Ketone Synthesis *via* Rhodium-Catalyzed Traceless Chelation-Controlled Hydroacylation Reactions

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A thesis submitted in partial fulfillment of the requirements for the degree of

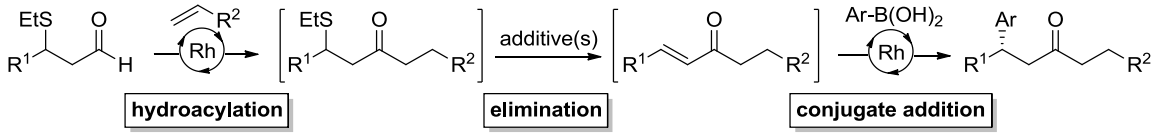
Doctor of Philosophy in Organic Chemistry

Abstract

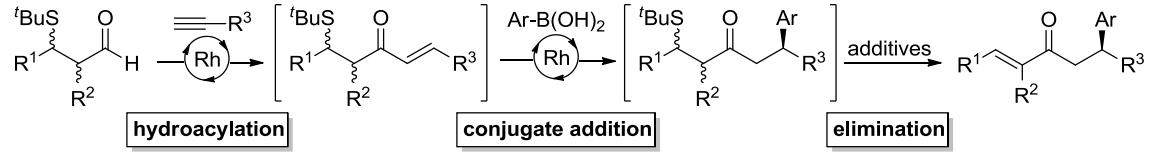
This thesis documents the development of rhodium-catalyzed traceless chelation-controlled hydroacylation reactions for the synthesis of a variety of ketone products.

Chapter 1 provides an overview of rhodium-catalyzed hydroacylation chemistry, focusing on the origin of chelation-controlled strategies and the benefits thereof.

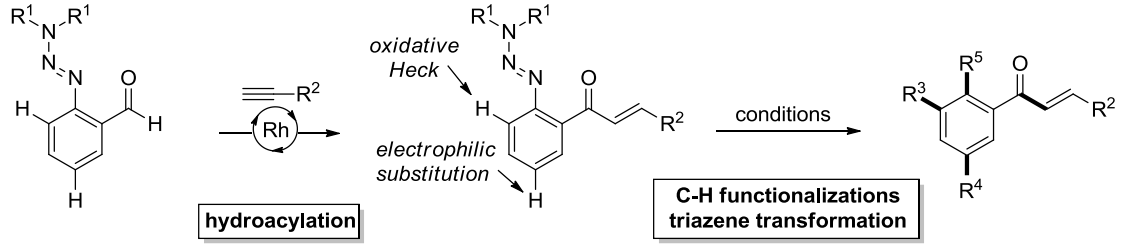
Chapter 2 describes a sequential reaction involving alkene hydroacylation, sulfide elimination and boronic acid conjugate addition, which affords products with the initial sulfide coordinating group replaced by a stereochemically defined aryl group.



Chapter 3 demonstrates a sequential process involving alkyne hydroacylation, boronic acid conjugate addition and sulfide elimination, which provides enantioenriched β'-aryl-α,β-unsaturated ketones in a highly efficient and selective manner.



Chapter 4 illustrates a versatile chelating group, triazene, for hydroacylation reactions. Subsequent functionalization of aromatic C-H bonds, promoted by the same chelating unit, offers highly substituted phenyl ketone products.



Chapter 5 documents experimental procedures and data.

Declaration

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

Two of the projects described in this thesis were developed in collaboration with other members in the Willis group and their contributions are clearly stated where appropriate.

The results discussed in Chapter 2 were carried out in collaboration with Dr. Anaïs Bouisseau, a former DPhil student in the Willis group, and have been published in *Chemistry – A European Journal* in 2016. Her part of work was submitted to the University of Oxford for a DPhil degree in 2017. The data obtained by Dr. Anaïs Bouisseau are not included in the experimental section.

The chemistry described in Chapter 4 was jointly carried out with Dr. Sangwon Seo, a former postdoctoral fellow, and Eva K. Paffenholz, a visiting student, and had not been published by the time this thesis was submitted. All data are detailed in the experimental section.

Ming Gao

April 2018

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A sincere thank you to my parents for their eternal love and encouragement – something that does not require many words. Big thanks to all my friends who have come to my life for the past 26 years, specially, Zhenbo and Nayeon during Oxford stay. Additionally, I would like to thank the Alternative Tuck Shop for providing fast, safe, tasty and filling sandwiches, and Tim/TQD/Yiding for being 'ATS mates', which ensured my efficiency during working days.

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Abbreviations

Ac	acetyl
acac	acetylacetone
app.	apparent
Ar	aryl
BAr^F	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
br.	broad
Bu	butyl
℃	degrees Celsius
cat.	catalyst
CI	chemical ionization
cod	cyclooctadiene
coe	cyclooctene
CuMeSal	copper(I) 3-methylsalicylate
CuTC	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
Cypent	cyclopentyl
d	doublet or deuterated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane

dcpe	1,1-bis(diphenylcyclohexyl)ethane
dcpm	1,1-bis(diphenylcyclohexyl)methane
DIBAL-H	diisobutylaluminium hydride
DMF	*N*,*N*-dimethylformamide
DPEPhos	bis((2-diphenylphosphino)phenyl)ether
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppm	1,1-bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
EI	electron ionization
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
et al.	et alii (Latin: and others)
g	gram(s)
h	hour(s)
Hex	*n*-hexyl
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry

Hz	Hertz
^{i}Pr	*iso*-propyl
IR	infrared
J	coupling constant
L	ligand or liter
LRMS	low resolution mass spectrometry
M	metal or molar
m	milli (10^{-3}) or multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Me-DuPhos	1,2-bis(2,5-dimethylphospholano)benzene
min	minutes
mol	mole(s)
m.p.	melting point
MS	mass spectrometry
MW	microwave irradiation
nbd	norbornadiene
NBS	*N*-bromosuccinimide
NMI	*N*-methyl imidazole
NMR	nuclear magnetic resonance
o	*ortho*
Oct	*n*-octyl

p	*para*
Pent	*n*-pentyl
Ph	phenyl
ppm	parts per million
Pr	*n*-propyl
q	quartet
R	generic group/substituent
rac	racemic
rt	room temperature
s	singlet
t	triplet
^{t}Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
Tf	trifluoromethanesulfonate/triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
δ	chemical shift
μ	micro (10^{-6})
ν_{max}	infrared absorption maximum

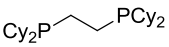
Ligands and chemical structures



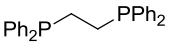
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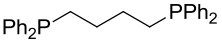
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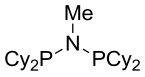
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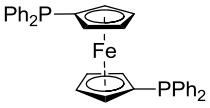
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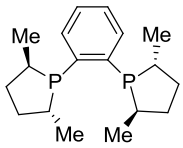
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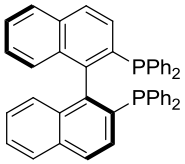
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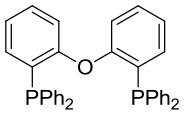
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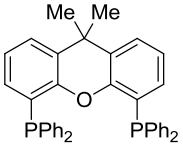
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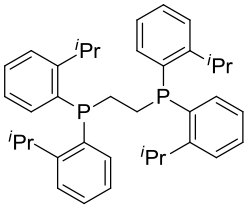
(*S*)-BINAP



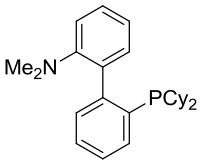
DPEPhos



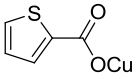
XantPhos



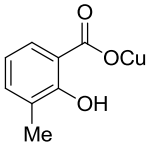
***o*-*i*Pr-dppe**



DavePhos



CuTC

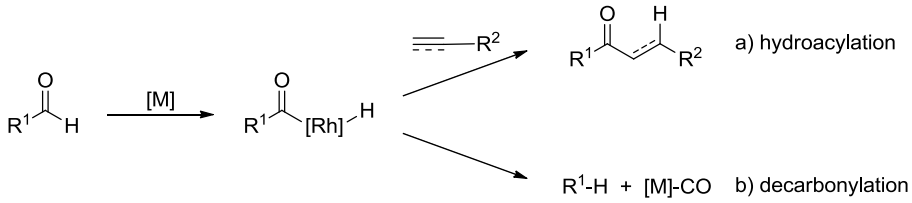


CuMeSal

Chapter 1

Introduction

The development of transition metal-catalyzed C-H bond activation processes is revolutionizing synthetic designs,[1] and has allowed novel catalytic reactions to proceed with high atom-economy.[2] As a powerful illustration, the hydroacylation of alkenes and alkynes, first described by Sakai *et al.*,[3] has emerged as an important tool for the synthesis of ketones and enones, respectively.[4] It is the formal addition of an acyl unit and a hydrogen atom across a C-C π bond, employing an aldehyde and an alkene or alkyne, and is inherently a 100% atom-economic process (Scheme 1.1a). Several metals can catalyze this reaction, including ruthenium,[5] cobalt,[6] nickel[7] and iridium,[8] and metal-free radical variants are also known.[9] However, rhodium catalysts have remained the most commonly used so far, and will be the focus of this thesis.



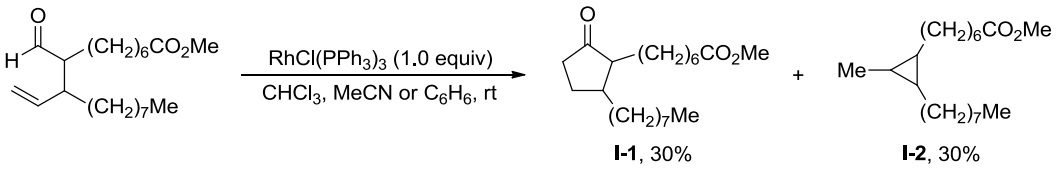
Scheme 1.1 Alkene and alkyne hydroacylation and decarbonylation

Different types of rhodium catalysts have been successfully utilized for hydroacylation

reactions, including Wilkinson's catalyst, neutral rhodium diene complexes and, most frequently, cationic rhodium bisphosphine complexes. The main obstacle stems from decarbonylation of the acyl-metal intermediate, generated from oxidative addition of an aldehyde, that gives rise to reductive side product (R^1-H) and an inactive metal carbonyl species (Scheme 1.1b).[10] The most common and effective approach to suppress this side reaction is the use of chelation-controlled strategies, which has allowed the development of highly efficient and versatile hydroacylation transformations. This chapter will outline the history of rhodium-catalyzed hydroacylation chemistry and then focus on the synthetic achievements from the use of various chelating atoms. A generally-accepted reaction mechanism of intermolecular hydroacylation will also be described.

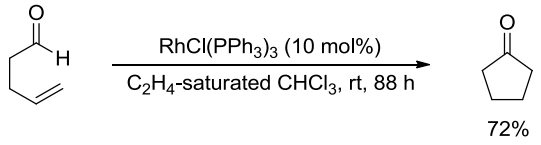
1.1 Rhodium-catalyzed intramolecular hydroacylation

Alkene hydroacylation was first described, in an intramolecular fashion, by Sakai *et al.* in their study towards the synthesis of prostaglandin derivatives (Scheme 1.2).[3] Using a stoichiometric amount of Wilkinson's catalyst, 4-enals cyclized to the desired cyclopentanone products **I-1**, together with reductive decarbonylative cyclopropane products **I-2**. This result illustrated that decarbonylation was such a facile process under rhodium catalysis that, even in competition with the formation of 5-membered ring systems, it could afford thermodynamically unfavored cyclopropanes in an effective manner. Nevertheless, the potential of a successful hydroacylation and the need to overcome decarbonylative side reactions drove the earlier research towards the synthesis of cyclopentanone products.



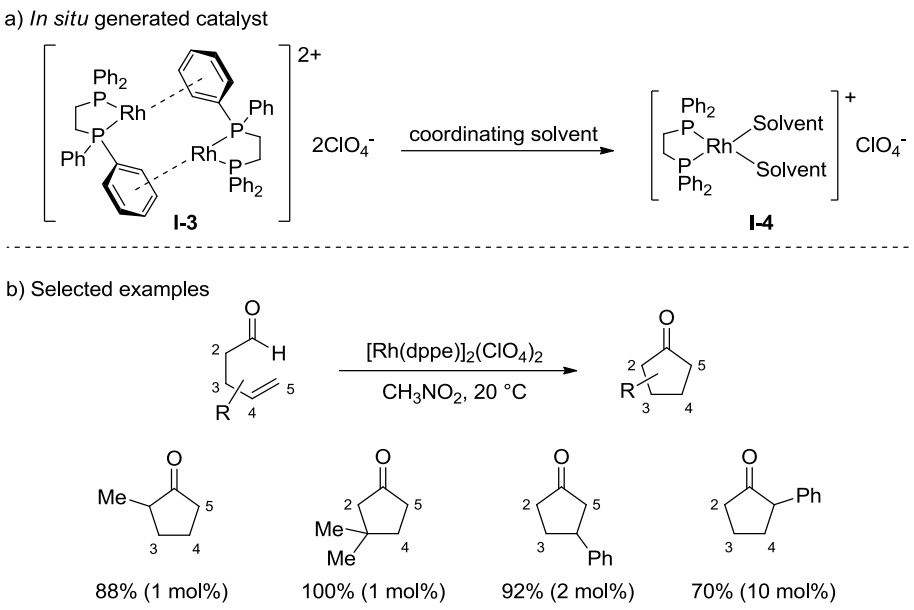
Scheme 1.2 First hydroacylation reactions employing Wilkinson's catalyst

Later in 1976, Miller and co-workers reported a related hydroacylation using a sub-stoichiometric amount of Wilkinson's catalyst (Scheme 1.3).[11] Key to suppressing the decarbonylative side reactions was the use of ethylene-saturated chloroform, with the ethylene probably occupying a vacant Rh coordination site. This technique allowed formation of the desired cyclopentanone in 72% yield after 88 h, employing 10 mol% of Wilkinson's catalyst, with only trace amounts of the decarbonylative product observed.



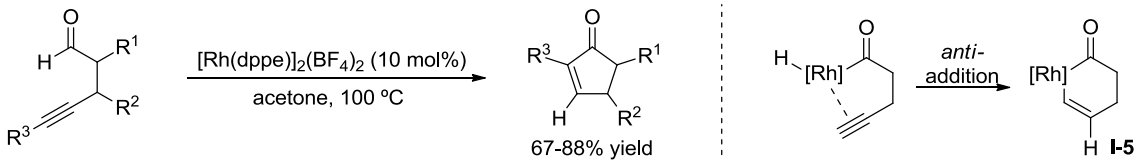
Scheme 1.3 Miller's hydroacylation using ethylene-saturated solvent

A significant breakthrough for this cyclization came in 1988 with the use of cationic Rh^{I} complexes pioneered by Bosnich,[12] in which an acceleration of the hydroacylation step over decarbonylation was realized. [Rh(dppe)]ClO_4 was identified as the optimal catalyst for this transformation, which existed as a catalytically inactive, phenyl-bridging dimer **I-3** in the solid state or non-coordinating solvents,[13] and could be generated *in situ* as disolvated monomer **I-4** (Scheme 1.4a). This highly efficient catalyst allowed the hydroacylative cyclization of a variety of 2-, 3-, 4- and 5-substituted 4-pentenals in good yields, with catalyst loadings as low as 1 mol% (Scheme 1.4b). Since this initial report, cationic rhodium complexes have become the most frequently employed and most effective catalysts for hydroacylation reactions.



Scheme 1.4 Bosnich's use of cationic Rh^{I} catalysis for hydroacylation

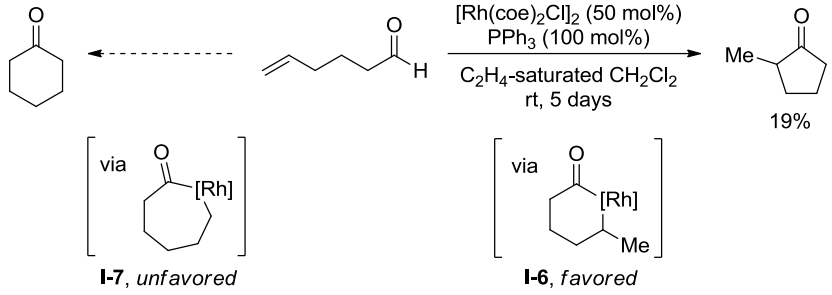
Fu and co-workers later utilized this catalytic system in the intramolecular hydroacylation of alkynes, which afforded diversely substituted cyclopentenones in good yields (Scheme 1.5).[14] Compared to its alkene variant, this process requires an unusual *anti*-addition of the metal hydride across the C-C π bond, which gives key intermediate **I-5**.



Scheme 1.5 Fu's hydroacylative route towards cyclopentenones

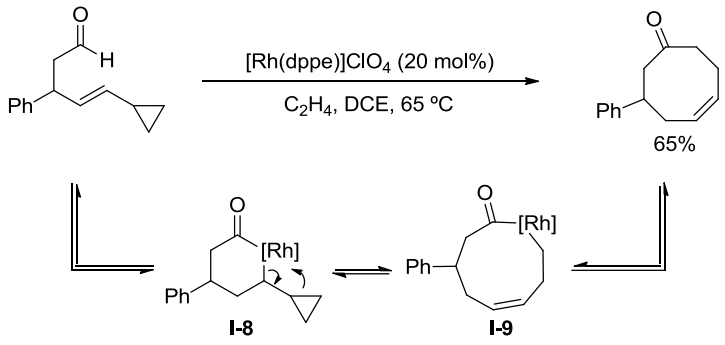
Despite the success in 5-membered ring synthesis *via* intramolecular hydroacylation, challenges remained in this area for the formation of larger ring systems, as exemplified in Larock's hydroacylation of 5-hexenal (Scheme 1.6).[15] A neutral rhodium diene dimer together with monophosphine ligand PPh_3 in ethylene-saturated CH_2Cl_2 promoted the hydroacylation of 5-hexenal to give 2-methyl-cyclopentanone in 19% yield, with no 6-membered ring formation observed. This suggested that the 6-membered metallacycle **I-6**, which was involved in the formation of cyclopentanone products, was favored over the

7-membered metallacycle **I-7**.



Scheme 1.6 Larock's hydroacylation of 5-hexenal

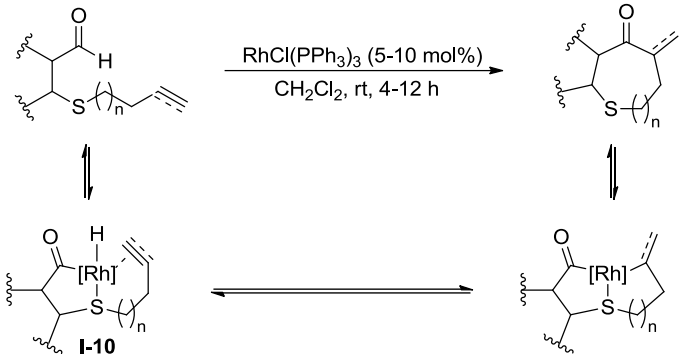
Instead of resorting to novel catalytic systems, Shair and co-workers managed to access 8-membered rings, cyclooctenones, by modifying the enal substrates (Scheme 1.7).[16] Incorporation of a cyclopropyl group led to a ring expansion of the acyl rhodium intermediate **I-8** to **I-9**, which, upon reductive elimination, gave the cyclooctenone product.



Scheme 1.7 Shair's synthesis of cyclooctenones

An alternative but highly efficient approach to access heterocycles with larger ring sizes was pioneered by Bendorf and co-workers, by the use of heteroatom chelation (Scheme 1.8).[17] The formation of chelation-stabilized intermediate **I-10** could inhibit reductive decarbonylation, and the desired sulfur-incorporated heterocycles were obtained employing low loadings of Wilkinson's catalyst under mild reaction conditions. Following this initial report, *O*- and *N*-containing heterocycles were synthesized by Dong[18] and Nguyen,[19] respectively. In addition, this powerful strategy has enabled the success of

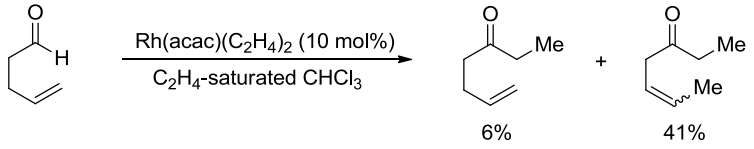
intermolecular hydroacylation processes.



Scheme 1.8 Chelation-assisted 7- and 8-membered ring formation

1.2 Rhodium-catalyzed intermolecular hydroacylation and chelation-controlled strategies

The synthetic utility of intramolecular hydroacylation reactions is inherently limited in the types of products it can provide and the need to prepare often complex substrates. Nevertheless, the development of intermolecular variants would provide versatile ketone products, potentially employing simple aldehydes and alkenes or alkynes. In Miller's study using ethylene-saturated chloroform, as was shown previously, they observed the intermolecular hydroacylation adduct in 6% yield, together with a subsequent alkene isomerization (Scheme 1.9).[11] Later, the hydroacylation of ethylene using benzaldehydes was realized by Marder and co-workers.[20] However, these transformations were plagued with low yields and high pressures of ethylene gas; as a consequence, synthetically friendly procedures were in demand.

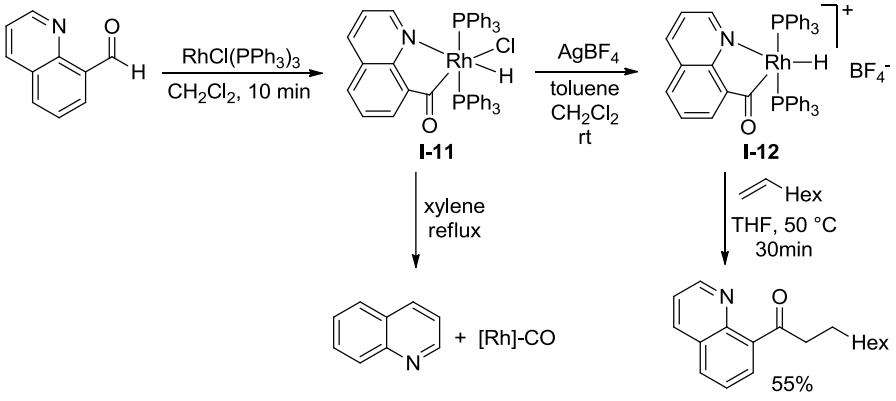


Scheme 1.9 Miller's hydroacylation of ethylene

The main challenge in developing intermolecular hydroacylation reactions is the prevention of decarbonylation pathways. In this context, the use of heteroatom chelation emerged as a successful strategy, which has allowed dramatic breakthroughs in this field. The majority of these transformations employed chelating aldehydes bearing *N*-, *O*-, *P*- and *S*-heteroatoms. Some examples with chelation derived from the unsaturated coupling partners are also known in the literature.[21]

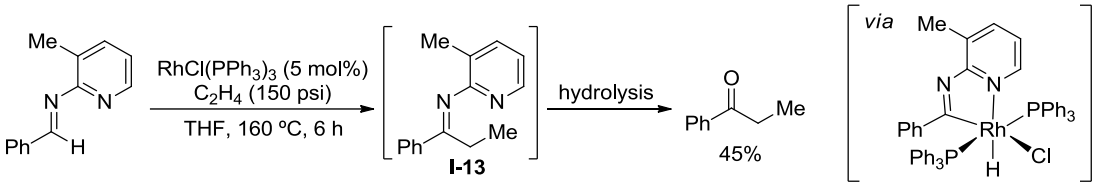
1.2.1 *N*-Chelation

Six years after Sakai's first intramolecular hydroacylation, Suggs reported its intermolecular variant *via* the use of *N*-chelation (Scheme 1.10).[22] It was found that treating 8-quinolinecarboxaldehyde with Wilkinson's catalyst gave an acylrhodium(III) hydride **I-11**, which was quite stable and did not undergo decarbonylation unless refluxed at elevated temperature in xylene. Further reacting **I-11** with $AgBF_4$ led to coordinatively unsaturated complex **I-12** in quantitative yield. Combining this complex with 1-octene at 50 ℃ afforded the desired hydroacylation product, 8-quinolinyl *n*-octyl ketone, in 55% yield. Notably, the coordinatively saturated complex **I-11** was not able to undergo alkene hydroacylation under these conditions.



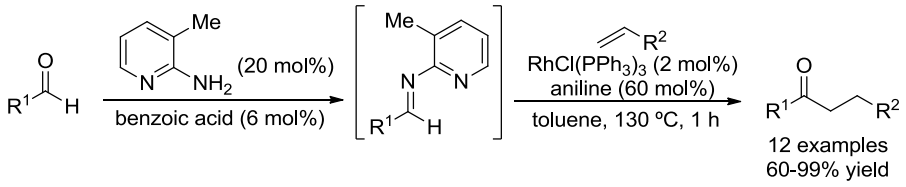
Scheme 1.10 First intermolecular hydroacylation employing heteroatom chelation

The same group also demonstrated that, by employing picolyl imines, they were able to achieve *N*-chelation-assisted hydroacylation in a catalytic manner (Scheme 1.11).[23] Using 5 mol% of Wilkinson's catalyst and high pressures of ethylene gas, a formal hydroacylation product **I-13** could be obtained, which, without isolation, underwent a hydrolysis to deliver the desired ketone product.



Scheme 1.11 Catalytic intermolecular hydroacylation using picolyl imines

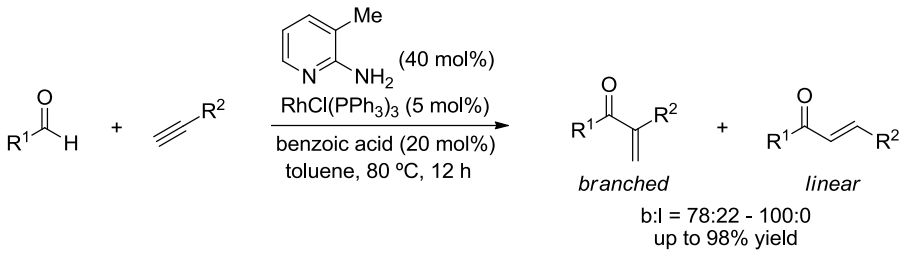
This field was further developed and improved in the 1990s by Jun and co-workers, who not only achieved catalytic hydroacylation using 8-quinolinecarboxaldehydes,[24] but also described a way to form and remove the picolyl imine directing group *in situ* so that only a sub-stoichiometric amount of picolyl amine was required.[25] In their latter methodology, a small amount of benzoic acid was utilized to catalyze imine formation, and the addition of aniline could catalyze its hydrolysis (Scheme 1.12). This elegant approach allowed all the reagents to be added in one-pot, moved away from high pressures of ethylene gas, and afforded alkene hydroacylation products in a 'traceless' manner.



Scheme 1.12 Jun's hydroacylation using a traceless chelating group

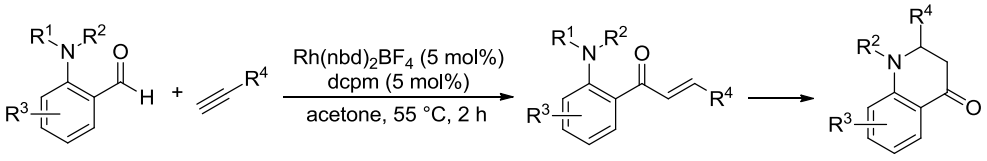
This picolyl imine system was extensively studied by several research groups, and a variety of both coupling partners could be successfully employed.[26] In Jun's

hydroacylation of terminal alkynes, they observed an exclusive formation of the branched regioisomer from aryl aldehydes, and a high branched to linear ratio with alkyl aldehydes (Scheme 1.13).[27] Later, Castillón illustrated that the use of sterically demanding ligands, *e.g.*, P^{t}Bu$_3$, could result in the reduction in the amount of the branched isomer.[28]



Scheme 1.13 Branched-selective hydroacylation of terminal alkynes

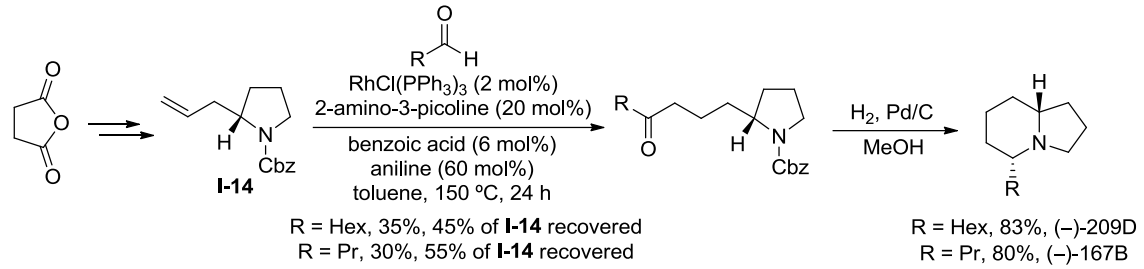
While cationic rhodium catalysis was not efficient for picolyl imines, as discussed in the mechanistic studies by Bo and Castillón,[29] it could promote a highly linear-selective alkyne hydroacylation employing 2-aminobenzaldehydes as the coupling partner.[30] Willis utilized the hydroacylation adducts, obtained from this method, for the synthesis of a variety of substituted dihydroquinolones, which demonstrated the synthetic utility of chelation-controlled hydroacylation reactions (Scheme 1.14).



Scheme 1.14 Willis' synthesis of dihydroquinolones from hydroacylation

The development of *N*-chelation based hydroacylation processes has led to the synthesis of gephyrotoxin alkaloids, (–)-167B and (–)-209D (Scheme 1.15).[31] The hydroacylative union of enantiomerically pure alkene **I-14** and an alkyl aldehyde under Jun's conditions afforded the corresponding ketone products in moderate yields, with significant amounts of **I-14** recovered in both cases. Subsequent cyclization under reductive

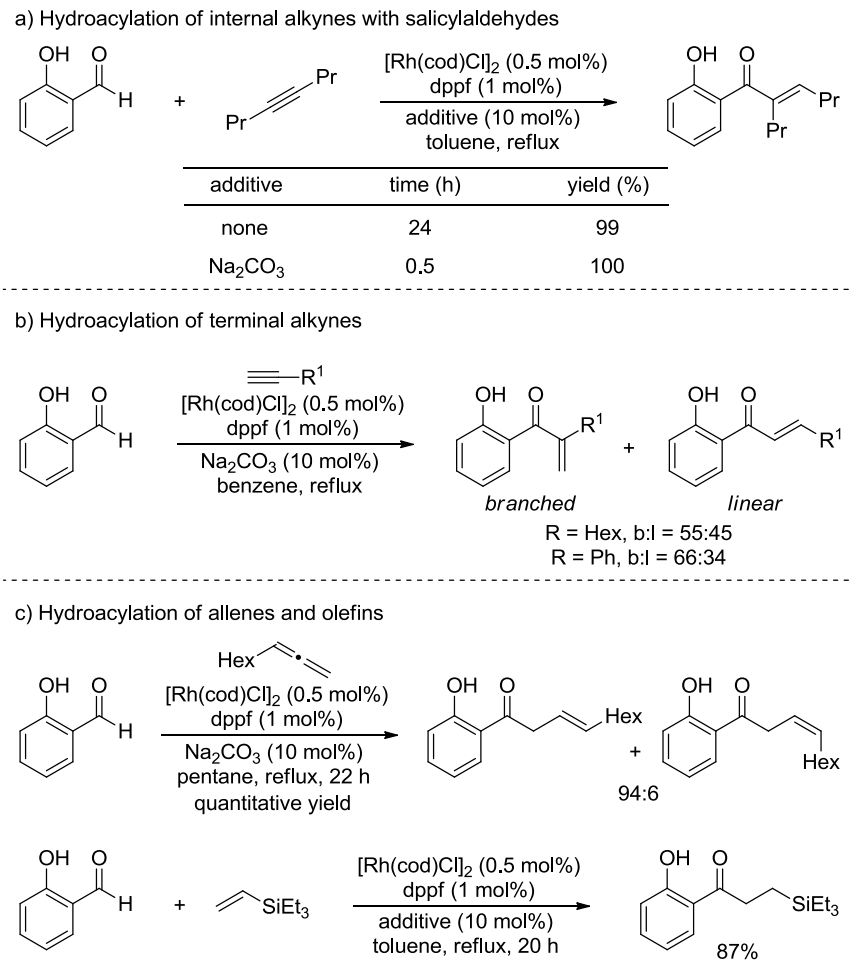
conditions yielded the final bicyclic natural products. In addition, Jun's conditions have also been applied to ^{18}F-labeling[32] and to polymer chemistry.[33]



Scheme 1.15 Total synthesis of natural products using hydroacylation

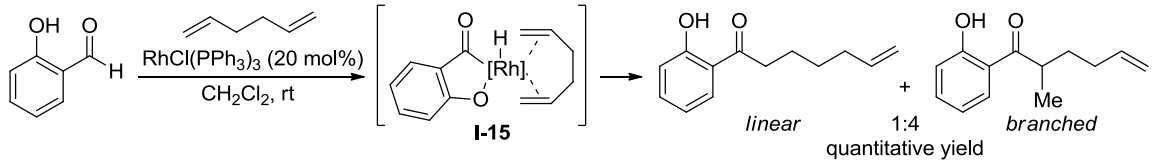
1.2.2 *O*-Chelation

Salicylaldehydes have been widely employed for intermolecular hydroacylation reactions due to their availability, and the first example was described in 1997 by Miura and co-workers.[34] The combination of low loadings of a neutral Rh precursor and a ferrocene-based bisphosphine ligand could promote the hydroacylation of 4-octyne, after refluxing in toluene for 24 h (Scheme 1.16a). The addition of sub-stoichiometric amounts of an inorganic base, Na_2CO_3, dramatically accelerated this transformation, possibly because it could facilitate oxygen coordination by deprotonating the phenol. When applying the optimized conditions to terminal alkynes, however, only a moderate level of regiocontrol was achieved (Scheme 1.16b). The same group later published a full paper for this process, which expanded the reaction scope to alkenes and allenes.[35] Generally, allenes were shown to be good substrates, producing β,γ-unsaturated ketones with excellent stereocontrol. In contrast, only one successful alkene hydroacylation example was described, utilizing triethyl(vinyl)silane (Scheme 1.16c).



Scheme 1.16 Miura's hydroacylation using salicylaldehydes

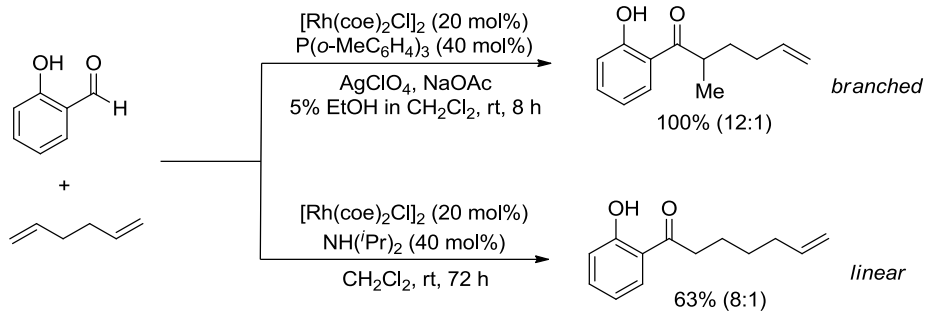
Later, Tanaka and Suemune employed salicylaldehydes in combination with 1,5-dienes to deliver hydroacylation products at ambient temperature using Wilkinson's catalyst (Scheme 1.17).[36] The authors believed, after conducting several control experiments, that the mild reaction conditions stemmed from a 'double chelation' intermediate **I-15**, which resulted in the facile formation of both linear and branched hydroacylation products in a moderate ratio. They also observed that some other neutral Rh complexes as well as



Scheme 1.17 Double-chelation-assisted alkene hydroacylation with salicylaldehydes

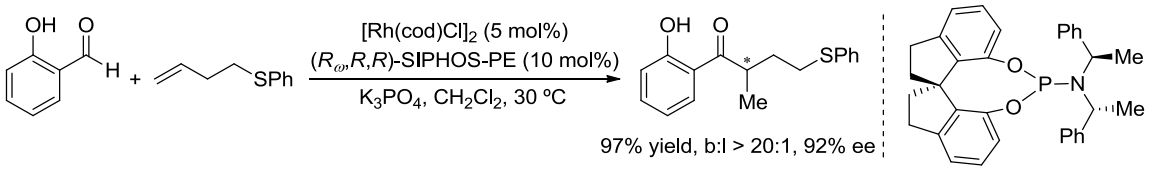
cationic Rh catalysts afforded product, although with different linear to branched ratios.

Suemune and co-workers thus carried out a catalyst screening, aiming to tune the regioselectivity.[37] It was found that by using different rhodium catalysts, together with additives, both regioisomers could be produced with good levels of selectivity (Scheme 1.18).



Scheme 1.18 Tunable regioselectivity using different catalyst systems

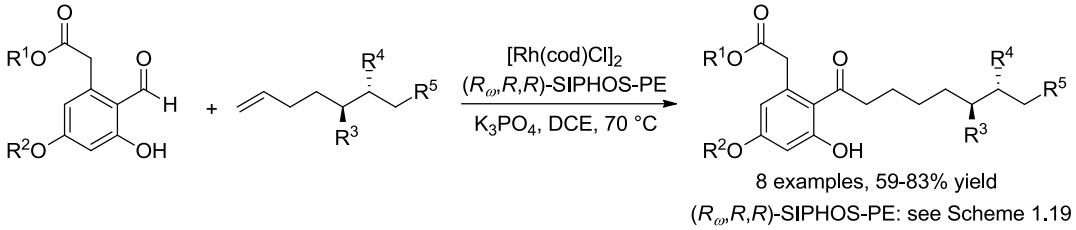
The intermolecular hydroacylation using salicylaldehydes could also be realized in an enantioselective fashion. For instance, in Bolm's *endo*-selective hydroacylation of norbornadiene, the use of a phosphoramidite ligand contributed to a moderate level of enantiocontrol.[38] Later, Dong developed a highly regio- and enantioselective hydroacylation employing homoallylic sulfides as the unsaturated coupling partner (Scheme 1.19).[39] Their success relied on the incorporation of a second coordinating heteroatom to the alkene, similar to the 'double chelation' system reported by Suemune.



Scheme 1.19 Dong's regio- and enantioselective hydroacylation using homoallylic sulfides

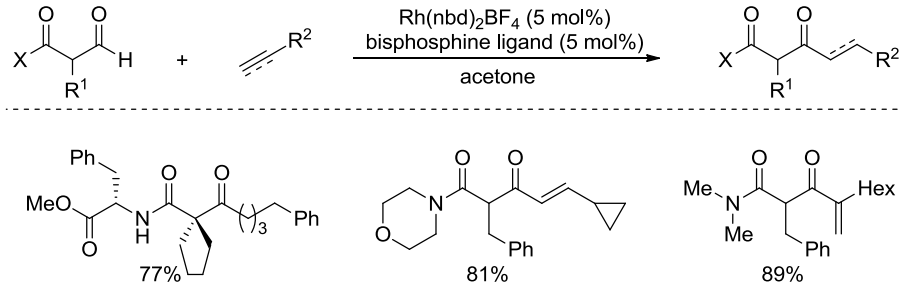
The synthetic utility of these reactions was illustrated in Dong's total synthesis of octaketide natural products.[40] They identified that the use of a chiral phosphoramidite

ligand, (R_ω,*R*,*R*)-SIPHOS-PE, could effectively suppress decarbonylation and favor the formation of linear regioisomer. Eight octaketide natural products were thus obtained through this method in a straightforward manner (Scheme 1.20).



Scheme 1.20 Total synthesis of octaketide natural products *via* hydroacylation

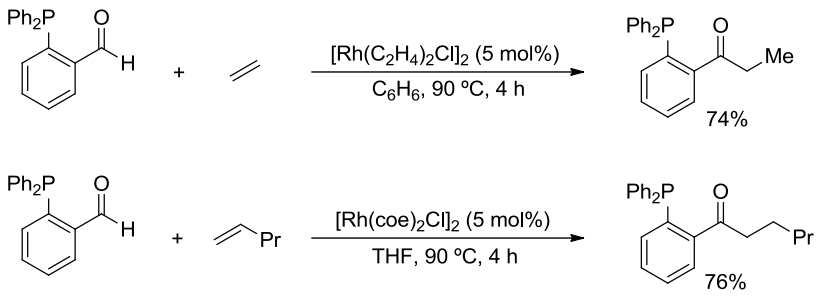
Moving away from salicylaldehydes, the Willis group has recently utilized carbonyl groups to control intermolecular hydroacylation reactions.[41] A broad variety of β-carbonyl-substituted aldehydes was combined with alkenes and alkynes under Rh^I catalysis to deliver synthetically useful 1,3-dicarbonyl compounds (Scheme 1.21), with a switchable linear/branched selectivity when alkynes were employed.



Scheme 1.21 Hydroacylation involving 1,3-dicarbonyl compounds

1.2.3 *P*-Chelation

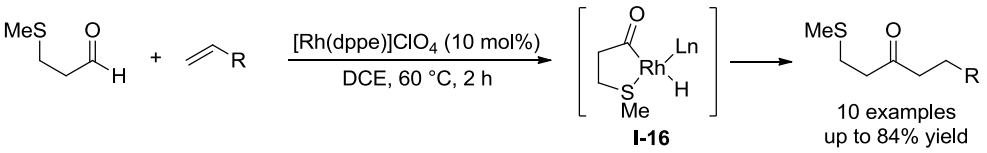
Hydroacylation based on *P*-chelation has remained scarce. Jun described one example with the use of diphenylphosphine as the coordinating unit (Scheme 1.22).[42] In their study, alkyl-substituted alkenes were shown to be good substrates, while styrenes were less efficient. Although successful, this area has not been since explored.



Scheme 1.22 Alkene hydroacylation employing *P*-chelation

1.3 Rhodium-catalyzed intermolecular hydroacylation using *S*-chelating aldehydes

Rh-catalyzed intermolecular hydroacylation reactions using *S*-chelating aldehydes have been widely explored by the Willis group, with the first example reported in 2004.[43] Starting from 3-(methylthio)propanal and employing a cationic Rh^{I} catalyst, the hydroacylation of a series of activated alkenes was achieved (Scheme 1.23). The authors proposed that decarbonylation pathways were diminished through the formation of a 5-membered acylrhodium species **I-16**.



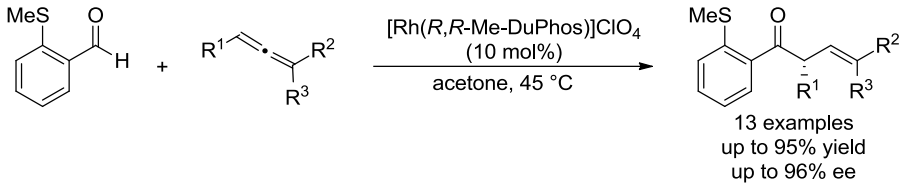
Scheme 1.23 First intermolecular hydroacylation using *S*-chelating aldehydes

Soon afterwards, Willis and co-workers described a second generation catalyst for this transformation, which lowered the catalyst loadings to 5 mol% and expanded the reaction scope to unactivated alkenes as well as alkynes.[44] Unlike $[Rh(dppe)]ClO_4$ (first generation), which had to be generated immediately before use by bubbling H_2 gas through $[Rh(dppe)(nbd)]ClO_4$, the second generation catalyst could be formed *in situ* from a

commercially available precursor, $[Rh(cod)Cl]_2$, a bisphosphine ligand, and $AgClO_4$. Key to achieving excellent reactivity was the use of a hemilabile oxygen-bridged bisphosphine ligand (P-O-P ligand), DPEPhos, while a rigid P-O-P ligand, XantPhos, was identified as being completely ineffective. The third generation catalyst came with the use of small bite-angle P-C-P (phosphine-carbon-phosphine) ligands, and has allowed hydroacylation reactions to proceed with catalyst loadings as low as 0.1 mol%.[45] The exploration of cationic Rh^I catalysts and understanding of reaction mechanisms have contributed to the development of a variety of hydroacylation processes, employing *S*-chelating aldehydes.

1.3.1 Extension of unsaturated coupling partners

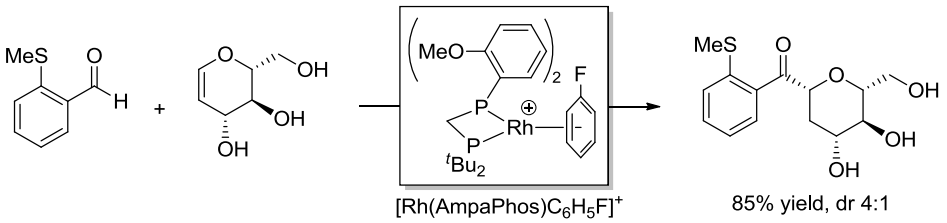
The highly active cationic Rh^I catalyst and the use of *S*-chelating aldehydes have enabled allenes to be employed as efficient coupling partners.[46] Under optimized reaction conditions involving a chiral bisphosphine ligand, Me-DuPhos, a series of allenes were combined with 2-sulfide-substituted benzaldehyde to give β,γ-unsaturated ketone adducts with a stereochemically defined α-carbon center (Scheme 1.24). A complete scope of this transformation was published one year later.[47]



Scheme 1.24 Hydroacylation of allenes with *S*-chelating aldehydes

By the time that the third generation catalyst was developed, the hydroacylation of alkenes (both activated and unactivated) and alkynes (both terminal and internal) had become possible. One challenge which remained was the use of internal alkenes for such

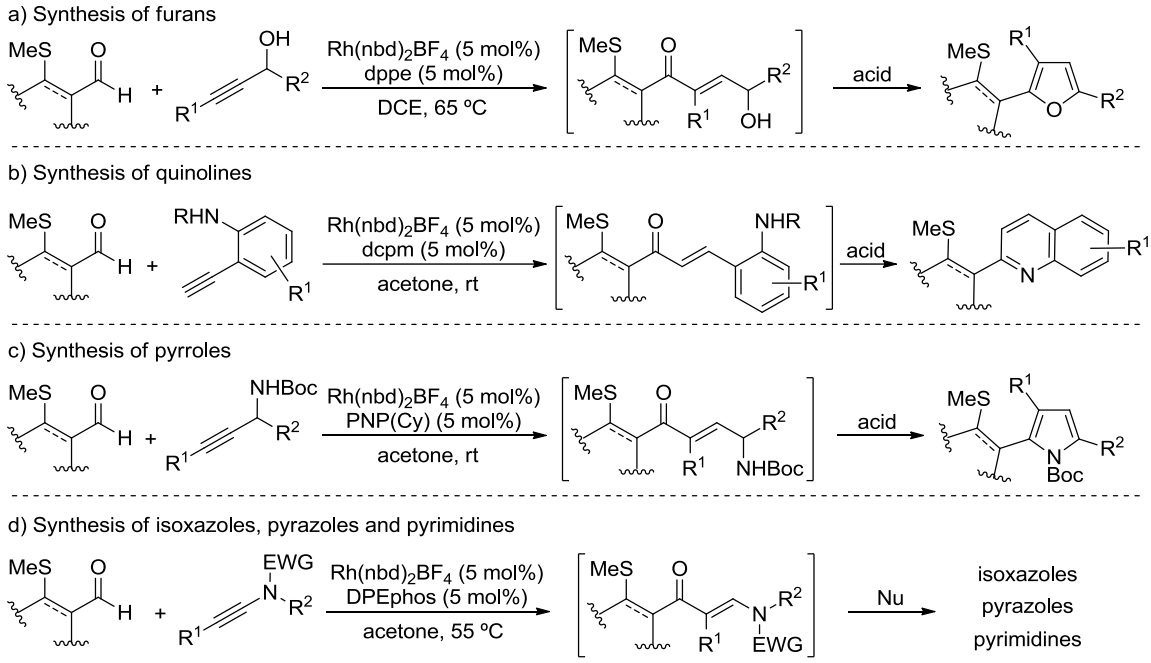
process, which was solved in 2015 with the advent of AmpaPhos.[48] This well-defined Rh/AmpaPhos catalyst allowed the hydroacylation of a series of 1,1- and 1,2-disubstituted olefins bearing diverse functionalities. A representative example is shown in Scheme 1.25.



Scheme 1.25 Hydroacylation of challenging alkenes

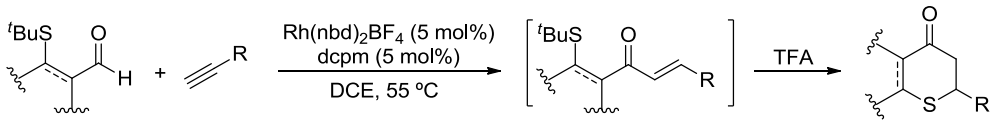
1.3.2 Synthesis of heterocyclic compounds

Versatility of the unsaturated coupling partners, derived from the use of *S*-chelating aldehydes, has led to the synthesis of a range of heterocyclic compounds. These transformations generally relied on the 1,3-, 1,4- or 1,5-relationships of the hydroacylation adducts, which could be subsequently cyclized to afford a variety of different heterocycles. This idea was first realized in 2011,[49] in which the hydroacylation of propargylic alcohols followed by an acid-catalyzed cyclization resulted in the formation of highly-substituted furans (Scheme 1.26a). This strategy was later applied to the synthesis of quinolines (Scheme 1.26b) and pyrroles (Scheme 1.26c), by employing *o*-alkynyl anilines and propargylic amines, respectively.[50] More recently, ynamides were shown to be effective coupling partners, and the corresponding linear-selective hydroacylation products, β-enaminones, could be treated with various nucleophiles to provide isoxazoles, pyrazoles and pyrimidines (Scheme 1.26d).[51]



Scheme 1.26 Synthesis of heterocyclic compounds *via* hydroacylation

A different concept was to incorporate the sulfide coordinating group into the final products, thus providing *S*-containing heterocycles. Willis and co-workers described successful hydroacylation reactions utilizing β-^{t}BuS-substituted aldehydes.[52] The products obtained, upon treatment of TFA, could undergo a thio-Michael addition process with the loss of a *tert*-butyl group to efficiently deliver thiochroman-4-ones and their derivatives (Scheme 1.27).

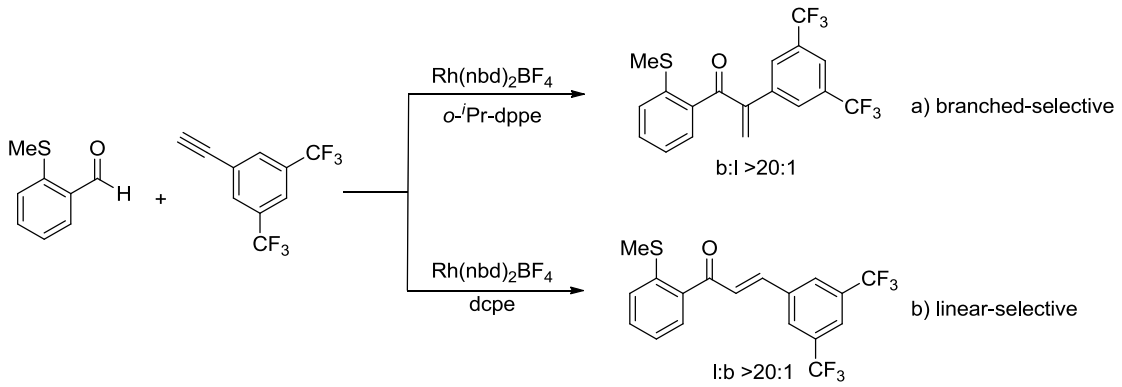


Scheme 1.27 Synthesis of thiochroman-4-ones and their derivatives

1.3.3 Control of regio- and enantioselectivities

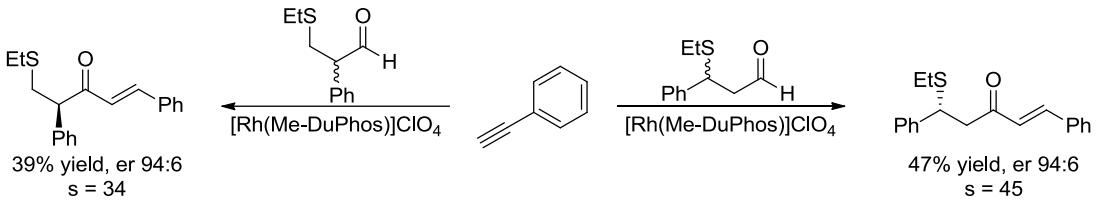
In earlier studies, linear-selective hydroacylation was typically observed. It was not until 2011 that highly branched-selective hydroacylation using *S*-chelating aldehydes was demonstrated.[53] Willis found that a bulky *ortho*-^{i}Pr-dppe derived catalyst could promote

the formation of branched adducts, which worked particularly well with electron-poor alkynes (Scheme 1.28a). One year later, a highly linear-selective variant was also described, in which the use of dcpe as the ligand proved to be optimal (Scheme 1.28b).[54]



Scheme 1.28 Control of regioselectivity for hydroacylation

Meanwhile, the hydroacylation with *S*-chelating aldehydes has been achieved in an enantioselective fashion. For example, the use of chiral Me-DuPhos derived catalyst resulted in the efficient kinetic resolution of both α- and β-substituted alkyl aldehydes, affording enantiomerically enriched α'- or β'-substituted enones, respectively, with useful levels of enantiocontrol (Scheme 1.29).[55]

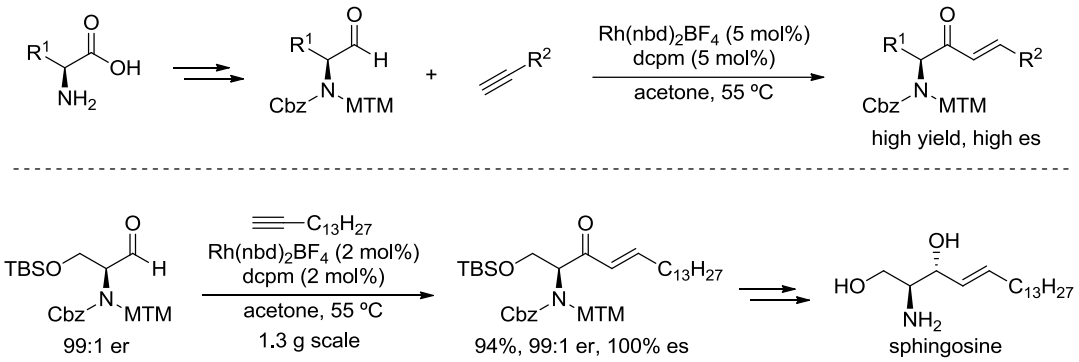


Scheme 1.29 Kinetic resolution of alkyl β-*S*-substituted aldehydes

1.3.4 From and towards naturally occurring molecules

Another approach to access stereogenic centers, apart from asymmetric catalysis of prochiral molecules, is to use chiral substrates directly. In this context, naturally occurring and abundant amino acids have received significant attention from synthetic chemists.

