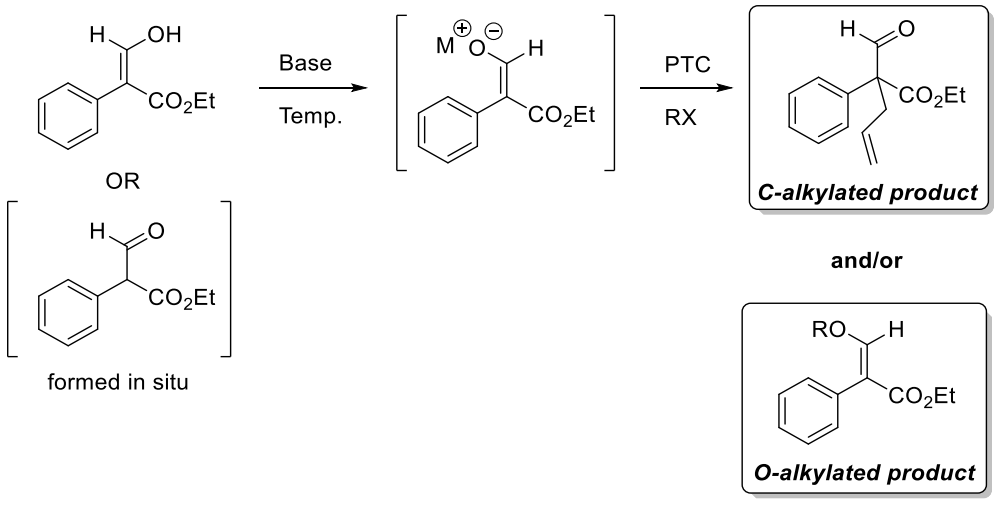
Figure 12. Mechanism for phase transfer catalyzed alkylation of Schiff bases.

The alkylation of compounds bearing active methylene or methine hydrogens typically occurs via the interfacial mechanism. That is, the rate determining step is the exchange of ions taking place at the interface between the conjugate base of the substrate and the quaternary ammonium salt, leading to the organic soluble enolate with a quaternary ammonium ion as the counterion. In the previous example (Figure 12) when the glycinate Schiff base comes in contact with the interface of the organic and aqueous faces, it meets the water soluble base, at which point the glycinate becomes deprotonated, forming the corresponding enolate. At this point it is crucial for the phase transfer catalyst to quickly exchange ions with the enolate, otherwise the enolate will directly react with the electrophile at the interface, leading to racemic product. Once the enolate exchanges ions with the phase transfer catalyst, it become organic soluble and goes deep into the organic

phase, where it reacts with the electrophile in a stereoselective manner by virtue of the tight ion pair formed between the prochiral enolate and the chiral quaternary ammonium ion.

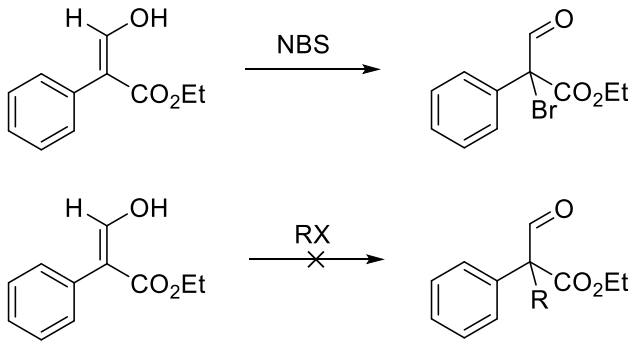
1.3.4.1. Phase transfer catalyzed alkylation of prochiral 3-hydroxy aryl acrylates

The initial strategy for the formation of α-aryl quaternary carbon centers was the phase transfer catalyzed alkylation of 3-hydroxy aryl acrylates (Scheme 30). Either purified 3-hydroxy acrylate could be used or the in situ formed aldehyde tautomer formed through the reaction of benzaldehyde and EDA in the presence of HBF_4 catalyst. Some of potential problems associated with the alkylation have been outlined above, namely, self aldol condensation and potential competition between C- vs O- alkylation. The latter was indeed a potential risk due to the high energy involved in breaking the conjugation present in the enol tautomer, leading to C-alkylated product.



Scheme 30. C-vs- O-alkylation of prochiral 3-hydroxy aryl acrylates.

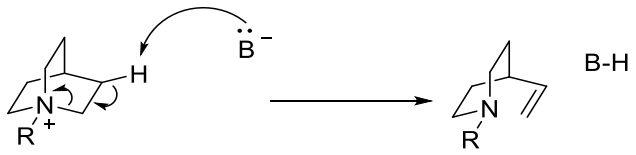
In contrast to the reaction of 3-hydroxy aryl acrylate with Br_2 at room temperature which does not require activation of the nucleophile via formation of the corresponding enolate in order for successful reaction to take place, alkyl halides are not strong enough electrophiles to react directly with the enol tautomer (Scheme 31). This is fortunate, since our initial goal was accomplishing the asymmetric alkylation of 3-hydroxy acrylates, and this could therefore be potentially accomplished through asymmetric phase transfer catalysis, whereby the water soluble enolate can be transferred to the organic layer for reaction with the organic soluble electrophile.



Scheme 31. Comparison of the reactivity of electrophiles.

It is obvious that highly polar solvents such as DMF and DMSO could be used in conjuction with stronger bases such as NaH in order to dissolve the metal enolate, facilitating nucleophilic attack in the organic phase, but this would face the obvious drawback of the reaction only being able to take place in an achiral fashion. Furthermore, as outlined above, alkylations of aldehydes with strong bases (NaH, MHMDS, etc) are highly susceptible to self-aldol condensation, rendering such a process impractical. Even

if a phase transfer catalyst could be utilized in such a reaction, such catalysts are susceptible to decomposition by strong bases via the Hoffmann elimination, whereby a β-hydrogen is abstracted by the base (Scheme 32).

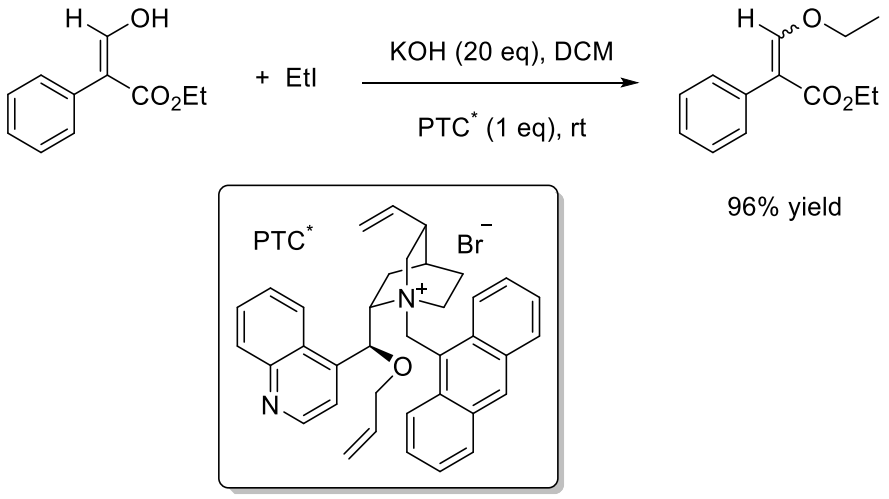


Scheme 32. Hoffmann elimination of β-hydrogens in quaternary ammonium salts.

Moreover, even in the case that problems such as the Hoffmann elimination could be avoided, there would be no guarantee that the respective counterions (the metal counterion of the enolate and the quaternary ammonium ion) would have been exchanged prior to the enolate reacting with the electrophile, thereby enabling the reaction to take place in an enantioselective fashion.

Either biphasic homogenous mixtures using aqueous bases, or heterogeneous systems using solid bases have both been employed successfully in phase transfer catalyzed alkylations.[15a] The mechanism for heterogeneous catalysis will involve deprotonation of the nucleophilic substrate at the interface between the organic solvent and the solid base, followed by exchange of counterions with the phase transfer catalyst at the same location. The mechanism for both cases is essentially the same, with the exception that in the homogenous case the exchange takes place in a liquid-lquid interface, but in the heterogeneous case in a solid-liquid interface.

The first attempt at forming the desired aldehyde bearing an α-aldehyde quaternary carbon center involved reaction with KOH and ethyl iodide as electrophile. Unfortunately, rather than the desired aldehyde product being obtained, the O-alkylated product was formed instead in good yield.



Scheme 33. First attempt at C-alkylation leading to undesired O-alkylated product.

It was clear that the highly conjugated nature of the nucleophilic substrate might prove problematic for obtaining high yields of C-alkylated product. On the other hand, and perhaps surprisingly, no detectable amount of the self-aldol condensation product was found to be formed. The self-aldol condensation could theoretically take place during the addition of base and subsequent mixing time, however this does not occur due to the insolubility of the metal salt in the organic phase, thereby preventing enolate from reacting with enol in the organic phase. Hence, if a biphasic homogenous system is used, the metal salt will dissolve immediately in the aqueous phase. If a solid base is employed

instead, the metal salt will precipitate out of the solution in the absence of the phase transfer catalyst, thereby preventing reaction of enolate with enol still unreacted with base via a self-aldol condensation. Thus, it is clear that carrying out the reaction via phase transfer catalysis carries the great advantage of preventing to a large degree the undesired self-aldol condensation product from being formed, a problem so commonly encountered with the alkylation of aldehydes under basic conditions.

In order to elucidate optimal reaction conditions for the alkylation of 3-hydroxy aryl acrylates that would give the highest possible C:O alkylated ratio an extensive screening of reaction conditions such as solvent, base and temperature was carried out (Scheme 30). Reactions carried out with strong bases having large, soft counterions yielded exclusively O-alkylated product (Table 4). No difference in the C:O ratio was observed if either the in situ formed aldehyde tautomer or the isolated enol tautomer was used.

Generally speaking, the ratio of C:O alkylation can be understood in terms of the strength of the ion pair in the enolate between the enolate oxygen and the metal counterion: bases with large counterions will be weakly coordinated to the enolate oxygen, thus creating a "naked" enolate that will react readily at the oxygen for nucleophilic attack of the electrophile. However, in the presence of the phase transfer catalyst there should theoretically be complete displacement of the metal counterion in the enolate by the quaternary ammonium ion, leading to the organic soluble enolate ion pair ($RO^{-}Q^{+}$) that can readily dissolve in the organic phase and react with the electrophile. Thus, theoretically, there should be no counter ion effect of the inorganic base employed under

Table 4. Reaction conditions leading to exclusive O-alkylation.

PTC	Solvent	Base	Electrophile
Cinchonidium[a]	DCM	KOH(s)/water	Ethyl iodide
Cinchonidium	THF	1 M KOH	Ethyl iodide
Cinchonidium	THF	KOH (s)	Ethyl iodide
Cinchonidium	Toluene	KOH (s)	4-(CF_3O)BnBr
Cinchonidium	DCM	KOH (s)	4-(CF_3O)BnBr
Cinchonidium	DCM	Sat. KOH	4-(CF_3O)BnBr
TBAI	DCM	Sat. KOH	4-(CF_3O)BnBr
TBAI	DCM	Sat. KOH	Allyl iodide
TBAI[b]	DCM	Sat. KOH	Allyl iodide
TBAI	DCM	Sat. RbOH	Allyl iodide
TBAI	DCM	$Ba(OH)_2$ (s)	Allyl iodide
TBAI	DCM	$CsOH \cdot H_2O$(s)	Allyl iodide
TBAI	DCM	Cs_2CO_3 (s)	Allyl iodide

a) "Cinchonidinium" = *O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide. b) Aldehyde used in situ.

phase transfer catalysis conditions. However, as bases of differing strength and with different counterions were employed it soon became evident that there was indeed a metal counter-ion effect on the ratio of C:O alkylation (Tables 5-7). Generally speaking, for bases weaker than KOH, C-alkylation was possible.

The reactions with bases having Li^+ counterions were in general not very successful in giving high yields of either C- or O-alkylated product (Table 5). It is possible that Li^+, being a hard, small ion, is tightly bound with the enolate oxygen, hindering the ion exchange with the phase transfer catalyst from taking place, preventing the organic soluble ion pair (RO^-Q^+) from being readily formed. Furthermore, it is known that

lithium enolates are prone to self-aldol condensations, and could explain the complex mixture of products observed in some cases. If this is the case, it would indicate that the size of the counterion affects the solubility of the enolate ion pair, with a tighter ion pair being more lipophilic and dissolving more readily in the organic solvent where it may react in the absence of catalyst.

Reactions involving sodium enolates (Table 6) in general gave higher yields of C-alkylated product than those involving lithium enolates. The best results involved using the rather weak base Na_2CO_3 and the even weaker base $NaHCO_3$. Interestingly, using the aldehyde in situ with NaOH as base led to poor conversion to C-alkylated product. Clearly, the base promoted aldehyde-enol tautomerisation takes place faster than the alkylation can occur.

Lastly, a screen was carried out on the alkylation of potassium enolates with bases weaker than KOH (Table 7). The C:O alkylated ratios utilizing K_2CO_3 and $KHCO_3$ were similar to those of comparable sodium bases although reaction rates were slightly improved due to the increased strength in basicity. Polar aprotic solvents (DMF, THF) were poor choice of solvents: with the former no reaction was observed, for the latter a complex mixture of products was observed. Interestingly, raising the temperature from -15 °C to 0 °C (Table 7, last two entries) resulted in an increase in the C:O ratio, implying that the C-alkylated product is the thermodynamic product and the O-alkylated product the kinetic one. This would be as expected, since formation of the C-alkylated product requires reaching the activation energy necessary to break the highly conjugated enol

tautomer, while the activation energy leading to the O-alkylated product would be expected to be much lower. As expected, switching from allyl iodide to allyl bromide as electrophile led to a slight decrease in the amount of C-alkylated product due to Br^- being a harder leaving group than I^- and thus more susceptible to attack at the harder oxygen (Table 7, compare second and third entries).

Table 5. Attempted alkylations with Li^+ inorganic bases.

Solvent	Base	C- vs O-alkylation (NMR ratios)
MeOH	Sat. Li_2CO_3	No reaction
DCM/Tol (1:5)	Sat. Li_2CO_3	Complex mix. of products
DCM	Sat. Li_2CO_3	1:2
DCM	Sat. LiOH	Low yield C-alkylated
DMF	Sat. Li_2CO_3	2:3

Thus, from these results one can conclude that there may be three modes of action possible for the phase transfer catalyzed alkylation of 3-hydroxy aryl acrylates depending on the reaction conditions. The first type of mechanism would involve the use of strong bases bearing large soft counter ions, leading exlusively to O-alkylated product (Figure 13). In this case, the metal exchanges rapidly with the quaternary ammonium ion of the phase transfer catalyst to form the enolate-quaternary ammonium ion pair (RO^-Q^+). This process probably takes place irreversibly and more rapidly in enolates bearing large soft counterions compared to other metals because as outlined above, the counterions are

loosely coordinated to the enolate oxygen, facilitating the ion exchange process with concomitant formation of the metal salt (MI).

Table 6. Attempted alkylations with Na^+ inorganic bases.

Solvent	Base	C- vs O-alkylation (NMR ratios)
DCM	$NaHCO_3$ (s)	2:3
DCM	Na_2CO_3 (s)	2:3
DCM	NaOH (s)	1:4
DCM[a]	NaOH (s)	1:4
DCM:Tol (1:5)	Na_2CO_3 (s)	1:1, complex mix. of products
DCM[a]	Sat. NaOH	Low yield C-alkylated
DCM (-78°C)	NaOH (s)	No reaction

a) Aldehyde used in situ. All reactions carried out in the presence of TBAI as phase transfer catalyst.

The second type would involve hydroxide bases weaker than KOH but with smaller, harder counterions, leading to some degree of C-alkylated product (Figure 14). Here, complete displacement of the metal counterion by the quaternary ammonium ion does not take place because of strong interactions between the enolate oxygen and metal, partially blocking the oxygen from nucleophilic attack, facilitating the C-alkylation pathway.

Table 7. Attempted alkylations with K^+ inorganic bases weaker than KOH.

Solvent	Base	C- vs O-alkylation (NMR ratios)
DCM	$KHCO_3$ (s)	2:3
DCM	$KHCO_3$ (aq)	2:3
DCM[a]	$KHCO_3$ (aq)	1:2
THF	$KHCO_3$ (s)	Complex mix. of products
DMF	$KHCO_3$ (s)	2:3
DMF (0 °C)	$KHCO_3$ (s)	No reaction
DCM (0° C)	K_2CO_3 (s)	2:3
DCM (-15 °C)	K_2CO_3 (s)	1:3

a) Allyl bromide used as electrophile. All reactions carried out in the presence of TBAI as phase transfer catalyst.

Lastly the third kind would involve the use of bases with CO_3^{2-} or HCO_3^- anions wherein, because of incomplete deprotonation of the acrylate acidic hydrogen, there takes place facile exchange between the quaternary ammonium ion and the metal ion (Figure 15). It is obvious that in reactions in which both C- and O-alkylated product are formed the mechanism in operation could take place with varying degrees of interaction between the enolate oxygen and metal (Figure 14). In the last mechanism type (Figure 15), the deprotonation step could either take place fully (in which case the mechanism would proceed as in Figure 13 and/or Figure 14) or partially, leading to an intermediate where the NBu_4^+ bridges both the anion of the base and the enolate oxygen.

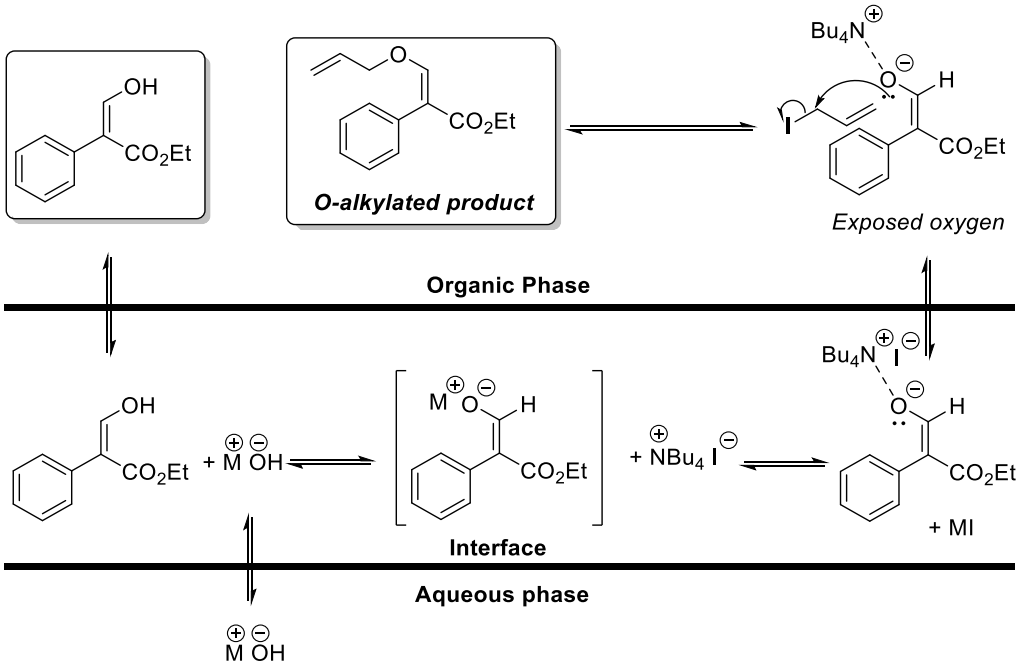


Figure 13. O-alkylation with strong bases bearing large soft counterions.

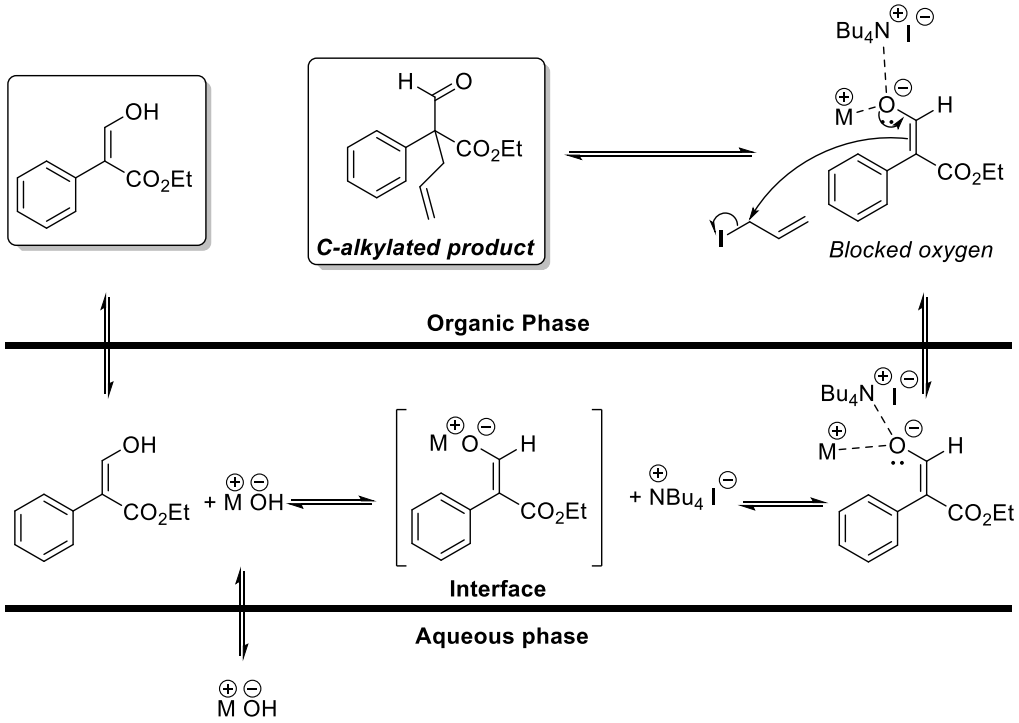


Figure 14. C-alkylation with OH^- bases weaker than KOH bearing hard counterions.

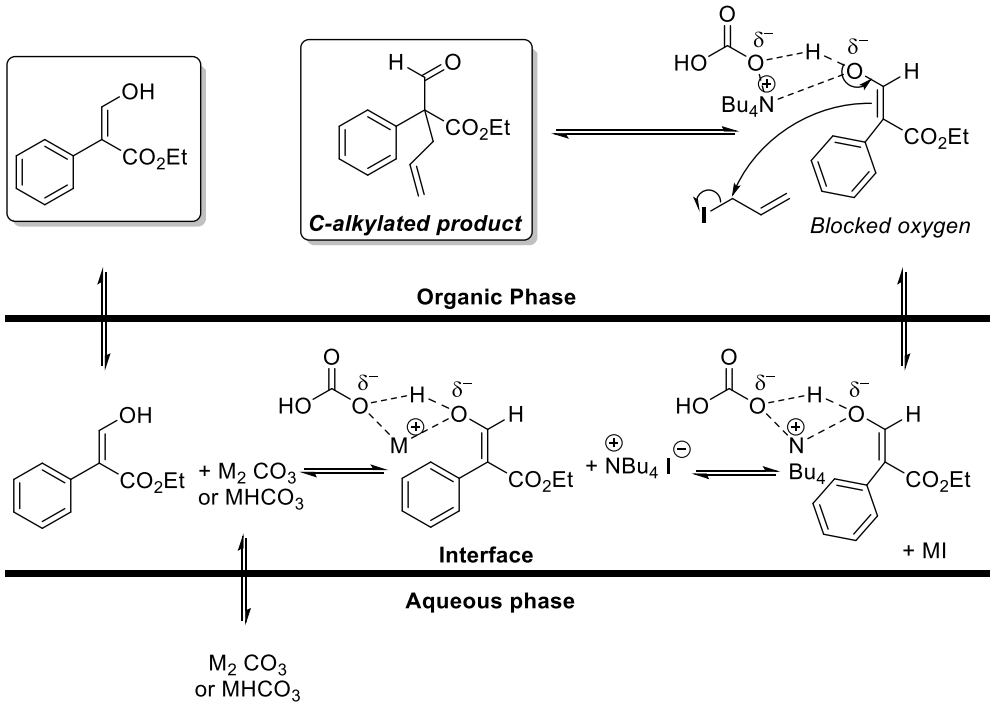


Figure 15. C-alkylation with K^+ bases weaker than KOH.

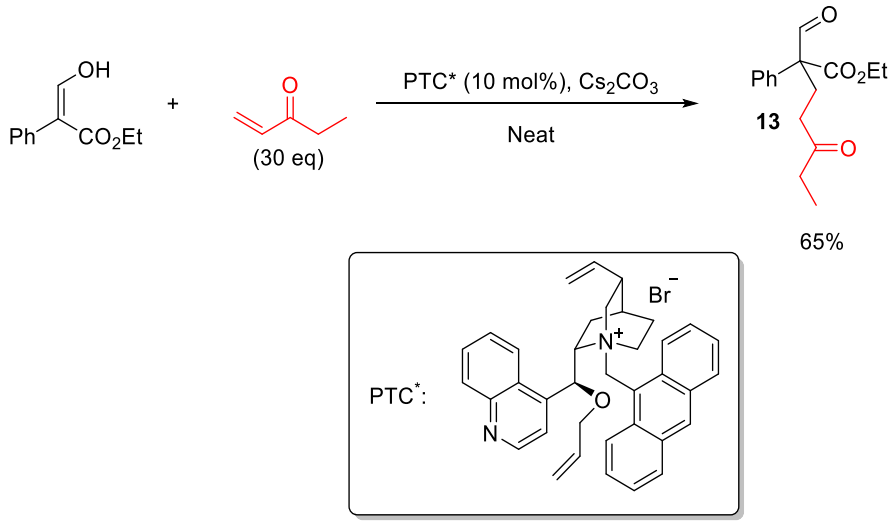
1.4. 3-hydroxy aryl acrylates as prochiral nucleophiles for organocatalytic asymmetric Michael additions

As outlined above (Scheme 4, Scheme 5) the organocatalytic Michael addition has been achieved with cinchona alkaloid based catalysts. However, the vast majority of examples to date are of cyclic systems (e.g. β-keto esters). It is important to note that so far there no known examples of aldehyde Michael adducts bearing quaternary carbon centers catalyzed by cinchona alkaloid organocatalysts. The use of cinchona alkaloid catalysts offered the potential of fine tuning the catalyst for obtaining optimal yield and enantiomeric excess (Figure 2, Figure 3). The structural richness of cinchona alkaloids

has been extensively exploited for the facile modification of the naturally occurring alkaloids to develop synthetic, tailor-made compounds for specific applications.[11]

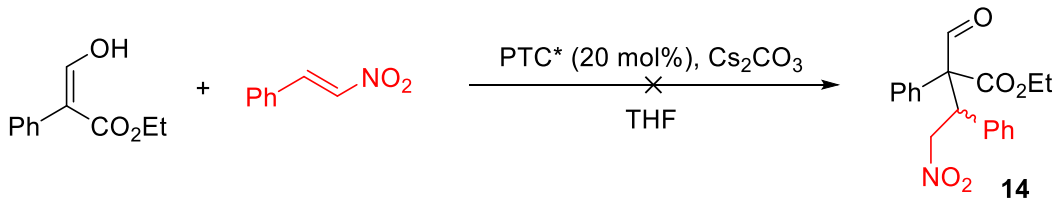
1.4.1. Phase transfer catalyzed asymmetric Michael addition

We decided to make an initial attempt at the organocatalytic Michael addition of prochiral 3-hydroxy aryl acrylates using phase transfer catalysis utilizing cinchonidinium derived chiral quaternary ammonium salts. Inspired by the report of a phase transfer catalyzed Michael addition of dimethyl malonates to cyclic enones that was carried out under neat conditions[49], we decided to employ the same tactic (Scheme 34). Surprisingly, the phase transfer catalyst proved to be very soluble in the large excess of ethyl vinyl ketone. The crude NMR for the reaction showed a singlet at δ9.87 ppm, implying that the desired product had indeed been formed. Gratifyingly, when the crude mixture was purified by flash chromatography, the desired Michael adduct **13** was indeed found to have been formed.



Scheme 34. Organocatalytic Michael addition to ethyl vinyl ketone.

Despite the initial success, it looked like the yield could be improved (65%). We then attempted to carry out the Michael addition with β-nitrostyrene as Michael acceptor in order to broaden the substrate scope; in this case neat conditions could not be carried out, so THF was chosen as the reaction solvent. Unfortunately, a complex reaction mixture brown/red in appearance was formed with no desired product. In fact, when the crude mixture was analyzed by TLC with 10% EtOAc/Hex, only a spot on the baseline could be observed.



Scheme 35. Attempted Michael addition with β-nitrostyrene.

Under phase transfer catalysis, β-nitro styrene proved to be a poor Michael acceptor for most screened inorganic bases ($KHCO_3$, Na_2CO_3, K_2CO_3), with poor yields or no product of Michael adduct **14** being obtained in all cases (Table 8).

Next, we attempted to carry out the phase transfer catalyzed Michael addition of 3-hydroxy aryl acrylates to ethyl vinyl ketone. In this case, satisfactory yields were obtained by carrying out the reaction with the cinchonidinium chiral phase transfer catalyst, DCM solvent, and 5 eq of Michael acceptor with a catalytic amount (.2 eq) of Cs_2CO_3 base (Entry 3, Table 9; Scheme 36). However, we were disappointed to find that the reaction gave essentially racemic Michael adduct product (4% ee).Thus far, the optimized reaction conditions had several drawbacks: the yield could potentially be

improved, moreover the enantiomeric excess could not be further improved by depressing the temperature due to the decreased reactivity at lower temperatures (Entries 4 and 5,Table 9).

Table 8. Reactions between 3-hydroxy aryl acrylates and β-nitro styrene.

Phase transfer catalyst	**Solvent**	**Temp. (°C)**	**Base**	**Yield (%)**
TBAI	DCM	rt	K_2CO_3	0
Cinchonidinium[a]	THF	rt	Cs_2CO_3	0
Cinchonidinium	THF	rt	K_2CO_3	Complex mixture of products
Cinchonidinium	THF	rt	$KHCO_3$	Complex mixture of products
Cinchonidinium	DCM	rt	$KHCO_3$	30
Cinchonidinium	DCM	rt	Na_2CO_3	33.
Cinchonidinium	DCM	-20	K_2CO_3	25

a) "Cinchonidinium" = *O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide. All reactions gave racemic product.

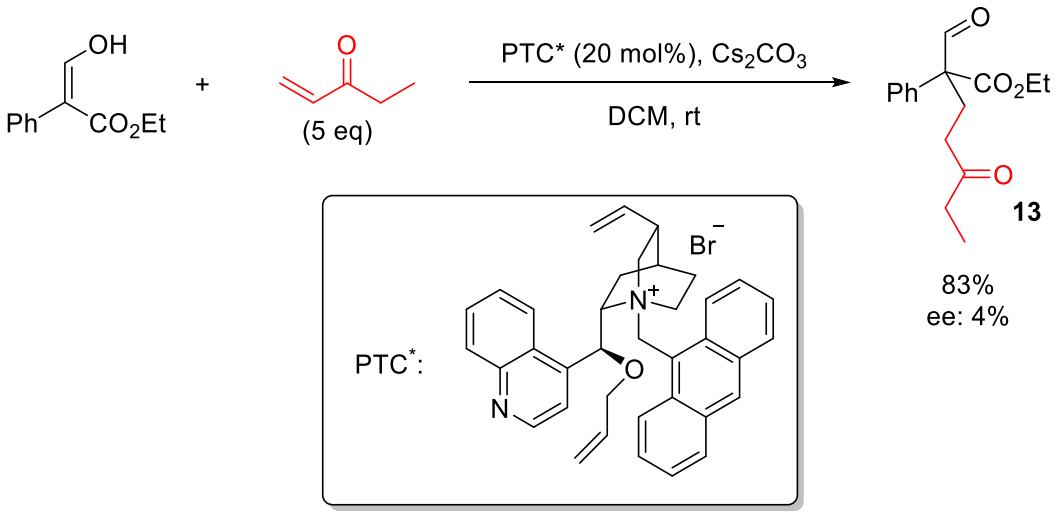
Table 9. Reactions between 3-hydroxy aryl acrylates and ethyl vinyl ketone.

Entry	Phase transfer catalyst	Eq. Michael acceptor	Solvent	Temp. (°C)	Base	Yield (%)
1	TBAI	1.5	DCM	rt	Cs_2CO_3	22
2	TBAI	30	-	rt	Cs_2CO_3	63
3	Cinchonidinium[a]	5	DCM	rt	Cs_2CO_3	83
4	Cinchonidinium	5	DCM	-38	Cs_2CO_3	0
5	Cinchonidinium	5	DCM	-25	Cs_2CO_3	0

a) "Cinchonidinium" = *O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide. ee: 4%

1.4.2. Cinchona alkaloid catalyzed asymmetric Michael addition

As outlined in section 1.1.4., the organocatalytic Michael addition has also been achieved via the use of cinchona alkaloid derived catalysts, derived from either quinine/quinidine or cinchonine/cinchonidine, bearing a tertiary amine in a chiral environment (Figure 16). With this knowledge in mind, we planned to use quinine analogs for the asymmetric Michael addition of 3-hydroxy aryl acrylates to α,β-unsaturated enones and β-nitrostyrene. The simplest structural modification that can be carried out on quinine is the demethylation of the aryl methyl ether, creating the analog known in the literature as *cupreine*, **15**. Demethylating the catalyst could potentially aid for both increasing the reactivity of the Michael substrate, by activating it for attack via hydrogen bonding, or by increasing the stereoinduction by helping to position the Michael substrate for attack by the prochiral nucleophile (Figure 18).



Scheme 36. Michael addition catalyzed by chiral phase transfer catalyst.

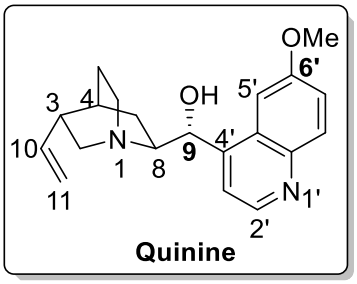
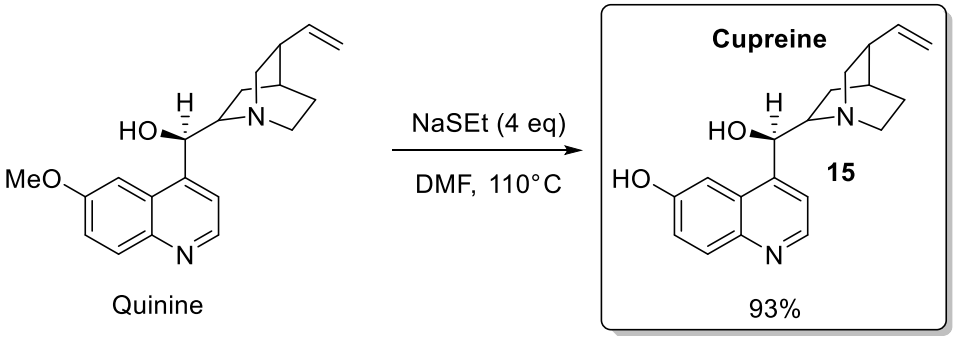


Figure 16. Numbering of atoms in quinine.

The most commonly used reagent to demethylate aryl methyl ethers in cinchona alkaloid based catalysts is sodium ethanethiolate.[50] The reaction proves efficient, but suffers from the obvious drawback of dealing with the associated strong odor of the reagent (Scheme 37). Moreover, the reaction work-up proves to be tedious, with any glassware used throughout both the reaction and the work-up having to be immersed in a bath of NaOCl (diluted commercial bleach proved effective for this purpose) in order to oxidize residual

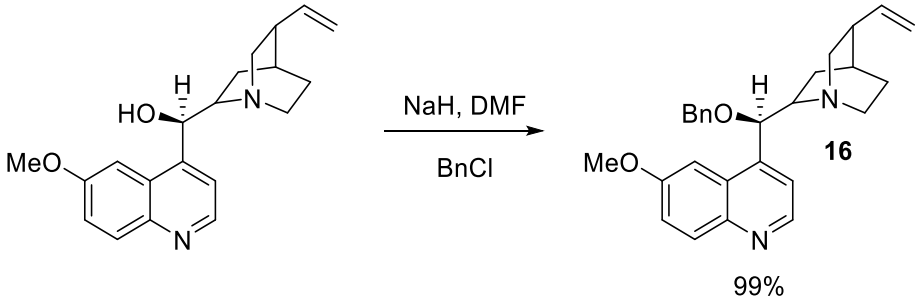
sulfur adsorbed on the surface that cannot be removed through conventional use of soap and water. Purification of the demethylated product via flash chromatography required addition of NH_4OH to the eluent (1% by volume) in order to avoid the streaking commonly encountered with amines. Triethylamine cannot be used for this purpose since the pK_a (ca 11) is higher than that of most phenols (pK_a ca 10). Because the pK_a of NH_4OH is about 9, the phenolic proton of cupreine will not protonate the ammonia to any significant extent. The DMF for this reaction and other subsequent reactions requiring this solvent was dried according to the recommendations of Burfield, advocating the use of sequential drying over 3Å sieves. From his studies, it was found that this technique gave, after 72 h, an extremely dry sample with a water content of 1.5 ppm.[51]



Scheme 37. Demethylation of quinine to furnish cupreine, 15.

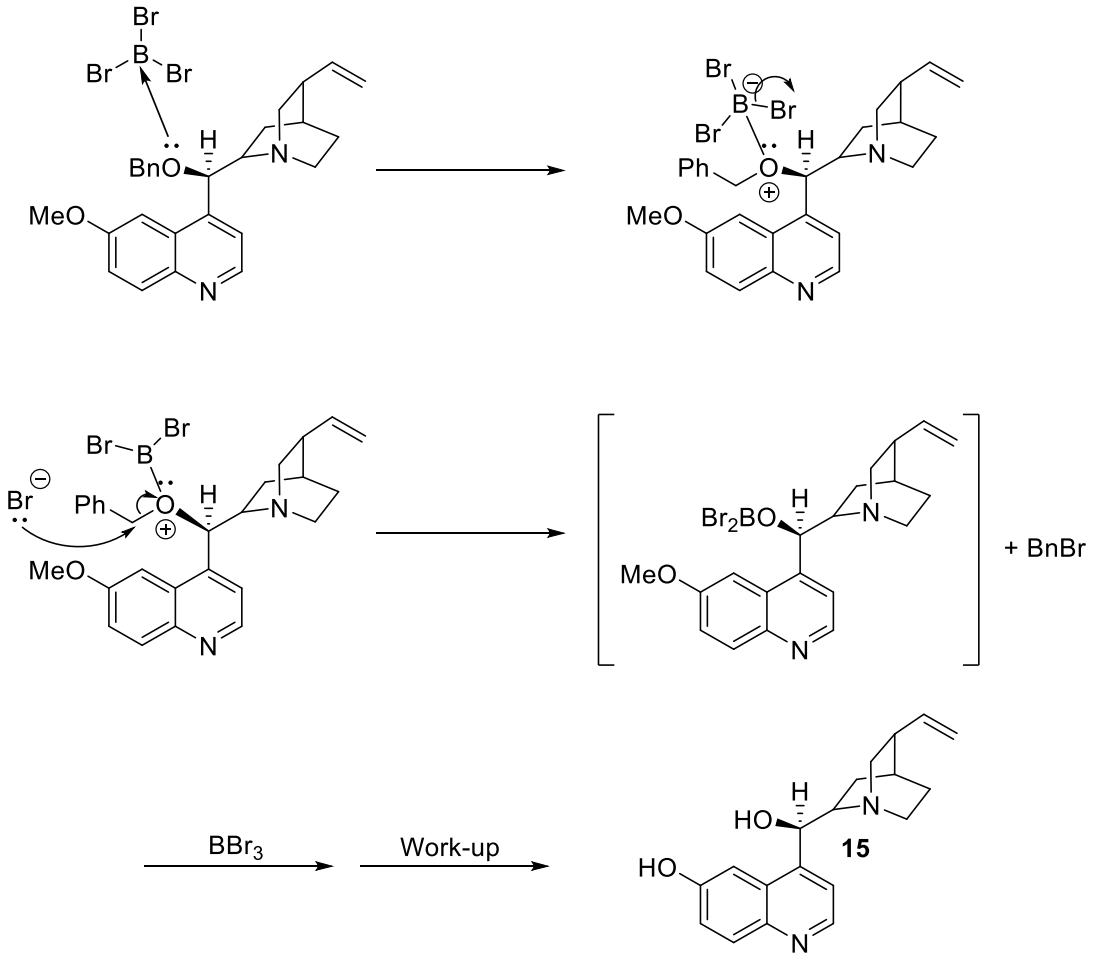
Next, we envisioned adding a sterically bulky group on the C-9 hydroxyl group. One of the simplest groups that can be added is a benzyl group, via a reaction with benzyl chloride to furnish benzylated quinine analog **16** (Scheme 38). In order to eventually obtain the quinine analog demethylated at C-6', it is necessary to carry out the alkylation before the deprotection step, in order to avoid the phenolic oxygen being alkylated in

conjunction with the C-9 oxygen. Sodium hydride was chosen as base to promote quantitative deprotonation of the C-9 hydroxyl. Despite chloride being a poorer leaving group than bromide or iodide, a harder anion was required as leaving group to avoid N-alkylation of the catalyst. The reaction proved to be straightforward with essentially quantitative conversion to product being obtained.



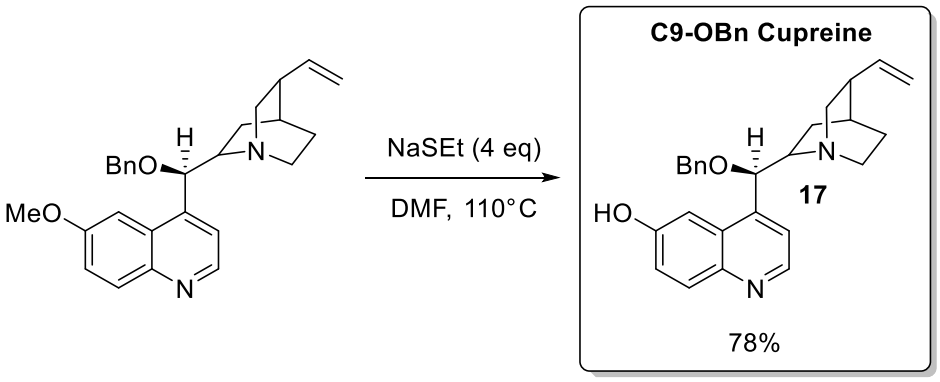
Scheme 38. Benzylation of quinine via reaction with benzyl chloride**.**

In order to remove the aryl methyl ether, we now envisioned carrying a deprotection with BBr_3[52], one of a number of Lewis acid reagents commonly used for this purpose,[53] and thereby avoid using the difficult to handle sodium ethanethiolate reagent with the resulting tedious work-up. Unfortunately, it was not entirely unexpected that BBr_3 cleaved off both the aryl methyl ether and the benzyl ether. Clearly, this Lewis acid can also bind to the basic oxygen of the benzyl ether and thereby effect the deprotection of the group (Scheme 39).



Scheme 39. Deprotection of aryl and benzyl ethers in the presence of BBr_3.

Eventually, the deprotection of the aryl methyl ether to form C9-OBn cupreine **17** was accomplished by the same established procedure outlined above using sodium ethanethiolate, albeit in slightly reduced yield, probably due to small amounts of nucleophilic cleavage of the benzyl ether (Scheme 40).

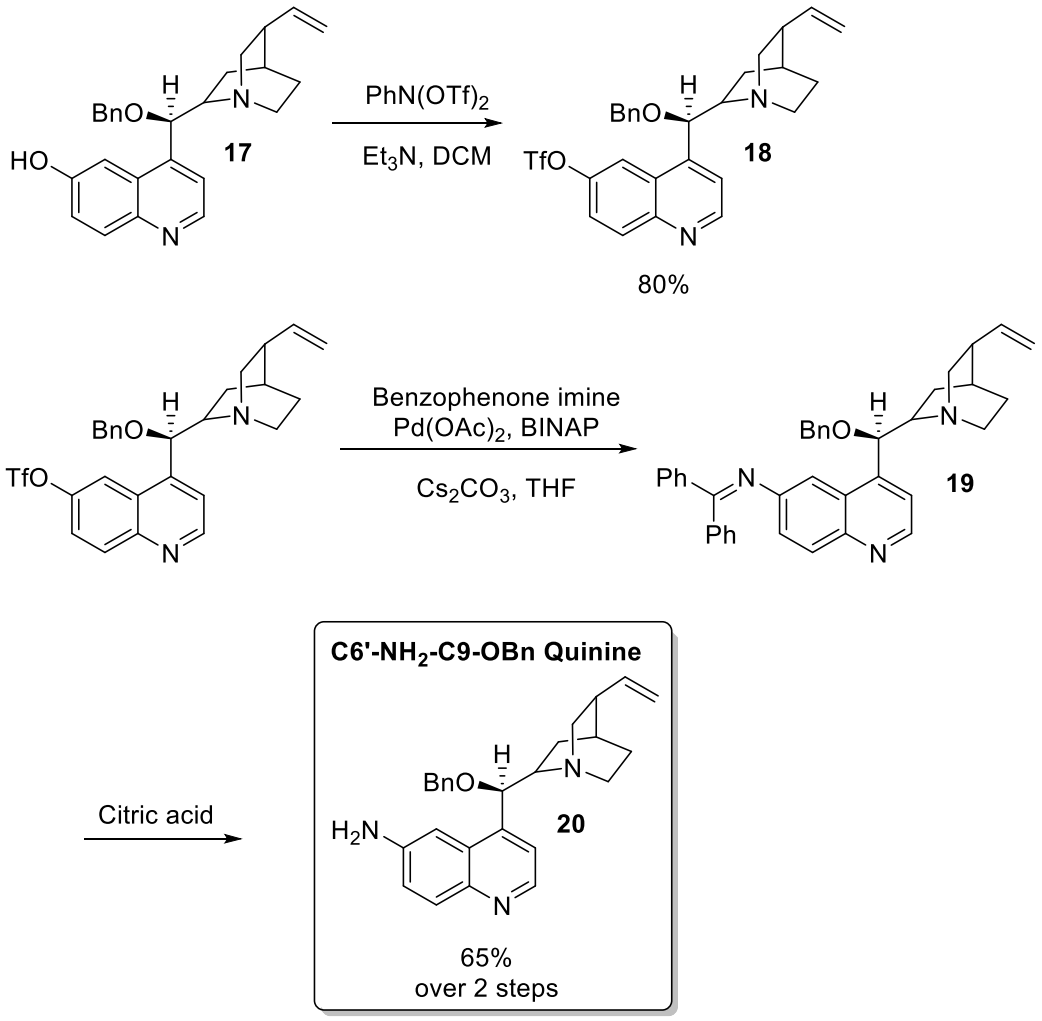


Scheme 40. Deprotection of aryl methyl ether of benzylated quinine analog.

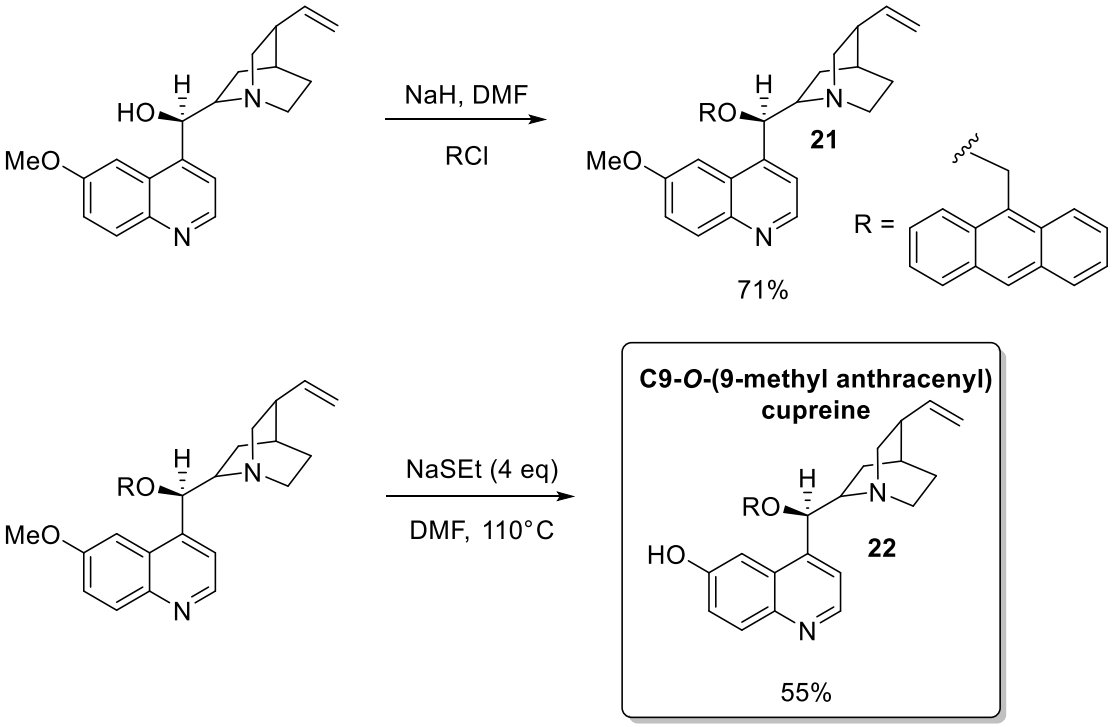
We next envisioned switching the C6' hydroxyl functionality to a primary amine. First, the hydroxyl group needed to be converted to a triflate functionality for the next coupling step. This was accomplished in good yield using *N*-Phenyl bis-(trifluoromethanesulfonimide) as the triflating agent. With quinine analog **18** bearing the triflate group at hand, we proceeded to accomplish the palladium catalyzed coupling step with benzophenone imine. The resulting imine intermediate **19** was isolated without purification, subjected to hydrolysis using citric acid, furnishing the free primary amine **20** at C6' (C6'-NH_2-C9-OBn Quinine, Scheme 41).

A moiety bulkier than a benzyl group could potentially be attached on the C9 oxygen, and we proposed to accomplish this via the attachment of a 9-methyl anthracenyl moiety. The alkylation was accomplished in moderately good yield by the reaction of the sodium hydride formed quinine alkoxide intermediate with 9-(chloromethyl)anthracene to afford alkylated analogue **21**. The final deprotection step to furnished cupreine analog **22** proceeded in modest yield, probably due to significant cleavage of the benzylic carbon by

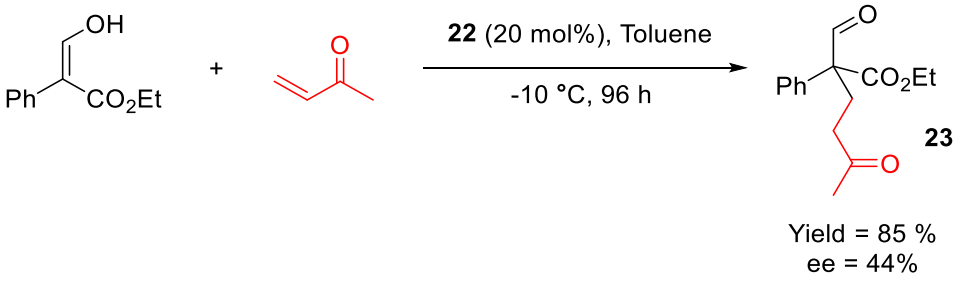
ethanethiolate anion. The benzylic carbocation in this case is expected to have a large degree of resonance stabilization because of the three conjugated aromatic rings, hence the transition state leading to the nucleophilic cleavage of the benzylic carbon-oxygen bond would be expected to be further stabilized, facilitating the thiolate promoted S_N2 cleavage (Scheme 42).



Scheme 41. Synthesis of quinine analog bearing a C6'-NH_2 functionality, 20.



Scheme 42. Synthesis of C9-*O*-(9-methyl anthracenyl) cupreine.



Scheme 43. Optimised reaction conditions for the organocatalytic Michael addition.

With the quinine analogs at hand, the next step was to screen the catalysts for the asymmetric Michael addition of 3-hydroxy aryl acrylates to Michael acceptors. For the Michael addition to methyl vinyl ketone optimised reaction conditions were found using catalyst **22** and toluene as solvent and by depressing the reaction temperature to -10 °C

(Scheme 43; Entry 1, Table 10). The loss of any stereocontrol with the use of higly polar aprotic solvents such as CH_3CN is worth noting (Entry 2; Table 10); this could possibly be due to hydrogen bonding interactions between the solvent and the phenolic hydrogen of the catalyst, thereby disrupting hydrogen bonding interactions between the Michael substrate and catalyst. Perhaps surprisingly, the attempt at carrying out the Michael addition with six membered Michael acceptors (Entry 3, Table 10) proved unsuccessful. The addition to sterically congested β-nitro styrene is a feasible reaction, so the explanation for the failure of the reaction with 2-cyclohexen-1-one based solely on steric reasons seems unlikely. Reaction of 3-hydroxy aryl acrylate with methyl vinyl ketone in the presence of catalyst **17** and THF as solvent afforded the Michael adduct in good yield but low enantioselectivity (Entry 4, Table 10). Surprisingly, cinchona alkaloid catalyst **20** bearing a primary amine functionality afforded the Michael with no stereoinduction and in low yield (Entry 5, Table 10). Catalyst $(DHQ)_2AQN$, used by Sharpless for the asymmetric aminohydroxylation, is able to catalyze the formation of Michael adduct **23** in good yield but unfortunately yielded racemic product (Entry 6, Table 10). The Michael addition with a hydrogen bonding thiourea catalyst (Figure 17) resulted in very poor yield and no stereoinduction (Entry 7, Table 10). In conclusion, it would appear that non polar solvents and bulky catalysts are required to optimize the enantiodifferentiation of the prochiral 3-hydroxy aryl acrylate substrate. In addition, cinchona alkaloid catalysts are clearly superior over hydrogen bonding thiourea catalysts. Moreover, the optimal hydrogen bonding group that allows for enantiodiscrimination in cinchona alkaloid catalysts is clearly the phenolic hydroxyl group.

Table 10. Michael addition of 3-hydroxy acrylate to methyl vinyl ketone.

Entry[a]	Catalyst[b]	Solvent	Temp. (°C)	Yield (%)	ee (%)
1	**22**	Toluene	-10	85	44
2	**22**	CH_3CN	-10	70%	0
3[c]	**17**	DCM	rt	-	-
4	**17**	THF	0 °C	89	31
5	**20**	DCM	-10 to rt	62	0
6	**$(DHQ)_2AQN$**	DCM	rt	86	0
7	**H-bonding catalyst[d]**	Toluene	-25 to 0	17	0

a) Reactions between 3-hydroxy aryl acrylate and methyl vinyl ketone. b) 20 mol% of catalyst used for all reactions. c) Reaction run with 5 eq. of 2-cyclohexen-1-one as Michael acceptor. d) Chiral hydrogen-bonding thiourea (Figure 17)

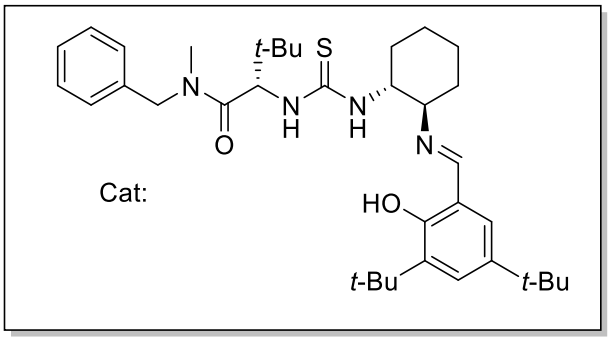
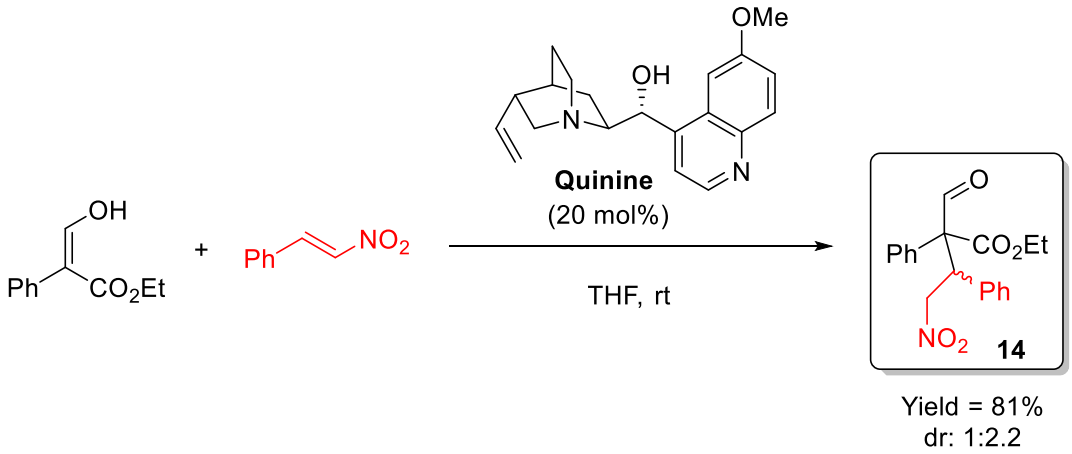


Figure 17. Chiral hydrogen bonding thio-urea.



Scheme 44. Cinchona alkaloid catalyzed Michael addition.

For the Michael addition of 3-hydroxy aryl acrylates to β-nitro styrene, optimized yield was achieved by using quinine as catalyst and THF as solvent (Entry 4, Scheme 44, Table 11) while the highest diastereomeric ratio (determined by integration of aldehyde singlets from crude NMR samples) was achieved by the use of cinchonine as catalyst, THF as solvent and at reduced temperature (-20 °C; Entry 2, Table 11). The reaction using the $(DHQ)_2AQN$ catalyst developed by Sharpless for the asymmetric aminohydroxylation and DCM as solvent also gave a satisfactory yield (Entry 5, Table 11).

Table 11. Screening of reaction conditions for asymmetric Michael addition.

Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)	dr
1	Cinchonine	THF	rt	39	1:2.2
2	Cinchonine	THF	-20	42	1:3.7
3	**15**	THF	rt	67	1:2.2
4	Quinine	THF	rt	81	1:2.2
5	$(DHQ)_2AQN$	DCM	-10	74	1:3.2

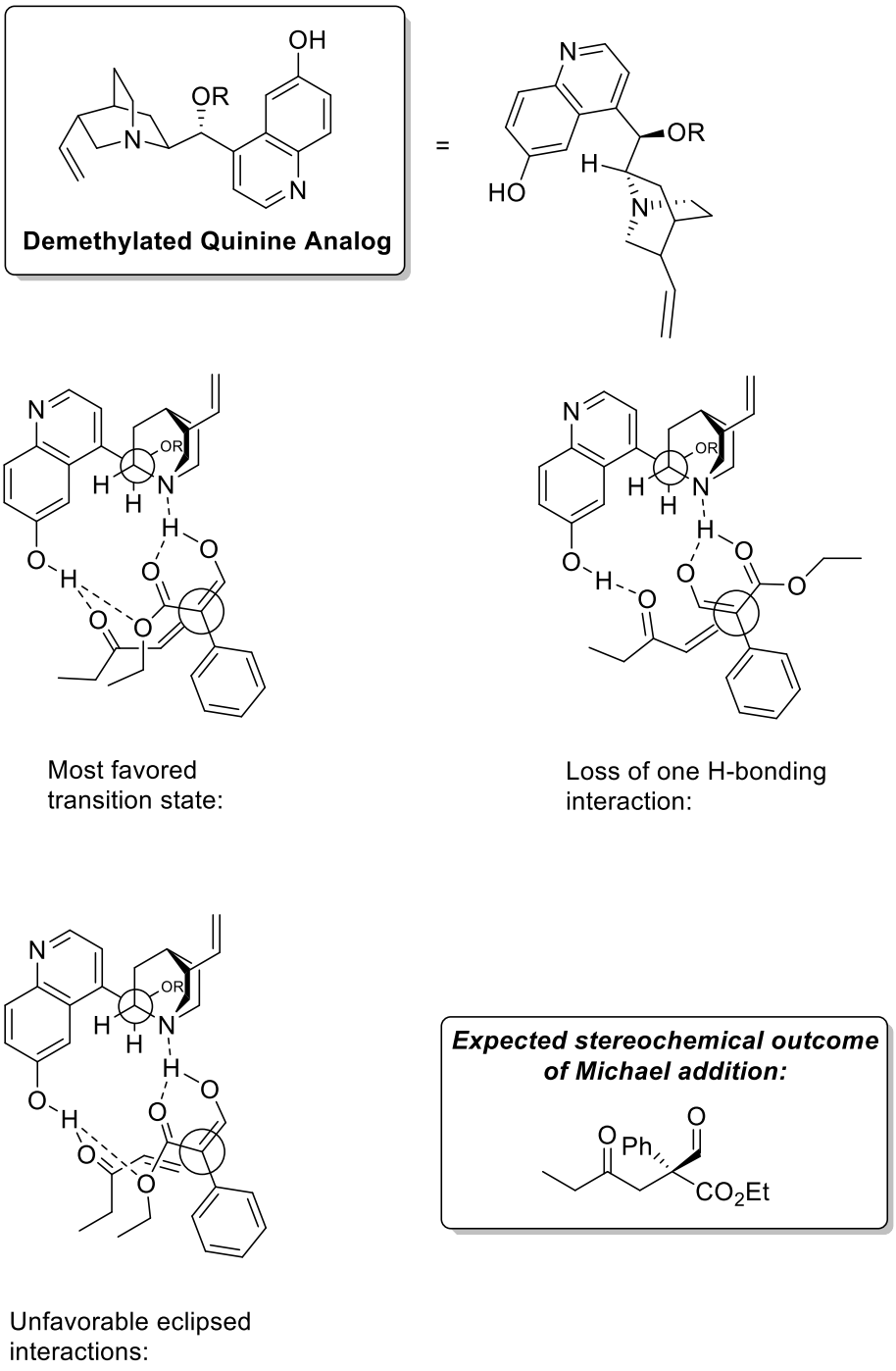
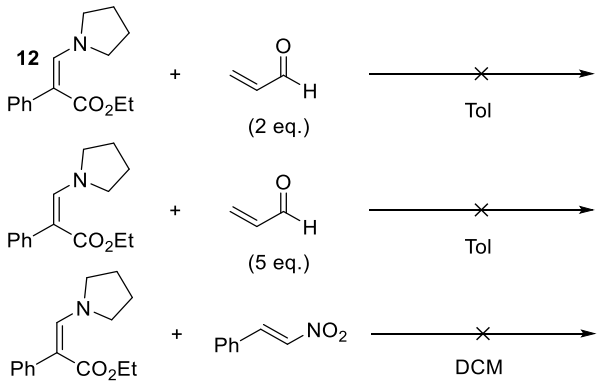


Figure 18. Possible transition states for asymmetric Michael addition.

1.4.3. Organocatalytic Michael addition using proline based catalysts

After ascertaining that aldehydes have been used extensively in the literature for the organocatalytic Michael addition using proline based catalysts, we set out to test whether 3-hydroxy aryl acrylates could also be used efficiently for the same reaction class. As will be seen below, and for the reasons set out in section 1.3.3.1., enamines derived from 3-hydroxy aryl acrylates turn out to be poor nucleophiles for such reactions.

