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Utilising a novel Ni/Zn catalytic system in small molecule synthesis

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Barbora Mala

Department of Chemistry

Lancaster University

February 2022

Declaration

I confirm that this thesis, submitted for the degree of Doctor of Philosophy has been composed entirely by myself and it is the result of my own work. This work has not been submitted in substantially the same form for the award of a higher degree elsewhere.

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Abstract

Utilising a novel Ni/Zn catalytic system in small molecule synthesis

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Transition metals have been used in C–C bond forming reactions for many decades. The use of palladium-based catalysts has dramatically increased in the last few years, however, there is a growing industrial need for low-cost, more abundant metals in catalysis. Nickel is often used as a replacement for palladium, as it is capable of catalysing many of the same reactions, whilst being significantly cheaper and more readily available. The most widely used Ni-catalyst, $Ni(cod)_2$, requires handling in a glove box, and although some catalytic systems employ air-stable pre-catalysts, these often require multiple step synthesis or an excess of reducing agents, making these reactions unfavourable for industrial scale up.

This work explored the application and robustness of a simple, novel Ni-based catalytic system to reactions that have previously utilised either Pd-based catalysts or $Ni(cod)_2$. The catalytic system described here comprises of a commercially available nickel salt ($NiBr_2.3H_2O$) and sub-stoichiometric amounts of zinc as the reducing agent. Utilising this system could ultimately allow for an easily scalable, and inexpensive benchtop synthesis.

Here this Ni/Zn catalytic system is used to successfully catalyse the direct allylation of simple ketones with allyl alcohols in the presence of pyrrolidine as a

co-catalyst. Substitution of the co-catalyst for a chiral pyrrolidine allowed for enantioselective allylation of ketones without the need for intricate chiral ligands. The system also successfully catalysed the allylation of branched aldehydes with allyl alcohols, although with a smaller substrate scope. Interestingly, this reaction did not require the use of a co-catalyst, highlighting the need to further explore the mechanism of this Ni/Zn system to fully understand and appreciate its potential.

Acknowledgments

Firstly, I would like to express my thanks to Professor Joe Sweeney for the opportunity to complete my PhD at Lancaster University and for his continued support and encouragement. I'd also like to thank Dr Julien Doulcet for his guidance and supervision throughout the project, and Dr Anthony Ball for setting the foundations for this work. Thank you to the rest of the Sweeney group members, past and present, for your constructive discussions, moral support, and making the last three years an enjoyable experience.

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I would also like to express my gratitude to my friends and family, who have always been there for me without judgement. Finally, my greatest thanks go to my fiancé, Dr David Townsend, who has been there for me throughout my PhD. Thank you for your unconditional love and support, for always believing in me and my abilities, and for encouraging me to keep focused, even when all work stopped during COVID. Without you I would not be the person I am today.

Contents

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Abbreviations

Ac	acyl
acac	acetylacetone
Ar	aryl
pin	pinacol
BDMAE	bis[2-(N,N-dimethylamino)ethyl] ether
Benz	benzoyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BiOX	bisoxazoline
bpy	2,2′-bipyridine
Bu	butyl
CDT	1,5,9-cyclododecatriene
cod	1,5-cyclooctadiene
cot	1,3,5,7-cyclooctatetraene
DCM	dichloromethane
dcype	1,2-bis(dicyclohexylphosphino)-ethane
DIBAL	diisobutylaluminium hydride
DMA	dimethylacetamide
DME	dimethoxyethane (glyme)
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppb	2-bis(diphenylphosphino)butane
dppbm	bis(diphenylphosphino)methane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DTBP	Di-tert-butyl peroxide
E	entegen (opposite, *trans*)
EDG	electron donating group
ee	enantiomeric excess
Et	ethyl
EWG	electron withdrawing group
FTIR	Fourier transform infrared spectroscopy
g	grams
h	hours
HIV	human immunodeficiency virus
Hz	Hertz

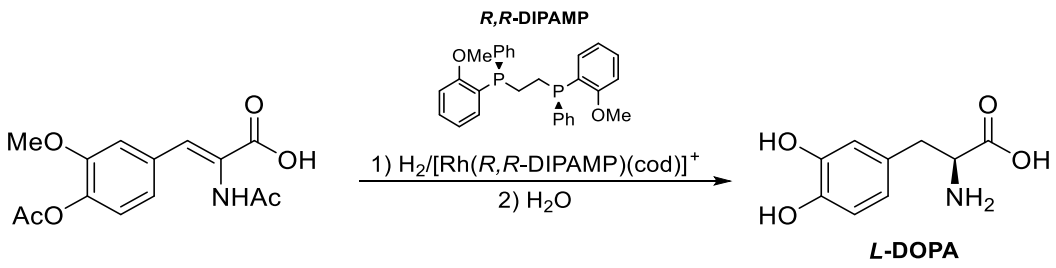
IT	ion trap
J	coupling constant (NMR)
L	undefined ligand
LA	Lewis acid
LCMS	liquid chromatography mass spectroscopy
L-DOPA	L-3,4-dihydroxyphenylalanine
HMDS	bis(trimethylsilyl)amide
M	undefined metal
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mol	moles
NHC	N-heterocyclic carbene
NHP	N-hydroxyphthalimide
NMP	N-methyl-2-Pyrrolidone
NMR	Nuclear Magnetic Resonance
Oct	octyl
OTf	triflate
PCy_3	tricyclohexylphosphine
Ph	phenyl
phen	phenanthroline
PMHS	Polymethylhydrosiloxane
PPh_3	triphenylphosphine
Pro	Proline
Pybox	bisoxazoline
R	undefined substituent
SPhos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TBS	*tert*-butyldimethylsilyl ether
THF	tetrahydrofuran
TOF	time of flight
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Ts	tosyl
UV	ultraviolet
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Z	zusammen (together, *cis*)

Chapter 1: Introduction to homogeneous nickel catalysis

1.1 Catalysis overview

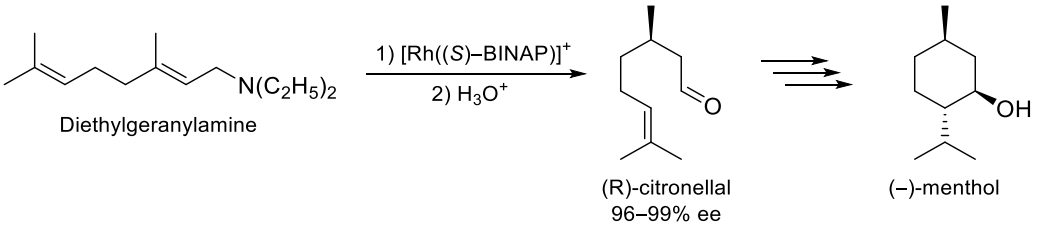
Catalysis provides an efficient and cost-effective delivery of a large number of compounds across many different chemical fields, including pharmaceuticals, biofuels, and polymers. In the last decade, it was estimated that 90% of all synthetic chemicals were made with methods that involve at least one catalytic process.[1,2] Transition metal catalysis is one of the most common catalytic methods employed in chemical synthesis. The advancement and the impact transition metal catalysis has had on the synthetic field has been recognised by the award of Nobel Prizes for several different transition metal catalysed reactions in the first decade of this century: Knowles, Noyori, and Sharpless in 2001; Grubbs, Chauvin, and Schrock in 2005; and Suzuki, Heck, and Negishi in 2010.[1]

The Knowles group demonstrated the synthesis of L-DOPA, a drug used in the treatment of Parkinson's disease, with rhodium-catalysed asymmetric hydrogenation (Scheme 1).[3] Noyori and co-workers highlighted the use of ruthenium catalysed asymmetric hydrogenation for the synthesis of *R*-1,2-propandiol which is a precursor for the antibacterial compound Levofloxacin.[4]



Scheme 1: Synthesis of L-DOPA as demonstrated by Knowles *et al.*

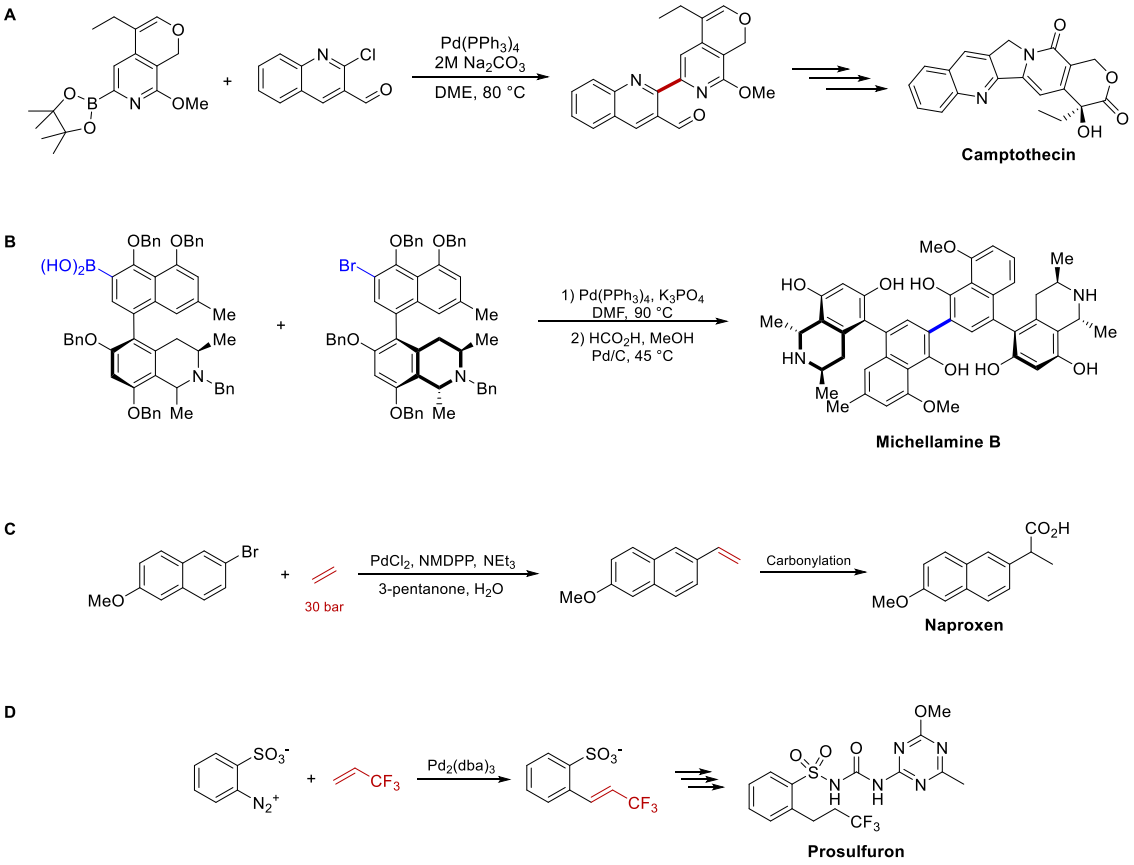
Most notably, Noyori's BINAP-Rh catalysed asymmetric isomerisation of allylic amines has been utilised in the industrial synthesis of menthol (Scheme 2), a widely used natural product found in common everyday items (such as cosmetics and toothpaste), with world demand exceeding the natural supply in 2007 at over 30,000 tonnes.[1,4,5] Grubbs catalysts have been widely employed in the olefin metathesis field. The first and second generation Grubbs catalysts were initially commercially utilised in the synthesis of poly-dicyclopentadiene resins, a class of exceptionally tough and corrosion resistant materials used in construction equipment and bodies of buses and tractors.[6]



Scheme 2: Rh-catalysed synthesis of menthol as developed by Noyori *et al.*

The Suzuki-Miyaura cross-coupling reaction has been employed in the total synthesis of a wide range of natural compounds; including camptothecin, a topoisomerase I inhibitor with anti-cancer activity;[7,8] palytoxin, a vasoconstrictor and the largest synthesised secondary metabolite at the time;[9] and michellamine B, a compound which impedes HIV viral replication,[9] just to name a few. The Heck reaction is a key step in the synthesis of anti-inflammatory Naproxen™, and the herbicide Prosulfuron™.[10] The Heck reaction is also employed in the synthesis of the idebenone,[11] a compound originally designed for the unsuccessful treatment of Alzheimer's disease, but has since been repurposed as the only current treatment for Leber's hereditary optic neuropathy.[12]

Negishi coupling has been overshadowed by the use of Suzuki and Heck reactions, owing to the air and moisture sensitivity of the organozinc reagents required.[13] Nevertheless, the Negishi coupling has been utilised in the synthesis of PDE472, a phosphodiesterase isoenzyme inhibitor used in the treatment of asthma.[14] For further examples of these reactions, in total synthesis of natural products and in industry, there are extensive reviews available in the literature.[7,9–11,15–17] All of these examples highlight the significance and importance of transition metal catalysis in synthetic applications for the development of therapeutics.



Scheme 3: Suzuki-Miyaura steps in the synthesis of Camptothecin (**A**), and Michellamine B (**B**); and Heck reaction steps in the synthesis of Naproxen (**C**), and Prosulfuron (**D**).

1.2 Alternatives to palladium

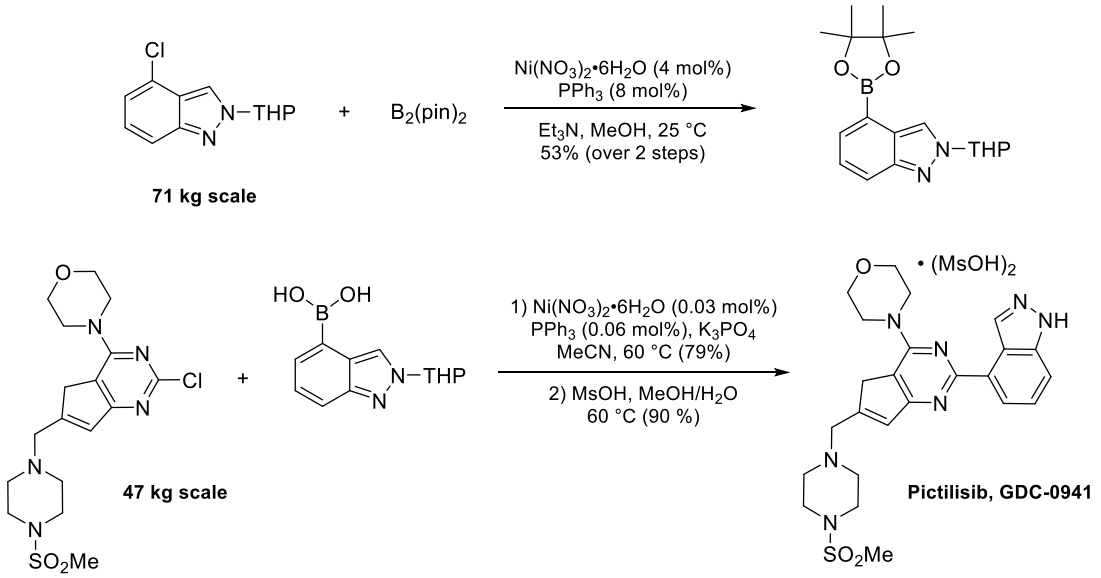
The 2010 Nobel prize in chemistry was awarded to Suzuki, Heck and Negishi for the advancements in "palladium-catalysed cross couplings in organic synthesis".[18] As a result, the use of palladium catalysts in cross-coupling reactions has dominated in the last couple of decades in comparison to other transition metals.[19] Pd-based catalysts have opened up the scope for a large number of novel carbon-carbon bond forming reactions: these catalysts are highly tolerant of many functional groups, and are also relatively stable to oxygen and moisture.[20] Many of the early cross-coupling developments involved the use of aryl halides as electrophiles and pre-functionalised organometallic species as nucleophiles. However, the scope of cross-coupling reactions has since significantly expanded.[21] Although palladium has dominated the field of transition metal catalysis, there is an ever-increasing need for lower-cost, more abundant metals in catalysis. As a result, the focus has now turned to other metals, such as nickel, as a cheaper, more abundant alternative to palladium in catalytic transformations.[22–24]

Nickel has been utilised in catalysis since the 1960s, when its catalytic properties were first serendipitously discovered by Ziegler, Wilke, and co-workers.[25] Wilke's contribution to organonickel chemistry included the synthesis of bis(1,5-cyclooctadiene)-nickel(0), [Ni(cod)$_2$], which is one of the most frequent sources of Ni^0 in chemical synthesis.[23] Since then, nickel has been used as a catalyst in a variety of cross-coupling reactions such as oligomerisations, cycloisomerisations, and reductive couplings.[23,25–27] In addition to the economic benefits, nickel is a more electropositive metal, meaning it is also capable of catalysing different bond formations to palladium, such as cross coupling of C–O and Csp^3–X bonds.[22,28,29]

This makes nickel attractive not only due to its economic benefits but also due to its versatility and unique ability to undergo reactions with less reactive electrophiles, thus creating opportunities for new transformations beyond the known limits of other metals.

Despite the benefits of nickel catalysis in cross-coupling reactions, many Ni-catalysed reactions often employ expensive, or air- and moisture- sensitive complexes, such as $Ni(cod)_2$. This sensitivity requires reactions that employ $Ni(cod)_2$ to be carried out in the absence of oxygen, often requiring the use of a glovebox, restricting its ease of use both academically and industrially, thereby often nullifying the economic advantages of using nickel.[30]

In light of this, considerable research has been conducted since its discovery to find an alternative source of Ni^0 for industrial applications. Genentech (USA) have employed an alternative nickel precatalyst, $Ni(NO_3)_2{\cdot}6H_2O$, in the borylation and Suzuki reaction steps in the synthesis of Pictilisib, a potential anticancer agent (Scheme 4).[31] Comparative reactions between this nickel system and palladium equivalent revealed that the use of nickel was not only cheaper, it also achieved better yields. Additionally, nickel residues were significantly easier to remove with simple aqueous washing, whereas palladium required the use of expensive metal scavengers and large solvent volumes.[31] This demonstrates that application of Ni-catalysed cross-coupling reactions in large scale catalytic processes is achievable and beneficial.



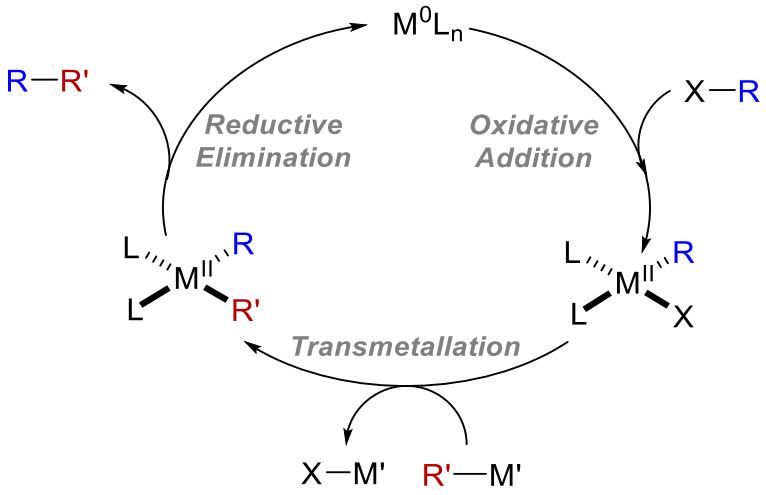
Scheme 4: The borylation and Suzuki reactions in the synthesis of Pictilisib utilising $Ni(NO_3)_2 \cdot 6H_2O$ as the catalyst.[31]

1.3 General features of Ni-catalysed reactions

Nickel is a group 10 metal, located just above palladium in the periodic table, therefore, it is capable of performing many of the same reactions as palladium. However, due to being a more electropositive metal, nickel also offers access to catalytic bond formations much different to palladium, such as those involving phenol-derived electrophiles.[22] Furthermore nickel has more oxidation states readily available in comparison to palladium, opening up the potential for different catalytic cycles, and thus many different transformations. Palladium catalysed reactions mostly involve Pd^0/Pd^{II} oxidation states in the catalytic cycle, which are also accessible by Ni, however, nickel catalytic cycles can also involve the Ni^I and Ni^{III} oxidations states which can affect the reactivity and allow for reactions to proceed via completely different (radical) pathways.[23,24]

1.3.1 Oxidative Addition

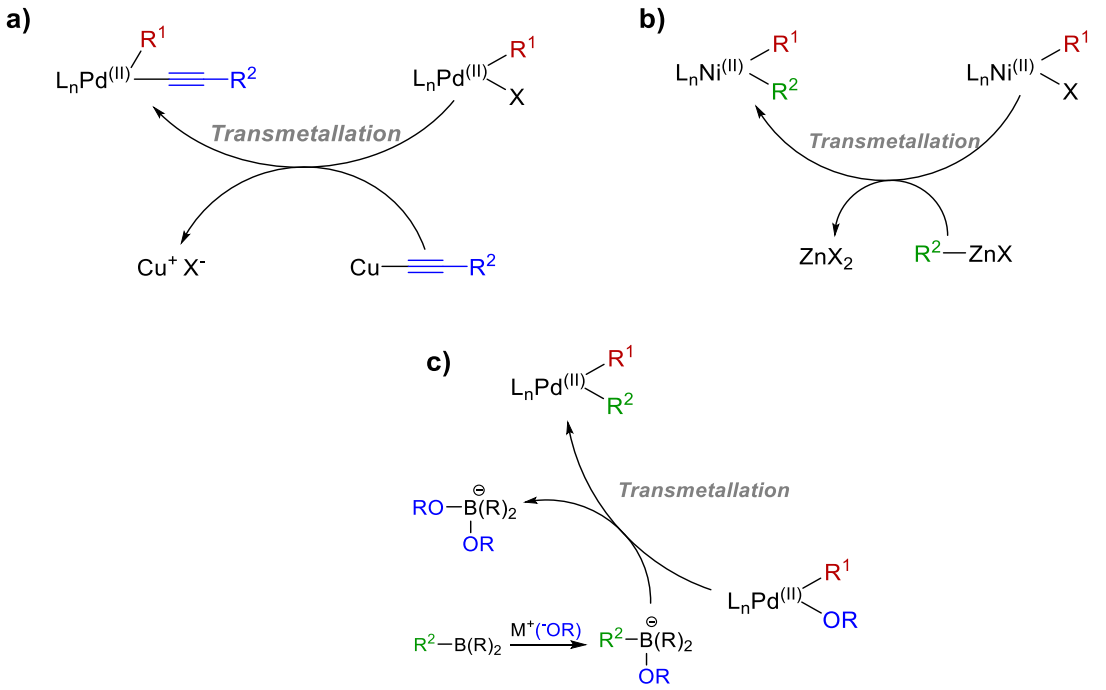
Typical transition metal catalysed reactions proceed via M^0/M^{II} intermediates (M = metal) through a series of steps involving oxidative addition, transmetallation, and subsequent reductive elimination (Scheme 5). As mentioned above, nickel is an electropositive metal, therefore it tends to undergo oxidative addition towards a large variety of compounds containing C–X bonds more readily than Pd and Pt (X = heteroatom).[24] This involves the oxidation of Ni^0 to Ni^{II}, and the cleavage of the C–X bond to form new Ni–C and Ni–X bonds. Oxidative addition of Ni^0 to π-bonds is also possible, breaking the π-bond and creating two new σ-bonds to the nickel, as before.[26] Furthermore, π-ligands, such as alkenes or alkynes, can undergo similar oxidative cyclization with aldehydes or ketones forming cyclised nickel intermediates, with oxidative addition of two butadiene molecules being perhaps the most well-known example.[26]



Scheme 5: Key mechanistic steps observed in typical metal-catalysed cross-coupling reactions.

1.3.2 Transmetallation

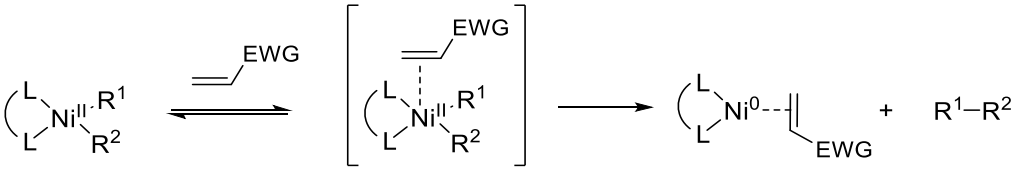
Transmetallation involves the transfer of ligands between two metals, forming and activating a new metal-carbon bond. It is one of the key mechanistic steps in most cross-coupling reactions.[32] For example, Grignard reagents tend to be largely reactive towards carbonyl groups, however, in the presence of catalytic amounts of a transition metal, such as cobalt or nickel, the reactivity of Grignard reagents drastically improves, allowing for coupling reactions with less reactive substrates such as alkyl halides.[26] The Suzuki-Miyaura reaction relies entirely on the transmetallation between boron and palladium/nickel;[33] the Negishi coupling involves transmetallation through organozinc compounds;[34] and the Sonogashira cross-coupling relies on transmetallation between palladium and copper cycles (Scheme 6).[35]



Scheme 6: Transmetallation steps in **a)** Sonogashira; **b)** Negishi; and **c)** Suzuki catalytic cycles.

1.3.3 Reductive Elimination

Reductive elimination is the opposite of oxidative addition – the formal oxidation state of nickel is reduced from +2 to 0, accompanied by the formation of a new C–C or C–X bond, resulting in an elimination of the coupled product. Reductive elimination is often the rate determining step, however, this process can be accelerated by the coordination of a fifth, electron deficient, ligand (Scheme 7). Conveniently, many Ni^{II} complexes have a vacant site for the fifth ligand due to having an unsaturated $d^8$16e configuration. The more electronegative this ligand, the easier and faster the reductive elimination.[26] For reductive elimination to occur, the two organic coupling ligands must be *cis* to one another. As such, bidentate ligands have been used to force the organic ligands closer together and encourage the formation of the (*Z*)-isomer thus encouraging reductive elimination.[26]



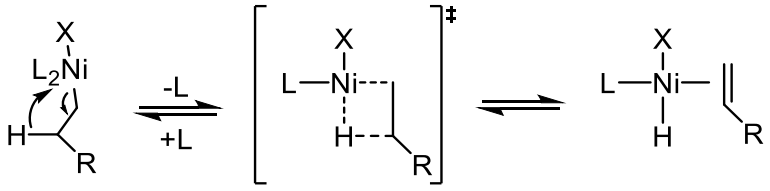
Scheme 7: Reductive elimination accelerated by the coordination of an electron deficient alkene.[26]

1.3.4 Migratory insertion and β-hydride elimination

Further to the typical mechanistic steps of metal-catalysed cross-coupling reactions, migratory insertion and β-hydride elimination are other common steps within catalytic processes. Migratory insertion involves the co-ordination of an unsaturated ligand (containing C=C, C≡C, or C=O groups) to a metal, followed by

the insertion of the unsaturated ligand into an M–R bond, thus forming a new C–C bond.[26] Insertion of alkenes into metal-aryl bonds is a common step in the Heck reaction, while consecutive insertion of alkenes into metal-alkyl bonds is key in olefin polymerisation reactions.[36] β-Hydride elimination involves the transfer of a hydrogen in a β-position on an alkyl ligand to the metal centre forming a new M–H bond and an alkene (Scheme 8).[26] β-Hydride elimination is often an unwanted side-reaction in many cross-coupling reactions, therefore it is crucial to control and reduce its occurrence, to maximise reaction yields. Conversely, in the Heck-Mizoroki reaction, β-hydride elimination is a key step in producing the desired substituted alkene.[37] In comparison to Pd-complexes, Ni-species readily undergo migratory insertion whereas β-hydride elimination is significantly slower, thus illustrating that nickel offers different reactivity compared to palladium.[24]

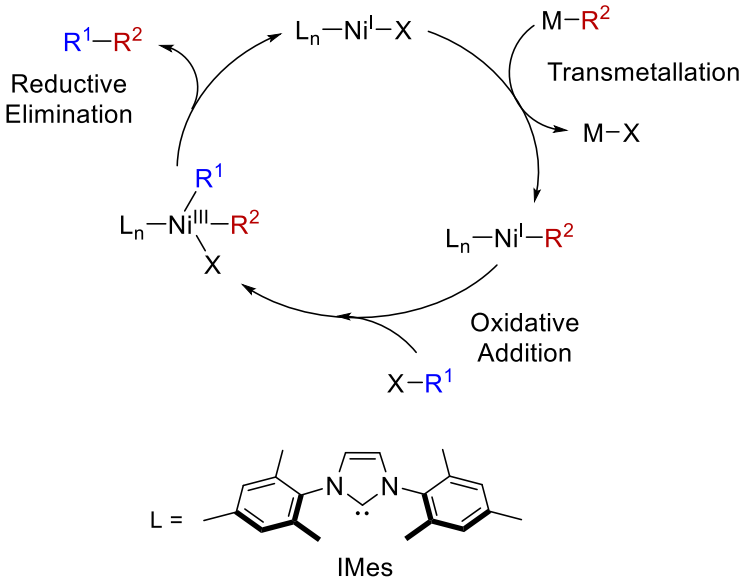
All of the features mentioned above can be taken advantage of and fine-tuned with appropriate ligands and reaction conditions to develop new reactions and potentially improve previously reported reaction yields and selectivity.[23,24,26]



Scheme 8: β-Hydride elimination (Left to right) and alkene insertion (right to left) with the concerted transition state displayed.

1.4 Alternative mechanistic routes

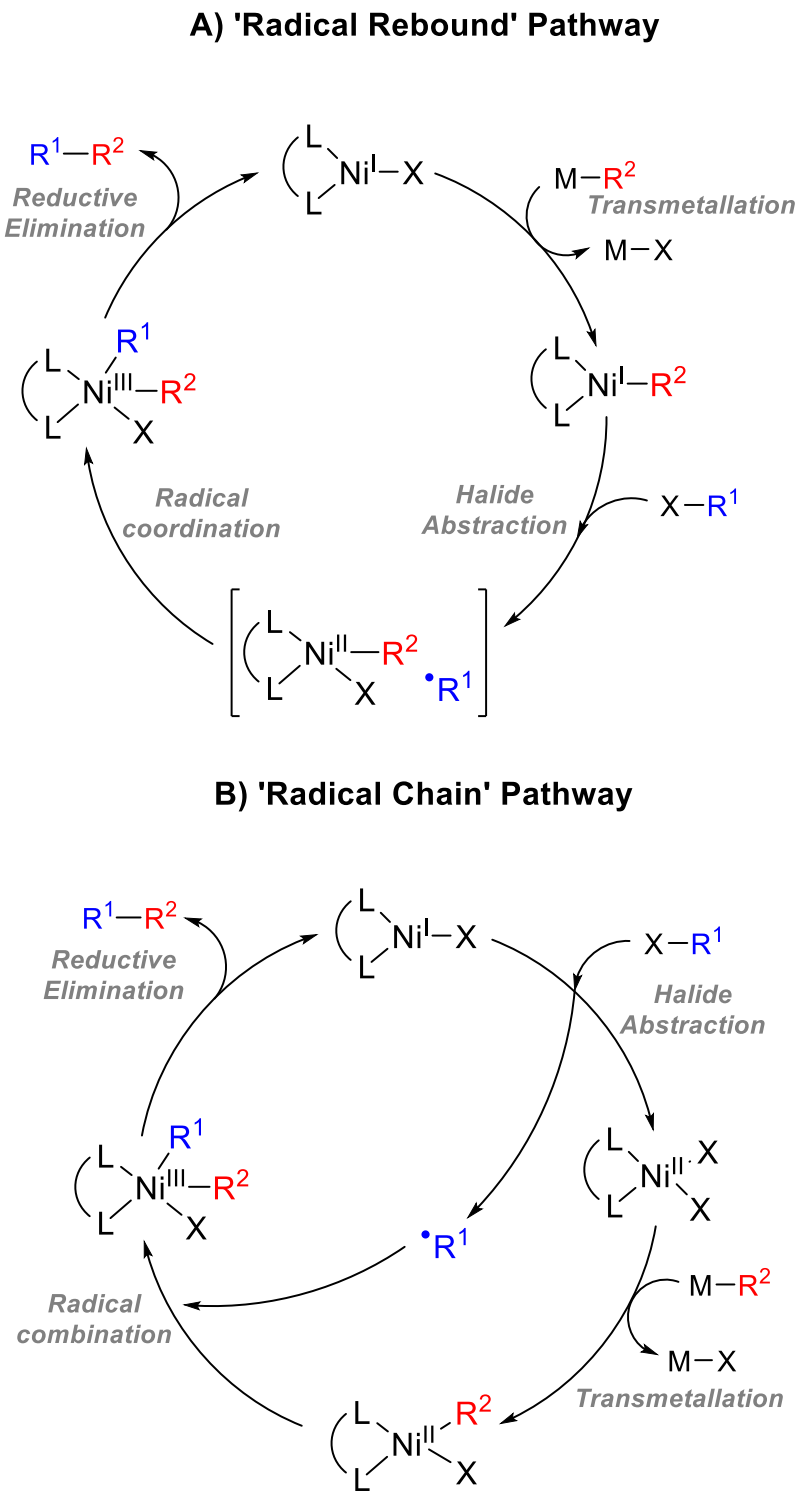
In addition to the common Ni^0 and Ni^{II} oxidation states, nickel can access Ni^I, Ni^{III} and Ni^{IV} oxidation states. As such, in addition to the typical two-electron Ni^0/Ni^{II} mechanism as mentioned above, nickel can also undergo a two-electron redox mechanism via Ni^I/Ni^{III}, as well as a single-electron process resulting in a radical mechanism.[38] In the case of a two-electron Ni^I/Ni^{III} cycle with an N-heterocyclic carbene ligand, IMes, it has been proposed that transmetallation of Ni^I species occurs prior to the oxidative addition, which forms Ni^{III} and is followed by facile reductive elimination (Scheme 9).[39]



Scheme 9: Two-electron pathway via Ni^I/Ni^{III} intermediates.[39]

Nickel catalysed cross-coupling reactions involving Csp^3 electrophiles often involve a single-electron transfer process resulting in Ni^{I}, Ni^{III} and organic radical intermediates. Two different radical pathways have been proposed and termed: 'radical rebound' and 'radical chain'.[38] Both pathways begin with a Ni^{I} –halide intermediate. In the 'radical rebound' pathway, the Ni^{I} –halide first undergoes transmetallation to form an Ni^{I} –alkyl intermediate. The Ni^{I} complex then undergoes radical oxidative addition of the electrophile, forming an Ni^{II} species and generating an alkyl radical. The alkyl radical coordinates to the Ni^{II} species forming Ni^{III} intermediate with two bound alkyl ligands, allowing for subsequent reductive elimination of the coupled product and regeneration of the starting Ni^{I} –halide complex (Scheme 10A). In the 'radical chain' pathway, the initial Ni^{I} –halide species abstracts a halide from the alkyl electrophile (thereby forming the organic radical) prior to the transmetallation step (Scheme 10B).[38] There is evidence to support both radical pathways, and their occurrence appears to be system dependent.[40–42]

In summary, the diverse mechanism available through nickel catalysis offer opportunities for achieving novel C–C bond forming transformations which are not accessible with palladium.



Scheme 10: The two possible single electron (radical) pathways involving Ni^{I} and Ni^{III} intermediates, and organic radicals.[38]

1.5 Advances in Ni-catalysed cross-coupling reactions

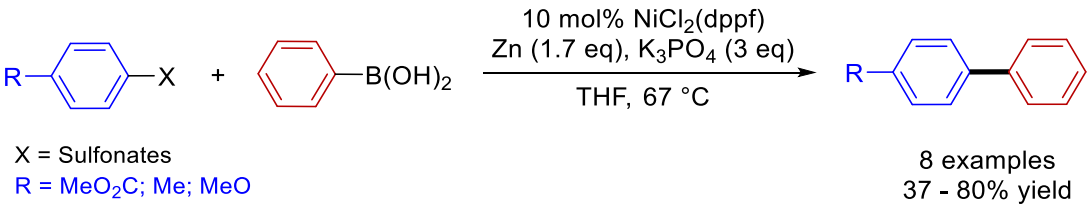
Transition metal-catalysed cross-coupling reactions are useful and widely used tools for the formation of C–C and C–X bonds. The use of palladium as a catalyst has dominated in this field, however, the interest is now shifting towards more abundant, and thus economically favourable metals in catalysis. As a result, the use of nickel in catalysis has become increasingly more common. Nickel is capable of catalysing many of the same reactions as palladium, in addition to its ability to activate less reactive electrophiles, such as phenols and their derivatives. The following section describes the numerous successful coupling reactions that employ Ni-based catalysts. There is a large variety in the nickel-based catalytic systems employed, however, a simple and general approach to nickel-based catalysts is currently lacking, which it could be argued is hindering the progress and wider application of nickel in industry.

1.5.1 Cross-coupling of aryl halides

1.5.1.1 Early work

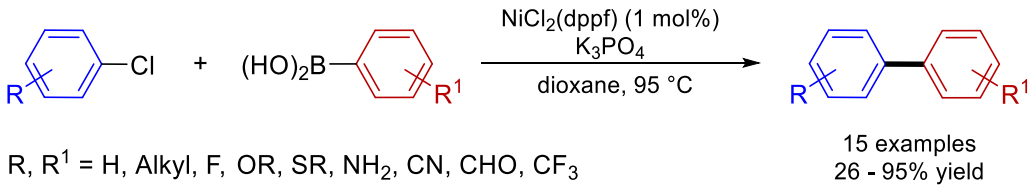
Many different electrophiles have been employed in Ni-catalysed cross-coupling reactions, however, aryl and vinyl electrophiles emerged as some of the most popular due to their general applicability, high tolerance of functional groups, and no β-hydride elimination.[43] The Suzuki-Miyaura cross-coupling has been one of the most popular approaches to constructing new C–C bonds since its discovery in 1979. It generally involves a reaction between an organic (pseudo) halide and organo-boron compounds, in the presence of a transition metal catalyst (usually palladium or nickel) and a base.[21] In 1995, Percec *et al* reported nickel's ability to

catalyse the cross-coupling of aryl mesylates and aryl sulfonates with phenylboronic acid, the first example of Ni catalysed Suzuki-Miyaura reaction (Scheme 11).[44] This not only potentially reduces costs, it may also allow for the use of less reactive electrophiles in Suzuki-Miyaura and potentially other C–C bond forming reactions.



Scheme 11: Example of the first reported Ni-catalysed Suzuki-Miyaura cross-coupling of aryl sulfonates with phenylboronic acid.[44]

Following on from the work reported by Percec in 1995, Miyaura and co-workers reported the first Ni-catalysed cross-coupling of aryl chlorides and phenylboronic acids in 1996, generating Ni^0 from $NiCl_2$(dppf) in the presence of a strong reducing agent, ^{n}BuLi, and K_3PO_4 base.[45] Following this work, Indolese demonstrated that the use of external reducing agents is not necessary for the coupling of aryl halides and boronic acids in the presence of $NiCl_2$(dppf) (Scheme 12).[46] Prior to this, aryl chlorides had rarely been used in Pd-catalysed cross-coupling reactions with phenylboronic acids due to slow oxidative addition hindering the reaction from proceeding.[45]

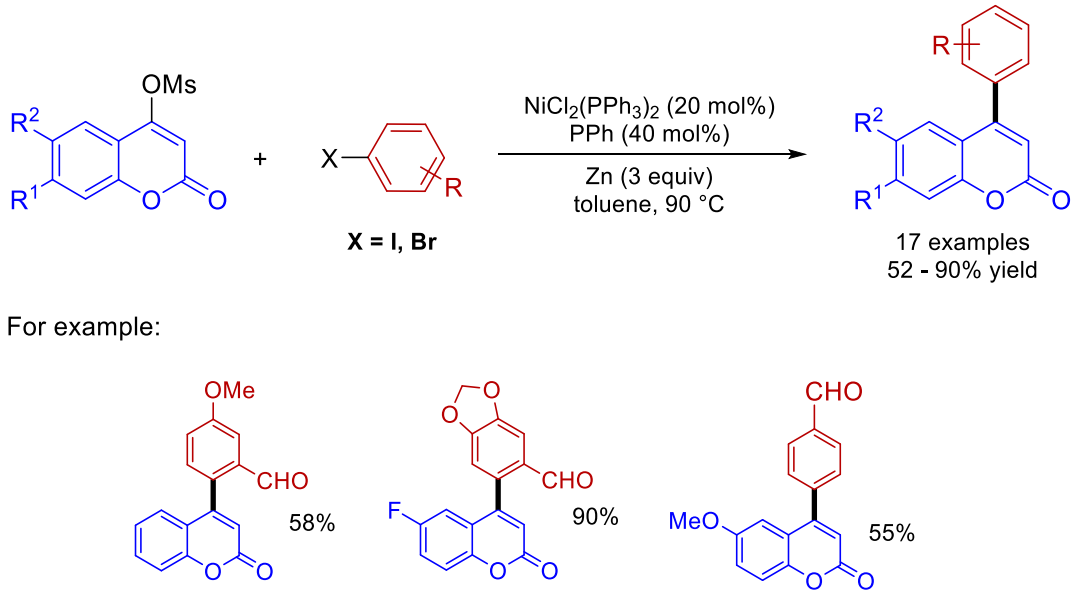


Scheme 12: Suzuki-type cross-coupling of aryl chlorides without the need for an external reducing agent.[46]

Since then, the use of nickel in cross-coupling reactions with aryl halides has undergone extensive investigations to understand, improve and expand the applicability of nickel in aryl halide coupling reactions. This involved many different Ni-catalyst systems ($NiCl_2(PPh_3)_2$, $Ni(cod)_2$, $NiCl_2(PCy_3)_2$, $NiCl_2$(dppf) and Ni(NHC)), reducing agents, bases, ligands, additives and solvents.[45,47–49]

1.5.1.2 Aryl halide coupling

Ni-catalysed cross-coupling of aryl halides has also been utilised in natural product synthesis, such as the synthesis of 4-aryl coumarins, a class of natural compounds with various biological activities, such as antibacterial, anti-HIV and anti-cancer activites.[50,51] The direct cross-coupling of 4-mesylcoumarins with aryl halides using a modified Ullmann-type coupling reaction was developed with a catalytic system compromised of $NiCl_2(PPh_3)_2$, PPh_3, and Zn (Scheme 13).[50]

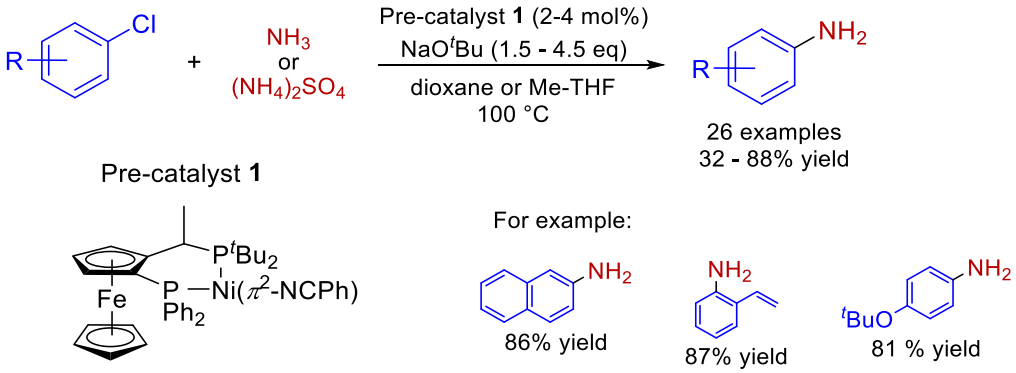


Scheme 13: Direct cross-coupling of 4-mesylcoumarins with aryl halides.[50]

More recently, a practical Ni catalyst for the Suzuki coupling of aryl halides has been reported.[52] This system, consisting of $NiCl_2$(dppp) and K_3PO_4 in dioxane, successfully catalysed the coupling of a large range of aryl bromide and chloride electrophiles with various boronic acids, demonstrating tolerance for a variety of functional groups including aldehydes, esters, and unprotected amino and hydroxy groups.[52]

Hartwig and Green also demonstrated nickel catalysed amination of aryl chlorides with ammonia, a reaction that was previously regarded as challenging due to ammonia often deactivating the catalyst, and due to the nucleophilic aniline formed during the reaction (Scheme 14).[53] The catalyst designed was a Ni^0 complex containing a biphosphine ligand with a large steric bulk, which preferentially binds ammonia over the aniline product; and a side-bound benzonitrile ligand, stabilising the Ni^0 intermediate and improving the efficiency

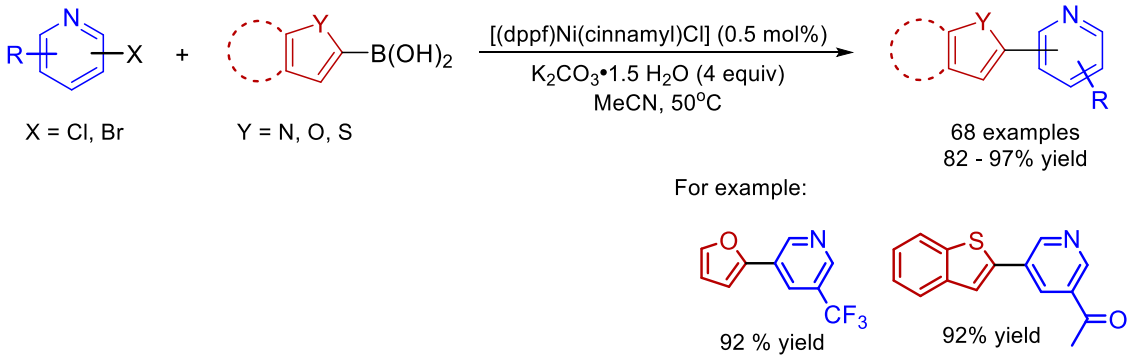
of oxidative addition. Furthermore, the same transformations are observed when ammonia is replaced by ammonium salts, which are inexpensive and easy to handle, expanding the scope and potential of this reaction.[53]



Scheme 14: Nickel catalysed amination of aryl chlorides with ammonia/ammonia salts.[53]

1.5.1.3 Coupling of heteroaryl halides

Nickel-catalysed synthesis of hetero-biaryl compounds was previously perceived as challenging due to the heteroaryl poisoning the catalyst by ligation. Nevertheless, in 2012, Hartwig and Ge reported the novel Ni^{II} precatalyst [(dppf)Ni(cinnamyl)Cl], capable of catalysing the synthesis of hetero-biaryl compounds in high yields, with low catalyst loading (0.5 mol% of Ni), making this a highly efficient and economically viable reaction (Scheme 15).[54]

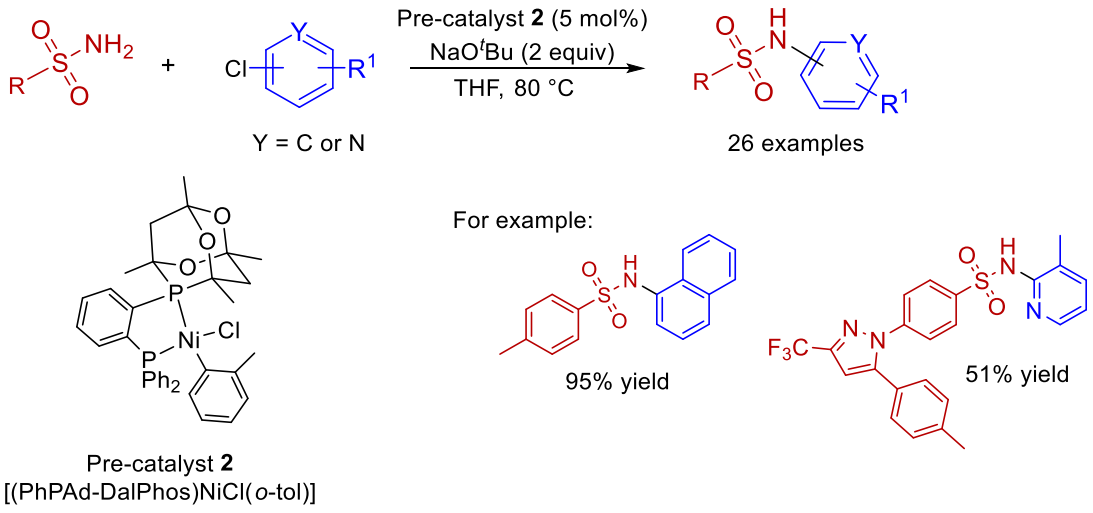


Scheme 15: Suzuki-Miyaura nickel catalysed synthesis of hetero-biaryl complexes.[54]

Recently, Ni-catalysis has been applied to the C–N cross-coupling of heteroaryl chlorides with sulfonamides to form secondary N-heteroaryl sulfonamides.[55] Sulfonamides are a common structural motif in medicinal chemistry, and their biological activity includes anti-bacterial, anti-cancer, and anti-malarial activities, just to name a few.[56,57] In this work, an air-stable Ni precatalyst (**2**) has been utilised in the presence of sodium tert-butoxide.[55] This enabled the C–N cross-coupling of primary sulfonamides with heteroaryl chloride electrophiles to furnish

secondary N-heteroaryl sulfonamides in high yields, with relatively low catalyst loading (5 mol%) and demonstrating a large substrate scope (Scheme 16).

Although Pd-catalysed cross-couplings of sulfonamides have been reported, their scope is limited, further highlighting the benefits of using nickel in catalysis.



Scheme 16: Cross-coupling of sulfonamides with heteroaryl chlorides.[55]

1.5.2 Cross-couplings involving C–O bonds

Although aryl and vinyl halides are popular in cross-coupling reactions, they are often toxic, expensive, and slow to prepare. Phenol derived electrophiles on the other hand are much easier to access since many phenols are naturally abundant. Alternatively, phenol derived electrophiles can be easily synthesised from other readily available aromatic species.[22] Other advantages of using phenol-derived electrophiles include the ability to easily introduce additional functional groups to the aromatic ring; such as esters, ethers, carbamates, and sulfamates, which can then be used as further cross-coupling partners. However, cross-coupling of phenol derivatives is not as straightforward as that of aryl halides due to the strength of the C–O bond being significantly higher than that of a C–Hal bond. (Hal = Cl, Br, or I). Consequently, phenols are often converted to more reactive species; such as aryl triflates, mesylates, tosylates, esters, carbamates or carbonates, in order to activate the C–O bond (Figure 1). [22,23]

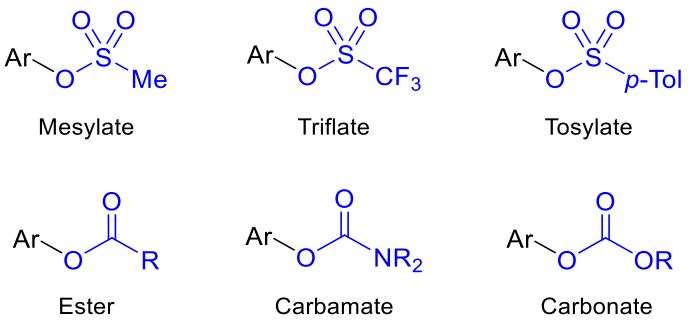
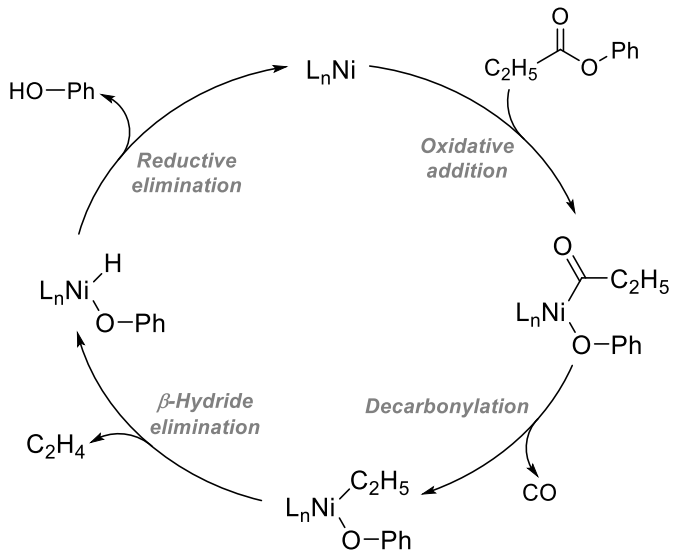


Figure 1: Examples of common phenol derived electrophiles.

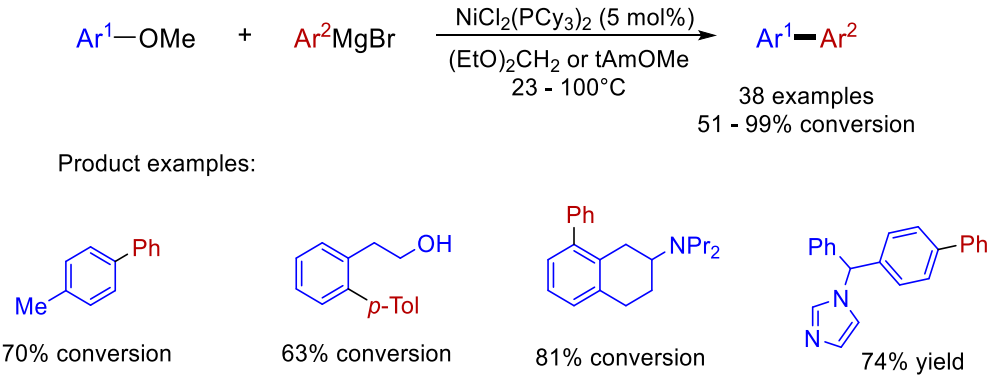
1.5.2.1 Coupling of phenol derived electrophiles

The ability of Ni^0 to activate C–O bonds was first recognised by Yamamoto and co-workers in 1976.[56] They were the first to report the ability of Ni to insert into a usually inert C–O acyl bond of an ester by oxidative addition (Scheme 17).[58,59] In 1979, the first catalytic use of phosphine–ligated nickel chloride in the cross-coupling reaction of aryl ethers with Grignard reagents was reported. However, at that point in time, the reaction displayed reactivity towards a limited range of aryl ethers.[60]



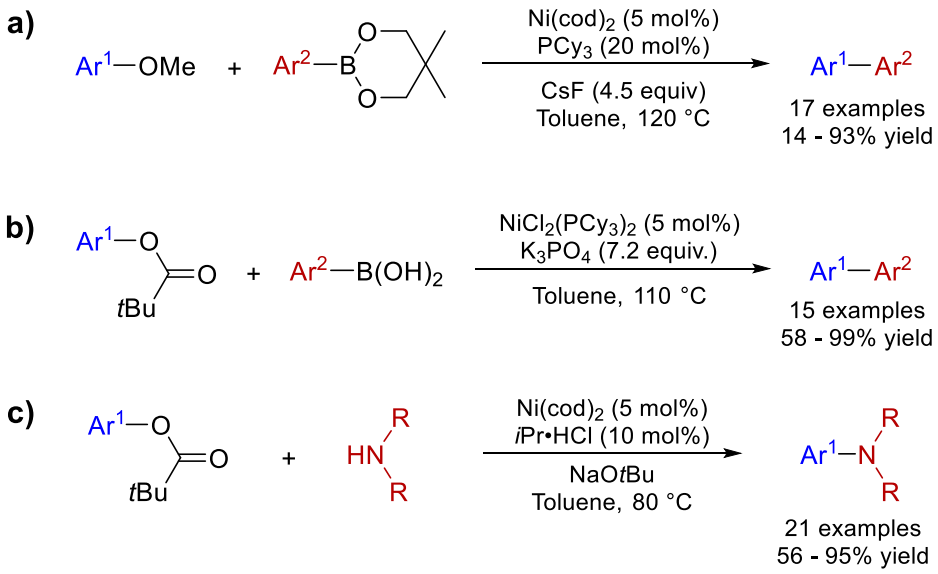
Scheme 17: C-O cleavage of esters as first presented by Yamamoto *et al*.[58,59]

Notable progress was made 25 years later, when Dankwardt reported a high-yielding Ni-catalysed cross-coupling of non-activated aryl ethers with aryl Grignard reagents.[61] This work significantly improved the scope of the reaction by using a PCy_3 ligand, instead of the (1,3-dppp) used 25 years earlier, and by using a non-polar solvent. As a result, the reaction was expanded to more versatile aryl ether derivatives, including heteroaryl ethers and anisole derivatives (Scheme 18).



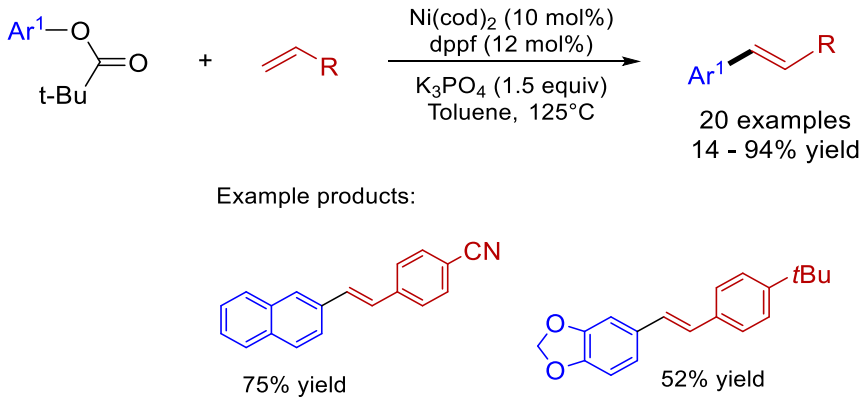
Scheme 18: Biaryl formation from aryl ethers and Grignard reagents as reported by Dankwardt.[61]

Another critical development in the coupling of phenol derivatives came in 2008 from the Chatani group, who reported the use of aryl methyl ethers with aryl boronic esters in the first nickel catalysed Suzuki-Miyaura cross-coupling of this type. Previously all similar reactions had utilised Grignard reagents (Scheme 19a).[62] In the same year, Garg and co-workers described the first Ni-catalysed Suzuki-Miyaura cross-coupling of *O*-acylated phenol derivatives, aryl pivalates, with boronic acids (Scheme 19b).[63] This was advantageous as *O*-acylated phenols are easy to prepare and are usually stable under a variety of reaction conditions.[63] The Chatani group later described the amination of aryl carboxylates in the presence of a nickel catalyst with a diverse range of aryl electrophiles (Scheme 19c).[64]



Scheme 19: a) Suzuki-Miyaura reaction forming biaryls from aryl ethers;[62] **b)** Suzuki-Miyaura coupling of aryl pivalates;[63] and **c)** amination of aryl pivalates.[64]

Following these initial reports, the range of cross-coupling partners for phenolic electrophiles has been expanded through the use of organozinc and aryl oxide reagents, resulting in many transformations to produce valuable biaryl compounds.[23] Other coupling reactions with phenol derivatives have since emerged. For example, in 2012, Watson and co-workers reported the first Ni-catalysed Heck cross-coupling of aryl pivalates with olefins.[65] They formed 1,2-disubstituted alkenes while avoiding the use of triflate groups and without producing halogenated waste (Scheme 20).[65] They also demonstrated the reaction's applicability to a range of different olefin partners, including styrenes and α-olefins, highlighting the scope of this reaction.

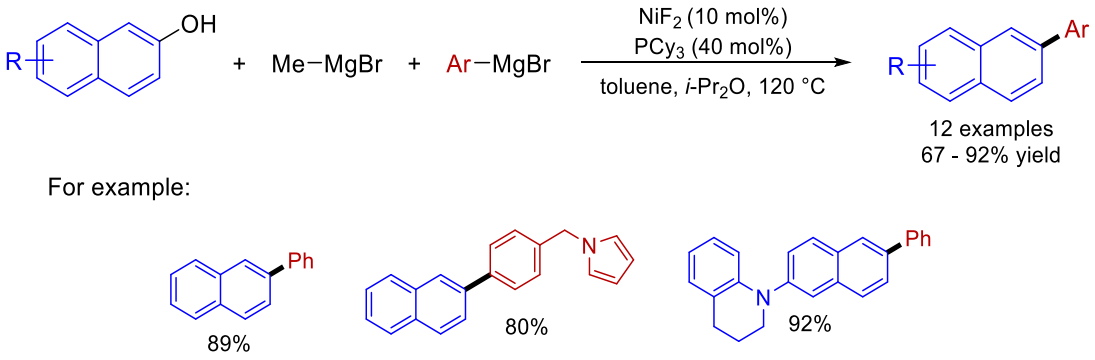


Scheme 20: Nickel catalysed Heck reaction of aryl pivalates.[65]

The methods mentioned here demonstrate that the ability of nickel to activate C–O bonds gives rise to the successful use of phenol derived electrophiles as viable alternatives to the previously traditional aryl halide electrophiles.

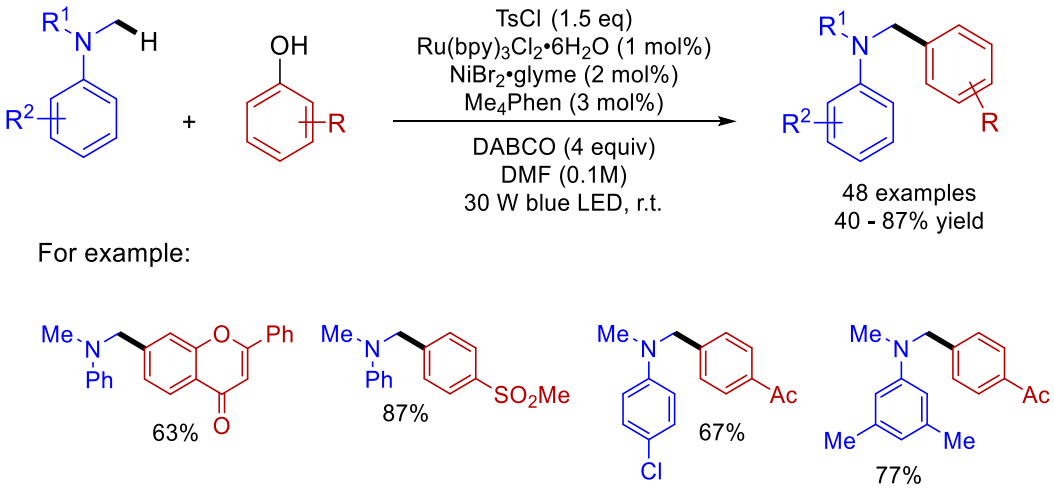
1.5.2.2 Direct coupling of phenol electrophiles

Due to the strength, and therefore high dissociative energy, of the C–O bond of phenol electrophiles, direct Ni-catalysed cross-coupling of phenols is seldom reported. The use of phenol electrophiles is attractive as it would allow for better atom economy and improved environmental impact. Although challenging, the direct cross-coupling of phenol electrophiles has been achieved. One strategy described the formation of a phenolic salt by the addition of MeMgBr prior to an addition of an aryl Grignard reagent in the presence of NiF_2/PCy_3 to form a biaryl product (Scheme 21).[66] Unfortunately, the reaction only proceeds with 2-napthol derivatives, however, this approach highlights a promising step towards improved atom and process economy of such reactions.



Scheme 21: Direct coupling of napthol electrophiles with aryl Grignard reagents.[66]

Recently, a one pot arylation of *N,N*-dimethylaniline derivatives with phenol electrophiles via photoredox/Ni dual catalysis has been developed as an *in situ* activation strategy to afford benzylic amines.[67] Photoredox catalysis offers unique C–C bond forming transformations via single electron transfer pathways, especially when combined with transition metal catalysis.[67] In this work, TsCl has been employed as an activation agent, $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ and $NiBr_2$·glyme as the catalysts, Me_4phen as the phosphine ligand, and DABCO as the base. The reaction demonstrated scope for a range of phenols not limited to 2-napthols, and for a small number of different *N,N*-dimethylaniline derivatives (Scheme 22). Although the activation of phenols is still required via the formation of tosylates *in situ*, the efficiency of this reaction is notable as the isolation and purification of the phenol intermediates is not needed, thus also highlighting the potential environmental impact of this approach. Nevertheless, the photoactive co-catalyst in this system, Ru, is an expensive and rare-Earth metal, potentially offsetting the economic benefits of using an inexpensive Ni-catalyst.



Scheme 22: Coupling of phenol electrophiles with *N,N*-dimethylaniline via photoredox/Ni dual catalysis.[67]

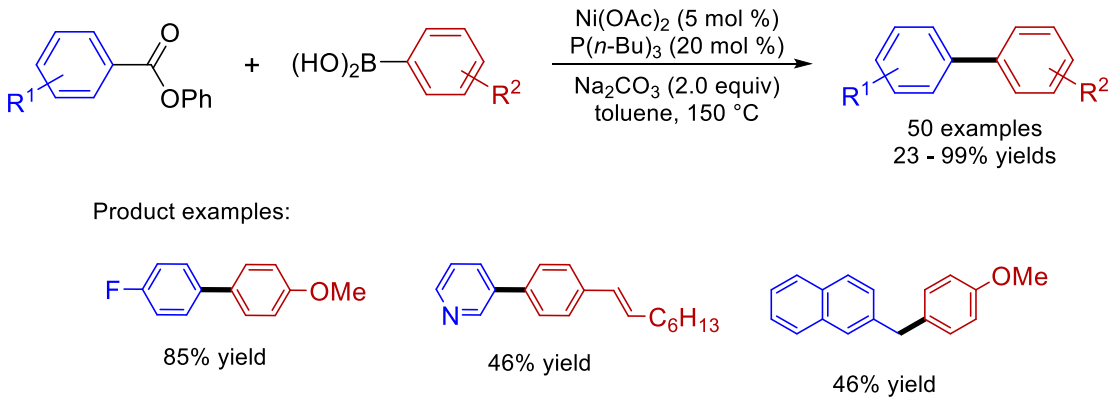
1.5.2.3 Decarbonylative reactions

Decarbonylative cross-coupling represents another strategy for forming desirable biaryl moieties. It allows for the utilisation of aryl esters, which is attractive not only due to the elimination of halide waste, but also due to the large number of esters which are commercially available.[68]

1.5.2.3.1 Decarbonylative cross-coupling of esters

In 2015, Suzuki-Miyaura decarbonylative cross-coupling of aryl esters with arylboronic acids in the presence of $Ni(cod)_2$, PCy_3 ligand and Cs_2CO_3 base was demonstrated.[69] This method provided a moderate substrate scope in modest yields, highlighting the potential for a new route of accessing biaryl compounds. A different group carried out a similar type of work simultaneously, significantly expanding on the original work. They reported successful decarbonylative cross-coupling of aryl esters with arylboronic acids, however, the method employed a

much cheaper, and air-stable nickel source, $Ni(OAc)_2$, in the presence of monodentate ligand, $P(n\text{-}Bu)_3$, and Na_2CO_3 base (Scheme 23).[70] This system displayed a broad scope for ester and boron substrates, including aliphatic coupling partners, with high yields, demonstrating the potential for inexpensive nickel precatalyst to be successfully applied for the cleavage of C–O bonds, thus forming desirable biaryl moieties from readily available precursors.

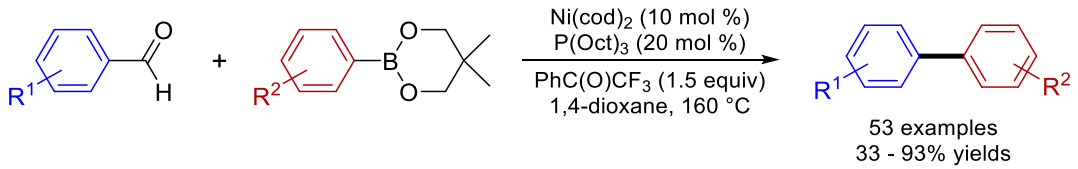


Scheme 23: Decarbonylative Suzuki-Miyaura cross-coupling of aryl esters.[70]

1.5.2.3.2.Decarbonylative cross-coupling of aldehydes

Recently, the first nickel-catalysed decarbonylative Suzuki-Miyaura cross-coupling of aromatic aldehydes for the formation of biaryl compounds has been reported.[71] Aldehydes are often inexpensive, readily available and do not require pre-functionalisation, as is sometimes the case with esters. Therefore, they represent an attractive electrophilic coupling partner for the formation of C–C bonds. Successful cross-coupling of aromatic aldehydes with organoboron compounds has been reported in the presence of $Ni(cod)_2$, $P(Oct)_3$ ligand, and $PhC(O)CF_3$ as a hydride acceptor, present to prevent the formation of an arene via

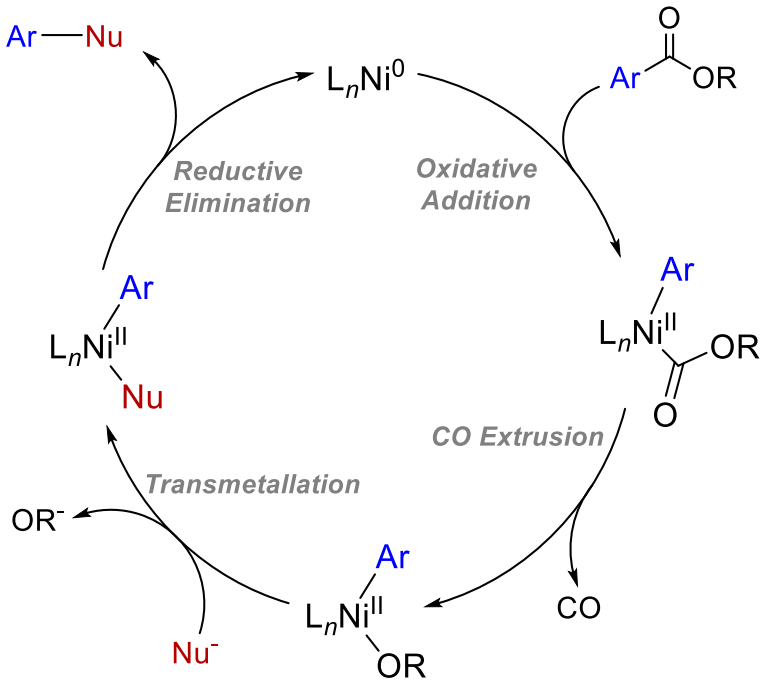
the undesired reductive elimination of arylnickel(II) hydride.[71] This system demonstrated broad scope for both coupling partners with moderate to high yields, offering novel opportunities for synthesising structurally diverse biaryls (Scheme 24).



Scheme 24: Decarbonylative cross-coupling of aromatic aldehydes for the formation of biaryl products.[71]

1.5.2.3.3 Mechanistic studies of decarbonylative coupling

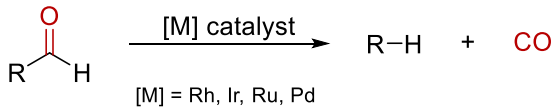
Several groups have undertaken mechanistic investigations of decarbonylative cross-coupling, however, some uncertainty remains and several possible mechanisms have so far been proposed. One proposed mechanism involves the oxidative addition into the C(acyl)–O bond of the ester, forming a Ni^{II}-acyl species. This intermediate then undergoes decarbonylation, releasing a molecule of CO and forming a Ni^{II}-aryl complex. This is then followed by the typical transmetallation and finally the reductive elimination steps to form the biaryl product (Scheme 25).[68,69] Although generally accepted, there is some disagreement in the order of the steps in this model, with some suggesting the transmetallation step takes place prior to the decarbonylation step.[68,70] Furthermore, evidence also suggests that oxidative addition into the C(aryl)–C bond occurs instead of into the C(acyl)–C bond.[72] Nevertheless, further research is required to fully understand these decarbonylative coupling reactions.



Scheme 25: Proposed mechanism for Ni-catalysed decarbonylative cross-coupling.

1.5.2.3.4 Ni-catalysed Tsuji-Wilkinson decarbonylation

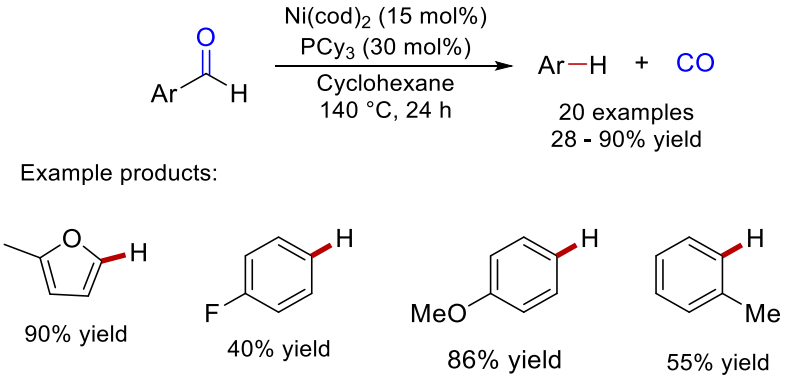
The Tsuji-Wilkinson decarbonylation is widely used in organic synthesis. It allows for the conversion of aldehydes and ketones into their parent alkanes, removing the carbonyl functional group and releasing a molecule of carbon monoxide in the process (Scheme 26).[73] Decarbonylation can only proceed in the presence of a transition metal catalyst and although decarbonylation of aldehydes was originally carried out in the presence of Rh, it has since been demonstrated to also proceed with catalysts based on Ir, Ru and Pd.[74] Nevertheless, the reaction conditions remain harsh (>180 °C) and employ rare-Earth metals as catalysts, making the whole process expensive and unsustainable. The utilisation of nickel in decarbonylative reactions has been restricted due to the propensity of nickel to form strong bonds with CO, thus deactivating the catalyst.[24] As a result, very few nickel mediated decarbonylation reactions have been reported.



Scheme 26: Tsuji-Wilkinson decarbonylation of aldehydes.[73]

In 2017, the first nickel-catalysed decarbonylation of aromatic aldehydes was developed, providing moderate yields in the presence of $Ni(cod)_2$, PCy_3, and at 140 °C over 24 h (Scheme 27).[74] Although this is an improvement on the previously used conditions of >180 °C, these temperatures would still be considered relatively harsh, in addition to utilising $Ni(cod)_2$, which offsets the economic

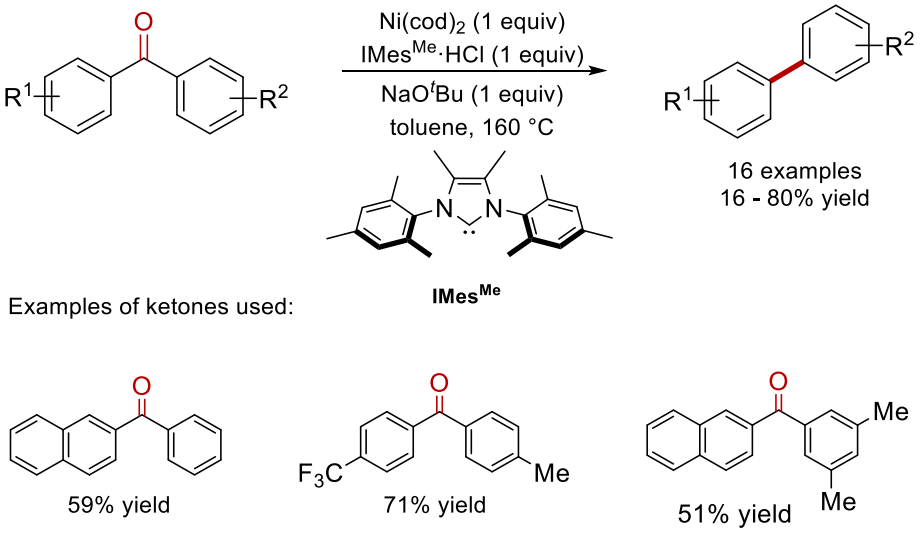
benefits of employing a nickel-based catalyst. Furthermore, the substrate scope presented is fairly limited.



Scheme 27: Ni-catalysed decarbonylation of aromatic aldehydes.[74]

In the same year, the Chatani group reported the first example of nickel-catalysed decarbonylation of simple diaryl ketones.[73] They also employed $Ni(cod)_2$ although this time in the presence of an NHC ligand ($IMes^{Me}$), and NaO^tBu (Scheme 28). The reaction was carried out at 160 °C over 18 h, giving moderate to high yields and demonstrating relatively broad substrate scope. Despite the high temperatures of 160 °C being far from ideal, the decarbonylation of ketones is typically more challenging than that of aldehydes, therefore, the need for higher temperatures is unsurprising. Recently Zhao *et al* have built on the work described by the Chatani

group by expanding the substrate scope of the reaction to heteroaryl ketones in addition to significantly lowering the catalyst loading to 10 mol%.[75]



Scheme 28: Nickel catalysed decarbonylation of ketones. [73]

Although the reaction conditions for these examples would still be considered harsh, these examples represent the potential for nickel to catalyse decarbonylative reactions, thus offering a less expensive alternative catalyst for the decarbonylation of aldehydes and ketones to the more commonly used rhodium-based catalysts. Nevertheless, the need for an air- and moisture- stable nickel catalyst remains.

1.5.3 Coupling of alkyl halides

1.5.3.1 Early discoveries and challenges

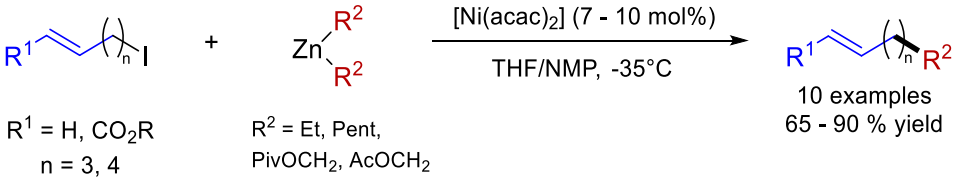
For many decades, cross-coupling reactions have largely focused on the coupling of aryl and vinyl electrophiles, thus generating new bonds between two sp^2 hybridised carbon atoms.[76] Although bonds between two sp^2 hybridised carbon atoms are common in many pharmacologically relevant compounds, Csp^3-Csp^3 bonds are significantly more abundant in natural products and complex organic molecules.[77]

As such, increasing the complexity of synthetic compounds through saturation allows access into a more diverse, three-dimensional chemical space, and increases the chance of finding biologically active molecules.[78] Increasing saturation has also shown to contribute towards improved potency, *in vivo* selectivity, and solubility. Therefore, organic chemists have gradually increased their focus on developing methods for forming Csp^3-Csp^3 bonds in a controlled and selective manner.

Nevertheless, the progress of developing catalytic methods to create new C–C bonds between two alkyl sp^3 centres has been challenging. This is due to a much slower oxidative addition of the alkyl electrophile to a metal catalyst, relatively slow transmetallation, and the propensity for the alkyl-metal intermediate to undergo intramolecular β-hydride elimination much more readily.[76] Despite these challenges, alkyl-alkyl cross-coupling has seen significant growth in the last few decades with metal catalysts such as Pd, Ni, Co, and Fe.[79]

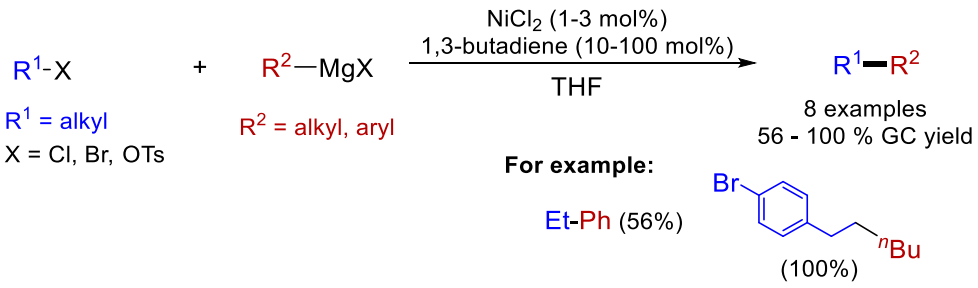
1.5.3.2 Primary alkyl electrophiles

Nickel catalysed Csp^3– Csp^3 cross-couplings were reported as far back as 1995 when a novel Ni-catalysed cross-coupling of polyfunctional primary alkyl iodides with diorganozinc reagents was developed, demonstrating a relatively large substrate scope (Error! Reference source not found.).[80–82]



Scheme 29: Negishi-type cross-coupling of primary alkyl iodides [80]

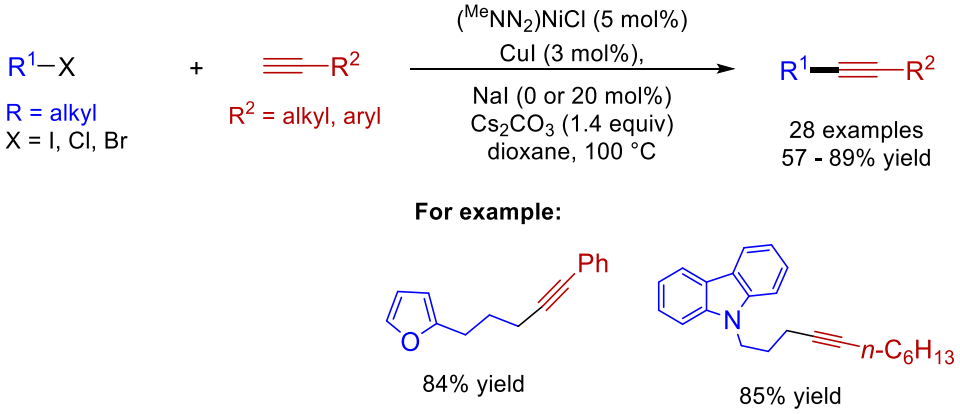
Further development in 2002 demonstrated the cross-coupling of alkyl halides and tosylates with Grignard reagents with the assistance of 1,3-butadiene (Scheme 30).[83] It is hypothesised that the butadiene forms a Ni(η^3-allyl) complex, thus facilitating the oxidative addition into the alkyl-halide bond.[83]



Scheme 30: Cross-coupling of alkyl halides with alkyl Grignard reagents[83]

Hu and co-workers also described the first Ni-catalysed Sonogashira coupling of nonactivated, β-hydrogen containing alkyl halides, utilising a Ni-pincer complex as

the catalyst (Scheme 31).[84] Up to this point, the electrophilic coupling partners for Sonogashira reactions had been largely limited to aryl and vinyl halides. They demonstrated tolerance for a range of functional groups, for both coupling partners, expanding the substrate scope of future Sonogashira coupling reactions. Although these reactions demonstrate progress in alkyl-alkyl coupling, they are all limited to primary alkyl electrophiles.