Willis and co-workers developed an elegant way to prepare α-amino aldehydes from the corresponding α-amino acids with full retention of the stereochemistry, and utilized these aldehydes in hydroacylation reactions by incorporating a methylthiomethyl (MTM) protecting group on nitrogen (Scheme 1.30).[56] A variety of enantioenriched enone products were obtained; the mild reaction conditions, made possible by the use of *S*-chelation, proved critical for obtaining high selectivities. This transformation led to the synthesis of sphingosine, which further demonstrated the synthetic utility of chelation-controlled hydroacylation reactions.

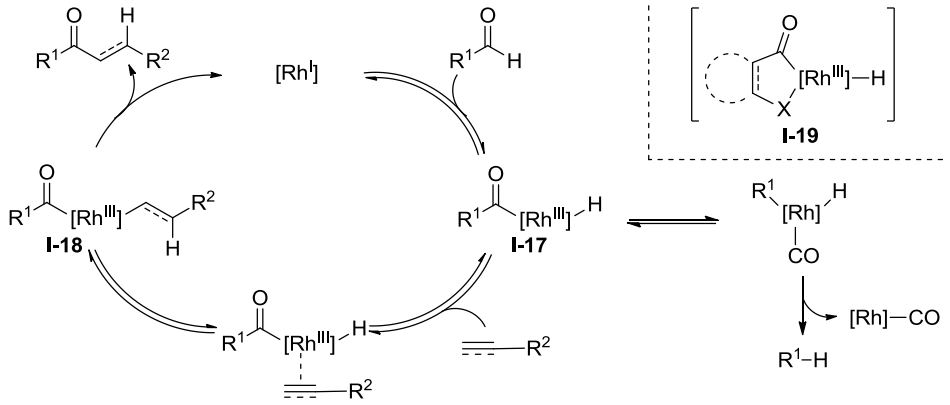


Scheme 1.30 α-Amino aldehydes for hydroacylation

1.4 Mechanistic studies

The mechanism of rhodium-catalyzed hydroacylation reactions has been extensively examined, with a variety of different experiments carried out for both intra- and intermolecular systems since Suggs' isolation of an acylrhodium hydride complex in 1978.[22a] Deuterium labelling studies by Miller elucidated the mechanism of intramolecular hydroacylation,[57] which were followed up by Bosnich's extensive NMR spectroscopy experiments[12] and Morehead and Sargent's computational studies.[58] Furthermore, Brookhart has applied computational methods to the understanding of

intermolecular hydroacylation.[59] Weller and Willis recently conducted mechanistic studies into the role of hemilabile P-O-P ligands as well as small bite-angle ligands, including isolation of key intermediate species, deuterium labelling and kinetic isotope effect experiments.[45a, 60] Presented herein is the generally accepted mechanism of Rh-catalyzed, linear-selective, intermolecular hydroacylation (Scheme 1.31). For individual catalytic systems, details can be found in their references.



Scheme 1.31 Generally accepted mechanism of Rh-catalyzed hydroacylation

The catalytic cycle leading to desired hydroacylation adducts involves three key steps: i) oxidative addition of a rhodium(I) complex into an aldehyde C-H bond to generate an acylrhodium(III) hydride **I-17**; ii) coordination of the unsaturated coupling partner, followed by *syn*-hydrometallation to afford intermediate **I-18**; iii) reductive elimination of **I-18** delivers the hydroacylation product and regenerates the rhodium(I) catalyst. Decarbonylation can occur from the unstable intermediate **I-17**, which undergoes extrusion of carbon monoxide to produce deactivated catalyst and the reduced substrate. The aforementioned chelation-controlled strategies rely on the formation of chelation-stabilized intermediate **I-19**, which, with the vacant coordinating site of the rhodium center occupied, can then go through the hydroacylation cycle.

1.5 Summary

With the advent of chelation-controlled strategies to suppress decarbonylative pathways, hydroacylation reactions have become an important complement to classic methods. These transformations have allowed the formation of both cyclic and acyclic ketones, and have been applied to the synthesis of several natural products and various types of heterocycles. Although successful, the presence of the coordinating groups has limited their synthetic utility to some extent. Therefore, the development of removable tethers, as well as new types of chelating units is in great synthetic demand.

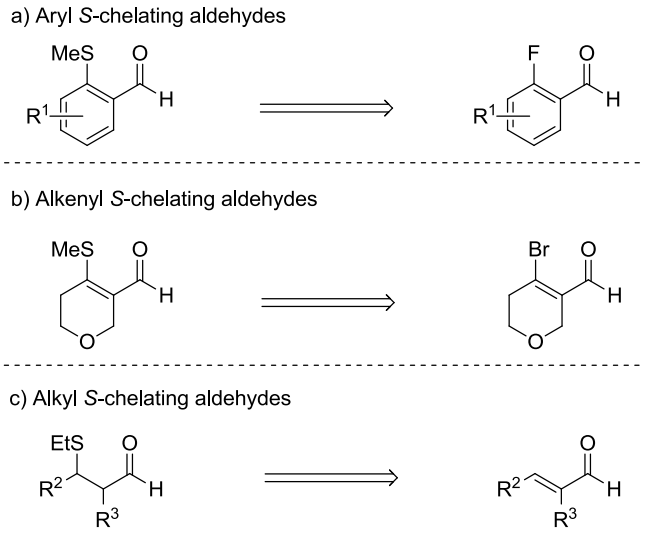
Chapter 2

Traceless chelation-controlled hydroacylation using alkyl aldehydes: developing a Rh-catalyzed three-component process towards β-aryl ketones

2.1 Introduction

2.1.1 Traceless chelation-controlled hydroacylation reactions

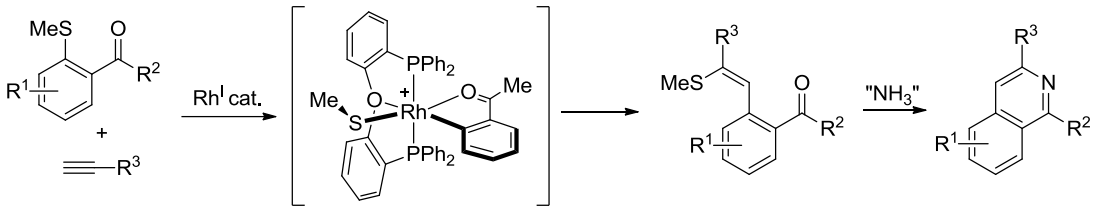
Chelation-controlled intermolecular hydroacylation reactions based on sulfur coordination have been extensively studied by the Willis group. These transformations possess the benefits from the use of a chelate: mild reaction conditions, good substrate scope and, by employing a defined catalyst system, controllable regio- and enantioselectivities. Moreover, all types of *S*-chelating aldehydes, be they aryl-, alkenyl- or alkyl-, are readily available through robust chemical reactions (Scheme 2.1), and have shown efficiency in hydroacylation processes. Therefore, considering the abundance of both coupling partners, *S*-chelation based hydroacylation reactions have become an appealing approach to access a variety of carbonyl-containing molecules.



Scheme 2.1 Availability of *S*-chelating aldehydes

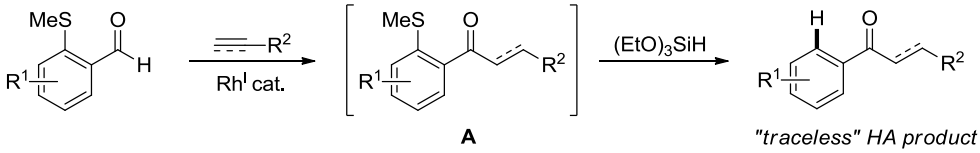
Despite the advantages that have been achieved by utilizing *S*-chelating aldehydes, one general limitation is that the coordinating group, essential for suppressing reductive decarbonylation, inevitably remains in the hydroacylation adducts. Although incorporation of the sulfide group could lead to various types of *S*-containing heterocycles,[52] it is not always desired. To address this issue, thus further enhancing the synthetic utility of chelation-controlled hydroacylation, the Willis group has developed Rh-catalyzed C-S activation processes that can remove or transform the sulfide group of the hydroacylation products. The success relies upon the carbonyl oxygen acting as a directing group to induce the insertion of rhodium catalyst in the C-S bond.

The first example was reported in 2012 (Scheme 2.2). Willis and co-workers discovered that aryl methyl sulfides could undergo a Rh-catalyzed alkyne carbothiolation process.[61] The resulting products were successfully applied to the synthesis of substituted isoquinolines.[62] This reaction was combined with an initial Rh-catalyzed alkene or alkyne hydroacylation in a cascade fashion, which added diversity to the products obtained.



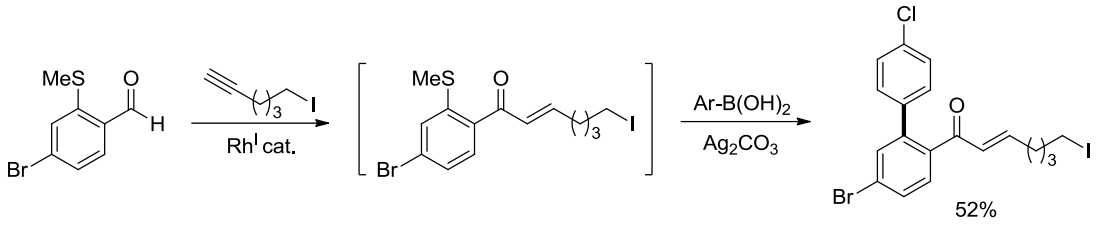
Scheme 2.2 Rh-catalyzed carbothiolation of alkynes

The Willis group also described a Rh-catalyzed sulfide reduction process which could remove the tether from the hydroacylation adducts (Scheme 2.3).[63] A silane was used as the hydrogen source. As before, this transformation was combined with an initial hydroacylation in a one-pot sequence, with both steps catalyzed by a single Rh^I catalyst added at the beginning of the reaction. Although the alkyne scope was limited due to the potential Rh-catalyzed conjugate reduction of α,β-unsaturated ketones **A**, this reaction demonstrated the concept of traceless chelation-controlled hydroacylation.



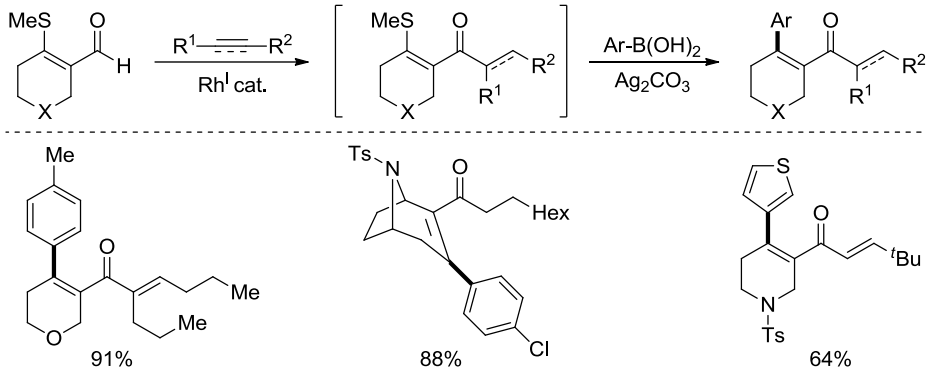
Scheme 2.3 Sequential Rh-catalyzed hydroacylation-sulfide reduction

The aryl sulfide group could also be employed as a pseudo halide for a Rh-catalyzed Suzuki-type coupling with aryl boronic acids (Scheme 2.4).[64] A stoichiometric amount of silver or copper salt, such as Ag_2CO_3, was required for turnover. This transformation could be combined in sequence with Rh-catalyzed alkene or alkyne hydroacylation, and has demonstrated orthogonal reactivity towards Pd-catalyzed Suzuki-Miyaura coupling of aryl bromides. Overall, this reaction resulted in traceless chelation-controlled hydroacylation products with the methyl sulfide replaced by an aryl group.



Scheme 2.4 Sequential Rh-catalyzed hydroacylation-Suzuki coupling

Besides aryl-*S*-chelating aldehydes, β-*S*-enals were also effective substrates for traceless chelation-controlled hydroacylation reactions, when combined with a Suzuki-type coupling (Scheme 2.5).[65] This sequential process served as a highly efficient method for the three-component construction of *N*-, *O*- and *S*-heterocycles.

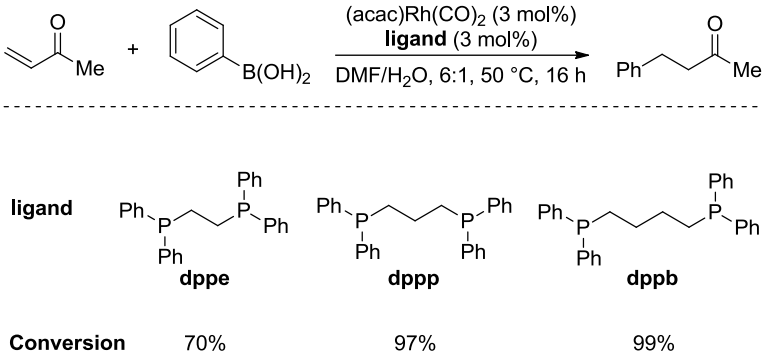


Scheme 2.5 Alkenyl-*S*-chelating aldehydes for traceless hydroacylation

To summarize, the Willis group has developed three types of Rh-catalyzed C-S activation processes, which, in combination with an initial chelation-controlled hydroacylation, lead to traceless products. These sequences were successful with both aryl- and alkenyl-*S*-chelating aldehydes that bear Csp^2-S bonds. These reactions possess the advantages of the use of chelation control, yet deliver products of traceless hydroacylation. In addition, the 'one-pot' nature of above-mentioned transformations averts the isolation of reaction intermediates, therefore reducing the waste generated and enhancing the synthetic efficiency.[66]

2.1.2 Rhodium-catalyzed conjugate addition of boronic acids

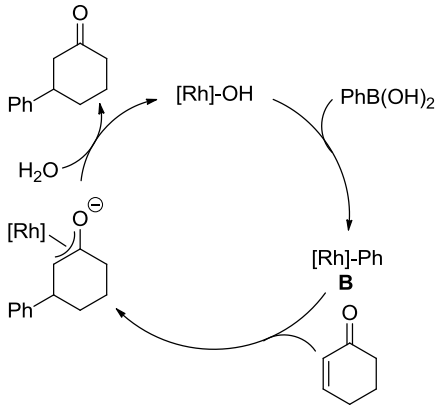
Boronic acids and their derivatives are readily available and bench stable reagents that have been widely utilized in transition metal-catalyzed transformations. However, it was not until 1997 that the first rhodium-catalyzed conjugate addition of boronic acids to α,β-unsaturated ketones was reported by Miyaura and co-workers (Scheme 2.6).[67] The combination of a neutral Rh precursor, (acac)Rh(CO)$_2$, and a bisphosphine ligand, dppb, efficiently catalyzed the union of phenylboronic acid and an enone, affording racemic β-phenyl ketone adducts in good to excellent yields. Monophosphine ligands were found to be less effective; bisphosphine ligands with a large bite-angle proved to have better performance than those with a smaller bite-angle. In addition, a solvent mixture with H_2O was crucial to achieve good reactivity.



Scheme 2.6 First Rh-catalyzed boronic acid 1,4-addition

One year later, Hayashi published the first enantioselective variation of this transformation.[68] Rh(acac)(C_2H_4)$_2$ was employed together with a chiral ligand, BINAP, to give products with excellent levels of enantiocontrol. Both cyclic and acyclic α,β-unsaturated ketones were successful substrates, with both electron-rich and electron-poor boronic acids being efficient coupling partners. The same group later reported their mechanistic studies in 2002, in which all the intermediates and their transformations were

observed in NMR spectroscopy experiments using a Rh/*rac*-BINAP system (Scheme 2.7).[69] A hydroxorhodium complex was identified as being highly active, which could undergo facile transmetalation with phenylboronic acid to give an aryl-rhodium intermediate **B**. Insertion of an α,β-unsaturated ketone to this intermediate, followed by hydrolysis afforded the desired β-phenyl ketone adduct and regenerated the active hydroxorhodium species. These early findings by Hayashi paved the way for future development of asymmetric Rh-catalyzed conjugate additions of organoboron reagents.

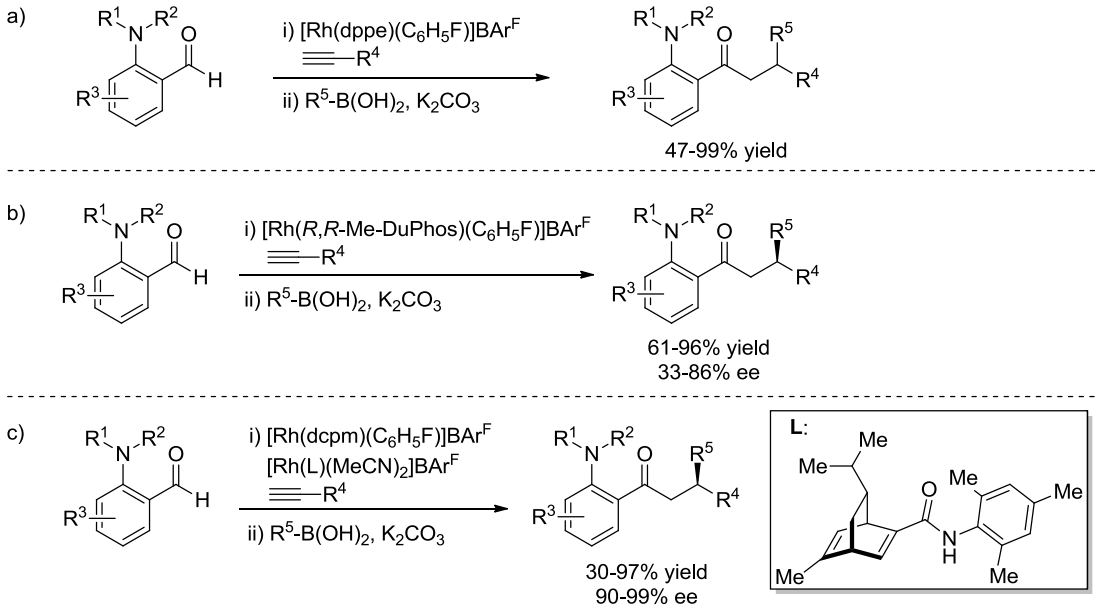


Scheme 2.7 General mechanism of Rh-catalyzed boronic acid 1,4-addition

Rhodium-catalyzed conjugate addition reactions have received significant attention since the initial report and have been utilized in the synthesis of bio-active molecules.[70] These reactions employ readily available starting materials and construct C-C bonds in a highly efficient and, if necessary, enantioselective manner. Three types of chiral ligands are normally used to attain high levels of enantiocontrol, namely chiral phosphine ligands, phosphoramidites, and chiral dienes.

As was shown above, the Rh^{I}-catalyzed boronic acid conjugate addition is a redox neutral process, with catalysts derived from large bite-angle bisphosphine ligands being most efficient. On the other hand, Rh^{I}-catalyzed hydroacylation reactions proceed *via* a

Rh^{I}/Rh^{III} cycle, and often utilize small bite-angle bisphosphine ligands. Despite the distinctive difference between their mechanisms, the Willis group has recently discovered an alkyne hydroacylation-boronic acid conjugate addition sequence, which was promoted by a single Rh^{I} catalyst (Scheme 2.8).[71] A preformed catalyst, $[Rh(dppe)(C_6H_5F)]BAr^F$, added at the beginning of the sequence, could efficiently catalyze both steps, enabling the delivery of racemic β-aryl ketones (Scheme 2.8a); the use of a chiral bisphosphine ligand, Me-DuPhos, allowed moderate to good levels of enantiocontrol to be obtained (Scheme 2.8b). Moreover, excellent enantioselectivities were achieved when employing a Rh-chiral diene complex (Scheme 2.8c). This work encouraged us to explore further combinations of Rh-catalyzed hydroacylation and boronic acid conjugate addition.

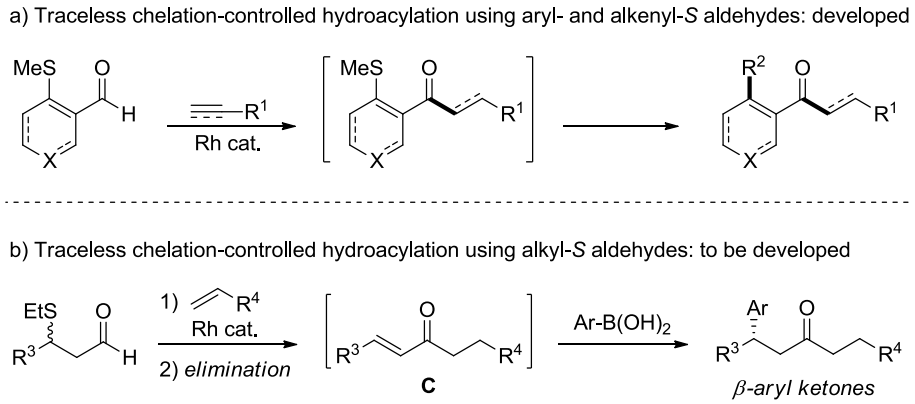


Scheme 2.8 Sequential hydroacylation-boronic acid conjugate addition

2.1.3 Project aims

Given the advantages of traceless chelation-controlled hydroacylation reactions, it would be desirable to extend such transformation to alkyl-*S*-chelating aldehydes (Scheme 2.9).

The nature of this type of substrate determined that removal of the sulfide group has to be achieved by a different pathway; sulfide elimination was proposed for this purpose, and enone products **C** could be obtained from an alkene hydroacylation-elimination sequence. Furthermore, we envisaged that enones **C** may undergo a Rh-catalyzed boronic acid conjugate addition reaction, affording β-aryl ketones, ideally, in an enantioselective fashion (Scheme 2.9b). Our goal was to find suitable reaction conditions which would allow the use of one or two rhodium complexes with a total catalyst loading no more than 10 mol%. Additionally, in order not to create two Michael acceptors on molecule **C**, which would add complexity, alkynes were not examined in the initial study. Finally, we intended to develop the whole sequence in a one-pot manner for synthetic practicability, and to utilize the products obtained in the synthesis of heterocyclic compounds.



Scheme 2.9 Proposed hydroacylation-elimination-1,4-addition sequence

2.2 Optimization of the reaction conditions

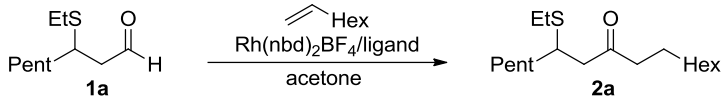
We first optimized the three individual steps separately and then combined them in a one-pot procedure. This project was in collaboration with Dr. Ana ïs Bouisseau, a former DPhil student in the Willis group; her studies are also discussed here for the understanding of the

entire project, and is clearly stated with a footnote where appropriate. The products prepared by Dr. Bouisseau are not included in the experimental section, and relevant data can be found in her thesis[72] or our published article.[73]

2.2.1 Optimization of alkene hydroacylation

Rhodium-catalyzed hydroacylation of alkenes using *S*-chelating aldehydes are known to be more challenging than that of alkynes. In earlier reports, it was only with activated alkenes that high yields could be obtained.[43] Recently, efficient transformations were achieved using a preformed Rh catalyst incorporating small bite-angle bisphosphine ligands.[45] Meanwhile, the Willis group has been employing a commercially available precatalyst, $Rh(nbd)_2BF_4$, together with a phosphine ligand to generate the active catalyst species, which does not require the use of a glovebox.[49] Based on this, we began our optimization by screening different bisphosphine ligands focusing on the small bite-angle variants, aiming at achieving successful hydroacylation of 1-octene with an easily accessible β-*S* aldehyde **1a** (Table 2.1). Of the various ligands tested in this standard reaction, large bite-angle ligands, such as DPEPhos and dppp, proved to be ineffective, which is in accordance with our previous studies (entries 1, 2); the use of smaller bite-angle ligands did improve the reaction (entries 3-5), and dcpm was identified as the most efficient, affording the desired hydroacylation adduct **2a** in 95% yield (entry 6). Increasing the concentration from 0.3 M to 1.0 M allowed the reaction to complete within 1 h at a lowered catalyst loading of 5 mol%, and ketone **2a** could thus be isolated in 99% yield (entry 7). In addition, it was realized, through reactions performed by Dr. Bouisseau, that a reaction temperature of 55 ℃ and the use of 3 equivalents of 1-octene were both crucial for this transformation.

Table 2.1 Ligand screening for the hydroacylation of 1-octene with aldehyde **1a**[a]



Entry	Ligand	Time (h)	Yield[b] (%)
1	DPEPhos	4	trace
2	dppp	3	5
3	dppe	3	29
4	dcpe	3	25
5	dppm	3	7
6	dcpm	1.5	95
7[c]	dcpm	1	100 (99)

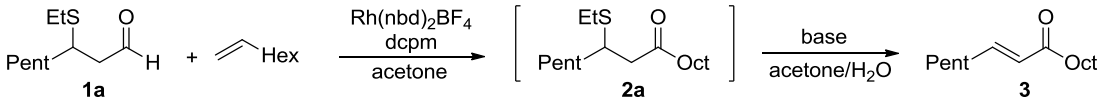
[a]Reaction conditions: **1a** (1.0 equiv), 1-octene (3.0 equiv), $Rh(nbd)_2BF_4$ (10 mol%), ligand (10 mol%), acetone (0.3 M), 55 ℃. [b]Determined by ^1H NMR spectroscopy, yields in parentheses are isolated yields, l:b >50:1. [c]Modified conditions: $Rh(nbd)_2BF_4$ (5 mol%), ligand (5 mol%), acetone (1.0 M); entry performed by Dr. Bouisseau.

2.2.2 Optimization of sulfide elimination

Having established the optimal conditions for the hydroacylation of 1-octene, we directed our attention to the elimination of β-sulfide. Sulfide is not a good leaving group for elimination, and traditional methods normally involve the transformation of the sulfide to a sulfoxide or sulfonium ion, which then serves as a better leaving group.[74] It was reasoned that these forcing conditions may be detrimental to rhodium catalysts, thus diminishing the possibility of one single Rh catalyst promoting the whole sequence. Aiming at developing a milder reaction, we initially chose to optimize the elimination step by screening different bases without the addition of an oxidant or an alkylating reagent, in the hope that it could proceed *via* an E1cB mechanism (Table 2.2). The elimination was performed in sequence

with an initial alkene hydroacylation, and H_2O was added to dissolve some of the inorganic bases. Without an additional base, a trace amount of the elimination product **3** was observed (entry 1). Bases that have been reported effective for conjugate addition reactions, such as NEt_3, K_2CO_3 and Cs_2CO_3, did not give satisfactory results for this elimination (entries 2-4). With $Zn(OTf)_2$, the elimination proceeded with a similar result as Cs_2CO_3 (entry 5). Pleasingly, by employing bases containing 'thiophilic' metal cations like silver or copper, dramatic improvements were observed (entries 6-10), with copper(I) 3-methylsalicylate (CuMeSal) being the most efficient (entry 10); the use of CuMeSal allowed the elimination to reach completion in 14 hours at 55 ℃. Dr. Bouisseau also evaluated some other copper salts, and none of them were superior to CuMeSal.

Table 2.2 Base screening for E1cB β-sulfide elimination[a]

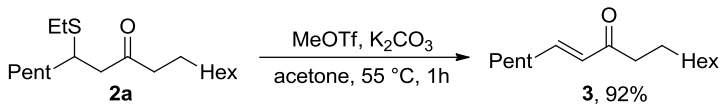


Entry	Base	**2a** : **3**[b]	Entry	Base	**2a** : **3**[b]
1	-	25 : 1[c]	6	AgOAc	0.3 : 1
2	NEt_3	9 : 1	7	Ag_2CO_3	0.1 : 1
3	K_2CO_3	7 : 1	8	CuOAc	0.8 : 1
4	Cs_2CO_3	14 : 1	9	CuTC	0.04 : 1
5	$Zn(OTf)_2$	12 : 1	10	CuMeSal	0 : 1 (81%)[d,e]

[a]Reaction conditions for elimination: base (1.0 equiv to **1a**), acetone (0.3 M), H_2O (0.7 M), 55 ℃, 14 h. [b]Ratio determined by ^1H NMR spectroscopy. [c]Ratio after hydroacylation (1 h) without an additional base. [d]Without H_2O. [e]Yields in parentheses are isolated yields.

While CuMeSal was capable of eliminating the β-sulfide, long reaction hours and a stoichiometric amount of copper salt were required. Therefore, we were also interested in other approaches that could eliminate the sulfide in a shorter reaction time and, preferably,

employ inexpensive bases. As was mentioned previously, the methylation-deprotonation method has been described in the literature. After a few attempts, Dr. Bouisseau identified modified conditions that were more compatible with our system: treating β-*S* ketone **2a** with methyl trifluoromethanesulfonate (MeOTf) and K_2CO_3 for 1 h in acetone afforded enone **3** in 92% yield (Scheme 2.10).



Scheme 2.10 Sulfide elimination using a methylation-deprotonation method

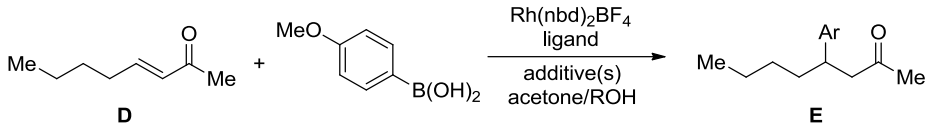
The two sets of conditions developed above are complementary to each other. Copper-mediated elimination requires longer duration, but is milder and more functional group tolerant; the methylation conditions are faster, but might alkylate sensitive moieties. Nevertheless, they together laid the foundation for our further optimization.

2.2.3 Optimization of boronic acid conjugate addition

Dr. Bouisseau carried out a comprehensive study on the conjugate addition step and key findings are summarized in Table 2.3. In accordance with the precedented discoveries, a rhodium complex bearing large bite-angle ligand, *rac*-BINAP, efficiently catalyzed the conjugate addition of 4-methoxyphenylboronic acid with α,β-unsaturated ketone **D**, affording ketone **E** in full conversion (entry 1); K_2CO_3 and H_2O were chosen initially as they were commonly employed in the literature. In order to examine the feasibility of utilizing one single catalyst for the whole sequence, dcpm was then evaluated in this transformation, as it was the best ligand for the hydroacylation of 1-octene. Surprisingly, this small bite-angle ligand was highly effective, with an even shorter reaction time required

for completion (entry 2). We were also pleased to find that a sub-stoichiometric amount of K_2CO_3 could promote the reaction to full conversion (entry 3). Switching the base to CuMeSal, the optimal reagent for elimination of the sulfide group, did not provide any desired 1,4-addition adduct **E** (entry 4). Furthermore, CuMeSal suppressed this transformation even in the presence of K_2CO_3 (entry 5). Pleasingly, the reactivity could be re-established by employing MeOH instead of H_2O (entry 6).

Table 2.3 Selected optimization of the conjugate addition step[a]



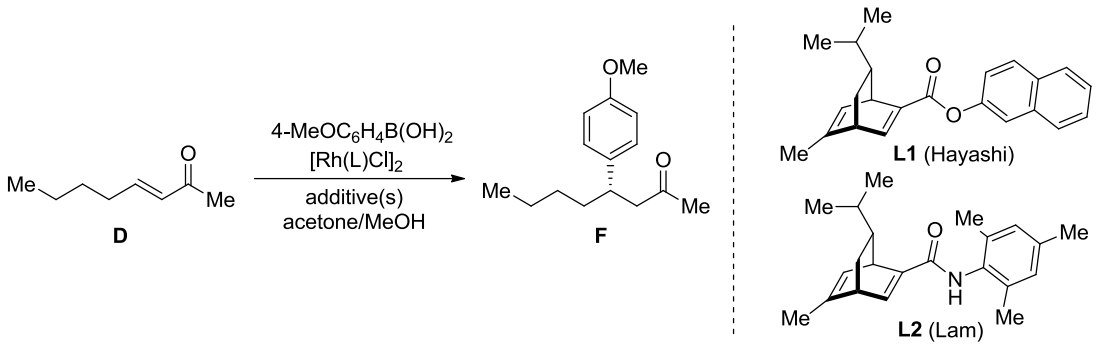
Entry	Ligand	Additive (equiv)	ROH (%)	Time	Yield[b] (%)
1	BINAP	K_2CO_3 (1.0)	H_2O (10%)	4 h	100
2	dcpm	K_2CO_3 (1.0)	H_2O (10%)	1 h	100
3	dcpm	K_2CO_3 (0.2)	H_2O (10%)	1 h	100
4	dcpm	CuMeSal (1.0)	H_2O (10%)	1 h	0
5	dcpm	K_2CO_3 (1.0) + CuMeSal (1.0)	H_2O (10%)	1 h	28
6	dcpm	K_2CO_3 (1.0) + CuMeSal (1.0)	MeOH (10%)	1 h	87

[a]Reaction conditions: **D** (1.0 equiv), boronic acid (2.0 equiv), $Rh(nbd)_2BF_4$ (10 mol%), ligand (10 mol%), additives (as indicated), acetone/ROH (0.1 M), 55 ℃; performed by Dr. Bouisseau. [b]Determined by ^1H NMR spectroscopy.

As the goal of this project was to develop a process involving an enantioselective conjugate addition, Dr. Bouisseau assessed two chiral diene ligands, **L1** and **L2**, which were developed by Hayashi[75] and Lam,[76] respectively (Table 2.4). To our delight, the use of these two ligands resulted in the formation of product **F** with excellent levels of enantiocontrol: both **L1** (entry 1) and **L2** (entry 2) promoted the conjugate addition under conditions optimized for the racemic reaction (see Table 2.3), yielding the desired adduct

in excellent yields and ee. With additional CuMeSal used together with K_2CO_3, the yield dropped slightly, but the enantioselectivity remained high (entry 3).

Table 2.4 Assessment of chiral diene ligands for the conjugate addition[a]



Entry	Additive (equiv)	L	Yield[b] (%)	Ee (%)
1	K_2CO_3 (1.0)	**L1**	94	98
2	K_2CO_3 (1.0)	**L2**	95	98
3	K_2CO_3 (1.0) + CuMeSal (1.0)	**L2**	88	98

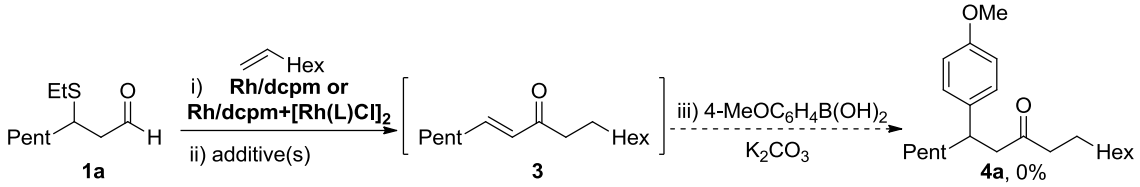
[a]Reaction conditions: **D** (1.0 equiv), boronic acid (2.0 equiv), $[Rh(L)Cl]_2$ (2.5 mol%), additives (as indicated), acetone/MeOH (9:1, 0.1 M), 55 ℃, 1 h; performed by Dr. Bouisseau. [b]Isolated yields.

2.2.4 Optimization of the hydroacylation-elimination-conjugate addition sequence

Having established the optimal reaction conditions for all of the three steps separately, we then focused on combining them in a one-pot procedure. Two strategies were proposed; i) a single catalyst or a combination of two catalysts, added at the beginning of the sequence, promoting both the hydroacylation and conjugate addition steps, as has been illustrated by previous work in the Willis group;[71] ii) two sets of catalysts, active for the hydroacylation and 1,4-addition respectively, are introduced to the reaction pot prior to each step.

The first strategy was proven unsuccessful after examinations performed by Dr. Bouisseau (Scheme 2.11). Since the Rh^I/dcpm complex was efficient for both the hydroacylation and conjugate addition steps from the individual studies, it was initially

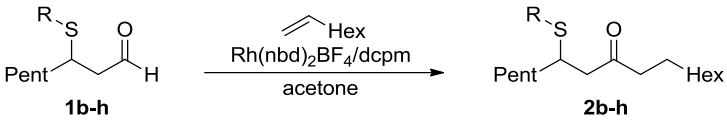
tested for the sequence. Although hydroacylation and elimination both proceeded well, we were never able to observe any conjugate addition adduct **4a**. Alternatively, addition of a combination of Rh/dcpm and Rh/chiral diene complexes at the start of the sequence also failed to afford any desired product **4a**. We reasoned that our developed conditions for the elimination step were poisonous to the rhodium catalysts, therefore resulting in failure.

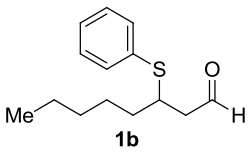
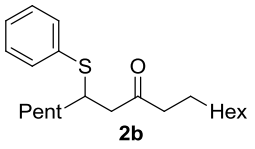
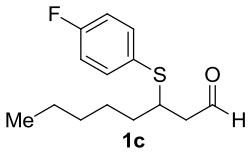
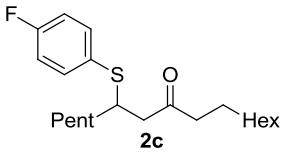
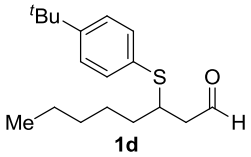
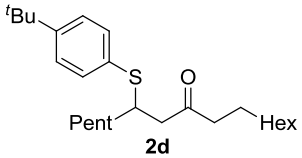
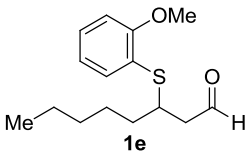
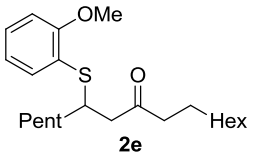
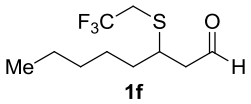
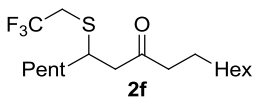
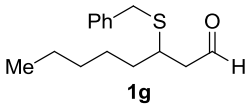
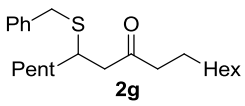
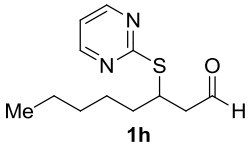
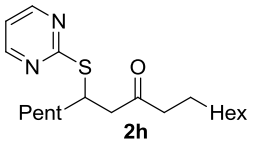


Scheme 2.11 Sequence promoted by Rh catalysts added at the beginning

The initial negative results drove us to rethink the elimination conditions. It was first postulated that, by varying the substituent on the sulfur, we might be able to achieve successful elimination with bases that are compatible with Rh catalysts. Therefore, we synthesized various β-*S* aldehydes and assessed them in the hydroacylation of 1-octene (Table 2.5). As electron-withdrawing groups may help to stabilize the sulfur anion formed from elimination, a set of phenyl sulfides was first employed (entries 1-4). However, none of these aldehydes resulted in satisfactory yields in hydroacylation, probably because of the decreased coordination ability of the sulfur, stemming from both steric and electronic reasons. We also tested aldehydes with other substituents on the sulfur, including a trifluoromethyl group (entry 5) and a benzyl group (entry 6); again, the yields were low. Finally, we utilized a pyrimidine-derived aldehyde **1h** for this reaction. However, we only observed full starting material recovery (entry 7). These results directed us to move away from our first strategy, and to explore the second one.

Table 2.5 Hydroacylation of 1-octene varying the *S*-substituent of the aldehyde[a]



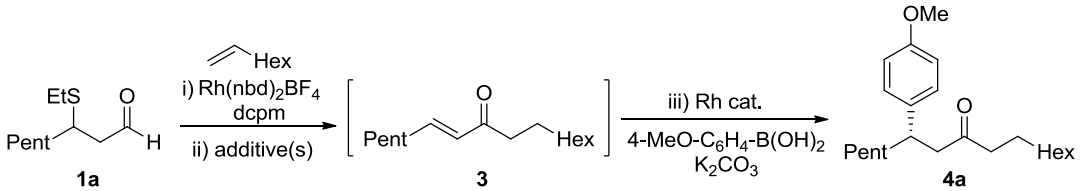
Entry	Aldehyde	Product	Yield[b] (%)
1			35
2			20
3			31
4			16
5			21
6			30
7			0

[a]Reaction conditions: **1b-h** (1.0 equiv), 1-octene (3.0 equiv), $Rh(nbd)_2BF_4$ (10 mol%), dcpm (10 mol%), acetone (0.3 M), 55 ℃, 1.5 h. [b]Isolated yields.

Our second strategy was successful: by adding a second Rh catalyst prior to the conjugate addition step, the desired product could be obtained (Table 2.6). We started optimizing the sequence using CuMeSal for elimination, with 2.0 equivalents of boronic

acid being employed for the conjugate addition step. When using *rac*-BINAP as the ligand for 1,4-addition together with $Rh(nbd)_2BF_4$, ketone **4a** was isolated in a 26% yield (entry 1). Switching the catalyst to either $[Rh(L1)Cl]_2$ (entry 2) or $[Rh(L2)Cl]_2$ (entry 3) provided the desired adduct in 82% and 83% yields, respectively, with excellent levels of enantiocontrol (98% ee) achieved in both cases. This suggested that chiral diene ligands are extremely effective in Rh-catalyzed conjugate addition processes. We were also pleased to find that our methylation-deprotonation conditions were compatible with the one-pot system; this method drastically shortened the reaction time and allowed a lower amount of boronic acid (1.5 equivalents) to be employed (entry 4). At this point, we have successfully optimized a hydroacylation-elimination-conjugate addition sequence using a total Rh catalyst loading of 10 mol%, affording enantioenriched β-aryl ketones in a one-pot manner.

Table 2.6 Selected optimization of the sequential procedure[a]



Entry	*Elimination (ii)*		*Conjugate addition (iii)*			*Results*	
	Additive (equiv)	time (h)	Rh cat. (mol%)	$ArB(OH)_2$ (equiv)	K_2CO_3 (equiv)	Yield[b] (%)	Ee (%)
1	CuMeSal (1.0)	14	$Rh(nbd)_2BF_4$ + BINAP (5)	2.0	1.0	26	-
2	CuMeSal (1.0)	14	$[Rh(L1)Cl]_2$ (2.5)	2.0	1.0	82	98
3	CuMeSal (1.0)	14	$[Rh(L2)Cl]_2$ (2.5)	2.0	1.0	83	98
4	MeOTf (1.5) + K_2CO_3 (2.5)	1	$[Rh(L1)Cl]_2$ (2.5)	1.5	0	85	97

[a]Reaction conditions: i) **1a** (1.0 equiv), 1-octene (3.0 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dcpm (5 mol%), acetone (1.0 M), 55 ℃, 1 h; ii) additives (as indicated), acetone (0.5 M), 55 ℃; iii) Rh cat. (as indicated), boronic acid (as indicated), K_2CO_3 (as indicated), acetone/MeOH (9:1, 0.1 M), 55 ℃, 1 h; entries 2-4 performed by Dr. Bouisseau; **L1** and **L2**: see Table 2.4. [b]Isolated yields.

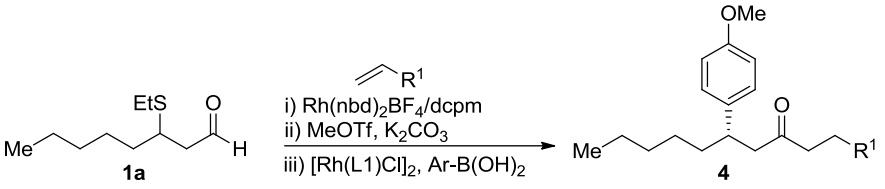
2.3 Variations of the reaction components

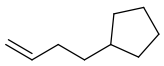
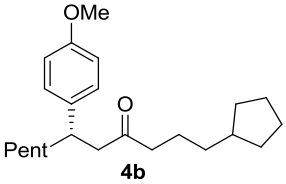
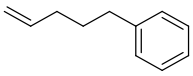
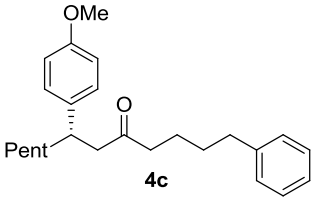
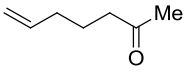
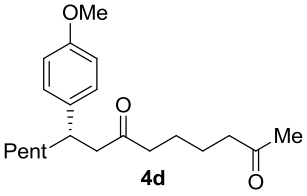
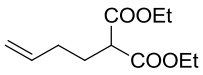
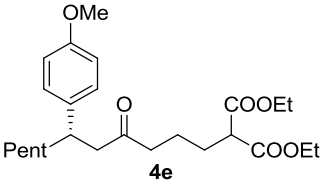
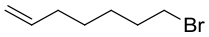
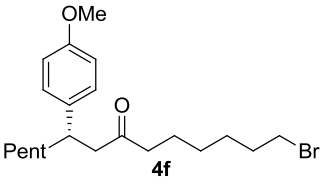
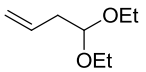
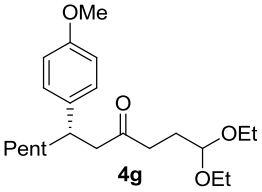
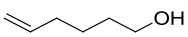
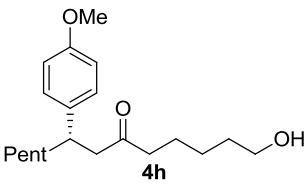
The scope of our developed methodology was jointly carried out with Dr. Bouisseau. While she explored the boronic acid scope and half of the aldehyde scope, I focused on the alkene scope and the other half of the aldehyde scope. In most cases, the MeOTf/K_2CO_3 conditions were applied for elimination, and **L1** (see Table 2.4) for conjugate addition. In the presence of sensitive functional groups, CuMeSal was employed instead of MeOTf/K_2CO_3; **L2** (see Table 2.4) was used for achieving excellent enantioselectivity with certain boronic acids.

2.3.1 Alkene scope

Having established the best reaction conditions for the hydroacylation-elimination-conjugate addition sequence, we directed our attention to the scope in respect to the alkene component, with aldehyde **1a** and 4-methoxyphenylboronic acid being the other two coupling partners (Table 2.7). Alkenes possessing alkyl, aryl or carbonyl groups were well tolerated, giving the corresponding ketones **4b-e** in good yields and excellent enantioselectivities (entries 1-4). Several other functional groups, such as an alkyl bromide and a diethyl acetal, could also be employed (entries 5, 6). Given the diverse synthetic utility of halide substituents, we performed a gram-scale reaction using 6-bromo-1-hexene; starting from 5.5 mmol of **1a**, 1.9 grams of ketone **4f** was isolated in good yield and ee, with only 2 mol% and 1 mol% of catalysts employed for the hydroacylation and conjugate addition steps, respectively (entry 5). The use of CuMeSal for the elimination step allowed the tolerance of a free hydroxyl group (entry 7) and a protected amine (entry 8). Finally, alkenes containing an acetate (entry 9) or phthalimide group (entry 10) were also excellent substrates for this sequential reaction.

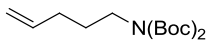
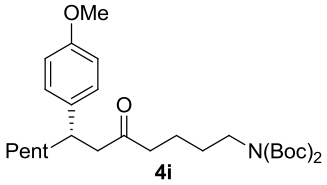
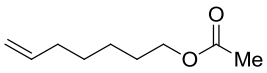
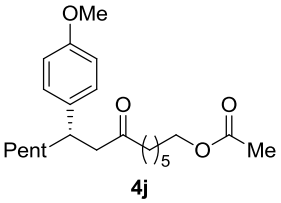
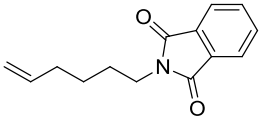
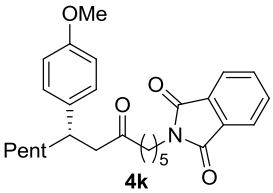
Table 2.7 Variation of the alkene component[a]



Entry	Alkene	Product	Yield[b] (%)	Ee (%)
1		 **4b**	75	91
2		 **4c**	84	93
3		 **4d**	84	94
4		 **4e**	60	93
5[c]		 **4f**	86	95
6[d]		 **4g**	42	95
7[e]		 **4h**	84	92

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Table 2.7, continued

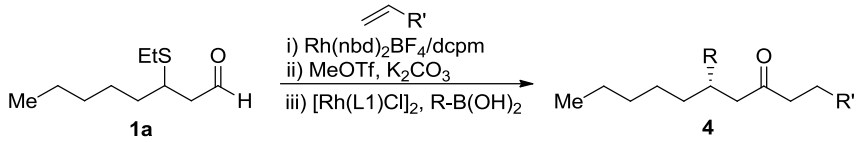
Entry	Alkene	Product	Yield[b] (%)	Ee (%)
8[e]		 **4i**	58	98
9		 **4j**	70	93
10		 **4k**	88	94

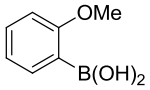
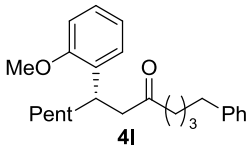
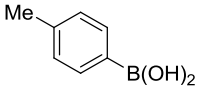
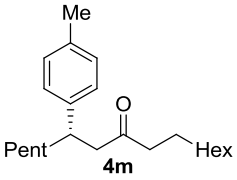
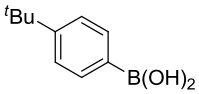
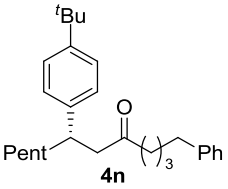
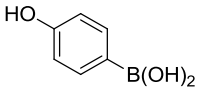
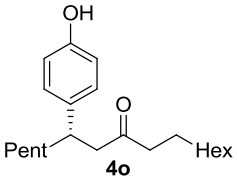
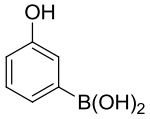
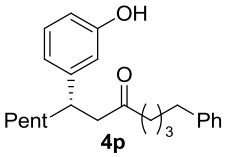
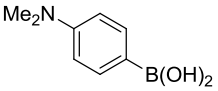
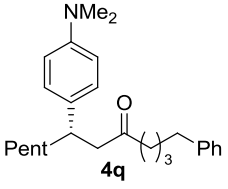
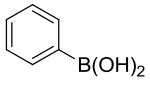
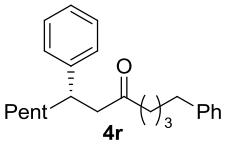
[a]Reaction conditions: i) **1a** (1.0 equiv), alkene (3.0 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dcpm (5 mol%), acetone (1.0 M), 55 ℃, 1 h; ii) MeOTf (1.5 equiv), K_2CO_3 (2.5 equiv), acetone (0.5 M), 55 ℃, 1 h; iii) $[Rh(L1)Cl]_2$ (2.5 mol%), 4-methoxyphenylboronic acid (1.5 equiv), acetone/MeOH (9:1, 0.1 M), 55 ℃, 1 h; **L1** and **L2**: see Table 2.4. [b]Isolated yields. [c]Gram scale with 5.5 mmol of **1a**, i) $Rh(nbd)_2BF_4$/dcpm (2 mol%), iii) $[Rh(L2)Cl]_2$ (1 mol%). [d]iii) boronic acid (3 equiv). [e]ii) CuMeSal (1.0 equiv).