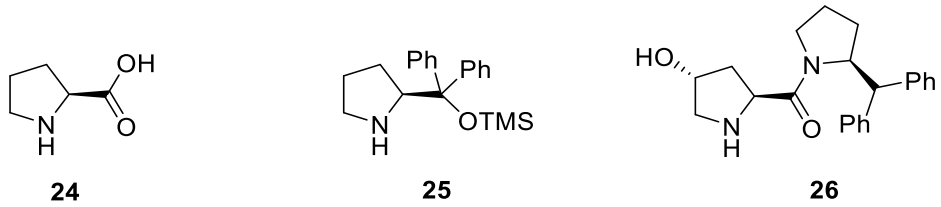
First, as a general proof of principle whether enamines in general are potential nucleophiles for such reactions, the reaction of enamines derived from the reaction of 3-hydroxy aryl acrylates and pyrrolidine with various Michael acceptors was tested (Scheme 45). In all cases, no product could be observed. We hypothesized that this could be the case due to the poorer nucleophilicity of enamines derived from pyrrolidine versus proline derivatives. With this in mind, various other proline derivatives were tested as potential catalysts for the organocatalytic Michael addition (Table 12, Figure 19).



Scheme 45. Attempted reaction of enamines with Michael acceptors.

Table 12. Screening of reaction conditions for enamine catalyzed Michael addition.

Catalyst	Michael Acceptor	Temp.	Reaction time (h)	Solvent	Additive
24	Acrolein (1 eq.)	rt	12	Toluene	-
25	Acrolein (2 eq.)	rt	12	Toluene	-
25	Ethyl vinyl ketone (2 eq.)	rt	12	Toluene	-
25	Methyl acrylate (2 eq.)	rt	12	Toluene	$BF_3 \cdot OEt_2$ (50 mol%)
25	β-nitro styrene (3 eq.)	rt	12	DCM	-
25	Ethyl vinyl ketone (3 eq.)	rt	12	DCM	-
25	Ethyl vinyl ketone (3 eq.)	rt	12	DCM	$HBF_4 \cdot OEt_2$ (20 mol%)
24	Ethyl vinyl ketone (3 eq.)	rt	12	DCM	Ethyl 3,4-dihydroxybenzo-ate (20 mol%)
26	Ethyl vinyl ketone (3 eq.)	rt	12	DCM	-
25	Ethyl vinyl ketone (3 eq.)	rt	12	DCM	TFA (20 mol%)
25	Ethyl vinyl ketone (3 eq.)	rt	12	Tol/ DCM (1:1)	Ethyl 3,4-dihydroxybenzo-ate (20 mol%)



24 **25** **26**

Figure 19. Proline based catalysts screened for organocatalytic Michael addition.

Unfortunately, no product was observed for the reaction between 3-hydroxy aryl acrylate and any of the screened Michael acceptors with any catalyst under the tested reaction conditions, probably for the same reasons as outlined in section 1.3.3.1. For several of the reactions (Table 12), additives were added to try to promote the reaction by activating the Michael acceptor for attack. Brønsted acids were used for this purpose ($HBF_4 \cdot OEt_2$, TFA), hydrogen bond donors (Ethyl 3,4-dihydroxybenzo-ate) as well as a strong Lewis acid ($BF_3 \cdot OEt_2$). It appears that despite the efforts involved in attempting to achieve the Michael addition, the enamine derived from 3-hydroxy aryl acrylate even with various different catalysts is too unreactive to react with Michael acceptors, because of the high energy involved in breaking the conjugation present in the Michael donor.

1.5. Summary

It is apparent that the direct alkylation of prochiral 3-hydroxy aryl acrylates via phase transfer catalysis is a challenging route to the formation of aldehydes bearing all carbon quaternary stereocenters. The main issue here is the propensity of these substrates to undergo O-alkylation rather than C-alkylation due to the highly conjugated nature of the prochiral substrates. Self-aldol condensation is also a potential side reaction leading to

the formation of complex mixture of products. Overall, the best yields of C-alkylated products were obtained with weaker bases, presumably due to the partial deprotonation of the enol proton, or due to the presence of a weak interaction between the metal ion and the enolate oxygen, both cases leading to the partial blocking of the oxygen available for nucleophilic attack. Overall, DCM proved to be the best solvent for the reaction due to the high solubility of the catalyst in this solvent. DCM:Tol (1:5) mixtures proved to give the highest C:O ratio (1:1) but formed the product in low yield because of the poor solubility of the catalyst in low polarity solvents. Future work could expand investigation of low polarity solvents as means of increasing C:O alkylated ratio by employing catalysts more soluble in these solvents.

The alkylation of 3-hydroxy aryl acrylates via enamine catalysis remains a considerable challenge in part because the highly conjugated nature of the starting material greatly lowers the nucleophilicity of the enamine substrates, with the further potential problem of *N*-alkylation of the catalysts. In the future it may be worth investigating whether some of the most potent electrophiles, such as carbenium ions, may be reactive enough to act as efficient electrophiles for the organocatalytic alkylation of 3-hydroxy aryl acrylates via enamine catalysis.

The Michael addition to 3-hydroxy aryl acrylates has proven to be a successful reaction, forming the Michael adducts in high yield albeit low enantioselectivity (44%, in the case of reaction with methyl vinyl ketone) and diastereoselectivity (1:3.7, in the case of reaction with β-nitro styrene). This reaction poses no problems in terms of O-alkylation

since the soft carbon nucleophile in the prochiral substrate will react readily with the soft electrophilic carbon at the β-position in the Michael acceptor. For the Michael addition to enones, it was found that the best stereoinduction was achieved by employing a catalyst bearing a bulky group on the C-9 position and a hydrogen bonding phenolic group on the C-6' position (catalyst **22**), the latter group aiding in the activation of the Michael acceptor as well as positioning the Michael substrate to increase the enantiodifferentiation in the transition state. Interestingly, the diastereoselective Michael addition to β-nitro styrene seemed to be less sensitive to hydrogen bonding groups on the C-6' position, with cinchonine providing the highest diastereoselectivity (1:3.7). Future studies in the organocatalytic Michael addition could involve further modification of the quinine based scaffold by introducing thio-urea moieties into the C-6' position.[50b] Adding bulky substituents with fewer rotational degrees of freedom to the C-9 position, such as a phenanthrene derivative, may also help improve the stereoinduction of the reaction.

1.6. General methods and experimental

General considerations: all starting materials and reagents were obtained from commercial sources and used as received unless otherwise noted. All solvents used were freshly distilled prior to use. ^{1}H and ^{13}C spectra were recorded on a Bruker DRX 300 operating at 300 MHz and 75 MHz, and referenced to the solvent used (7.27 and 77.00 ppm for $CDCl_3$). Analytical thin layer chromatography was performed using EMD Chemicals TLC Glass plates, Silica Gel 60 F254. Flash column chromatography was performed using Biosolve 60 Å (0.032–0.063 mm) silica gel.

1.6.1. Synthesis of 3-hydroxy aryl acrylates

Method 1 (Reaction with HBF_4):

As an example of a typical reaction, benzaldehyde (0.77 ml, 7.6 mmol) was dissolved in DCM (19 mL), followed by addition of $HBF_4 \cdot OEt_2$ (52 µL, 0.381 mmol, 10 mol%). The mixture was allowed to cool down to -78 °C, at which point EDA (0.434 g, 3.81 mmol) was added slowly dropwise over a period of ca. 5 minutes. After complete consumption of EDA was identified by TLC analysis, the reaction mixture was allowed to slowly warm up to 0 °C, at which point the reaction was quenched by addition of water and extracted with DCM. The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was adsorbed onto silica and purified by chromatography (SiO_2, 2% EtOAc/Hex) to yield 3-hydroxy aryl acrylate (0.44 g, 60% yield) as a light yellow oil. Elution of product from the column can be easily identified

when a pink band reaches the bottom of the silica. Heating product at elevated temperatures (above 50 °C) for prolonged times causes self-polymerization of product, as indicated by a change of the oil to a dark pink color.

Method 2 (Reaction with TfOH):

As an example of a typical reaction, benzaldehyde (0.96 ml, 9.43 mmol) was dissolved in DCM (39 mL), followed by addition of TfOH (140 μL, 1.57 mmol, 20 mol%). After 1-2 minutes of stirring, the reaction mixture turned an intense pink colour. The mixture was then allowed to cool down to -78 °C, at which point EDA (0.896 g, 7.85 mmol) was added slowly dropwise, at a suitable rate to ensure continuous off-gassing (this usually meant adding over a period of ca. 5 minutes). After 30 minutes of stirring, reaction completion was confirmed by TLC, at which point the reaction mixture was allowed to slowly warm up to 0 °C. The reaction was then quenched by slow addition of water; at the point in which the TfOH is neutralized the color of the reaction mixture changes from deep pink to yellow. The aqueous layer was extracted with DCM, the combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by chromatography (SiO_2, 2% EtOAc/Hex) to yield 3-hydroxy aryl acrylate (1.086 g, 72% yield) as a light yellow oil.

1.6.2. Alkylation reactions

Reactions of 3-hydroxy aryl acrylates with electrophiles under phase transfer catalysis:

Method 1 (Reaction of 3-hydroxy aryl acrylate with electrophile in the presence of a solid base):

As an example of a typical reaction, 3-hydroxy aryl acrylate (50 mg, 0.26 mmol) was allowed to dissolve in DCM (2.6 ml) and this was followed by the addition of TBAI (33 mg, 0.089 mmol, 35 mol%). Next, Na_2CO_3 (276 mg, 2.6 mmol, 10 eq.) was slowly added with vigorous stirring and allowed to stir for 5 minutes. At this point, allyl iodide (48 μL, 0.52 mmol) was slowly added via syringe. After a few minutes, the color of the reaction mixture changed from light yellow/brown to an almost colorless cloudy mixture. The reaction was allowed to stir overnight under N_2, at which point TLC analysis confirmed reaction completion. The reaction was quenched with sat. NH_4Cl and allowed to stir for a few minutes, the layers were separated and the aqueous layer was then extracted with DCM. The combined organic extracts were dried over Na_2SO_4 and passed through a 1 cm high Celite pad in a 4 cm diameter fritted funnel (medium porosity) to remove small amounts of residual precipitates. The resulting yellow solution was then concentrated under vacuum, leaving a dark yellow oil that turns dark violet if exposed to the air overnight due to oxidation of allyl iodide. The crude mixture was adsorbed onto silica and purified by chromatography (SiO_2, 10% EtOAc/Hex). I_2 was used to aid in the identification of the product in the fractions being eluted from the column. The combined

fractions were concentrated and yielded the C-alkylated product (60 mg, 40% yield) as a light yellow oil.

Method 2 (Reaction of 3-hydroxy aryl acrylate with electrophile in the presence of an aqueous base): Same procedure as above (***Method 1***), aqueous base added slowly dropwise via syringe.

Reactions of enamine derived from 3-hydroxy aryl acrylate with electrophiles:

Formation of enamine 12:

To a flask were added benzaldehyde (478 μL, 4.717 mmol), followed by DCM (20 mL). At this point TfOH (83 μL, 0.943 mmol) was added slowly dropwise via syringe at rt with stirring, and after 1-2 minutes the mixture turned a deep pink color. The reaction mixture was allowed to cool down to -78 °C, after which EDA (448 mg, 3.93 mmol) was added slowlydropwise via syringe over a period of ca. 5 minutes. The reaction was allowed to stir for 30 minutes, and the flask was allowed to slowly warm up to rt. Next, pyrrolidine (3.94 mL, 47.2 mmol) was added slowly dropwise via syringe at this temperature. As the pyrrolidine was slowly added with stirring, the appearance of the reaction mixture gradually changed from light yellow to dark yellow. After stirring for about 10 minutes, 4Å powdered molecular sieves (1.2 g, 300 mg $mmol^{-1}$ limiting reagent) were added, and the mixture was allowed to stir for a total of 24 hours, at which time TLC analysis showed the reaction to have reached completion. The reaction mixture was

filtered through a fritted funnel (medium porosity). The solvent was then concentrated under vacuum to leave a dark yellow oil, and the crude mixture was purified by chromatography (SiO_2, 20% EtOAc/Hex) to furnish enamine **12** (675 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (s, 1 H), 7.41 – 7.09 (m, 5 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 1.78 – 1.65 (m, 4 H), 1.84 – 1.56 (m, 4 H), 1.21 (t, *J* = 7.1 Hz, 3 H).^{13}C NMR (75 MHz, $CDCl_3$): δ 145.74, 132.23, 132.17, 126.80, 126.74, 125.86, 125.79, 59.34, 51.40, 25.20, 14.55.

General procedure for reaction of enamine 12 with electrophiles:

To a flask was added enamine **12** (73.5 mg, 0.3 mmol), followed by enough solvent to make up a 0.1 M solution of the reactant. The reactant was dissolved into the solvent through vigorous stirring, and the electrophile was next added through the septum under a positive pressure of Ar slowly dropwise over a period of ca. 1 minute. The reaction was allowed to stir for 24 hours and on the following day reaction completion was determined by TLC analysis.

1.6.3. Phase transfer catalyzed Michael addition of 3-hydroxy aryl acrylate with enones

General procedure (neat reaction with ethyl vinyl ketone):

To a flask was added 3-hydroxy aryl acrylate (0.136 g, 0.708 mmol) followed by ethyl vinyl ketone (2.1 mL, 21.2 mmol) and TBAI (52 mg, 0.142 mmol, 20 mol%), the latter dissolving readily in the neat reaction mixture. Next, Cs_2CO_3 (46 mg, 0.142 mmol, 20 mol%) was added slowly to the mixture with vigorous stirring, which turned cloudy initially but after 1-2 minutes of stirring turned into a colorless solution. After 2 hours, reaction completion was confirmed by TLC analysis. The reaction was then diluted with EtOAc and quenched with sat. NH_4Cl. The layers were then separated and the aqueous layer extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by chromatography (SiO_2, 20% EtOAc/Hex) to yield the Michael adduct (123 mg, 63% yield) as a colorless oil.

General procedure (reaction with enone in solvent):

To a flask was added 3-hydroxy aryl acrylate (235 mg, 1.22 mmol), followed by DCM (1.22 mL), ethyl vinyl ketone (0.61 mL, 6.11 mmol) and *O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (148 mg, 0.244 mmol, 20 mol%). The chiral phase transfer catalyst dissolved completely in the reaction mixture after stirring vigorously for a few minutes. Next, Cs_2CO_3 (80 mg, 0.244 mmol, 20 mol%) was added slowly to the reaction mixture with vigorous stirring, turning the reaction mixture cloudy.

After 3 hours, reaction completion was confirmed by TLC analysis. At this point, the reaction mixture was diluted with DCM and quenched with half sat. NH_4Cl. The organic layer was removed and the aqueous layer extracted with DCM; the combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. Vide supra for purification of crude reaction mixture.

1.6.4. Cinchona alkaloid catalyzed Michael addition between 3-hydroxy aryl acrylates and Michael acceptors

Synthesis of quinine based catalysts:

Procedure for formation of cupreine 15 from quinine:

To a three necked flask fitted with a condenser and a thermometer were added quinine (0.5 g, 1.54 mmol) followed by NaSEt (0.519 g, 6.16 mmol) and anhydrous DMF via syringe (10 mL). At this point the color of the reaction mixture turned light brown. The reaction was then heated to 110 °C with the aid of an oil bath and stirred overnight (12 h) under Ar. The following morning, the reaction was quenched with enough sat. NH_4Cl to change the pH to 7-8 and then diluted with H_2O (10 mL). The solution was diluted with EtOAc (50 mL), the layers were separated and the aqueous layer extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (4 × 10 mL) and dried over Na_2SO_4. The DMF was removed by azeotropic distillation with xylenes, leaving a white solid. The crude mixture was purified by chromatography (SiO_2,

EtOH:EtOAc:NH_4OH = 4:6:0.5) to yield cupreine **15** as a white solid (445 mg, 93% yield). ^1H NMR (300 MHz, CD_3OD) δ 8.58 (d, J = 4.8 Hz, 1H), 7.89 (d, J = 9.2 Hz,1H), 7.61 (d, J = 4.8 Hz, 1H), 7.32 (dd, J = 2.4 Hz, 9.2 Hz, 1 H), 7.28 (d, J = 2.4 Hz, 1H), 5.69-5.78 (m, 1H), 5.51 (d, J = 3.2 Hz, 1H), 4.95 (d, J = 17.2 Hz, 1H), 4.88 (d, J = 9.2 Hz, 1H), 3.66-3.73 (m, 1H), 3.05-3.13 (m, 2H), 2.63-2.74 (m, 2H), 2.34 (br, 1H), 1.80-1.89 (m, 2H), 1.77-1.78 (m, 1H), 1.54-1.61(m, 1H), 1.39-1.46(m, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 157.9, 149.8, 147.4, 144.0, 142.6, 131.4, 128.4, 123.3, 119.8, 115.0, 105.1, 72.2, 60.9, 57.6, 48.4, 44.2, 40.9, 29.2, 28.1, 21.8.

***Formation of cupreine 15 from C9-OBn quinine*:**

To a flask was added C9-OBn quinine **16** (257 mg, 0.62 mmol) followed by DCM (7 mL). The mixture was cooled down to -78 °C, at which point BBr_3 (1.36 mL, 1.36 mmol) was added slowly via syringe. The mixture was stirred at this temperature for 30 minutes, before letting it warm up to 0 °C, at which temperature the mixture was stirred for 12 h. The following day the reaction was quenched by slow addition of MeOH (0.55 mL, 13.6 mmol) and allowed to stir for 30 minutes. The mixture was then diluted with H_2O (10 mL) and neutralised with NH_4OH to pH = 10, the layers were separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic extracts were then washed with brine and dried over Na_2SO_4. The solvent was concentrated under vacuum, leaving a yellow solid. The crude product was purified by chromatography (SiO_2, EtOH:EtOAc:NH_4OH = 4:6:0.5) to yield cupreine **15** as a white solid (154 mg, 80% yield).

***Formation of C9-OBn quinine 16*:**

A flask was charged with quinine (1g, 3.08 mmol) and anhydrous DMF (31 mL) via syringe. The reaction mixture was cooled down to 0 °C, at which point, NaH (60% dispersion in mineral oil; 0.148g, 3.696 mmol) was slowly added and the mixture was allowed to stir at this temperature for 30 minutes. Next, benzyl chloride (425 µL, 3.696 mmol) was slowly added via syringe to the reaction mixture which was then allowed to warm up to rt and stirred under Ar for 12 h. After this time, the reaction was cooled again to 0 °C and quenched by the dropwise addition of sat. NH_4Cl (50 mL). The crude mixture was diluted with EtOAc (50 mL) allowing for separation of layers, the aqueous layers was then extracted with EtOAc (3 × 30 mL). Combined organic layers were washed with water (5 × 15 mL), washed with brine and dried over Na_2SO_4. Residual DMF was removed by azeotropic distillation with xylenes, leaving behind benzylated analogue **16** as a beige-yellow oil (1.27 g, 99% yield) which was pure enough for synthetic use.[50a]

***Formation of C9-OBn cupreine 17*:**

To a flask was added NaH (60% dispersion in mineral oil; 247 mg, 6.18 mmol) followed by anhydrous DMF (5 mL) and EtSH (0.46 mL, 6.18 mmol) added slowly dropwise at 0 °C, the mixture was then stirred at this temperature for 1 hour. A separate flask was charged with C9-OBn quinine **16** (641 mg, 1.55 mmol) and anhydrous DMF (5 mL), this mixture was then transferred via cannula to the flask containing the in situ formed NaSEt, at this point the mixture turned cloudy yellow. The reaction mixture was heated to 110 °C

with the aid of an oil bath and stirred for 10 hours under Ar. After this time, the reaction was quenched by the slow dropwise addition of sat. NH_4Cl (10 mL) and was then diluted with H_2O (8 mL). The solution was adjusted to pH = 2 by the slow dropwise addition of conc. HCl. The aqueous phase was next washed with EtOAc (2 × 15 mL), and the mixture was adjusted to pH = 8 by the slow dropwise addition of NH_4OH. Finally, the aqueous phase was extracted with EtOAc (3 × 20 mL), washed with brine and dried over Na_2SO_4. The DMF was removed by azeotropic distillation with xylenes, and the crude product was purified by chromatography (SiO_2, Et_3N:EtOH:EtOAc = 0.5:1:9) to yield C9-OBn cupreine **17** as a white powder (484 mg, 78% yield). ^1H NMR (300 MHz, DMSO-d_6) δ (ppm) 10.03 (br, 1H), 8.63 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.70-7.15 (m, 8H), 5.92-5.77 (m, 1H), 5.14-4.82 (m, 3H), 4.34 (d, J = 11.6 Hz, 1H), 4.27 (d, J = 11.6 Hz, 1H), 3.30-2.94 (m , 2H), 2.88-2.70 (m, 1H), 2.50-2.10 (m, 3H), 1.94-1.32 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d6) δ (ppm) 155.4, 146.6, 144.3, 143.4, 142.3, 138.1, 131.3, 128.2, 127.7, 127.6, 127.5, 121.4, 114.2, 104.7, 70.5, 59.9, 56.0, 54.9, 41.7, 39.4, 27.4, 27.3, 24.6.

Formation of C9-OBn-C6'-OTf- quinine 18 from C9-OBn cupreine 17:

To a flask was added C9-OBn cupreine **17** (928 mg, 2.31 mmol), followed by anhydrous DCM (17 mL) and *N*,*N*-bis(trifluoromethylsulfonyl)aniline (993 mg, 2.78 mmol). Next, Et_3N (0.74 mL, 5.33 mmol) was added via syringe and the mixture was allowed to stir for 12 h under Ar. After this time, the solvent was removed under vacuum, leaving a dark yellow oil. The crude mixture was purified by chromatography (SiO_2,

EtOAc:EtOH:NH_4OH = 100:1:1) to yield C9-OBn-C6'-OTf **18** (987 mg, 80% yield) as a dark yellow translucent solid.[50b]

Formation of C6'-NH_2-C9-OBn Quinine 20 from C9-OBn-C6'-OTf-quinine 18:

A flask under Ar was charged with C9-OBn-C6'-OTf-quinine **18** (227 mg, 0.43 mmol) and dissolved in THF (1.9 mL). To the reaction flask were next added with stirring $Pd(OAc)_2$ (5.7 mg, 0.0255 mmol), BINAP (24 mg, 0.0388 mmol), Cs_2CO_3 (198 mg, 0.609 mmol) and finally benzophenone imine (74 μL, 0.44 mmol). The reaction mixture was then heated to 70 °C with the aid of an oil bath and after a few minutes of stirring the solution gradually turned a lighter red colour. After 24 hours of stirring at the aforementioned temperature, the reaction mixture was cooled to rt, diluted down with DCM (10 mL) and filtered through a 1 cm high Celite pad (medium porosity, 4 cm diameter, ca 1 cm high), which was washed with DCM (10 mL). The solvent was concentrated under reduced pressure, leaving crude imine **19** as an orange solid. To the crude solid was next added THF (1.6 mL), followed by 10% citric acid (3.3 mL), and the mixture was allowed to stir for 24 hours. After this time, the mixture was quenched by slow dropwise addtion of sat. Na_2CO_3 and was then diluted with EtOAc (10 mL). The layers were separated and the aqueous layer extracted with DCM (2 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum to yield a crude green solid. The crude mixture was purified by chromatography (SiO_2, EtOAc:MeOH:NH_4OH = 100:15:1) to afford C6'-NH_2-C9-OBn Quinine **20** (111 mg, 65% yield) as a translucent yellow solid.[50b]

***Formation of C9-O-(9-methyl anthracenyl) quinine 21*:**

To a flask under Ar was added quinine (680 mg, 2.10 mmol), followed by anhydrous DMF (4 mL) and slow addition of NaH (60% dispersion in mineral oil; 235 mg, 5.87 mmol) with stirring at rt. After addition was complete, the reaction mixture was allowed to stir for 1 hour and 30 minutes, at which point 9-(Chloromethyl)anthracene (475 mg, 2.10 mmol) was added with stirring at rt. After stirring for 2 hours, additional DMF (2 mL) was charged to the reaction flask to help with dissolution of starting materials. After stirring for 12 h, the reaction mixture was quenched with brine (10 mL). A viscous material remained undissolved in the reaction flask, which slowly dissolved by addition of EtOAc (25 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 × 25 mL). Combined organic extracts were washed with H_2O (3 × 10 mL), washed with brine, dried over Na_2SO_4, and concentrated under vacuum to leave a orange solid. The crude mixture was purified by chromatography (SiO_2, MeOH:EtOAc:Et_3N = 20:80:0.5) to yield C9-O-(9-methyl anthracenyl) **21** as a yellow translucent solid (765 mg, 71% yield).[50b]

Formation of C9-O-(9-methyl anthracenyl) cupreine 22 from C9-O-(9-methyl anthracenyl) quinine 21:

To a flask under Ar was added NaH (60% dispersion in mineral oil; 335 mg, 8.36 mmol) followed by anhydrous DMF (8 mL). The solution was allowed to cool down to 0 °C and EtSH (0.62 mL, 8.36 mmol) was added slowly dropwise via syringe, the mixture was

then stirred at this temperature for 30 minutes. The mixture was warmed to rt at stirred for a few more minutes. To a separate flask was added C9-O-(9-methyl anthracenyl) quinine **21** (1.076 g, 2.09 mmol) followed by anhydrous DMF (5 mL). This mixture was then transferred via cannula to the mixture containing the in situ formed NaSEt, the flask containing substrate was rinsed with a further 2 mL and the rinsed was transferred through via cannula. The mixture was then heated to 110 °C with the aid of an oil bath for 9 h. The following day, the reaction was quenched by slow dropwise addition of sat NH_4Cl (15 mL), and addition of H_2O (15 mL). The reaction mixture was diluted with EtOAc (30 mL), the layers were separated and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was concentrated under vacuum. Residual DMF was removed by azeotropic distillation with xylenes. The crude product was purified by chromatography (SiO_2, MeOH:EtOAc:NH_4OH = 4:100:1) to yield C9-O-(9-methyl anthracenyl) cupreine **22** (578 mg, 55% yield) as a translucent dark yellow solid.[50b]

Cinchona alkaloid catalyzed Michael addition between 3-hydroxy aryl acrylate and enone:

To a flask was added **22** (104 mg, 0.208 mmol), followed by toluene (1 mL) and 3-hydroxy aryl acrylate (200 mg, 1.04 mmol) at rt with stirring. The mixture was allowed to cool down to -10 °C, at which point methyl vinyl ketone was added slowly dropwise over a perios of ca. 2 minutes. The reaction was allowed to stir for 96 hours, at which point the reaction was allowed to warm up to room temperature, and the mixture was passed

through a silica plug (3 cm silica in fritted funnel of medium porosity and 1 inch diameter). The plug was washed with DCM (25 mL), the solvent was concentrated under vacuum and the flask placed under high vacuum overnight in order to remove excess methyl vinyl ketone. The product was purified by chromatography (SiO_2, 10% EtOAc/Hexane) to yield **23** (232 mg, 85% yield) in 44% ee as a colorless oil.

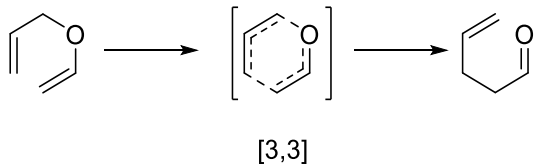
Cinchona alkaloid catalyzed Michael addition between 3-hydroxy aryl acrylate and β-nitrostyrene:

To a flask was added $(DHQ)_2AQN$ (89.2 g, 0.104 mmol) followed by DCM (2 mL) and 3-hydroxy aryl acrylate (100 mg, 0.520 mmol) with stirring at rt. The mixture was allowed to stir for ca. 5 minutes, at which point it was cooled down to -10 °C, and at this point β-nitrostyrene (155 mg, 1.04 mmol) was added to the flask. The reaction mixture was allowed to stir at this temperature for 96 hours, at which point the mixture was passed through a silica plug (3 cm silica in fritted funnel of medium porosity and 1 inch diameter). The plug was washed with DCM (25 mL) and the solvent was concentrated under vacuum to yield a crude yellow crystalline solid. The crude mixture was purified by chromatography (SiO_2, 15% EtOAc/Hex) to yield **14** (131 mg, 74% yield, 1:3.2 dr) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1 H_b), 9.75 (s, 1 H_a), 7.51 – 7.02 (m, 20 $H_{a,b}$), 5.32 (dd, J = 13.7, 11.4 Hz, 1 H_a), 5.17 (dd, J = 13.5, 11.0 Hz, 1 H_b), 4.87 – 4.72 (m, 2 $H_{a,b}$), 4.66 – 4.53 (m, 2 $H_{a,b}$), 4.42 – 4.34 (m 3 $H_{a,b}$), 4.23 (q, J = 7.1 Hz, 1 H_a), 1.30 (t, J = 7.1 Hz, 3 H_a), 1.20 (t, J = 7.1 Hz, 3 H_b).

CHAPTER II: STUDIES ON THE CLAISEN REARRANGEMENT AS A ROUTE TO QUATERNARY STEREOCENTERS

2.1. Introduction

The [3,3] sigmatropic rearrangement of allyl vinyl ethers leads to γ,δ-enones and is known as the *Claisen* rearrangement,[54] discovered over 100 years ago[55] and it has proven to be a powerful tool in the chest-box of the organic chemist. The reaction is mechanistically analogous to the Cope rearrangement. Both the Claisen and Cope rearrangements are known as protocols to reliable generate defined configured tertiary and quaternary carbon centers as well as complicated C atom-heteroatom bonds. The Claisen rearrangement is the most used [3,3]-sigmatropic rearrangement due to the ease by which the allyl vinyl ether system can usually be made, along with the smooth and frequently irreversible product formation, making this reaction widely applicable for the synthesis of numerous organic intermediates. The [3,3] sigmatropic rearrangement is characterized by a highly ordered transition state where the repulsive interactions are minimized (Scheme 46).



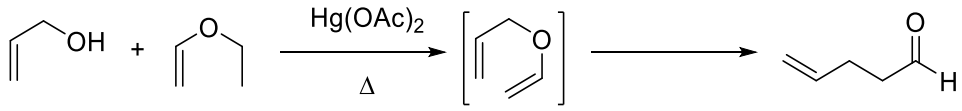
Scheme 46. Transition state for the Claisen rearrangement.

As a result of the highly ordered nature of the six membered transition state, predictions are possible on the stereochemical outcome of the reaction based on the stereochemistry at the double bond. Over the years the usefulness of the Claisen rearrangement has been realized and the reaction has drawn the attention of numerous research groups, which has been reflected in the large amounts of papers published in the literature on this reaction.[56] Because the product is a carbonyl compound, the equilibrium is usually favorable for product formation.

The Claisen rearrangement has been an effective tool for the formation of quaternary stereocenters for a long time.[6] However, until very recently with the advent of true asymmetric catalysis (see section 2.1.3) the Claisen rearrangement has mostly been used for the diastereoselective formation of quaternary stereocenters due to the highly ordered nature of the chair-like transition state.[57] The enantioselective variant of the reaction for the asymmetric synthesis of quaternary stereocenters often required the use of chiral auxiliaries[58] or the use of stoichiometric amounts of chiral catalysts due to product inhibition of the catalyst.[56] A review of the literature also notes the conspicuous absence of the formation of aldehydes bearing quaternary stereocenters via the truly catalytic Claisen rearrangement. All of these factors make the catalytic Claisen rearrangement a particularly challenging reaction.

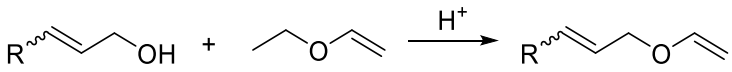
2.1.1. Synthesis of allyl vinyl ethers

The reactants can be made from allylic alcohols by mercuric ion-catalyzed exchange with ethyl vinyl ether.[59] The allyl vinyl ether does not necessarily have to be isolated but is usually prepared under conditions which lead to its rearrangement. The simplest of all Claisen rearrangements, the conversion of allyl vinyl ether to 4-pentenal, typifies this process (Scheme 47).



Scheme 47. In situ formation of allyl vinyl ether followed by Claisen rearrangement.

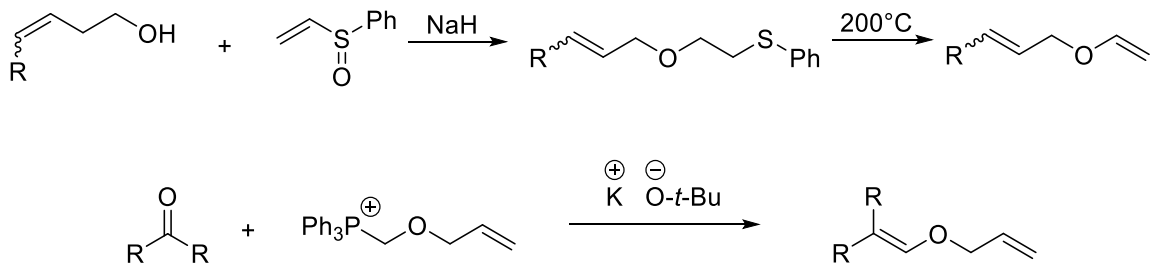
Acid catalyzed cleavage can also be used to prepare the vinyl ethers (Scheme 48):



Scheme 48. Preparation of allyl vinyl ethers through acid catalyzed cleavage.

Allyl vinyl ethers can also be generated by thermal elimination reactions. For example, base-catalyzed conjugate addition of allyl alcohols to phenyl vinyl sulfone generates 2-(phenylsulfinyl)ethyl ethers, which can undergo elimination at 200°C, and it is at this temperature that the [3,3] rearrangement proceeds. Allyl vinyl ethers have also been

prepared by Wittig reactions using ylides generated from allyloxymethylphosphonium salts (Scheme 49).

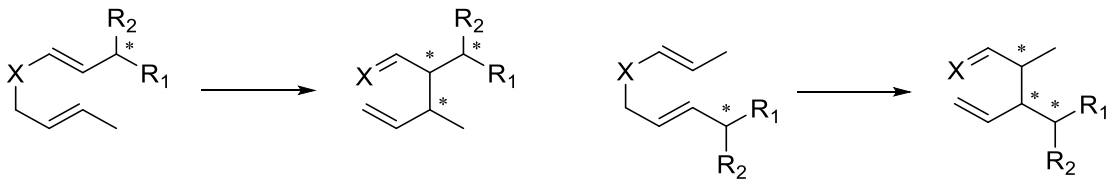


Scheme 49. Preparation of allyl vinyl ethers through the Wittig reaction.

2.1.2. Asymmetric Claisen rearrangement

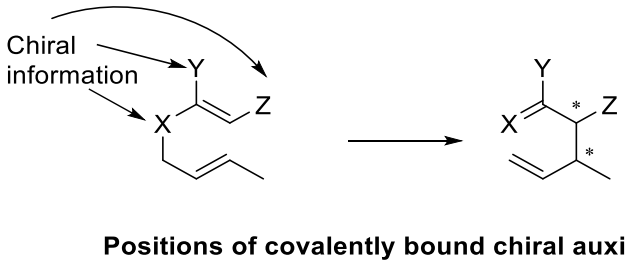
In order to make chiral Claisen rearrangement products via an asymmetric route several possibilities exist. If no external asymmetric induction is applied, the two separate enantiomers can be separated via resolution but this obviously suffers from the disadvantage of losing 50% of the unwanted enantiomer, a highly undesired outcome. The first possibility is to transfer chirality from either the allylic or vinylic fragment of the allyl vinyl ether to the chiral carbon through a complete [1,3]-chirality transfer (remote stereocontrol), although other positions in the allyl vinyl ether substrate have also be used to transfer the chirality. Alternatively, more than one chiral center can be used to transfer the stereochemical information. The chiral allylic fragment can be obtained by such well known processes like the Sharpless asymmetric epoxidation[60], enantioselective reduction of carbonyl compounds[61] and enzymatic processes[62]. In the diastereoselective

reaction proceeding through remote stereocontrol the chiral center is usually present present to position one and six (Scheme 50).



Scheme 50. Diastereoselective reaction proceeding through remote stereocontrol.

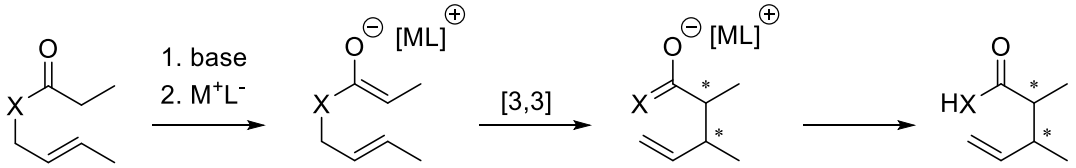
Secondly, the asymmetric induction can be achieved through the use of a chiral auxiliary. A review of the literature reveals the predominance of the chiral auxiliary in three main positions of the allyl vinyl ether (X, Y, Z; Scheme 51).



Scheme 51. Asymmetric induction through the use of a chiral auxiliary.

Thirdly, asymmetric induction can be achieved through external asymmetric induction via the use of a chiral catalyst. While there are numerous reports in the literature for

examples that use stoichiometric quantities of catalyst (vide infra), the use of *catalytic* quantities has thus far not found widespread use and is limited to certain specific types of substrate class (vide infra). The former case, where stoichiometric quantities are required has usually been used in the ester and amide enolate Claisen rearrangement. The ester or amide substrate is reacted with a strong base at low temperature, forming the allyl vinyl ether Claisen substrate in situ. Next, a Lewis acid together with the corresponding chiral ligand is added which coordinates with the oxygen of the in situ formed enolate (Scheme 52). The disadvantage here is the requirement of adding equimolar quantities of chiral Lewis acid complexes, necessary because the metal complex binds more strongly to the carbonyl product than to the starting material. Hence, the reason for the sparsity of examples in the literature for reaction that employ *catalytic* quantities of Lewis acid.

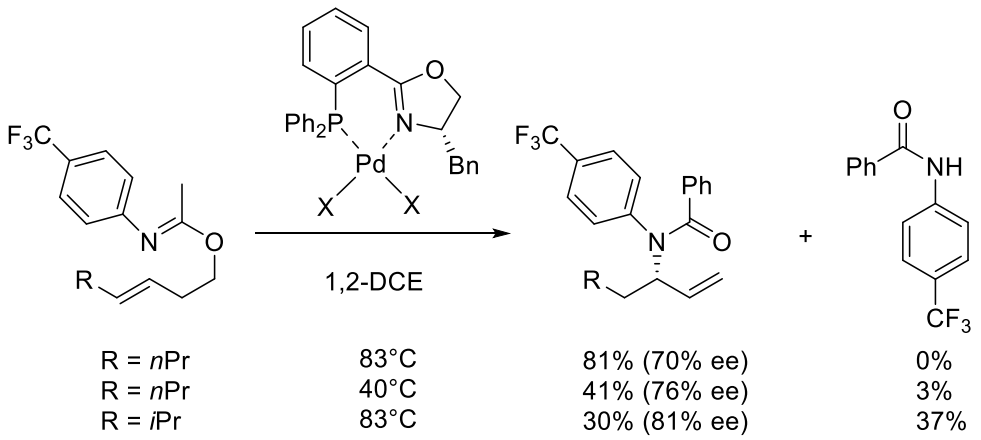


Scheme 52. Ester enolate Claisen rearrangement.

2.1.3. Asymmetric catalytic Claisen rearrangement

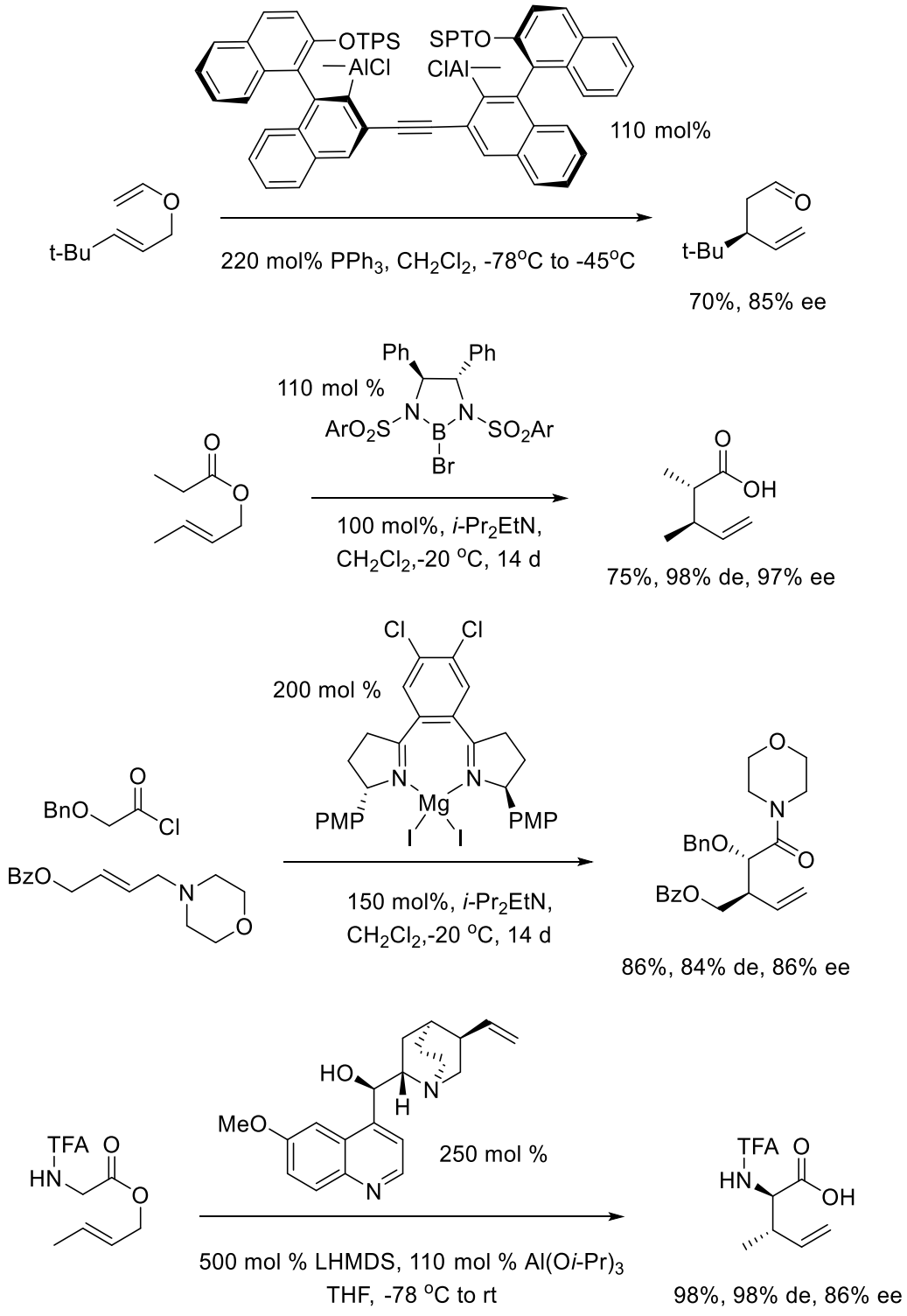
The first examples of a truly catalytic reaction were reported by Overman et al.[63] of the conversion of allyl amidates into the corresponding carbamates employing chiral palladium catalysts. Uozumi and Hayashi tested a series of chiral oxazoline substituted

ligands in the palladium(II)-catalyzed rearrangement of a *N*-(4-(trifluoromethyl)phenyl)[64] substituted allyl imidate (Scheme 53).



Scheme 53. Catalytic conversion of allyl amidates to carbamates.

It has been known for more than 20 years that achiral Al(III) Lewis acids are able to accelerate the aliphatic Claisen rearrangement, however, as mentioned previously, their applicability as catalysts is prevented by product inhibition.[65] Al (III), B(III), and Mg(II) *chiral* Lewis acid complexes have been effective for the asymmetric reaction but have not found applicability for a catalytic version of the reaction.[66] In an interesting version of the asymmetric reaction, quinine was used in greater than stoichiometric amounts as a chiral base to effect an asymmetric Ireland-Claisen rearrangement (Scheme 54).[67]



Scheme 54. Asymmetric Claisen rearrangements.

A limited number of truly catalytic *achiral* metal catalysts that accelerate the Claisen rearrangement have been reported, such as Pd(II) complexes,[68] lanthanide (III) complexes[69] and $TiCl_4$[70]. Substituents on the allyl vinyl ether have a dramatic effect on the rate of both metal promoted and metal catalyzed Claisen rearrangements. Hence, if a particular metal Lewis acid is found to effectively catalyze the Claisen rearrangement of a particular allyl vinyl ether substrate, this does not immediately qualify the metal as a catalyst for a broad range of allyl vinyl ether substrates. Therefore, substrate structure, the nature of the metal and associated ligands, as well as the structure of the product have to be adjusted carefully to achieve efficient metal catalysis and avoid side reactions such as ionization[71] and/or product inhibition of the catalyst.

The breakthrough in the development of a truly catalytic version of the Claisen rearrangement of simple allyl vinyl ethers only came as recently as 2001 when Hiersemann et al. reported the discovery that several metal triflates, such as $Cu(OTf)_2$, Lanthanide$(OTf)_3$ and $Sc(OTf)_3$, catalyzed the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers.[72] A report on the asymmetric version of the same reaction catalyzed by Cu^{2+} complexes followed soon afterwards.[73] The identification of $Cu(OTf)_2$ as an efficient catalyst led to the report of the very first asymmetric and truly catalytic Claisen rearrangement using the well known chiral copper(II) bis(oxazolines) (Figure 20).

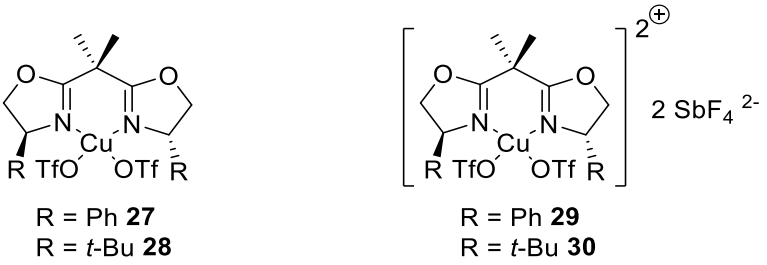
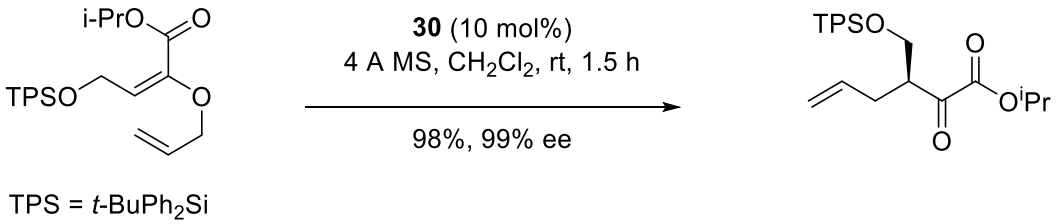


Figure 20. First catalysts for asymmetric Claisen rearrangement.

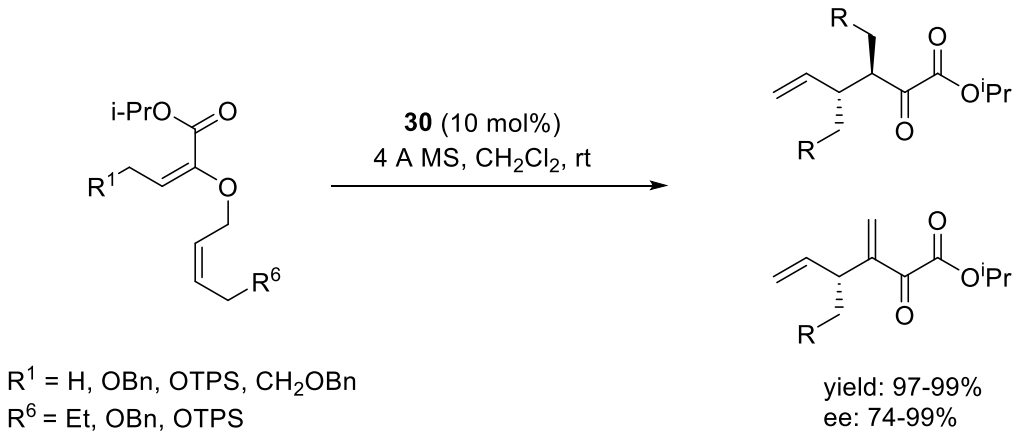
Using this approach enantiomeric excess values in the range 80-90% were reported. Further studies into the substrate scope of the Claisen rearrangement using the aforementioned 2-alkoxycarbonyl-substituted allyl vinyl ethers led to the discovery that the known bench stable [Cu{(*S*,*S*)-*t*-Bu-box}](H_2O)(SbF_6)$_2$ (Figure 20) complex combines efficient enantioface-differentiating capability and high Lewis acidity, proving to be a powerful catalyst for the asymmetric Claisen rearrangement (Scheme 55).



Scheme 55. Cu^{2+} Lewis acid catalyzed rearrangement with complex **30**.

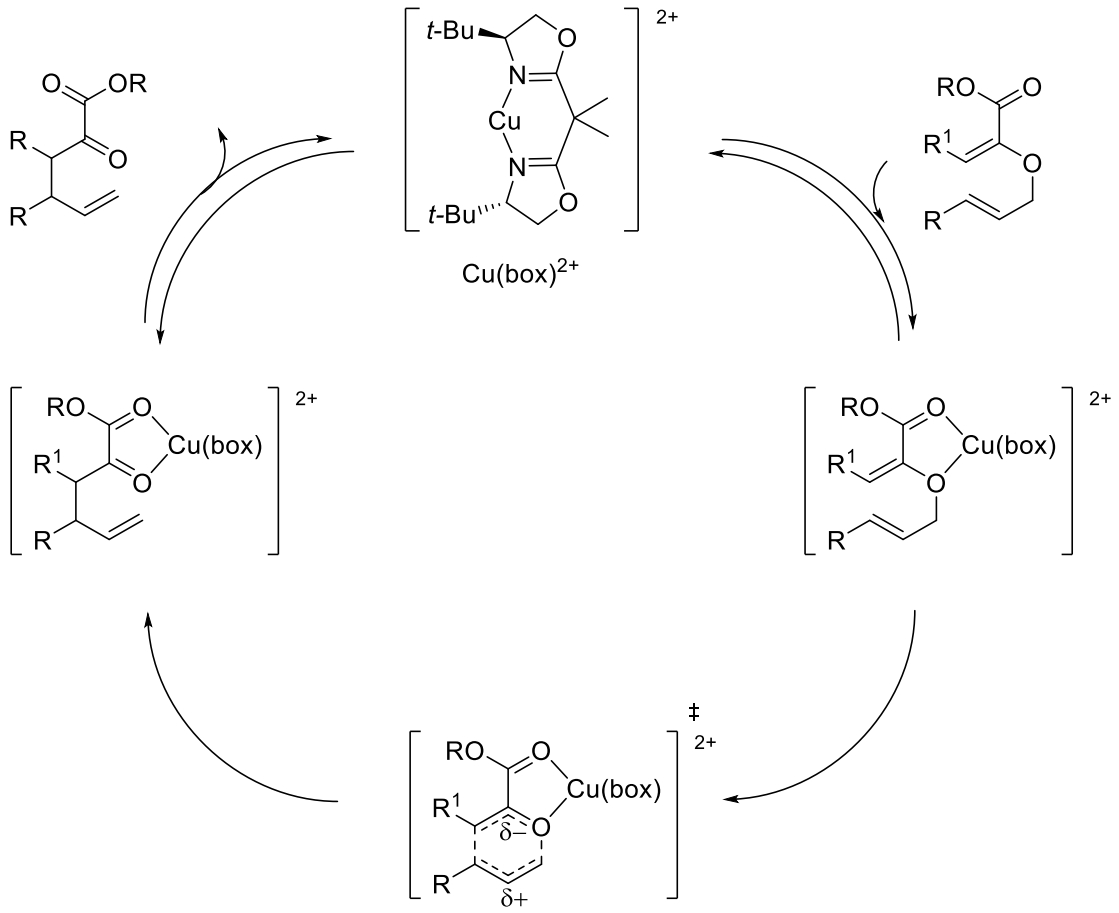
Further extension of this work led to a report of the catalytic asymmetric Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers containing two stereogenic double bonds (Scheme 56).[73b] The results clearly demonstrated a remarkable

influence of the configuration of the double bond of the allyl vinyl ether and the nature of the catalyst on the stereoselectivity of the rearrangement. Generally, use of an allyl vinyl ether containing an *E*-configured allylic double bond frequently provides decreased diastereoselectivities.



Scheme 56. Catalytic asymmetric Claisen rearrangement with catalyst **30**.

With the knowledge of earlier studies on the thermal Claisen rearrangement, the authors suggest the catalytic cycle for the Cu(box)-complex (Figure 20) catalyzed reaction (Scheme 57) proceeds via a highly polarized pericyclic transition state of considerably lower activation energy (Figure 21).



Scheme 57. Proposed cat. cycle for the (*S*,*S*)-**30**-catalyzed Claisen rearrangement.

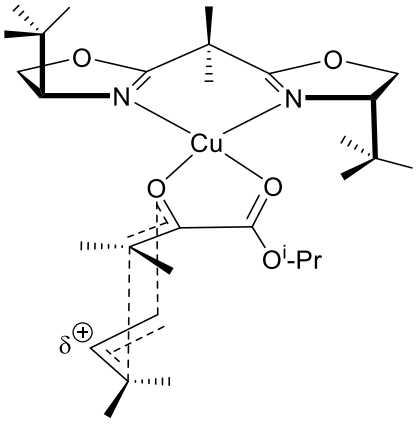
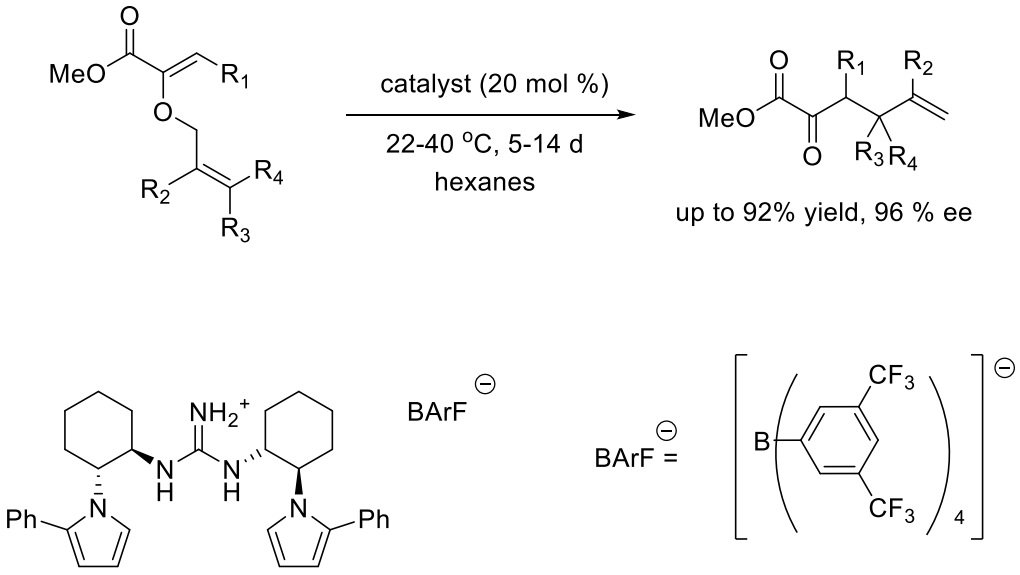


Figure 21. Transition state for the (*S*,*S*)-**30** catalyzed Claisen rearrangement.

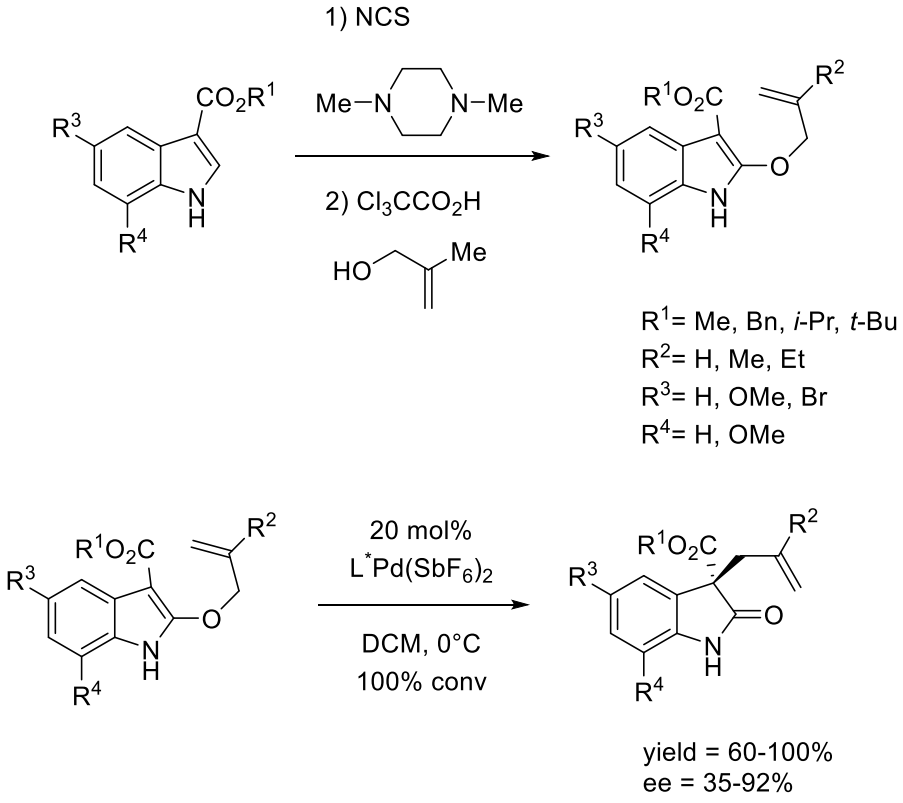
In 2008 the Jacobsen group reported on the first catalytic asymmetric Claisen rearrangement with a hydrogen-bond donor catalyst.[74] Guanidinium catalysts proved ineffective to effect asymmetric induction, whilst high enantioselectivities were obtained in the reaction carried out between 22 and 40°C over a period of several days with a guanidinium BArF catalyst (Scheme 58). Optimal rates and enantioselectivities were observed in hexanes, despite the fact that the guanidinium BArF catalyst is virtually insoluble in the solvent, use of DCM or benzene resulted in slightly diminished enantioselection, while no catalysis was observed with ethereal solvents such as Et_2O or TBME.



Scheme 58. Catalytic Claisen rearrangement with chiral guanidinium catalyst.

In the same year and virtually simultaneously with the report by Jacobsen, the Kozlowski group[75] discovered that allyloxy-indoles are another class of substrates that permit

catalytic turnover. Using palladium complexes, they reported on the first asymmetric catalytic Meerwein-Eschenmoser Claisen rearrangement, which involves the transformation of 2-amino allyl vinyl ethers to γ,δ-unsaturated amides. The formation of the intermediate hemiaminal usually requires forcing conditions, rendering the reaction unsuitable for asymmetric catalysis in ordinary cases. Indole containing Claisen subtrates were used for the reaction; despite the high activation energy typically required for dearomatization accompanying the rearrangement, the substrates were amenable to catalysis probably due to the nucleophilic nature of the C-3 carbon of the indole ring (Scheme 59). The reaction was proposed to proceed via a chair-like transition state, with both the oxygen of the allyl vinyl ether and the carbonyl oxygen of the ester moiety binding to the Pd(II) catalyst (Figure 22).



Scheme 59. Catalytic Meerwein-Eschenmoser Claisen rearrangement.

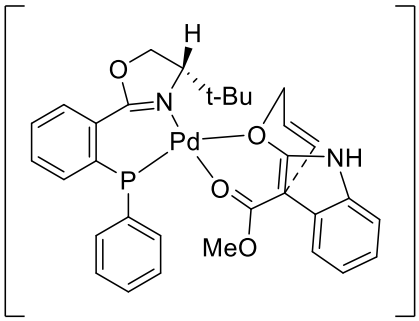
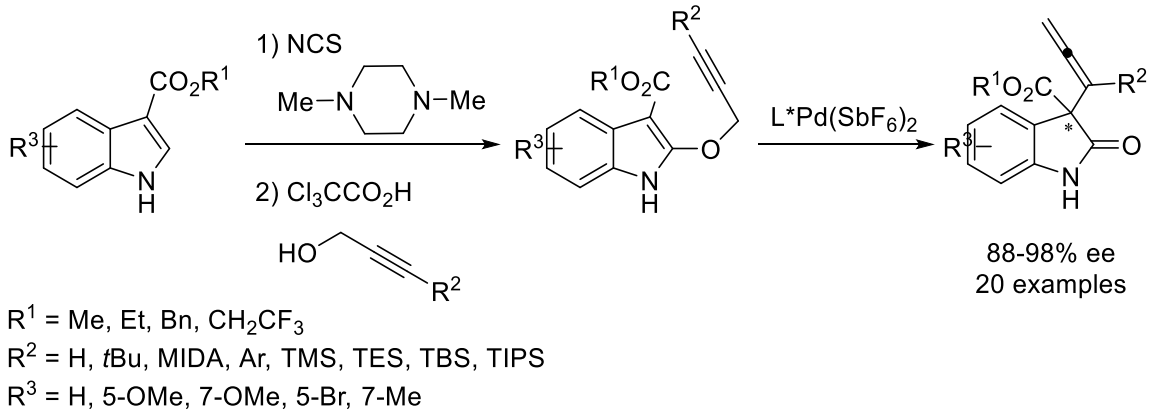


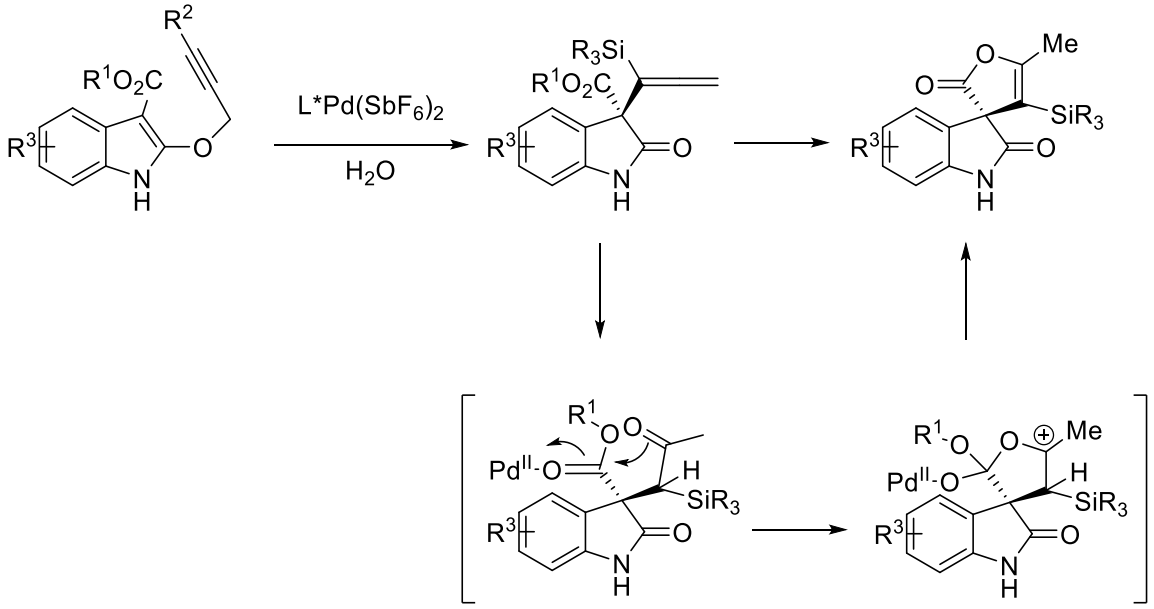
Figure 22. Transition state for the Meerwein-Eschenmoser Claisen rearrangement.