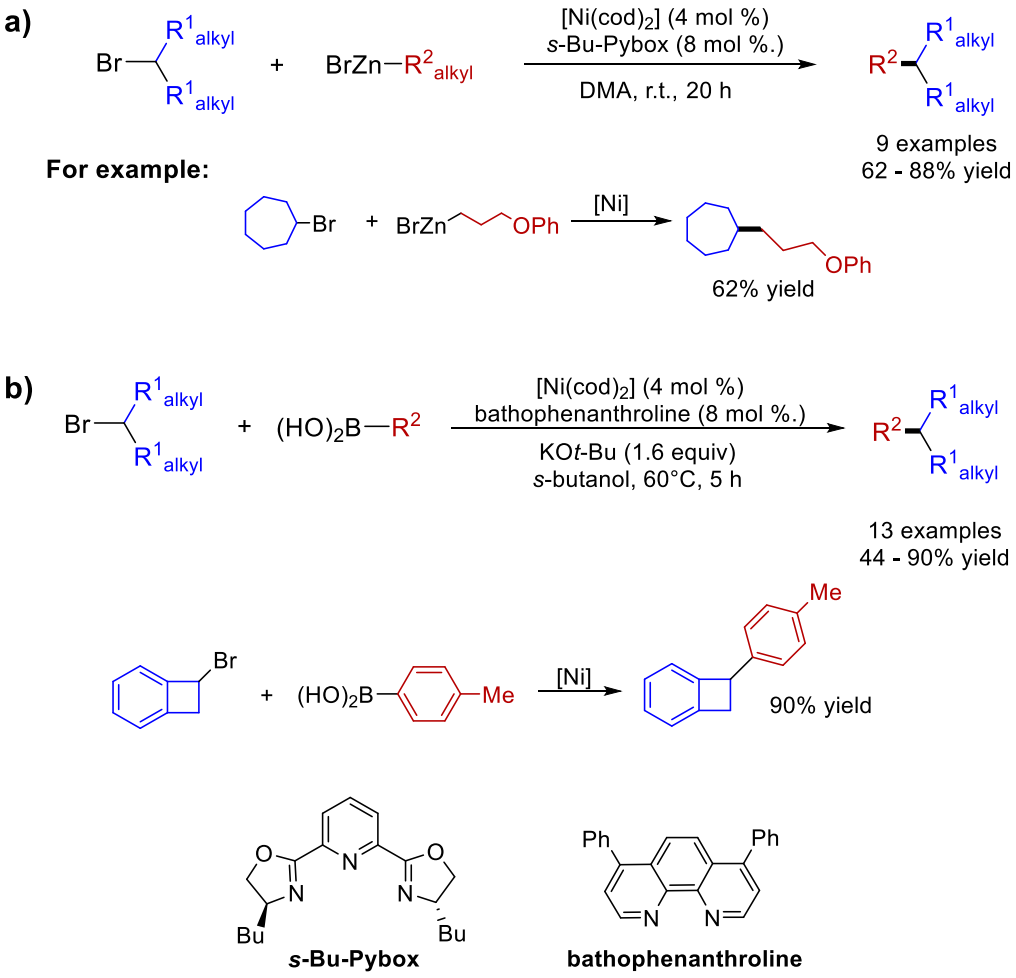


Scheme 31: Sonogashira coupling of nonactivated alkyl halides[84]

1.5.3.3 Secondary alkyl electrophiles

A breakthrough in the field of Csp^3–Csp^3 cross-coupling came in 2003 when Fu *et al* reported the first Negishi and Suzuki cross-couplings of secondary, nonactivated alkyl bromides and iodides containing β-hydrogens (Scheme 32).[85,86] The use of multidentate chelating ligands, such as Pybox or bipyridines, proved crucial in the success of these reactions, perhaps due to their ability to block the otherwise vacant coordination site, thus slowing β-hydride elimination.[23] These results offered up new opportunities in asymmetric synthesis of tertiary or

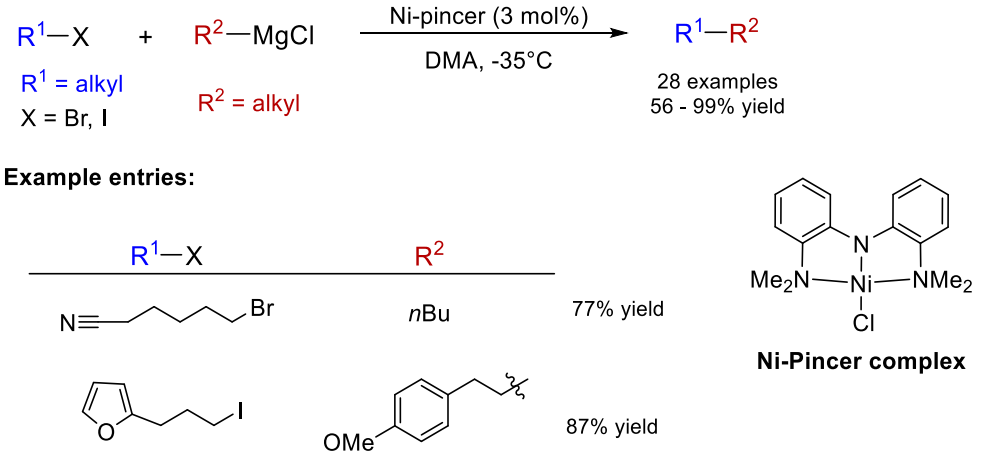
quaternary carbon stereocentres which are a common feature in naturally occurring molecules, but their synthesis has remained a challenge.



Scheme 32: a) Negishi and **b)** Suzuki-Miyaura cross-coupling of nonactivated secondary alkyl halides.[85,86]

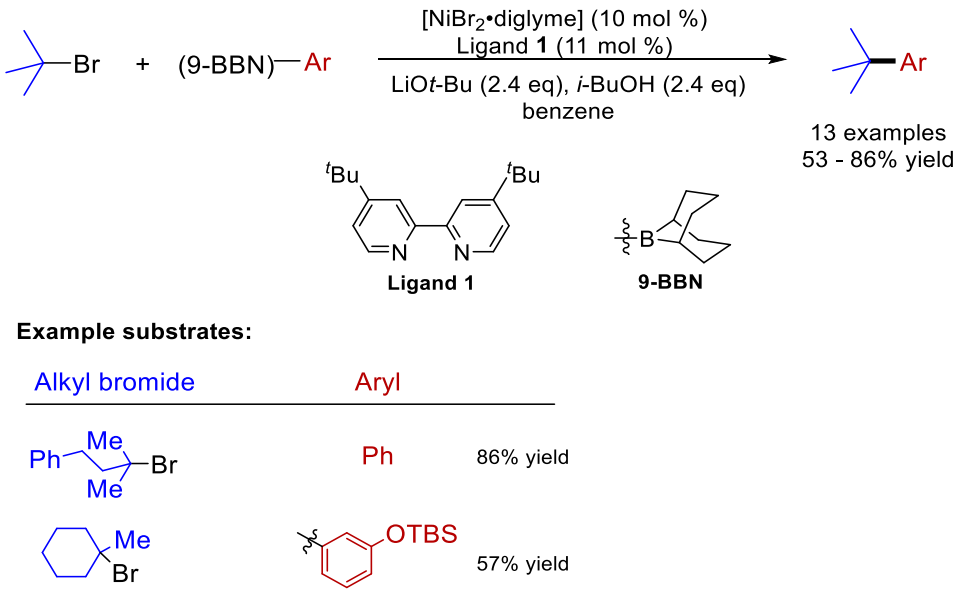
Another notable contribution to the field was the development of a novel Ni-pincer complex for the catalysis of alkyl-alkyl cross-coupling of non-activated primary and secondary alkyl halides with alkyl Grignard reagents under mild conditions

and with tolerance for a range of functional groups (Scheme 33).[87,88] This Ni-pincer complex was further applied for the Suzuki cross-coupling of alkyl halides[89]



Scheme 33: Alkyl-alkyl cross-coupling utilising a Ni-pincer complex.

In 2011, the Fu group extended the alkyl-alkyl Suzuki cross-coupling to secondary alkyl chlorides, which were previously observed to be unreactive.[90] They also reported the first nickel-catalysed borylation of nonactivated tertiary electrophiles with B_2pin_2, later extending this to Suzuki-Miyaura reactions (Scheme 34).[91,92] Notably, this reaction did not lead to isomerisation of the alkyl group. Nevertheless, the use of tertiary electrophiles in cross-coupling remains limited, and the full potential of these reactions has not yet been reached.



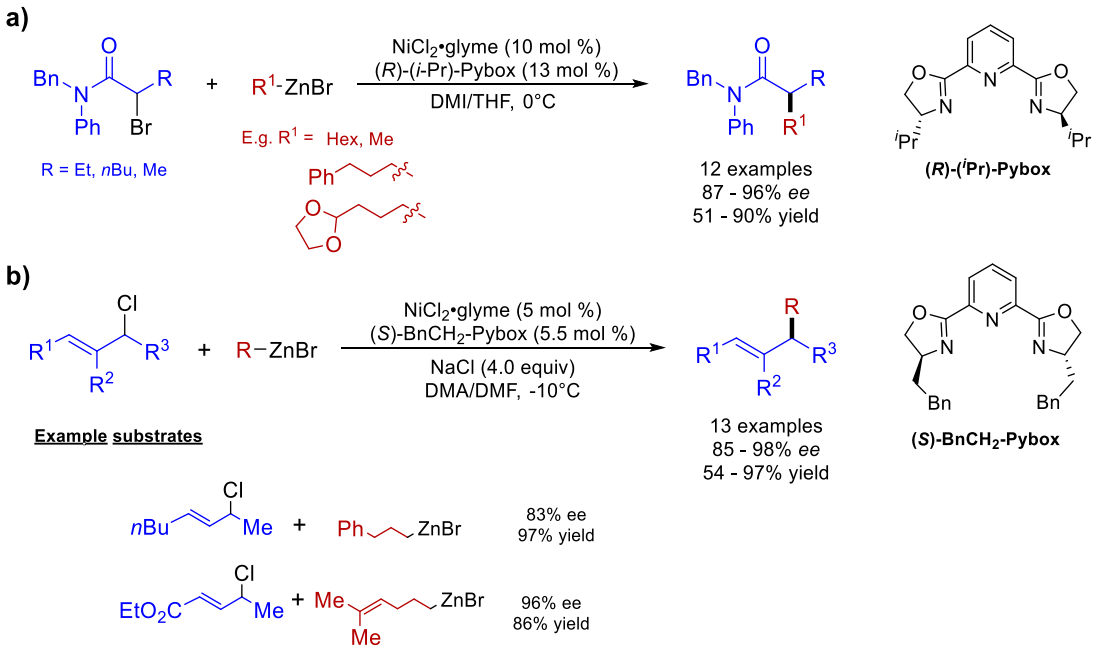
Scheme 34: The first nickel catalysed cross-coupling of unactivated tertiary alkyl halides as reported by Fu *et al.*[91,92]

1.5.3.4 Asymmetric cross-coupling of alkyl halides

Enantioselective catalysis is of significant interest in terms of Csp^3– Csp^3 bond formation. Following on from the initial research on coupling of alkyl halides, the Fu group described the first nickel-catalysed enantioselective cross-coupling of alkyl electrophiles in 2005. They reported enantioselective Negishi cross-coupling of α-bromo amides with organozinc reagents the presence of a chiral Pybox ligand with good yields and high enantiomeric excess, highlighting the potential of these types of reactions for synthetic chemistry (Scheme 35a).[93] They also demonstrated that their catalytic system was highly selective for α-bromo amides in the presence of other primary or secondary alkyl bromides.

Further reports from the Fu group have described asymmetric Ni-catalysed Negishi cross-couplings of allylic chlorides and racemic propargylic halides with alkylzinc reagents (Scheme 35b);[94] asymmetric γ-alkylation of carbonyl

compounds via Suzuki cross-couplings;[95] enantioselective cyclization through alkyl halide couplings;[96] and enantioconvergent cross-couplings of racemic secondary and tertiary electrophiles with alkenes;[97] to name a few examples. The impressive publications by the Fu group within this field demonstrate the versatility of utilising nickel catalysts for complex reactions.

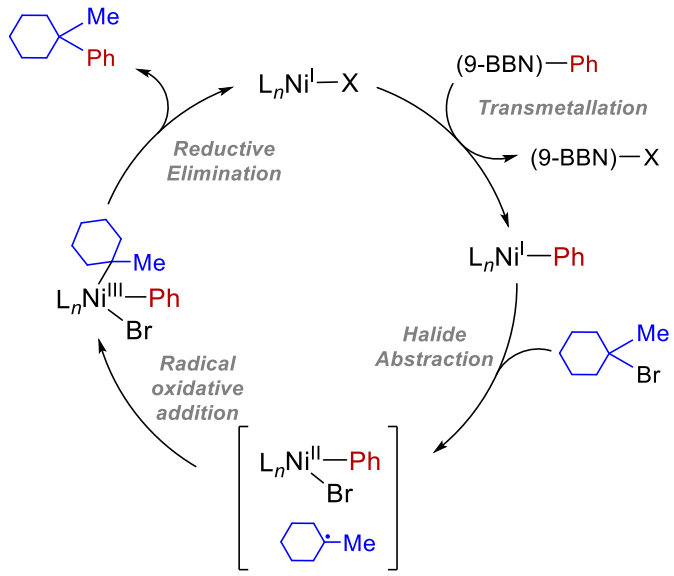


Scheme 35: a) Enantioselective, nickel catalysed Negishi coupling of secondary alkyl electrophiles;[93] **b)** Negishi cross-coupling of allylic halides.[94]

1.5.3.5 Mechanisms of alkyl-alkyl coupling

Various mechanistic studies suggest that Ni-catalysed alkyl-alkyl cross-coupling reactions proceed via radical pathways. For example, mechanistic studies of the cross-coupling reactions developed by the Fu group appear to follow the 'radical rebound' pathway mentioned earlier (**Section 1.4**).[91,92] The Ni^{I} complex undergoes transmetallation giving an Ni^{I}-alkyl species. Radical oxidative addition of the alkyl halide electrophile follows, forming a Ni^{II} species, which combines with

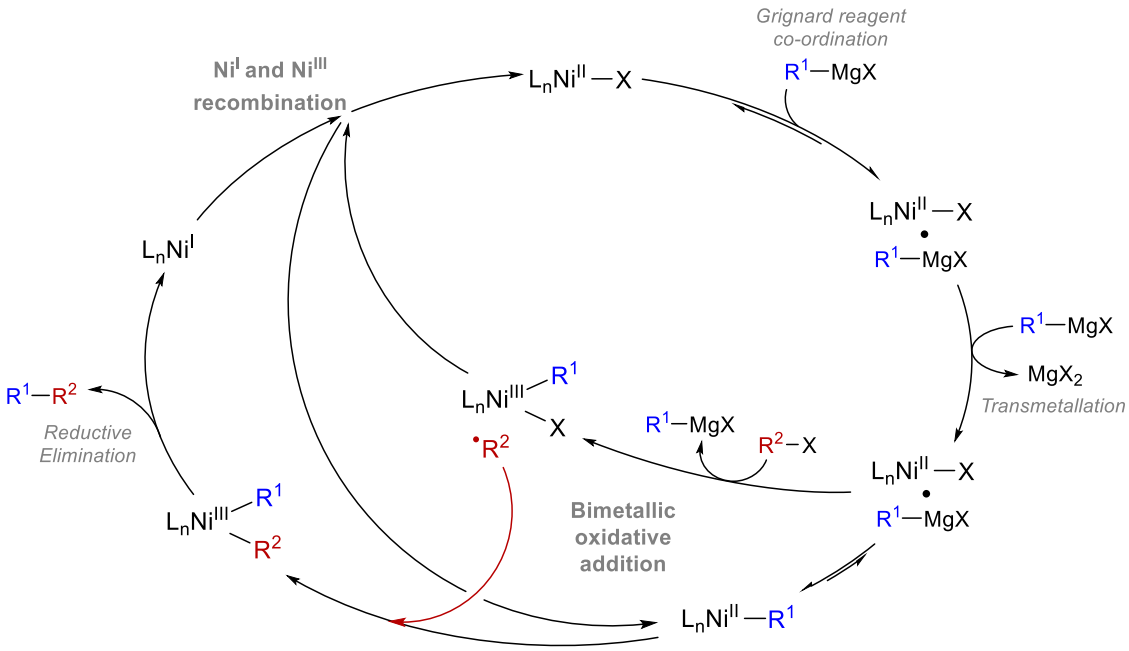
the alkyl radical producing a Ni^{III} bis(alkyl) intermediate. The product can then reductively eliminate, and thus regenerate the Ni^{I} catalyst (Scheme 36).



Scheme 36: Proposed mechanism for alkyl-alkyl cross-coupling as reported by Fu *et al.*[91,92]

The Kumada-type reactions with the Ni-pincer complex were reported to undergo a more complicated radical mechanism which involves the co-ordination of a Grignard reagent to the Ni-complex, transmetallation with a different molecule of a Grignard reagent, and generation of the alkyl radical via a bimetallic oxidative addition of the alkyl halide electrophile.[98] This leads to the formation of two Ni-complexes: a Ni^{III}-alkyl halide species and a Ni^{III}-bis(alkyl) intermediate, the latter can reductively eliminate to form the coupled product. This produces an unstable Ni^{I} intermediate in the process, which recombines with the initial Ni^{III}-alkyl halide species generating a Ni^{II}-halide and Ni^{II}-alkyl complexes, both of which can re-enter the catalytic cycle (Scheme 37).

The progress made in alkyl-alkyl cross-coupling reactions could be attributed to the fact that nickel can access a variety of oxidation states not available to other transition metals frequently utilised in catalysis, and thus facilitate alternative mechanisms to access the previously inaccessible reactions.



Scheme 37: The proposed mechanism for Kumada-type alkyl-alkyl cross-coupling with Ni-pincer catalyst.

1.5.4 C–H functionalisation

Traditional cross-coupling reactions generally rely on the use of pre-functionalised substrates, such as halides or organometallic reagents. Direct addition to a C–H bond would remove this need and significantly improve the atom economy of coupling reactions. Nevertheless, direct C–H functionalisation is not

without challenges, especially when considering site selectivity, since usually, there are multiple C–H bonds present within a molecule.[23] The progress with nickel-catalysed C–H activation has been somewhat slower in comparison to palladium. Nevertheless, examples of nickel mediated C–H activation have been reported as far back as 1963 when Kleiman and Dubeck reported nickel addition into the C–H bond in the *ortho* position of azobenzene.[99]

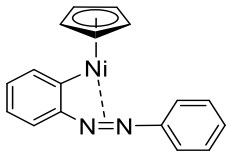
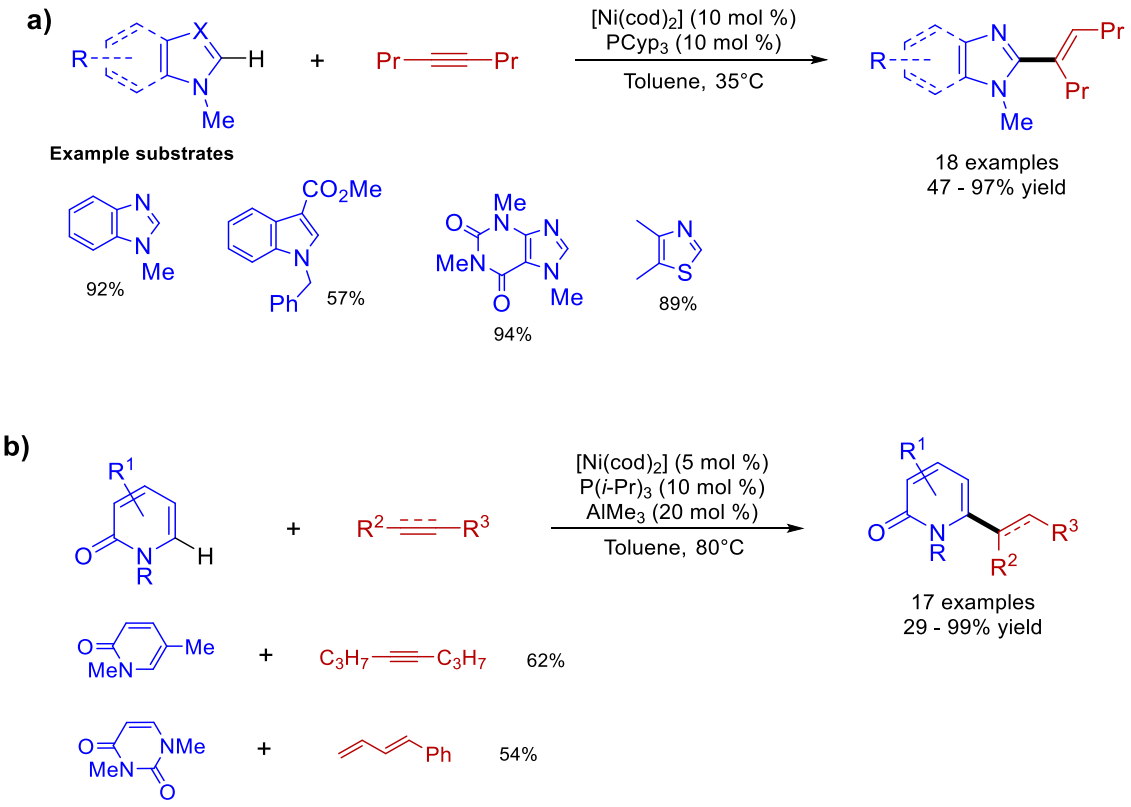


Figure 2: First reported example of Ni insertion in an ortho C-H bond.[99]

Since this discovery of nickel's ability to insert into C–H bonds, many reports on C–H activation and functionalisation by nickel have been published. The Hiyama group have made notable contributions within this field. In 2006, they reported one of the first examples of nickel catalysed activation of Ar–H bond for the hydroheteroarylation of alkynes under mild conditions in the presence of $Ni(cod)_2$ and tricyclopentylphosphine ($PCyp_3$) (Scheme 38a).[100] The Hiyama group has since further expanded the application of this nickel system to the addition pyridine-*N*-oxides across alkynes via C–H activation, which readily deoxygenate to provide a variety of substituted pyridines.[101] They also demonstrated the direct alkenylation of pyridines with a nickel-Lewis acid (LA) catalyst system.[102] They later utilised the Ni-LA catalyst system to selectively functionalise the C(6)–H bond of pyridone derivatives, a structural motif commonly found in pharmacologically

relevant compounds. Previously only C(5) selective direct transformations had been achieved, therefore the direct alkylation of the C(6) opens up the door to a variety of functionalisations of pyridone derivatives (Scheme 38b).[103,104]



Scheme 38: a) Hydro-heteroarylation of 4-octyne with indole derivatives;[100] **b)** alkenation/alkylation of pyridone derivatives.[103]

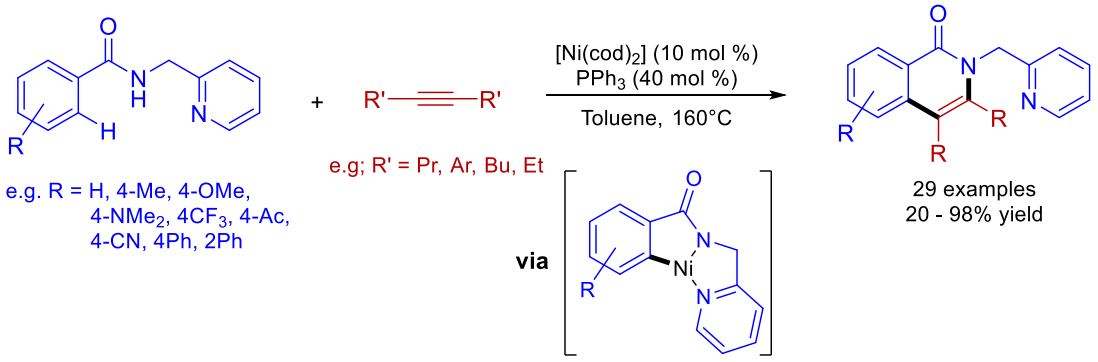
1.5.4.1 Chelation assisted C-H activation

Significant advancements in the field of C–H functionalisation were made by the Chatani group, who described the Ni-catalysed transformation of an *ortho*-aryl C–H bond with the aid of chelation.[105] In this work, they achieved regioselective oxidative cycloaddition of aromatic amides containing a 2-pyridinylmethylamine

directing group to alkynes using a $Ni(cod)_2/PPh_3$ as the catalytic system (Scheme 39). This marked the first example of Ni-catalysed *ortho* C–H bond cleavage since the initial publication in 1963. Although similar reactions have been demonstrated using rhodium or ruthenium as the catalysts, nickel offers a much cheaper alternative, despite initially utilising the air- and moisture- sensitive $Ni(cod)_2$. Since then, bidentate chelating directing groups have been widely utilised in Ni-catalysed functionalisation of C–H bonds.[106,107] The group went on to develop this work by utilising an 8-aminoquinoline moiety as the directing group for the first example of nickel catalysed ortho alkylation of benzamides and acrylamide derivatives with nonactivated alkyl halides.[108]

In 2014, bidentate chelation was then reported in assisting nickel-catalysed C–H functionalisation of arenes and indoles with challenging secondary alkyl halides, utilising $NiCl_2(DME)$ rather than $Ni(cod)_2$, in the presence of BDMAE ligand and LiO^tBu base in the catalytic system.[109] Nickel catalysed Csp^2–H transformations have been accomplished for other useful compounds including: anilines, precursors for many industrial chemicals such as dyes and pharamceuticals;[110,111]

indoles, structural motifs appearing in biologically active natural products;[112] and chiral oxazolines, ligands often used for enantioselective transfomations.[113]

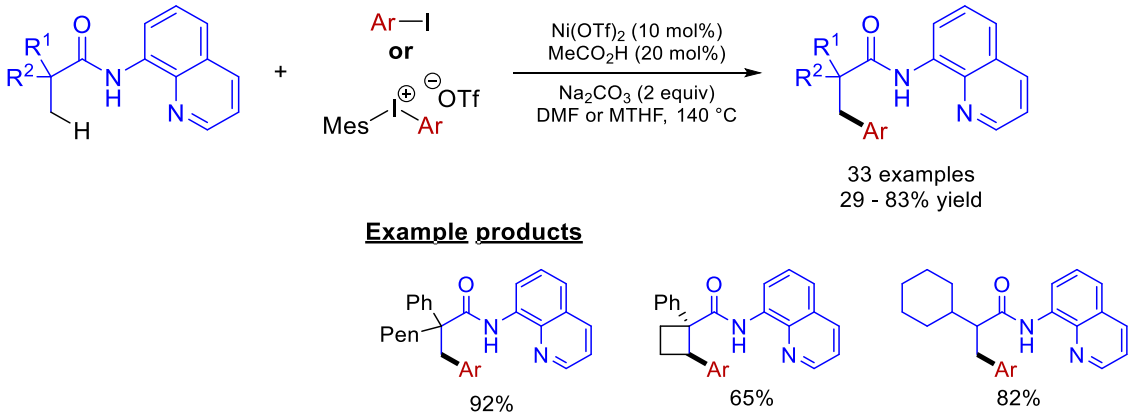


Scheme 39: Chelation assisted nickel-catalysed regioselective cycloaddition of the *ortho*-aryl C-H bond.[105]

1.5.4.2 Functionalisation of Csp³–H bonds

C–C bond formation via C*sp²*–H functionalisation has been well established over the last couple of decades. As such, the focus has recently turned to the more challenging task of direct and selective functionalisation of inert, nonactivated C*sp³*–H bonds. Many C*sp³*–H activations have relied on the use of palladium-based catalysts as the more traditional metal catalyst utilised in cross-coupling reactions. Nevertheless, nickel is emerging as a preferred alternative, due to slower β-hydride elimination in addition to being more cost-effective.[114] As such, the selective nickel-catalysed cross-coupling of *sp³* hybridised C–H bonds has been explored.

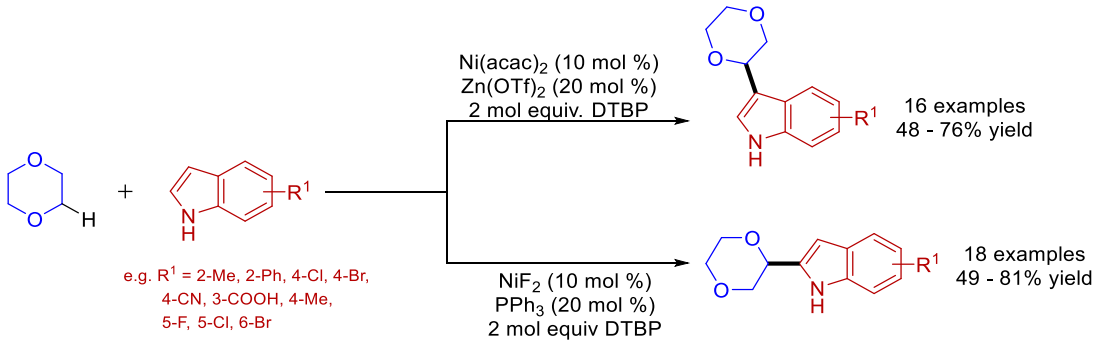
Some of the early examples of functionalisation of Csp^3–H bonds include work by the Chatani group who utilised the bidentate auxiliary system with an 8-aminoquinolyl moiety as the directing group.[115,116] They demonstrated the successful direct arylation of nonactivated Csp^3–H bonds of aliphatic amides with aryl iodides[115] and diaryliodonium salts[116] with a high functional group compatibility (Scheme 40).



Scheme 40: Direct arylation of nonactivated Csp^3–H bonds of aliphatic amides.[115,116]

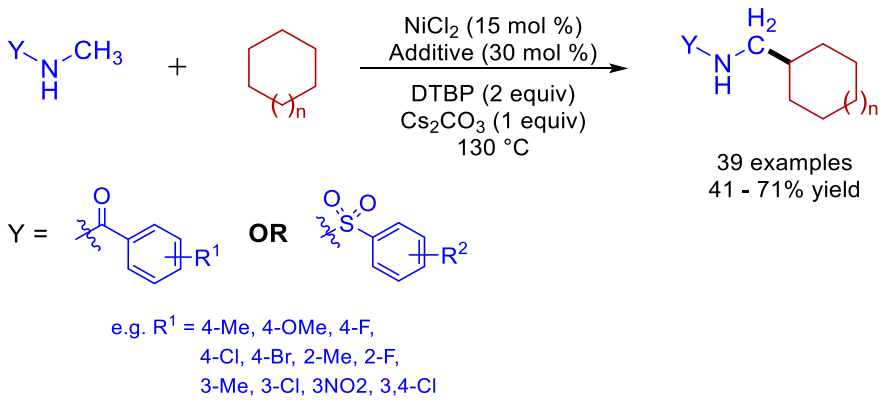
Moving away from the chelation assisted C–H functionalisation, the Ni-catalysed regioselective coupling of inactive Csp^3–H bond of cyclic ethers with indole derivatives has been achieved.[117] Interestingly, the C–H site selectivity of the reaction could be tuned to either C2 or C3, simply by adjusting the catalytic system from NiF_2/PPh_3 to $Ni(acac)_2/Zn(OTf)_2$, respectively (Scheme 41). Nickel catalysed reductive arylation of benzylic Csp^3-H bonds with alkenes has more recently been

reported. This allows access to a selection of 1,1-diarylalkane compounds, structural motifs often found in medicinal compounds.[118]



Scheme 41: Catalyst dependent regioselective coupling of cyclic ethers with indole derivatives.[117]

Nickel catalysed C*sp*^{3}–H transformations have also been demonstrated in the cross-dehydrogenative coupling of *N*-Methylamides with C*sp*^{3}–H bonds of cyclic alkanes (Scheme 42).[119] *N*-Methylamides are structural motifs often found in agrochemicals and pharmaceuticals.[119] This reaction not only utilises a cost-effective nickel catalyst, it proved to be highly selective, tolerant to a range of functional groups, solvent free, and did not require the synthesis of an extraneous directing group, thus highlighting the potential environmental benefits.



Scheme 42: Cross-dehydrogenative coupling of *N*-methylamides with cyclic alkanes.

Direct C–H functionalisation offers an attractive synthetic route, eliminating the need for pre-functionalisation such as halogenation, metalation or borylation. Furthermore, nickel's ability to provide access to these industrially relevant structural motifs is highly attractive as it provides a significantly cheaper alternative to other metal catalysts capable of C–H bond activation, such as palladium or rhodium.

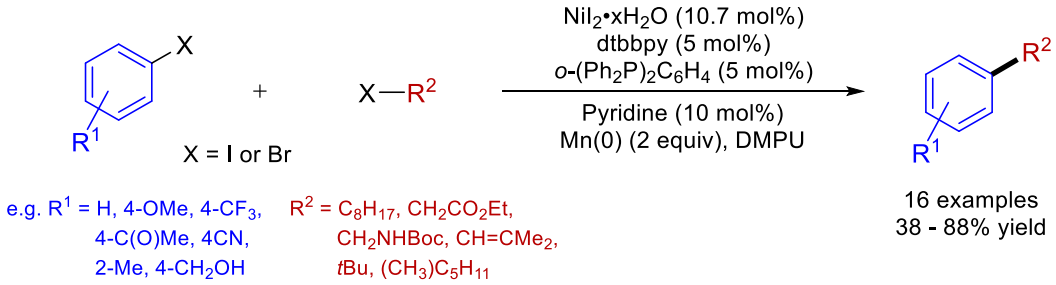
1.5.5 Cross-electrophile coupling

The cross-coupling of carbon nucleophiles with carbon electrophiles has been well established in the last few decades. However, these reactions usually require stoichiometric amounts of organometallic reagents. Furthermore, there are many more commercially available carbon electrophiles than there are carbon nucleophiles, and nucleophilic reagents can be costly and unstable.[120] One strategy that avoids the use of carbon nucleophiles is the direct cross-coupling of two electrophiles. These reactions are not without their own challenges, since two electrophiles are used, they can both be activated and therefore be susceptible to forming two homodimers, rather than the desired cross-coupled product.

1.5.5.1 Coupling of halide electrophiles

The first nickel-catalysed cross-electrophile coupling of aryl halides with alkyl halides (sometimes also referred to as reductive cross-coupling) was reported in 2010 by the Weix group (Scheme 43).[121] Using reaction conditions of NiI_2, bipyridyl and phosphine ligands, and stoichiometric amounts of manganese, this group successfully demonstrated high selectivities for the cross-coupling reaction over dimerisation without the formation of an organometallic intermediate.[121] Later on, they further developed their method for the coupling of aryl and vinyl halides with alkyl bromides, utilising zinc as the reducing agent.[122] Further development also extended this work to the coupling of alkylated pyridines, allowing for the synthesis of functionalised molecules not easily accessed by conventional cross-coupling reactions.[123] This work was then enhanced by the application of pyridyl carboxamidine ligands under a standard set of conditions,

significantly increasing the scope and ease of cross-electrophile coupling across a wide range of challenging *N*-heteroaryl halides.[124]

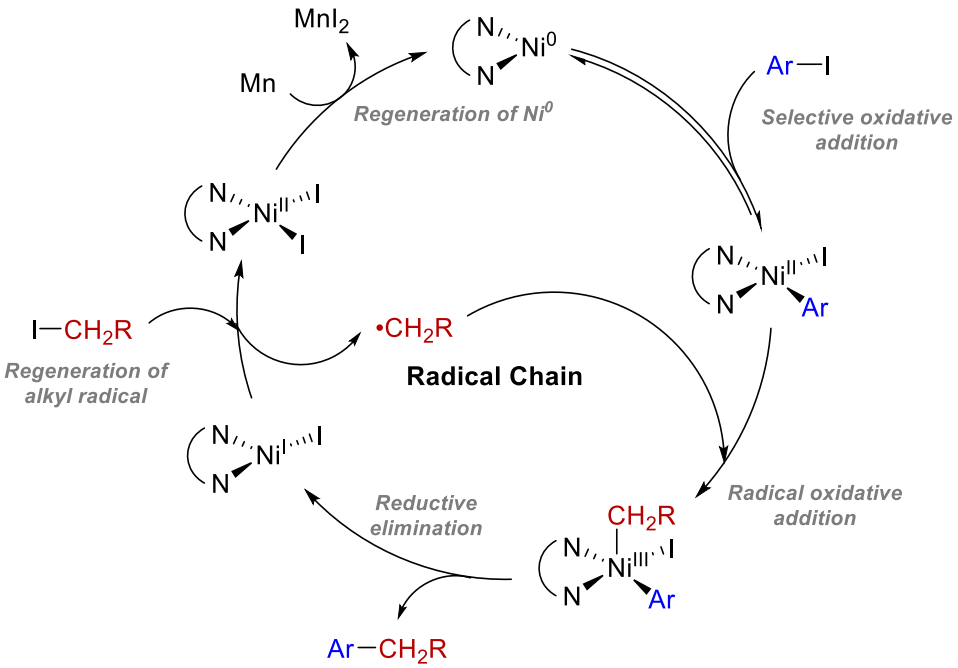


Scheme 43: The first example of nickel catalysed cross-electrophile coupling of aryl halides with alkyl halides.[121]

Extensive studies into the mechanism of the reaction between aryl halides and alkyl halides were carried out to gain a deeper understanding of the selectivities of these reactions.[125] Their research revealed that a catalyst capable of both single and two-electron processes is essential to support the typical oxidative addition of one electrophile, and the single electron process of the other.

The aryl halide undergoes faster oxidative addition with Ni^0 in comparison to the alkyl halide, resulting in only the aryl halide undergoing the typical two-electron oxidative addition, whereas radicals form more readily from alkyl halides in comparison to aryl halides. As such, only alkyl radicals are formed through single electron transfer, rationalising the selectivity and formation for the cross-coupled products.[126] The proposed mechanism proceeds via a combination of the typical two-electron process and the radical chain pathway previously mentioned in **Section 1.4.** The aryl halide undergoes oxidative addition with Ni^0, forming an

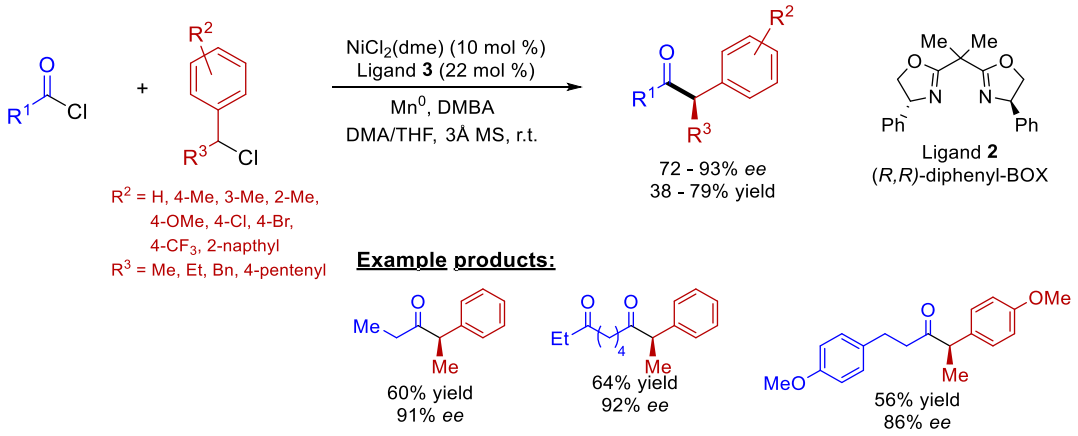
aryl-Ni^{II} complex. This then reacts with an alkyl radical forming a diorgano-Ni^{III} intermediate. This allows for the reductive elimination of the cross-coupled product, generating an Ni^{I} species in the process. The Ni^{I} species then reacts with another alkyl iodide molecule, forming Ni^{II}-diiodide and generating the alkyl radical. In the last step, the Ni^{II} diiodide is reduced by the reductant (Mn or Zn), thus regenerating Ni^{0} (Scheme 44).[126]



Scheme 44: The proposed mechanism for the nickel-catalysed cross-electrophile coupling.

1.5.5.2 Enantioselective cross-electrophile coupling

Asymmetric reductive cross-coupling is also of interest as this would provide a useful alternative to traditional transmetallating agents, such as Grignard or organolithium reagents. In 2013, Reisman and co-workers developed the first nickel catalysed enantioselective reductive acyl cross-coupling reaction, synthesising α,α-disubstituted ketones from acyl chlorides and secondary benzylic chlorides (Scheme 45).[127] They utilised a chiral diphenyl-Box ligand in the presence of $NiCl_2$(dme) with manganese as the reductant. The reaction demonstrated high enantioselectivities, good yields and good tolerance of functional groups.



Scheme 45: Nickel catalysed enantioselective reductive cross-coupling of acyl chlorides with benzylic chlorides;[127]

Later, in 2015, the Reisman group described the asymmetric reductive cross-coupling between α-chloronitriles and heteroaryl iodides using a novel chiral PHOX ligand with the catalytic system mentioned above, which allowed for the synthesis of α,α-disubstituted nitriles.[128] This reaction is tolerant of N- and S-

heterocyclic coupling partners, and provides a route to synthesising a variety of enantioenriched heterocyclic products.

More recently, in 2017, the same group described the synthesis of enantioenriched 1,1-diarylalkanes, motifs often present in commercial pharmaceuticals, by the Ni-catalysed reductive cross-coupling of heteroaryl iodides and benzylic chlorides.[129] The success of this reaction relied on the synthesis of the novel chiral ligand 4-heptyl-BiOX, which improved the enantioselectivity and yields in comparison to previously reported BiOX ligands.

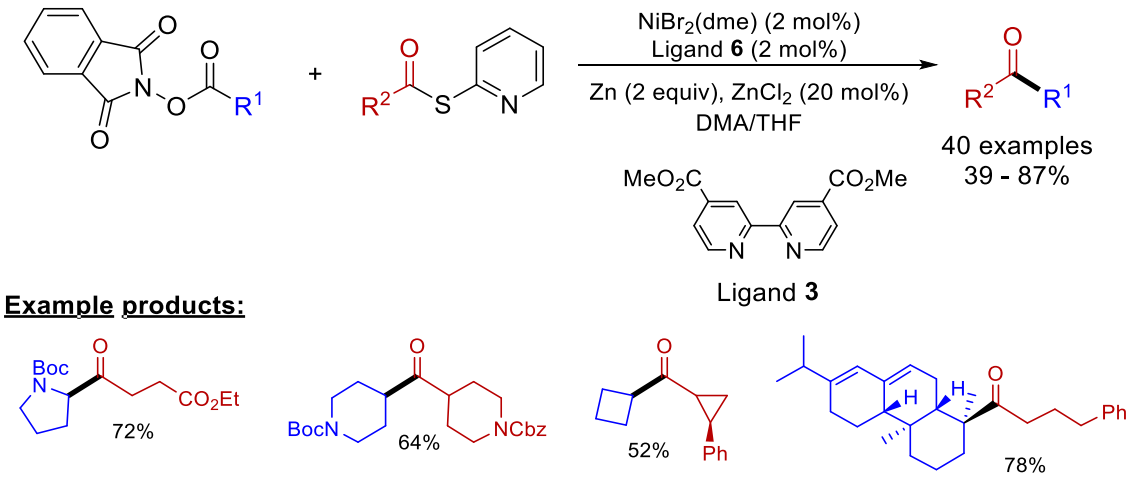
Research into asymmetric reductive cross-coupling is ongoing, however, it is a promising alternative to accessing enantiomeric products with potential applications in medicine and pharmaceuticals.

1.5.5.3 Coupling of ester electrophiles

Nickel catalysed cross-electrophile coupling has also been utilised for intramolecular reductive cyclization of benzylic esters and aryl halides for the synthesis of indanes and tertralins – structural motifs found in natural products and pharmaceutical compounds.[130] This procedure focused on the cross-coupling of C–O electrophiles with halides, rather than just two halide electrophiles, in the presence of $NiBr_2$.glyme, zinc and a bipyridyl ligand. The utilisation of a chiral starting material demonstrated stereospecific coupling in high enantioselectivity, highlighting the potential of this reaction.

The Weix group recently reported decarboxylative cross-electrophile coupling of two different esters for the synthesis of ketones – some of the most versatile

functional groups in organic chemistry.[131] Their approach involved the coupling of N-hydroxyphthalimide (NHP) esters with thioesters with the aim of one component (NHP ester) acting as the radical donor, and the thioester preferentially forming a Ni^{II}-acyl species, thus resulting in selective coupling of the two different esters. They demonstrated successful cross-coupling of the two ester components in the presence of $NiBr_2$.glyme, zinc and a simple bipyridyl ligand, with a broad scope in both ester components with moderate to high yields, offering a general route to a variety of ketone products (Scheme 46).



Scheme 46: Synthesis of ketones via cross-coupling of two different esters.[131]

1.5.6 Cross-coupling involving C–N bonds

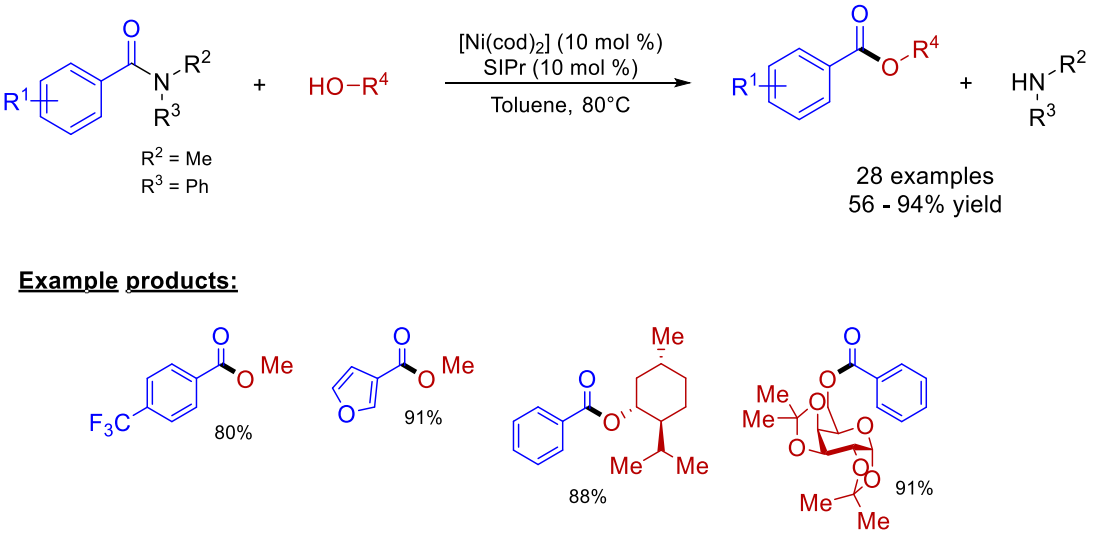
1.5.6.1 Coupling through C–N bond cleavage

1.5.6.1.1 Activation of amide C–N bonds

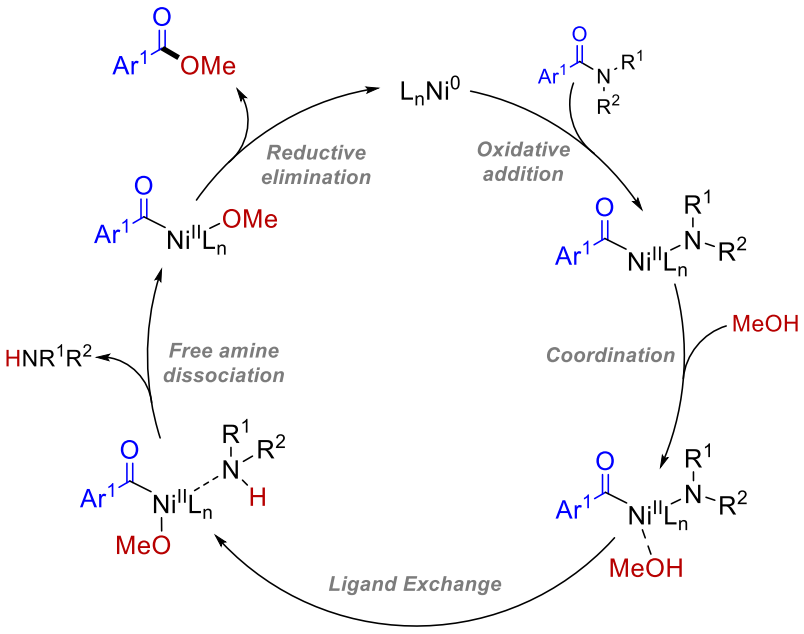
The development of nickel-catalysed cross-coupling of amides by C–N cleavage is still relatively new; direct metal-catalysed activation of amide C–N bonds was first reported in 2015 by Garg *et al.*[132] Amides are present in a large variety of natural and synthetic compounds, and they are the key building blocks for all proteins. Amide C–N bonds are naturally very strong as a result of resonance stabilisation, therefore they are generally poor electrophiles and difficult to break using traditional synthetic chemistry.[132] Consequently, amides are generally well suited for multistep synthesis as they tend to be stable to a large range of reaction conditions. Nevertheless, Garg and co-workers have recently reported the first nickel-catalysed transformations of amides to esters and ketones by activation of the usually unreactive C–N bonds.[132,133]

The transformation of amides to esters has always been challenging, often requiring harsh acidic or basic conditions, while also using a large excess of nucleophiles. However, the Garg group have demonstrated the conversion of amide to ester of benzamide and its derivatives, using a variety of alcohol nucleophiles with relatively mild conditions (Scheme 47), albeit in the presence of $Ni(cod)_2$.[132] The proposed mechanism for transformation of amides to esters proceeds via oxidative addition of nickel into the C–N bond, forming acyl-Ni^{II} species. The next step involves coordination, ligand exchange, and the deprotonation of methanol; allowing for the dissociation of a free amine. Finally,

reductive elimination yields the desired ester product, regenerating the catalyst in the process (Scheme 48).

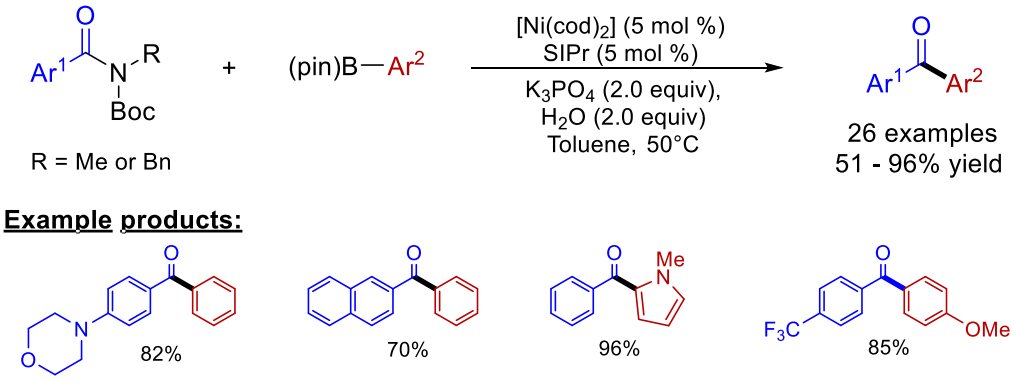


Scheme 47: Transformation of amides to esters by nickel catalysed activation of the C-N bond.[132]



Scheme 48: Proposed mechanism for the Ni-catalysed conversion of amides to esters.

The Garg group were also the first to report Ni-catalysed Suzuki-Miyaura amide cross-coupling with boronic esters to create new C–C bonds, forming ketone products, including the synthesis of a microtubule inhibitor, MPT0B002, a potential candidate for the treatment of chronic myeloid leukemia,[134] again using relatively mild reaction conditions (Scheme 49).[133] Since their initial work on the coupling of amides, the Garg group have also reported the esterification and Suzuki-Miyaura cross-couplings of aliphatic amides.[135,136]

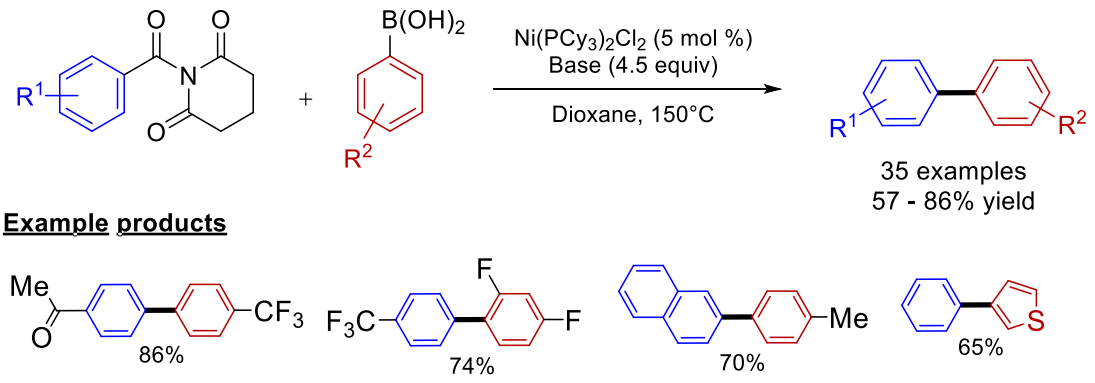


Scheme 49: Suzuki-Miyaura cross-coupling of amides in the presence of a nickel catalyst.[133]

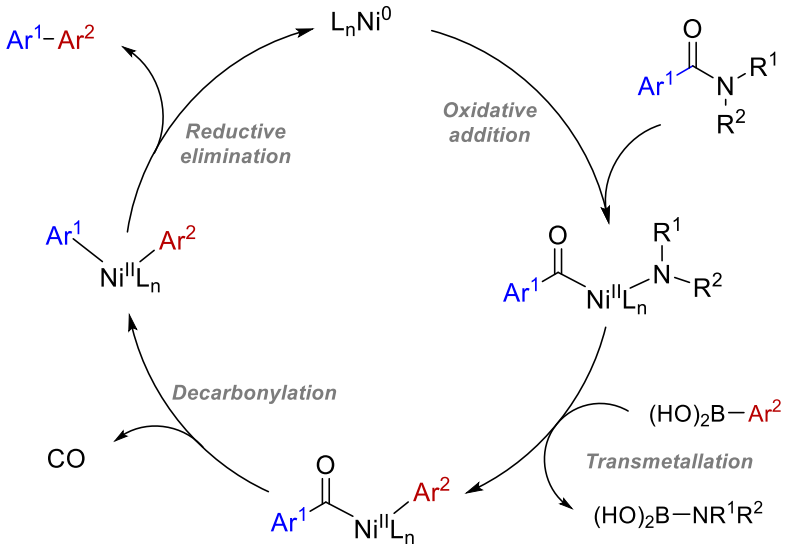
Recently, they have demonstrated benchtop Suzuki-Miyaura coupling of aliphatic amides, in the presence of $Ni(cod)_2$ and Benz-Icy.HCl using a paraffin encapsulation strategy. This encapsulation approach allows for reactions utilising $Ni(cod)_2$ to be set up outside the glovebox, thus increasing the ease and accessibility of Ni-catalysed reactions.[137] Although this approach is promising, the glovebox is still initially required to encapsulate the $Ni(cod)_2$, thereby potentially still limiting its scalability. Also, the addition of a paraffin capsule to the reaction

could cause undesired side reactions, meaning extensive optimisations would potentially be required with each new substrate. Furthermore, any paraffin remnants could prove difficult to remove from the products in the final purification steps.

Since the publications by Garg, others have turned their focus to amide cross-coupling. The first synthesis of biaryl compounds through Suzuki-Miyaura cross-coupling of amides by cleavage of the C–N bond was developed in 2016. This method employed an air stable $Ni(PCy_3)_2Cl_2$ complex without the need for further ligands, and displayed a large scope for amide substrates (Scheme 50).[138] The proposed reaction mechanism varies slightly from that reported by Garg as it also involves a decarbonylation step prior to reductive elimination, promoting the formation of biaryl products instead of the ketone product (Scheme 51). The synthesis of diaryl ketones through the first Ni-catalysed Negishi cross-coupling of primary amides has also been reported under mild conditions, utilising an air stable nickel precatalyst, and demonstrating tolerance for a variety of functional groups.[139]



Scheme 50: Decarbonylative biaryl synthesis via nickel catalysed Suzuki-Miyaura cross-coupling.[138]



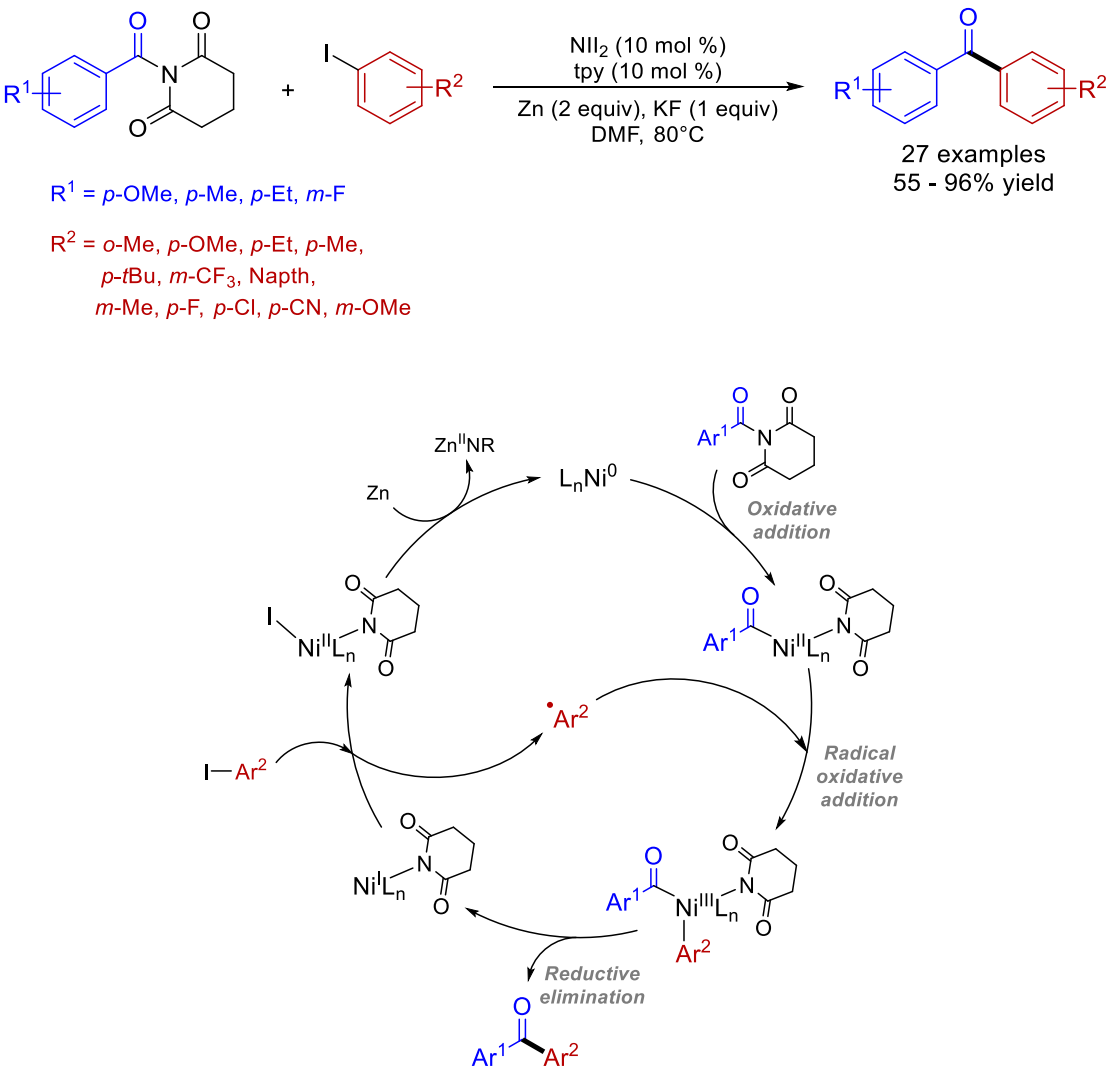
Scheme 51: Proposed mechanism for the amide cross-coupling with a boronic acid, via a decarbonylation step, forming the biaryl product.

The works presented here again highlight the versatility of nickel by showcasing its ability to activate and cleave the inert C–N bonds of amides leading to the construction of novel C–C and C–O bonds. Furthermore, the methodologies described here displayed high functional group tolerance, selectivities towards amides, and relatively mild reaction conditions.

1.5.6.1.2 Cross-electrophile coupling of amides

As previously mentioned (**Section 1.5.5**), the coupling of two electrophiles is of increasing interest as it eliminates the need for often unstable nucleophiles, in addition to allowing for the use of more widely commercially available substrates.[120] The direct coupling of aryl amides with aryl iodide electrophiles to furnish diaryl ketones has only recently been reported for the first time in 2017.[140] This reaction proceeds in the presence of nickel iodide, excess zinc, a tridentate terpyridine ligand, and potassium fluoride as an additive (Scheme 52). The reaction demonstrated excellent yields, with a reasonable substrate scope and functional group tolerance for either electrophile, demonstrating the potential of this reaction.

The proposed reaction mechanism is a combination of the 'radical chain' pathway involving Ni^{I}/Ni^{III} steps; and the traditional coupling involving Ni^{0}/Ni^{II} steps, similarly to the reductive cross coupling of aryl halides with alkyl halides. The amide undergoes oxidative addition into the C–N bond, forming an acyl-Ni^{II} complex. This then undergoes radical oxidative addition of an aryl radical, formed from the reduction of iodobenzene with an active Ni^{I} species, generating an aryl-acyl-Ni^{III} intermediate. Reductive elimination of the Ni^{III} intermediate forms the desired product and the active Ni^{I} species which reduces iodobenzene forming a Ni^{II} iodide intermediate and another aryl radical. The Ni^{II} iodide complex then undergoes reduction by zinc, regenerating the active Ni^{0} catalyst.[140]



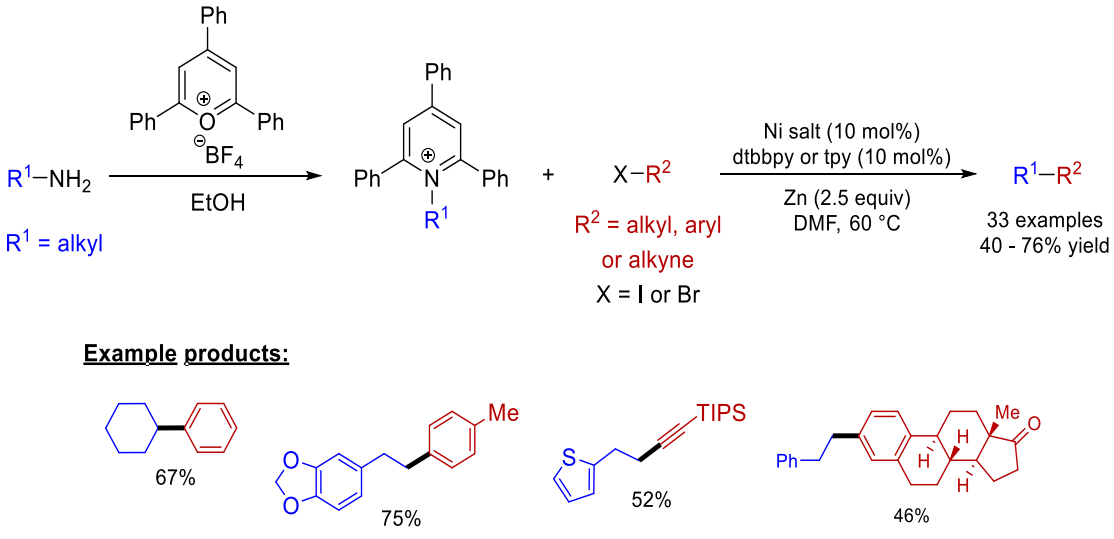
Scheme 52: Reductive coupling or aryl amides with aryl iodides and the proposed mechanism for the formation of diaryl ketones.[140]

1.5.6.1.3 C–N activation of primary amine derivatives

Also in 2017, Watson and co-workers reported the first Ni-catalysed Suzuki-type cross-coupling of Katritzky alkyl pyridinium salts, derived from primary amines, with aryl boronic acids.[141] This work demonstrated the introduction of nonactivated alkyl groups onto arenes via C–N bond activation of an amine derivative. The reactions demonstrated broad substrate scope and functional

group tolerance in addition to allowing for the installation of primary and secondary alkyl groups.

Another group expanded on this work by applying Katritzky pyridinium salts to deaminative cross-electrophile coupling of alkyl and aryl halides through C–N activation.[142] The coupling of alkyl amine-derived pyridinium salts with a variety of *sp*³, *sp*² and *sp* C–C bonds was successfully demonstrated with a broad functional group tolerance (Scheme 53). Furthermore, a one-pot reaction without the isolation of the alkylpyridinium salt was also demonstrated, highlighting the potential ease of this reaction.[142] They adjusted the nickel salt and bipyridine ligand used for the coupling depending on the type of halide electrophile being used. For example, aryl iodides gave optimal yields with $NiBr_2$.diglyme and a tridentate ligand, while bromo-alkynes gave best results in the presence of $Ni(acac)_2$ and a bipyridyl ligand.



Scheme 53: Deaminative cross-electrophile coupling of Katrizky salts with alkyl and aryl halides.

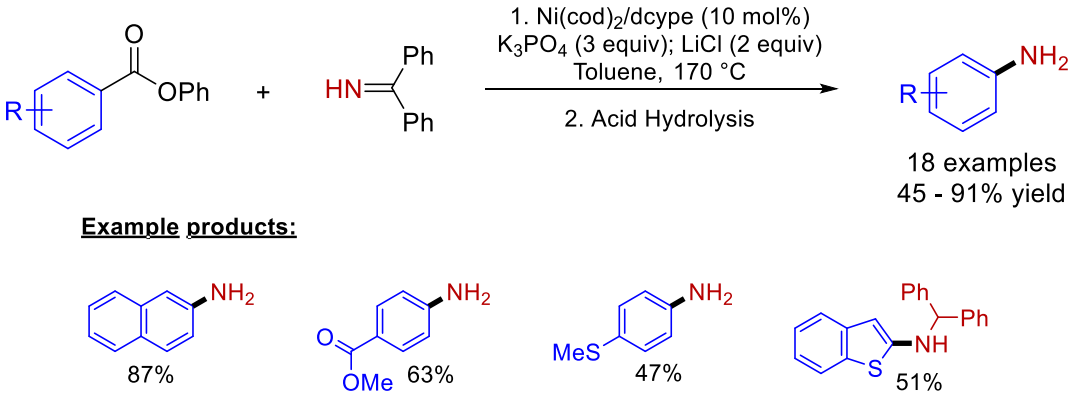
1.5.6.2 Formation of C–N bonds via cross-coupling

1.5.6.2.1 Decarbonylative amination

The synthesis of C–N bonds is of interest due to the prevalence of aniline structures and N-heterocycles in natural products, medicinal chemistry, organic materials and catalytic systems.[143,144] An extensive review on palladium catalysed C–N cross-coupling reactions has been published,[144] however, the use of nickel in these transformations is less explored, perhaps due to the widespread success and applicability of Pd-based catalytic systems.

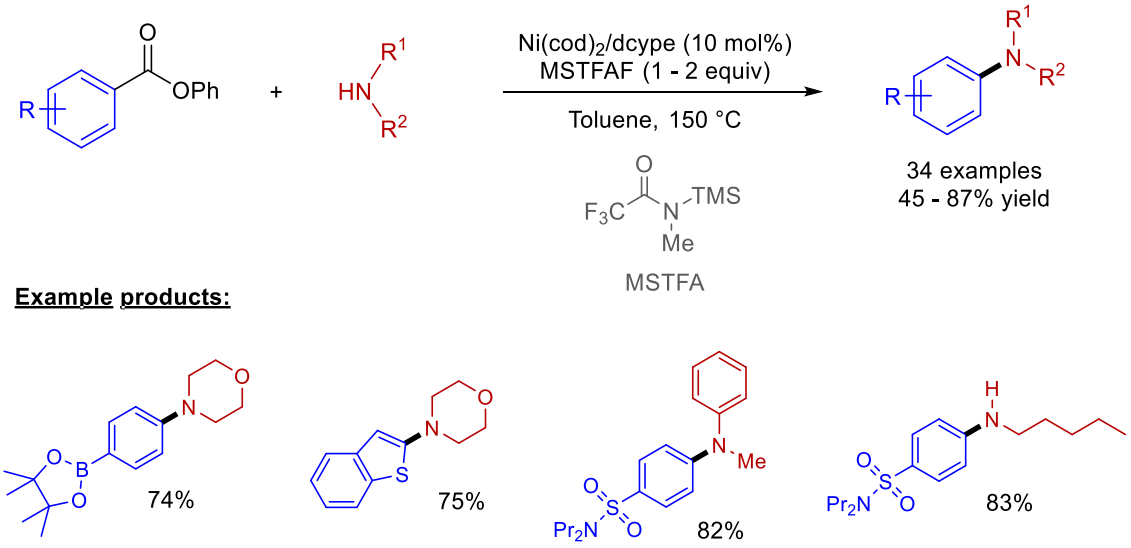
The focus is now shifting towards decarbonylative coupling reactions that employ aryl carboxylic acids and their derivatives due to their abundance, low cost and stability. Ni-catalysed decarboxylative coupling of carboxylic acids with amines to furnish C–N bonds presents an attractive challenge due to its potential economic and practical benefits, but such processes were not reported until very recently and remain limited. The first nickel-catalysed one-step decarboxylative amination process was developed in 2017, coupling imines with aryl esters in the presence of $Ni(cod)_2$/dcype, K_3PO_4 base and LiCl additive (Scheme 54).[145] Imines were chosen as the coupling partners to prevent the formation amide by-products, with a final acid hydrolysis step yielding the desired aryl amine product. Unfortunately,

with more nucleophilic amine sources, such as morpholine or aniline, only the amide product was obtained.



Scheme 54: Ni-catalysed decarbonylative amination via the coupling of aryl esters with imines.[145]

The scope of this reaction has recently been expanded by slight alteration of the reaction conditions (Scheme 55).[146] This coupling reaction of aromatic ester electrophiles with amines also employs Ni(cod)$_2$/dcype, however, it is base-free and involves the formation of silyl amines *in situ*. Silyl amines are inert to the unwanted acyl transfer, but do engage in transmetallation thus preventing the formation of undesired amides and allowing for the reaction scope to be expanded to simple amines; such as morpholine, aniline and indole nucleophiles.



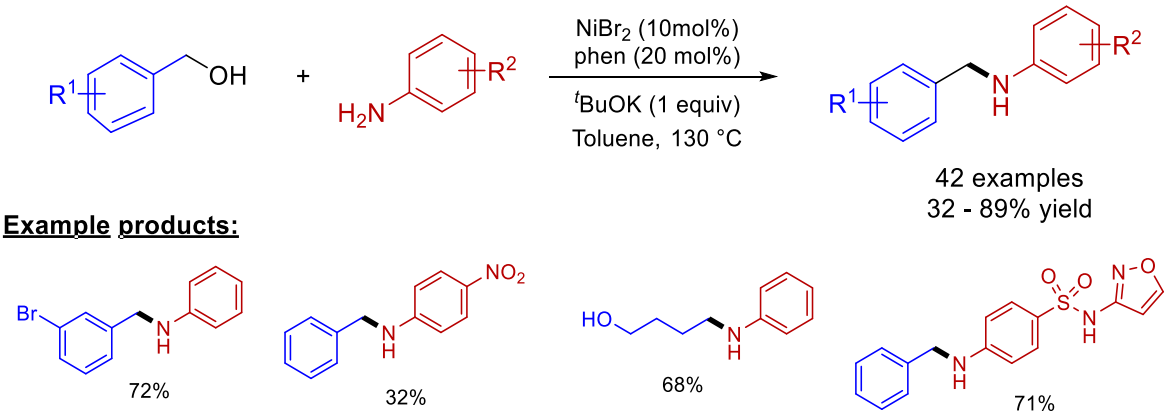
Scheme 55: Ni-catalysed decarbonylative amination via the coupling of aryl esters with amines[146]

Although the versatility of these reactions is promising in employing inexpensive starting materials, the reactivity of electron rich and sterically hindered electrophiles remains limited, and $Ni(cod)_2$ is used as the Ni^0 source, limiting this reaction to a glovebox. The high temperatures (>170°C) and sometimes high catalyst loading (20 mol%) required for these reactions to proceed also need to be addressed to truly reach the full potential of these transformations. It is worth bearing in mind that these are relatively new reactions, therefore a more suitable Ni-based catalyst may still be developed.

1.5.6.2.2 Coupling of anilines

Anilines are attractive due to their high reactivity in electrophilic aromatic substitutions and thus are common coupling partners in Pd-catalysed N-arylation reactions. The lack of β-hydrogens eliminates the potentially competing β-hydrogen elimination, increasing the efficiency of these reactions.[144] However, many of these reactions employ aryl halides or triflates, resulting in stoichiometric production of hazardous waste. The direct use of alcohols as coupling partners in amination reactions presents a promising alternative, generating water as the only stoichiometric by-product. Recently, the direct Ni-catalysed amination of benzyl and alkyl alcohols with anilines has been reported, utilising $NiBr_2$ with 1,10-phenanthroline as the ligand, and a ^{t}BuOK base (Scheme 56).[147] This system successfully achieved moderate to high yields with a wide range of substrates, demonstrating tolerance for a variety of functional groups. Another group recently described the direct synthesis of quinoxalines via the coupling of 1,2-diamines and 2-nitroanilines with 1,2-diols with a similar Ni-based catalyst system.[148]

These examples highlight the applicability of simple Ni-based systems for the cross-coupling of readily available alcohols and amines, reducing the hazardous waste usually associated with these types of reactions, and improving atom economy.

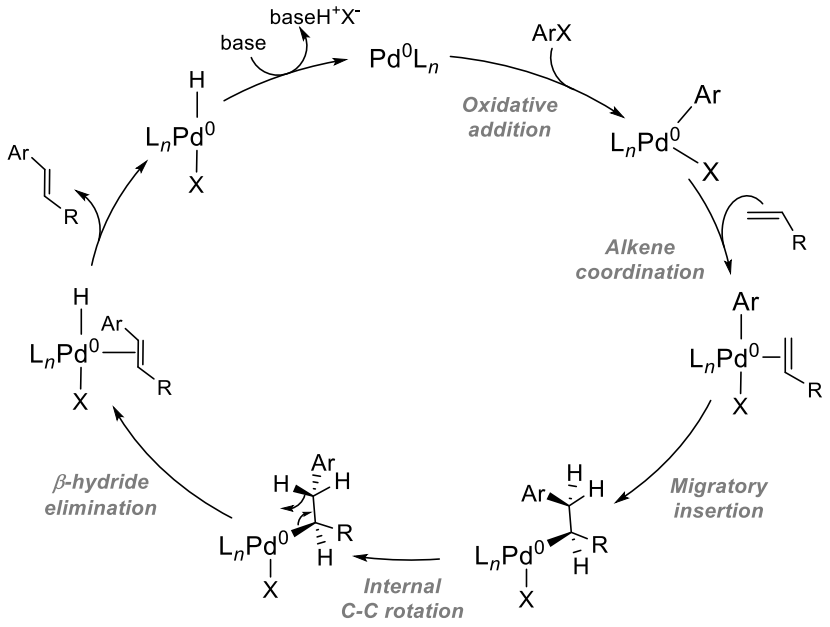


Scheme 56: Amination of alkyl and benzyl alcohols with aniline derivatives;[147]

1.5.7 Heck-type reactions

1.5.7.1 Traditional Heck reactions

The Mizoroki-Heck reaction is another powerful C–C bond forming process and provides an effective route for the synthesis of functionalised alkenes typically through the coupling of aryl/vinyl halides or triflates with olefins.[149] The Heck reaction differs from cross-coupling reactions in that the transmetallation step is omitted, and instead an alkene coordinates to the metal complex following oxidative addition of an aryl halide. The complex then undergoes migratory insertion of the alkene into the M-aryl bond, followed by β-hydride elimination, thus forming the desired substituted alkene (Scheme 57).[149] Although nickel complexes tend to undergo facile migratory insertion, the β-hydride elimination step tends to be slow in comparison to palladium, often requiring harsh reactions conditions, such as high temperatures, prolonged reaction times, and highly polar solvents, for the reaction to proceed.[24] As such, the development of nickel-based catalysts suitable for Heck-type reactions has been scarce.

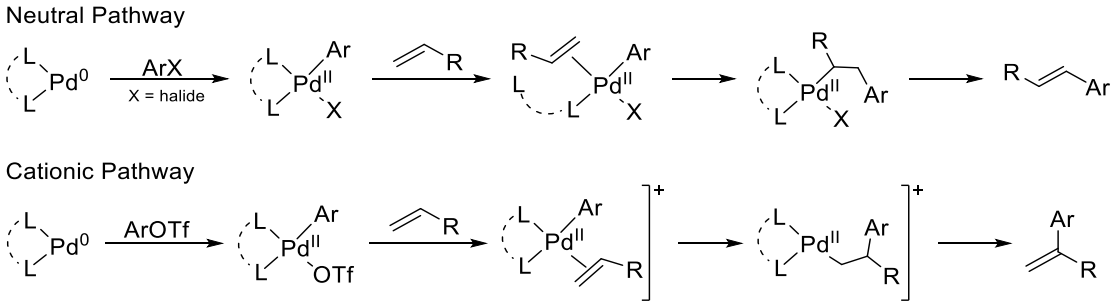


Scheme 57: General mechanism of the Heck reaction.

In addition to slow β-hydride elimination presenting a challenge, one of the most crucial aspects of the Heck reaction is controlling the stereo- and regioselectivity. In theory, migratory insertion can occur at either end of the alkene, giving either 1,1- or 1,2-disubstituted alkenes. Electron-poor alkenes, such as acrylates and styrenes, will generally form the *trans* isomer of the 1,2-disubtituted product mainly due to steric effects.[149,150] Electron-rich alkenes present more of a challenge as they usually produce a mixture of regio- and stereoisomers. The stereoselectivity can be controlled by adjusting the nature of the π-complex intermediate through careful selection of ligands, substrates, additives and solvents.[149,150]

Prior to migratory insertion, alkene association can occur via two different pathways, neutral or cationic (Scheme 58).[149] The pathway that is observed is

highly dependent on the nature of the ligands and substrates used, and directly impacts the regioselectivity of the reaction.



Scheme 58: Neutral vs cationic pathways of the Heck reaction.

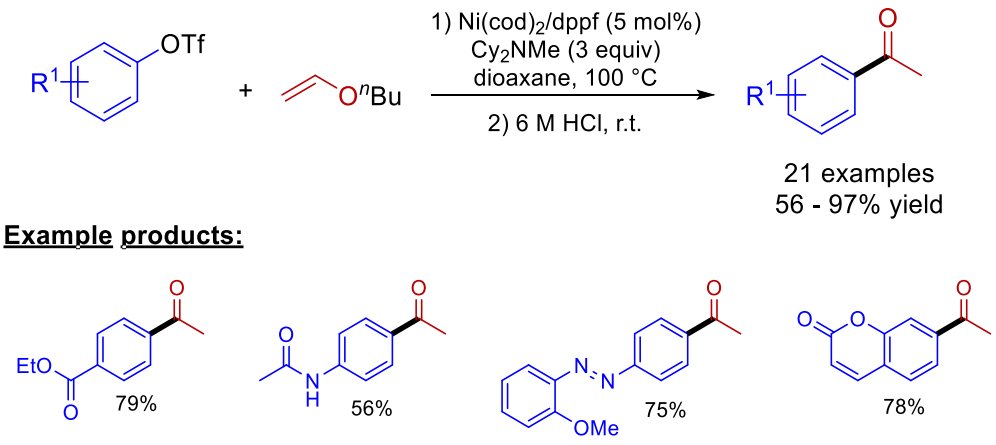
A neutral pathway is usually observed when alkyl halides are utilised in the reaction. Palladium-halide bonds are relatively strong in comparison to Pd-PR_3 bonds, meaning it is the neutral ligand that is forced to dissociate from the metal complex to vacate a site for the incoming alkene, thus forming a neutral palladium complex.[149] The neutral pathway is sensitive to steric factors; therefore, it is more likely to yield the 1,2-subsituted product where the aryl group migrates onto the less substituted carbon of the alkene.[149]

A cationic pathway is observed when aryl triflates are used. In this case, the Pd–OTf are relatively labile, therefore the triflate anion is most likely to dissociate upon coordination of the alkene rather than the phosphine ligand, thus forming a positive Pd(II) complex. Alternatively, halide scavengers, such as silver (I) salts, can be employed to abstract the halide ion from the palladium complex if aryl halides are used in the reaction.[149] The cationic pathway is more sensitive to electronic effects, resulting in aryl substitution onto the carbon of the alkene with lower charge density. For example, when electron donating group is present on

the alkene, substitution will occur on the α-carbon, resulting in the 1,1-substituted product.[149]

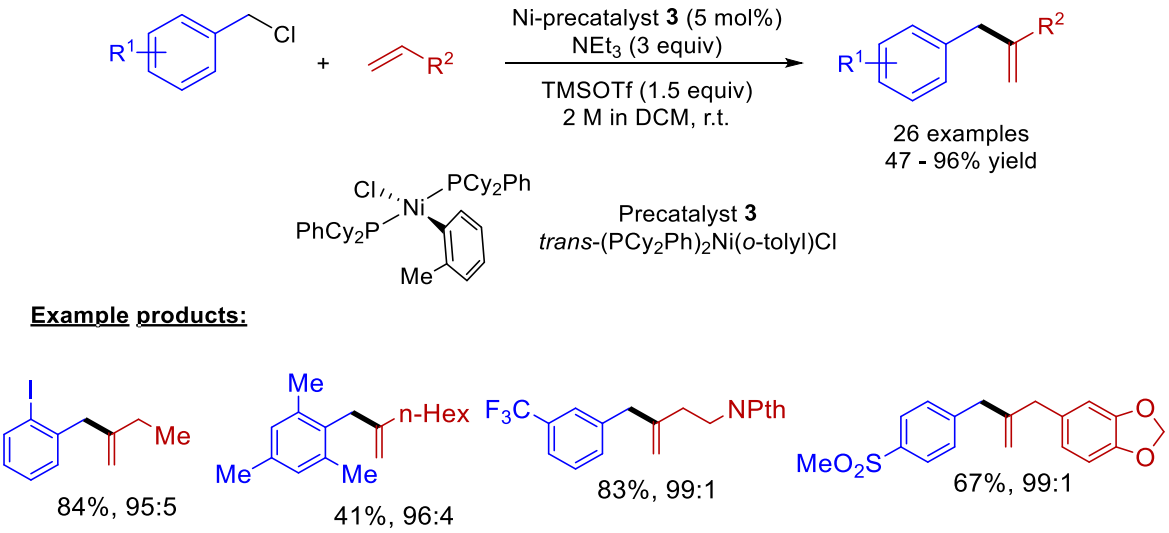
Interest lies in the selective construction of 1,1-disubstituted products due to their prevalence in biologically active compounds.[151] Although the palladium catalysed Heck reaction is well understood, nickel presents an attractive, and inexpensive alternative for these types of reactions as it offers opportunities to further tune selectivity.

Despite the challenges, reports of nickel-based catalysts in Heck-type reactions have increased in the last decade. In 2011, the first Ni-catalysed, highly selective Heck reaction of electron rich alkenes with aryl triflates under mild conditions was reported.[150] The reaction utilised $Ni(cod)_2$ as the source of Ni^0, a bidentate phosphine ligand, dppf, and aryl triflates to encourage the cationic mechanistic pathway and thus selective the formation of 1,1-disubstituted products (Scheme 59).[150]



Scheme 59: Heck reaction of aryltriflates with electron rich alkenes.[150]

In the same year, Jamison co-workers presented a novel Ni-catalysed, highly selective formation of 1,1-disubstituted alkenes via benzylation of simple alkenes under mild conditions utilising $Ni(cod)_2$ and a monodentate phosphate ligand.[151] The Jamison group later developed this work by employing an easily synthesised, air-stable nickel precatalyst, removing the need for a glove box and thus making these reactions more practical (Scheme 60).[152] Furthermore, they expanded on their substrate scope for both the benzyl chloride and terminal alkene substrates. Additionally, the Jamison group have also reported highly selective addition of aryl triflates and sulfonates to electronically unbiased terminal alkenes,[29] highlighting the potential of Ni-catalysed Heck reactions as viable alternatives to Pd-catalysed equivalents.