2.3.2 Boronic acid scope

The boronic acid scope was investigated by Dr. Bouisseau. Aldehyde **1a** was employed and choice of the alkene coupling partner was dependent on the ease of separating pairs of enantiomers using chiral HPLC (Table 2.8). The transformation was successfully applied to phenyl boronic acids bearing a variety of both electron-donating (entries 1-6) and electron-withdrawing (entries 8-10) groups, with substituents being tolerated at all positions of the benzene ring. Notable amongst these examples are the use of free hydroxyl groups (**4o, p**), a basic amine (**4q**) and reactive ester (**4t**) and cyano (**4u**) groups. Additionally, boronic acids incorporating a naphthyl (entry 11), heterocycles (entries 12, 13) and an olefin (entry 14) were all effective coupling partners.

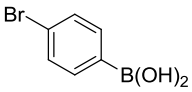
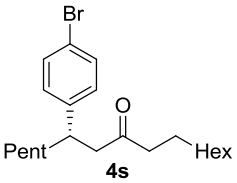
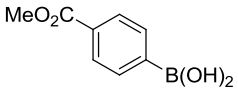
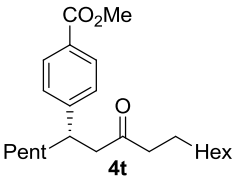
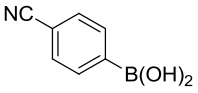
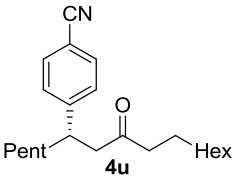
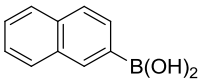
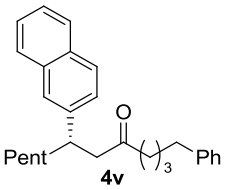
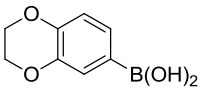
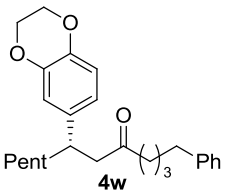
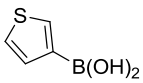
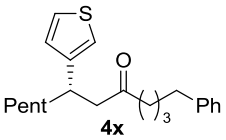
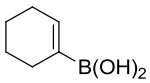
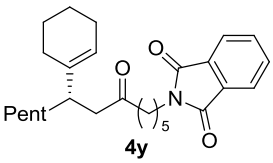
Table 2.8 Variation of the boronic acid component[a]



Entry	Boronic acid	Product	Yield[b] (%)	Ee (%)
1			63	93
2			80	92
3			84	95
4			82	94
5			79	93
6			58	96
7[c]			83	94

continued on the next page

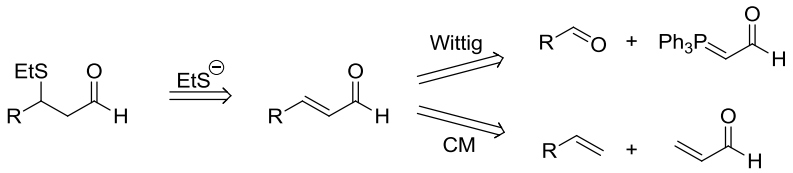
Table 2.8, continued

Entry	Boronic acid	Product	Yield[b] (%)	Ee (%)
8[d]		 **4s**	64	93
9[d]		 **4t**	82	93
10		 **4u**	55	91
11		 **4v**	75	95
12		 **4w**	82	94
13		 **4x**	27	94
14		 **4y**	63	89

[a]Reaction conditions: i) **1a** (1.0 equiv), alkene (3.0 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dcpm (5 mol%), acetone (1.0 M), 55 ℃, 1 h; ii) MeOTf (1.5 equiv), K_2CO_3 (2.5 equiv), acetone (0.5 M), 55 ℃, 1 h; iii) $[Rh(L1)Cl]_2$ (2.5 mol%), boronic acid (1.5 equiv), acetone/MeOH (9:1, 0.1 M), 55 ℃, 1 h; **L1** and **L2**: see Table 2.4; performed by Dr. Bouisseau. [b]Isolated yields. [c]iii) $[Rh(L2)Cl]_2$. [d]1,2-Dichloroethane (DCE) instead of acetone, iii) $[Rh(L2)Cl]_2$.

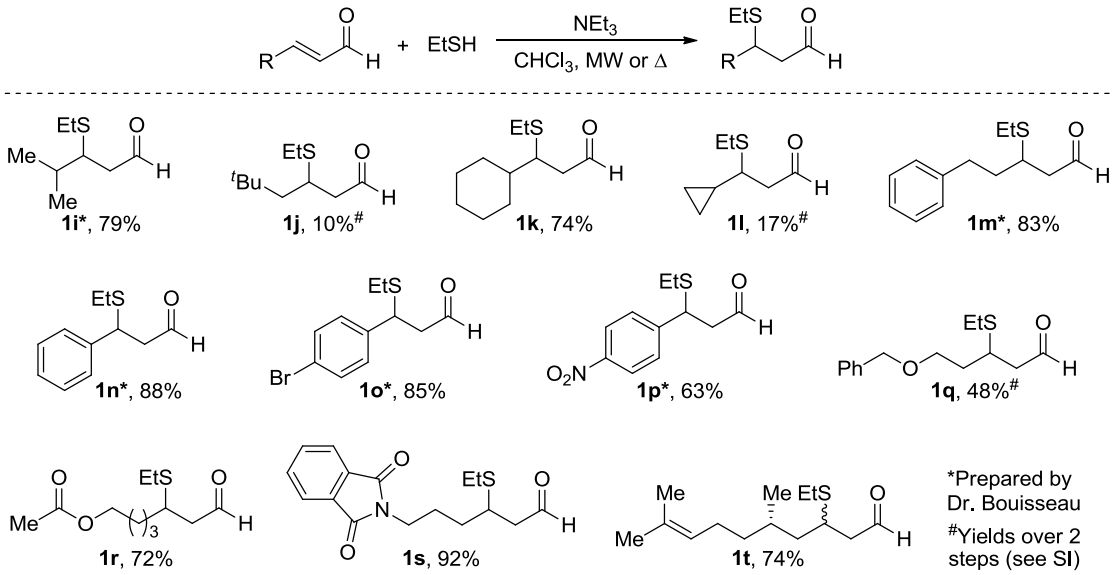
2.3.3 Aldehyde scope

Alkyl β-*S*-substituted aldehydes were prepared *via* thio-Michael addition of α,β-unsaturated aldehydes; α,β-unsaturated aldehydes were either commercially available or synthesized from a Wittig reaction or an olefin cross metathesis (Scheme 2.12).



Scheme 2.12 Disconnection of the aldehyde starting material

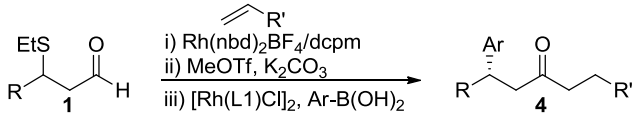
A series of starting aldehydes were subsequently synthesized (Scheme 2.13), including β-alkyl-substituted (**1i-m**) and β-aryl-substituted (**1n-p**) examples. We were also able to access aldehydes bearing heteroatoms (**1q-s**), as well as a stereogenic center (**1t**).

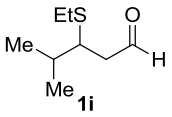
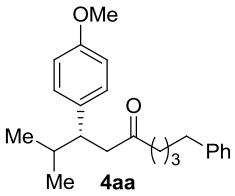
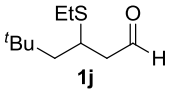
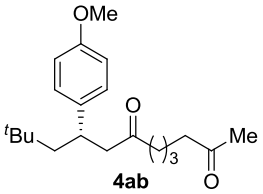
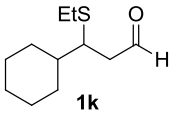
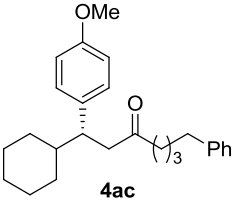
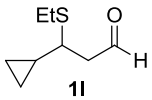
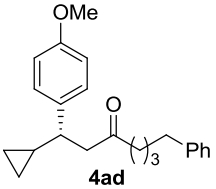
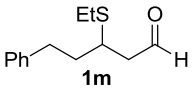
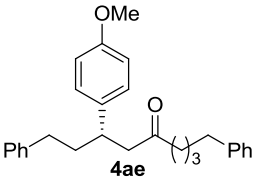
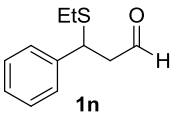
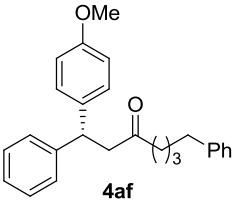
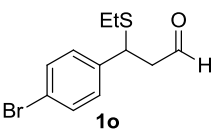
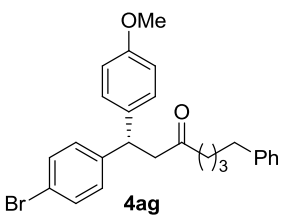


Scheme 2.13 List of β-EtS-substituted aldehydes

With robust methods for starting material synthesis established, we set about evaluating the aldehyde scope (Table 2.9). A variety of β-alkyl substituted aldehydes were explored, illustrating the tolerance of the chemistry to different steric demand (entries 1-5). In a similar manner, aryl substituents with various electronic properties were also

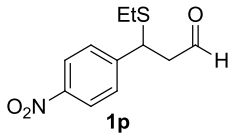
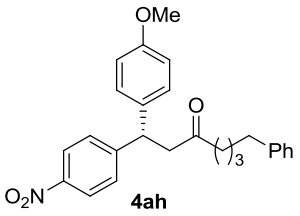
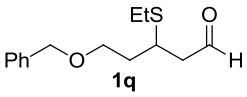
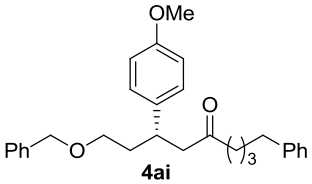
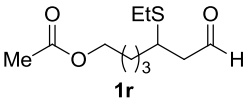
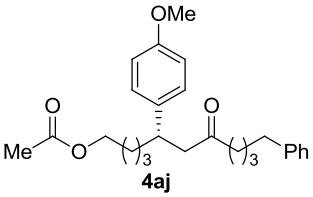
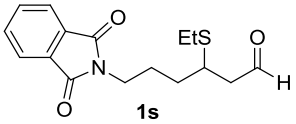
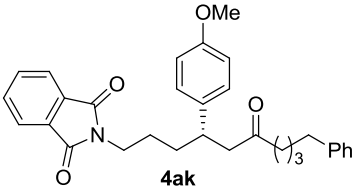
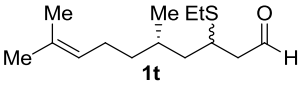
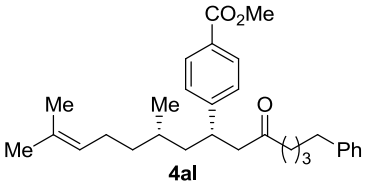
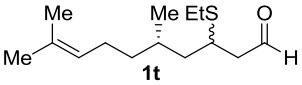
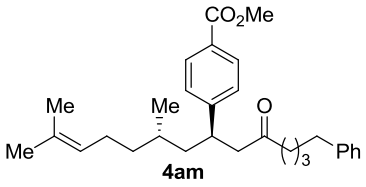
Table 2.9 Variation of the aldehyde component[a]



Entry	Aldehyde	Product	Yield[b] (%)	Ee (%)
1[c]	 **1i**	 **4aa**	82	98
2	 **1j**	 **4ab**	61	95
3	 **1k**	 **4ac**	72	98
4[d]	 **1l**	 **4ad**	54	98
5[c]	 **1m**	 **4ae**	63	90
6[c]	 **1n**	 **4af**	85	97
7[c]	 **1o**	 **4ag**	60	98

continued on the next page

Table 2.9, continued

Entry	Aldehyde	Product	Yield[b] (%)	Ee (%)
8[c]	 **1p**	 **4ah**	44	98
9	 **1q**	 **4ai**	83	92
10	 **1r**	 **4aj**	87	93
11	 **1s**	 **4ak**	78	93
12[e]	 **1t**	 **4al**	66	>99 (dr >20:1)
13[f]	 **1t**	 **4am**	62	99 (dr 8:1)

[a]Reaction conditions: i) **1** (1.0 equiv), alkene (3.0 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dcpm (5 mol%), acetone (1.0 M), 55 ℃, 1 h; ii) MeOTf (1.5 equiv), K_2CO_3 (2.5 equiv), acetone (0.5 M), 55 ℃, 1 h; iii) $[Rh(L1)Cl]_2$ (2.5 mol%), boronic acid (1.5 equiv), acetone/MeOH (9:1, 0.1 M), 55 ℃, 1 h; **L1** and **L2**: see Table 2.4. [b]Isolated yields. [c]Performed by Dr. Bouisseau. [d]ii) CuMeSal (1.0 equiv). [e]DCE instead of acetone, iii) $[Rh(L2)Cl]_2$. [f]iii) $Rh(nbd)_2BF_4$/(*S*)-BINAP (5 mol%), boronic acid (3.0 equiv).

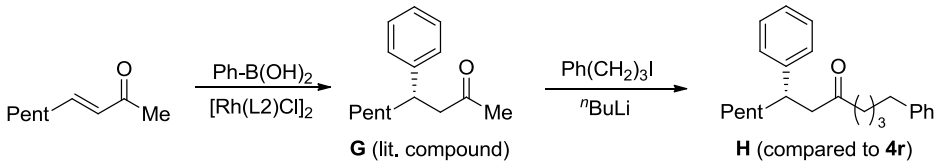
incorporated, yielding products with excellent levels of enantiocontrol (entries 6-8). Other functional groups, including an ether (entry 9), an ester (entry 10) and a phthalimide (entry 11) were well tolerated. Pleasingly, an (*S*)-citronellal unit could also be introduced, giving (*S*,*S*)-ketone **4al** in good yield with excellent diastereocontrol (entry 12); the diastereomeric (*S*,*R*)-product **4am** could be accessed by using a Rh^{I}/(*S*)-BINAP catalyst for the conjugate addition step, although the stereoselectivity was reduced in this case.

Together with the compounds prepared in the alkene and boronic acid scope studies, we have demonstrated that our developed methodology can tolerate a broad range of functional groups. However, this three-component process has certain limitations. For instance, alkenes, including acrylates, styrenes and 1,2-disubstituted variants, could not undergo efficient hydroacylation under the standard condition with a dcpm derived catalyst, which could potentially be solved by using other catalyst systems developed by the Willis group.[43a, 48] α-Substituted aldehydes were not successful, as the corresponding conjugate addition would proceed through a different mechanism and would require ligands effective for enantioselective protonation.[77]

2.4 Determination of the absolute configuration

With three reaction components of the developed sequence explored, we moved on to determining absolute configuration of the products (Scheme 2.14). This part was carried out by Dr. Bouisseau. She first synthesized (*S*)-4-phenylnonan-2-one **G**, whose absolute configuration was verified by comparing with the optical rotation value reported in the literature: $[\alpha]_D^{25}$: +18.7 (*c* = 1.0, $CHCl_3$, 98% ee for **G**); literature values: $[\alpha]_D^{20}$: +16.9

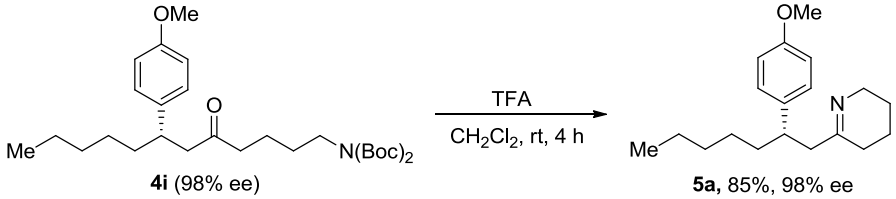
(c = 0.5, $CHCl_3$, 92% ee for (*S*)-enantiomer),[78] $[\alpha]_D^{20}$: –17.0 (c = 1.3, $CHCl_3$, 92% ee for (*R*)-enantiomer).[68-69] This compound was then alkylated with an alkyl iodide to afford (*S*)-β-phenyl ketone **H**; and we compared its optical rotation value with compound **4r** (see Table 2.8), which was prepared from our sequential methodology: $[\alpha]_D^{25}$: +17.4 (c = 0.5, $CHCl_3$, 98% ee for **H**) compared to $[\alpha]_D^{25}$: +17.9 (c = 0.5, $CHCl_3$, 94% ee for **4r**). The absolute configuration of compound **4r** was therefore determined as (*S*)-enantiomer. The stereochemistry for the remaining products was assigned by analogy. The stereochemical outcome obtained for this reaction is in agreement with previous reports from the literature.[71, 75-76, 79]



Scheme 2.14 Determination of the absolute configuration

2.5 Applications in the synthesis of heterocycles

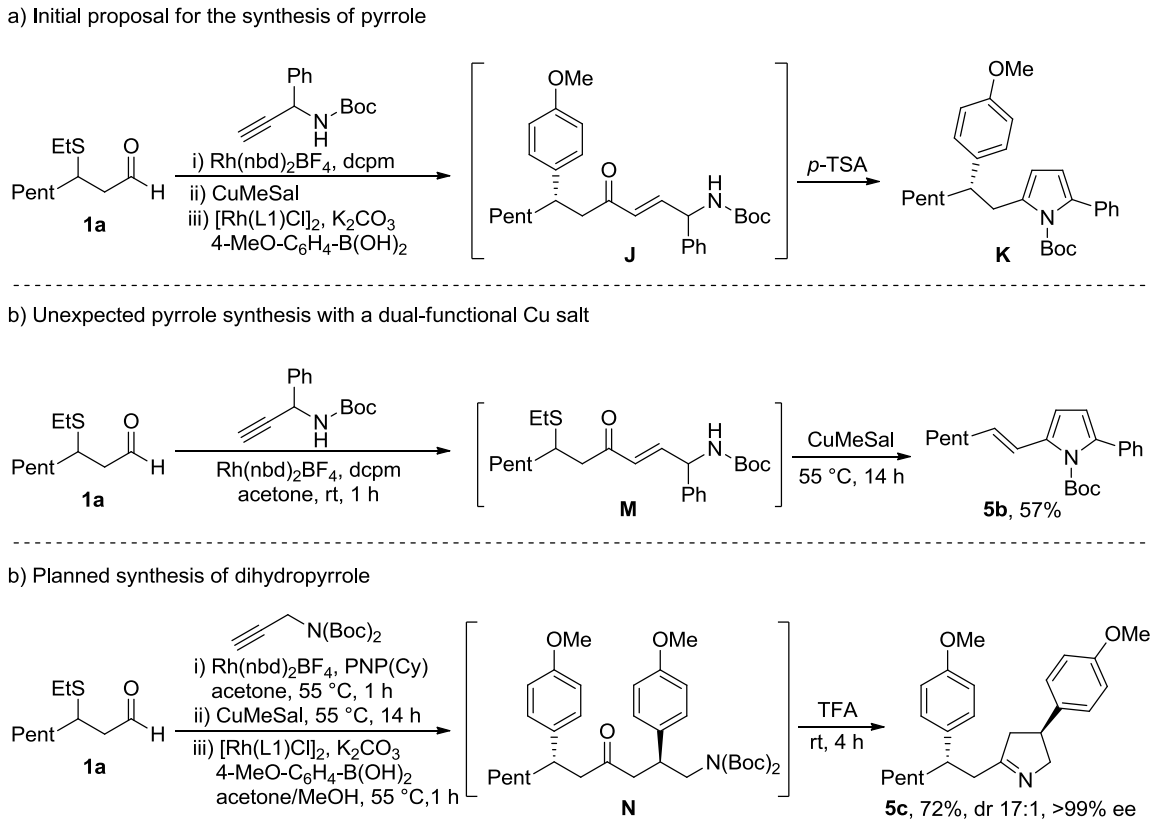
The Willis group has demonstrated the utility of hydroacylation adducts in the synthesis of heterocyclic compounds, as was discussed in Chapter 1. We envisaged that our developed method could add diversity to these syntheses, giving products without the presence of a chelating group. For instance, treating ketone **4i** (see Table 2.7), obtained from our sequential procedure, with TFA at room temperature afforded tetrahydropyridine **5a** in 85%



Scheme 2.15 Synthesis of tetrahydropyridine

yield without any loss of enantiopurity (Scheme 2.15).

In another study, we initially tried to synthesize substituted pyrroles following our previous reported method.[50b] It was hypothesized that the hydroacylation of a Boc-protected propargylic amine followed by elimination could afford a divinyl ketone, which would then react selectively with a boronic acid to give intermediate **J**; subsequent cyclization of **J** could afford pyrrole **K** (Scheme 2.16a) with retention of the stereochemistry. In reality, we unexpectedly found that under the elimination conditions with CuMeSal, hydroacylation product **M** could undergo an elimination-cyclization cascade, yielding pyrrole **5b** in 57% isolated yield (Scheme 2.16b). With this result in hand, we then postulated another route utilizing a double Boc-protected propargylic amine to avoid cyclization under the elimination conditions. Pleasingly, this reaction proceeded well;

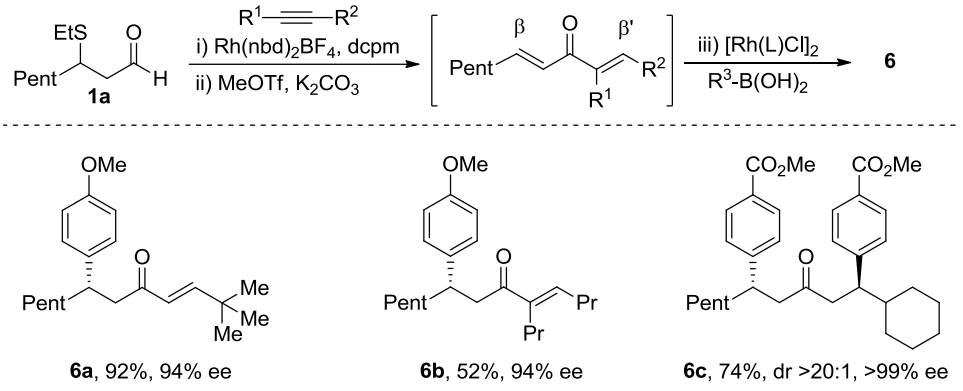


Scheme 2.16 Synthesis of pyrrole and dihydropyrrole

double addition intermediate **N** could be obtained *via* the three component sequence; filtering the reaction mixture through a short pad of SiO_2 and treatment with TFA yielded dihydropyrrole **5c** with excellent stereocontrol (Scheme 2.16c).

2.6 Towards regioselective mono-conjugate addition

As was shown previously, an alkyne hydroacylation-elimination sequence using alkyl β-*S* aldehydes would afford divinyl ketones, with easy variation of substituents at both sides of the carbonyl. We began to wonder if the selectivity could be controlled between the two Michael acceptors (β and β') of the divinyl ketone under conjugate addition conditions (Scheme 2.17). The introduction of a sterically demanding *tert*-butyl group at β'-position suppressed the subsequent conjugate addition, giving β-aryl enone **6a** with excellent regiocontrol. Selective mono-conjugate addition could also be achieved by employing an internal alkyne; the presence of an α'-substituent attenuated nucleophilic addition to the



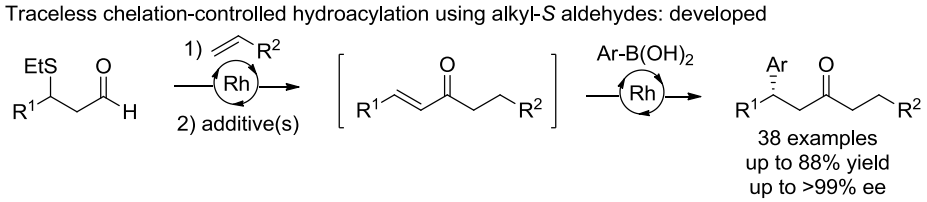
Reaction conditions: i) **1** (1.0 equiv), alkyne (1.3 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dcpm (5 mol%), acetone (1.0 M), 55 ℃, 1 h; ii) MeOTf (1.5 equiv), K_2CO_3 (2.5 equiv), acetone (0.5 M), 55 ℃, 1 h; iii) $[Rh(L1)Cl]_2$ (2.5 mol%), boronic acid (1.5 equiv), acetone/MeOH (9:1, 0.1 M), 55 ℃, 1 h. **6c**: DCE was used instead of acetone; iii) boronic acid (3.0 equiv), $[Rh(L2)Cl]_2$ (2.5 mol%), 3h; **L1** and **L2**: see Table 2.4.

Scheme 2.17 Conjugate addition to divinyl ketones

β-carbon, affording product **6b** in a moderate yield. However, when the steric difference between β- and β'-positions were not substantial enough to favor the addition to either of the electrophilic carbons, as was in the case of using cyclohexylacetylene, double addition product **6c** was thereby obtained in good yield and excellent stereocontrol.

2.7 Summary and outlook

In conclusion, we have developed a one-pot alkene hydroacylation-elimination-boronic acid conjugate addition sequence for the enantioselective synthesis of β-aryl ketones, employing easily accessible starting materials and commercially available catalysts (Scheme 2.18). This methodology possesses the benefits of chelation-controlled hydroacylation – efficient reactions, good substrate scope, and mild reaction conditions – yet delivers products of traceless hydroacylation with the initial *S*-substituent replaced by a stereochemically defined aryl group. Good variation of the three components is possible. This reaction is scalable to gram scale with low catalyst loadings and can be applied to the synthesis of heterocyclic compounds, which further demonstrates its synthetic utility.



Scheme 2.18 traceless chelation-controlled hydroacylation using alkyl *S*-aldehydes

Meanwhile, we observed that it was challenging to achieve regioselective mono-conjugate addition to divinyl ketones, unless a carefully selected substrate was employed. It would be synthetically useful if we could develop an approach that delivers β'-substituted enones in a selective manner. Research towards this goal is presented in Chapter 3.

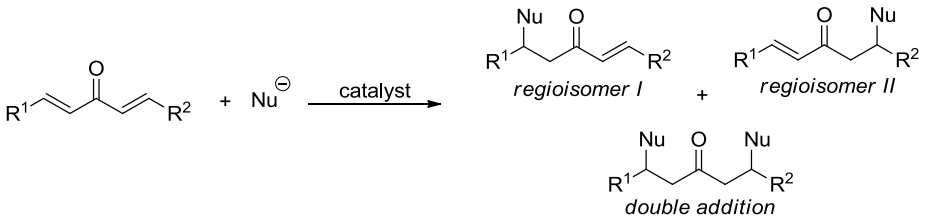
Chapter 3

Construction of β'-aryl enones utilizing a rhodium-catalyzed alkyne hydroacylation-conjugate addition-elimination sequence

3.1 Introduction

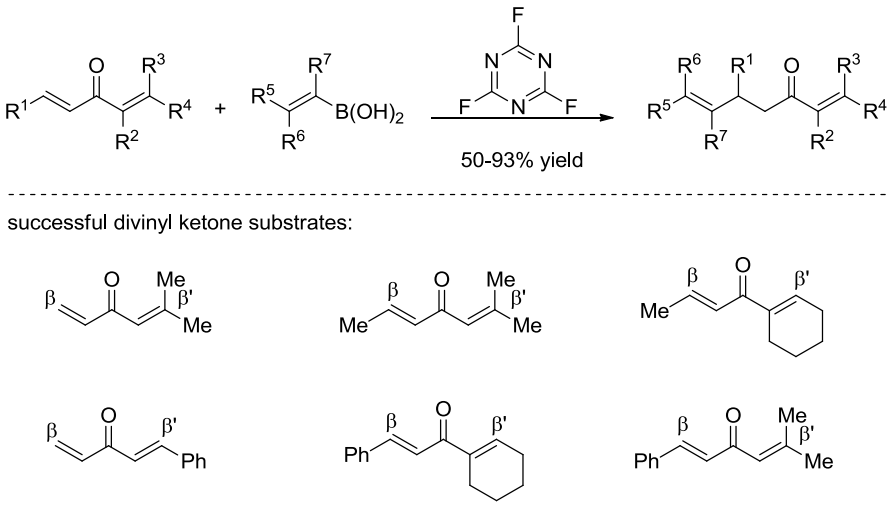
3.1.1 Conjugate addition of nucleophiles to divinyl ketones

Enantiomerically enriched β'-substituted enones are versatile synthetic building blocks.[80] A simple and conceptually attractive route to these molecules involves a catalyst-controlled regio- and enantioselective addition of nucleophiles to divinyl ketones (Scheme 3.1). However, as was described at the end of the previous chapter, this approach suffers from selectivity issues; the formation of two possible regioisomers as well as the double-addition products is possible.



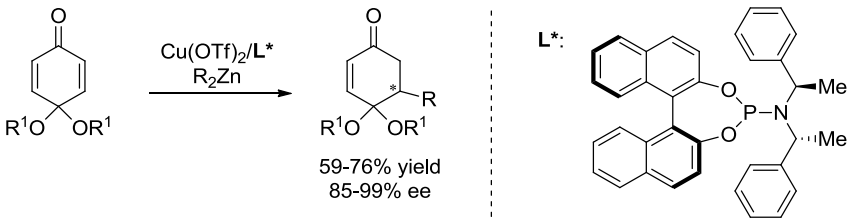
Scheme 3.1 Conjugate addition to divinyl ketones

Several research groups have published different approaches to control regioselectivity in this addition process. In 1998, Hara and co-workers reported a regioselective 1,4-addition of alkenyl boronic acids to divinyl ketones (Scheme 3.2).[80a] In their research, six divinyl ketone substrates were successfully employed, to which the addition of nucleophiles favored the β-position over β'. Their good selectivity relied on the presence of a less substituted β-position or on the existence of an α'-substituent.



Scheme 3.2 Mono-addition of alkenyl boronic acids to divinyl ketones

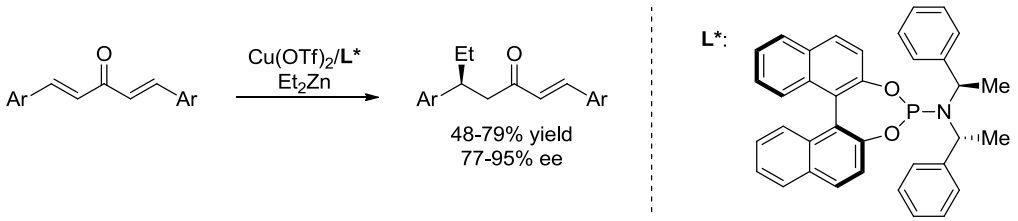
In 1999, Feringa and co-workers reported an enantioselective conjugate addition of organozinc reagents to symmetrical cyclohexadienones catalyzed by a $Cu(OTf)_2$-phosphoramidite complex (Scheme 3.3).[80b] Mono-addition products were isolated in moderate to good yields with excellent levels of enantiocontrol.



Scheme 3.3 Enantioselective mono-addition using organozinc reagents

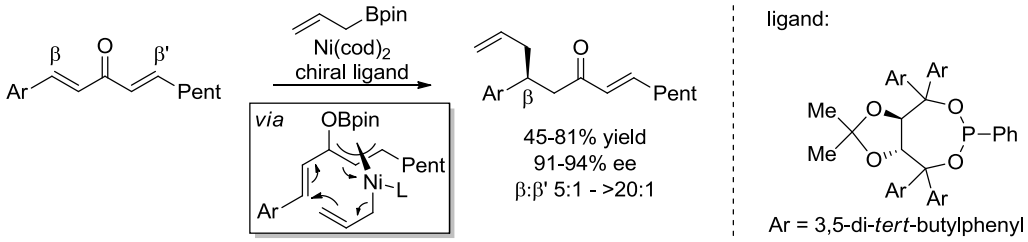
More recently, they applied the same catalytic system to the enantioselective mono-

conjugate addition on symmetrical *acyclic* divinyl ketones (Scheme 3.4).[80c] In this report, only β,β'-aryl-substituted substrates were successfully used. In addition, any nucleophilic reagents other than diethylzinc decreased the enantioselectivity dramatically.



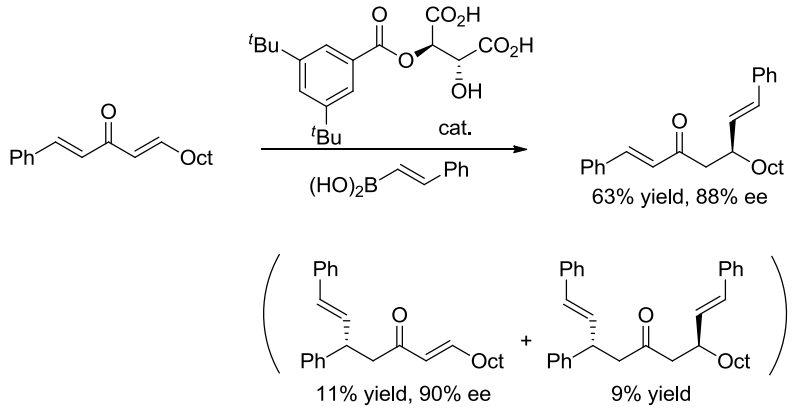
Scheme 3.4 Enantioselective mono-addition to linear divinyl ketones

In 2008, Morken and co-workers developed a Ni-catalyzed enantioselective conjugate allylation of unsymmetrical divinyl ketones using allyl pinacol boronate (Scheme 3.5).[80f] A variety of mono-addition products were synthesized with good to excellent regiocontrol (β:β' 5:1 to >20:1), suggesting that the initial Lewis acid activation prefers to take place at the alkyl-substituted β'-position.



Scheme 3.5 Enantioselective mono-allylation to unsymmetrical divinyl ketones

More recently, Sugiura and co-workers applied their *O*-monoacyltartaric acid-catalyzed conjugate olefination to unsymmetrical divinyl ketones (Scheme 3.6).[80h] Although a moderate selectivity was observed in some cases, they also isolated the alternative regioisomer and the double addition product, which impairs synthetic efficiency. In addition, a discrimination between the β- and β'-substituents (alkyl/aryl) was essential for attaining good selectivity.

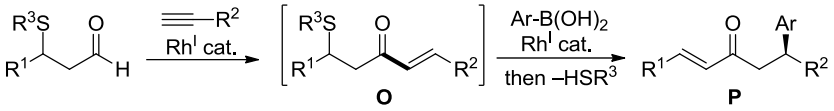


Scheme 3.6 Enantioselective mono-olefination catalyzed by *O*-monoacyltartaric acid

To summarize, although the regioselective mono-conjugate addition to divinyl ketones is known in the literature, these processes required careful selection of the substrates. High selectivity has only been achieved when a significant steric and/or electronic variation existed between the two Michael acceptors, or when a symmetrical divinyl ketone was employed. This has limited the number of β'-substituted enones that can be accessed. Therefore, it would be synthetically useful if we could establish a robust method to access these compounds in a highly selective manner.

3.1.2 Project aims

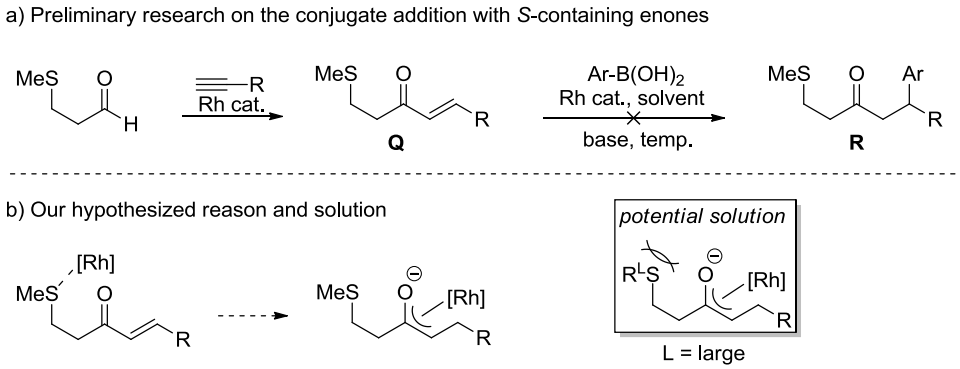
In this context, we postulated a different route based on our previous study (Scheme 3.7). Our design relies on three key operations: (i) rhodium-catalyzed alkyne hydroacylation with a β-*S*-substituted alkyl aldehyde to provide β'-substituted enone **O**; (ii) rhodium-catalyzed enantioselective conjugate addition of an aryl boronic acid to enone **O**; and (iii) elimination of the β-*S*-substituent to provide β'-substituted enone **P**. This approach, employing three readily available starting materials, inherently averts the selectivity issue raised from 1,4-addition to divinyl ketones and, given our previous success, should be achievable in an efficient manner.[52]



Scheme 3.7 Our proposed route to β'-aryl enones

3.2 Optimization of the reaction conditions

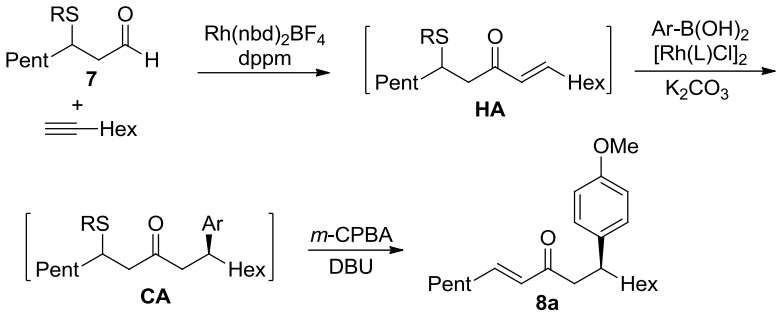
Preliminary research has been conducted in the Willis group with the goal of achieving a successful conjugate addition using hydroacylation products **Q** containing a methyl sulfide group (Scheme 3.8a).[81] However, desired ketone products **R** were not observed, possibly due to sulfur inhibition of the Rh catalyst (Scheme 3.8b, left), although the methyl sulfide was an effective directing group for hydroacylation. We hypothesized that increasing the steric bulk attached to the sulfur may help to diminish the catalyst poisoning effect, hence allowing the conjugate addition to take place (Scheme 3.8b, right).



Scheme 3.8 Conjugate addition using *S*-containing enones

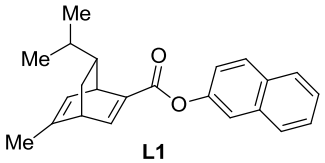
To test our hypothesis, we prepared a series of β-*S*-substituted octenal derivatives as our evaluation substrates and studied their addition to 1-octyne as the first step of our planned sequence (Table 3.1). Small bite-angle ligand dppm was used as the ligand of choice for the hydroacylation step and chiral diene ligand **L1** for the conjugate addition step. Although we could achieve successful hydroacylation reactions using aldehydes

Table 3.1 Optimization of reaction conditions[a]

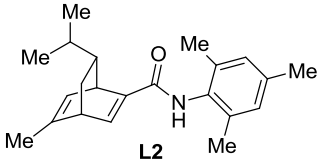


Entry	R	L	Yield[b] (sequence)	Ee (sequence)
1[c]	Et	**L1**	0%	-
2[d]	^{i}Pr	**L1**	0%	-
3	^{t}Bu	**L1**	75%	95%
4	^{t}Bu	**L2**	73%	94%
5	^{t}Bu	**L3**	75%	–88%
6	^{t}Bu	-	<5%	-

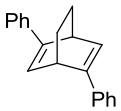
[a]Reaction conditions: **7** (1.0 equiv), 1-octyne (1.1 equiv), $Rh(nbd)_2BF_4$ (3 mol%), dppm (3 mol%), DCE (1.0 M), 55 ℃, 1 h; then 4-MeO-C_6H_4-$B(OH)_2$ (1.5 equiv), $[Rh(L1)Cl]_2$ (2.5 mol%), K_2CO_3 (1.0 equiv), DCE/MeOH (9:1, 0.1 M), 55 ℃, 1.5 h; then filter through a pad of SiO_2, CH_2Cl_2 (0.1 M), *m*-CPBA (1.5 equiv), 0 ℃, 15 min, then DBU (2.5 equiv), rt, 2.5 h. [b]Isolated yields. [c]100% conversion to **HA**; 0% conversion to **CA**. [d]100% conversion to **HA**; 34% conversion to **CA**; elimination not performed.



L1



L2

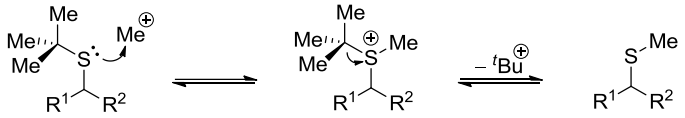


L3

bearing EtS-, ^{i}PrS- and ^{t}BuS-substituents, it was only with the sterically demanding ^{t}BuS-substituted example that efficient conjugate addition took place (entries 1-3). For the experiments in which a successful hydroacylation-conjugate addition sequence was achieved, elimination of the sulfide was realized by treatment with *m*-CPBA and then DBU; using this protocol, a sequence combining β-^{t}BuS-substituted aldehyde **7a**, 1-octyne and

4-methoxyphenylboronic acid afforded β'-aryl enone **8a** in 75% yield and 95% ee, with a total catalyst loading of 8 mol% (entry 3). Two alternative chiral diene ligands, **L2** and **L3**,[82] were also evaluated in the conjugate addition step, providing the final product **8a** in 94 and –88% ee, respectively (entries 4, 5). Entry 6, in which no additional catalyst was added in the 1,4-addition step, confirms that the dppm-derived catalyst is not effective for the conjugate addition, which is essential for achieving high levels of enantiocontrol.

Elimination of the *tert*-butyl sulfide unit using our previously developed methods (Chapter 2) was not effective. Treating the mixture with MeOTf/K_2CO_3 led to a complex reaction, with a methyl-*tert*-butyl exchange observed by ^{1}H NMR spectroscopy (Scheme 3.9). The reaction with CuMeSal resulted in recovery of the starting material, probably because the steric hindrance was preventing the Lewis acid activation of the sulfide.



Scheme 3.9 Methyl-*tert*-butyl exchange

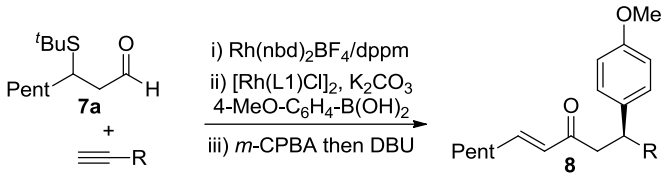
3.3 Evaluation of the reaction scope

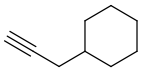
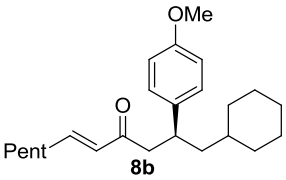
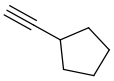
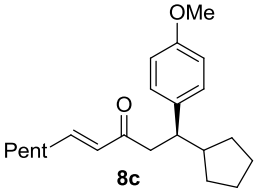
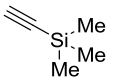
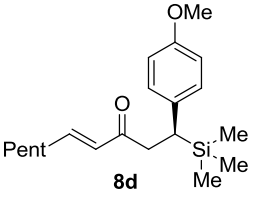
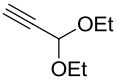
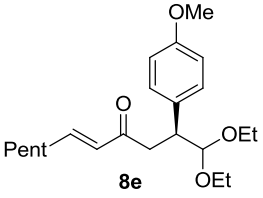
3.3.1 Alkyne scope

With optimized reaction conditions in hand, we first examined the scope with respect to the alkyne coupling partner, with aldehyde **7a** and 4-methoxyphenylboronic acid being held constant (Table 3.2). Alkynes with different levels of steric demand were all successfully utilized, yielding the corresponding enones **8b-d** in good yields and excellent enantioselectivities (entries 1-3). A variety of functional groups, including a diethyl acetal

(entry 4), alkyl chloride (entry 5), phenyl (entry 6) and a silyl-protected alcohol (entry 7), were all well-tolerated. Arylalkynes could also be employed in this transformation (entries 8, 9), and a gram-scale reaction using phenylacetylene was performed; starting with 5.0 mmol of aldehyde **7a**, 1.5 grams of the desired product **8i** was isolated in good yield and ee, employing 1 and 2 mol% of catalyst for the hydroacylation and conjugate addition steps respectively (entry 8). In addition, a thiophene-derived alkyne was used successfully, giving product **8k** in 75% yield and 94% ee (entry 10).

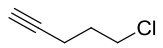
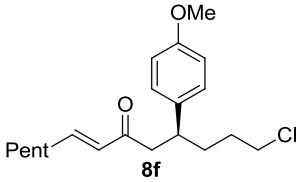
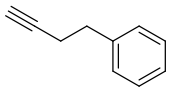
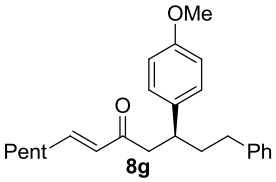
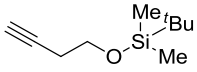
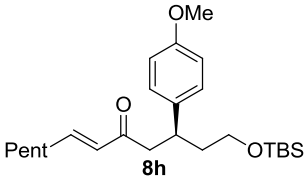
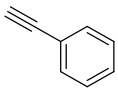
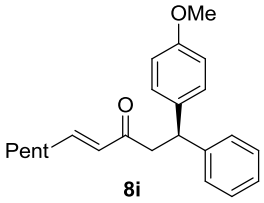
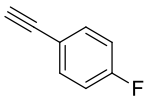
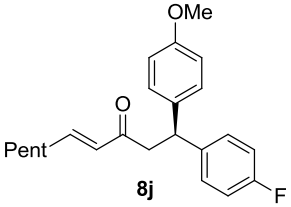
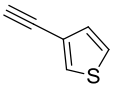
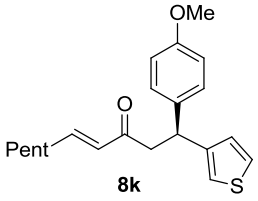
Table 3.2 Variation of the alkyne coupling partner[a]



Entry	Alkyne	Product	Yield[b] (%)	Ee (%)
1			70	97
2[c]			61	92
3			66	92
4			71	97

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Table 3.2, continued

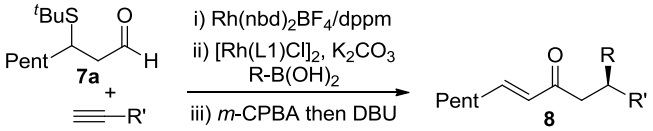
Entry	Alkyne	Product	Yield[b] (%)	Ee (%)
5		 **8f**	76	94
6		 **8g**	71	98
7		 **8h**	60	97
8[d]		 **8i**	80	95
9		 **8j**	78	96
10		 **8k**	75	94

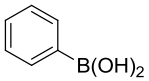
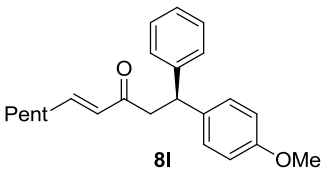
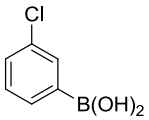
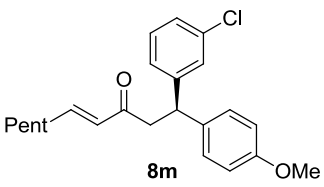
[a]Reaction conditions: i) **7a** (1.0 equiv), alkyne (1.1 equiv), $Rh(nbd)_2BF_4$ (3 mol%), dppm (3 mol%), DCE (1.0 M), 55 ℃, 1 h; ii) 4-MeO-C_6H_4-$B(OH)_2$ (1.5 equiv), $[Rh(L1)Cl]_2$ (2.5 mol%), K_2CO_3 (1.0 equiv), DCE/MeOH (9:1, 0.1 M), 55 ℃, 1.5 h; iii) filter through a pad of SiO_2, CH_2Cl_2 (0.1 M), *m*-CPBA (1.5 equiv), 0 ℃, 15 min, then DBU (2.5 equiv), rt, 2.5 h; **L1** and **L2**: see Table 3.1. [b]Isolated yields. [c]ii) $[Rh(L2)Cl]_2$ was used. [d]5.0 mmol of **7a**, 1 mol% of $Rh(nbd)_2BF_4$/dppm, 2 mol% of $[Rh(L1)Cl]_2$.

3.3.2 Boronic acid scope

We then evaluated a variety of boronic acids for our developed transformation, together with aldehyde **7a** and two different alkynes (Table 3.3). The reaction was successfully applied to aryl boronic acids bearing both electron-withdrawing (entries 2-4) and electron-donating (entries 5-8) substituents, which could be placed at all positions of the benzene ring. Notably, enantiomeric product pairs were obtained by varying the alkyne and boronic acid coupling partners (**8i**/**8l**, **8j**/**8o**). The reaction could also tolerate a naphthyl group (entry 9) and an olefin (entry 10), yielding corresponding enones with excellent levels of enantiocontrol. However, when a boronic acid bearing an aryl bromide was employed with either an alkyl or aryl-substituted alkyne (entries 11, 12), we were only able to obtain a moderate ee. Moreover, the use of 3,4-disubstituted phenyl boronic acid resulted in a dramatic drop in the enantioselectivity (entry 13). The decrease in ee with boronic acids bearing an aryl halide may be due to the coordination of the halide to the rhodium catalyst.

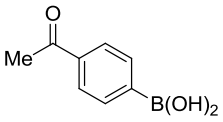
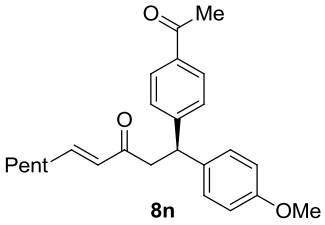
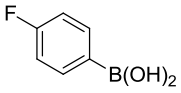
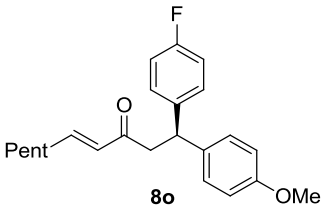
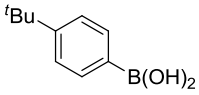
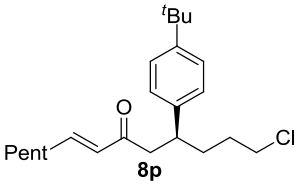
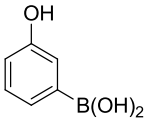
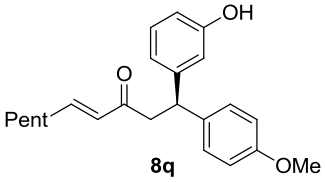
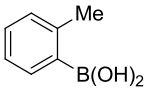
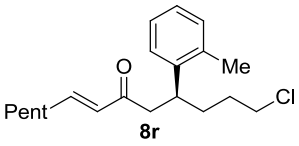
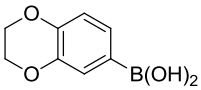
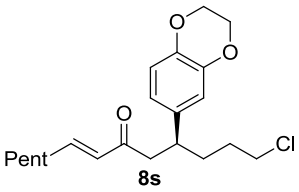
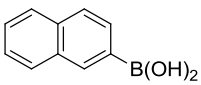
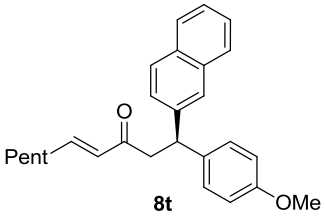
Table 3.3 Variation of the boronic acid coupling partner[a]



Entry	Boronic acid	Product	Yield[b] (%)	Ee (%)
1			70	95
2[c]			78	85

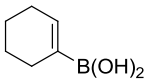
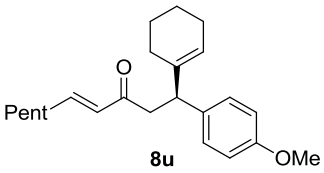
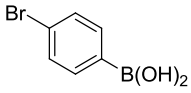
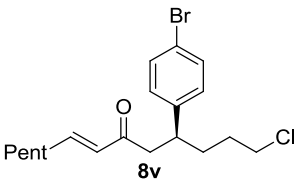
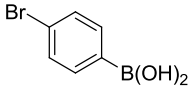
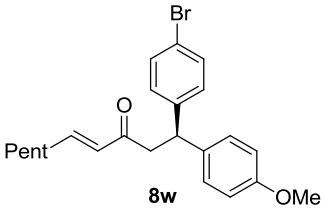
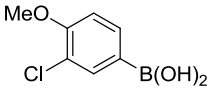
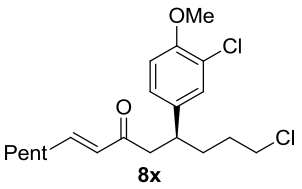
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Table 3.3, continued

Entry	Boronic acid	Product	Yield[b] (%)	Ee (%)
3[c]		 **8n**	77	91
4		 **8o**	79	90
5		 **8p**	75	89
6		 **8q**	61	93
7		 **8r**	76	90
8[c]		 **8s**	76	90
9		 **8t**	81	87

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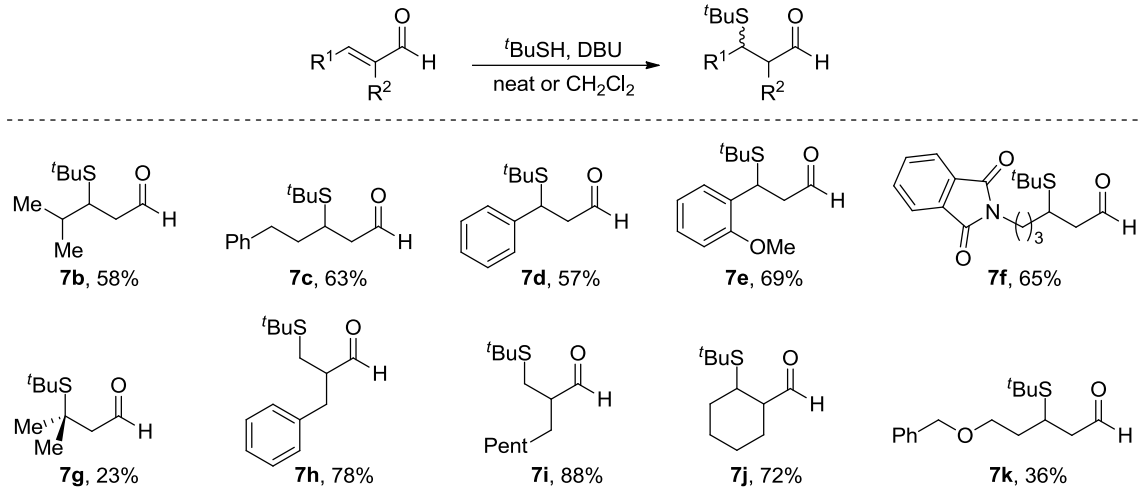
Table 3.3, continued

Entry	Boronic acid	Product	Yield[b] (%)	Ee (%)
10[c]		 **8u**	44	94
11[c]		 **8v**	78	79
12[c]		 **8w**	71	78
13		 **8x**	79	60

[a]Reaction conditions: i) **7a** (1.0 equiv), alkyne (1.1 equiv), $Rh(nbd)_2BF_4$ (3 mol%), dppm (3 mol%), DCE (1.0 M), 55 ℃, 1 h; ii) boronic acid (1.5 equiv), $[Rh(L1)Cl]_2$ (2.5 mol%), K_2CO_3 (1.0 equiv), DCE/MeOH (9:1, 0.1 M), 55 ℃, 1.5 h; iii) filter through a pad of SiO_2, CH_2Cl_2 (0.1 M), *m*-CPBA (1.5 equiv), 0 ℃, 15 min, then DBU (2.5 equiv), rt, 2.5 h; **L1** and **L2**: see Table 3.1. [b]Isolated yields. [c]ii) $[Rh(L2)Cl]_2$ was used.