Very recently, in 2012 Marisa Kozlowski et al[76] reported the first asymmetric synthesis of allenyl oxindoles and spirooxindoles by the catalytic enantioselective Saucy-Marbet Claisen rearrangement, namely, the transformation of propargyl ethers to provide β-substituted allenyl carbonyls (Scheme 60). The reaction gives rise to two classes of chiral oxindoles containing newly formed quaternary centers: allenyl compounds and spirocyclic lactones through a tandem rearrangement (Scheme 61). The tandem reactions of silyl-substituted substrates permit rapid assembly of complex spirooxindoles, an important class of biologically active structures in one operation. The discovery provides promise for the general use of alkynyl vinyl ethers in catalytic, asymmetric rearrangement reactions, providing an alternative route to valuable allenes.



Scheme 60. Saucy–Marbet Claisen rearrangement.

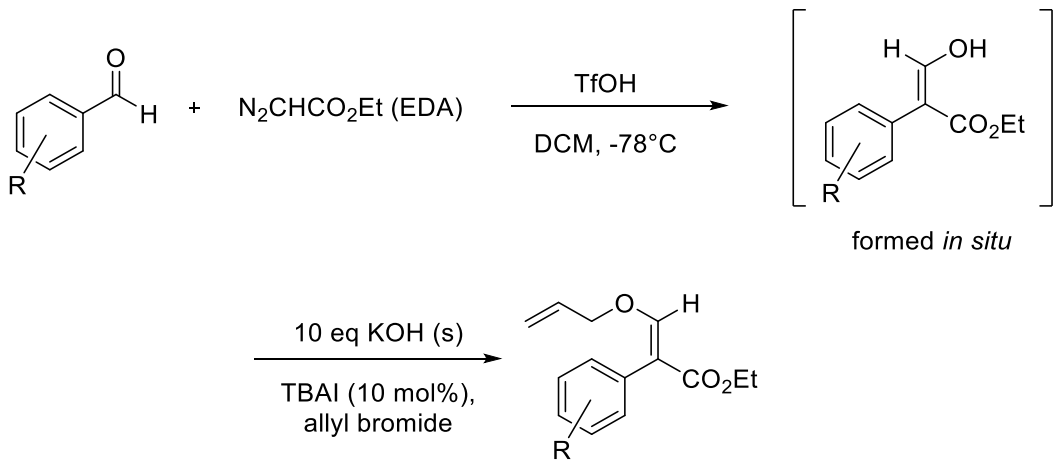
NCS=N-chlorosuccinimide, MIDA=N-methyliminodiacetic acid, TMS=trimethylsilyl, TES=triethylsilyl, TBS=tert-butylsilyl, TIPS=triisopropylsilyl.



Scheme 61. Tandem formation of a spirocyclic oxindole.

2.2. Claisen rearrangement of allyl vinyl ethers derived from 3-hydroxy aryl acrylates

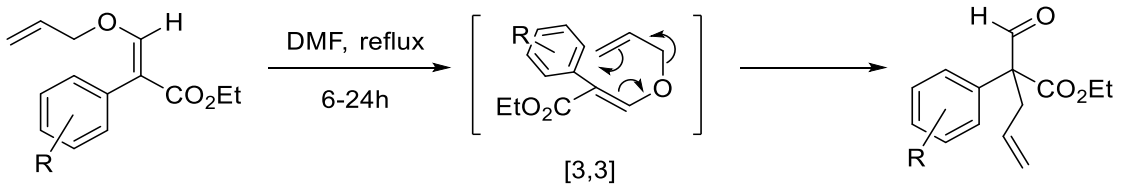
As outlined in section 1.3.4.1., it is evident that the O-alkylation of 3-hydroxy aryl acrylates is strongly favored under phase transfer catalysis conditions. Fortunately, good use can be made of these O-alkylated products (allyl vinyl ethers) by effecting an indirect C-alkylation through the Claisen rearrangement. The allyl vinyl ether Claisen substrates can be made through a practical one-pot protocol (Scheme 62) whereby the in situ formed 3-hydroxy aryl acrylate is reacted with allyl bromide to provide the O-alkylated products in mostly good yields.



Scheme 62. One-pot synthesis of O-alkylated allyl vinyl ethers.

2.2.1. Thermal Claisen rearrangement of allyl vinyl ethers derived from 3-hydroxy aryl acrylates

Thermal Claisen rearrangements are frequently carried out at high temperature with high boiling polar aprotic solvents such as DMF and DMSO.[54] Bearing this in mind, the thermal Claisen rearrangement was attempted with refluxing DMF. Gratifyingly, it was found that the reaction proceeded smoothly in good yield to furnish the corresponding C-alkylated product (Ar = Phenyl, Scheme 63). With the knowledge of this precedent, a series of O-allylated analogues were then prepared for carrying out the thermal Claisen rearrangement (Scheme 63, Table 13).[77] Unsurpringly, lower yields are observed by carrying out the [3,3] rearrangement with lower boiling solvents (xylenes) for most substrates; due to the high activation energy required to break the conjugation present in the O-allylated substrates. However, the 4-MeC_6H_4 analogue could be converted to product with refluxing xylenes with a much simplified work-up whereby the solvent is evaporated at the vapor pressure of a regular aspirator and a water bath temperature of ca. 50 °C. Generally speaking, there is a greater difference in the yield of C-allylated products than in the O-allylated substrates between different substrates. The yield of C-allylated products seems to be hindered by the presence of electron withdrawing substituents (Entries 3 and 5, Table 13).



Scheme 63. Thermal Claisen rearrangement of O-alkylated substrates.

Table 13. Formation of O-alkylated and C-alkylated products.

Entry	Ar	Yield O-allylated (a) (%)	Yield C-allylated (b) (%)
1a,b	C_6H_5	71	89
2a,b	4-MeC_6H_4	80	85
3a,b	2,4-$Cl_2C_6H_3$	82	69
4a,b	4-$MeOC_6H_4$	66	88
5a,b	4-FC_6H_4	65	55
6a,b	5-Br-2-$MeOC_6H_3$	72	90
7a,b	4-*t*-BuC_6H_4	84	91

In order to determine the stereochemistry at the double bond, a NOESY 2D experiment was carried out on the O-allylated substrate which determined *E* stereochemistry to be present (Figure 23). It is possible that unfavorable steric interactions are present in the *Z*-stereoisomer between the allyl group and the ethyl ester moiety. The *E*-product could be favored due to weak π-interactions between the p-orbitals in the vinyl moiety of the allyl group and the p-orbitals of the phenyl ring (Figure 23).

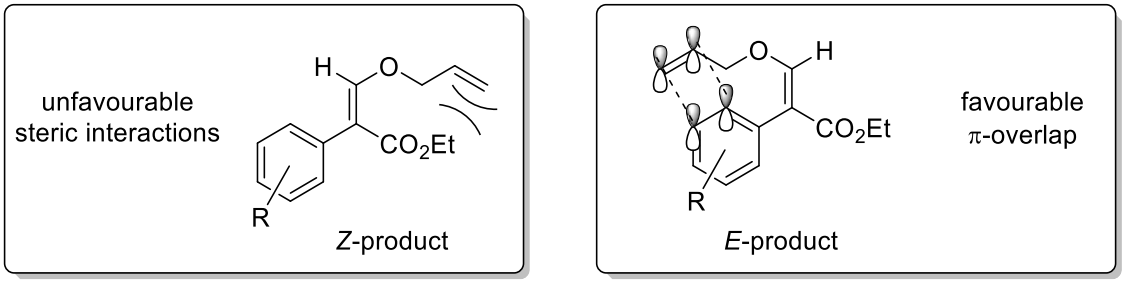
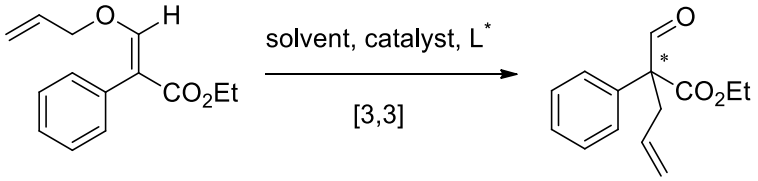


Figure 23. Steric/electronic interactions present in *E* and *Z* stereoisomers.

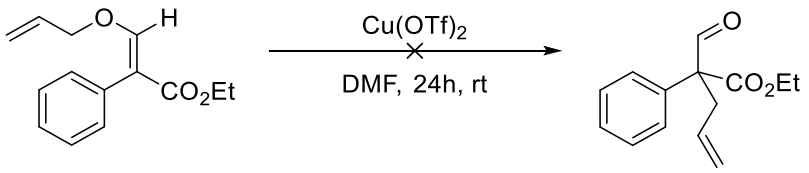
2.2.2. *Attempted catalytic Claisen rearrangement of allyl vinyl ethers derived from 3-hydroxy aryl acrylates*

With the knowledge that allyl vinyl ethers derived from 3-hydroxy aryl acrylates are viable precursors for the thermal Claisen rearrangement, we set out to investigate whether the *catalytic* asymmetric Claisen rearrangement was a viable procedure (Scheme 64).



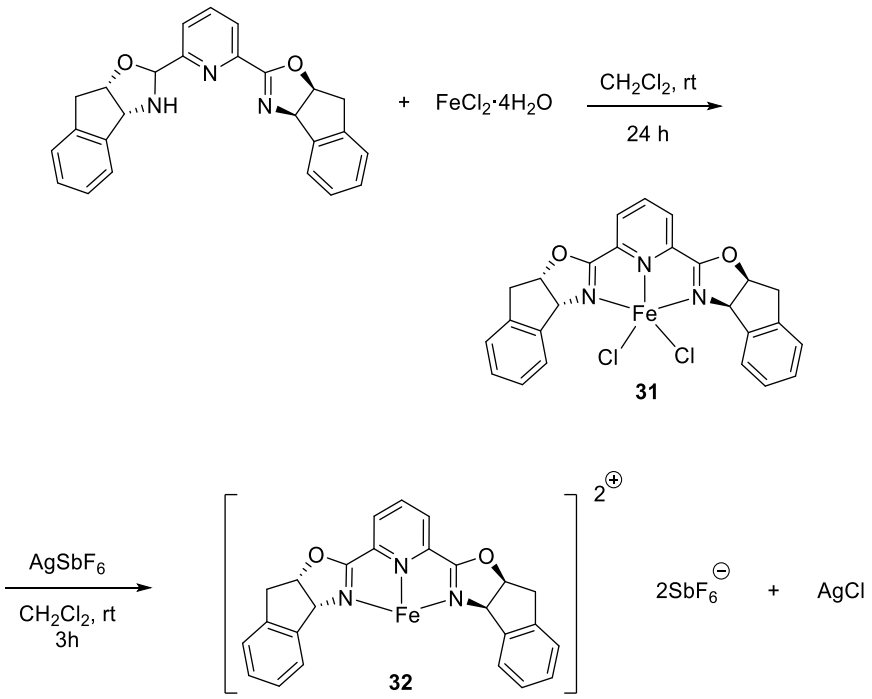
Scheme 64. Hypothetical asymmetric Claisen rearrangement of allyl vinyl ether.

Following from the reports by Hiersemann[73], we first decided to investigate the possibility of whether Cu(II) would be an efficient catalyst for the catalytic Claisen rearrangement. Our first attempt involved using allyl vinyl ether **1a** (Table 13) as Claisen substrate and $Cu(OTf)_2$ as catalyst and DMF as solvent. Unfortunately, no reaction was observed even after stirring the reaction mixture for 24 hours (Scheme 65).



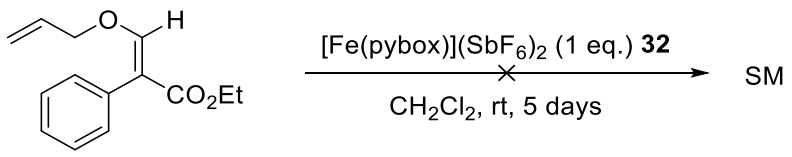
Scheme 65. Attempted Claisen rearrangement with $Cu(OTf)_2$ catalyst.

A brief foray was made into the investigation of Fe(II) as a possible Lewis acid for the catalytic Claisen rearrangement. First, we decided to make Fe(II) pybox complexes with a SbF_6^- counterion to increase the Lewis acidity of the Fe(II) metal center (Scheme 66). This involved first preparing the dark red $Fe(pybox)Cl_2$ complex **31**, followed by displacement of the chloride counterions with the more weakly coordinating SbF_6^- by the addition of $AgSbF_6$, resulting in a deep red solution of $[Fe(pybox)](SbF_6)_2$ complex **32**.



Scheme 66. Formation of $[Fe(pybox)](SbF_6)_2$ complex **32**.

Unfortunately, when the reaction was attempted with **1a** (Table 13) and 1 eq. of catalyst **32** no reaction was observed even after stirring for 5 days, possibly due to the weak Lewis acidity of the iron metal center (Scheme 67).



Scheme 67. Attempted Claisen rearrangement of **1a** (Table 13) with catalyst **32**.

Considering the report by Kozlowski[75] of the Meerwein-Eschenmoser Claisen rearrangement (transformation of 2-amino allyl vinyl ethers into γ,δ-unsaturated amides), we hypothesized that the transition state for the [3,3] rearrangement of allyl vinyl ethers derived from 3-hydroxy aryl acrylates should be remarkably similar to the one described in the report by Kozlowski (cf. Figure 22 and 24).

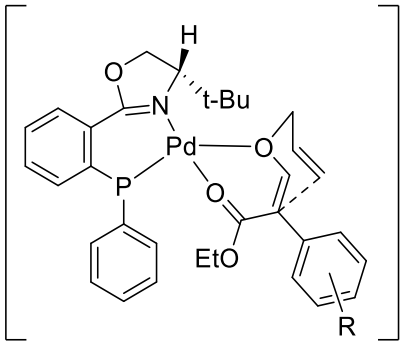
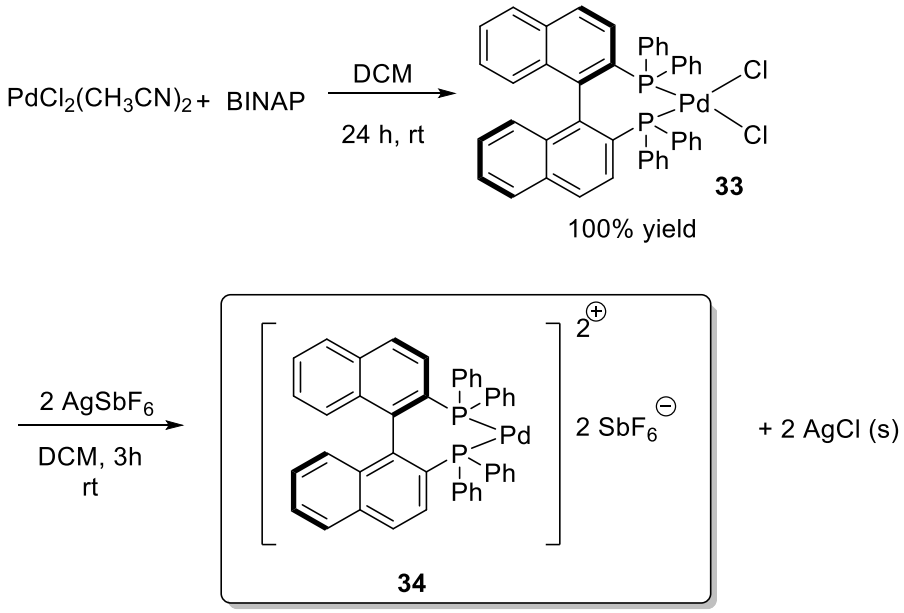
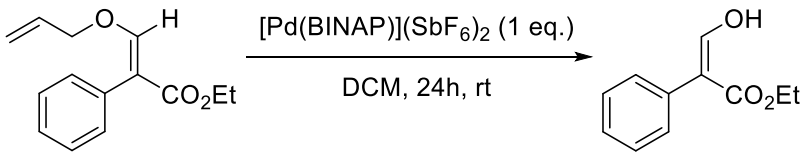


Figure 24. Proposed transition state for Claisen rearrangement of AVE's.

Because of the similarity in these two transition states, we decided to first attempt the Pd^{2+} Lewis acid catalyzed Claisen rearrangement as reported by Kozlowski.[75] To do this, we first needed to prepare the Pd^{2+} catalyst complex; a weakly coordinating counterion (SbF_6^-) was chosen to increase the Lewis acidity of the metal complex. This was achieved by displacing chloride from Pd(BINAP)Cl_2 complex **33** via a displacement reaction with $AgSbF_6$ to form the corresponding SbF_6^- complex **34**. A white AgCl precipitate ensued, which was filtered off through a PTFE filter.

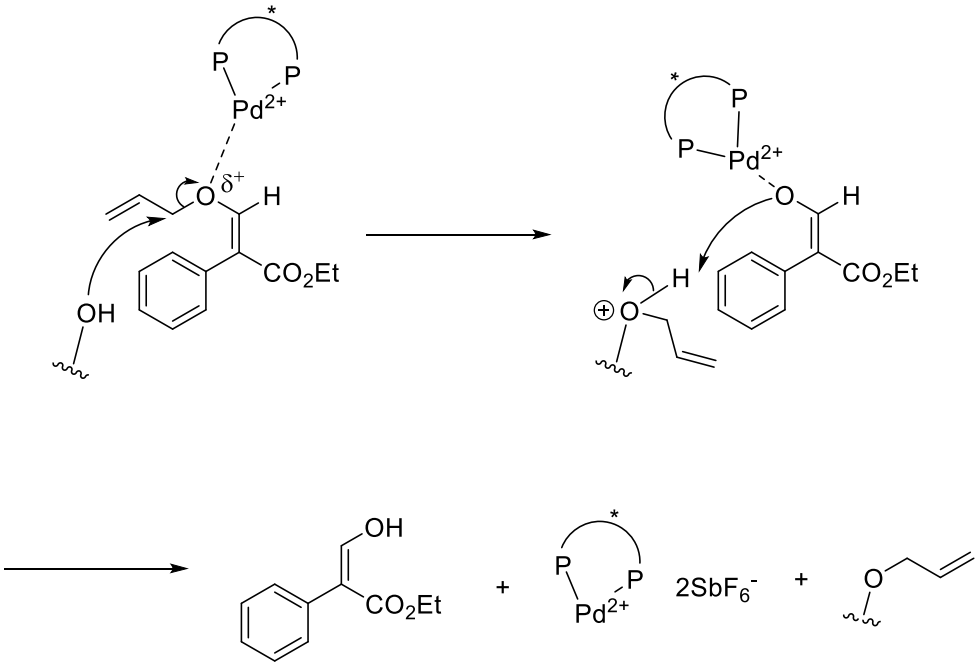


Scheme 68. Synthesis of [Pd(BINAP)]$(SbF_6)_2$ Lewis acid.



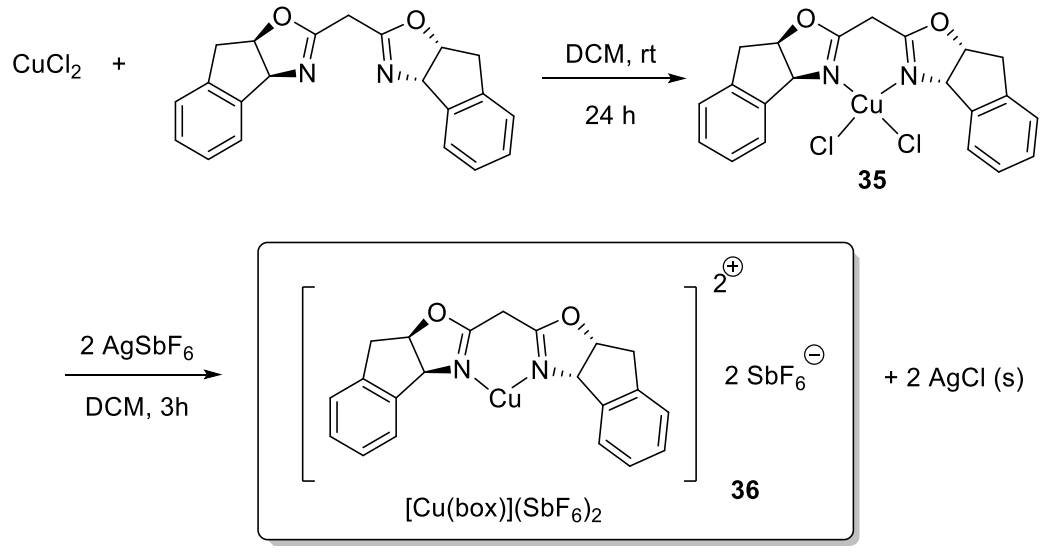
Scheme 69. Attempted $[Pd(BINAP)](SbF_6)_2$ catalyzed Claisen rearrangement.

Unfortunately, upon attempting to carry out the catalytic asymmetric Claisen rearrangement with $[Pd(BINAP)](SbF_6)_2$ it was found that cleavage of the allyl-oxygen bond took place (Scheme 69). Presumably, the oxygen of the allyl vinyl ether binds to the Pd^{2+} catalyst, and the bond between the oxygen and the allylic carbon is then cleaved with ease during the work-up when the reaction mixture is passed through a silica plug (Scheme 70).



Scheme 70. Proposed mechanism for cleavage of carbon-oxygen allylic bond.

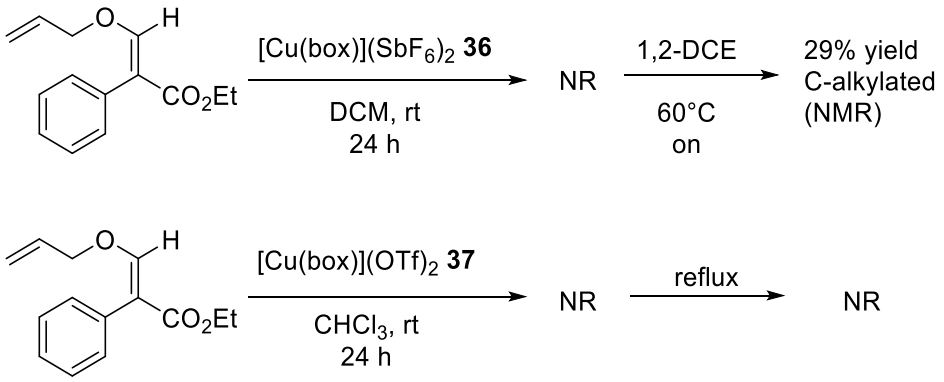
We proposed that other Lewis acids such as Cu^{2+} might circumvent the problem of the enol oxygen-allylic carbon bond cleavage. With this idea in mind, we set out to form a $Cu(box)^{2+}$ complexes (Scheme 71). The procedure for the synthesis of the $[Cu(box)](SbF_6)_2$ catalyst was essentially the same as that for the formation of the $[Pd(BINAP)](SbF_6)_2$ complex (Scheme 68), whereby the $Cu(box)Cl_2$ complex **35** is first formed, and the chlorides are then exchanged with SbF_6^- via a displacement reaction with $AgSbF_6$ to form the desired Cu^{2+} catalyst **36**.



Scheme 71. Formation of $[Cu(box)](SbF_6)_2$ Lewis acid complex.

When the Claisen rearrangement was attempted with Cu^{2+} catalyst **36**, no product was observed to have been formed at rt (Scheme 72). The solvent was then removed under N_2. dry 1,2-DCE was added to the mixture and the reaction was heated to 60 °C. A small amount of C-alkylated product (29%) was observed to have been formed through analysis

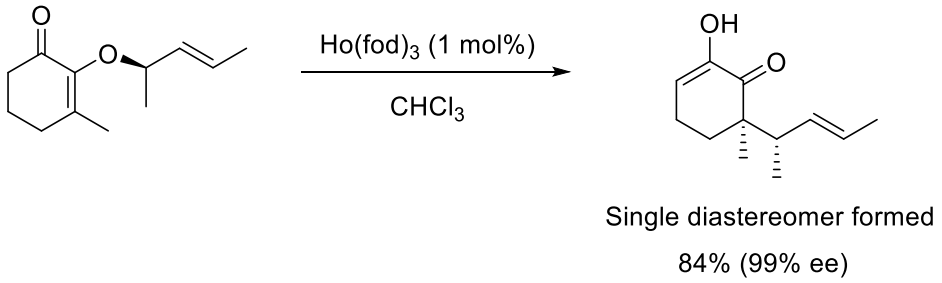
of a crude NMR of a reaction aliquot. At this temperature, the reaction mixture turned cloudy, implying that decomposition of the catalyst might have taken place at higher temperatures. The Claisen rearrangement was then attempted with $[Cu(box)](OTf)_2$ catalyst **37** (made easily by the addition of $Cu(OTf)_2$ to 1 eq. of box ligand) bearing the more strongly coordinating triflate counterion, which should decrease the Lewis acidity of the catalyst but should also decrease the possibility of enol oxygen-allylic carbon bond cleavage (Scheme 72). However, in this case no product was observed to be formed at either rt or under refluxing $CHCl_3$. The absence of formation of the cleavage product (acrylate) seems to indicate that Cu^{2+} catalyst **37** is a weaker Lewis acid than **34**. The Claisen rearrangement was also attempted using simple $Cu(OTf)_2$ with both DMF and DCM as solvent but resulted in no product formation.



Scheme 72. Attempted Claisen rearrangements using Cu^{2+} complexes **36** and **37**.

The next attempt at achieving the catalytic Claisen rearrangement was via the use of Lanthanide Lewis acids. The first report of a Lanthanide metal Lewis acid catalyzed Claisen rearrangement was by Trost et al, wherein a $Ho(fod)_3$ catalyst (1 mol%) was able

to effect a enantio- and diastereoselective rearrangement of chiral allyl vinyl ether substrates via 1,3-transfer of chirality.[69c]

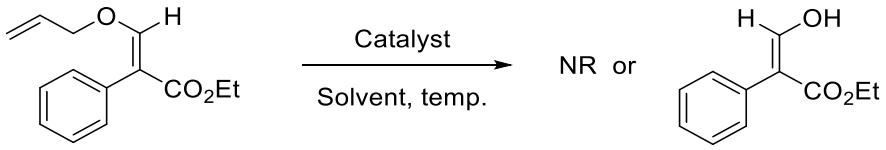


Scheme 73. Enantio- and diastereoselective Claisen rearrangement.

Given the easy access to O-allylated substrates derived from 3-hydroxy aryl acrylates, this looked like an attractive route to the formation of C-alkylation products. Moreover, an asymmetric Tsuji-Trost *O-allylation* (as compared to the usual C-alkylation) could potentially afford the chiral O-alkylated substrates necessary to afford the diastereomeric products in a enantio- and diastereoselective fashion. With this idea in mind, we set out to screen a variety of Lanthanide Lewis acids and different reaction conditions for the catalytic reaction (Table 14). Perhaps surprisingly, no product was observed in all cases. The reason for this is probably the same as that of the unreactivity of our Claisen rearrangement substrates with the aforementioned Cu^{2+} complexes, namely, that the activation energy for breaking the conjugation present in the O-allylated substrates is high enough that Lewis acids such as Cu^{2+} and Lanthanide metals are not strong enough to enable the substrate to reach the activation energy required to form the 6-membered transition state leading to C-alkylated product.

Table 14. Attempted Claisen rearrangement with Lanthanide Lewis acids.

Metal	Solvent (reflux)	Reaction time (h)
$YbCl_3 \cdot (H_2O)_6$	DCM	12
$Yb(FOD)_3$	$CHCl_3$	12
$Ho(FOD)_3$	DCE	12
$Pr(FOD)_3$	DCE	12
$Er(FOD)_3$	DCE	12
EuL_3^*	DCE	12



Scheme 74. Screening of reaction conditions for attempted Claisen rearrangement.

A more thorough screening of Lewis acids was accomplished by testing Lewis acids of greatly varying Lewis acidity (Table 15). Again, no C-alkylated product was observed to be formed in any of the screened reactions. It appears that cleavage of the enol oxygen-allylic carbon tends to take place under relatively strong Lewis acids ($BF_3 \cdot OEt_2$, $PdCl_2(CH_3CN)_2$, Table 15).

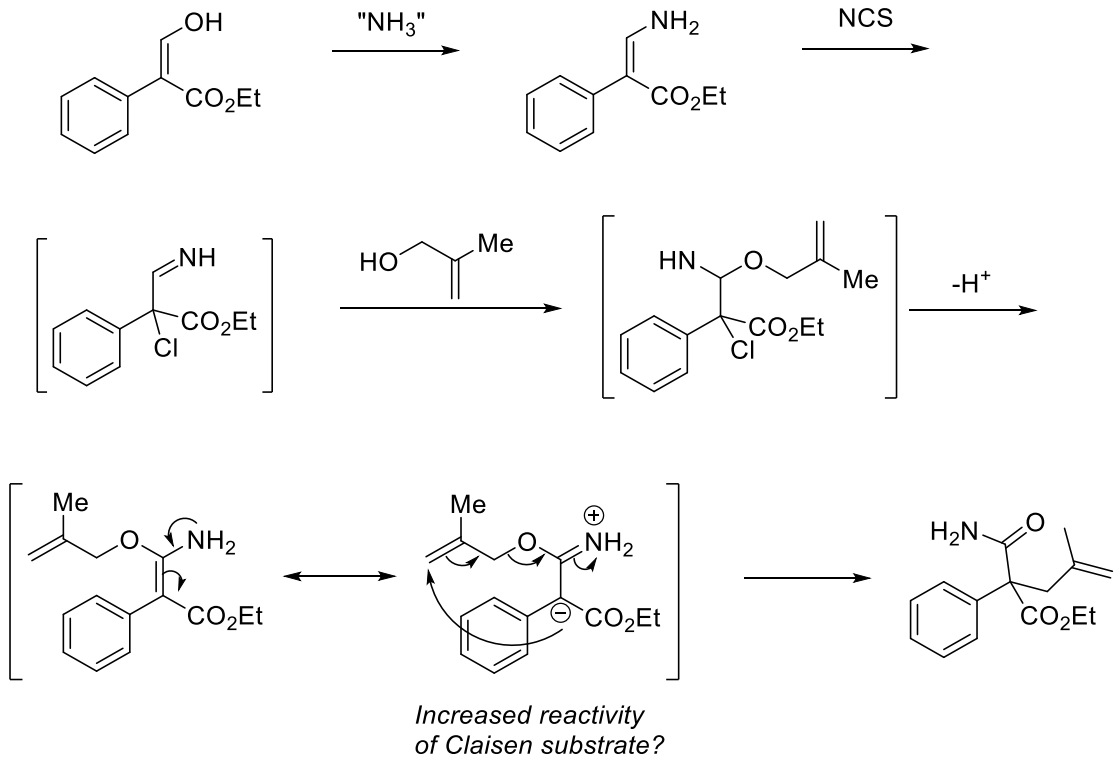
Table 15. Screening of reaction conditions for attempted Claisen rearrangement.

Metal	Ligand	Product	Temp. (°C)
$Zn(OTf)_2$	Bis-oxazoline	NR	rt
$Zn(SbF_6)_2$	Bis-oxazoline	NR	rt
$Ni(SbF_6)_2$	BINAP	NR	rt
$PdCl_2(CH_3CN)_2$	-	SM + acrylate	rt
$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	-	NR	rt to 50
$BF_3 \cdot OEt_2$	-	SM + acrylate	rt
$Fe(SbF_6)_2$	PyBox	NR	rt
$[Rh(COD)Cl]_2$	DACH-Phenyl Trost	NR	50
$(Cp^*RhCl)_2$	-	NR	rt to 50

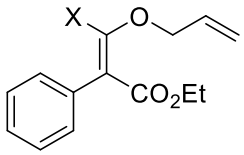
2.3. Summary

It is apparent that while the *thermal* Claisen rearrangement of O-alkylated allyl vinyl ethers derived from 3-hydroxy aryl acrylates is a feasible reaction and indeed proceeds in good yields for a variety of different analogs bearing different aryl substituents, the *catalytic* Claisen rearrangement has thus far not been possible. The catalytic reaction results in no product being formed, or for stronger Lewis acids, cleavage of the bond between the enol oxygen and the allylic carbon. Only low yields of product have been observed (29% C-alkylated) for the Claisen rearrangement with the $[Cu(box)](SbF_6)_2$ metal complex at elevated temperature (60 °C).

It is clear if an efficient reaction is to be achieved, future work may have to employ a different approach. One possible area of exploration for future work could be investigating the Meerwein-Eschenmoser-Claisen rearrangement of 2-amino allyl vinyl ethers derived from 3-hydroxy aryl acrylates. This variant of the Claisen rearrangement is particularly appealing because the main problem associated with allyl vinyl ethers derived from 3-hydroxy aryl acrylates seems to be their low reactivity, and the 2-amino group present in substrates of the Meerwein-Eschenmoser Claisen rearrangement is said to increase the rate of the [3,3] rearrangement pericyclic step.[78] The enamine could be readily accessed through the reaction of 3-hydroxy aryl acrylate with NH_3 in dry solvent or alternatively NH_4OAc (soluble in alcohols), which could then serve as a substrate for forming 2-amino allyl vinyl ethers (Scheme 75). Alternatively, the 2- position could also be substituted with other groups which have been shown to accelerate the Claisen rearrangement (Figure 25).[56a]



Scheme 75. Proposed formation of γ,δ-unsaturated amides.



X = -OSi(CH$_3$)$_3$, -CH$_3$, -CH$_2$SO$_2$Ph, -F

Figure 25. Groups at the 2-position amenable to being added or changed.

2.4. General methods and experimental

General considerations: For reactions involving refluxing DMF (Table 13) and Claisen rearrangement reactions involving Pd(II), the solvent was degassed by flushing the solvent for 30 minutes with N_2 while stirring the solvent with a magnetic stirring bar. All reactions carried out under Lewis acid catalysis were carried out with solvent dried under conventional methods and under a positive pressure of either Ar or N_2.

2.4.1. Formation of O-allylated substrates for Claisen rearrangement

O-allylated Claisen substrates (**1**-**7**, Table 13) could be prepared via a one pot protocol starting from the aromatic aldehyde by either one of the two general procedures outlined below (***Method 1*** and ***Method 2***).

2.4.2. Experimental procedures for thermal Claisen Rearrangement

Method 1 (synthesis of ethyl (E)-3-(allyloxy)-2-phenylacrylate, (1a, Table 13):

To a flask was added anhydrous DCM (8 mL), followed by $HBF_4 \cdot OEt_2$ (52 µL, 0.381 mmol) and benzaldehyde (0.386 mL, 3.8 mmol) at rt with stirring. Next, to a pressure equalizing addition funnel was added DCM (2 mL) followed by EDA (0.2 mL, 1.90 mmol). The reaction flask was allowed to cool to -78 °C and was stirred at this temperature for 30 minutes. After this time, the EDA/DCM mixture was added slowly

dropwise to the reaction flask at -78 °C. The reaction was allowed to stir at this temperature for 12 hours, and was then allowed to warm up slowly to rt, at which point 50% KOH (1.4 mL, 19.0 mmol) was added via a syringe slowly dropwise over a period of ca. 1-2 minutes, followed by TBAI (70 mg, 0.190 mmol, 10 mol%) and allyl bromide (165 μL, 1.90 mmol). The reaction mixture was allowed to stir for a further 12 hours at rt, at which point the reaction was quenched by the addition of water (15 mL). The mixture was stirred for a further 5 minutes, and the mixture was diluted with DCM (10 mL). The phases were separated, and the aqueous phase extracted with DCM (2 × 25 mL). The combined organic phases were dried over Na_2SO_4 and passed through a Celite pad (1 cm high, 4 cm diameter fritted funnel, medium porosity). The solvent was concentrated under vacuum to yield a yellow crude oil which was purified by chromatography (SiO_2, 10% EtOAc/Hex) to yield ethyl (*E*)-3-(allyloxy)-2-phenylacrylate (Entry **1**, Table 13; 269 mg, 61% yield) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.45-7.30 (m, 5H), 5.92 (m, 1H), 5.4 (d, *J* = 17.4 Hz, 1H), 5.3 (d, *J* = 10.5 Hz, 1H), 4.53 (d, *J* = 4.0 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 157.6, 132.7, 132.4, 130.2, 127.6, 126.9, 119.3, 111.9, 74.9, 60.2, 14.3. HRMS: 233.1169 [calcd. for $C_{14}H_{16}O_3$ (M+H): 233.1177].

Method 2 (synthesis of (E)-Ethyl 3-(allyloxy)-2-p-tolylacrylate; Entry 2a, Table 13):

To a flask was added anhydrous DCM (52 mL), followed by TfOH (221 μL) and *p*-tolualdehyde (1.47 mL, 12.5 mmol) at rt with stirring. The reaction mixture was cooled down to -78 °C, at which point EDA (94 wt.%, 1.14 mL, 10.4 mmol) was slowly added

dropwise via syringe. The reaction mixture was stirred at this temperature for 1 hour, and was allowed to warm up slowly to rt, at which point 50% KOH (7.8 mL, 0.104 mol) was added slowly dropwise via syringe. The mixture was stirred for 1-2 minutes and TBAI (384 mg, 1.04 mmol, 10 mol%) was then added to the reaction flask. Finally, allyl bromide (0.90 mL, 10.4 mmol) was added via syringe slowly dropwise to the reaction flask with stirring. The reaction mixture was allowed to stir at this temperature for 12 hours, at which point the mixture was quenched with sat. NH_4Cl (35 mL) and stirred vigorously for ca. 5 minutes. The layers were separated, and the aqueous layer extracted with DCM (2 × 25 mL). Combined organic extracts were washed with brine (25 mL), and dried over Na_2SO_4. The mixture was then passed through a Celite pad (1 cm high, 4 cm diameter fritted funnel, medium porosity). The solvent was concentrated under vacuum to yield a dark yellow/red crude oil which was purified by chromatography (SiO_2, 10% EtOAc/Hex) to yield (*E*)-Ethyl 3-(allyloxy)-2-p-tolylacrylate (Entry **2**, Table 13; 1.52g, 63%) yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.37–7.22 (m, 4H), 5.95 (m, 1H), 5.4 (d, *J* = 18.8 Hz, 1H), 5.35 (d, *J* = 10.5 Hz, 1H), 4.53 (d, *J* = 5.1 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 157.5, 136.5, 132.6, 129.7, 129.3, 127.7, 118.6, 111.9, 74.9, 60.2, 21.2, 14.4. HRMS: 247.1358 [calcd. for $C_{15}H_{18}O_3$ (M+H): 247.1363].

Method 3 (Preparation of O-allylated Claisen substrates (a, Table 13) directly from 3-hydroxy aryl acrylates):

As an example of a general procedure, ethyl (*Z*)-3-hydroxy-2-phenylacrylate **10** (1 mmol) was dissolved in anhydrous DCM (5 mL), followed by addition of 50% KOH (10 eq.) added

slowly at room temperature dropwise via syringe. The mixture is allowed to stir for 1-2 minutes, at which point TBAI (10 mol%) is added, followed by allyl bromide (1.2 eq.). The reaction mixture is allowed to stir for 12 hours at rt, at which point the reaction is quenched by the addition of sat. NH_4Cl. The mixture is allowed to stir vigorously for ca. 5 minutes, and the layers are then separated. The aqueous layer is extracted with DCM (2 × 25 mL), the combined organic extracts are then washed over brine (25 mL) and dried over Na_2SO_4, The solution is then passed through a Celite pad (1 cm high, 4 cm diameter fritted funnel, medium porosity), the solvent is concentrated under vacuum and the product purified by chromatography (SiO_2, 10% EtOAc/Hex) to yield **1a** (71% yield) as a yellow oil.

(E)-Ethyl 3-(allyloxy)-2-(2,4-dichlorophenyl)acrylate (3a, Table 13).

According to the general procedure in ***Method 2***, the O-alkylated compound was synthesized in 61% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 2.6 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.27–7.17 (m, 2H), 5.86 (m, 1H), 5.35 (d, *J* = 12.5 Hz, 1H), 5.3 (d, *J* = 4.4 Hz, 1H), 4.52 (d, *J* = 4.2 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 166.6, 158.7, 135.2, 133.8, 133.0, 132.1, 130.7, 130.2, 129.1, 119.0, 109.3, 75.1, 60.4, 14.2. HRMS: 301.0472 [calcd. for $C_{14}H_{14}Cl_2O_3$ (M+H): 301.0398].

(E)-Ethyl 3-(allyloxy)-2-(4-methoxyphenyl)acrylate (4a, Table 13).

According to the general procedure in ***Method 2***, the O-alkylated compound was synthesized in 50% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (s, 1H),

7.33 (m, 2H), 6.92 (m, 2H), 5.93 (m, 1H), 5.4 (d, *J* = 17.9 Hz, 1H), 5.3 (d, *J* = 10.4 Hz, 1H), 4.52 (d, *J* = 5.4 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 157.1, 132.5, 131.2, 129.5, 124.9, 118.7, 113.8, 111.5, 74.8, 60.2, 55.1, 14.3. HRMS: 263.1260 [calcd. for $C_{15}H_{18}O_4$ (M+H): 263.1283].

(E)-Ethyl 3-(allyloxy)-2-(4-fluorophenyl)acrylate (5a, Table 13).

According to the general procedure in ***Method 2***, the O-alkylated compound was synthesized in 55 % yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 4.0 Hz, 1H), 7.36 (m, 2H), 7.05 (m, 2H), 5.90 (m, 1H), 5.35 (d, *J* = 14.7 Hz, 1H), 5.3 (d, *J* = 5.4 Hz, 1H), 4.53 (d, *J* = 5.4 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) . ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 163.3, 158.2, 132.3, 131.8, 128.5, 118.9, 114.7, 111.0, 75.0, 60.3, 14.3. HRMS: 253.1237 [calcd. for $C_{14}H_{15}FO_3$ (M+H): 251.1083].

(E)-Ethyl 3-(allyloxy)-2-(5-bromo-2-methoxyphenyl)acrylate (6a, Table 13).

According to the general procedure in ***Method 2***, the O-alkylated compound was synthesized in 63% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.39–7.28 (m, 2H), 6.77 (d, *J* = 8.7 Hz, 1H), 5.93 (m, 1H), 5.32 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 9.6 Hz, 1H), 4.48 (d, *J* = 5.4 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 157.8, 156.4, 134.2, 132.4,

131.4, 124.2, 118.6, 112.4, 112.1, 108.0, 74.8, 60.1, 55.6, 14.3. HRMS: 341.0120 [calcd. for $C_{15}H_{17}BrO_4$ (M+H): 341.0388].

(E)-Ethyl 2-(4-t-butylphenyl)-3-(allyloxy)acrylate (7a, Table 13).

According to the general procedure in ***Method 2***, the O-alkylated compound was synthesized in 72 % yield as a yellow oil. HRMS: 289.1797 [calcd. for $C_{18}H_{24}O_3$ (M+H): 289.1803]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.41–7.35 (m, 4H), 5.93 (m, 1H), 5.38 (d, *J* = 18.9 Hz, 1H), 5.32 (d, *J* = 10.8 Hz, 1H), 4.54 (d, *J* = 5.4 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.36 (s, 9H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 157.8, 149.5, 132.5, 129.5, 128.3, 124.5, 118.7, 111.6, 74.9, 60.2, 34.4, 31.2, 14.3.

Synthesis of ethyl 2-formyl-2-phenylpent-4-enoate (1b, Table 13). General procedure.

(*E*)-Ethyl-3-(allyloxy)-2-arylacrylate (**1a,** Table 13; 100 mg, 0.430 mmol) was added to a flask, followed by DMF (5 mL). The solvent was degassed by flushing N_2 through the solvent for 30 minutes and was then heated under reflux for 12 hours under N_2 with the aid of an oil bath, at which point the flask was cooled to rt. The reaction mixture was then diluted with Et_2O (20 mL) and H_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and washed with brine. Residual DMF was removed by azeotropic distillation with xylenes. The crude mixture was purified by chromatography (SiO_2, 10% EtOAc/Hex) to yield **1b** (89 mg, 89% yield) as a light yellow oil. ^{1}H NMR (300 MHz,

$CDCl_3$): δ 9.95 (s, 1H), 7.44–7.23 (m, 5H), 5.76 (m, 1H), 5.13 (d, *J* = 18 Hz, 1H), 5.07 (d, *J* = 9.9 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.14 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.88 (dd, *J* = 8.1, 13.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.3, 170.6, 135.0, 132.6, 129.0, 128.5, 127.8, 119.1, 65.6, 61.6, 37.5, 14.0. HRMS: 233.1000 [calcd. for $C_{14}H_{16}O_3$ (M+H): 233.1177].

Ethyl 2-formyl-2-p-tolylpent-4-enoate (2b, Table 13).

Following the general procedure outlined above for the synthesis of **1b**, **2b** was synthesized in 85% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.28–7.12 (m, 4H), 5.75 (m, 1H), 5.15 (d, *J* = 18.3 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.12 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.88 (dd, *J* = 8.1, 13.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 196.3, 170.8, 137.9, 132.8, 130.0, 129.0, 127.4, 118.9, 65.3, 61.5, 36.5, 20.8, 14.0. HRMS: 247.1346 [calcd. for $C_{15}H_{18}O_3$ (M+H): 247.1334].

Ethyl 2-(2,4-dichlorophenyl)-2-formylpent-4-enoate (3b, Table 13).

Following the general procedure outlined above for the synthesis of **1b**, **3b** was synthesized in 69% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.32 (s, 1H), 7.72 (s, 1H), 7.44–7.28 (m, 2H), 5.75 (m, 1H), 5.2-5.1 (m, 2H), 4.25 (q, *J* = 7.1, 2H), 3.10 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.94 (dd, *J* = 7.2, 14.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 198.0, 169.9, 134.6, 134.5, 133.9, 131.1, 130.5, 127.3,

119.9, 64.0, 61.9, 37.7, 13.9. HRMS: 301.0397 [calcd. for $C_{14}H_{14}Cl_2O_3$ (M+H): 301.0398].

Ethyl 2-formyl-2-(4-methoxyphenyl)pent-4-enoate (4b, Table 13).

Following the general procedure outlined above for the synthesis of **1b**, **4b** was synthesized in 88% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.28–6.86 (m, 4H), 5.80 (m, 1H), 5.13 (d, *J* = 18.6 Hz, 1H), 5.08 (d, *J* = 9.9 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.10 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.87 (dd, *J* = 7.8, 13.8 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 170.9, 159.2, 132.7, 128.8, 126.8, 119.0, 114.4, 64.9, 61.5, 55.4, 36.5, 14.0. HRMS: 263.1284 [calcd. for $C_{15}H_{18}O_4$ (M+H): 263.1283].

Ethyl 2-(4-fluorophenyl)-2-formylpent-4-enoate (5b, Table 13).

Following the general procedure outlined above for the synthesis of **1b**, **5b** was synthesized in 55% yield as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.28–7.07 (m, 4H), 5.73 (m, 1H), 5.20-5.05 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.11 (dd, *J* = 6.6, 14.1 Hz, 1H), 2.88 (dd, *J* = 7.8, 14.1 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.0, 170.5, 160.5, 132.3, 130.7, 129.2, 116.1, 115.8, 65.0, 61.8, 36.8, 14.0. HRMS: 251.1072 [calcd. for $C_{14}H_{15}FO_3$ (M+H): 251.1083].

Ethyl 2-(5-bromo-2-methoxyphenyl)-2-formylpent-4-enoate (6b, Table 13).

Following the general procedure outlined above for the synthesis of **1b**, **6b** was synthesized in 90% yield as a yellow oil. ^{1}H NMR δ: 10.1 (s, 1H), 7.42–7.31 (m, 2H), 6.75 (d, *J* = 8.7 Hz, 1H), 5.77 (m, 1H), 5.15-5.05 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.00 (dd, *J* = 6.6, 13.8 Hz, 1H), 2.80 (dd, *J* = 7.8, 13.8 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H) . ^{13}C NMR δ: 197.8, 170.6, 155.5, 132.0, 130.8, 128.7, 128.0, 119.1, 113.4, 112.6, 68.0, 61.2, 55.7, 36.5, 14.0. HRMS: 347.0244 [calcd. for $C_{15}H_{17}BrO_4$ (M+Li): 346.9698].

Ethyl 2-(4-tert-butylphenyl)-2-formylpent-4-enoate (7b, Table 13).

Following the general procedure outlined above for the synthesis of **1b**, **6b** was synthesized in 91% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.42 (d, *J* = 6.7 Hz, 2H), 7.18 (d, *J* = 6.7 Hz, 2H), 5.90 (m, 1H), 5.15 (d, *J* = 18.9 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.15 (dd, *J* = 6.3, 14.1 Hz, 1H), 2.86 (dd, *J* = 8.1, 13.8 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2, 170.8, 151.0, 132.8, 131.8, 126.8, 126.4, 119.3, 65.2, 61.5, 36.5, 34.4, 31.1, 14.0. HRMS: 289.1809 [calcd. for $C_{18}H_{24}O_3$ (M+H): 289.1804].

2.4.3. Experimental procedures for catalytic Claisen rearrangement.

Synthesis of Fe(pybox)Cl_2 complex 31.

To a flask was added $FeCl_2 \cdot 4H_2O$ (55 mg, 0.277 mmol) followed by pybox ligand (107 mg, 0.272 mmol) and 2.5 mL of anhydrous THF. After a few minutes of stirring a bright red solution was formed, the mixture was then allowed to stir for 24 hours. After this time, the solvent was concentrated under reduced pressure and the product was washed with ice cold petroleum ether (2 × 25 mL) leaving Fe(pybox)Cl_2 **31** (130 mg, 90% yield).

Synthesis of [Fe(pybox)]$(SbF_6)_2$ complex 32.

To a flask with Fe(pybox)Cl_2 **31** (111 mg, 0.213 mmol) was added anhydrous DCM (4.3 mL). To a separate flask was added $AgSbF_6$ (147 mg, 0.427 mmol), followed by anhydrous DCM (13 mL). The $AgSbF_6$ solution was transferred to the mixture containing iron catalyst via cannula and the solution was stirred in the absence of light for 3 hours. The AgCl precipitate was filtered through a PTFE filter leaving a deep red solution of [Fe(pybox)]$(SbF_6)_2$ complex **32**. To this solution was added slowly dropwise 2.1 mL of a 0.1 M solution of allyl vinyl ether **1a**. The reaction mixture was allowed to stir for 24 hours at rt, at which time reaction progress was monitored by TLC.

Synthesis of Pd(BINAP)Cl_2 complex 33

To a 100 mL flask was added anhydrous DCM (34 mL), followed by $Pd(CH_3CN)_2Cl_2$ (280 mg, 1.08 mmol) (at this point reaction mixture turned orange in color) and *R*-BINAP (671 mg, 1.08 mmol) (at this point reaction mixture started turning yellow within a few minutes of stirring). The reaction was allowed to stir for 24 hours; after this time the solvent was concentrated under vacuum to yield Pd(BINAP)Cl_2 **33** (862 mg, 100% yield) as a bright yellow solid.

Synthesis of [Pd(BINAP)]$(SbF_6)_2$ complex 34

To a flask was added $AgSbF_6$ (148 mg, .431 mmol) which was dissolved in anhydrous DCM (15 mL). In a separate flask, complex **33** (172 mg, 0.215 mmol) was dissolved in DCM (13 mL). The flask containing the dissolved $AgSbF_6$ was transferred to the flask containing dissolved catalyst via cannula. The reaction mixture was stirred for 3 hours in the absence of light, at which point the mixture was filtered through a PTFE filter to remove AgCl precipitate, yielding a clear yellow 0.0154 M solution of complex **34**.

Attempted Claisen rearrangement reaction of 1a (Table 13) with [Pd(BINAP)]$(SbF_6)_2$ complex 34

To the clear golden yellow solution of complex **34** was added dropwise 2.15 mL of a 0.1 M solution of allyl vinyl ether **1a** (Error! Reference source not found.) dissolved in DCM.

he reaction mixture was then allowed to stir for 24 hours and after this time reaction completion was monitored by TLC analysis.

Synthesis of Cu(box)Cl_2 complex 35 and [Cu(box)]$(SbF_6)_2$ complex 36. Attempted Claisen rearrangement reaction of 1a (Table 13) with complex 36.

To a flask was added $CuCl_2$ (30 mg, 0.223 mmol) followed by the box ligand (74 mg, 0.223 mmol) and 7.4 mL of anhydrous DCM. The mixture turned from magenta/purple gradually into a green color over a period of 30 minutes and the solution was allowed to stir at rt over a period of 24 hours to form a 0.030 M solution of Cu(box)Cl_2 complex **35**. After this time, to the mixture was added $AgSbF_6$ (171 mg, 0.491 mmol) and a white AgCl precipitate started to form immediately. The mixture was allowed to stir in the absence of light for 3h, and after this time the AgCl precipitate was filtered through a PTFE filter, resulting in a clear green 0.030 M solution of [Cu(box)]$(SbF_6)_2$ complex **36**. To this solution was added dropwise a 0.1 M solution of allyl vinyl ether **1a** (Table 13) dissolved in DCM (2.2 mL, 0.223 mmol), and the reaction was stirred for 24 hours; after this time reaction completion was monitored by TLC analysis.

Synthesis of [Cu(box)]$(OTf)_2$ complex 37

To a flask was added $Cu(OTf)_2$ (66 mg, 0.183 mmol) followed by box ligand (60 mg, 0.183 mmol) and anhydrous $CHCl_3$ (5.7 mL). As soon as the solvent was added, the solution turned deep blue but after a few minutes of stirring turned into a clear green

solution. After stirring for 12 hours, the mixture was a light green color, and at this point 1.8 mL of a 0.1 M solution of allyl vinyl ether **1a** (Table 13) dissolved in $CHCl_3$ was added dropwise to the reaction flask and was allowed to stir for 24 hours at rt. Reaction completion was monitored by TLC analysis.

Attempted Claisen rearrangement with Lanthanide Lewis acids (Table 14)

As an example of a general procedure, to a flask was added $Yb(FOD)_3$ (56 mg, 0.0528 mmol) followed by anhydrous $CHCl_3$ (2 mL). Next was added 0.53 mL of a 0.1 M solution of the allyl vinyl ether dissolved in $CHCl_3$ and the resulting solution was allowed to stir overnight. The reaction was allowed to stir for 12 hours at rt, and at this time the reaction progress was monitored by TLC. Since no formation of product was detected, the solvent was heated to reflux with the aid of an oil bath and was stirred for a further 6 hours. After this time reaction progress was again monitored by TLC.

CHAPTER III: ASYMMETRIC SYNTHESIS OF ALDEHYDES BEARING QUATERNARY CARBON CENTERS VIA THE DECARBOXYLATIVE ASYMMETRIC ALLYLIC ALKYLATION

3.1. Introduction

The palladium catalyzed asymmetric allylic alkylation (Tsuji-Trost reaction) reaction has emerged as a powerful tool for the creation of quaternary stereocenters with high chemo-, regio-, and stereoselectivity.[79] The term "Tsuji-Trost reaction" is a generic term used to describe two reaction classes. The first class utilizes a nucleophile that is coupled intermolecularly with a Pd π-allyl complex (typically generated from allyl acetate or allyl carbonate). In the second class an allyl enol carbonate or β-keto ester forms an *in situ* generated enolate nucleophile via decarboxylation that reacts intramolecularly with the corresponding *in situ* generated Pd π-allyl complex. "Soft" nucleophiles such as malonates (whose corresponding pK_a's are < 20) are often used for attack on the *π*-allyl palladium intermediate in the intermolecular version of the reaction.

The basic mechanism involves a Pd catalyzed oxidative addition step between the allylic carbon and oxygen of the precursor to the Pd π-allyl complex, with comcommitant decarboxylation in the case of a carbonate or β-keto ester. In all cases a common electrophilic Pd π-allyl complex is formed, which can be reacted with a variety of nucleophiles.[80] Quaternary stereocenters can be formed on a prochiral nucleophilic partner or, more commonly, on the electrophilic partner.

3.1.1. Decarboxylative asymmetric allylic alkylation (DAAA)

Catalytic cross-coupling reactions have had a deep impact on the synthesis of pharmaceuticals, biologically active natural products, and materials.[81] Such reactions typically involve the oxidative addition of an aryl or alkyl halide to a metal in a low oxidation state, followed by transmetalation and reductive elimination of the desired product (Figure 26).[82]

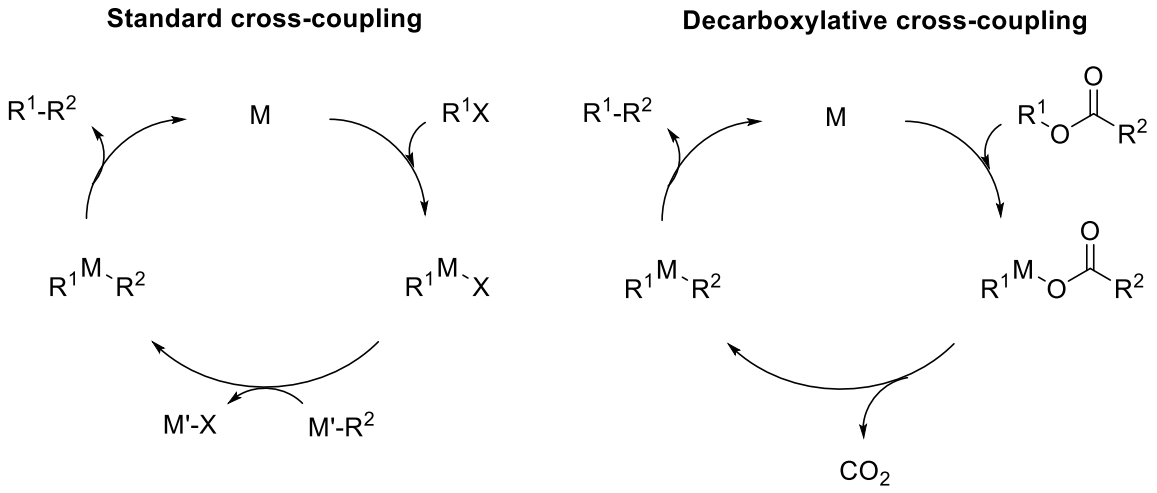


Figure 26. Standard cross-coupling versus decarboxylative coupling.

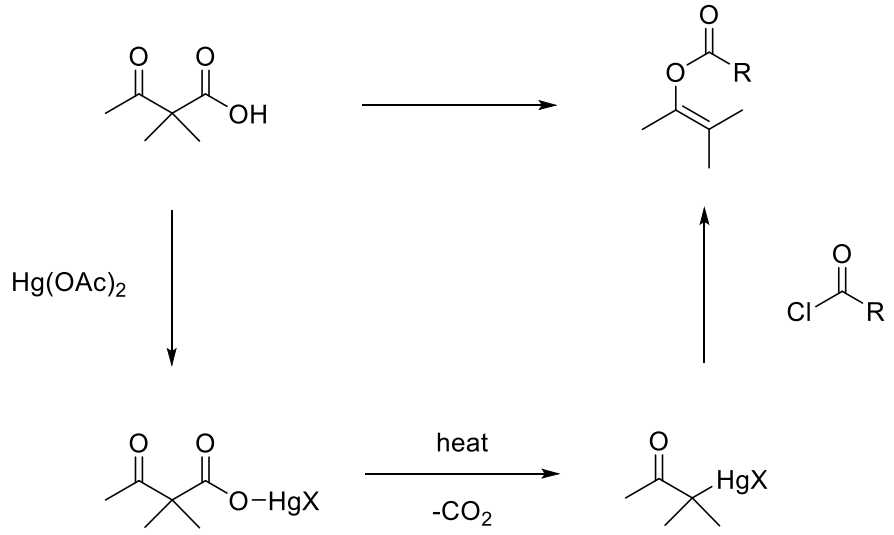
In cross-coupling reactions relatively expensive, toxic, or highly basic reagents are used in the transmetalation steps and these must be prepared from other functional precursors. Product purification is complicated by stoichiometric quantities of hazardous byproducts that are produced from the reagents required for transmetalation. Therefore, it has been recognized that it is highly desirable to develop new strategies for the generation of organometallic intermediates that utilize inexpensive substrates, proceed under mild

conditions, and are environmentally benign. One such strategy is decarboxylative coupling. Decarboxylative coupling reactions utilize decarboxylative metalation to generate organometallic intermediates that are coupled via reductive elimination (Figure 26). As compared to traditional cross-coupling methods, decarboxylative coupling has several potential advantages: (i) carboxylic acid derivatives are ubiquitous and inexpensive reactants; (ii) decarboxylation can drive the formation of reactive intermediates under neutral conditions; and (iii) the only stoichiometric byproduct is CO_2, which is non-flammable, non-toxic, and easily removed from the reaction medium. Moreover, decarboxylation allows the site-specific generation and coupling of reactive intermediates, in contrast to reactions that generate reactive intermediates by C-H activation, where regioselective formation of specific intermediates can be difficult.[83]

Enolates used for the intermolecular variant of the Tsuji-Trost reaction include Sn[84], B[85], Mg[86] and Li[87] enolates, as well as silyl enol ethers[88]. While these methods are able to utilize the power of the Tsuji-Trost reaction, they suffer from the need to pre-form the enolate in order to activate it for reaction with the Pd π-allyl complex. This typically requires subjecting the nucleophiles to stoichiometric amounts of strong base, leading to concomitant large amounts of salt waste. The ideal alternative synthesis is one which bypasses the use of strong bases and which forms easily removed waste; in addition the nucleophile would not have to be preformed, thus allowing for greater synthetic efficiency. Thus, an alternative strategy for the in-situ formation of enolates that encompasses the previously mentioned favourable characteristics (easily removed waste, no salt byproducts) is highly desirable. This can be accomplished through the

decarboxylative allylic alkylation (DAA) or for the asymmetric variant, the decarboxylative asymmetric allylic alkylation (DAAA). Indeed, the in-situ generation of nucleophiles via decarboxylation distinguishes the DAA reactions as an important subset of Tsuji-Trost reactions.

In 1950 Nesmeyanov et al. showed that, upon the application of heat, mercury enolates could be preformed in-situ by the decarboxylation of *β*-keto carboxylates[89] (Scheme 76).

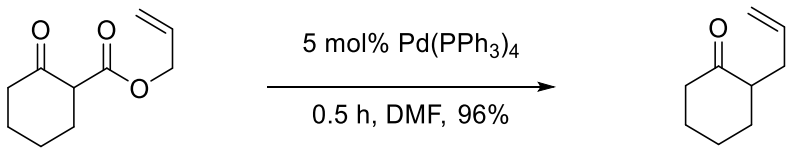


Scheme 76. Formation of mercury enolate via decarboxylation.

The enolate was next reacted with an acyl chloride, giving *O*-acylation to afford the corresponding *O*-acylated enols. While Nesmeyanov utilized stoichiometric quantities of metal for the decarboxylative acylation, his research set the stage for catalytic transformations in the 1960's using metals like Ni(II) and Mn(II), which were shown to decarboxylate malonic acids via a proposed intermediate metal enolate. The synthetic

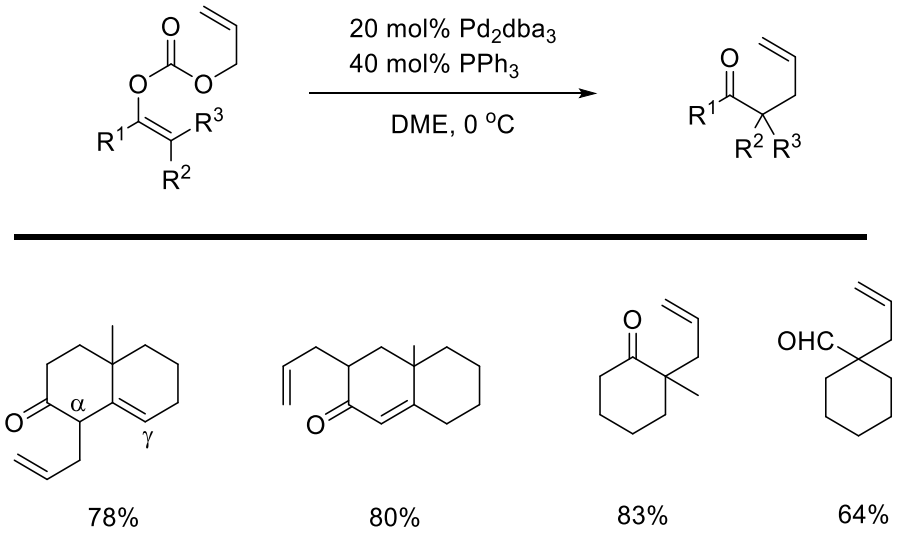
potential of these transformations was not yet realized since these reactions were carried out for further understanding of enzymatic decarboxylations.