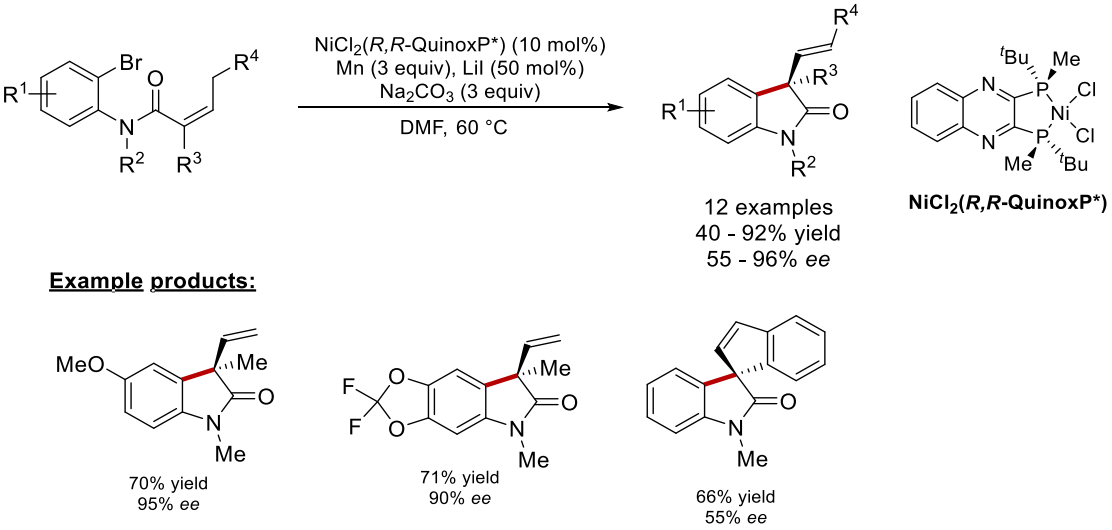


Scheme 60: Formation of 1,1-disubstituted alkenes.[152]

1.5.7.2 Intramolecular Heck cyclization reactions

The palladium-catalysed intramolecular Heck reaction is well established as one of the most commonly used methods for the constructions of small, medium and large rings, including the preparation of heterocycles and asymmetric construction of quaternary carbon centres.[149] The development of nickel-based catalysts for Heck cyclisation reactions has been significantly slower in comparison to palladium-based catalysts, perhaps due to the high energy barrier for β-hydride elimination required in the presence of nickel.

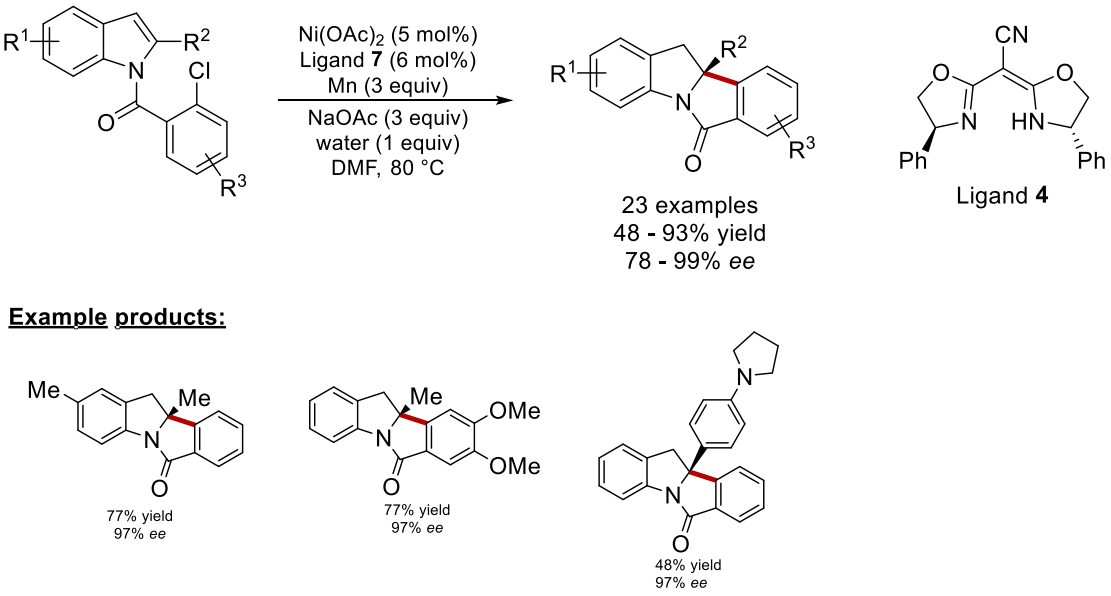
Nevertheless, few examples of enantioselective nickel-catalysed Heck cyclisations have emerged in the last decade. In 2014, an example of a nickel-catalysed stereospecific intramolecular Heck reaction of secondary benzylic ethers functionalised with a pendant alkene was reported. This reaction was carried out in the presence of $Ni(cod)_2$ with monodentate phosphine ligand, PCy_3, furnishing methylenecyclopentanes with a tertiary chiral centre in a selective manner although the substrate scope was limited.[153] In 2016, the first example of the formation of quaternary stereocentres by Ni-catalysed intramolecular Heck cyclisation in the presence of an air-stable precatalyst, $NiCl_2(P^nBu_3)_2$ was described.[154] In 2017, the same group also reported the enantioselective formation of some of these quaternary stereocentres, this time utilising a $NiCl_2$ complex with a P-chiral bisphosphine ligand, QuinoxP*, demonstrating the first enantioselective Ni-catalysed Heck cyclisation reaction (Scheme 61).[155]



Scheme 61: Examples of enantioselective intramolecular Heck cyclization reactions.[155]

Since these initial examples of Ni-catalysed Heck cyclisation reactions, further examples have since been reported. A general Ni-catalysed approach for the Heck-cyclisation of nonactivated alkyl bromines has been developed using inexpensive $NiBr_2$.glyme as the precatalyst with xantphos as the ligand, demonstrating good regioselectivity across a range of substrates.[156] Another group reported the first Ni-catalysed enantioselective reductive Heck cyclisation of aryl chlorides,

furnishing substituted indolines in the presence of $Ni(OAc)_2$ or $NiCl_2(dme)$ and a chiral oxazoline-based ligand (Scheme 62).[157]



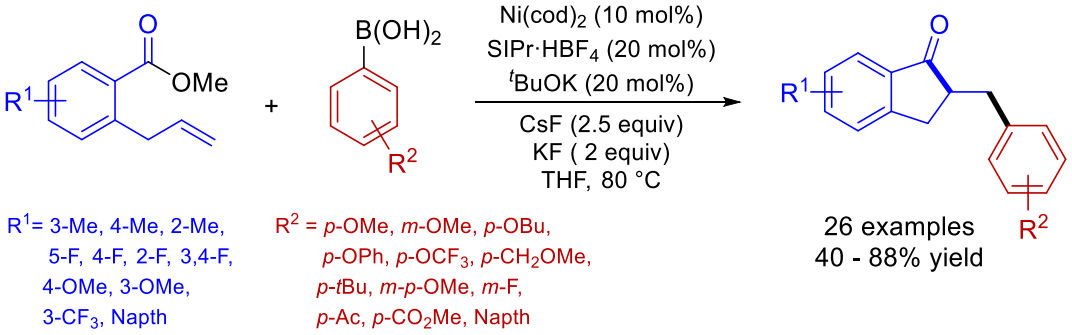
Scheme 62: Heck cyclisation of aryl chlorides, forming substituted indolines.[157]

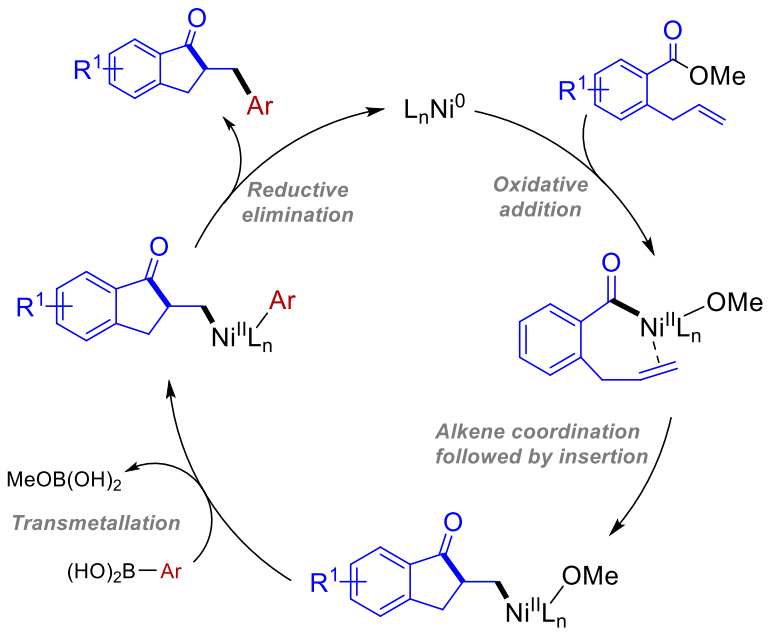
These examples highlight the potential for nickel to selectively catalyse intramolecular Heck reactions, with the latter examples also utilising inexpensive and air-stable nickel precatalysts. However, these examples utilise excess (3 equivalents) of manganese as the reducing agent for nickel to produce Ni^0 *in situ*, resulting in large amount of metal waste and reducing the overall atom economy of these reactions.

In 2019, a highly enantioselective Ni-catalysed intramolecular reductive Heck cyclisation of aryl bromides with tethered nonactivated alkenes was successfully demonstrated. This reaction achieved the synthesis of benzene-fused cyclic

compounds containing a quaternary carbon centre in the presence of an air-stable Ni-salt, $Ni(BF_4)_2.6H_2O$, as the nickel precatalyst with a chiral PyrOX ligand.[158]

Finally, a novel Ni-catalysed tandem Heck-type cyclisation followed by Suzuki-Miyaura coupling was recently developed, utilising methyl ester electrophiles as the coupling partners (Scheme 63).[159] These transformations represent the first generalised approach for the formation of carbonyl-containing products from methyl esters with nucleophilic coupling partners. The proposed mechanism suggests oxidative addition of the ester C(acyl)-O bond to Ni^0, forming an acyl-Ni^{II} complex, allowing for the coordination of the tethered alkene. This is followed by insertion of the alkene into the acyl-Ni^{II} bond, giving a σ-Ni^{II} intermediate which then undergoes transmetallation with aryl boronic acid, and finally reductive elimination to yield the desired product. The examples presented here highlight the ability of nickel to undergo oxidative addition to a large variety of electrophiles, including traditionally unreactive electrophiles, thus offering an array of novel catalytic pathways and transformations.





Scheme 63: Ni-catalysed tandem intramolecular Heck-cyclization followed by Suzuki-Miyaura coupling and the mechanism proposed for this reaction.

1.5.8 Allylic substitutions

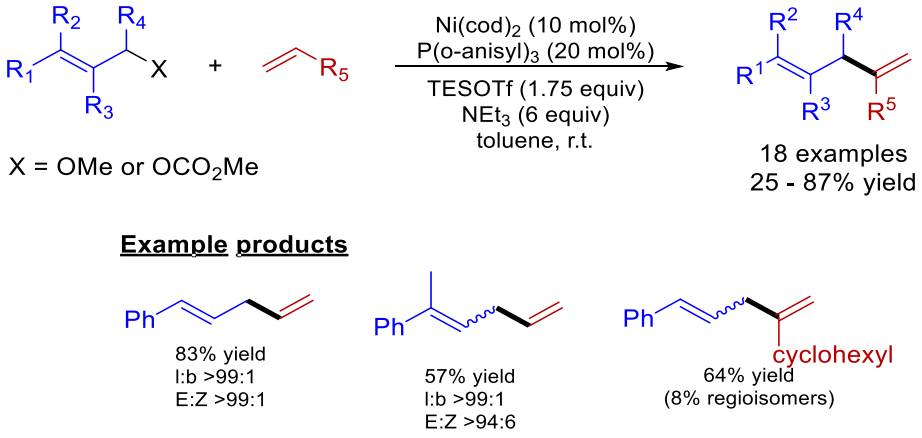
Transition metal catalysed asymmetric allylic alkylations were first reported by Tsuji in 1965 and later developed by Trost in 1973.[160,161] Since then, allylic alkylation has proven to be an extremely useful tool for creating chiral tertiary and quaternary carbon stereocentres. Allylic substitution reactions may proceed via several different mechanistic pathways, which have been found to be dependent on the nature of the nucleophile, metal catalyst and the ligands used. The first reports of allylic alkylations were carried out in the presence of palladium; however, metals such as Mo, W, Cu, Rh, Ru, and Ir have also been demonstrated as successful catalysts for allylic substitutions. [162]

1.5.8.1 Allylic alkylation with hard nucleophiles

Although nickel-catalysed allylic alkylation reactions have been reported as far back as 1973, the use of palladium has dominated in this field.[163,164] One reason for this could be that nickel-catalysed allylic substitutions have been mostly limited to hard nucleophiles, with which it is harder to control selectivity. Conversely, palladium catalysts generally react well with soft nucleophiles thus allowing for better stereocontrol.[165] From a mechanistic point of view, hard nucleophiles bind directly to the metal centre prior to C–C bond formation with the allyl groups, whereas 'soft' nucleophiles attack the Ni(π-allyl) intermediate externally.[165]

Nevertheless, the number of nickel-catalysed allylic alkylations has been on the rise. Many early examples of Ni-catalysed allylic transformations focused on the coupling of allyl alcohol derivatives with alkyl Grignard reagents to form substituted allyl alkanes.[166–168] Since then, numerous reports on coupling of allylic

electrophiles with 'hard' alkyl nucleophiles have emerged, including Ni-catalysed Negishi cross-coupling of allylic halides with alkylzinc reagents;[94] Kumada type coupling of allyl carbonates with tertiary alkyl Grignard reagents;[169] and Ni-catalysed Suzuki-Miyaura cross-coupling of allylic pivalates with aryl boroxines.[170] Allylic substitution of nonactivated alkenes with allyl alcohol derivatives to form 1,4-dienes have also been reported. 1,4-dienes are structural motifs commonly found in natural products (Scheme 64). Additionally, simple alkenes represent attractive coupling partners as they are inexpensive and readily available.[171]



Scheme 64: Allylic alkylation of simple alkenes with allyl alcohol derivatives.[171]

1.5.8.2 Allylic alkylation with soft nucleophiles

Although the use of hard organometallic reagents in the Ni-catalysed allylic alkylations dominated the field in the early years, the use of soft nucleophiles such as malonate esters,[172] β-keto esters and β-diketones,[173] dialkyl amines,[174,175] and amides[176] have been reported in successful allylation reactions. The allylic

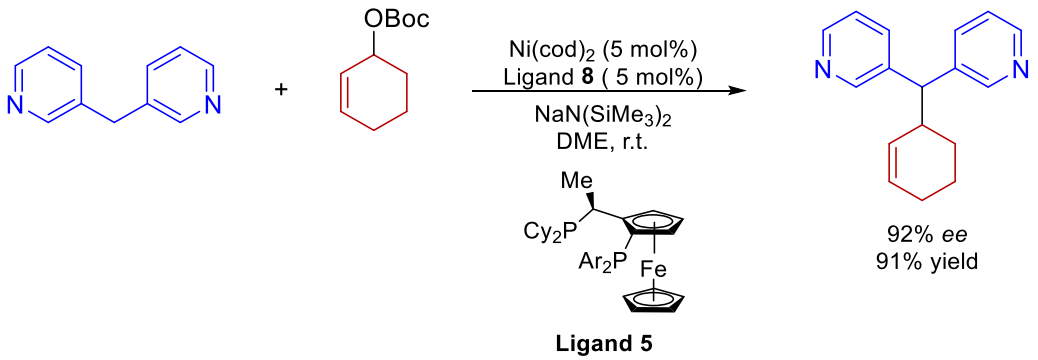
alkylation of dimethyl malonates with allylic acetates in the presence of $Ni(cod)_2$, and a diphosphine ligand has been developed. Although successful, the reaction displayed poor enantioselectivity, in addition to utilising the air- and moisture-sensitive $Ni(cod)_2$.[172]

The N-allylation of amides and sulfonamides with allyl alcohol substrates has recently been reported in the presence of $Ni(dppmb)_2$, providing a solvent and additive free method for the N-protection of amides where water is the only by-product.[176] Despite this method providing an eco-friendly route to protected amides, the reaction gives a mixture of mono- and di-allylated products in an uncontrollable manner, hindering its use.

A robust nickel-catalyst system for the synthesis of allylated diaryl compounds has recently been developed.[165] Diarylmethyl compounds are structural moieties present in many bioactive molecules, utilised in medical applications such as breast cancer treatment and as inhibitor of HIV protease.[165,177] The allylic alkylation of a variety of diarylmethyl pronucleophiles was successfully demonstrated in the presence of $Ni(cod)_2$, dppf and $NaN(SiMe_3)_2$ with relatively broad scope and high yields (Scheme 65). Additionally, substitution of dppf for a Josiphos-type ligand allowed for asymmetric allylic alkylation with high *ee* values and high yields, demonstrating that nickel-catalysed asymmetric allylic substitutions are not limited to hard nucleophiles but can be applied to a range of soft nucleophiles, expanding the scope of these reactions.[165]

The progress in nickel-catalysed allylic substitutions has proven promising, however, most of the transformations presented here use $Ni(cod)_2$ as the source of Ni^0. As repeatedly highlighted, $Ni(cod)_2$ is extremely air- and moisture-

sensitive, therefore difficult and impractical to handle, again limiting the large-scale potential of nickel-catalysed allylations. Allylic alkylation of 1,3-dicarbonyls with an air-stable Ni^0 precatalyst has been reported; this is discussed in more detail in **section 1.5.9.2.**

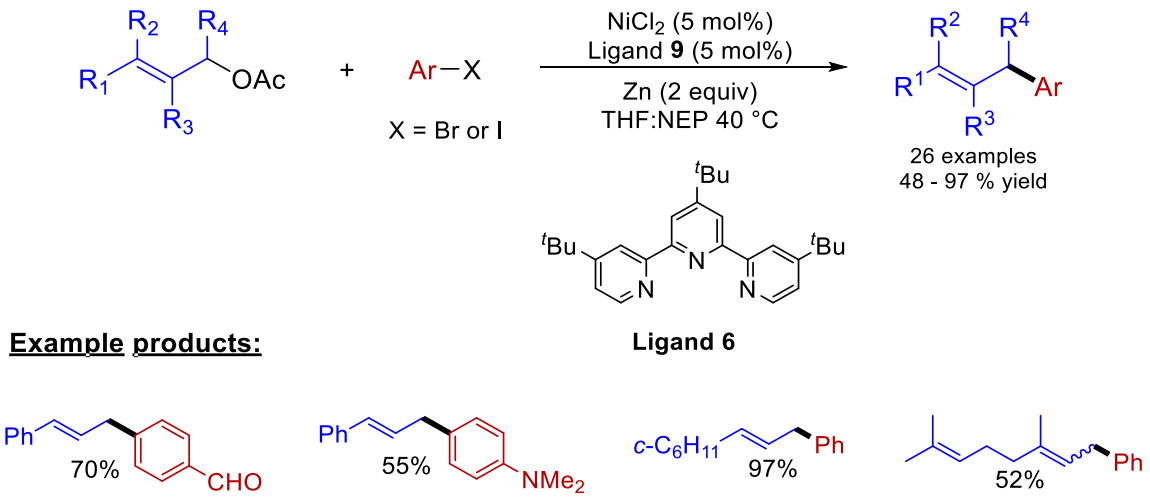


Scheme 65: Example of enantioselective allylic alkylation of diarylmethyl.[165]

1.5.8.3 Reductive Allylation with halide electrophiles

The poor selectivities in Ni-catalysed allylation reactions associated with the use of hard organometallic nucleophiles have been improved in the last couple of decades with the use of soft nucleophiles, such as malonates etc. However, in the last decade, reductive coupling of alkyl and aryl halides with allylic derivatives has emerged as another strategy to improve regioselectivities. Additionally, alkyl halides are generally more readily available and more practical to use in comparison to organometallic reagents, therefore reductive coupling between alkyl halides and allylic electrophiles is of increasing interest.[178]

In 2012, in an early example of reductive allylation, an efficient nickel-catalysed allylation of alkyl halides with allyl acetates was reported. The system of $Ni(cod)_2$, Zn, a tridentate chelating ligand and Cu or Mg additive displayed tolerance for a range of functional groups, with excellent stereo- and regio-selectivities.[178] Later in the same year, a different group demonstrated coupling of allylic acetates with a significantly broader scope for both organic halides and allyl acetates (Scheme 66).[179] Furthermore, their catalytic system employed $NiCl_2$ as a precatalyst, a much cheaper and practical precursor for Ni^0.



Scheme 66: Coupling of allylic acetates with aryl halides in the presence of $NiCl_2$.[179]

Up to this point, the scope for aryl halides had been limited to simple allylic acetates. Nevertheless, in 2013, allylation of aryl bromides with a range of substituted allyl acetates was achieved by utilising NiI_2, Zn as a reductant, and a novel bidentate ligand in the catalytic system, thus improving on the substrate scope previously reported.[180] Various mechanistic pathways have been suggested, including a radical chain pathway and a single electron process, however, detailed mechanistic studies to back up these claims are lacking.[179] For further examples of

reductive allylic coupling reactions and mechanistic insights, an extensive review on Ni-catalysed reductive couplings has recently been published.[181]

1.5.9 Recent notable developments of nickel catalysts

As mentioned, $Ni(cod)_2$ remains as one of the most common sources of Ni^0 in nickel catalysed reactions, requiring the use of a glovebox. Several strategies have been employed to utilise alternative air-stable sources as Ni^0 precatalysts, some of which have been presented earlier.

These include the synthesis of Ni^0 precatalyst complexes with sophisticated and novel ligands, however, these often require multi-step synthesis, increasing the overall complexity and cost of such Ni-catalysed reactions. Another strategy is to utilise cheap and commercially available Ni^{II} salts which are reduced *in situ* to generate the active Ni^0 species, however, this approach often requires excess amounts of reducing agents producing large quantities of metal waste. The use of paraffin capsules has allowed for benchtop handling of $Ni(cod)_2$ as described in **Section 1.5.6.1.1** but the glovebox is still required to charge the capsule with $Ni(cod)_2$**.**

These numerous approaches highlight the ability and applicability of nickel to large variety of reactions, previously predominantly studied with palladium. However, the development of a single nickel catalytic approach which can be applied to a range of reactions would allow for a rapid transition away from palladium without the need for extensive trialling and optimisations.

1.5.9.1 Air-stable Ni^0-olefin catalyst

Recently, a novel air-stable Ni^0-olefin catalyst featuring 4,4'-bis(trifluoromethyl)-stilbene, termed $Ni(^Fstb)_3$, has been explored.[182] Other olefin-based catalysts have been explored as alternatives to $Ni(cod)_2$, such as $Ni(cot)_2$ or Ni(CDT), however, these are equally unstable in air, leading to their decomposition outside of the glovebox.

The unprecedented stability of this novel $Ni(^Fstb)_3$ precatalyst is hypothesized to be due to the 'propeller-like' staggered arrangement of the stilbene ligands, shielding the nickel centre, thereby preventing oxidation. As such, this complex is stable for months when frozen, and can be handled on the benchtop without the need for a glovebox. Additionally, the complex can be synthesised from the relatively inexpensive $Ni(acac)_2$, however, an argon atmosphere is required for its synthesis.

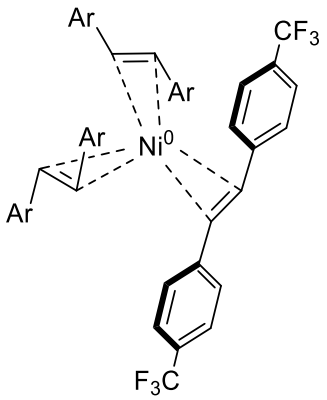


Figure 3: Structure of the air-stable Ni^0 precatalyst, $Ni(^Fstb)_3$

The complex displayed facile ligand exchange with ligands typically employed in Ni-catalysis, such as dppf or PPh_3, allowing for the formation of well-defined Ni^0-ligand complexes. This Ni^0 precursor was evaluated in a variety of coupling reactions, including but not restricted to: biaryl Suzuki coupling, alkyl-alkyl Negishi coupling, ester formation through C–N bond activation, and the Heck reaction of benzyl chloride and ethylene.

The yields achieved in the presence of $Ni(^Fstb)_3$ were comparable to those previously obtained with $Ni(cod)_2$. This highlights the efficiency of the novel catalyst, making it a promising candidate for a practical source of Ni^0 on the benchtop. Some of the reactions conducted required higher temperatures to achieve the same yields as $Ni(cod)_2$, perhaps due to the increased stability of $Ni(^Fstb)_3$. Despite examining a range of different reaction types, only one example of each was tested, therefore there is a need to further probe the full scope of this catalytic system before its potential can be fully appreciated.

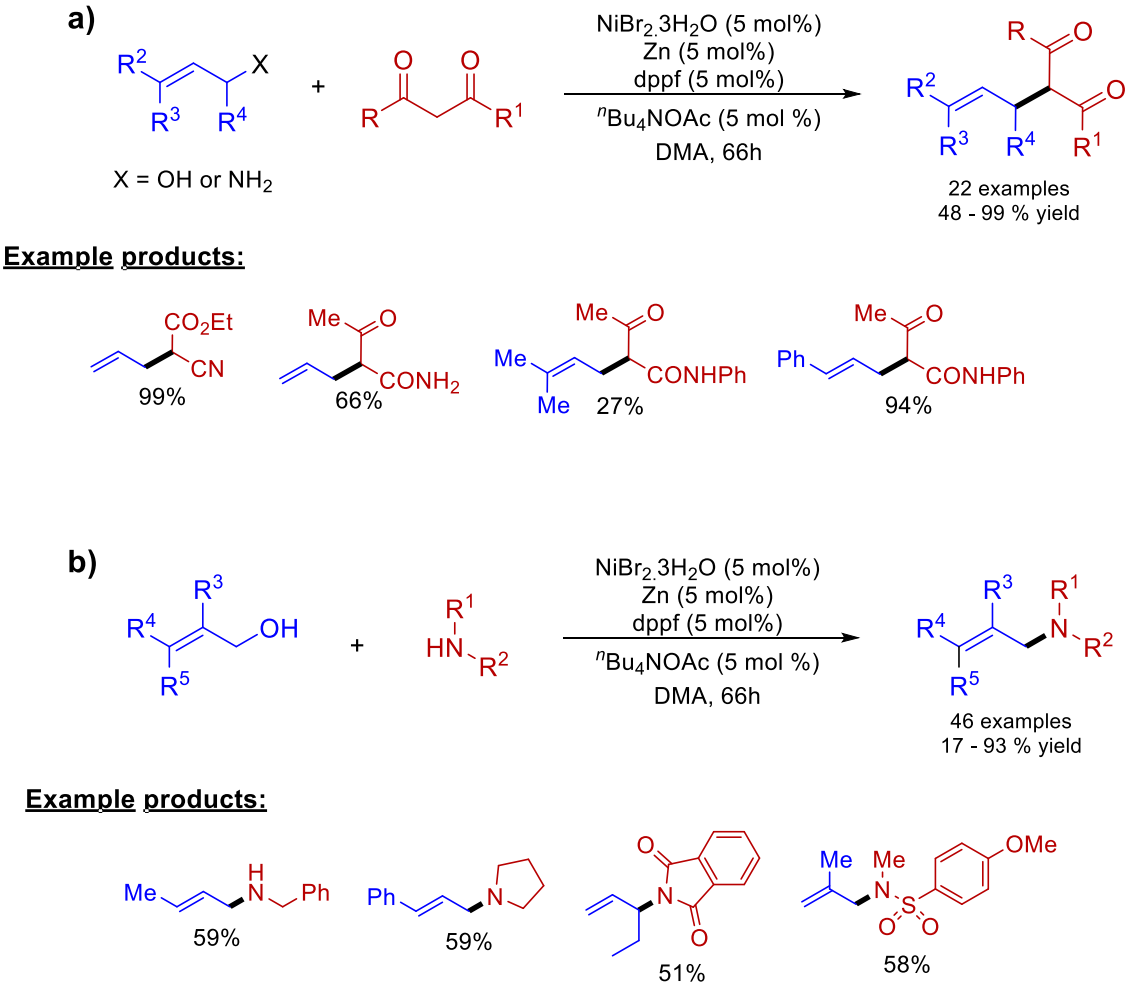
1.5.9.2 'Totally catalytic' nickel system

Recently, the Sweeney group described a simple yet robust nickel precatalyst system in allylations of malonates, β-keto esters, β-diketones, and β-ketoamides by allyl alcohols and allyl amines (Scheme 67a).[183] The optimised system consisted of catalytic amounts of the inexpensive and commercially available $NiBr_2$ salt as the Ni^0 precursor, and catalytic quantities of zinc as the reducing agent. Interestingly, the optimised Ni-catalytic system displayed selectivities towards the monoallylated products, which previous nickel-catalysed allylations were unable to achieve.[183,184] Furthermore, in comparison to similar reactions, this system does

not require a base or an activator, it consists of air-stable, inexpensive and readily available reagents, and utilises sub-stoichiometric amount of the metal reductant, highlighting the practicality of the system.[183]

The applicability of this Ni/Zn precatalyst system was further probed by the Sweeney group by exploring the direct amination of allyl alcohols for the formation of allylamines (Scheme 67b).[185] Allylic amines are useful building blocks for a large number of applications in the pharmaceutical industry, either as intermediates for bioactive compounds or as commercially available products (such as flunarizine, an anti-migraine drug). Allylamines can be challenging to synthesise, often undergoing over-alkylation, while also producing stoichiometric amounts of waste. This system was successfully employed in the direct amination of allyl alcohols with both nucleophilic and electron-deficient nitrogen nucleophiles. Furthermore, this is the first reported nickel-catalysed allylic amination process that generates Ni^0 *in situ* from a simple Ni^{II} salt.[185]

This catalytic system not only provides an inexpensive, practical and scalable process for the synthesis of allylamines and allylated 1,3-dicarbonyls, it allows for the direct use of allyl alcohols or amines as substrates. This significantly reduces the metal waste produced and results in stoichiometric amounts of water or ammonia as the only by-products, highlighting the potential positive environmental impact of this catalytic system. The reaction also does not require the use of a glovebox. This system has so far only been applied to the two reactions mentioned here, therefore, its applicability to different types of reactions needs to be explored to determine its robustness as a general nickel catalytic system.



Scheme 67: Utilisation of the totally catalytic Ni/Zn system for **a)** C-allylation using allyl alcohols and allyl amines;[183] and **b)** Direct amination of allyl alcohols.[185]

1.6 Conclusion

Although palladium-based catalysts have received the most attention from synthetic organic chemists in the last few decades, the use of nickel in the catalysis of C–C bond formations has significantly increased. As presented here, nickel is capable of catalysing many of the same reactions as palladium and, considering the significant price difference between palladium and nickel, this offers substantial financial benefits.

The field of nickel catalysis has significantly expanded in the last couple of decades, however, challenges of its wider application remain. Nickel catalysts are highly reactive meaning the catalytic systems can be difficult to control, often resulting in poor selectivities. Nevertheless, the increased reactivity of nickel over palladium can also be viewed as an advantage as it offers opportunities for transformations involving less reactive electrophiles, such as phenols or amides. Nickel catalysts can also access different oxidation states to palladium, resulting in new reactivity patterns and new catalytic pathways involving radical intermediates, but also increasing the complexity of these systems.

The increased understanding of the mechanistic steps involved in many nickel-catalysed reactions has led to the design of new catalysts accomplishing a range of new bond forming reactions. Highly selective nickel catalysed transformations have been achieved, as demonstrated by the Fu, Reisman and Jamison groups, just to name a few, highlighting the increased understanding and the potential of nickel systems. Furthermore, the ability to access more oxidation states, namely Ni^{I} and Ni^{III}, has been highly advantageous in cross-electrophile coupling.

Despite the advances in nickel catalysis, the highly air- and moisture- sensitive $Ni(cod)_2$ remains as one of the most common sources of Ni^0, requiring the use of a glovebox for many nickel-catalysed reactions. This limits the practicality and applicability of nickel catalysts to industrial processes and potentially offsets the economic benefits of employing nickel. Some groups have developed elegant, yet often complex, Ni^0 precatalysts, while others have employed inexpensive nickel salts with super-stoichiometric quantities of reducing agents, such as Zn or Mn, to reduce Ni^{II} to Ni^0 *in situ*. However, the use of complex ligands can limit the number of suitable substrates, often increasing the complexity and cost of the reaction, while utilisation of super-stoichiometric quantities of reducing agents leads to large amount of metal waste, making these reactions atom inefficient.

In light of these limitations, research efforts have focused on the development of a catalytic system that addresses these issues. In 2020, a simple, air-stable Ni^0 precursor, $Ni(^Fstb)_3$, was developed, allowing for reactions that have previously utilised $Ni(cod)^2$ to be carried out on the benchtop, significantly improving the practicality and potential scalability of these reactions. The Sweeney group have recently developed the first ''totally catalytic'' Ni/Zn system in response to these issues. They employed an inexpensive, commercially available, and air-stable nickel bromide salt with sub-stoichiometric amounts of zinc as the reducing agent and showed great success with two separate allylation reactions.

These two alternative approaches to the same problem highlight great progress in making nickel-catalysed reactions more practical, applicable and potentially scalable. Both of these approaches show great promise at becoming the general

catalytic nickel system for future Ni-catalysed reactions. However, further exemplification is required to fully appreciate and understand their potential.

1.7 Project Aims

The aim of this research project is to further probe the applicability and scope the Sweeney Ni/Zn system. This system has demonstrated a broad substrate scope in the two reactions studied, however, the challenge now lies in exploring its applicability to a greater variety of reactions that have previously employed $Ni(cod)_2$, complex nickel pre-catalysts, or expensive palladium catalysts; as well as testing its ability to catalyse novel bond forming reactions with potentially challenging substrates.

Chapter 2 of this thesis focuses on applying the Ni/Zn system to the direct allylation of simple ketones with allyl alcohols in the presence of pyrrolidine as a co-catalyst. This reaction has previously only been demonstrated with a palladium-based catalyst. Furthermore, the utilisation of allyl alcohols without the need for pre-functionalisation would reduce the waste produced during the reaction since water would be the only by-product.

Chapter 3 directly follows on from the work in chapter 2 and aims to explore the enantioselective potential of the allylation of ketones in the presence of chiral pyrrolidine derivatives. A successful outcome of this reaction would be the first example of enantioselective synthesis utilising the novel Ni/Zn catalytic system.

Finally, chapter 4 focuses on further expanding the applicability of the Ni/Zn system by exploring its potential to catalyse the α-allylation of α-branched aldehydes with allyl alcohols. If successful, this reaction would highlight the robustness of this catalytic system to variety of different, and often challenging, substrates.

Chapter 2: Application of the 'totally catalytic' Ni/Zn system for direct allylation of ketones with allyl alcohols

2.1 Introduction to 'total catalysis'

Transition metal catalysis has been widely used in organic chemistry for decades with palladium in particular having received much interest in cross-coupling reactions.[186–190] Pd-based catalysts have opened the door to a large number of carbon-carbon bond forming reactions as they are highly tolerant of many functional groups, and they are also relatively stable to oxygen and moisture. The versatility of Pd catalysts has led to their wide adoption by organic chemists, however, there is an increasing need for lower-cost, Earth abundant metals in catalysis. As a result, the focus has now turned to nickel as a sustainable, cheaper, alternative for palladium in catalytic transformations.[20,22–24]

Nickel(0) complexes and salts have been utilised in catalysis since the 1960s when their catalytic properties were first discovered by Ziegler, Wilke, and co-workers.[25] Since then, nickel has been used as a catalyst in a large number of cross-coupling reactions: such as oligomerisations, cycloisomerisations, and reductive couplings.[23,25] Additionally, nickel is a more electropositive metal, meaning it is also capable of catalysing bond formations different to Pd, such as cross coupling of phenol derivatives,[61–64] making Ni attractive not only due to its economic benefits but also due to its versatility and unique ability to undergo reactions with less reactive electrophiles, thus creating opportunities for new transformations.

Nevertheless, the scale up of nickel-catalysed cross-coupling reactions into industrial application has been hindered by the lack of an air-stable, easily

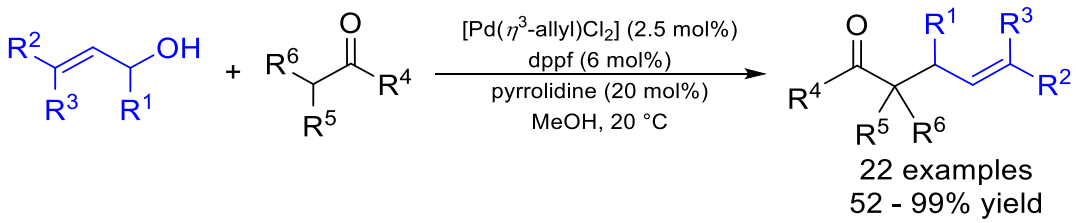
accessible Ni^0 source. The most widely used Ni^0 catalyst, $Ni(cod)_2$, is highly air and moisture sensitive, meaning it requires handling in a glove box.[191] Some catalytic systems employ air-stable nickel pre-catalysts, which often require multiple step synthesis or superstoichiometric amounts of reducing agents, making the reaction complicated and atom inefficient.[183,184] As such, the application of nickel-based catalyst in organic synthesis on an industrial scale is limited.

Transition metal catalysed asymmetric allylic alkylations, as first reported by Tsuji in 1965, are a powerful and widely used tool for introducing new chiral carbon centres to molecules.[160,161] Furthermore, the introduced allylic moiety allows for further functionalisation of the C–C double bond. Commonly, allylic alkylations are carried out in the presence of palladium, however, these reactions have also been reported in the presence of Cu, Fe, Ir, Mo, Ni, Rh, Ru, and W based catalysts.[162]

Many allylic alkylation reactions have focused on the coupling of carbonyl compounds with allylic electrophiles, such as allyl halides and allyl acetates, to form either homoallylic alcohols or α-substituted aldehydes and ketones.[192–194] In recent years, the interest has grown in the direct use of allyl alcohols in allylic alkylation reactions instead of the conventional activated allylic compounds which often require synthetic preparation.[195,196] The use of allyl alcohols would eliminate the need for pre-functionalisation, thus improving the overall atom economy of the reaction. Additionally, the only stoichiometric by-product in allylation reactions with allyl alcohols would be water, highlighting the potential positive environmental impact of using ally alcohols.[196]

However, allyl alcohols are usually less electrophilic, thus potentially requiring higher catalyst loading, higher temperatures, and chemical additives.[184]

Nevertheless, the direct use of allylic alcohols for the allylation of simple ketones has been reported by Zhang *et al* in the presence of a palladium catalyst with pyrrolidine as an organic co-catalyst at room temperature and using methanol as the solvent, highlighting potential for these types of reactions.[197]



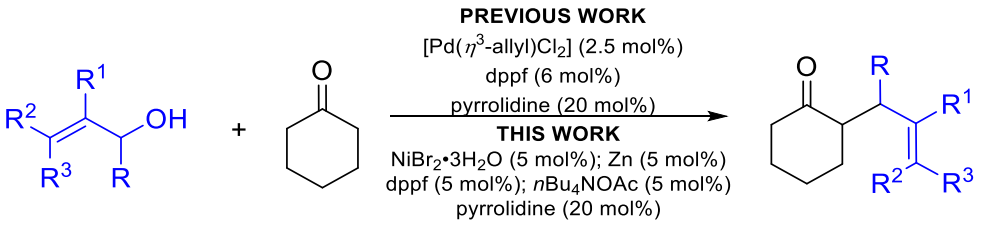
Scheme 68: Direct allylation of ketones with allyl alcohols. [197]

Nickel catalysed allyl-transfer reactions were first reported in 1973 by Tojo *et al*, however, palladium has received the most attention in this field, perhaps due to the many different mechanisms of allylic transfer reactions possible in the presence of $Ni(cod)_2$.[163] Nevertheless, the number of nickel-catalysed allylations has been on the rise. Mashima and co-workers have recently demonstrated asymmetric allylic alkylation of *β*-ketoesters with allylic alcohols using a nickel/chiral disphosphine system, resulting in the construction of quaternary carbon centres with high yields and enantioselectivity.[184] This work was recently adopted and built upon by Stoltz *et al* who focused on the enantioselective allylic alkylation of α-substituted lactones and lactams with allylic alcohols, yielding α-quaternary products with high yields and enantiomeric excess.[198]

Recent efforts within the Sweeney group have focused on the development of a 'totally catalytic' Ni/Zn system, which employs the cheap, commercially available

nickel salt, $NiBr_2.H_2O$, and equimolar amounts of zinc as the precatalyst, making this the first catalytic system utilising both Ni and Zn at sub-stoichiometric loading. This totally catalytic system has been applied to two separate allylation reactions: direct allylation of β-ketoesters, and direct amination of allyl alcohols.[183,185] Nevertheless, the application of nickel catalysis to the allylation of simple ketones with allyl alcohols has not yet been reported.

Here we demonstrate the successful application of the totally catalytic Ni/Zn system to the direct allylation of ketones with allyl alcohols, highlighting the potential for this system to catalyse novel reactions. Additionally, the successful outcome of this reaction would highlight the robustness and applicability of this Ni/Zn catalytic system, with the potential to explore other previously reported literature reactions which either use complex Ni-based catalysts, $Ni(cod)_2$, or Pd-based catalysts. This would not only reduce the cost of such reactions but it would also make Ni(0) reactions more scalable and thus more accessible to industrial application.



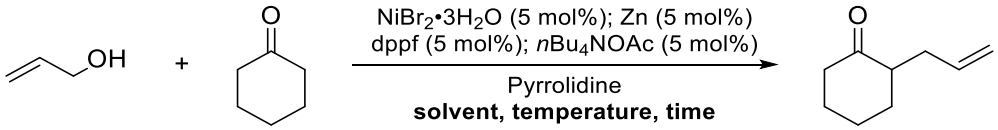
2.2 Results and Discussion

2.2.1 Optimisation of reaction conditions

The Ni/Zn system was initially tested on the allylation of cyclohexanone with allyl alcohol, employing the previously reported optimal conditions for the totally catalytic Ni/Zn system, as reported by Sweeney *et al.* (Table 1, entry 1).[183] These conditions were then further probed and optimised to determine the best system for this reaction in particular (Tables 1 – 3). An extensive optimisation was not carried out due to the similarities of this reaction to the one reported by Sweeney *et al.*[183]

This initial screening delivered the product in 50% yield. Further optimisation revealed a 67% yield is possible when using methanol as the solvent, however, upon application of these conditions to a variety of allyl alcohols, the reactions did not work, therefore DMA was used as the solvent for these reactions.

Table 1: Optimisation of reaction conditions



Entry	Ligand	Solvent	Pyrrolidine (mol%)	T (°C)	Time (h)	Isolated Yield (%)
1	dppf	DMA	20	50	66	50
2	dppf	DMA	20	50	18	15
3	dppf	DMA	20	80	18	15
4	dppb	DMA	20	50	66	0
5	dppf	DMF	20	50	66	52
6	dppf	MeOH	20	50	66	67
7	dppf	DMA	20	50	66	21[a]
8	dppf	DMA	0	50	66	0
9	dppf	DMA	10	50	66	13
10	dppf	DMA	40	50	66	71
11	dppf	DMA	20	50	66	15[b]
12	dppf	DMA	20	50	66	0[c]
13	dppf	DMA	10	50	66	0[d]
14	dppf	DMA	10	50	66	0[e]
15	-	DMA	10	50	66	0

Reaction conditions: Allyl alcohol (1.0 mmol), cyclohexanone (1.0 mmol), $NiBr_2 \cdot 3H_2O$ (0.05 mmol), dppf (0.05mmol), *n*Bu_4NOAc (0.05 mmol), zinc (0.05 mmol), pyrrolidine (0.2 mmol); DMA, 50°C, 66 h, sealed vial; [a] Without *n*Bu_4NOAc; [b] Reaction with $Ni(OAc)_2$ (0.05 mmol), conversion (%) determined by ^1H NMR; [c] Reaction with $Ni(OH)_2$ (0.05 mmol); [d] Reaction without $NiBr_2 \cdot 3H_2O$; [e] Reaction without zinc.

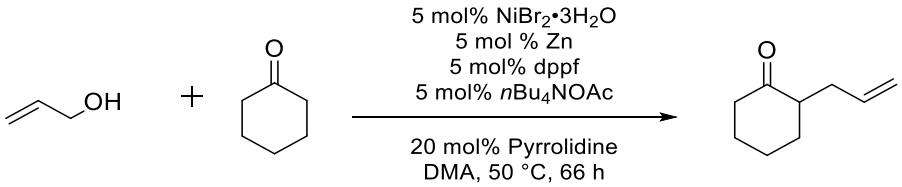
Once the optimum conditions were determined, a stoichiometry study was carried out to determine the optimal ratios of allyl alcohol to ketone to maximise the yield. The results showed that the yield was reduced in the presence of a large excess of allyl alcohol (Table 2, entries 1 vs 5). This could be due to the increased concentration of allyl alcohol slowing down enamine formation, thus lowering the

yield. Furthermore, the yield significantly increased in the presence of excess cyclohexanone, suggesting easier/more efficient enamine formation due to the increase in cyclohexanone concentration thus leading to a faster and a more efficient reaction.

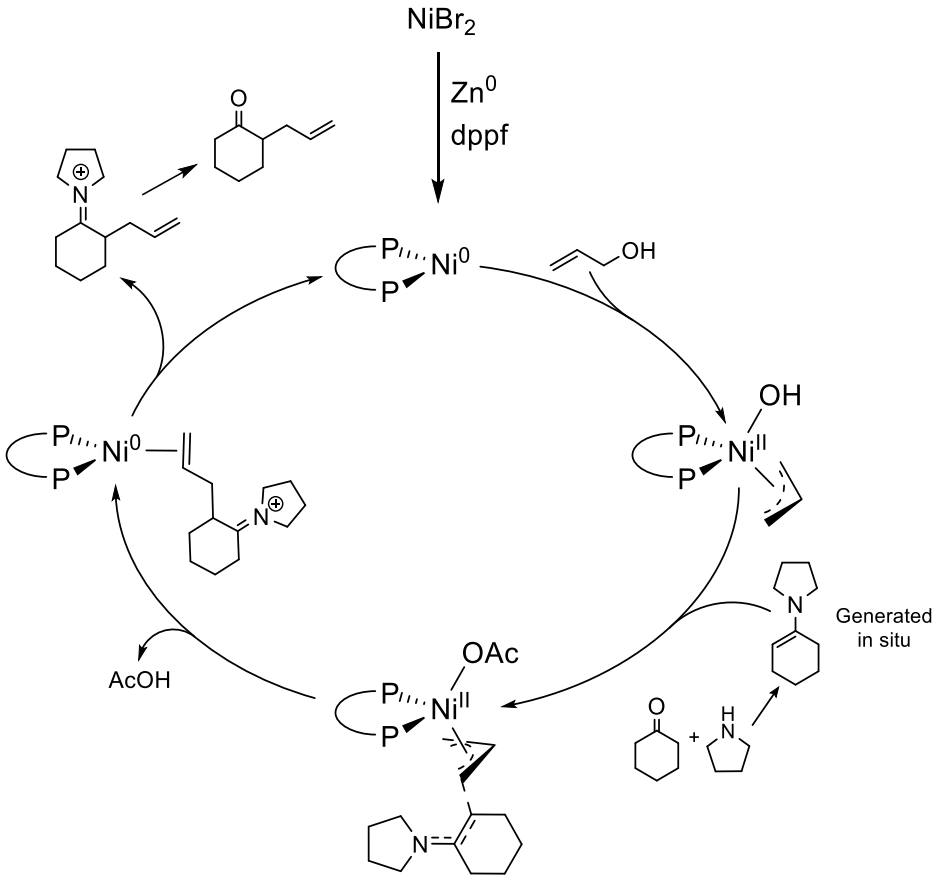
It should be noted that the yield was significantly lower and did not follow the general observed trend when 2:1 ratio of allyl alcohol to cyclohexanone was used in the reaction (23% yield, Table 2, entry 4). However, it is unclear as to why this is the case. The reaction yield was highest with 40 mol% loading of pyrrolidine (See Table 1, entries **1**, and **8 – 10**), however, it was decided the optimal amount of pyrrolidine to use would be 20 mol% in order to keep the concentration as low as possible while also maximising yields. No reaction is observed in the absence of pyrrolidine suggesting the enamine intermediate formation is crucial for the reaction to proceed successfully. The reaction was also attempted with nickel acetate and nickel hydroxide as these are cheaper sources of nickel. Nickel acetate did catalyse the reaction, resulting in 15% conversion based on the consumption of the starting material as determined by NMR. However, this is significantly lower than when using nickel bromide. The desired product was not observed in the presence of nickel hydroxide, only the starting materials could be seen by NMR, suggesting the reaction did not proceed in the presence of nickel hydroxide, perhaps due to its limited solubility in DMA.

Having determined the optimal conditions for the reaction, the system was next tested with a variety of allyl alcohols and ketones to test the scope and breadth of the reaction.

Table 2: Stoichiometry study



Entry	Allyl Alcohol (mmol)	Cyclohexanone (mmol)	Isolated Yield (%)
1	5	1	30
2	4	1	34
3	3	1	48
4	2	1	23
5	1	1	50
6	1	2	51
7	1	3	57
8	1	4	76
9	1	5	77



Scheme 69: Proposed reaction mechanism

2.2.2 Allyl alcohol substrate scope

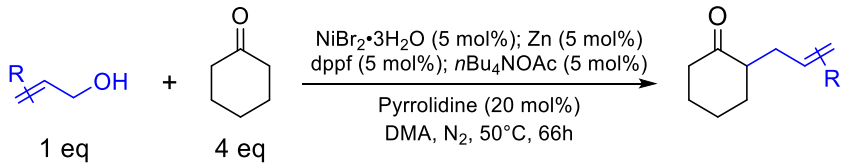
Once the optimal conditions for the reaction of allyl alcohol with cyclohexanone had been identified (Table 1, entry 1), the scope of the reaction was explored with a variety of allyl alcohols, delivering a selection of allylated products (**Table 3**). Increasing the chain length from 3 to 5 carbons appears to have a negative influence on the efficiency of the reaction, with the yield decreasing as the chain length increases (compounds **1-4**). This holds true up to chain length of 6 for (*Z*)-2-hexen-1-ol, however, (*E*)-2-hexen-1-ol does not follow this trend, with the yield more similar to **1**. (*E*)-2-hexen-1-ol may be able to twist into a favourable chair-like conformation in the transition state thus potentially stabilising the η^3-allyl intermediate and increasing the yield as a result.

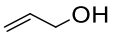
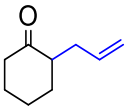
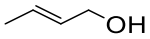
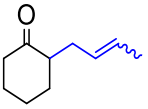
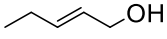
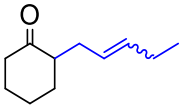
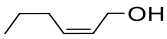
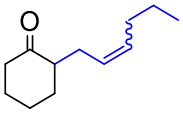
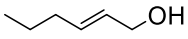
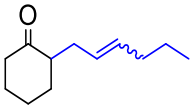
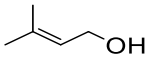
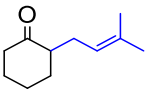
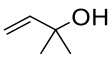
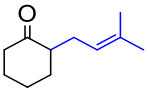
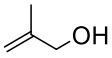
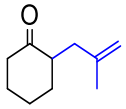
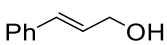
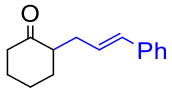
Increased branching of the allyl alcohol also appears to decrease the yield, again suggesting that steric hindrance plays a part in the efficiency of the reaction (compounds **6, 7 & 9**), perhaps due to slower oxidative addition of the allyl alcohol as the chain length increases. Given the increased steric bulk of the *trans*-1-methyl-3-phenyl-2-propen-1-ol substrate to synthesise compound **9,** the yield was significantly affected, resulting in a difficult purification process meaning the compound could only be isolated in 9% yield and as 83% pure. Introduction of the phenyl group (**8**) significantly improved the yield, perhaps due to increased stabilisation of the η^3-allyl intermediate with delocalisation from the phenyl ring. Electron withdrawing groups on the phenyl ring appear to reduce the yield, suggesting a destabilising effect, meanwhile electron donating groups have very little effect.

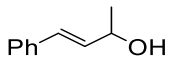
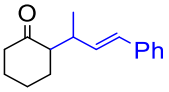
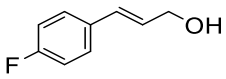
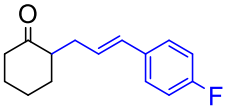
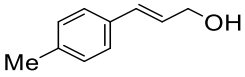
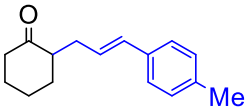
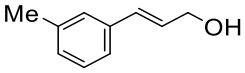
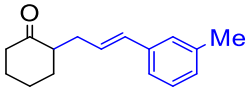
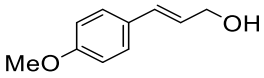
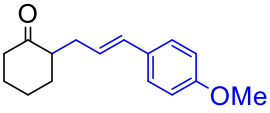
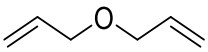
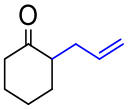
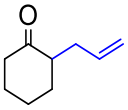
The use of diallyl amine instead of allyl alcohol was also explored, yielding the desired, monoallylated product in 43% yield (Table 3, entry 16). The application of diallyl amine potentially removes the need for pyrrolidine within the reaction and may also offer the opportunity to transfer multiple allyl groups.

2-Methylene-1,3-propanediol was unsuccessful in the reaction, perhaps due to co-ordination of the two OH groups to the nickel, thus preventing oxidative addition into the C–O bond. In the case with 4-chloro- and 4-(dimethyl)amino-cinnamyl alcohol, oxidative addition into the C–Cl and C–N bonds, respectively, may be faster than the oxidative addition into the C–O bond of the alcohol thus preventing the reaction from proceeding.[199]

Table 3: Scope of Ni-catalysed allylation of ketones with various allyl alcohols.



Entry	Allyl Alcohol	Product	Isolated Yield /%
1		**1** 	76
2		**2** 	64* linear/branched = 9:1
3		**3** 	42*
4		**4** 	44* linear/branched = 96:4
5		**5** 	74*
6		**6** 	38 linear/branched = 4:1
7		**6** 	50 linear/branched = 17:3
8		**7** 	66
9		**8** 	84

10		**9** 	9 *d.r.* = 2:1 linear/branched = 85:15
11		**10** 	75
12		**11** 	64
13		**12** 	57
14		**13** 	86
15		**1** 	10
16		**1** 	43[a]

Reaction conditions: allyl alcohol (1.0 mmol), cyclohexanone (4.0 mmol), $NiBr_2 \cdot 3H_2O$ (0.05 mmol), dppf (0.05mmol), *n*Bu_4NOAc (0.05 mmol), zinc (0.05 mmol), pyrrolidine (0.2 mmol), DMA, 50°C, 66 h, sealed vial; [a] no pyrrolidine & no $^{n}Bu_4NOAc$; **E*/*Z* isomeric ratios could not be determined by ^1H NMR due to the overlapping nature of the peaks

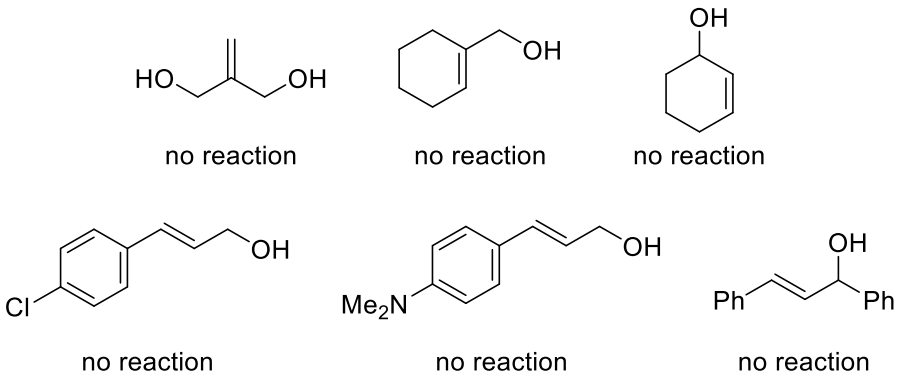


Figure 4: Other allyl alcohol substrates tested in this reaction.

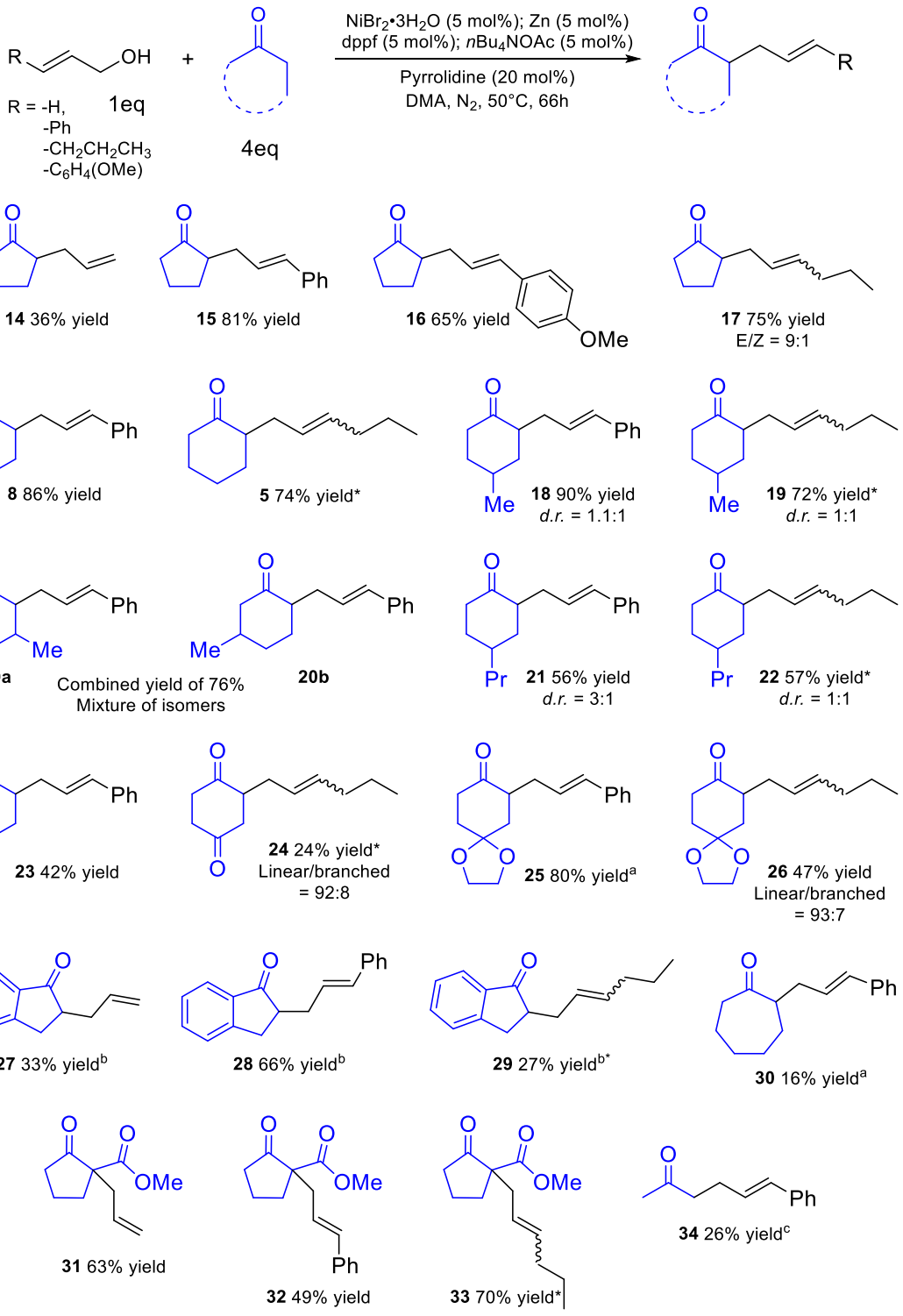
2.2.3 Screening of ketones and aldehydes

Having shown scope for a variety of allyl alcohols, the simple Ni/Zn catalytic system was further tested with a range of ketones and aldehydes using cinnamyl alcohol and (*E*)-2-hexen-1-ol as exemplar alcohols (Scheme 70). These substrates were chosen as these gave the highest isolated yields with cyclohexanone (compounds **5** and **8**). The reactions with cyclopentanone (**14 – 16**) and 3- or 4-substituted cyclohexanones proceeded in moderate to good yields (**18 – 26**), however, the reactions with cycloheptanone, aliphatic ketones, 2-substituted cyclic ketones, and aldehydes proved more challenging, giving lower yields or no reaction at all (Compounds **30** and **34**). Cycloheptanone (**30**) reacted in lower yield, perhaps due to the increased ring size and thus increased flexibility and stability of the ring, resulting in a less reactive compound and a much slower enamine formation, even at higher temperatures and increased pyrrolidine loading.

Disappointingly, the yields of the reactions with 1-indanone were modest, even at increased temperature, catalyst loading, and reaction time (compounds **27 – 29**). Although it could be expected that the aromatic moiety would have a stabilising effect on any intermediates, it is possible that this mechanism is highly sensitive to increased steric hindrance. This was demonstrated with increasing chain length of the allyl alcohols in compounds **1** to **4** and as such, it is possible that the bulk of the phenyl ring of indanone is having an unexpected negative impact on the yield of the reaction. Alternatively, the increased stabilising effect from the aromatic moiety could be hindering the *in situ* enamine formation. Literature suggests[200,201] that high pyrrolidine loading, high temperatures (reflux), and dry conditions are

required for the synthesis of the enamine of 1-indanone, therefore, under the conditions present here, the enamine formation would be slow, therefore limiting the progress of the reaction.

Disappointingly, the reaction was unsuccessful with acyclic ketones, other than acetone, or aldehydes, contrary to the results previously demonstrated by Zhang *et al* with their palladium-based system.[197] This highlights a potential limitation of this Ni/Zn system for this reaction. The reaction of propiophenone was repeated with allyl alcohol to determine whether it is the cinnamyl alcohol that is limiting the reaction from proceeding; however, no product was observed. This suggests the allyl alcohol substrate is not the limiting agent in this reaction. The formation of enamines with acyclic ketones may be much slower than their cyclic counterparts, perhaps due to the increased ring strain of cyclic ketones, meaning the reaction may be much slower, or it may not proceed as desired at all. Some studies have been carried out that show slow formation of enamines with aliphatic ketones in comparison to cyclic ketones, supporting this hypothesis.[202]



Scheme 70: Scope of Ni-catalysed allylation with cinnamyl alcohol and (*E*)-2-hexen-1-ol; Reaction conditions: Allyl alcohol (1.0 mmol), ketone (4.0 mmol), NiBr2·3H2O (0.05 mmol), dppf (0.05mmol), ^{n}Bu4NOAc (0.05 mmol), zinc (0.05 mmol), pyrrolidine (0.2 mmol), DMA, 50°C, 66 h, sealed vial; [a] 10 mol% catalyst**, excess acetone (25x, 2mL); [b] 80°C, 10 mol% catalyst; [c] 80°C. (**10

mol% catalyst = 10 mol% $NiBr_2.3H_2O$, 10 mol% Zn, 10 mol% $^nBu_4NOAc$, 10 mol% dppf); *E/Z isomeric ratios could not be determined by ^1H NMR due to the overlapping nature of the peaks.

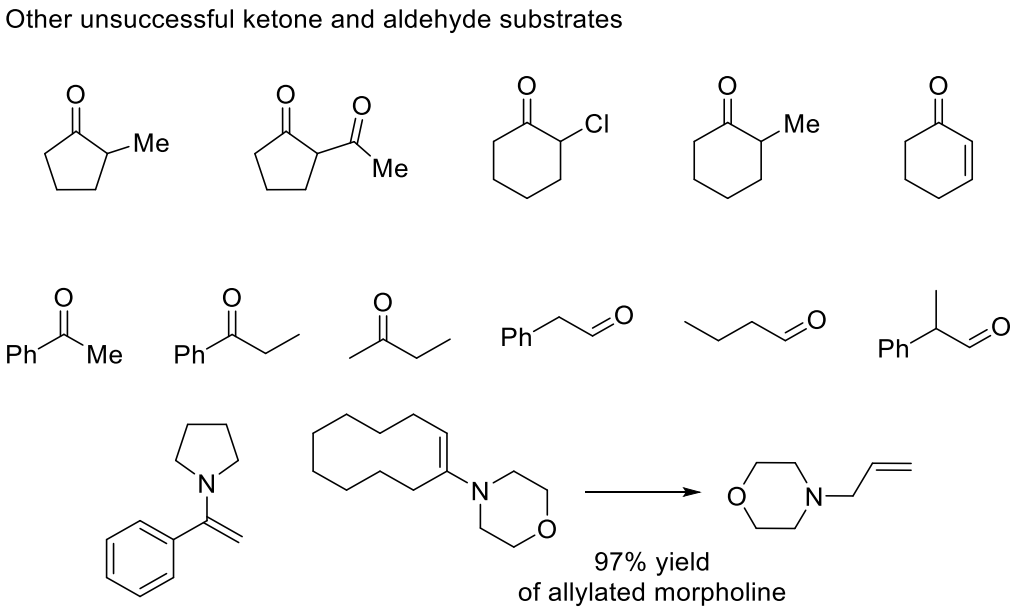
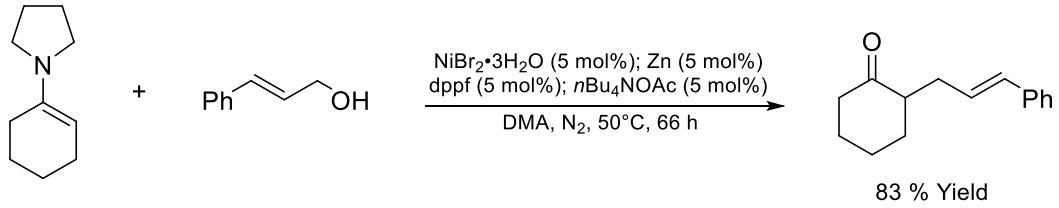


Figure 5: Unreactive ketone and aldehyde substrates trialled in this reaction.

One strategy to overcome the issue with acyclic ketones was to synthesise the enamines of the unsuccessful ketone substrates prior to the reaction to determine whether the enamine formation is hindered *in situ* and thus preventing the allylation from proceeding.

Initially pre-made enamine of cyclohexanone was used in the reaction with cinnamyl alcohol to check whether the direct use of enamines would still produce the desired product. This reaction was indeed successful and gave the same product yield as when the enamine is formed *in situ* (Scheme 71).



Scheme 71: Utilising pre-made cyclohexanone enamine.

Unfortunately, this approach of using pre-made enamines of the unsuccessful ketones failed to produce the desired allylated products, returning the starting ketone upon work up. This suggests that there are other factors within the reaction limiting the formation of the desired product. It may be that the enamine is unstable under the reaction conditions employed thus preventing the reaction from proceeding as expected.

Since the reaction does proceed with excess acetone, the increased chain length of the other ketones could be reason for the lack of reaction due to increased steric hindrance. Cyclohexanone and cyclopentanone enamine intermediates may be destabilised by their cyclic conformations due to increased bond angle strain, whereas acyclic ketones will not have any ring strain, thus they would be more stable and less reactive.

2-Substituted cyclohexanone and cyclopentanone substrates also do not produce the allylated product. This result is not unexpected as no di-allylation (2,2- or 2,6) has been observed with any of the substrates tested. Surprisingly, the reaction with 2-methoxycarbonylcyclopentanone does proceed successfully in moderate yields resulting in the 2,2-disubtituted cyclopentanone products (**31 – 33**). This could be due to the lower pK_a of the α-H of the β-keto ester, making the enamine formation easier and thus more favourable. Furthermore, the methoxycarbonyl

group can stabilise the intermediate state by resonance, giving justification as to why this particular 2- substituted cyclopentanone proceeds with the allylation as desired. It should be noted that a similar effect is not seen with the diketone 2-acetylcyclopentanone. Unsurprisingly, no substitution is observed at the 5-position of 2-methoxycarbonylcyclopentanone. These results further highlight how increased steric hindrance of the substrate, in this case a substitution in the 2- position, significantly impacts the outcome of the reaction.

2.2.3.1 Isomers and other impurities

Many of the products described, displayed a degree of E/Z isomerism, regioisomerism (in terms of linear or branched products), and diastereisomerism. Given the nature of these compounds, a mixture of these different isomers could sometimes be observed in the NMR. Best efforts have been made to attempt to quantify the extent of isomerism in the relevant compounds as detailed below.

In the ^{1}H NMR spectra of several compounds (namely **8**, **9**, **14**, **15** and **27**), minor traces of impurities other than the isomers described above are also present, which were accounted for in the reported yield. However, in all cases, the NMRs are clean enough to easily identify the desired compounds with confidence with reference to published NMR data in literature.[197,203,204] As these are known compounds, and given the restricted access to the departmental facilities during my final 12-months, further effort improve the purity of these compounds was not attempted, as priority was given to expand the scope of this work.

Some of the compounds also display regioisomerism in the form of branching. The presence of branched isomers was determined and calculated using the ^{1}H NMR,

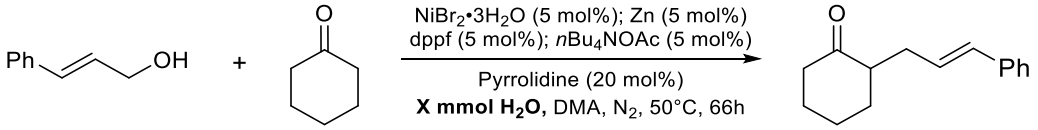
where extra peaks corresponding to the terminal geminal protons could be observed.

2.2.4 Mechanistic studies

2.2.4.1 Tolerance of the catalytic system to moisture

The moisture sensitivity of the allylation reaction was studied to determine whether the presence of water would affect the outcome of the reaction. The reaction of cinnamyl alcohol with cyclohexanone was repeated in the presence of 1 mmol water, 10 mmol water, 1:1 DMA and water, and in water only. In the case of small amounts of water (1 and 10 mmol), the yield of the reaction was unaffected, whereas at higher loading (55 and 110 mmol), the reaction did not proceed. This highlights the catalytic system's and the reaction's tolerance to the presence of water, however, it also shows that this tolerance is limited and a reaction in large excess of water is not possible. Nevertheless, these results show that the reaction does not necessarily have to be carried out in dry conditions (under nitrogen and in dry solvent), which would not only reduce the cost of these types of reactions, but also improves their practicality and applicability to scale up processes.

Table 4: Water tolerance study

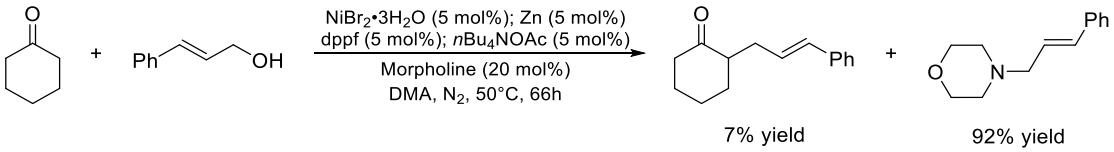


Entry	H_2O (mmol)	Isolated yield (%)
1	0	86
2	1	86
3	10	85
4	55	0
5	110	0

Reaction conditions: Cinnamyl alcohol (1.0 mmol), ketone (4.0 mmol), $NiBr_2 \cdot 3H_2O$ (0.05 mmol), dppf (0.05mmol), nBu$_4$NOAc (0.05 mmol), zinc (0.05 mmol), pyrrolidine (0.2 mmol), DMA, 50°C, 66 h, sealed vial.

2.2.4.2 Reaction with morpholine

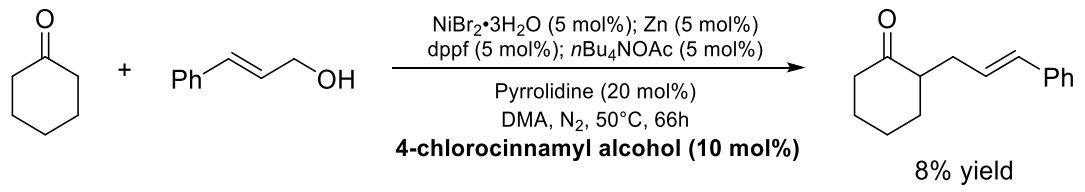
Based on the result of the reaction of cinnamyl alcohol with 1-morpholino-1-cyclododecene, the reaction of cyclohexanone with cinnamyl alcohol was repeated in the presence of morpholine as the co-catalyst instead of pyrrolidine. This yielded the N-allylated morpholine as the product instead of the desired allylated ketone. This could be due to morpholine being more nucleophilic than the pyrrolidine, therefore reacting with the cinnamyl alcohol before it has a chance to form the enamine with the cyclohexanone.



Scheme 72: Allylation reaction in the presence of morpholine as co-catalyst

2.2.4.3 Test for Cl poisoning the catalyst

Tests were carried out whether the presence of a chloro substituent on the substrates (whether on the cyclohexanone or allyl alcohol) was poisoning the catalyst and thus impeding the reaction from proceeding as normal, or whether the substrates were undergoing other side-reactions. The reaction of cinnamyl alcohol with cyclohexanone was used in this study in the presence of 10 mol% 4-chlorocinnamyl alcohol. The reaction yielded only 8% of the desired 2-cinnnamylcyclohexanone, suggesting the presence of chloride does hinder the reaction by interfering with the nickel catalyst. It is likely the 4-chlorocinnamyl alcohol is preferentially undergoing oxidative addition into the C–Cl bond, instead of the C–O bond as required,[199] forming nickel chloride in the process and preventing the nickel from forming the η^3-allyl intermediate with the allyl alcohol and thus from reacting with the enamine of the cyclohexanone.



Scheme 73: Allylation reaction in the presence of 4-chlorocinnamyl alcohol (10 mol%).

2.3. Conclusion

The totally catalytic Ni/Zn system, as first reported by Sweeney *et al,*[183] has successfully been applied to the direct allylation of cyclic ketones with allyl alcohols, yielding a variety of allylated products in moderate to high yields (34 examples, 11 – 86% yield). The system employs pyrrolidine as an organic co-catalyst to activate the ketone through the formation of an enamine intermediate, formed *in situ*. The tolerance of this reaction and the catalytic system to a range of functional groups has been successfully demonstrated, including fluoro-, methoxy, and carboxylate- groups just to name a few.

The number of reactions utilising simple ketones with simple allyl alcohols are limited, presumably due to the low electrophilicity of the allyl alcohol in comparison to activated allylic substrates.[194] As such, functionalised allyl alcohol derivatives are often used to improve reactivity.[195] As shown here, allylation of simple ketones directly with allyl alcohols is achievable, improving the atom economy of these types of reactions, and the ease of synthesis of allylated ketones.

Here, a variety of simple cyclic ketones have been successfully allylated, however, the allylation of acyclic ketones has remained a challenge, with only acetone successfully yielding the desired product in moderate yield (**34**, 26% yield). This could be due to the lower reactivity of the acyclic ketones, meaning different approaches and/or additives may be needed, such as the use of a strong base, in the catalytic system to encourage allylation of acyclic ketones with allyl alcohols.

Chapter 3. Asymmetric allylation of ketones with a chiral amine

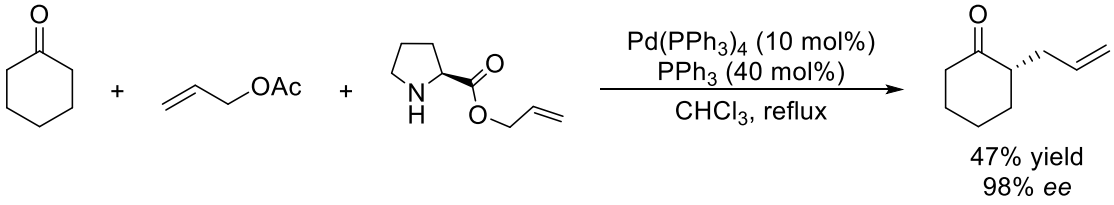
3.1 Introduction

In the examples of allylic alkylation of ketones discussed in Chapter 2, most substrates lead to the formation of a new chiral carbon centre. As such, the enantioselective synthesis of these compounds is of interest. Enantioselective allylation reactions of ketones with allyl alcohols would provide a simple and direct route to enantio-enriched compounds containing a C–C double bond that could be further functionalised to furnish a variety of molecules.

There are many different approaches to asymmetric synthesis, including the use of metal-based catalytic methods with chiral ligands, chiral bases, and/or chiral organocatalysts. Many groups have focused on enantioselective synthesis of allylated ketones via the formation of metal enolates. This approach usually involves the use of strong bases, such as LiHMDS, and Lewis acids, such as LiCl, in the presence of a metal catalyst, most commonly Pd, and a chiral ligand; an extensive review on the asymmetric allylic alkylation of ketone enolates has recently been published.[205]

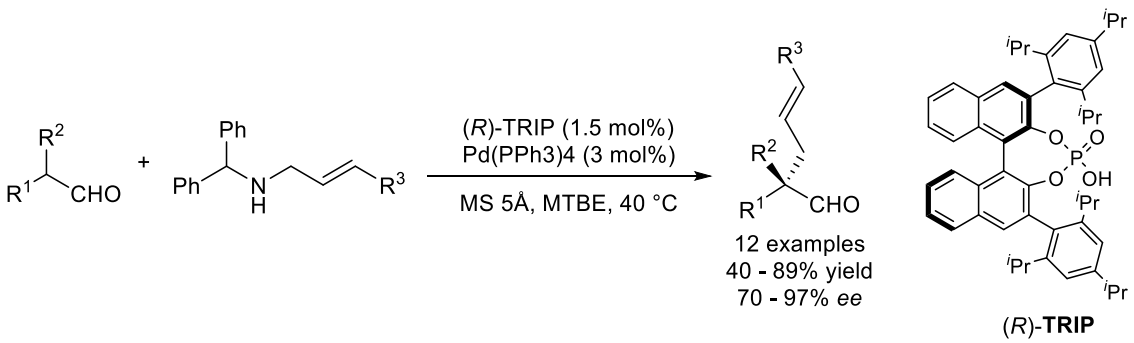
Enamines are attractive alternatives to the utilisation of ketone enolates as they are easily accessible from ketones and secondary amines, eliminating the need for harsh reactions conditions, including the use of strong bases such as LiHMDS or NaH.[201,205] Palladium catalysed asymmetric allylic alkylation of ketones via a chiral enamine intermediate was first reported in 1994.[206] This work successfully utilised chiral (*S*)-proline allyl ester as the chiral directing group, in the presence

of Pd and PPh_3, to obtain α-allylated carbonyls with high enantioselectivity (Scheme 74).



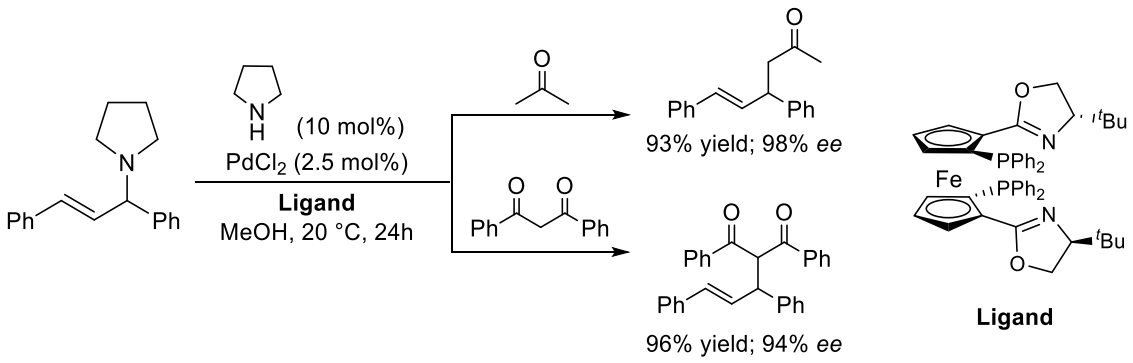
Scheme 74: The first Pd-catalysed asymmetric α-allylation of ketones with chiral allyl esters.[206]

Since then, however, the progress with enantioselective allylic alkylations of ketones and aldehydes via a chiral enamine intermediate has been limited. Significant progress has been made in understanding and utilising the dual catalysis approach of a transition metal catalyst with a secondary amine (usually pyrrolidine),[207–209] nevertheless, only a handful of groups report enantioselective α-allylation of carbonyl compounds. In 2007, List *et al.* reported asymmetric α-allylation of branched aldehydes utilising a 3-component catalytic system comprising a chiral phosphoric acid ((*R*)-TRIP), $Pd(PPh_3)_4$, and an secondary allyl amine (Scheme 75).[210] Further development of this method allowed for the use of allyl alcohols directly in combination with the secondary amine, benzhydrylamine.[211]



Scheme 75: Asymmetric allylation of branched aldehydes utilising a chiral phosphoric acid.[210]

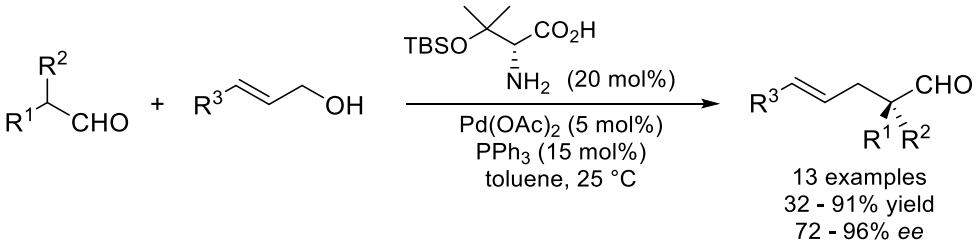
Reports of enantioselective allylation of ketones utilising the dual catalysis approach are even more scarce in comparison to the aldehydes. In 2011, Zhang *et al.* reported two examples of palladium catalysed enantioselective allylation of ketones (acetone and 1,3-diphenyl-1,3-propanedione) with an allyl amine in the presence of pyrrolidine as the co-catalyst, and a chiral ferrocene-based phosphino-oxazoline ligand, demonstrating high yields and high enantioselectivity (Scheme 76).[212] Further work by this group also showcased enantioselective allylation of cyclohexanone with allylic alkyl ethers,[203] and direct allylation of acetone with an allyl alcohol,[197] both of which utilised the same Pd-based catalytic system and the same chiral ligand. In all examples, excellent yields and high enantiomeric excess was obtained, albeit with a limited substrate scope.



Scheme 76: Enantioselective allylation of ketones utilising a chiral ferrocene-based phosphino-oxazoline ligand.[212]

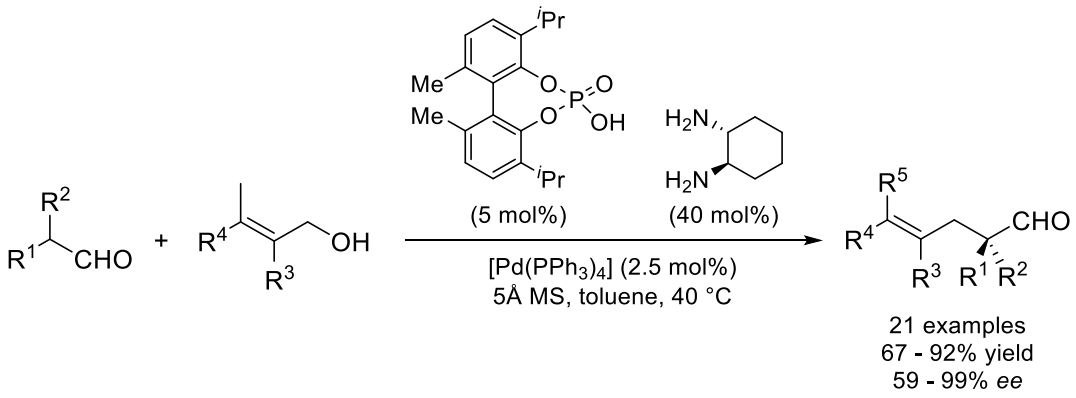
The examples thus far have focused on enantioselective synthesis of allylated aldehydes and ketones with the utilisation of a chiral ligand. Very few groups have focused on utilising a chiral amine co-catalyst to aid with the enantioselectivity.