3.3.3 Aldehyde scope

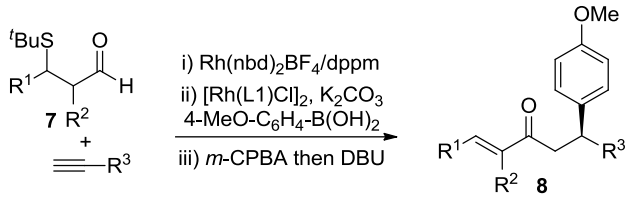
Our starting aldehydes were prepared through thio-Michael addition to α,β-unsaturated aldehydes, using DBU as a base. The synthesis of β-substituted acroleins has been discussed in Chapter 2; α-substituted acroleins could be easily accessed according to a procedure reported by Pihko employing formaldehyde.[83] A set of starting aldehydes was subsequently obtained (Scheme 3.10), including both β- (**7b-g, k**) and α-substituted (**7h, i**) examples. We could also access a cyclohexene-derived, α,β-disubstituted aldehyde **7j**.

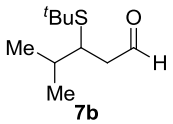
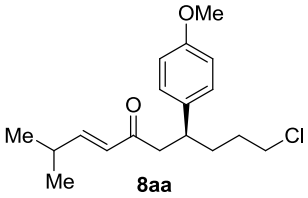
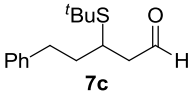
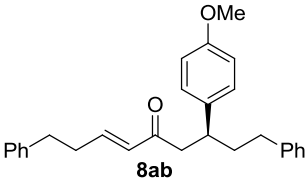
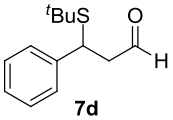
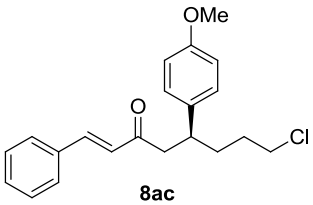
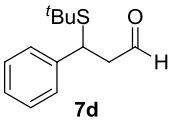
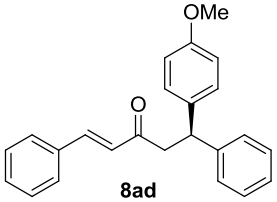
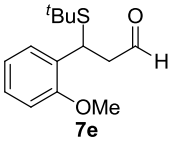
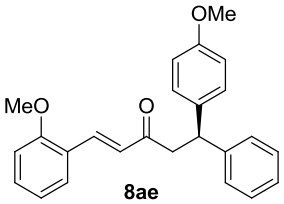
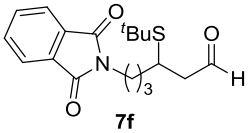
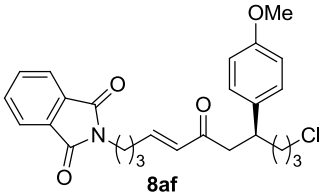


Scheme 3.10 Preparation of β-^{t}BuS-substituted aldehydes

With robust methods for starting material synthesis established, we then examined the aldehyde scope for this transformation (Table 3.4). Aldehydes bearing a variety of β-substituents were shown to be effective substrates, including alkyl (entries 1, 2), aryl (entries 3-5), phthalimide (entry 6), and a β,β-dimethyl-substituted example (entries 7, 8). Notably, **8ab** and **8ad** are the formal mono-addition products from symmetrical divinyl ketones. Next, α-substituted aldehydes were also successfully employed, although, in these cases, the elimination step required a longer reaction time, potentially due to a lower rate of deprotonation (entries 9, 10). In addition, we succeeded in applying an α,β-disubstituted aldehyde to this transformation, affording the corresponding cyclohexene-derived ketone **8ak** (entry 11). Finally, the use of aldehyde bearing a benzyl ether group gave product **8al** in a moderate ee (entry 12); perhaps the π-interactions, between the terminal phenyl group of the substrate and the naphthyl group of the ligand, compromised their steric repulsion, which is critical for high levels of enantiocontrol.[75, 84]

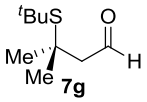
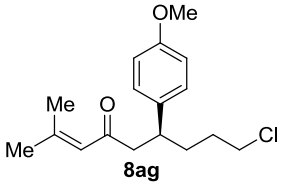
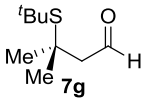
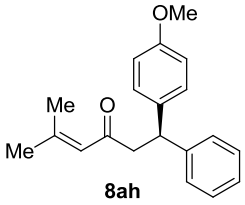
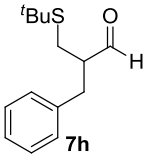
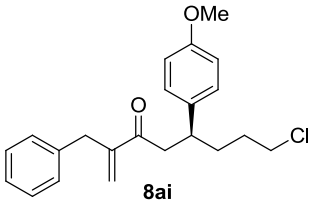
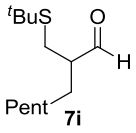
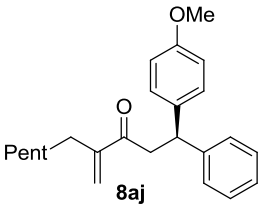
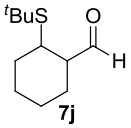
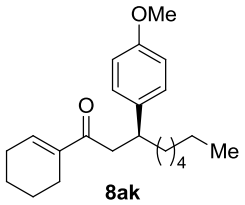
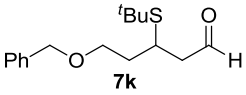
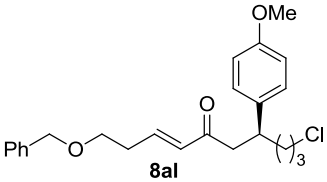
Table 3.4 Variation of the aldehyde coupling partner[a]



Entry	Aldehyde	Product	Yield[b] (%)	Ee (%)
1	 **7b**	 **8aa**	77	95
2	 **7c**	 **8ab**	66	93
3	 **7d**	 **8ac**	82	92
4	 **7d**	 **8ad**	81	97
5	 **7e**	 **8ae**	81	96
6	 **7f**	 **8af**	77	85

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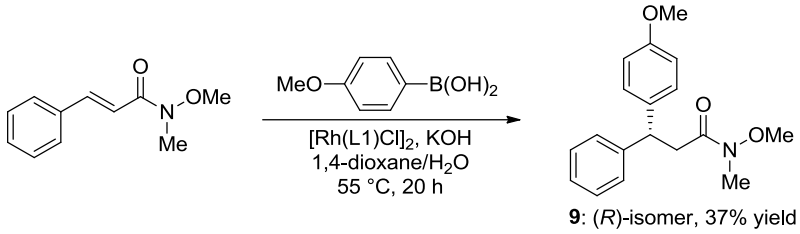
Table 3.4, continued

Entry	Aldehyde	Product	Yield[b] (%)	Ee (%)
7	 **7g**	 **8ag**	76	85
8	 **7g**	 **8ah**	70	88
9[c]	 **7h**	 **8ai**	53	93
10[c]	 **7i**	 **8aj**	61	90
11[d]	 **7j**	 **8ak**	50	96
12	 **7k**	 **8al**	78	77

[a]Reaction conditions: i) **7** (1.0 equiv), alkyne (1.1 equiv), $Rh(nbd)_2BF_4$ (3 mol%), dppm (3 mol%), DCE (1.0 M), 55 ℃, 1 h; ii) 4-MeO-C_6H_4-$B(OH)_2$ (1.5 equiv), $[Rh(L1)Cl]_2$ (2.5 mol%), K_2CO_3 (1.0 equiv), DCE/MeOH (9:1, 0.1 M), 55 ℃, 1.5 h; iii) filter through a pad of SiO_2, CH_2Cl_2 (0.1 M), *m*-CPBA (1.5 equiv), 0 ℃, 15 min, then DBU (2.5 equiv), rt, 2.5 h; **L1** and **L2**: see Table 3.1. [b]Isolated yields. [c]Reaction stirred for 14 h after addition of DBU. [d]iii) toluene (0.1 M), *m*-CPBA (1.5 equiv), 0 ℃, 15 min, then DBU (2.5 equiv), reflux (120 ℃), 1.5 h.

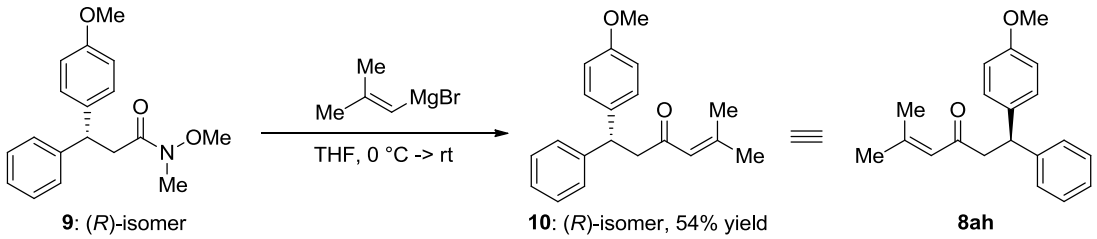
3.4 Determination of the absolute configuration

We then set about determining the absolute configuration of the products obtained from our developed sequence. First, we synthesized amide **9** from a conjugate addition to α,β-unsaturated Weinreb amide (Scheme 3.11); its absolute configuration was determined by comparing the optical rotation value with that reported in the literature: $[\alpha]_D^{25}$: –4.4 (*c* = 1.0, $CHCl_3$ for **9**); literature value: $[\alpha]_D^{20}$: –4.1 (*c* = 1.3, $CHCl_3$ for (*R*)-enantiomer).[85]



Scheme 3.11 1,4-Addition to Weinreb amide for the determination of absolute configuration

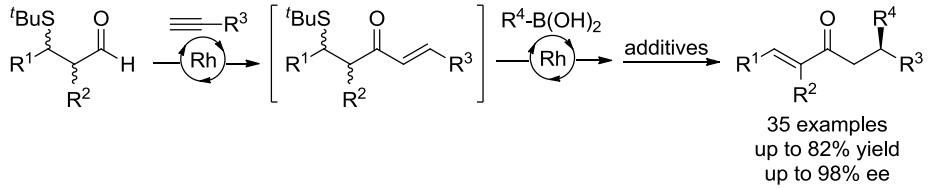
Compound **9** was then reacted with 2-methyl-1-propenylmagnesium bromide, affording β'-aryl-substituted enone **10** (Scheme 3.12). The optical rotation value of **10** was compared with **8ah** (see Table 3.4), which was prepared from our sequential procedure: $[\alpha]_D^{25}$: +3.5 (*c* = 1.0, $CHCl_3$, 80% ee), (*R*)-isomer for **10**; $[\alpha]_D^{25}$: +5.1 (*c* = 1.0, $CHCl_3$, 88% ee) for **8ah**. Therefore, **8ah** was determined as (*R*)-isomer. The stereochemistry for the remaining products was assigned by analogy. The stereochemical outcome obtained for this reaction is in agreement with previous reports from the literature.[71, 75-76, 79]



Scheme 3.12 Determination of the absolute configuration

3.5 Summary and outlook

In conclusion, we have developed a Rh^{I}-catalyzed alkyne hydroacylation-boronic acid conjugate addition-sulfide elimination sequence, leading to highly functionalized β'-aryl enones with excellent levels of enantiocontrol (Scheme 3.13). This three-component procedure serves as an efficient alternative to the mono-conjugate addition of aryl boronic acids to divinyl ketones, employing readily available starting materials and commercially available catalysts. Key to achieving this transformation is the use of a bulky *tert*-butyl sulfide coordinating group, which works efficiently for the hydroacylation step and minimizes sulfur poisoning in the conjugate addition step. The products obtained, featuring a remaining Michael acceptor, are useful building blocks for further functionalizations.



Scheme 3.13 A hydroacylation-conjugate addition-elimination sequence to β'-aryl enones

This work, together with that in Chapter 2, demonstrates our effort in developing traceless chelation-controlled hydroacylation reactions using *alkyl* aldehydes, which has only been achieved with aryl- and alkenyl-variants before. To further extend the synthetic utility of chelation-controlled hydroacylation reactions, we aimed at identifying a versatile chelating group which, ideally, can promote more than one C-H functionalization process and can be transformed to a broader range of functional groups. Research towards this goal is presented in Chapter 4.

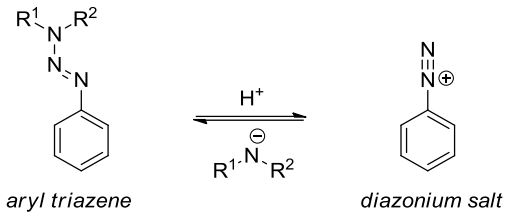
Chapter 4

Exploiting 2-triazenylbenzaldehydes for chelation-controlled hydroacylation and subsequent aromatic C-H functionalizations

4.1 Introduction

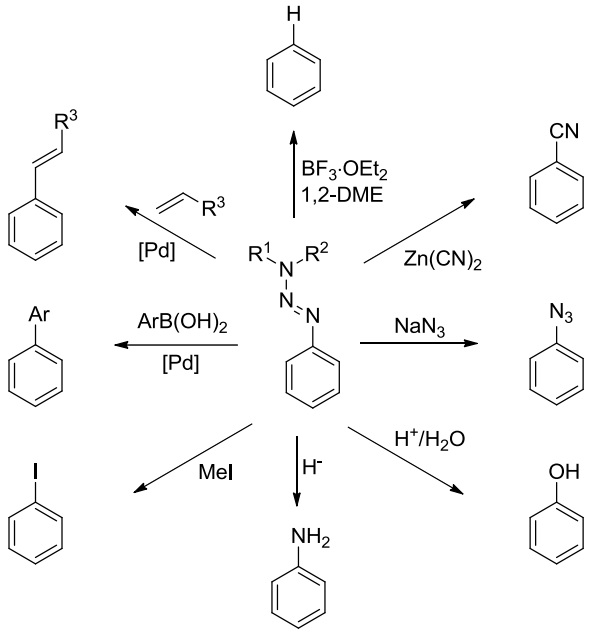
4.1.1 Triazenes in organic synthesis

Triazenes are a class of synthetically useful compounds. They can be seen as protected diazonium salts, and this interconversion is shown in Scheme 4.1. Under acidic conditions, a triazene is decomposed to a diazonium salt; inversely, the diazonium salt can react with a deprotonated amine to form a triazene. Compared to diazonium salts, triazenes are soluble in organic solvents, which makes them more attractive for organic synthesis. For example, this type of compound has been employed as a protecting group in natural product synthesis,[86] and has found applications in combinatorial chemistry[87] and polymer chemistry.[88] Over the past few decades, triazenes have been extensively studied by various research groups, with several review articles having been published.[89]



Scheme 4.1 Interconversion between a triazene and a diazonium salt

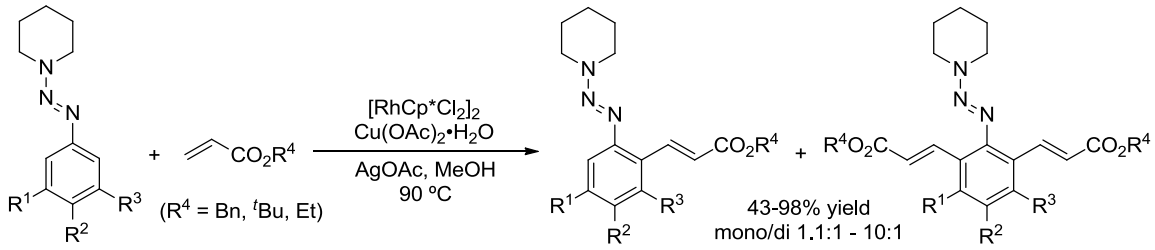
As a masked diazonium salt, the triazene group can be transformed into a broad variety of functional groups *via* Sandmeyer-type reactions.[90] More recently, they have also been employed in transition metal-catalyzed processes.[91] A brief summary is presented in Scheme 4.2.



Scheme 4.2 An overview of triazene transformations

Owing to their unique reactivity, organic chemists have begun to utilize triazenes as a traceless directing group in metal-catalyzed C-H functionalization reactions. As a representative example, the rhodium-catalyzed *ortho* C-H olefination reaction, using triazene as a directing group, was described by Huang and co-workers in 2012.[92] In their study, a variety of aryl triazenes were successfully combined with electron-deficient

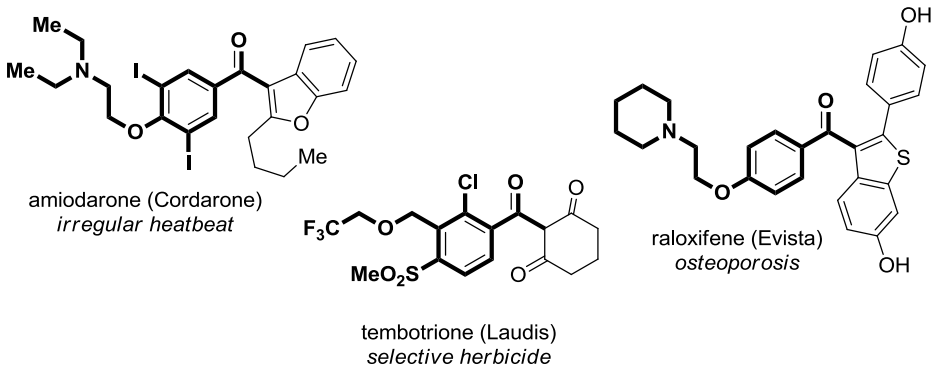
alkenes under rhodium(III) catalysis, affording oxidative Heck products in good to excellent yields. However, when employing substrates without a substituent *ortho* to the triazene group, the authors only observed moderate to good ratios of mono to di-functionalization (Scheme 4.3).



Scheme 4.3 Rhodium-catalyzed, triazene directed *ortho*-olefination

4.1.2 Project aims

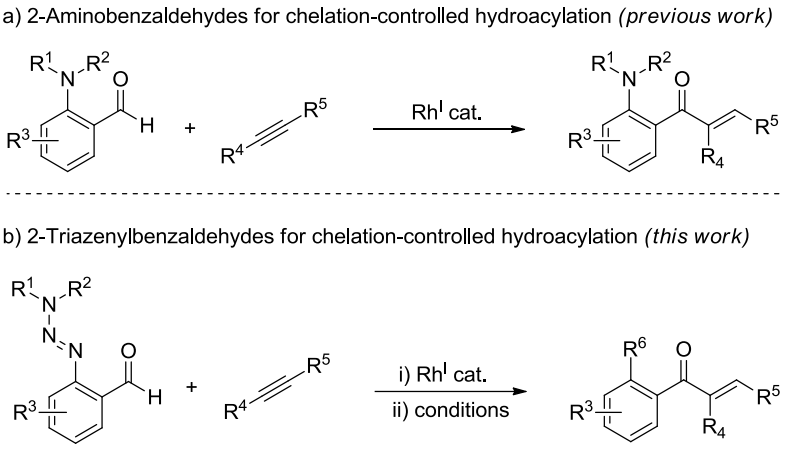
Substituted phenyl ketones are valuable synthetic building blocks in organic chemistry. They are found in several biologically active molecules used in pharmaceutical and agrichemical industries (Scheme 4.4).[93] Therefore, efficient access to this moiety is of great importance.



Scheme 4.4 Bioactive molecules containing a phenyl ketone moiety

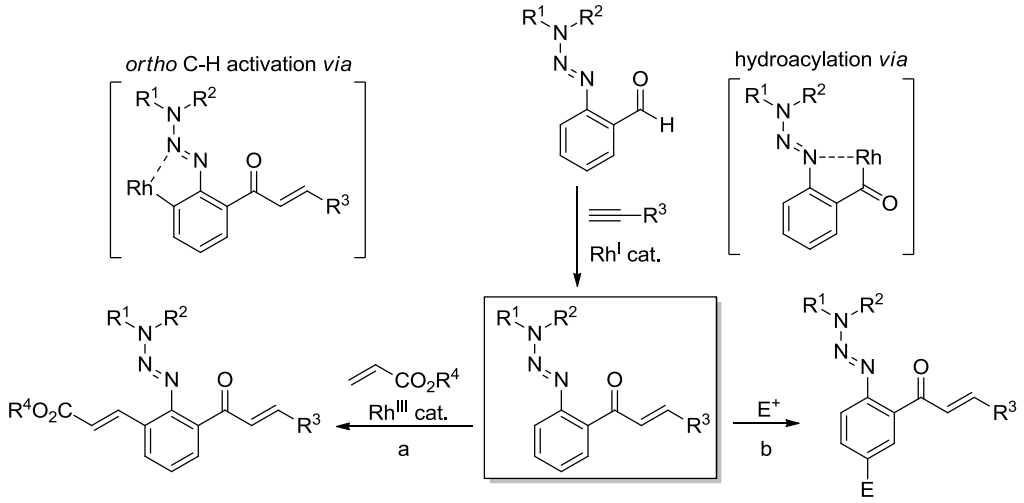
The Willis group has been continuously investigating new chelating groups for traceless hydroacylation processes that would afford versatile ketone products since 2013. Attracted by the number of transformations that a triazene group may undergo, and given

our previous success in the use of *N*-chelating aldehydes (Scheme 4.5a),[30] we postulated that 2-triazenylbenzaldehydes may undergo a rhodium-catalyzed hydroacylation, which, in combination with other transformations, could yield products with the triazene replaced by a variety of different functional groups (Scheme 4.5b).



Scheme 4.5 Our proposed traceless hydroacylation employing 2-triazenylbenzaldehydes

In addition, the versatility of the triazene group may provide us the possibility of further functionalizations, and subsequent access to multi-substituted phenyl ketones. For example, the hydroacylation adducts could undergo a triazene-directed, Rh^{III}-catalyzed *ortho* C-H olefination process; no selectivity issues are raised from this transformation, as one of the *ortho*-positions to the triazene is already occupied by the carbonyl moiety



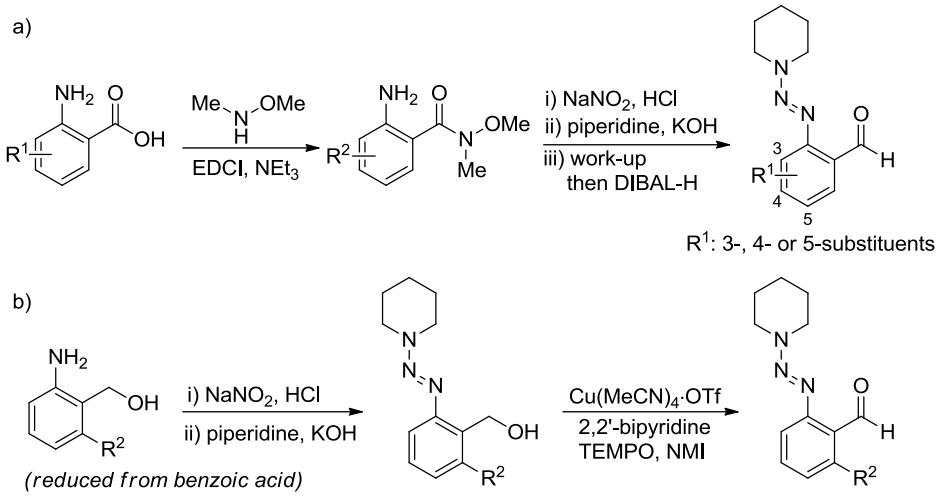
Scheme 4.6 Postulated transformations promoted by the triazene group

(Scheme 4.6a). Then, we may achieve a successful electrophilic aromatic substitution from the hydroacylation products, potentially under mild reaction conditions, due to the electron-donating property of the triazene moiety (Scheme 4.6b). Furthermore, the triazene unit could be removed or transformed into a variety of functional groups, thus adding diversity to the products obtained.

This project was performed in collaboration with a former postdoctoral fellow, Dr. Sangwon Seo and a visiting student, Eva K. Paffenholz. None of this work is yet published, and so the whole story is presented here for the understanding of the entire project. Their contributions are clearly stated where appropriate. Paffenholz performed the initial optimizations for hydroacylation;[94] Dr. Seo continued her optimization, and identified optimal conditions for triazene removal. Dr. Seo and I divided the work of preparing starting aldehydes and of examining the scope of the hydroacylation-triazene removal sequence. Dr. Seo studied the hydroacylation-*ortho* C-H olefination sequence while I explored the hydroacylation-electrophilic aromatic substitution sequence. In addition, I carried out reactions to transform the triazene unit and to synthesize multi-functionalized products.

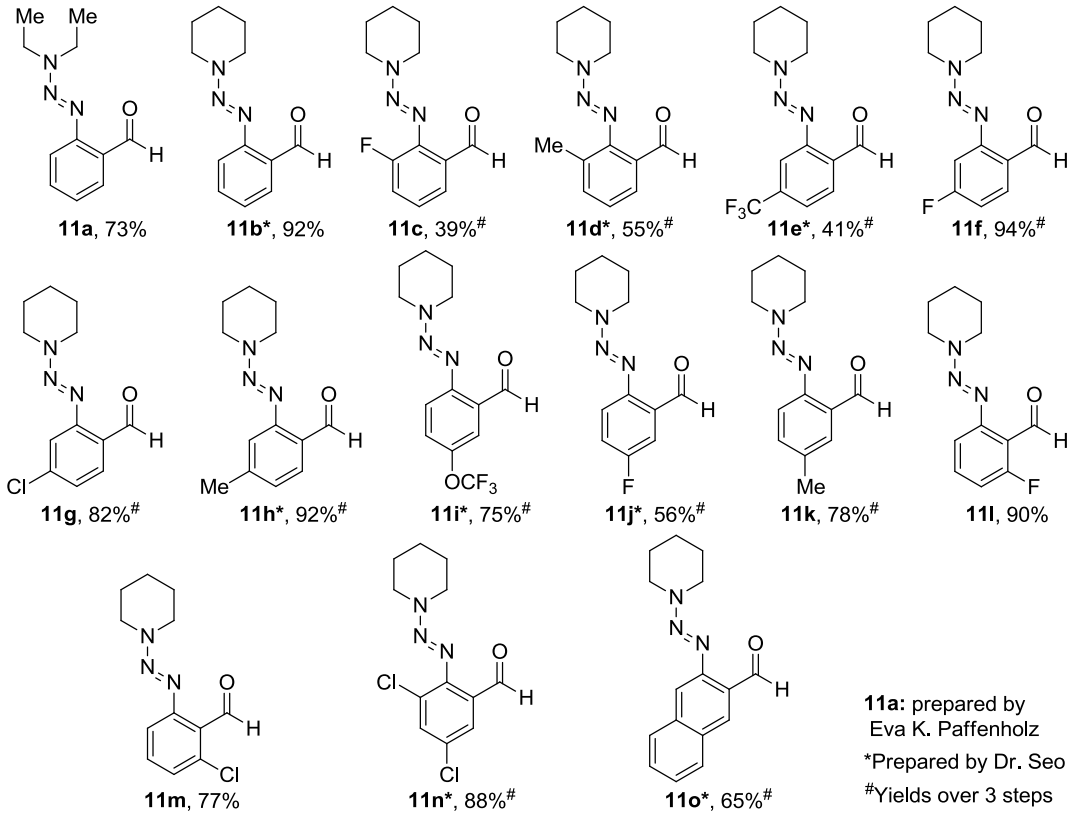
4.2 Preparation of 2-triazenylbenzaldehydes

In the literature, aryl triazenes have been synthesized by a one-pot procedure, starting from aniline derivatives.[95] To access triazenes with an *ortho*-formyl group, two sets of conditions were developed, starting from commercially available 2-aminobenzoic acids. For the synthesis of 2-triazenylbenzalehydes with 3-, 4- or 5-substituents, we utilized a



Scheme 4.7 Preparation of starting aldehydes

DIBAL-H reduction on a Weinreb amide as the key step (Scheme 4.7a). However, in the preparation of the 6-substituted variants, this reduction failed, possibly due to the steric hindrance from the 1-position; therefore a benzylic alcohol oxidation procedure reported by Stahl was employed instead (Scheme 4.7b).[96]



Scheme 4.8 List of triazene starting aldehydes

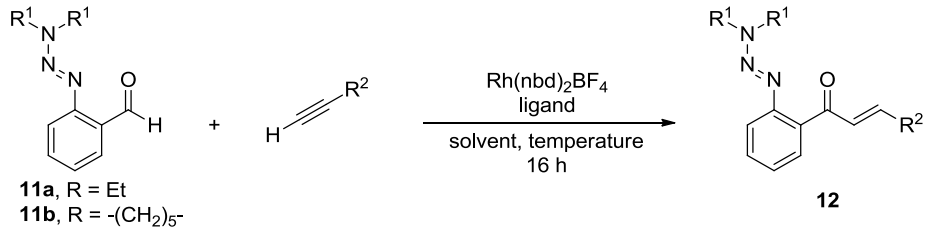
With these conditions in hand, a set of aldehydes was prepared in collaboration with Dr. Seo (Scheme 4.8). 2-Triazenylbenzaldehydes with substituents at all positions of the benzene ring were successfully obtained, including both electron-deficient and electron-rich examples (**11a-n**). In addition, an aldehyde with a naphthalene core was also synthesized (**11o**). Of these starting aldehydes, **11l** and **11m**, bearing a 6-substituent, were prepared using the method shown in Scheme 4.7b; the rest were synthesized following the procedure presented in Scheme 4.7a.

4.3 Optimization of the reaction conditions for hydroacylation

Having established robust methods for starting material synthesis, we then began our optimization for the hydroacylation of alkynes (Table 4.1, performed by Eva K. Paffenholz and Dr. Seo). Initially, the *N*,*N*-diethyl triazene **11a** was employed as the aldehyde component, together with 3.0 equivalents of 1-octyne as the coupling partner (entries 1-7); the active rhodium catalyst was generated *in situ* from commercially available $Rh(nbd)_2BF_4$ and a bisphosphine ligand. The use of 10 mol% of a dcpm or dppe derived catalyst, at a temperature of 55 ℃ in acetone, both led to the desired ketone product **12a** in moderate yields (entries 1, 2). Increasing the reaction temperature to 80 ℃ and switching the solvent to DCE did not affect the yield appreciably (entries 3, 4). Pleasingly, the reaction proceeded more efficiently at room temperature (entries 5, 6); with the Rh^I/dppe complex, **12a** was obtained in 89% isolated yield (entry 6). However, the yield dropped dramatically when a catalyst loading of 5 mol% was employed (entry 7). With the aim of lowering the catalyst loading from 10 mol% to 5 mol%, we evaluated another aldehyde bearing a different

triazene unit. To our delight, the hydroacylation using the piperidine variant, **11b**, with 5 mol% catalyst loading in acetone, afforded ketone **12b** in 85% yield as determined by ^{1}H NMR spectroscopy (entry 8). Notably, the amount of the alkyne coupling partner was reduced to 1.5 equivalents in this case. Furthermore, by employing CH_2Cl_2 as the solvent, ketone **11b** was isolated in 93% yield (entry 9). Two other alkynes, incorporating a sterically demanding *tert*-butyl group or a phenyl group, were also evaluated and both afforded the desired adducts in excellent yields (entries 10, 11).

Table 4.1 Optimization of hydroacylation using a triazene chelating group[a]



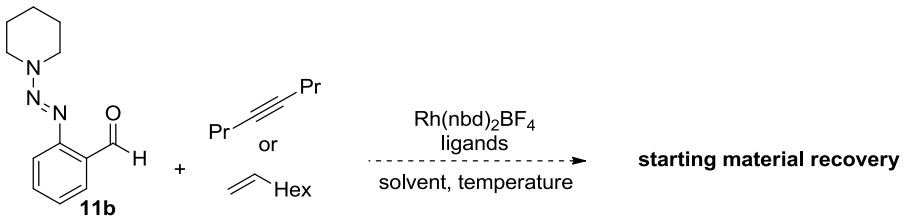
11a, R = Et
11b, R = -$(CH_2)_5$-

12

Entry	Aldehyde	R^2	Ligand (mol%)	Solvent	Temp. (°C)	Yield[b] (%)
1	**11a**	Hex	dcpm (10)	acetone	55	**12a**, 39
2	**11a**	Hex	dppe (10)	acetone	55	**12a**, 44
3	**11a**	Hex	dcpm (10)	DCE	80	**12a**, 43
4	**11a**	Hex	dppe (10)	DCE	80	**12a**, 33
5	**11a**	Hex	dcpm (10)	acetone	23	**12a**, 70
6	**11a**	Hex	dppe (10)	acetone	23	**12a**, 93 (89)
7	**11a**	Hex	dppe (5)	acetone	23	**12a**, 33
8[c]	**11b**	Hex	dppe (5)	acetone	23	**12b**, 85
9[c]	**11b**	Hex	dppe (5)	CH_2Cl_2	23	**12b**, 96 (93)
10[c]	**11b**	^{t}Bu	dppe (5)	CH_2Cl_2	23	**12c**, (97)
11[c]	**11b**	Ph	dppe (5)	CH_2Cl_2	23	**12d**, (89)

[a]Reaction conditions: **11** (1.0 equiv), alkyne (3.0 equiv), $Rh(nbd)_2BF_4$ (as indicated), ligand (as indicated), solvent (1.0 M); entries 1-7 performed by Eva K. Paffenholz, entries 8-11 by Dr. Seo. [b]Determined by ^{1}H NMR spectroscopy using nitromethane as an internal standard, yields in parentheses are isolated yields, l:b >50:1. [c]Alkyne (1.5 equiv).

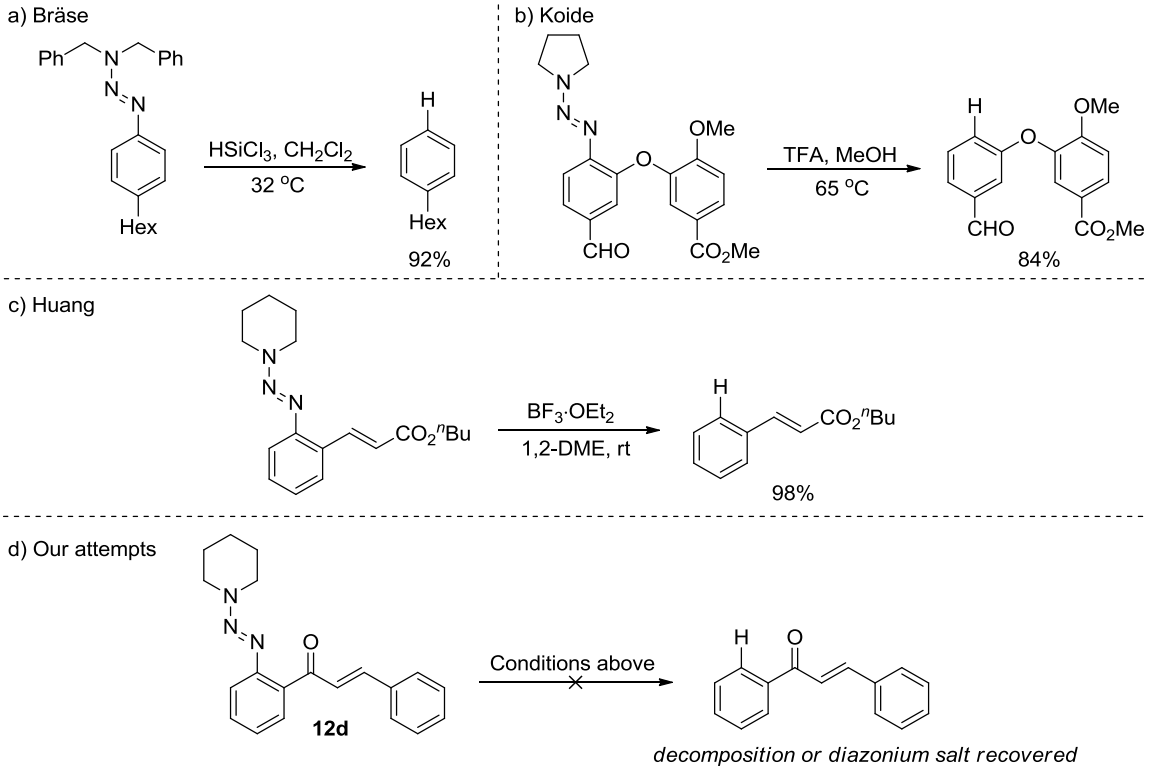
Unfortunately, the reaction did not proceed when employing internal alkynes, or alkenes; even with the use of different ligands and solvents at various temperatures, we only isolated the aldehyde starting material (Scheme 4.9).



Scheme 4.9 Limitation of the developed hydroacylation process

4.4 Optimization of the triazene removal

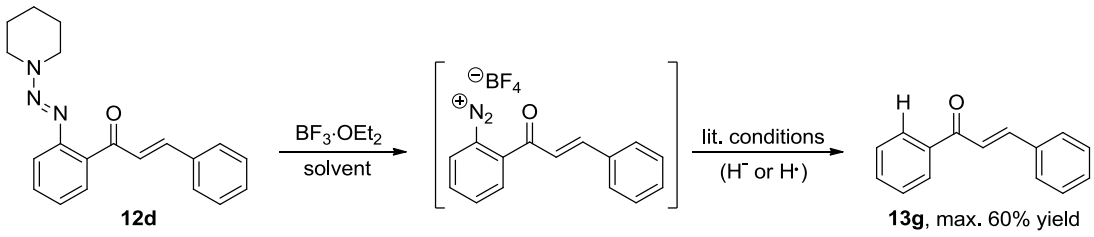
Replacement of the triazene unit by hydrogen atom is known in the literature under Lewis or Brønsted acid conditions (Scheme 4.10a-c).[97] However, when applying these conditions to our hydroacylation adduct **12d**, no desired product was observed (Scheme 4.10d);



Scheme 4.10 Removal of the triazene: literature examples and initial attempts

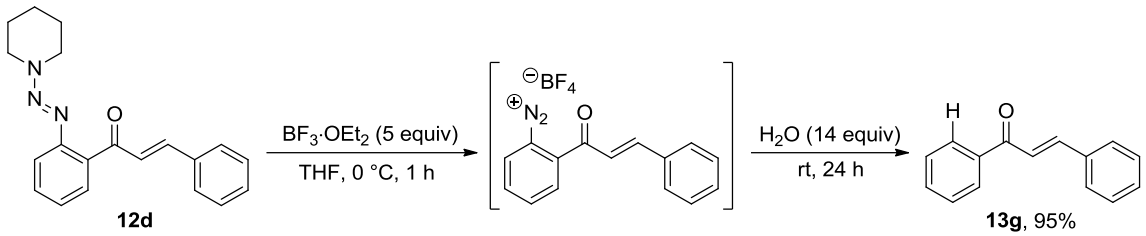
conditions a and b led to decomposition of the starting material; diazonium salt was obtained under conditions c. We reasoned that the failure may be due to the existence of a Michael acceptor in our molecule, which jeopardizes the hydrogen atom transfer to the desired position, which is essential for the removal of the triazene.[97b]

Dr. Seo then resorted to literature conditions that were used to reduce diazonium salts;[98] the diazonium salt was formed *in situ* from treatment of **12d** with a Lewis acid, $BF_3{\cdot}OEt_2$. A variety of additives, together with different solvents were evaluated. However, none of these conditions provided synthetically useful yields (Scheme 4.11).



Scheme 4.11 Further optimization of triazene removal

Finally, after further optimization, Dr. Seo discovered that by simply adding a small amount of H_2O after the formation of the diazonium salt in THF, full reduction of the triazene could be achieved, which gave product **13g** in 95% isolated yield (Scheme 4.12). It was crucial to employ THF as the solvent; other solvents, including 1,2-dimethoxyethane and 1,4-dioxane, under the same conditions, resulted in poor yields. We believe that this process proceeds *via* a radical mechanism,[97b] and the critical role of THF suggests that the hydrogen comes from this solvent. It is not fully understood why H_2O is needed, but it helps solubilize the otherwise insoluble diazonium salt. These optimized conditions were utilized for our further studies.

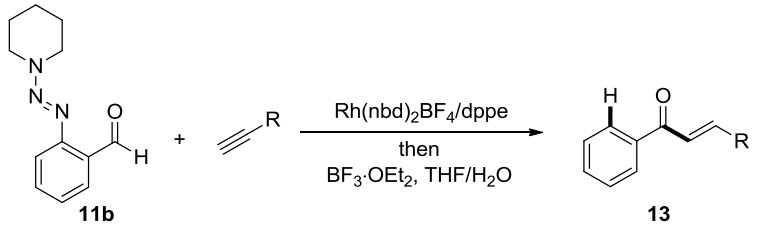


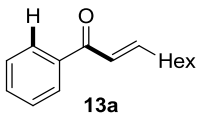
Scheme 4.12 The optimized conditions for triazene removal

4.5 Sequential hydroacylation-triazene removal

With both conditions for hydroacylation and triazene removal established, we then evaluated the possibility of combining them in a sequential procedure. First, a variety of different alkynes was assessed for this transformation, with aldehyde **11b** as the other coupling partner (Table 4.2). A simple filtration through SiO_2 between the hydroacylation and triazene removal steps helped to provide efficient reactions. Alkyl alkynes with different levels of steric demand were well tolerated, affording the desired ketone adducts in good to excellent yields (entries 1-5). Pleasingly, an enyne (entry 6), phenylacetylene (entry 7) and a ferrocene derived alkyne (entry 8) could also be successfully employed, demonstrating the functional group compatibility of our developed transformation.

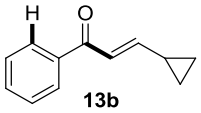
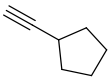
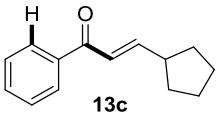
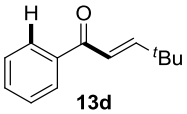
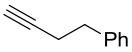
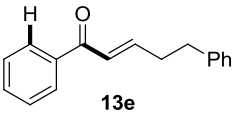
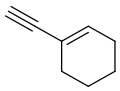
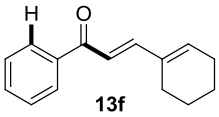
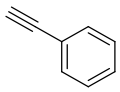
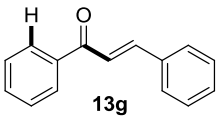
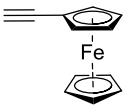
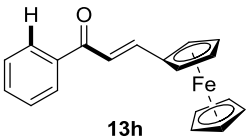
Table 4.2 Sequential hydroacylation-triazene removal: alkyne scope[a]



Entry	Alkyne	Product	Yield[b] (%)
1			86

continued on the next page

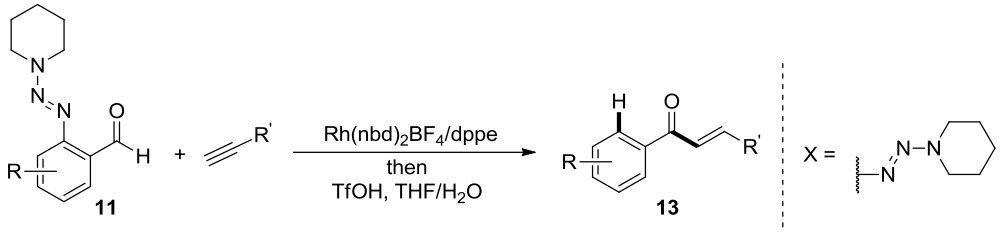
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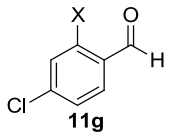
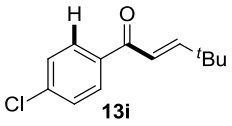
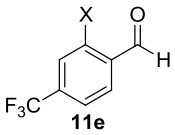
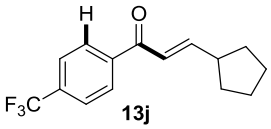
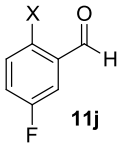
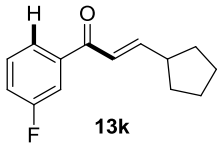
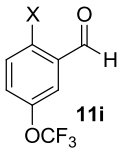
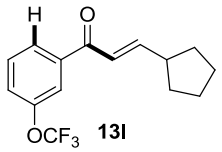
Entry	Alkyne	Product	Yield[b] (%)
2		 **13b**	64
3		 **13c**	85
4		 **13d**	91
5		 **13e**	70
6		 **13f**	80
7		 **13g**	83
8		 **13h**	52

[a]Reaction conditions: **11b** (1.0 equiv), alkyne (1.5 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dppe (5 mol%), CH_2Cl_2 (1.0 M), rt, 16 h, then SiO_2 filtration, $BF_3{\cdot}OEt_2$ (5-10 equiv), THF (0.05 M), 0 ℃, 1 h, then H_2O, rt, 24 h; performed by Dr. Seo. [b]Isolated yields.

We then set about examining the aldehyde scope (Table 4.3). $BF_3{\cdot}OEt_2$ was not effective for the formation of diazonium salts from aryl triazenes bearing strong electron-withdrawing substituents; therefore triflic acid was used instead, as it is acidic enough to protonate the piperidine nitrogen of the triazene moiety. Triazene aldehydes with chloro (entry 1), trifluoromethyl (entry 2), fluoro (entry 3) and trifluoromethoxy (entry 4) substituents at 4- or 5-positions were all shown to be efficient substrates for this transformation, providing the corresponding products in good yields.

Table 4.3 Sequential hydroacylation-triazene removal: aldehyde scope[a]

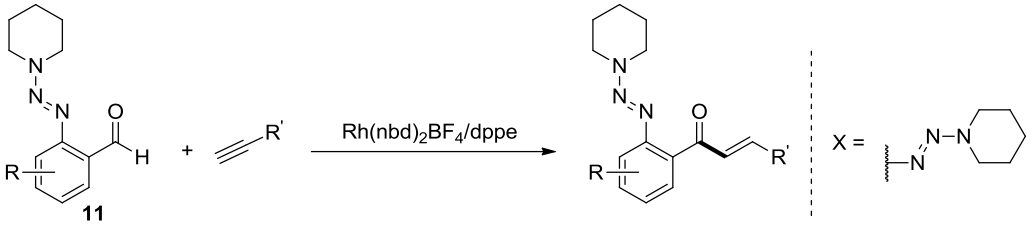


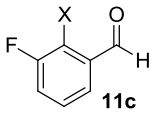
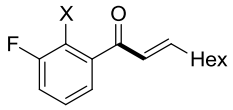
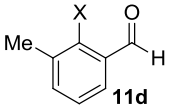
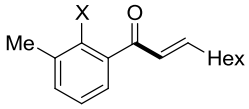
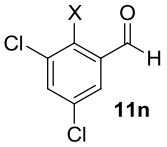
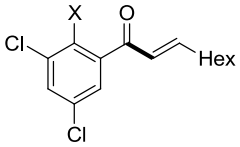
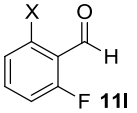
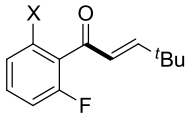
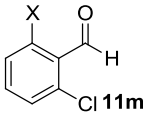
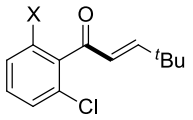
Entry	Aldehyde	Product	Yield[b] (%)
1	 **11g**	 **13i**	72
2	 **11e**	 **13j**	59
3	 **11j**	 **13k**	62
4	 **11i**	 **13l**	60

[a]Reaction conditions: **11** (1.0 equiv), alkyne (1.5 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dppe (5 mol%), CH_2Cl_2 (1.0 M), rt, 16 h, then SiO_2 filtration, TfOH (3.4 equiv), THF (0.05 M), 0 ℃, 1 h, then H_2O, rt, 24 h. [b]Isolated yields.

When employing 3- or 6-substituted 2-triazenylbenzaldehydes, the reaction proceeded dependently on the size of the substituents (Table 4.4). For example, increasing the steric bulk at 3-position gave rise to a decrease in yield, with 3-chloro substituent completely shutting down the reaction (entries 1-3). Likewise, 6-fluorobenzaldehyde **11l** was an effective substrate (entry 4), while the 6-chloro variant did not show any reactivity at all (entry 5).

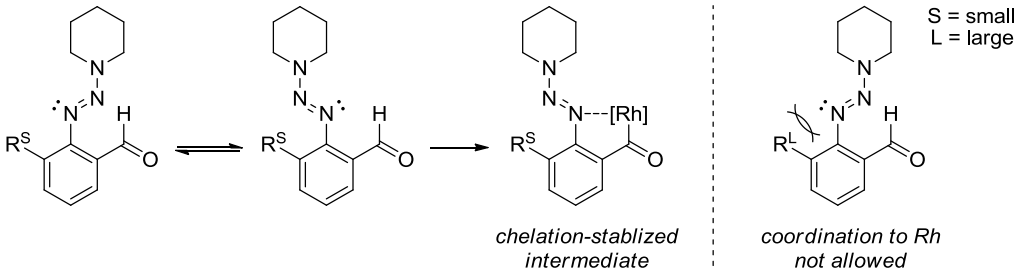
Table 4.4 Evaluation of aldehydes for hydroacylation[a]



Entry	Aldehyde	Alkyne	Product	Yield[b] (%)
1[c]	 **11c**			80
2[c]	 **11d**			4
3[c]	 **11n**			0
4	 **11l**			99
5	 **11m**			0

[a]Reaction conditions: **11** (1.0 equiv), alkyne (1.5 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dppe (5 mol%), CH_2Cl_2 (1.0 M), rt, 16 h. [b]Determined by ^1H NMR spectroscopy. [c]Performed by Dr. Seo.

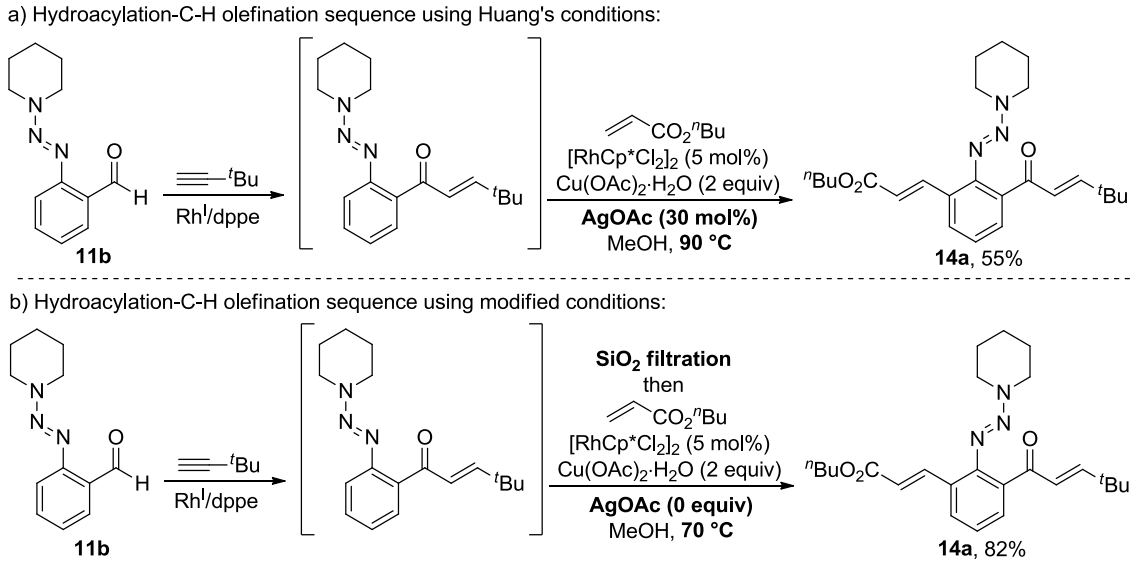
The trend in reactivity for 3-substituted aldehydes can be explained by the mode of coordination (Scheme 4.13). With a small substituent at 3-position, it is possible that the lone pair of electrons, of the coordinating nitrogen atom, points towards the acyl moiety and coordinates to the rhodium in subsequent reactions; however, if a large substituent exists, this lone pair of electrons is forced away, preventing the formation of the chelation-stabilized, 5-membered acyl rhodium species.