The decarboxylative *allylation* of *β*-keto allyl esters (Scheme 77) was first accomplished almost simultaneously in 1980 by Tsuji and coworkers[90] and in the same year by Saegusa and coworkers.[91] As with previous methods, enolates are formed in-situ through decarboxylation, thus avoiding the use of preformed enolate equivalents. One advantage of the decarboxylative allylation (DcA) is the fact that the pH of the solution is formally neutral, also, both the nucleophile and the electrophile are formed in situ, moreover as these are formed in catalytic concentrations it is to be expected that functional group tolerance will be greater. Thus, decarboxylative allylation is a powerful tool at the hands of the organic chemist.



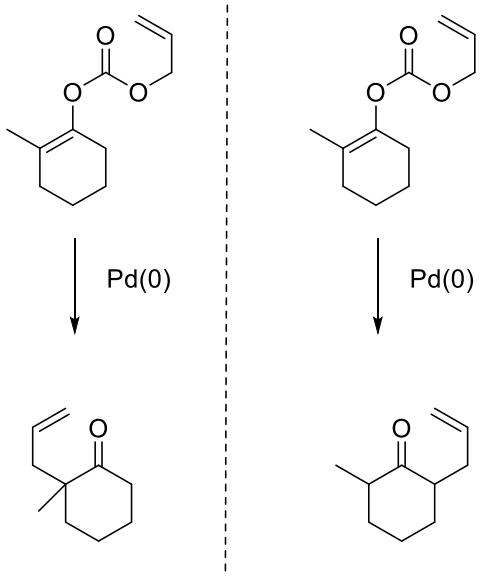
Scheme 77. DcA of cyclic β-keto ester.

Shortly after his work on the allylation of *β*-keto esters, Tsuji reported the use of allyl enol carbonates (decarboxylative allylic alkylation, DAA) to effect the same overall synthetic transformation as the DcA of *β*-keto esters (Scheme 78).[92]



Scheme 78. DcA of allyl enol carbonates.

As with the DcA of *β*-keto esters the reaction if regiospecific, but in the case of the DAA reaction, the correct regioisomer of the carbonate has to be made first in order to obtain the desired regioisomeric product (Scheme 79).



Scheme 79. Regiospecificity in the DcA of allyl enol carbonates.

However, enol carbonate precursors allow the formation of homoallylic aldehydes (Scheme 78), not possible with the use of the corresponding *β*-oxo ester, presumably due to the instability of the reactants. Tsuji showed that either *β*-keto esters or enol carbonates undergo kinetic α-allylation of the dienolate rather than the possible *γ*-allylation (Scheme 78). Moreover the mild conditions prevent isomerization of the double bond to give the α,*β*-unsaturated enone.

The allylic moiety attached to the nucleophilic carbon during the DcA reaction is of great synthetic utility, and is one of the main reasons for the great synthetic utility of the Tsuji-Trost reaction in any of its variants.

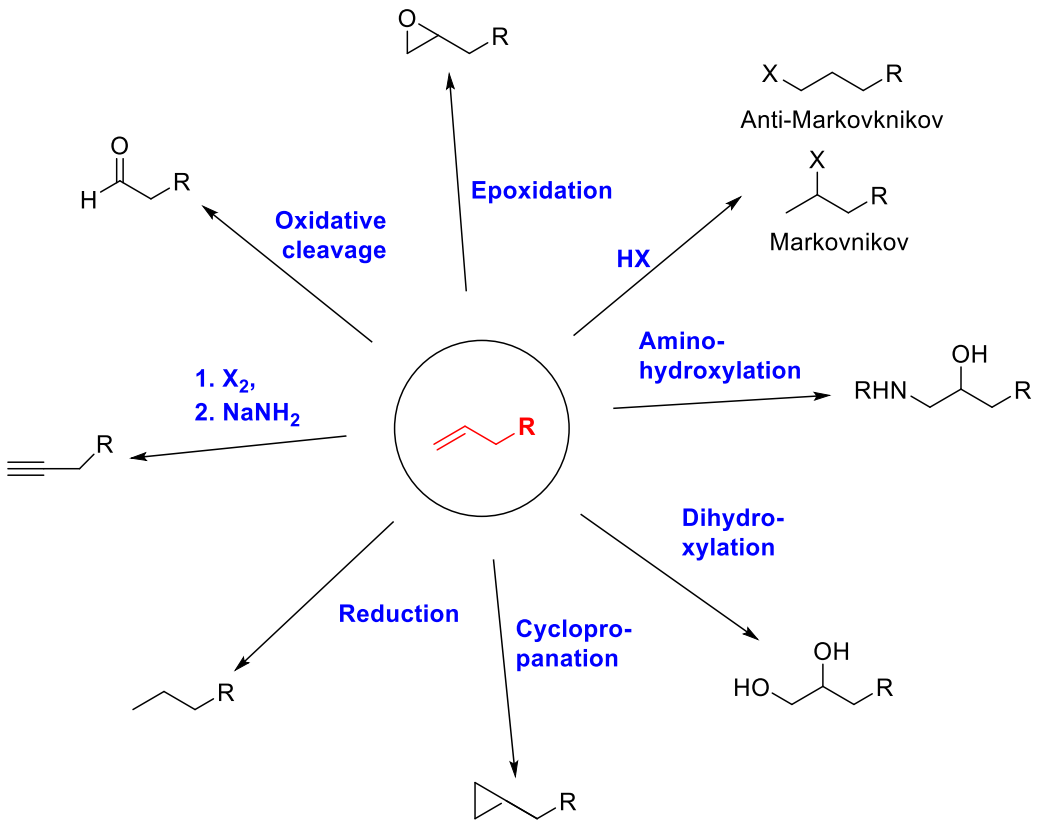
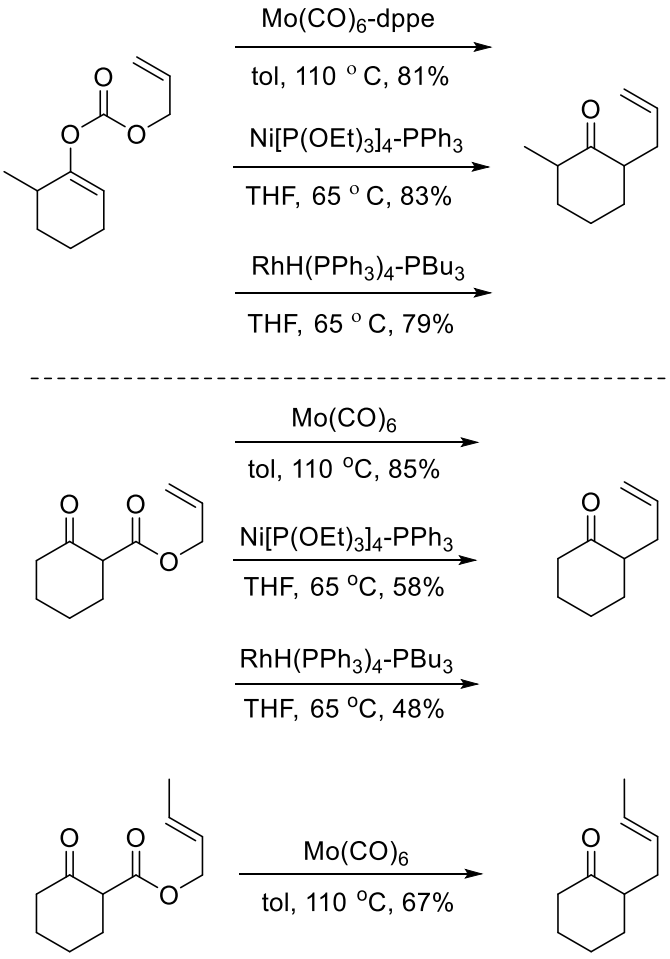


Figure 27. Possible synthetic transformations of the allyl group.

3.1.2. Catalysis with Molybdenum, Nickel and Rhodium

Although palladium based catalysts have been used for DcA reactions more widely than any other transition metals, several other metals have been successfully employed for the DcA of enolates. Tsuji et al, have demonstrated that Mo, Ni and Rh catalysts are capable carrying out the DcA of cyclic allyl enol carbonates or cyclic *β*-keto esters (Scheme 80).[93]

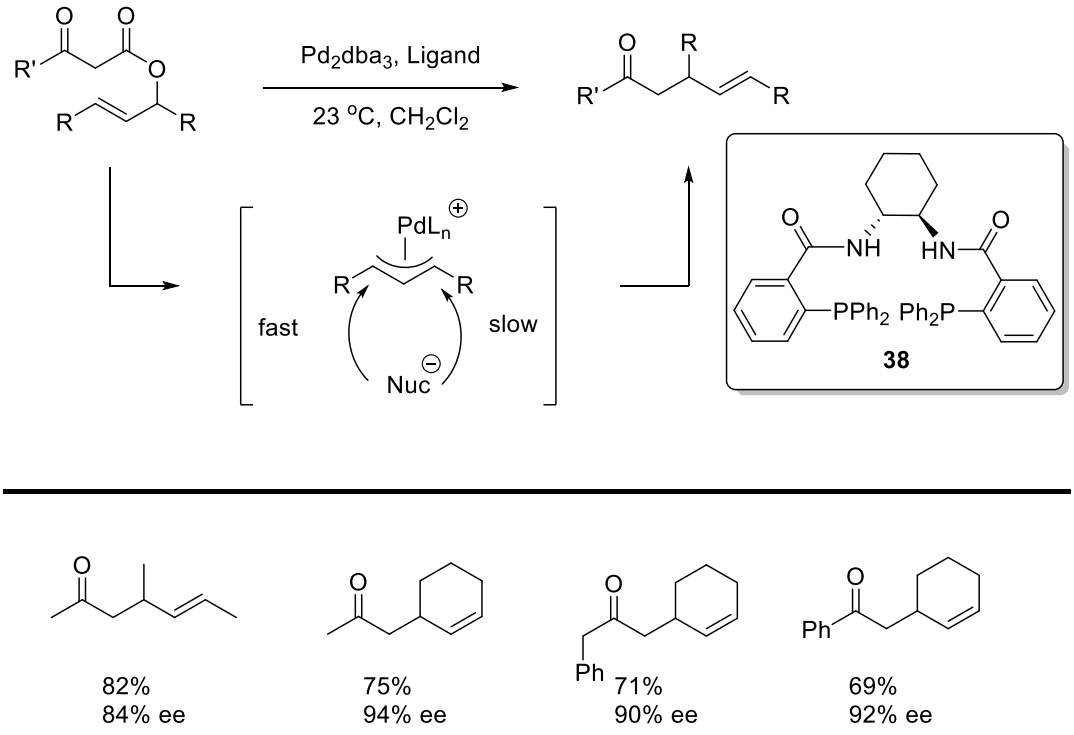


Scheme 80. DcA with Mo, Ni and Rh.

Thus far, little research has been carried out on these transformations and tt is clear from these examples that the DcA reaction is not catalysed out exclusively by Pd. Some investigation has also been carried out on the Ru catalyzed reaction.[94]

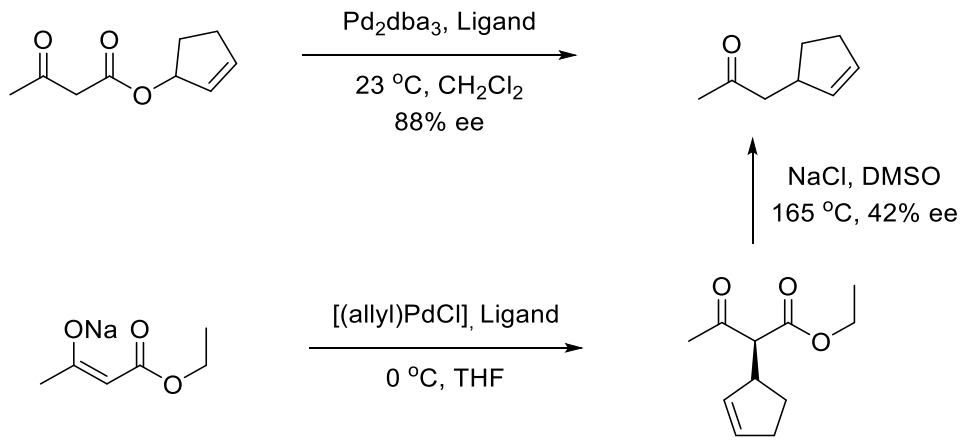
3.1.3. Asymmetric DcA of enolates

Although the first reports of the formation of allylic ketones via the the Pd-catalyzed DcA reaction took place in 1980[95] the first *enantioselective* variants did not appear until 2004 when the Trost ligand **38** was used by Burger and Tunge to effect the enantioselective DcA of *β*-keto esters.[96] In this work, the stereochemistry of the homoallylic ketone product was controlled at the *β* position.



Scheme 81. First enantioselective DcA of ketones.

In addition, by comparison with the same product derived from the Tsuji-Trost reaction with the same ligand, the enantioselectivity is higher in the DcA than that of the two-step Tsuji-Trost/decarboxylation pathway[97] (Scheme 82).



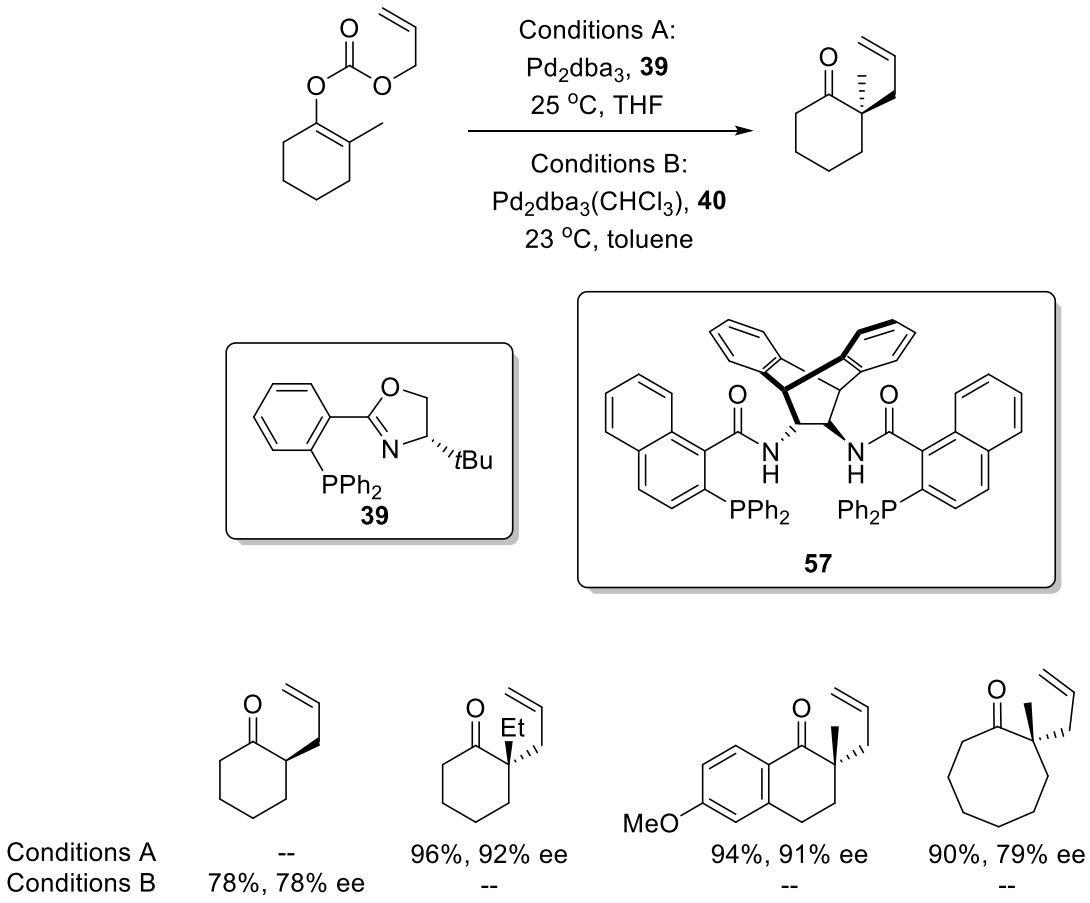
Scheme 82. Comparison of DcA and traditional two-step method.

3.1.4. Decarboxylative Asymmetric Allylic Alkylation (DAAA) of Allyl Enol Carbonates

3.1.4.1. Cyclic Stereocontrol

Behenna and Stoltz[98], and later Trost et al.[99] demonstrated the ability to control the stereochemistry at the α-position via the enantioselective decarboxylative asymmetric allylic alkylation reaction (DAAA). In these reactions, the inconvenience of having to synthesize the allyl enol carbonate precursors is mitigated by the high ee's obtained in the reaction forming cyclic ketone products. Both Stoltz and Trost demonstrated the ability to carry out the enantioselective allylation in high yield and good to excellent enantioselectivity. Stoltz's method (conditions A) was used to quaternarize the α-position,

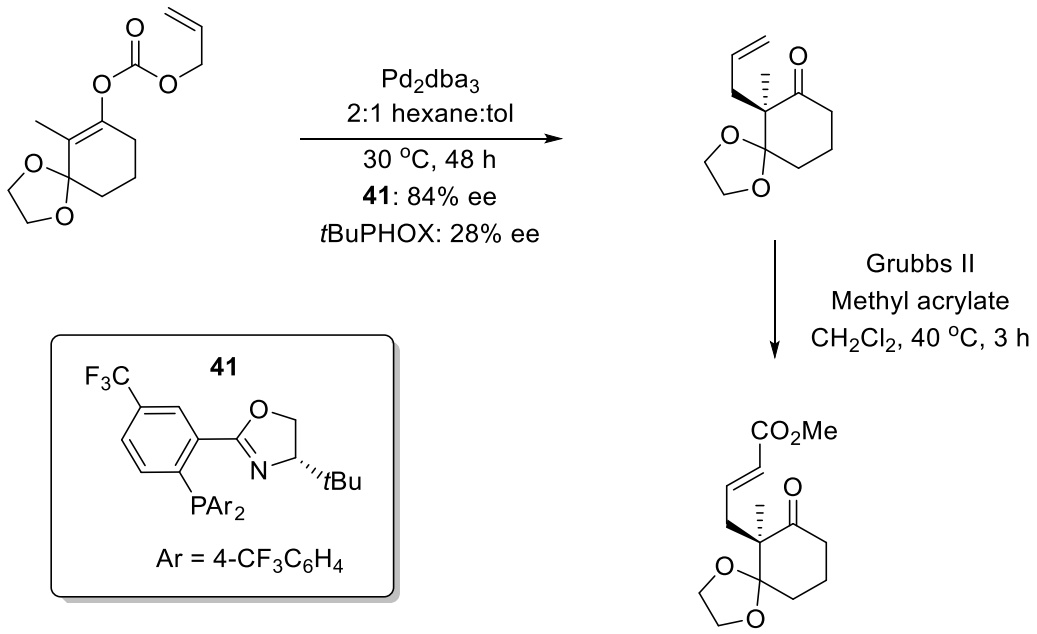
whereas Trost (conditions B) described formation of both quaternary and tertiary α-stereocenters (Scheme 83).



Scheme 83. Decarboxylative allylation of allyl enol carbonates.

While the Trost ligands and *t*-butyl PHOX ligands are the most generally applicable ligands for the decarboxylative coupling of enol carbonates, ligand modifications can have a significant influence on the enantioselectivity of DAAA reactions. An electron deficient *tert*-butyl PHOX derivative, (*S*)-**41**, has been shown to be superior to the Trost ligand **38** for the asymmetric synthesis of a protected diketone (Scheme 84).[100] The authors also reported improved ee's by using hexane-toluene mixtures, presumably due to

the presence of tighter ion pair between the metal center and the enolate in the presence of lower polarity solvents.

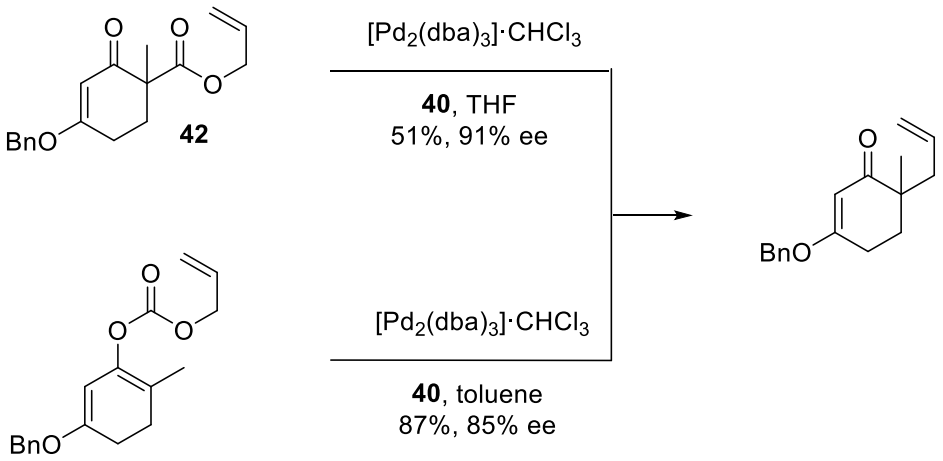


Scheme 84. Superior ee's with an electron-deficient PHOX ligand.

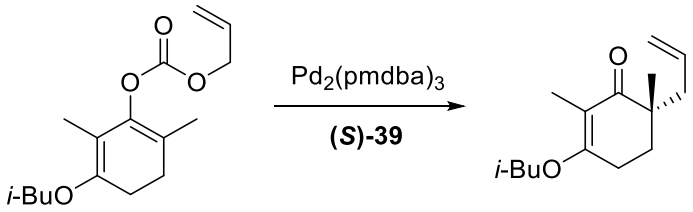
The DAAA of vinylogous ester derivatives has been carried out by both Trost[101] (Scheme 85) and Stoltz[102] (Scheme 86). Treatment of β-ketoester **42** with ANDEN-ligand **40** provided the product in high ee; however the reaction was slow and yielded product in low yield (Scheme 85), probably due to the electronics of the enolate which are akin to the malonates, known to be sluggish reactants for DcA reactions.

Schulz and Blecher developed a reaction that they termed the AREA reaction (asymmetric ring-expanding allylation).[103] In this reaction, allyl carbonates derived from

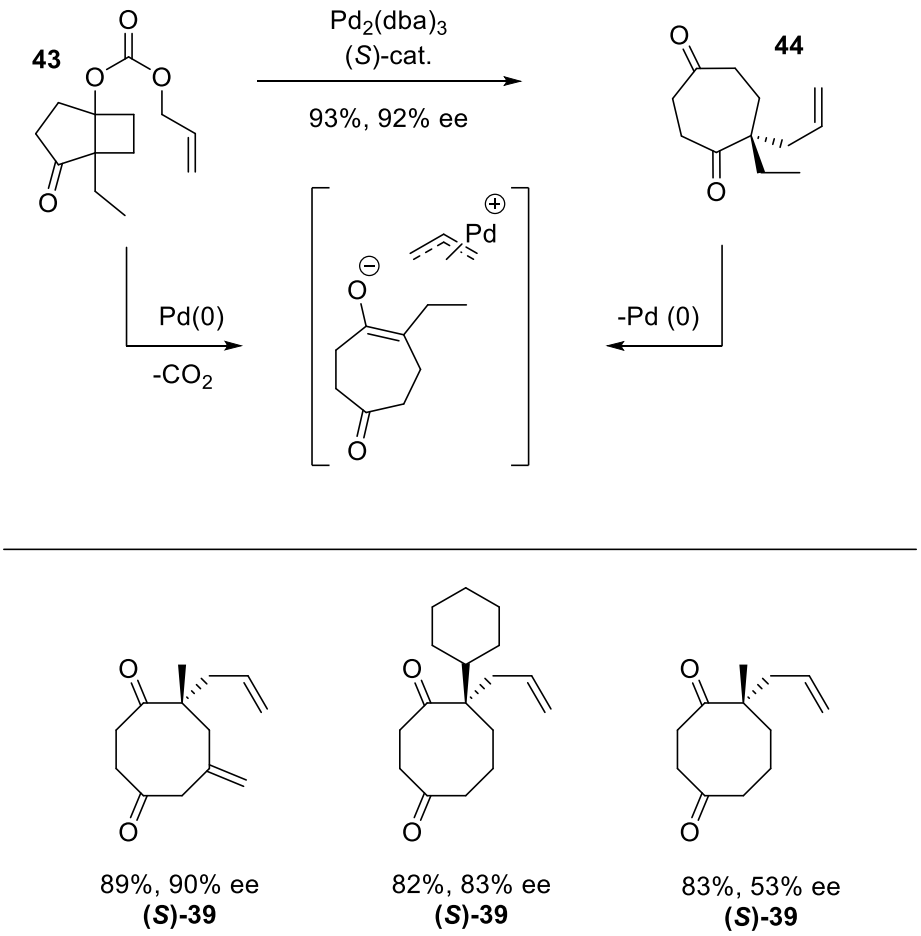
1,3-hydroxy fused bicyclic systems such as **43** (Scheme 87) undergo enantioselective Pd-catalyzed ring opening, ring expanding allylation to form tertiary and quaternary stereocenters resulting in selectively allylated cyclic 1,4-diketones **30** (Scheme 87).



Scheme 85. DcA of vinylogous ester enolates.

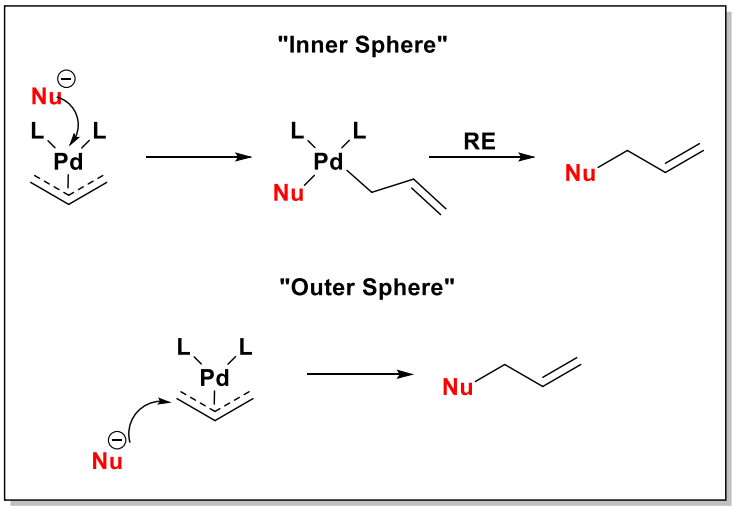


Scheme 86. Asymmetric DcA of vinylogous ester derivatives with PHOX-ligand.



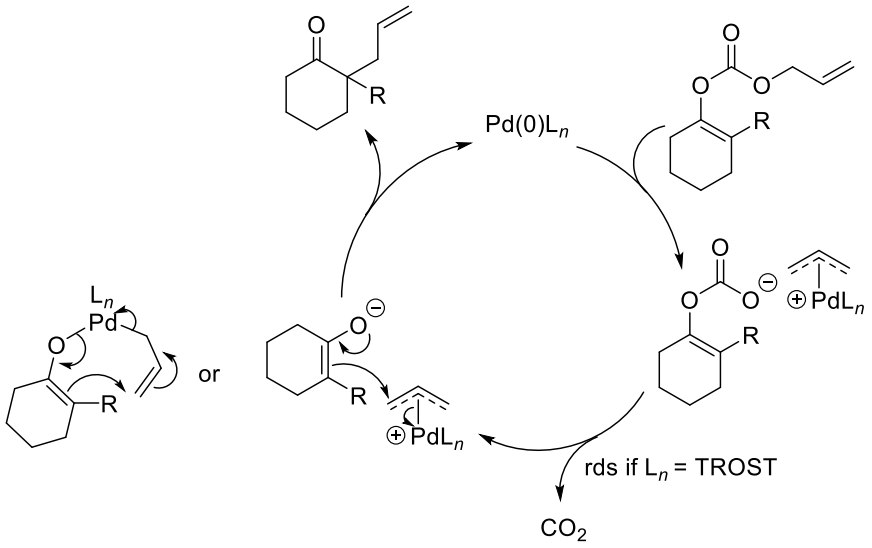
Scheme 87. Examples of the AREA reaction.

The mechanism of the DAAA reaction can occur through either outer sphere or inner sphere mechanisms (Scheme 88). From the literature, it is fairly evident that more in-depth mechanistic studies are required to ascertain the mechanism which can change among other factors by the ligand class used (Trost or Stoltz-PHOX type ligand), solvent polarity etc.



Scheme 88. Inner sphere and outer sphere mechanisms for the DAAA.

In the outer sphere mechanism attack of uncoordinated enolate occurs to the π-allyl complex; this type of mechanism is said to be favored by Trost type ligands (Scheme 89). In the inner sphere mechanism formation of a 7-membered cyclic transition state undergoes reductive elimination, and this type of mechanism is said to be favored by Stoltz type ligands.



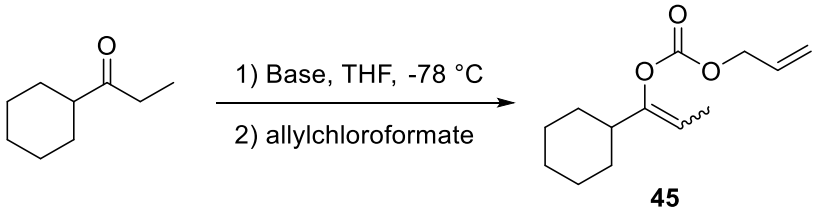
Scheme 89. Mechanism of the DAAA using Stoltz type ligands.

3.1.4.2. Acyclic Stereocontrol

The apparent mixture of enolate geometries generated via decarboxylation is a general problem for DcA reactions, however some solutions to this problem have been encountered. An enolate with a predefined geometry can be formed via the placement of appropriate functional groups that will sterically hinder either of the two stereoisomers. However, a more simple approach is via the formation of an allyl enol carbonate with a predefined geometry.

Preparation and reactivity of allyl enol carbonates

Besides intrinsic electronic and steric effects, the double bond geometry of an acyclic ketone is also controlled by the choice of base, solvent and reaction temperature.[104] Usually the preformed enolate is stable at lower temperature as long as there is no external proton source that could cause equilibration of the two enolate geometries; this enolate geometry can then be rapidly trapped at low temperature by reaction with allyl chloroformate. For example, deprotonation of cyclohexyl ethyl ketone by $(PhMe_2Si)_2NLi$ in THF at -78 °C followed by quenching the produced lithium enolate with allylchloroformate (Scheme 90) gives *Z*-**45** in 56% yield and greater than 49/1 *Z*/*E* selectivity (^{1}H NMR) (entry 1, Table 16).

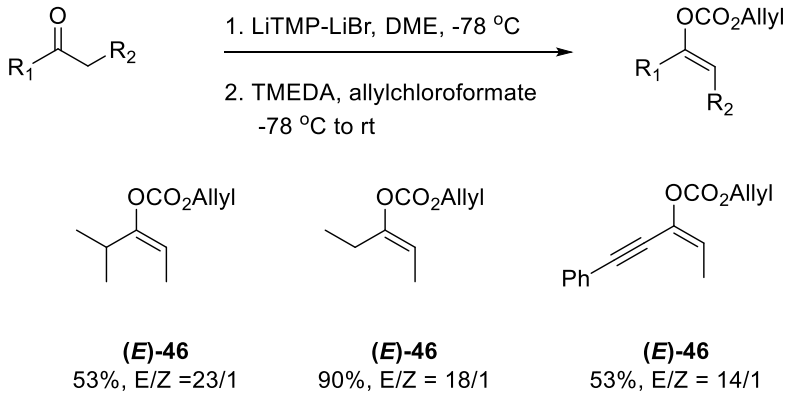


Scheme 90. Formation of acyclic allyl enol carbonates.

Table 16. Stereoselective formation of acyclic allyl enol carbonates.

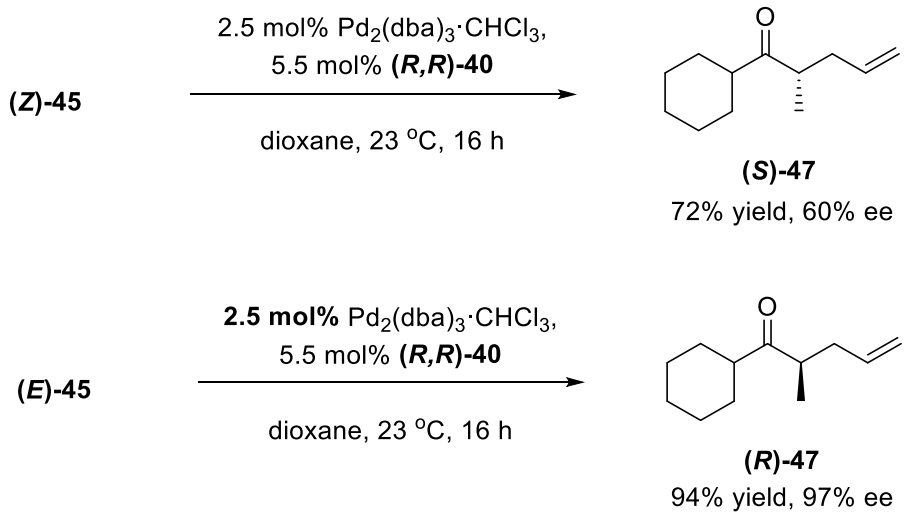
Entry	Base	Yield (%)	*Z*/*E*
1	$(PhMe_2Si)_2NLi$	56	>49/1
2	LDA, TMEDA	91	1.6/1
3	LiTMP-LiBr-TMEDA	87	1/3

In the presence of LDA/TMEDA as base, the ratio of *E*-**45** to *Z*-**45** increased to 1:1.6 (entry 2, Table 16). Switching from LDA to (LiTMP-LiBr)[105], *E*-**45** was obtained as the major isomer with a 3:1 *E*/*Z* ratio (entry 3, Table 16). Several *E*-enol carbonates were prepared in this fashion in good yields and high *E*/*Z* selectivity (Scheme 91).



Scheme 91. Preparation of *E*-enol carbonates.

Different stereoisomers (*Z*/*E*) of allyl enol carbonates turn out to have different *reactivities*, in addition to usually providing opposite enantiomers.[106] In addition, the enantiomeric excess value of each enantiomer will not be equal in magnitude. For example, when both isomers of **45** are prepared and subjected to optimized palladium-catalyzed DAAA conditions, *E*-**45** is found to be considerably more reactive than its isomer. In addition, the yield obtained from *E*-**45** is lower than that of its isomer (72% vs 94%) (Scheme 92).



Scheme 92. Differences in reactivity between opposite stereoisomers.

These results indicate the absence of an equilibrium between the *E* and *Z* enolates made possible by the presence of an external proton source (the product), as well as the π-allyl palladium reacting with the enolate from the same face. The different enantioselectivities may be interpreted by cartoon models developed by Trost (Figure 28). The *E* enolate attacking the π-allyl palladium complex from the *si* face (**A**), with both the methyl and cyclohexyl groups on the "flap" side of the complex, should be more favoured than the

enolate attacking from the *re* face (**B**), with the cyclohexyl moiety encountering substantial steric repulsion from the π-allyl palladium complex (Figure 28).

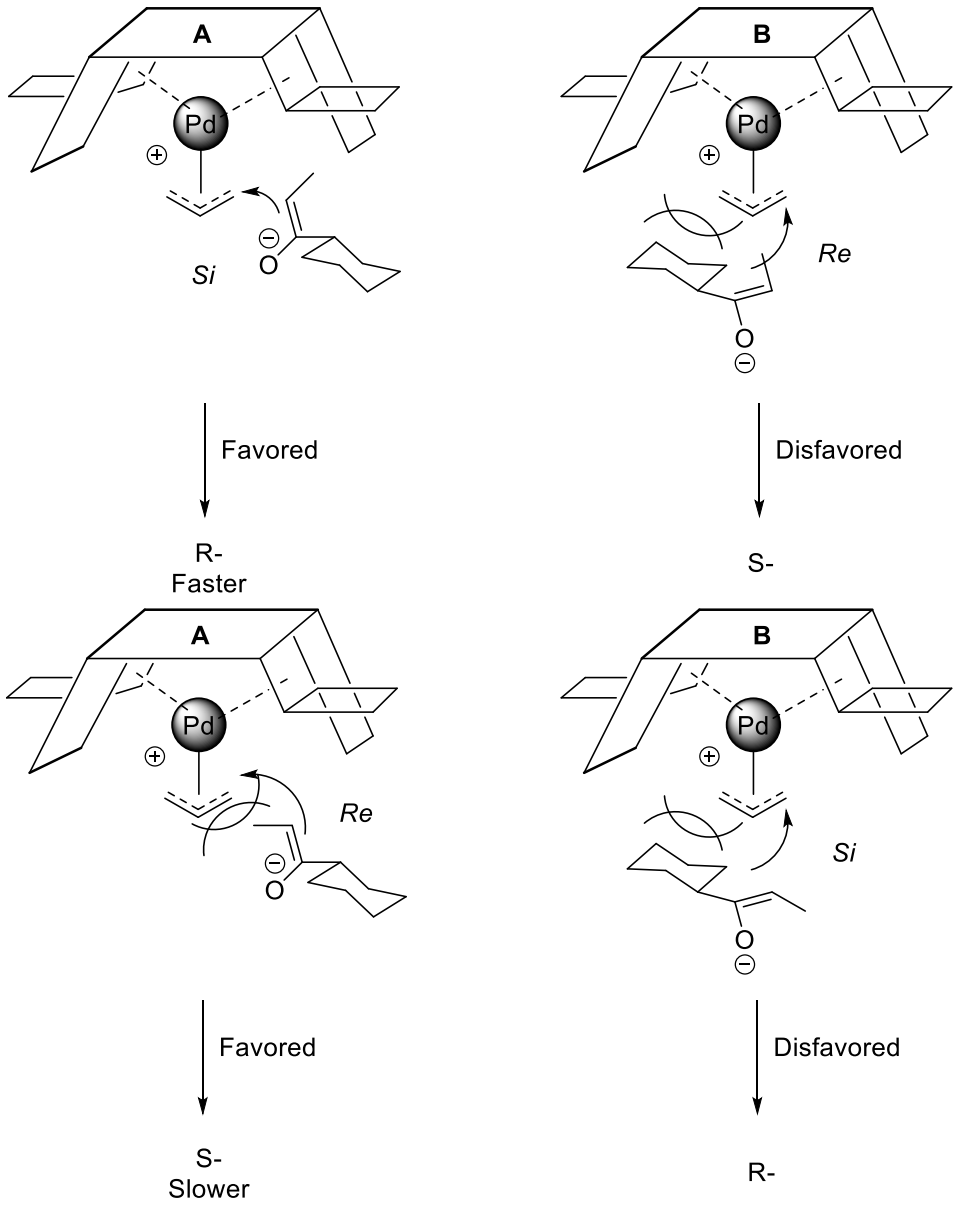
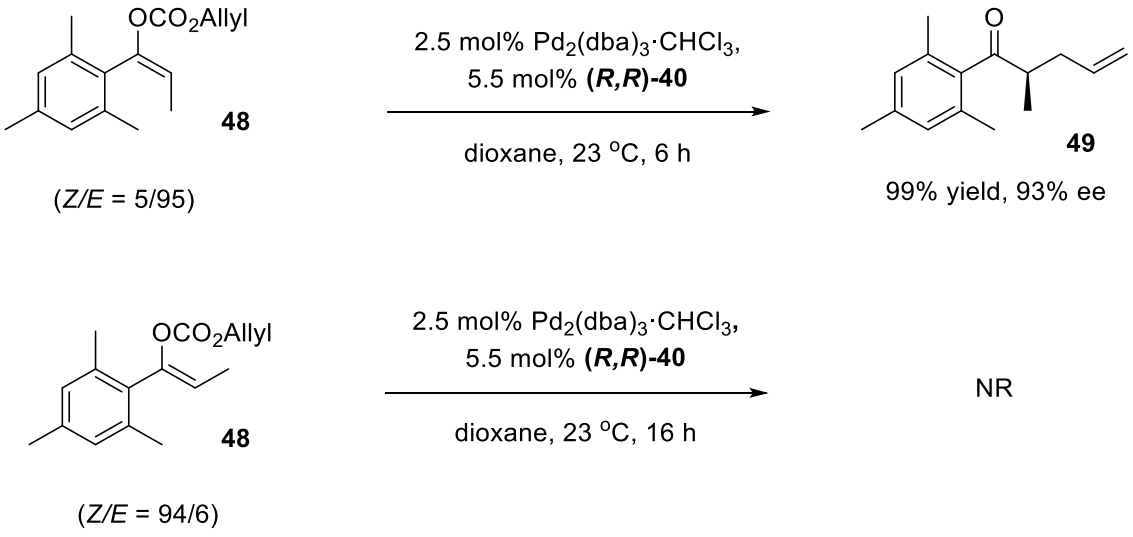


Figure 28. Cartoon models rationalizing reactivity and selectivity for *E*- and *Z*-**45**.

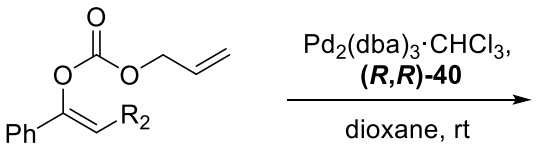
In the allylation of the *Z* enolate, no matter which side the enolate attacks from, the substrate encounters some steric repulsion with the metal complex (the methyl group in **C** and the cyclohexyl moiety in **D**). Although attack from the *re* face should be favoured, leading to the *S* stereoisomer, the difference in energy between **C** and **D** is smaller than that between **A** and **B**, thus leading to reduced enantioselectivity (Figure 28).

Likewise, the DAAA reaction of the *E* isomer **48** led to the formation of ketone **49** in excellent yield and enantioselectivity, while the *Z* isomer was completely unreactive even at rt (Scheme 93).



Scheme 93. Differences in reactivity between stereoisomers of allyl enol carbonates.

Interestingly and in start contrast, the phenyl analogue of **48** (*Z*-**50**) did prove to be reactive, the ketone product (*S*-**51**) being formed with excellent yield and enantioselectivity (Scheme 94).

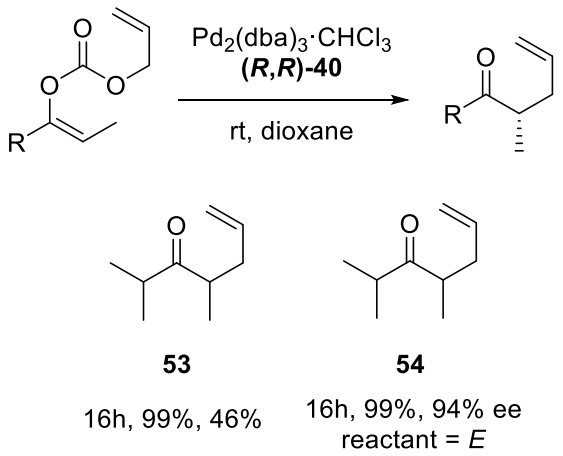


R_2	substrate (*Z*/*E*)	product	time (h)	yield	ee
Me	**50** (>98/2)	***S*-51**	3	96	94

Scheme 94. Comparison in reactivity between **48** and *Z*-**50.**

This result clearly demonstrates dramatic changes in the reactivity of allyl enol carbonates by subtle structural changes in the substrates. As expected from the model shown above (Figure 28), the *Z* isomer leads to the formation of the *S* homoallylated ketone.

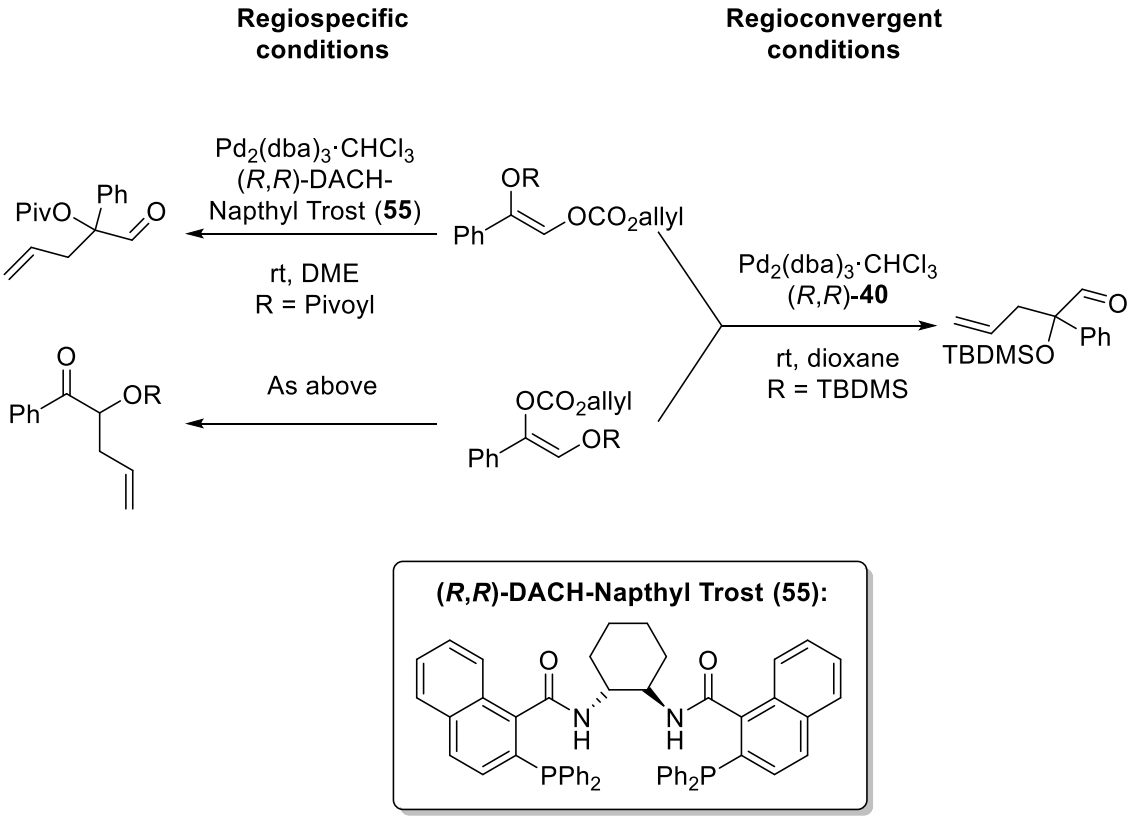
Another striking example of difference in reactivity between two different isomers is that of the DAAA reaction of carbonate substrate **52** leading to the formation of homoallylic ketones **53** and **54**; while both isomers are highly reactive, the difference in enantiomeric excess is nearly 50% (Scheme 95).[10]



Scheme 95. Difference in reactivity between stereoisomeric allyl enol carbonates.

3.1.5. Formation of homoallylic aldehydes via the DAAA

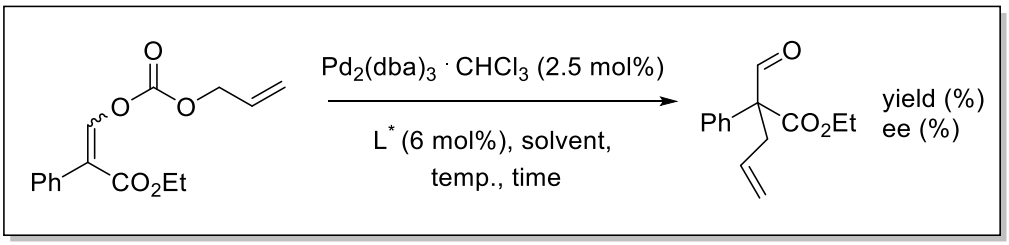
The DAAA of prochiral enolate equivalents leading to the formation of aldehyde products has received surpringly little attention in the literature thus far. The first such reaction was reported by Trost in 2007[107] wherein he described the regioconvergent generation of α-tertiary hydroxy aldehydes from protected α-hydroxy enol carbonates (Path A, Scheme 96). A later report demonstrated the dramatic effect of changing the ligand on the outcome of the reaction, so that the reaction was changed to regiospecific rather than regioconvergent (Path B, Scheme 96).[108] So far, no reaction has been reported in the literature of the DAAA reaction leading to the formation of aldehydes bearing *quaternary* carbon centers.



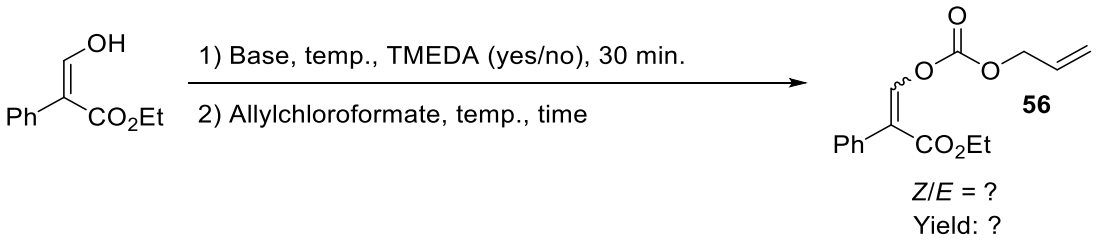
Scheme 96. First synthesis of homoallylic aldehydes via the DAAA.

3.2. Synthesis of allyl enol carbonates derived from 3-hydroxy aryl acrylates

Our first efforts towards the DAAA of allyl enol carbonates derived from 3-hydroxy aryl acrylates (Scheme 97) were directed towards forming these carbonates in a stereoselective fashion (Scheme 98), for the reasons outlined in section 3.1.4., i.e. because of potential differences in reactivity and stereoselectivity with different stereoisomers.



Scheme 97. Formation of aldehydes via the DAAA.



Scheme 98. Stereoselective synthesis of allyl enol carbonates for the DAAA.

Most commonly, the basic procedure for preparing allyl enol carbonates for the DAAA involves addition of a strong base to convert the carbonyl quantitatively to enolate, followed by addition of allylcloroformate to convert the enolate to the corresponding allyl enol carbonate. The only major variation in this procedure involves the optional addition of TMEDA, which is known to act as a chelating agent for a variety of metal ions, especially Li^+. Thus, the addition of TMEDA can potentially speed up the reaction by creating a more "naked" enolate which will be more accessible to attack by the electrophile. Interestingly, a SciFinder search resulted in no hits for structures similar to the allyl enol carbonate that we desired to form, demonstrating the novel aspect of our research. With these ideas in mind, we set out to develop a stereoselective synthesis of our desired allyl enol carbonates (Scheme 98).

Table 17. Screening of reaction conditions for formation of allyl enol carbonates.

Entry	Base	Temp. 1 (°C)	Temp. 2 (°C)	Rxn time for 2	TMEDA added?	*Z*/*E* ratio	Yield (%)
1	LiHMDS (1M in Tol.)	-15	-78 to rt	o/n	No	4:1	95
2	**LiHMDS**	**0**	**0**	**1 h**	**Yes**	**40:1**	**98[a]**
3	NaHMDS (1M in THF)	-15	-78 to rt	o/n	No	3:2	68
4	NaHMDS	0	rt	o/n	No	1:1	77
5	**NaHMDS**	**0**	**0**	**o/n**	**No**	**50:1**	**93**
6	NaHMDS	0	0	o/n	Yes	1:40	40[b]
7	NaHMDS	0	0	72 h	Yes	1:40	0[c]
8	NaHMDS	rt	rt	3 h	Yes	1:99	48[d]
9	NaHMDS	rt	rt	3 h	Yes	1:99	56[e]
10	**NaHMDS**	**rt**	rt	**40 min**	**Yes**	**1:99**	**98[f]**

a) After 72 h, large amount of product decarboxylated. b) Large amount of side product formed. c) Aliquots taken every 24h, increasing amount of product with singlet @ 7.8 ppm. d) Inverse addition (acrylate added directly to NaHMDS and TMEDA mixture). e) Quench used: NH4Cl, Distilled water. f) Rxn passed through silica plug, aq work-up avoided.

Gratifyingly, we were able to develop a stereoselective synthesis for the formation of both *E* and *Z* allyl carbonate **56**. The use of NaHMDS base proved optimal for the generation of both the *E* and *Z* stereoisomers (Entries 5 and 10, Table 17), although the formation of the *Z* stereoisomer in large *Z*/*E* ratio required the absence of addition of TMEDA (Entry 5). Interestingly, LiHMDS also yielded the *Z* stereoisomer in a large *Z*/*E* ratio but in this case with the addition of TMEDA (Entry 2). It is worth noting that all the

reactions with large *Z*/*E* ratios were conducted at or below 0 °C. Hence, it would appear that the *Z* stereoisomer is a kinetic product. As the reactions were conducted at more elevated temperatures (Entries 3 and 4), the *Z*/*E* ratio was noticeably lowered. A striking reversal in the stereoselectivity was observed by the addition of TMEDA for reactions conducted with NaHMDS (cf. Entries 5 and 6), but the greatest *Z*/*E* ratio was observed for reaction carried out at rt (Entries 8-10). Even as the problem of stereoselectively forming the allyl enol carbonates was solved, low yields were a persistent problem (Entries 6-9). For these reactions, commonly a large amount of starting material (3-hydroxy aryl acrylate) was found, together with an unidentified side product with a singlet at δ 7.8 ppm. It was proposed that the recovered starting material could be due to decarboxylation of the allyl enol carbonate taking place under the aqueous work-up conditions. To solve this problem, we developed an extremely simple work-up procedure for a reaction that used a small excess of 3-hydroxy aryl acrylate (1.2 eq) whereby the contents of the reaction flask were passed through a silica plug when reaction was complete (ca. 40 minutes). By following this method, very high yields and very clean reaction mixtures could be obtained (Entry 10) and the allyl enol carbonate product could be used without further purification for the DAAA.

In order to determine the absolute stereochemistry of the stereoisomers of carbonate **56**, a 2D NOESY experiment was carried out. In the *Z*-stereoisomer, a NOESY signal should be present between the ortho proton of the phenyl group and vinylic proton (Figure 29). Gratifyingly, we detected such a signal for carbonate *Z*-**56**, with a singlet at δ 7.56 for the vinylic proton (Figure 30). Furthermore, a weak NOESY signal might be present between

the allylic protons and the methylene protons of the ethyl ester. Such a signal was also present, allowing for a clear assignment of *Z* stereochemistry to carbonate **56** with a singlet at δ 7.56 (Figure 31).

Figure 29. Comparison of possible NOE signals in *E*- and *Z*- **56**.

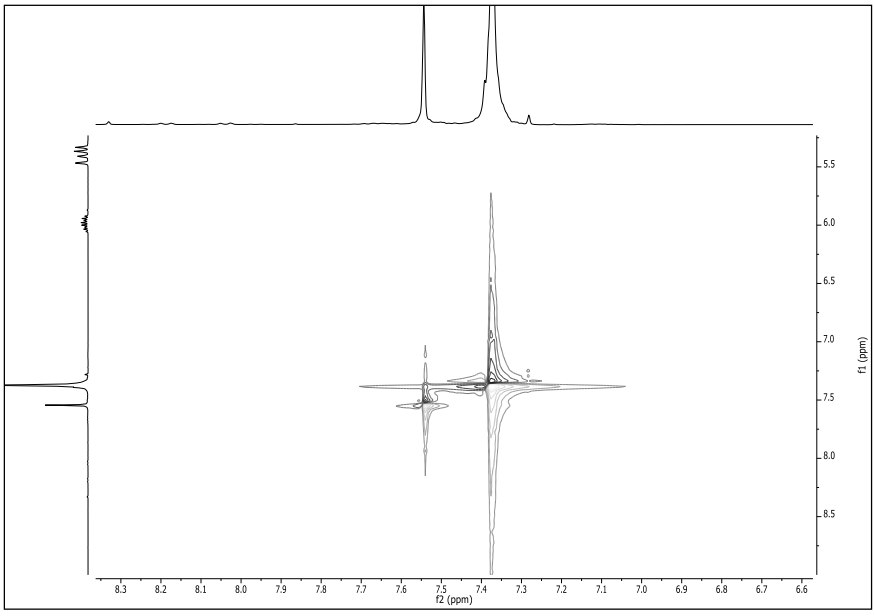


Figure 30. NOESY signal between vinylic proton and aromatic protons.

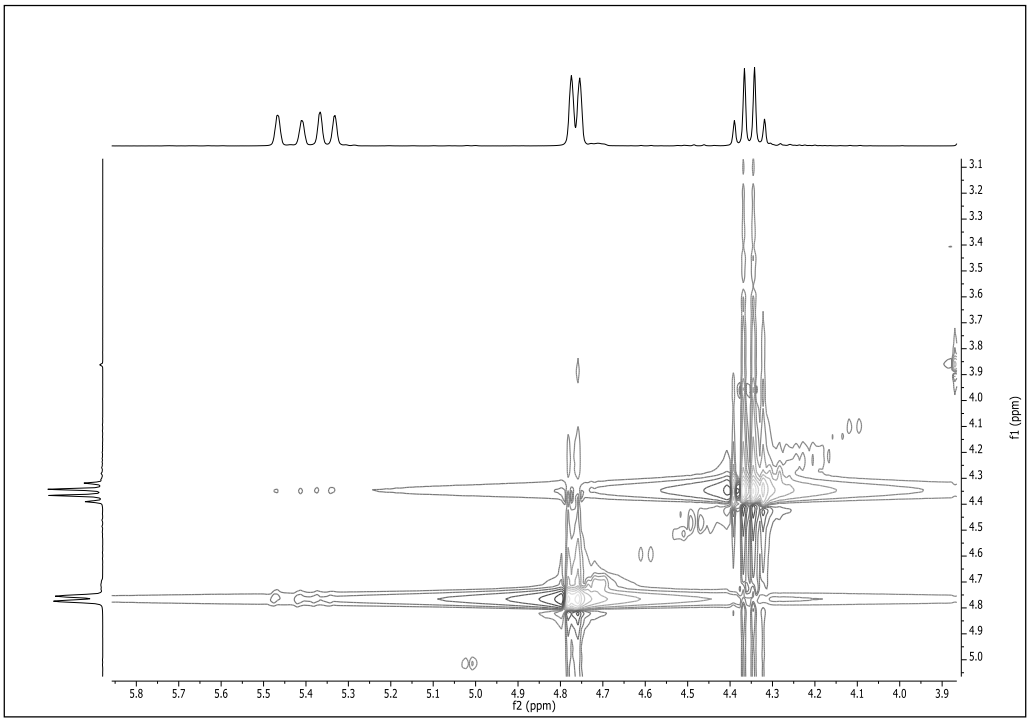


Figure 31. NOESY signal between allylic protons and methylene protons.

Stereoisomer **56** exhibiting a singlet at δ8.3 in the ^{1}H spectrum displayed no such NOESY signal, further allowing for a clear assignment of *E*-stereochemistry for this stereoisomer.

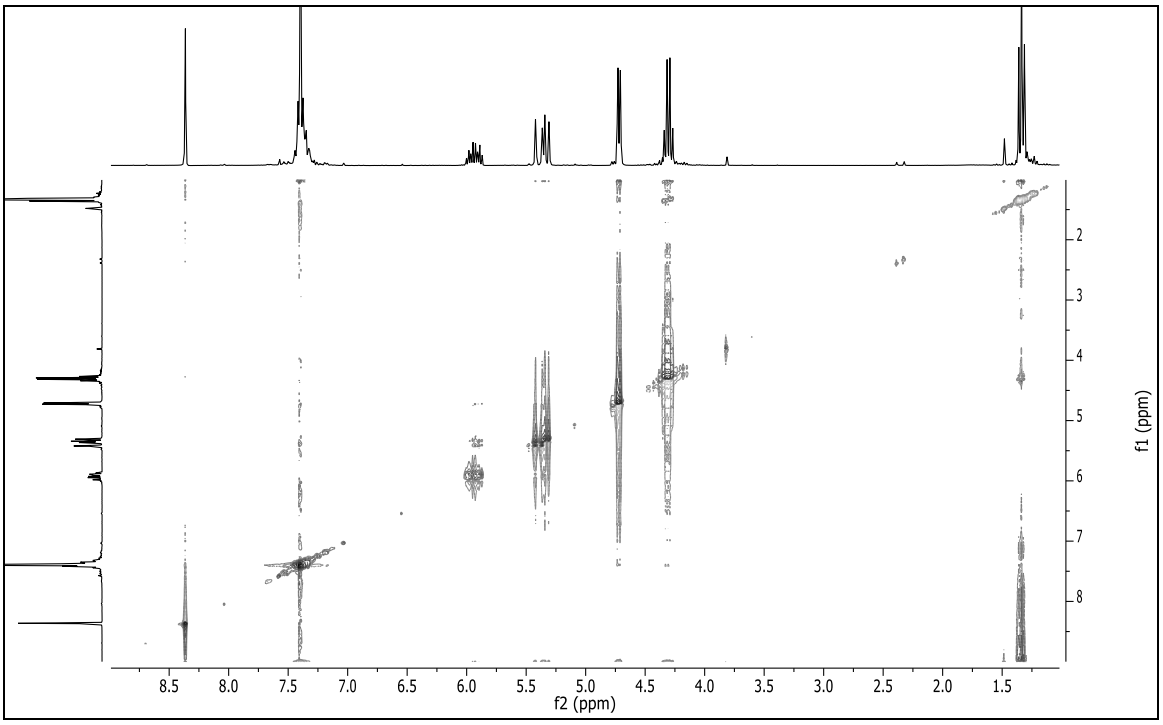
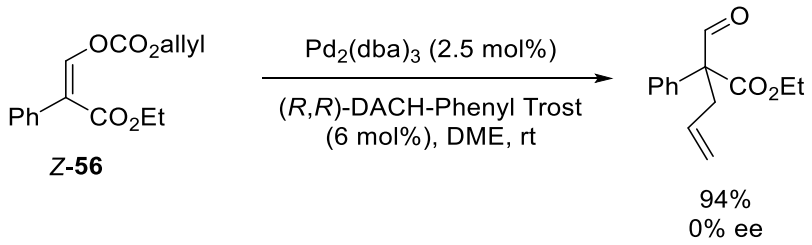


Figure 32. NOESY spectra for *E*-**56**.

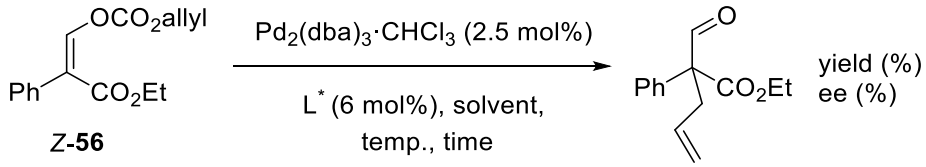
3.3. DAAA of allyl enol carbonates leading to aldehydes bearing quaternary carbon centers with Pd (0)

With a stereoselective synthesis of *E*- and *Z*- **56** at hand, we could now screen reaction conditions for the DAAA reaction resulting in optimal yield and stereoselectivity. Our first attempt at such a reaction was encouraging in forming the product in very high yield but unfortunately yielded the product with no stereoinduction (Scheme 99).



Scheme 99. First attempted DAAA reaction with *Z*-**56**.

Further reactions were carried out with *Z*-**56** to ascertain reaction conditions that could afford the product with some degree of stereoinduction (Scheme 100, Table 18)



Scheme 100. Initial screening of reaction conditions for the DAAA of *Z*-**56**.