In 2012, palladium catalysed highly enantioselective α-allylation of aldehydes was described in the presence of a 2- substituted chiral pyrrolidine using allyl acetates as the allylic substrate.[213] Another group described Pd-catalysed α-allylation of α-branched aldehydes with allyl alcohols directly in the presence of an amino acid, OTBS-3-hydroxy-D-valine, as the amine co-catalyst (Scheme 77).[214] This catalytic system demonstrated excellent enantioselectivity in addition to good functional group tolerance.



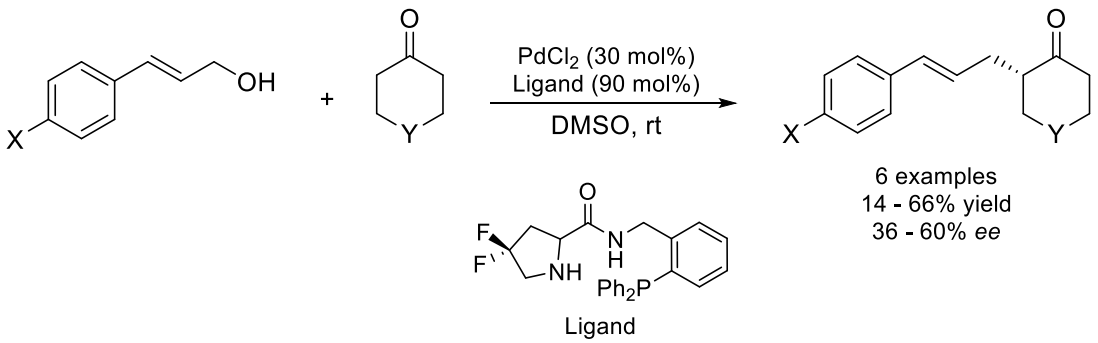
Scheme 77: Asymmetric allylic alkylation of branched aldehydes in the presence of a chiral amino acid as the co-catalyst.[214]

Most recently, in 2021, Bica-Schroder *et al.* reported a Pd-based catalytic system comprising of a simple phosphoric acid and a simple chiral amine, which allowed for the straightforward enantioselective synthesis of allylated branched aldehydes from allyl alcohols (Scheme 78).[215] This method demonstrated broad reaction scope, functional group tolerance and excellent yields in addition to high enantioselectivity.



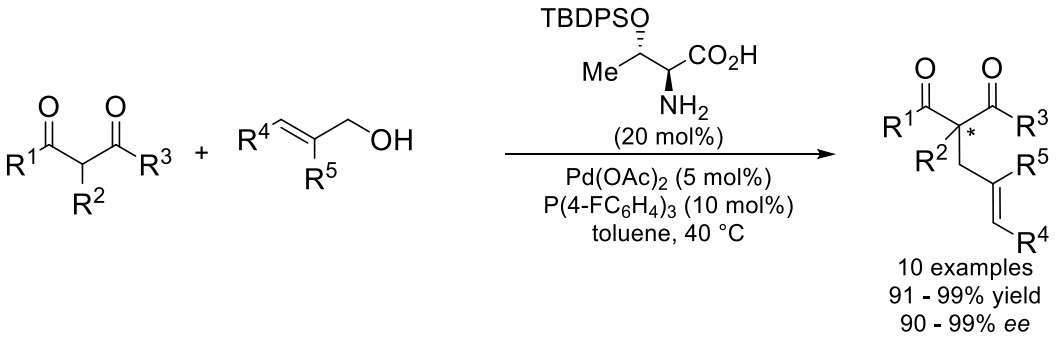
Scheme 78: Asymmetric allylation of branched aldehydes utilising a simple phosphoric acid and a simple secondary amine.[215]

The examples highlighted above are notable, however, apart from the original study in 1994, only a few reports of allylation of ketones in the presence of a chiral amine co-catalyst have been reported. Shibasaki *et al.* have described the asymmetric allylation of ketones with allyl alcohols utilising a phosphine ligand bearing a chiral proline moiety through an amide bond (Scheme 79).[216] They anticipated it would result in the tethering of the metal complex to the proline, and ultimately the enamine intermediate, which was hoped to encourage allylation in an enantioselective manner. Although successful, this approach only provided the corresponding allylated ketones in moderate yields and enantioselectivity, and with a limited substrate scope.



Scheme 79: Asymmetric allylation of ketones utilising a phosphine ligand bearing a chiral amine moiety.[216]

In 2017, Yoshida reported the asymmetric allylic alkylation of α-substituted β-keto esters with allyl alcohols, utilising a Pd-based catalytic system alongside an amino acid, demonstrating high yields and enantioselectivities, however the substrate scope was relatively limited (Scheme 80).[217] The substrate scope was further expanded in 2019 by a different group who used the same dual-catalytic system, however, they employed allyl amines instead of allyl alcohols in the reaction.[218] Both of these examples only utilised α-substituted β-keto esters, limiting further scope of this reaction. As such, no reports of chiral amine-assisted asymmetric synthesis of simple allylated ketones have been identified.



Scheme 80: Asymmetric allylation of β-ketoesters with allyl alcohols using a chiral amino acid as the co-catalyst.

All of the examples highlighted here utilise Pd-based catalytic systems; no examples of nickel catalysed asymmetric allylation of simple ketones have been reported so far. With this in mind, we aimed to explore the potential of our Ni/Zn system for the asymmetric allylation of cyclic ketones in the presence of a chiral amine, utilising the optimal reaction conditions obtained in Chapter 2.

3.2 Initial screen and optimisation

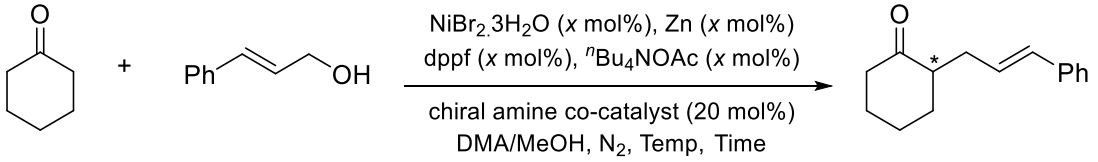
A variety of chiral pyrrolidines and prolines of were selected and trialled in the reaction (**Figure 7**). Cyclohexanone with cinnamyl alcohol were used as the exemplar substrates as this combination gave the highest yield when pyrrolidine was used (**Chapter 2**, compound **8**). Same reaction conditions as that in Chapter 2 were initially employed to increase the chance of success. Some experiments were carried out in 50% MeOH (1 mL) to aid with solubility of the prolines.

Initially, *L*-Proline (**P1**) was trialled in the reaction as it is readily available and has previously been successfully used in Pd-catalysed allylation reactions, albeit not with an enantioselective purpose.[209] Unfortunately no reaction took place with proline, suggesting the enamine intermediate was unable to form. Simple ester derivatives of proline were trialled next as, again, they are inexpensive and readily available. *D*-Proline methyl ester hydrochloride (**P2**) was successful at co-catalysing the allylation of cyclohexanone in 40% yield and with 16% *ee* (Table 5, entry 2). This was promising as a first trial and highlighted the potential for chiral amines to direct enantioselectivity within dual-catalysed mechanisms. Reducing the reaction temperature but increasing the reaction time improved the reaction yield and selectivity (Table 5, entry 3). It should be noted that the free base of **P2**

did not provide the product, suggesting the HCl may be involved in the mechanism. *L*-Proline tert-butyl ester hydrochloride (**P3**) was also trialled, initially giving a lower yield but significantly better *ee* values in comparison to **P2** (Table 5, entry 4).

After these initial results, a quick optimisation in the presence of **P3** was carried out to determine the best temperature, reaction time, and Ni-catalyst loading for optimal yields and enantioselectivity. **P3** was used in the optimisation as it produced better *ee* values in comparison **P2**, even at 50 °C. Lowering the temperature to 25 °C, and increasing the reaction time only yielded trace amounts of the desired product (Table 5, entry 5 & 6). Increasing the catalyst loading to 10 mol% at 25 °C finally resulted in 63% yield and 50% *ee* (Table 5, entry 7). Interestingly, further increase to 20 mol% of catalyst loading resulted in a decrease in both, the reaction yield and selectivity (Table 5, entry 8). At 20 mol%, the reaction is quite concentrated for the volume of solvent used (1ml DMA/1 mL MeOH) therefore not all of the reagents may be fully dissolved, and this may be interfering with the progress of the reaction. Based on this quick optimisation, the conditions in Table 5, entry 7 were used for the subsequent pyrrolidine and proline catalyst screen.

Table 5: Optimisation of reaction conditions.



Entry	Co-catalyst	Ni/Zn loading (mol%)	Temp (°C)	Time (h)	Isolated Yield (%)	ee (%)
1	P1	5	50	66	nr	-
2	**P2**	5	50	66	40	16
3	P2	5	**25**	**162**	55	32
4	**P3**	5	50	66	33	40
5	P3	5	**25**	66	trace	-
6	P3	5	25	**162**	trace	-
7	P3	**10**	25	162	**63**	**50**
8	P3	**20**	25	162	44	45

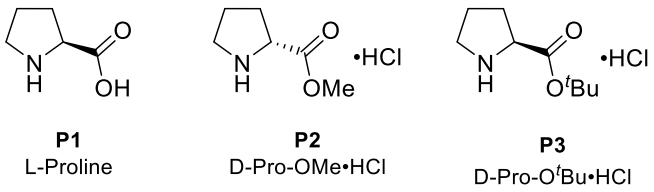


Figure 6: Initial proline derivatives tested.

3.3 Chiral amine catalyst screen

After the initial success of the asymmetric screen with the two proline esters, variety of proline and pyrrolidine derivatives were selected, and further asymmetric reactions were carried out. Table 6 summarises the chiral amines tested, and the outcomes of these reactions with the successful substrates highlighted in green. Out of the total 15 amines tested, only 7 produced quantifiable yields and *ee* values.

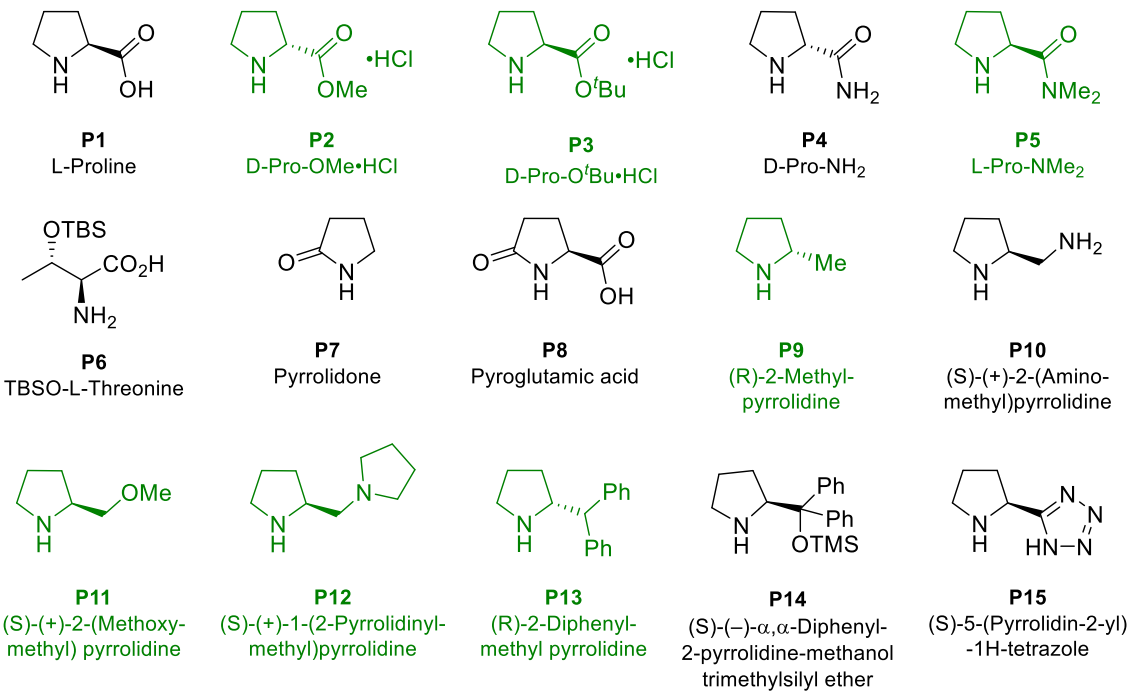
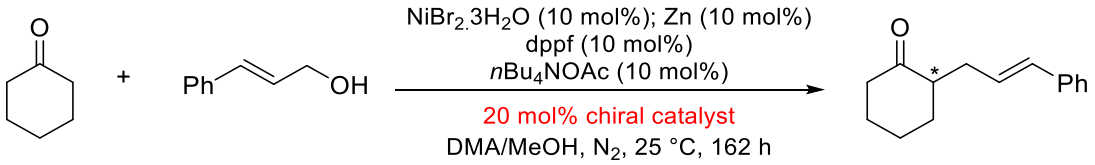


Figure 7: Chiral pyrrolidine substrates tested in the enantioselective reaction of cinnamyl alcohol and cyclohexanone.

Table 6: Results of the chiral pyrrolidine screen.



Co-catalyst	Isolated Yield (%)	*ee* (%)
P1	nr	-
P2	55	32
P3	63	**50**
P4	trace	-
P5	29	44
P6	nr	-
P7	nr	-
P8	nr	-
P9	85	8
P10	nr	-
P11	67	44
P12	10	48
P13	50	42
P14	nr	-
P15	nr	-

*nr = no reaction

All of the proline derivatives were successful, however, (*L*)-Prolinamide (**P4**) only yielded trace amounts of the desired product which could not be isolated. The only other amino acid tested within this reaction was TBSO-L-Threonine (**P6**) as this has previously been reported as a successful amine co-catalyst in the asymmetric allylation of β-keto esters.[217,218] Similarly to *L*-Proline, no reaction was observed with **P6**.

This chiral amine screen reveals it is a delicate balance of sterics which dictate the outcome of the reaction. Small functional groups in the 2-position increase the reaction yield, however, too small a group and the enantioselectivity is poor. For

example, the use of (*R*)-2-methylpyrrolidine (**P9**) resulted in a comparative yield as when using pyrrolidine (85%), however giving a product with only 8% *ee*. Conversely, (*R*)-2-diphenylmethylpyrrolidine (**P13**) gave a reduced yield of 50%, however, the enantiomeric excess was significantly higher at 42%. Too large a substituent and no reaction takes place, perhaps due to the inability of the intermediate enamine to get close enough to the metal centre for allyl transfer to occur (**P14** & **15**). Additionally, some of these catalysts work in the reaction as a free base, whereas others work best as the HCl salt. Further analysis of this observation may provide insight into the reaction mechanism.

Unprotected carboxylic acid and primary amine groups also appear to hinder the progress of the reaction (**P1**, **4**, **6**, **8**, and **10**). It could be possible that these substrates are acting as bi-dentate ligands, co-ordinating to the nickel centre, thus simultaneously preventing the enamine formation and deactivating the metal catalyst. Nickel is known to bind to amino acids through the carboxylate and amino groups (O and N donor atoms respectively), forming a stable, 5-membered chelate.[219] Therefore, it is not surprising that the reaction has not proceeded as desired with the unprotected amino acids **P1** and **P6**.

Despite the number of different amines trialled, the highest enantiomeric excess value achieved was 50% in the presence of **P3** (L-Pro-O^{t}Bu.HCl). **P12** yielded a comparative *ee* value of 48%, however, the yield was very modest at only 10%. Therefore, **P3** remained as the best chiral amine for selectivity in this study, with a relatively good yield.

3.4 Summary

In summary, this screen of chiral pyrrolidines has explored and highlighted the potential for the α-allylation of ketones to proceed in an enantioselective manner if a suitable chiral amine is used. The bulk of the substituents and any functional groups must be taken into account when selecting a suitable pyrrolidine derivative. Based on the results with *L*-Pro-O^{t}Bu.HCl (**P3**), various proline esters with larger ester groups could be explored to further probe the enantioselectivity of this reaction. Both the yield and *ee* value improved when the temperature of the reaction was lowered, therefore reducing the temperature even further could potentially improve on these *ee* values.

Additionally, only 2-subtituted chiral pyrrolidines were screened in this initial study, however, it would be interesting to see if and how the selectivity would be affected if substituents are introduced in the 3- position or even multiple positions. Another way to encourage enantioselectivity would be to employ chiral phosphine ligands which are often used in number of transition metal catalysed asymmetric transformations.

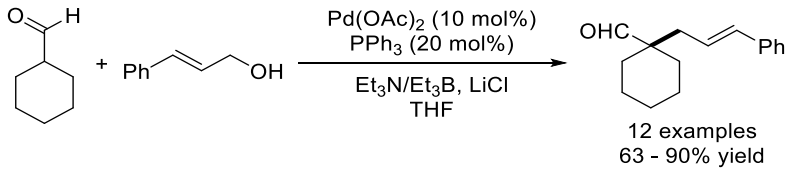
Finally, chiral phosphine ligands are often employed to encourage enantioselectivity within a reaction, and co-operative asymmetric allylation in the presence of phosphine covalently tethered to a proline has previously been demonstrated.[219] This is a route that could be explored with the Ni/Zn system, and further development of the phosphine or proline moieties could result in even better selectivity than previously reported.

Chapter 4: Application of the 'totally catalytic' Ni/Zn system for the direct allylation of aldehydes with allyl alcohols

4.1 Introduction

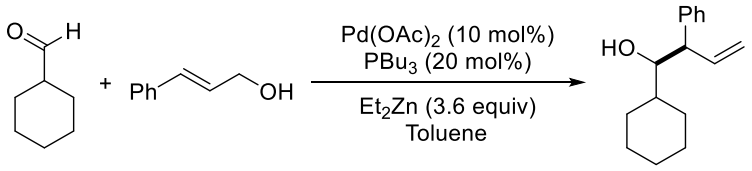
As previously discussed, allylic alkylation is a useful and versatile tool for the introduction of novel chiral tertiary and quaternary carbon centres while also allowing for further functionalisation of the newly incorporated C–C double bond. In the previous chapter, the allylic alkylation of ketones with allyl alcohols in the presence of the Ni/Zn catalytic system has been successfully demonstrated. This chapter will focus on utilising the Ni/Zn system for the α-allylation of aldehydes with a variety of allyl alcohols.

Pd-catalysed α-allylation of aldehydes with allyl alcohols was reported for the first time in 2001 (Scheme 81);[220] previously allylic acetates,[221] carbonates,[222] and amines[206] had been employed resulting in undesired by-products and poor atom economy. The success of this reaction relied on the utilisation of bases (Et_3N or Et_3B) to eliminate the formation of biallyl products, and on the addition of LiCl to inhibit nucleophilic allylation at the carbonyl.



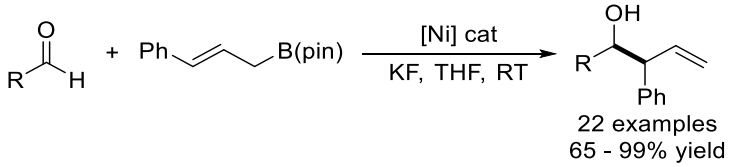
Scheme 81: Example of the first α-allylic alkylation of aldehydes with allyl alcohols.[220]

Many alkylation reactions of aldehydes have focused on nucleophilic alkylation, producing homoallylic alcohols. These are a result of nucleophilic addition of the allyl moiety at the carbonyl atom, rather than electrophilic alkylation at the carbon α to the carbonyl. In 2003, it was reported that substituting Et_3B with Et_2Zn in a catalytic system similar to the above inhibits electrophilic alkylation and the reaction proceeds via nucleophilic addition to selectively yield the homoallylic product (Scheme 82).[223]



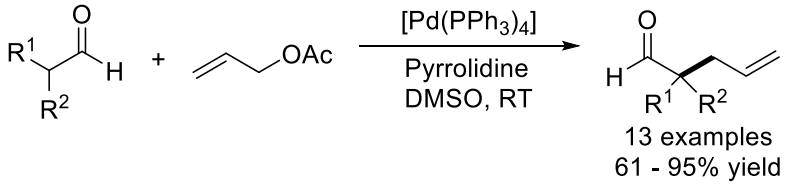
Scheme 82: Nucleophilic allylic alkylation forming the homoallylic product.[223]

Over the years, various different approaches have emerged for the synthesis of homoallyl alcohols. For example, one group reported the use of a Se-Pd(II) pincer complex catalyst in the presence of allyltributyltin;[224] another group described allylboration of aldehydes in the presence of $Ni(OAc)_2$ (Scheme 83);[225] while another demonstrated Ni-catalysed reductive allylation with allyl acetates,[226] just to name a few.



Scheme 83: Nickel catalysed formation of homoallyl alcohols utilising allyl boranes.[225]

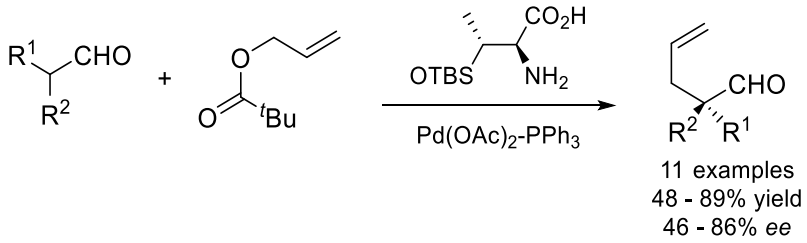
Although much of the focus has been on the synthesis of homoallylic alcohols, examples of palladium-based α-allylations of aldehydes have also been reported in the last couple of decades. Utilising Et_3B was proven to be one route of obtaining α-allylated aldehydes, however, since then researchers have focused on utilising amine-based organocatalysts in tandem with transition-metal catalysts as an alternate route to obtaining α-allylated aldehydes via the formation of enamine intermediates *in situ*. The first example of utilising this dual catalysis for the allylation of aldehydes was reported in 2006 in the presence of a $Pd(PPh_3)_4$ and pyrrolidine, however, the scope of this reaction was limited and only moderate yields were obtained (Scheme 84).[207]



Scheme 84: First example of dual catalysis of Pd and pyrrolidine to furnish α-allylated aldehydes.[207]

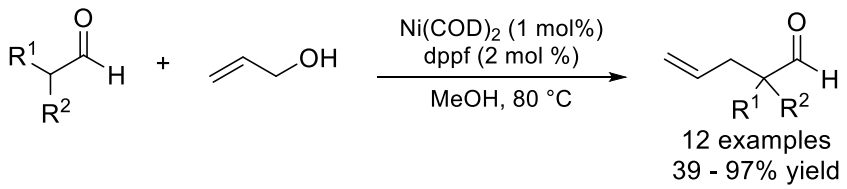
Nevertheless, further research has demonstrated that utilising the enamine catalysis pathway is an effective method for yielding α-allylated aldehydes, and allows for direct allylation with allyl alcohols. Various groups have reported the use of pyrrolidine,[207] proline,[227] benzhydrylamine,[228] and amino acids[229] as the amine source, giving moderate to high yields, and demonstrating relatively wide substrate scope overall. Additionally, the use of chiral amines, such as amino acids, has allowed for enantioselective synthesis of α-branched aldehydes (Scheme 85).[213,229] Another approach to obtain allylated aldehydes has been to utilise a

Brønsted acid (benzoic acid) as a cocatalyst with Pd, however, this method is less widely used in comparison to the enamine approach.[230]



Scheme 85: Enantioselective synthesis of α-allylated aldehydes utilising an amino acid as the organic co-catalyst.[229]

The progress with Pd-catalysed α-allylation of aldehydes has been significant, however, as highlighted here, many of the approaches still require various additives for successful reactions and optimal yields. To date only one report of nickel-based α-allylation of aldehydes with allyl alcohols had been published. This reaction was performed under relatively mild conditions in the presence of $Ni(cod)_2$ and dppf in methanol and at 80 °C (Scheme 86). No further additives were required, however, non-branched linear aldehydes were prone to aldol condensation and overalkylation.[231]



Scheme 86: First Ni-catalysed α-allylation of aldehydes with allyl alcohols.[231]

The limited reports of nickel-based catalysts for these types of reactions may suggest lack of reactivity within these systems, and the Ni-catalysed amine and base free conditions suggest a different mechanistic pathway to the reactions that have utilised Pd-based catalysts. Here, the previously described totally catalytic nickel system has been employed for the direct α-allylation of branched aldehydes with allyl alcohols, highlighting its wider applicability.

4.2 Results and discussion

4.2.1 Optimisation of reaction conditions

To test whether an aldehyde allylation would be successful with our Ni/Zn catalytic system, a reaction between allyl alcohol and 2-phenylpropanal was initially carried out under similar reaction conditions to those reported in literature as above (MeOH, 80°C, Scheme 86).[231] 2-Phenylpropanal was chosen as it cannot undergo diallylation, and the product cannon be enolised thus preserving the integrity of the chiral centre. The reaction was screened with and without pyrrolidine, as amine-based co-catalysts are fairly common in allylation reactions,[201] and pyrrolidine has previously been successfully used as a co-catalyst in the allylation of ketones (Chapter 2). Surprisingly, the initial screen with pyrrolidine as the co-catalyst did not yield the desired product (Table 7, entry 1). The removal of pyrrolidine from the reaction did produce the product, however, only in a 5% yield (Table 7, entry 2). Nevertheless, this did highlight the potential for using the Ni/Zn catalytic system for the α-allylation of aldehydes, therefore further reaction optimisations were carried out.

The first simple attempt to improve the yield was to use DMA as the solvent in conjunction, and instead of MeOH (Table 7, entries 3 – 5). This revealed that using DMA as a solvent by itself gave superior yield to MeOH (5 vs 61%, Table 7, entries 2 vs 5). Interestingly, utilising pyrrolidine as a co-catalyst provided no benefits and actually proved slightly detrimental to the yield (31% with vs 35% without, Table 7, entries 3 vs 4). This would suggest an alternative reaction mechanism for the allylation of aldehydes to the one described for the allylation of ketones (Chapter 2) as the enamine intermediate is not essential or necessary for the reaction to proceed (whereas it is crucial for the allylation of ketones). It may be that an enolisation of the α-carbon is taking place, resulting in a reactive enolate intermediate instead.

Having identified that the reaction is likely to proceed via a mechanism different to that observed in the allylation of ketones, a more extensive ligand and solvent screen was carried out to determine the optimal conditions. Interestingly, only dppb and BINAP ligands (in addition to dppf) resulted in a successful reaction and quantifiable yields. All three ligands are di-phosphines with a relatively large bite angle, resulting in bidentate co-ordination and possibly better stabilisation of the Ni^0 state, thus leading to the successful outcomes of these reactions. The reaction yield significantly decreased upon the addition of water (32%, Table 7, entry 6) therefore only anhydrous solvents were used in the solvent screen.

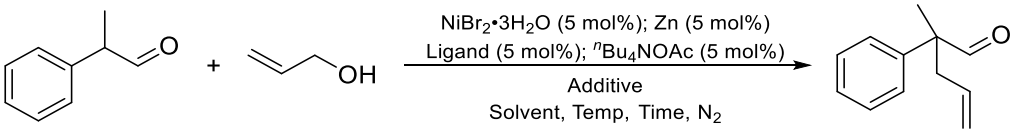
Polar aprotic solvents of various polarities were used, with the yield increasing as the polarity of the solvent increases. Although enol tautomer is thought to be less polar than its ketone form,[232] in this case a polar aprotic solvent may stabilise the enol form through hydrogen bonding of the enol -OH. Since the solvents are

aprotic, this stabilisation is not possible in the keto form. Additionally, the enol form will also be stabilised by conjugation of the double bond with the phenyl group.

The solvent screen revealed DMSO to be a slightly better solvent than DMA (69 vs 61%, Table 7, entries 18 vs 5); and the reaction time of 66 hours at 80 °C also remained optimal. The removal of $^{n}Bu_4NOAc$ from the reaction resulted in a slight increase in the yield (Table 7, entry 24), therefore it was omitted from further optimisation and substrate screening reactions. Nickel hydroxide was also tested as a different source of Ni in the reaction giving a reaction yield of 40% (Table 7, entries 25). $Ni(OH)_2$ was also used in combination with nickel bromide, however this offered no significant benefits to the reaction yield (Table 7, entry 26). It has previously been shown that both Ni and Zn are essential for these reactions to proceed.[183]

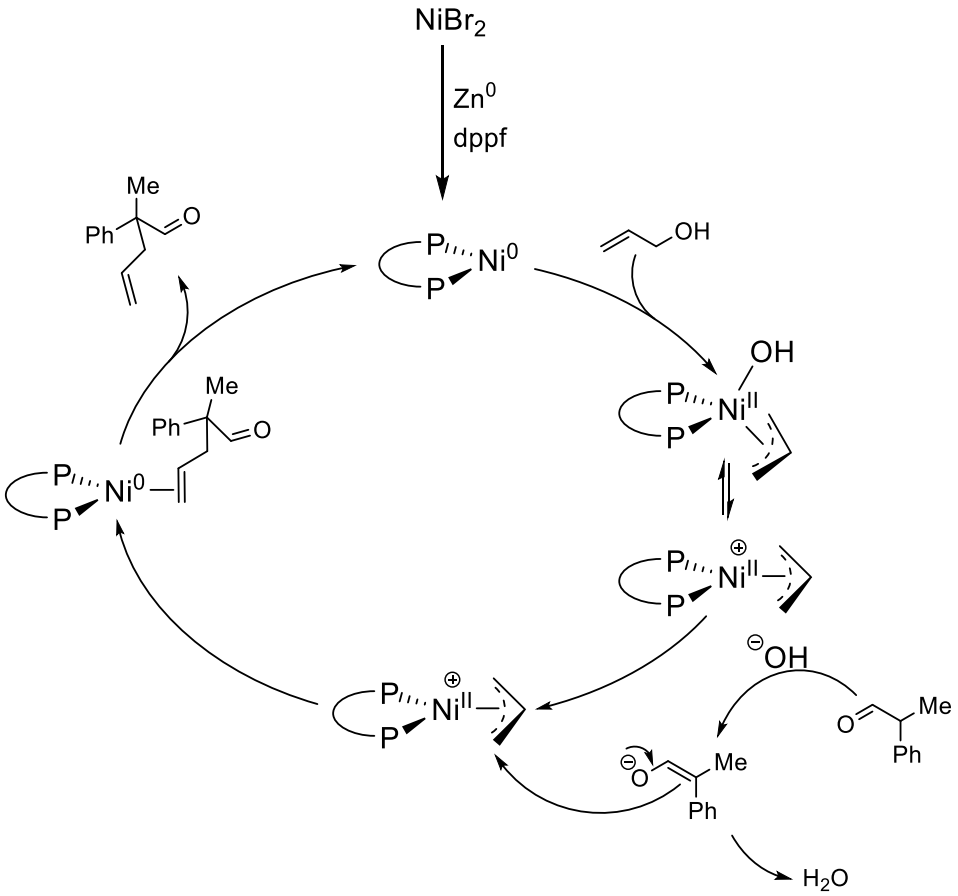
Finally, triethylamine was used at 20 mol% as an additive which resulted in a 11% increase in the product's yield (75 to 86%, Table 7, entries 24 & 27). The final optimised catalytic system consisted of 5 mol% of $NiBr_2.3H_2O$, Zn and dppf; and 20 mol% of NEt_3 in DMSO at 80 °C for 66 hours.

Table 7: Optimisation of reaction conditions.



Entry	Ligand	Solvent	Temp (°C)	Time (h)	Isolated Yield (%)
1	dppf	MeOH	80	66	0[a]
2	dppf	MeOH	80	66	5
3	dppf	MeOH/DMA	80	66	31[a]
4	dppf	MeOH/DMA	80	66	35
5	dppf	DMA	80	66	61
6	dppf	DMA	80	66	32[b]
7	**dppb**	DMA	80	66	51
8	**dppe**	DMA	80	66	6
9	**dppp**	DMA	80	66	0
10	**rac-BINAP**	DMA	80	66	34
11	**SPhos**	DMA	80	66	0
12	**XantPhos**	DMA	80	66	0
13	**-**	DMA	80	66	0
14	dppf	**DMF**	80	66	47
15	dppf	**THF**	80	66	9
16	dppf	**MeCN**	80	66	21
17	dppf	**NMP**	80	66	40
18	dppf	**DMSO**	80	66	69
19	dppf	**DMSO/DMA**	80	66	57
20	dppf	DMSO	80	**18**	41
21	dppf	DMSO	80	**42**	60
22	dppf	DMSO	80	**1 week**	34
23	dppf	DMSO	**50**	66	30
24	dppf	DMSO	80	66	75[c]
25	dppf	DMSO	80	66	40[c,d,e]
26	dppf	DMSO	80	66	73[c,d]
27	dppf	DMSO	80	66	86[c,f]
28	dppf	DMSO	80	66	0[g]
29	dppf	DMSO	80	66	0[h]

Reaction conditions: Allyl alcohol (1.0 mmol), 2-phenylpropanal (1.0 mmol), $NiBr_2 \cdot 3H_2O$ (0.05 mmol), dppf (0.05mmol), $^nBu_4NOAc$ (0.05 mmol), zinc (0.05 mmol), sealed vial; [a] With pyrrolidine (0.2 mmol); [b] With 1.0 mmol H_2O [c] Without $^nBu_4NOAc$; [d] With $Ni(OH)_2$; [e] without $NiBr_2 \cdot 3H_2O$; [f] With NEt_3 (0.2 mmol); [g] Without $NiBr_2 \cdot 3H_2O$, with NEt_3; [h] Without zinc, with NEt_3.

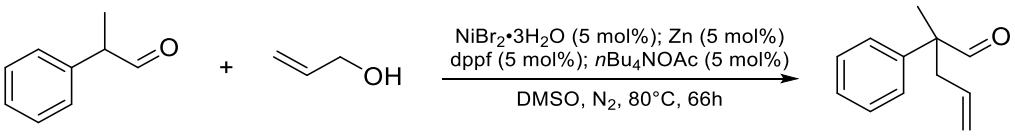


Scheme 87: Proposed reaction mechanism based on previous work by Sauthier *et al.*[233]

A stoichiometry study with systematic alterations to the ratio of aldehyde to allyl alcohol was carried out alongside the other optimisation tests, therefore only partially optimised reaction conditions were employed (Table 8). Nevertheless, the stoichiometry study revealed a pattern of improvement in the yield with increasing ratio of aldehyde to allyl alcohol. Large excess of allyl alcohol had a large detrimental impact on the reaction yield, going from 67% at 1:1 to 26% yield at 4:1 (44% decrease in yield). Although increasing the ratio of aldehyde did improve the reaction yield, the percentage difference is not as significant as with the high ratio of allyl alcohol. From 1:1 and up to 3:1 of aldehyde to allyl alcohol, the yield

remains mostly unaffected, and at 4:1, the yield increased by only 13% (up from 67% to 80%, Table 8, entries 4 vs 7). Additionally, utilising an excess of aldehyde was detrimental to the purification process, as the excess aldehyde could not be separated easily, which resulted in lower isolated yields. As such, a ratio of 1:1 was utilised for the substrate scope, improving separation during purification and therefore obtaining higher yields of products.

Table 8: Stoichiometry Study



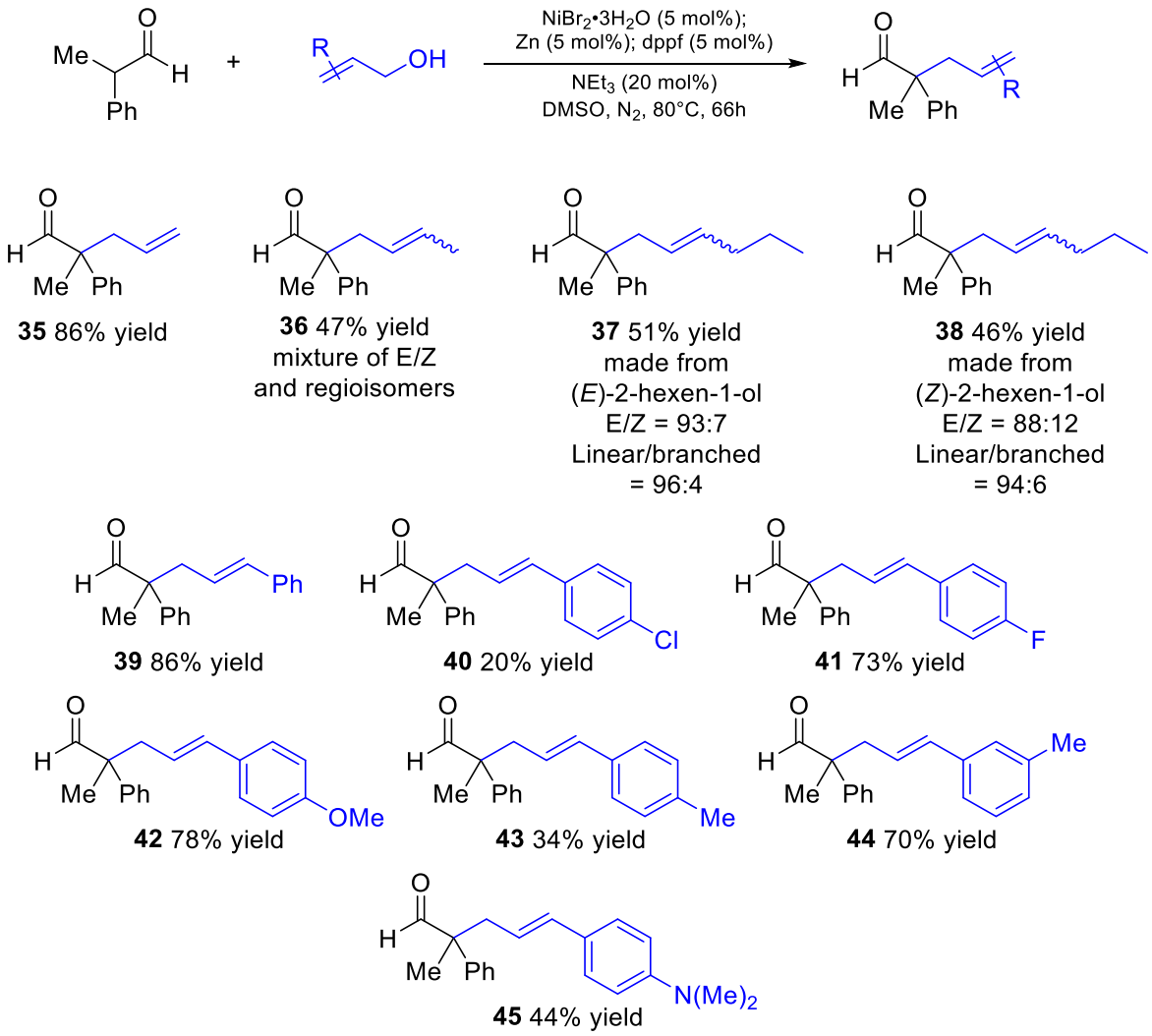
Entry	Allyl Alcohol (mmol)	Aldehyde (mmol)	Isolated Yield (%)
1	4	1	26
2	3	1	34
3	2	1	55
4	1	1	67
5	1	2	68
6	1	3	70
7	1	4	80

4.2.2 Allyl alcohol substrate scope

Once the optimal reaction conditions had been identified, the next step was to evaluate the scope and breadth of this reaction. A number of different allyl alcohol substrates were initially tested with 2-phenylpropanal, producing a selection of 11 different α-allylated branched aldehydes (Scheme 88). The chain length of the allyl alcohol does appear to have an impact on the reaction yield, with the yield decreasing as the chain length increases from 3 to 4 carbons. However, any further

increase in the chain length appears to have a minimal impact on the yield (4, 5 and 6). The difference between (*E*)- and (*Z*)-2-hexen-1-ol is minimal, unlike with the ketone allylation where (*E*)-2-hexen-1-ol provided a much higher yield, similar to that of allyl alcohol. This would suggest that, in this case, the (*E*)-2-hexen-1-ol used does not have a role in stabilising any intermediate transition states. Contrary to the allylation of ketones, the reactions with branched allyl alcohols were unsuccessful, highlighting the differences in mechanisms between the two substrate types, and suggesting steric hindrance is a significant factor within the aldehyde reaction mechanism.

Utilising various cinnamyl alcohol substrates within the reaction proved successful, however, there does not appear to be any obvious trend as to whether and electron donating or electron withdrawing group on the phenyl ring of the cinnamyl alcohol has an effect on the reaction yield. Interestingly, the reaction did proceed with 4-chlorocinnamyl alcohol, which is in contrast to what was observed in the allylation of ketones in which the chloro- substituent was hypothesised to 'poison' the catalyst, thus preventing the desired reaction from proceeding. In the allylation of aldehydes, the reaction mechanism differs significantly, as it does not go via an enamine intermediate, therefore the desired reaction may be able to potentially outcompete any side reactions to some extent. The reaction yield is still very low (20%), which would suggest the chloro- substituent is still a limiting factor in this case as the reaction with 4-fluorocinnamyl alcohol gives a significantly higher yield (**41**, 73%).



Scheme 88: Scope of Ni-catalysed allylation of 2-phenylpropanal with various allyl alcohols; Reaction conditions: allyl alcohol (1.0 mmol), 2-phenylpropanal (1.0 mmol), $NiBr_2 \cdot 3H_2O$ (0.05 mmol), dppf (0.05mmol), zinc (0.05 mmol), NEt_3 (0.20 mmol), DMSO, 80°C, 66 h, sealed vial.

Unsuccessful allyl alcohol substrates

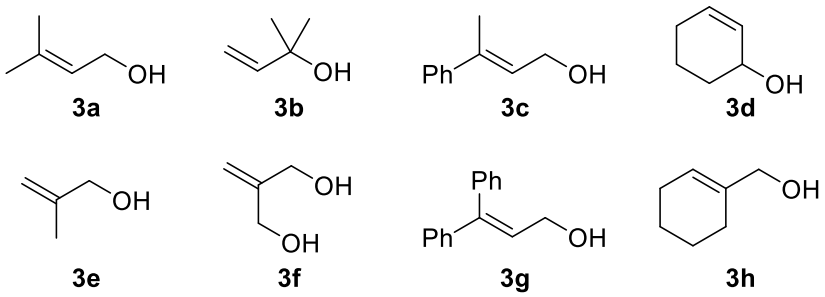


Figure 8: Unsuccessful allyl alcohol substrates

4.2.3 Aldehyde substrate scope

The scope of the reaction with various allyl alcohols was limited to linear allyl alcohols, therefore we were keen to explore the scope with different aldehyde substrates. Allyl alcohol was used as the exemplar alcohol as to minimise steric hindrance and therefore increase the chance of a successful outcome. Disappointingly, the reaction with a variety of aldehydes was even less successful. Initially, aliphatic aldehydes of various chain lengths and different extent of branching were trialled, however all of these were unsuccessful at yielding the desired products (Figure 9). Some of these aldehydes (**3i, 3j, 3m** and **3n**) underwent self-aldol reactions instead, as observed by NMR, highlighting some of the difficulties with coupling of aldehydes.

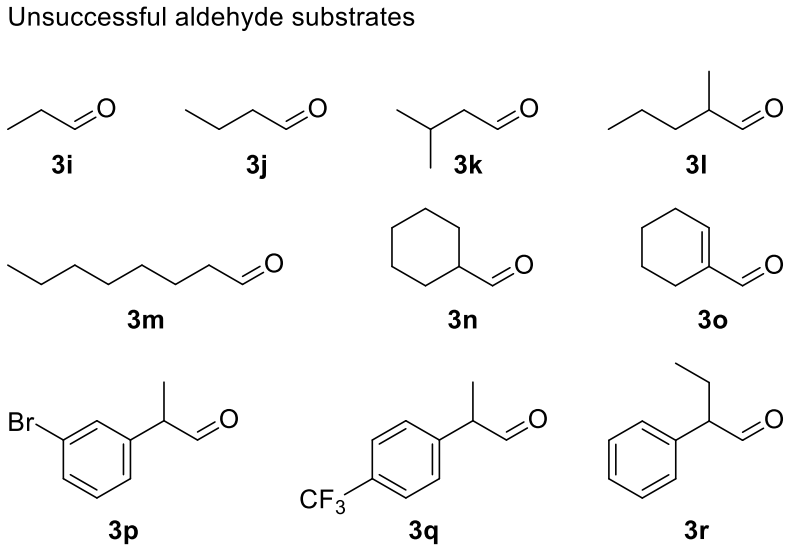
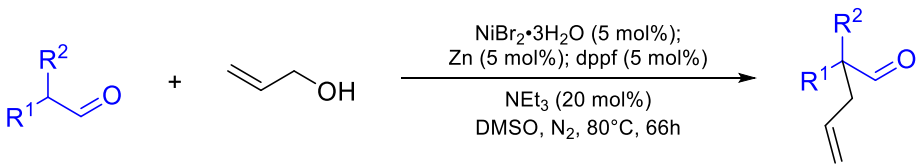


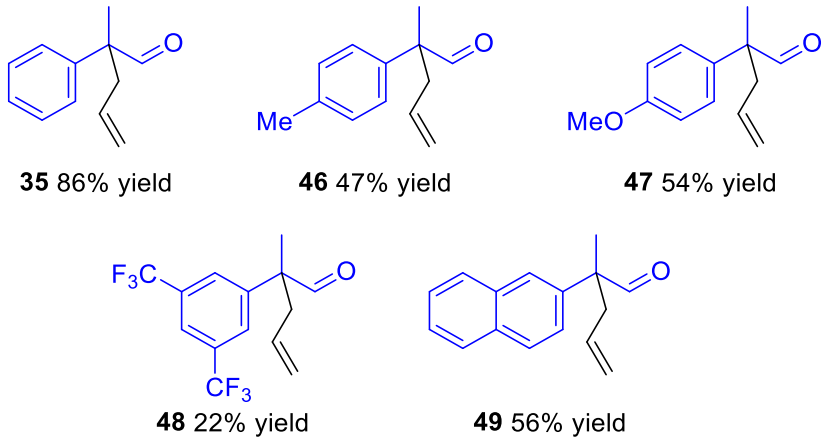
Figure 9: Unsuccessful aldehydes substrates.

Following this screen, a variety of α-branched aryl acetalaldehydes were synthesised to determine the impact of steric and electronics within the phenylacetaldehyde series (Scheme 89). Nevertheless, out of these 7 α-branched

aromatic aldehydes synthesised, only 4 produced the desired allylated product; furthermore, only compound **49** was able to be isolated as a pure product. Compounds **46**, **47, and 48** can be observed by NMR as 67%, 81%, and 80% pure respectively, however, multiple purification attempts did not yield the pure products. One strategy to overcome the difficulties with separation would have been to reduce the aldehyde prior to purification, however, time constraints and limited starting material availability meant that this option could not be explored further.

Based on the handful of α-branched aromatic aldehydes that have yielded the desired products, there does not appear to be an obvious inductive effect from the substituted groups on the phenyl ring on the reaction yield. Compounds with electron withdrawing groups in the meta position (**48**) suffer significant reduction in reaction yield. This however does not explain why 2-(4-trifluoromethyl)phenylpropanal (**3q**) did not react in the reaction, as based on this hypothesis, one would expect yields similar to, or better than compound **46**. Given the limited scope and unpredictability of this reaction, these hypotheses are merely speculative. The reaction was unsuccessful with a larger alkyl group on the α-carbon (**3r**), once again highlighting that steric factors are of importance when considering this reaction.





35 86% yield **46** 47% yield **47** 54% yield

48 22% yield **49** 56% yield

Scheme 89: Scope of Ni-catalysed allylation of aldehydes with allyl alcohol; Reaction conditions: allyl alcohol (1.0 mmol), aldehyde (1.0 mmol), $NiBr_2 \cdot 3H_2O$ (0.05 mmol), dppf (0.05mmol), zinc (0.05 mmol), NEt_3 (0.20 mmol), DMSO, 80°C, 66 h, sealed vial.

4.3 Summary

In this chapter, the 'totally catalytic' Ni/Zn system has been applied to the direct allylation of α-branched aldehydes with allyl alcohols, albeit with limited success, yielding a small variety of products in moderate yields (15 examples, 20 – 86% yield). Although the initial optimisation of **35** appeared promising, achieving 86% yield when fully optimised, the scope and breath of this reaction, especially with different aldehydes, was limited. Once again, the tolerance for a range of functional groups has been demonstrated within the allyl alcohol substrate screen, including chloro-, fluoro-, methoxy-, and amino- groups. The reaction showed no scope for branched allyl alcohols, suggesting steric effect is a critical factor within this mechanism.

Unlike in the allylation of ketones in Chapter 2, this reaction is thought to proceed via an enol-based mechanism without an organic co-catalyst. While the removal of pyrrolidine from the reaction is desirable from an atom economy perspective, this alternate mechanistic pathway is not currently understood enough to capitalise on the full scope of the reaction.

Sauthier *et al* have previously demonstrated α-allylation of branched aldehydes, and tandem self-aldol/allylation of aliphatic aldehydes with allyl alcohols in the presence of $Ni(cod)_2$ and dppf.[231] They demonstrated a relatively wide scope for a variety of branched and linear aldehydes, however, their scope for different allyl alcohols was limited. Using our Ni/Zn system, the opposite was true with a wider allyl alcohol scope. Their method required the use of a glovebox due to the utilisation of $Ni(cod)_2$, allowing for completely anhydrous reaction conditions, whilst our catalytic system avoids the use of a glove box meaning fully anhydrous

environment cannot be guaranteed. These contradicting results highlight the potential moisture sensitivity of this reaction mechanism. Molecular sieves could be trialled within the reaction mixture to test this theory, and to explore whether the aldehyde scope would be more successful in anhydrous conditions that do not require the use of a glove box. Alternatively, small amounts of water could be added to the reaction to test its tolerance to moisture.

In summary, the applicability of the 'totally catalytic' Ni/Zn system for the direct allylation of α-branched aldehydes with allyl alcohols has been demonstrated, however, the scope and breadth of this reaction remains limited and further studies could be carried out to try and improve this.

Chapter 5: Discussion

Transition metal catalysis is a useful and widely used method in the field of chemical synthesis.[1] Many different transition metals have been employed in the synthesis of a wide variety of chemical compounds, as highlighted by the number of different chemical syntheses that have been awarded the Nobel prize since the early 2000's (3 separate Nobel prizes shared amongst 9 chemists).[1] Palladium-based catalysts have largely dominated the field of transition metal catalysis since the discovery of its ability to catalyse a large variety of novel cross-coupling reactions in organic synthesis.[19] In addition to its vast applicability, palladium-based catalysts are generally tolerant of many different functional groups, and are relatively stable to air and moisture, making these catalysts attractive to work with as they do not require extensive measures to ensure water and oxygen free environments.[20]

Although the use of palladium catalysts in organic synthesis is widely studied and understood, it is a rare, precious metal, with a high material cost (£61/g).[234] Nickel lies in the same group in the periodic table as palladium, often offering similar reactivities in cross-coupling reactions. As a result, the research into utilising nickel in organic catalysis as an inexpensive (£0.015/g)[235] and more abundant alternative to palladium has gained significant traction in the last decade.[23] Additionally, nickel tends to be more reactive than palladium, offering novel C–C bond forming pathways, or allowing for the use of less reactive substrates.[24]

As detailed in Chapter 1, many different nickel catalysts have been developed over the last couple of decades. Usually, one of three nickel sources is employed in nickel-based catalysis: i) $Ni(cod)_2$, ii) pre-synthesised air-stable nickel pre-

catalysts, or iii) nickel salts. All of these approaches have their advantages; however, each of these catalysts also have their drawbacks, which can outweigh the benefits in the adoption of a single method for wide scale use. $Ni(cod)_2$, although used as the most common source of Ni^0 in a large proportion of nickel-catalysed reactions,[23] requires an oxygen free environment when handled, hindering the scale up of reactions utilising $Ni(cod)_2$ or increasing the cost of manufacturing. Air-stable nickel pre-catalysts often require intricate ligands made via a multi-step process, reducing the ease with which these reactions can be carried out. This increases the overall cost of these reactions, and also results in an overall poor atom economy of such reactions. Nickel salts often require super-stoichiometric amounts of metal reducing agents to reduce Ni^{II} to the active Ni^0 species *in situ*, again resulting in poor atom economy as well as large amounts of metal waste.

Recently, the Sweeney group developed the first nickel-based precatalytic system which utilises equimolar amounts of zinc as the reducing agent relative to the nickel salt in a two-step process. This was originally applied to two separate reactions: allylation of β-keto carbonyls[183] and amination of allyl alcohols.[185] This equimolar Ni/Zn catalytic system significantly reduced the amount of metal waste produced in comparison to previously studies. Additionally, it also allowed for the direct use of allyl alcohols and amines where water is the only by-product, making this a relatively environmentally friendly catalytic system. Furthermore, the inexpensive $NiBr_2$ salt can be handled on the benchtop, removing the need for a glovebox, and making reactions utilising this catalytic system easier and more accessible.

The aim of this research project was to further probe the applicability of this Ni/Zn catalytic system to other reactions. Chapter 2 describes the successful application of the Ni/Zn system to the direct allylation of cyclic ketones with various allyl alcohols, producing allylated products in respectable yields (34 examples, 11 – 86% yield), and displaying tolerance for a range of functional groups (-F, -OMe, -CO_2Me). This reaction required the use of pyrrolidine as an organic co-catalyst, meaning the reaction proceeded via an enamine-based mechanism, expanding the scope of reactive nucleophiles from the previous two studies published by the Sweeney group.

Chapter 3 explored the asymmetric allylation of ketones in the presence of chiral pyrrolidines. Various chiral pyrrolidines and prolines were trialled, with only a small number of these yielding the desired product. The successful reactions did proceed in enantioselective manner, however, the highest enantiomeric excess achieved was 50%, even at re-optimised conditions to ensure the best selectivity possible. Nevertheless, this highlights the potential of these reactions to proceed in an enantioselective manner in the presence of our Ni/Zn catalyst and a chiral pyrrolidine. To expand on this work, a synergistic asymmetric allylation with a chiral phosphine ligand alongside a chiral pyrrolidine could be explored to further improve the enantiomeric excess.

In Chapter 4, the Ni/Zn catalytic system was applied to the α-allylic alkylation of α-branched aldehydes, this time without the need for the organic co-catalyst, resulting in a different mechanistic pathway to the allylation of cyclic ketones. The substrate scope with aldehydes was much smaller in comparison to the cyclic ketones (15 examples, 22 – 86% yield), highlighting a potential lack of

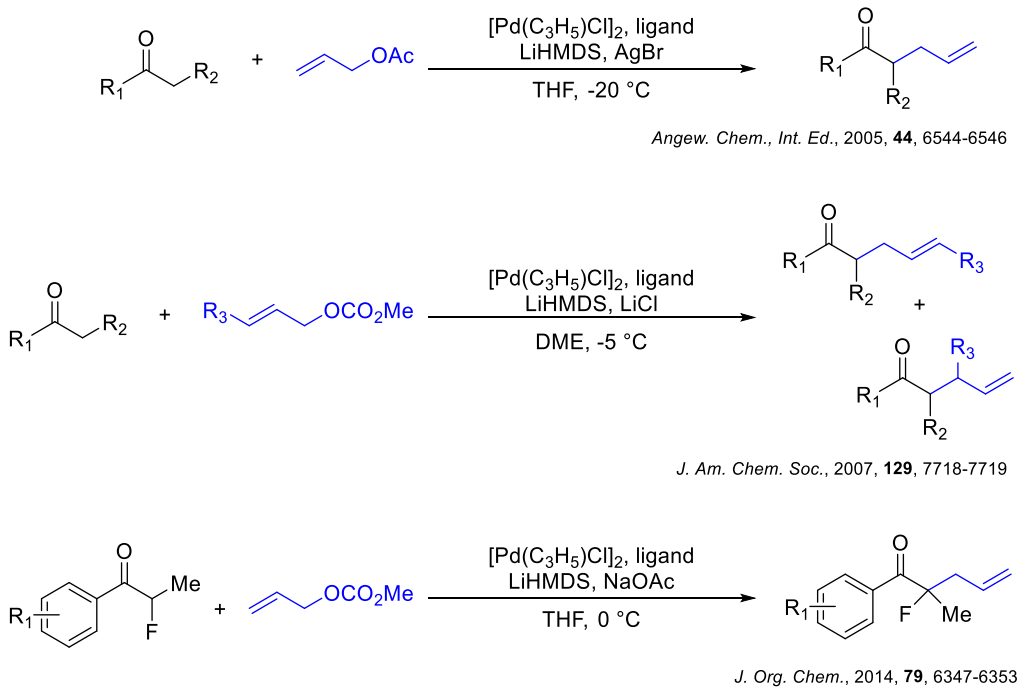
understanding of this catalytic system, and the different mechanistic routes it can undergo. To make this Ni/Zn catalytic system truly applicable across a wide range of reactions, further mechanistic studies would be needed to help with its application in future C–C bond forming reactions.

The applicability of the Ni/Zn system has had mixed success amongst the two different allylation reactions for aldehydes and ketones. Nevertheless, this highlights the potential for the Ni/Zn system to catalyse the allylation of simple carbonyl compounds without the need for a glove box. Additionally, the direct use of allyl alcohols in both reactions eliminates the need for pre-functionalisation of the allyl alcohol, a feature often required when Pd-based catalysts are used. This not only improves the atom economy and ease of carrying out allylation reactions, thus reducing the overall reaction cost; but water is the only stoichiometric by-product, therefore, allylation reactions directly with allyl alcohols provide a relatively environmentally friendly synthesis.

5.1 Future work

There are several possible next steps following on from the work described within this thesis. Perhaps the most logical direction would involve continuing on the work in Chapter 2, with the focus shifting to the allylation of acyclic ketones with allyl alcohol utilising the Ni/Zn system. Only a few examples in literature report direct allylation of acyclic ketones, and most of these examples employ pre-functionalised allyl alcohols, either as allyl acetates or allyl carbonates, and utilise a palladium based catalytic system containing ferrocene ligands (Scheme 90).[236–238] The referenced examples use LiHMDS as a base in excess, without the use of pyrrolidine-based reagents as co-catalysts. The use of these methods suggests an

alternative mechanism through an enolate intermediate, rather than the enamine-based mechanism proposed here, for a successful allylation of acyclic ketones to occur. Therefore, a similar approach utilising a strong base could be explored using the Ni/Zn system. If successful, this approach may also be trialled with the α-allylation of aldehyde substrates that have proven unsuccessful with this catalytic system (see Chapter 4), although this approach may lead to self-aldol reactions instead.

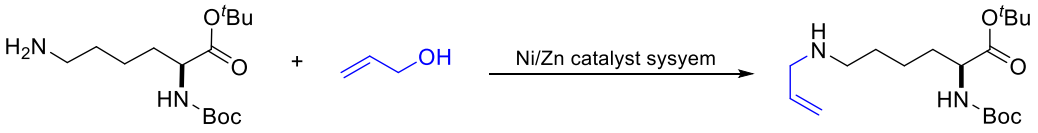


Scheme 90: Literature examples of allylation of acyclic ketones.

Another direction this project could take would be to demonstrate the applicability of the Ni/Zn catalytic system in further cross-coupling reactions that have previously employed $Ni(cod)_2$ or Pd-based catalysts. Some reactions that could be trialled include the Suzuki-Miyaura coupling or the Heck reaction, both of which are routinely utilised in industry.[16] The utilisation of the Ni/Zn system could

offer a scalable, sustainable, and more environmentally friendly alternative to Pd in these reactions.

Finally, in addition to proving the Ni/Zn catalytic system's applicability to well-studied reactions, it would be interesting to explore its ability to catalyse novel C–C and C–X bond forming reactions. The Sweeney group has demonstrated the N-allylation of secondary and tertiary amines utilising the Ni/Zn system.[185] It would therefore be interesting to explore whether allylic amination could be achieved with N-containing amino acid side chains, such as lysine (Scheme 91). There are a handful of examples of palladium catalysed N^{α}-allylation of amino acids in literature, however, there are currently no examples that functionalise the side chain. Introduction of an allyl group onto a side chain for an amino acid could allow for the incorporation of an allylated amino acid into a peptide chain. Furthermore, the placement of two allyl groups onto a peptide chain could offer the opportunity for a ring closing metathesis reaction (RCM) to produce a 'stapled peptide', a motif which is of increasing interest in drug design and therapeutics.[239–241]



Scheme 91: A possible example of N-allylation of amino acid side chain.

In conclusion, the challenge for future work based on this thesis lies in further testing the robustness of this practical and scalable 'totally catalytic' Ni/Zn system in a variety of different C–C bond forming reactions. This one-pot nickel-based catalytic system utilises an inexpensive, air-stable Ni^0 precursor; reduces the metal waste produced; improves the ease of carrying out nickel-based reactions; and yields results similar to, or better than, palladium-based systems. Therefore, it's conceivable that this system could rival palladium catalysts as a more sustainable and cheaper alternative on an industrial scale.

Chapter 6: Experimental

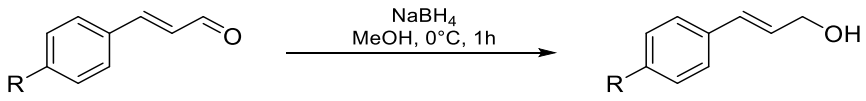
6.1 General Methods

Unless otherwise stated, all reactions were carried out under an inert atmosphere of nitrogen, in glassware which had been oven dried. Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific, Fluorochem, and Tokyo Chemical Industry UK, and were not purified further unless stated. Solvents were purchased anhydrous and stored over molecular sieves. Thin layer chromatography was performed on aluminium sheets coated with Merck silica gel 60 F254 with visualisation using potassium permanganate solution, and/or scrutinised under 254 nm UV light. Column chromatography was performed using Silica 60 (40-63 microns) supplied by Fisher or Sigma unless otherwise stated.

Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) with the appropriate deuterated solvent. Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra are relative to the deuterated solvent peak and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (*J*) are quoted in Hz and are averaged between coupling partners and rounded to the nearest 0.1 Hz. Mass spectrometry was performed using a Shimadzu LCMS-IT-TOF instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Agilent Technologies Cary 630 FTIR instrument with wavenumbers being reported in cm^{-1}. Chiral HPLC analysis was performed using Shimadzu NexeraX2 UHPLC instrument equipped with a UV detector with a CHIRALPAK OD-H column.

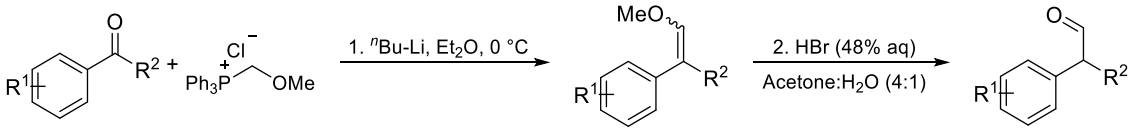
6.2 General Procedures

6.2.1 General procedure 1: Synthesis of allyl alcohol substrates from aldehydes[197]



Substituted cinnamyl aldehyde (1 equivalent) was dissolved in methanol (3 mL/mmol of aldehyde) and cooled to 0 °C in an ice bath. Sodium borohydride (1.2 equivalents) was slowly added to the solution and the reaction was left to stir for 50 minutes. After 50 minutes, the reaction was quenched with water (20 mL), and the product was extracted with DCM (3 x 25 mL). The organic fractions were combined, dried using $MgSO_4$, and the solvent was removed under reduced pressure resulting in the pure product.

6.2.2 General Procedure 2: Synthesis of branched aldehydes from acetophenones

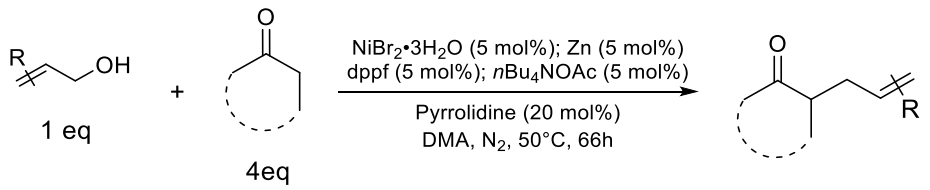


(Methoxymethyl)triphenylphosphonium chloride (2.74 g, 8 mmol, 1.6 eq.) was suspended in anhydrous Et_2O (15 mL) and the mixture was cooled to 0 °C. To this suspension, ^{n}BuLi (3.2 mL, 2.5M in hexane, 8 mmol, 1.6 eq.) was slowly added over 5 minutes until the mixture turned dark red. After stirring at 0 °C for 30 minutes, a solution of ketone (5 mmol, 1 eq.) in anhydrous Et_2O was added (5 mL). The mixture was left to stir at 0 °C for 30 minutes before warming to RT and leaving to stir for 16 h. Water (50 mL) was added to quench the reaction and the mixture was

extracted with Et_2O (3 x 20 mL). The organic fractions were combined, dried with $MgSO_4$, and solvent evaporated under reduced pressure. The methyl enol ether product was purified by flash column chromatography on silica gel using 1% Et_2O in hexane unless otherwise stated.

The pure methyl enol ether was dissolved in acetone and water mixture (4:1, 25 mL), and cooled to 0 °C under an inert atmosphere. Concentrated HBr (48%, 2 mL) was slowly added to the solution, and the mixture was left to warm to room temperature and to stir for 16 h. The reaction was neutralised by saturated $NaHCO_3$ (approx. 15 mL) and the solution was extracted with Et_2O (3 x 20 mL). The organic fractions were washed with brine (25 mL), dried using $MgSO_4$, and the solvent was removed under reduced pressure. The branched aldehyde was obtained after purification by flash column chromatography on silica gel (1:9 Et_2O/Hexane) unless otherwise stated.

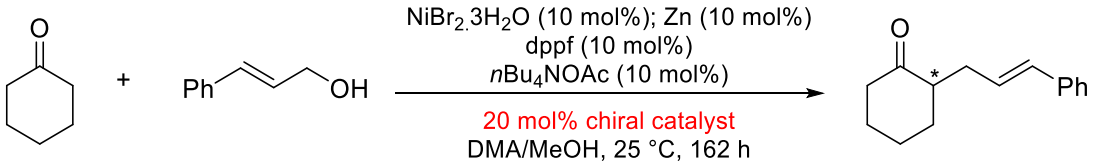
6.2.3 General procedure 3: Allylation of ketones



$NiBr_2.3H_2O$ (13.6 mg, 0.05 mmol, 0.05 eq.), Zn (3.2 mg, 0.05 mmol, 0.05 eq.), dppf (27.7 mg, 0.05 mmol, 0.05 eq.) and $^nBu_4NOAc$ (15 mg, 0.05 mmol, 0.05 eq.) were placed in a reaction vial which was then sealed and flushed with nitrogen. Dry DMA (2.00 ml/mmol allyl alcohol) was then added to the reaction vial and this was left to stir at room temperature for 15 minutes. Allyl alcohol (1 mmol, 1 eq.) was added to the resulting solution, followed by the ketone (4 mmol, 4 eq.), and finally by the pyrrolidine (16.5 µL, 0.2 mmol, 0.2 eq.). The reaction was left to stir at 50 °C for 66

hours unless otherwise stated. After 66 hours, the reaction was left to cool before dilution with ethyl acetate (20 mL/mmol). This mixture was washed with saturated sodium bicarbonate solution (20 mL/mmol), water (20 mL/mmol), and brine (20 mL/mmol). The organic layer was dried with $MgSO_4$, and solvent evaporated under reduced pressure. The product was purified by flash column chromatography (1:9, EtOAc : hexane) on silica gel, unless otherwise stated.

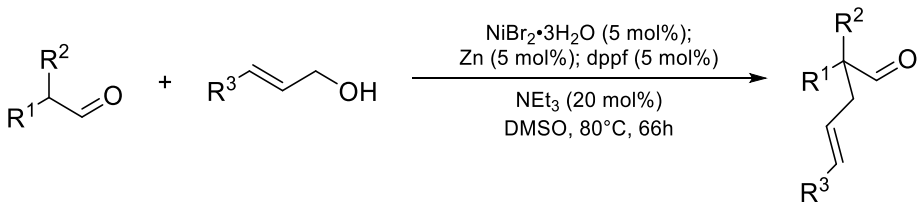
6.2.4 General procedure 4: Enantioselective allylation of ketones



$NiBr_2.3H_2O$ (27.2 mg, 0.10 mmol, 0.1 eq.), Zn (6.4 mg, 0.10 mmol, 0.1 eq.), dppf (55.4 mg, 0.10 mmol, 0.1 eq.) and $^nBu_4NOAc$ (30 mg, 0.10 mmol, 0.1 eq.) were placed in a reaction vial which was then sealed and flushed with nitrogen. Anhydrous DMA (2.0 mL/ mmol of allyl alcohol) was then added to the reaction vial and this was left to stir at room temperature for 15 minutes. Allyl alcohol (1 mmol, 1 eq.) was added to the resulting solution, followed by the ketone (4 mmol, 4 eq.), and finally by the chiral pyrrolidine or proline (0.2 mmol, 0.2 eq.). Where the proline was insoluble in DMA, a solution of proline in MeOH (0.2 mmol in 1 mL) was prepared separately and added to the reaction mixture. In these circumstances only 1 mL of DMA was added in the first step. The reaction was left to stir at 25 °C for 162 hours (1 week) unless otherwise stated. After 1 week, the reaction was diluted with ethyl acetate (20 mL/mmol). This mixture was washed with saturated sodium bicarbonate solution (20 mL/mmol), water (20 mL/mmol), and brine (20 mL/mmol). The organic layer was dried with $MgSO_4$, and solvent

evaporated under reduced pressure. The product was purified by flash column chromatography (1:9, EtOAc/hexane) on silica gel, unless otherwise stated.

6.2.5 General procedure 5: Allylation of aldehydes

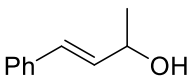


$NiBr_2.3H_2O$ (13.6 mg, 0.05 mmol, 0.05eq.), Zn (3.2 mg, 0.05mmol, 0.05eq.), dppf (27.7 mg, 0.05 mmol, 0.05eq.), and NEt_3 (27 µL, 0.2 mmol, 0.2eq.) were placed in a reaction vial which was then sealed and flushed with nitrogen. Dry DMSO (1.00 ml/mmol aldehyde) was then added to the reaction vial and this was left to stir at room temperature for 15 minutes. Allyl alcohol (1 mmol, 1 eq.) was added to the resulting solution, followed by the aldehyde (1 mmol, 1 eq.). The reaction was left to stir at 80 °C for 66 hours unless otherwise stated. After 66 hours, the reaction was left to cool before dilution with ethyl acetate (20 mL/mmol). This mixture was washed with aqueous HCl (2M, 20 mL/mmol), water (20 mL/mmol), and brine (20 mL/mmol). The organic layer was dried with $MgSO_4$, and solvent evaporated under reduced pressure. The product was purified by flash column chromatography (2:3 DCM/hexane) on silica gel, unless otherwise stated.

6.3 Experimental data

6.3.1 Synthesis of allyl alcohol substrates

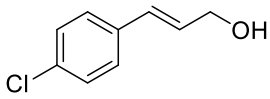
(*E*)-4-Phenylbut-3-en-2-ol[197]



According to general procedure 1, $NaBH_4$ (501 mg, 12 mmol) was added to a solution of (*E*)-4-phenyl-3-buten-2-one (1.52 g, 10.4

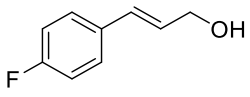
mmol) in MeOH (30 mL) at 0 °C. After work-up, the product was obtained as a yellow oil (1.54 g, 10.3 mmol, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (d, *J* = 6.4 Hz, 3H), 2.84 (s, 1H), 4.47-4.55 (m, 1H), 6.30 (dd, *J* = 16.0 Hz, 6.4 Hz, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 7.26-7.32 (m, 1H), 7.33-7.39 (m, 2H), 7.39-7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 68.9, 126.5, 127.6, 128.6, 129.3, 133.7, 136.8; IR υ_{max} (cm^{-1}): 3337 (OH), 2970 (CH), 2871 (CH), 1492 (CH), 1448 (CH), 1138, 1056 (CO), 963 (CC), 745 (CC), 691 (CH).

4-Chlorocinnamyl alcohol[197]



According to general procedure 1, $NaBH_4$ (136 mg, 3.6 mmol) was added to a solution of 4-chlorocinnamaldehyde (0.5 g, 3 mmol) in MeOH (10 mL) at 0 °C. After work-up, the product was obtained as a pale yellow solid (481 mg, 2.85 mmol, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 1H), 4.35 (dd, *J* = 5.6 Hz, 1.6 Hz, 2H), 6.36 (dt, *J* = 15.9 Hz, 5.6 Hz, 1H), 6.60 (dt, *J* = 15.9 Hz, 1.5 Hz, 1H), 7.28-7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.7 , 127.7, 128.8, 129.2, 129.8, 133.3, 135.2; IR υ_{max} (cm^{-1}): 3224 (OH), 2926 (CH), 1906 (ArCH), 1451 (CH), 1086 (CO), 972 (CC), 842 (CCl).

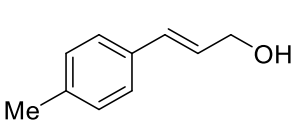
4-Fluorocinnamyl alcohol[242]



According to general procedure 1, $NaBH_4$ (227 mg, 6 mmol) was added to a solution of 4-fluorocinnamaldehyde (655 µL, 5 mmol) in MeOH (10 mL) at 0 °C. After work-up the product was obtained as a yellow solid (753 mg, 4.9 mmol, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83 (s, 1H), 4.33 (d, J = 2.4 Hz, 2H), 6.29 (dt, *J* = 15.8 Hz, 5.7 Hz, 1H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.98-7.06 (m, 2H), 7.32-7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.6, 115.5 (d, *J* = 21.6 Hz), 127.9 (d, *J* = 8.0 Hz), 128.3 (d, *J* = 2.3 Hz), 130.0, 132.8 (d, *J* = 3.4

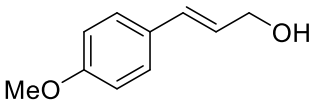
Hz), 163.6; IR υ_{max} (cm^{-1}): 3246 (OH), 2875 (CH), 1597 (CC), 1505 (ArCC), 1457 (CH), 1086 (CO), 1004 (CF), 967 (CC), 846 (CF).

4-Methyl-cinnamyl alcohol[197]



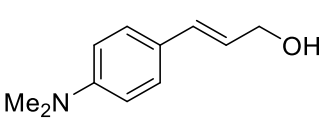
According to general procedure 1, $NaBH_4$ (136 mg, 3.6 mmol) was added to a solution of 4-methylcinnamaldehyde (438 mg, 3 mmol) in MeOH (10 mL) at 0 °C. After work-up, the product was obtained as a yellow solid (440 mg, 2.97 mmol, 99% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 1H), 2.37 (s, 3H), 4.33 (dd, *J* = 5.9 Hz, 1.4 Hz, 2H), 6.34 (dt, *J* = 15.8 Hz, 5.8 Hz, 1H), 6.60 (d, J = 15.8 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 64.1, 126.5, 127.5, 129.4, 131.3, 134.0, 137.7; IR υ_{max} (cm^{-1}): 3274 (OH), 2853 (CH), 1509 (ArCC), 1410 (OH), 1198 (CO), 971 (CC), 792 (CH).

4-Methoxy-cinnamyl alcohol[197]



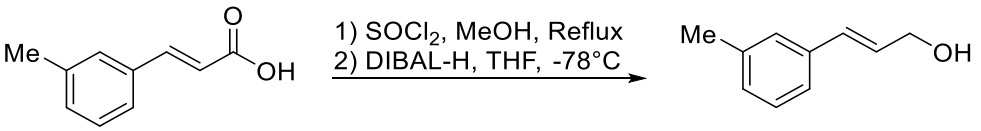
According to general procedure 1, $NaBH_4$ (501 mg, 12 mmol) was added to a solution of 4-methoxycinnamaldehyde (1.62 g, 10 mmol) in MeOH (30 mL) at 0 °C. After work-up, the product was obtained as a yellow solid (1.52 g, 9.3 mmol, 93% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 1.60 (s, 1H), 3.83 (s, 3H), 4.31 (dd, *J* = 5.9 Hz, 1.3 Hz, 2H), 6.26 (dt, *J* = 15.8 Hz, 6 Hz, 1H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.86-6.91 (m, 2H), 7.31-7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 64.1, 114.1, 126.3, 127.7, 129.5), 131.0, 159.3; IR υ_{max} (cm^{-1}): 3362 (OH), 2842 (CH), 1602 (CC), 1442 (OH), 1241 (ArCO), 1084 (CO), 1004 (CC), 967 (CC), 775 (CH);).

4-(Dimethyl)amino-cinnamyl alcohol[216]



According to general procedure 1, $NaBH_4$ (227 mg, 6 mmol) was added to a solution of 4-(dimethyl)aminocinnamaldehyde (0.88 g, 5 mmol) in MeOH (15 mL) at 0 °C. The desired product was obtained as an orange solid (872 mg, 4.92 mmol, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 1H), 2.98 (s, 6H), 4.30 (d, *J* = 6.1 Hz, 2H), 6.21 (dt, *J* = 15.8 Hz, 6.2 Hz, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.7 (d, *J* = 8.7 Hz, 2H), 7.3 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.4, 64.2, 112.3, 124.0, 127.5, 129.0, 131.9, 150.2.

3-methylcinnamyl alcohol[197]

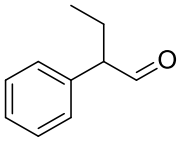


3-methylcinnamyl alcohol was prepared by the same route as reported by Doye *et al*.[243] To a suspension of 3-methylcinnamic acid (324 mg, 2 mmol, 1 eq.) in methanol (10 mL) thionyl chloride was added (220 μL, 3 mmol, 1.5eq.). The reaction mixture was heated under reflux (65 °C) for 2 hours. The solvent was removed under reduced pressure and the solid was placed under an inert nitrogen atmosphere and re-dissolved in dry THF (10 mL). This was cooled to -78 °C, a solution of DIBAL-H in hexane (1 M, 8 mL, 4 eq.) was slowly added, and the resulting mixture was stirred at -78 °C for 2.5 hours. MeOH was added (5 mL), followed by saturated $NaHCO_3$ (15 mL) and the solution left to warm to room temperature. HCl (1 M, approx. 100 mL) was added while stirring until the while precipitate dissolved. The product was extracted with hexane (3 x 50 mL), the organic fractions were combined, and dried with $MgSO_4$. The solvent was removed

under reduced pressure and the product was isolated as a colourless oil (282 mg, 1.9 mmol, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.44 (s, 1H), 4.33 (dd, *J* = 5.8 Hz, 1.5 Hz, 2H), 6.37 (dt, *J* = 15.9 Hz, 5.8 Hz, 1H), 6.61 (d, *J* = 15.9 Hz, 1H), 7.10 (m, 1H), 7.19 – 7.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 63.7, 123.6, 127.2, 128.3, 128.5, 131.2, 136.7, 138.2; IR υ_{max} (cm^{-1}): 3306 (OH), 2918 (CH), 2858 (CH), 1448 (CH), 1377, 1082 (CO), 997 (CC), 963 (CC), 760 (CH), 689 (CC).

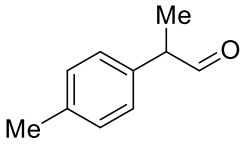
6.3.2 Synthesis of branched aldehydes

2-(1-tosyl-1H-indol-5-yl)propanal[244]



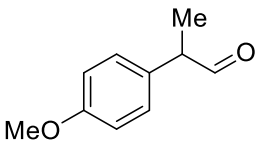
Prepared according to general procedure 2 from propiophenone (664 µL, 5.0 mmol). The product was purified by flash column chromatography and isolated as a colourless oil (180 mg, 1.2 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.75 – 1.83 (m, 1H), 2.08 – 2.20 (m, 1H), 3.39 – 3.46 (m, 1H), 7.20 – 7.23 (m, 2H), 7.31 – 7.35 (m, 1H), 7.37 – 7.40 (m, 2H), 9.70 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 22.9, 60.8, 127.5, 128.8, 129.0, 136.3, 201.0.

2-(*p*-Tolyl)propanal[244]



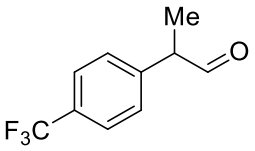
Prepared according to general procedure 2 from 4'-Methylacetophenone (671 mg, 5.0 mmol). The product was purified by flash column chromatography and isolated as a colourless oil (326 mg, 2.2 mmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, *J* = 7.0 Hz, 3H), 2.38 (s, 3H), 3.63 (q, *J* = 7.0 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 9.69 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 21.0, 52.6, 128.2, 129.8, 134.6, 137.2, 201.2.

2-(4-Methoxyphenyl)propanal[244]



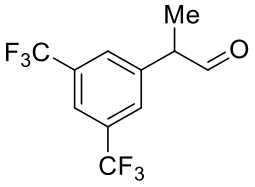
Prepared according to general procedure 2 from 4'-Methoxyacetophenone (376 mg, 2.5 mmol). The product was purified by flash column chromatography and isolated as a colourless oil (105 mg, 0.64 mmol, 26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (d, *J* = 7.0 Hz, 3H), 3.83 (s, 3H), 3.60 (qd, *J* = 7.0, 1.4 Hz, 1H), 6.91 – 6.96 (m, 2H), 7.12 – 7.17 (m, 2H), 9.67 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 52.1, 55.3, 114.5, 129.3, 129.5, 159.0, 201.1.

2-(4-(Trifluoromethyl)phenyl)propanal[244]



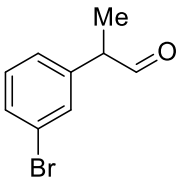
Prepared according to general procedure 2 from 4'-(trifluoromethyl)acetophenone (940 mg, 5.0 mmol). The product was purified by flash column chromatography and isolated as a colourless oil (242 mg, 1.2 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (d, *J* = 7.1 Hz, 3H), 3.74 (q, *J* = 7.1 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 9.72 (d, *J* = 1.2 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 52.7, 123.9 (q, *J* = 270.2 Hz), 126.0 (q, *J* = 3.8 Hz), 126.6 (m), 128.6, 141.7 (m), 200.1.

2-(3,5-Bis(trifluoromethyl)phenyl)propanal[244]



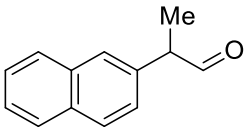
Prepared according to general procedure 2 from 3',5'-Bis(trifluoromethyl)-acetophenone (900 μL, 5.0 mmol). The product was purified by flash column chromatography and isolated as a pale yellow oil (157 mg, 0.60 mmol, 11%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (d, *J* = 7.2 Hz, 3H), 3.84 (q, *J* = 7.2 Hz, 1H), 7.69 (s, 2H), 7.86 (s, 1H), 9.75 (d, *J* = 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 52.3, 121.6, 127.8 (q, *J* = 173.3 Hz), 128.9 (q, *J* = 19.7 Hz), 132.5, 140.2, 199.0.

2-(3-Bromophenyl)propanal[244]



Prepared according to general procedure 2 from 4'-bromoacetophenone (664 μL, 5.0 mmol). The product was purified by flash column chromatography and isolated as a colourless oil (217 mg, 1.0 mmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (d, *J* = 7.1 Hz, 3H), 3.63 (qd, *J* = 7.1, 1.2 Hz, 1H), 7.14 – 7.18 (m, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 1.8 Hz, 1H), 7.46 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 9.69 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 52.5, 123.1, 126.9, 130.5, 130.7, 131.3, 139.9, 200.2.