Scheme 4.13 Proposed chelation-mode for hydroacylation

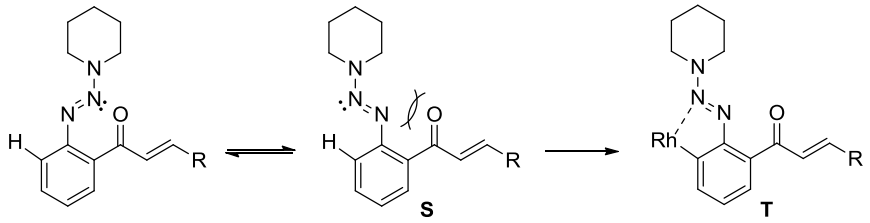
4.6 Sequential hydroacylation-*ortho* C-H olefination

We next directed our attention to the hydroacylation-*ortho* C-H olefination sequence (work performed by Dr. Seo). Using exactly the same conditions from Huang and co-workers (Scheme 4.3),[92] a 55% isolated yield of **14a** was achieved for the sequential process starting from aldehyde **11b** (Scheme 4.14a). On further optimization, it was realized that a simple filtration through SiO_2 was essential for good conversion; this may be due to removal of the initial Rh^I catalyst. The reaction proceeded efficiently in the absence of AgOAc at a lower temperature, affording desired adduct **14a** in 82% yield (Scheme 4.14b).



Scheme 4.14 Optimization of the *ortho* C-H olefination process

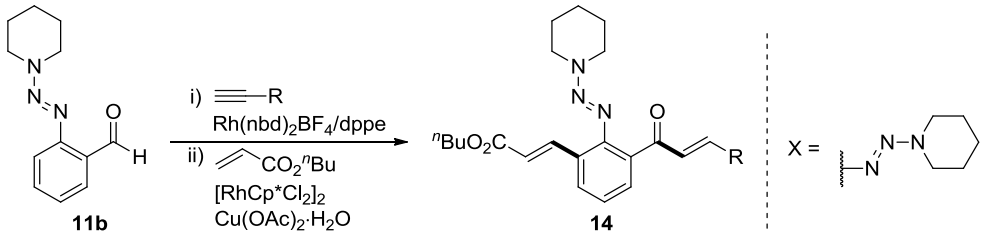
The milder reaction conditions required for this C-H olefination process may stem from the presence of a carbonyl group *ortho* to the triazene (Scheme 4.15). Steric repulsion from the existing *ortho*-substituent forces the triazene group to adopt a configuration (**S**) that is required for coordination (**T**), and therefore lowers the reaction temperature.

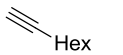
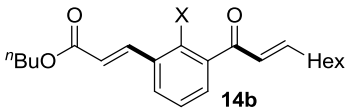
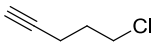
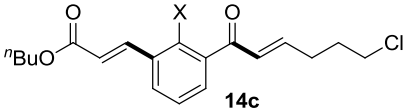
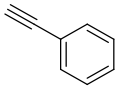
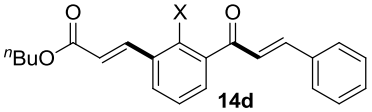
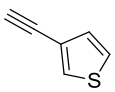
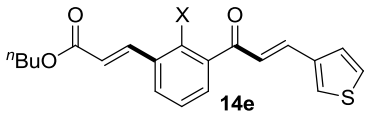


Scheme 4.15 Coordination in the C-H olefination process

Having established the optimal reaction conditions, Dr. Seo then examined the scope for this three-component sequence. For the variation of the alkyne components (Table 4.5),

Table 4.5 Sequential hydroacylation-*ortho* C-H olefination: alkyne scope[a]

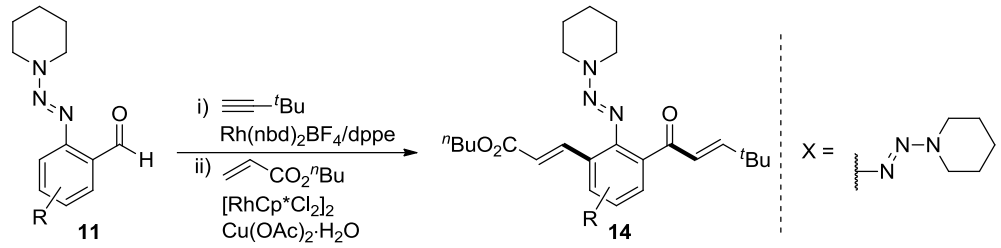


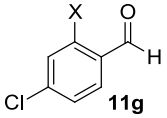
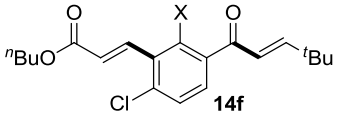
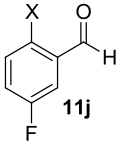
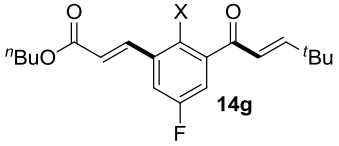
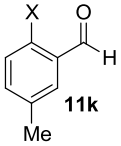
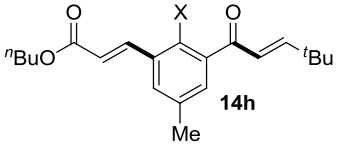
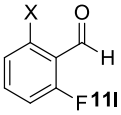
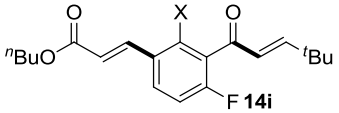
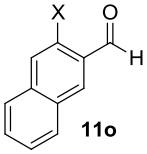
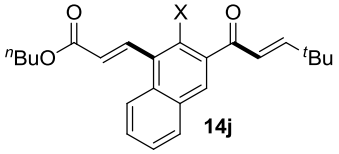
Entry	Alkyne	Product	Yield[b] (%)
1		 **14b**	74
2		 **14c**	73
3		 **14d**	81
4		 **14e**	56

[a]Reaction conditions: i) **11b** (1.0 equiv), alkyne (1.5 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dppe (5 mol%), CH_2Cl_2 (1.0 M), rt, 16 h, then SiO_2 filtration, ii) butyl acrylate (2.5 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv), MeOH (0.15 M), 70 ℃, 6-16 h; performed by Dr. Seo. [b]Isolated yields.

aldehyde **11b** and butyl acrylate were held constant. Alkynes bearing an alkyl chain (entry 1) or an alkyl chloride (entry 2) were both efficient substrates, yielding desired products **14b** and **14c** in 74% and 73% yields, respectively. Pleasingly, it was also possible to employ phenylacetylene (entry 3) and a thiophene derived alkyne (entry 4) for this transformation.

Table 4.6 Sequential hydroacylation-*ortho* C-H olefination: aldehyde scope[a]



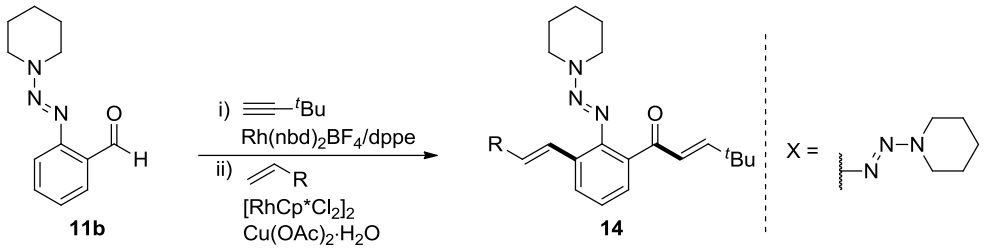
Entry	Aldehyde	Product	Yield[b] (%)
1	 **11g**	 **14f**	57
2	 **11j**	 **14g**	62
3	 **11k**	 **14h**	79
4	 **11l**	 **14i**	89 (1.2 g scale)
5	 **11o**	 **14j**	49

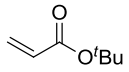
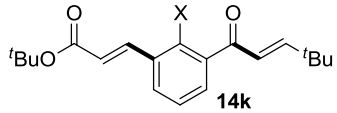
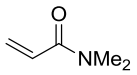
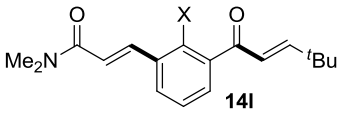
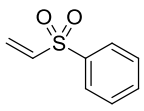
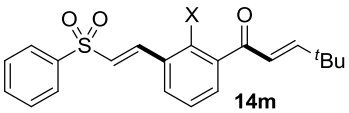
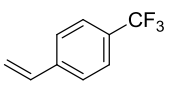
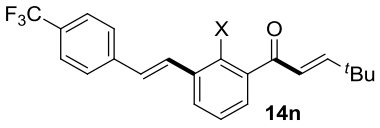
[a]Reaction conditions: i) **11** (1.0 equiv), alkyne (1.5 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dppe (5 mol%), CH_2Cl_2 (1.0 M), rt, 16 h, then SiO_2 filtration, ii) butyl acrylate (2.5 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), $Cu(OAc)_2·H_2O$ (2 equiv), MeOH (0.15 M), 70 ℃, 6-16 h; entries 1-3, 5 performed by Dr. Seo. [b]Isolated yields.

Next, a set of different aldehydes was evaluated for this reaction in combination with *tert*-butylacetylene and butyl acrylate (Table 4.6). 2-Triazenylbenzaldehydes with substituents at 4- (entry 1), 5- (entries 2, 3), or 6- (entry 4) positions were all successfully employed, giving tetrasubstituted benzenes in good to excellent yields. Notably, a large scale reaction was carried out; starting with 3.0 mmol of aldehyde **11l**, 1.2 grams of enone **14i** could be obtained in 89% yield (entry 4). In addition, a naphthaldehyde **11o** was shown to be a good substrate for this transformation (entry 5).

The scope with respect to the alkene components was the last Dr. Seo examined (Table 4.7). First, it was possible to employ *tert*-butyl acrylate for this reaction (entry 1),

Table 4.7 Sequential hydroacylation-*ortho* C-H olefination: alkene scope[a]

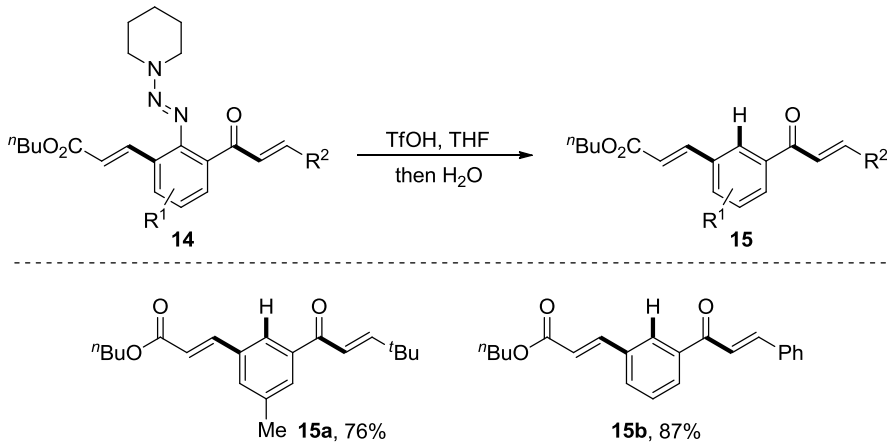


Entry	Alkene	Product	Yield[b] (%)
1		 **14k**	77
2		 **14l**	61
3		 **14m**	68
4		 **14n**	58

[a]Reaction conditions: i) **11b** (1.0 equiv), alkyne (1.5 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dppe (5 mol%), CH_2Cl_2 (1.0 M), rt, 16 h, then SiO_2 filtration, ii) alkene (2.5 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), $Cu(OAc)_2·H_2O$ (2 equiv), MeOH (0.15 M), 70 ℃, 6-16 h; performed by Dr. Seo. [b]Isolated yields.

which has been described in Huang's report.[92] Moreover, electron-deficient olefins absent from Huang's study were also excellent substrates, including an acrylamide (entry 2), a phenyl sulfone (entry 3) and a substituted styrene (entry 4); the corresponding adducts were obtained in good yields over the two-step sequence.

We have successfully expanded the three reaction components for our developed hydroacylation-*ortho* C-H olefination sequence, leading to highly-substituted aromatic compounds in an efficient manner. As before, the triazene group could be subsequently removed, employing our previously described method, to afford *meta*-substituted phenyl ketones in good yields (Scheme 4.16).



Scheme 4.16 Removal of the triazene group

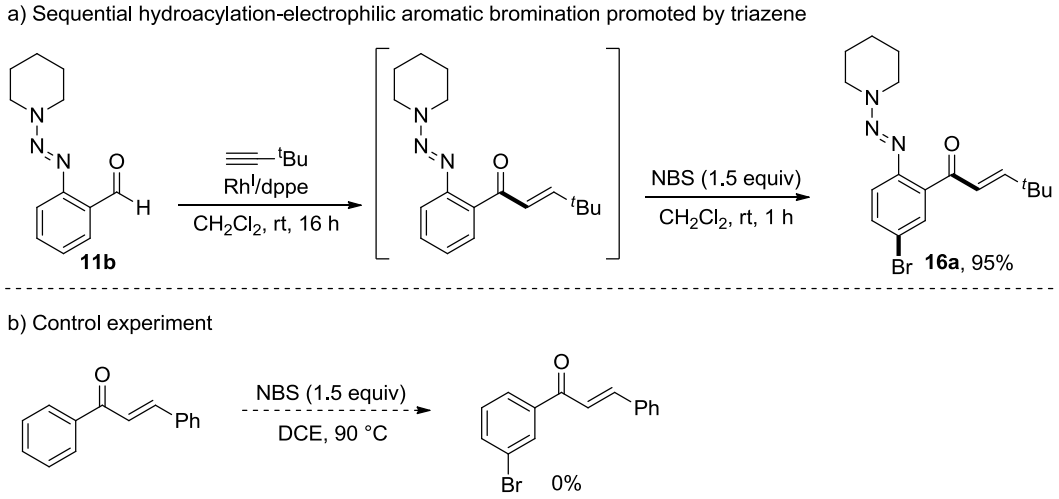
4.7 Exploring electrophilic aromatic substitution reactions with aryl triazenes

4.7.1 Electrophilic aromatic bromination

Having utilized the triazene unit as a bifunctional directing group in metal-catalyzed C-H activation processes, we then directed our attention to its potential application in electrophilic aromatic substitution reactions. Electrophilic aromatic substitution reactions

represent a straightforward approach to introduce functionalities to electron-rich aromatic compounds.[99] We envisaged that the electron-donating nature of the triazene unit should allow simple installation of electrophiles into the benzene core, which would give access to diversely functionalized products.

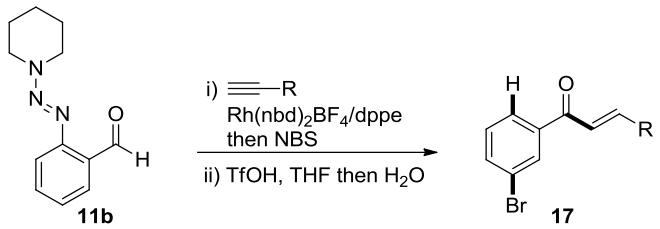
Initially, bromination was of particular interest due to the versatility of aryl bromides. Although modern metal-catalyzed C-H bromination processes have been developed,[100] the direct electrophilic aromatic bromination remains a simple and straightforward tool.[101] This protocol, typically employing an electrophilic bromine source such as NBS, can proceed under mild conditions without metal catalysis. However, forcing conditions are required when utilizing electron-poor aromatic compounds, which restricts the incorporation of sensitive functional groups. In this context, we postulated that the triazene group could be explored as an electron donor, which would promote electrophilic bromination under mild reaction conditions. We also aimed to combine this transformation with an initial hydroacylation to access highly substituted ketone adducts.

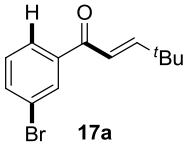
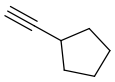
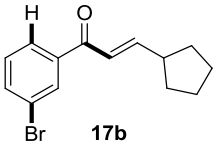
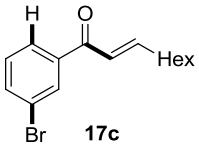
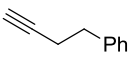
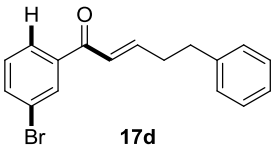
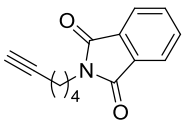
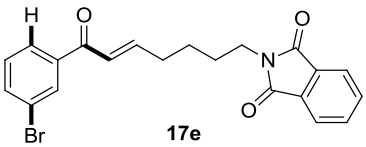


Scheme 4.17 Triazene-promoted electrophilic aromatic bromination

To our delight, it was found that one-pot addition of NBS following a successful hydroacylation reaction resulted in the desired *para*-selective bromination product **16a** in 95% yield over two steps (Scheme 4.17a); the regioselectivity was confirmed by ^{1}H NMR spectroscopy. A control experiment, in which treating chalcone with NBS led to no brominated product, proved the critical role of the triazene unit for this process (Scheme 4.17b).

Table 4.8 Sequential hydroacylation-bromination-triazene removal: alkyne scope[a]



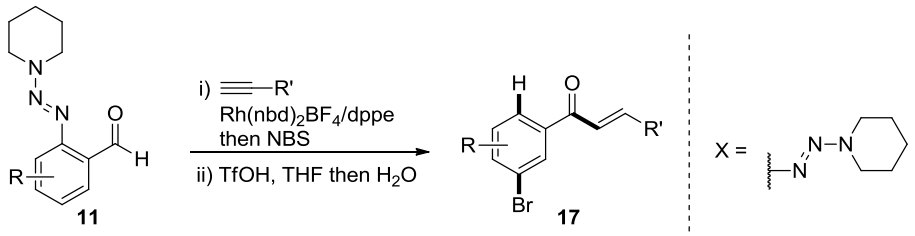
Entry	Alkyne	Product	Yield[b] (%)
1		 **17a**	i: 95, ii: 80; sequential: 77
2		 **17b**	i: 87, ii: 77; sequential: 61
3		 **17c**	sequential: 65
4		 **17d**	sequential: 51
5		 **17e**	i: 79, ii: 65; sequential: 50

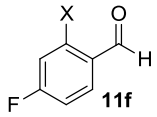
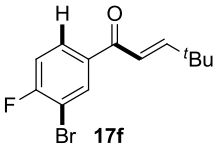
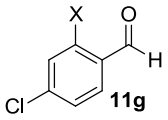
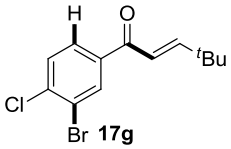
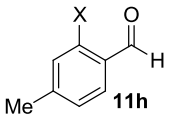
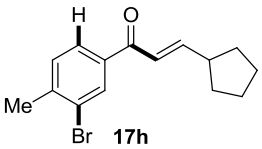
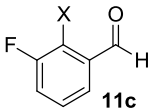
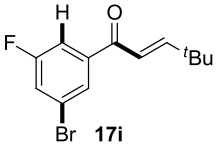
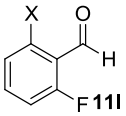
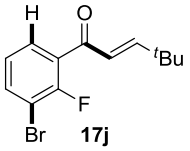
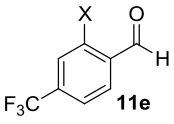
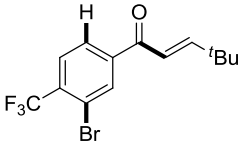
[a]Reaction conditions: i) **11b** (1.0 equiv), alkyne (1.5 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dppe (5 mol%), CH_2Cl_2 (1.0 M), rt, 16 h, then NBS (1.5 equiv), CH_2Cl_2 (0.2 M), rt, 1 h, then SiO_2 filtration, ii) TfOH (3.4 equiv), THF (0.05 M), 0 ℃, 1 h, then H_2O, rt, 24 h. [b]Isolated yields.

With the conditions for electrophilic aromatic bromination identified, we began our evaluation of different reaction components; triazene removal was also incorporated into this sequential procedure to deliver directing group-free products. The scope with respect to the alkyne component was first examined (Table 4.8), with aldehyde **11b** held constant. Steps i and ii could be performed separately, or could be combined in sequence. As shown in the table, alkyl alkynes possessing different levels of steric demand were all tolerated in this reaction, affording the final products in generally good yields (entries 1-3). Pleasingly, alkynes containing aromatic functionalities could also be employed, including a phenyl group and a phthalimide; and the bromination only took place at the benzene core bearing a triazene unit (entries 4, 5).

Next, we assessed a series of aldehydes for this sequence (Table 4.9). Aldehydes with 4-substituents, be they electron-withdrawing or electron-donating, were shown to be efficient substrates, affording 5-brominated products in good yields (entries 1-3). 3-Fluoro-substituted aldehyde **11c** was also successfully employed in the hydroacylation-aromatic bromination sequence, however, with a much lower efficiency in the subsequent triazene removal (entry 4). The introduction of a fluoride at the 6-position required elevated reaction temperature for electrophilic bromination, and an inseparable mixture of 5- and 3-brominated products were isolated in a 5:1 ratio; the single isomer could be obtained after triazene removal (entry 5). Finally, a strong electron-withdrawing trifluoromethyl group completely shut down the electrophilic aromatic substitution (entry 6).

Table 4.9 Sequential hydroacylation-bromination-triazene removal: aldehyde scope[a]

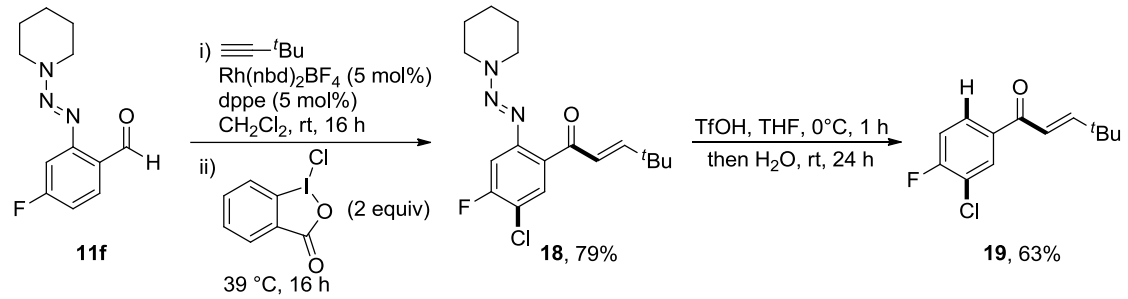


Entry	Aldehyde	Product	Yield[b] (%)
1	 **11f**	 **17f**	i: 92, ii: 82; sequential: 73
2	 **11g**	 **17g**	i: 90, ii: 79; sequential: 71
3	 **11h**	 **17h**	i: 81, ii: 70; sequential: 53
4[c]	 **11c**	 **17i**	i: 80, ii: 26
5[d]	 **11l**	 **17j**	i: 86, ii: 81
6	 **11e**		i: 0

[a]Reaction conditions: i) **11** (1.0 equiv), alkyne (1.5 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dppe (5 mol%), CH_2Cl_2 (1.0 M), rt, 16 h, then NBS (1.5 equiv), CH_2Cl_2 (0.2 M), rt, 1 h, then SiO_2 filtration, ii) TfOH (3.4 equiv), THF (0.05 M), 0 ℃, 1 h, then H_2O, rt, 24 h.. [b]Isolated yields. [c]Bromination at 39 ℃. [d]Bromination at 35 ℃, an inseparable 5:1 mixture of regioisomers isolated for step i, single isomer isolated for step ii.

4.7.2 Other electrophiles

Recently, Xue and co-workers described a simple and efficient electrophilic aromatic chlorination process, employing a hypervalent iodine reagent, 1-chloro-1,2-benziodoxol-3-one.[102] Pleasingly, this reagent could promote the chlorination of our hydroacylation adduct in the presence of a triazene unit; one-pot addition of this reagent to the hydroacylation reaction mixture, followed by stirring at 39 ℃ for 16 h, afforded the 5-chlorinated product **18** in 79% isolated yield over 2 steps. Subsequent removal of the triazene gave the directing group-free enone **19** (Scheme 4.18).

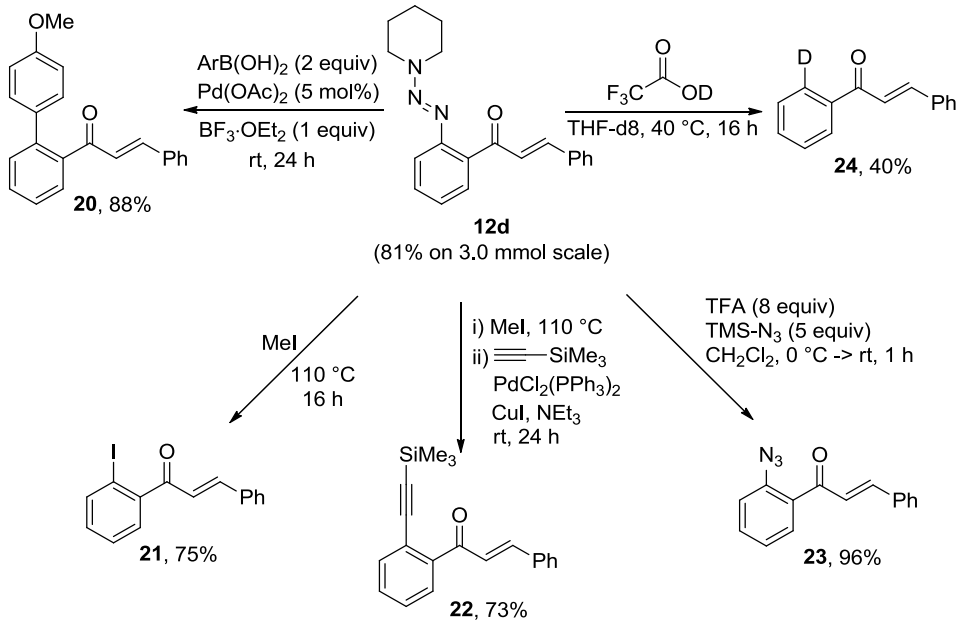


Scheme 4.18 Triazene-promoted electrophilic aromatic chlorination

We have explored a variety of other electrophiles in combination with the hydroacylation adduct, including F^+,[103] I^+,[104] NO_2^+,[105] F_3CS^+,[106] $PhSe^+$,[107] NCS^+,[108] F_3C^+,[109] and Friedel-Crafts[110] or Mannich[111] type reagents. In general, under these conditions, sometimes in the presence of a Lewis acid, a lack of reactivity was observed at low temperatures and decomposition of starting materials was detected at elevated temperatures.

4.8 Transformations of the triazene group

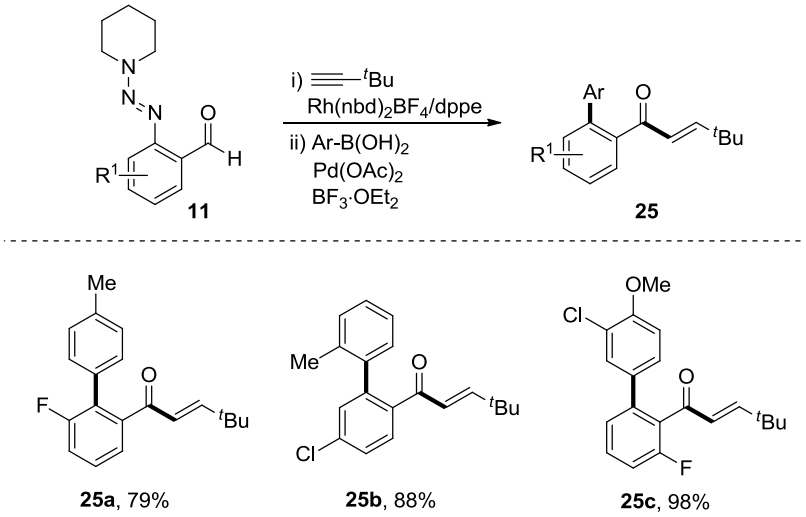
With our success in utilizing 2-triazenylbenzaldehydes for several sequential reactions, as was discussed above, we next investigated the transformations that the triazene unit could undergo (Scheme 4.19). The hydroacylation adduct **12d** could be prepared on a 3.0 mmol scale, which was then subjected to various reaction conditions. A palladium-catalyzed, phosphine free, Suzuki-type coupling with an aryl boronic acid in the presence of $BF_3{\cdot}OEt_2$ gave the arylated product **20** in 88% yield.[112] Treatment with methyl iodide resulted in the corresponding 2-iodophenyl ketone **21**, which could be subsequently employed in a Pd-catalyzed Sonogashira coupling to afford alkynylated product **22**.[112] Moreover, azide **23** could be synthesized by reacting **12d** with TFA and TMS-N_3.[113] Finally, it was possible to replace the triazene with deuterium (**24**), by utilizing deuterated TFA in deuterated THF.[114]



Scheme 4.19 Transformations of the triazene group

Palladium-catalyzed Suzuki coupling has emerged as a powerful tool to construct C-C bonds.[115] In this context, we decided to further explore the Suzuki-type coupling using the

aryltriazenes obtained from our developed hydroacylation method. Pleasingly, this coupling was successfully combined in sequence with a Rh-catalyzed hydroacylation (Scheme 4.20). Aryl boronic acids with substituents at different positions of the benzene ring were successfully employed together with three different aldehydes, which resulted in an efficient double C-C bond formation. It is noticeable that in products **25b** and **25c**, the arylchloride remained intact in this transformation, possibly due to the low temperature and phosphine-free conditions.



Reaction conditions: i) **11** (1.0 equiv), alkyne (1.5 equiv), $Rh(nbd)_2BF_4$ (5 mol%), dppe (5 mol%), CH_2Cl_2 (1.0 M), rt, 16 h; then SiO_2 filtration, ii) boronic acid (2.0 equiv), $Pd(OAc)_2$ (5 mol%), $BF_3{\cdot}OEt_2$ (2.0 equiv), 1,4-dioxane (0.1 M), rt, 24 h.

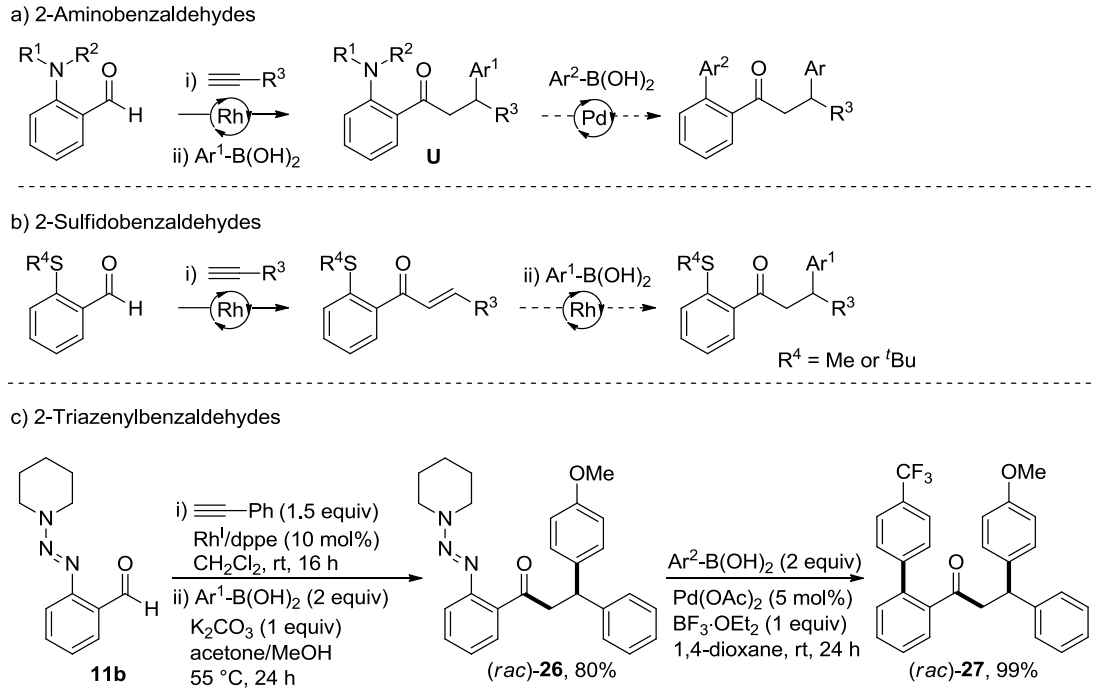
Scheme 4.20 Sequential hydroacylation-Suzuki coupling

4.9 Synthetic utility of the developed methodology

4.9.1 Hydroacylation-boronic acid conjugate addition sequence

According to previous studies in the Willis group, 2-aminobenzaldehydes could undergo a hydroacylation-boronic acid conjugate addition sequence to afford **U**, which, however,

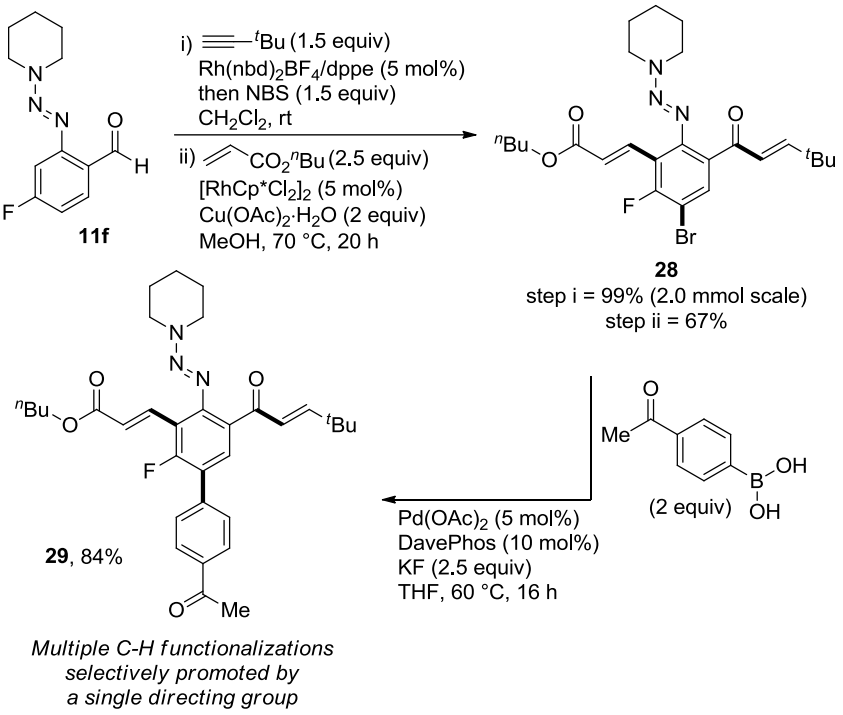
would not serve as pseudo halides to react further with aryl boronic acids under palladium catalysis (Scheme 4.21a).[71] On the other hand, although 2-sulfidobenzaldehydes are efficient substrates for chelation-controlled hydroacylation, and the resulting 2-sulfidophenyl ketones could potentially be employed in subsequent Suzuki-type coupling,[64] they were not successful in the 1,4-addition step (Scheme 4.21b). Pleasingly, with our newly-developed 2-triazenylbenzaldehydes, this sequence became possible. Aldehyde **11b** first underwent an alkyne hydroacylaton-boronic acid conjugate addition sequence using a single Rh^I/dppe catalyst, yielding product **26** in 80% yield over two steps; enantioselective variation could potentially be achieved using a chiral ligand for the conjugate addition step. Product **26** was then subjected to Suzuki conditions, resulting in the formation of **27** in 99% yield (Scheme 4.21c). The orthogonal reactivities under two different catalytic systems allowed the controlled installation of different aromatic functional groups selectively at different positions.



Scheme 4.21 Sequential hydroacylation-conjugate addition and subsequent Suzuki coupling

4.9.2 Synthesis of pentasubstituted benzene

Finally, to illustrate the synthetic utility, we combined all the developed transformations to access a multi-functionalized phenyl ketone (Scheme 4.22). Alkyne hydroacylation, *para*-bromination and *ortho*-olefination could be incorporated together, on a 2.0 mmol scale, to achieve three C-H functionalizations, which were selectively promoted by a single directing group and afforded highly substituted product **28**. This product, bearing an aryl bromide, could undergo a Pd-catalyzed Suzuki-type coupling, resulting in arylated product **29** without affecting either the enone or triazene units.



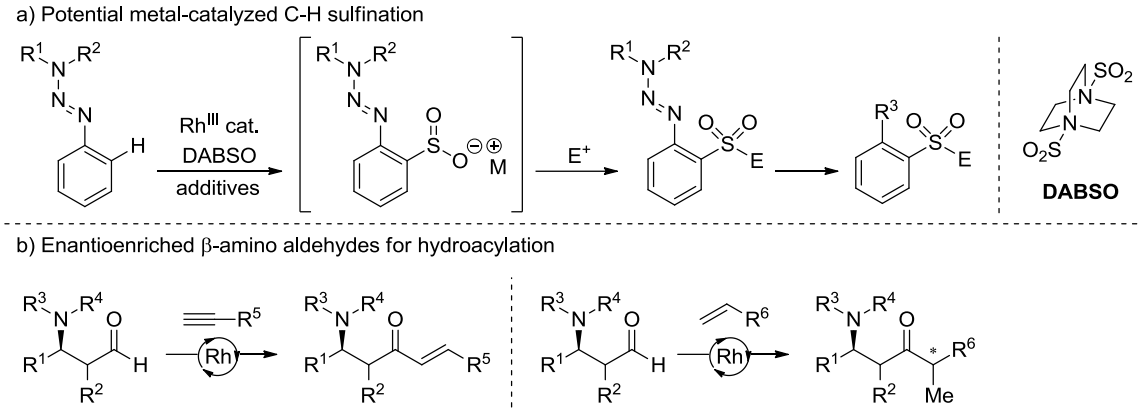
Scheme 4.22 Synthesis of a pentasubstituted benzene

4.10 Summary and outlook

In conclusion, a novel coordinating unit for chelation-controlled hydroacylation reactions has been developed, based on the use of a triazene group. This tether has not only allowed

an alkyne hydroacylation to proceed at room temperature, but also promoted subsequent *ortho* C-H olefination and electrophilic aromatic substitution reactions. Moreover, we were able to transform this chelating unit to a variety of functional groups, leading to directing group-free products.

This chemistry demonstrates the concept of one single directing group assisting three mechanistically distinctive C-H functionalizations, which enhances efficiency in organic synthesis. Future work may include the exploration of further triazene-promoted transformations, and the combination of them to deliver synthetically useful building blocks. For example, we could explore a metal-catalyzed C-H sulfination process employing an SO_2 surrogate, DABSO.[116] Subsequent transformations of the triazene unit could provide diversely *ortho*-substituted phenyl sulfonyl derivatives (Scheme 4.23a).



Scheme 4.23 Potential future work

In addition, given our success in utilizing alkyl *S*-chelating aldehydes for hydroacylation (Chapters 2, 3), and in employing aryl *N*-chelating aldehydes (this chapter), we could exploit *alkyl* aldehydes bearing an *N*-chelating unit for hydroacylation reactions. For instance, enantioenriched β-amino aldehydes may undergo an alkyne hydroacylation under mild reaction conditions; it may also be combined with an alkene to give branched-

selective hydroacylation adducts bearing a new stereogenic center, in which the regio- and enantioselectivities could be tuned by either the substrate or the catalyst (Scheme 4.23b).

Chapter 5

Experimental section

5.1 General considerations

Reagents were purchased from Sigma-Aldrich Co. LLC., Fisher Scientific UK Ltd., Fluorochem Ltd., Tokyo Chemical Industry UK Ltd. or Strem Chemicals Inc. and were used as supplied unless otherwise stated. Alkenes and alkynes were distilled and stored at −20 ℃. Acetone was distilled over Drierite® under N_2 and degassed by bubbling a flow of N_2 gas for 30 min; 1,2-dichloroethane was distilled over CaH_2 under N_2 and degassed by bubbling a flow of N_2 gas for 30 min. The other solvents were collected fresh from an in-house solvent purification system, which involves passing the solvent through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Glassware was oven-dried (100 ℃), and allowed to cool to room temperature under vacuum once assembled. Cooling to 0 ℃ was achieved using ice-water bath; cooling to −20 ℃ was achieved using dry ice-acetone bath. Microwave conditions were achieved using a CEM Discover-S microwave synthesizer. Reactions were monitored by thin layer chromatography (TLC) using pre-coated aluminum-backed silica plates (Merck Kieselgel

60 F254); plates were visualized under ultraviolet light (254 nm) followed by staining with $KMnO_4$. Flash column chromatography was carried out using Geduran® Si 60, 40-63 micron silica gel; the compound to be purified was either loaded as oil or pre-absorbed onto silica. Pressure was applied to the column head by hand bellows. Petrol refers to the fraction of light petroleum ether boiling in the range 40-60 ℃. Rhodium complexes, $[Rh(L)Cl]_2$, were prepared using literature methods,[71, 75-76, 79] weighed under air and stored under N_2. 1,1-Dicyclohexyl-*N*-(dicyclohexylphosphino)-*N*-methylphosphinamine (PNP(Cy)) was synthesized by another Willis group member according to a reported procedure and was weighed under air and stored in a Schlenk tube under N_2 after use.[45b] Diastereomeric ratios (dr) were determined by ^{1}H NMR spectroscopy analysis on the crude mixture.

^{1}H NMR spectra were obtained on a Brüker AVIII400 (400 MHz) spectrometer using the residual solvent as an internal standard. ^{13}C NMR spectra were obtained on a Brüker AVIII400 (101 MHz) spectrometer using the residual solvent as an internal standard. ^{19}F NMR spectra were obtained on a Brüker AVIII400 (377 MHz) spectrometer using the ^{1}H decoupling method. Acquisitions were carried out at room temperature. Chemical shifts (δ) are reported in parts per million (ppm) from the residual solvent peak and coupling constants (*J*) were given in Hertz (Hz) and rounded to the nearest 0.5 Hz. Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), quintet (p), multiplet (m), broad (br.), and apparent (app.).

Low resolution ESI mass spectra were recorded on a Waters LCT Premier spectrometer. High resolution mass spectra were recorded either on a Brüker MicroTOF spectrometer under electrospray ionization conditions (ESI) or on a Waters LCT Premier spectrometer

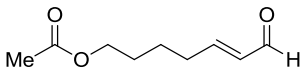
under the conditions of chemical ionization (CI) by the internal service at Chemistry Research Laboratory, University of Oxford. Samples for mass spectra were prepared as 1 mg/mL solution in MeOH (LRMS, HRMS-ESI) or submitted neat (HRMS-CI). Values quoted are a ratio of mass to charge in Daltons and relative intensities of peaks observed are quoted as a percentage. High resolution values are calculated to four decimal places from the molecular formula, all found within a tolerance of five ppm.

Infrared spectra were recorded as thin films ($CHCl_3$) on a Brüker Tensor 27 FT-IR spectrometer. Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1. Optical rotations were measured on a Schmidt Haensch UniPol L2000 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC in a Dionex P680 chromatograph with a Dionex UVD170U detector (Daicel Chiralpak AD-H, AS-H, IC, IA-3, ID-3, OD-H, AY-H columns).

5.2 Data for Chapter 2

5.2.1 Synthesis of starting materials

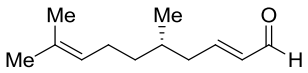
(*E*)-7-Oxohept-5-en-1-yl acetate, SM1



A 50 mL round-bottom flask charged with Hoveyda-Grubbs Catalyst 2nd Generation (47 mg, 0.075 mmol) (weighed with minimal light) was evacuated and back-filled with N_2 gas. Degassed CH_2Cl_2 (10 mL), 5-hexenyl acetate (0.24 mL, 1.5 mmol) and distilled acrolein (0.30 mL, 4.5 mmol) were added to the flask and the resulting solution was stirred at 23 ℃ for 20 h. The reaction mixture was filtered through a pad of Celite® and

concentrated under reduced pressure. Purification by flash column chromatography (gradient petrol/EtOAc, 9:1 to 7:3) afforded *the title compound* (234 mg, 92% yield) as a pale yellow oil. **δ_H** (400 MHz, $CDCl_3$): 9.48 (d, *J* = 8.0 Hz, 1H, C*H*O), 6.82 (dt, *J* = 15.5, 6.5 Hz, 1H, C*H*=CH-CO), 6.10 (ddt, *J* = 15.5, 8.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.05 (t, *J* = 6.5 Hz, 2H, CO_2-CH_2), 2.39-2.32 (m, 2H, CH_2-CH=CH), 2.02 (s, 3H, CH_3-CO), 1.70-1.61 (m, 2H, CO_2-CH_2-CH_2), 1.61-1.52 (m, 2H, CH_2-CH_2-CH=CH); **δ_C** (101 MHz, $CDCl_3$): 194.0, 171.2, 157.9, 133.3, 64.0, 32.3, 28.2, 24.3, 21.0; **HRMS** (ESI^+) $C_9H_{14}O_3Na$ requires 193.0835 $[M+Na]^+$, found 193.0836; **ν_{max}** (film)/cm^{-1} 2944, 2867, 2740, 1734, 1687, 1638, 1458, 1436, 1388, 1366, 1235, 1137, 1039.

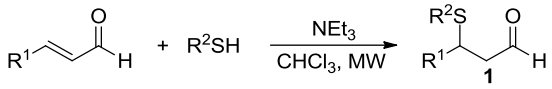
(*S*,*E*)-5,9-Dimethyldeca-2,8-dienal, SM2



A solution of (triphenylphosphoranylidene)acetaldehyde (2.74 g, 9.0 mmol) and (*S*)-(−)-citronellal (1.1 mL, 6.0 mmol) in $CHCl_3$ (3.3 mL) was refluxed with a condenser at 62 ℃ for 60 h and then concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (0.54 g, 50% yield, 97% ee) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 9.49 (d, *J* = 8.0 Hz, 1H, C*H*O), 6.81 (dt, *J* = 15.5, 7.5 Hz, 1H, C*H*=CH-CO), 6.09 (ddt, *J* = 15.5, 8.0, 1.5 Hz, 1H, CH=C*H*-CO), 5.09-5.03 (m, 1H, C*H*=C$(CH_3)_2$), 2.38-2.29 (m, 1H, C$H_a$$H_b$-CH=CH-CO), 2.21-2.12 (m, 1H, $CH_a$$H_b$-CH=CH-CO), 2.06-1.90 (m, 2H, CH_2-CH=C$(CH_3)_2$), 1.74-1.63 (m, 4H, C*H*-CH_3 and $(CH_3)_a$-C=CH), 1.58 (s, 3H, $(CH_3)_b$-C=CH), 1.40-1.30 (m, 1H, CH_2-C$H_c$$H_d$-CH-$CH_3$), 1.25-1.15 (m, 1H, CH_2-$CH_c$$H_d$-CH-$CH_3$), 0.91 (d, *J* = 6.5 Hz, 3H, CH-CH_3); **δ_C** (101 MHz, $CDCl_3$): 194.1, 157.9, 134.3, 131.7, 124.3, 40.2, 36.8, 32.2, 25.8, 25.5, 19.6, 17.7; **HRMS**

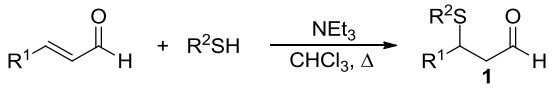
(CI$^+$) $C_{12}H_{21}O$ requires 181.1587 $[M+H]^+$, found 181.1594; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2964, 2915, 2730, 1691, 1637, 1454, 1379, 1146; the **ee** was determined by HPLC using a Chiralpak AY-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 7.83 min, τ_{minor} = 6.70 min (97% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +9.1 (c = 1.0, $CHCl_3$).

General Procedure A: microwave-assisted synthesis of β-*S*-substituted aldehydes.



In a microwave reaction vial, thiol (2.0 equiv) and triethylamine (0.1-0.2 equiv) were added to a solution of α,β-unsaturated aldehyde (1.0 equiv) in $CHCl_3$. The reaction mixture was subjected to microwave irradiation at 100 ℃ for 1.5 h. After cooling to room temperature, the solution was concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding β-*S*-substituted aldehyde.

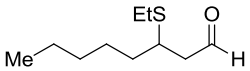
General Procedure B: microwave-free synthesis of β-*S*-substituted aldehydes.



In a round bottom flask fitted with a condenser (used when employing volatile reagents), thiol (1.05-2.0 equiv) and triethylamine (0.1-0.2 equiv) were added to a solution of α,β-unsaturated aldehyde (1.0 equiv) in $CHCl_3$ and the resulting mixture was stirred at 40 ℃ for 14 h. The solution was concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding β-*S*-substituted aldehyde.

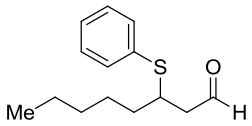
Note: aldehydes (**1i**, **1m-p**) prepared by Dr. Bouisseau are not included.

3-(Ethylthio)octanal, 1a



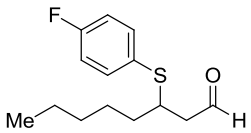
Prepared according to General Procedure B, using ethanethiol (2.2 mL, 30 mmol), triethylamine (0.21 mL, 1.5 mmol), *trans*-2-octenal (2.2 mL, 15 mmol) and $CHCl_3$ (15 mL). Purification by flash column chromatography (petrol/Et_2O, 98:2) afforded the title compound (2.40 g, 85% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 9.77 (t, *J* = 2.0 Hz, 1H, C*H*O), 3.23-2.98 (m, 1H, S-C*H*), 2.67-2.60 (m, 2H, CH_2-CO), 2.54 (q, *J* = 7.5 Hz, 2H, S-CH_2), 1.64-1.55 (m, 2H, CH-CH_2-CH_2), 1.48-1.26 (m, 6H, 3 × CH_2), 1.24 (t, *J* = 7.5 Hz, 3H, S-CH_2-CH_3), 0.88 (t, *J* = 7.0 Hz, 3H, CH_2-CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 201.3, 48.9, 39.4, 35.4, 31.7, 26.6, 24.6, 22.6, 14.9, 14.1; **LRMS** (ESI^+) 243.1 ([M+MeOH+Na]$^+$, 100%); data consistent with literature.[55]

3-(Phenylthio)octanal, 1b



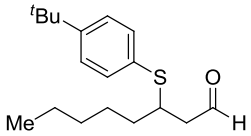
Prepared according to General Procedure B, using benzenethiol (0.35 mL, 3.3 mmol), triethylamine (0.04 mL, 0.30 mmol), *trans*-2-octenal (0.47 mL, 3.0 mmol) and $CHCl_3$ (3.0 mL). The resulting mixture was stirred at 23 ℃ for 14 h. Purification by flash column chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (597 mg, 84% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 9.79 (t, *J* = 2.0 Hz, 1H, C*H*O), 7.48-7.42 (m, 2H, Ar-*H*), 7.37-7.27 (m, 3H, Ar-*H*), 3.58 (p, *J* = 6.5 Hz, 1H, S-C*H*), 2.67 (dd, *J* = 6.5, 2.0 Hz, 2H, CH_2-CO), 1.68-1.61 (m, 2H, S-CH-CH_2-CH_2), 1.61-1.42 (m, 2H, S-CH-CH_2-CH_2), 1.39-1.25 (m, 4H, 2 × CH_2), 0.91 (t, *J* = 7.0 Hz, 3H, CH_3); **δ_C** (101 MHz, $CDCl_3$): 201.0, 133.8, 133.2, 129.2, 127.7, 48.7, 43.3, 34.8, 31.6, 26.7, 22.6, 14.1; **HRMS** (ESI^+) $C_{14}H_{20}OSNa$ requires 259.1127 [M+Na]$^+$, found 259.1128; **ν_{max}** (film)/cm^{-1} 2929, 2857, 1723, 1584, 1479, 1439, 1025, 747, 693.

3-((4-Fluorophenyl)thio)octanal, 1c



Prepared according to General Procedure B, using 4-fluorobenzenethiol (0.51 mL, 4.8 mmol), triethylamine (0.06 mL, 0.40 mmol), *trans*-2-octenal (0.63 mL, 4.0 mmol) and $CHCl_3$ (4.0 mL). The resulting mixture was stirred at 23 ℃ for 14 h. Purification by flash column chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (1.01 g, 98% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 9.75 (t, *J* = 2.0 Hz, 1H, C*H*O), 7.45-7.39 (m, 2H, Ar-*H*), 7.05-6.99 (m, 2H, Ar-*H*), 3.44 (p, *J* = 6.5 Hz, 1H, S-C*H*), 2.61 (dd, *J* = 6.5, 1.5 Hz, 2H, CH_2-CO), 1.62-1.53 (m, 2H, S-CH-CH_2-CH_2), 1.53-1.42 (m, 2H, S-CH-CH_2-CH_2), 1.36-1.22 (m, 4H, 2 × CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_3); **δ_C** (101 MHz, $CDCl_3$): 200.8, 162.9 (d, $J_{C\text{-}F}$ = 248.5 Hz), 136.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 128.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 116.3 (d, $J_{C\text{-}F}$ = 21.5 Hz), 48.6, 44.0, 34.8, 31.6, 26.7, 22.6, 14.1; **δ_F** (377 MHz, $CDCl_3$): –113.2; **HRMS** (ESI^+) $C_{15}H_{23}FO_2SNa$ requires 309.1295 $[M+MeOH+Na]^+$, found 309.1297; **ν_{max}** (film)/cm^{-1} 2930, 2858, 1724, 1590, 1490, 1224, 833.