Table 18. Initial screening of reaction conditions for the DAAA of *Z*-**56**.

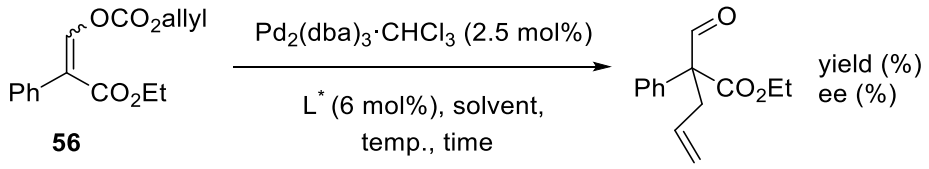
Entry	Ligand	Solvent	Yield (%)	ee (%)	Temp. (°C)	Reaction Time (h)
1	(*R*,*R*)-**55**	DME	-[a]	-	rt	12
2	(*R*,*R*)-**38**	THF	77	18	rt	12
3	(*R*,*R*)-**55**	THF	-[a]	-	rt	12
4	**(*R*,*R*)-40**	**THF**	**5**	**61**	**rt**	**12**
5	(*S*)-**39**	THF	86	0	rt	12

a) Scrambling of carbonate stereochemistry took place (i.e. partial conversion of stereoisomer Z-56 to E-56).

Interestingly, scrambling of carbonate stereochemistry was observed in the reactions carried out with (*R*,*R*)- DACH-Napthyl Trost ligand with either DME or THF catalyst (Entries 1 and 3, Table 18). To the best of our knowledge, the scrambling of carbonate stereochemistry has thus far not been reported in the literature. The scrambling step probably occurs after the decarboxylation step of the reaction mechanism, with fast equilibrium between *E*- and *Z*- stereochemistries of the corresponding enolates. It is worth noting that the opposite carbonate stereosimer (*vide infra*), *E*-**56** has not been observed to undergo scrambling to the opposite stereochemistry. This seems to indicate that formation of the *E*-stereoisomer is more thermodynamically favored and that it is therefore the thermodynamic product. In terms of yield, the most successful reaction was carried out with (*S*)-*t*-butyl PHOX ligand **39** (Entry 5), which unfortunately yielded racemic product. We decided to investigate further the reaction carried out with the sterically bulky ligand (*R*,*R*)-ANDEN-Phenyl Trost ligand **40** which yielded the product in very low yield (5%) but encouraging enantiomeric excess (61% ee, Entry 4).

A more thorough screening of reaction conditions was undertaken spanning a wider variety of solvents, ligands and reaction temperature (Table 19). First, reactions employing *Z*-**56** were tested for reactivity and stereoinduction (Entries 1-7, Table 19). Optimal reaction conditions were achieved with a non-polar solvent (toluene) and a more bulky ligand (ANDEN-Phenyl Trost, (*R*,*R*)-**40**, (Entry 7, Table 19). While the *Z*-isomer proved largely unreactive at temperatures below 0 °C, a big change in reactivity and stereoinduction was observed in changing to carbonate substrate *E*-**56** (Entry 8, Table 19**)**. Interestingly, lowering the polarity of the solvent by using either 1:1 or 2:1 Tol:Hex

mixtures had a marked in improvement in both the stereoselection and the reactivity of the carbonate substrates (Entries 10 and 14, Table 19) with the DcA being able to be carried out in essentially quantitative yield and moderate stereoselection. A novel ligand, (*R*,*R*)-ANDEN-Naphtyl **57** (Scheme 102) was prepared and the DAAA was carried out with toluene at rt (Entry 9, Table 19). Surprisingly, the use of ligand **57** led to the formation of some O-alkylated product (ca. 10 % yield) and to a rather poor stereoselection (21% ee). Overall, it is clear than (*R*,*R*)-ligand **40** and either 1:1 or 1:2 Tol:Hex mixtures provide the optimal result in terms of stereoinduction and yield. The use of Tol:Hex mixtures in the DAAA has also been reported by Stoltz and he claims that these very low polarity systems help to improve stereoinduction by helping to form tight ion pairs via the formation of "solvent cages", hence bringing the enolate and Pd π-allyl complex closer together.

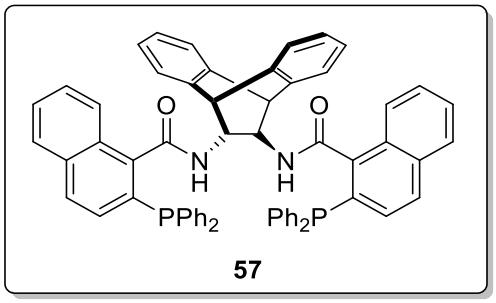


Scheme 101. Optimization of reaction conditions for DAAA of carbonate **56**.

Table 19. Optimization of reaction conditions for DAAA of carbonate **56**.

Entry	Ligand	Solvent	Yield (%)	ee (%)	Temp. (°C)	Reaction Time (h)	(*Z*/*E*)
1	(*R*,*R*)-**40**	DCM	67[a]	22	rt	24	*Z*-**56**
2	(*R*,*R*)-**55**	Toluene	99	8	rt	24	*Z*-**56**
3	(*R*,*R*)-**38**	Toluene	99	12	rt	24	*Z*-**56**
4	*S*-**39**	Toluene	47	8	rt	24	*Z*-**56**
5	(*R*,*R*)-**40**	Toluene	99	45	rt	24	*Z*-**56**
6	(*R*,*R*)-**40**	Toluene	99	46	0	72	*Z*-**56**
7	(*R*,*R*)-**40**	Toluene	-25°C: 5%[b] -10°C: 18% 0°C: 99%	At 0°C: 46	-20 to 0	72	*Z*-**56**
8	(*R*,*R*)-**40**	**Toluene**	**89**	**52**	**-20**	**48**	***E*-56**
9	(*R*,*R*)-**57**	Toluene	90[c]	21	rt	24	*E*-**56**
10	(*R*,*R*)-**40**	***Tol:Hex 1:1***	***99***	***66***	***-20***	***24***	***E***
11	(*R*,*R*)-**40**	Tol:Hex 1:1	No Reaction	-	-40	24	*E*
12	(*R*,*R*)-**40**	Tol:Hex 1:2	99	63	rt	24	*E*
13	(*R*,*R*)-**40**	Tol:Hex 1:2	99	62	-78 to rt	24	*E*
14	***(R,R)-40***	***Tol:Hex 1:2***	***99***	***66***	***-20***	***24***	***E***
15	(*R*,*R*)-**40**	THF	74[d]	58	-20	72	*E*

a) 33% O-alkylated. b) NMR yields. c) 10% O-alkylated. d) Some decarboxylation to 3-hydroxy aryl acrylate observed (26%).



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Scheme 102. Novel ANDEN-Napthyl ligand.

Carbonate analog substrates were prepared (**58-63**, Table 20) and tested for the DAAA reaction first using the optimized reaction conditions elucidated for the reaction of *E*-**56** (Table 20). It is interesting to note that for all substrates (with the exception of 1,2-dichloro substrate **62**) slight improvement in stereoselection was observed by using THF as solvent instead of Tol:Hex mixtures. For analogue **61**, the improvement both in stereoselection and yield by the use of THF is remarkable, with the aldehyde product being obtained in very high yield (96%) and good enantiomeric excess (78%) (Entry 9, **Table 20**). Interestingly, in this case, the use of non-polar solvents *hinders* to a striking degree both of these reaction parameters.

Lastly, a screen of reaction conditions was undertaken on the DAAA of carbonate **64** (ethyl (E)-3-(((allyloxy)carbonyl)oxy)-2-(2-nitrophenyl)acrylate) (Table 21). Extensive optimization of reaction conditions had to be undertaken due to large amounts of O-alkylated product formed, even with the commonly successful solvent system Hex:Tol mixtures (Entries 3-5, Table 21). More polar solvents such as THF (Entries 1 and 2) and DCM (Entry 6) also did not prove to be satisfactory solvents for the DAAA (Entries 1 and 2). THF forms a very large amount of O-alkylated product formed even at rt (Entry

2), while the use of DCM leads to no reaction taking place at rt (Entry 3). An initial screen using a 1:2 Tol:Hex mixture showed carbonate **64** was unreactive at -20 °C, but formed mostly O-alkylated product together with a small amount of C-alkylated product (Entry 4). Increasing the temperature to rt and using a 1:1 Tol:Hex mixture (Entry 6) led to a considerable increase in the C:O ratio and an ee of 42%. Gratifyingly, using a 1:1 Tol:Hex mixture at 40 °C led to the product being formed in 99% yield (Entry 7), but unfortunately with poor stereoinduction (31%). Decreasing the polarity further to almost pure hexane (Entry 10) led to a large amount of O-alkylated product being formed (C:O = 1:5.3). Interestingly, using ligand (*R*,*R*)-**55** led to a striking increase in the amount of O-alkylated product being formed (cf. Entries 7 and 8). These results taken in conjuction seem to imply that the main factor leading to C-alkylation versus O-alkylation is the reaction temperature with the C-alkylated product being the thermodynamic product and the O-alkylated product being the kinetic product. The solvent and ligand used for the DcA also play a critical role in determining the C:O ratio.

Table 20. Optimization of reaction conditions for the DAAA of *E*-**56** analogues.

Entry	Ar	Solvent	Yield (%)	ee (%)
1	4-Me (**58**)	1:2 Tol:Hex	99	54
2	**4-Me**	**THF**	**99**	**61**
3	4-F (**59**)	1:2 Tol:Hex	99	61
4	**4-F**	**THF**	**99**	**65**
5	4-MeO (**60**)	1:2 Tol:Hex	81	56
6	**4-MeO**	**THF**	**99**	**59**
7	5-Br-2-MeO (**61**)	1:2 Tol:Hex	79	17
8	5-Br-2-MeO	Toluene	85	24
9	**5-Br-2-MeO**	**THF**	**96**	**78**
10	**2,4-dichloro**[a] **(62)**	**1:2 Tol:Hex**	**99**	**53**
11	2,4-dichloro[b]	THF	10	49
12	naphthyl (**63**)	1:1 Tol:Hex	100	-[c]
13	naphthyl	THF	100	-[c,d]

All reactions carried out with ANDEN-Phenyl Trost ligand at -20 °C and for 24 h unless otherwise noted. a) Reaction run at rt; at -25°C and 0°C yield low, with some O-alkylated product formed. b) 67% yield O-alkylated, some decarboxylation to acrylate (8%), reaction carried out for 72 h. c) No resolution of peaks observed. d) Reaction carried out for 72 h.

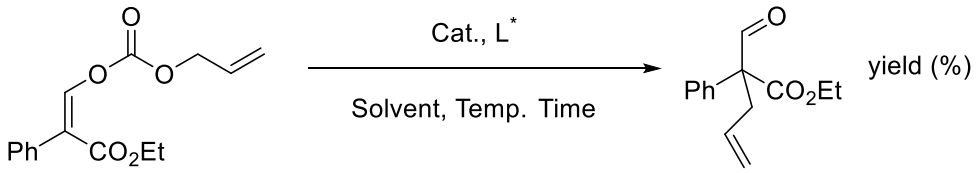
Table 21. Optimisation of reaction conditions for the DAAA of carbonate **64**.

Entry	Ligand	Solvent	Yield (%), C:O	ee (%)	Temp. (° C)	Reaction Time (h)
1	(*R*,*R*)-**40**	THF	0	-	-20-rt	72
2	(*R*,*R*)-**40**	THF	6, 1:16.8	-	rt	12
3	(*R*,*R*)-**40**	DCM	No rxn		rt	12
4	(*R*,*R*)-**40**	1:2 Tol: Hex	23[a], 1:3.4	-	-20-0	48
5	(*R*,*R*)-**40**	1:1 Tol:Hex	21, 1:3.8	12	0	12
6	(***R*,*R***)-**40**	**1:1 Tol:Hex**	**46, 1:1.2**	**42**	**rt**	**12**
7	(***R*,*R***)-**40**	**1:1 Tol:Hex**	**99, 100% C**	**31**	**40**	**12**
8	(*R*,*R*)-**55**	1:1 Tol:Hex	26, 1:3	24	40	24
9	(*R*,*R*)-**55**	1:1 Tol:Hex	23, 1:3	36	50	48
10	(*R*,*R*)-**40**	1:14 Tol:Hex	16, 1:5.3	21	rt	12
11	(***R*,*R***)-**40**	**Tol**	**99, 100% C**	**32**	**rt**	**12**

a) After 24h at -20 °C no product formed

3.4. DAAA of allyl enol carbonates leading to aldehydes bearing quaternary carbon centers with Rh (I)

Given the little amount of investigation that has so far been undertaken in studying the DAAA with metals other than Pd, we decided to pursue an investigation whether the reaction could proceed under Rh (I) catalysis, and if this was indeed the case, whether it would proceed with acceptable stereoinduction (Scheme 103, Table 22).



Scheme 103. DAAA under Rh (I) catalysis.

Table 22. DAAA under Rh (I) catalysis

Metal complex (% cat loading)	**Ligand**	**Solvent**	**Temp. (°C)**	**Reaction time (h)**	**Yield (%)**	**ee (%)**
TangPhos Rhodium(I) (10%)	-	THF	50	72	5	-
$[Rh(COD)Cl]_2$ (10%)	*t*-butyl PHOX	DCM:Tol (1:1)	50	24	81	0
$[Rh(COD)Cl]_2$ (10%)	DACH-Phenyl Trost	Toluene	rt to 50	48	40	0
Rh(acac)(COD) (10%)	DACH-Phenyl Trost	Toluene	rt to 50	48	45	0
$[Rh(COD)Cl]_2$ (2.5%)	ANDEN-Phenyl Trost	Toluene	50	48	86[a]	9

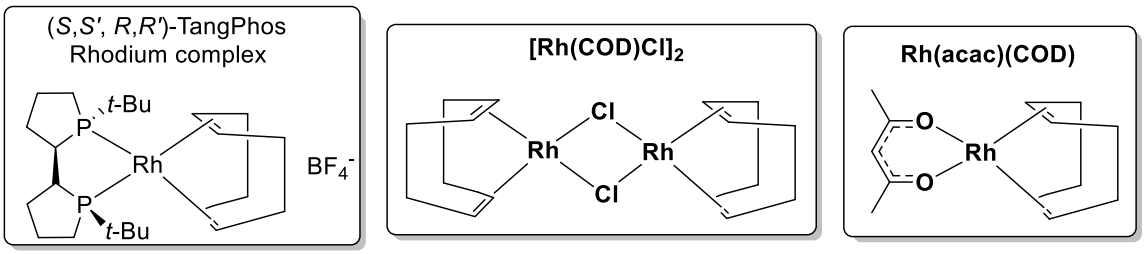


Figure 33. Metal complexes for the DAAA under Rh (I) catalysis.

From the results (Table 22) it is evident that the DAAA is indeed a feasible reaction but that it proceeds under clearly much higher temperatures than those normally required

under Pd catalysis (usually -20 °C). Thus, one can surmise that the crucial oxidative addition step and/or decarboxylation occur more slowly and with more difficulty with Rh (I). However, as compared to the examples reported thus far in the literature (see section 3.1.2.) the reaction conditions employed are generally milder (50 °C as compared to temperatures up to 110 °C previously employed). Unfortunately, the reactions all occurred with very little to no stereoinduction. The yields for the reaction were acceptable in some cases, but overall did not match those of the reaction with Pd, where the products are obtained in essentially quantitative yields in most cases. Interestingly, small amounts of O-alkylated product could be observed in some of the reactions, a problem not commonly encountered with the Pd catalyzed reaction.

In conclusion, the DAAA reaction with Rh (I) has been shown to be a feasible reaction but would require much greater optimization of reaction parameters and screening of ligands in order to match the results obtained with Pd. The work with Rh (I) is further made difficult by the required higher temperature, which might hinder the enantioselectivity of the reaction.

3.5 Summary

The stereoselective formation of allyl enol carbonates derived from 3-hydroxy aryl acrylates proved to be a considerable challenge but was ultimately successfully achieved. A stereoselective synthesis of these carbonates was devised that can form the *Z*- or *E*-stereoisomer in very high *Z*/*E* ratios (50:1 and 1:99 respectively). The stereochemical outcome depends on the choice of base, addition of TMEDA and reaction temperature. The addition of TMEDA caused a remarkable change from predominant *Z*-stereochemistry to predominant *E*-stereochemistry when NaHMDS was used. When LiHMDS is used, at lower temperatures (up to 0 °C), even with the addition TMEDA, there is little equilibration of the enolate stereochemistries leading to the *Z*-carbonate (the kinetic product) being predominantly formed. The *Z*- and *E*- stereoisomers have different reactivities towards the DAAA reaction, with the *E*-stereoisomer displaying both greater reactivity and enantio-differentiation with chiral ligands.

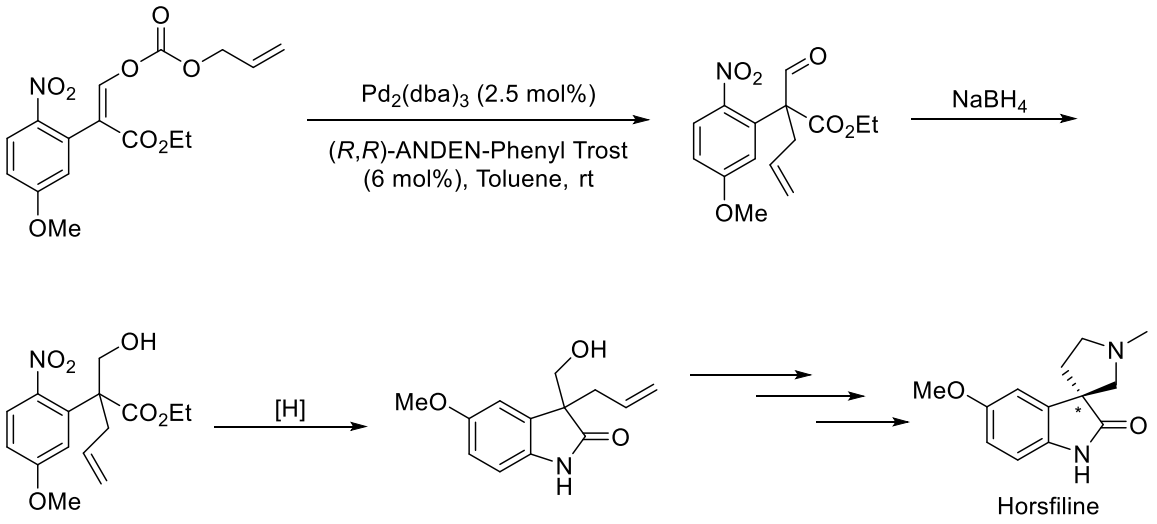
The DAAA of allyl enol carbonates derived from 3-hydroxy aryl acrylates has proven to be a powerful method for the formation of aldehydes bearing all carbon quaternary stereocenters, forming most aldehyde analogues in essentially quantitative yields (up to 99% even at -20 °C) and moderate to good enantioselectivities (up to 78%). Generally speaking, either THF or very non-polar solvent mixtures (either 1:1 Tol:Hex of 1:2 Tol:Hex mixtures) were found to be the optimal solvents for the reaction. The use of nonpolar solvent mixtures in some substrates has been reported to produce a higher affinity between the chiral Pd center and the intermediate enolate than when the reaction

is conducted in more polar solvents, resulting in higher enantioselectivities. [109] Interestingly, for some substrates, similar enantioselectivities have been reported with either polar (THF) or non polar (Tol:Hex) solvent mixtures.[110] This seems to imply that the achievement of tight ion pairs leading to enhanced stereoselectivity may be achieved with both polar and non-polar solvent mixtures and that generalizations about which solvent system will afford the greatest stereoselectivity should be avoided. In other words, the optimal solvent system for each reaction is highly substrate specific and for some substrates both polar and non-polar solvents will result in satisfactory enantioselectivity. Among the ligands that were screened for the DAAA, the stereoinduction showed a marked improvement by employing the most sterically demanding ligand, (*R*,*R*)-ANDEN Phenyl Trost.

Some substrates (such as the 2-nitro carbonate analog) proved to have very different reactivity under the optimized reaction conditions of most substrates (*vide supra*) and required extensive screening of reaction conditions in order to improve yield and enantioselectivity. Interestingly, while potential O-alkylation of the enolate from the Pd π-allyl complex was not an issue for the majority of analogues, this did prove to be a problem for analogues of increased polarity with electron withdrawing groups, such as the 2,4-dichloro analogue (Table 20) and even more so the 2-nitro carbonate analog (Table 21). The latter carbonate formed almost exclusively O-alkylated product with THF at rt and ANDEN ligand (Entry 2, Table 21). There was also a very clear pattern of increased C- vs O- alkylation as the temperature was increased (Entries 5-7), implying

that the O-alkylated product is the kinetic and the C-alkylated product the thermodynamic product.

Future work could involve the synthesis of the 2-nitro-5-OMe carbonate analogue that could be used as an intermediate leading up to the synthesis of the simplest spiro-oxindole natural product, horsfiline (Scheme 104). The DAAA reaction of this analog could provide further evidence of the potential importance of this substitution pattern for providing enantiodifferentiation in the transition state leading up to the alkylated product, such as the example of the enhanced enantiomeric excess observed in the DAAA of 5-Br-2-OMe carbonate **61** (78% ee). In addition, it might be worth exploring the DAAA reaction with metals other than Pd, such as Ir(I), Mo (0), Ni (0), or further exploring the work already undertaken with Rh(I).



Scheme 104. Synthesis of Horsfiline from 2-nitro-5-OMe carbonate intermediate.

3.6. General methods and experimental

All reactions were carried with distilled solvent dried under conventional techniques. For the synthesis of aldehydes via the DAAA, solvent was degassed by flushing with Ar and stirring the solvent for 30 minutes. Reaction progress for all reactions was monitored by taking a crude aliquot out of the reaction mixture (0.1 mL), quenching the reaction, concentrating the solvent under vacuum and taking a ^{1}H NMR out of the resulting crude sample. $Pd_2(dba)_3 \cdot CHCl_3$ catalyst used for DAAA reactions was carefully stored under Ar in a freezer at -20 °C.

Procedure for synthesis of allyl enol carbonate E-56

To a flask was added anhydrous THF (7 mL) via syringe, followed by NaHMDS (1M solution in THF; 1.73 mL, 1.73 mmol, 1 eq) and TMEDA (0.26 mL, 1.73 mmol), both reagents being added at room temperature. After the mixture is stirred for 5 min, aryl acrylate **10** (400 mg, 2.08 mmol) is dissolved in anhydrous THF (2 mL) in a separate flask and is then transferred to the reaction flask containing the NaHMDS/TMEDA mixture via syringe at room temperature. The flask is rinsed with additional THF (1 mL) to aid in the quantitative transfer of substrate **10** (total volume of THF in reaction flask 10 mL). The mixture is allowed to stir at room temperature for 20 min, at which point allylchloroformate (0.184 mL, 1.73 mmol) is added dropwise via syringe at rt. The resulting solution is then allowed to stir at room temperature for 45 minutes. The reaction is monitored by taking a small aliquot (0.1 mL) via syringe from the reaction flask,

passing it through a small silica plug (pasteur pippete is used for this purpose), concentrating the solvent under vacuum and taking a ^{1}H NMR. After this time, the reaction mixture is passed through a silica plug (4 cm diameter medium porosity fritted funnel, 2 cm of silica). The silica plug is rinsed through with additional solvent (25 mL) to ensure quantitative elution of product. The solvent is then concentrated under reduced pressure at room temperature (carbonate may decarboxylate at higher temperatures) yielding carbonate *E*-**56** as a yellow oil, the product being pure enough for synthetic purposes. ^{1}H NMR (300 MHz, , $CDCl_3$): δ 8.36 (s, 1 H), 7.40 (s, 5 H), 5.94 (ddt, *J* = 17.0, 10.1, 6.0 Hz, 1 H), 5.39 (dd, *J* = 17.3, 1.4 Hz, 1 H), 5.32 (d, *J* = 12.0 Hz, 1 H), 4.72 (dt, *J* = 6.1, 1.2 Hz, 2 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

Procedure for synthesis of allyl enol carbonate Z-56

To a dry flask was added anhydrous THF (3 mL), via syringe and the flask was cooled to 0 °C. Next LiHMDS (1M solution in toluene; 937 μL, 0.937 mmol) was added via syringe, followed by TMEDA (140 μL, 0.937 mmol). The reaction mixture was stirred for 5 minutes, after which 3-hydroxy aryl acrylate **10** (180 mg, 0.937 mmol) dissolved in THF (0.9 mL) was added dropwise via syringe to the reaction mixture at 0 °C. The resulting solution was stirred for 30 minutes, at which point allylchloroformate (100 μL, 0.937 mmol) was added dropwise via syringe. The resulting solution was allowed to stir for 1 hour. After this time, the mixture was poured into a silica plug (4 cm diameter medium porosity fritted funnel, 2 cm of silica). The silica plug is rinsed through with additional solvent (25 mL) to ensure quantitative elution of product. The solvent is then

concentrated under reduced pressure at room temperature (carbonate may decarboxylate at higher temperatures) yielding carbonate *Z*-**56** as a yellow oil, the product being pure enough for synthetic purposes. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (s, 1 H), 7.35 (s, 5 H), 6.03 – 5.90 (m, 1 H), 5.42 (dd, *J* = 17.3, 1.6 Hz, 1 H), 5.33 (dd, *J* = 10.5, 1.1 Hz, 1 H), 4.74 (dd, *J* = 5.9, 1.5 Hz, 2 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 1.33 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.35, 152.03, 140.14, 133.17, 130.75, 128.58, 128.57, 128.21, 127.74, 120.37, 119.82, 69.60, 61.26, 14.19.

Synthesis of E-58: ethyl (E)-3-(((allyloxy)carbonyl)oxy)-2-(p-tolyl)acrylate

E-**58** was synthesized by the general procedure outlined for the formation of *E*-**56**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (s, 1 H), 7.28 – 7.19 (m, 4 H), 6.08 – 5.78 (m, 1 H), 5.52 – 5.22 (m, 2 H), 4.72 (d, *J* = 6.0 Hz, 2 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 2.38 (s, 3 H), 1.33 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.49, 151.85, 145.56, 137.80, 130.54, 128.70, 120.22, 118.65, 69.79, 61.10, 21.31, 14.28.

Synthesis of E-59: ethyl (E)-3-(((allyloxy)carbonyl)oxy)-2-(4-fluorophenyl)acrylate

E-**59** was synthesized by the general procedure outlined for the formation of *E*-**56**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (s, 1 H), 7.46 – 7.25 (m, 2 H), 7.18 – 6.98 (m, 2 H), 6.06 – 5.85 (m, 1 H), 5.50 – 5.15 (m, 2 H), 4.73 (dd, *J* = 6.0, 1.1 Hz, 2 H), 4.40 – 4.04 (m, 2 H), 1.33 (t, J = 9.0 Hz, 3 H).^{13}C NMR (75 MHz, $CDCl_3$): δ 166.19, 164.00, 160.72,

151.67, 146.01, 145.99, 131.85, 131.83, 131.74, 131.72, 130.41, 127.06, 127.01, 120.39, 117.65, 115.14, 114.85, 69.93, 61.23, 14.24.

Synthesis of E-60: ethyl (E)-3-(((allyloxy)carbonyl)oxy)-2-(4-methoxyphenyl)acrylate

E-**60** was synthesized by the general procedure outlined for the formation of *E*-**56**.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, *J* = 1.0 Hz, 1 H), 7.47 – 7.18 (m, 2 H), 6.93 (dd, *J* = 8.9, 1.1 Hz, 2 H), 6.11 – 5.78 (m, 1 H), 5.56 – 5.15 (m, 2 H), 4.73 (q, *J* = 6.0 Hz, 2 H), 4.40 – 4.18 (m, 2 H), 3.84 (s, 3 H), 1.33 (t, *J* = 9.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.59, 159.23, 151.84, 145.28, 132.58, 131.18, 130.52, 123.35, 120.23, 118.25, 114.23, 113.44, 77.46, 77.04, 76.61, 69.79, 61.09, 55.21, 30.92, 14.26.

Synthesis of E-61: ethyl (E)-3-(((allyloxy)carbonyl)oxy)-2-(5-bromo-2-methomethoxy-phenyl)acrylate

E-**61** was synthesized by the general procedure outlined for the formation of *E*-**56**.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.43 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.34 – 7.26 (m, 1 H), 6.81 (d, *J* = 8.8 Hz, 1 H), 5.94 (ddt, *J* = 17.1, 10.3, 6.0 Hz, 1 H), 5.47 – 5.24 (m, 2 H), 4.72 (dt, *J* = 6.0, 1.2 Hz, 2 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 3.77 (s, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H).^{13}C NMR (75 MHz, $CDCl_3$) δ 156.26, 151.63, 146.37, 133.81, 132.38, 130.46, 122.67, 120.28, 115.03, 112.58, 112.38, 69.84, 61.04, 14.24.

Synthesis of E-62: ethyl (E)-3-(((allyloxy)carbonyl)oxy)-2-(2,4-dichlorophenyl)acrylate

E-**62** was synthesized by the general procedure outlined for the formation of *E*-**56**.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (s, 1 H), 7.47 (s, 1 H), 7.29 (d, *J* = 8.1 Hz, 1 H), 7.18 (d, *J* = 8.2 Hz, 1 H), 6.00 – 5.77 (m, 1 H), 5.49 – 5.18 (m, 2 H), 4.72 (d, *J* = 6.0 Hz, 2 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H).^{13}C NMR (75 MHz, $CDCl_3$): δ 165.12, 151.37, 147.35, 134.83, 132.46, 130.28, 129.38, 129.29, 126.99, 120.49, 115.98, 70.04, 61.36, 14.18.

Synthesis of E-63: ethyl (E)-3-(((allyloxy)carbonyl)oxy)-2-(naphthalen-2-yl)acrylate

E-**63** was synthesized by the general procedure outlined for the formation of *E*-**56**.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (s, 1 H), 7.98 – 7.74 (m, 4 H), 7.54 – 7.48 (m, 3 H), 6.11 – 5.76 (m, 1 H), 5.52 – 5.10 (m, 2 H), 4.72 (dd, *J* = 6.0, 1.3 Hz, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H)^{13}C NMR (75 MHz, $CDCl_3$): δ 166.48, 151.83, 146.24, 133.03, 132.92, 130.47, 129.46, 128.70, 128.29, 127.64, 127.60, 127.46, 126.37, 126.05, 120.24, 118.77, 69.87, 61.26, 36.67, 24.73, 23.41, 14.30.

Synthesis of E-64: (E)-ethyl 3-(((allyloxy)carbonyl)oxy)-2-(2-nitrophenyl)acrylate

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (s, 1 H), 8.12 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.67 – 7.61 (m, 1 H), 7.51 (td, *J* = 7.9, 1.5 Hz, 1 H), 7.38 (dd, *J* = 7.6, 1.5 Hz, 1 H), 5.89 (ddt, *J* = 16.6, 10.4, 6.0 Hz, 1 H), 5.46 – 5.20 (m, 2 H), 4.69 (dt, *J* = 6.0, 1.3 Hz, 2 H), 4.20 (q, *J* =

7.1 Hz, 2 H), 1.22 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.71, 148.15, 145.90, 133.31, 132.84, 130.28, 129.38, 126.99, 124.72, 120.43, 116.48, 70.05, 61.41, 14.03.

Procedure for DAAA of allyl enol carbonates

To a dry flask was added $Pd_2(dba)_3$ (4.7 mg, 0.0045 mmol) followed by (*R*,*R*)-ANDEN-phenyl Trost ligand. To the flask was added a mixture of dry and degassed 2:1 Hexane:Toluene (6 mL) at room temperature and the mixture was allowed to stir for 30 minutes. After several minutes of stirring, the mixture turned into a bright yellow color (occasionally a slight pink hue is observable) with a small amount of beige precipitate. The resulting mixture was cooled down to -20 °C and was transferred via cannula to a separate flask containing allyl enol carbonate substrate dissolved in 2:1 Hexane:Toluene (1 mL) which was already cooled down to -20 °C. The reaction mixture is allowed to stir at this temperature for 24 hours, after which time the mixture is observed a cloudy yellow/green solution and is allowed to warm to room temperature. The solution is then passed through a silica plug (1 cm fritted funnel, 2 cm silica, medium porosity filter) which is washed through with DCM (25 mL) to allow for quantitative elution of the resulting C-allylated product. The solvent is concentrated under vacuum to yield **x** as a yellow oil. For all the substrates tested so far, the resulting yield is quantitative and the NMR is pure enough to be reported without further purification.

Synthesis of 2-nitro acrylate: (Z)-ethyl 3-hydroxy-2-(2-nitrophenyl)acrylate

To a flask was added 2-nitrobenzaldehyde (0.907 g, 6 mmol), followed by anhydrous DCM (25 mL). The reactant was allowed to still dissolve, and $HBF_4 \cdot OEt_2$ (136 µL, 1 mmol) was added carefully via syringe at room temperature. The reaction mixture was cooled down to 0 °C, at which point EDA (1 mL [5M] solution, 5 mmol) was added slowly dropwise over a period of ca. 5 minutes. The reaction mixture was allowed to stir for 12 hours, at which point the reaction flask was allowed to warm up to room temperature. Next, the reaction was quenched by the addition of water (20 mL) added at room temperature. The resulting solution was stirred for 5 minutes, the layers were separated and the aqueous phase extracted with DCM (2 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was concentrated under vacuum to yield 2-nitro acrylate as a yellow oil (581 mg, 49% yield).

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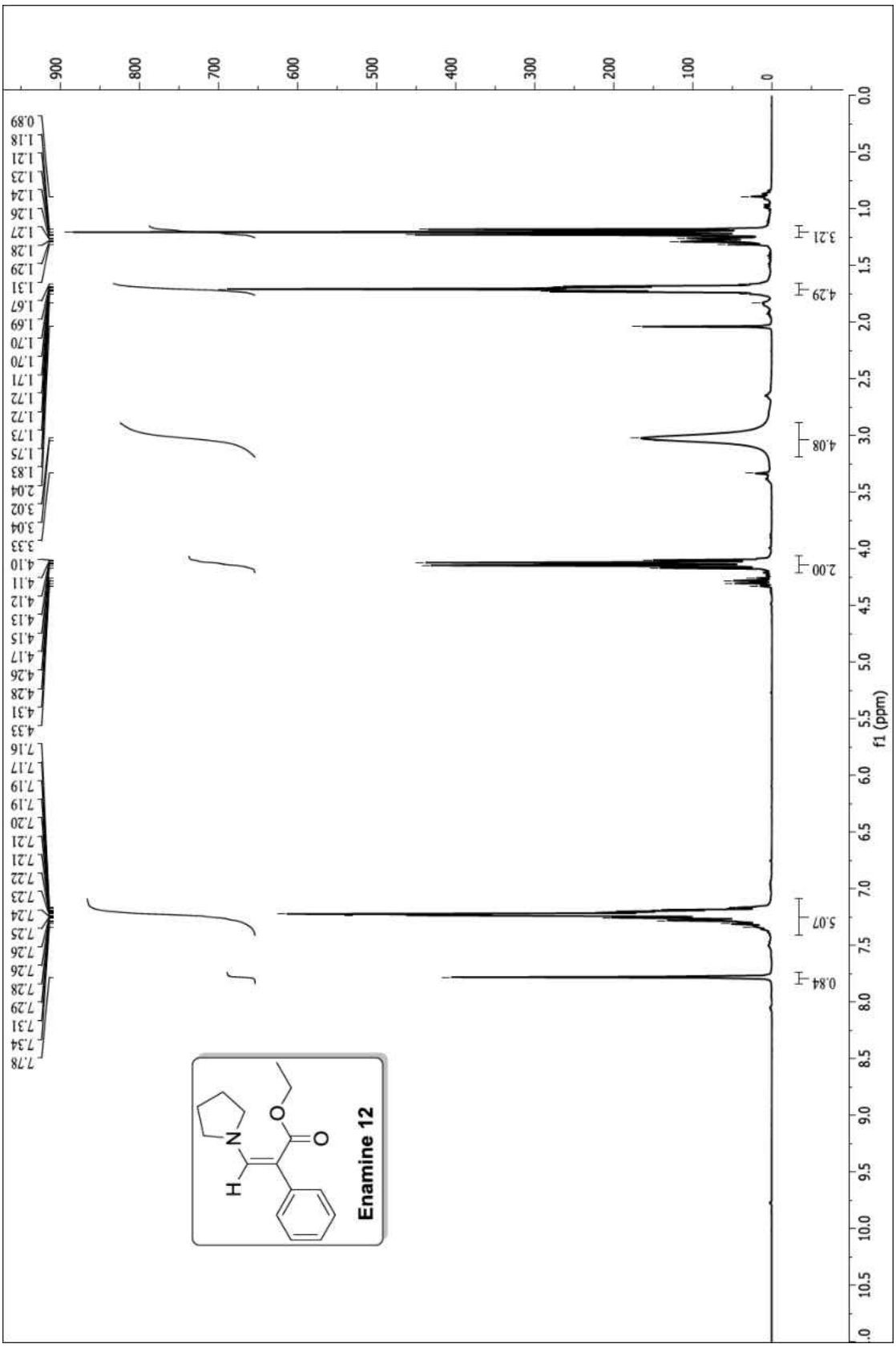
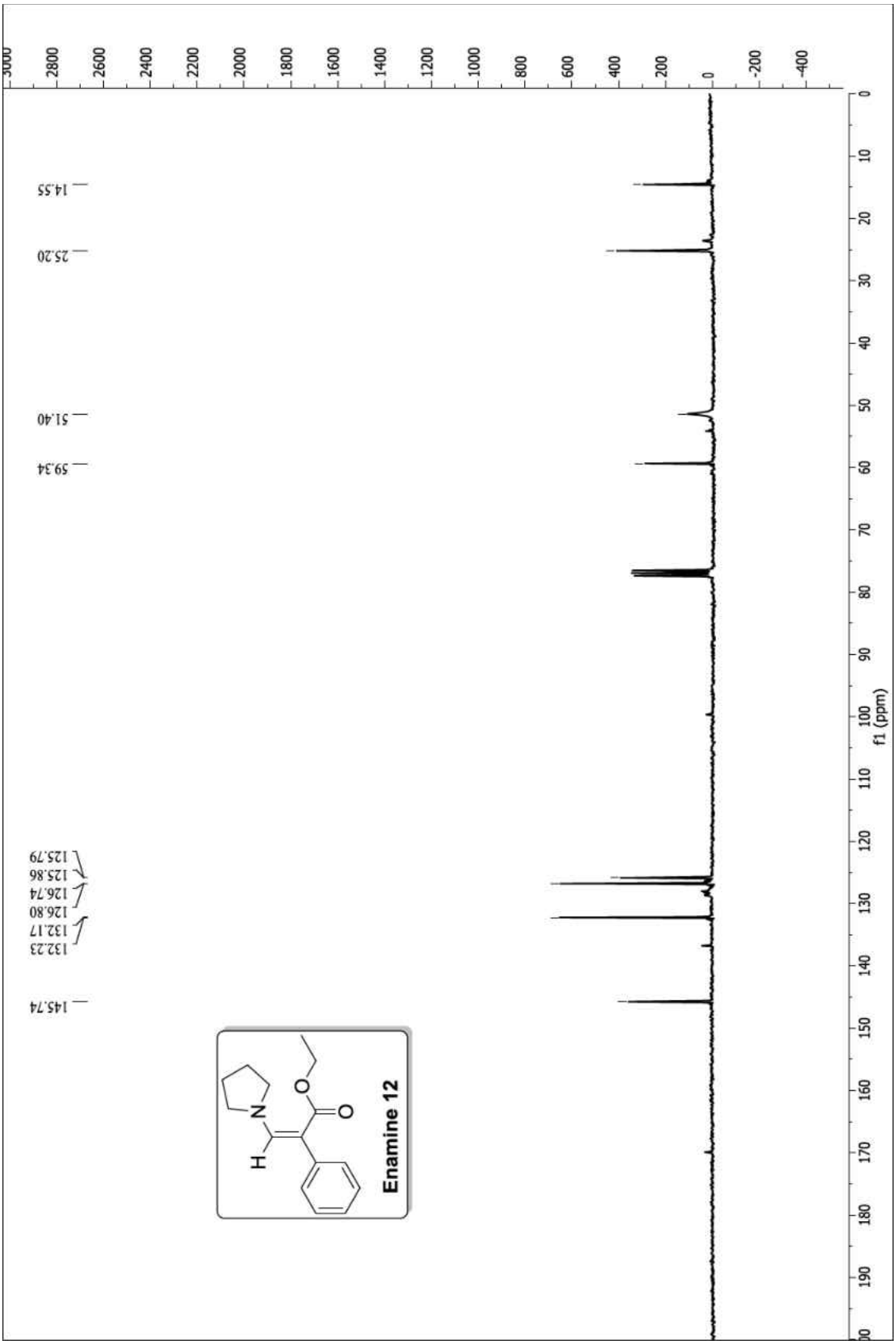
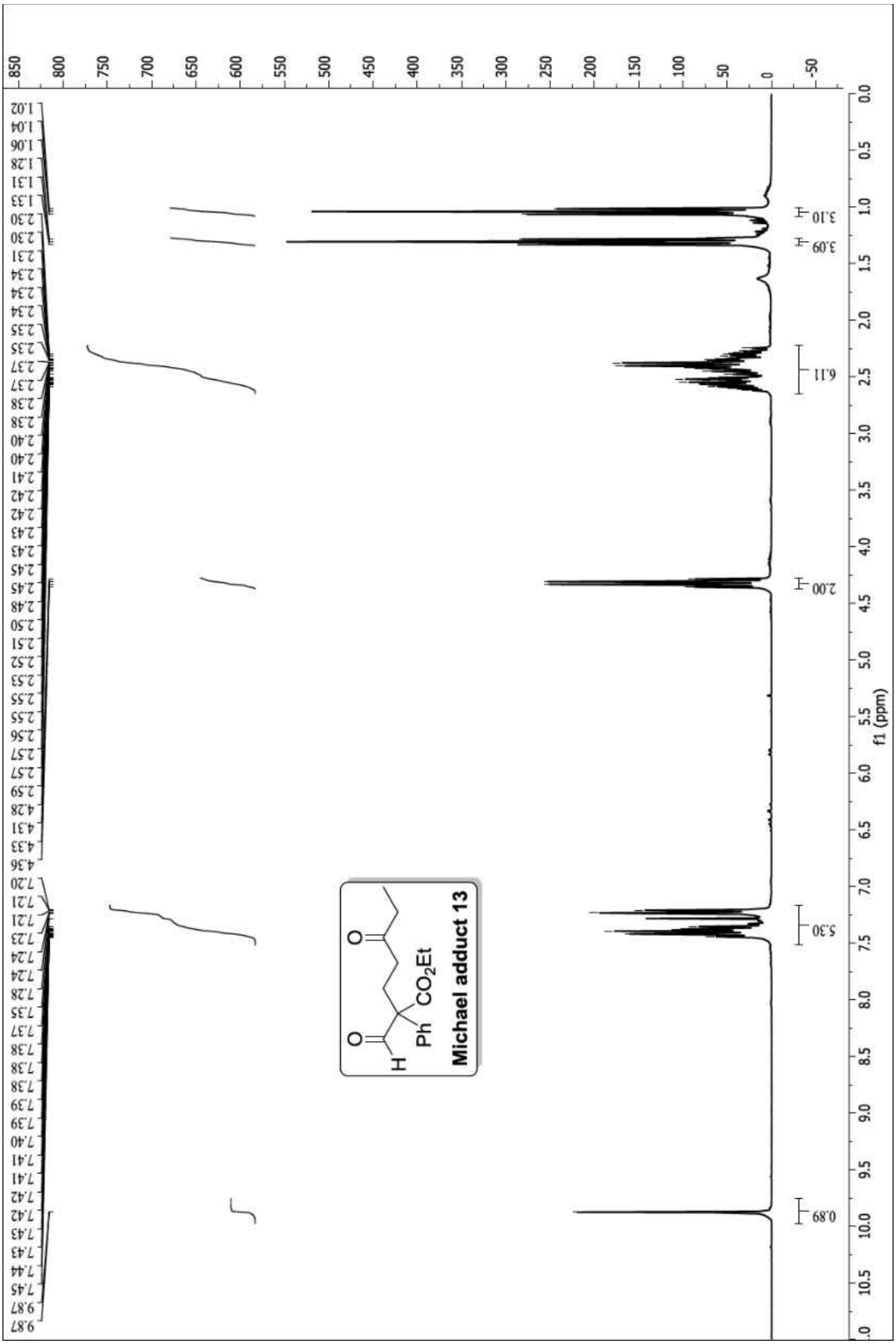
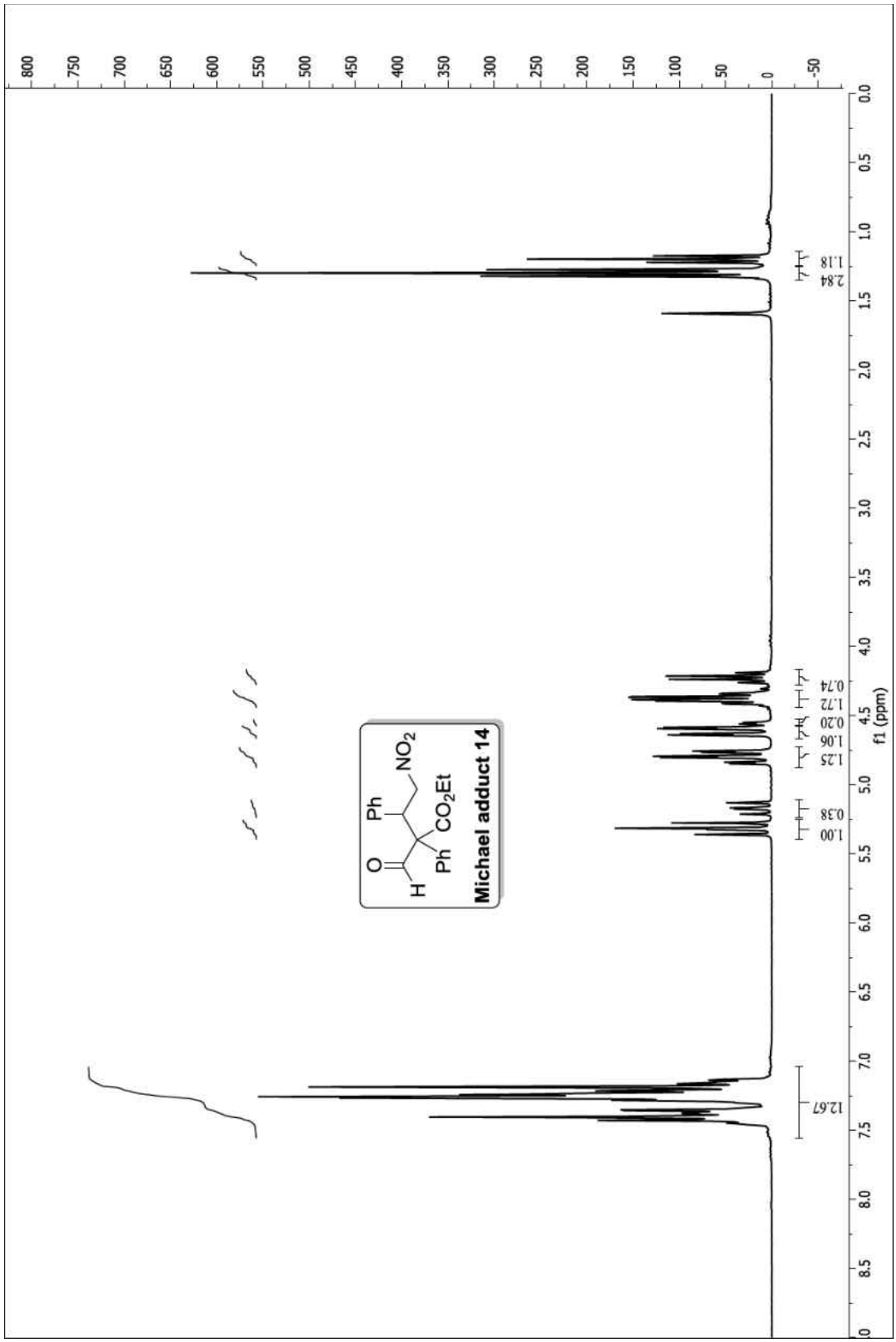
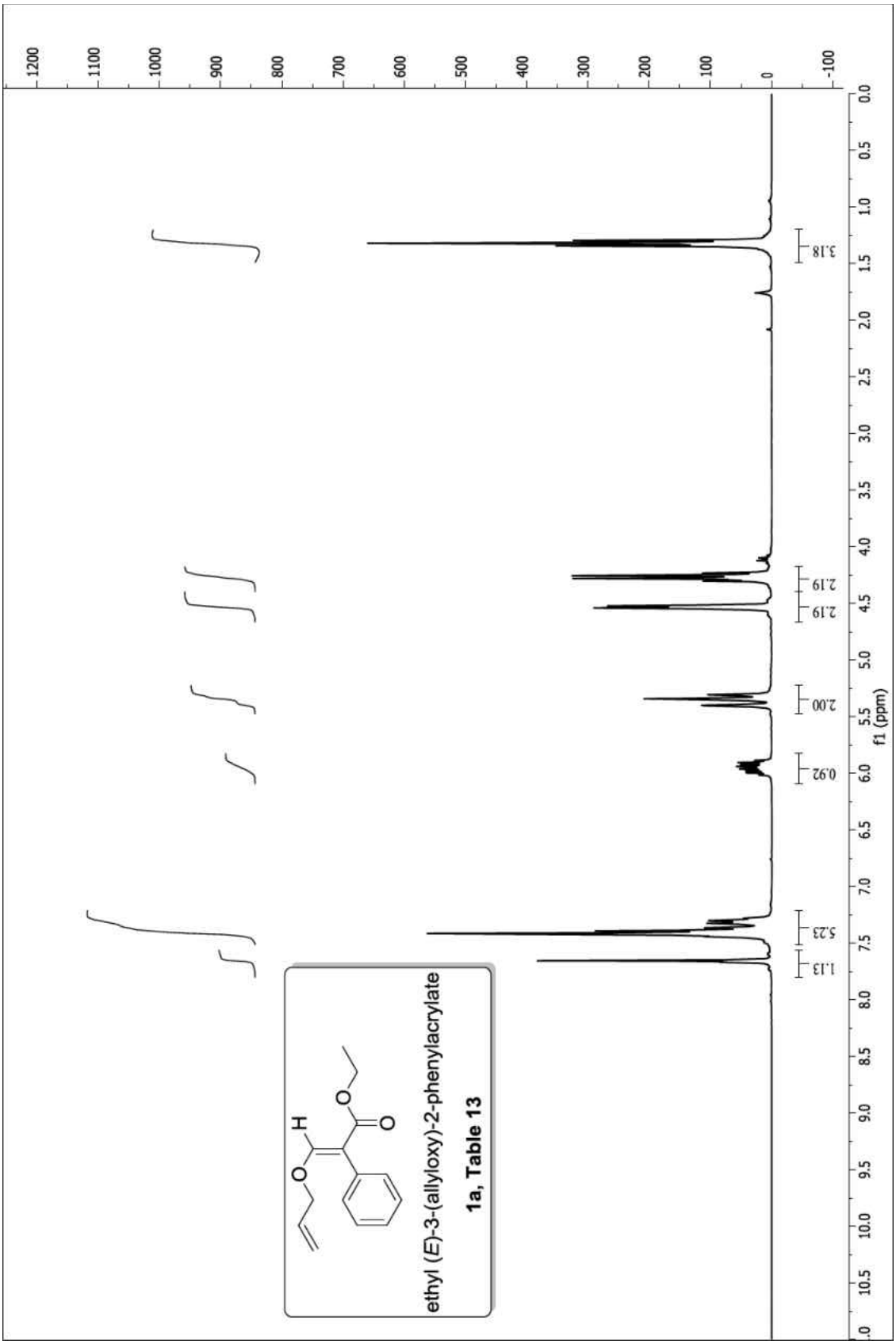
APPENDIX A: NMR SPECTRA

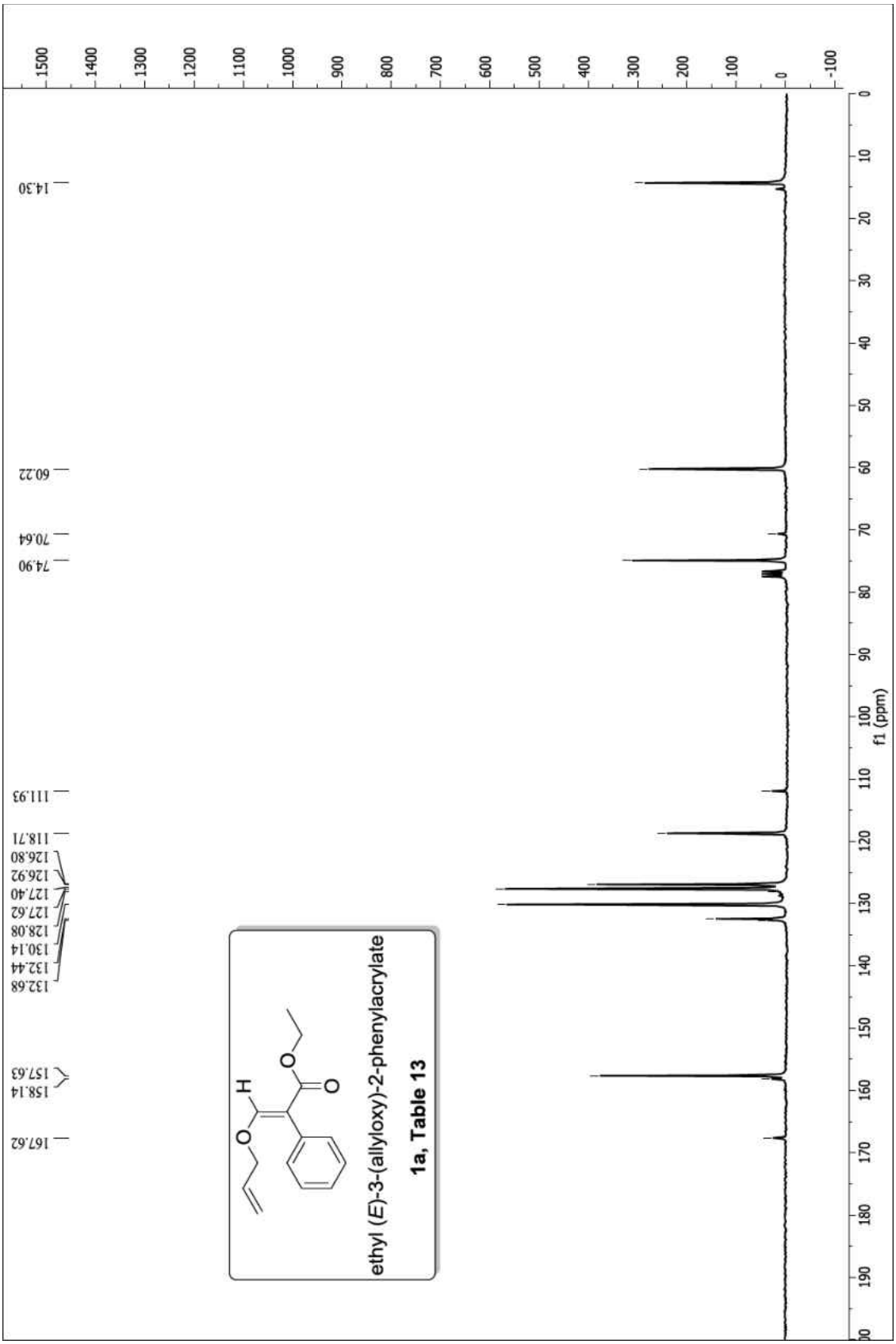

Enamine 12
f1 (ppm)

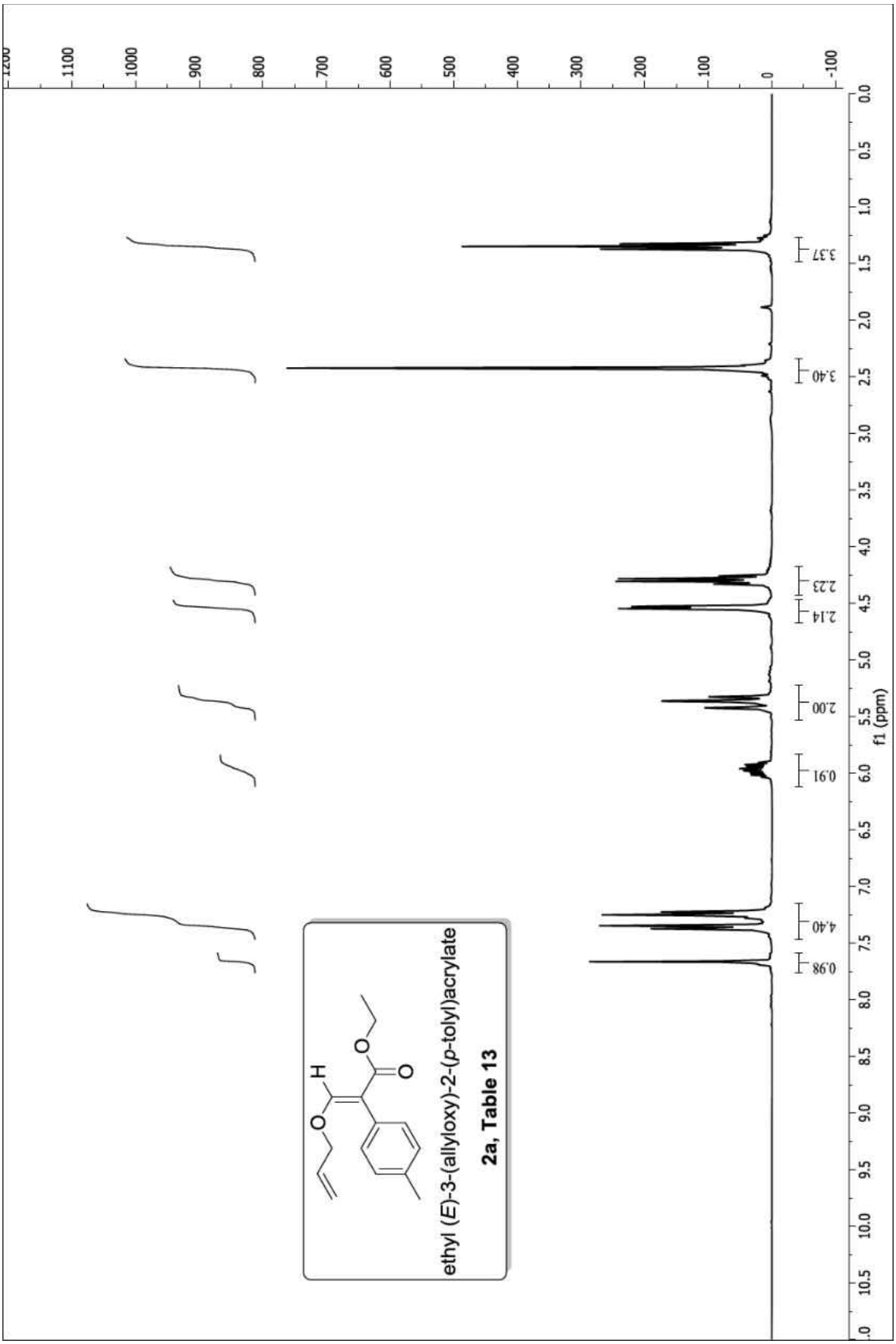

14.55
25.20
51.40
59.34
125.79
125.86
126.74
126.80
132.17
132.23
145.74
Enamine 12
f1 (ppm)

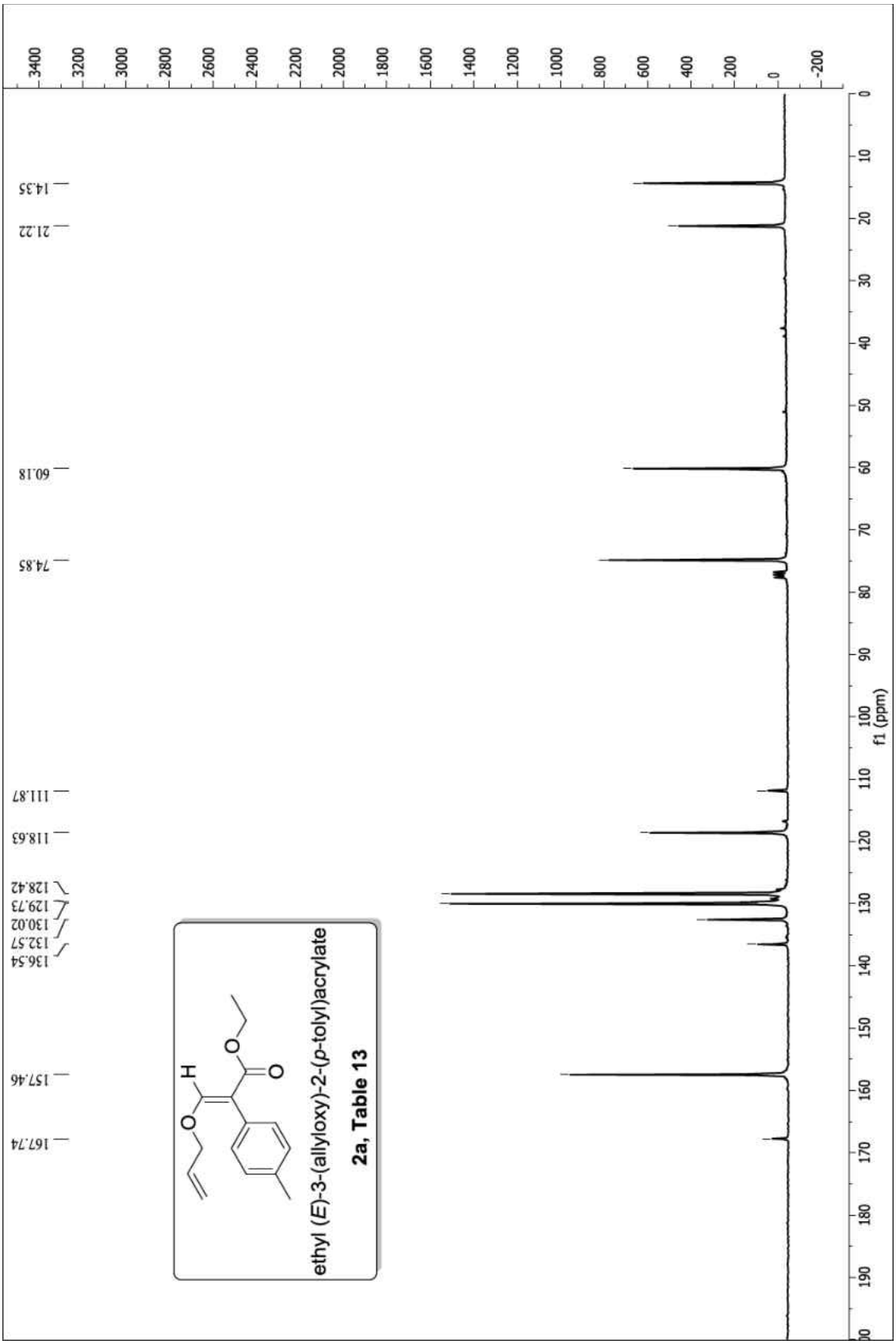

Michael adduct 13
Ph
CO2Et
H
O
O
0.89
5.30
2.00
6.11
3.09
3.10
f1 (ppm)