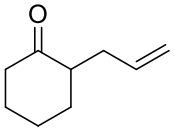
2-(Naphthalen-2-yl)propanal[244]



Prepared according to general procedure 2 from 2-acetylnapthalene (851 mg, 5.0 mmol). The product was purified by flash column chromatography and isolated as a white solid (276 mg, 1.5 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (d, *J* = 7.1 Hz, 3H), 3.83 (qd, *J* = 7.0, 1.3 Hz, 1H), 7.34 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.48 – 7.55 (m, 2H), 7.70 (d, *J* = 1.3 Hz, 1H), 7.82 – 7.90 (m, 3H), 9.79 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 53.1, 126.1, 126.2, 126.4, 127.2, 127.7, 128.8, 132.6, 133.6, 135.1, 201.0.

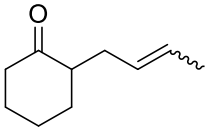
6.3.3 Allylation of ketones

2-Allylcyclohexanone (1)[197]



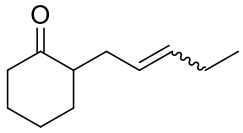
According to general procedure 3, allyl alcohol (68 µL, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (104 mg, 0.76 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 – 1.44 (m, 1H), 1.63 – 1.76 (m, 2H), 1.82 – 1.93 (m, 1H), 1.94 – 2.03 (m, 1H), 2.03 – 2.10 (m, 1H), 2.11 – 2.20 (m, 1H), 2.26 – 2.46 (m, 3H), 2.49 – 2.60 (m, 1H), 4.96 – 5.10 (m, 2H), 5.71 – 5.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 27.9, 33.4, 33.8, 42.0, 50.3, 116.2, 136.5, 212.5; IR υ_{max} (cm^{-1}): 2931 (CH), 1707 (CO), 1640 (CC), 1431 (CH), 995 & 909 (CC); HRMS (APCI) HRMS (APCI) m/z $[C_9H_{14}O]^+$ expected 139.1117, found 139.1115.

2-(But-2-enyl)cyclohexanone (2)[197]



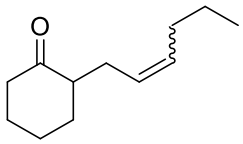
According to general procedure 3, crotyl alcohol (85 µL, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a colourless oil (97 mg, 0.64 mmol, 64%; linear/branched = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 – 1.38 (m, 1H), 1.56 – 1.72 (m, 5H), 1.80 – 1.95 (m, 2H), 1.98 – 2.07 (m, 1H), 2.07 – 2.16 (m, 1H), 2.23 – 2.33 (m, 2H), 2.34 – 2.48 (m, 2H), 5.30 – 5.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 24.9, 28.1, 32.6, 33.4, 42.1, 50.8, 126.8, 128.9, 213.0; IR υ_{max} (cm^{-1}): 2931 (CH), 1709 (CO), 1448 (CC), 1125 (CH), 967 (CC); HRMS (APCI) m/z $[C_{10}H_{16}O]^+$ expected 153.1274, found 153.1276.

2-(pent-2-enyl)cyclohexanone (3)[245]



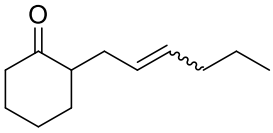
According to general procedure 3, (*E*)-2-penten-1-ol (101 µL, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a colourless oil (70 mg, 0.42 mmol, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 – 0.99 (t, *J* = 7.45 Hz, 3H), 1.29 – 1.43 (m, 1H), 1.58 – 1.74 (m, 2H), 1.82 – 2.17 (m, 6H), 2.24 – 2.52 (m, 4H), 5.29 – 5.41 (m, 1H), 5.41 – 5.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 24.9, 25.6, 27.9, 32.5, 33.3, 42.0, 50.8, 126.6, 134.0, 213.1 ; IR υ_{max} (cm^{-1}): 2931 (CH), 1709 (CO), 1448 (CH), 1125, 967 (CC).

(*Z*)-2-(hexan-2-enyl)cyclohexanone (4)



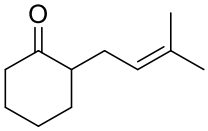
According to general procedure 3, (*Z*)-2-hexen-1-ol (118 µL, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a colourless oil (80 mg, 0.44 mmol, 44%; linear/branched = 96:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J = 7.3 Hz, 3H), 1.29 – 1.39 (m, 3H), 1.59 – 1.69 (m, 2H), 1.78 – 2.16 (m, 6H), 2.23 – 2.34 (m, 2H), 2.34 – 2.49 (m, 2H), 5.26 – 5.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 22.7, 24.8, 28.0, 32.6, 33.2, 34.7, 42.0, 50.9, 127.7, 132.2, 212.9; IR υ_{max} (cm^{-1}): 2929 (CH), 2860 (CH), 1709 (CO), 1448 (CH), 1125, 967 (CC); HRMS (APCI) m/z $[C_{12}H_{20}O]^{+}$ expected 181.1587, found 181.1587.

(*E*)-2-(hexan-2-enyl)cyclohexanone (5)[246]



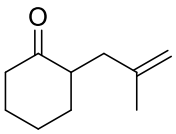
According to general procedure 3, (*E*)-2-hexen-1-ol (118 µL, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a colourless oil (133 mg, 0.74 mmol, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, J = 7.4 Hz, 3H), 1.26 – 1.39 (m, 3H), 1.55 – 1.71 (m, 2H), 1.78 – 2.14 (m, 6H), 2.21 – 2.48 (m, 4H), 5.25 – 5.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 ($1CH_3$), 22.6, 25.0, 27.9, 32.4, 33.2, 34.6, 41.9, 50.7, 127.7, 132.2, 212.9; IR υ_{max} (cm^{-1}): 2929 (CH), 2860 (CH), 1709 (CO), 1448 (CH), 1125, 967 (CC); HRMS (APCI) m/z $[C_{12}H_{20}O]^+$ expected 181.1587, found 181.1581.

2-(2-methyl-but-2-enyl)cyclohexanone (6)[197]



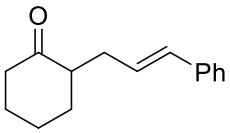
According to general procedure 3, 3-methyl-2-buten-1-ol (101 µL, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a colourless oil (63 mg, 0.38 mmol, 38%; linear/branched = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 – 1.35 (m, 1H), 1.52 – 1.72 (m, 8H), 1.79 – 1.90 (m, 2H), 1.96 – 2.08 (m, 2H), 2.23 – 2.57 (m, 4H), 5.03 – 5.4=34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 15.4, 24.6, 27.9, 32.9, 39.2, 41.8, 48.4, 120.5, 133.0, 213.3; IR υ_{max} (cm^{-1}): 2931 (CH), 2860 (CH), 1709 (CO), 1448 (CH), 833 (CC); HRMS (APCI) m/z $[C_{11}H_{18}O]^+$ expected 167.1430, found 167.1430.

2-(2-methyl-prop-1-enyl)cyclohexanone (7)[227]



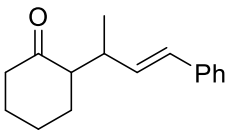
According to general procedure 3, 2-methyl-2-propen-1-ol (84 µL, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a colourless oil (100 mg, 0.66 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 – 1.34 (m, 1H), 1.59 – 1.69 (m, 5H), 1.77 – 1.93 (m, 2H), 1.96 – 2.12 (m, 2H), 2.24 – 2.34 (m, 1H), 2.35 – 2.49 (m, 2H), 2.53 (dd, *J* = 14.4, 4.9 Hz, 1H), 4.62 (m, 1H), 4.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 24.9, 28.1, 33.3, 37.4, 42.1, 48.4, 111.9, 143.4, 212.7; IR υ_{max} (cm^{-1}): 2931 (CH), 1709 (CO), 1647 (CC), 1448 (CH), 885 (CC); HRMS (APCI) m/z $[C_{10}H_{16}O]^+$ expected 153.1274, found 153.1268.

(*E*)-2-cinnamylcyclohexanone (8)[197]



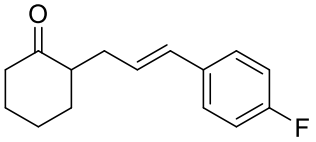
According to general procedure 3, cinnamyl alcohol (130 µL, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (180 mg, 0.84 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 – 1.48 (m, 1H), 1.63 – 1.76 (m, 2H), 1.83 – 1.92 (m, 1H), 2.14 – 2.23 (m, 1H), 2.27 – 2.38 (m, 1H), 2.38 – 2.49 (m, 2H), 2.64 – 2.75 (m, 1H), 6.17 – 6.28 (m, 1H), 6.41 (d, *J* = 15.8 Hz, 1H), 7.17 – 7.24 (m, 1H), 7.26 – 7.38,(m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 27.9, 33.0, 33.6, 42.1, 50.7, 126.0, 127.0, 128.3, 128.5, 131.6, 137.6, 212.4 ; IR υ_{max} (cm^{-1}): 2931(CH), 2858 (CH), 1703 (CO), 1448 (CH), 1127, 967 (CC), 736 (CH), 691 (CC); HRMS (APCI) m/z $[C_{12}H_{20}O]^+$ expected 215.1430, found 215.1425.

(*E*)-2-(4-Phenylbut-3-en-2-yl)cyclohexanone (9)[197]



According to general procedure 3, (*E*)-4-Phenylbut-3-en-2-ol (148 mg, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a brown oil (20 mg, 0.09 mmol, 9%; *d.r.* = 2:1; (4-Phenylbut-3-en-2-yl)/(1-Phenylbut-2-en-1-yl) = 85:15). Major product: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 – 1.16 (m, 3H), 1.57 – 1.80 (m, 4H), 1.94 – 2.11 (m, 2H), 2.25 – 2.46 (m, 3H), 2.83 – 2.95 (m, 1H), 6.06 – 6.32 (m, 1H), 6.39 (dd, *J* = 15.8, 7.4 Hz, 1H), 7.17 – 7.25 (m, 1H), 7.29 – 7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 24.6, 27.6, 29.1, 35.7, 42.3, 55.6, 126.0, 126.9, 128.4, 128.5, 129.0, 134.3, 212.0 ; IR υ_{max} (cm^{-1}): 2931 (CH), 2862 (CH), 1701 (CO), 1448 (CH), 967 (CC), 751 (CH), 695 (CC); HRMS (APCI) m/z $[C_{16}H_{20}O]^+$ expected 229.1587, found 229.1579.

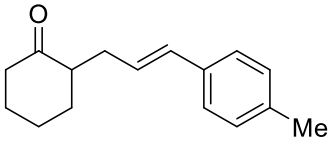
(*E*)-2-(4-fluoro)cinnamylcyclohexanone (10)[216]



According to general procedure 3, 4-fluorocinnamyl alcohol (152 mL, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (175 mg, 0.75 mmol, 75%; *d.r.* = 2:1; linear/branched = 85:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 – 1.47 (m, 1H), 1.62 – 1.77 (m, 2H), 1.84 – 1.94 (m, 1H), 2.02 – 2.23 (m, 3H), 2.29 – 2.49 (m, 3H), 2.62 – 2.72 (m, 1H), 6.08 – 6.19 (m, 1H), 6.73 (d, *J* = 15.7 Hz, 1H), 6.99 (t, *J* = 8.8 Hz, 2H), 7.28 – 7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1 , 27.9 , 33.0 , 33.7 , 42.2 , 50.8 , 115.3 (d, *J* = 21 Hz), 127.4 (d, *J* = 7 Hz), 128.1 (d, *J* = 2.2 Hz), 130.4, 133.7 (d, *J* = 3.4 Hz), 162 (d, *J* = 244 Hz), 212.6 ; IR υ_{max} (cm^{-1}): 2931 (CH), 2860 (CH), 1705 (CO), 1599 (CC_{Ar}) 1507 (CC_{Ar}) 1448

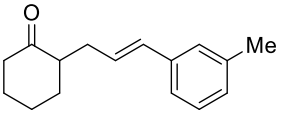
(CH), 1222 (CF), 1157, 967 (CC), 834 (CH), 766 (CH); HRMS (APCI) m/z $[C_{15}H_{17}FO]^+$ expected 223.1336, found 233.1328.

(*E*)-2-(4-methyl)cinnamylcyclohexanone (11)[197]



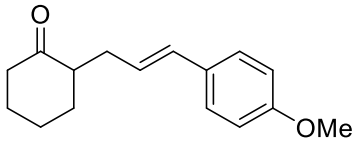
According to general procedure 3, 4-methylcinnamyl alcohol (148 mg, 1.0 mmol) and cyclohexanone (414 μL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (145 mg, 0.64 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 – 1.50 (m, 1H), 1.65 – 1.74 (m, 2H), 1.84 – 1.95 (m, 1H), 2.02 – 2.25 (m, 3H), 2.29 – 2.49 (m, 6H), 2.64 – 2.74 (m, 1H), 6.12 – 6.22 (m, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 25.1, 28.0, 33.1, 33.7, 42.2, 50.9, 125.8, 127.2, 129.1, 131.5, 135.0, 136.7, 212.6; IR υ_{max} (cm^{-1}): 2927 (CH), 2857 (CH), 1705 (CO), 1511 (CC_{Ar}), 1448 (CH), 1127, 967 (CC), 792 (CH); HRMS (APCI) m/z $[C_{16}H_{20}O]^+$ expected 229.1587, found 229.1579.

(*E*)-2-(3-methyl)cinnamylcyclohexanone (12)[197]



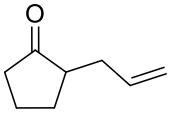
According to general procedure 3, 3-methylcinnamyl alcohol (74 mg, 0.5 mmol) and cyclohexanone (207 μL, 2.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a colourless oil (65 mg, 0.29 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ): δ 1.36 – 1.50 (m, 1H), 1.61 – 1.77 (m, 2H), 1.83 – 1.95 (m, 1H), 2.02 – 2.25 (m, 3H), 2.29 – 2.49 (m, 6H), 2.64 – 2.74 (m, 1H), 6.17 – 6.27 (m, 1H), 6.39 (d, *J* = 15.7 Hz, 1H), 7.01 – 7.06 (m, 1H), 7.14 – 7.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 25.1, 27.8, 33.1, 33.7, 42.3, 50.9, 123.2, 126.7, 127.8, 128.1, 128.4, 131.7, 137.5 138.0, 212.5; IR υ_{max} (cm^{-1}): 2929 (CH), 2857 (CH), 1709 (CO), 1448 (CH), 1127, 967 (CC), 775 (CH), 693 (CC); HRMS (APCI) m/z $[C_{16}H_{20}O]^+$ expected 229.1587, found 229.1590.

(*E*)-2-(4-methoxy)cinnamylcyclohexanone (13)[197]



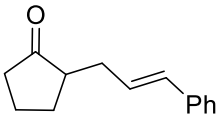
According to general procedure 3, 4-methoxycinnamyl alcohol (164 mg, 1.0 mmol) and cyclohexanone (414 µL, 4.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (209 mg, 0.86 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 – 1.49 (m, 1H), 1.60 – 1.75 (m, 2H), 1.83 – 1.92 (m, 1H), 2.02 – 2.23 (m, 3H), 2.28 – 2.45 (m, 3H), 2.62 – 2.71 (m, 1H), 3.80 (s, 3H), 6.01 – 6.12 (m, 1H), 6.34 (d, *J* = 15.7 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 28.0, 33.0, 33.5, 42.2, 50.9, 55.3, 113.9, 126.1, 127.2, 130.4, 131.1, 158.9, 212.6; IR υ_{max} (cm^{-1}): 2931 (CH), 2857 (CH, 1705 (CO), 1606 (CC_{Ar}), 1509 (CC_{Ar}), 1446 (CH), 1243 (CO), 1174, 1127, 1032 (CO), 967 (CC), 821 (CH); HRMS (APCI) m/z $[C_{16}H_{20}O]^+$ expected 245.1536, found 245.1529.

2-Allylcyclopentanone (14)[204]



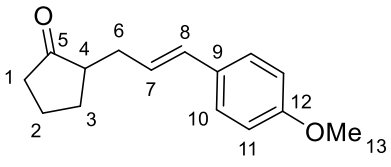
According to general procedure 3, allyl alcohol (68 µL, 1.0 mmol) and cyclopentanone (89 µL, 1.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (36 mg, 0.36 mmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 – 1.65 (m, 1H), 1.74 – 1.87 (m, 1H), 1.97 – 2.26 (m, 5H), 2.27 – 2.40 (m, 1H), 2.47 – 2.58 (m, 1H), 5.00 – 5.13 (m, 2H), 5.72 – 5.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 28.9, 33.9, 38.1, 48.6, 116.4, 135.9; IR υ_{max} (cm^{-1}): 2924 (CH), 2857 (CH), 1725 (CO), 1326 (CH), 799 (CC).

2-Cinnamylcyclopentanone (15)[197]



According to general procedure 3, cinnamyl alcohol (130 µL, 1.0 mmol) and cyclopentanone (88.5 µL, 1.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (164 mg, 0.81 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 – 1.70 (m, 1H), 1.72 – 1.86 (m, 1H), 1.96 – 2.06 (m, 1H), 2.07 – 2.18 (m, 1H), 2.18 – 2.39 (m, 4H), 2.61 – 2.75 (m, 1H), 6.19 (dt, *J* = 15.7 Hz, 8.6 Hz, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 7.19 – 7.25 (m, 1H), 7.28 – 7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 29.0, 33.1, 38.1, 49.0, 126.0, 127.2, 127.7, 128.6, 131.8, 137.4, 200.4; IR υ_{max} (cm^{-1}): 2959 (CH), 2875 (CH), 1733 (CO), 1597 (CC_{Ar}), 1449 (CH), 1153, 965 (CC), 747 (CH), 691 (CC); HRMS (APCI) m/z $[C_{14}H_{16}O]^+$ expected 201.1274, found 201.1264.

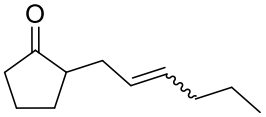
(*E*)-2-(4-methoxy)cinnamylcyclohexanone (16)



According to general procedure 3, 4-methoxycinnamyl alcohol (164 mg, 1.0 mmol) and cyclopentanone (89 µL, 1.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (146 mg, 0.65 mmol, 65%, R_f = 0.35). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 – 1.73 (m, 1H, H3), 1.74 – 1.90 (m, 1H, H2), 1.95 – 2.05 (m, 1H, H2), 1.98 – 2.20 (m, 1H, H1), 2.20 – 2.30 (m, 3H, H3, H4, H6), 2.30 – 2.40 (m, 1H, H1), 2.57 – 2.72 (m, 1H, H6), 3.81 (s, 3H, H13), 5.98 – 6.09 (m, 1H, H7), 6.38 (d, 1H, *J* = 15.5 Hz, H8), 6.86 (d, J = 8.7 Hz, 2H, H11), 7.29 (d, J = 8.7 Hz, 2H, H10); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6 (C2), 29.0 (C3), 33.0 (C6), 38.2 (C1), 49.1 (C4), 55.2 (C13), 113.9 (C11), 125.4 (C7), 127.1 (C10), 130.2 (C9), 131.1 (C8), 158.8 (C12), 220.6 (C5); IR υ_{max} (cm^{-1}): 2961 (CH), 2842 (CH),

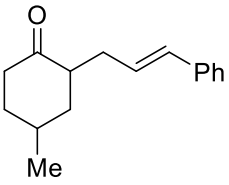
1729 (CO), 1701 (CO), 1604 (CC), 1246 (CO), 1146 (CC), 965 (CC), 801 (CH); HRMS (APCI) m/z $[C_{15}H_{18}O_2]^+$ expected 253.1199, found 253.1203.

(*E*)-2-(hexan-2-enyl)cyclopentanone (17)[247]



According to general procedure 3, (*E*)-2-hexene-1-ol (118 µL, 1.0 mmol) and cyclopentanone (90 µL, 1.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (124 mg, 0.75 mmol, 75%; *E*/*Z* = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 7.4 Hz, 3H), 1.31 – 1.41 (m, 2H), 1.52 – 1.63 (m, 1H), 1.69 – 1.82 (m, 1H), 1.91 – 2.03 (m, 4H), 2.06 – 2.20 (m, 3H), 2.25 – 2.35 (m, 1H), 2.37 – 2.47 (m, 1H), 5.28 – 5.36 (m, 1H), 5.40 – 5.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 20.6, 22.5, 28.8, 32.6, 34.5, 38.2, 49.0, 127.1, 132.5, 200.8; IR υ_{max} (cm^{-1}): 2957 (CH), 2871 (CH), 1735 (CO), 1453 (CH), 1153 (CO), 967 (CC); HRMS (APCI) m/z $[C_{11}H_{18}O]^+$ expected 167.1430, found 167.1435.

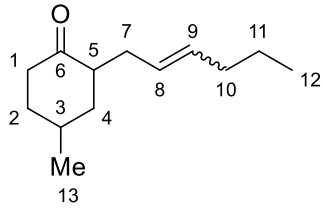
2-Cinnamyl-4-methylcyclohexanone (18)[197]



According to general procedure 3, cinnamyl alcohol (130 µL, 1.0 mmol) and 4-methylcyclohexanone (123 µL, 1.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a brown oil (206 mg, 0.90 mmol, 90%; *d.r.* = 1.1:1). ^{1}H NMR (400 MHz, $CDCl_3$,): δ 1.01 (d, J = 6.5 Hz, 1.56H, *y*-CH_3), 1.12 (d, J = 6.8 Hz, 1.28H, *x*-CH_3), 1.35 – 1.47 (m, 0.6H), 1.59 – 1.69 (m, 0.5H), 1.71 – 1.83 (m, 1H), 1.93 – 2.07 (m, 1.7H), 2.09 – 2.19 (m, 1.5H), 2.27 – 2.75 (m, 4.9H), 6.13 – 6.28 (m, 1H), 6.40 (d, *J* = 5.5 Hz, 0.6H), 6.44 (d, J = 5.5 Hz, 0.4H), 7.19 – 7.26 (m, 1H), 7.27 – 7.40 (m, 4H,); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 21.3, 26.6, 32.0, 32.8, 34.0, 34.1, 34.8, 35.9 , 37.9, 40.8, 41.5, 41.7, 47.6, 49.6, 126.0, 126.1, 126.9, 127.1, 127.7, 128.5, 131.6, 131.8, 137.3, 137.5,

212.4, 213.6 ; IR υ_{max} (cm^{-1}): 2924 (CH), 2868 (CH), 1701 (CO), 1597 (CC_{Ar}), 1451 (CC_{Ar}), 1023, 965 (CC), 747 (CH), 695 (CC); HRMS (APCI) m/z $[C_{16}H_{20}O]^+$ expected 229.1587, found 229.1579.

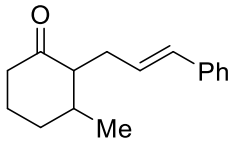
(*E*)-2-(hexan-2-enyl)-4-methylcyclohexanone (19)

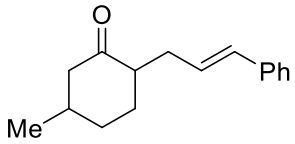


According to general procedure 3, (*E*)-2-hexen-1-ol (118 µL, 1.0 mmol) and 4-methylcyclohexanone (123 µL, 1.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (140 mg, 0.72 mmol, 72%; *d.r.* = 1:1, R_f = 0.41). ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.4 Hz, 3H, H12), 0.98 – 1.01 (d, J = 6.5 Hz, 1.6H, H13), 1.05 – 1.08 (d, J = 6.7 Hz, 1.6H, H13), 1.33 – 1.40 (m, 2.2H, H2, H11), 1.50 – 1.70 (m, 1.4H, H2, H7), 1.74 (m, 0.58H, H7), 1.83 – 2.17 (m, 5.8H, H2, H3, H5, H7), 2.29 – 2.52 (m, 4H, H1, H2, H4, H5), 5.25 – 5.39 (m, 1H, H8), 5.39 – 5.50 (m, 1H, H9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (C12), 13.6 (C12), 20.0 (C13), 21.3 (C13), 22.5 (C11), 22.6 (C11), 26.4 (C3), 32.0 (C3), 32.2 (C7), 33.9 (C4), 34.2 (C2), 34.5 (C10), 34.6 (C10), 35.9 (C2), 37.9 (C1), 38.7 (C7), 41.5 (C1), 41.6 (C4), 48.1 (C5), 49.6 (C5), 127.0 (C8), 127.7 (C8), 132.2 (C9), 132.6 (C9), 212.7 (C6), 214.2 (C6); IR υ_{max} (cm^{-1}): 2926 (CH), 2870 (CH), 1710 (CO), 1459 (CH), 1127, 967 (CC); HRMS (APCI) m/z $[C_{13}H_{22}O]^+$ expected 195.1743, found 195.1738.

2-Cinnamyl-3-methylcyclohexanone (20a) and

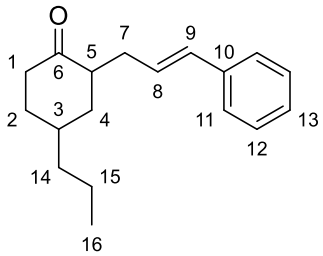
2-Cinnamyl-5-methylcyclohexanone (20b)[227]





According to general procedure 3, cinnamyl alcohol (132 µL, 1.0 mmol) and 3-methylcyclohexanone (122 µL, 1.0 mmol) were heated at 50 °C for 66 h. After work-up, the product was isolated as a pale yellow oil (175 mg, 0.76 mmol, 76% yield). The products were isolated together as a mixture of the two regioisomers. Additionally, each of the regioisomers also contains a combination of diastereoisomers. These were unable to be identified but are present in the ratio of 68:19:3:10. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 – 1.14 (m, 3H), 1.36 – 1.43 (m, 1H), 1.69 – 2.06 (m, 3H), 2.08 – 2.32 (m, 3H), 2.33 – 2.54 (m, 2H), 2.56 – 2.76 (m, 1H), 6.13 – 6.31 (m, 1H), 6.37 – 6.46 (m, 1H), 7.18 -7.25 (m, 1H), 7.26 – 7.38 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 32.6, 32.7, 34.0, 35.6, 49.8, 50.5, 126.0, 126.1, 126.9, 128.4, 131.5, 137.5, 211.8; IR υ_{max} (cm^{-1}): 2924 (CH), 2868 (CH), 1701 (CO), 1449 (CH), 1099 (CO), 1015 (CC).

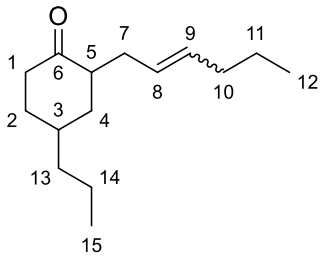
2-Cinnamyl-4-propylcyclohexanone (21)



According to general procedure 3, cinnamyl alcohol (130 µL, 1.0 mmol) and 4-propylcyclohexanone (155 µL, 1.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a brown oil (142 mg, 0.55 mmol, 55%; *d.r.* = 3:1, R_f = 0.28). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 – 1.00 (m, 3.3H, H16), 1.11 (q, *J* = 12.8 Hz, 0.7H, H4), 1.22 – 1.46 (m, 5.3H, H1, H2, H14, H15), 1.63 – 1.71 (m, 0.6H, H2), 1.74 – 1.87 (m, 1.5H, H4, H3), 1.88 – 2.02 (m, 0.6H, H2), 2.06 – 2.23 (m, 2.2H, H4, H7), 2.26 – 2.75 (m, 4.6H, H1, H5, H7, H14), 6.12 -6.29 (m, 1H, H8), 6.37

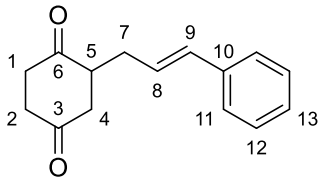
– 6.46 (m, 1H, H9), 7.18 – 7.25 (m, 1H, H13), 7.28 – 7.39 (m, 4H, H11, H12); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (C16), 14.3 (C16), 20.3 (C15), 20.6 (C15), 31.4 (C3), 31.9 (C2), 32.9 (C7), 33.8 (C2), 34.0 (C7), 35.9 (C1), 36.6 (C3), 36.8 (C4), 38.1 (C16), 38.2 (C16), 39.9 (C4), 41.5 (C1), 47.6 (C5), 49.6 (C5), 126.0 (C12), 126.1 (C12), 126.9 (C13), 127.1 (C13), 127.7 (C8), 128.5 (C8), 131.5 (C9), 131.8 (C9), 137.4 (C10), 137.6 (C10), 212.6 (C6), 213.8 (C6); IR υ_{max} (cm^{-1}): 2926 (CH), 2870 (CH), 1701 (CO), 1449 (CC), 1025, 698 (CC); HRMS (APCI) m/z $[C_{18}H_{24}O]^+$ expected 257.1900, found 257.1904.

(*E*)-2-(hexan-2-enyl)-4-propylcyclohexanone (22)



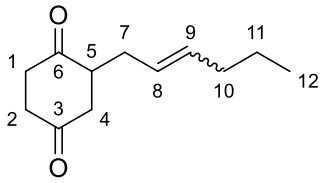
According to general procedure 3, (*E*)-2-hexen-1-ol (118 µL, 1.0 mmol) and 4-propylcyclohexanone (155 µL, 1.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (127 mg, 0.57 mmol, 57%; *d.r.* = 1:1, R_f = 0.24). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.4 Hz, 3H, H12), 0.91 – 0.96 (m, 3H, H15), 0.96 – 1.06 (m, 1H, H4), 1.29 – 1.42 (m, 6H, H2, H4, H11, H13, H14), 1.49 – 1.70 (m, 1H, H7), 1.70 – 2.21 (m, 6.6H, H2, H3, H4, H7), 2.26 – 2.47 (m, 4H, H1, H5, H7, H13), 5.25 – 5.50 (m, 2H, H8, H9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (C12), 13.6 (C12), 14.1 (C15), 14.2 (C15), 20.3 (C14), 20.5 (C14), 22.5 (C11), 22.6 (C11), 31.1 (C3), 32.2 (C7), 32.3 (C7), 33.8 (C2), 34.5 (C10), 34.6 (C10), 36.4 (C4), 36.5 (C3), 36.6 (C1), 38.0 (C13), 38.2 (C13), 39.6 (C4), 41.4 (C1), 48.1 (C5), 49.6 (C5), 127.0 (C8), 127.8 (C8), 132.1 (C9), 132.6 (C9), 212.9 (C6), 214.3 (C9); IR υ_{max} (cm^{-1}): 2924 (CH), 2862 (CH), 1710 (CO), 1459 (CH), 1127 , 967 (CC); HRMS (APCI) m/z $[C_{15}H_{26}O]^+$ expected 223.2066, found 223.2051.

2-cinnamyl-1,4-cyclohexanedione (23)



According to general procedure 3, cinnamyl alcohol (132 µL, 1.0 mmol) and 1,4-cyclohexanedione (112 mg, 1.0 mmol) were heated at 50 °C for 66 h. After work-up, the product was isolated as a pale-yellow oil (95 mg, 0.42 mmol, 42%, R_f = 0.21). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 – 2.48 (m, 1H, H7), 2.50 – 2.62 (m, 1H, H4), 2.63 – 2.92 (m, 7H, H1, H2, H4, H5, H7), 6.13 (dt, *J* = 15.7, 7.5 Hz, 1H, H8), 6.45 (d, *J* = 15.7 Hz, 1H, H9)), 7.21 – 7.26 (m, 1H, H13), 7.29 – 7.37 (m, 4H, H11, H12); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.0 (C7), 36.7 (C), 37.0 (C1), 42.2 (C4), 46.1 (C5), 125.6 (C8), 126.1 (C12), 127.4 (C13), 128.5 (C11), 133.4 (C9), 136.9 (C10), 208.1 (C3), 209.1 (C6); IR υ_{max} (cm^{-1}): 2918 (CH), 2849 (CH), 1701 (CO), 1412 (CH), 1267, 1142 (CO), 963 (CC), 736 (CH), 691 (CC); HRMS (APCI) m/z $[C_{15}H_{16}O]^+$ expected 229.1223, found 229.1218.

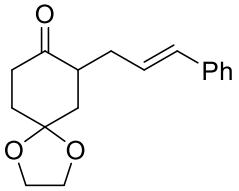
(*E*)-2-(hexan-2-enyl)-1,4-cyclohexanedione (24)



According to general procedure 3, (*E*)-2-hexen-1-ol (118 µL, 1.0 mmol) and 1,4-cyclohexanedione (112 mg, 1.0 mmol) were heated at 50 °C for 66h. After work-up, the product was isolated as a pale-yellow oil (46 mg, 0.24 mmol, 24% yield; *E*/*Z* = 9:1; linear/branched = 92:8, R_f = 0.19). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.4 Hz, 3H, H12), 1.37 (sxt, *J* = 7.4 Hz, 2H, H11), 1.97 (q, *J* = 7.1 Hz, 2H, H10), 2.14 – 2.24 (m, 1H, H2), 2.43 – 2.55 (m, 2H, H4, H7), 2.60 – 2.81 (m, 6H, H1, H2, H4, H5, H7), 5.25 – 5.36 (m, 1H, H8), 5.44 – 5.54 (m, 1H, H9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (C12), 22.4 (C11), 32.7 (C7), 34.5 (C10), 36.7 (C2), 37.0 (C1), 42.0 (C4), 46.0 (C5),

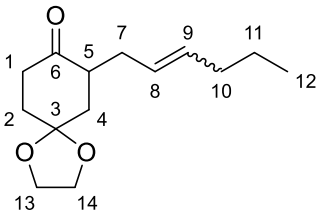
125.3 (C8), 134.5 (C9), 208.5 (C3), 209.4 (C6); HRMS (APCI) m/z $[C_{12}H_{18}O_2]^+$ expected 195.1380, found 195.1383.

2-cinnamyl-1,4-Cyclohexanedione monoethylene acetal (25)[227]



According to general procedure 3, cinnamyl alcohol (132 µL, 1.0 mmol) and 1,4-cyclohexanedione mono ethylene acetal (156 mL, 1.0 mmol) were heated at 50 °C for 66 h. After work-up, the product was isolated as a pale yellow oil (86 mg, 0.32 mmol, 32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (t, *J* = 13.3 Hz, 1H), 1.94 – 2.11 (m, 2H), 2.12 – 2.26 (m, 2H), 2.42 (ddd, *J* = 14.4, 5.0, 3.2 Hz, 1H), 2.64 – 2.74 (m, 2H), 2.76 – 2.85 (m, 1H), 3.98 – 4.08 (m, 4H), 6.13 – 6.23 (m, 1H), 6.41 (d, *J* = 15.8 Hz, 1H), 7.19 – 7.24 (m, 1H), 7.27 – 7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.6, 34.6, 38.2, 40.1, 46.3, 64.7, 107.4, 126.0, 127.0, 127.6, 128.4, 132.1, 137.4, 210.7; IR υ_{max} (cm^{-1}): 2955 (CH), 2875 (CH), 1701 (CO), 1125 (CO), 1097 (CO), 1045, 957 (CC), 924 (CC); HRMS (APCI) m/z $[C_{17}H_{20}O_3]^+$ expected 273.1485, found 273.1472.

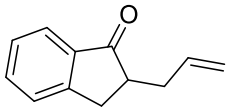
(*E*)-2-(hexan-2-enyl)- 1,4-Cyclohexanedione monoethylene acetal (26)



According to general procedure 3, (*E*)-2-hexen-1-ol (118 µL, 1.0 mmol) and 1,4-cyclohexanedione mono ethylene acetal (156 mL, 1.0 mmol) were heated at 50 °C for 66 h. After work-up, the product was isolated as a pale yellow oil (112 mg, 0.47 mmol, 47%; linear/branched = 93:7, R_f = 0.30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.3 Hz, 3H, H12), 1.29 – 1.41 (m, 2H, H11), 1.68 (t, *J* = 12.8 Hz, 1H, H4), 1.89 – 2.14 (m, 6H, H2, H4, H7, H10), 2.32 – 2.51 (m, 2H, H1, H7), 2.56 – 2.71 (m, 2H, H1, H5), 3.96 – 4.10 (m, 4H, H13, H14), 5.24 – 5.51 (m, 2H, H8, H9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (C12), 22.6 (C11), 32.0 (C7), 34.5 (C2), 34.6 (C10), 38.1 (C1), 39.8

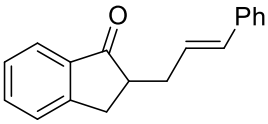
(C4), 46.3 (C5), 64.5 + 64.7 (C13, C14), 107.5 (C3), 127.0 (C5), 132.8 (C9), 211.1 (C6); IR υ_{max} (cm^{-1}): 2957 (CH), 2875 (CH), 1712 (CO), 1436 (CH), 1362 (CH), 1263 (CO), 1116, 1043 (CO), 946 (CC); HRMS (APCI) m/z $[C_{14}H_{22}O_3]^+$ expected 239.1642, found 239.1632.

2-allyl-1-indanone (27)[203]



According to a modification of general procedure 3, using 10 mol% catalyst loading, allyl alcohol (68 µL, 1.0 mmol) and 1-indanone (132 mg, 1.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a pale yellow oil (56 mg, 0.33 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 – 2.37 (m, 1H), 2.67 – 2.82 (m, 2H), 2.88 (dd, *J* = 17.3, 3.7 Hz, 1H), 3.3 (dd, *J* = 17.4, 7.8 Hz, 1H), 5.03 – 5.17 (m, 2H), 5.76 – 5.88 (m, 1H), 7.37 (t. *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = Hz, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.0, 35.5, 46.5, 116.9, 123.9, 126.6, 127.3, 134.7, 135.4, 136.6, 153.7, 208.1; IR υ_{max} (cm^{-1}): 2926 (CH), 1701 (CO), 1604 (CC), 1258 (CH), 1067 (CC), 916 (CC), 741 (CH).

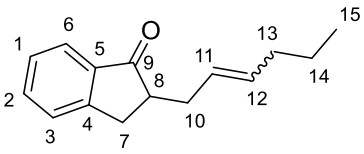
2-Cinnamyl-1-indanone (28)[197]



According to a modification of general procedure 3, using 10 mol% catalyst loading, cinnamyl alcohol (130 µL, 1.0 mmol) and indanone (132 mg, 1.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a colourless oil (160 mg, 0.66 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.4 – 2.52 (m, 1H), 2.83 – 3.00 (m, 3H), 3.29 (dd, *J* = 17.5 Hz, 7.5 Hz, 1H), 6.19 – 6.29 (m, 1H), 6.51 (d, *J* = 15.7 Hz, 1H), 7.21 – 7.26 (m, 1H), 7.27 – 7.38 (m, 4H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.7 Hz). 7.61 (t, *J* = 7.4 Hz, 1H), 7.81 (d, *J* =

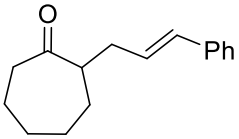
7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.1, 34.9, 47.1, 124.0, 126.1, 126.7, 127.2, 127.3, 127.5, 128.5, 132.2, 134.8, 136.7, 137.2, 153.7, 208.0; IR υ_{max} (cm^{-1}): 3026 (CH), 2920 (CH), 1701 (CO), 1604 (CC_{Ar}), 1463 (CH), 965 (CC), 739 (CH), 691 (CC); HRMS (APCI) m/z $[C_{18}H_{16}O]^+$ expected 249.1274, found 249.1266.

(*E*)-2-(hexan-2-enyl)-1-indanone (29)



According to a modification of general procedure 3, using 10 mol% catalyst loading, (*E*)-2-hexen-1-ol (118 μL, 1.0 mmol) and 1-indanone (132 mg, 1.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a colourless oil (58 mg, 0.27 mmol, 27%, R_f = 0.26). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.4 Hz, 3H, H15), 1.36 (sx, *J* = 7.4 Hz, 2H, H14), 1.96 (q, *J* = 6.9 Hz, 2H, H13), 2.17 – 2.27 (m, 1H, H10), 2.60 – 2.79 (m, 2H, H8, H10), 2.88 (dd, *J* = 17.3, 3.7 Hz, 1H, H7), 3.27 (dd, *J* = 17.3, 7.8 Hz, 1H, H7), 5.34 – 5.45 (m, 1H, H11), 5.47 – 5.58 (m, 1H. H12), 7.38 (t, *J* = 7.3 Hz, 1H, H2), 7.46 (d, *J* = 7.6 Hz, 1H, H3), 7.59 (m, 1H, H1), 7.76 (d, *J* = 7.6 Hz, 1H, H6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (C15), 22.5 (C14), 32.0 (C7), 34.4 (C10), 34.6 (C13), 47.1 (C8), 123.8 (C6), 126.5 (CC3), 126.7 (C11), 127.3 (C2), 133.0 (C12), 134.7 (C1), 136.8 (C4), 153.9 (C5), 208.5 (C9); IR υ_{max} (cm^{-1}): 2927 (CH), 2871 (CH), 1701 (CO), 1604 (CC), 1284 (CH), 1069 (CC), 747 (CH); HRMS (APCI) m/z $[C_{15}H_{18}O]^+$ expected 215.1430, found 215.1432.

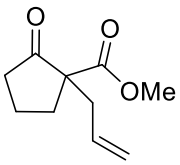
2-Cinnamylcycloheptanone (30)[197]



According to general procedure 3, cinnamyl alcohol (130 μL, 1.0 mmol) and cycloheptanone (118 μL, 1.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a brown oil (36 mg, 0.16 mmol, 16%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 – 1.53 (m, 3H), 1.58 – 1.74 (m,

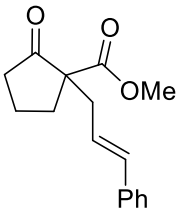
1H), 1.80 – 1.98 (m, 4H), 2.18 – 2.33 (m, 1H), 2.48 – 2.56 (m, 2H), 2.57 – 2.72 (m, 2H), 6.10 – 6.24 (m, 1H), 6.42 (d, *J* = 15.9 Hz, 1H), 7.18 – 7.25 (m, 1H), 7.27 – 7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 28.8, 29.5, 30.6, 35.5, 43.2, 52.0, 126.0, 127.0, 128.0, 128.4, 131.8, 137.4, 215.5; IR υ_{max} (cm^{-1}): 2924 (CH), 2853 (CH), 1697 (CO), 1448 (CH), 1162, 963 (CC), 935 (CC), 743 (CH), 691 (CC); HRMS (APCI) m/z $[C_{16}H_{20}O]^+$ expected 229.1587, found 229.1586.

2-allyl-2-methoxycarbonylcyclopentanone (31)[248]



According to general procedure 3, allyl alcohol (68 μL, 1.0 mmol) and methyl cyclopentanone-2-carboxylate (124 μL, 1.0 mmol) were heated at 50 °C for 66h. After work-up, the product was isolated as a pale-yellow oil (114 mg, 0.63 mmol, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 – 2.07 (m, 3H), 2.15 – 2.28 (m, 1H), 2.29 – 2.51 (m, 3H), 2.58 – 2.69 (m, 1H), 3.64 – 3.70 (m, 3H), 5.00 – 5.14 (m, 2H), 5.58 – 5.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 32.0, 37.8, 38.0, 52.5, 59.9, 119.0, 132.9, 171.3, 214.4; IR υ_{max} (cm^{-1}): 2955 (CH), 2914 (CH), 1750 (CO), 1720 (CO), 1435 (CH), 1224 (CO), 1131 (CC), 920 (CH).

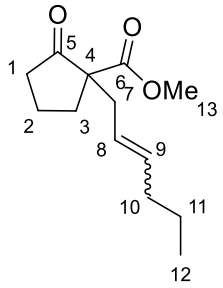
2-Cinnamyl-2-methoxycarbonylcyclopentanone (32)[227]



According to general procedure 3, cinnamyl alcohol (132 μL, 1.0 mmol) and methyl cyclopentanone-2-carboxylate (124 μL, 1.0 mmol) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (127 mg, 0.49 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88 – 2.01 (m, 1H), 2.01 – 2.12 (m, 2H), 2.23 – 2.35 (m, 1H), 2.41 – 2.61 (m, 3H), 2.85 (ddd, J = 13.9, 7.3, 1.3 Hz, 1H), 3.75 (s, 3H), 6.10 (dt, J = 15.8, 7.6 Hz, 1H), 6.47 (d, J = 15.8 Hz, 1H), 7.20 – 7.27 (m, 1H), 7.29 – 7.28 (m, 4H). ^{13}C NMR (100 MHz,

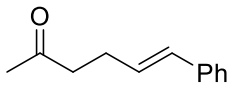
$CDCl_3$): δ 19.5, 32.2, 37.1, 38.1, 52.6, 60.3, 124.4, 126.2, 127.4, 128.5, 134.1, 137.0, 171.4, 214.6; IR υ_{max} (cm^{-1}): 3026 (CH), 2953 (CH), 1748 (CO), 1720 (CO), 1433 (CH), 1146 (CO), 967 (CH), 743 (CC), 693 (CH).

(*E*)-2-(hexan-2-enyl)-2-methoxycarbonylcyclopentanone (33)



According to general procedure 3, (*E*)-2-hexen-1-ol (118 μL, 1.0 mmol) and methyl cyclopentanone-2-carboxylate (124 μL, 1.0 mmol) were heated at 50 °C for 66h. After work-up, the product was isolated as a pale-yellow oil (157 mg, 0.70 mmol, 70% yield, R_f = 0.45). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J = 7.5 Hz, 3H, H12), 1.28 – 1.39 (sxt, *J* = 7.3 Hz, 2H, H11), 1.84 – 2.05 (m, 5H, H2, H3, H10), 2.19 –2.29 (m, 1H, H1), 2.29 – 2.37 (m, 1H, H7), 2.38 – 2.44 (m, 1H, H1), 2.45 – 2.50 (m, 1H, H3), 2.59 (dd, J = 13.8, 7.1 Hz, 1H, H7), 3.69 (s, 3H, H13), 5.20 – 5.32 (m, 1H, H9), 5.43 – 5.56 (m, 1H, H8); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (C12), 19.4 (C2), 22.4 (C11), 31.9 (C3), 34.6 (C10), 36.8 (C7), 38.1 (C1), 52.4 (C13), 60.3 (C4), 124.1 (C9), 135.4 (C8), 171.4 (C6), 214.7 (C5); IR υ_{max} (cm^{-1}): 2957 (CH), 1720 (CO), 1435 (CH), 1203 (CO), 1149, 971 (CC); HRMS (APCI) m/z $[C_{13}H_{20}O_3]^+$ expected 225.1485, found 145.1481.

(*E*)-6-phenylhex-5-en-2-one (34)[227]

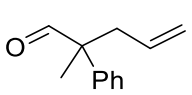


According to a modification to general procedure 3, cinnamyl alcohol (132 μL, 1.0 mmol) and acetone (2 mL) were heated at 50 °C. After work-up, the product was isolated as a pale-yellow oil (36 mg, 0.20 mmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.46 – 2.55 (m, 2H), 2.64 (t, J = 7.2 Hz, 2H), 6.22 (dt, J = 15.8, 6.7 Hz, 1H), 6.43 (d, J = 15.8 Hz, 1H), 7.19 – 7.25 (m, 1H), 7.29 – 7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.1, 30.0, 43.1, 126.0,

127.1, 128.5, 128.8, 130.7, 137.4, 208.0; IR υ_{max} (cm^{-1}): 3024 (CH), 2899 (CH), 1710 (CO), 1356 (CH), 1159, 963 (CC).

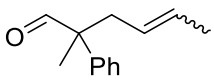
6.3.4 Allylation of aldehydes

2-methyl-2-phenylpent-4-enal (35)[233]



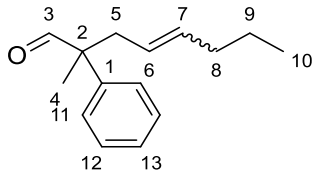
According to general procedure 5, allyl alcohol (68 µL, 1.0 mmol) and 2-phenylpropanal (134 µL, 1.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a pale-yellow oil (165 mg, 0.86 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 3H), 2.58 – 2.77 (m, 2H), 4.99 – 5.14 (m, 2H), 5.47 – 5.66 (m, 1H), 7.23 – 7.34 (m, 3H), 7.36 – 7.45 (m, 2H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 40.6, 53.6, 118.6, 127.1, 127.3, 128.8, 133.1, 139.4, 201.9; IR υ_{max} (cm^{-1}): 2976 (CH), 2929 (CH),1720 (CO), 1682 (CC), 1446 (CH), 1265, 1026 (CC), 762 (CH), 698 (CC).

2-methyl-2-phenylhex-4-enal (36) [233]



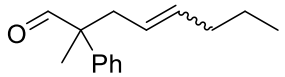
According to general procedure 5, allyl alcohol (85 µL, 1.0 mmol) and 2-phenylpropanal (134 µL, 1.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a pale-yellow oil as a mixture of isomers (89 mg, 0.89 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, *J* = 6.81 Hz, 0.4H), 1.08 (d, *J* = 6.81 Hz, 0.5H) 1.40 – 1.48 (m, 2.7H), 1.60 – 1.97 (m, 1.7H), 2.63 (d, *J* = 7.2 Hz, 2H), 2.69 (d, *J* = 7.2 Hz, 0.14H), 3.08 – 3.20 (m, 0.3H), 4.89 – 5.02 (m, 0.33H), 5.08 – 5.29 (m, 0.9H), 5.44 – 5.64 (m, 0.7), 5.69 – 5.83 (m, 0.1H), 7.26 – 7.34 (m, 2H), 7.38 – 7.43 (m, 3H), 9.54 (s, 0.48H), 9.56 (s, 0.06H), 9.64 (s, 0.13H), 9.65 (s, 0.14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.9, 14.2, 14.3, 14.6, 14.9, 17.9, 18.8, 19.0, 33.2, 39.3, 41.9, 42.1, 53.8, 56.7, 56.8, 115.7, 116.2, 125.3, 127.1, 127.2, 127.5, 127.6, 128.6, 128.7, 128.8, 129.3, 138.6, 139.4, 139.9, 202.2, 202.3, 202.4.

(*E*)-2-methyl-2-phenyloct-4-enal (37)



According to general procedure 5, (*E*)-2-hexen-1-ol (118 µL, 1.0 mmol) and 2-phenylpropanal (134 µL, 1.0 mmol) were heated at 80 °C. After work-up, the product was purified by flash column chromatography (2:3 DCM/hexane) on silica gel and isolated as a pale-yellow oil as a mixture of isomers (major product reported) (110 mg, 0.51 mmol, 51%; *E*/*Z* = 9:1; linear/branched = 95:5, R_f = 0.32). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, *J* = 7.3 Hz, 3H, H10), 1.33 (sxt, *J* = 7.3 Hz, 2H, H9), 1.44 (s, 3H, H4), 1.93 (q, *J* = 7.0 Hz, 2H, H8), 2.63 (d, *J* = 7.3 Hz, 2H, H5), 5.13 – 5.23 (m, 1H, H6), 5.41 – 5.52 (m, 1H, H7), 7.25 – 7.34 (m, 3H, H12, H13), 7.37 – 7.43 (m, 2H, H11), 9.55 (s, 1H, H3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (C10), 19.0 (C4), 22.5 (C9), 34.6 (C8), 39.3 (C5), 53.8 (C2), 124.3 (C6), 127.1 (C12), 127.2 (C13), 128.7 (C11), 134.8 (C7), 139.9 (C1), 202.4 (C3); IR υ_{max} (cm^{-1}): 2959 (CH), 2931 (CH), 1720 (CO), 1684 (CC), 1448 (CH), 1358 (CC), 1265, 760 (CH), 698 (CC); HRMS (APCI) m/z $[C_{15}H_{20}O]^+$ expected 217.1587, found 217.1579

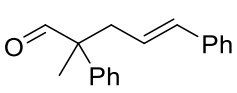
(E)-2-methyl-2-phenyloct-4-enal (38)



According to general procedure 5, (*Z*)-2-hexen-1-ol (118 µL, 1.0 mmol) and 2-phenylpropanal (68 µL, 1.0 mmol) were heated at 80 °C. After work-up, the product was purified by flash column chromatography (2:3 DCM/hexane) on silica gel and isolated as a colourless oil as a mixture of isomers – major product reported (100 mg, 0.46 mmol, 46%; *E*/*Z* = 9:1; linear/branched = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.4 Hz, 3H), 1.29 – 1.38 (m, 2H), 1.45 (s, 3H), 1.89 – 1.98 (q, *J* = 7.2 Hz, 2H), 2.64 (d, *J* = 7.3 Hz,

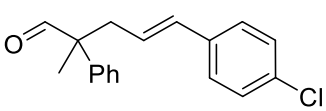
2H), 5.14 – 5.25 (m, 1H), 5.42 – 5.53 (m, 1H), 7.26 – 7.33 (m , 3H), 7.37 – 7.44 (m, 2H), 9.55 (s, 1H); 13.5, 19.0, 22.5, 34.6, 39.4, 53.9, 124.3, 127.1, 128.7, 139.9, 202.3; IR υ_{max} (cm^{-1}): 2959 (CH), 2931 (CH), 1720 (CO), 1684 (CC), 1446 (CH), 1265, 1026 (CC), 760 (CH), 698 (CC).

(*E*)-2-methyl-2,5-diphenylpent-4-enal (39)[233]



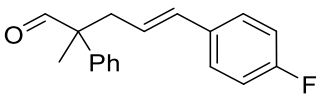
According to general procedure 5, cinnamyl alcohol (132 µL, 1.0 mmol) and 2-phenylpropanal (528 µL, 4.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a pale-yellow oil (216 mg, 0.86 mmol, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 3H), 2.76 – 2.90 (m, 2H), 5.97 (dt, *J* = 15.7, 7.4 Hz, 1H), 6.42 (d, *J* = 15.7 Hz, 1H), 7.19 – 7.36 (m, 8H), 7.40 – 7.47 (m, 2H), 9.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 39.9, 54.1, 124.9, 126.1, 127.2, 127.4, 128.4, 128.9, 133.6, 137.2, 139.4, 202.0; IR υ_{max} (cm^{-1}): 2926 (CH), 1718 (CO), 1684 (CC), 1448 (CH), 1265, 1025 (CC), 758 (CH), 698 (CC).

(*E*)-5-(4-chlorophenyl)-2-methyl-2-phenylpent-4-enal (40)[249]



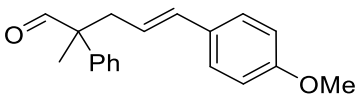
According to general procedure 5, 4-chlorocinnamyl alcohol (169 mg, 1.0 mmol) and 2-phenylpropanal (134 µL, 1.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a as a pale-yellow oil (77 mg, 0.26 mmol, 26% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (s, 3H), 2.74 – 2.88 (m, 2H), 5.88 – 5.98 (m, 1H), 6.36 (d, *J* = 15.7 Hz, 1H), 7.16 – 7.20 (m, 2H), 7.22 – 7.25 (m, 3H), 7.32 – 7.36 (m, 2H), 7.40 – 7.45 (m, 2H), 9.58 (s, 1H); IR υ_{max} (cm^{-1}): 2974 (CH), 2927 (CH), 1718 (CO), 1684 (CC), 1490 (CH), 1269, 1088 (CC), 1013 (CCl), 758 (CH), 698 (CC).

(*E*)-5-(4-fluorophenyl)-2-methyl-2-phenylpent-4-enal (41)[249]



According to general procedure 5, 4-fluorocinnamyl alcohol (152 mg, 1.0 mmol) and 2-phenylpropanal (134 µL, 1.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a pale-yellow oil (196 mg, 0.73 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 3H), 2.75 – 2.90 (m, 2H), 5.18 – 5.94 (m, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 6.97 (t, *J* = 8.6 Hz, 2H), 7.20 – 7.26 (m, 2H), 7.29 – 7.38 (m, 3H), 7.40 – 7.48 (m, 2H), 9.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 39.9, 54.1 115.4 (d, *J* = 22.2 Hz), 124.6 (d, *J* = 1.7 Hz), 127.1, 127.4, 127.6 (d, *J* = 8 Hz), 128.9, 132.3, 133.4 (d, *J* = 3.2 Hz),139.4, 162.1 (d, *J* = 244 Hz), 201.9; IR υ_{max} (cm^{-1}): 2974 (CH), 2929 (CH), 1720 (CO), 1684 (CC), 1597 (CC), 1507 (CH), 1224, 1155 (CC), 833 (CF), 760 (CH), 698 (CC).

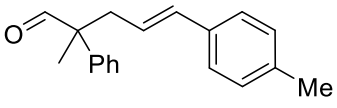
(*E*)-5-(4-methoxyphenyl)-2-methyl-2-phenylpent-4-enal (42)[249]



According to general procedure 5, 4-methoxycinnamyl alcohol (164 mg, 1.0 mmol) and 2-phenylpropanal (134 µL, 1.0 mmol) were heated at 80 °C. After work-up, the product was purified by flash column chromatography (1:9 EtOAc/Hexane) on silica gel and isolated as a colourless oil (218 mg, 0.78 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (s, 3H), 2.76 – 2.89 (m, 2H), 3.80 (s, 3H), 5.75 – 5.89 (dt, *J* = 7.4, 15.7 Hz, 1H), 6.37 (d, *J* = 15.7 Hz, 1H), 6.81 – 6.87 (m, 2H), 7.19 – 7.24 (m, 2H), 7.30 – 7.37 (m, 3H), 7.40 – 7.46 (m, 2H), 9.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 39.9, 54.1, 55.2, 113.9, 122.6, 127.2, 127.3, 127.4, 128.3, 128.9, 130.0, 132.9, 139.6,

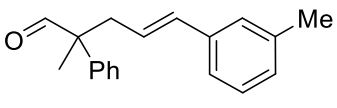
158.9, 202.1 ; IR υ_{max} (cm^{-1}): 2963 (CH), 2933 (CH), 1718 (CO), 1684 (CC), 1599 (CO), 1511 (CH), 1244, 1161 (CC), 1026 (CO), 760 (CH), 698 (CC).

(*E*)-2-methyl-2-phenyl-5-(p-tolyl)pent-4-enal (43)[249]



According to general procedure 5, 4-methylcinnamyl alcohol (148 mg, 1.0 mmol) and 2-phenylpropanal (134 µL, 1.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a colourless oil (105 mg, 0.39 mmol, 39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 3H), 2.34 (s, 3H), 2.77 – 2.89 (m, 2H), 5.85 – 5.98 (m, 1H), 6.40 (d, *J* = 15.7 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.29 – 7.37 (m, 3H), 7.39 – 7.47 (m, 2H), 9.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 21.1, 39.9, 54.1, 123.8, 126.0, 127.1, 127.3, 128.9, 129.1, 133.4, 134.4, 137.0, 139.5, 202.0; IR υ_{max} (cm^{-1}): 2974 (CH), 2924 (CH), 1718 (CO), 1701 (CO), 1684 (CC), 1446(CH), 1265, 1071 (CC), 1019 (CO), 758 (CH), 698 (CC).

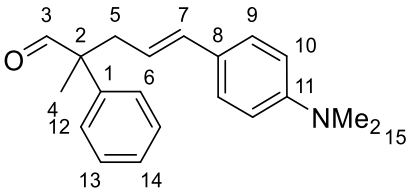
(*E*)-2-methyl-2-phenyl-5-(m-tolyl)pent-4-enal (44)[249]



According to general procedure 5, 3-methylcinnamyl alcohol (148 mg, 1.0 mmol) and 2-phenylpropanal (134 µL, 1.0 mmol) were heated at 80 °C. After work-up, the product was isolated as a colourless oil (185 mg, 0.70 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 3H), 2.34 (s, 3H), 2.80 – 2.89 (m, 2H), 5.89 – 6.04 (m, 1H), 6.41 (d, *J* = 15.8 Hz, 1H), 7.02 – 7.14 (m, 3H), 7.15 – 7.24 (m, 1H), 7.30 – 7.39 (m, 3H), 7.40 – 7.49 (m, 2H), 9.60 (s, 1H); 19.0, 21.3, 40.0, 54.1, 123.3, 124.6, 126.8, 127.2, 127.4, 128.1, 128.4, 128.9, 133.7, 137.1, 138.0, 139.5, 202.0; IR υ_{max} (cm^{-1}): 2974 (CH), 2926 (CH), 1720

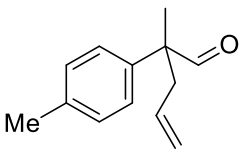
(CO), 1701 (CO), 1684 (CC), 1446(CH), 1265, 1157 (CC), 1026 (CO), 760 (CH), 698 (CC).

(*E*)-5-(4-(dimethyl)aminophenyl)-2-methyl-2-phenylpent-4-enal (45)



According to general procedure 5, 4-(dimethyl)amino-cinnamyl alcohol (177 mg, 1.0 mmol) and 2-phenylpropanal (134 μL, 1.0 mmol) were heated at 80 °C. After work-up, the product was purified by flash column chromatography (1:9 EtOAc/Hexane) on silica gel and isolated as a colourless oil (128 mg, 0.44 mmol, 44%, R_f = 0.31). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (s, 3H, H4), 2.78 – 2.85 (m, 2H, H5), 2.95 (s, 6H, H15), 5.74 (dt, *J* = 15.7, 7.5 Hz, 1H, H6), 6.33 (d, *J* = 15.7 Hz, 1H, H7), 6.62 – 6.69 (m, 2H, H9), 7.15 – 7.21 (m, 2H, H10), 7.28 – 7.35 (m, 3H, H13, H14), 7.38 – 7.45 (m, 2H, H12), 9.60 (s, 1H, H3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0 (C4), 40.0 (C5), 40.5 (C15), 54.2 (C2), 112.4 (C9), 120.3 (C6), 125.9 (C8), 127.0 (C10), 127.2 (C13), 127.3 (C14), 128.8 (C12), 133.4 (C7), 139.8 (C1), 149.9 (C11), 202.4 (C3); IR υ_{max} (cm^{-1}): 2961 (CH), 2866 (CH), 1720 (CO), 1610 (CN), 1518 (CC), 1347 (CN), 1164 (CC), 1064 (CO), 907 (CN), 728 (CH), 698 (CC); HRMS (APCI) m/z $[C_{20}H_{23}NO]^+$ expected 294.1852, found 294.1852.

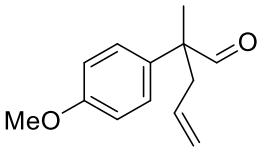
2-(4-methylphenyl)-2-methylpent-4-enal (46)[230]



According to general procedure 5, allyl alcohol (150 μL, 2.2 mmol) and 2-(*p*-Tolyl)propanal (326 mg, 2.2 mmol) were heated at 80 °C. After work-up, the product was purified by flash column chromatography (2:3 DCM/hexane) on silica gel and isolated as a colourless oil (196 mg, 1.1 mmol, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 3H), 2.37 (s, 3H), 2.63 – 2.75 (m, 2H), 5.03 – 5.14 (m, 2H), 5.53 – 5.65 (m, 1H), 7.15

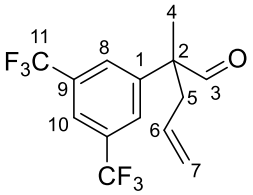
– 7.18 (m, 2H), 7.30 – 7.41 (m, 2H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 20.9, 40.5, 53.2, 118.5, 124.7, 127.0, 129.5, 133.3, 137.0, 202.1.

2-(4-methoxyphenyl)-2-methylpent-4-enal (47)[230]



According to general procedure 5, allyl alcohol (41 μL, 0.6 mmol) and 2-(4-methoxyphenyl)propanal (105 mg, 0.6 mmol) were heated at 80 °C. After work-up, the product was purified by flash column chromatography (2:3 DCM/hexane) on silica gel and isolated as a colourless oil (66 mg, 0.32 mmol, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H), 2.58 – 2.72 (m, 2H), 3.82 (s, 3H), 5.02 – 5.10 (m, 2H), 5.51 – 5.63 (s, 1H), 6.87 – 6.92 (m, 2H), 7.34 – 7.42 (m, 2H), 9.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 40.5, 55.2, 113.6, 114.2, 118.4, 126.3, 128.3, 130.6, 133.3, 201.9.

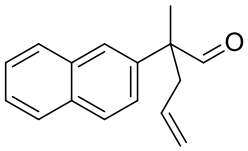
2-(3,5-Bis(trifluoromethyl)phenyl)-2-methylpent4-enal (48)



According to general procedure 5, allyl alcohol (41 μL, 0.6 mmol) and 2-(3,5-bis(trifluoromethyl)phenyl)propanal (157 mg, 0.6 mmol) were heated at 80 °C. After work-up, the product was purified by flash column chromatography (2:3 DCM/hexane) on silica gel and isolated as a colourless oil (40 mg, 0.13 mmol, 22% yield, R_f = 0.33). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 3H, H4), 2.68 – 2.78 (m, 2H, H5), 5.05 – 5.15 (m, 2H, H7), 5.46 – 5.59 (m, 1H, H6), 7.72 (s, 2H, H8), 7.85 (s, 1H, H10), 9.59 (s, 1H, H3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (C4), 40.8 (C5), 53.8 (C2), 120.0 (C7), 121.4 (m, *J* = 3.7 Hz, C10), 123.16 (q, *J* = 272 Hz, C11), 127.5 (m, C8), 131.4 (C6), 132.1 (q, *J* = 33.0 Hz, C9), 142.4 (C1), 200.4 (C3); IR υ_{max} (cm^{-1}): 2983 (CH), 1623 (CO),

1375 (CF), 1274 (CH), 1121 (CC), 898 (CC), 844 (CC), 706 (CH), 682 (CC); HRMS (APCI) m/z $[C_{12}H_{14}OF_6 + Na]^+$ expected 311.0841, found 311.0846.

2-(Naphthalen-2-yl)-2-methylpent-4-enal (49)[250]



According to general procedure 5, allyl alcohol (100 μL, 1.5 mmol) and 2-(Naphthalen-2-yl)propanal (276 mg, 1.5 mmol) were heated at 80 °C. After work-up, the product was purified by flash column chromatography (2:3 DCM/hexane) on silica gel and isolated as an orange oil (190 mg, 0.85 mmol, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 3H), 2.75 (dd, *J* = 14.2, 7.8 Hz, 1H), 2.86 (dd, *J* = 14.2, 6.8 Hz, 1H), 5.03 – 5.17 (m ,2H), 5.53 – 5.67 (m, 1H), 7.37 – 7.42 (m, 1H), 7.51 – 7.54 (m, 2H), 7.74 (s, 1H), 7.85 – 7.90 (m, 3H), 9.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 40.5, 53.8, 118.7, 125.0, 126.2, 126.3, 126.4, 127.5, 128.0, 128.6, 132.4, 133.1, 133.4, 136.8, 201.9; IR υ_{max} (cm^{-1}): 2976 (CH), 2931 (CH), 1720 (CO), 1373 (CC), 1274 (CC), 1190 (CC), 915 (CH), 857 (CH), 814 (CC), 745 (CH).

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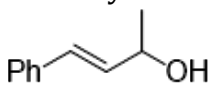
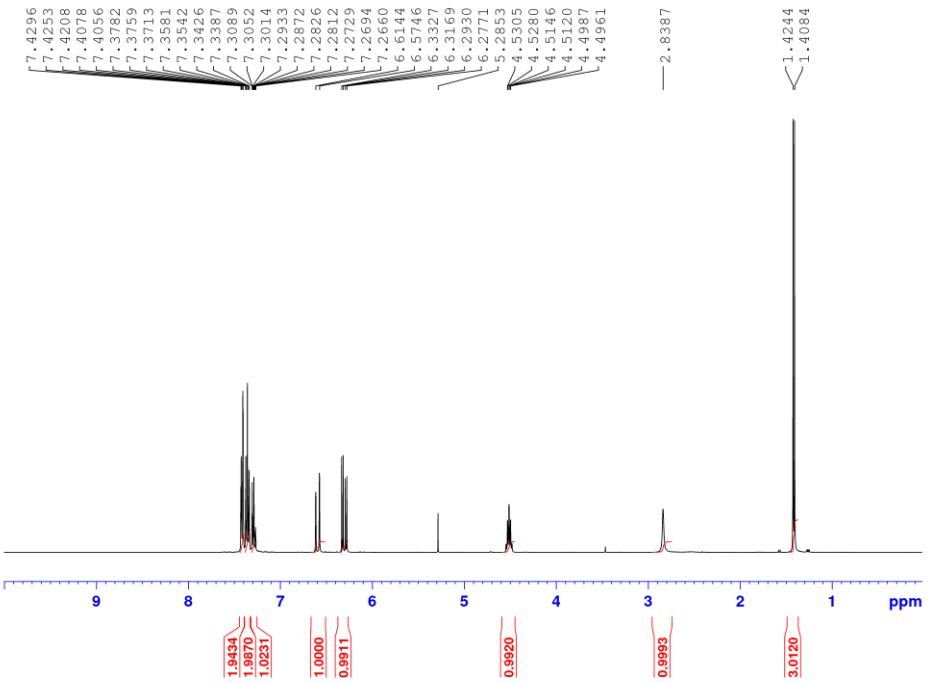
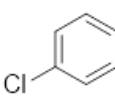
8. Appendix

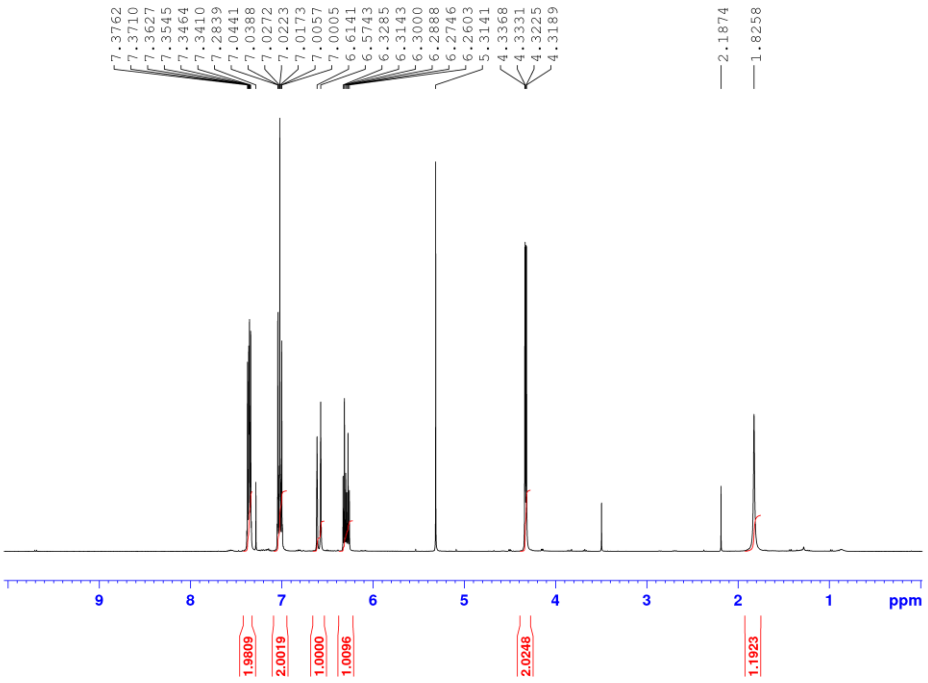
8.1 NMR Data

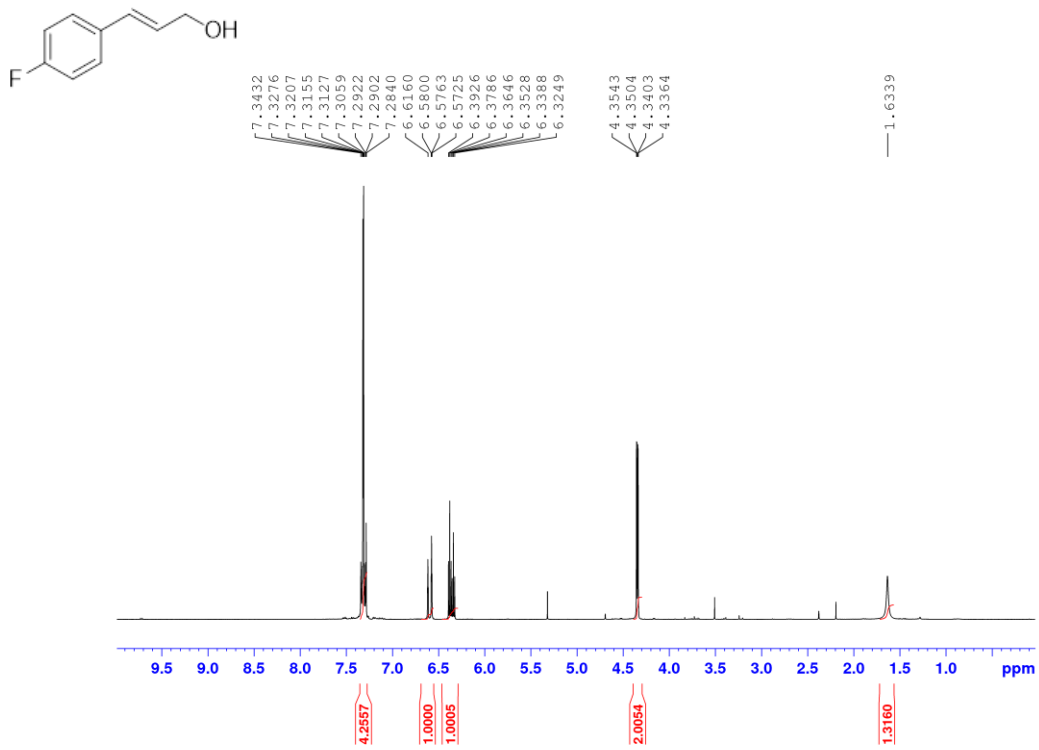
8.1.1 Allyl alcohols







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6.6160
6.5800
6.5763
6.5725
6.3926
6.3786
6.3646
6.3528
6.3388
6.3249
4.3543
4.3504
4.3403
4.3364
1.6339
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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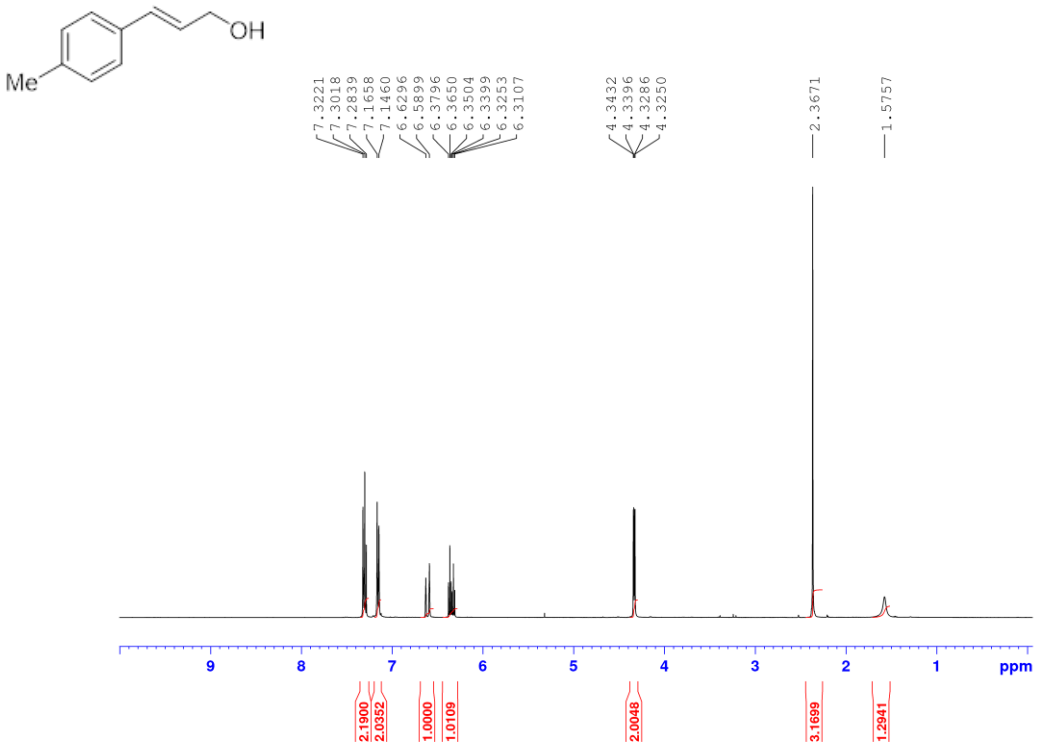
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6.3399
6.3253
6.3107
4.3432
4.3396
4.3286
4.3250
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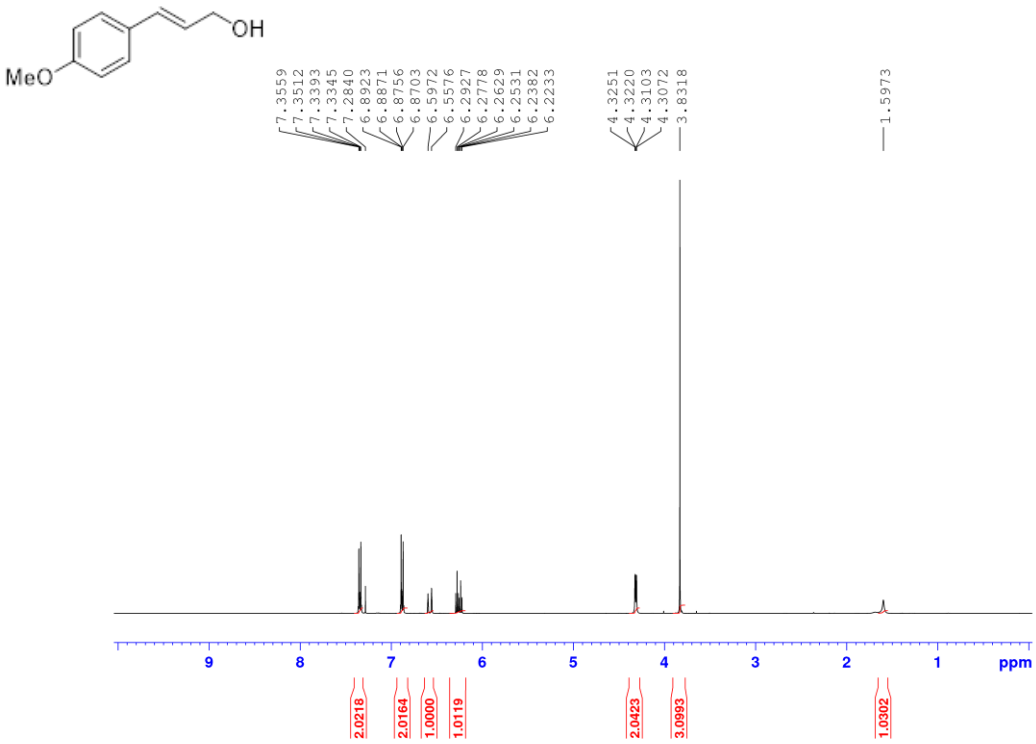
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7
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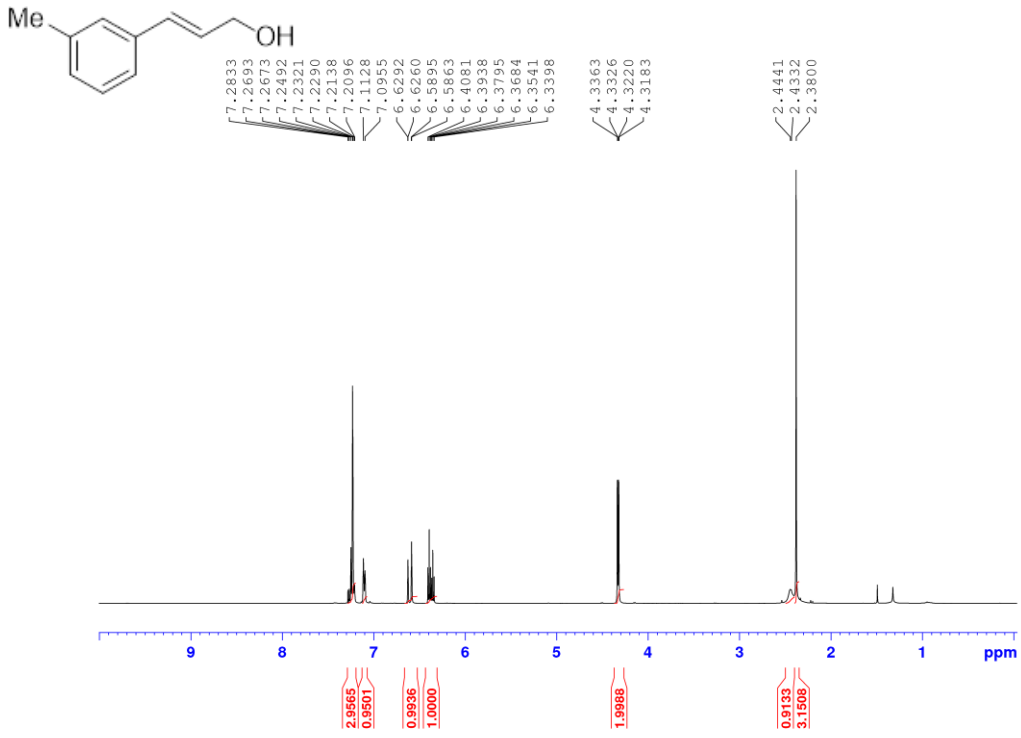
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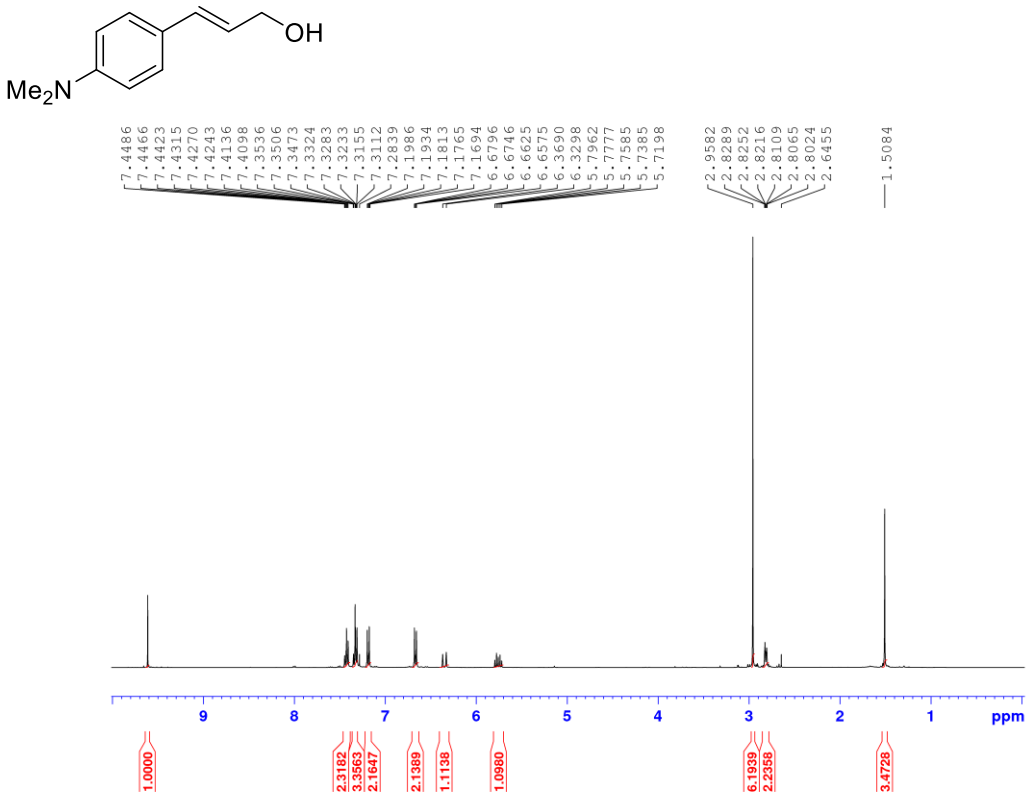
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8
7
6
5
4
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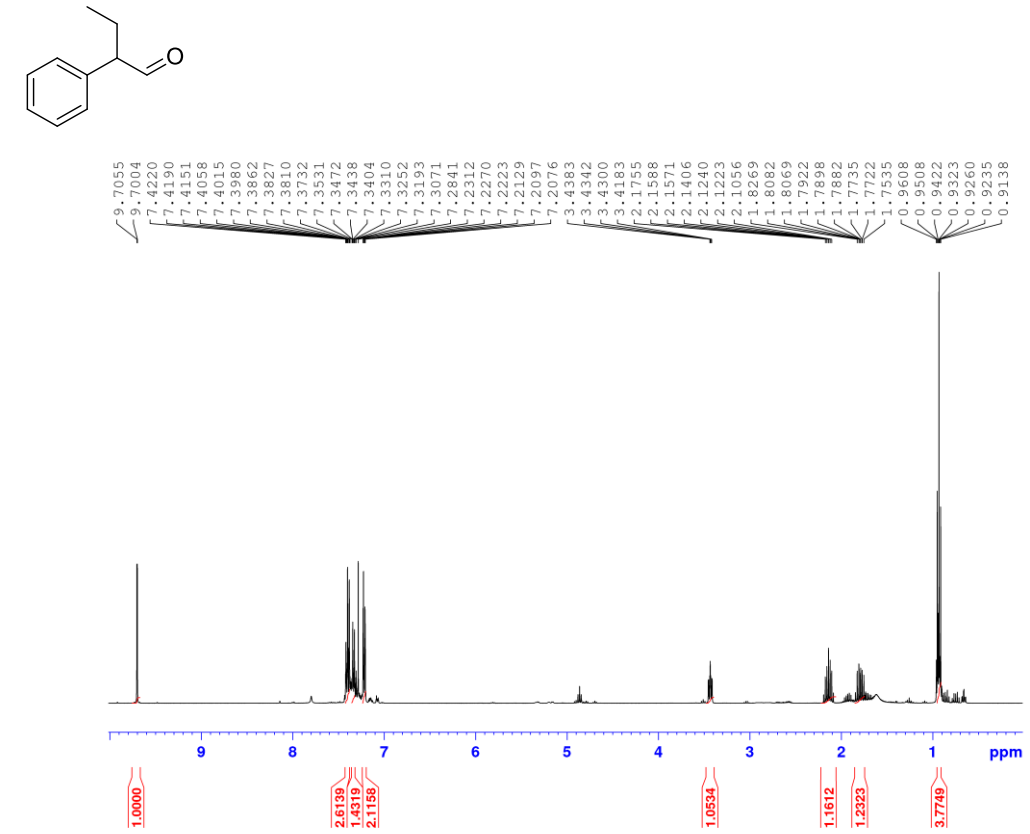
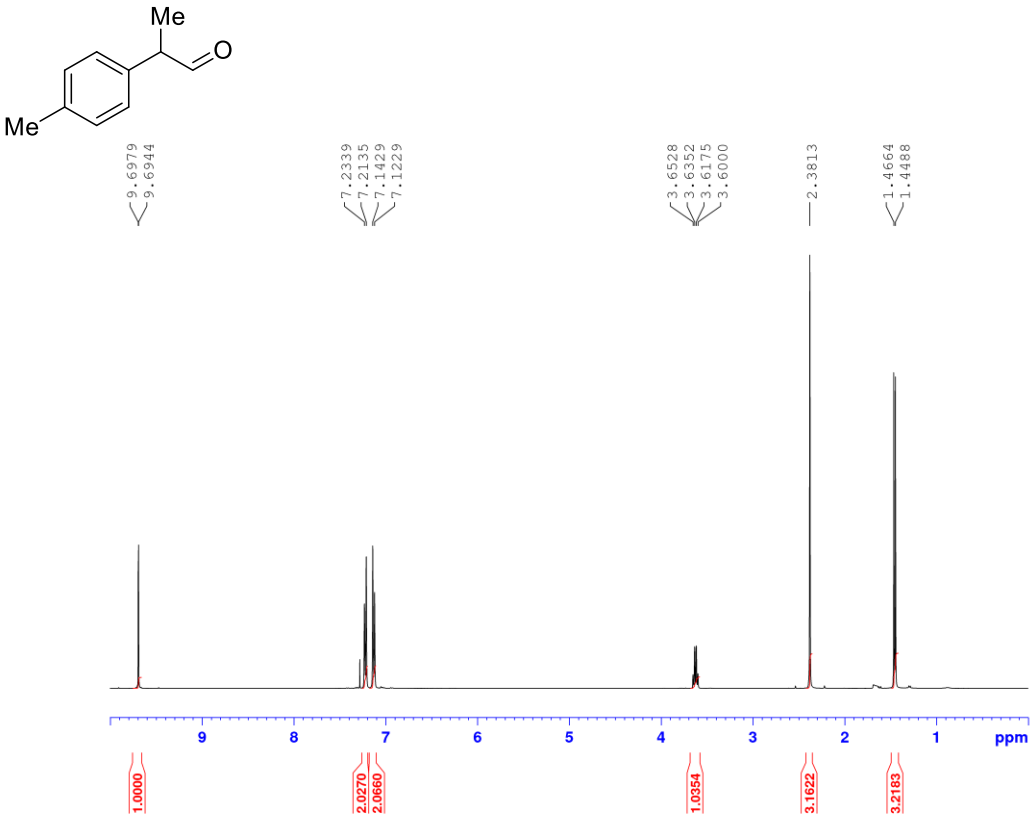
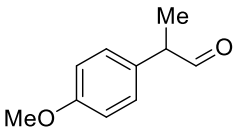
8.1.2 Branched aldehydes