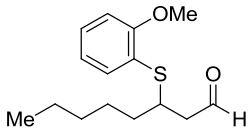
3-((4-(*tert*-Butyl)phenyl)thio)octanal, 1d



Prepared according to General Procedure B, using 4-(*tert*-butyl)benzenethiol (0.72 mL, 4.2 mmol), triethylamine (0.06 mL, 0.40 mmol), *trans*-2-octenal (0.63 mL, 4.0 mmol) and $CHCl_3$ (4.0 mL). The resulting mixture was stirred at 23 ℃ for 14 h. Purification by flash column chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (956 mg,

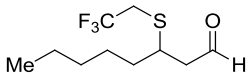
82% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 9.76 (t, *J* = 2.0 Hz, 1H, C*H*O), 7.37-7.31 (m, 4H, Ar-*H*), 3.48 (p, *J* = 6.5 Hz, 1H, S-C*H*), 2.62 (dd, *J* = 6.5, 2.0 Hz, 2H, CH_2-CO), 1.64-1.57 (m, 2H, S-CH-CH_2-CH_2), 1.56-1.40 (m, 2H, S-CH-CH_2-CH_2), 1.36-1.25 (m, 13H, C(CH_3)$_3$ and 2 × CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 201.2, 151.1, 133.3, 129.9, 126.2, 48.6, 43.4, 34.8, 34.7, 31.6, 31.3, 26.7, 22.6, 14.1; **HRMS** (ESI^+) $C_{19}H_{32}O_2SNa$ requires 347.2015 $[M+MeOH+Na]^+$, found 347.2015; **ν_{max}** (film)/cm^{-1} 2958, 2930, 2860, 1723, 1462, 1394, 1363, 1268, 1120, 1014, 829, 726.

3-((2-Methoxyphenyl)thio)octanal, 1e



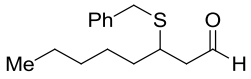
Prepared according to General Procedure A, using 2-methoxybenzenethiol (0.29 mL, 2.4 mmol), triethylamine (0.03 mL, 0.20 mmol), *trans*-2-octenal (0.30 mL, 2.0 mmol) and $CHCl_3$ (2.0 mL). Purification by flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (431 mg, 81% yield) as a pale yellow oil. **δ_H** (400 MHz, $CDCl_3$): 9.76 (t, *J* = 2.0 Hz, 1H, C*H*O), 7.38 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.27 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Ar-*H*), 6.91 (td, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 6.88 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 3.87 (s, 3H, OCH_3), 3.70-3.62 (m, 1H, S-C*H*), 2.61 (dd, *J* = 6.5, 2.0 Hz, 2H, CH_2-CO), 1.65-1.58 (m, 2H, S-CH-CH_2-CH_2), 1.57-1.42 (m, 2H, S-CH-CH_2-CH_2), 1.35-1.21 (m, 4H, 2 × CH_2), 0.87 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 201.6, 159.2, 134.4, 129.4, 121.8, 121.1, 111.1, 55.8, 48.7, 41.5, 35.0, 31.7, 26.7, 22.6, 14.1; **HRMS** (ESI^+) $C_{15}H_{23}O_2S$ requires 267.1413 $[M+H]^+$, found 267.1414; **ν_{max}** (film)/cm^{-1} 2957, 2930, 2857, 1721, 1581, 1476, 1462, 1432, 1272, 1243, 1071, 1024, 751.

3-((2,2,2-Trifluoroethyl)thio)octanal, 1f



Prepared according to General Procedure A, using 2,2,2-trifluoroethanethiol (0.22 mL, 2.4 mmol), triethylamine (0.06 mL, 0.40 mmol), *trans*-2-octenal (0.30 mL, 2.0 mmol) and $CHCl_3$ (2.0 mL). Purification by flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (382 mg, 79% yield) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 9.77 (t, *J* = 1.5 Hz, 1H, C*H*O), 3.28 (p, *J* = 6.5 Hz, 1H, S-C*H*), 3.24-3.04 (m, 2H, S-CH_2-CF_3), 2.73 (dd, *J* = 6.5, 1.5 Hz, 2H, CH_2-CO), 1.64-1.57 (m, 2H, S-CH-CH_2-CH_2), 1.51-1.37 (m, 2H, S-CH-CH_2-CH_2), 1.36-1.22 (m, 4H, 2 × CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 200.2, 125.8 (q, $J_{C\text{-}F}$ = 276.0 Hz), 49.4, 41.0, 35.3, 33.8 (q, $J_{C\text{-}F}$ = 33.0 Hz), 31.6, 26.4, 22.6, 14.1; $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$): –66.3; **HRMS** (ESI^+) $C_{11}H_{21}F_3O_2SNa$ requires 297.1107 $[M+MeOH+Na]^+$, found 297.1108; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2932, 2860, 1725, 1310, 1269, 1242, 1123, 1077, 842, 638.

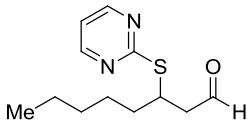
3-(Benzylthio)octanal, 1g



Prepared according to General Procedure A, using phenylmethanethiol (0.28 mL, 2.4 mmol), triethylamine (0.06 mL, 0.40 mmol), *trans*-2-octenal (0.30 mL, 2.0 mmol) and $CHCl_3$ (2.0 mL). Purification by flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (480 mg, 96% yield) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 9.58 (t, *J* = 2.0 Hz, 1H, C*H*O), 7.27-7.14 (m, 5H, Ar-*H*), 3.67 (s, 2H, Ar-CH_2), 2.98-2.89 (m, 1H, S-C*H*), 2.58-2.46 (m, 2H, CH_2-CO), 1.57-1.42 (m, 2H, S-CH-CH_2-CH_2), 1.38-1.24 (m, 2H, S-CH-CH_2-CH_2), 1.24-1.08 (m, 4H, 2 × CH_2), 0.80 (t, *J* = 7.0 Hz, 3H, CH_3); $\boldsymbol{\delta_C}$ (101 MHz,

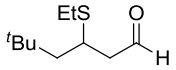
$CDCl_3$): 201.2, 138.3, 129.0, 128.7, 127.3, 48.8, 39.2, 35.5, 35.2, 31.6, 26.5, 22.6, 14.1; **HRMS** (ESI^+) $C_{16}H_{26}O_2SNa$ requires 305.1546 $[M+MeOH+Na]^+$, found 305.1544; ν_{max} (film)/cm^{-1} 2955, 2928, 2857, 1722, 1454, 767, 700.

3-(Pyrimidin-2-ylthio)octanal, 1h



Prepared according to General Procedure B, using pyrimidine-2-thiol (0.27 g, 2.4 mmol), triethylamine (0.06 mL, 0.40 mmol), *trans*-2-octenal (0.30 mL, 2.0 mmol) and $CHCl_3$ (2.0 mL). The resulting mixture was refluxed at 70 ℃ for 14 h. Purification by flash column chromatography (petrol/Et_2O, 1:4) afforded *the title compound* (290 mg, 61% yield) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 9.80 (s, 1H, C*H*O), 8.50 (d, *J* = 5.0 Hz, 2H, Ar-*H*), 6.97 (t, *J* = 5.0 Hz, 1H, Ar-*H*), 4.26 (p, *J* = 6.5 Hz, 1H, S-C*H*), 2.94-2.79 (m, 2H, CH_2-CO), 1.79-1.72 (m, 2H, S-CH-CH_2-CH_2), 1.59-1.39 (m, 2H, S-CH-CH_2-CH_2), 1.36-1.23 (m, 4H, 2 × CH_2), 0.89-0.84 (m, 3H, CH_3); δ_C (101 MHz, $CDCl_3$): 201.2, 172.0, 157.4, 116.8, 49.1, 39.9, 34.4, 31.6, 26.7, 22.6, 14.1; **HRMS** (ESI^+) $C_{13}H_{22}O_2N_2SNa$ requires 293.1294 $[M+MeOH+Na]^+$, found 293.1293; ν_{max} (film)/cm^{-1} 2928, 2857, 1721, 1565, 1547, 1378, 1190, 801, 774, 749, 630.

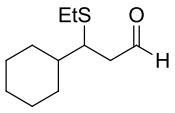
3-(Ethylthio)-5,5-dimethylhexanal, 1j



A solution of (triphenylphosphoranylidene)acetaldehyde (3.01 g, 9.9 mmol) and 3,3-dimethylbutyraldehyde (1.1 mL, 9.0 mmol) in $CHCl_3$ (30 mL) was refluxed with a condenser at 62 ℃ for 24 h. The mixture was filtered through a pad of SiO_2 using 10% Et_2O in petrol (b.p. 30-40 ℃) and concentrated under reduced pressure at room temperature

(volatile) to afford a yellow oil (129 mg), which was used in the next step without further purification. General Procedure B was then followed, using this product (129 mg, 1.0 mmol), ethanethiol (0.15 mL, 2.0 mmol), triethylamine (0.03 mL, 0.20 mmol) and $CHCl_3$ (1.0 mL). The resulting mixture was stirred in a sealed tube at 40 ℃ for 20 h. Additional ethanethiol (0.07 mL, 1.0 mmol) was added, and the solution stirred at 40 ℃ for a further 40 h. Purification by flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (162 mg, 10% yield over two steps) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 9.77 (m, 1H, C*H*O), 3.20-3.13 (m, 1H, S-C*H*), 2.71 (ddd, *J* = 17.0, 5.5, 1.5 Hz, 1H, C$H_a$$H_b$-CO), 2.64 (ddd, *J* = 17.0, 7.5, 2.5 Hz, 1H, C$H_a$$H_b$-CO), 2.54 (q, *J* = 7.5 Hz, 2H, S-CH_2-CH_3), 1.63 (dd, *J* = 14.5, 5.5 Hz, 1H, C$H_c$$H_d$-CH-$CH_2$-CO), 1.51 (dd, *J* = 14.5, 6.0 Hz, 1H, C$H_c$$H_d$-CH-$CH_2$-CO), 1.25 (t, *J* = 7.5 Hz, 3H, S-CH_2-CH_3), 0.96 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 201.4, 50.7, 49.5, 35.2, 31.5, 29.9, 24.6, 14.6; **HRMS** (ESI^+) $C_{11}H_{24}O_2SNa$ requires 243.1389 $[M+MeOH+Na]^+$, found 243.1389; **ν_{max}** (film)/cm^{-1} 2956, 2869, 1723, 1469, 1366, 1248.

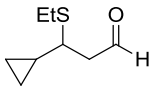
3-Cyclohexyl-3-(ethylthio)propanal, 1k



Prepared according to General Procedure B, using ethanethiol (0.22 mL, 2.94 mmol), triethylamine (0.04 mL, 0.29 mmol), (*E*)-3-cyclohexylacrylaldehyde[117] (203 mg, 1.47 mmol) and $CHCl_3$ (1.5 mL). The resulting mixture was stirred in a sealed tube at 40 ℃ for 20 h. Purification by flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (219 mg, 74% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 9.78 (dd, *J* = 2.5, 1.5 Hz, 1H, C*H*O), 3.02-2.96 (m, 1H, S-C*H*), 2.72-2.52 (m, 4H, CH_2-CO and S-CH_2-CH_3),

1.82-1.62 (m, 5H, Cy-*H*), 1.57-1.47 (m, 1H, Cy-*H*), 1.26-1.02 (m, 8H, S-CH_2-C*H*$_3$ and 5 × Cy-*H*); **δC** (101 MHz, $CDCl_3$): 201.7, 46.7, 45.8, 42.6, 30.2, 30.0, 26.49, 26.47, 26.4, 26.3, 14.9; **HRMS** (ESI^+) $C_{12}H_{24}O_2SNa$ requires 255.1389 $[M+MeOH+Na]^+$, found 255.1389; **ν_{max}** (film)/cm^{-1} 2925, 2852, 1724, 1449.

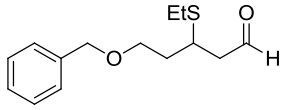
3-Cyclopropyl-3-(ethylthio)propanal, 1l



A solution of (triphenylphosphoranylidene)acetaldehyde (3.01 g, 9.9 mmol) and cyclopropanecarboxaldehyde (0.67 mL, 9.0 mmol) in $CHCl_3$ (30 mL) was refluxed with a condenser at 62 ℃ for 16 h. The mixture was filtered through a pad of SiO_2 using 20% Et_2O in petrol (b.p. 30-40 ℃) and concentrated under reduced pressure at room temperature (volatile) to afford a yellow oil (695 mg), which was used in the next step without further purification. General Procedure B was then followed, using this product (510 mg, 5.2 mmol), ethanethiol (0.44 mL, 6.0 mmol), triethylamine (0.08 mL, 0.60 mmol) and $CHCl_3$ (3.0 mL). The resulting mixture was stirred at 23 ℃ for 72 h. Purification by flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (176 mg, 17% yield over two steps) as a colorless oil. **δH** (400 MHz, $CDCl_3$): 9.80 (t, *J* = 2.0 Hz, 1H, C*H*O), 2.81-2.68 (m, 2H, C*H*$_2$-CO), 2.65 (qd, *J* = 7.5, 1.5 Hz, 2H, S-C*H*$_2$-CH_3), 2.54 (dt, *J* = 9.5, 7.0 Hz, 1H, S-C*H*), 1.25 (t, *J* = 7.5 Hz, 3H, S-CH_2-C*H*$_3$), 0.97 (dtt, *J* = 9.5, 8.0, 5.0 Hz, 1H, C*H*-CH_2-CH_2), 0.71-0.63 (m, 1H, CH-C*H*$_a$H$_b$-CH$_c$H$_d$), 0.60-0.52 (m, 1H, CH-CH$_a$H$_b$-C*H*$_c$H$_d$), 0.42-0.35 (m, 1H, CH-CH$_a$*H*$_b$-CH$_c$H$_d$), 0.26-0.19 (m, 1H, CH-CH$_a$H$_b$-CH$_c$*H*$_d$); **δC** (101 MHz, $CDCl_3$): 201.0, 49.6, 44.3, 24.9, 17.2, 14.9, 5.9, 4.9; **HRMS** (ESI^+) $C_8H_{14}OSNa$ requires 181.0658 $[M+Na]^+$, found 181.0658; **ν_{max}** (film)/cm^{-1} 3003, 2969,

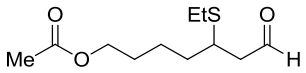
2928, 2872, 2828, 1721, 1452, 1264.

5-(Benzyloxy)-3-(ethylthio)pentanal, 1q



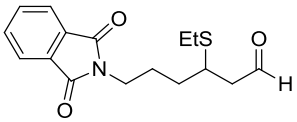
A solution of (triphenylphosphoranylidene)acetaldehyde (1.00 g, 3.3 mmol) and 3-benzyloxypropionaldehyde (0.47 mL, 3.0 mmol) in $CHCl_3$ (10 mL) was refluxed with a condenser at 62 ℃ for 60 h. The mixture was concentrated under reduced pressure and purified by flash column chromatography (petrol/Et_2O, 4:1) to afford the enal (contains ~10% unreacted 3-benzyloxypropionaldehyde, not isolable from SiO_2) as a pale yellow oil (355 mg), which was used in the next step without further purification. General Procedure B was then followed, using this product (355 mg), ethanethiol (0.27 mL, 3.6 mmol), triethylamine (0.05 mL, 0.36 mmol) and $CHCl_3$ (1.8 mL). Purification by flash column chromatography (gradient petrol/Et_2O, 88:12 to 82:18) afforded *the title compound* (365 mg, 48% yield over two steps) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 9.75 (dd, *J* = 2.5, 1.5 Hz, 1H, C*H*O), 7.38-7.25 (m, 5H, Ar-*H*), 4.49 (s, 2H, Ph-CH_2), 3.71-3.56 (m, 2H, Ph-CH_2-O-CH_2), 3.39-3.30 (m, 1H, S-C*H*), 2.72 (ddd, *J* = 17.0, 6.0, 1.5 Hz, 1H, C$H_a$$H_b$-CO), 2.64 (ddd, *J* = 17.0, 8.0, 2.5 Hz, 1H, $CH_a$$H_b$-CO), 2.55 (qd, *J* = 7.5, 0.5 Hz, 2H, S-CH_2-CH_3), 1.98-1.83 (m, 2H, CH_2-CH_2-CH), 1.24 (t, *J* = 7.5 Hz, 3H, S-CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 201.0, 138.3, 128.5, 127.84, 127.81, 73.2, 67.4, 49.1, 36.6, 35.5, 24.8, 14.9; **HRMS** (ESI^+) $C_{14}H_{20}O_2SNa$ requires 275.1076 $[M+Na]^+$, found 275.1078; **ν_{max}** (film)/cm^{-1} 3031, 2927, 2861, 2725, 1722, 1454, 1364, 1264.

5-(Ethylthio)-7-oxoheptyl acetate, 1r



Prepared according to General Procedure B, using ethanethiol (0.18 mL, 2.42 mmol), triethylamine (0.03 mL, 0.24 mmol), **SM1** (207 mg, 1.21 mmol) and $CHCl_3$ (1.2 mL). The resulting mixture was stirred at 23 ℃ for 22 h. Purification by flash column chromatography (gradient petrol/EtOAc, 90:10 to 85:15) afforded *the title compound* (202 mg, 72% yield) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 9.77 (t, *J* = 2.0 Hz, 1H, C*H*O), 4.05 (t, *J* = 6.5 Hz, 2H, CO_2-CH_2), 3.11 (p, *J* = 7.0 Hz, 1H, S-C*H*), 2.66 (dd, *J* = 7.0, 2.0 Hz, 2H, CH_2-CO), 2.54 (q, *J* = 7.5 Hz, 2H, S-CH_2-CH_3), 2.03 (s, 3H, CH_3-CO), 1.67-1.56 (m, 4H, 2 × CH_2), 1.55-1.40 (m, 2H, CH_2), 1.23 (t, *J* = 7.5 Hz, 3H, S-CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 201.0, 171.3, 64.3, 49.1, 39.2, 34.9, 28.5, 24.7, 23.4, 21.1, 14.8; **HRMS** (ESI^+) $C_{11}H_{21}O_3S$ requires 233.1206 $[M+H]^+$, found 233.1208; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2931, 2868, 2726, 1724, 1455, 1388, 1366, 1236, 1036.

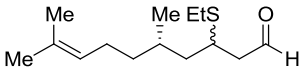
6-(1,3-Dioxoisoindolin-2-yl)-3-(ethylthio)hexanal, 1s



Prepared according to General Procedure B, using ethanethiol (0.19 mL, 2.5 mmol), triethylamine (0.03 mL, 0.25 mmol), (*E*)-6-(1,3-dioxoisoindolin-2-yl)hex-2-enal[118] (303 mg, 1.25 mmol) and $CHCl_3$ (1.3 mL). The resulting mixture was stirred at 23 ℃ for 22 h. Purification by flash column chromatography (gradient petrol/EtOAc, 9:1 to 8:2) afforded *the title compound* (350 mg, 92% yield) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 9.73 (t, *J* = 2.0 Hz, 1H, C*H*O), 7.85-7.79 (m, 2H, Ar-*H*), 7.73-7.67 (m, 2H, Ar-*H*), 3.69 (t, *J* = 7.0 Hz, 2H, N-CH_2), 3.19-3.11 (m, 1H, S-C*H*), 2.64 (dd, *J* = 7.0, 2.0 Hz, 2H, CH_2-CO),

2.52 (q, *J* = 7.5 Hz, 2H, S-C*H*$_2$-CH$_3$), 1.94-1.74 (m, 2H, N-CH$_2$-C*H*$_2$), 1.68-1.58 (m, 2H, C*H*$_2$-CH-CH$_2$-CO), 1.21 (t, *J* = 7.5 Hz, 3H, S-CH$_2$-C*H*$_3$); **δC** (101 MHz, $CDCl_3$): 200.8, 168.5, 134.1, 132.1, 123.3, 49.1, 38.8, 37.6, 32.4, 26.0, 24.6, 14.8; **HRMS** (ESI^+) $C_{17}H_{23}O_4NSNa$ requires 360.1240 $[M+MeOH+Na]^+$, found 360.1231; **νmax** (film)/cm^{-1} 2929, 2869, 2727, 1771, 1704, 1615, 1437, 1396, 1371, 1361, 1263, 1188, 1052.

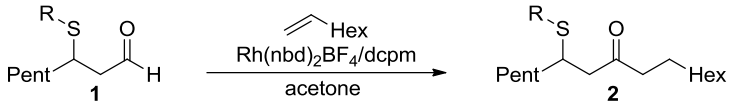
(5*S*)-3-(Ethylthio)-5,9-dimethyldec-8-enal, 1t



Prepared according to General Procedure B, using ethanethiol (0.22 mL, 3.0 mmol), triethylamine (0.04 mL, 0.3 mmol), **SM2** (270 mg, 1.5 mmol) and $CHCl_3$ (1.5 mL). The resulting mixture was stirred at 23 ℃ for 24 h. Purification by flash column chromatography (petrol/Et_2O, 97:3) afforded *the title compound* (268 mg, 74% yield) as a pale yellow oil. The compound was isolated as an inseparable mixture of diastereoisomers. **δH** (400 MHz, $CDCl_3$): 9.79-9.76 (m, 1H, C*H*O), 5.11-5.05 (m, 1H, C*H*=C), 3.22-3.13 (m, 1H, S-C*H*), 2.69-2.49 (m, 4H, C*H*$_2$-CO and S-C*H*$_2$-CH$_3$), 2.06-1.88 (m, 2H, C*H*$_2$-CH=C), 1.75-1.10 (m, 14H, C*H*$_2$-C*H*(CH$_3$)-C*H*$_2$, 2 × C*H*$_3$-C=CH and S-CH$_2$-C*H*$_3$), 0.91 (m, 3H, CH-C*H*$_3$); **δC** (101 MHz, $CDCl_3$) (*denotes the second diastereoisomer): 201.4, 201.4*, 131.6, 131.5*, 124.7*, 124.6, 49.8*, 48.8, 43.2, 42.7*, 37.3, 37.2*, 37.0*, 36.8, 30.02, 29.99*, 25.8, 25.8*, 25.5*, 25.4, 24.5, 24.0*, 19.7, 19.4*, 17.8, 17.8*, 14.9, 14.8*; **HRMS** (CI^+) $C_{14}H_{27}OS$ requires 243.1777 $[M+H]^+$, found 243.1778; **νmax** (film)/cm^{-1} 2965, 2915, 2849, 2725, 1724, 1453, 1378, 1265.

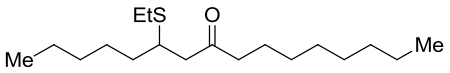
5.2.2 Hydroacylation

General Procedure C: hydroacylation of 1-octene.



A microwave reaction vial charged with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 10 mol%) and dcpm (6.1 mg, 0.015 mmol, 10 mol%) was evacuated and back-filled with N_2 gas for 3 times. Acetone was added to dissolve the solids. H_2 gas was bubbled through the solution for 2 min, and the solution then purged with N_2 gas until dryness. Acetone (0.50 mL, 0.3 M) was added and the resulting mixture was transferred to a N_2-purged reaction vial containing aldehyde **1** (0.15 mmol, 1.0 equiv). 1-Octene (71 μL, 0.45 mmol, 3.0 equiv) was then added and the reaction mixture stirred at 55 ℃ for 1.5 h. The mixture was allowed to cool to room temperature, concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding hydroacylation adduct.

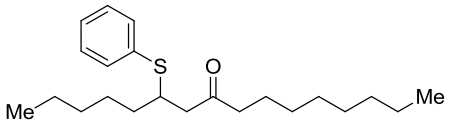
6-(Ethylthio)hexadecan-8-one, 2a



Prepared according to General Procedure C, using **1a** (28 mg). Purification by flash column chromatography (petrol/Et_2O, 98:2) afforded *the title compound* (35 mg, 77% yield) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 3.15-3.07 (m, 1H, S-C*H*), 2.67 (dd, *J* = 16.5, 7.0 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.58 (dd, *J* = 16.5, 6.5 Hz, 1H, CH-CH$_a$$H_b$-CO), 2.51 (q, *J* = 7.5 Hz, 2H, S-CH_2-CH_3), 2.40 (td, *J* = 7.0, 1.5 Hz, 2H, CO-CH_2-CH_2), 1.60-1.46 (m, 4H, CO-CH_2-CH_2 and S-CH-CH_2-CH_2), 1.46-1.33 (m, 2H, S-CH-CH_2-CH_2), 1.33-1.19 (m, 17H, 7 × CH_2 and S-CH_2-CH_3), 0.90-0.83 (m, 6H, 2 × CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 209.6, 49.0, 43.9, 40.5, 35.5, 31.9, 31.8, 29.5, 29.32, 29.26, 26.6, 25.1, 23.8, 22.8, 22.7, 15.0, 14.21,

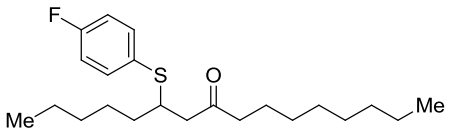
14.16; **HRMS** (ESI$^+$) $C_{18}H_{36}OSNa$ requires 323.2379 $[M+Na]^+$, found 323.2376; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2956, 2925, 2855, 1714, 1457, 1375, 724.

6-(Phenylthio)hexadecan-8-one, 2b



Prepared according to General Procedure C, using **1b** (35 mg). Purification by flash column chromatography (petrol/Et_2O, 98:2) afforded *the title compound* (18 mg, 35% yield) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.42-7.37 (m, 2H, Ar-*H*), 7.31-7.20 (m, 3H, Ar-*H*), 3.66-3.58 (m, 1H, S-C*H*), 2.69 (dd, *J* = 17.0, 6.0 Hz, 1H, CH-CH_aH_b-CO), 2.60 (dd, *J* = 17.0, 7.5 Hz, 1H, CH-CH$_a$*H*$_b$-CO), 2.36 (t, *J* = 7.5 Hz, 2H, CO-CH_2-CH$_2$), 1.65-1.37 (m, 6H, CO-CH$_2$-CH_2 and S-CH-CH_2-CH_2), 1.32-1.18 (m, 14H, 7 × CH_2), 0.90-0.84 (m, 6H, 2 × CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 209.4, 134.9, 132.2, 129.0, 127.1, 48.3, 43.9, 43.8, 35.0, 31.9, 31.7, 29.5, 29.31, 29.26, 26.7, 23.8, 22.8, 22.7, 14.2, 14.1; **HRMS** (ESI$^+$) $C_{22}H_{37}OS$ requires 349.2560 $[M+H]^+$, found 349.2558; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2955, 2926, 2855, 1714, 1584, 1466, 1439, 1131, 1090, 1025, 746, 692.

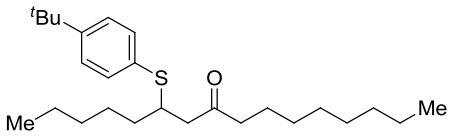
6-((4-Fluorophenyl)thio)hexadecan-8-one, 2c



Prepared according to General Procedure C, using **1c** (38 mg). Purification by flash column chromatography (petrol/Et_2O, 98:2) afforded *the title compound* (11 mg, 20% yield) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.44-7.37 (m, 2H, Ar-*H*), 7.03-6.96 (m, 2H, Ar-*H*), 3.53-3.45 (m, 1H, S-C*H*), 2.65 (dd, *J* = 17.0, 6.5 Hz, 1H, CH-CH_aH_b-CO), 2.57 (dd, *J* = 17.0, 7.0 Hz, 1H, CH-CH$_a$*H*$_b$-CO), 2.36 (t, *J* = 7.5 Hz, 2H, CO-CH_2-CH$_2$), 1.60-1.36 (m,

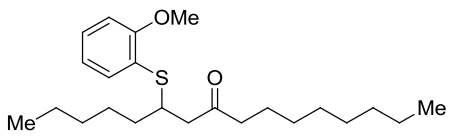
6H, CO-CH_2-CH_2 and S-CH-CH_2-CH_2), 1.34-1.18 (m, 14H, 7 ×CH_2), 0.87 (t, J = 7.0 Hz, 6H, 2 ×CH_3); **δC** (126 MHz, $CDCl_3$): 209.3, 162.6 (d, $J_{C\text{-}F}$ = 247.5 Hz), 135.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 129.6 (d, $J_{C\text{-}F}$ = 3.5 Hz), 116.1 (d, $J_{C\text{-}F}$ = 22.0 Hz), 48.2, 44.9, 43.8, 35.0, 32.0, 31.7, 29.5, 29.31, 29.26, 26.6, 23.8, 22.8, 22.7, 14.23, 14.15; **δF** (377 MHz, $CDCl_3$): −114.2; **HRMS** (ESI^+) $C_{22}H_{35}FOSNa$ requires 389.2285 $[M+Na]^+$, found 389.2291; **νmax** (film)/cm^{-1} 2955, 2927, 2856, 1715, 1590, 1490, 1466, 1224, 832, 725.

6-((4-(*tert*-Butyl)phenyl)thio)hexadecan-8-one, 2d



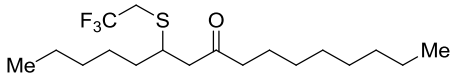
Prepared according to General Procedure C, using **1d** (44 mg). Purification by flash column chromatography (petrol/Et_2O, 98:2) afforded *the title compound* (19 mg, 31% yield) as a pale yellow oil. **δH** (400 MHz, $CDCl_3$): 7.35-7.28 (m, 4H, Ar-*H*), 3.60-3.51 (m, 1H, S-C*H*), 2.69 (dd, J = 17.0, 6.0 Hz, 1H, CH-CH_aH_b-CO), 2.58 (dd, J = 17.0, 7.5 Hz, 1H, CH-CH_aH_b-CO), 2.35 (t, J = 7.5 Hz, 2H, CO-CH_2-CH_2), 1.60-1.40 (m, 6H, CO-CH_2-CH_2 and S-CH-CH_2-CH_2), 1.30 (s, 9H, C(CH_3)$_3$), 1.29-1.22 (m, 14H, 7 ×CH_2), 0.87 (t, J = 7.0 Hz, 6H, 2 ×CH_3); **δC** (101 MHz, $CDCl_3$): 209.6, 150.5, 132.5, 131.0, 126.1, 48.5, 44.0, 43.8, 35.0, 34.7, 32.0, 31.7, 31.4, 29.5, 29.32, 29.27, 26.7, 23.8, 22.8, 22.7, 14.23, 14.16; **HRMS** (ESI^+) $C_{26}H_{45}OS$ requires 405.3186 $[M+H]^+$, found 405.3168; **νmax** (film)/cm^{-1} 2956, 2927, 2856, 1715, 1463, 1363, 1268, 1120, 1014, 829, 724.

6-((2-Methoxyphenyl)thio)hexadecan-8-one, 2e



Prepared according to General Procedure C, using **1e** (40 mg). Purification by flash column chromatography (petrol/Et_2O, 96:4) afforded *the title compound* (9 mg, 16% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.33 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.22 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Ar-*H*), 6.90 (td, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 6.85 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 3.88 (s, 3H, OCH_3), 3.75 (app. tt, *J* = 7.5, 5.5 Hz, 1H, S-C*H*), 2.69 (dd, *J* = 17.0, 5.5 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.61 (dd, *J* = 17.0, 8.0 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.34 (t, *J* = 7.5 Hz, 2H, CO-CH_2-CH_2), 1.63-1.40 (m, 6H, CO-CH_2-CH_2 and S-CH-CH_2-CH_2), 1.33-1.19 (m, 14H, 7 × CH_2), 0.90-0.84 (m, 6H, 2 × CH_3); **δ_C** (101 MHz, $CDCl_3$): 209.7, 158.6, 132.6, 128.4, 123.0, 121.1, 110.8, 55.9, 48.5, 43.7, 41.6, 34.9, 31.9, 31.8, 29.5, 29.31, 29.26, 26.7, 23.8, 22.8, 22.7, 14.24, 14.18; **HRMS** (ESI^+) $C_{23}H_{38}O_2SNa$ requires 401.2485 $[M+Na]^+$, found 401.2487; **ν_{max}** (film)/cm^{-1} 2957, 2927, 2855, 1713, 1581, 1477, 1463, 1272, 1244, 1071, 1026, 751.

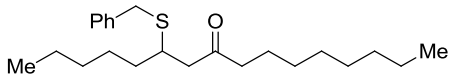
6-((2,2,2-Trifluoroethyl)thio)hexadecan-8-one, 2f



Prepared according to General Procedure C, on a 0.10 mmol scale, using **1f** (24 mg, 0.10 mmol). Purification by flash column chromatography (petrol/Et_2O, 96:4) afforded *the title compound* (7 mg, 21% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 3.30-3.17 (m, 2H, S-CH_2-CF_3), 3.14-3.01 (m, 1H, S-C*H*), 2.75 (dd, *J* = 17.5, 7.5 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.66 (dd, *J* = 17.5, 6.0 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.40 (t, *J* = 7.5 Hz, 2H, CO-CH_2-CH_2), 1.62-1.50 (m, 4H, CO-CH_2-CH_2 and S-CH-CH_2-CH_2), 1.49-1.34 (m, 2H, S-CH-CH_2-CH_2), 1.34-1.20 (m, 14H, 7 × CH_2), 0.91-0.84 (m, 6H, 2 × CH_3); **δ_C** (101 MHz, $CDCl_3$): 209.0, 125.8 (q, $J_{C\text{-}F}$ = 276.0 Hz), 49.3, 43.7, 42.4, 35.5, 34.3 (q, $J_{C\text{-}F}$ = 33.0 Hz), 32.0, 31.6, 29.5,

29.31, 29.26, 26.5, 23.8, 22.8, 22.6, 14.2, 14.1; **δ_F** (377 MHz, $CDCl_3$): –66.4; **HRMS** (ESI^+) $C_{18}H_{33}F_3OSNa$ requires 377.2096 $[M+Na]^+$, found 377.2095; **ν_{max}** (film)/cm^{-1} 2956, 2927, 2857, 1715, 1466, 1309, 1269, 1243, 1123, 1076, 842, 638.

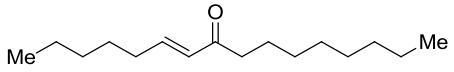
6-(Benzylthio)hexadecan-8-one, 2g



Prepared according to General Procedure C, using **1g** (38 mg). Purification by flash column chromatography (petrol/Et_2O, 97:3) afforded *the title compound* (16 mg, 30% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.34-7.20 (m, 5H, Ar-*H*), 3.73 (s, 2H, Ph-CH_2), 3.06 (p, *J* = 6.5 Hz, 1H, S-C*H*), 2.64 (dd, *J* = 16.5, 7.0 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.56 (dd, *J* = 16.5, 6.5 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.32 (t, *J* = 7.5 Hz, 2H, CO-CH_2-CH_2), 1.59-1.42 (m, 4H, CO-CH_2-CH_2 and S-CH-CH_2-CH_2), 1.42-1.13 (m, 16H, 8 × CH_2), 0.91-0.82 (m, 6H, 2 × CH_3); **δ_C** (101 MHz, $CDCl_3$): 209.5, 138.8, 129.1, 128.6, 127.1, 49.0, 43.7, 40.7, 36.0, 35.3, 32.0, 31.7, 29.5, 29.33, 29.28, 26.4, 23.8, 22.8, 22.7, 14.24, 14.15; **HRMS** (ESI^+) $C_{23}H_{38}OSNa$ requires 385.2536 $[M+Na]^+$, found 385.2534; **ν_{max}** (film)/cm^{-1} 2955, 2927, 2855, 1714, 1454, 701.

5.2.3 Sequential hydroacylation-elimination

(*E*)-Hexadec-6-en-8-one, 3

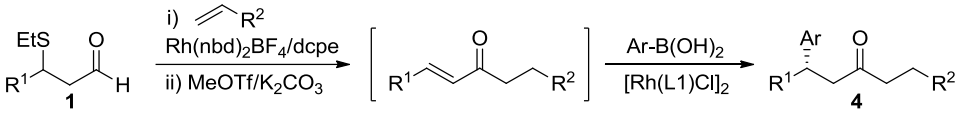


General Procedure C was first followed, using $Rh(nbd)_2BF_4$ (11.2 mg, 0.030 mmol), dcpm (12.3 mg, 0.030 mmol), **1a** (113.0 mg, 0.60 mmol), 1-octene (0.28 mL, 1.8 mmol) and acetone (0.60 mL, 1.0 M). The reaction mixture was allowed to cool to room temperature before copper(I) 3-methylsalicylate (128.8 mg, 0.60 mmol) and acetone

(0.60 mL) were added. The resulting suspension was stirred at 55 ℃ for 14 h and then cooled to room temperature. After removing the precipitates by filtering through a pad of SiO_2, the filtrate was concentrated under reduced pressure and purified by flash column chromatography (petrol/Et_2O, 98:2) to afford *the title compound* (116.0 mg, 81% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 6.82 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 6.08 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 2.52 (t, *J* = 7.5 Hz, 2H, CO-CH_2), 2.23-2.16 (m, 2H, CH_2-CH=CH), 1.64-1.55 (m, 2H, CO-CH_2-CH_2), 1.50-1.42 (m, 2H, CH_2-CH_2-CH=CH), 1.37-1.20 (m, 14H, 7 × CH_2), 0.88 (app. q, *J* = 7.0 Hz, 6H, 2 × CH_3); **δ_C** (101 MHz, $CDCl_3$): 201.2, 147.5, 130.5, 40.3, 32.6, 32.0, 31.5, 29.54, 29.48, 29.3, 27.9, 24.5, 22.8, 22.6, 14.2, 14.1; **HRMS** (ESI^+) $C_{16}H_{31}O$ requires 239.2369 $[M+H]^+$, found 239.2370; **ν_{max}** (film)/cm^{-1} 2957, 2927, 2856, 1698, 1676, 1631, 1466, 983, 723.

5.2.4 One-pot synthesis of enantioenriched β-aryl ketones

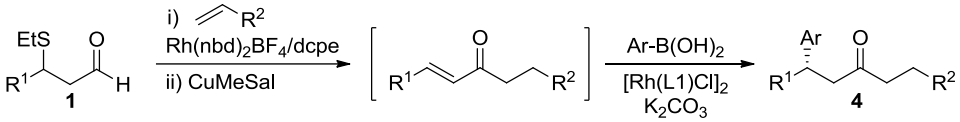
General Procedure D: sequential hydroacylation-elimination-conjugate addition.



Acetone (~0.5 mL) was added to a microwave reaction vial charged with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 5 mol%) and dcpm (6.1 mg, 0.015 mmol, 5 mol%) (previously evacuated and back-filled with N_2 gas). The solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until dryness. Acetone (0.30 mL, 1.0 M) was added and the resulting solution was transferred to a N_2-purged microwave reaction vial containing aldehyde **1** (0.30 mmol, 1.0 equiv). Alkene (0.90 mmol, 3.0 equiv) or alkyne (0.39 mmol, 1.3 equiv) was added and the reaction mixture was stirred at 55 ℃ for 1 h. The mixture was allowed

to cool to room temperature and transferred to a N_2-purged microwave reaction vial charged with K_2CO_3 (103.7 mg, 0.75 mmol, 2.5 equiv). Acetone (0.30 mL) then MeOTf (51 μL, 0.45 mmol, 1.5 equiv) were added. The resulting suspension was stirred at 55 ℃ for 1 h, then cooled to room temperature and transferred to a microwave reaction vial charged with boronic acid (0.45 or 0.90 mmol, 1.5 or 3.0 equiv) and $[Rh(L1)Cl]_2$ (7.1 mg, 0.0075 mmol, 2.5 mol%) (previously evacuated and back-filled with N_2 gas). Acetone (2.1 mL) and methanol (0.30 mL) were added and the mixture stirred at 55 ℃ for 1 h. Upon completion, the reaction mixture was filtered through a pad of SiO_2 and the filtrate concentrated under reduced pressure. Purification by flash column chromatography afforded the corresponding β-aryl ketone.

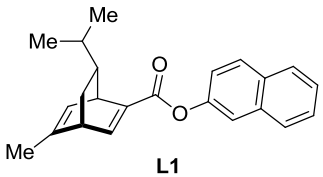
General Procedure E: sequential hydroacylation-elimination-conjugate addition employing copper(I) 3-methylsalicylate (CuMeSal).



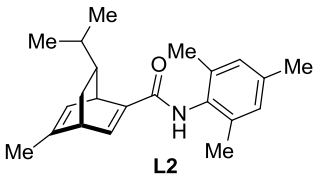
Acetone (~0.5 mL) was added to a microwave reaction vial charged with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 5 mol%) and dcpm (6.1 mg, 0.015 mmol, 5 mol%) (previously evacuated and back-filled with N_2 gas). The solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until dryness. Acetone (0.30 mL, 1.0 M) was added and the resulting solution was transferred to a N_2-purged microwave reaction vial containing aldehyde **1** (0.30 mmol, 1.0 equiv). Alkene (0.90 mmol, 3.0 equiv) or alkyne (0.39 mmol, 1.3 equiv) was added and the reaction mixture was stirred at 55 ℃ for 1 h. The mixture was allowed to cool to room temperature and transferred to a N_2-purged microwave reaction vial charged with CuMeSal (64.4 mg, 0.30 mmol, 1.0 equiv). Acetone (0.30 mL) was added and the

resulting suspension was stirred at 55 ℃ for 14 h, cooled to room temperature and filtered (through a thin Celite® layer under inert atmosphere) into a microwave reaction vial charged with boronic acid (0.60 mmol, 2.0 equiv), K_2CO_3 (41.5 mg, 0.30 mmol, 1.0 equiv) and $[Rh(L1)Cl]_2$ (7.1 mg, 0.0075 mmol, 2.5 mol%) (previously evacuated and back-filled with N_2 gas). Acetone (2.1 mL) and methanol (0.30 mL) were added and the mixture stirred at 55 ℃ for 1 h. Upon completion, the reaction mixture was filtered through a pad of SiO_2 and the filtrate concentrated under reduced pressure. Purification by flash column chromatography afforded the corresponding β-aryl ketone.

When 1,2-dichloroethane (DCE) is mentioned, it indicates that DCE was used instead of acetone for the whole process (volumes not modified). When $[Rh(L2)Cl]_2$ is mentioned, it indicates that $[Rh(L2)Cl]_2$ was used instead of $[Rh(L1)Cl]_2$ for the conjugate addition step.



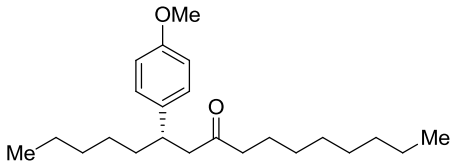
L1



L2

Note: products (**4l-y**, **4aa**, **4ae-ah**) synthesized by Dr. Bouisseau are not included.

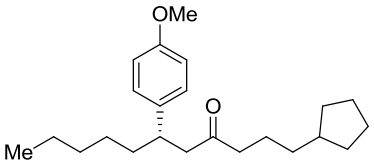
(*S*)-6-(4-Methoxyphenyl)hexadecan-8-one, 4a



Prepared according to General Procedure D, using **1a** (56 mg), 1-octene (0.14 mL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (petrol/Et_2O, 99:1) afforded *the title compound* (88 mg, 85% yield, 97% ee) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.08 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.77

(s, 3H, OCH_3), 3.10-3.03 (m, 1H, CH-CH_2-CO), 2.66 (dd, J = 13.5, 5.0 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.61 (dd, J = 13.5, 4.5 Hz, 1H, CH-$CH_a$$H_b$-CO), 2.31-2.14 (m, 2H, CO-CH_2-CH_2), 1.60-1.40 (m, 4H, 2 ×CH_2), 1.29-1.08 (m, 16H, 8 ×CH_2), 0.88-0.82 (m, 6H, 2 ×CH_2-CH_3); **δC** (101 MHz, $CDCl_3$): 210.7, 158.1, 136.9, 128.5, 113.9, 55.3, 50.4, 43.8, 40.6, 36.7, 31.93, 31.86, 31.8, 29.5, 29.2, 27.2, 23.7, 22.8, 22.6, 14.21, 14.16; **HRMS** (ESI^+) $C_{23}H_{38}O_2Na$ requires 369.2764 $[M+Na]^+$, found 369.2763; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2925, 2855, 1713, 1611, 1512, 1373, 1246; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 9.09 min, τ_{minor} = 9.58 min (97% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +20.0 ($c$ = 1.0, $CHCl_3$).

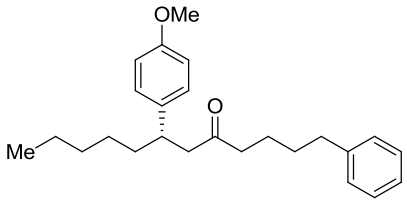
(*S*)-1-Cyclopentyl-6-(4-methoxyphenyl)undecan-4-one, 4b



Prepared according to General Procedure D, using **1a** (56 mg), allylcyclopentane (0.13 mL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (petrol/Et_2O, 97:3) afforded *the title compound* (78 mg, 75% yield, 91% ee) as a colorless oil. **δH** (400 MHz, $CDCl_3$): 7.08 (d, J = 8.5 Hz, 2H, Ar-H), 6.81 (d, J = 8.5 Hz, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 3.11-3.02 (m, 1H, CH-CH_2-CO), 2.66 (dd, J = 14.0, 5.5 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.60 (dd, J = 14.0, 5.0 Hz, 1H, CH-$CH_a$$H_b$-CO), 2.26 (dt, J = 16.5, 7.5 Hz, 1H, CO-C$H_c$$H_d$-$CH_2$), 2.18 (dt, J = 16.5, 7.5 Hz, 1H, CO-$CH_c$$H_d$-$CH_2$), 1.75-1.39 (m, 12H, 6 ×CH_2), 1.27-0.93 (m, 9H, CO-$(CH_2)_3$-CH and 4 ×CH_2), 0.82 (t, J = 7.0 Hz, 3H, CH_2-CH_3); **δC** (101 MHz, $CDCl_3$): 210.8, 158.0, 136.9, 128.5, 113.9, 55.3, 50.4, 44.0, 40.6, 40.0, 36.7, 35.7, 32.7, 31.9, 27.2, 25.3, 22.9, 22.7, 14.2; **HRMS** (ESI^+)

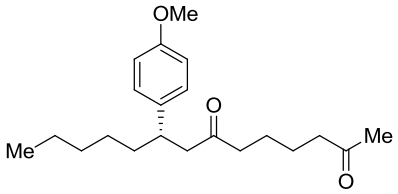
$C_{23}H_{36}O_2Na$ requires 367.2608 $[M+Na]^+$, found 367.2610; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2928, 2857, 1712, 1611, 1512, 1456, 1247, 1178, 1038; the **ee** was determined by HPLC using Chiralpak IC/AS-H columns in series (^{n}hexane/^{i}PrOH, 99:1); flow rate 0.70 mL/min; τ_{major} = 20.15 min, τ_{minor} = 21.51 min (91% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +19.9 (c = 1.0, $CHCl_3$).

(*S*)-7-(4-Methoxyphenyl)-1-phenyldodecan-5-one, 4c



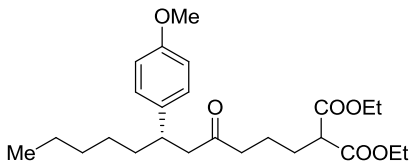
Prepared according to General Procedure D, using **1a** (56 mg), 4-phenyl-1-butene (0.14 mL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (petrol/Et_2O, 96:4) afforded *the title compound* (92 mg, 84% yield, 93% ee) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.32-7.25 (m, 2H, Ar-*H*), 7.23-7.13 (m, 3H, Ar-*H*), 7.10 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.84 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.80 (s, 3H, OCH_3), 3.14-3.04 (m, 1H, C*H*-CH_2-CO), 2.68 (dd, *J* = 14.0, 6.0 Hz, 1H, CH-CH_aH_b-CO), 2.63 (dd, *J* = 14.0, 5.5 Hz, 1H, CH-CH_aH_b-CO), 2.57 (t, *J* = 7.0 Hz, 2H, CH_2-Ph), 2.38-2.21 (m, 2H, CO-CH_2-CH_2), 1.64-1.47 (m, 6H, 3 × CH_2), 1.31-1.05 (m, 6H, 3 × CH_2), 0.85 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 210.4, 158.1, 142.4, 136.8, 128.5 (2C), 128.4, 125.8, 113.9, 55.3, 50.4, 43.5, 40.7, 36.7, 35.8, 31.9, 31.0, 27.2, 23.3, 22.6, 14.2; **HRMS** (ESI^+) $C_{25}H_{34}O_2Na$ requires 389.2462 $[M+Na]^+$, found 389.2451; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2927, 2856, 1712, 1611, 1512, 1455, 1247, 1178, 1036; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 15.99 min, τ_{minor} = 18.79 min (93% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +19.6 (c = 1.0, $CHCl_3$).

(*S*)-9-(4-Methoxyphenyl)tetradecane-2,7-dione, 4d



Prepared according to General Procedure D, using **1a** (56 mg), 5-hexen-2-one (0.10 mL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (gradient petrol/Et_2O, 9:1 to 7:3) afforded *the title compound* (84 mg, 84% yield, 94% ee) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.06 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.77 (s, 3H, OCH_3), 3.09-2.99 (m, 1H, C*H*-CH_2-CO), 2.65 (dd, *J* = 14.0, 6.0 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.60 (dd, *J* = 14.0, 5.0 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.34 (t, *J* = 7.0 Hz, 2H, CH_2-CO-CH_3), 2.31-2.13 (m, 2H, CH_2-CO-CH_2-CH_2), 2.09 (s, 3H, CO-CH_3), 1.60-1.46 (m, 2H, CH_2-CH_2-CH), 1.45-1.38 (m, 4H, CH_2-CH_2-CH_2-CO-CH_3), 1.27-1.02 (m, 6H, 3 × CH_2), 0.81 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 210.1, 208.9, 158.1, 136.7, 128.5, 113.9, 55.3, 50.4, 43.5, 43.4, 40.7, 36.7, 31.8, 30.0, 27.2, 23.2, 23.0, 22.6, 14.2; **HRMS** (ESI^+) $C_{21}H_{32}O_3Na$ requires 355.2244 $[M+Na]^+$, found 355.2244; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2956, 2928, 2856, 1712, 1611, 1512, 1465, 1357, 1246, 1178, 1036; the **ee** was determined by HPLC using a Chiralpak IC column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 99.08 min, τ_{minor} = 110.04 min (94% ee); $\boldsymbol{[\alpha]_D^{25}}$: +23.4 (c = 1.0, $CHCl_3$).

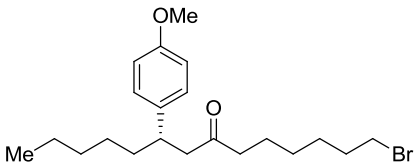
(*S*)-Diethyl 2-(6-(4-methoxyphenyl)-4-oxoundecyl)malonate, 4e



Prepared according to General Procedure D, using **1a** (56 mg), diethyl allylmalonate

(0.18 mL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (gradient petrol/Et_2O, 9:1 to 7:3) afforded *the title compound* (78 mg, 60% yield, 94% ee) as a pale yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.06 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.17 (app. qd, *J* = 7.0, 1.5 Hz, 4H, 2 × CO_2-C*H*$_2$-CH_3), 3.77 (s, 3H, OC*H*$_3$), 3.24 (t, *J* = 7.5 Hz, 1H, C*H*-CO_2Et), 3.09-2.99 (m, 1H, C*H*-CH_2-CO), 2.65 (dd, *J* = 13.0, 5.0 Hz, 1H, CH-C*H*$_a$H$_b$-CO), 2.60 (dd, *J* = 13.0, 4.5 Hz, 1H, CH-CH$_a$*H*$_b$-CO), 2.37-2.15 (m, 2H, CO-C*H*$_2$-CH_2), 1.80-1.71 (m, 2H, C*H*$_2$-CH-CO_2Et), 1.60-1.43 (m, 4H, C*H*$_2$-CH-CH_2-CO and CO-CH_2-C*H*$_2$), 1.29-1.02 (m, 12H, 2 × CO_2-CH_2-C*H*$_3$ and 3 × C*H*$_2$), 0.81 (t, *J* = 7.0 Hz, 3H, CH_2-CH_2-C*H*$_3$); **δ_C** (101 MHz, $CDCl_3$): 209.6, 169.4, 158.1, 136.7, 128.4, 113.9, 61.5, 55.3, 52.0, 50.4, 43.1, 40.7, 36.7, 31.8, 28.2, 27.2, 22.6, 21.3, 14.19, 14.17; **HRMS** (ESI^+) $C_{25}H_{38}O_6Na$ requires 457.2561 $[M+Na]^+$, found 457.2558; **ν_{max}** (film)/cm^{-1} 2956, 2930, 2858, 1749, 1731, 1513, 1463, 1369, 1247, 1178, 1035; the **ee** was determined by HPLC using a Chiralpak AS-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 19.17 min, τ_{minor} = 23.34 min (94% ee); $[\alpha]_D^{25}$: +19.2 (c = 1.0, $CHCl_3$).