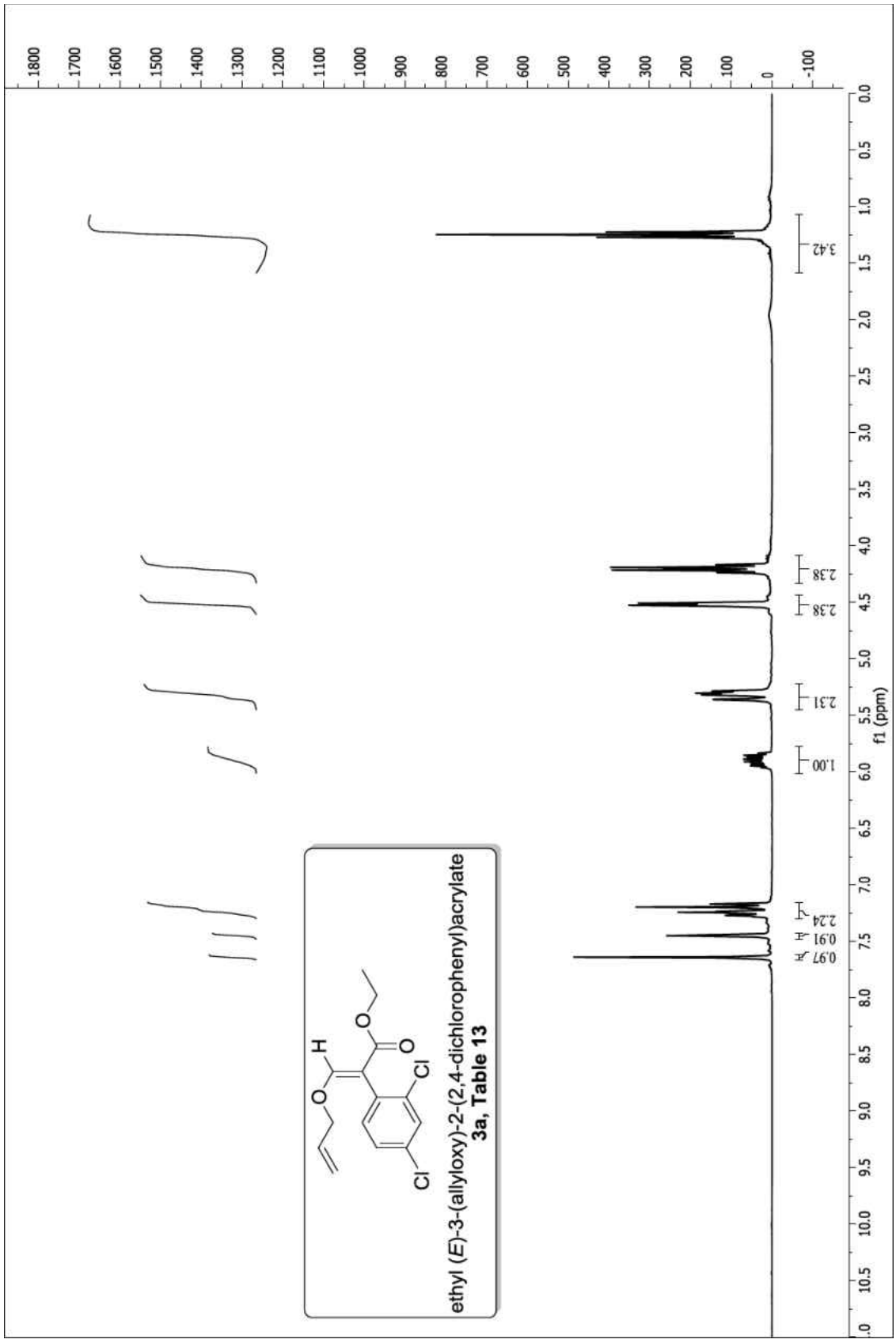

Michael adduct 14
Ph
NO2
O
H
Ph
CO2Et
12.67
1.00
0.38
1.25
1.06
0.20
1.72
0.74
2.84
1.18
f1 (ppm)

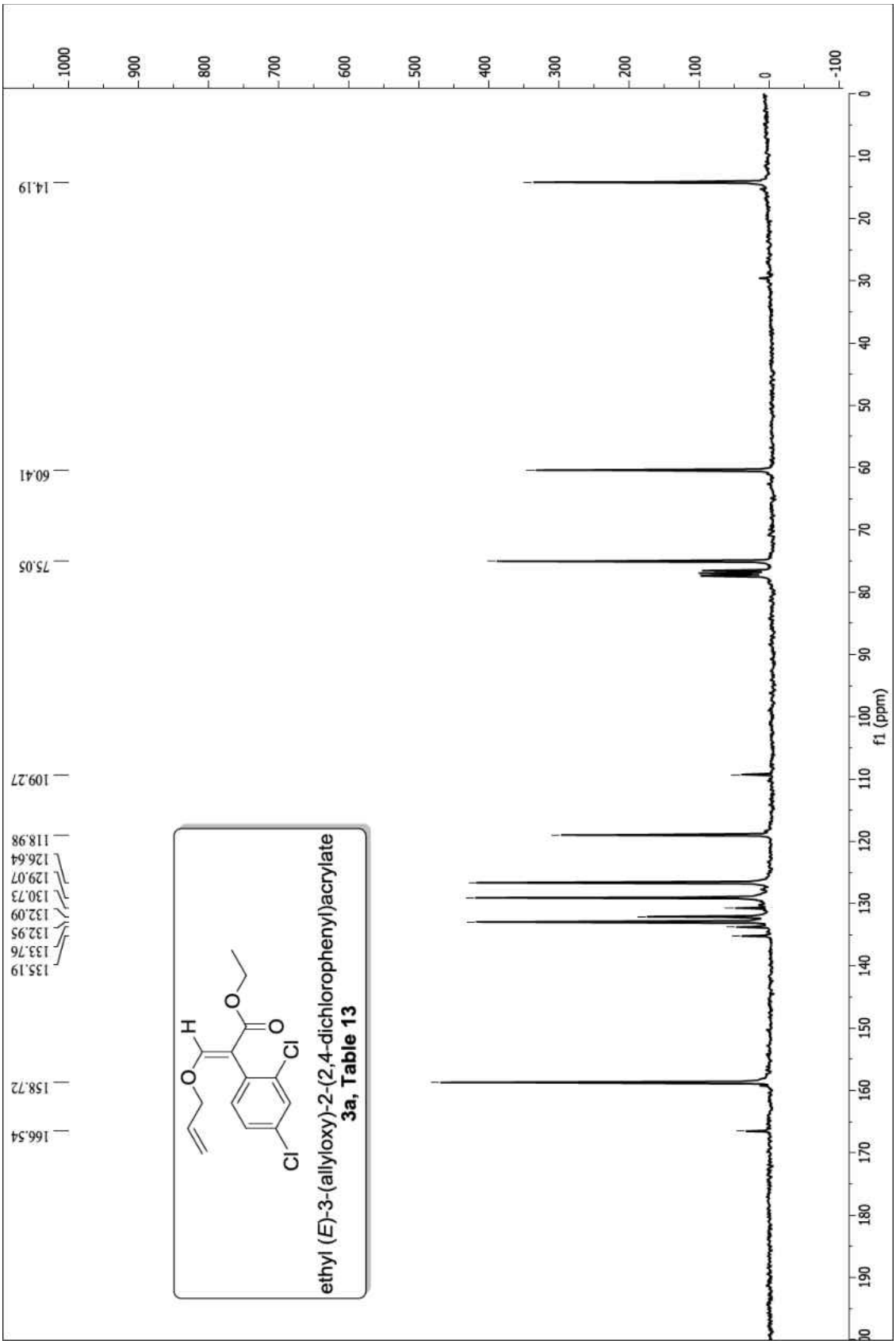

ethyl (E)-3-(allyloxy)-2-phenylacrylate
1a, Table 13
3.18
2.19
2.19
2.00
0.92
5.23
1.13
f1 (ppm)

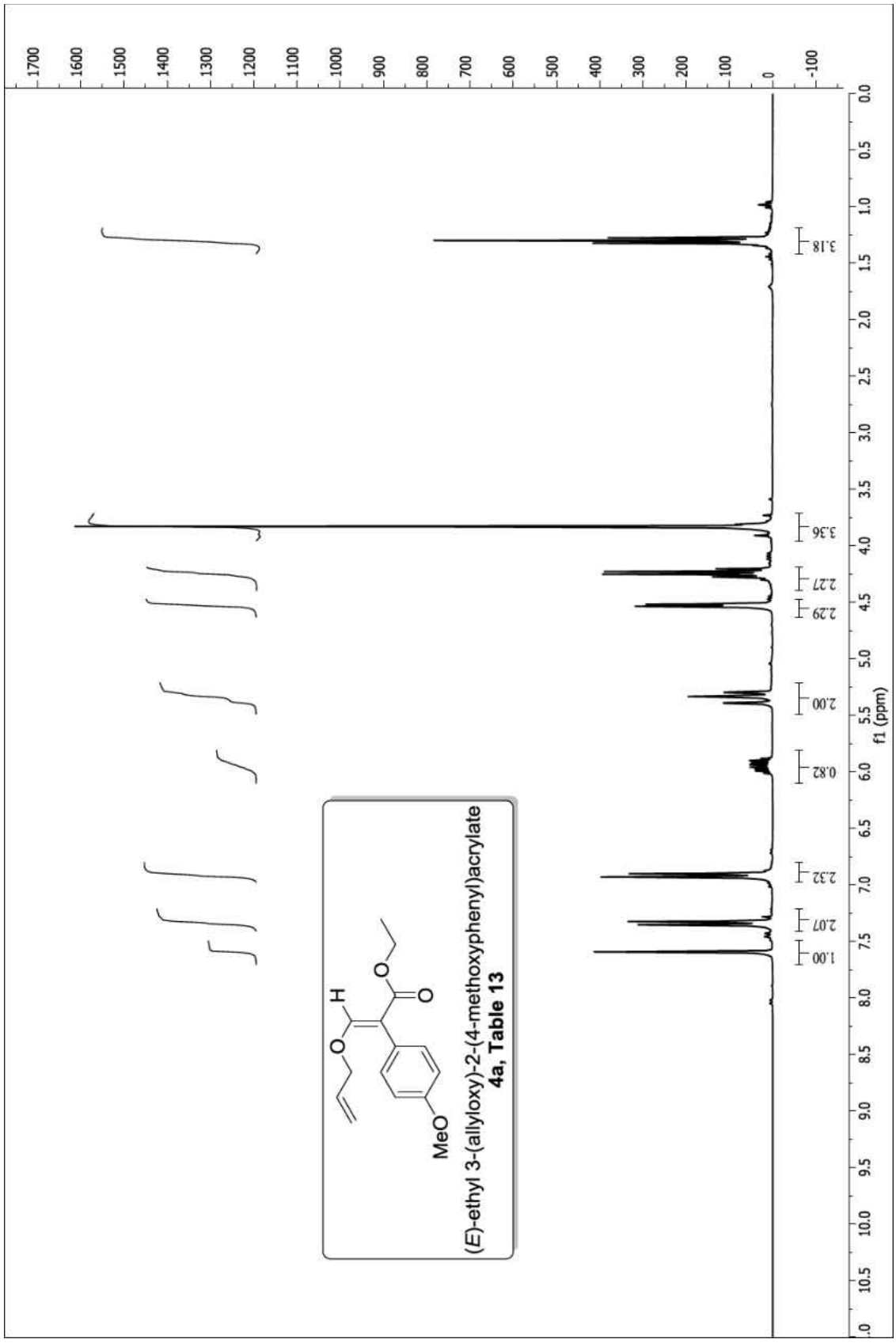

ethyl (E)-3-(allyloxy)-2-phenylacrylate
1a, Table 13
14.30
60.22
70.64
74.90
111.93
118.71
126.80
126.92
127.40
127.62
128.08
130.14
132.44
132.68
157.63
158.14
167.62
f1 (ppm)

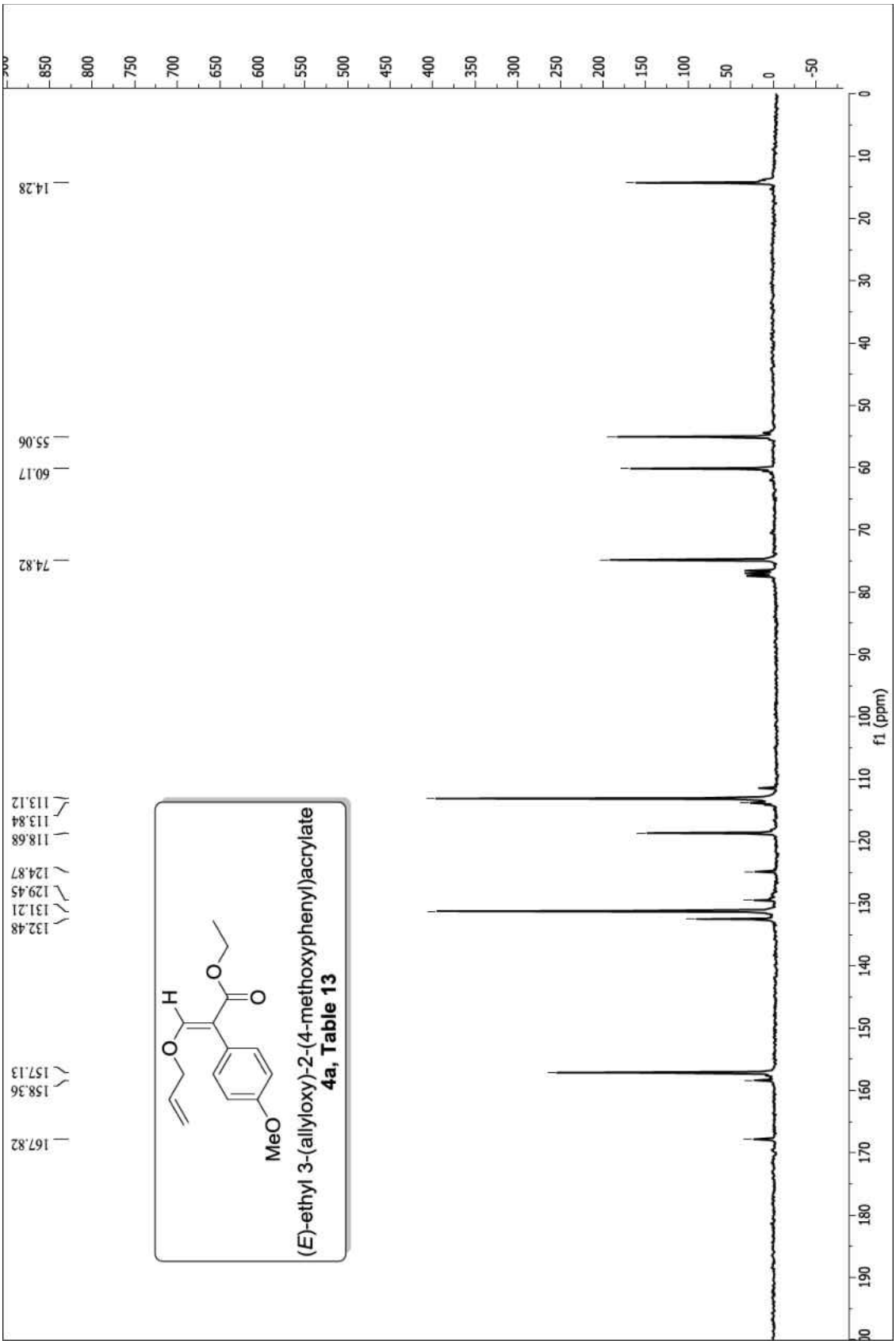

ethyl (E)-3-(allyloxy)-2-(p-tolyl)acrylate
2a, Table 13
0.98
4.40
0.91
2.00
2.14
2.23
3.40
3.37
f1 (ppm)

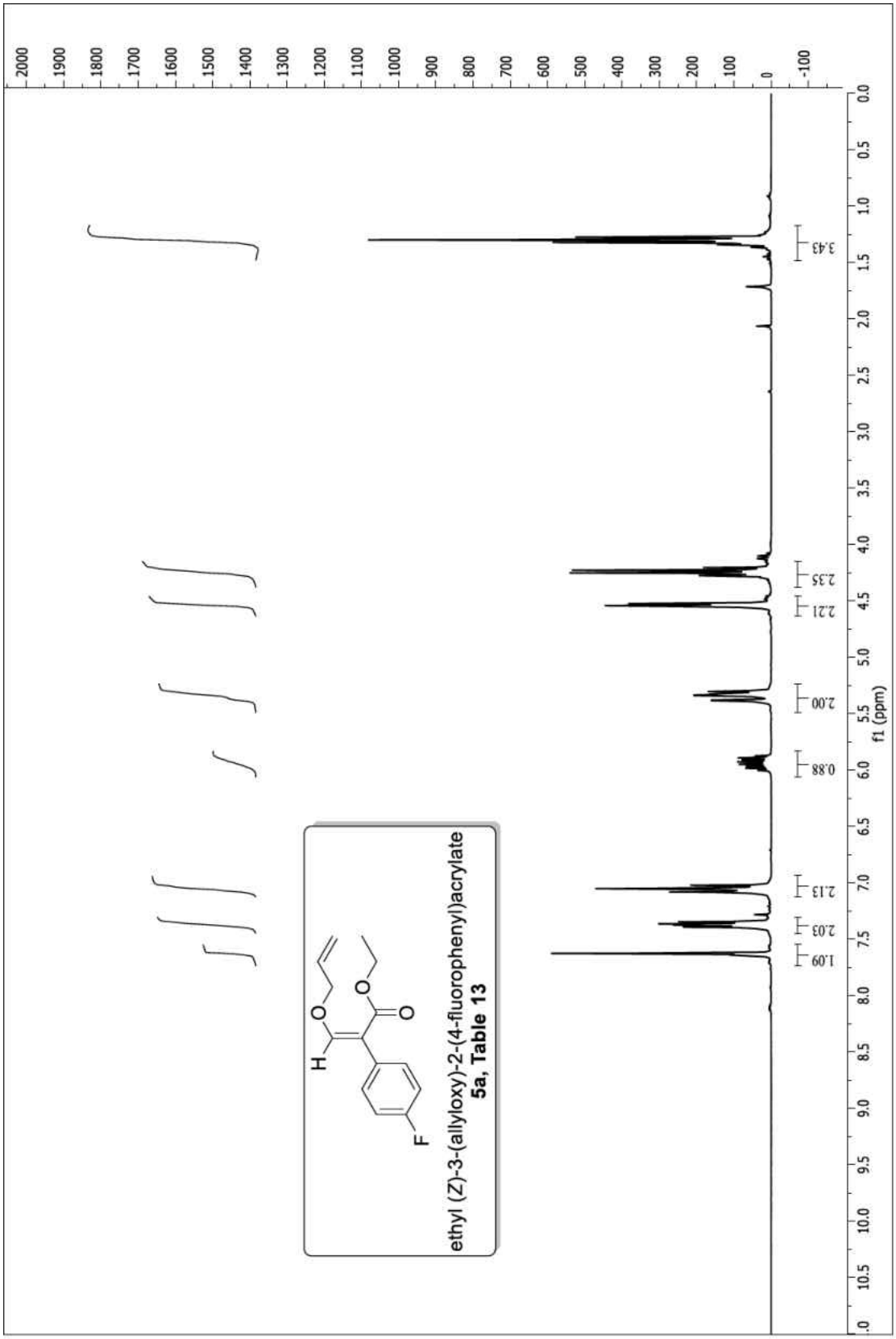

ethyl (E)-3-(allyloxy)-2-(p-tolyl)acrylate
2a, Table 13
167.74
157.46
136.54
132.57
130.02
129.73
128.42
118.63
111.87
74.85
60.18
21.22
14.35
f1 (ppm)

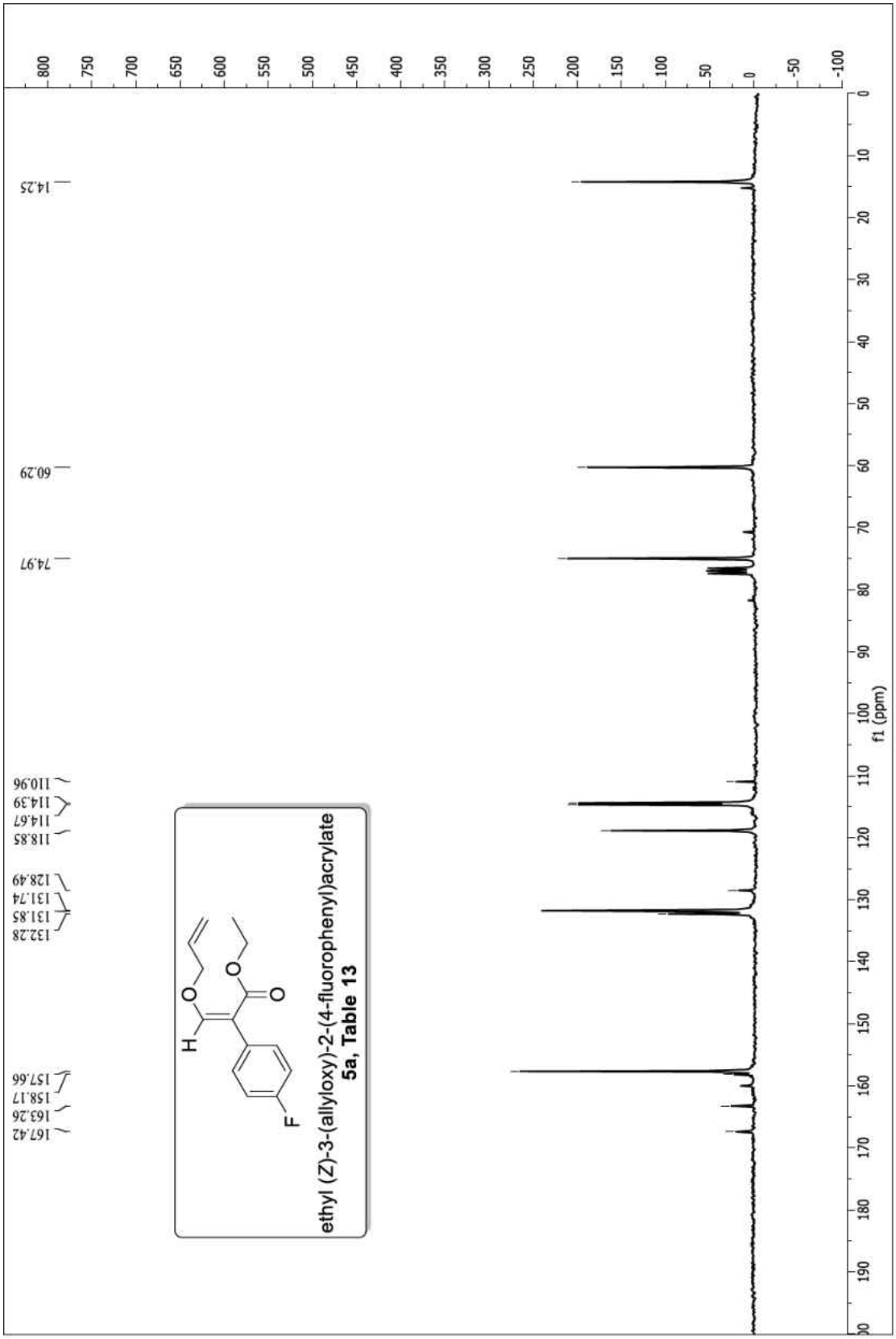

ethyl (E)-3-(allyloxy)-2-(2,4-dichlorophenyl)acrylate
3a, Table 13
3.42
2.38
2.38
2.31
1.00
0.97
0.91
2.24
f1 (ppm)

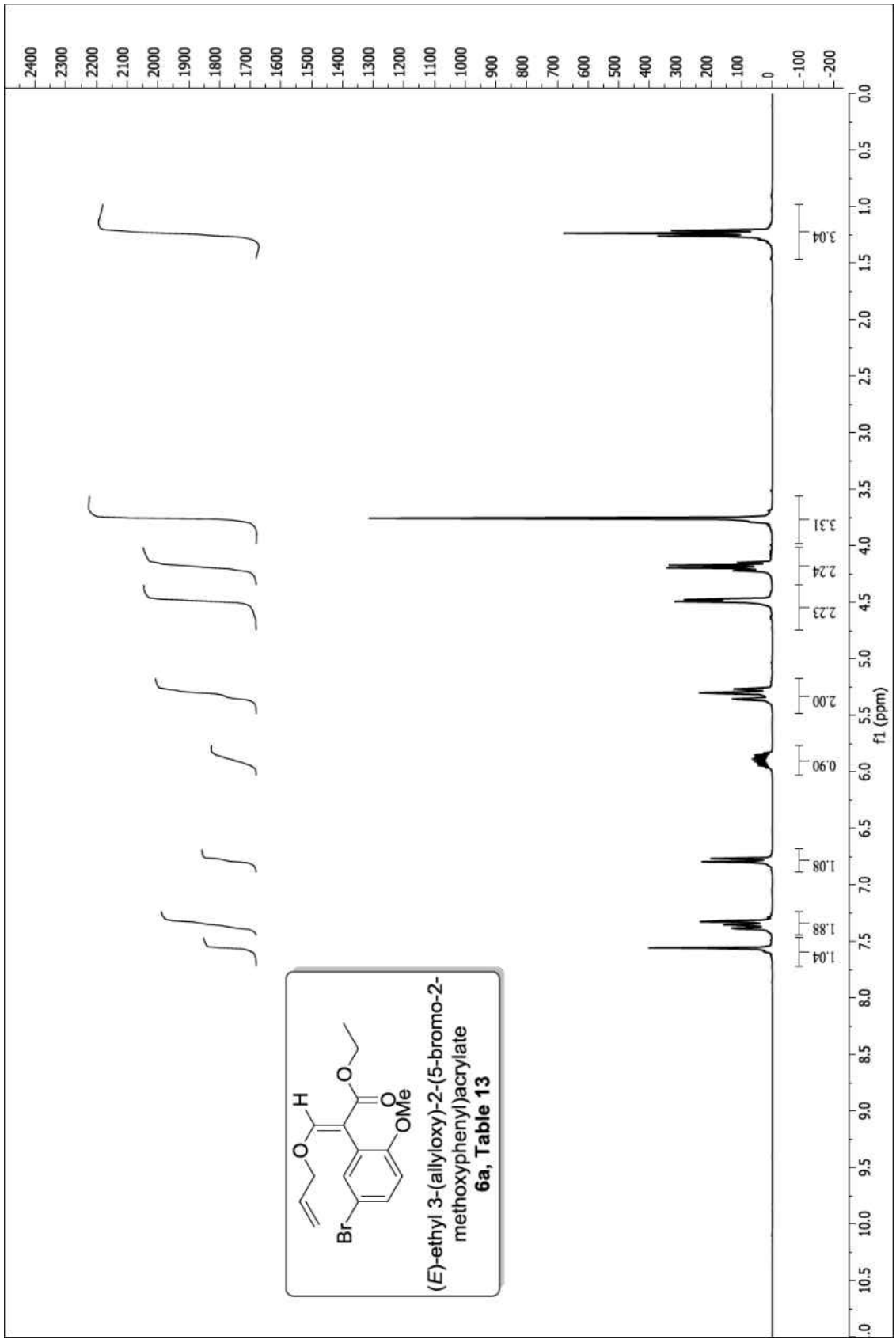

ethyl (E)-3-(allyloxy)-2-(2,4-dichlorophenyl)acrylate
3a, Table 13
166.54
158.72
135.19
133.76
132.95
132.09
130.73
129.07
126.64
118.98
109.27
75.05
60.41
14.19
f1 (ppm)

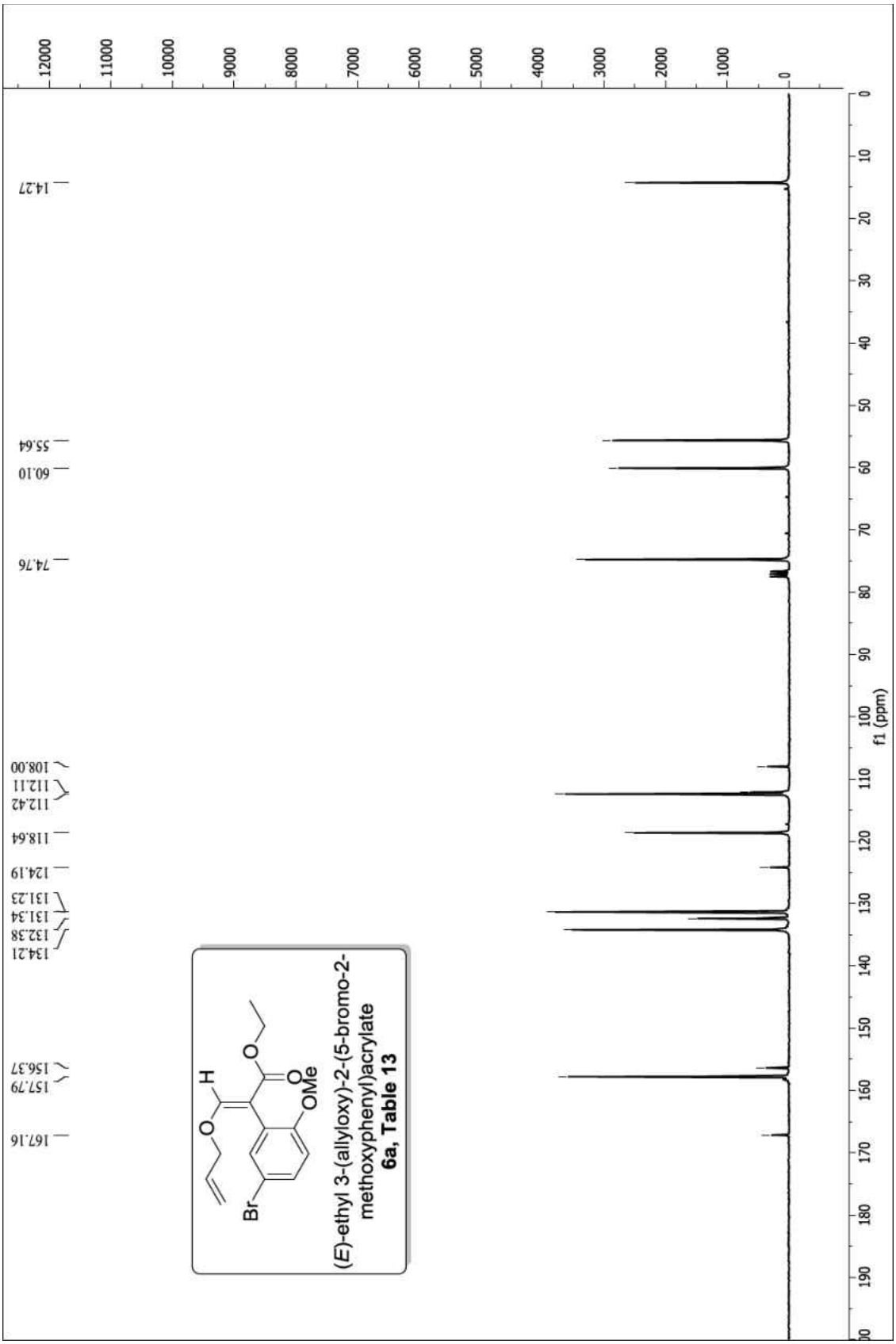

(E)-ethyl 3-(allyloxy)-2-(4-methoxyphenyl)acrylate
4a, Table 13
MeO
O
O
H
O
3.18
3.36
2.27
2.29
2.00
0.82
2.32
2.07
1.00
f1 (ppm)

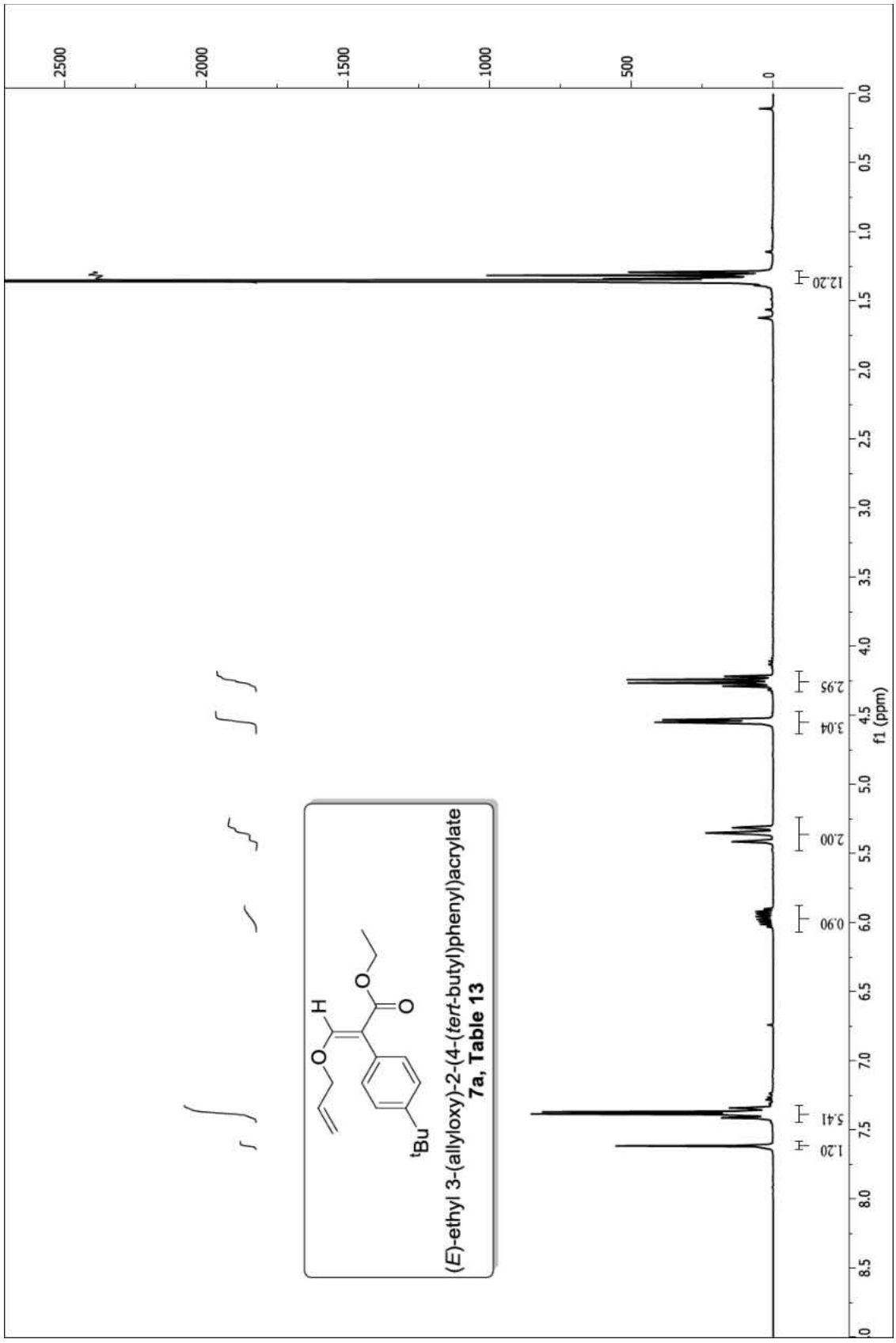

(E)-ethyl 3-(allyloxy)-2-(4-methoxyphenyl)acrylate
4a, Table 13
MeO
167.82
158.36
157.13
132.48
131.21
129.45
124.87
118.68
113.84
113.12
74.82
60.17
55.06
14.28
f1 (ppm)

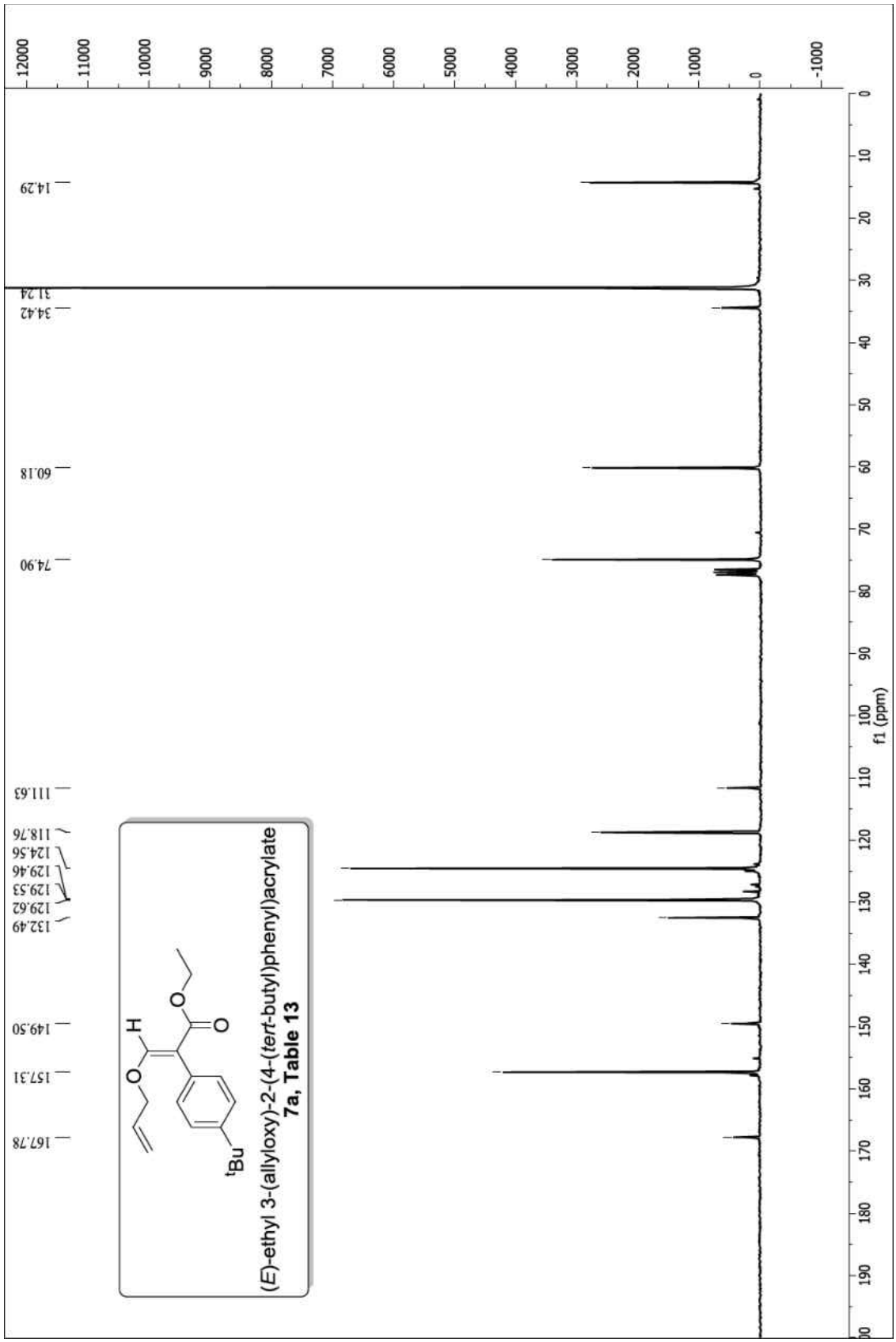

ethyl (Z)-3-(allyloxy)-2-(4-fluorophenyl)acrylate
5a, Table 13
3.43
2.35
2.21
2.00
0.88
2.13
2.03
1.09
f1 (ppm)

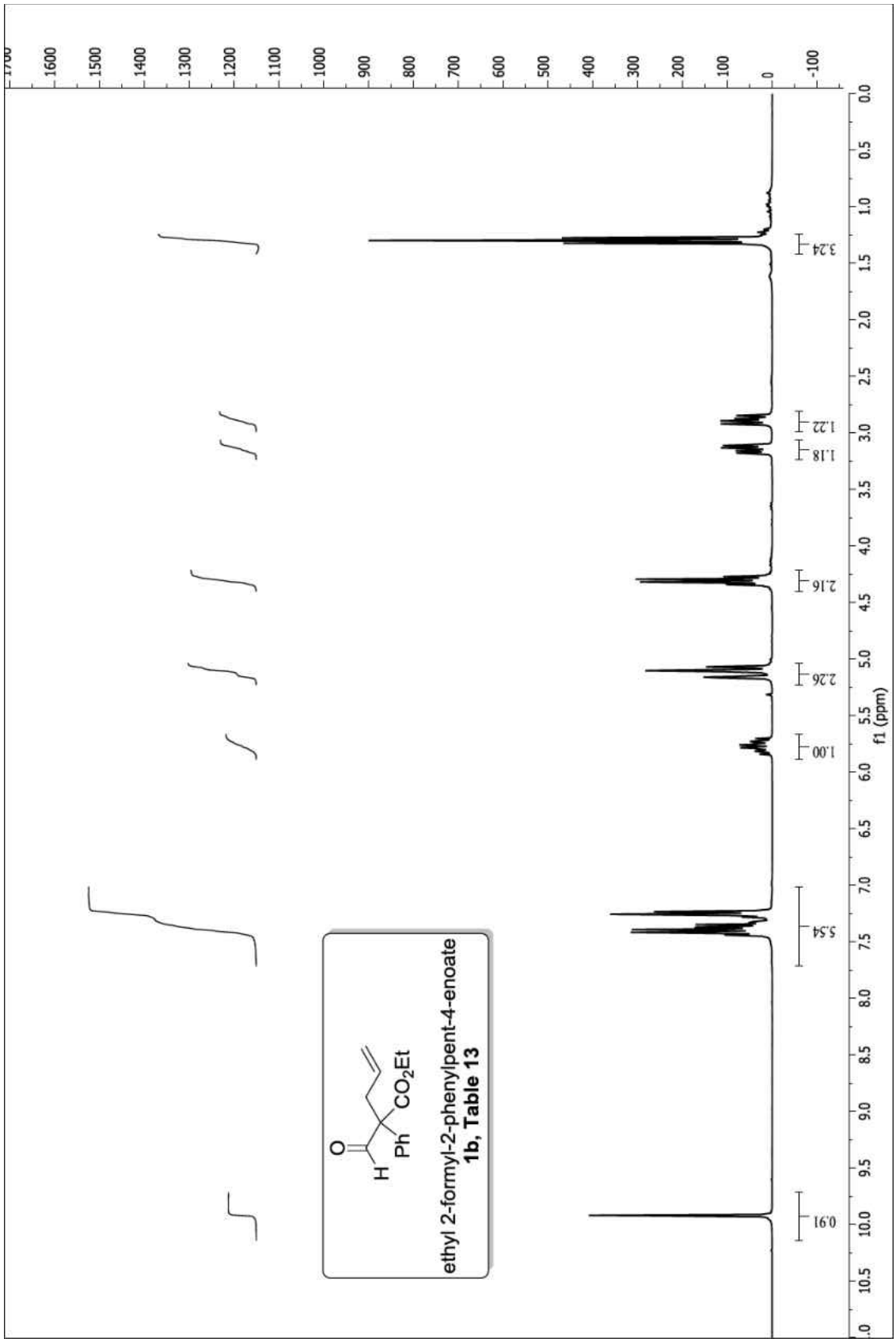

ethyl (Z)-3-(allyloxy)-2-(4-fluorophenyl)acrylate
5a, Table 13
14.25
60.29
74.97
110.96
114.39
114.67
118.85
128.49
131.74
131.85
132.28
157.66
158.17
163.26
167.42
f1 (ppm)

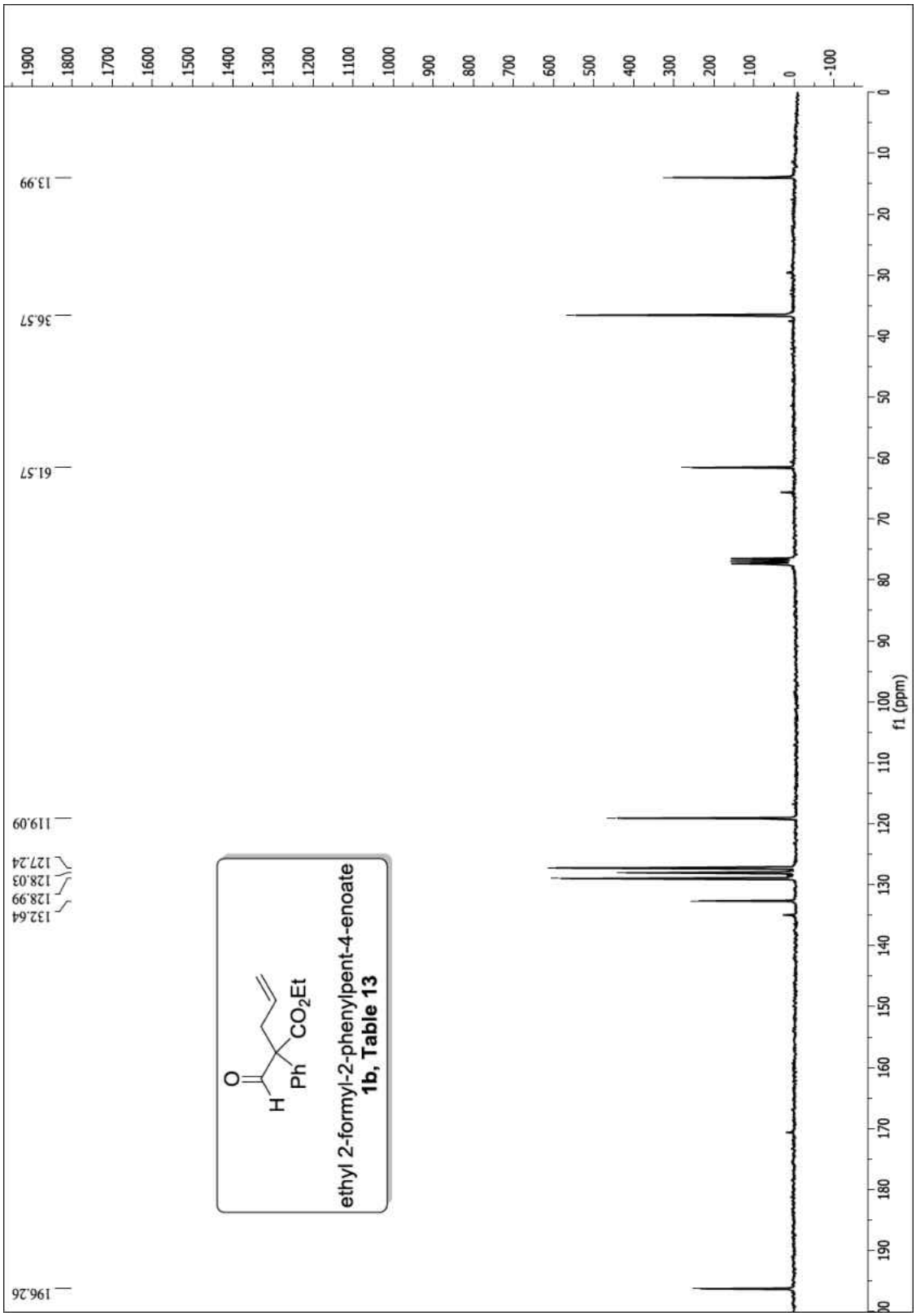

(E)-ethyl 3-(allyloxy)-2-(5-bromo-2-methoxyphenyl)acrylate
6a, Table 13
f1 (ppm)

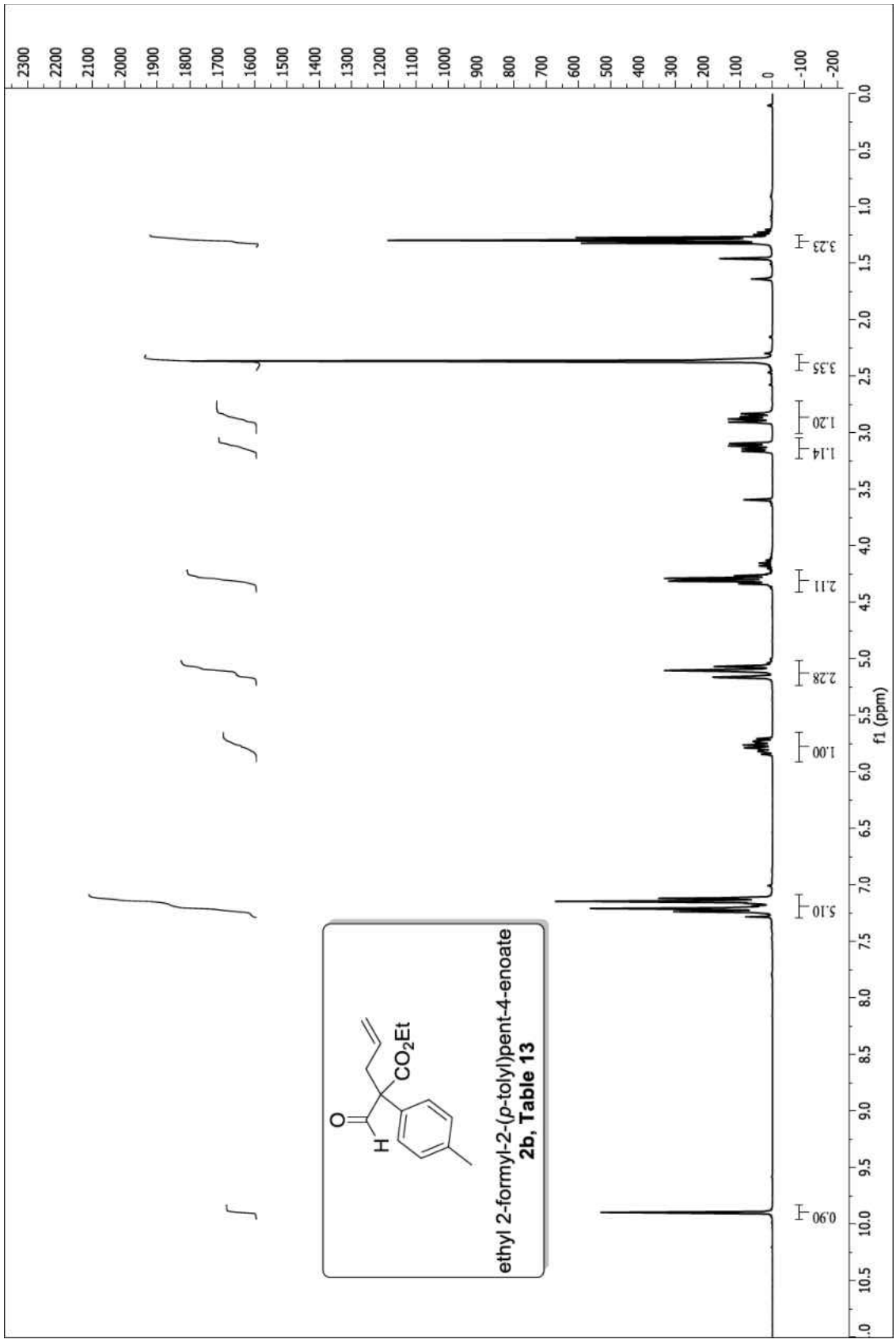

(E)-ethyl 3-(allyloxy)-2-(5-bromo-2-methoxyphenyl)acrylate
6a, Table 13
Br
OMe
167.16
157.79
156.37
134.21
132.38
131.34
131.23
124.19
118.64
112.42
112.11
108.00
74.76
60.10
55.64
14.27
f1 (ppm)

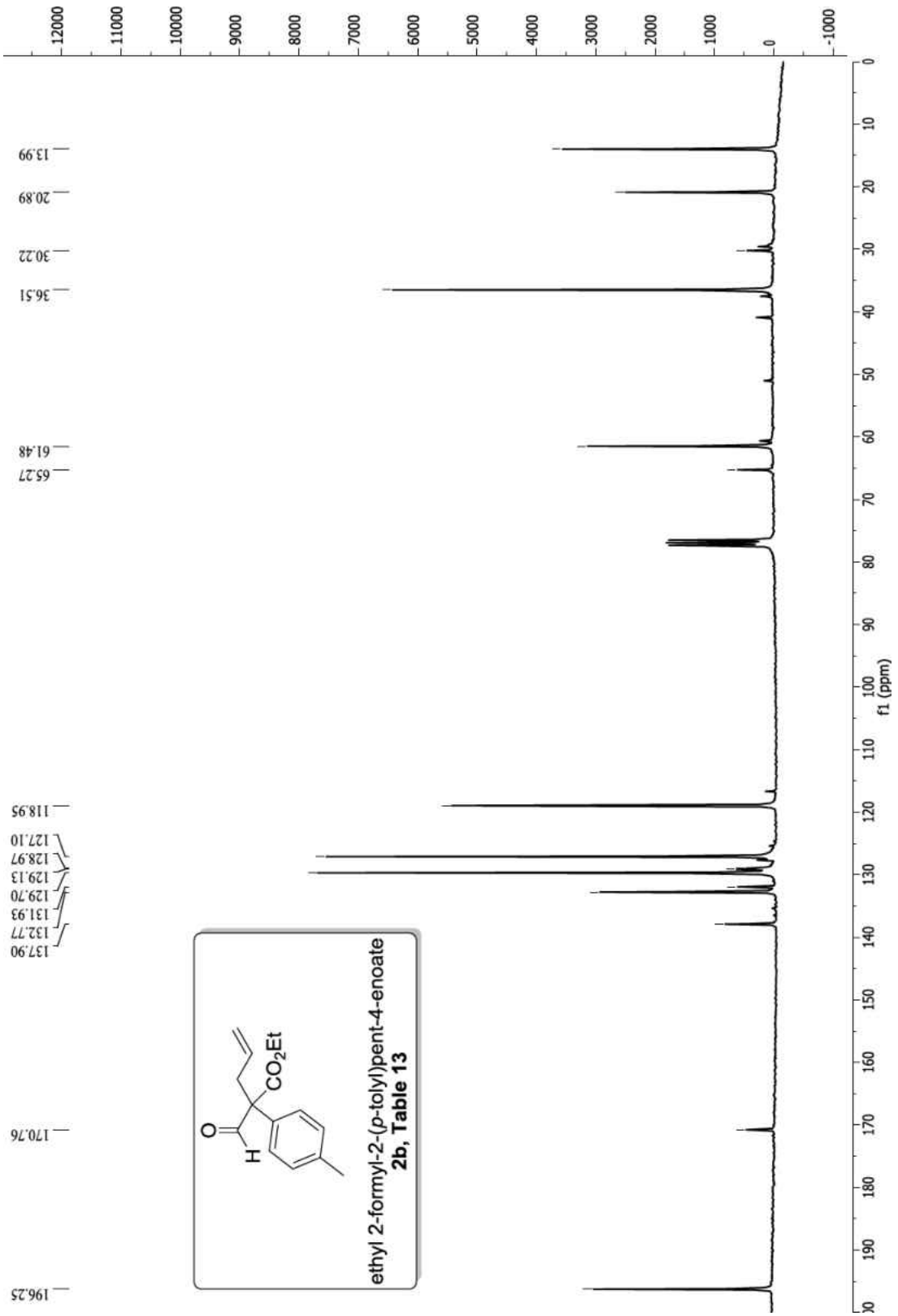

(E)-ethyl 3-(allyloxy)-2-(4-(tert-butyl)phenyl)acrylate
7a, Table 13
tBu
12.20
2.95
3.04
2.00
0.90
5.41
1.20
f1 (ppm)

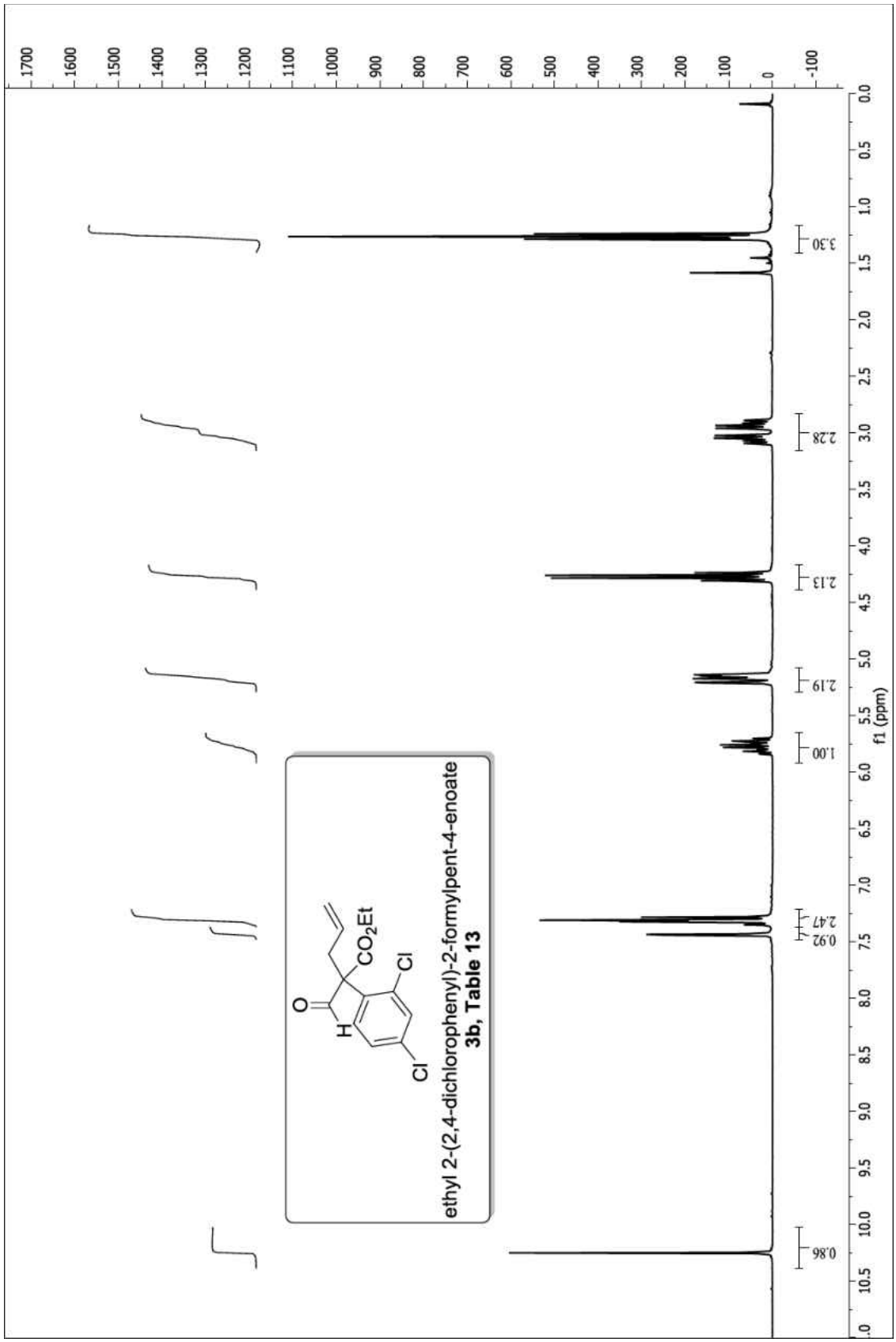

(E)-ethyl 3-(allyloxy)-2-(4-(tert-butyl)phenyl)acrylate
7a, Table 13
tBu
14.29
31.24
34.42
60.18
74.90
111.63
118.76
124.56
129.46
129.53
129.62
132.49
149.50
157.31
167.78
f1 (ppm)

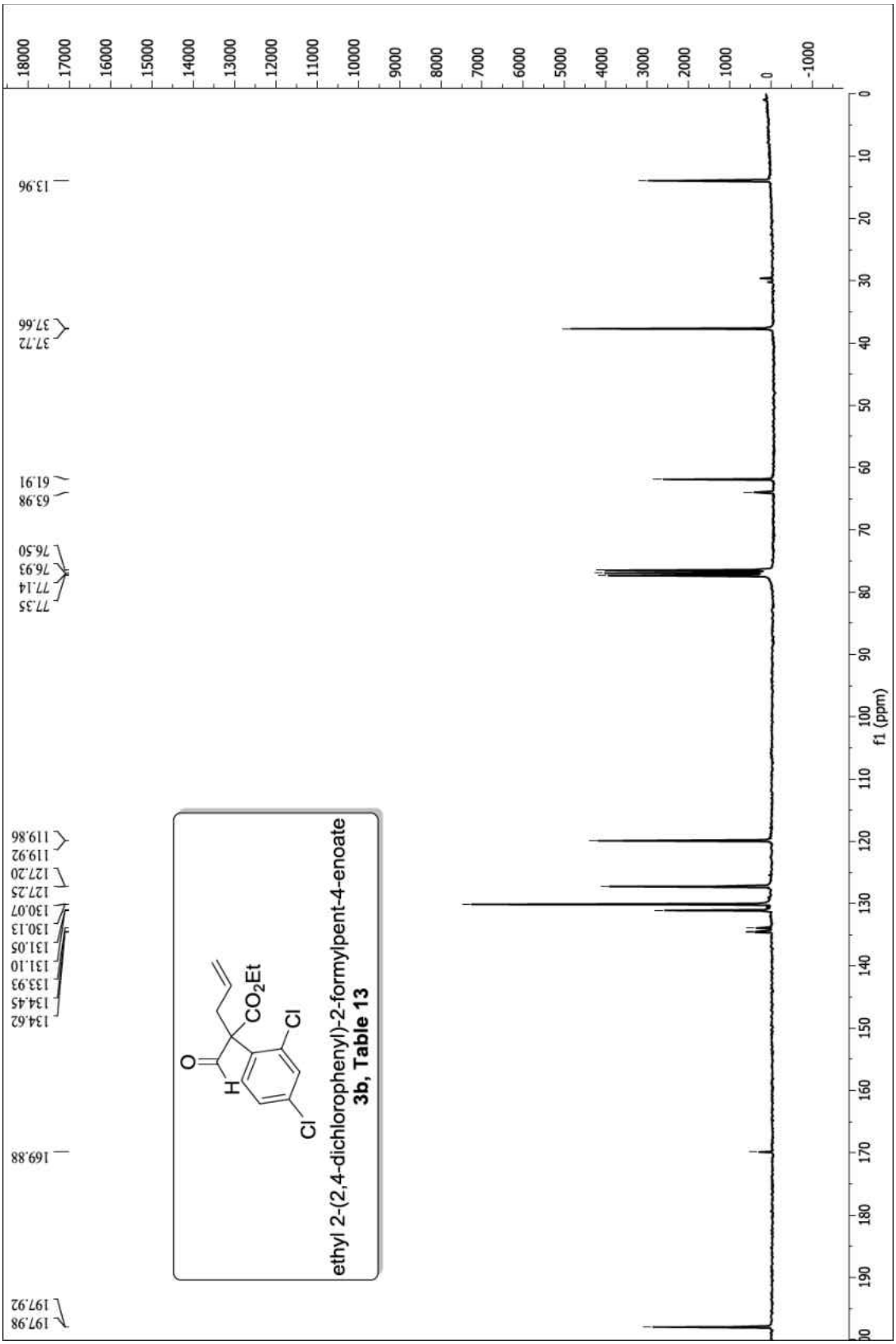

ethyl 2-formyl-2-phenylpent-4-enoate
1b, Table 13
O
H
Ph
CO2Et
0.91
5.54
1.00
2.26
2.16
1.18
1.22
3.24
f1 (ppm)