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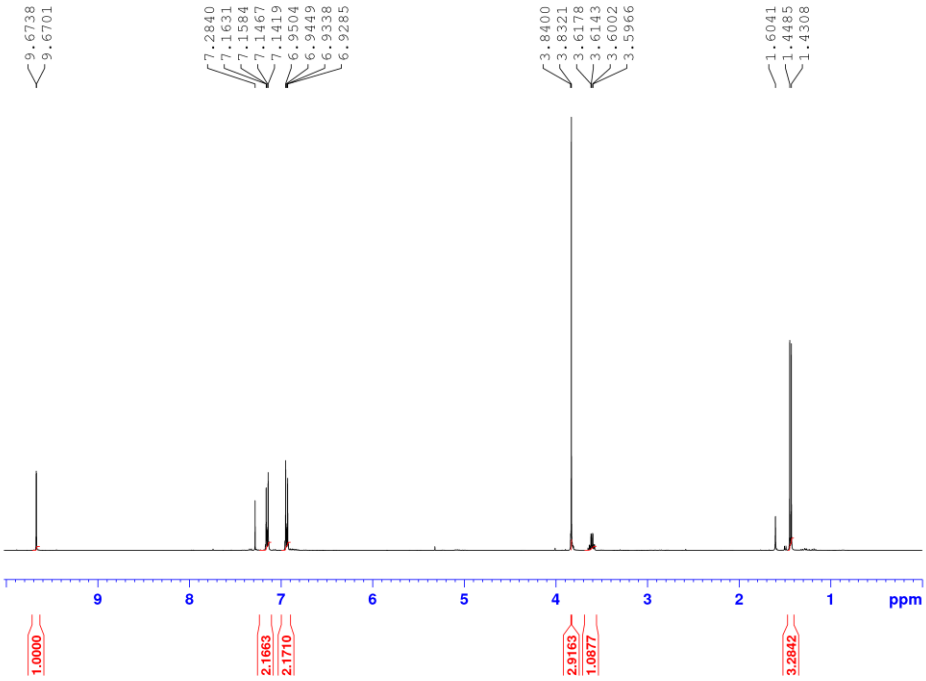
O
MeO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9
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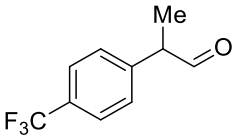
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O
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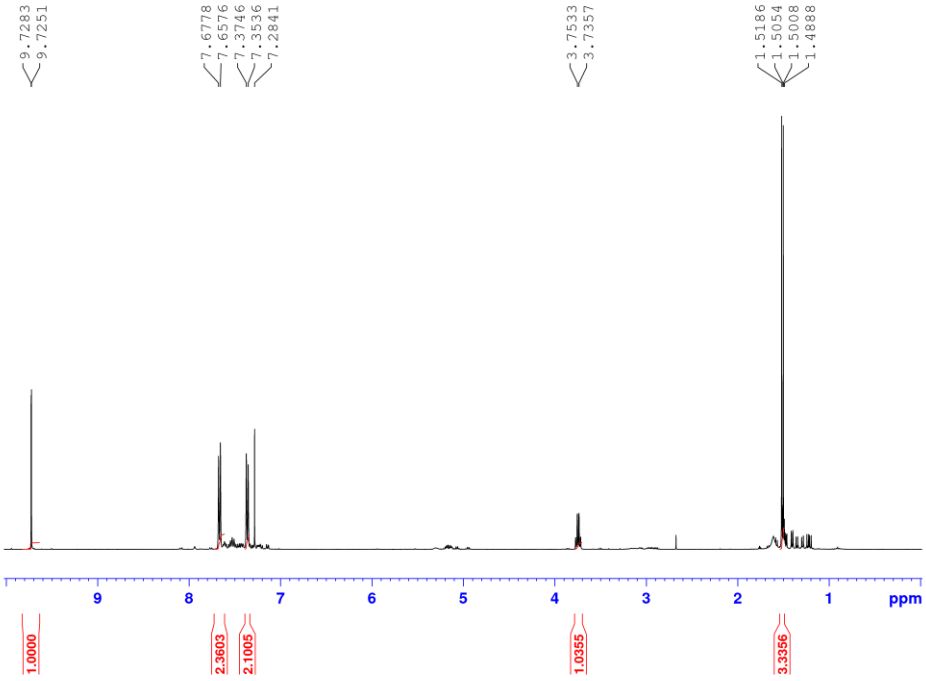
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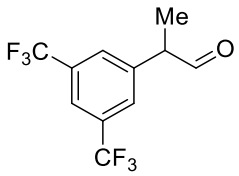
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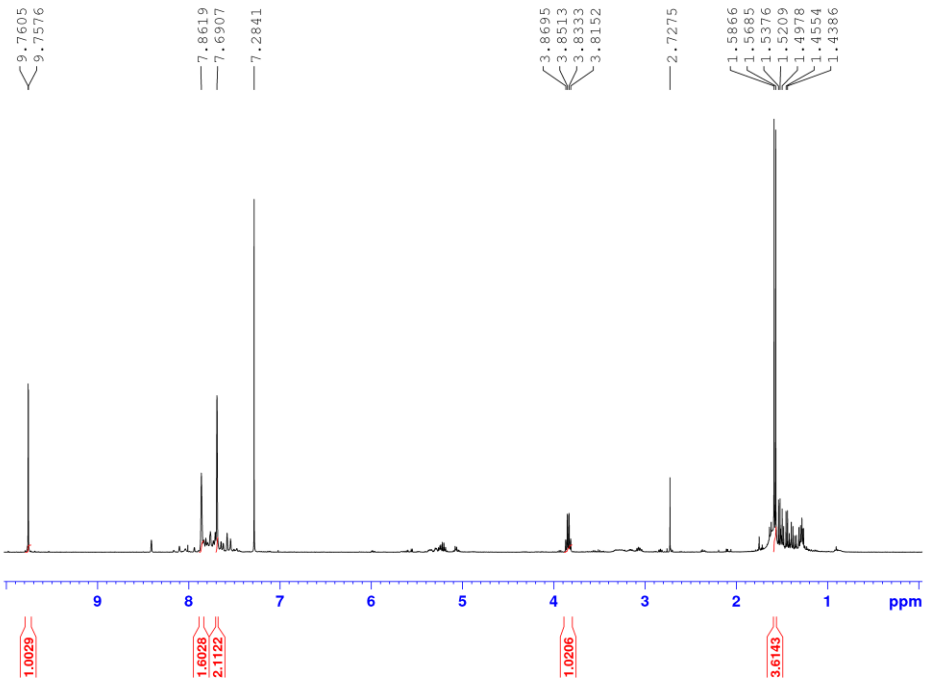
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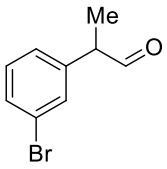
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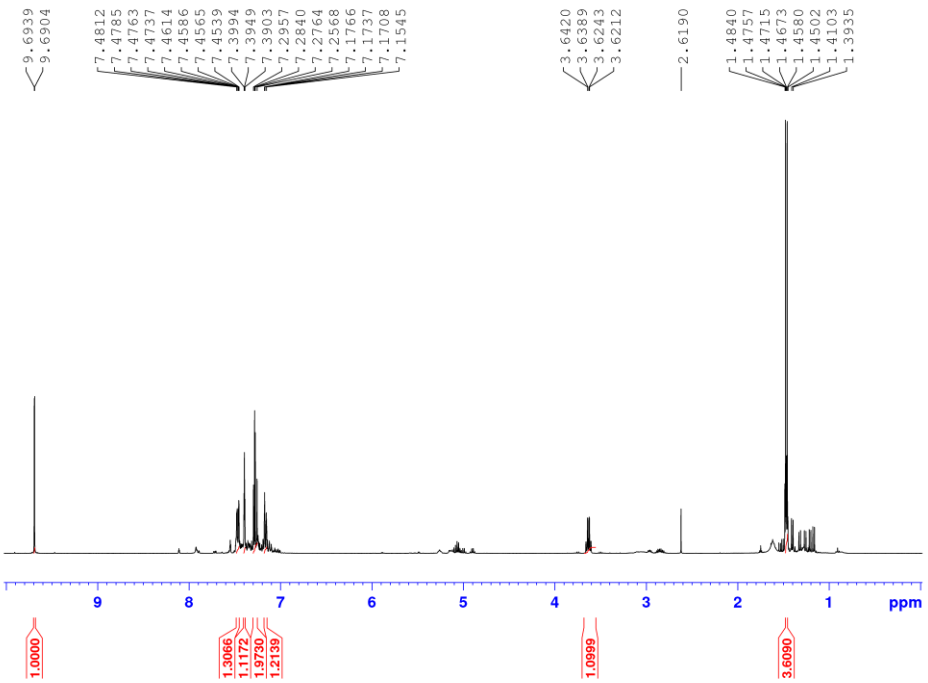
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1.4840
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1.4715
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1.4103
1.3935
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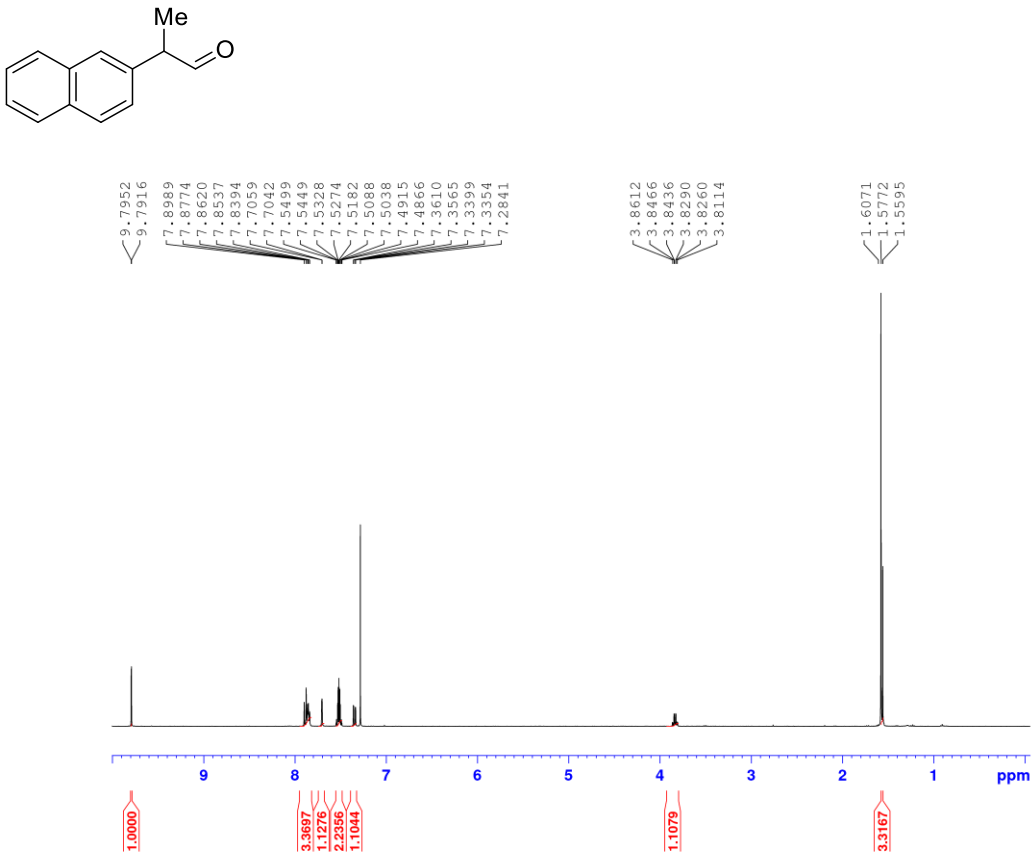
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7.4915
7.4866
7.3610
7.3565
7.3399
7.3354
7.2841
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3.8290
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1.6071
1.5772
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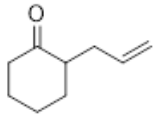
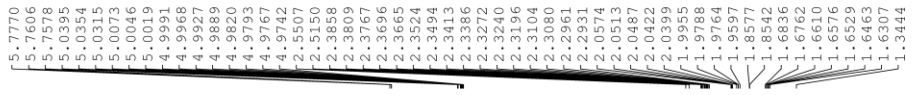
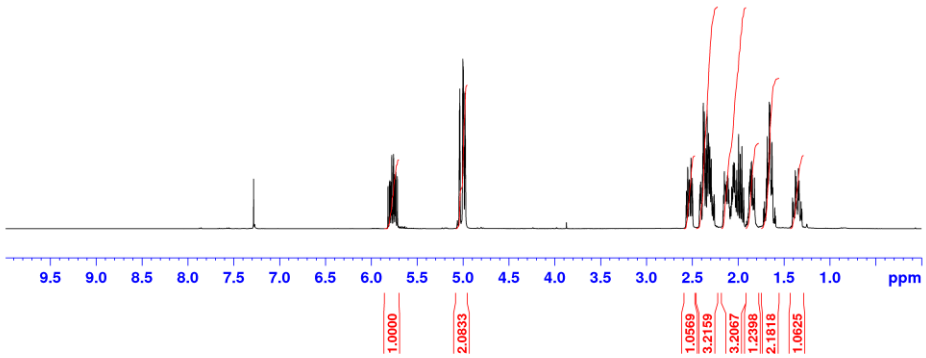
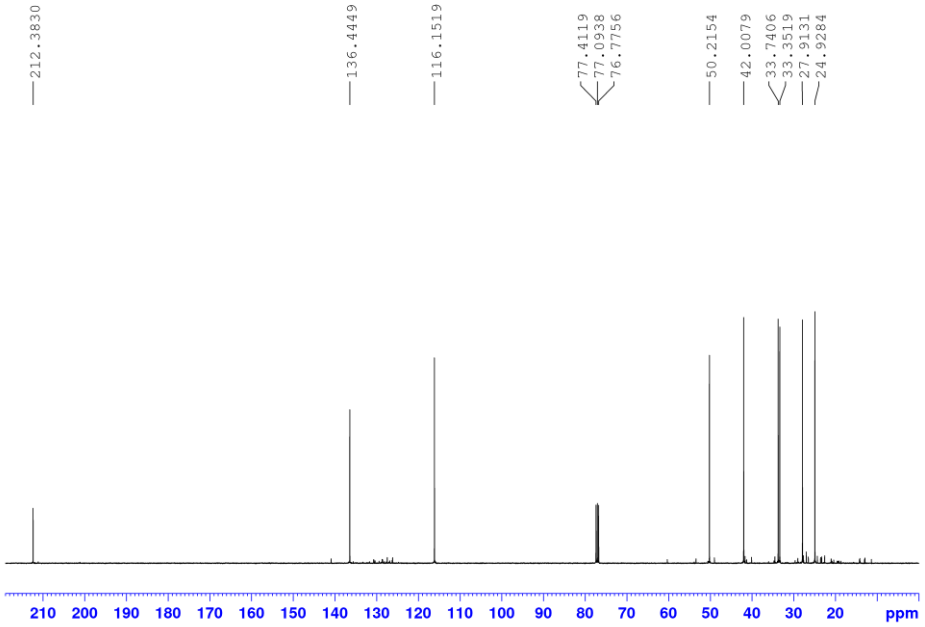
8.1.3 Allylated ketones

1









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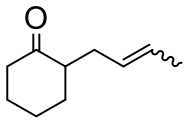

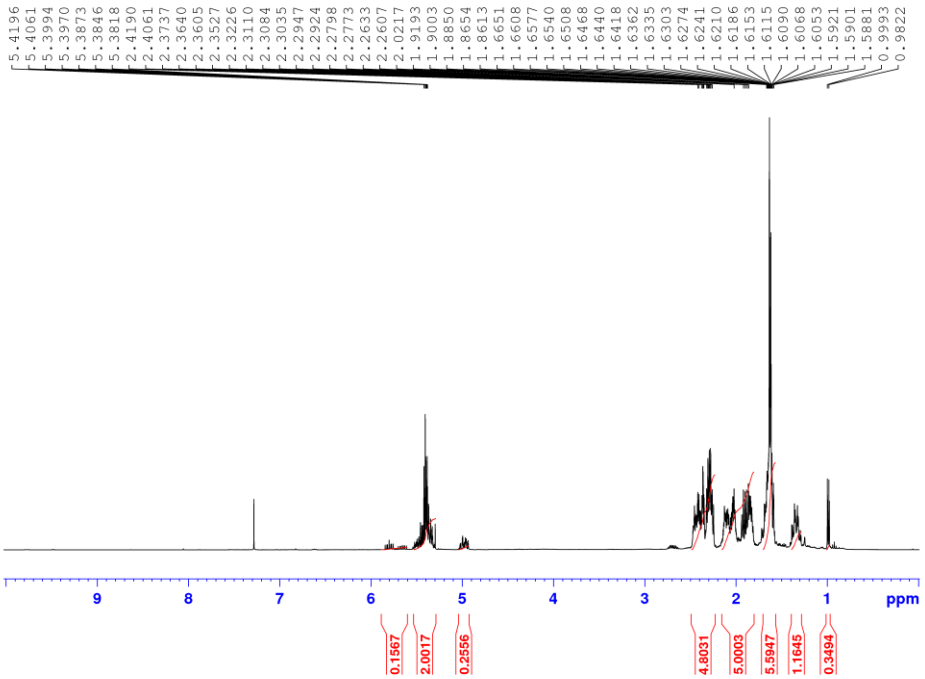
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2.2947
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2.2798
2.2773
2.2633
2.2607
2.0217
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1.8850
1.8654
1.8613
1.6651
1.6608
1.6577
1.6540
1.6508
1.6468
1.6440
1.6418
1.6362
1.6335
1.6303
1.6274
1.6241
1.6210
1.6186
1.6153
1.6115
1.6090
1.6068
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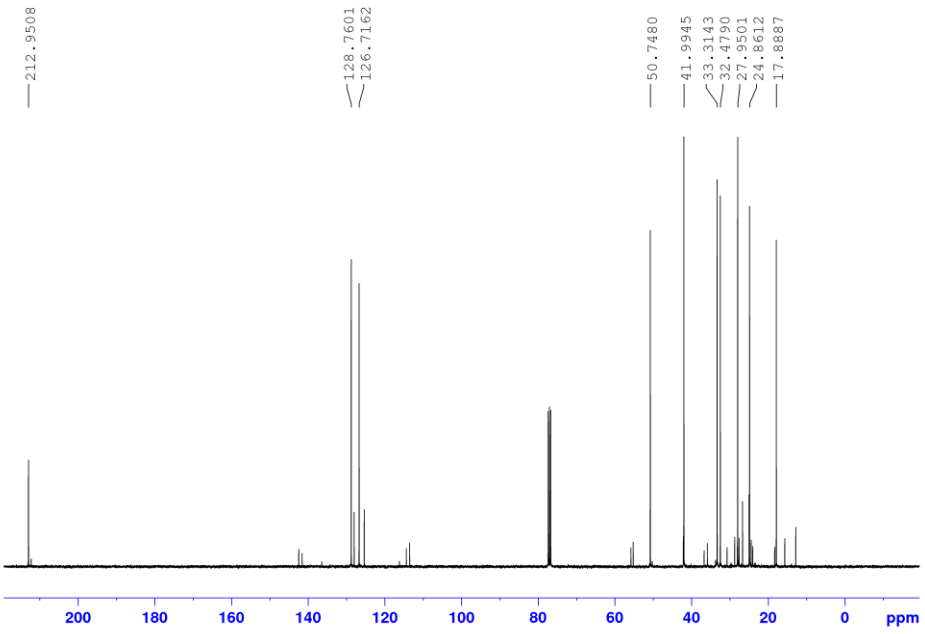
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120
100
80
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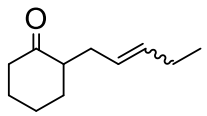
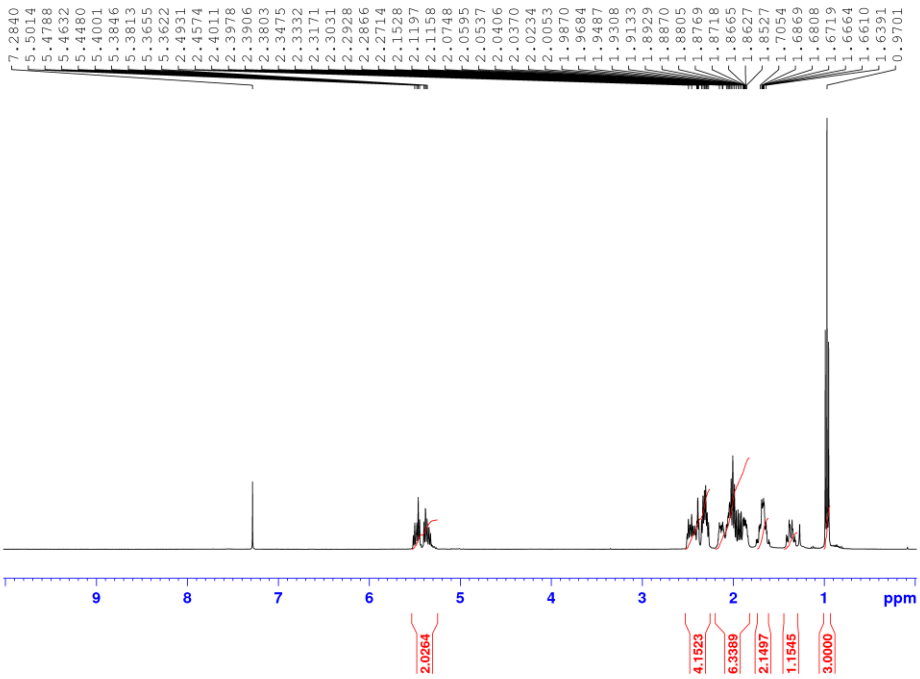
40
20
0
ppm

3

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5.3655
5.3622
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2.4574
2.4011
2.3978
2.3906
2.3803
2.3475
2.3332
2.3171
2.3031
2.2928
2.2866
2.2714
2.1528
2.1197
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2.0748
2.0595
2.0537
2.0406
2.0370
2.0234
2.0053
1.9870
1.9684
1.9487
1.9308
1.9133
1.8929
1.8870
1.8805
1.8769
1.8718
1.8665
1.8627
1.8527
1.7054
1.6869
1.6808
1.6719
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1.6610
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0.9701
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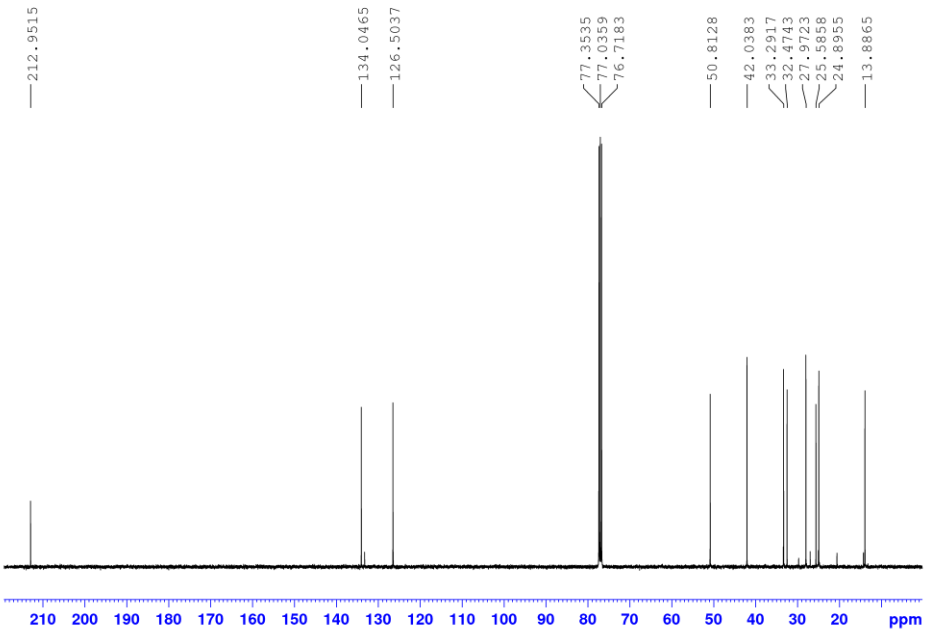
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150
140
130
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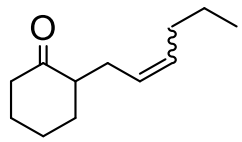
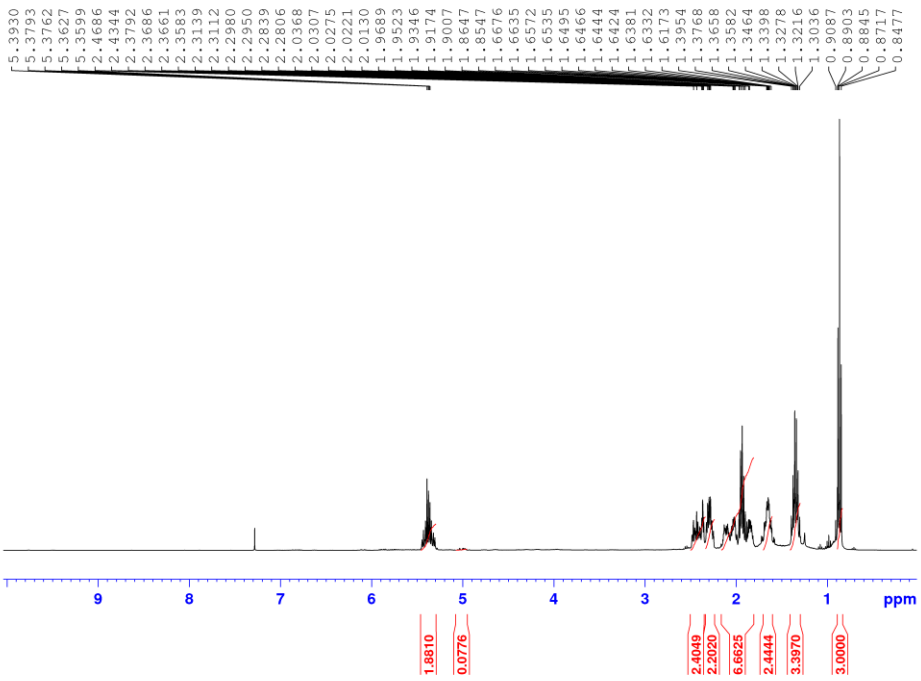
30
20
ppm

4

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2.3583
2.3139
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2.2980
2.2950
2.2839
2.2806
2.0368
2.0307
2.0275
2.0221
2.0130
1.9689
1.9523
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1.6635
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1.6535
1.6495
1.6466
1.6444
1.6424
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1.3658
1.3582
1.3464
1.3398
1.3278
1.3216
1.3036
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0.8903
0.8845
0.8717
0.8477
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8
7
6
5
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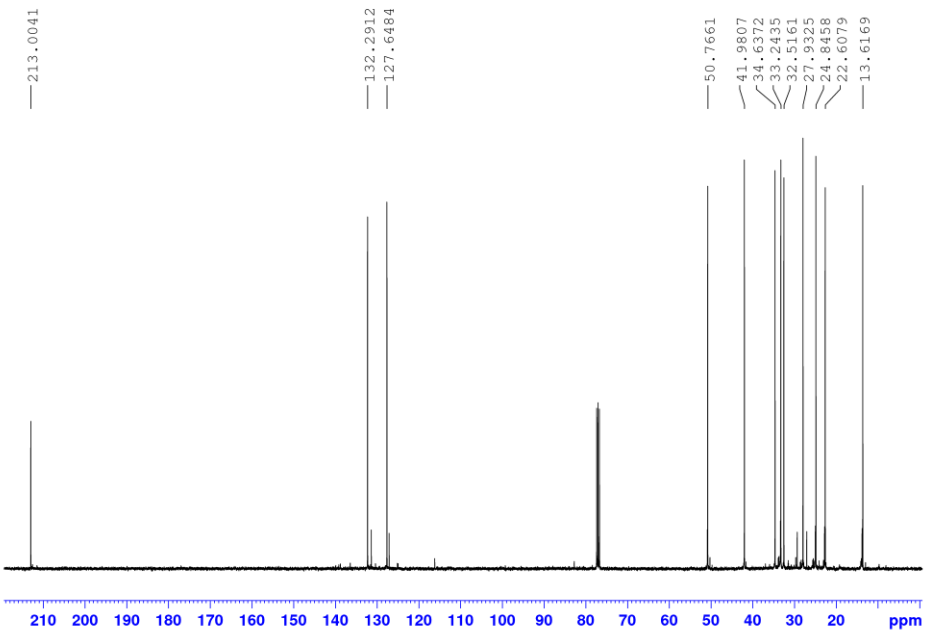
3.0000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150
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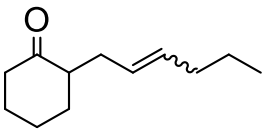
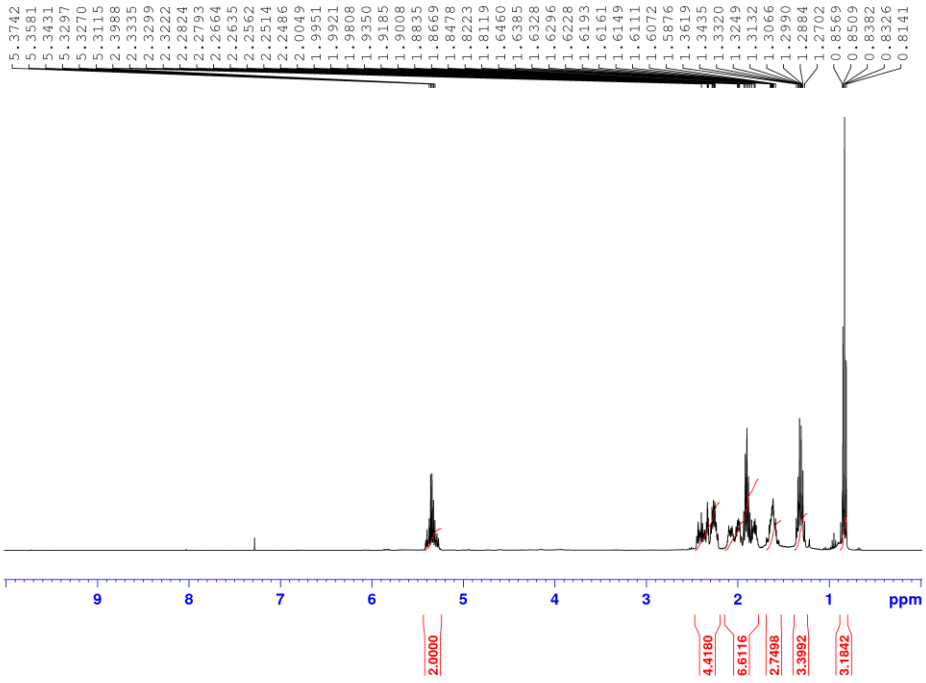
30
20
ppm

5

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2.3299
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2.2793
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2.2635
2.2562
2.2514
2.2486
2.0049
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1.9921
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1.9185
1.9008
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1.8223
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1.6385
1.6328
1.6296
1.6228
1.6193
1.6161
1.6149
1.6111
1.6072
1.5876
1.3619
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1.3320
1.3249
1.3132
1.3066
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1.2702
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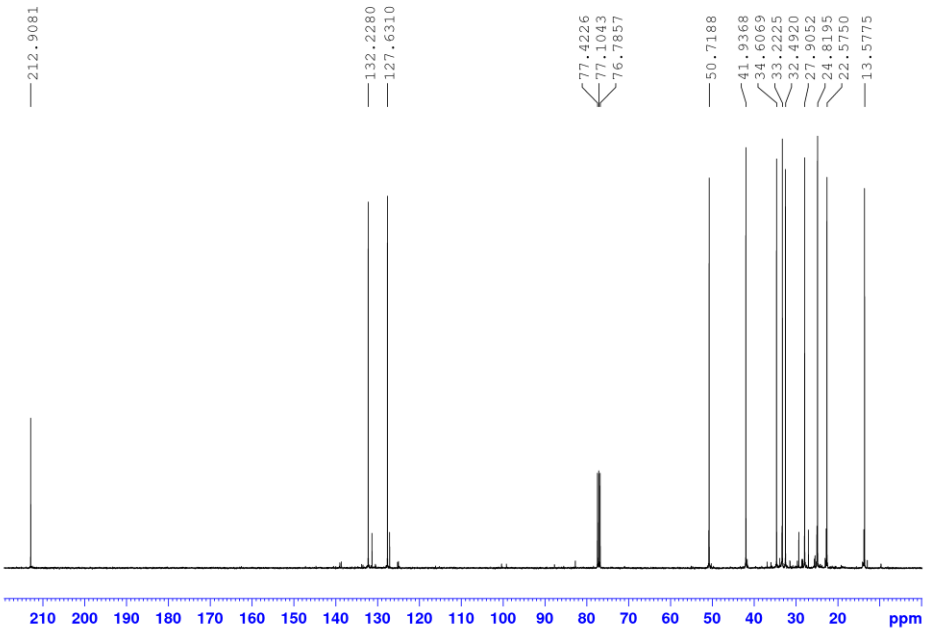
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27.9052
24.8195
22.5750
13.5775
210
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150
140
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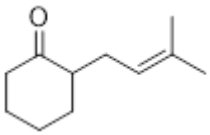
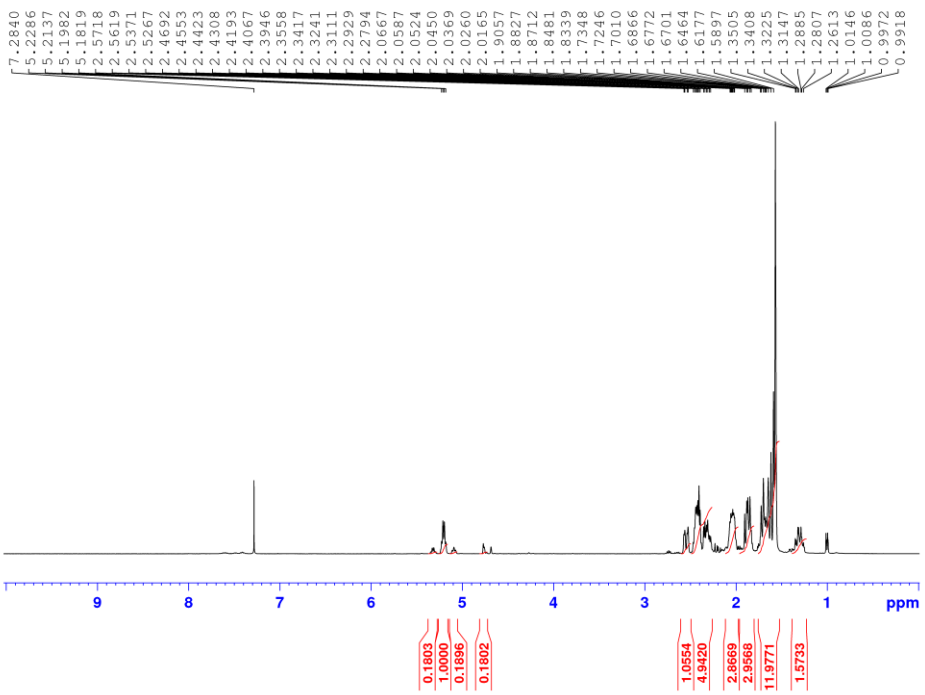
30
20
ppm

6

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2.3558
2.3417
2.3241
2.3111
2.2929
2.2794
2.0667
2.0587
2.0524
2.0450
2.0369
2.0260
2.0165
1.9057
1.8827
1.8712
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1.8339
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1.7246
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1.6866
1.6772
1.6701
1.6464
1.6177
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1.3505
1.3408
1.3225
1.3147
1.2885
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1.0146
1.0086
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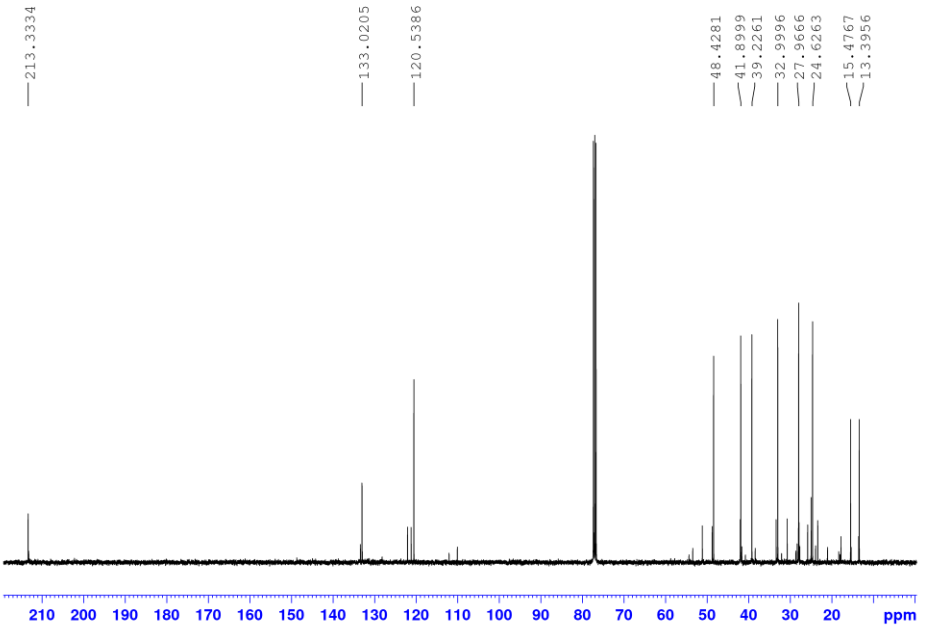
1.5733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150
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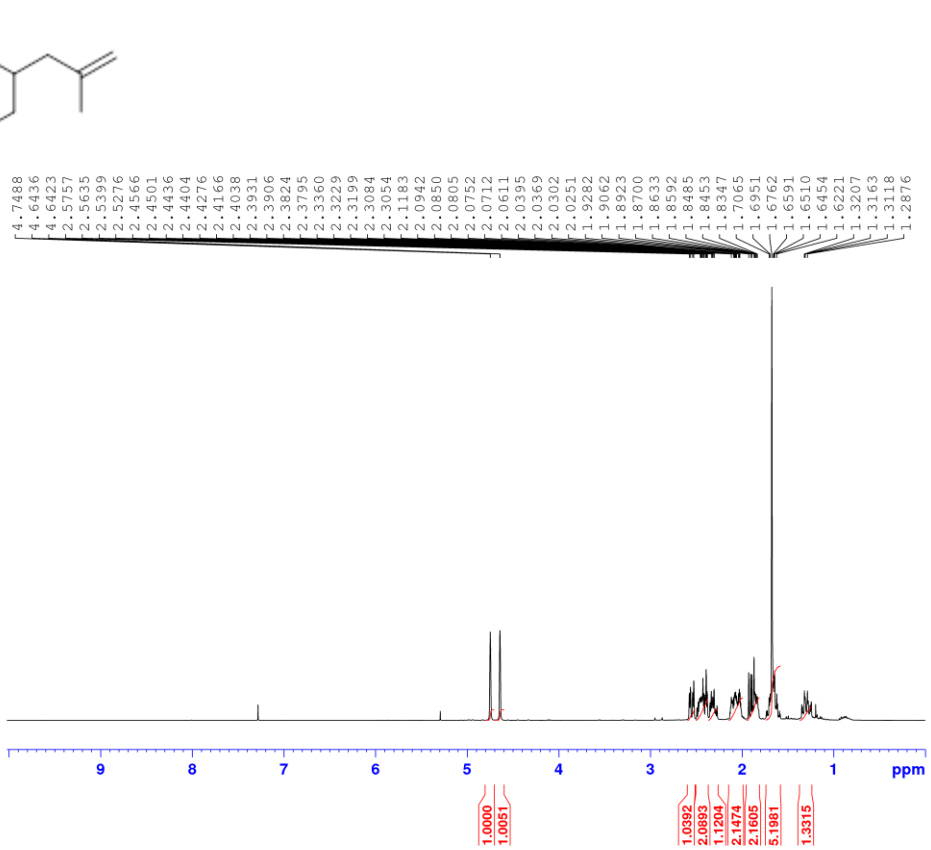
30
20
ppm

7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2.4276
2.4166
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2.3931
2.3906
2.3824
2.3795
2.3360
2.3229
2.3199
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2.3054
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2.0850
2.0805
2.0752
2.0712
2.0611
2.0395
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2.0302
2.0251
1.9282
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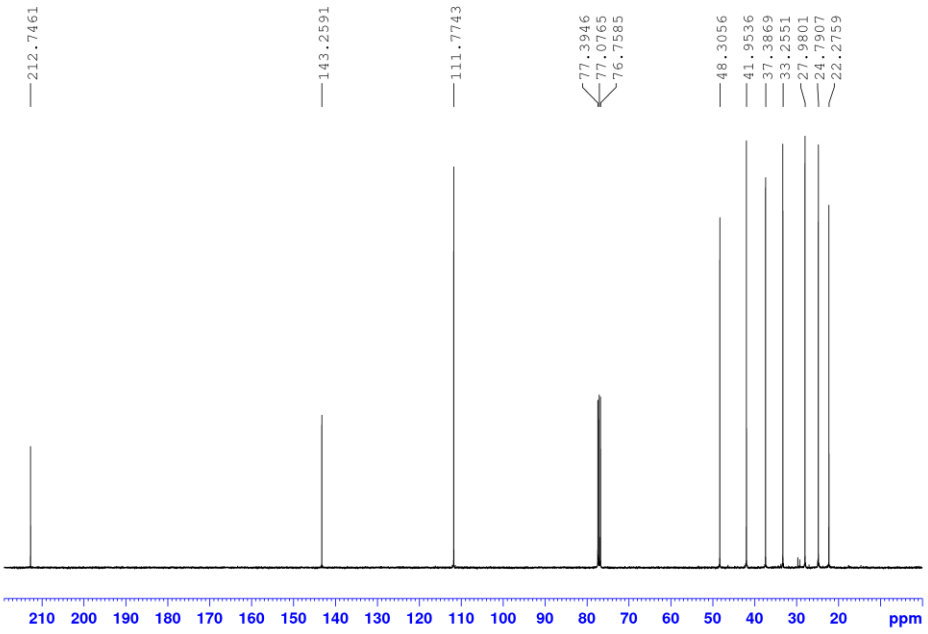
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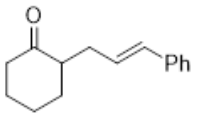
8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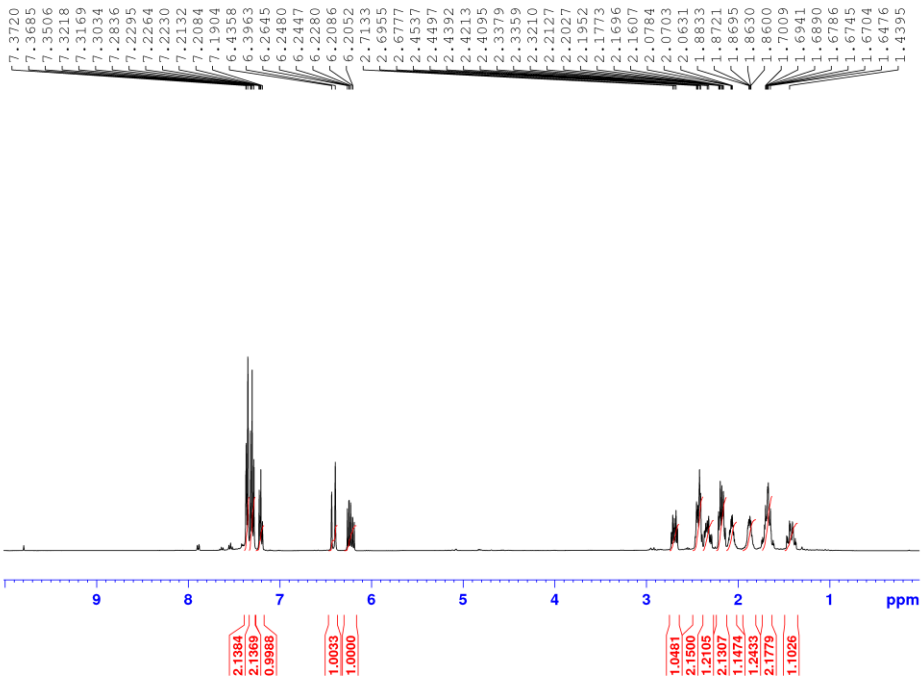
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7.2084
7.1904
6.4358
6.3963
6.2645
6.2480
6.2447
6.2280
6.2086
6.2052
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2.6777
2.4537
2.4497
2.4392
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2.3379
2.3359
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2.2127
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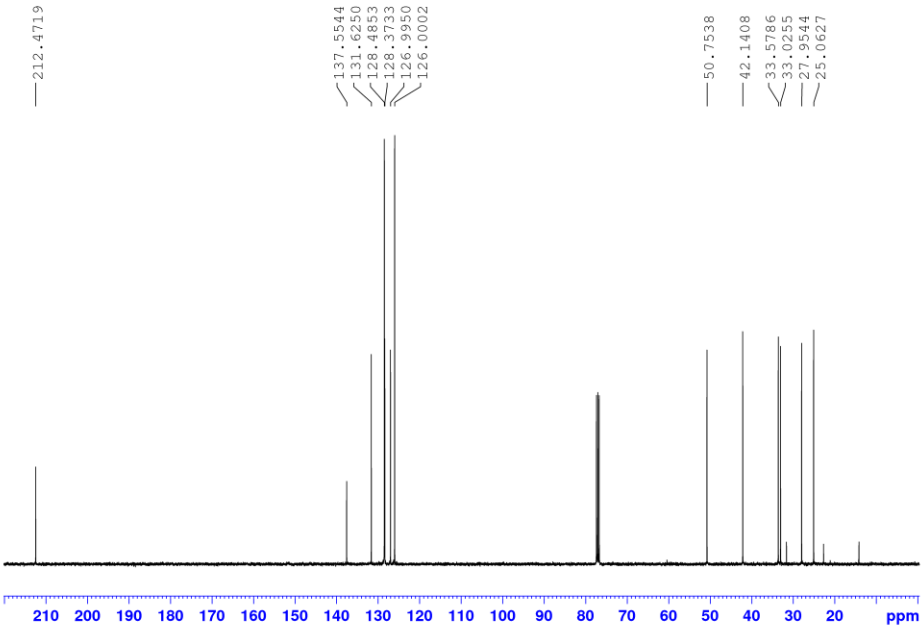
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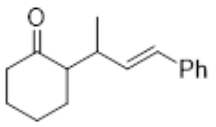
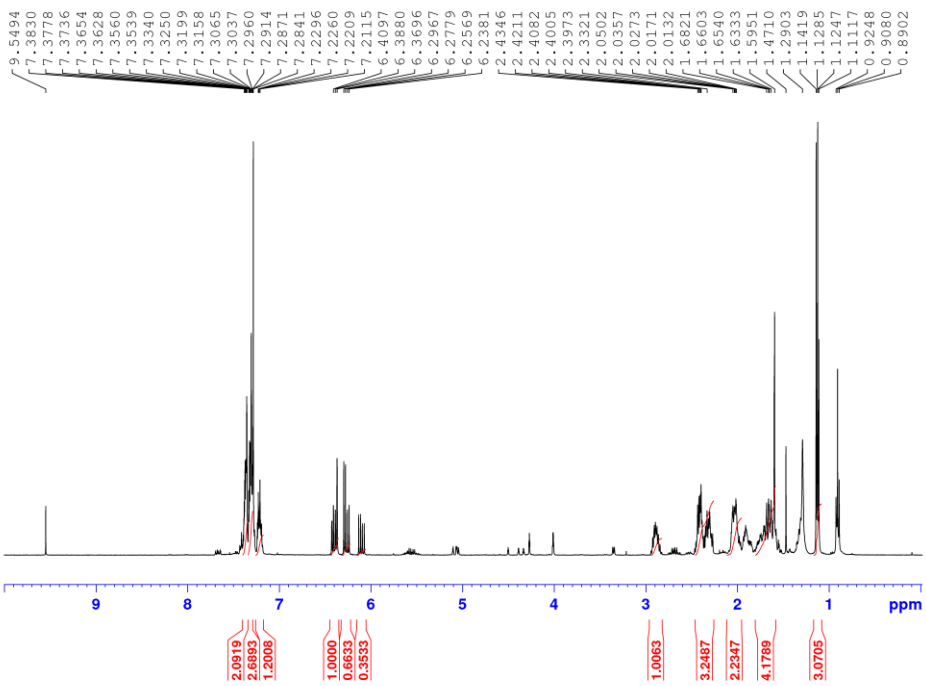
ppm

9


O
Ph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2.0132
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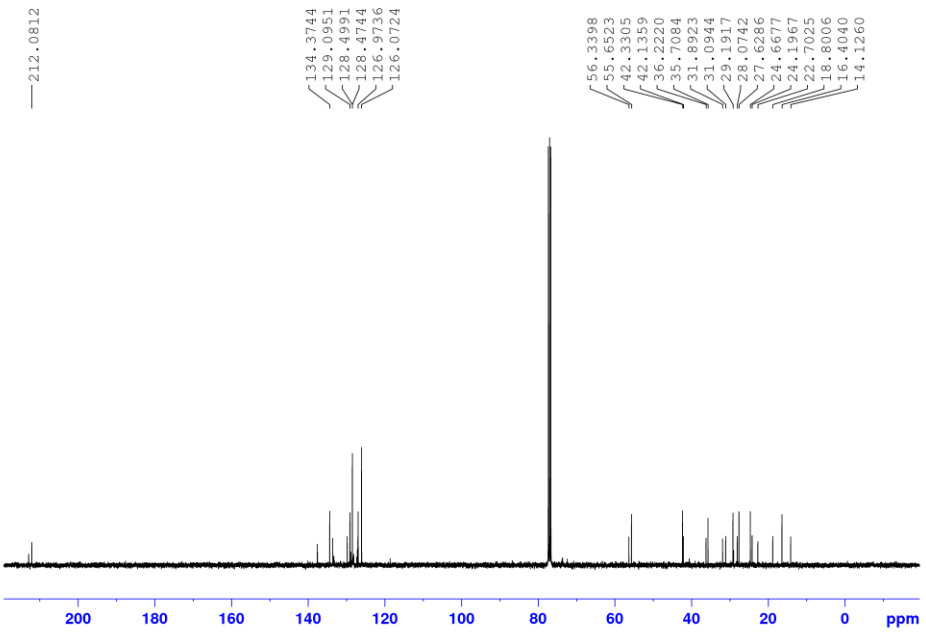
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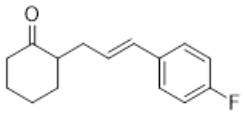
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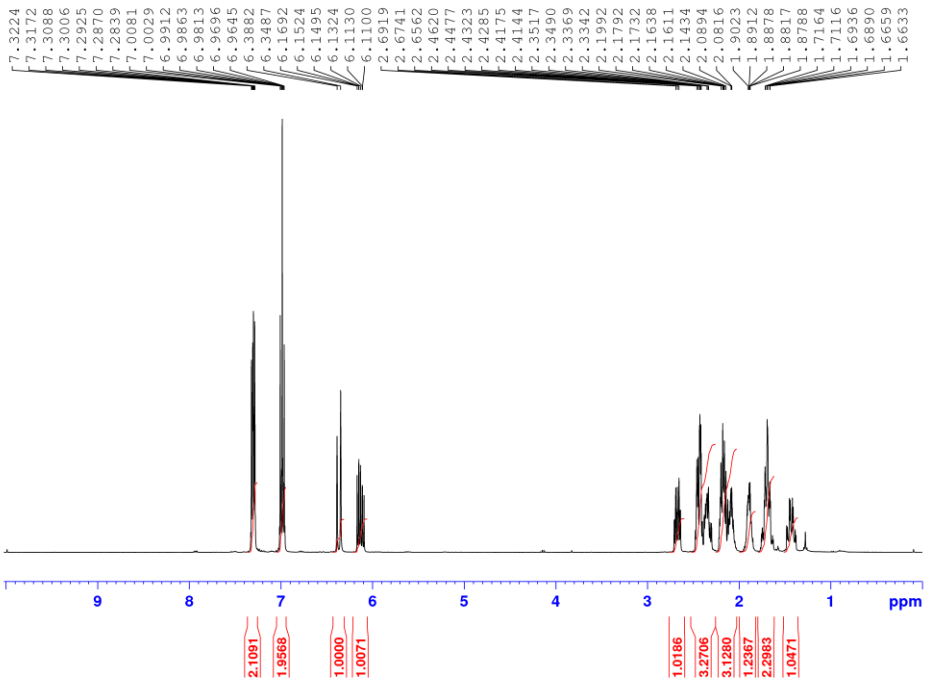
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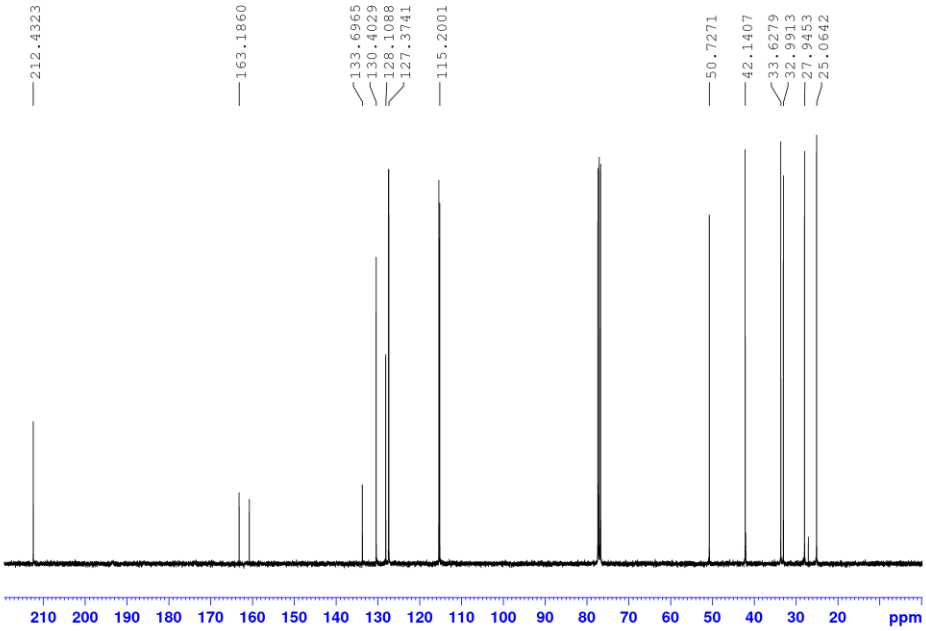
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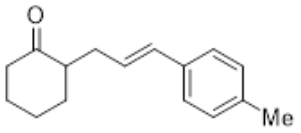
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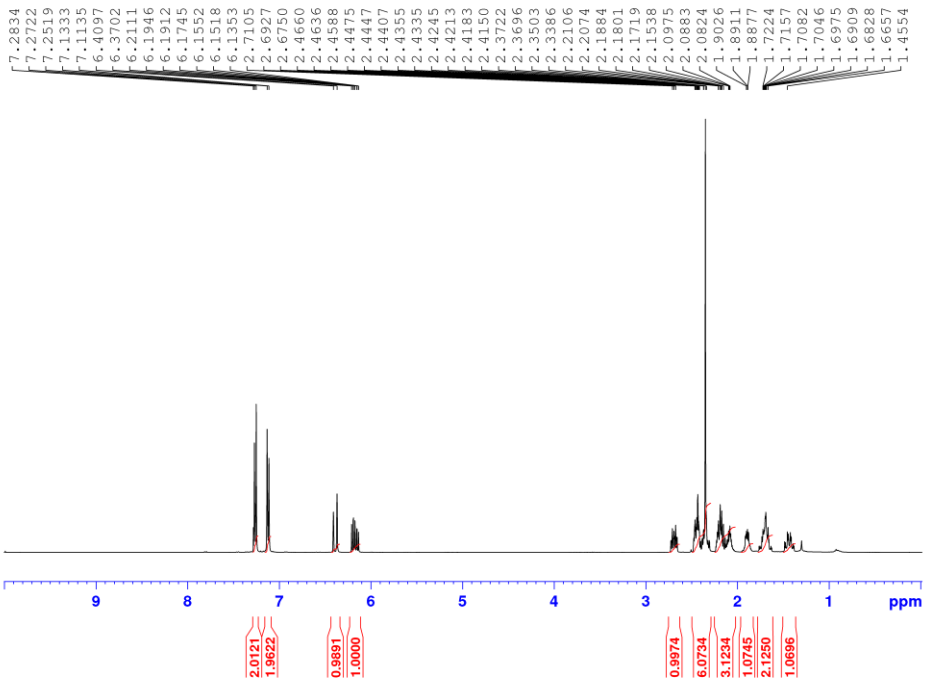
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2.4447
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2.3386
2.2106
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2.1801
2.1719
2.1538
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1.7082
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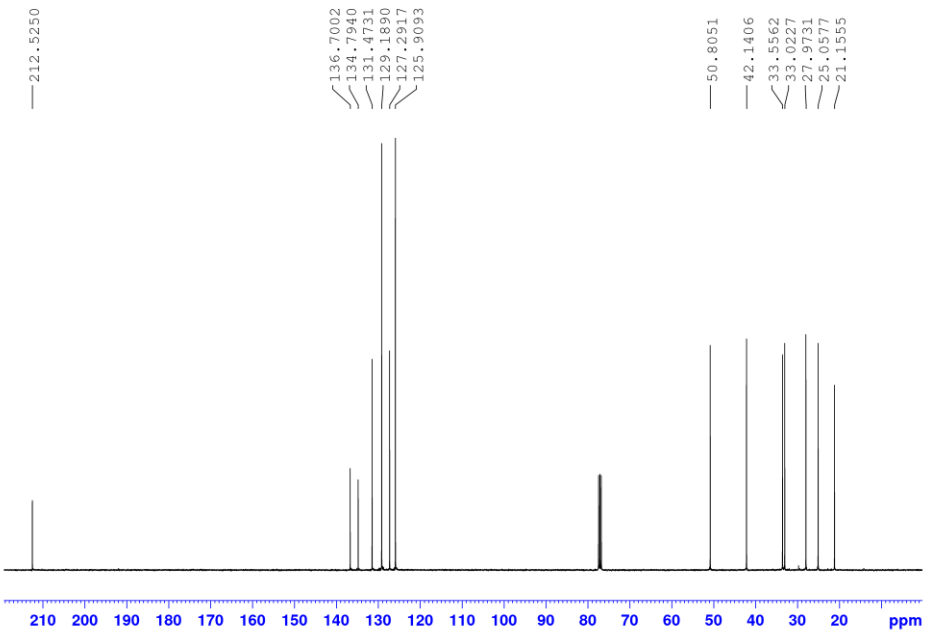
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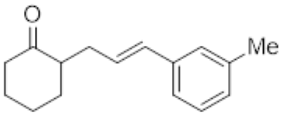
12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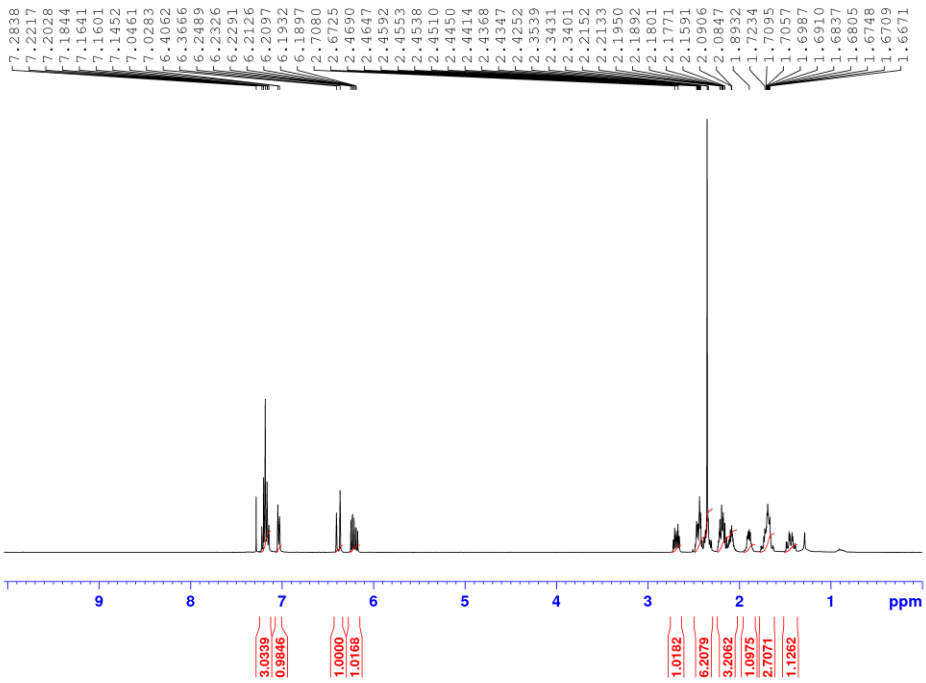
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6.2097
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6.1897
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2.4690
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2.4592
2.4553
2.4538
2.4510
2.4450
2.4414
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2.3539
2.3431
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2.1892
2.1801
2.1771
2.1591
2.0906
2.0847
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1.7095
1.7057
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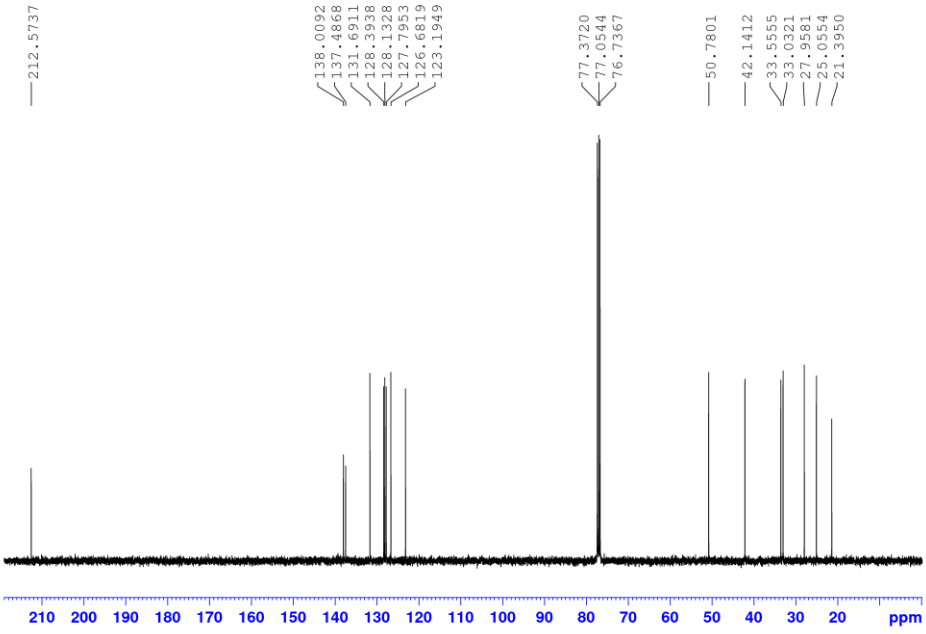
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76.7367
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42.1412
33.5555
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27.9581
25.0554
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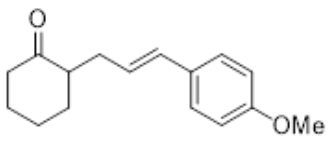
ppm

13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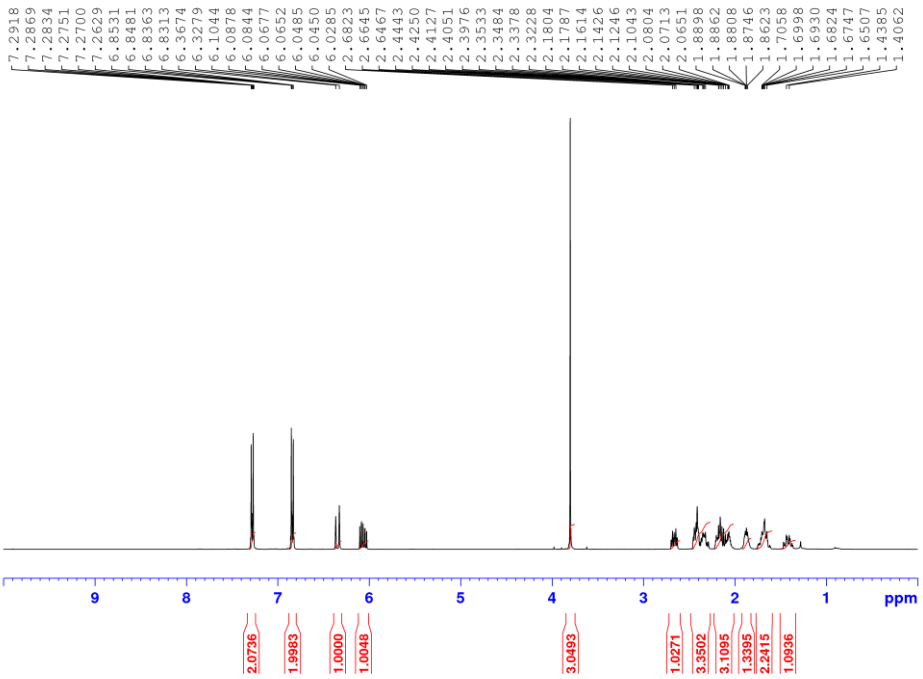
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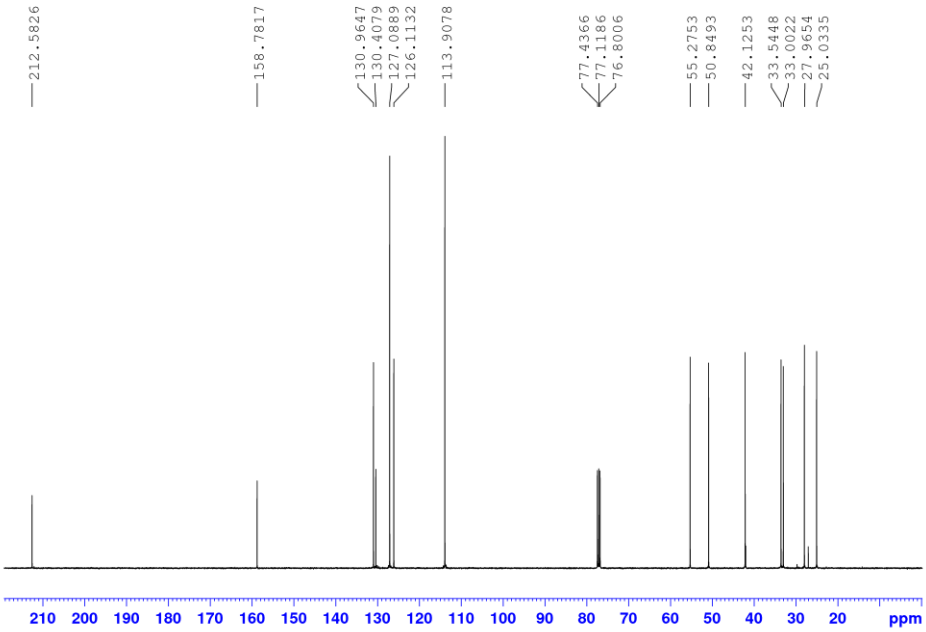
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33.0022
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140
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120
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70
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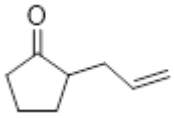
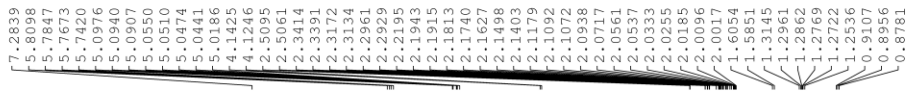
30
20
ppm

14

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5.0474
5.0441
5.0186
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4.1246
2.5095
2.5061
2.3414
2.3391
2.3172
2.3134
2.2961
2.2929
2.2195
2.1943
2.1915
2.1813
2.1740
2.1627
2.1498
2.1403
2.1179
2.1092
2.1072
2.0938
2.0717
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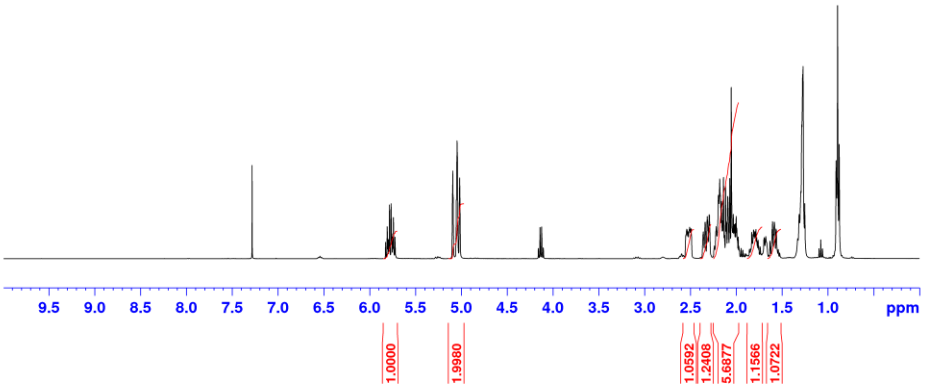
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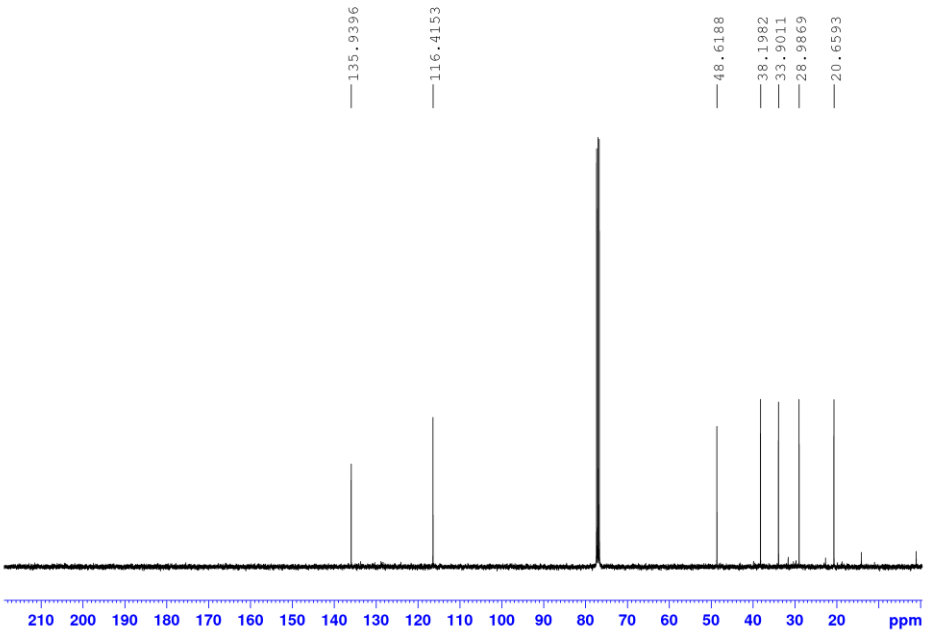
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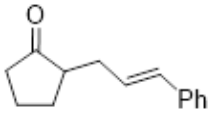
15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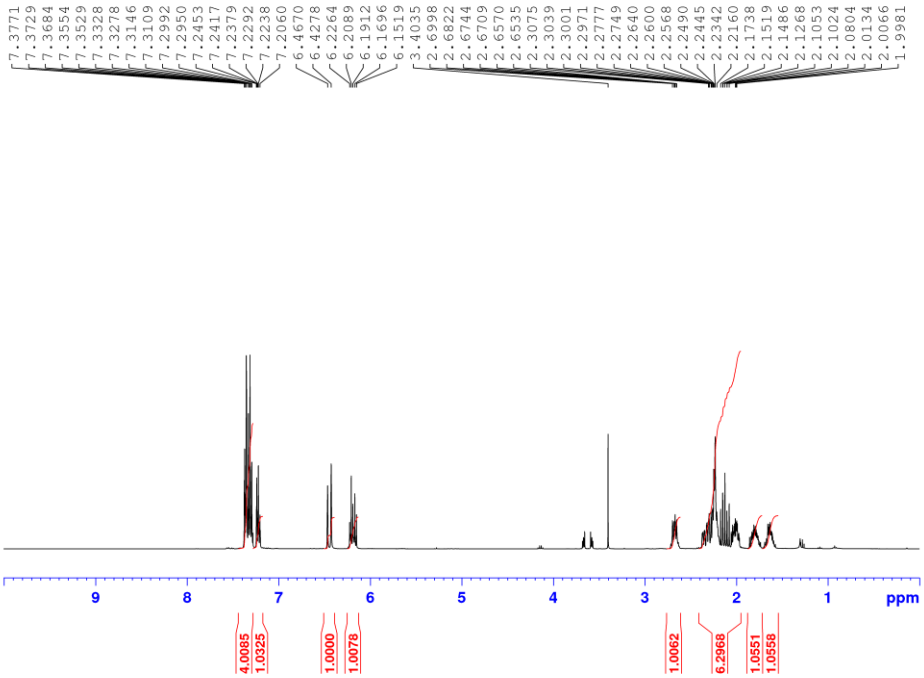
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7.2417
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7.2292
7.2238
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6.4278
6.2264
6.2089
6.1912
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6.1519
3.4035
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2.6744
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2.2640
2.2600
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2.2490
2.2445
2.2342
2.2160
2.1738
2.1519
2.1486
2.1268
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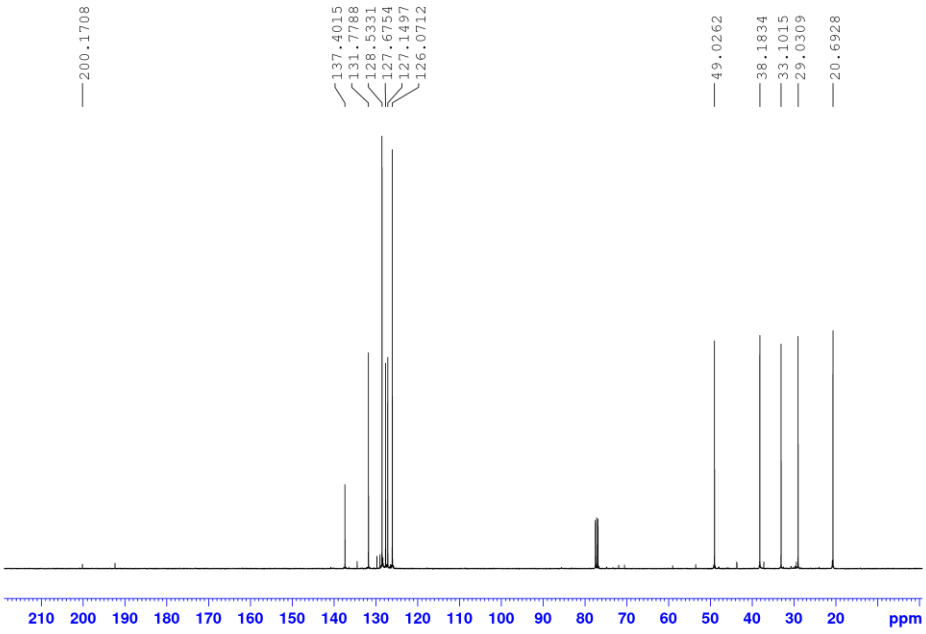
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200
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150
140
130
120
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70
60
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40
30
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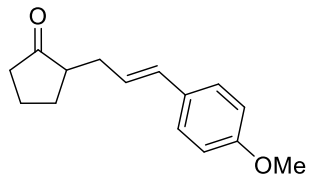
ppm