(*S*)-1-Bromo-9-(4-methoxyphenyl)tetradecan-7-one, 4f



Prepared according to General Procedure D, using **1a** (56 mg), 6-bromo-1-hexene (0.12 mL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (petrol/Et_2O, 96:4) afforded *the title compound* (101 mg, 85% yield, 92% ee) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.07 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.78 (s, 3H, OC*H*$_3$), 3.36 (t, *J* = 7.0 Hz, 2H, C*H*$_2$-Br), 3.11-3.01 (m, 1H,

C*H*-CH_2-CO), 2.66 (dd, *J* = 14.5, 6.5 Hz, 1H, CH-C*H*$_a$H$_b$-CO), 2.60 (dd, *J* = 14.5, 6.0 Hz, 1H, CH-CH$_a$*H*$_b$-CO), 2.32-2.14 (m, 2H, CO-C*H*$_2$-CH$_2$), 1.84-1.75 (m, 2H, C*H*$_2$-CH$_2$-Br), 1.62-1.50 (m, 2H, CH$_2$-C*H*$_2$-CH), 1.50-1.40 (m, 2H, CO-CH$_2$-C*H*$_2$), 1.39-1.29 (m, 2H, C*H*$_2$-CH$_2$-CH$_2$-Br), 1.28-1.02 (m, 8H, 4 × C*H*$_2$), 0.82 (t, *J* = 7.0 Hz, 3H, CH$_2$-C*H*$_3$); **δc** (101 MHz, $CDCl_3$): 210.4, 158.1, 136.8, 128.5, 113.9, 55.3, 50.5, 43.5, 40.7, 36.7, 33.9, 32.6, 31.9, 28.3, 28.0, 27.2, 23.3, 22.6, 14.2; **HRMS** (ESI$^+$) $C_{21}H_{33}O_2{}^{79}BrNa$ requires 419.1556 [^{79}BrM+Na]$^+$, found 419.1554, $C_{21}H_{33}O_2{}^{81}BrNa$ requires 421.1536 [^{81}BrM+Na]$^+$, found 421.1534; **ν_{max}** (film)/cm^{-1} 2928, 2856, 1712, 1611, 1512, 1462, 1246, 1178, 1037; the **ee** was determined by HPLC using a Chiralpak AS-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 0.60 mL/min; τ_{major} = 12.91 min, τ_{minor} = 15.42 min (92% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +19.6 (c = 1.0, $CHCl_3$).

Gram-scale preparation:

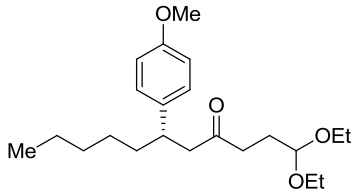
- $Rh(nbd)_2BF_4$ (41 mg, 0.11 mmol, 2 mol%), dcpm (45 mg, 0.11 mmol, 2 mol%), **1a** (1.04 g, 5.5 mmol), 6-bromo-1-hexene (2.2 mL, 16.5 mmol) in acetone (2.0 mL, 2.75 M) for the hydroacylation step.

- K_2CO_3 (1.90 g, 13.75 mmol), MeOTf (0.93 mL, 8.25 mmol) and additional acetone (total 11.0 mL, 0.5 M) for the elimination step.

- 4-methoxyphenylboronic acid (1.25 g, 8.25 mmol), additional K_2CO_3 (380 mg, 2.75 mmol, 0.5 equiv) and $[Rh(L2)Cl]_2$ (51 mg, 0.055 mmol, 1 mol%) with additional acetone (total 49 mL) and methanol (5.5 mL) for the conjugate addition step.

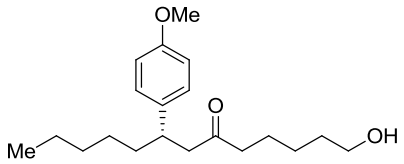
- purification by flash column chromatography (petrol/Et_2O, 96:4) afforded *the title compound* (1.87 g, 86% yield, 95% ee) as a colorless oil.

(*S*)-1,1-Diethoxy-6-(4-methoxyphenyl)undecan-4-one, 4g



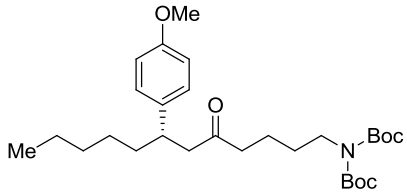
Prepared according to General Procedure D, using **1a** (56 mg), 3,3-diethoxy-1-propene (0.14 mL) and 4-methoxyphenylboronic acid (137 mg). The conjugate addition step was carried out for 14 h. Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (46 mg, 42% yield, 95% ee) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.07 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.38 (t, *J* = 5.5 Hz, 1H, C*H*-OEt), 3.77 (s, 3H, OCH_3), 3.62-3.53 (m, 2H, O-CH_2-CH_3), 3.47-3.35 (m, 2H, O-CH_2-CH_3), 3.11-3.02 (m, 1H, C*H*-CH_2-CO), 2.68 (dd, *J* = 13.0, 4.5 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.63 (dd, *J* = 13.0, 4.0 Hz, 1H, CH-$CH_a$$H_b$-CO), 2.39 (dt, *J* = 17.5, 7.0 Hz, 1H, CO-C$H_c$$H_d$-$CH_2$), 2.28 (dt, *J* = 17.5, 7.0 Hz, 1H, CO-$CH_c$$H_d$-$CH_2$), 1.81-1.73 (m, 2H, CO-$CH_2$-C$H_2$), 1.61-1.44 (m, 2H, C$H_2$-CH-$CH_2$-CO), 1.26-1.04 (m, 12H, 2 × O-CH_2-CH_3 and 3 × CH_2), 0.82 (t, *J* = 7.0 Hz, 3H, CH_2-CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 209.8, 158.1, 136.8, 128.5, 113.9, 102.1, 61.7, 61.6, 55.3, 50.5, 40.6, 38.5, 36.7, 31.9, 27.6, 27.2, 22.6, 15.41, 15.40, 14.2; **HRMS** (ESI^+) $C_{22}H_{36}O_4Na$ requires 387.2506 $[M+Na]^+$, found 387.2502; **ν_{max}** (film)/cm^{-1} 2972, 2929, 2873, 1714, 1611, 1513, 1458, 1373, 1248, 1122, 1062; the **ee** was determined by HPLC using a Chiralpak IC column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 17.33 min, τ_{minor} = 19.99 min (95% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +14.3 (c = 1.0, $CHCl_3$).

(*S*)-1-Hydroxy-8-(4-methoxyphenyl)tridecan-6-one, 4h



Prepared according to General Procedure E, using **1a** (56 mg), 4-penten-1-ol (93 μL) and 4-methoxyphenylboronic acid (91 mg). Purification by flash column chromatography (petrol/Et_2O, 1:1) afforded *the title compound* (81 mg, 84% yield, 92% ee) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.07 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.77 (s, 3H, OCH_3), 3.57 (t, *J* = 6.5 Hz, 2H, CH_2-OH), 3.10-3.00 (m, 1H, C*H*-CH_2-CO), 2.65 (dd, *J* = 14.5, 6.5 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.60 (dd, *J* = 14.5, 5.5 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.29 (dt, *J* = 17.0, 7.5 Hz, 1H, CO-C$H_c$$H_d$-$CH_2$), 2.19 (dt, *J* = 17.0, 7.5 Hz, 1H, CO-C$H_c$$H_d$-$CH_2$), 1.61-1.43 (m, 6H, 3 × CH_2), 1.26-1.05 (m, 8H, 4 × CH_2), 0.81 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δc** (101 MHz, $CDCl_3$): 210.6, 158.0, 136.8, 128.5, 113.9, 62.8, 55.3, 50.5, 43.6, 40.7, 36.7, 32.5, 31.8, 27.2, 25.3, 23.2, 22.6, 14.2; **HRMS** (ESI^+) $C_{20}H_{32}O_3Na$ requires 343.2244 $[M+Na]^+$, found 343.2243; **ν_{max}** (film)/cm^{-1} 3397 (br.), 2928, 2858, 1710, 1611, 1513, 1462, 1247, 1178, 1038; the **ee** was determined by HPLC using a Chiralpak IC column (^{n}hexane/^{i}PrOH, 95:5); flow rate 1.0 mL/min; τ_{major} = 44.76 min, τ_{minor} = 58.30 min (92% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +24.5 (c = 1.0, $CHCl_3$).

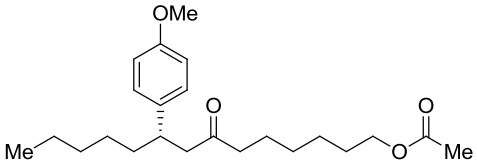
(*S*)-*N*,*N*-Di-Boc-1-amino-7-(4-methoxyphenyl)dodecan-5-one, 4i



Prepared according to General Procedure E, on a 0.20 mmol scale, using **1a** (38 mg, 0.20 mmol), di-*tert*-butyl *N*-3-butenylimino dicarboxylate[119] (0.16 mL) and 4-methoxy

phenylboronic acid (61 mg). Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (59 mg, 58% yield, 98% ee) as a pale yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.06 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.77 (s, 3H, OC*H*$_3$), 3.49 (t, *J* = 6.5 Hz, 2H, C*H*$_2$-N), 3.10-3.01 (m, 1H, C*H*-CH_2-CO), 2.68-2.56 (m, 2H, CH-C*H*$_2$-CO), 2.36-2.15 (m, 2H, CO-C*H*$_2$-CH_2), 1.65-1.42 (m, 24H, 2 × C(C*H*$_3$)$_3$ and 3 × C*H*$_2$), 1.26-1.04 (m, 6H, 3 × C*H*$_2$), 0.81 (t, *J* = 6.5 Hz, 3H, CH_2-C*H*$_3$); **δ_C** (101 MHz, $CDCl_3$): 210.0, 158.1, 152.8, 136.8, 128.5, 113.9, 82.3, 55.3, 50.4, 46.1, 43.2, 40.6, 36.7, 31.9, 28.6, 28.2, 27.2, 22.6, 20.8, 14.2; **HRMS** (ESI^+) $C_{29}H_{47}O_6NNa$ requires 528.3296 $[M+Na]^+$, found 528.3287; **ν_{max}** (film)/cm^{-1} 2956, 2931, 2856, 1747, 1714, 1691, 1513, 1458, 1367, 1247, 1178, 1136, 1037; the **ee** was determined by HPLC using a Chiralpak IA-3 column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 6.89 min, τ_{minor} = 7.59 min (98% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +12.0 (c = 1.0, $CHCl_3$).

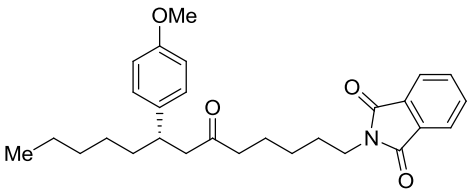
(*S*)-9-(4-Methoxyphenyl)-7-oxotetradecyl acetate, 4j



Prepared according to General Procedure D, using **1a** (56 mg), 5-hexenyl acetate (0.14 mL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (gradient petrol/Et_2O, 90:10 to 85:15) afforded *the title compound* (79 mg, 70% yield, 93% ee) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.07 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.01 (t, *J* = 6.5 Hz, 2H, CO_2-C*H*$_2$), 3.77 (s, 3H, OC*H*$_3$), 3.10-3.01 (m, 1H, C*H*-CH_2-CO), 2.66 (dd, *J* = 14.0, 6.0 Hz, 1H, CH-C*H*$_a$H$_b$-CO), 2.60 (dd, *J* = 14.0, 5.0 Hz, 1H, CH-CH_a*H*$_b$-CO), 2.27 (dt, *J* = 17.0, 7.5 Hz, 1H, CO-C*H*$_c$H$_d$-CH_2),

2.18 (dt, *J* = 17.0, 7.5 Hz, 1H, CO-CH_cH_d-CH_2), 2.03 (s, 3H, CO-CH_3), 1.60-1.40 (m, 6H, CO_2-CH_2-CH_2, CH_2-CH_2-CH and CO-CH_2-CH_2), 1.31-1.05 (m, 10H, 5 × CH_2), 0.82 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δC** (101 MHz, $CDCl_3$): 210.5, 171.3, 158.1, 136.8, 128.5, 113.9, 64.6, 55.3, 50.4, 43.6, 40.7, 36.7, 31.8, 28.8, 28.5, 27.2, 25.8, 23.4, 22.6, 21.1, 14.2; **HRMS** (ESI^+) $C_{23}H_{36}O_4Na$ requires 399.2506 $[M+Na]^+$, found 399.2501; **ν_{max}** (film)/cm^{-1} 2928, 2857, 1737, 1712, 1611, 1512, 1463, 1366, 1244, 1178, 1037; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 14.58 min, τ_{minor} = 16.20 min (93% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +18.2 (c = 1.0, $CHCl_3$).

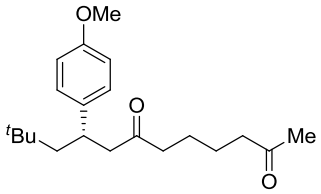
(*S*)-2-(8-(4-Methoxyphenyl)-6-oxotridecyl)isoindoline-1,3-dione, 4k



Prepared according to General Procedure D, using **1a** (56 mg), 2-(pent-4-en-1-yl)isoindoline-1,3-dione[120] (194 mg) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (petrol/Et_2O, 3:1) afforded *the title compound* (119 mg, 88% yield, 94% ee) as an off-white solid. **M.p.** (Et_2O): 39-41 ℃; **δ_H** (400 MHz, $CDCl_3$): 7.88-7.83 (m, 2H, Ar-*H*), 7.76-7.70 (m, 2H, Ar-*H*), 7.06 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.80 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.76 (s, 3H, OCH_3), 3.62 (t, *J* = 7.5 Hz, 2H, CH_2-N), 3.09-2.99 (m, 1H, C*H*-CH_2-CO), 2.64 (dd, *J* = 13.5, 5.5 Hz, 1H, CH-CH_aH_b-CO), 2.59 (dd, *J* = 13.5, 4.5 Hz, 1H, CH-CH_aH_b-CO), 2.27 (dt, *J* = 17.0, 7.5 Hz, 1H, CO-CH_cH_d-CH_2), 2.17 (dt, *J* = 17.0, 7.5 Hz, 1H, CO-CH_cH_d-CH_2), 1.64-1.43 (m, 6H, CH_2-CH_2-N, CH_2-CH_2-CH and CO-CH_2-CH_2), 1.27-1.02 (m, 8H, 4 × CH_2), 0.81 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δC** (101 MHz, $CDCl_3$): 210.3, 168.5, 158.0, 136.8, 134.0, 132.3, 128.5, 123.3, 113.9,

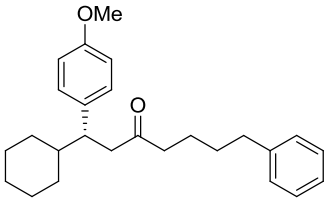
55.3, 50.4, 43.4, 40.7, 37.9, 36.6, 31.8, 28.5, 27.2, 26.4, 23.1, 22.6, 14.2; **HRMS** (ESI^+) $C_{28}H_{36}O_4N$ requires 450.2639 $[M+H]^+$, found 450.2635; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2928, 2857, 1772, 1709, 1611, 1512, 1466, 1438, 1396, 1369, 1246, 1178, 1037; the **ee** was determined by HPLC using a Chiralpak AS-H column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 30.49 min, τ_{minor} = 37.93 min (94% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +15.9 (c = 1.0, $CHCl_3$).

(*S*)-9-(4-Methoxyphenyl)-11,11-dimethyldodecane-2,7-dione, 4ab



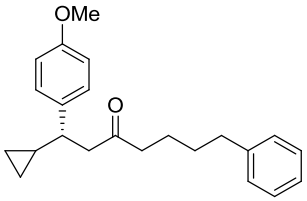
Prepared according to General Procedure D, on a 0.20 mmol scale, using **1j** (38 mg, 0.20 mmol), 5-hexen-2-one (70 μL) and 4-methoxyphenylboronic acid (46 mg). Purification by flash column chromatography (gradient petrol/Et_2O, 9:1 to 3:1) afforded *the title compound* (40 mg, 60% yield, 95% ee) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.10 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.79 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.77 (s, 3H, OCH_3), 3.27-3.19 (m, 1H, C*H*-CH_2-CO), 2.62 (dd, *J* = 15.5, 8.0 Hz, 1H, CH-CH_aH_b-CO), 2.55 (dd, *J* = 15.5, 6.5 Hz, 1H, CH-CH_aH_b-CO), 2.36-2.11 (m, 4H, 2 × CH_2-CH_2-CO), 2.09 (s, 3H, CO-CH_3), 1.69-1.44 (m, 2H, CH_2-CH-CH_2-CO), 1.43-1.38 (m, 4H, 2 × CH_2), 0.76 (s, 9H, C(CH_3)$_3$); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 209.9, 208.8, 158.0, 138.2, 128.7, 113.9, 55.3, 52.9, 50.0, 43.53, 43.49, 37.7, 31.4, 30.2, 30.0, 23.3, 22.9; **HRMS** (ESI^+) $C_{21}H_{32}O_3Na$ requires 355.2244 $[M+Na]^+$, found 355.2242; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2950, 1713, 1512, 1465, 1364, 1246; the **ee** was determined by HPLC using a Chiralpak IC column (^{n}hexane/^{i}PrOH, 95:5); flow rate 1.0 mL/min; τ_{major} = 38.42 min, τ_{minor} = 33.58 min (95% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +43.9 (c = 1.0, $CHCl_3$).

(*R*)-1-Cyclohexyl-1-(4-methoxyphenyl)-7-phenylheptan-3-one, 4ac



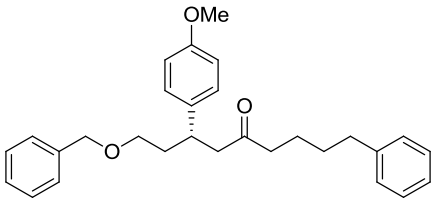
Prepared according to General Procedure D, using **1k** (60 mg), 4-phenyl-1-butene (0.14 mL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (82 mg, 72% yield, 98% ee) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.28-7.23 (m, 2H, Ar-*H*), 7.19-7.09 (m, 3H, Ar-*H*), 7.02 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.79 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.75 (s, 3H, OCH_3), 2.88 (ddd, *J* = 9.5, 7.5, 5.5 Hz, 1H, C*H*-CH_2-CO), 2.75 (dd, *J* = 15.5, 5.5 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.67 (dd, *J* = 15.5, 9.5 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.51 (t, *J* = 7.0 Hz, 2H, CH_2-Ph), 2.28 (dt, *J* = 17.0, 7.0 Hz, 1H, CO-C$H_c$$H_d$-$CH_2$), 2.17 (dt, *J* = 17.0, 7.0 Hz, 1H, CO-C$H_c$$H_d$-$CH_2$), 1.80-1.68 (m, 2H, Cy-*H*), 1.65-1.55 (m, 2H, Cy-*H*), 1.50-1.34 (m, 5H, CO-CH_2-CH_2-CH_2 and Ar-CH-C*H*), 1.27-0.71 (m, 6H, Cy-*H*); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 210.8, 158.0, 142.4, 135.6, 129.3, 128.5, 128.4, 125.8, 113.6, 55.3, 46.9, 46.6, 43.5, 43.2, 35.8, 31.4, 30.9, 30.8, 26.6, 26.5 (2C), 23.3; **HRMS** (ESI^+) $C_{26}H_{34}O_2Na$ requires 401.2451 $[M+Na]^+$, found 401.2449; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 3027, 2925, 2851, 1712, 1611, 1511, 1451, 1246; the **ee** was determined by HPLC using a Chiralpak AS-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 9.92 min, τ_{minor} = 13.14 min (98% ee); $\boldsymbol{[\alpha]_D^{25}}$: +30.9 (c = 1.0, $CHCl_3$).

(*R*)-1-Cyclopropyl-1-(4-methoxyphenyl)-7-phenylheptan-3-one, 4ad



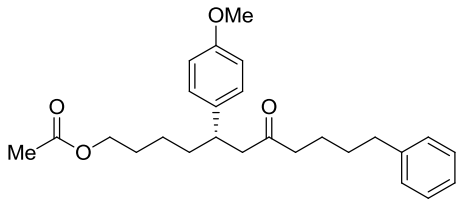
Prepared according to General Procedure E, using **1l** (47 mg), 4-phenyl-1-butene (0.14 mL) and 4-methoxyphenylboronic acid (91 mg). Purification by flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (54 mg, 54% yield, 98% ee) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.30-7.24 (m, 2H, Ar-*H*), 7.20-7.11 (m, 5H, Ar-*H*), 6.83 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.77 (s, 3H, OCH_3), 2.83-2.78 (m, 2H, CH-CH_2-CO), 2.55 (t, *J* = 7.0 Hz, 2H, CH_2-Ph), 2.43-2.22 (m, 3H, C*H*-CH_2-CO and CO-CH_2-CH_2), 1.55-1.49 (m, 4H, CO-CH_2-CH_2-CH_2), 1.02-0.92 (m, 1H, Ar-CH-C*H*), 0.57-0.49 (m, 1H, CH-C$H_a$$H_b$-$CH_c$$H_d$), 0.44-0.36 (m, 1H, CH-$CH_a$$H_b$-C$H_c$$H_d$), 0.21 (td, *J* = 9.5, 5.0 Hz, 1H, CH-$CH_a$$H_b$-$CH_c$$H_d$), 0.13 (td, *J* = 9.5, 5.0 Hz, 1H, CH-$CH_a$$H_b$-$CH_c$$H_d$); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 210.2, 158.1, 142.3, 136.7, 128.5, 128.4 (2C), 125.8, 113.9, 55.3, 49.9, 45.6, 43.8, 35.8, 31.0, 23.3, 17.8, 5.4, 4.3; **HRMS** (ESI^+) $C_{23}H_{28}O_2Na$ requires 359.1982 $[M+Na]^+$, found 359.1984; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 3026, 3000, 2934, 2858, 1711, 1611, 1512, 1455, 1245; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 18.76 min, τ_{minor} = 22.94 min (98% ee); $\boldsymbol{[\alpha]_D^{25}}$: –17.9 (c = 1.0, $CHCl_3$).

(*S*)-1-(Benzyloxy)-3-(4-methoxyphenyl)-9-phenylnonan-5-one, 4ai



Prepared according to General Procedure D, using **1q** (76 mg), 4-phenyl-1-butene (0.14 mL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (petrol/Et_2O, 85:15) afforded *the title compound* (107 mg, 83% yield, 92% ee) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.35-7.23 (m, 7H, Ar-*H*), 7.19-7.10 (m, 3H, Ar-*H*), 7.08 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.80 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.42 (d, *J* = 12.0 Hz, 1H, Ph-C$H_a$$H_b$-O), 4.38 (d, *J* = 12.0 Hz, 1H, Ph-C$H_a$$H_b$-O), 3.77 (s, 3H, OC$H_3$), 3.36-3.24 (m, 3H, C*H*-CH_2-CO and Ph-CH_2-O-CH_2), 2.70 (dd, *J* = 13.5, 5.0 Hz, 1H, CH-C$H_c$$H_d$-CO), 2.65 (dd, *J* = 13.5, 4.0 Hz, 1H, CH-C$H_c$$H_d$-CO), 2.53 (t, *J* = 7.0 Hz, 2H, CH_2-CH_2-Ph), 2.34-2.17 (m, 2H, CO-CH_2-CH_2), 2.01-1.91 (m, 1H, O-CH_2-C$H_e$$H_f$), 1.83-1.73 (m, 1H, O-$CH_2$-C$H_e$$H_f$), 1.54-1.45 (m, 4H, 2 × CH_2); **δ_C** (101 MHz, $CDCl_3$): 209.9, 158.2, 142.4, 138.6, 136.0, 128.6, 128.49, 128.46, 128.4, 127.8, 127.6, 125.8, 114.0, 73.0, 68.3, 55.3, 50.1, 43.3, 37.4, 36.5, 35.8, 31.0, 23.3; **HRMS** (ESI^+) $C_{29}H_{34}O_3Na$ requires 453.2400 $[M+Na]^+$, found 453.2401; **ν_{max}** (film)/cm^{-1} 3028, 2933, 2858, 1712, 1611, 1512, 1454, 1366, 1248; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 25.36 min, τ_{minor} = 29.33 min (92% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –8.2 (c = 1.0, $CHCl_3$).

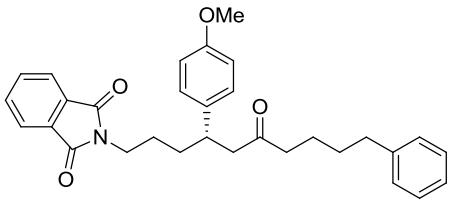
(*S*)-5-(4-Methoxyphenyl)-7-oxo-11-phenylundecyl acetate, 4aj



Prepared according to General Procedure D, on a 0.20 mmol scale, using **1r** (46 mg, 0.20 mmol), 4-phenyl-1-butene (0.09 mL) and 4-methoxyphenylboronic acid (46 mg). Purification by flash column chromatography (gradient petrol/Et_2O, 9:1 to 8:2) afforded *the*

title compound (72 mg, 87% yield, 93% ee) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.28-7.23 (m, 2H, Ar-*H*), 7.19-7.10 (m, 3H, Ar-*H*), 7.06 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.02-3.91 (m, 2H, CO_2-CH_2), 3.76 (s, 3H, OCH_3), 3.11-3.02 (m, 1H, C*H*-CH_2-CO), 2.69-2.57 (m, 2H, CH-CH_2-CO), 2.54 (t, *J* = 7.0 Hz, 2H, CH_2-Ph), 2.35-2.15 (m, 2H, CO-CH_2-CH_2), 2.00 (s, 3H, CH_3-CO), 1.63-1.47 (m, 8H, 4 × CH_2), 1.26-1.09 (m, 2H, CH_2); **δ_C** (101 MHz, $CDCl_3$): 210.1, 171.3, 158.2, 142.3, 136.3, 128.5 (2C), 128.4, 125.8, 114.0, 64.4, 55.3, 50.3, 43.5, 40.4, 36.1, 35.5, 31.0, 28.5, 23.8, 23.3, 21.1; **HRMS** (ESI^+) $C_{26}H_{34}O_4Na$ requires 433.2349 $[M+Na]^+$, found 433.2340; **ν_{max}** (film)/cm^{-1} 3027, 2935, 2859, 1736, 1712, 1611, 1512, 1455, 1365, 1245, 1179, 1035; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 31.92 min, τ_{minor} = 36.98 min (93% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +13.6 (c = 1.0, $CHCl_3$).

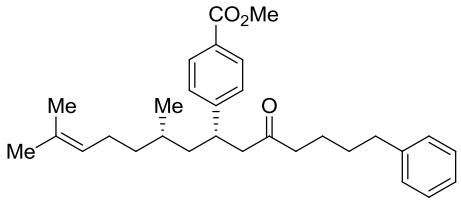
(*S*)-2-(4-(4-Methoxyphenyl)-6-oxo-10-phenyldecyl)isoindoline-1,3-dione, 4ak



Prepared according to General Procedure D, on a 0.20 mmol scale, using **1s** (61 mg, 0.20 mmol), 4-phenyl-1-butene (0.09 mL) and 4-methoxyphenylboronic acid (46 mg). Purification by flash column chromatography (gradient petrol/Et_2O, 9:1 to 7:3) afforded *the title compound* (76 mg, 79% yield, 93% ee) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.83-7.78 (m, 2H, Ar-*H*), 7.72-7.66 (m, 2H, Ar-*H*), 7.28-7.22 (m, 2H, Ar-*H*), 7.18-7.09 (m, 3H, Ar-*H*), 7.05 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.78 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.74 (s, 3H, OCH_3), 3.61 (t, *J* = 6.5 Hz, 2H, N-CH_2), 3.13-3.05 (m, 1H, C*H*-CH_2-CO), 2.67 (dd, *J* = 16.0, 8.0 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.60 (dd, *J* = 16.0, 6.5 Hz, 1H, CH-C$H_a$$H_b$-CO), 2.52 (t, *J* = 7.0

Hz, 2H, CH_2-Ph), 2.33-2.16 (m, 2H, CO-CH_2-CH$_2$), 1.68-1.45 (m, 8H, 4 × CH_2); **δ_C** (101 MHz, $CDCl_3$): 209.9, 168.5, 158.2, 142.3, 135.9, 134.0, 132.2, 128.5 (2C), 128.4, 125.8, 123.3, 114.0, 55.3, 50.2, 43.5, 40.2, 38.0, 35.8, 33.8, 30.9, 26.7, 23.3; **HRMS** (ESI^+) $C_{31}H_{34}O_4N$ requires 484.2482 $[M+H]^+$, found 484.2481; **ν_{max}** (film)/cm^{-1} 3027, 2935, 2858, 1771, 1709, 1611, 1512, 1454, 1437, 1396, 1370, 1248, 1179, 1033; the **ee** was determined by HPLC using a Chiralpak IA-3 column (^{n}hexane/^{i}PrOH, 95:5); flow rate 1.0 mL/min; τ_{major} = 42.42 min, τ_{minor} = 54.57 min (93% ee); $[\alpha]_D^{25}$: +4.1 (c = 1.0, $CHCl_3$).

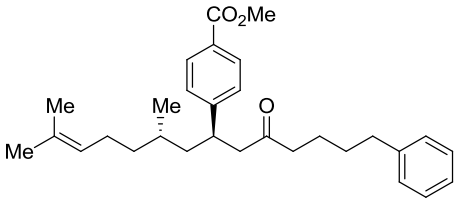
Methyl 4-((7*S*,9*S*)-9,13-dimethyl-5-oxo-1-phenyltetradec-12-en-7-yl)benzoate, 4al



Prepared according to General Procedure D, on a 0.20 mmol scale, using **1t** (48 mg, 0.20 mmol), 4-phenyl-1-butene (0.09 mL), 4-(methoxycarbonyl)phenylboronic acid (54 mg) and $[Rh(L2)Cl]_2$ (4.6 mg) in DCE. The conjugate addition step was carried out with additional K_2CO_3 (14 mg, 0.10 mmol, 0.5 equiv). dr >20:1. Purification by flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (59 mg, 66% yield, >99% ee) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.94 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.28-7.22 (m, 4H, Ar-*H*), 7.19-7.13 (m, 1H, Ar-*H*), 7.11 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 5.06-4.99 (m, 1H, C*H*=C(CH$_3$)$_2$), 3.89 (s, 3H, CO$_2$-CH_3), 3.37-3.29 (m, 1H, C*H*-CH$_2$-CO), 2.72-2.58 (m, 2H, CH-CH_2-CO), 2.53 (t, *J* = 7.0 Hz, 2H, CH_2-Ph), 2.35-2.16 (m, 2H, CO-CH_2-CH$_2$), 2.03-1.92 (m, 1H, CH_aH$_b$-CH=C(CH$_3$)$_2$), 1.88-1.76 (m, 1H, CH$_a$$H_b$-CH=C(CH$_3$)$_2$), 1.66 (s, 3H, (C$H_3$)$_c$(CH$_3$)$_d$-C=CH), 1.57 (s, 3H, (CH$_3$)$_c$(C$H_3$)$_d$-C=CH), 1.55-1.38 (m, 7H, C*H*-CH$_3$ and 3 × CH_2), 1.24-1.14 (m, 1H, CH$_2$-CH_eH$_f$-CH-CH$_3$), 1.13-1.04 (m, 1H, CH$_2$-

CH_eH_f-CH-CH_3), 0.80 (d, *J* = 6.5 Hz, 3H, CH-CH_3); **δ_C** (101 MHz, $CDCl_3$): 209.5, 167.1, 150.7, 142.3, 131.4, 129.9, 128.5, 128.40, 128.35, 127.7, 125.9, 124.8, 52.1, 49.8, 44.0, 43.5, 38.8, 36.1, 35.8, 30.9, 29.9, 25.8, 25.2, 23.3, 20.3, 17.8; **HRMS** (ESI^+) $C_{30}H_{40}O_3Na$ requires 471.2870 $[M+Na]^+$, found 471.2867; **ν_{max}** (film)/cm^{-1} 2951, 2915, 2852, 1721, 1610, 1435, 1278, 1180, 1113, 1019; the **ee** was determined by HPLC using two Chiralpak AD-H columns in series (^{n}hexane/^{i}PrOH, 99:1); flow rate 0.8 mL/min; τ_{major} = 61.81 min, τ_{minor} = 85.69 min (>99% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –1.2 (c = 1.0, $CHCl_3$).

Methyl 4-((7*R*,9*S*)-9,13-dimethyl-5-oxo-1-phenyltetradec-12-en-7-yl)benzoate, 4am

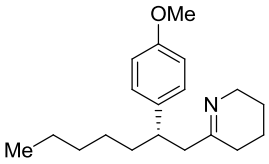


Prepared according to General Procedure D, on a 0.20 mmol scale, using **1t** (48 mg, 0.20 mmol), 4-phenyl-1-butene (0.09 mL) and 4-(methoxycarbonyl)phenylboronic acid (108 mg). A mixture of $Rh(nbd)_2BF_4$ (3.7 mg, 0.010 mmol) and (*S*)-BINAP (6.2 mg, 0.010 mmol) was used instead of $[Rh(L1)Cl]_2$; the conjugate addition step was carried out with additional K_2CO_3 (28 mg, 0.20 mmol, 1.0 equiv) for 4 h. dr 8:1. Purification by flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (56 mg, 62% yield, 99% ee) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.87 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.21-7.14 (m, 4H, Ar-*H*), 7.12-7.06 (m, 1H, Ar-*H*), 7.04 (d, *J* = 7.0 Hz, 2H, Ar-*H*), 4.91-4.84 (m, 1H, C*H*=$C(CH_3)_2$), 3.82 (s, 3H, CO_2-CH_3), 3.31-3.22 (m, 1H, C*H*-CH_2-CO), 2.61 (dd, *J* = 16.5, 7.5 Hz, 1H, CH-CH_aH_b-CO), 2.53 (dd, *J* = 16.5, 6.5 Hz, 1H, CH-CH_aH_b-CO), 2.46 (t, *J* = 7.0 Hz, 2H, CH_2-Ph), 2.29-2.08 (m, 2H, CO-CH_2-CH_2), 1.83-1.69 (m, 2H, CH_2-CH=$C(CH_3)_2$), 1.54 (s, 3H, $(CH_3)_c(CH_3)_d$-C=CH), 1.46 (s, 3H, $(CH_3)_c(CH_3)_d$-C=CH), 1.44-

0.95 (m, 9H, C*H*-CH_3 and 4 × CH_2), 0.79 (d, *J* = 6.0 Hz, 3H, CH-CH_3); **δC** (101 MHz, $CDCl_3$): 209.4, 167.1, 150.2, 142.2, 131.3, 129.9, 128.5, 128.4, 127.8, 127.7, 125.9, 124.7, 52.1, 50.5, 43.5, 43.1, 38.8, 37.9, 35.5, 30.9, 29.9, 25.8, 25.4, 23.3, 19.1, 17.7; the **ee** was determined by HPLC using two Chiralpak AD-H columns in series (^{n}hexane/^{i}PrOH, 99:1); flow rate 0.8 mL/min; τ_{major} = 75.33 min, τ_{minor} = 59.12 min (99% ee).

5.2.5 Heterocycle synthesis and mono-conjugate addition

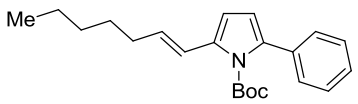
(*S*)-6-(2-(4-Methoxyphenyl)heptyl)-2,3,4,5-tetrahydropyridine, 5a



Trifluoroacetic acid (0.13 mL, 1.72 mmol) was added to a solution of **4i** (44 mg, 0.086 mmol) in CH_2Cl_2 (0.5 mL). The resulting solution was stirred at 23 ℃ for 4 h and cooled to 0 ℃. The pH was adjusted to 12-13 using 1 M aqueous solution of NaOH and the mixture extracted with CH_2Cl_2 (4×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (1 drop of triethylamine/100 mL acetone) afforded *the title compound* (21 mg, 85% yield, 98% ee, 100% es) as a yellow oil. **δH** (400 MHz, $CDCl_3$): 7.07 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.78 (s, 3H, OCH_3), 3.55-3.45 (m, 2H, CH_2-N), 2.91-2.82 (m, 1H, Ar-C*H*), 2.44 (dd, *J* = 13.5, 7.0 Hz, 1H, CH-C$H_a$$H_b$-C=N), 2.30 (dd, *J* = 13.5, 8.5 Hz, 1H, CH-C$H_a$$H_b$-C=N), 1.94 (dt, *J* = 13.0, 6.5 Hz, 1H, CH_2-C$H_c$$H_d$-C=N), 1.78 (dt, *J* = 13.0, 6.0 Hz, 1H, CH_2-C$H_c$$H_d$-C=N), 1.65-1.40 (m, 6H, 3 × CH_2), 1.24-1.06 (m, 6H, 3 × CH_2), 0.81 (t, *J* = 6.5 Hz, 3H, CH_2-CH_3); **δC** (101 MHz, $CDCl_3$): 170.5, 157.9, 137.3, 128.6, 113.7, 55.3, 49.3, 48.8, 43.2, 36.5, 32.0, 30.2,

27.2, 22.7, 21.9, 19.7, 14.2; **HRMS** (ESI$^+$) $C_{19}H_{30}NO$ requires 288.2322 $[M+H]^+$, found 288.2319; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2928, 2853, 1658, 1611, 1512, 1464, 1246, 1178, 1039; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 96:4); flow rate 1.0 mL/min; τ_{major} = 8.21 min, τ_{minor} = 7.33 min (98% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +42.3 (c = 1.0, $CHCl_3$).

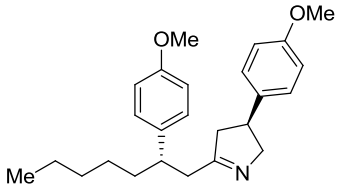
(*E*)-*tert*-Butyl 2-(hept-1-en-1-yl)-5-phenyl-1*H*-pyrrole-1-carboxylate, 5b



Acetone was added to a microwave reaction vial charged with $Rh(nbd)_2BF_4$ (3.7 mg, 0.010 mmol) and dcpm (4.1 mg, 0.010 mmol) (previously evacuated and back-filled with N_2 gas). The solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until dryness. Acetone (0.20 mL) was added and the resulting solution was transferred to a N_2-purged microwave reaction vial containing **1a** (37.7 mg, 0.20 mmol) and *tert*-butyl (1-phenylprop-2-yn-1-yl)carbamate[50b] (60.1 mg, 0.26 mmol). The reaction mixture was stirred at 23 ℃ for 1 h and transferred to a N_2-purged microwave reaction vial charged with CuMeSal (42.9 mg, 0.20 mmol). Acetone (0.20 mL) was added and the resulting suspension was stirred at 55 ℃ for 14 h. Upon completion, the mixture was filtered through a pad of SiO_2 and the filtrate concentrated under reduced pressure. Purification by flash column chromatography (petrol/EtOAc, 95:5) afforded *the title compound* (38.6 mg, 57% yield) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.29-7.17 (m, 5H, Ar-*H*), 6.71 (dm, *J* = 15.5 Hz, 1H, CH_2-CH=C*H*), 6.26 (d, *J* = 3.5 Hz, 1H, Ar-C=CH-C*H*), 6.07 (d, *J* = 3.5 Hz, 1H, Ar-C=C*H*-CH), 6.00 (dt, *J* = 15.5, 7.0 Hz, 1H, CH_2-C*H*=CH), 2.16-2.09 (m, 2H, CH_2-CH=CH), 1.44-1.22 (m, 6H, 3 × CH_2), 1.18 (s, 9H, C(CH_3)$_3$), 0.83 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101

MHz, $CDCl_3$): 150.2, 136.0, 135.30, 135.27, 131.9, 128.4, 128.0, 126.9, 120.6, 113.1, 108.3, 83.9, 33.2, 31.6, 29.2, 27.4, 22.7, 14.2; **HRMS** (CI^+) $C_{22}H_{30}NO_2$ requires 340.2271 $[M+H]^+$, found 340.2276; ν_{max} (film)/cm^{-1} 2957, 2927, 2856, 1740, 1476, 1370, 1305, 1146, 1076.

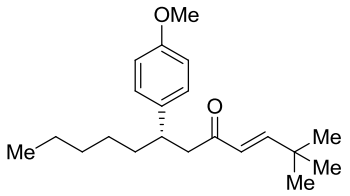
(*S*)-3-(4-Methoxyphenyl)-5-((*S*)-2-(4-methoxyphenyl)heptyl)-3,4-dihydro-2*H*-pyrrole, 5c



General Procedure E was first followed, on a 0.20 mmol scale, using **1a** (38 mg, 0.20 mmol), di-*tert*-butyl prop-2-ynylimidodicarbonate[121] (66 mg) and 4-methoxyphenyl boronic acid (122 mg, 0.80 mmol, 4.0 equiv). The hydroacylation step was carried out, using PNP(Cy) (4.2 mg) instead of dcpm, at 23 ℃ for 3 h. The filtrate was concentrated under reduced pressure and dissolved in CH_2Cl_2 (2.0 mL), followed by the addition of trifluoroacetic acid (0.31 mL, 4.0 mmol). The resulting mixture was stirred at 23 ℃ for 4 h and cooled to 0 ℃. The pH was adjusted to 12-13 using 1 M aqueous solution of NaOH and the mixture extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. dr 17:1. Purification by flash column chromatography (gradient petrol/EtOAc, 9:1 to 7:3) afforded *the title compound* (55 mg, 72% yield, >99% ee) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 7.10 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.83 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.76 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.15 (dd, *J* = 15.5, 8.5 Hz, 1H, C$H_a$$H_b$-N), 3.85-3.70 (m, 7H, 2 × OCH_3 and C$H_a$$H_b$-N), 3.34-3.25 (m, 1H, C*H*-CH_2-N), 2.99-2.90 (m, 1H, CH_2-CH_2-C*H*-CH_2), 2.79 (dd, *J* = 17.5, 9.5 Hz, 1H, C$H_c$$H_d$-CH-$CH_2$-N), 2.71 (dd, *J* = 14.0, 6.5 Hz, 1H, CH_2-CH_2-CH-

CH_eH$_f$), 2.61 (dd, *J* = 14.0, 9.0 Hz, 1H, CH_2-CH_2-CH-CH$_e$$H_f$), 2.28 (dd, *J* = 17.5, 6.5 Hz, 1H, CH$_c$$H_d$-CH-$CH_2$-N), 1.70-1.49 (m, 2H, CH_2-CH_2-CH-CH_2), 1.28-1.11 (m, 6H, 3 × CH_2), 0.82 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δC** (101 MHz, $CDCl_3$): 177.0, 158.07, 158.06, 137.5, 137.0, 128.6, 127.7, 114.0, 113.9, 69.1, 55.4, 55.3, 47.3, 43.1, 41.9, 41.2, 37.1, 31.9, 27.2, 22.7, 14.2; **HRMS** (ESI$^+$) $C_{25}H_{34}NO_2$ requires 380.2584 $[M+H]^+$, found 380.2589; **νmax** (film)/cm^{-1} 2928, 2856, 1642, 1611, 1584, 1512, 1463, 1301, 1246, 1178, 1037; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 97:3); flow rate 1.0 mL/min; τ_{major} = 30.31 min, τ_{minor} = 21.10 min (>99% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +113.8 (c = 1.0, $CHCl_3$).

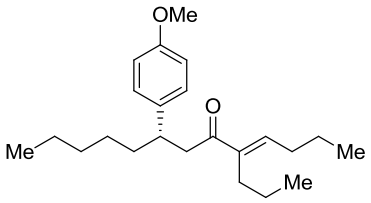
(*S*,*E*)-7-(4-Methoxyphenyl)-2,2-dimethyldodec-3-en-5-one, 6a



Prepared according to General Procedure D, using **1a** (56 mg), 3,3-dimethyl-1-butyne (48 μL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (petrol/Et_2O, 96:4) afforded *the title compound* (87 mg, 92% yield, 94% ee) as a pale yellow oil. **δH** (400 MHz, $CDCl_3$): 7.09 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.68 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 5.89 (d, *J* = 16.0 Hz, 1H, CO-C*H*), 3.77 (s, 3H, OCH_3), 3.13-3.04 (m, 1H, C*H*-CH_2-CO), 2.80 (dd, *J* = 14.0, 6.0 Hz, 1H, CH-CH_aH$_b$-CO), 2.75 (dd, *J* = 14.0, 5.5 Hz, 1H, CH-CH$_a$$H_b$-CO), 1.68-1.48 (m, 2H, CH_2-CH_2-CH), 1.27-1.07 (m, 6H, 3 × CH_2), 1.02 (s, 9H, C(CH_3)$_3$), 0.82 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δC** (101 MHz, $CDCl_3$): 200.6, 158.0, 157.2, 137.1, 128.5, 125.9, 113.9, 55.3, 48.1, 41.0, 36.5, 33.8, 31.9, 28.8, 27.2, 22.6, 14.2; **HRMS** (ESI$^+$) $C_{21}H_{33}O_2$ requires 317.2475

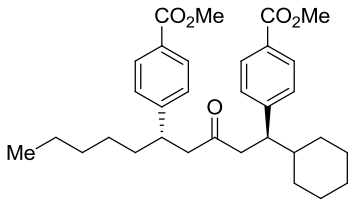
$[M+H]^+$, found 317.2478; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2958, 2929, 2860, 1672, 1622, 1513, 1463, 1365, 1301, 1247, 1178, 1039; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 9.98 min, τ_{minor} = 11.22 min (94% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +9.1 (c = 1.0, $CHCl_3$).

(*S*,*E*)-8-(4-Methoxyphenyl)-5-propyltridec-4-en-6-one, 6b



Prepared according to General Procedure D, using **1a** (56 mg), 4-octyne (57 μL) and 4-methoxyphenylboronic acid (68 mg). Purification by flash column chromatography (gradient petrol/Et_2O, 99:1 to 97:3) afforded *the title compound* (54 mg, 52% yield, 93% ee) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.08 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.48 (d, *J* = 7.5 Hz, 1H, CO-C=C*H*), 3.77 (s, 3H, OCH_3), 3.15-3.06 (m, 1H, C*H*-CH_2-CO), 2.91 (dd, *J* = 15.5, 7.0 Hz, 1H, CH-CH_aH_b-CO), 2.82 (dd, *J* = 15.5, 7.0 Hz, 1H, CH-CH_aH_b-CO), 2.22-2.13 (m, 4H, CH_2-C=CH-CH_2), 1.65-1.48 (m, 2H, CH_2-CH-CH_2-CO), 1.48-1.39 (m, 2H, C=CH-CH_2-CH_2), 1.28-1.06 (m, 8H, 4 × CH_2), 0.93 (t, *J* = 7.5 Hz, 3H, C=CH-CH_2-CH_2-CH_3), 0.82 (t, *J* = 7.5 Hz, 6H, 2 × CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 201.2, 158.0, 142.8, 142.5, 137.4, 128.6, 113.8, 55.3, 45.1, 41.5, 36.5, 31.9, 31.0, 27.8, 27.3, 22.7, 22.5, 22.3, 14.3, 14.2, 14.1; **HRMS** (ESI^+) $C_{23}H_{36}O_2Na$ requires 367.2608 $[M+Na]^+$, found 367.2608; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2958, 2929, 2871, 1667, 1512, 1463, 1378, 1247, 1178, 1103, 1039; the **ee** was determined by HPLC using a Chiralpak IA-3 column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 5.69 min, τ_{minor} = 6.32 min (93% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –13.3 (c = 1.0, $CHCl_3$).

Dimethyl 4,4'-((1*R*,5*S*)-1-cyclohexyl-3-oxodecane-1,5-diyl)dibenzoate, 6c

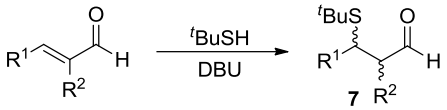


Prepared according to General Procedure D, using **1a** (56 mg), ethynylcyclohexane (51 μL), 4-methoxycarbonylphenylboronic acid (162 mg) and $[Rh(L2)Cl]_2$ (7.0 mg) in DCE. The conjugate addition step was carried out with additional K_2CO_3 (41 mg, 0.30 mmol, 1.0 equiv) for 6 h. dr >20:1. Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (113 mg, 74% yield, >99% ee) as a white solid. **M.p.** (Et_2O): 113-117 ℃; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.91 (app. dd, *J* = 8.5, 1.5 Hz, 4H, Ar-*H*), 7.13 (app. dd, *J* = 8.5, 5.5 Hz, 4H, Ar-*H*), 3.89 (s, 6H, 2 × CO_2-C*H*$_3$), 3.11-3.02 (m, 1H, CH_2-C*H*-CH_2-CO), 2.93 (td, *J* = 8.0, 6.0 Hz, 1H, Cy-C*H*), 2.72-2.41 (m, 4H, C*H*$_2$-CO-C*H*$_2$), 1.69-1.52 (m, 4H, Cy-*H*), 1.41-0.90 (m, 13H, 5 × Cy-*H* and 4 × C*H*$_2$), 0.84-0.63 (m, 5H, 2 × Cy-*H* and CH_2-C*H*$_3$); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 208.3, 167.1 (2C), 150.4, 149.4, 129.9, 129.6, 128.5, 128.33, 128.28, 127.7, 52.1, 50.6, 47.2, 46.9, 42.8, 40.9, 36.1, 31.7, 31.1, 30.8, 27.0, 26.4, 26.3, 22.5, 14.1; **HRMS** (ESI^+) $C_{32}H_{42}O_5Na$ requires 529.2924 $[M+Na]^+$, found 529.2917; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2928, 2854, 1720, 1610, 1435, 1279, 1181, 1112; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 97:3); flow rate 1.0 mL/min; τ_{major} = 54.84 min, τ_{minor} = 41.98 min (>99% ee); $\boldsymbol{[\alpha]_D^{25}}$: +35.0 (c = 1.0, $CHCl_3$).

5.3 Data for Chapter 3

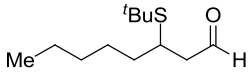
5.3.1 Preparation of starting aldehydes

General Procedure F: synthesis of β-^{t}BuS-substituted aldehydes.



α,β-Unsaturated aldehyde (1.0 equiv) was added dropwise to a mixture of *tert*-butylthiol (1.1-2.0 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.1-0.5 equiv) and the reaction mixture stirred at 23 ℃ for 30 min. The crude was subjected to flash column chromatography to afford the corresponding aldehyde.

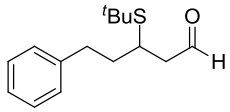
3-(*tert*-Butylthio)octanal, 7a



Prepared according to General Procedure F, using *trans*-2-octenal (3.0 mL, 20 mmol), *tert*-butylthiol (2.5 mL, 22 mmol) and DBU (0.30 mL, 2.0 mmol). Flash column chromatography (petrol/Et_2O, 98:2) afforded the title compound (3.34 g, 77% yield) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 9.76 (t, *J* = 2.0 Hz, 1H, C*H*O), 3.08 (p, *J* = 6.5 Hz, 1H, S-C*H*), 2.71 (ddd, *J* = 17.0, 6.5, 2.0 Hz, 1H, CH_aH_b-CO), 2.64 (ddd, *J* = 17.0, 7.0, 2.0 Hz, 1H, CH_aH_b-CO), 1.62-1.55 (m, 2H, S-CH-CH_2-CH_2), 1.48-1.35 (m, 2H, S-CH-CH_2-CH_2), 1.32 (s, 9H, SC(CH_3)$_3$), 1.31-1.22 (m, 4H, 2 ×CH_2), 0.87 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 201.8, 50.8, 43.9, 37.7, 37.1, 31.8, 31.6, 26.7, 22.7, 14.2; **HRMS** (ESI^+) $C_{13}H_{28}O_2NaS$ requires 271.1702 $[M+MeOH+Na]^+$, found 271.1702; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2958, 2928, 2860, 1723, 1460, 1365, 1162; data consistent with literature.[52]

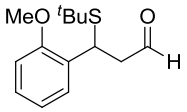
Compounds **7b**, **7d** have been reported in the literature.[52]

3-(*tert*-Butylthio)-5-phenylpentanal, 7c



Prepared according to General Procedure F, using (*E*)-5-phenylpent-2-enal[73] (376 mg, 2.4 mmol), *tert*-butylthiol (0.30 mL, 2.6 mmol) and DBU (0.04 mL, 0.24 mmol). Flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (380 mg, 63% yield) as a pale yellow oil. **δ_H** (400 MHz, $CDCl_3$): 9.77 (t, *J* = 2.0 Hz, 1H, C*H*O), 7.32-7.26 (m, 2H, Ar-*H*), 7.22-7.16 (m, 3H, Ar-*H*), 3.15 (p, *J* = 6.5 Hz, 1H, S-C*H*), 2.85-2.67 (m, 4H, CH_2-CO and Ph-CH_2), 2.02-1.85 (m, 2H, Ph-CH_2-CH_2), 1.32 (s, 9H, SC(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 201.4, 141.5, 128.6, 128.5, 126.1, 50.8, 44.1, 39.2, 36.6, 33.2, 31.6; **HRMS** (ESI^+) $C_{15}H_{23}OS$ requires 251.1464 $[M+H]^+$, found 251.1466; **ν_{max}** (film)/cm^{-1} 2960, 2861, 1721, 1497, 1456, 1365, 1161, 749, 700.