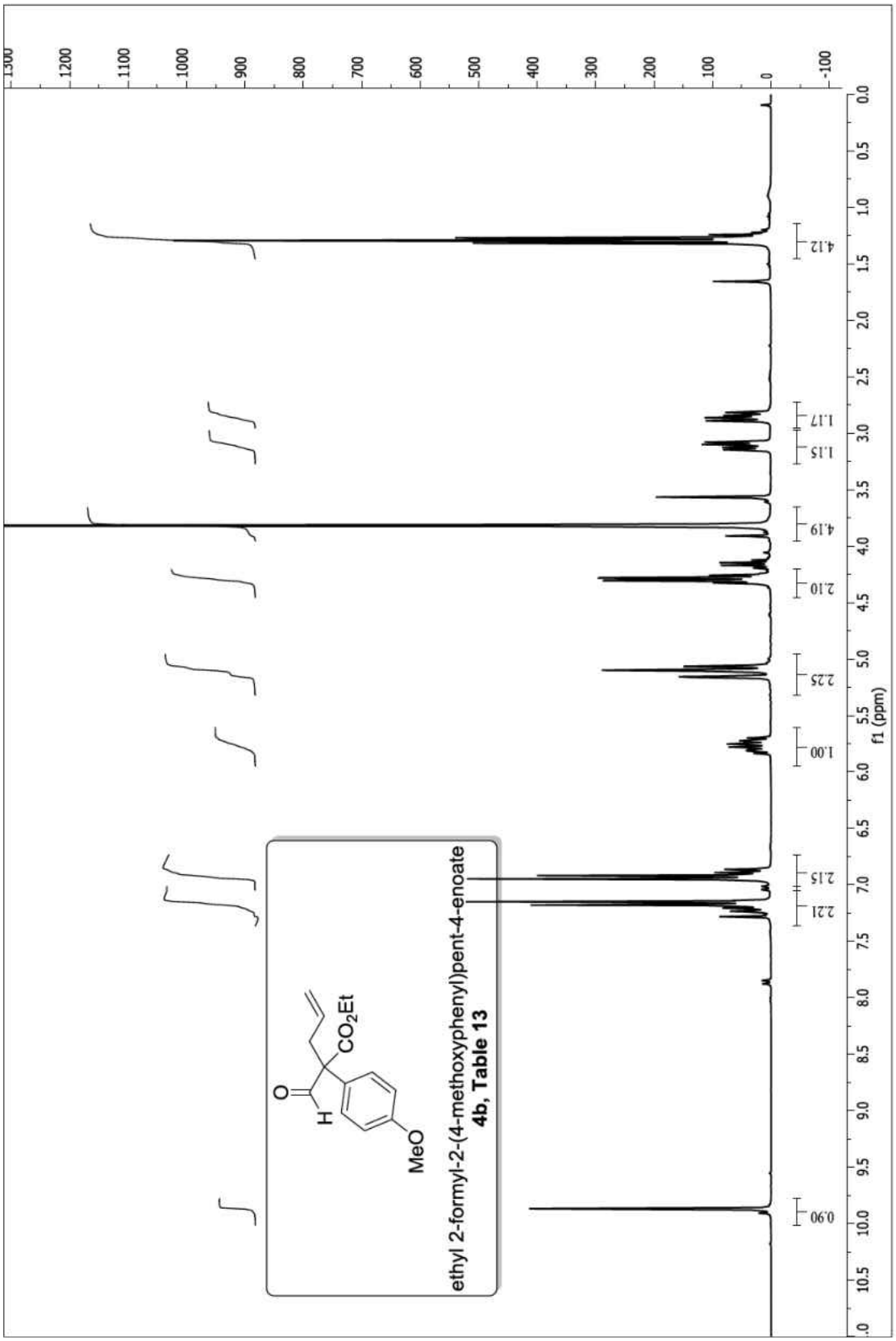

196.26
132.64
128.99
128.03
127.24
119.09
61.57
36.57
13.99
ethyl 2-formyl-2-phenylpent-4-enoate
1b, Table 13
f1 (ppm)

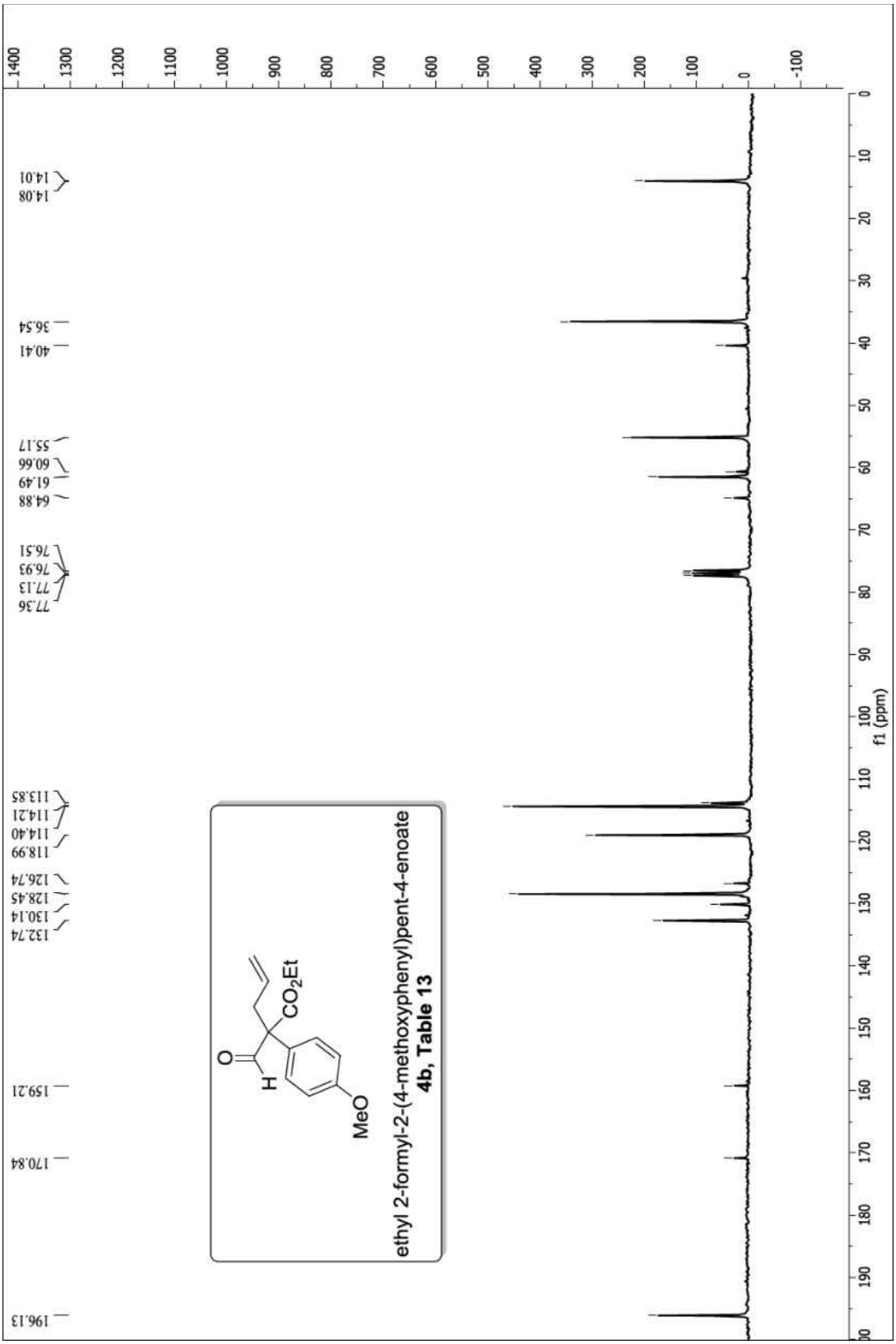

ethyl 2-formyl-2-(p-tolyl)pent-4-enoate
2b, Table 13
CO2Et
O
H
0.90
5.10
1.00
2.28
2.11
1.20
1.14
3.35
3.23
f1 (ppm)

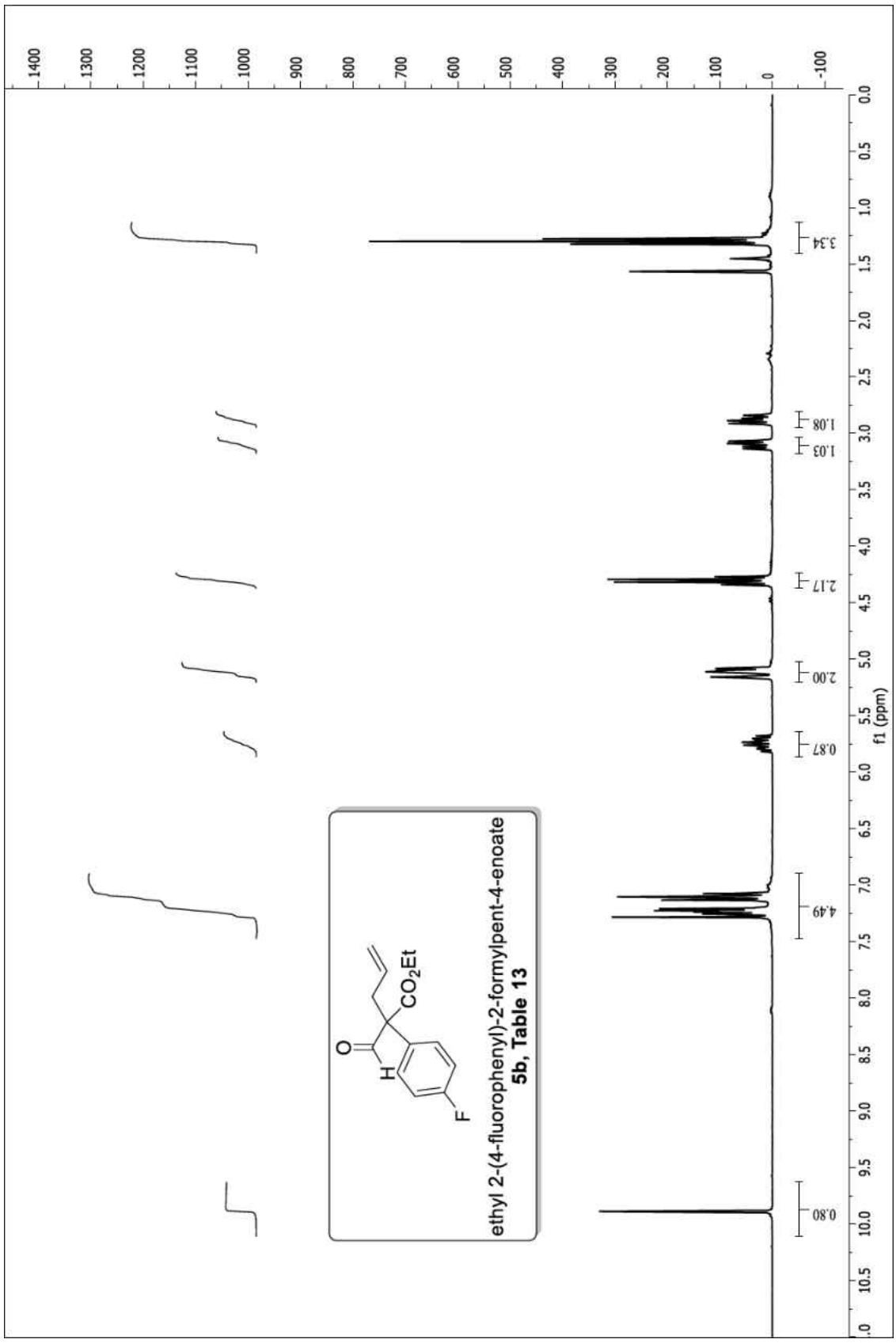

ethyl 2-formyl-2-(p-tolyl)pent-4-enoate
2b, Table 13
CO2Et
O
H
196.25
170.76
137.90
132.77
131.93
129.70
129.13
128.97
127.10
118.95
65.27
61.48
36.51
30.22
20.89
13.99
f1 (ppm)

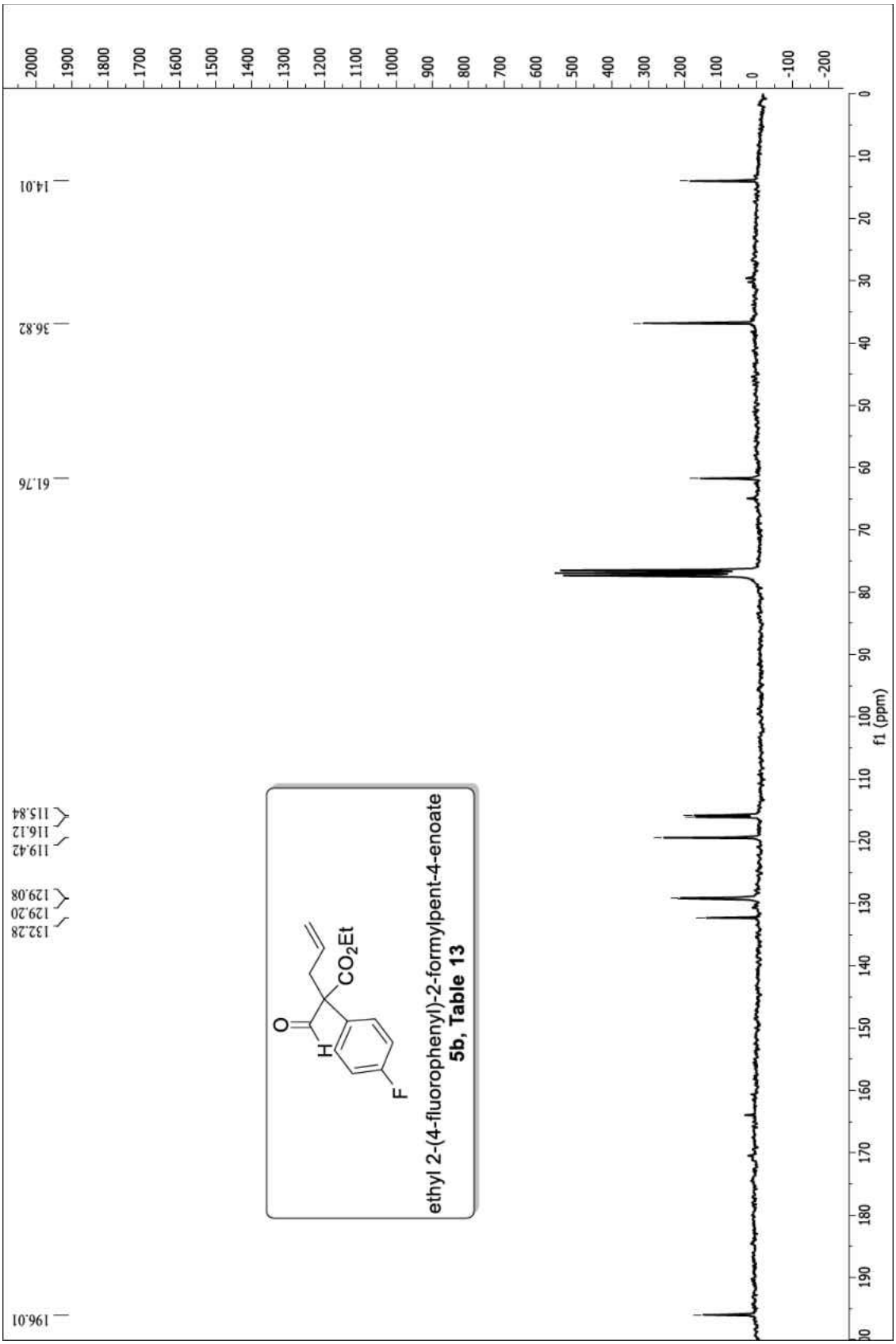

ethyl 2-(2,4-dichlorophenyl)-2-formylpent-4-enoate
3b, Table 13
CO2Et
Cl
Cl
O
H
3.30
2.28
2.13
2.19
1.00
0.92
2.47
0.86
f1 (ppm)

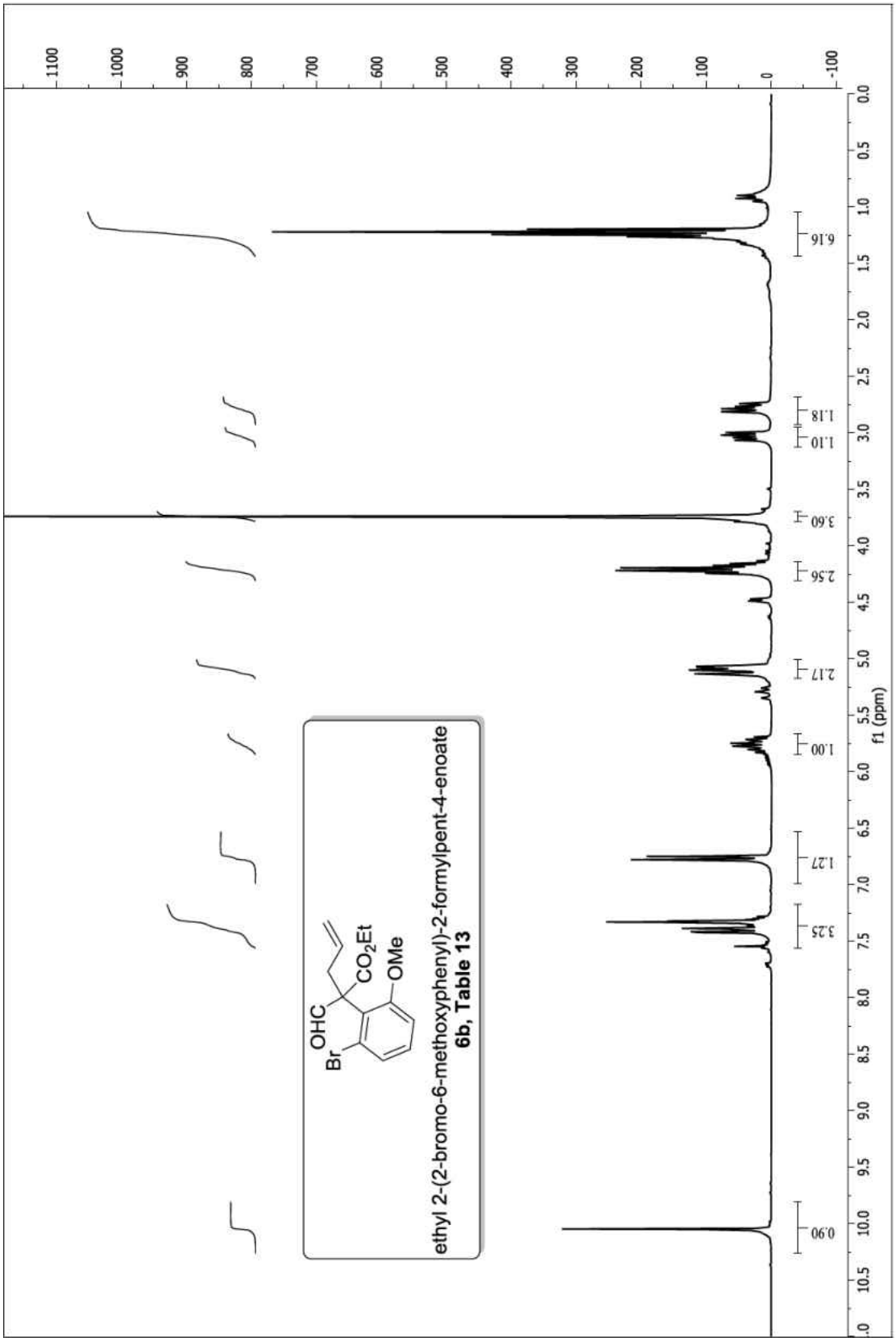

ethyl 2-(2,4-dichlorophenyl)-2-formylpent-4-enoate
3b, Table 13
O
H
CO2Et
Cl
Cl
f1 (ppm)
197.98
197.92
169.88
134.62
134.45
133.93
131.10
131.05
130.13
130.07
127.25
127.20
119.92
119.86
77.35
77.14
76.93
76.50
63.98
61.91
37.72
37.66
13.96

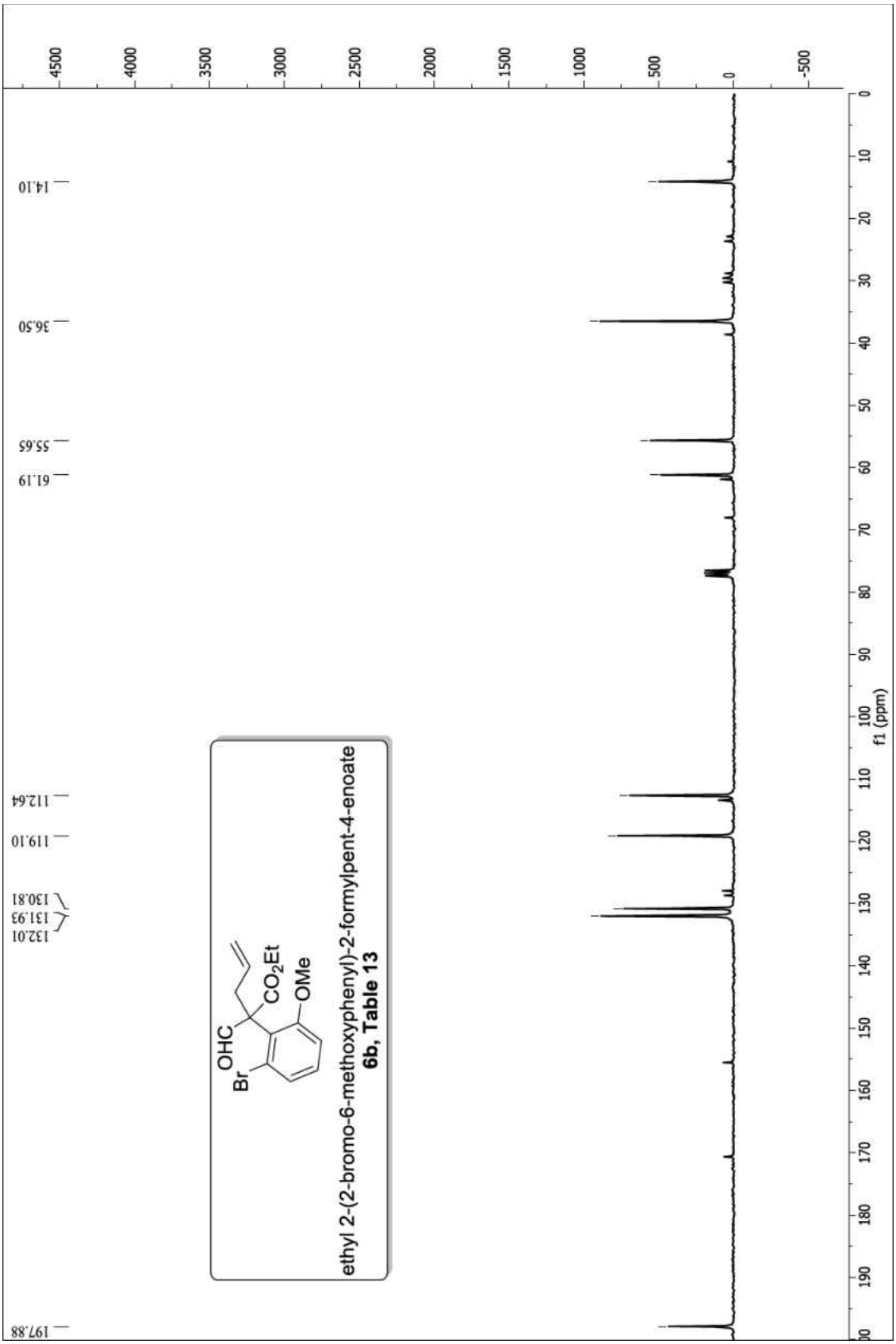

ethyl 2-formyl-2-(4-methoxyphenyl)pent-4-enoate
4b, Table 13
MeO
CO2Et
O
H
f1 (ppm)
0.90
2.21
2.15
1.00
2.25
2.10
4.19
1.15
1.17
4.12

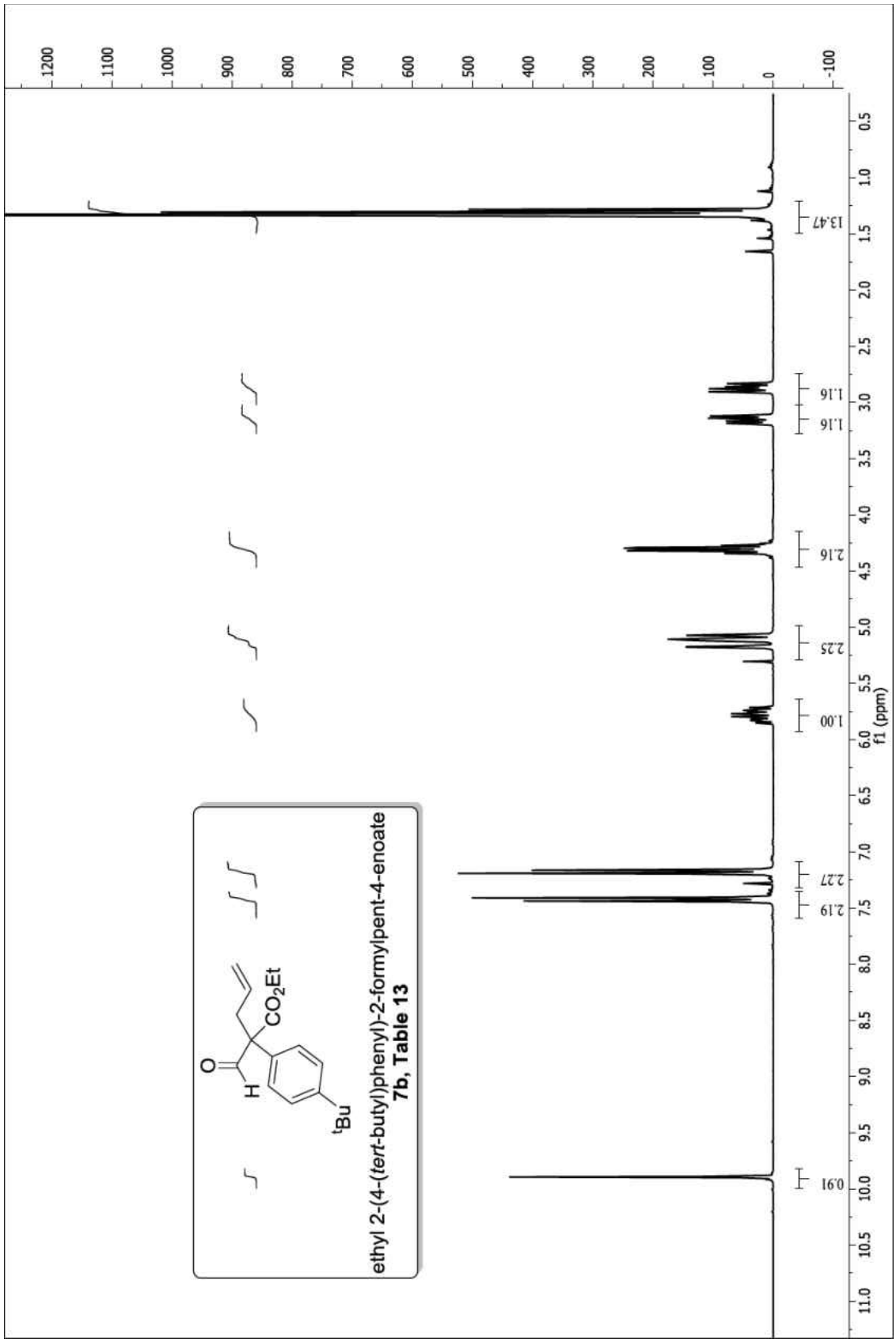

ethyl 2-formyl-2-(4-methoxyphenyl)pent-4-enoate
4b, Table 13
CO2Et
O
H
MeO
14.01
14.08
36.54
40.41
55.17
60.66
61.49
64.88
76.51
76.93
77.13
77.36
113.85
114.21
114.40
118.99
126.74
128.45
130.14
132.74
159.21
170.84
196.13
f1 (ppm)

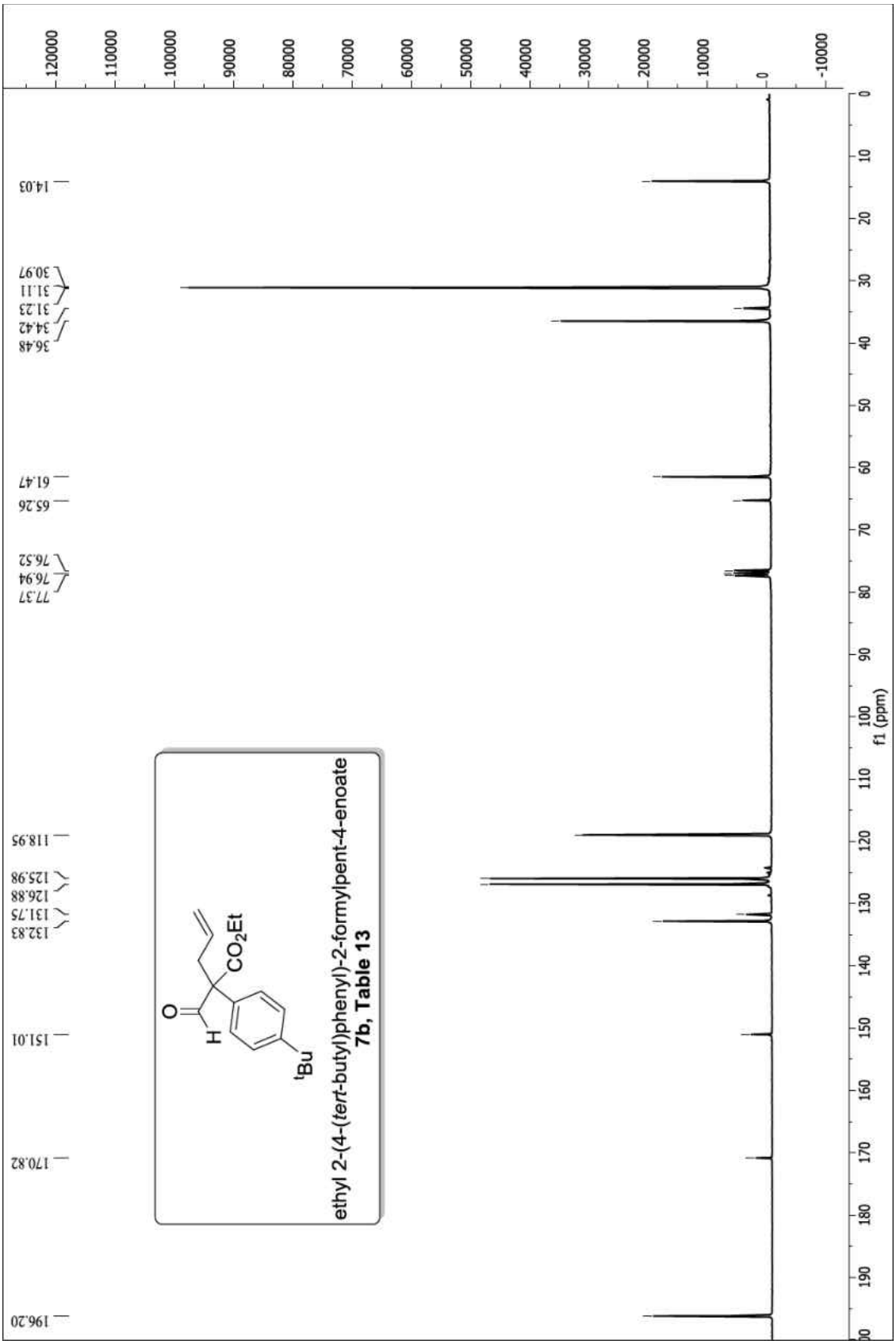

ethyl 2-(4-fluorophenyl)-2-formylpent-4-enoate
5b, Table 13
CO2Et
O
H
F
3.34
1.08
1.03
2.17
2.00
0.87
4.49
0.80
f1 (ppm)

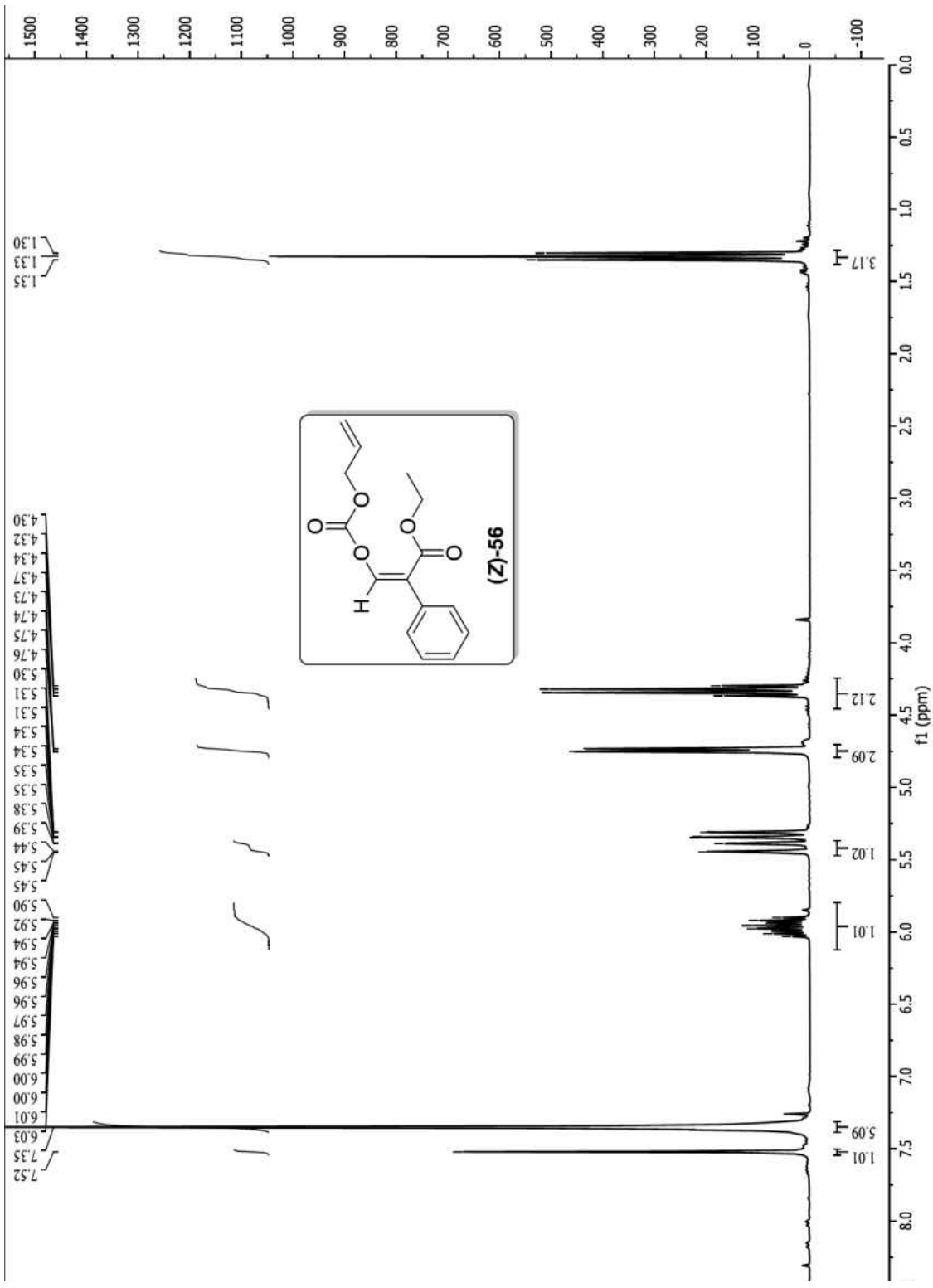

196.01
132.28
129.20
129.08
119.42
116.12
115.84
61.76
36.82
14.01
CO2Et
O
H
F
ethyl 2-(4-fluorophenyl)-2-formylpent-4-enoate
5b, Table 13
f1 (ppm)

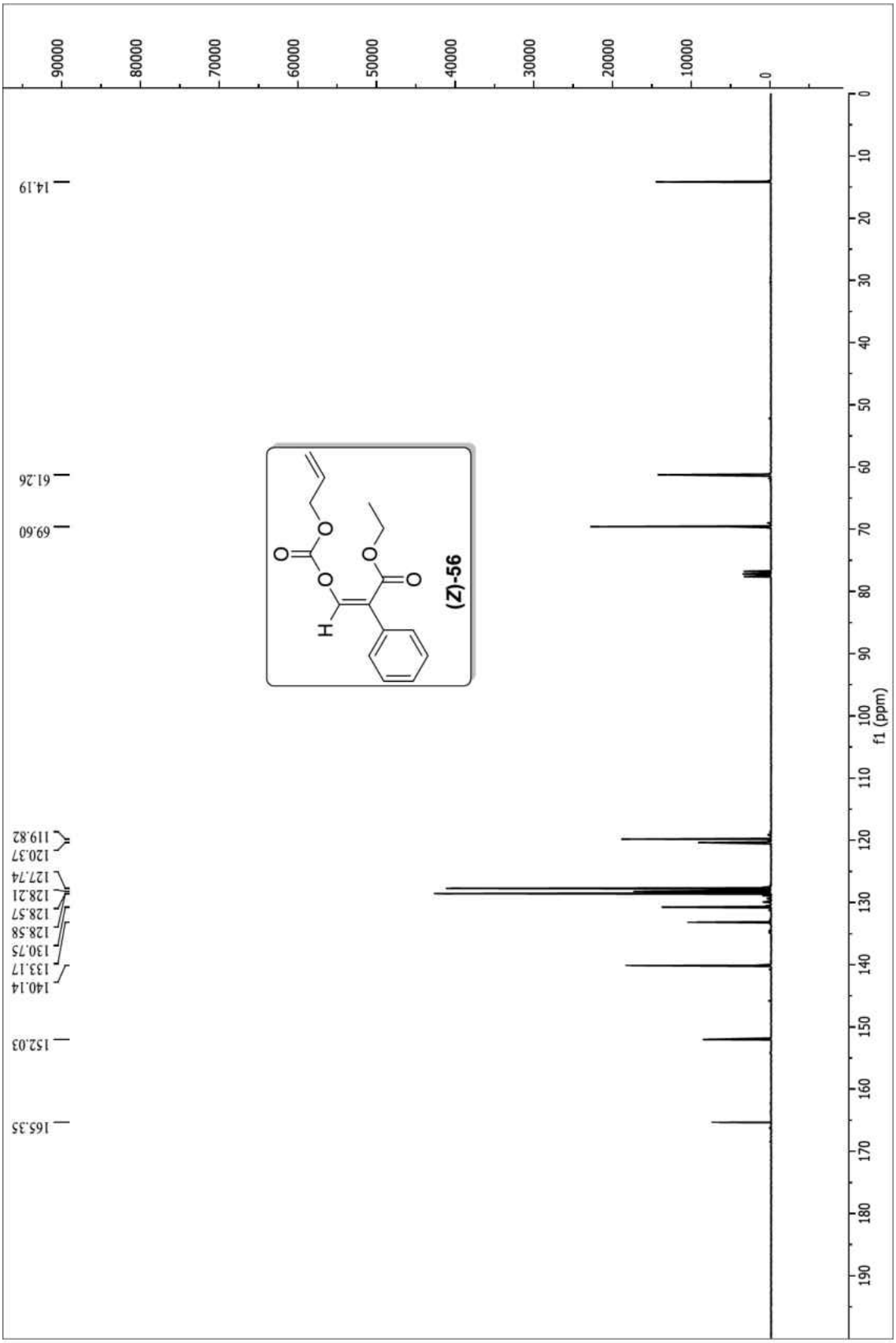

ethyl 2-(2-bromo-6-methoxyphenyl)-2-formylpent-4-enoate
6b, Table 13
OHC
Br
CO2Et
OMe
f1 (ppm)

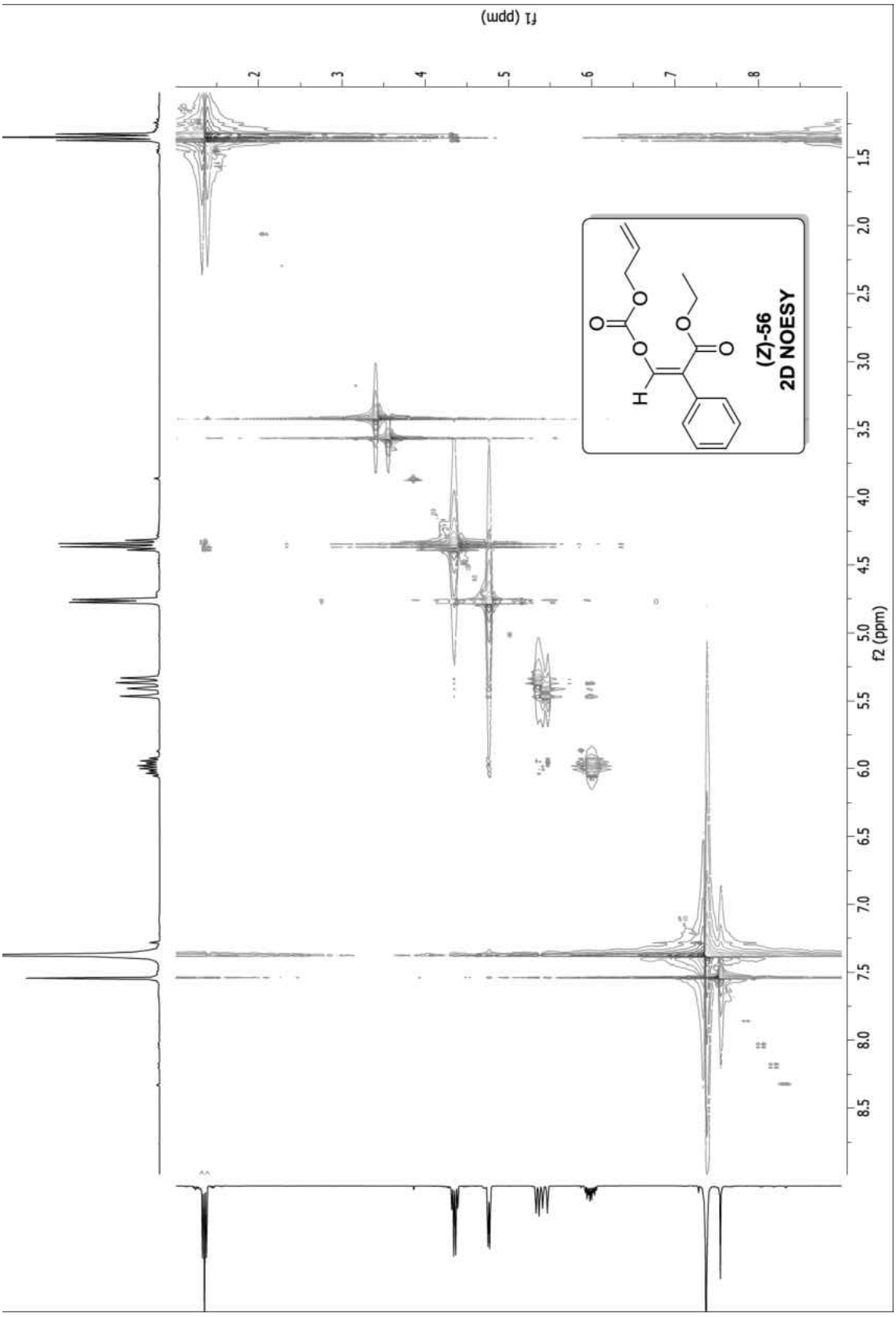

ethyl 2-(2-bromo-6-methoxyphenyl)-2-formylpent-4-enoate
6b, Table 13
OHC
Br
CO2Et
OMe
197.88
132.01
131.93
130.81
119.10
112.64
61.19
55.65
36.50
14.10
f1 (ppm)

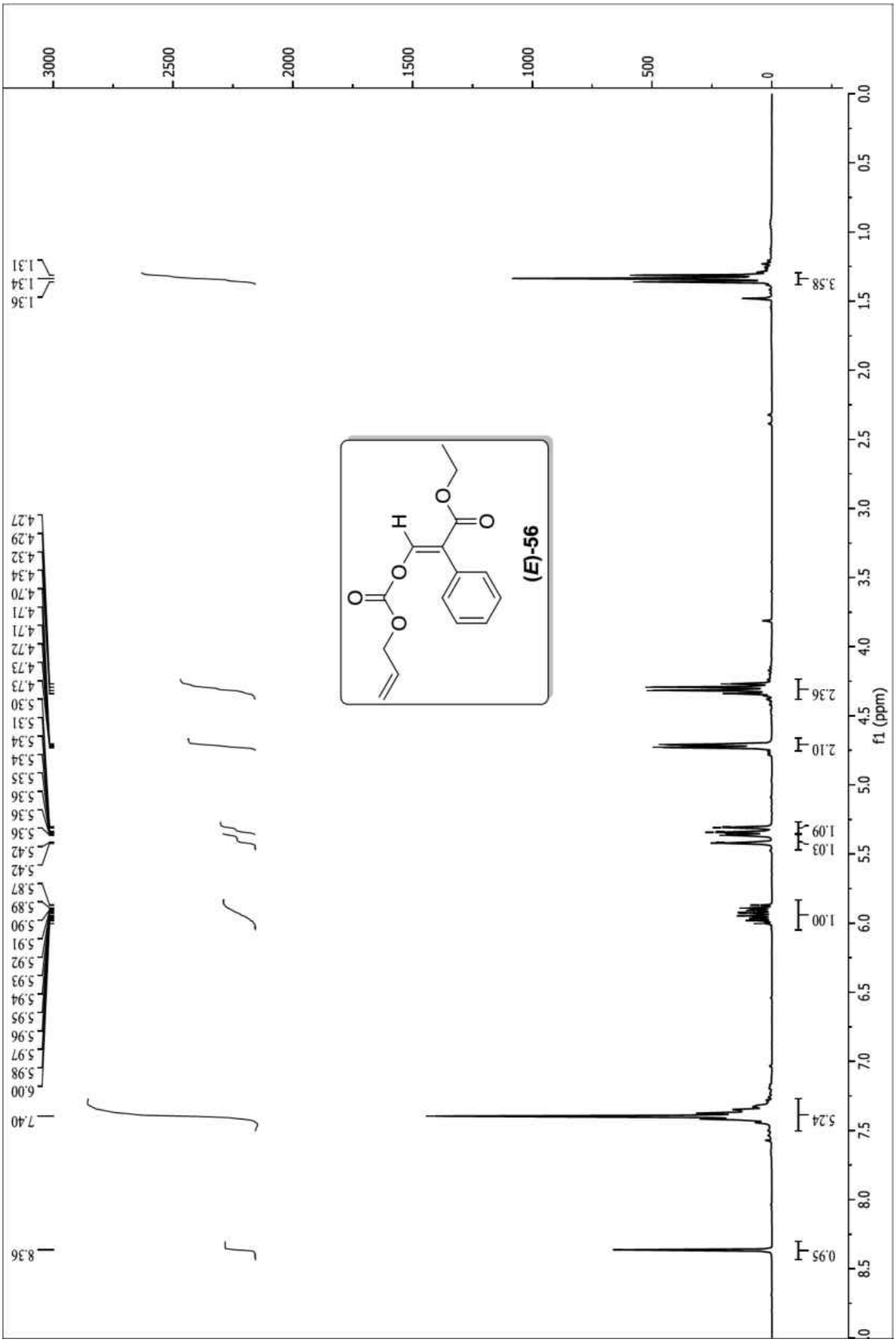

ethyl 2-(4-(tert-butyl)phenyl)-2-formylpent-4-enoate
7b, Table 13
O
H
CO2Et
tBu
13.47
1.16
1.16
2.16
2.25
1.00
2.27
2.19
0.91
f1 (ppm)

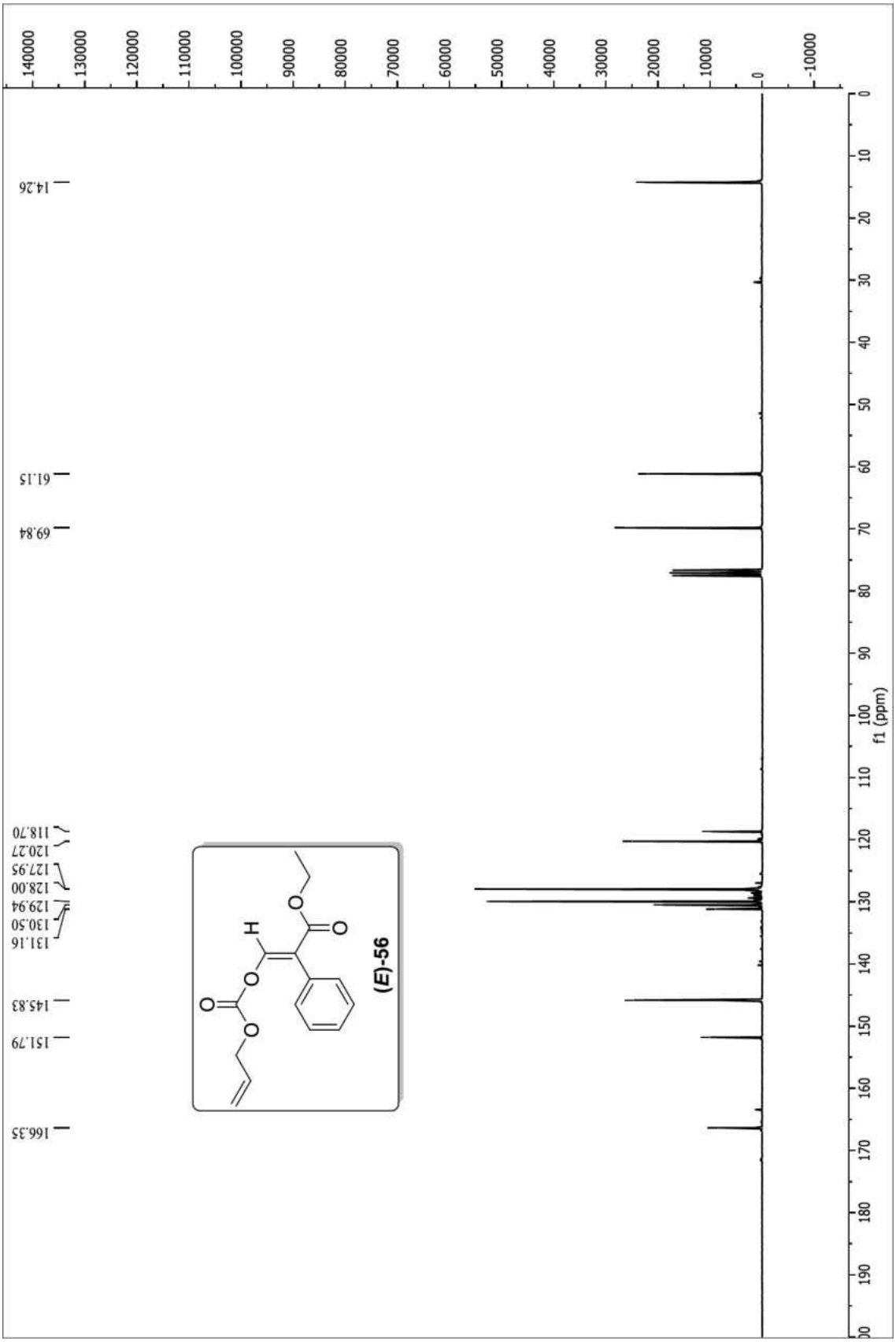

ethyl 2-(4-(tert-butyl)phenyl)-2-formylpent-4-enoate
7b, Table 13
CO2Et
O
H
tBu
f1 (ppm)
14.03
30.97
31.11
31.23
34.42
36.48
61.47
65.26
76.52
76.94
77.37
118.95
125.98
126.88
131.75
132.83
151.01
170.82
196.20

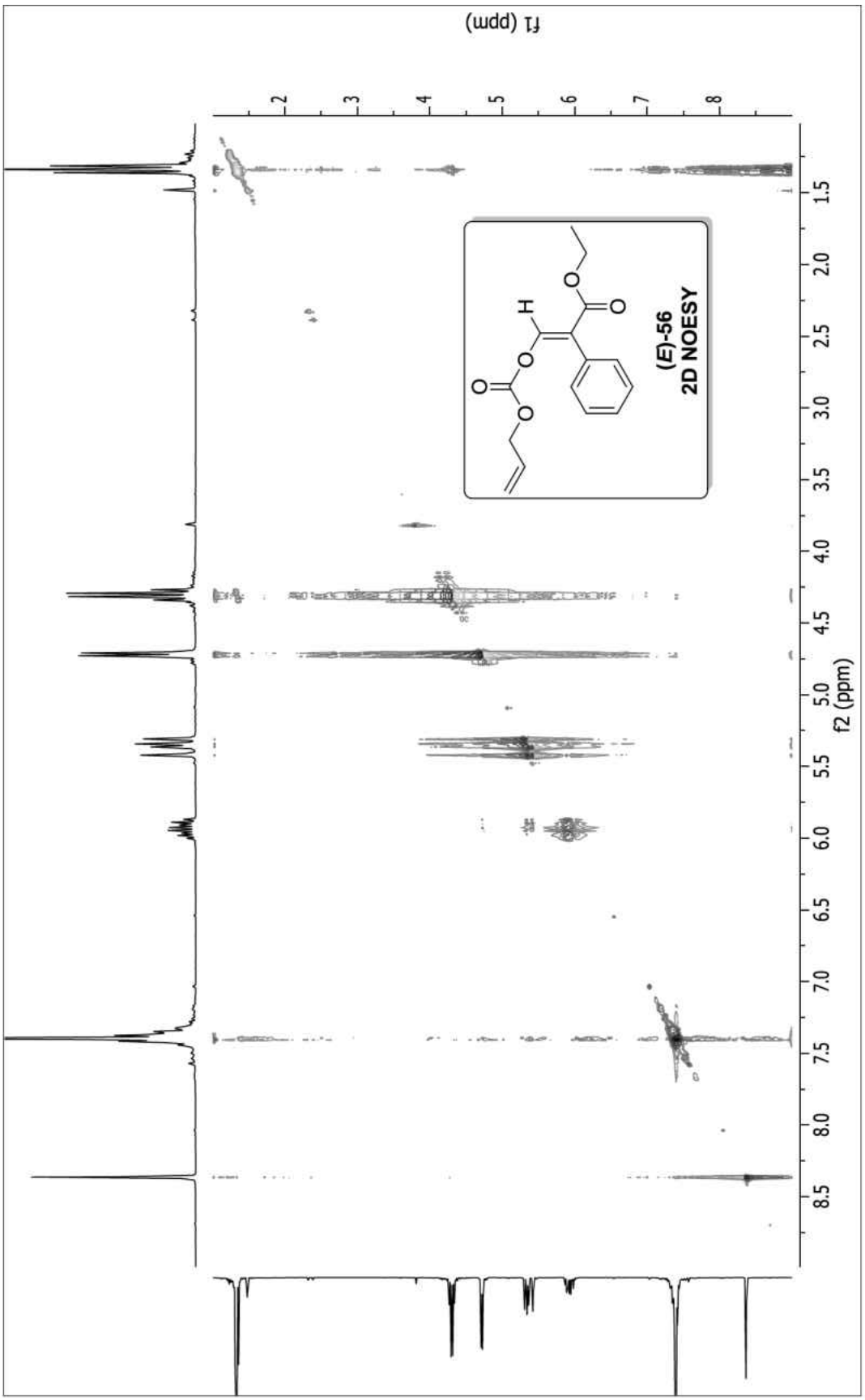

(Z)-56
f1 (ppm)

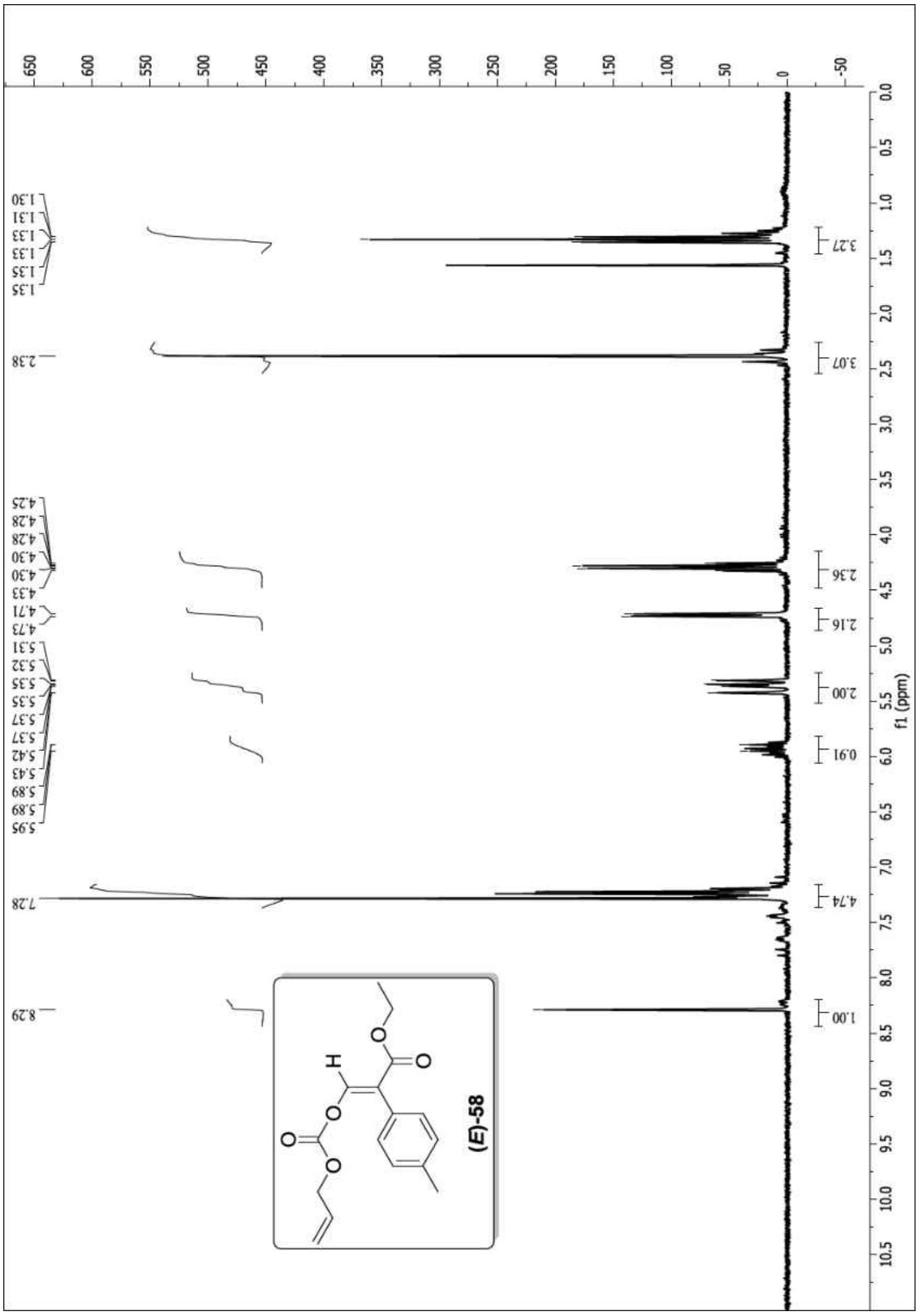

14.19
61.26
69.60
119.82
120.37
127.74
128.21
128.57
128.58
130.75
133.17
140.14
152.03
165.35
(Z)-56
f1 (ppm)

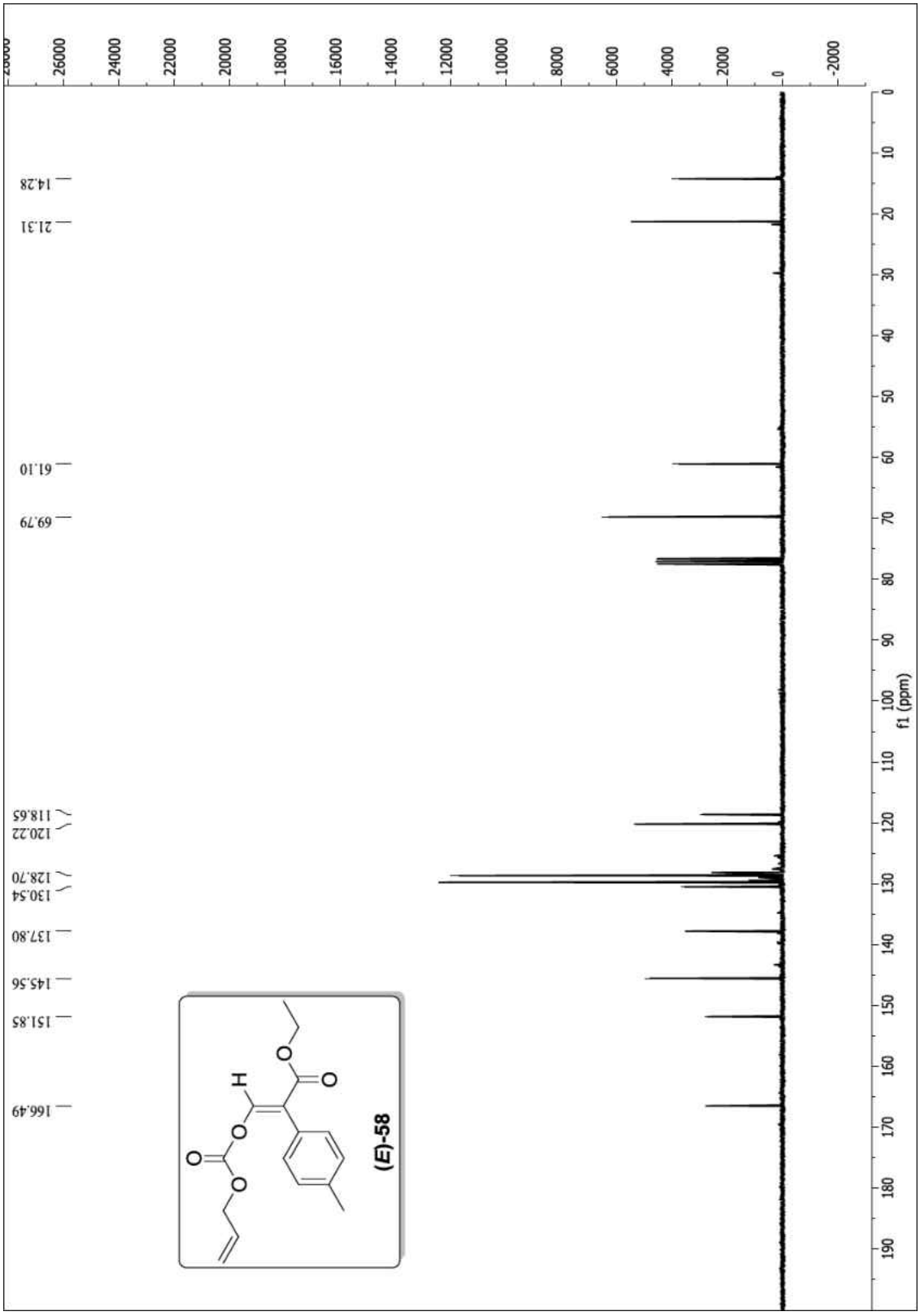

f1 (ppm)
f2 (ppm)
(Z)-56
2D NOESY

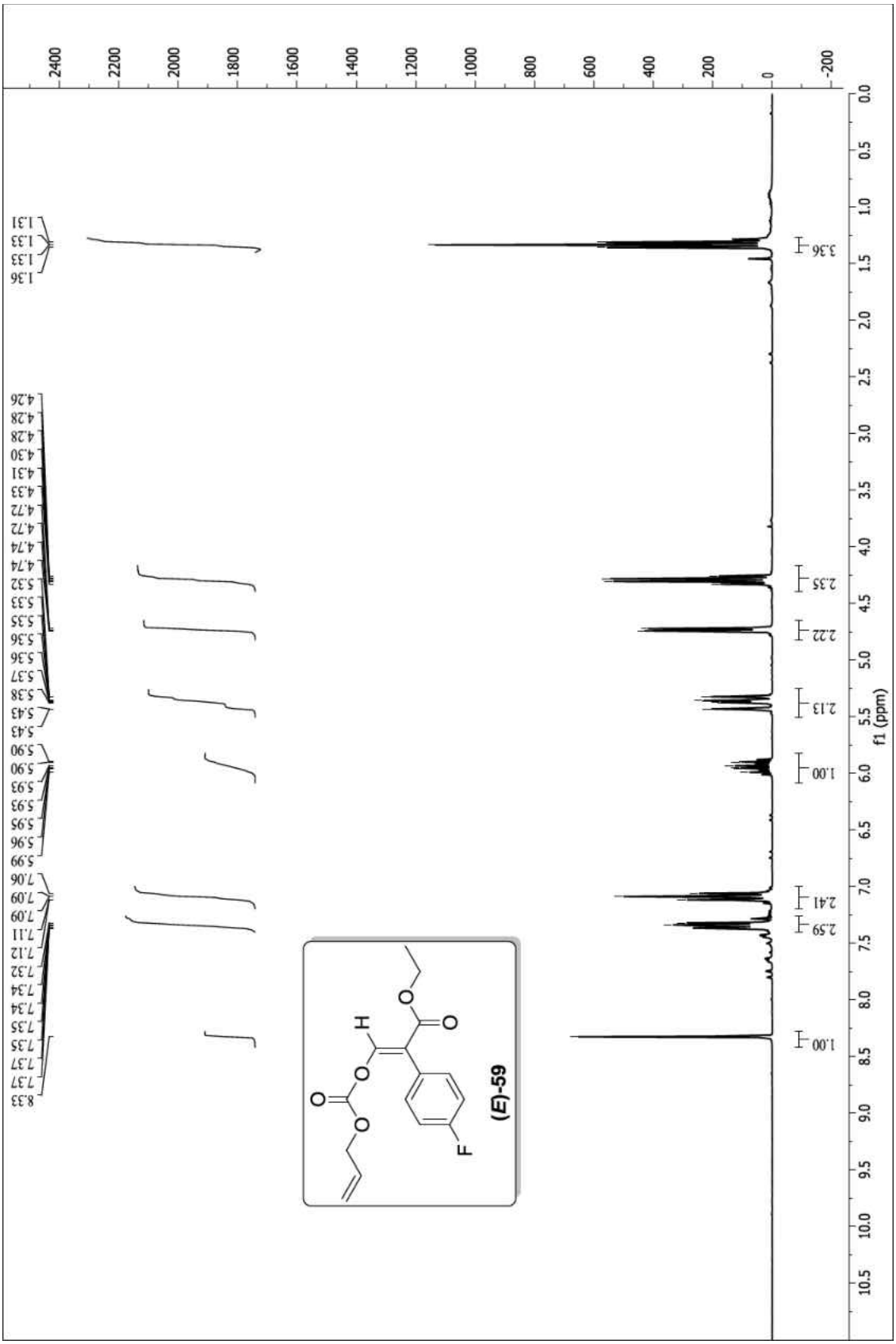

(E)-56
f1 (ppm)