16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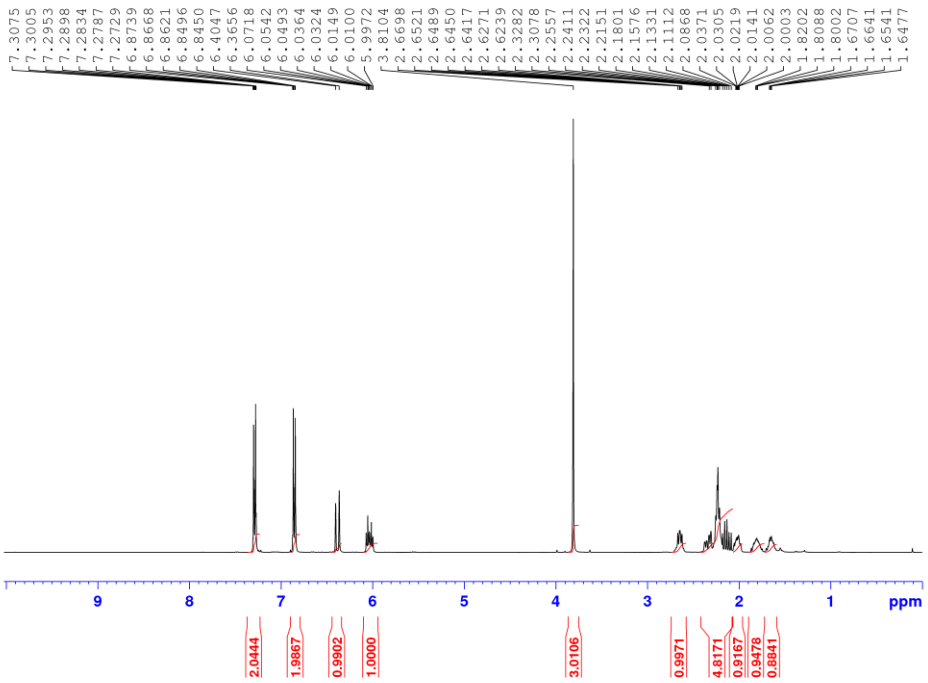
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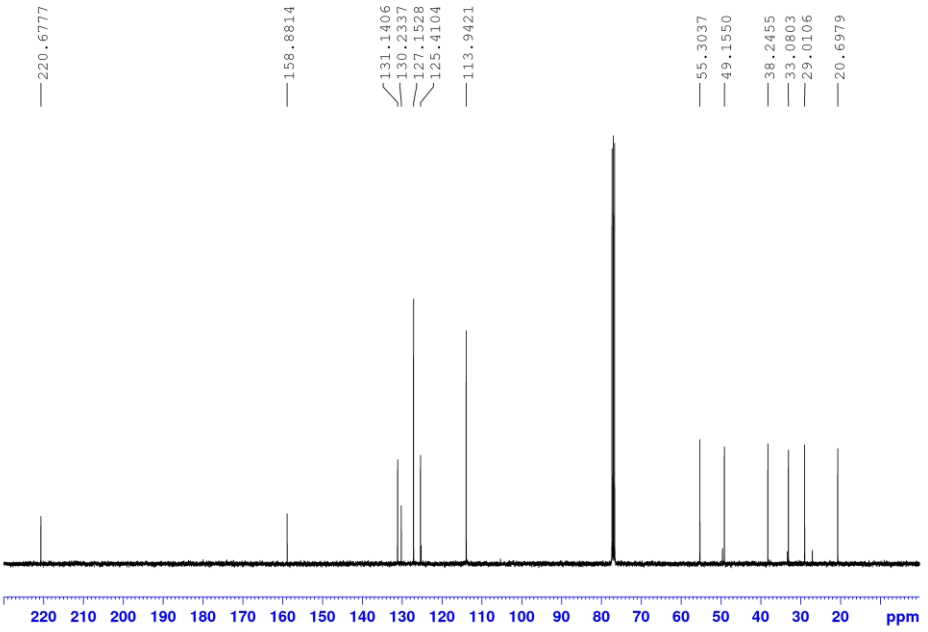
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29.0106
20.6979
220
210
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150
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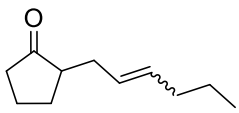
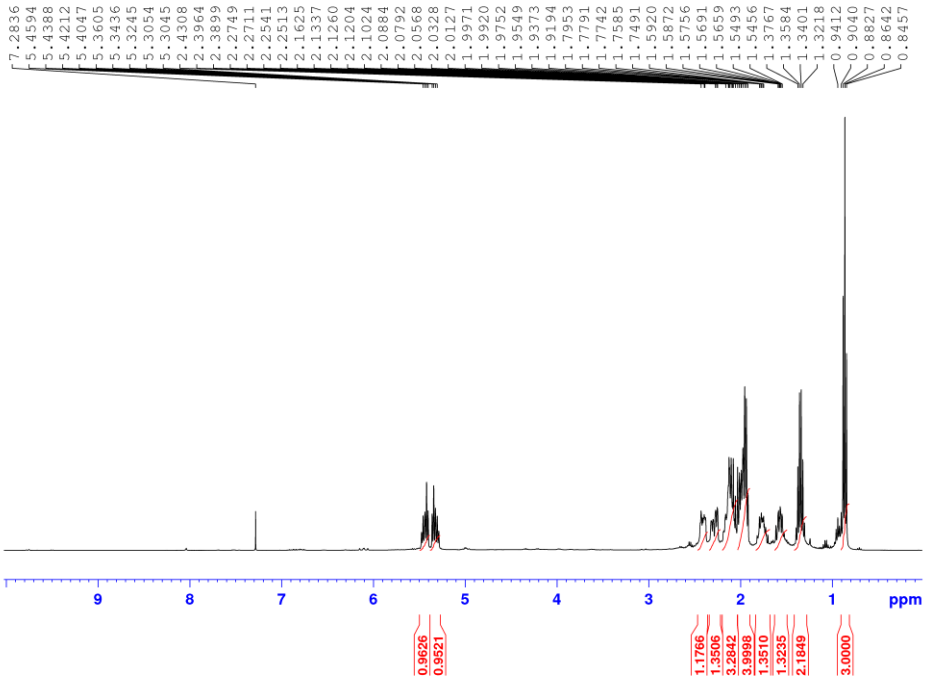
30
20
ppm

17

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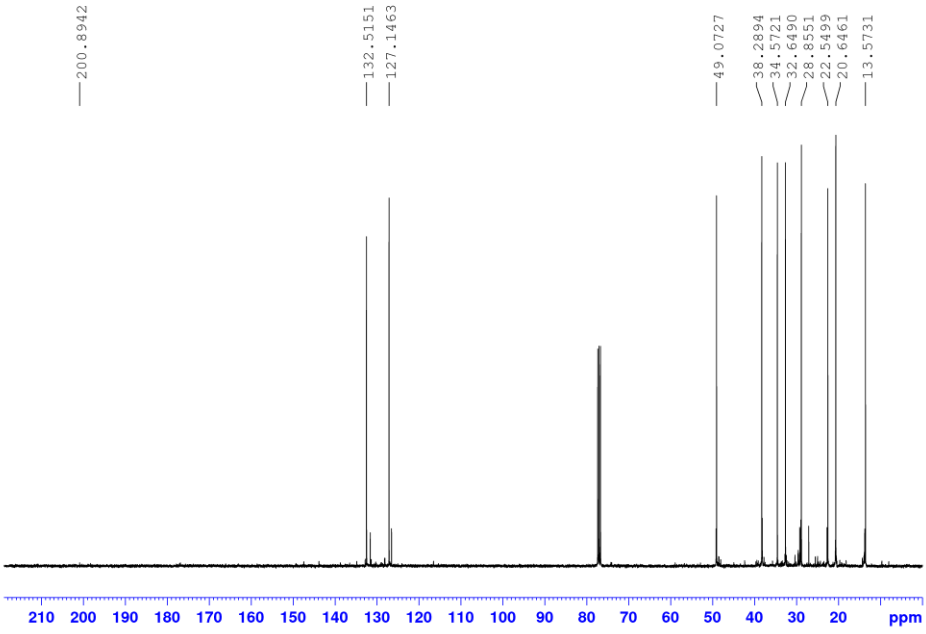
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200
190
180
170
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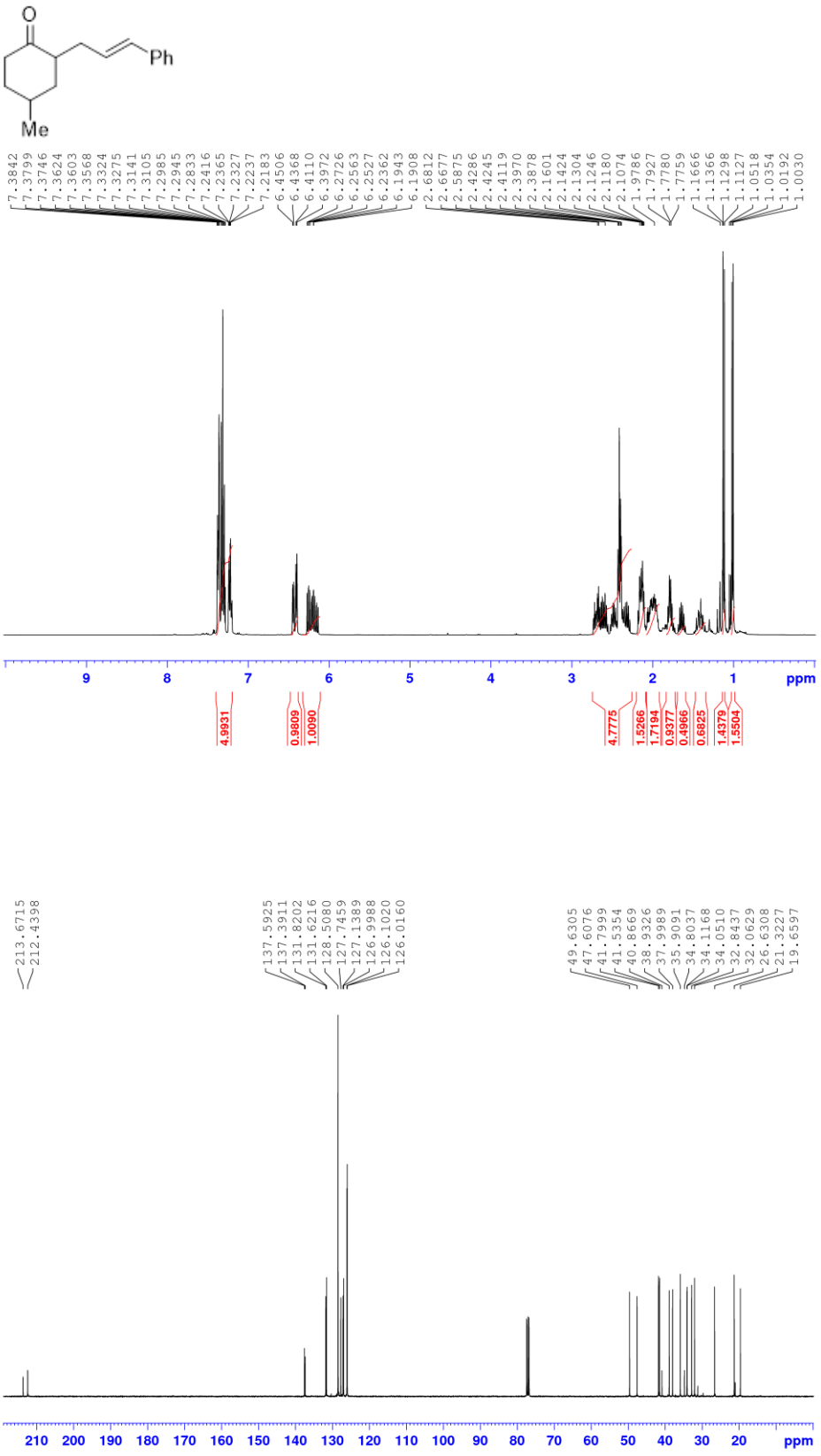
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

18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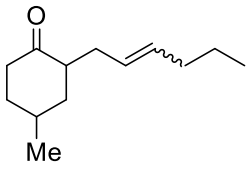
19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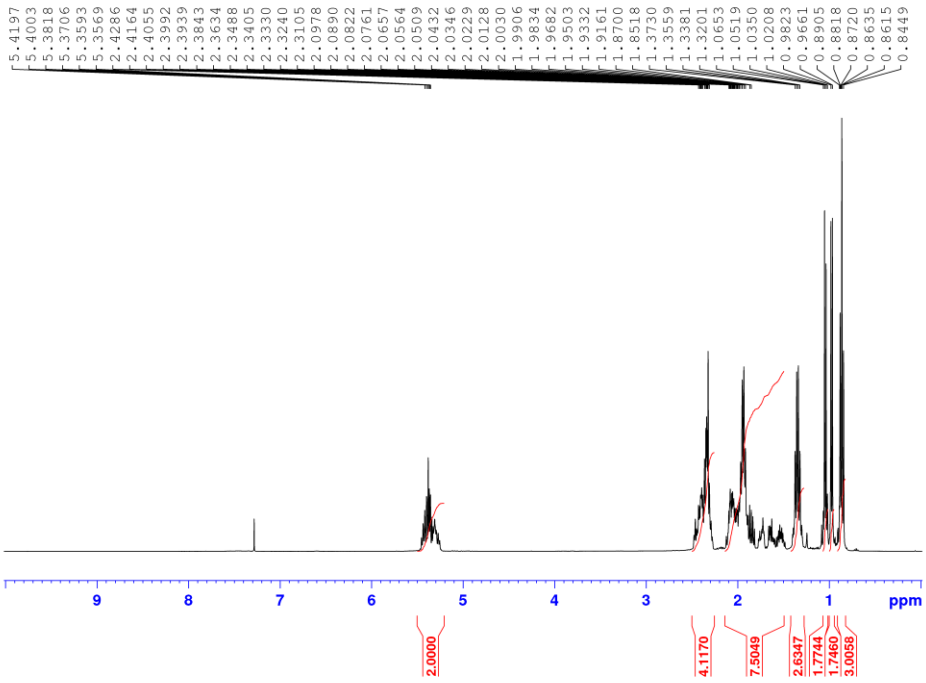
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2.0890
2.0822
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2.0564
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0.8615
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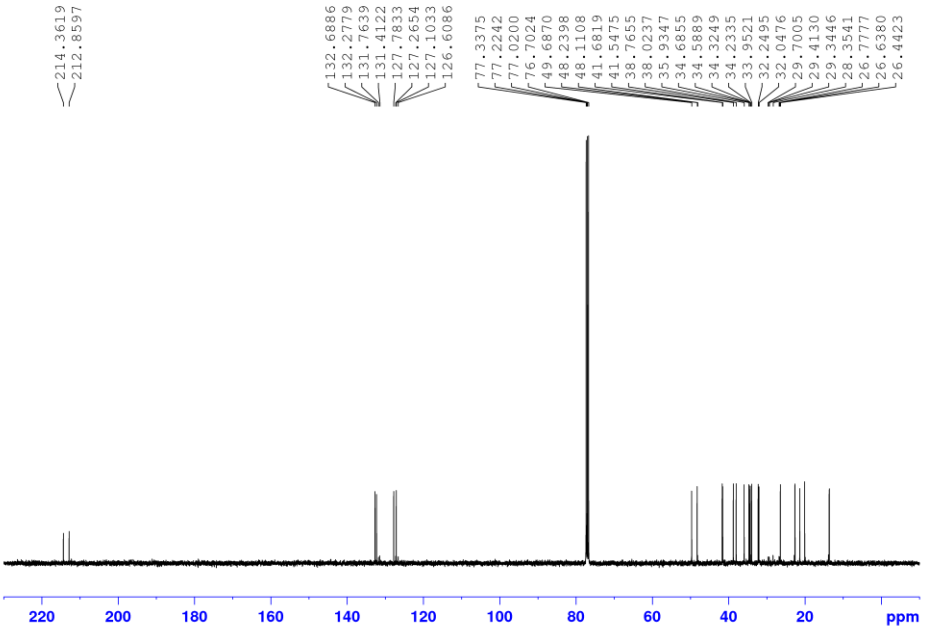
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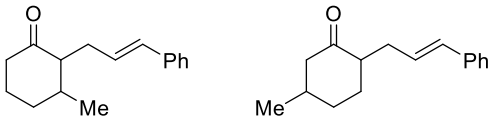
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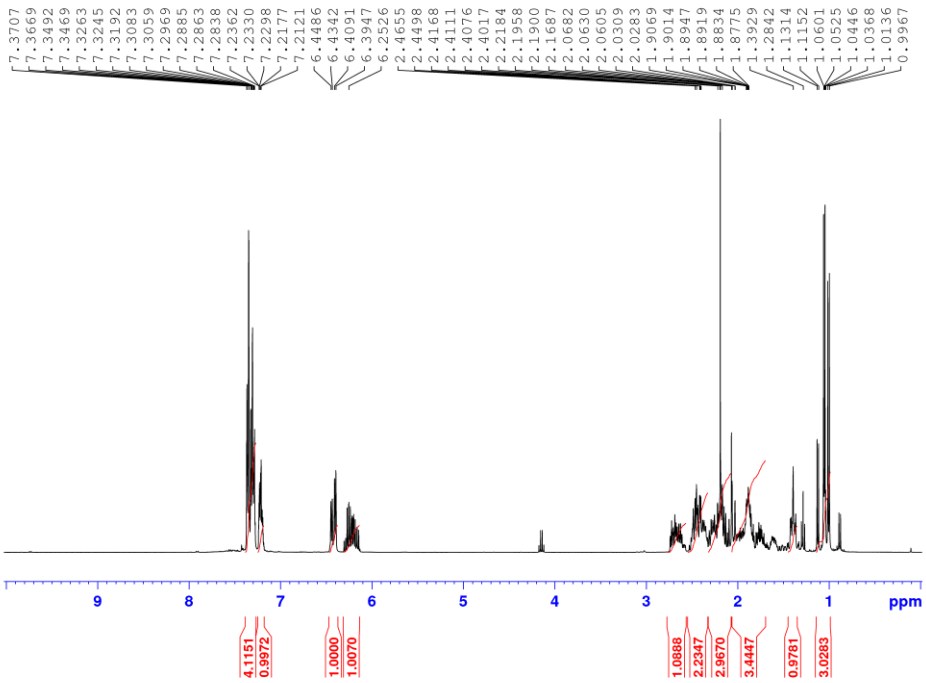
Me
O
Ph
Me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7.2838
7.2362
7.2330
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7.2177
7.2121
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6.4342
6.4091
6.3947
6.2526
2.4655
2.4498
2.4168
2.4111
2.4076
2.4017
2.2184
2.1958
2.1900
2.1687
2.0682
2.0630
2.0605
2.0309
2.0283
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1.9014
1.8947
1.8919
1.8834
1.8775
1.3929
1.2842
1.1314
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1.0525
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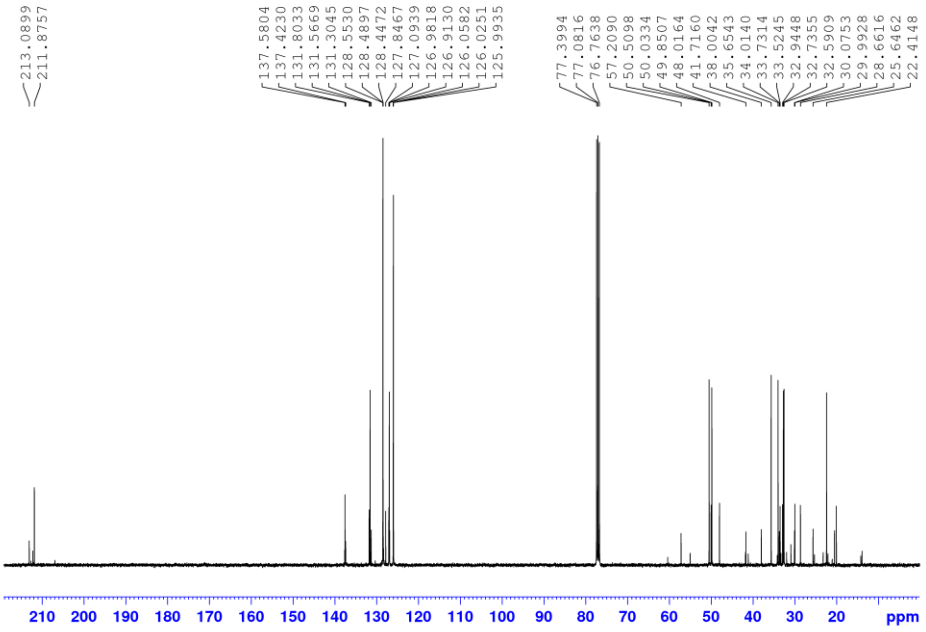
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126.0582
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76.7638
57.2090
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41.7160
38.0042
35.6543
34.0140
33.7314
33.5245
32.9448
32.7355
32.5909
30.0753
29.9928
28.6616
25.6462
22.4148
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70
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30
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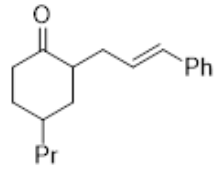
ppm

21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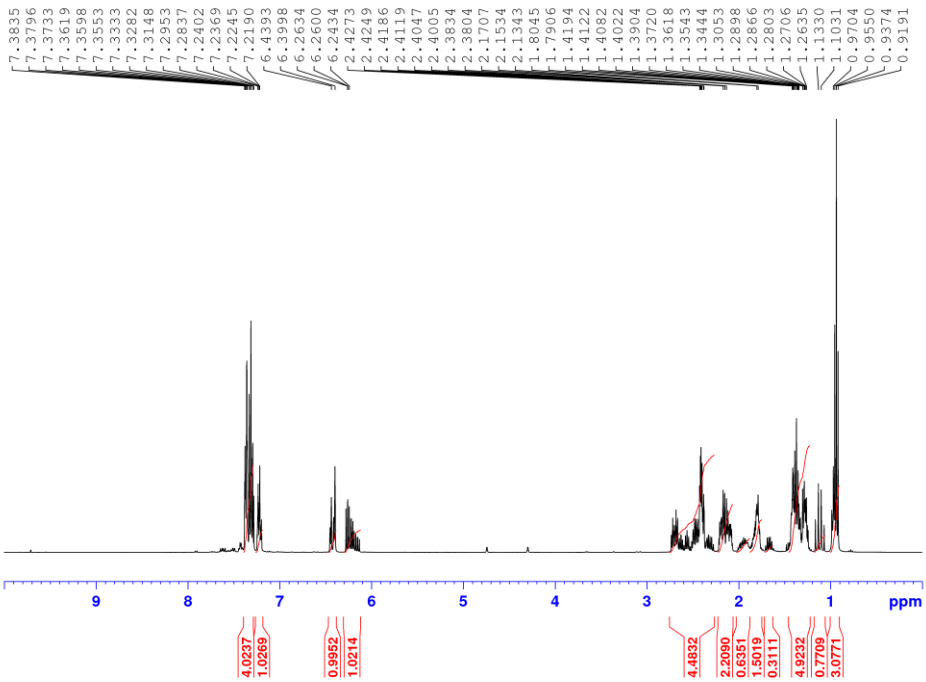
Ph
Pr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7.2369
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7.2190
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6.2634
6.2600
6.2434
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2.4249
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2.3804
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2.1534
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1.4122
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1.3904
1.3720
1.3618
1.3543
1.3444
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1.2803
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1.2635
1.1330
1.1031
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0.9191
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1
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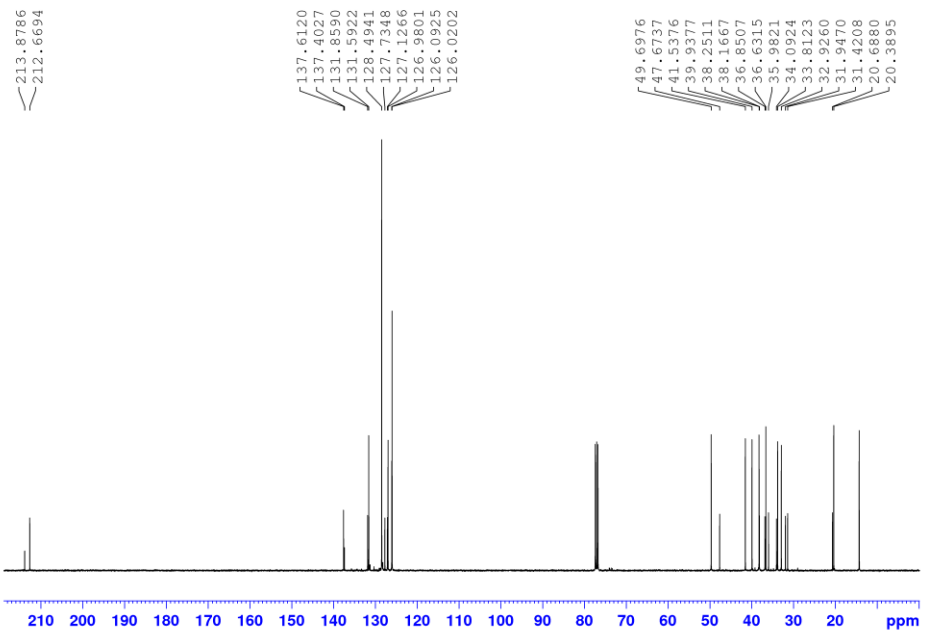
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41.5376
39.9377
38.2511
38.1667
36.8507
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35.9821
34.0924
33.8123
32.9260
31.9470
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20.3895
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150
140
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30
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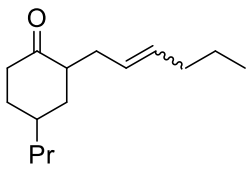
ppm

22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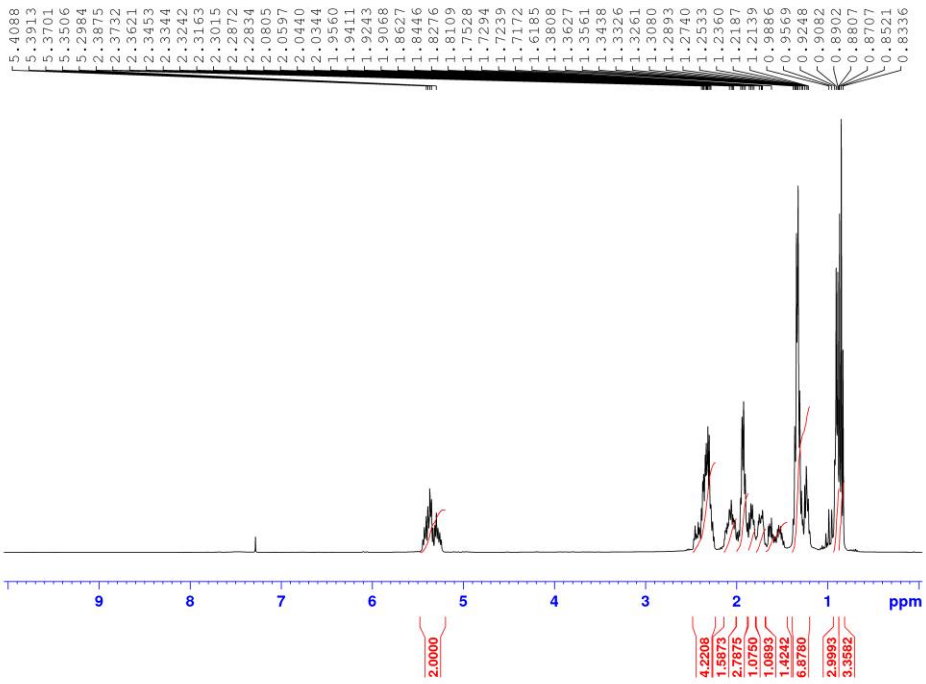
Pr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2.3242
2.3163
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2.2834
2.0805
2.0597
2.0440
2.0344
1.9560
1.9411
1.9243
1.9068
1.8627
1.8446
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1.8109
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1.7294
1.7239
1.7172
1.6185
1.3808
1.3627
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1.3438
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1.2360
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0.9082
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0.8807
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0.8521
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8
7
6
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4
3
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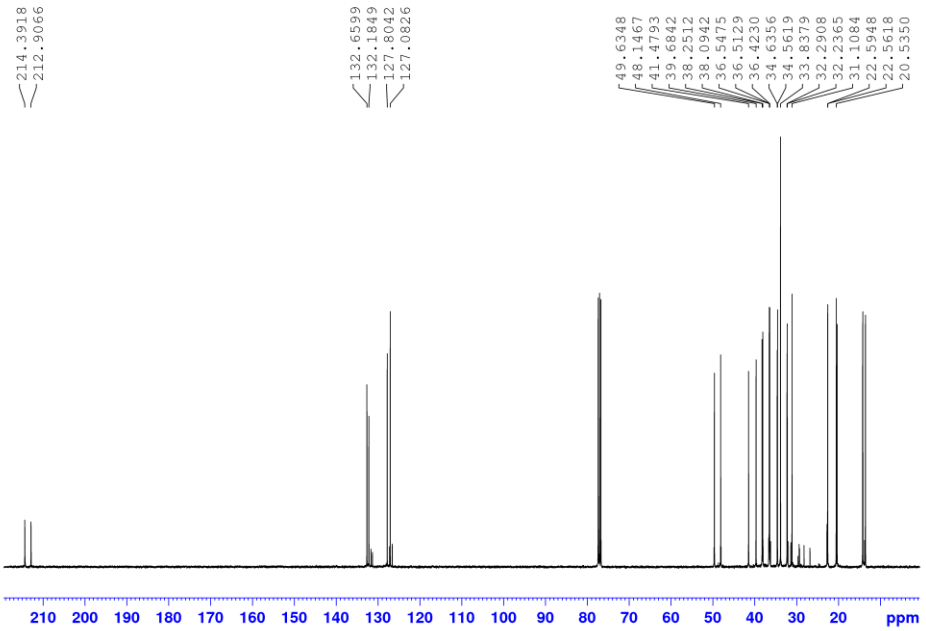
3.3582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36.5129
36.4230
34.6356
34.5619
33.8379
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32.2365
31.1084
22.5948
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20.5350
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150
140
130
120
110
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70
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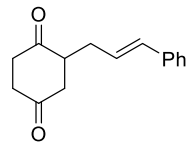
30
20
ppm

23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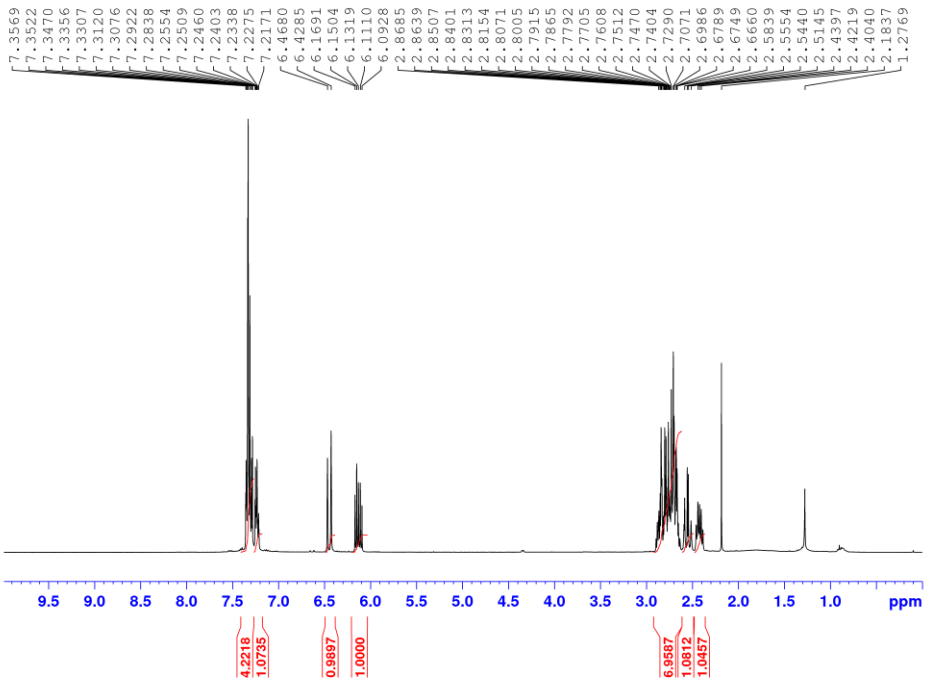
Ph
O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7.2460
7.2403
7.2338
7.2275
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6.4285
6.1691
6.1504
6.1319
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6.0928
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2.8639
2.8507
2.8401
2.8313
2.8154
2.8071
2.8005
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2.7865
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2.7705
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2.7290
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2.5554
2.5440
2.5145
2.4397
2.4219
2.4040
2.1837
1.2769
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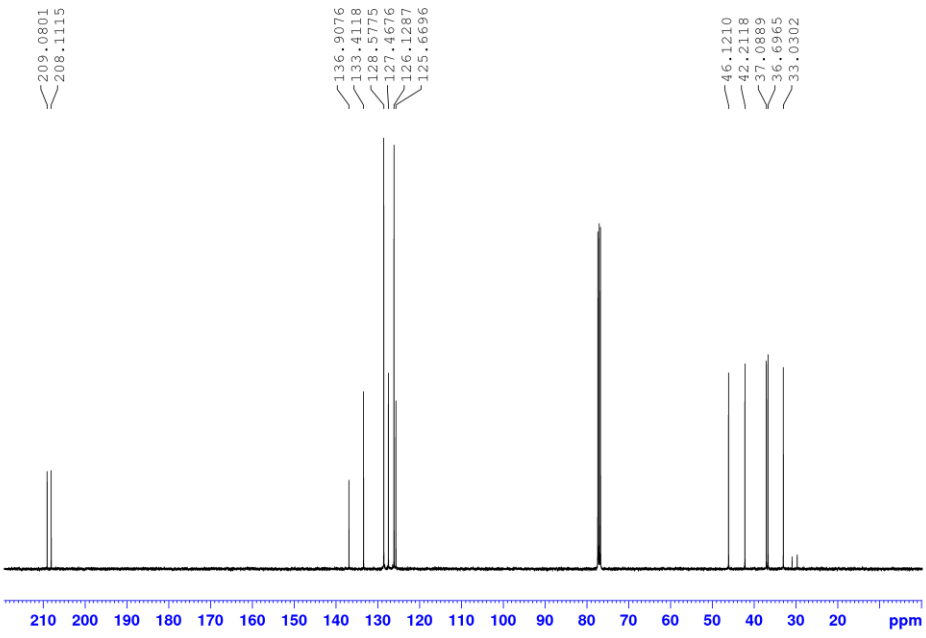
1.0812
1.0457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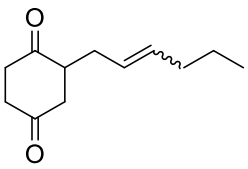
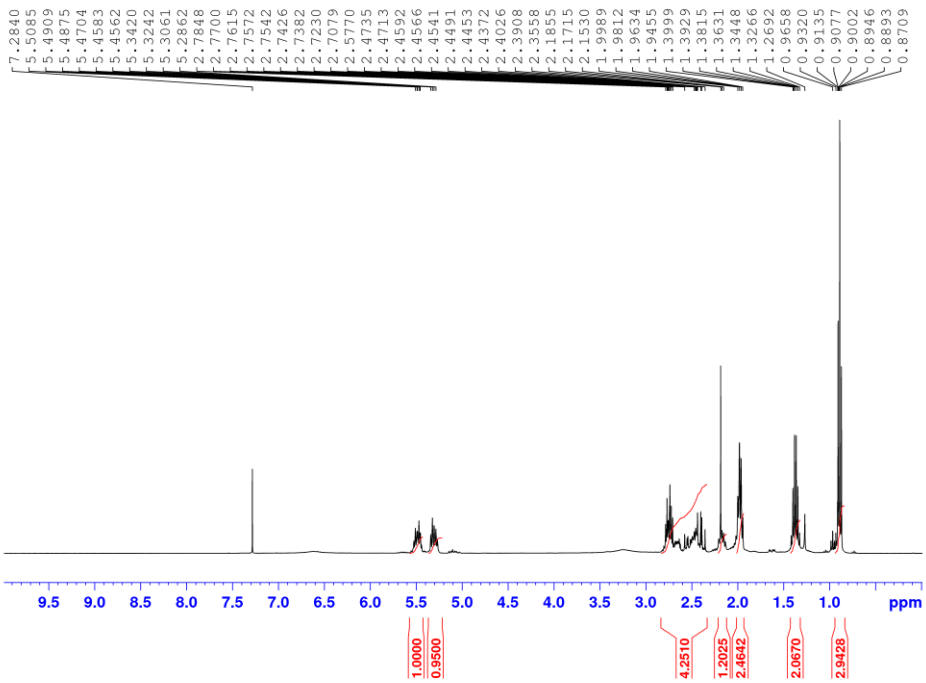
24

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2.7700
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2.7572
2.7542
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1.9634
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1.3999
1.3929
1.3815
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1.3448
1.3266
1.2692
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0.9135
0.9077
0.9002
0.8946
0.8893
0.8709
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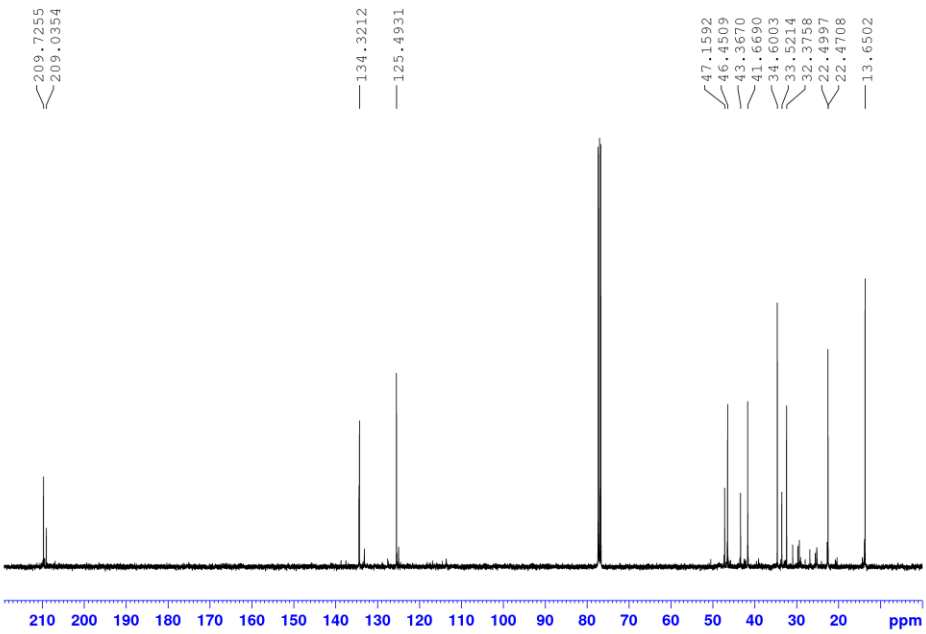
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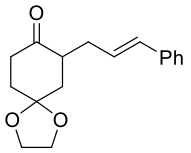
22.4708
13.6502
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

25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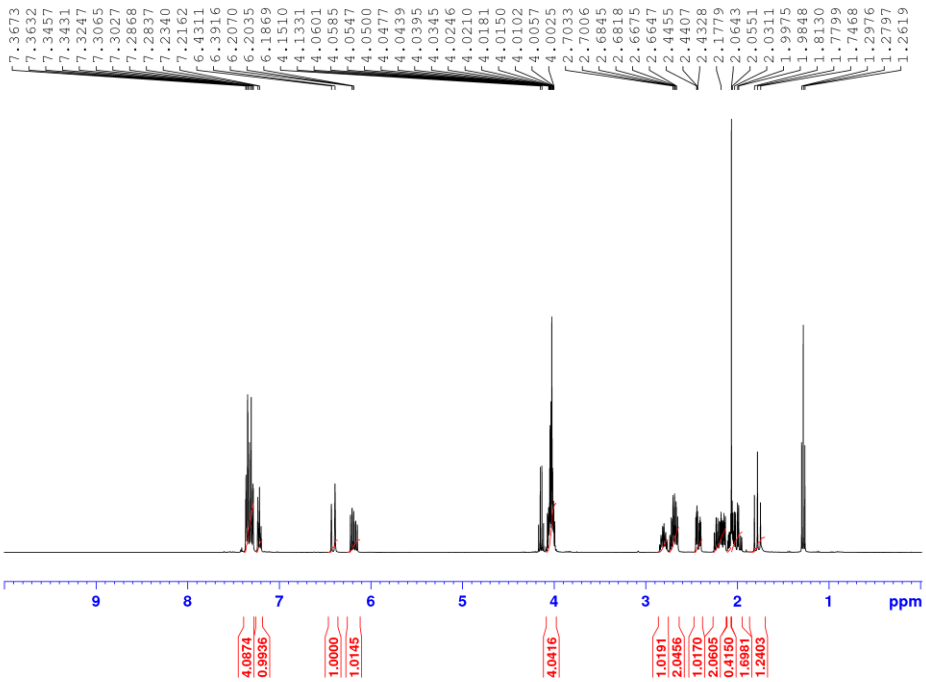
Ph
O
O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6.2070
6.2035
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4.1331
4.0601
4.0585
4.0547
4.0500
4.0477
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4.0395
4.0345
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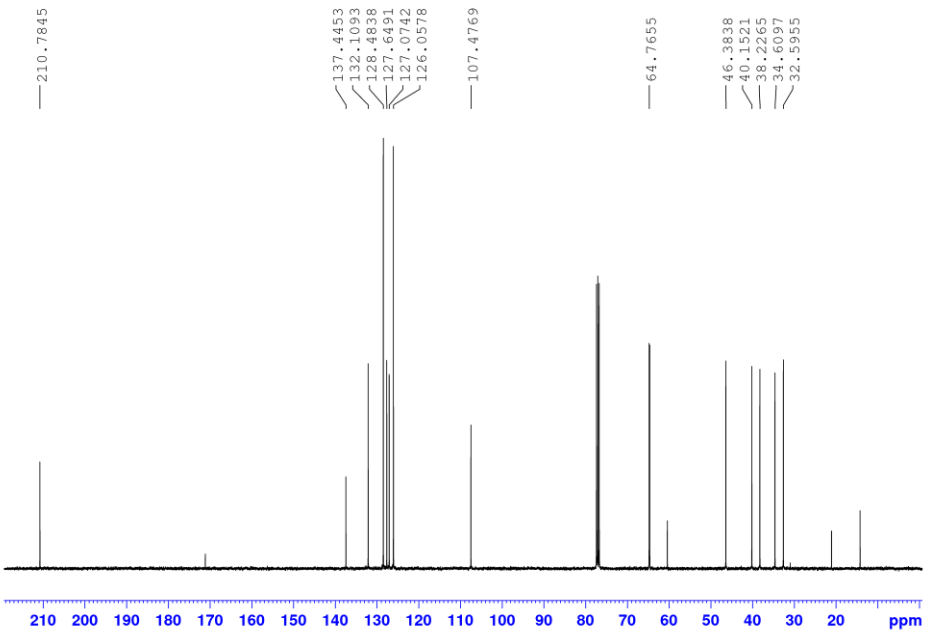
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126.0578
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64.7655
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40.1521
38.2265
34.6097
32.5955
210
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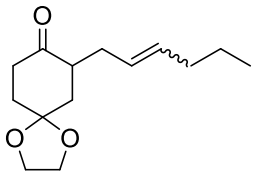
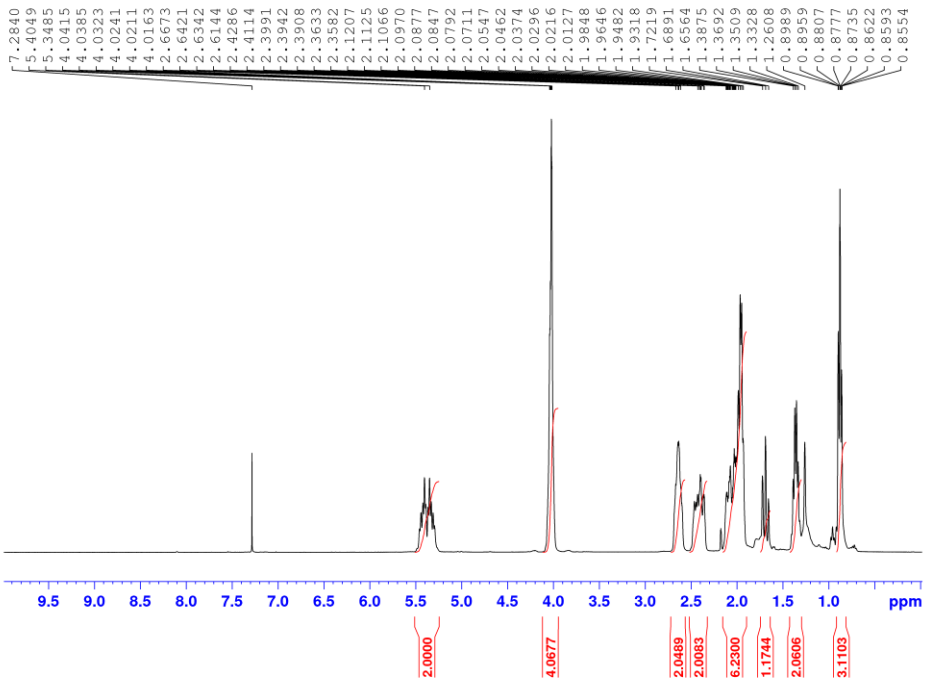
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

26

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2.1125
2.1066
2.0970
2.0877
2.0847
2.0792
2.0711
2.0547
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2.0374
2.0296
2.0216
2.0127
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1.9482
1.9318
1.7219
1.6891
1.6564
1.3875
1.3692
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1.3328
1.2608
0.8989
0.8959
0.8807
0.8777
0.8735
0.8622
0.8593
0.8554
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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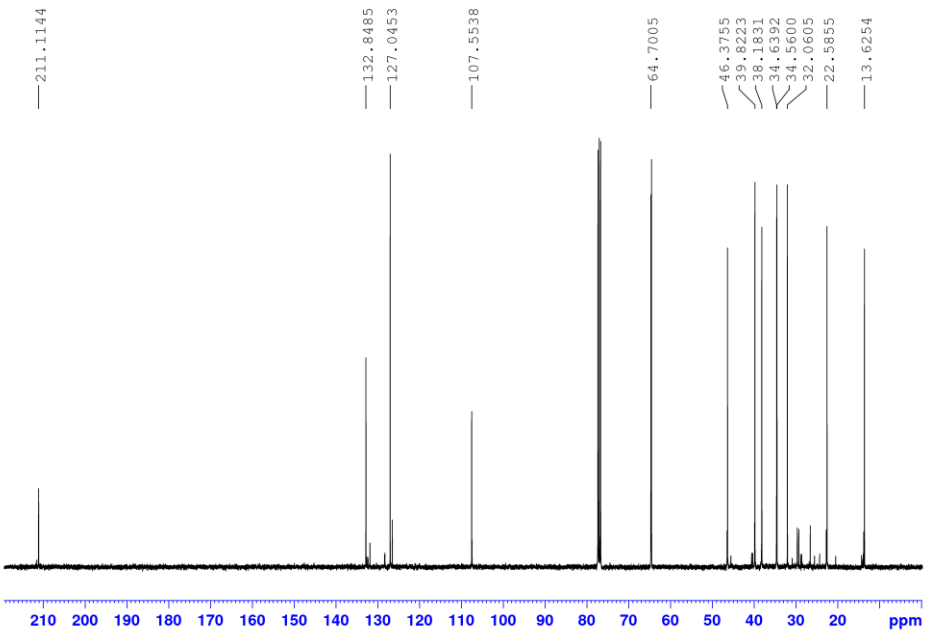
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32.0605
22.5855
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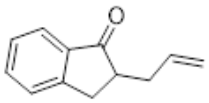
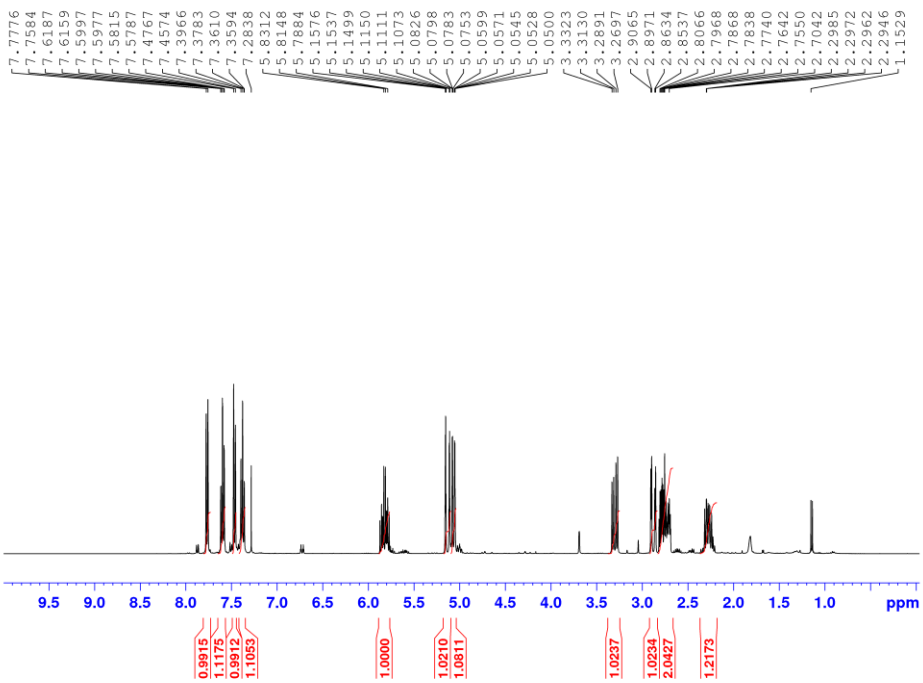
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

27

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7.3610
7.3594
7.2838
5.8312
5.8148
5.7884
5.1576
5.1537
5.1499
5.1150
5.1111
5.1073
5.0826
5.0798
5.0783
5.0753
5.0599
5.0571
5.0545
5.0528
5.0500
3.3323
3.3130
3.2891
3.2697
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2.8971
2.8634
2.8537
2.8066
2.7968
2.7868
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2.7740
2.7642
2.7550
2.7042
2.2985
2.2972
2.2962
2.2946
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9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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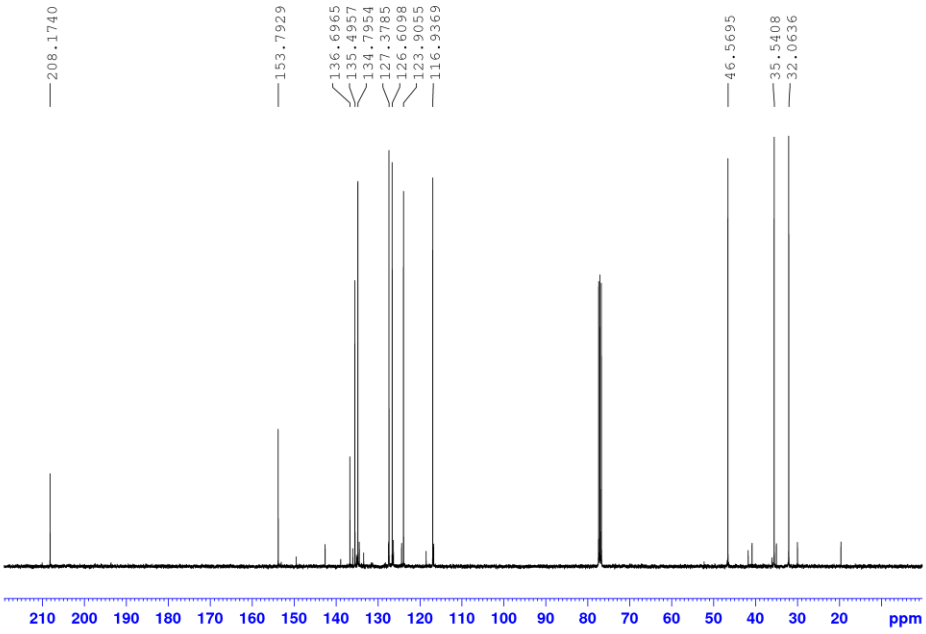
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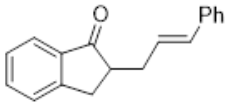
46.5695
35.5408
32.0636
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

28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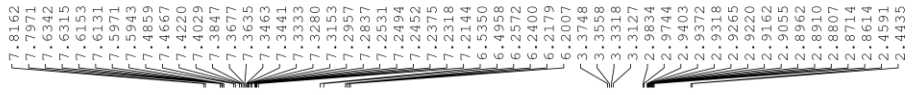
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7.4859
7.4667
7.4220
7.4029
7.3847
7.3677
7.3635
7.3463
7.3441
7.3333
7.3280
7.3153
7.2957
7.2837
7.2531
7.2494
7.2452
7.2375
7.2318
7.2144
6.5350
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6.2400
6.2179
6.2007
3.3748
3.3558
3.3318
3.3127
2.9834
2.9744
2.9403
2.9372
2.9318
2.9265
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2.8910
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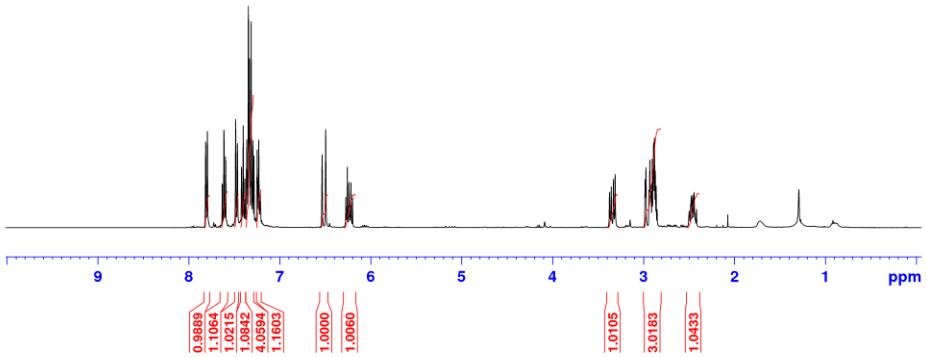
2.4591
2.4435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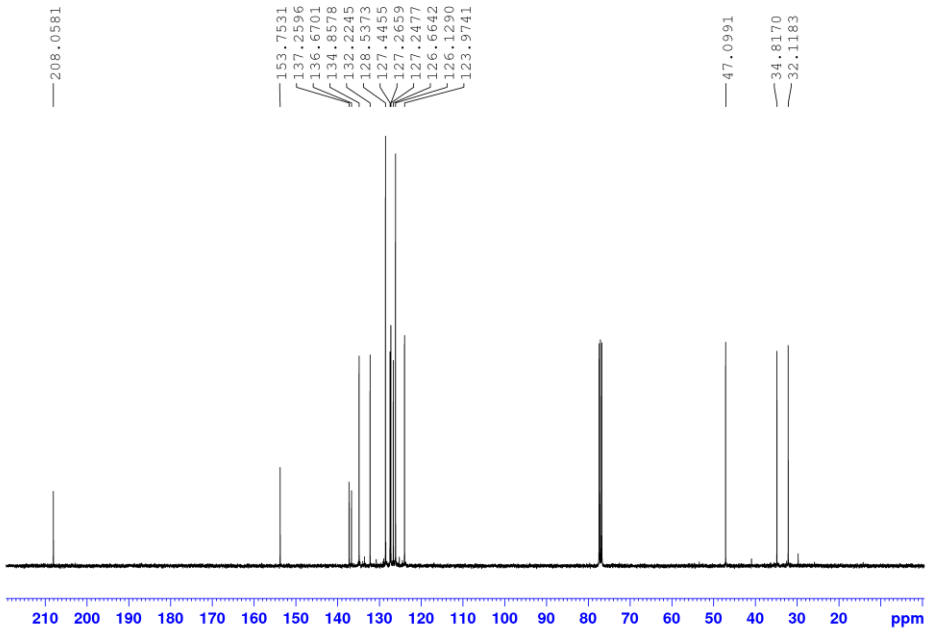
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126.1290
123.9741
47.0991
34.8170
32.1183
210
200
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150
140
130
120
110
100
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70
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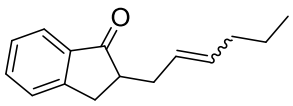
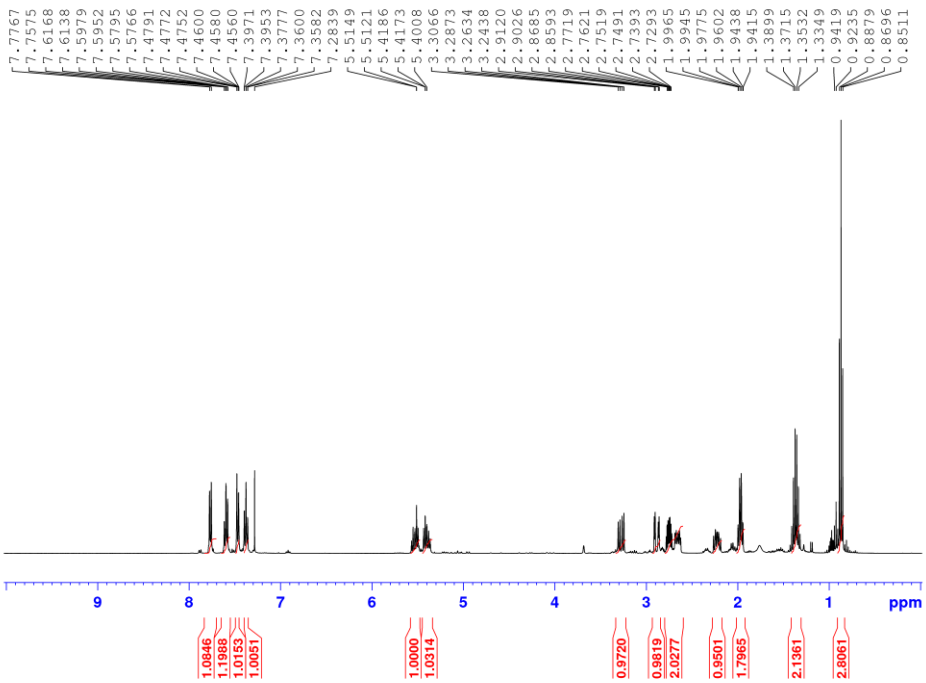
40
30
20
ppm

29

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7.4600
7.4580
7.4560
7.3971
7.3953
7.3777
7.3600
7.3582
7.2839
5.5149
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5.4173
5.4008
3.3066
3.2873
3.2634
3.2438
3.2120
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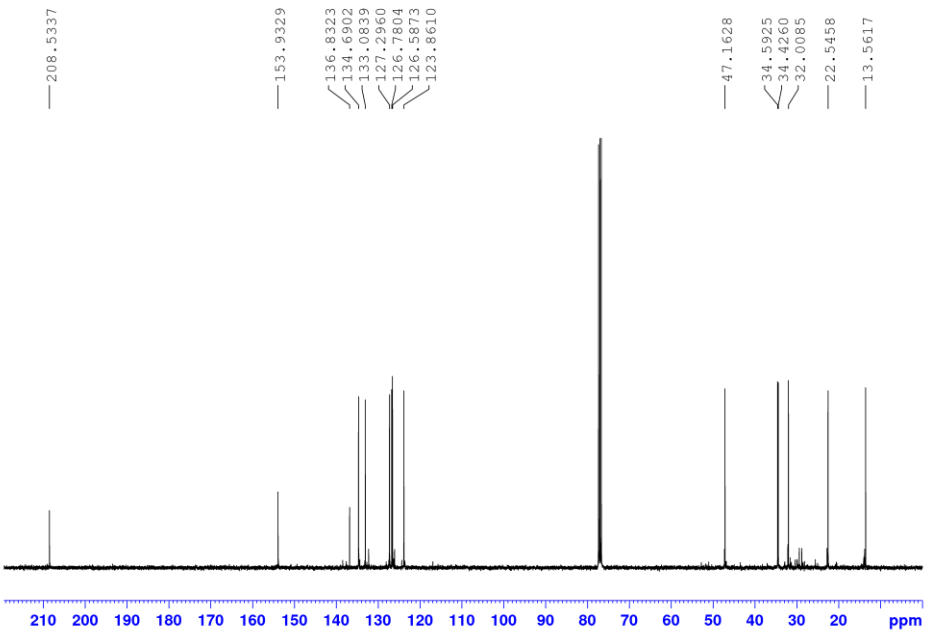
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32.0085
22.5458
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210
200
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150
140
130
120
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100
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80
70
60
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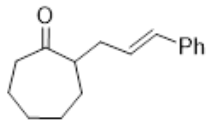
40
30
20
ppm

30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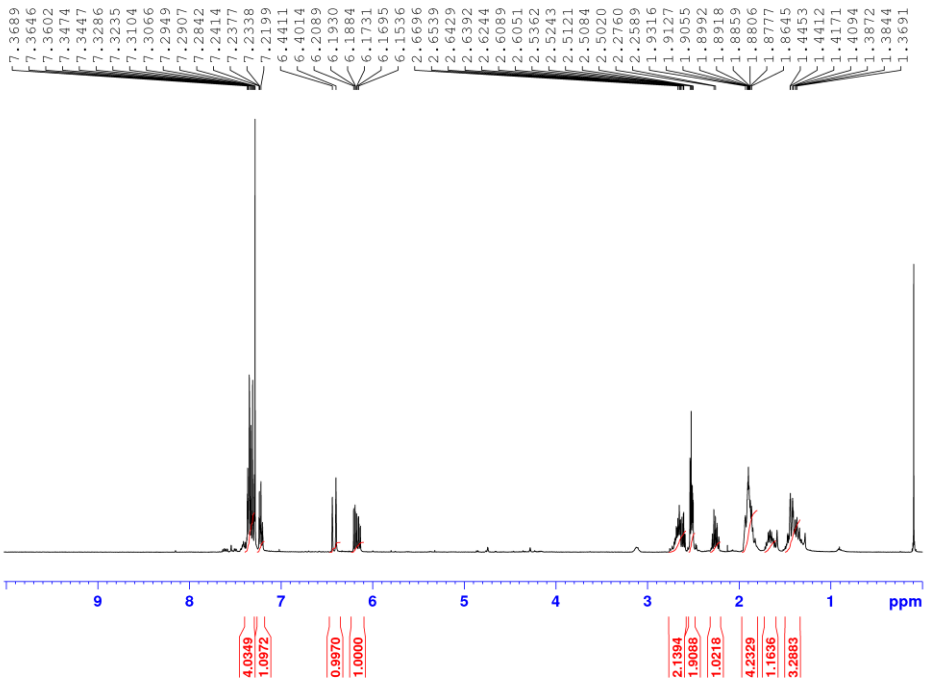
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7.2907
7.2842
7.2414
7.2377
7.2338
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6.4014
6.2089
6.1930
6.1884
6.1731
6.1695
6.1536
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2.5243
2.5121
2.5084
2.5020
2.2760
2.2589
1.9316
1.9127
1.9055
1.8992
1.8918
1.8859
1.8806
1.8777
1.8645
1.4453
1.4412
1.4171
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1.3872
1.3844
1.3691
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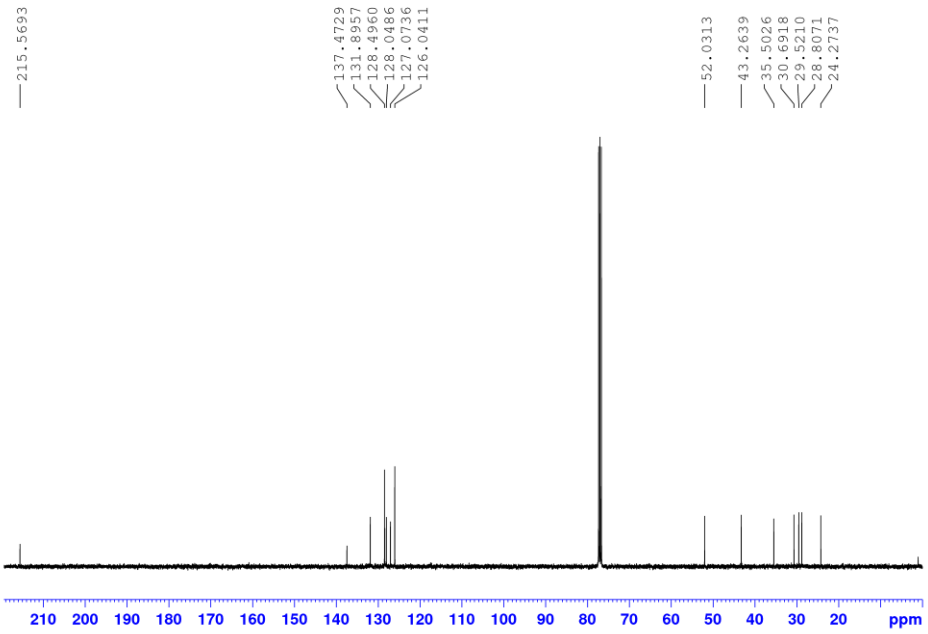
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24.2737
210
200
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150
140
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120
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70
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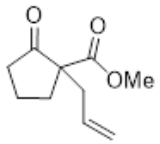
20
ppm

31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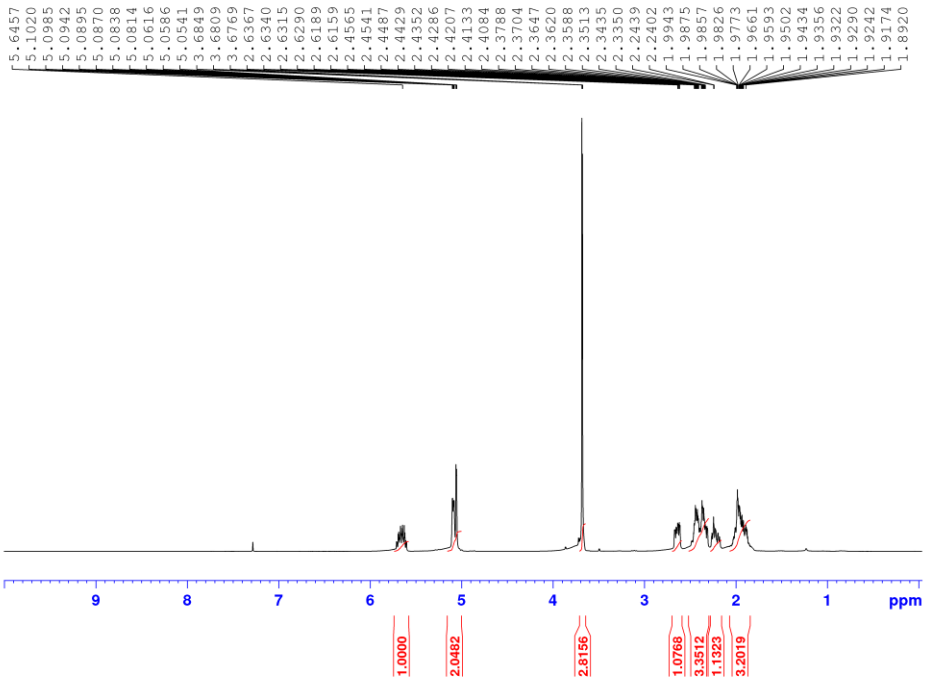
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2.6290
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2.3435
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2.2439
2.2402
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1.9875
1.9857
1.9826
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1.9502
1.9434
1.9356
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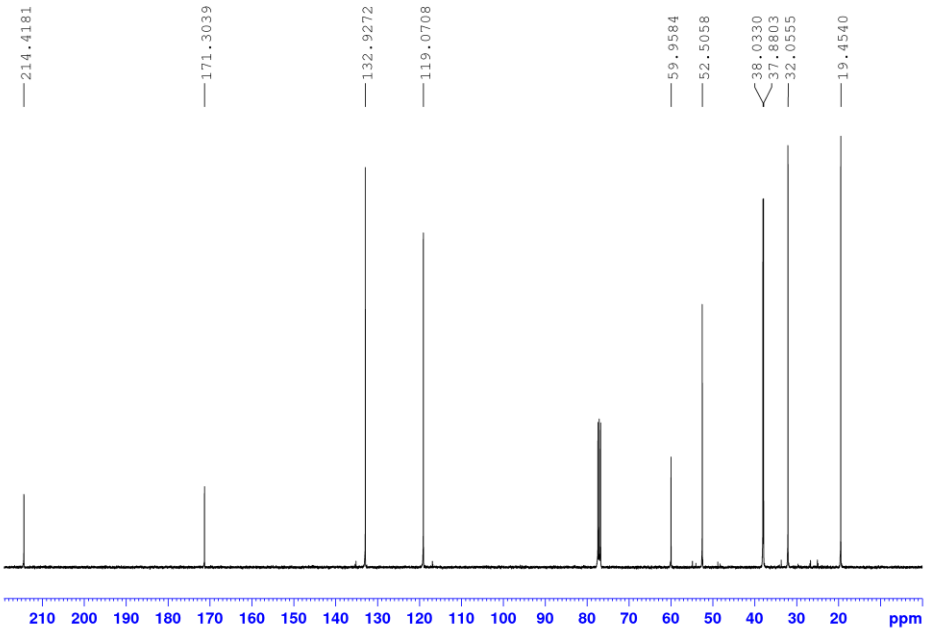
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180
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150
140
130
120
110
100
90
80
70
60
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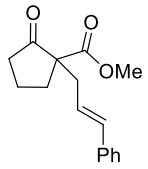
40
30
20
ppm

32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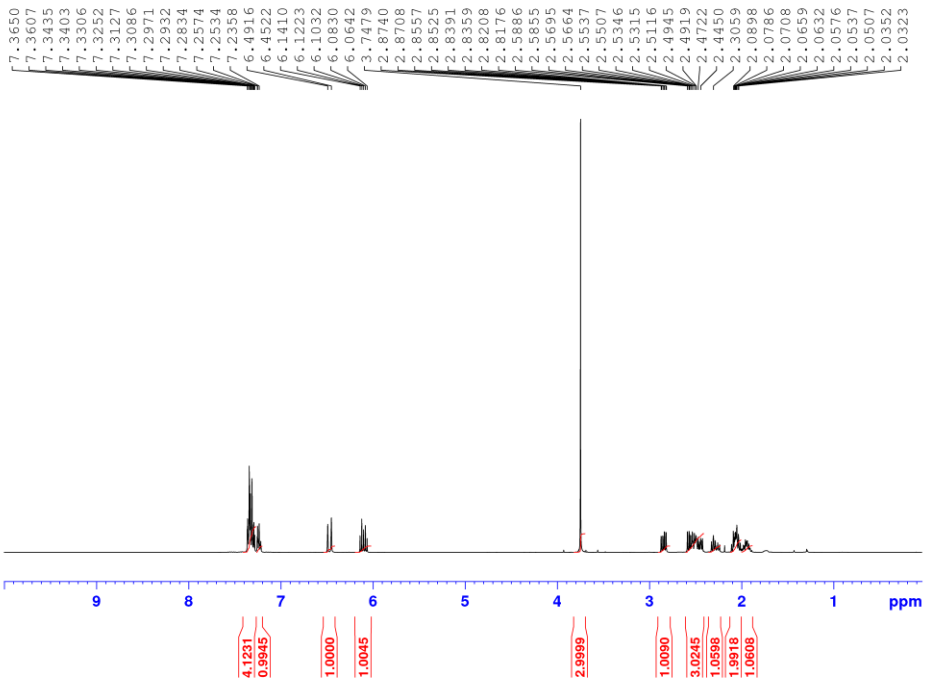
OMe
Ph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7.2834
7.2574
7.2534
7.2358
6.4916
6.4522
6.1410
6.1223
6.1032
6.0830
6.0642
3.7479
2.8740
2.8708
2.8557
2.8525
2.8391
2.8359
2.8208
2.8176
2.5886
2.5855
2.5695
2.5664
2.5537
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2.5346
2.5315
2.5116
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2.4919
2.4722
2.4450
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2.0786
2.0708
2.0659
2.0632
2.0576
2.0537
2.0507
2.0352
2.0323
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8
7
6
5
4
3
2
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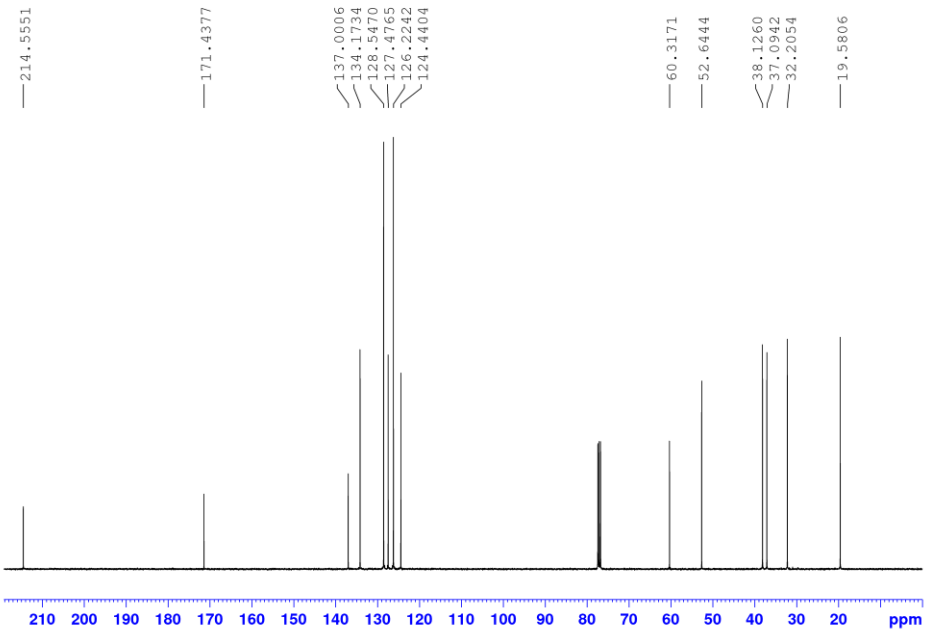
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32.2054
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200
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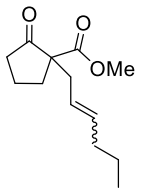
20
ppm

33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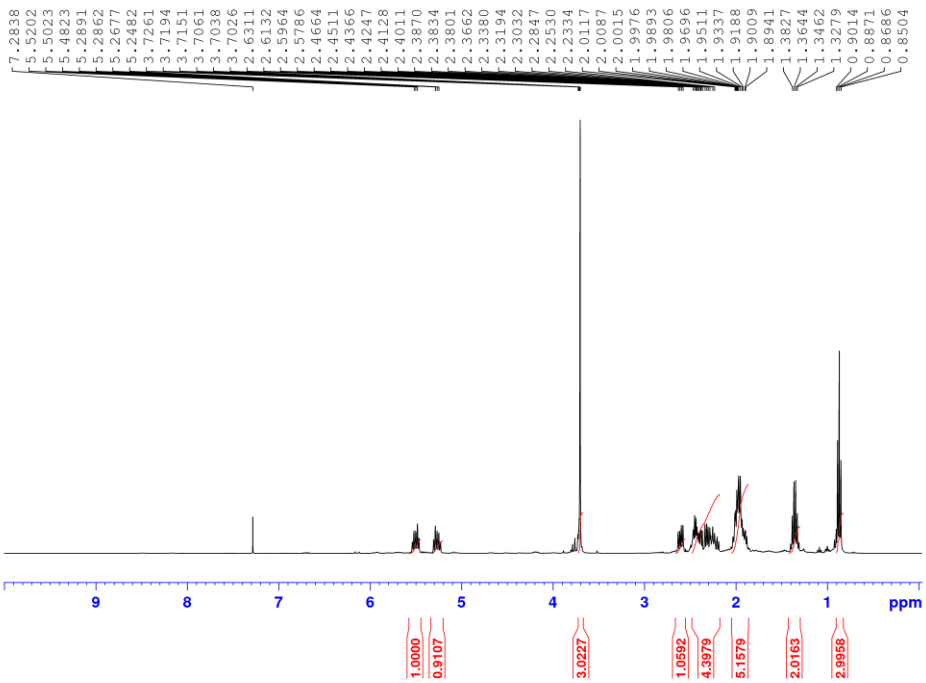
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3.7061
3.7038
3.7026
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2.4664
2.4511
2.4366
2.4247
2.4128
2.4011
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2.3662
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2.2530
2.2334
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1.9337
1.9188
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1.3827
1.3644
1.3462
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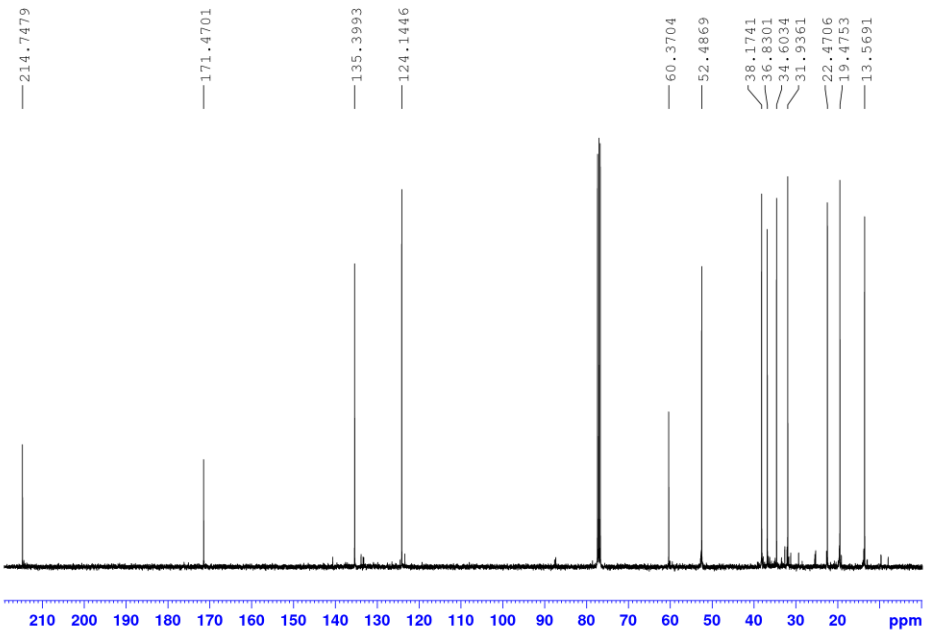
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19.4753
13.5691
210
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150
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120
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70
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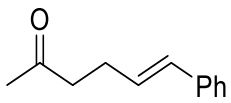
40
30
20
ppm

34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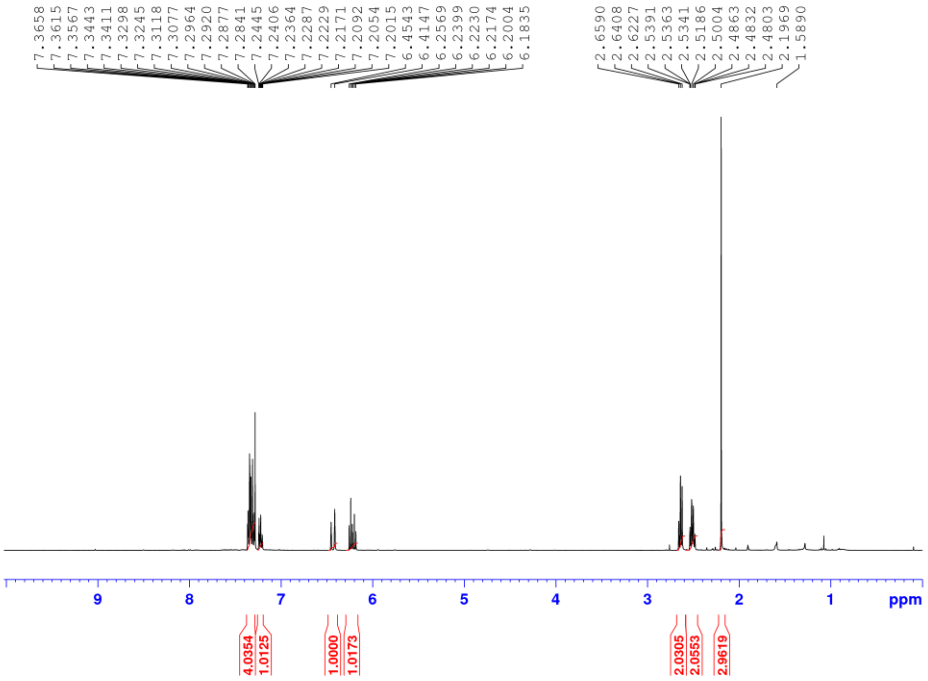
Ph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7.2406
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7.2171
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6
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4
3
2
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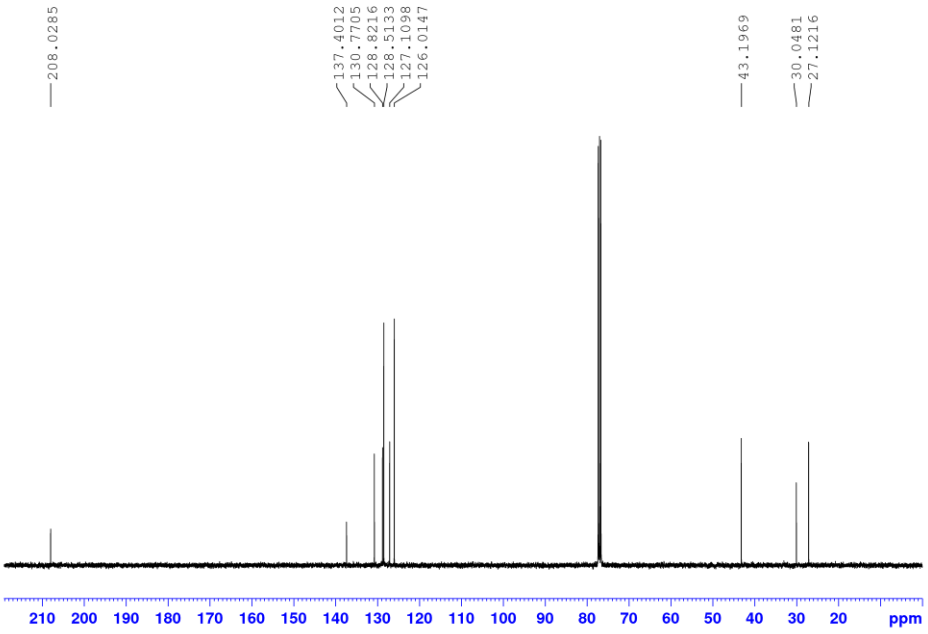
2.9619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128.5133
127.1098
126.0147
43.1969
30.0481
27.1216
210
200
190
180
170
160
150
140
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120
110
100
90
80
70
60
50
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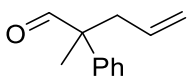
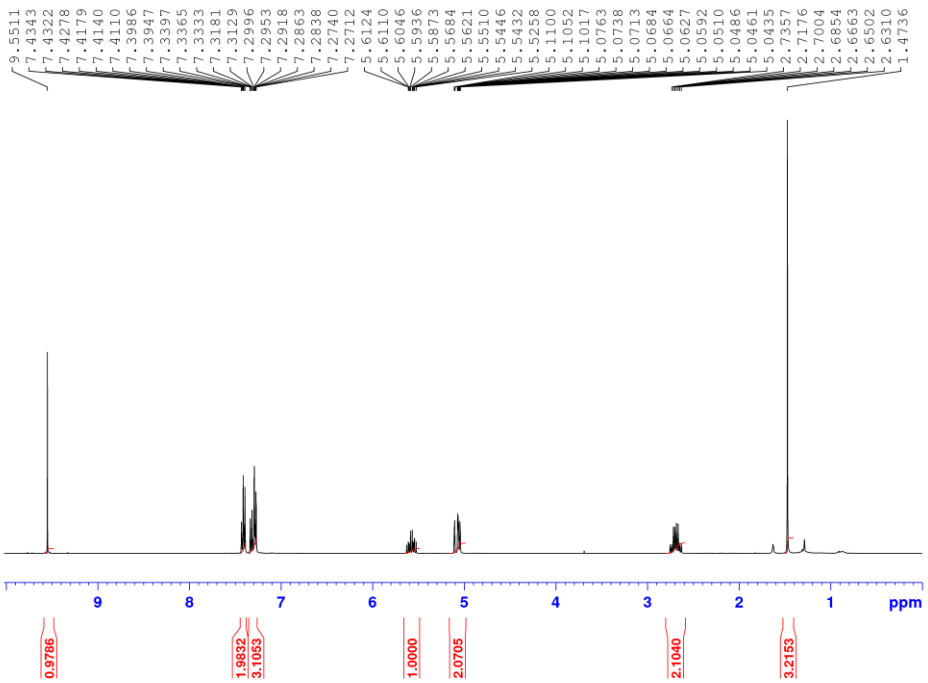
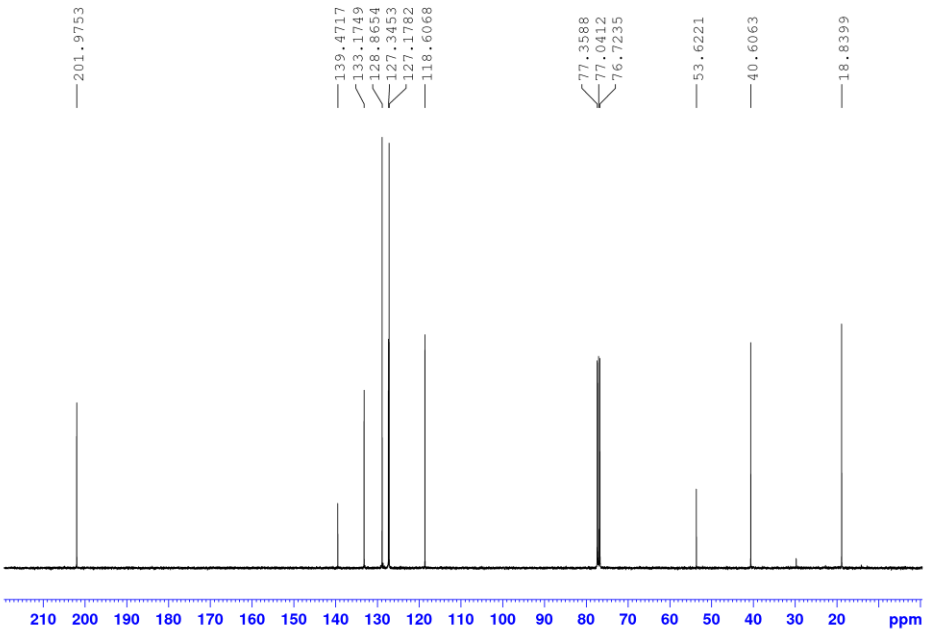
30
20
ppm

8.1.4 Allylated aldehydes

35







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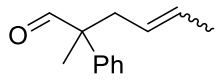
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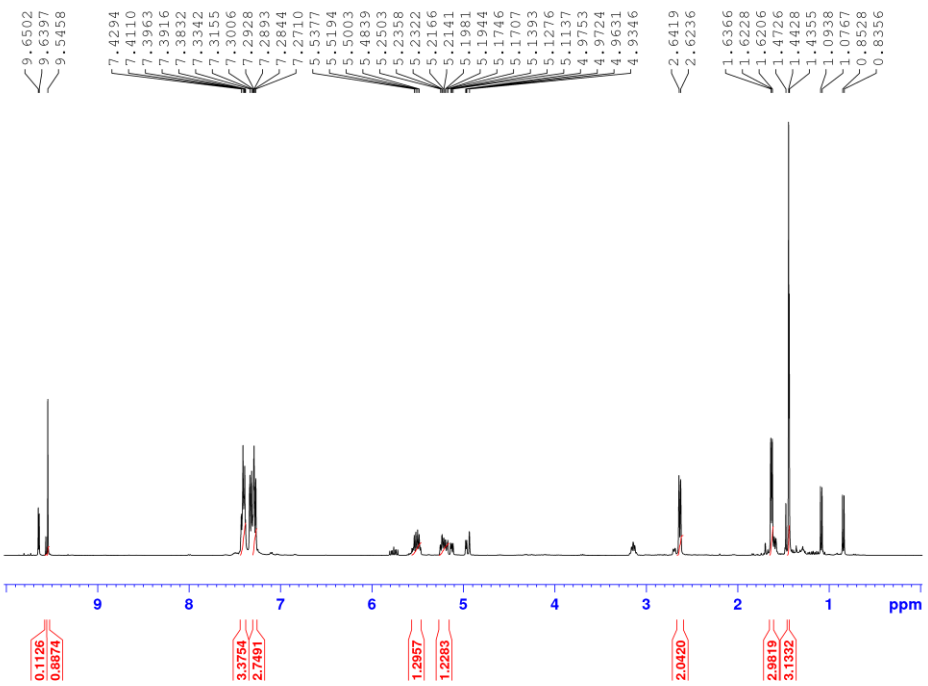
Ph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7.2928
7.2893
7.2844
7.2710
5.5377
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5.5003
5.4839
5.2503
5.2358
5.2322
5.2166
5.2141
5.1981
5.1944
5.1746
5.1707
5.1393
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2.6236
1.6366
1.6228
1.6206
1.4726
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1.0938
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0.8528
0.8356
9
8
7
6
5
4
3
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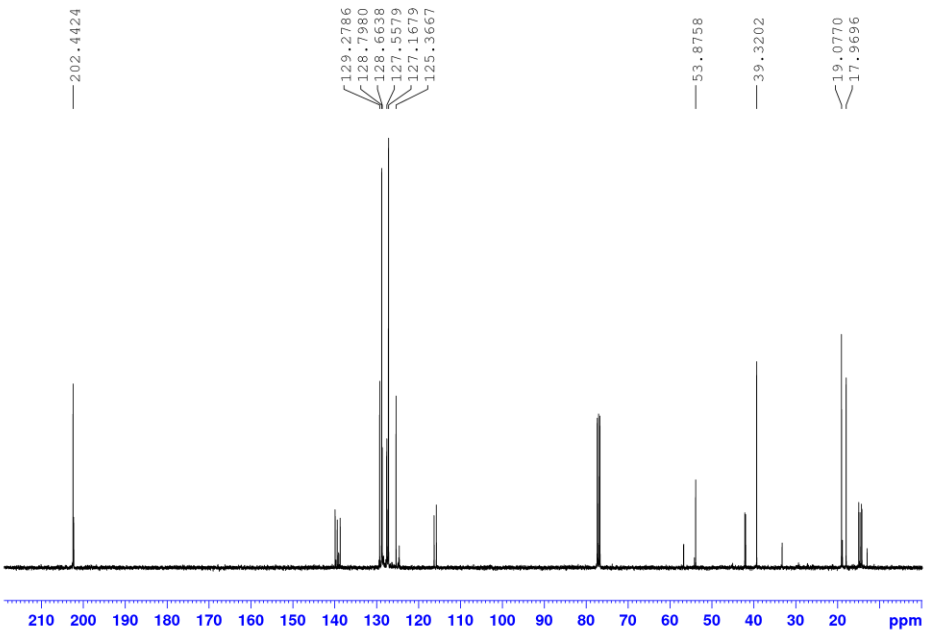
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19.0770
17.9696
210
200
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150
140
130
120
110
100
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80
70
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30
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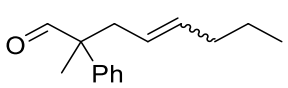
ppm

37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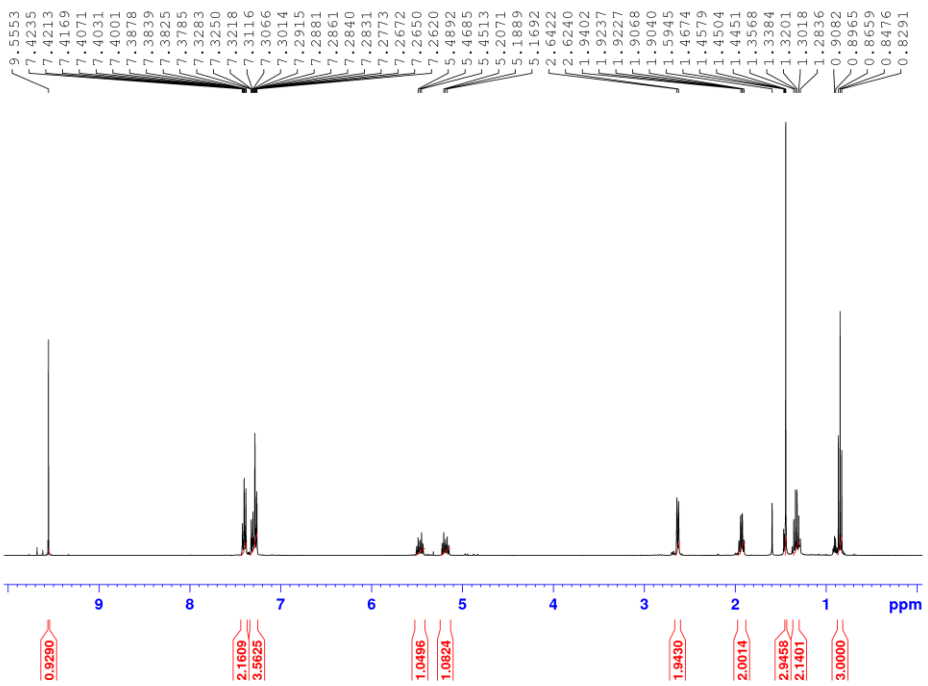
Ph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7.3825
7.3785
7.3283
7.3250
7.3218
7.3116
7.3066
7.3014
7.2915
7.2881
7.2861
7.2840
7.2831
7.2773
7.2672
7.2650
7.2620
5.4892
5.4685
5.4513
5.2071
5.1889
5.1692
2.6422
2.6240
1.9402
1.9237
1.9227
1.9068
1.9040
1.5945
1.4674
1.4579
1.4504
1.4451
1.3568
1.3384
1.3201
1.3018
1.2836
0.9082
0.8965
0.8659
0.8476
0.8291
9
8
7
6
5
4
3
2
1
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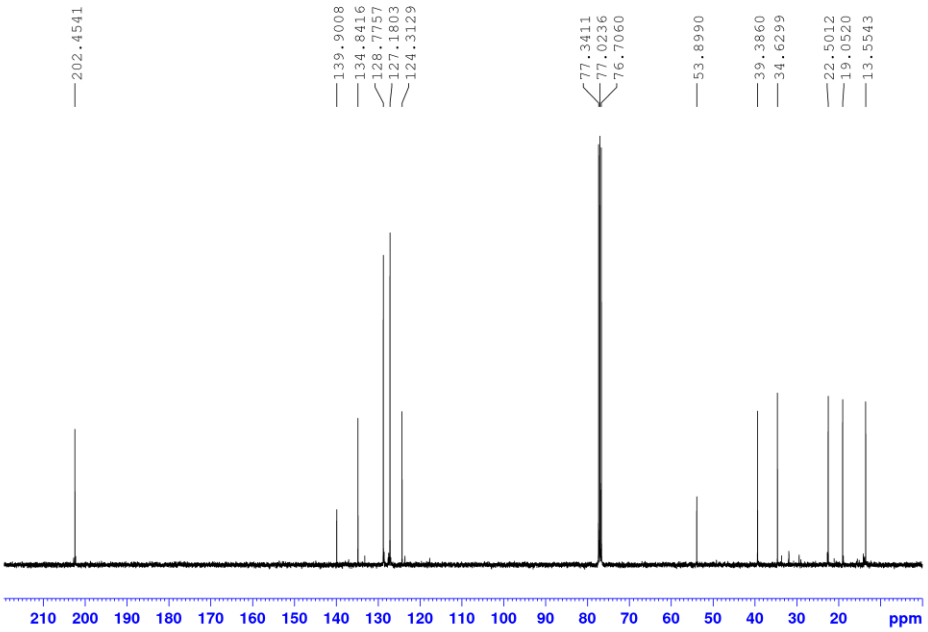
3.0000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76.7060
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39.3860
34.6299
22.5012
19.0520
13.5543
210
200
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180
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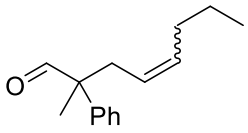
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

38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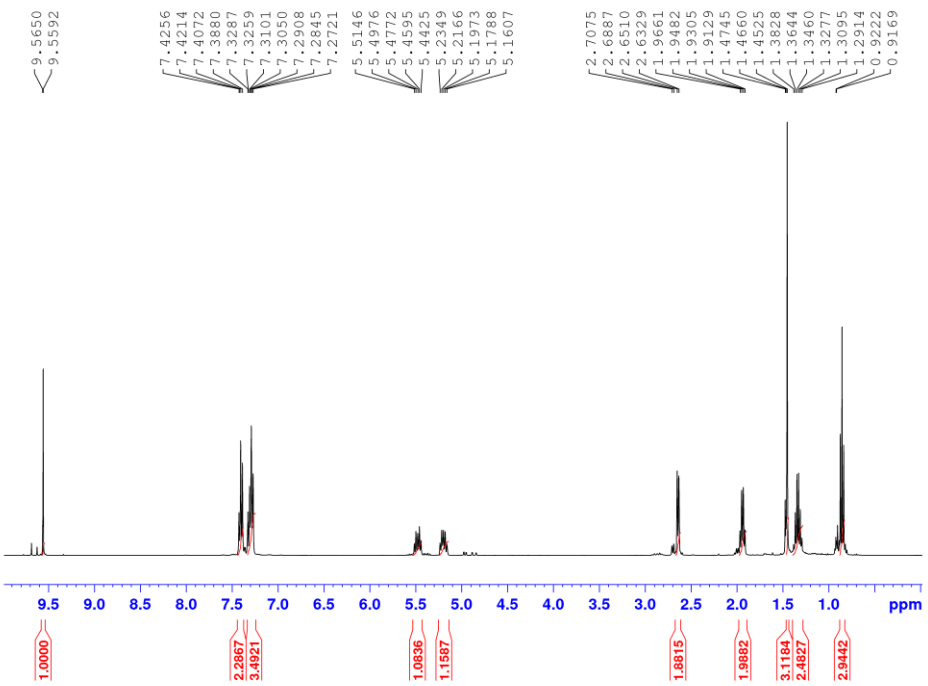
Ph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7.3101
7.3050
7.2908
7.2845
7.2721
5.5146
5.4976
5.4772
5.4595
5.4425
5.2349
5.2166
5.1973
5.1788
5.1607
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1.9482
1.9305
1.9129
1.4745
1.4660
1.4525
1.3828
1.3644
1.3460
1.3277
1.3095
1.2914
0.9222
0.9169
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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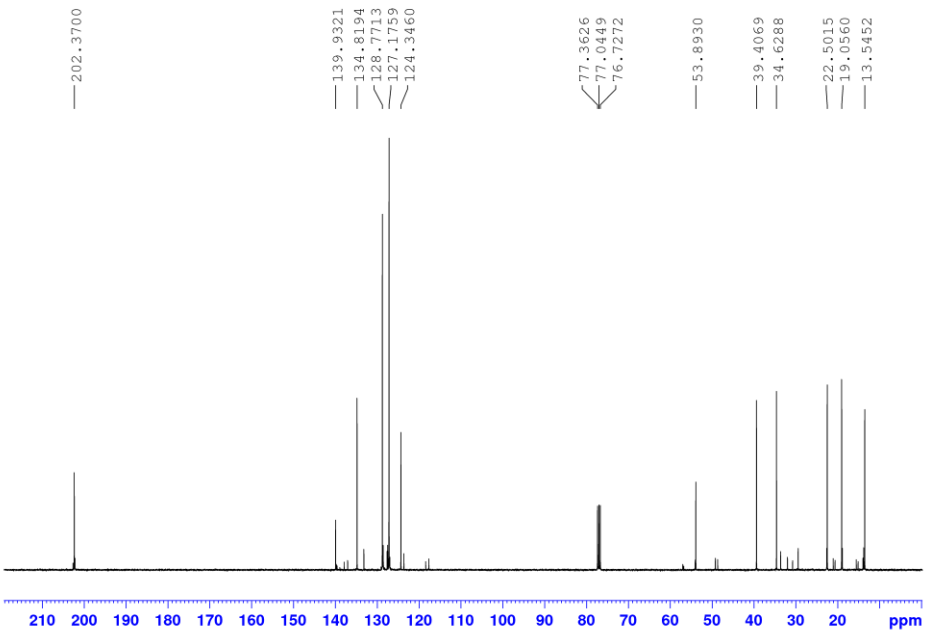
1.8815
1.9882
3.1184
2.4627
2.9442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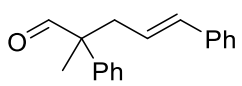
34.6288
22.5015
19.0560
13.5452
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

39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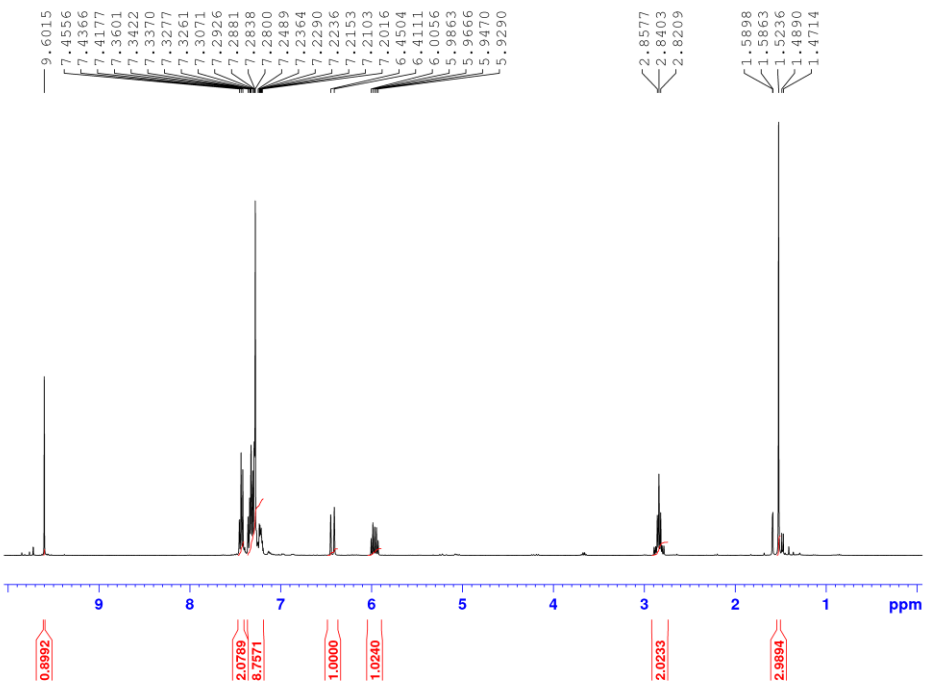
Ph
Ph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7.2926
7.2881
7.2838
7.2800
7.2489
7.2364
7.2290
7.2236
7.2153
7.2103
7.2016
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6.4111
6.0056
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5.9666
5.9470
5.9290
2.8577
2.8403
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1.5898
1.5863
1.5236
1.4890
1.4714
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8
7
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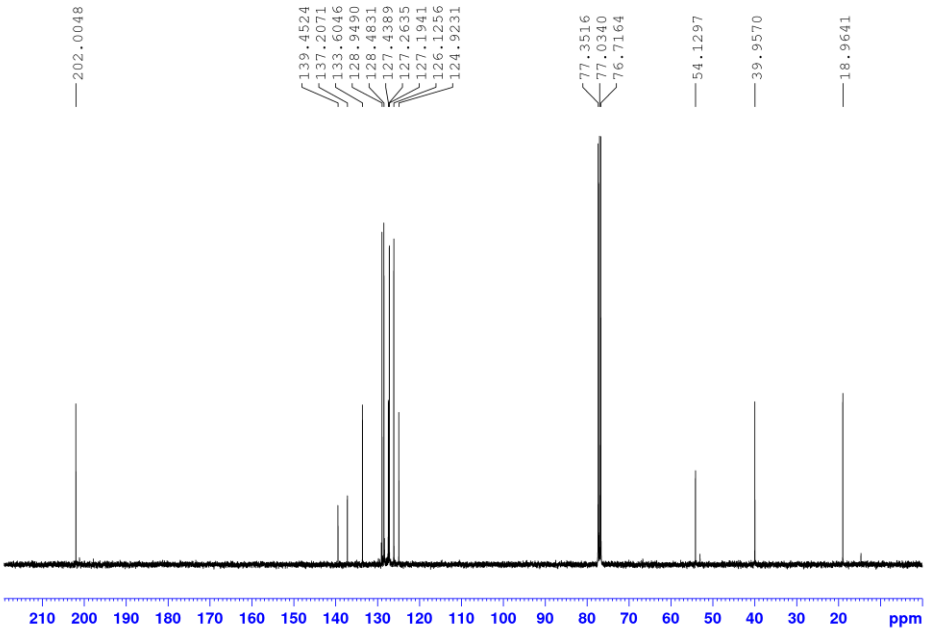
2.0233
2.9894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76.7164
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39.9570
18.9641
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30
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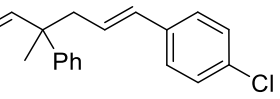
ppm

40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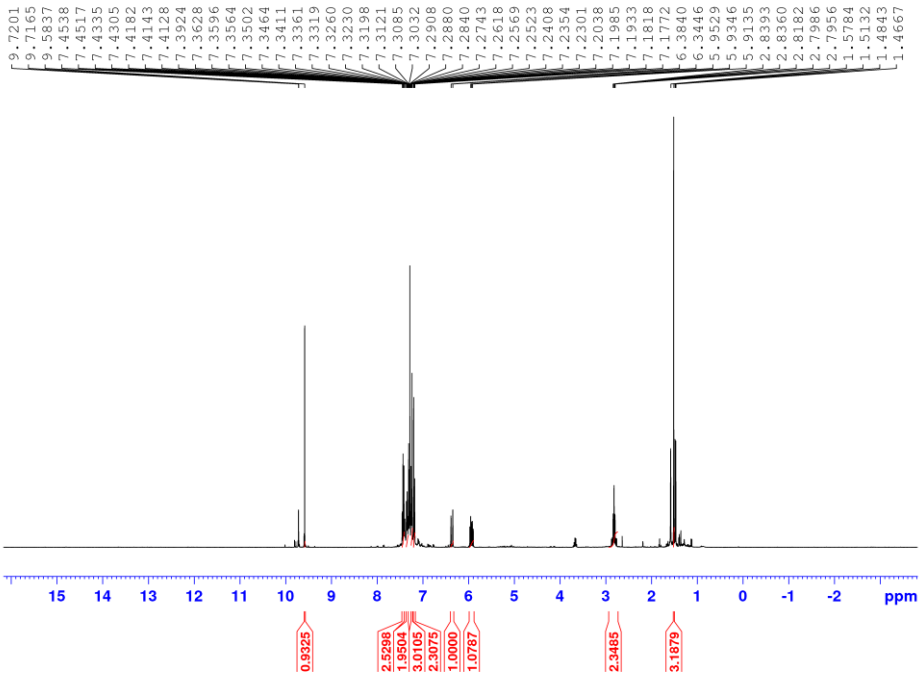
Ph
Cl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7.3924
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7.3596
7.3564
7.3502
7.3464
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7.3361
7.3319
7.3260
7.3230
7.3198
7.3121
7.3085
7.3032
7.2908
7.2880
7.2840
7.2743
7.2618
7.2569
7.2523
7.2408
7.2354
7.2301
7.2038
7.1985
7.1933
7.1818
7.1772
6.3840
6.3446
5.9529
5.9346
5.9135
2.8393
2.8360
2.8182
2.7986
2.7956
1.5784
1.5132
1.4843
1.4667
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14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
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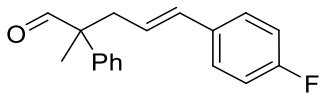
2.3485
3.1879

41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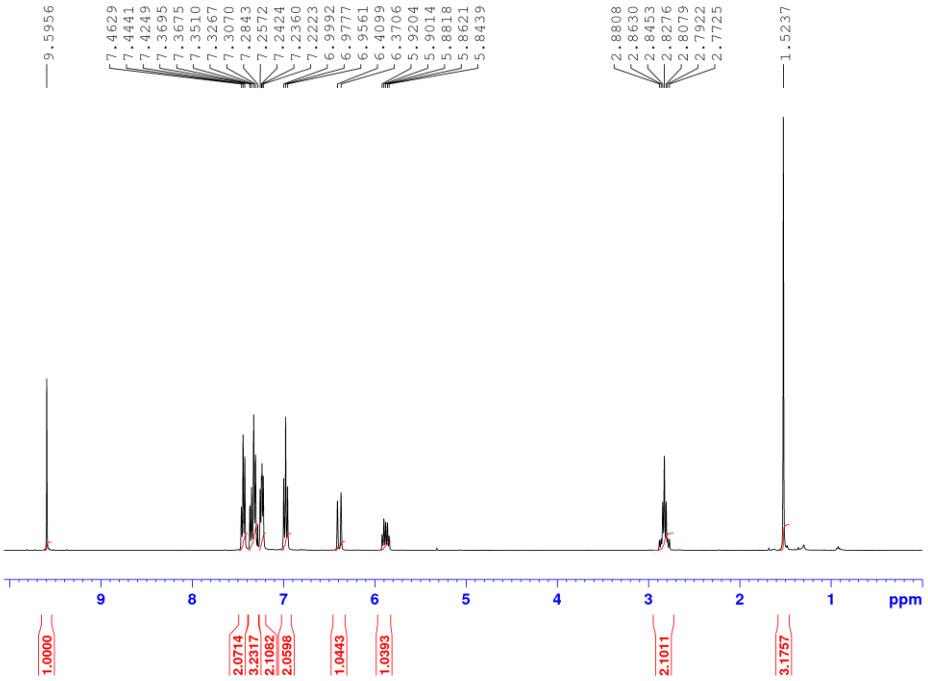
Ph
F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7.2360
7.2223
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6.9561
6.4099
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5.9014
5.8818
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5.8439
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2.8630
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2.8276
2.8079
2.7922
2.7725
1.5237
9
8
7
6
5
4
3
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1.0443
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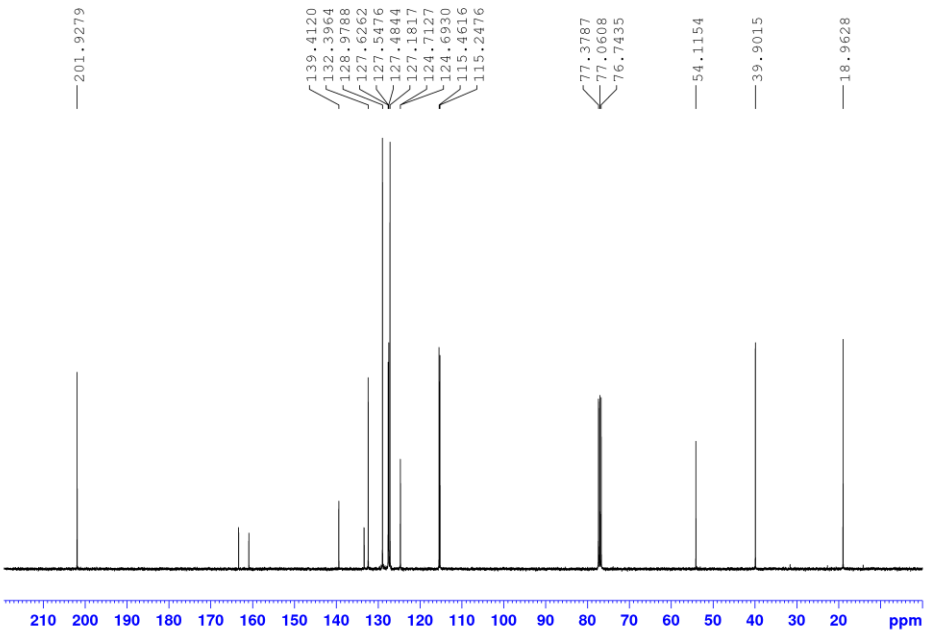
2.1011
3.1757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115.4616
115.2476
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77.0608
76.7435
54.1154
39.9015
18.9628
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200
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180
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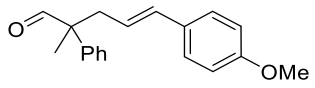
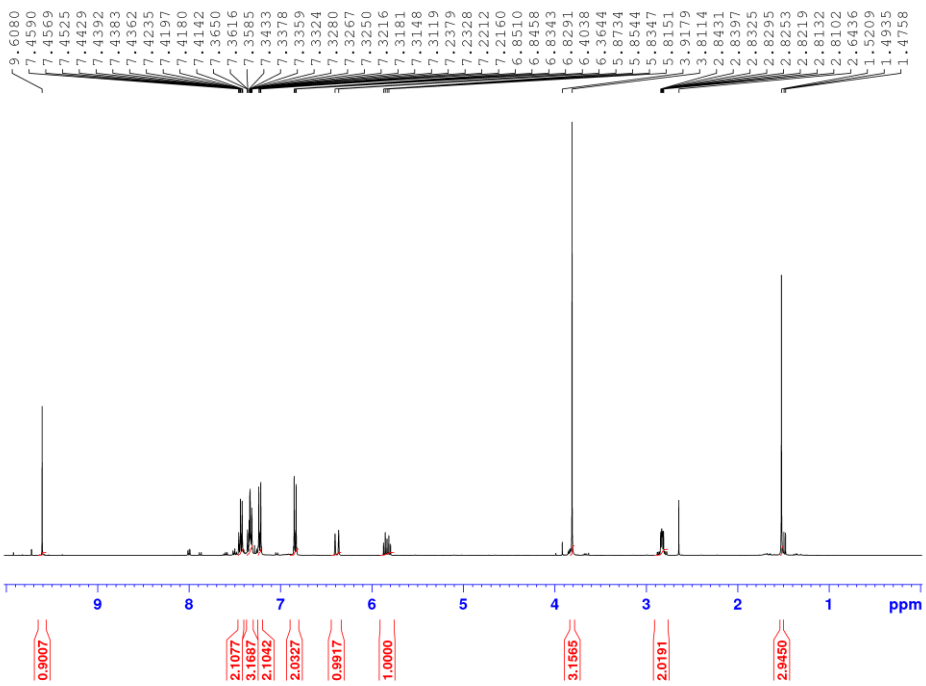
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

42


O
Ph
OMe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7.3324
7.3280
7.3267
7.3250
7.3216
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7.3148
7.3119
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7.2328
7.2212
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6.3644
5.8734
5.8544
5.8347
5.8151
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3.8114
2.8431
2.8397
2.8325
2.8295
2.8253
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8
7
6
5
4
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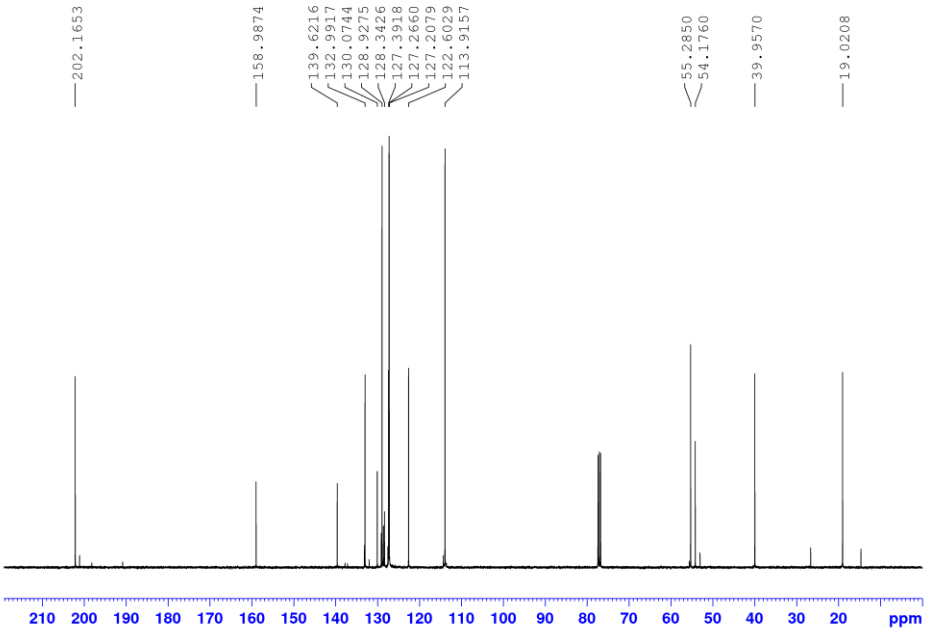
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54.1760
39.9570
19.0208
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140
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110
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70
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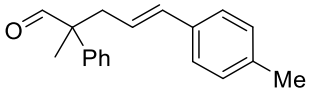
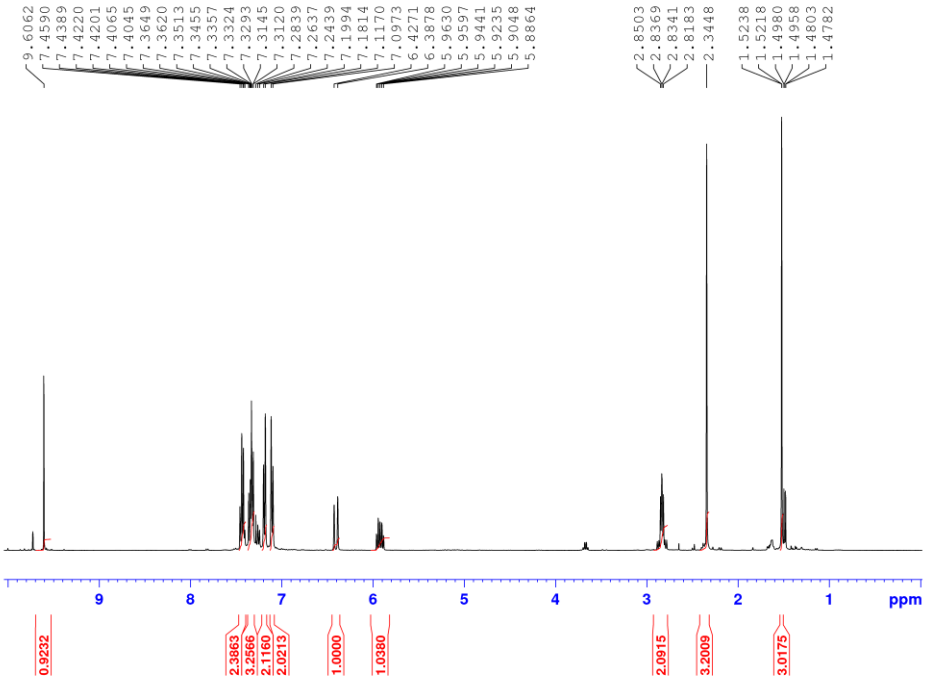
50
40
30
20
ppm

43


O
Ph
Me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7.3455
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7.3324
7.3293
7.3145
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7.2439
7.1994
7.1814
7.1170
7.0973
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6.3878
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5.9597
5.9441
5.9235
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5.8864
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2.8183
2.3448
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1.4958
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1.4782
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8
7
6
5
4
3
2
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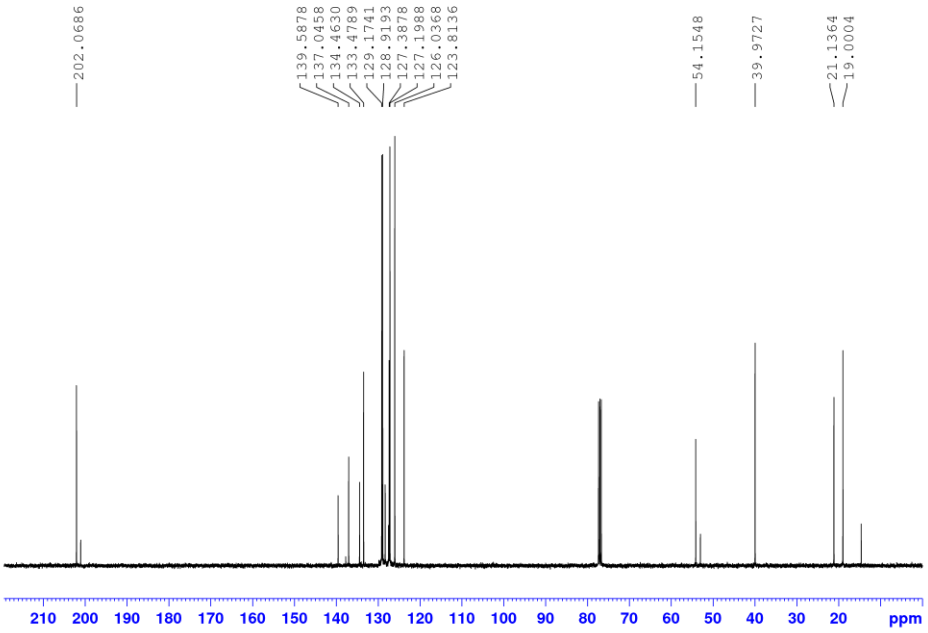
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19.0004
210
200
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180
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80
70
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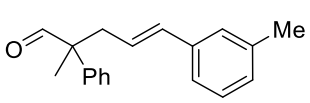
40
30
20
ppm

44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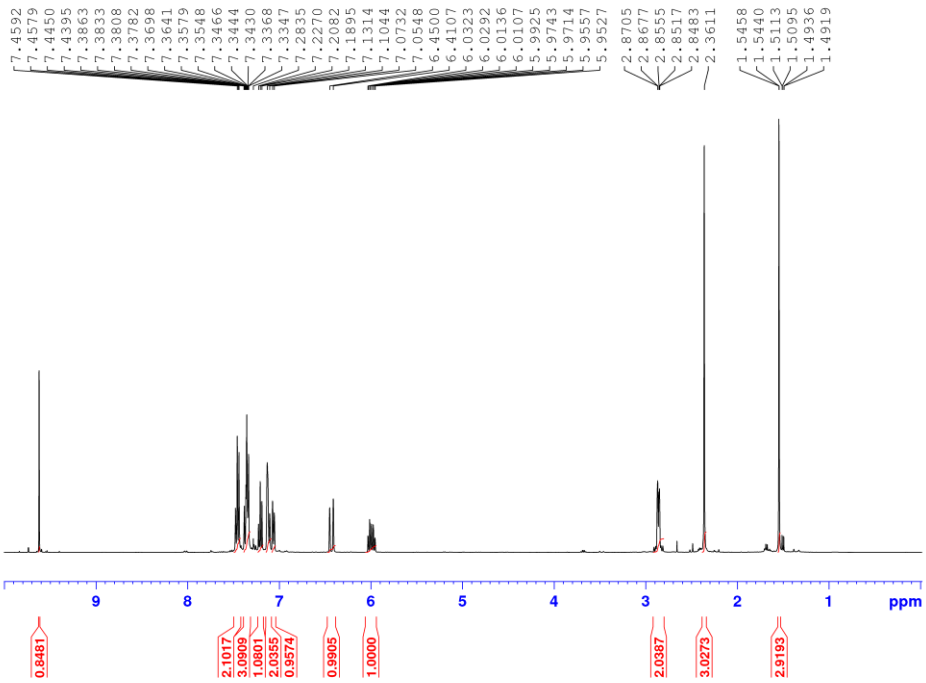
Ph
Me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7.3579
7.3548
7.3466
7.3444
7.3430
7.3368
7.3347
7.2835
7.2270
7.2082
7.1895
7.1314
7.1044
7.0732
7.0548
6.4500
6.4107
6.0323
6.0292
6.0136
6.0107
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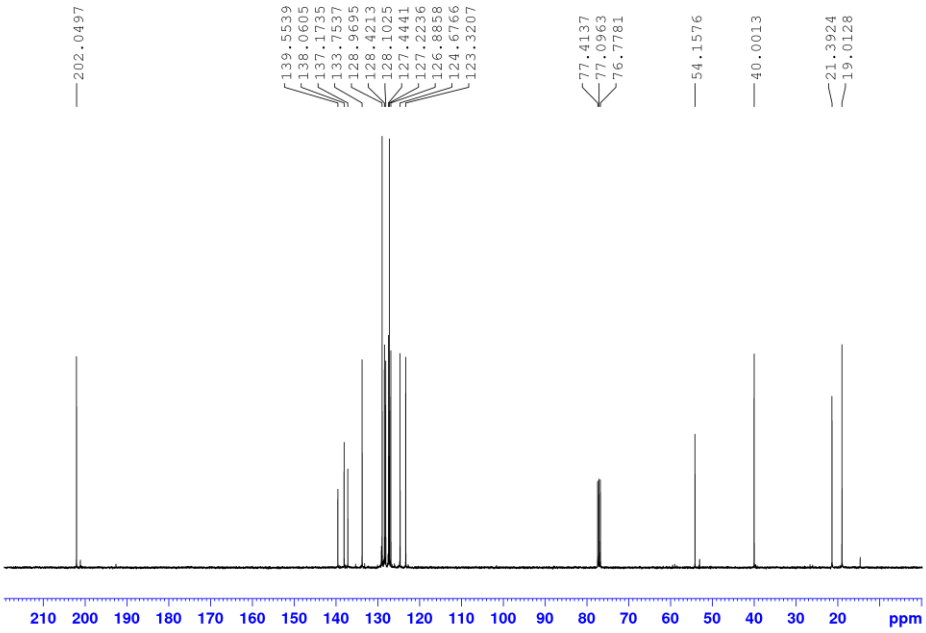
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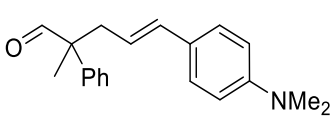
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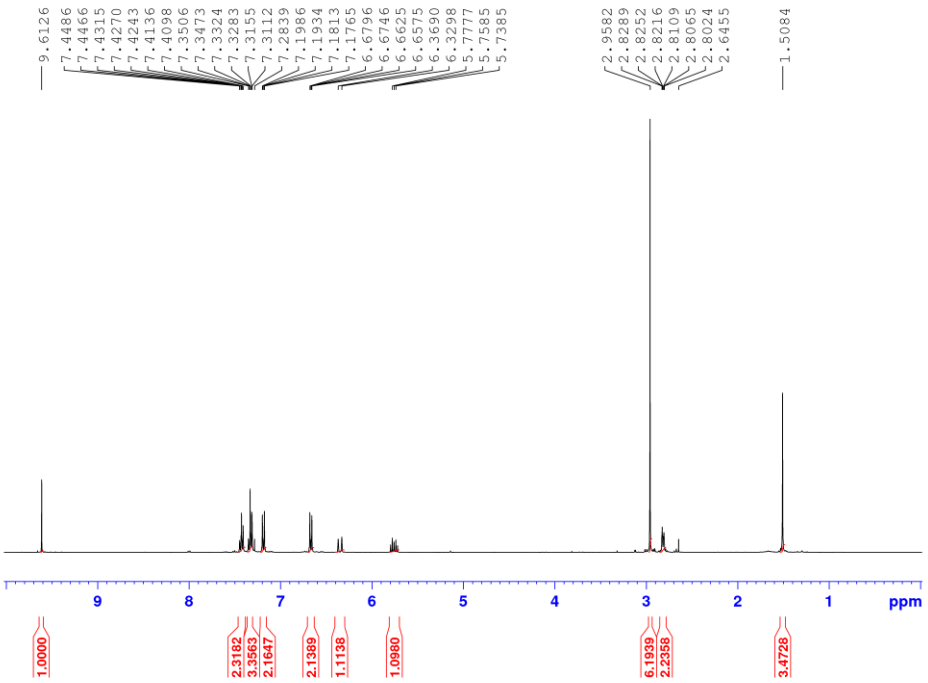
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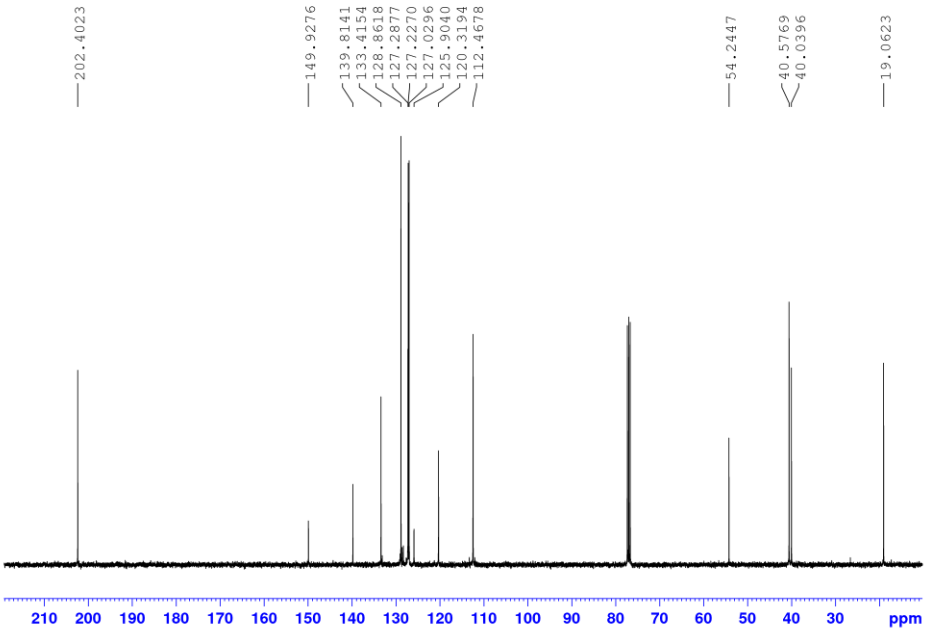
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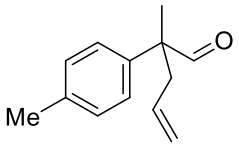
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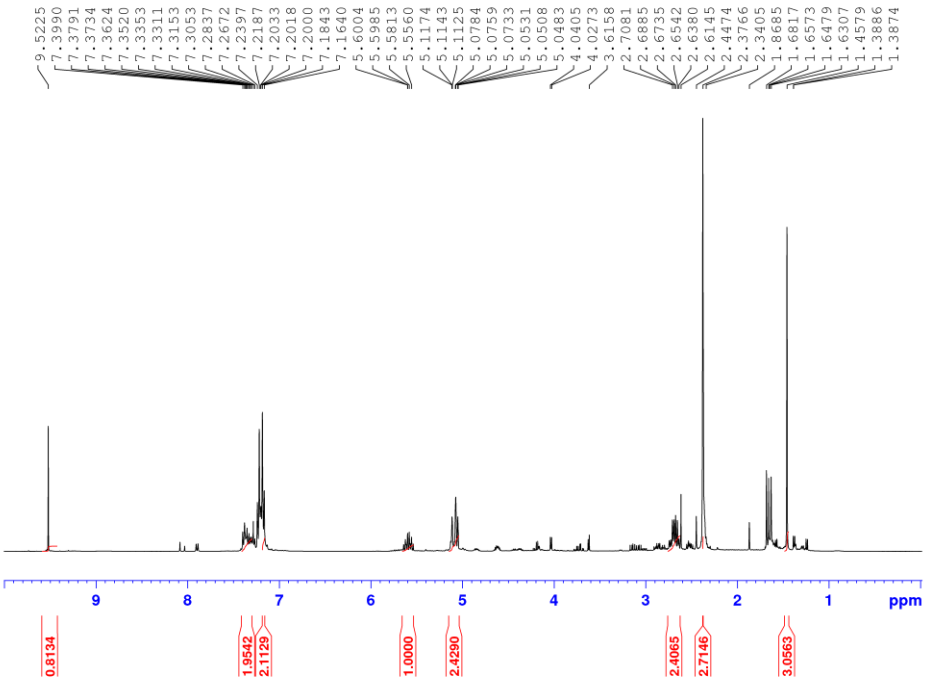
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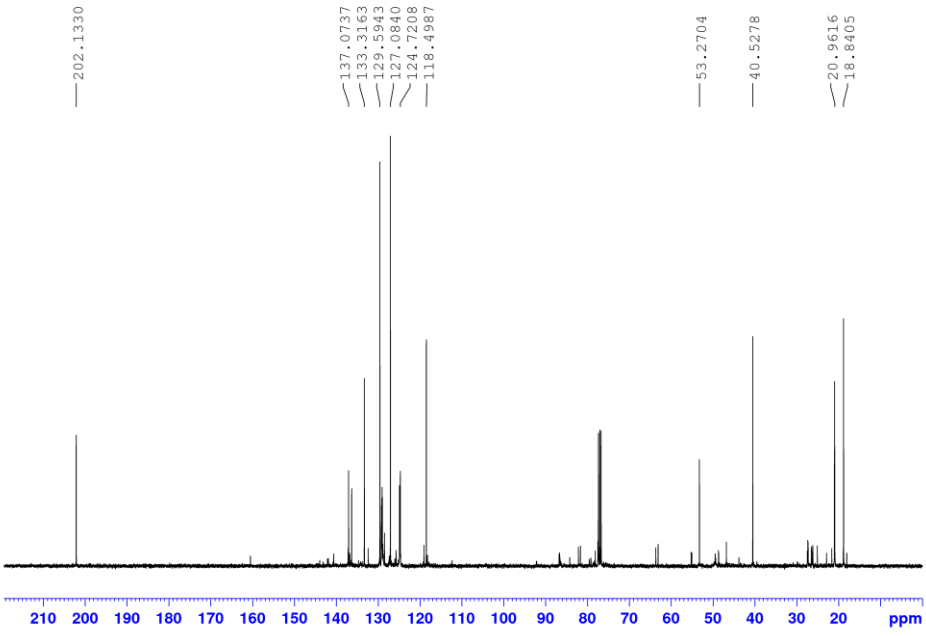
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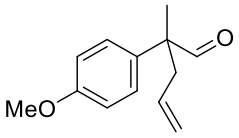
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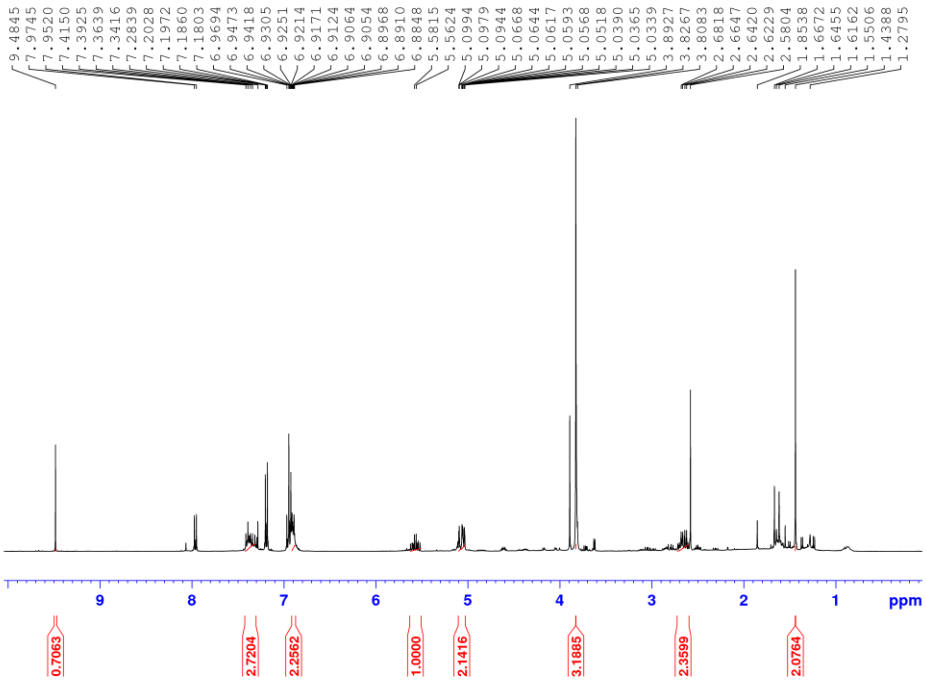
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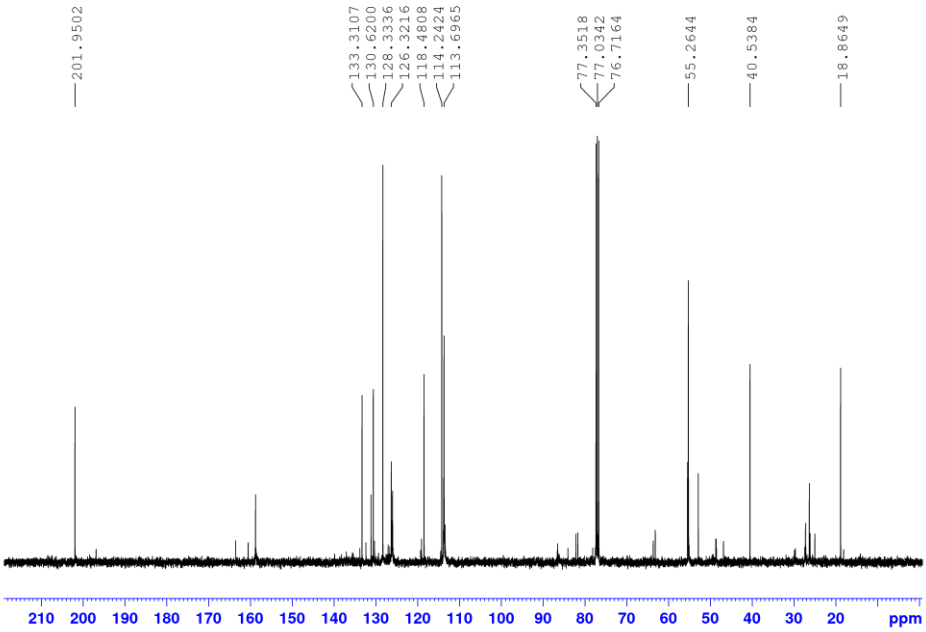
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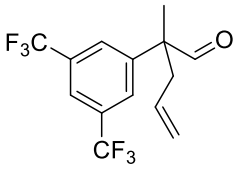
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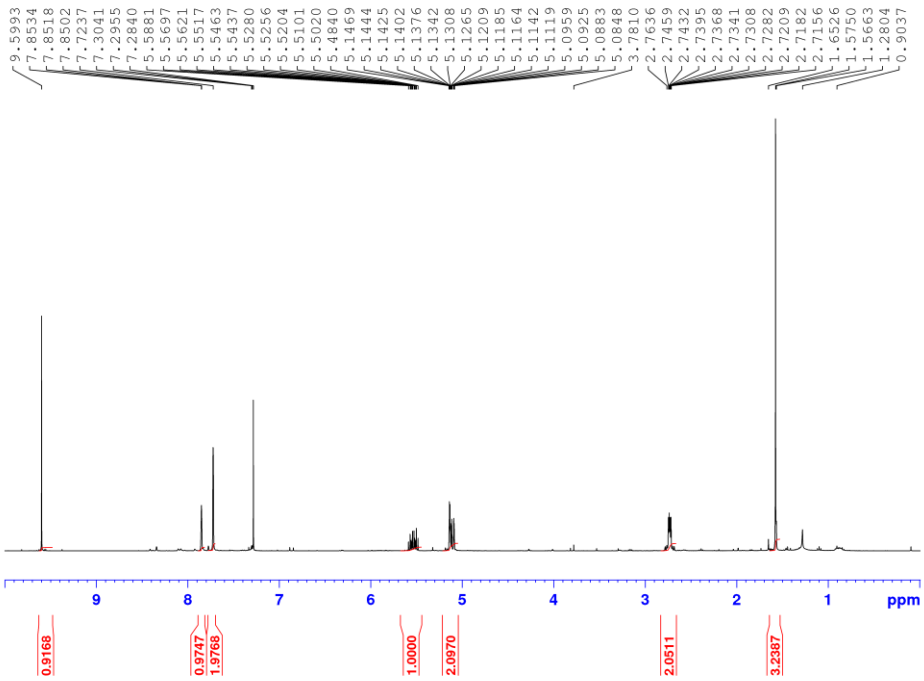
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5.1142
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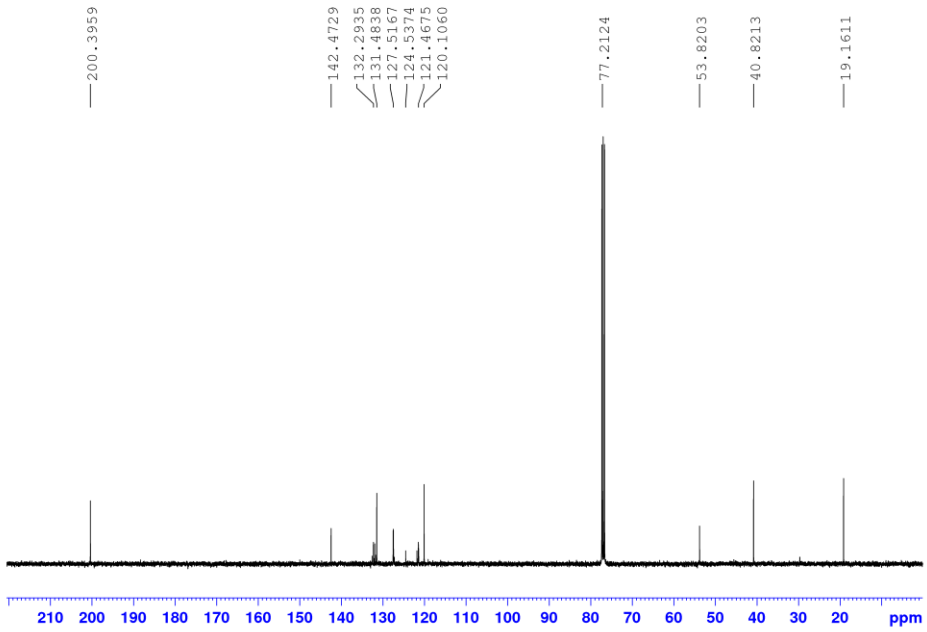
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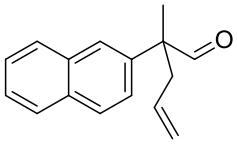
30
20
ppm

49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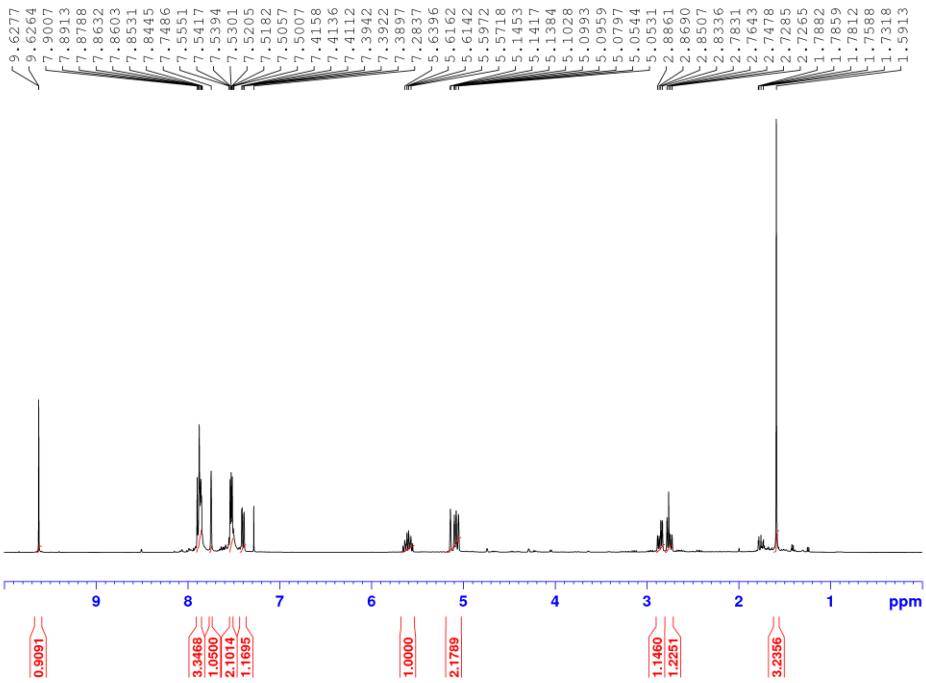
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7.5301
7.5205
7.5182
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7.4112
7.3942
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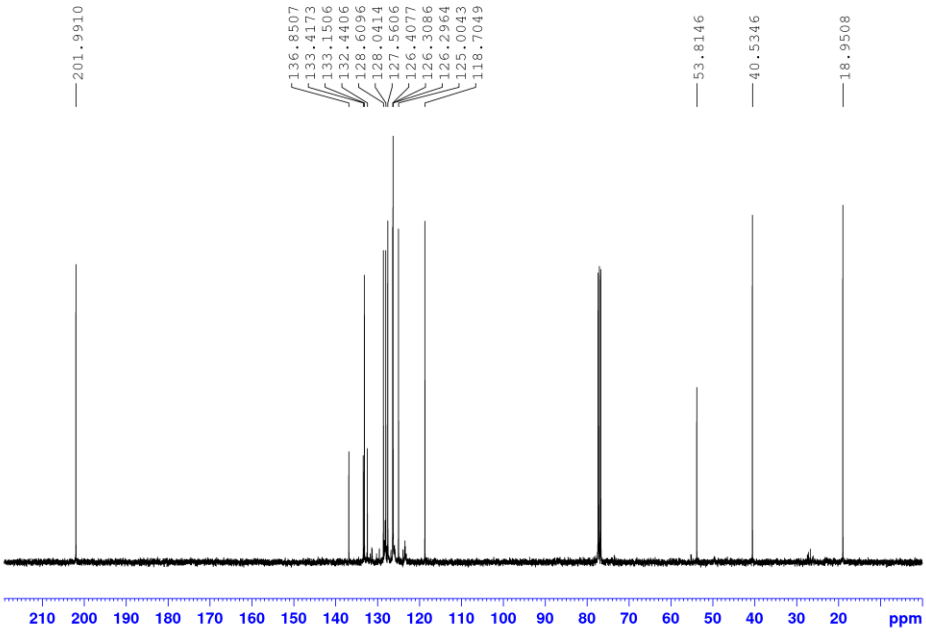
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170
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150
140
130
120
110
100
90
80
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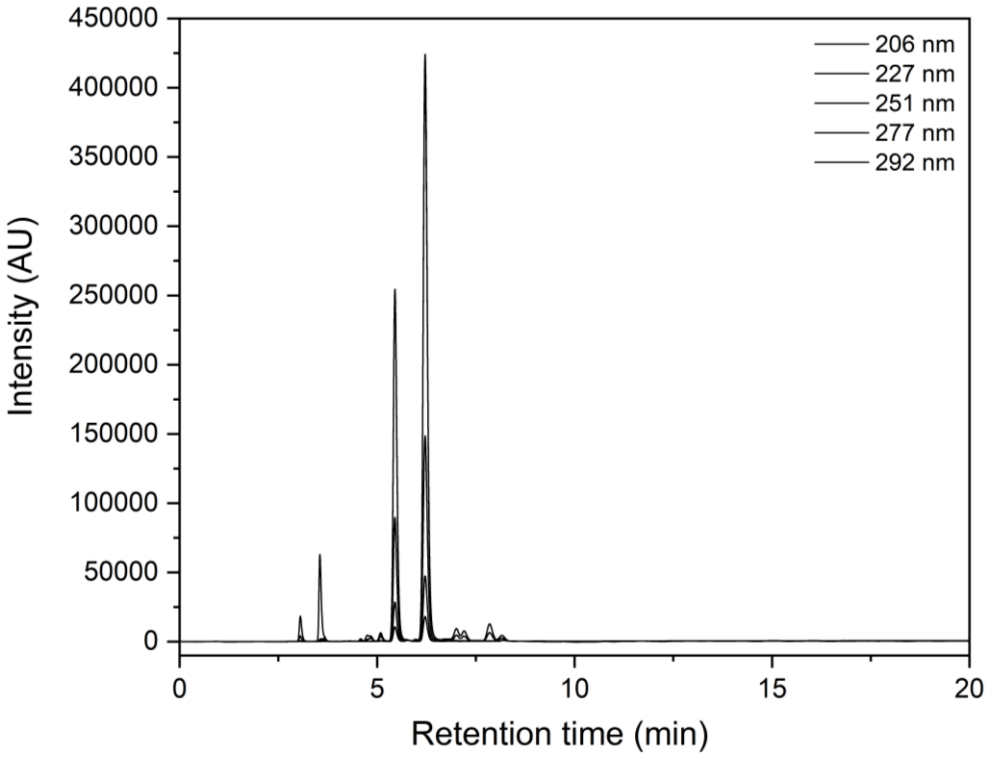
30
20
ppm

8.2 Chiral HPLC analysis

Chromatogram of 2-cinnamylcyclohexanone in the presence of **P2** (32% *ee*).



PDA Ch1 206 nm	Peak #	Ret. time	Area	Area%
	1	5.454	1652074	34.477
	2	6.218	3139753	65.523

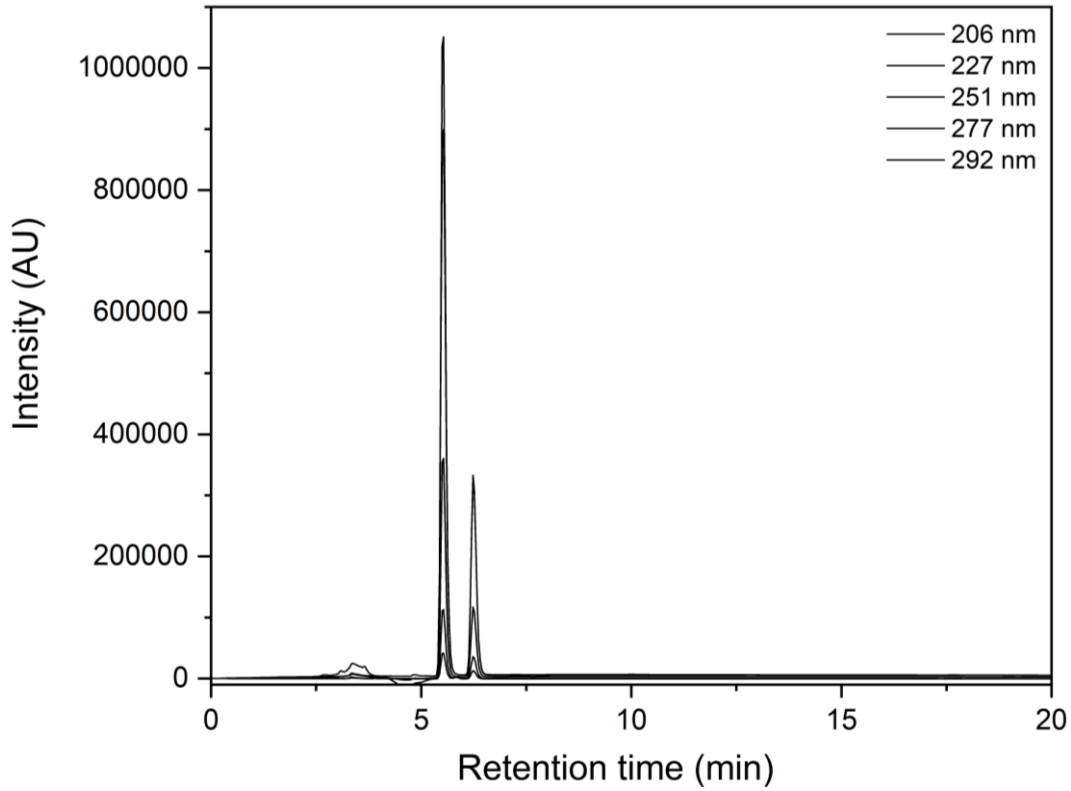
PDA Ch2 227 nm	Peak #	Ret. time	Area	Area%
	1	5.454	576037	34.042
	2	6.218	1116104	65.958

PDA Ch3 251 nm	Peak #	Ret. time	Area	Area%
	1	5.454	1639592	33.988
	2	6.218	3184451	66.012

PDA Ch4 277 nm	Peak #	Ret. time	Area	Area%
	1	5.454	183693	34.142
	2	6.218	354337	65.858

PDA Ch5 292 nm	Peak #	Ret. time	Area	Area%
	1	5.454	19862	32.368
	2	6.218	41501	67.632

Chromatogram of 2-cinnamylcyclohexanone in the presence of **P3** (50% *ee*).



PDA Ch1 206 nm	Peak #	Ret. time	Area	Area%
	1	5.52	8302165	72.874
	2	6.242	3090334	27.126

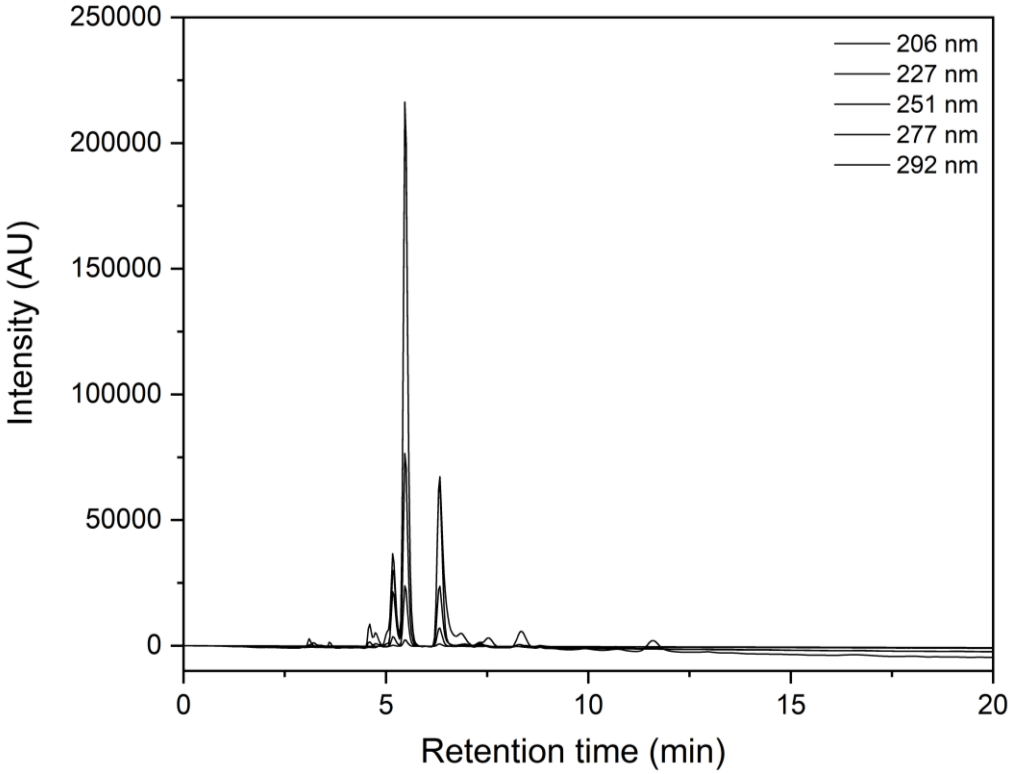
PDA Ch2 227 nm	Peak #	Ret. time	Area	Area%
	1	5.519	3108853	74.565
	2	6.242	1060484	25.435

PDA Ch3 251 nm	Peak #	Ret. time	Area	Area%
	1	5.518	8695882	74.93
	2	6.242	2909528	25.07

PDA Ch4 277 nm	Peak #	Ret. time	Area	Area%
	1	5.519	965609	75.113
	2	6.242	319939	24.887

PDA Ch5 292 nm	Peak #	Ret. time	Area	Area%
	1	5.518	351590	74.732
	2	6.242	118876	25.268

Chromatogram of 2-cinnamylcyclohexanone in the presence of **P5** (44% *ee*).



PDA Ch1 206 nm	Peak #	Ret. time	Area	Area%
	1	5.478	1765000	67.987
	2	6.327	831074	32.013

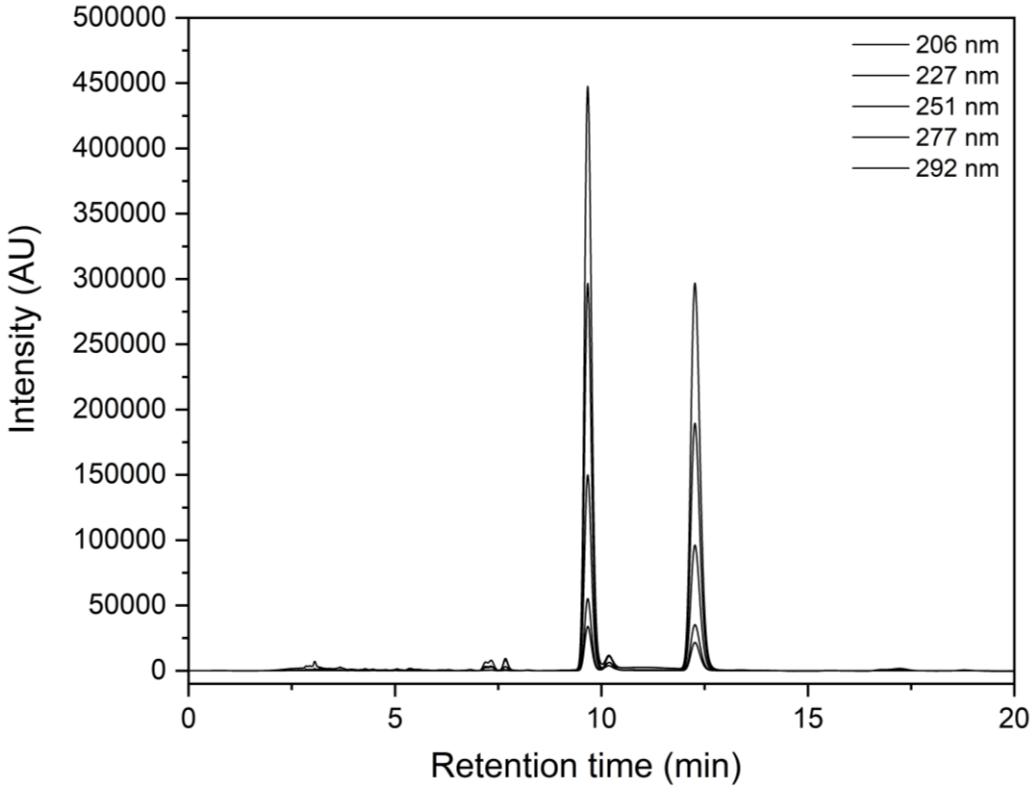
PDA Ch2 227 nm	Peak #	Ret. time	Area	Area%
	1	5.477	636852	71.576
	2	6.324	252907	28.424

PDA Ch3 251 nm	Peak #	Ret. time	Area	Area%
	1	5.478	1766881	74.241
	2	6.323	613057	25.759

PDA Ch4 277 nm	Peak #	Ret. time	Area	Area%
	1	5.478	195577	74.32
	2	6.323	67580	25.68

PDA Ch5 292 nm	Peak #	Ret. time	Area	Area%
	1	5.478	20875	68.842
	2	6.323	9448	31.158

Chromatogram of 2-cinnamylcyclohexanone in the presence of **P9** (8% ee).



PDA Ch1 206 nm	Peak #	Ret. time	Area	Area%
	1	9.67	5534638	53.541
	2	12.266	4802498	46.459

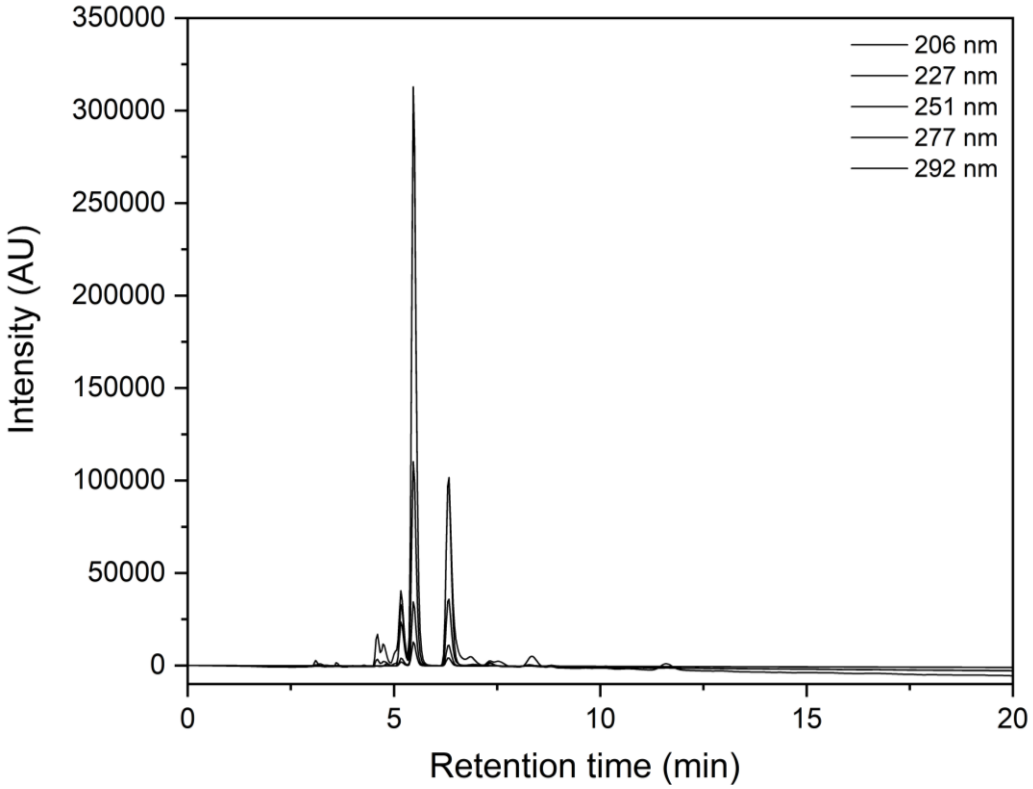
PDA Ch2 227 nm	Peak #	Ret. time	Area	Area%
	1	9.67	1804126	54.093
	2	12.266	1531127	45.907

PDA Ch3 251 nm	Peak #	Ret. time	Area	Area%
	1	9.67	3560969	54.131
	2	12.266	3017464	45.869

PDA Ch4 277 nm	Peak #	Ret. time	Area	Area%
	1	9.67	660061	54.268
	2	12.266	556247	45.732

PDA Ch5 292 nm	Peak #	Ret. time	Area	Area%
	1	9.408	405859	54.352
	2	11.96	340869	45.648

Chromatogram of 2-cinnamylcyclohexanone in the presence of **P11** (44% *ee*)



PDA Ch1 206 nm	Peak #	Ret. time	Area	Area%
	1	5.476	2491335	69.265
	2	6.322	1105463	30.735

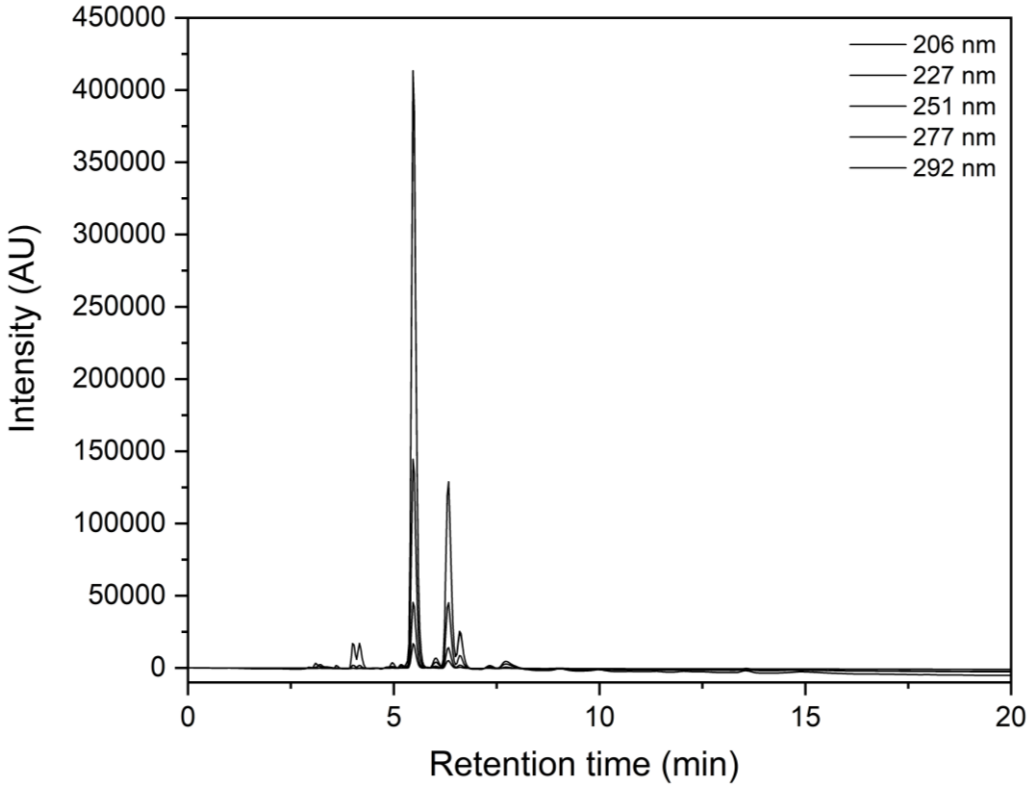
PDA Ch2 227 nm	Peak #	Ret. time	Area	Area%
	1	5.475	905028	71.793
	2	6.321	355582	28.207

PDA Ch3 251 nm	Peak #	Ret. time	Area	Area%
	1	5.475	2511489	73.079
	2	6.321	925209	26.921

PDA Ch4 277 nm	Peak #	Ret. time	Area	Area%
	1	5.475	277218	72.965
	2	6.321	102715	27.035

PDA Ch5 292 nm	Peak #	Ret. time	Area	Area%
	1	5.475	104095	72.338
	2	6.32	39806	27.662

Chromatogram of 2-cinnamylcyclohexanone in the presence of **P12** (48% *ee*).



PDA Ch1 206 nm	Peak #	Ret. time	Area	Area%
	1	5.478	3319930	73.97
	2	6.325	1168257	26.03

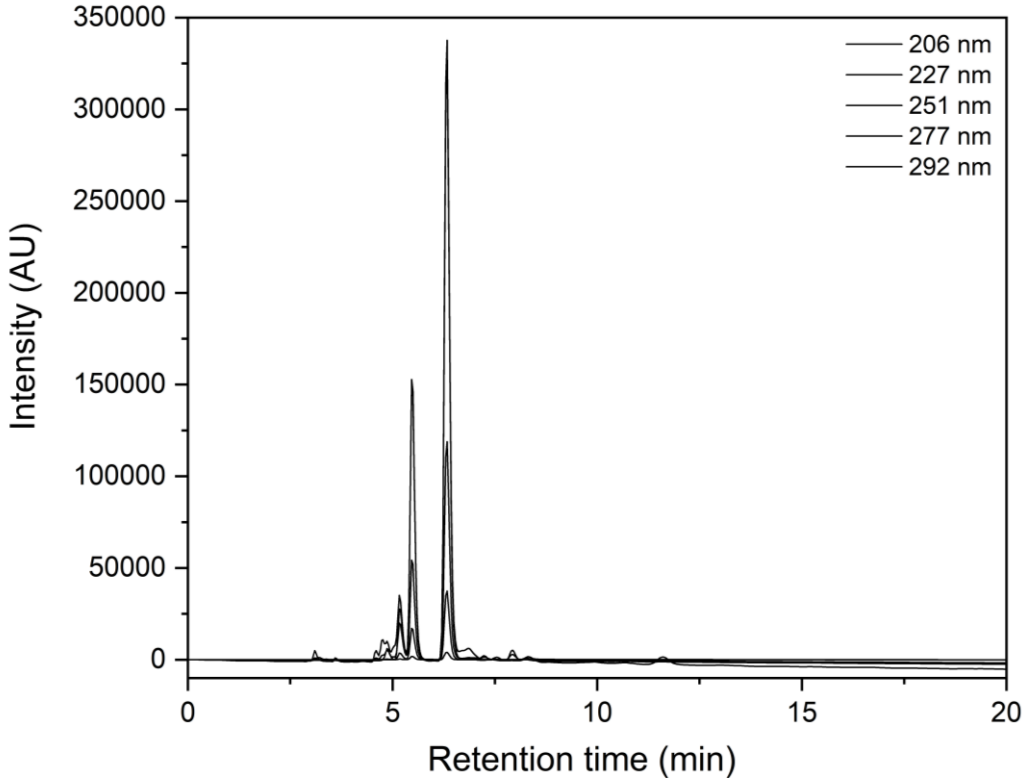
PDA Ch2 227 nm	Peak #	Ret. time	Area	Area%
	1	5.478	1199723	73.775
	2	6.325	426475	26.225

PDA Ch3 251 nm	Peak #	Ret. time	Area	Area%
	1	5.478	3386699	73.746
	2	6.325	1205657	26.254

PDA Ch4 277 nm	Peak #	Ret. time	Area	Area%
	1	5.478	365973	72.973
	2	6.325	135547	27.027

PDA Ch5 292 nm	Peak #	Ret. time	Area	Area%
	1	5.478	38138	73.688
	2	6.325	13618	26.312

Chromatogram of 2-cinnamylcyclohexanone in the presence of **P13** (42% *ee*).



.

PDA Ch1 206 nm	Peak #	Ret. time	Area	Area%
	1	5.48	1279017	29.468
	2	6.325	3061331	70.531

PDA Ch2 227 nm	Peak #	Ret. time	Area	Area%
	1	5.48	466563	29.925
	2	6.325	1092542	70.074

PDA Ch3 251 nm	Peak #	Ret. time	Area	Area%
	1	5.48	1275015	29.464
	2	6.324	3052247	70.535

PDA Ch4 277 nm	Peak #	Ret. time	Area	Area%
	1	5.48	139217	29.338
	2	6.325	335301	70.66139

PDA Ch5 292 nm	Peak #	Ret. time	Area	Area%
	1	5.48	14582	28.274
	2	6.325	36991	71.725