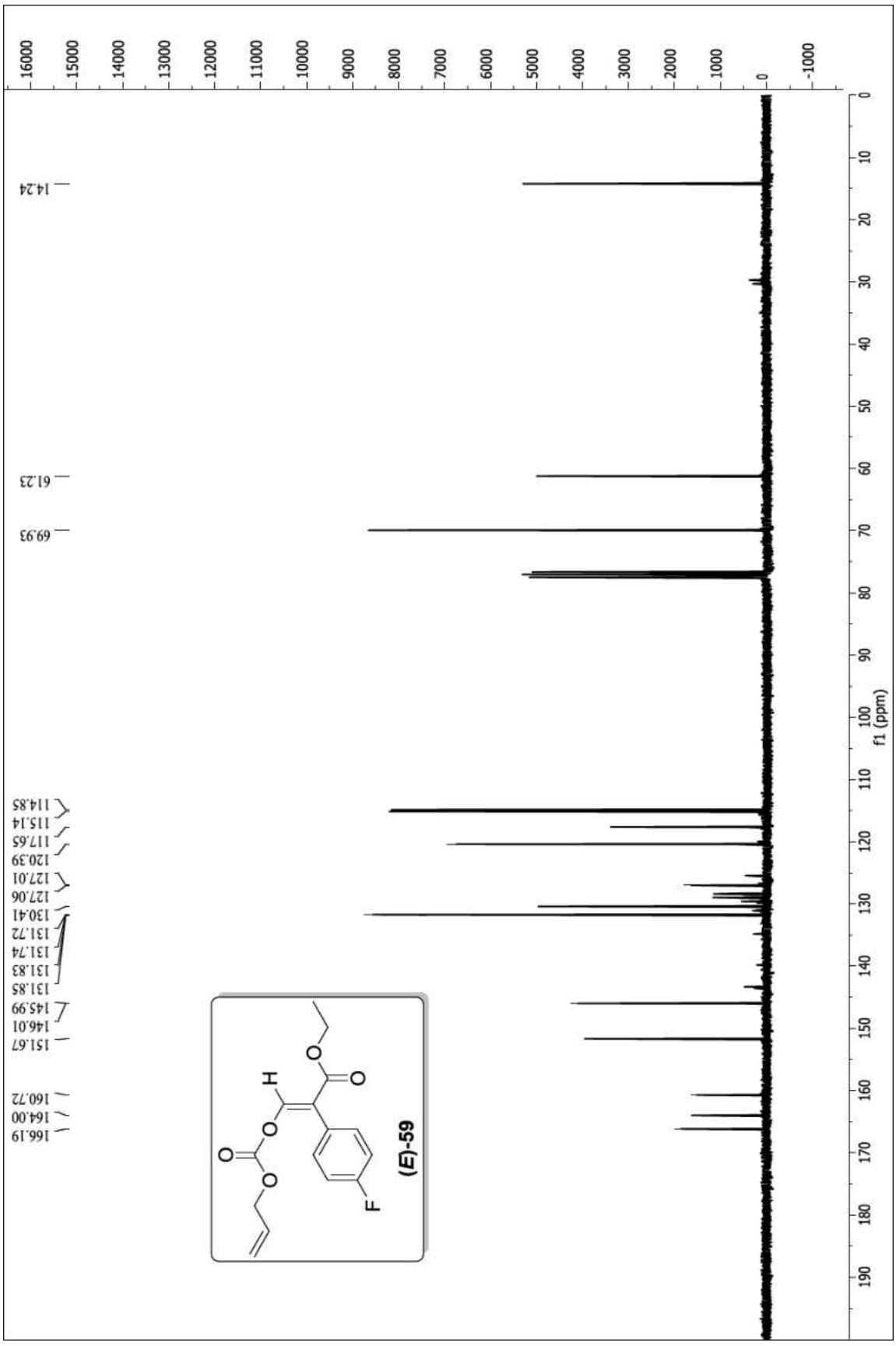

14.26
61.15
69.84
118.70
120.27
127.95
128.00
129.94
130.50
131.16
145.83
151.79
166.35
(E)-56
f1 (ppm)

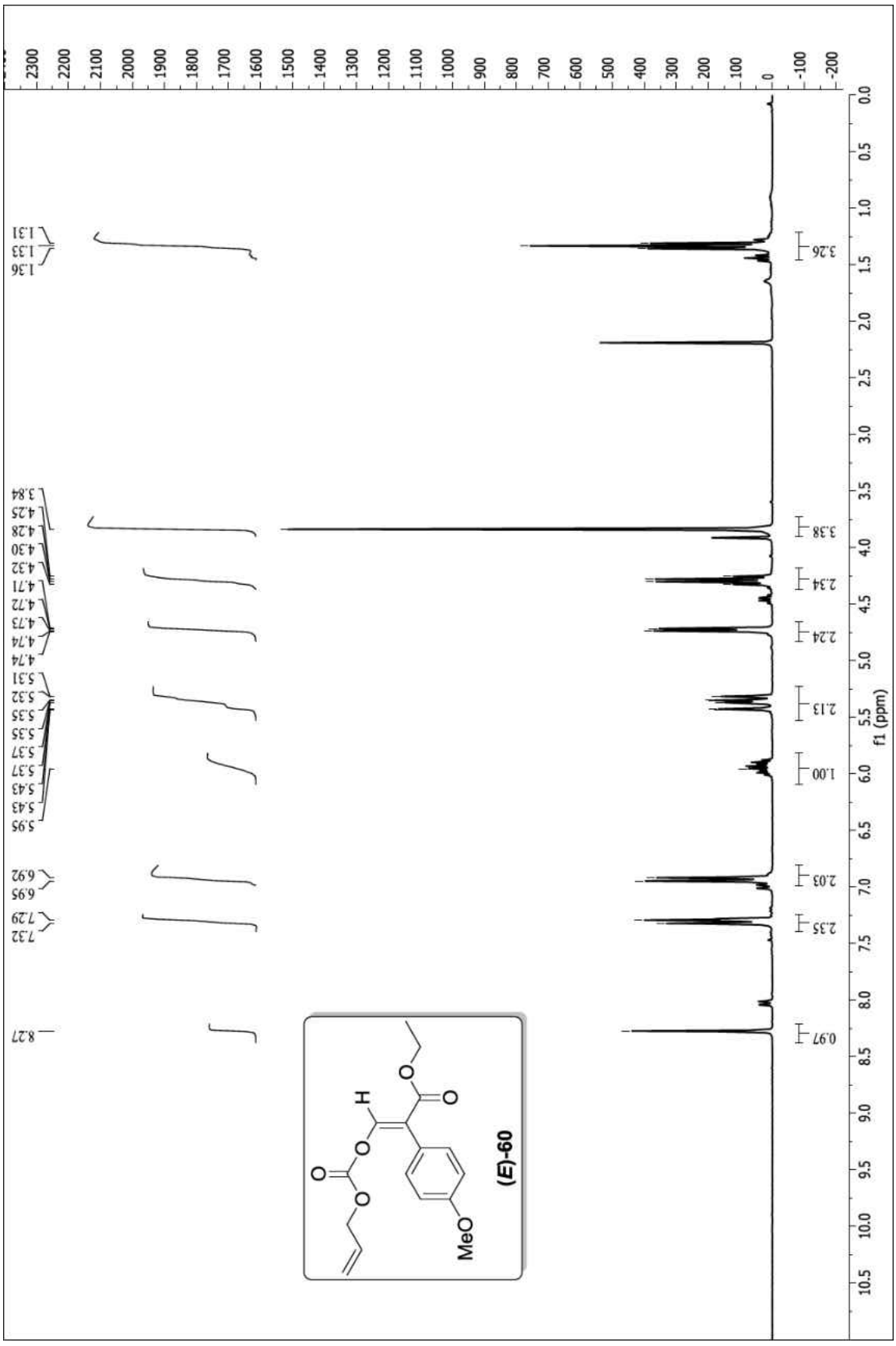

f1 (ppm)
f2 (ppm)
(E)-56
2D NOESY

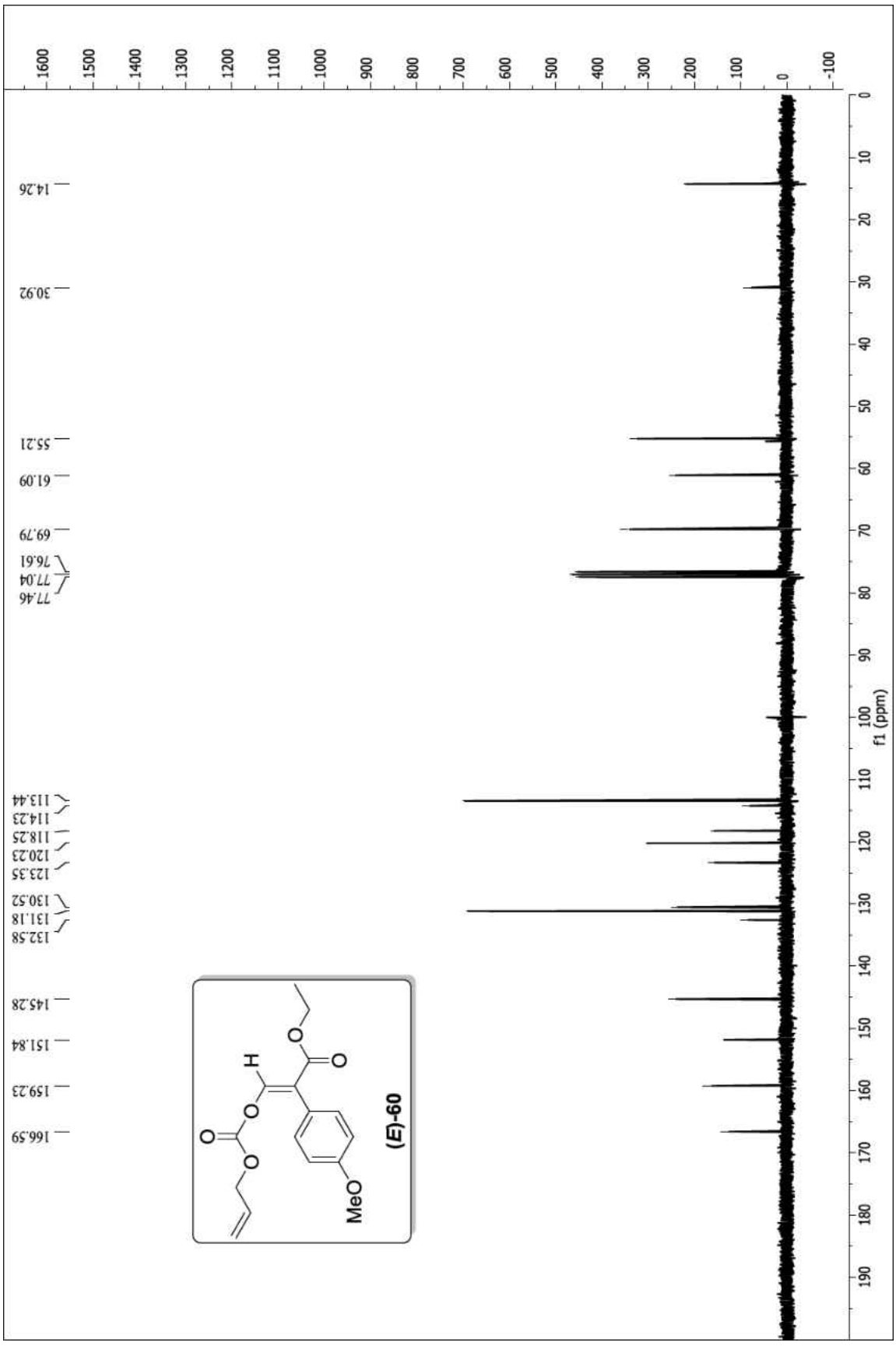

(E)-58
f1 (ppm)

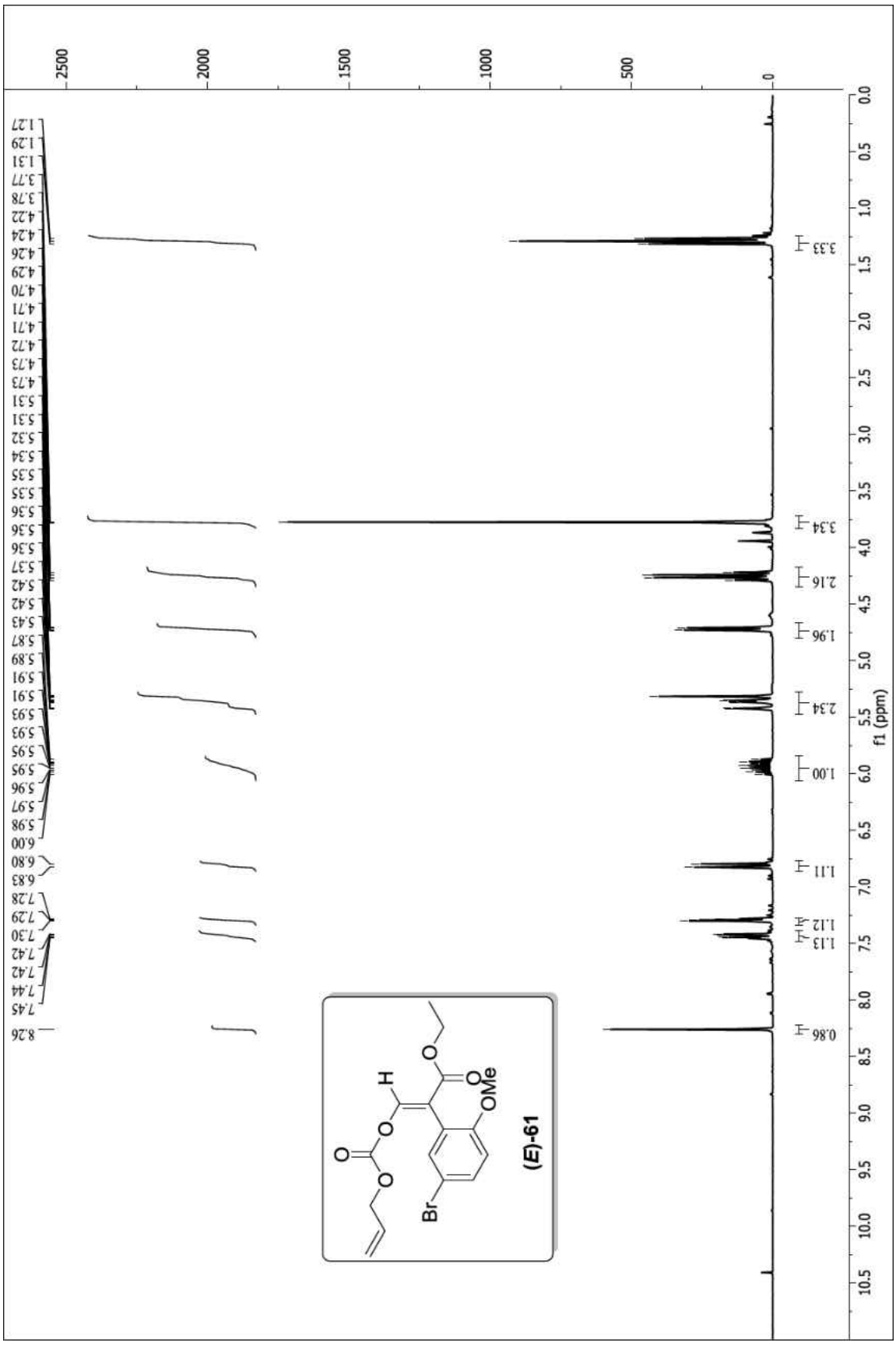

14.28
21.31
61.10
69.79
118.65
120.22
128.70
130.54
137.80
145.56
151.85
166.49
(E)-58
f1 (ppm)

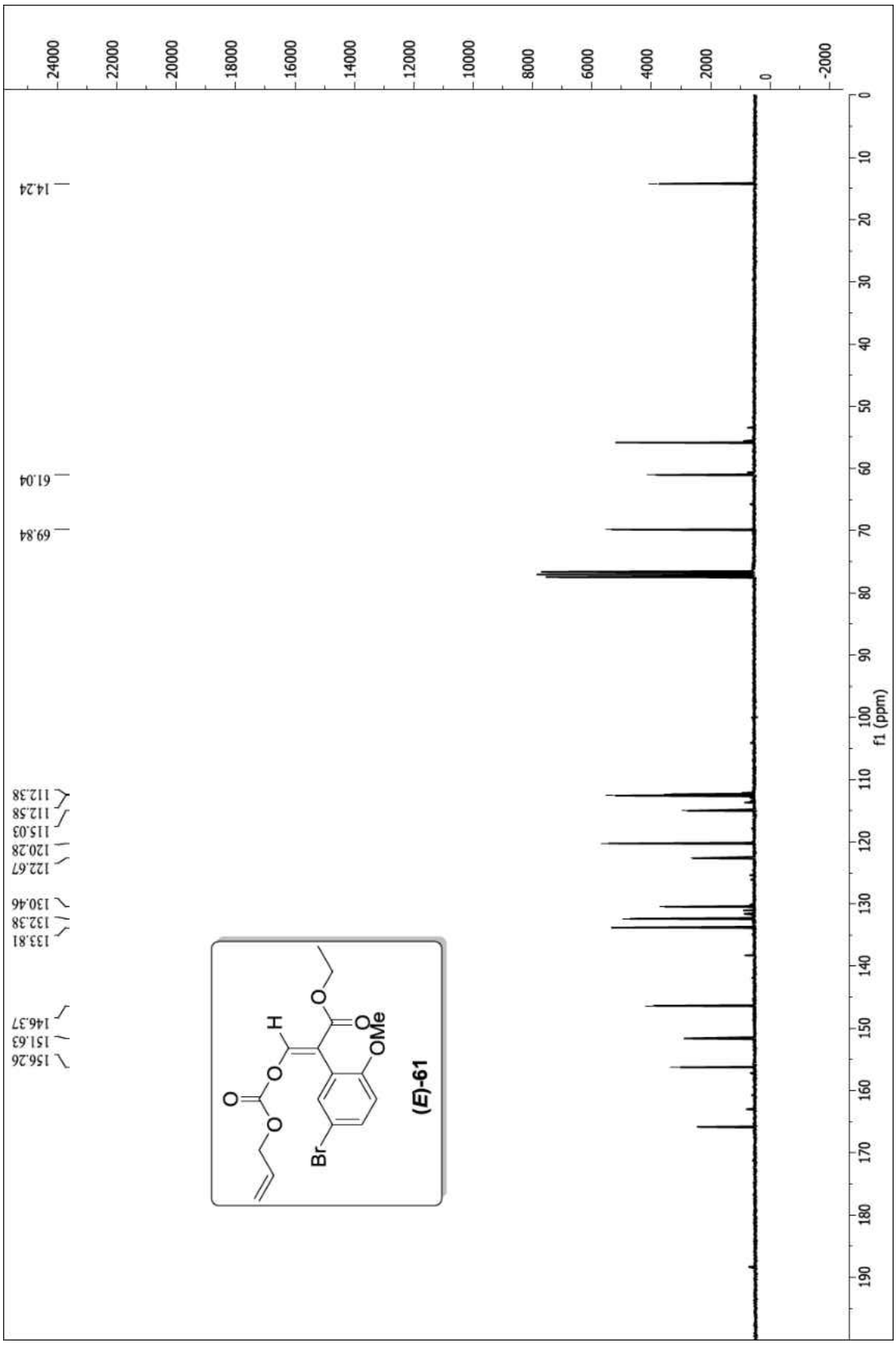

(E)-59
F
f1 (ppm)

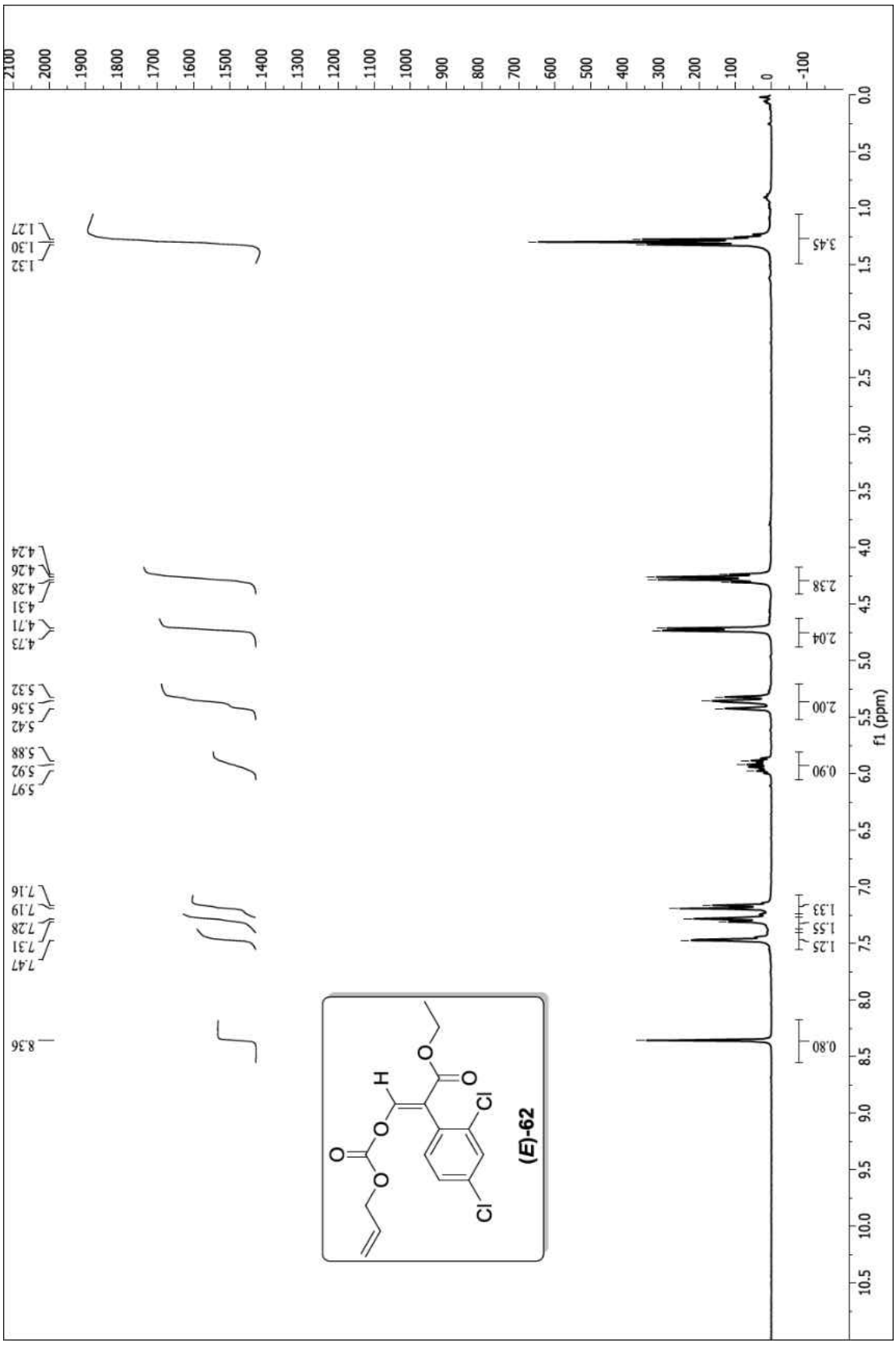

166.19
164.00
160.72
151.67
146.01
145.99
131.85
131.83
131.74
131.72
130.41
127.06
127.01
120.39
117.65
115.14
114.85
69.93
61.23
14.24
(E)-59
F
f1 (ppm)

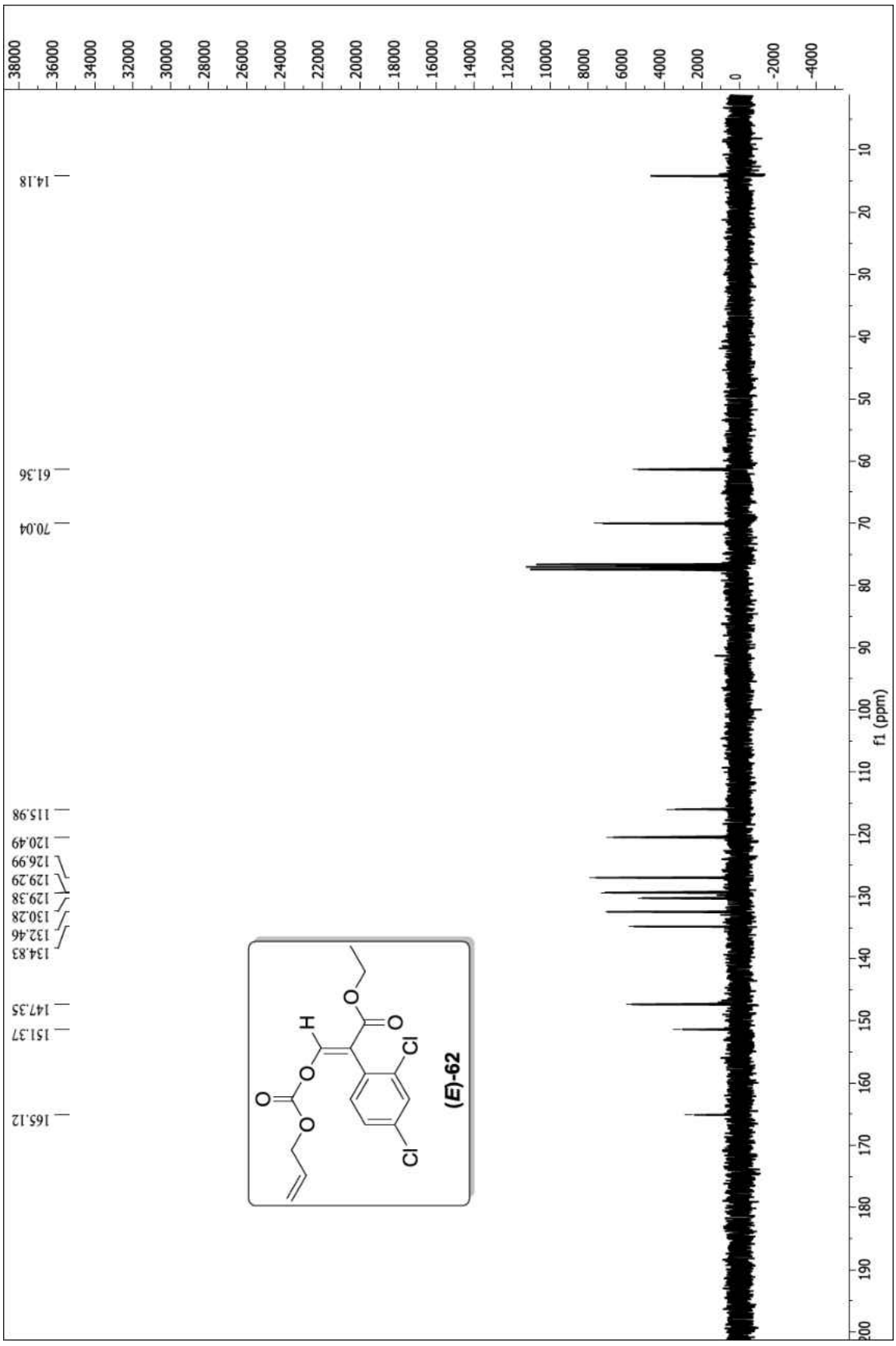

(E)-60
MeO
f1 (ppm)

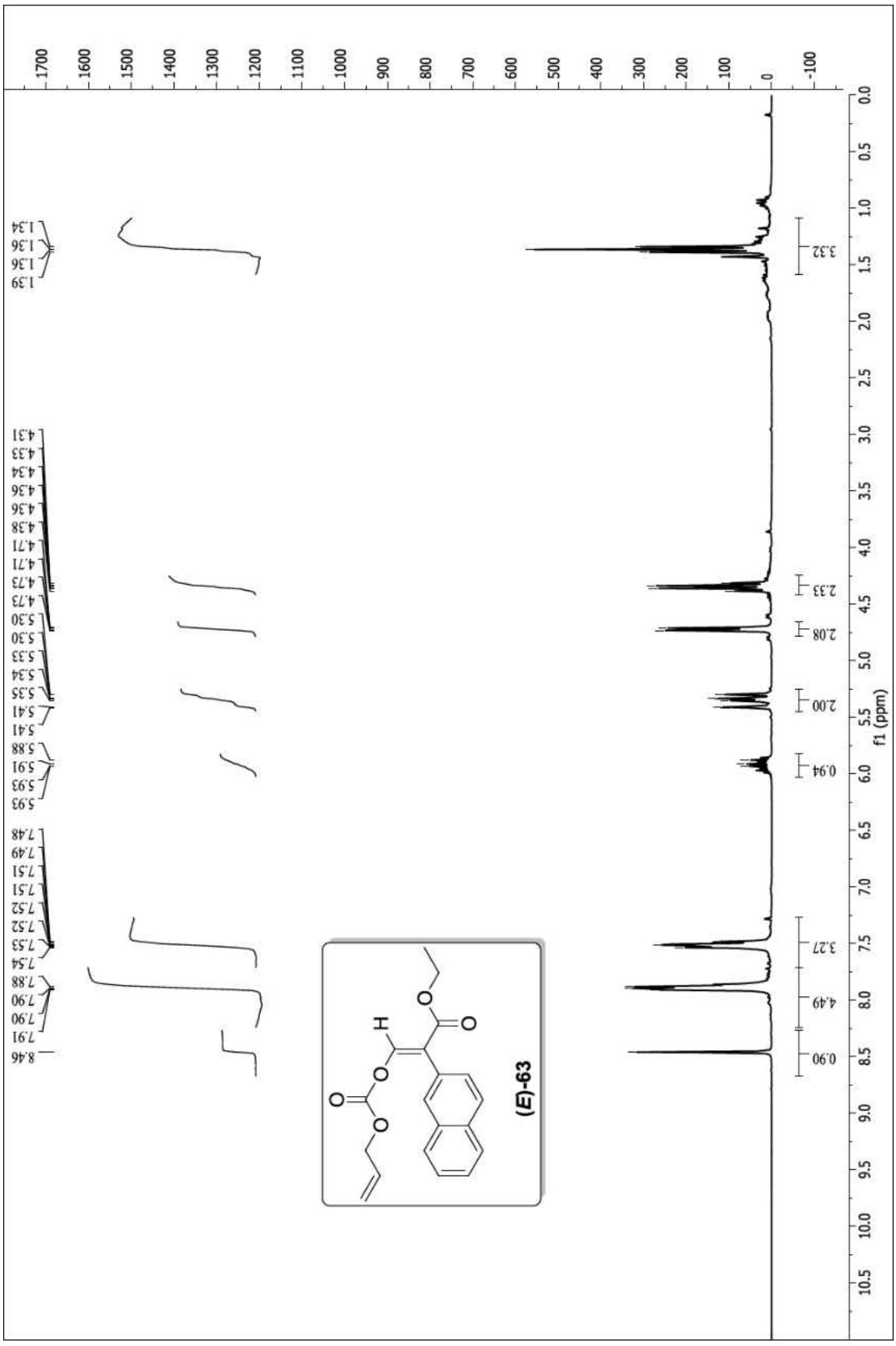

(E)-60
MeO
166.59
159.23
151.84
145.28
132.58
131.18
130.52
123.35
120.23
118.25
114.23
113.44
77.46
77.04
76.61
69.79
61.09
55.21
30.92
14.26
f1 (ppm)

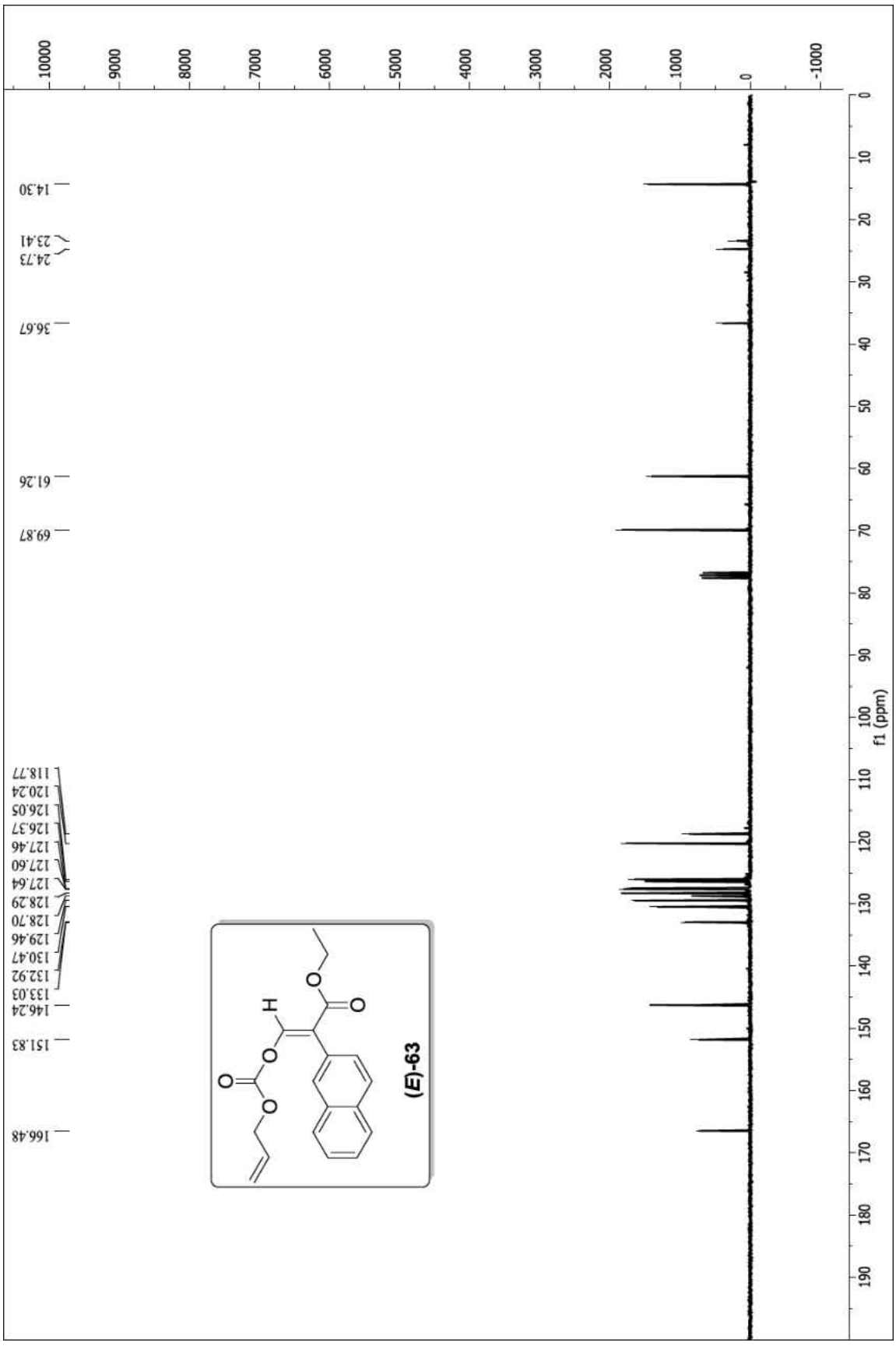

(E)-61
f1 (ppm)

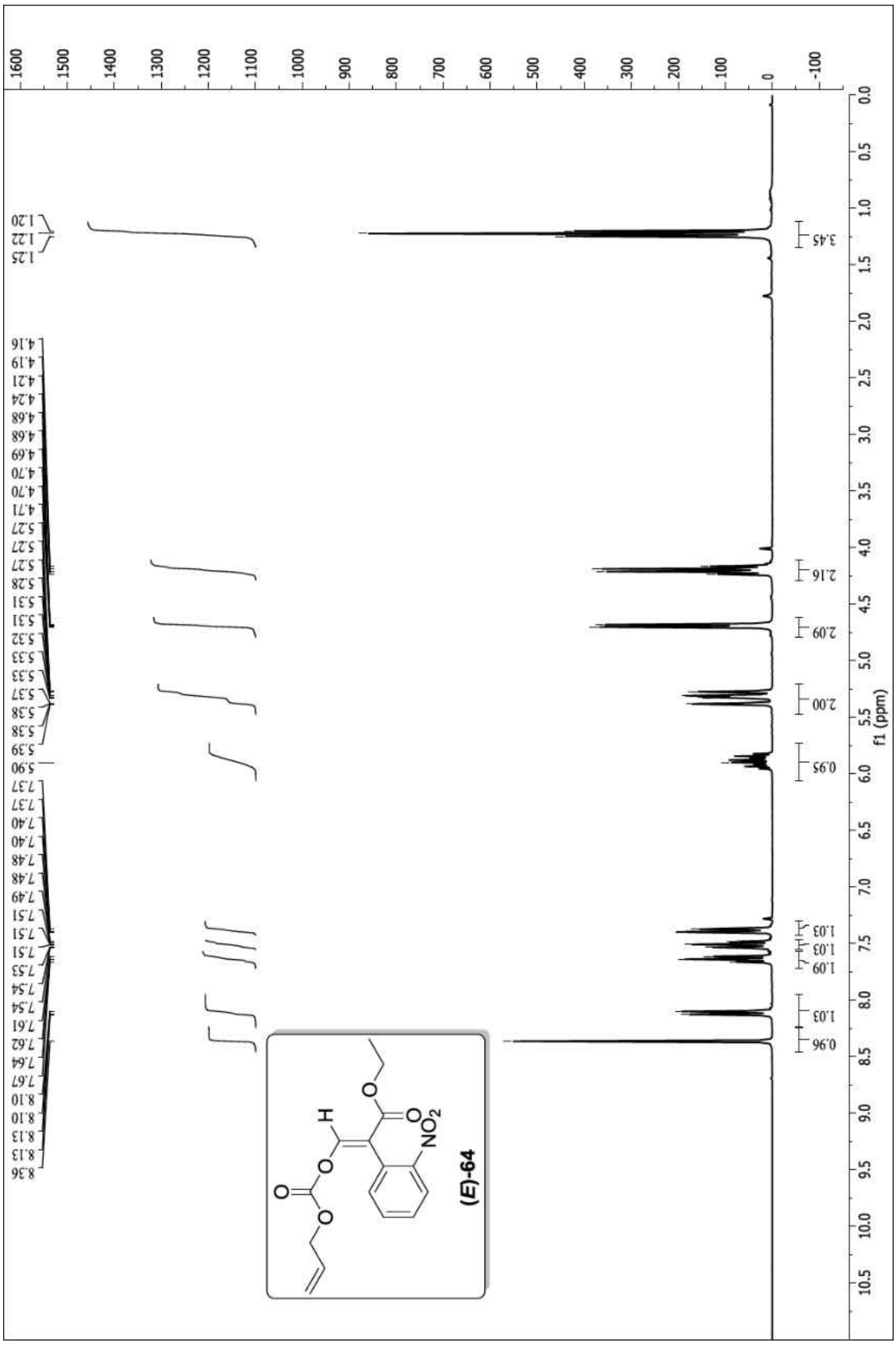

14.24
61.04
69.84
112.38
112.58
115.03
120.28
122.67
130.46
132.38
133.81
146.37
151.63
156.26
(E)-61
f1 (ppm)

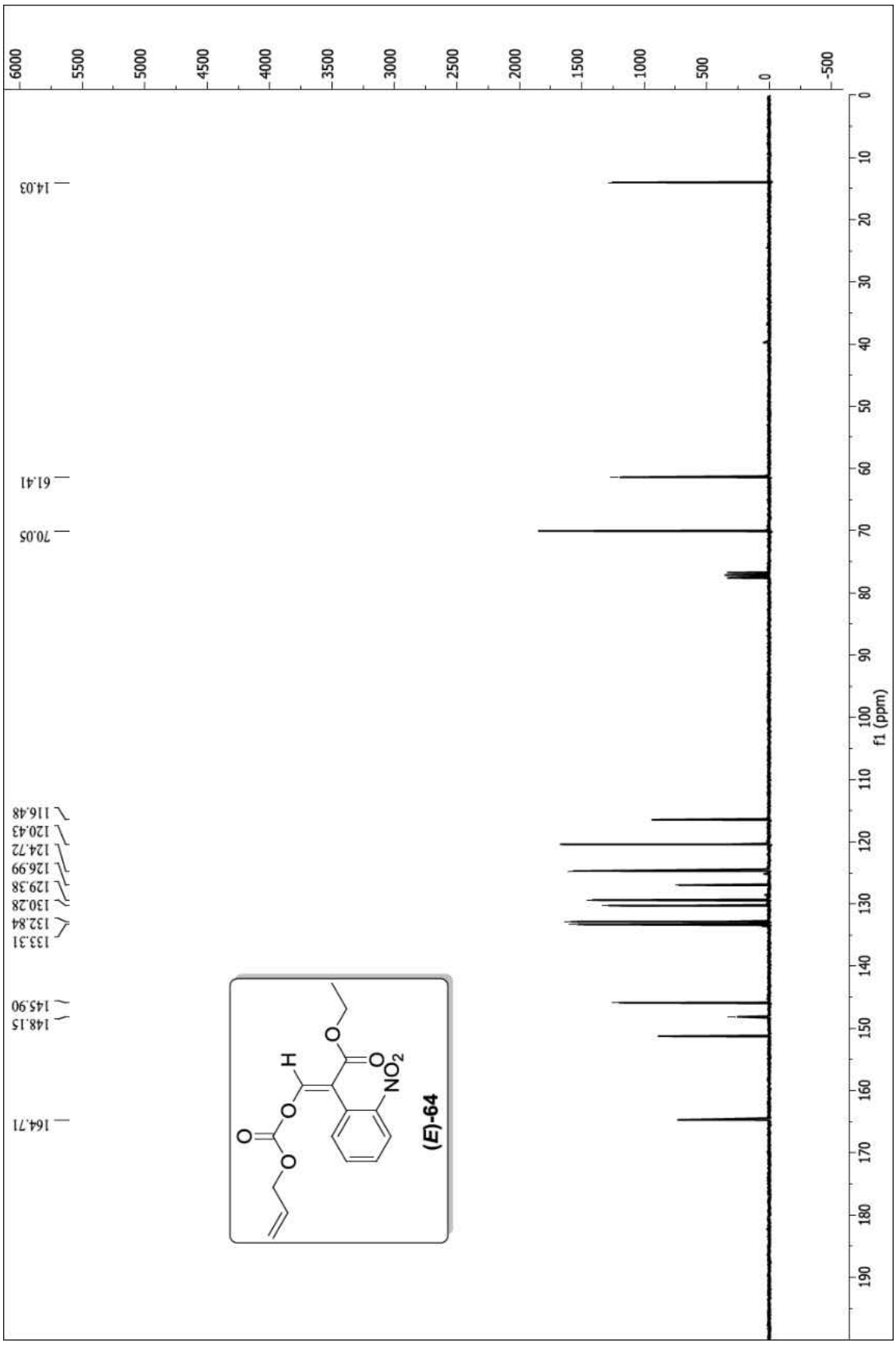

(E)-62
f1 (ppm)


14.18
61.36
70.04
115.98
120.49
126.99
129.29
129.38
130.28
132.46
134.83
147.35
151.37
165.12
(E)-62
Cl
Cl
f1 (ppm)


(E)-63
f1 (ppm)

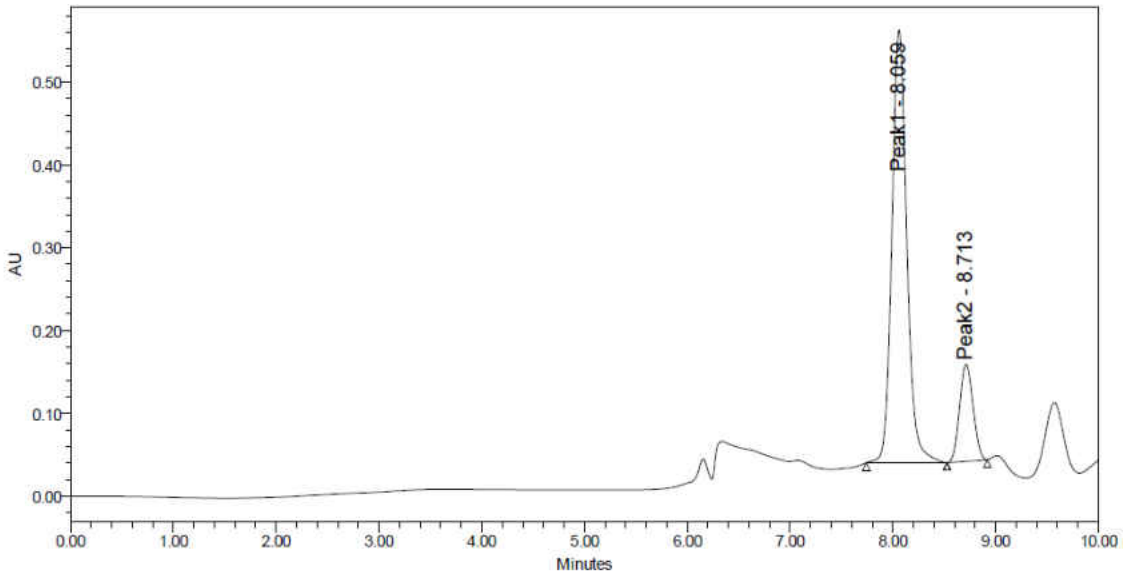

14.30
23.41
24.73
36.67
61.26
69.87
118.77
120.24
126.05
126.37
127.46
127.60
127.64
128.29
128.70
129.46
130.47
132.92
133.03
146.24
151.83
166.48
(E)-63
f1 (ppm)


(E)-64
f1 (ppm)


14.03
61.41
70.05
116.48
120.43
124.72
126.99
129.38
130.28
132.84
133.31
145.90
148.15
164.71
(E)-64
f1 (ppm)

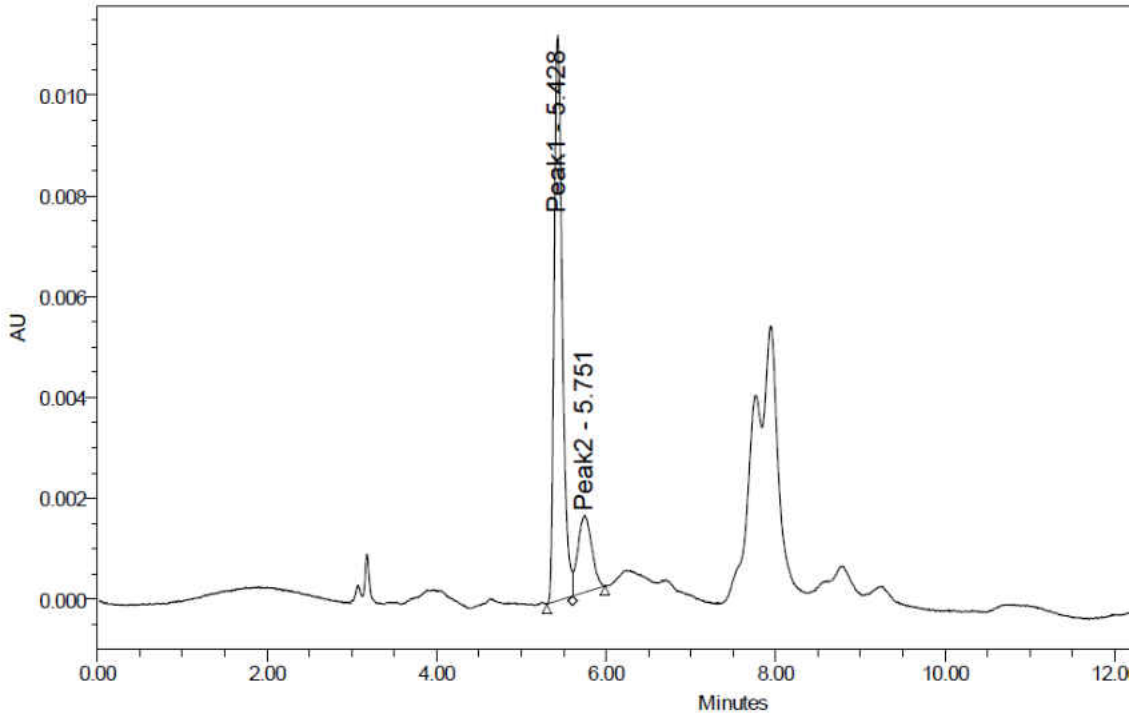
APPENDIX B: HPLC CHROMATOGRAMS

Entry 11, Table 19



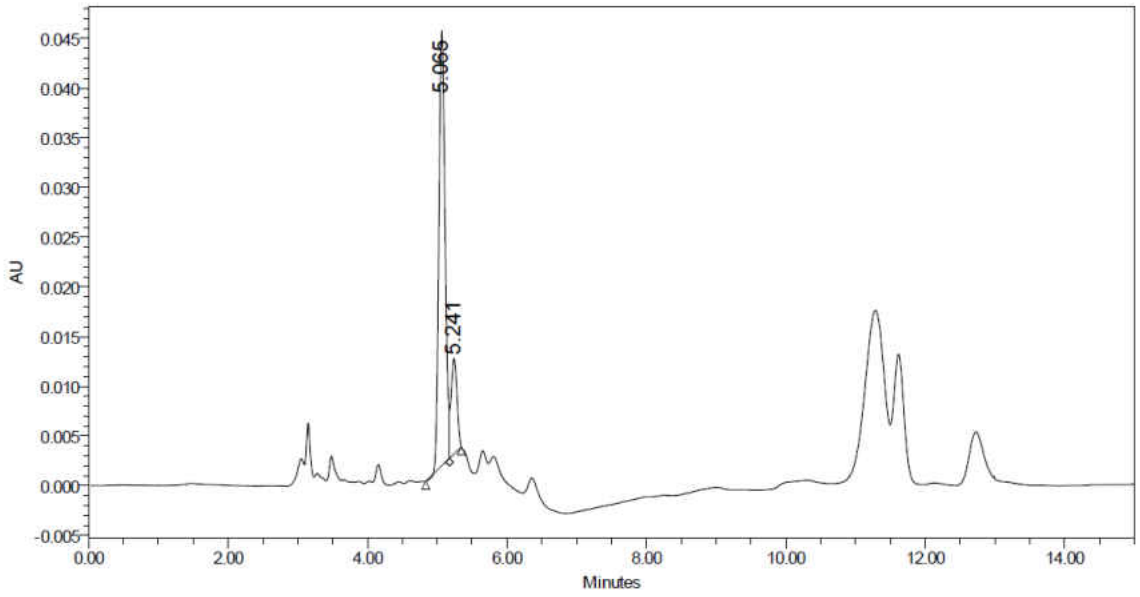
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	8.059	5252167	83.11	522111	81.70
2	Peak2	8.713	1067604	16.89	116956	18.30

Enry 2, Table 20



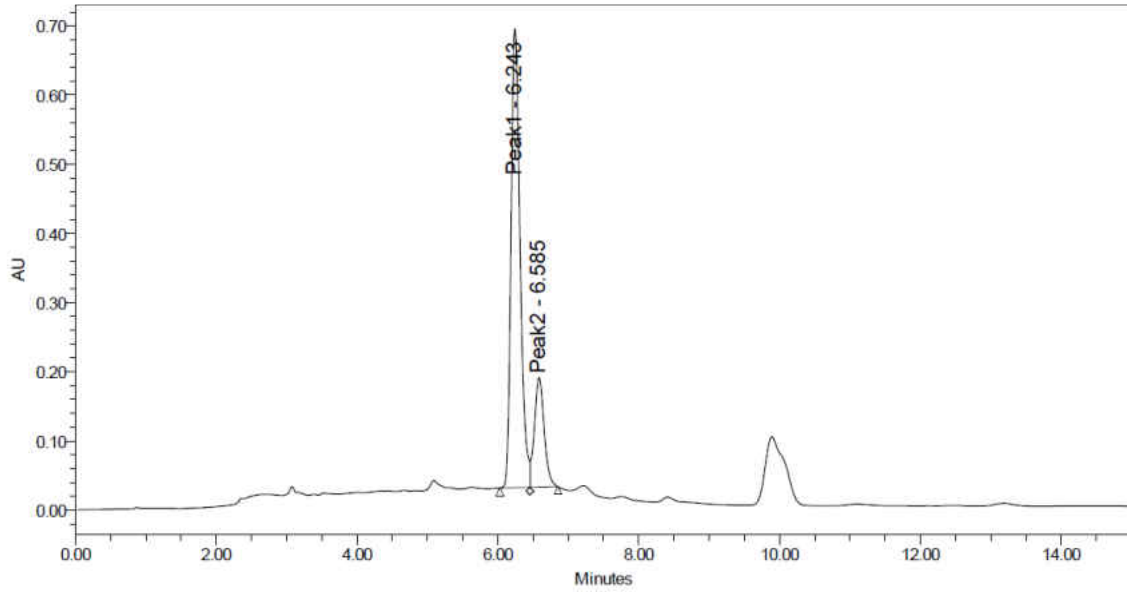
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	5.428	74636	80.97	11203	88.07
2	Peak2	5.751	17541	19.03	1518	11.93

Entry 4, Table 20



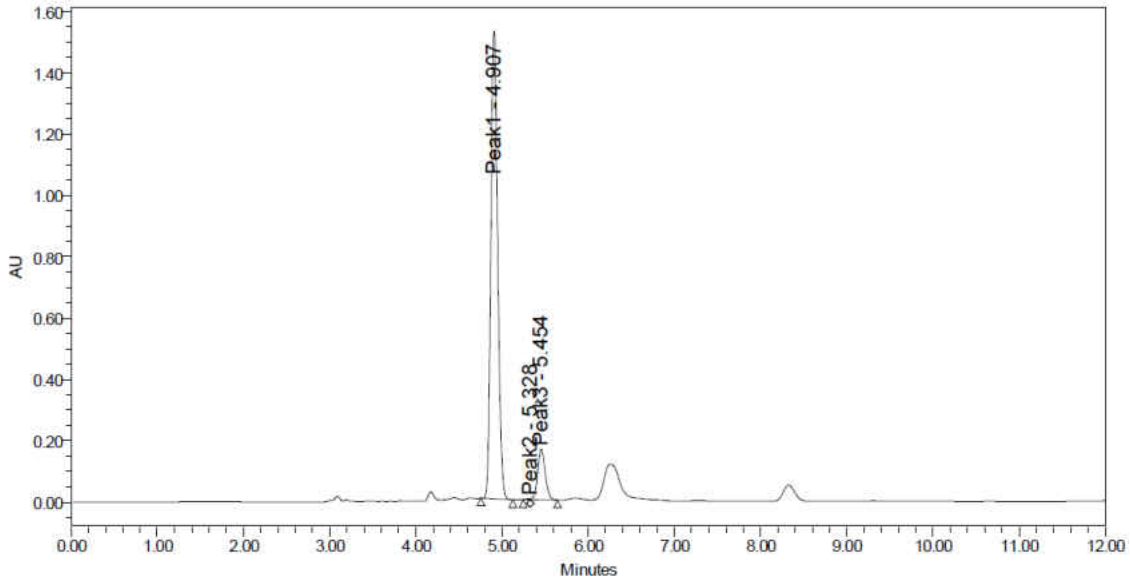
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	5.065	270675	82.67	43726	81.99
2	5.241	56736	17.33	9608	18.01

Entry 6, Table 20



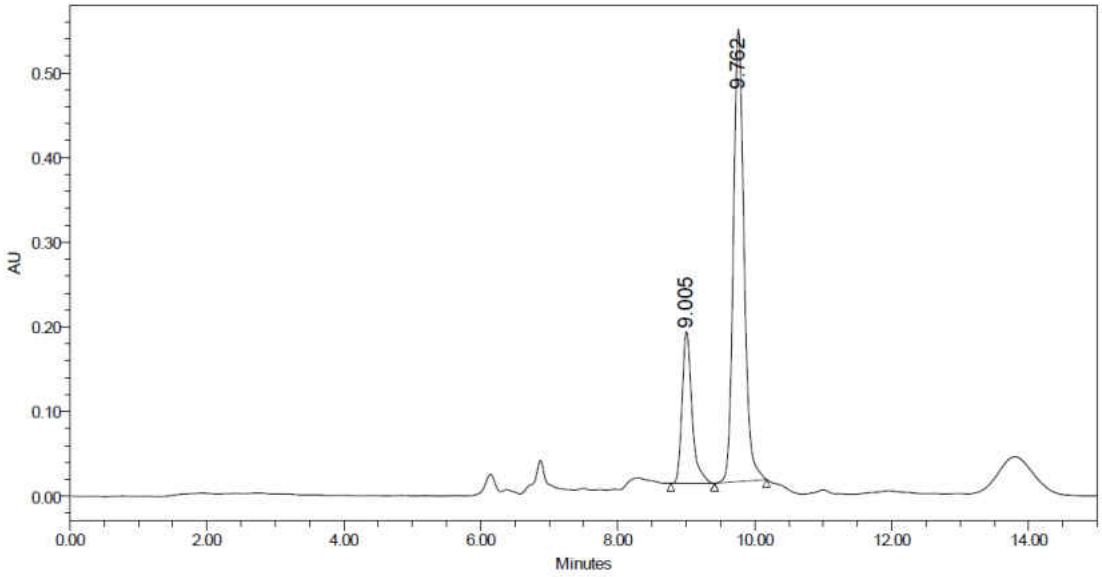
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	6.243	5900485	79.31	662809	80.70
2	Peak2	6.585	1538858	20.69	158528	19.30

Entry 20, Table 20



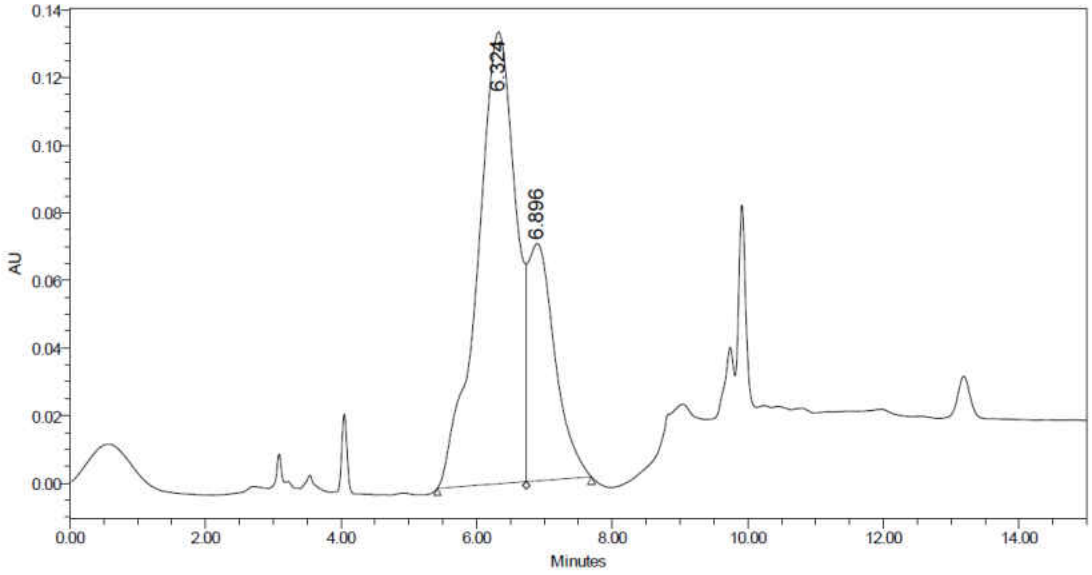
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	4.907	8191600	89.02	1524219	90.09
2	Peak2	5.328	8013	0.09	3288	0.19
3	Peak3	5.454	1002732	10.90	164398	9.72

Entry 10, Table 20



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	9.005	1796282	23.69	178717	25.07
2	9.762	5784933	76.31	534095	74.93

Entry 13, Table 20



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	6.324	5234034	72.85	133582	65.56
2	6.896	1950471	27.15	70172	34.44

CURRICULUM VITAE

Eduardo Alberch

Date of birth: 02/16/1983

Place of birth: Barcelona (Spain)

Education:

- BSc. Chemistry (upper 1st degree, honors), University of Manchester, UK, May 2005
- MSc. Chemistry, The University of Chicago, USA, June 2006.

Dissertation title: *I. Studies on the organocatalytic formation of quaternary stereocenters. II. Studies on the Claisen rearrangement as a route to quaternary stereocenters. III. Asymmetric synthesis of aldehydes bearing quaternary carbon centers via the decarboxylative asymmetric allylic alkylation.*

Publications:

- E. Alberch, N. Uddin, M. Shevyrev, M. M. Hossain, *ARKIVOC* **2010**, *(iv)*, 139-146**.**
- The Chemistry of Organoiron Compounds (Patai's Chemistry of Functional Groups). Volume editors: Ilan Marek and Zvi Rappoport. *The chemistry of iron-alkyl complexes.* E. Alberch. J. Ulicki. S. Asad, M. Mahmun. Wiley Feb. 2014.

Awards:

- Astra-Zeneca award due to outstanding academic achievement (2002-2005)