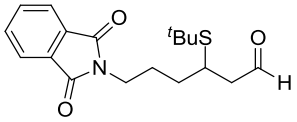
3-(*tert*-Butylthio)-3-(2-methoxyphenyl)propanal, 7e



Prepared according to General Procedure F, using *o*-methoxycinnamaldehyde (1.3 g, 8 mmol, dissolved in 4 mL CH_2Cl_2 for addition), *tert*-butylthiol (1.8 mL, 16 mmol) and DBU (0.60 mL, 4 mmol). The reaction mixture was stirred at 23 ℃ for 1.5 h. Flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (1.4 g, 69% yield) as a white solid. **M.p.** (Et_2O): 30-33 ℃; **δ_H** (400 MHz, $CDCl_3$): 9.66 (dd, *J* = 2.5, 1.5 Hz, 1H, C*H*O), 7.52 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.20 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Ar-*H*), 6.94 (td, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 6.84 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 4.84 (dd, *J* = 8.5, 7.0 Hz, 1H, S-C*H*), 3.87 (s, 3H, OCH_3), 2.86 (ddd, *J* = 16.5, 7.0, 1.5 Hz, 1H, C$H_a$$H_b$-CO), 2.78

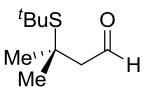
(ddd, J = 16.5, 8.5, 2.5 Hz, 1H, CH_aH_b-CO), 1.24 (s, 9H, SC(CH_3)$_3$); **δC** (101 MHz, $CDCl_3$): 200.9, 155.7, 131.9, 129.1, 128.2, 121.0, 110.6, 55.5, 50.8, 44.5, 34.8, 31.3; **HRMS** (ESI^+) $C_{14}H_{21}O_2S$ requires 253.1257 $[M+H]^+$, found 253.1257; ν_{max} (film)/cm^{-1} 2960, 1722, 1599, 1489, 1460, 1365, 1287, 1241, 1161, 1105, 1050, 1027, 752.

3-(*tert*-Butylthio)-6-(1,3-dioxoisoindolin-2-yl)hexanal, 7f



Prepared according to General Procedure F, using (*E*)-6-(1,3-dioxoisoindolin-2-yl)hex-2-enal[118] (335 mg, 1.4 mmol, dissolved in 0.7 mL CH_2Cl_2 for addition), *tert*-butylthiol (0.17 mL, 1.54 mmol) and DBU (0.02 mL, 0.14 mmol). Flash column chromatography (petrol/EtOAc, 4:1) afforded *the title compound* (305 mg, 65% yield) as a white solid. **M.p.** (EtOAc): 63-65 ℃; **δH** (400 MHz, $CDCl_3$): 9.73 (t, J = 1.5 Hz, 1H, C*H*O), 7.86-7.80 (m, 2H, Ar-*H*), 7.73-7.67 (m, 2H, Ar-*H*), 3.69 (t, J = 7.0 Hz, 2H, CH_2-N), 3.16-3.07 (m, 1H, S-C*H*), 2.75-2.63 (m, 2H, CH_2-CO), 1.95-1.54 (m, 4H, 2 × CH_2), 1.30 (s, 9H, SC(CH_3)$_3$); **δC** (101 MHz, $CDCl_3$): 201.2, 168.5, 134.1, 132.2, 123.3, 51.2, 44.0, 37.8, 36.4, 34.4, 31.5, 26.1; **HRMS** (CI^+) $C_{18}H_{24}NO_3S$ requires 334.1471 $[M+H]^+$, found 334.1474; ν_{max} (film)/cm^{-1} 2959, 1771, 1706, 1395, 1364, 1188, 719.

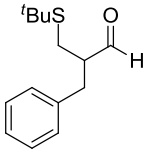
3-(*tert*-Butylthio)-3-methylbutanal, 7g



Prepared according to General Procedure F, using 3-methylcrotonaldehyde (0.96 mL, 10 mmol), *tert*-butylthiol (1.2 mL, 11 mmol) and DBU (0.15 mL, 1.0 mmol). After stirring at 23 ℃ for 1.5 h, additional *tert*-butylthiol (1.0 mL, 9 mmol, 0.9 equiv) and DBU (0.30 mL,

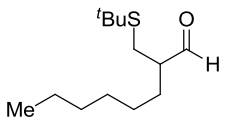
2.0 mmol, 0.2 equiv) were added and the mixture stirred for another 1.5 h. Flash column chromatography (petrol/Et_2O, 96:4) afforded *the title compound* (400 mg, 23% yield) as a pale yellow oil. **δ_H** (400 MHz, $CDCl_3$): 9.86 (t, *J* = 3.0 Hz, 1H, C*H*O), 2.61 (d, *J* = 3.0 Hz, 2H, CH_2-CO), 1.51 (s, 6H, 2 ×CH_3), 1.41 (s, 9H, SC(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 202.4, 56.1, 46.7, 46.1, 33.3, 31.5; **HRMS** (EI^+) $C_9H_{18}OS$ requires 174.1073 $[M]^+$, found 174.1072; ***ν*max** (film)/cm^{-1} 2964, 1719, 1463, 1365, 1161, 1130, 1041.

2-Benzyl-3-(*tert*-butylthio)propanal, 7h



Prepared according to General Procedure F, using 2-benzylacrylaldehyde[83] (439 mg, 3.0 mmol), *tert*-butylthiol (0.37 mL, 3.3 mmol) and DBU (0.04 mL, 0.3 mmol). Flash column chromatography (petrol/Et_2O, 96:4) afforded *the title compound* (556 mg, 78% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 9.74 (d, *J* = 1.5 Hz, 1H, C*H*O), 7.33-7.18 (m, 5H, Ar-*H*), 3.06 (dd, *J* = 13.5, 6.0 Hz, 1H, S-CH_aH$_b$), 2.90 (dd, *J* = 13.5, 7.0 Hz, 1H, S-CH$_a$$H_b$), 2.86-2.75 (m, 2H, C*H*-CO and CH_cH$_d$-Ph), 2.64 (dd, *J* = 11.5, 5.5 Hz, 1H, CH$_c$$H_d$-Ph), 1.29 (s, 9H, SC(C$H_3$)$_3$); **$\delta_C$** (101 MHz, $CDCl_3$): 203.2, 138.2, 129.2, 128.7, 126.7, 53.2, 42.7, 34.6, 30.9, 26.6; **HRMS** (CI^+) $C_{14}H_{21}OS$ requires 237.1308 $[M+H]^+$, found 237.1314; ***ν*max** (film)/cm^{-1} 2961, 1726, 1497, 1456, 1365, 1162, 742, 700.

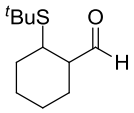
2-((*tert*-Butylthio)methyl)octanal, 7i



Prepared according to General Procedure F, using 2-methyleneoctanal[83] (516 mg, 3.7 mmol), *tert*-butylthiol (0.46 mL, 4.1 mmol) and DBU (0.06 mL, 0.37 mmol). Flash

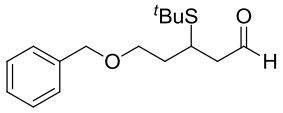
column chromatography (petrol/Et_2O, 98:2) afforded *the title compound* (752 mg, 88% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 9.63 (d, *J* = 2.0 Hz, 1H, C*H*O), 2.80 (dd, *J* = 12.0, 7.5 Hz, 1H, S-C*H*$_a$H$_b$), 2.65 (dd, *J* = 12.0, 6.0 Hz, 1H, S-CH$_a$*H*$_b$), 2.51-2.42 (m, 1H, C*H*-CO), 1.76-1.64 (m, 1H, CH_2-C*H*$_c$H$_d$-CH), 1.64-1.51 (m, 1H, CH_2-CH$_c$*H*$_d$-CH), 1.36-1.21 (m, 17H, SC(C*H*$_3$)$_3$ and 4 × C*H*$_2$), 0.87 (t, *J* = 7.0 Hz, 3H, CH_2-C*H*$_3$); **δ_C** (101 MHz, $CDCl_3$): 203.9, 51.6, 42.5, 31.7, 30.9, 29.4, 28.9, 27.1, 26.8, 22.7, 14.2; **HRMS** (ESI^+) $C_{13}H_{27}OS$ requires 231.1777 $[M+H]^+$, found 231.1780; ***ν*max** (film)/cm^{-1} 2958, 2927, 2858, 1727, 1460, 1365, 1163.

2-(*tert*-Butylthio)cyclohexanecarbaldehyde, 7j



Prepared according to General Procedure F, using 1-cyclohexene-1-carboxaldehyde (0.57 mL, 5.0 mmol), *tert*-butylthiol (0.62 mL, 5.5 mmol) and DBU (0.07 mL, 0.5 mmol). After stirring at 23 ℃ for 0.5 h, additional *tert*-butylthiol (0.56 mL, 5.0 mmol, 1.0 equiv) and DBU (0.30 mL, 2.0 mmol, 0.4 equiv) were added and the mixture stirred for another 1 h. Flash column chromatography (petrol/Et_2O, 98:2) afforded *the title compound* (725 mg, 72% yield) as a colorless oil. The compound was isolated as a mixture of diastereoisomers. **δ_H** (400 MHz, $CDCl_3$): 9.67-9.64 (m, 1H, C*H*O), 2.84-2.75 (m, 1H, S-C*H*), 2.29-2.20 (m, 1H, C*H*-CO), 2.14-2.06 (m, 1H, Cy-*H*), 1.87-1.78 (m, 1H, Cy-*H*), 1.77-1.61 (m, 2H, Cy-*H*), 1.55-1.41 (m, 2H, Cy-*H*), 1.39-1.23 (m, 11H, 2 × Cy-*H* and SC(C*H*$_3$)$_3$); **δ_C** (101 MHz, $CDCl_3$): 204.3, 55.0, 44.0, 40.3, 36.5, 31.7, 27.3, 25.7, 24.1; **HRMS** (CI^+) $C_{11}H_{21}OS$ requires 201.1308 $[M+H]^+$, found 201.1312; ***ν*max** (film)/cm^{-1} 2930, 2857, 1724, 1448, 1365, 1161.

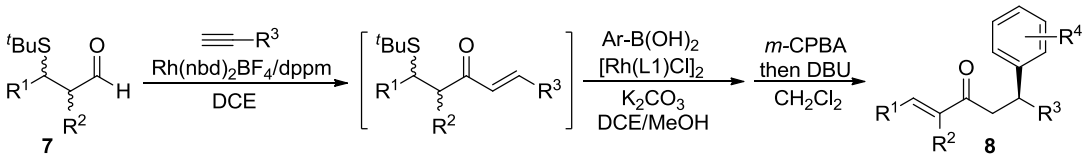
5-(Benzyloxy)-3-(*tert*-butylthio)pentanal, 7k



Prepared according to General Procedure F, using (*E*)-5-(benzyloxy)pent-2-enal[122] (228 mg, 1.2 mmol), *tert*-butylthiol (0.15 mL, 1.32 mmol) and DBU (0.02 mL, 0.12 mmol). Flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (120 mg, 36% yield) as a pale yellow oil. **δ_H** (400 MHz, $CDCl_3$): 9.74 (t, *J* = 2.0 Hz, 1H, C*H*O), 7.38-7.25 (m, 5H, Ar-*H*), 4.50 (d, *J* = 12.0 Hz, 1H, Ph-CH_aH_b), 4.46 (d, *J* = 12.0 Hz, 1H, Ph-CH_aH_b), 3.70-3.63 (m, 1H, BnO-CH_cH_d), 3.60-3.53 (m, 1H, BnO-CH_cH_d), 3.32 (p, *J* = 6.5 Hz, 1H, S-C*H*), 2.78 (ddd, *J* = 17.0, 6.5, 2.0 Hz, 1H, CH_eH_f-CO), 2.66 (ddd, *J* = 17.0, 6.5, 2.0 Hz, 1H, CH_eH_f-CO), 1.95-1.88 (m, 2H, CH_2), 1.34 (s, 9H, SC(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 201.6, 138.4, 128.5, 127.82, 127.76, 73.1, 67.5, 51.0, 44.1, 37.4, 34.2, 31.5; **HRMS** (CI^+) $C_{16}H_{25}O_2S$ requires 281.1570 $[M+H]^+$, found 281.1569; ***ν_{max}*** (film)/cm^{-1} 2960, 2861, 1722, 1455, 1365, 1162, 1101, 1027, 737, 698.

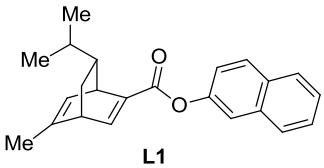
5.3.2 Enantioselective synthesis of β'-aryl-α,β-unsaturated ketones

General procedure G: sequential hydroacylation-conjugate addition-elimination.

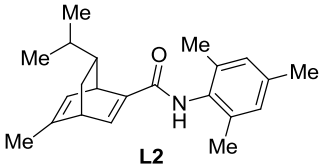


A microwave reaction vial charged with $Rh(nbd)_2BF_4$ (3.4 mg, 0.009 mmol, 3 mol%) and dppm (3.6 mg, 0.009 mmol, 3 mol%) was evacuated and back-filled with N_2 gas for 3 times. 1,2-Dichloroethane (DCE) (0.25 mL) was added to dissolve the solids. The resulting solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until 0.1 mL of the solution

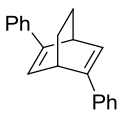
was left. This solution was transferred to a N_2-purged microwave reaction vial containing aldehyde **7** (0.30 mmol, 1.0 equiv) with the aid of DCE (0.2 mL) to rinse the remainder. Alkyne (0.33 mmol, 1.1 equiv) was added and the reaction mixture stirred at 55 ℃ for 1 h then cooled to room temperature. The solution was transferred to a microwave reaction vial charged with boronic acid (0.45 mmol, 1.5 equiv), K_2CO_3 (41.5 mg, 0.30 mmol, 1.0 equiv) and $[Rh(L1)Cl]_2$ (7.1 mg, 0.0075 mmol, 2.5 mol%) (previously evacuated and back-filled with N_2 gas) with the aid of DCE (2.4 mL). Methanol (0.3 mL) was added and the resulting suspension stirred at 55 ℃ for 1.5 h. The mixture was filtered through a short plug of SiO_2, washed with Et_2O and the filtrate concentrated under reduced pressure. It was then diluted in CH_2Cl_2 (3.0 mL) and cooled to 0 ℃, followed by the addition of *m*-CPBA (77%, 100.9 mg, 0.45 mmol, 1.5 equiv). After stirring at 0 ℃ for 15 min, DBU (0.11 mL, 0.75 mmol, 2.5 equiv) was added and the reaction mixture stirred at 23 ℃ for 2.5 h. Water (3 mL) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography afforded the corresponding product.



L1

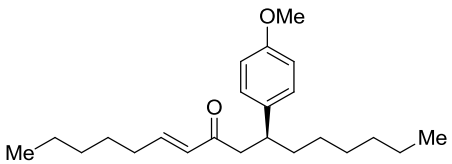


L2



L3

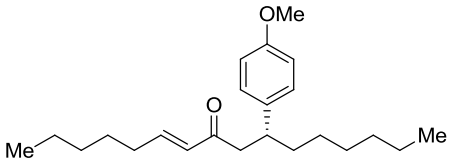
(*S*,*E*)-10-(4-Methoxyphenyl)hexadec-6-en-8-one, 8a



Prepared according to General Procedure G, using **7a** (65 mg), 1-octyne (49 μL) and

4-methoxyphenylboronic acid (68 mg). Flash column chromatography (gradient petrol/Et_2O, 98:2 to 96:4) afforded *the title compound* (78 mg, 75 % yield, 95% ee) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.09 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.72 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 5.99 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.77 (s, 3H, OCH_3), 3.14-3.05 (m, 1H, Ar-C*H*), 2.79 (dd, *J* = 13.5, 5.0 Hz, 1H, C$H_a$$H_b$-CO), 2.74 (dd, *J* = 13.5, 5.0 Hz, 1H, C$H_a$$H_b$-CO), 2.18-2.10 (m, 2H, CH_2-CH=CH), 1.67-1.47 (m, 2H, CH_2-CH-CH_2-CO), 1.45-1.36 (m, 2H, CH_2-CH_2-CH=CH), 1.34-1.04 (m, 12H, 6 × CH_2), 0.88 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3), 0.83 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 199.9, 158.0, 147.8, 137.0, 130.8, 128.5, 113.8, 55.3, 47.8, 40.9, 36.6, 32.5, 31.8, 31.4, 29.4, 27.9, 27.5, 22.7, 22.5, 14.2, 14.1; **HRMS** (CI^+) $C_{23}H_{37}O_2$ requires 345.2788 $[M+H]^+$, found 345.2781; **ν_{max}** (film)/cm^{-1} 2955, 2926, 2856, 1694, 1670, 1626, 1613, 1584, 1512, 1464, 1366, 1301, 1247, 1177, 1109, 1038, 983, 829; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 10.26 min, τ_{minor} = 12.46 min (95% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +3.2 (*c* = 1.0, $CHCl_3$).

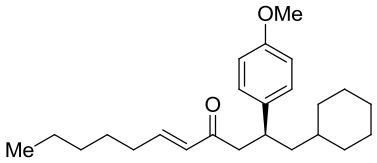
(*R*,*E*)-10-(4-Methoxyphenyl)hexadec-6-en-8-one, 8a'



Prepared according to General Procedure G, using **7a** (65 mg), 1-octyne (49 μL) and 4-methoxyphenylboronic acid (68 mg). An *in situ* generated catalyst from $[Rh(C_2H_4)_2Cl]_2$ (2.9 mg, 2.5 mol%) and **L3** (4.6 mg, 6 mol%), pre-stirred under N_2 in DCE (0.4 mL) at 23 ℃ for 30 min, was employed instead of $[Rh(L1)Cl]_2$. Flash column chromatography

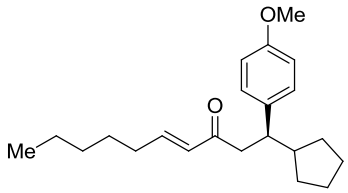
(gradient petrol/Et_2O, 98:2 to 96:4) afforded *the title compound* (78 mg, 75% yield, 88% ee) as a colorless oil. The **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 12.21 min, τ_{minor} = 10.33 min (88% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –2.8 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-Cyclohexyl-2-(4-methoxyphenyl)undec-5-en-4-one, 8b



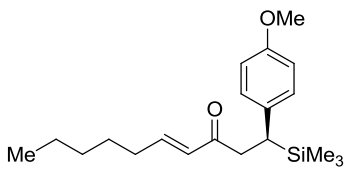
Prepared according to General Procedure G, using **7a** (65 mg), 3-cyclohexyl-1-propyne (48 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (gradient petrol/Et_2O, 96:4 to 94:6) afforded *the title compound* (75 mg, 70 % yield, 97% ee) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.09 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.70 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 5.97 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.78 (s, 3H, OCH_3), 3.30-3.21 (m, 1H, Ar-C*H*), 2.76 (dd, *J* = 15.5, 7.5 Hz, 1H, CH_aH$_b$-CO), 2.68 (dd, *J* = 15.5, 7.0 Hz, 1H, CH$_a$$H_b$-CO), 2.17-2.10 (m, 2H, CH_2-CH=CH), 1.85-1.76 (m, 1H, Cy-*H*), 1.67-1.20 (m, 12H, 4 × Cy-*H* and 4 × CH_2), 1.16-0.97 (m, 4H, Cy-*H*), 0.92-0.78 (m, 5H, 2 × Cy-*H* and CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 199.9, 158.0, 147.7, 137.1, 130.8, 128.5, 113.9, 55.3, 48.3, 44.3, 37.9, 34.8, 34.2, 32.6, 32.5, 31.4, 27.9, 26.7, 26.3, 26.2, 22.5, 14.1; **HRMS** (ESI^+) $C_{24}H_{37}O_2$ requires 357.2788 $[M+H]^+$, found 357.2787; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2922, 2851, 1694, 1671, 1627, 1613, 1512, 1448, 1363, 1301, 1247, 1177, 1109, 1039, 983, 828; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 11.80 min, τ_{minor} = 15.13 min (97% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –3.5 (*c* = 1.0, $CHCl_3$).

(*R*,*E*)-1-Cyclopentyl-1-(4-methoxyphenyl)dec-4-en-3-one, 8c



Prepared according to General Procedure G, using **7a** (65 mg), cyclopentylacetylene (38 μL) and 4-methoxyphenylboronic acid (68 mg). $[Rh(L2)Cl]_2$ (6.9 mg) was used instead of $[Rh(L1)Cl]_2$. Flash column chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (60 mg, 61% yield, 92% ee) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.07 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.78 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.66 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 5.93 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.76 (s, 3H, OCH_3), 2.95-2.81 (m, 3H, Ar-C*H* and CH_2-CO), 2.14-2.07 (m, 2H, CH_2-CH=CH), 2.07-1.97 (m, 1H, Ar-CH-C*H*), 1.89-1.80 (m, 1H, Cyp-*H*), 1.70-1.59 (m, 1H, Cyp-*H*), 1.58-1.16 (m, 11H, 5 × Cyp-*H* and 3 × CH_2), 1.06-0.95 (m, 1H, Cyp-*H*), 0.87 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 200.1, 157.9, 147.6, 136.9, 130.7, 128.9, 113.6, 55.2, 46.9, 46.61, 46.59, 32.5, 31.61, 31.56, 31.4, 27.9, 25.4, 25.1, 22.5, 14.1; **HRMS** (CI^+) $C_{22}H_{33}O_2$ requires 329.2475 $[M+H]^+$, found 329.2477; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2952, 2931, 2861, 1693, 1669, 1626, 1612, 1583, 1511, 1464, 1361, 1336, 1303, 1285, 1246, 1178, 1108, 1038, 982, 829; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 15.25 min, τ_{minor} = 24.70 min (92% ee); $\boldsymbol{[\alpha]_D^{25}}$: +14.5 (*c* = 1.0, $CHCl_3$).

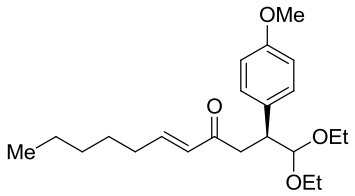
(*S*,*E*)-1-(4-Methoxyphenyl)-1-(trimethylsilyl)dec-4-en-3-one, 8d



Prepared according to General Procedure G, using **7a** (65 mg), ethynyltrimethylsilane

(46 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (66 mg, 66% yield, 92% ee) as a pale yellow oil. **δ_H** (400 MHz, $CDCl_3$): 6.94 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.80-6.71 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.05 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.75 (s, 3H, OCH_3), 3.01 (dd, *J* = 16.5, 10.5 Hz, 1H, C$H_a$$H_b$-CO), 2.77 (dd, *J* = 16.5, 4.5 Hz, 1H, C$H_a$$H_b$-CO), 2.65 (dd, *J* = 10.5, 4.5 Hz, 1H, Ar-C*H*), 2.18-2.10 (m, 2H, CH_2-CH=CH), 1.45-1.36 (m, 2H, CH_2-CH_2-CH=CH), 1.33-1.20 (m, 4H, 2 × CH_2), 0.88 (t, *J* = 6.5 Hz, 3H, CH_2-CH_3), –0.053 (s, 9H, Si(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 200.0, 157.0, 147.4, 135.1, 130.1, 128.4, 113.7, 55.3, 41.1, 32.5, 31.4, 30.7, 27.9, 22.5, 14.1, –2.8; **HRMS** (ESI^+) $C_{20}H_{33}O_2Si$ requires 333.2244 $[M+H]^+$, found 333.2239; **ν_{max}** (film)/cm^{-1} 2955, 2930, 2859, 1673, 1628, 1509, 1463, 1301, 1246, 1178, 1108, 1038, 984, 839, 755; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 7.92 min, τ_{minor} = 14.49 min (92% ee); $[\alpha]_D^{25}$: +2.2 (*c* = 1.0, $CHCl_3$).

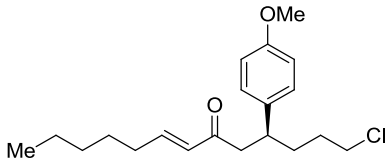
(*S*,*E*)-1,1-Diethoxy-2-(4-methoxyphenyl)undec-5-en-4-one, 8e



Prepared according to General Procedure G, using **7a** (65 mg), 3,3-diethoxy-1-propyne (47 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (petrol/Et_2O, 88:12) afforded *the title compound* (77 mg, 71% yield, 97% ee) as a pale yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.20 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82-6.73 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.02 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.47 (d, *J* = 5.0 Hz, 1H, C*H*(OEt)$_2$), 3.76 (s, 3H, OCH_3), 3.69 (dq, *J* = 9.0, 7.0 Hz, 1H, OC$H_a$$H_b$-$CH_3$), 3.57 (dq,

J = 9.0, 7.0 Hz, 1H, OC*H*$_c$H$_d$-CH$_3$), 3.53-3.46 (m, 1H, Ar-C*H*), 3.45-3.34 (m, 2H, OCH$_a$*H*$_b$-CH$_3$ and OCH$_c$*H*$_d$-CH$_3$), 3.09 (dd, *J* = 16.5, 5.0 Hz, 1H, C*H*$_e$H$_f$-CO), 2.91 (dd, *J* = 16.5, 9.0 Hz, 1H, CH$_e$*H*$_f$-CO), 2.18-2.11 (m, 2H, C*H*$_2$-CH=CH), 1.46-1.36 (m, 2H, C*H*$_2$-CH$_2$-CH=CH), 1.34-1.20 (m, 4H, 2 × C*H*$_2$), 1.16 (t, *J* = 7.0 Hz, 3H, OCH$_a$H$_b$-C*H*$_3$), 1.09 (t, *J* = 7.0 Hz, 3H, OCH$_c$H$_d$-C*H*$_3$), 0.88 (t, *J* = 7.0 Hz, 3H, CH$_2$-CH$_2$-C*H*$_3$); **δC** (101 MHz, $CDCl_3$): 199.4, 158.3, 147.5, 132.9, 130.8, 129.8, 113.6, 105.9, 63.8, 63.1, 55.3, 44.3, 41.0, 32.5, 31.4, 27.9, 22.5, 15.3 (2C), 14.1; **HRMS** (ESI$^+$) $C_{22}H_{34}O_4Na$ requires 385.2349 $[M+Na]^+$, found 385.2345; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2972, 2929, 2872, 1695, 1671, 1628, 1614, 1513, 1464, 1443, 1372, 1247, 1178, 1113, 1060, 829; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 95:5); flow rate 1.0 mL/min; τ_{major} = 6.12 min, τ_{minor} = 7.49 min (97% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –0.6 (*c* = 1.0, $CHCl_3$).

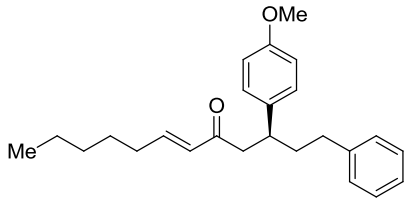
(*S*,*E*)-1-Chloro-4-(4-methoxyphenyl)tridec-7-en-6-one, 8f



Prepared according to General Procedure G, using **7a** (65 mg), 5-chloro-1-pentyne (35 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (78 mg, 77% yield, 94% ee) as a pale yellow oil. **δH** (400 MHz, $CDCl_3$): 7.10 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.74 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 6.00 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.78 (s, 3H, OC*H*$_3$), 3.45 (t, *J* = 6.5 Hz, 2H, C*H*$_2$-Cl), 3.18-3.09 (m, 1H, Ar-C*H*), 2.86-2.73 (m, 2H, C*H*$_2$-CO), 2.18-2.11 (m, 2H, C*H*$_2$-CH=CH), 1.85-1.52 (m, 4H, C*H*$_2$-C*H*$_2$-CH$_2$-Cl), 1.45-1.36 (m, 2H, C*H*$_2$-CH$_2$-CH=CH), 1.34-1.20 (m, 4H, 2 × C*H*$_2$), 0.88 (t, *J* = 7.0 Hz, 3H,

CH_2-C*H*$_3$); **δC** (101 MHz, $CDCl_3$): 199.4, 158.3, 148.1, 136.1, 130.7, 128.5, 114.1, 55.3, 47.7, 45.1, 40.2, 33.6, 32.5, 31.4, 30.7, 27.9, 22.5, 14.1; **HRMS** (CI^+) $C_{20}H_{30}{}^{35}ClO_2$ requires 337.1929 $[M+H]^+$, found 337.1933; $\boldsymbol{\nu}_{\mathbf{max}}$ (film)/cm^{-1} 2955, 2929, 2858, 1693, 1669, 1626, 1612, 1583, 1513, 1461, 1366, 1302, 1247, 1178, 1110, 1036, 984, 830; the **ee** was determined by HPLC using a Chiralpak ID-3 column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 16.83 min, τ_{minor} = 18.59 min (94% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +2.8 (*c* = 1.0, $CHCl_3$).

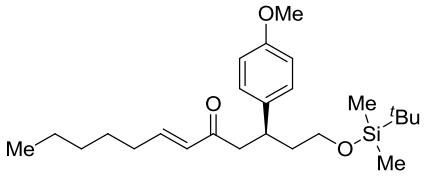
(*S*,*E*)-3-(4-Methoxyphenyl)-1-phenyldodec-6-en-5-one, 8g



Prepared according to General Procedure G, using **7a** (65 mg), 4-phenyl-1-butyne (46 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (78 mg, 71% yield, 98% ee) as a pale yellow oil. **δH** (400 MHz, $CDCl_3$): 7.27-7.22 (m, 2H, Ar-*H*), 7.18-7.08 (m, 5H, Ar-*H*), 6.86 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.72 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 5.98 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.80 (s, 3H, OC*H*$_3$), 3.22-3.13 (m, 1H, Ar-C*H*), 2.83 (dd, *J* = 14.0, 5.0 Hz, 1H, C*H*$_a$H$_b$-CO), 2.78 (dd, *J* = 14.0, 5.5 Hz, 1H, CH$_a$*H*$_b$-CO), 2.45 (t, *J* = 8.0 Hz, 2H, C*H*$_2$-Ph), 2.17-2.10 (m, 2H, C*H*$_2$-CH=CH), 2.04-1.94 (m, 1H, C*H*$_c$H$_d$-CH$_2$-Ph), 1.92-1.80 (m, 1H, CH$_c$*H*$_d$-CH$_2$-Ph), 1.44-1.35 (m, 2H, C*H*$_2$-CH$_2$-CH=CH), 1.34-1.20 (m, 4H, 2 × C*H*$_2$), 0.89 (t, *J* = 7.0 Hz, 3H, CH$_2$-C*H*$_3$); **δC** (101 MHz, $CDCl_3$): 199.6, 158.2, 147.9, 142.3, 136.4, 130.7, 128.6, 128.5, 128.4, 125.8, 114.0, 55.3, 47.8, 40.6, 38.2, 33.8, 32.5, 31.4, 27.9, 22.5, 14.1; **HRMS** (CI^+) $C_{25}H_{33}O_2$ requires 365.2475 $[M+H]^+$, found 365.2479; $\boldsymbol{\nu}_{\mathbf{max}}$ (film)/cm^{-1} 3027, 2954, 2928, 2857, 1693, 1668, 1626, 1612, 1583, 1512, 1455, 1364, 1301,

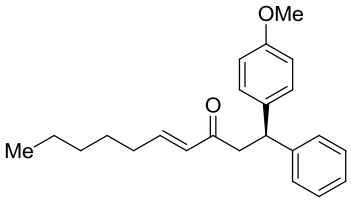
1247, 1178, 1110, 1035, 984, 831, 749, 700; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 23.69 min, τ_{minor} = 30.28 min (98% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +8.8 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(4-methoxyphenyl)dodec-6-en-5-one, 8h



Prepared according to General Procedure G, using **7a** (65 mg), 4-(*tert*-butyl dimethylsilyloxy)-1-butyne (68 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (gradient petrol/Et_2O, 96:4 to 94:6) afforded *the title compound* (75 mg, 60% yield, 97% ee) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.10 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.73 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 5.99 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.77 (s, 3H, OCH_3), 3.50-3.36 (m, 2H, CH_2-O), 3.34-3.25 (m, 1H, Ar-C*H*), 2.86-2.75 (m, 2H, CH_2-CO), 2.18-2.10 (m, 2H, CH_2-CH=CH), 1.92-1.83 (m, 1H, CH_aH$_b$-CH_2-O), 1.80-1.69 (m, 1H, CH_a*H*$_b$-CH_2-O), 1.45-1.36 (m, 2H, CH_2-CH_2-CH=CH), 1.35-1.20 (m, 4H, 2 × CH_2), 0.91-0.84 (m, 12H, C(CH_3)$_3$ and CH_2-CH_3), –0.03 (app. d, *J* = 3.0 Hz, 6H, 2 × Si-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 199.6, 158.1, 147.8, 136.3, 130.6, 128.6, 113.9, 61.0, 55.3, 47.7, 39.3, 37.5, 32.5, 31.5, 27.9, 26.1, 22.5, 18.4, 14.1, –5.2; **HRMS** (ESI^+) $C_{25}H_{42}O_3NaSi$ requires 441.2795 $[M+Na]^+$, found 441.2790; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2954, 2929, 2857, 1695, 1671, 1627, 1613, 1513, 1464, 1361, 1302, 1248, 1178, 1110, 1038, 833, 776; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 5.13 min, τ_{minor} = 5.64 min (97% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –2.1 (*c* = 1.0, $CHCl_3$).

(*R*,*E*)-1-(4-Methoxyphenyl)-1-phenyldec-4-en-3-one, 8i



Prepared according to General Procedure G, using **7a** (65 mg), phenylacetylene (36 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (gradient petrol/Et_2O, 95:5 to 93:7) afforded *the title compound* (81 mg, 80% yield, 95% ee) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.29-7.11 (m, 7H, Ar-*H*), 6.84-6.75 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.05 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.61 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.76 (s, 3H, OCH_3), 3.26 (d, *J* = 7.5 Hz, 2H, CH_2-CO), 2.20-2.13 (m, 2H, CH_2-CH=CH), 1.46-1.37 (m, 2H, CH_2-CH_2-CH=CH), 1.34-1.22 (m, 4H, 2 × CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 198.6, 158.1, 148.1, 144.6, 136.4, 130.6, 128.9, 128.6, 127.8, 126.4, 114.0, 55.3, 46.4, 45.4, 32.6, 31.4, 27.8, 22.6, 14.1; **HRMS** (CI^+) $C_{23}H_{29}O_2$ requires 337.2162 $[M+H]^+$, found 337.2165; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 3060, 2956, 2929, 2857, 1694, 1671, 1626, 1612, 1584, 1511, 1495, 1463, 1453, 1302, 1248, 1035, 984, 832, 700; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 25.22 min, τ_{minor} = 38.12 min (95% ee); $\boldsymbol{[\alpha]_D^{25}}$: –2.8 (*c* = 1.0, $CHCl_3$).

Gram-scale preparation:

- $Rh(nbd)_2BF_4$ (19 mg, 0.05 mmol, 1 mol%), dppm (19 mg, 0.05 mmol, 1 mol%), **7a** (1.08 g, 5.0 mmol), phenylacetylene (0.60 mL, 5.5 mmol) and DCE (5 mL) for the hydroacylation step;

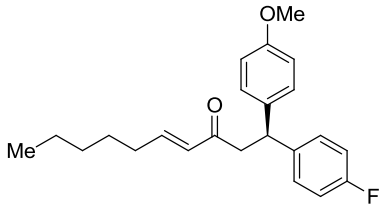
- 4-methoxyphenylboronic acid (1.14 g, 7.5 mmol), K_2CO_3 (0.69 g, 5.0 mmol),

$[Rh(L1)Cl]_2$ (94 mg, 0.1 mmol, 2 mol%), additional DCE (40 mL), MeOH (5 mL) for the conjugate addition step;

- *m*-CPBA (77%, 1.68 g, 7.5 mmol), CH_2Cl_2 (50 mL), DBU (1.9 mL, 12.5 mmol) for the elimination step;

- flash column chromatography (gradient petrol/Et_2O, 95:5 to 93:7) afforded *the title compound* (1.45 g, 86% yield, 95% ee) as a pale yellow oil.

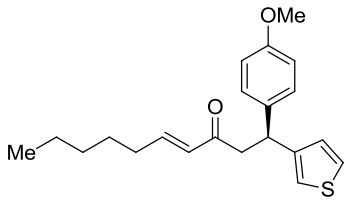
(*S*,*E*)-1-(4-Fluorophenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8j



Prepared according to General Procedure G, using **7a** (65 mg), 1-ethynyl-4-fluorobenzene (38 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (83 mg, 78% yield, 96% ee) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.20-7.14 (m, 2H, Ar-*H*), 7.12 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.98-6.91 (m, 2H, Ar-*H*), 6.85-6.76 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.06 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.60 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.76 (s, 3H, OCH_3), 3.23 (d, *J* = 7.5 Hz, 2H, CH_2-CO), 2.21-2.13 (m, 2H, CH_2-CH=CH), 1.47-1.38 (m, 2H, CH_2-CH_2-CH=CH), 1.36-1.21 (m, 4H, 2 × CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 198.4, 161.4 (d, $J_{C\text{-}F}$ = 244.5 Hz), 158.2, 148.3, 140.3 (d, $J_{C\text{-}F}$ = 3.0 Hz), 136.2, 130.5, 129.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 128.8, 115.3 (d, $J_{C\text{-}F}$ = 21.5 Hz), 114.0, 55.3, 46.4, 44.6, 32.6, 31.4, 27.8, 22.5, 14.1; **δ_F** (377 MHz, $CDCl_3$): −117.0; **HRMS** (ESI^+) $C_{23}H_{27}O_2FNa$ requires 377.1887 $[M+Na]^+$, found 377.1886; **ν_{max}** (film)/cm^{-1} 2956, 2930, 2858, 1694, 1672, 1626, 1609, 1508, 1463, 1302, 1248, 1223, 1179, 1159, 1035, 826; the

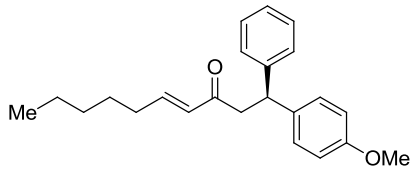
ee was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 31.52 min, τ_{minor} = 52.12 min (96% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –4.8 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-(4-Methoxyphenyl)-1-(thiophen-3-yl)dec-4-en-3-one, 8k



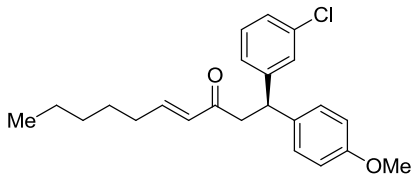
Prepared according to General Procedure G, using **7a** (65 mg), 3-ethynylthiophene (33 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (77 mg, 75% yield, 94% ee) as a yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.21 (dd, *J* = 5.0, 3.0 Hz, 1H, Ar-*H*), 7.14 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.95-6.92 (m, 1H, Ar-*H*), 6.88 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar-*H*), 6.84-6.75 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.05 (d, *J* = 16.0 Hz, 1H, CH=C*H*-CO), 4.65 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.77 (s, 3H, OCH_3), 3.25 (dd, *J* = 16.0, 7.0 Hz, 1H, CH_aH_b-CO), 3.18 (dd, *J* = 16.0, 7.5 Hz, 1H, CH_aH_b-CO), 2.20-2.13 (m, 2H, CH_2-CH=CH), 1.47-1.38 (m, 2H, CH_2-CH_2-CH=CH), 1.36-1.22 (m, 4H, 2 × CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 198.6, 158.2, 148.2, 145.5, 136.1, 130.6, 128.9, 127.8, 125.7, 120.3, 114.0, 55.3, 46.8, 41.3, 32.6, 31.5, 27.9, 22.6, 14.1; **HRMS** (ESI^+) $C_{21}H_{26}O_2NaS$ requires 365.1546 $[M+Na]^+$, found 365.1544; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2955, 2928, 2857, 1693, 1669, 1626, 1611, 1584, 1510, 1463, 1358, 1302, 1247, 1178, 1110, 1092, 1035, 983, 829, 787; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 33.85 min, τ_{minor} = 60.91 min (94% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +37.3 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-(4-Methoxyphenyl)-1-phenyldec-4-en-3-one, 8l



Prepared according to General Procedure G, using **7a** (65 mg), 4-ethynylanisole (43 μL) and phenylboronic acid (55 mg). Flash column chromatography (gradient petrol/Et_2O, 95:5 to 93:7) afforded *the title compound* (70 mg, 70% yield, 95% ee) as a yellow oil. **Characterization data**: see compound **8i**; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 37.99 min, τ_{minor} = 25.77 min (95% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +4.3 (*c* = 1.0, $CHCl_3$).

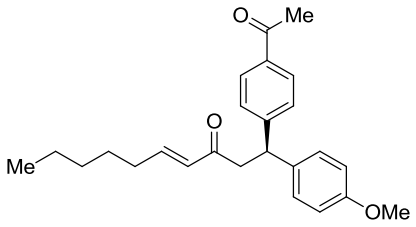
(*R*,*E*)-1-(3-Chlorophenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8m



Prepared according to General Procedure G, on a 0.20 mmol scale, using **7a** (43 mg, 0.20 mmol), 4-ethynylanisole (29 μL) and 3-chlorophenylboronic acid (47 mg). $[Rh(L2)Cl]_2$ (4.6 mg) was used instead of $[Rh(L1)Cl]_2$. Flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (58 mg, 78% yield, 85% ee) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.22-7.08 (m, 6H, Ar-*H*), 6.86-6.77 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.06 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.59 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.76 (s, 3H, OCH_3), 3.24 (d, *J* = 7.5 Hz, 2H, CH_2-CO), 2.21-2.14 (m, 2H, CH_2-CH=CH), 1.48-1.38 (m, 2H, CH_2-CH_2-CH=CH), 1.37-1.21 (m, 4H, 2 × CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 198.1, 158.3, 148.4, 146.7, 135.6, 134.4,

130.5, 129.8, 128.8, 127.9, 126.6, 126.2, 114.1, 55.3, 46.0, 45.0, 32.6, 31.4, 27.8, 22.5, 14.1; **HRMS** (ESI^+) $C_{23}H_{27}O_2{}^{35}ClNa$ requires 393.1592 $[M+Na]^+$, found 393.1590; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2957, 2930, 2856, 1696, 1671, 1628, 1611, 1571, 1511, 1463, 1429, 1302, 1248, 1179, 1080, 1036, 984, 831, 788, 693; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 17.38 min, τ_{minor} = 14.83 min (85% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –4.4 (*c* = 1.0, $CHCl_3$).

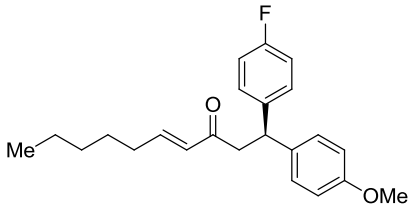
(*S*,*E*)-1-(4-Acetylphenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8n



Prepared according to General Procedure G, on a 0.20 mmol scale, using **7a** (43 mg, 0.20 mmol), 4-ethynylanisole (29 μL) and 4-acetylphenylboronic acid (49 mg). $[Rh(L2)Cl]_2$ (4.6 mg) was used instead of $[Rh(L1)Cl]_2$. Flash column chromatography (gradient petrol/Et_2O, 4:1 to 3:1) afforded *the title compound* (59 mg, 77% yield, 91% ee) as a white solid. **M.p.** (Et_2O): 27-29 ℃; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.86 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.31 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.12 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.86-6.77 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.06 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.67 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.75 (s, 3H, OCH_3), 3.34-3.22 (m, 2H, CH_2-CO), 2.55 (s, 3H, CO-CH_3), 2.21-2.13 (m, 2H, CH_2-CH=CH), 1.47-1.37 (m, 2H, CH_2-CH_2-CH=CH), 1.36-1.21 (m, 4H, 2 × CH_2), 0.88 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 198.0, 197.8, 158.3, 150.2, 148.5, 135.5, 135.4, 130.4, 128.83, 128.78, 128.1, 114.1, 55.3, 45.9, 45.3, 32.6, 31.4, 27.8, 26.7, 22.5, 14.1; **HRMS** (ESI^+) $C_{25}H_{30}O_3Na$ requires 401.2087 $[M+Na]^+$, found 401.2086;

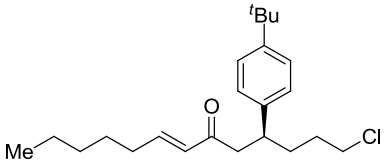
$\boldsymbol{\nu}_{\mathbf{max}}$ (film)/cm^{-1} 2956, 2930, 1681, 1606, 1512, 1358, 1269, 1249, 1179, 1035, 955, 824; the **ee** was determined by HPLC using a Chiralpak IA-3 column (^{n}hexane/^{i}PrOH, 94:6); flow rate 1.0 mL/min; τ_{major} = 30.55 min, τ_{minor} = 32.97 min (91% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –18.4 (*c* = 1.0, $CHCl_3$).

(*R*,*E*)-1-(4-Fluorophenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8o



Prepared according to General Procedure G, using **7a** (65 mg), 4-ethynylanisole (43 μL) and 4-fluorophenylboronic acid (63 mg). Flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (84 mg, 79% yield, 90% ee) as a yellow oil. **Characterization data**: see compound **8j**; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 47.41 min, τ_{minor} = 30.43 min (90% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +6.0 (*c* = 1.0, $CHCl_3$).

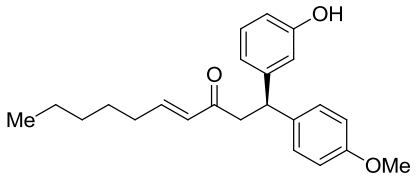
(*S*,*E*)-4-(4-(*tert*-Butyl)phenyl)-1-chlorotridec-7-en-6-one, 8p



Prepared according to General Procedure G, using **7a** (65 mg), 5-chloro-1-pentyne (35 μL) and 4-*tert*-butylphenylboronic acid (80 mg). Flash column chromatography (petrol/Et_2O, 96:4) afforded *the title compound* (82 mg, 75% yield, 89% ee) as a colorless oil. $\boldsymbol{\delta}_{\mathbf{H}}$ (400 MHz, $CDCl_3$): 7.29 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.10 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.75 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 6.01 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.45 (t, *J* = 6.5 Hz, 2H, CH_2-Cl), 3.21-3.11 (m, 1H, Ar-C*H*), 2.84 (dd, *J* = 15.0, 5.5 Hz, 1H,

C*H*$_a$H$_b$-CO), 2.79 (dd, *J* = 15.0, 7.0 Hz, 1H, CH$_a$*H*$_b$-CO), 2.19-2.11 (m, 2H, C*H*$_2$-CH=CH), 1.86-1.53 (m, 4H, C*H*$_2$-C*H*$_2$-CH$_2$-Cl), 1.46-1.36 (m, 2H, C*H*$_2$-CH$_2$-CH=CH), 1.35-1.21 (m, 13H, 2 × C*H*$_2$ and C(C*H*$_3$)$_3$), 0.88 (t, *J* = 7.0 Hz, 3H, CH$_2$-C*H*$_3$); **δC** (101 MHz, CDCl$_3$): 199.4, 149.3, 148.0, 141.0, 130.7, 127.2, 125.5, 47.5, 45.2, 40.4, 34.5, 33.4, 32.5, 31.50, 31.46, 30.7, 27.8, 22.5, 14.1; **HRMS** (ESI$^+$) $C_{23}H_{36}{}^{35}ClO$ requires 363.2449 $[M+H]^+$, found 363.2451; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2957, 2929, 2861, 1695, 1671, 1628, 1510, 1461, 1410, 1362, 1305, 1269, 1200, 1111, 1018, 983, 830, 726, 648; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 8.99 min, τ_{minor} = 10.58 min (89% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +1.7 (*c* = 1.0, CHCl$_3$).

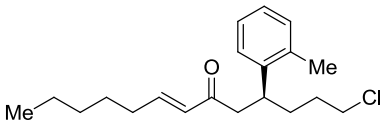
(*R*,*E*)-1-(3-Hydroxyphenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8q



Prepared according to General Procedure G, on a 0.20 mmol scale, using **7a** (43 mg, 0.20 mmol), 4-ethynylanisole (29 μL) and 3-hydroxyphenylboronic acid (41 mg). Flash column chromatography (gradient petrol/Et$_2$O, 80:20 to 70:30) afforded *the title compound* (43 mg, 61% yield, 93% ee) as a yellow oil. **δH** (400 MHz, CDCl$_3$): 7.15-7.07 (m, 3H, Ar-*H*), 6.87-6.74 (m, 4H, 3 × Ar-*H* and C*H*=CH-CO), 6.71-6.68 (m, 1H, Ar-*H*), 6.62 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, Ar-*H*), 6.14 (s, 1H, O*H*), 6.06 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.54 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.74 (s, 3H, OC*H*$_3$), 3.24 (d, *J* = 7.5 Hz, 2H, C*H*$_2$-CO), 2.20-2.12 (m, 2H, C*H*$_2$-CH=CH), 1.46-1.37 (m, 2H, C*H*$_2$-CH$_2$-CH=CH), 1.36-1.21 (m, 4H, 2 × C*H*$_2$), 0.89 (t, *J* = 7.0 Hz, 3H, CH$_2$-C*H*$_3$); **δC** (101 MHz, CDCl$_3$): 199.6, 158.1, 156.1, 149.0, 146.2, 136.1, 130.4, 129.7, 128.8, 119.8, 115.0, 114.0, 113.5, 55.3, 46.1, 45.4, 32.6,

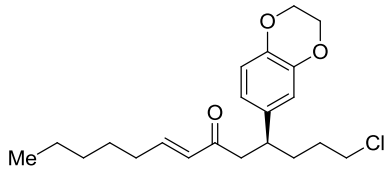
31.4, 27.8, 22.5, 14.1; **HRMS** (ESI$^+$) $C_{23}H_{28}O_3Na$ requires 375.1931 $[M+Na]^+$, found 375.1926; $\boldsymbol{\nu}_{\mathbf{max}}$ (film)/cm^{-1} 3389 (br.), 2957, 2930, 2856, 1657, 1613, 1586, 1511, 1454, 1248, 1179, 1035, 832, 789, 697; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 88:12); flow rate 1.0 mL/min; τ_{major} = 17.16 min, τ_{minor} = 20.38 min (93% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +3.5 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-Chloro-4-(*o*-tolyl)tridec-7-en-6-one, 8r



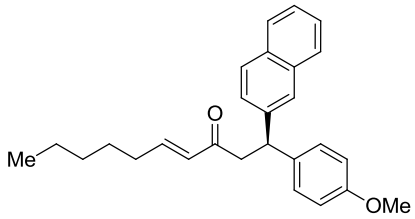
Prepared according to General Procedure G, using **7a** (65 mg), 5-chloro-1-pentyne (35 μL) and *o*-tolylboronic acid (61 mg). Flash column chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (74 mg, 76% yield, 90% ee) as a colorless oil. $\boldsymbol{\delta}_{\mathbf{H}}$ (400 MHz, $CDCl_3$): 7.20-7.15 (m, 2H, Ar-*H*), 7.14-7.04 (m, 2H, Ar-*H*), 6.75 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 6.00 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.57-3.48 (m, 1H, Ar-C*H*), 3.44 (t, *J* = 6.5 Hz, 2H, CH_2-Cl), 2.88-2.74 (m, 2H, CH_2-CO), 2.36 (s, 3H, Ar-CH_3), 2.19-2.11 (m, 2H, CH_2-CH=CH), 1.88-1.51 (m, 4H, CH_2-CH_2-CH_2-Cl), 1.46-1.36 (m, 2H, CH_2-CH_2-CH=CH), 1.36-1.20 (m, 4H, 2 × CH_2), 0.88 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta}_{\mathbf{C}}$ (101 MHz, $CDCl_3$): 199.3, 148.1, 142.5, 136.2, 130.6 (2C), 126.4, 126.2, 125.7, 47.1, 45.2, 35.3, 33.6, 32.5, 31.4, 30.5, 27.8, 22.5, 20.0, 14.1; **HRMS** (EI$^+$) $C_{20}H_{29}{}^{35}ClO$ requires 320.1901 $[M]^+$, found 320.1907; $\boldsymbol{\nu}_{\mathbf{max}}$ (film)/cm^{-1} 2957, 2929, 2859, 1695, 1670, 1627, 1491, 1460, 1367, 1303, 1159, 1110, 983, 758, 727, 645; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 7.75 min, τ_{minor} = 10.71 min (90% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –1.4 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-Chloro-4-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)tridec-7-en-6-one, 8s



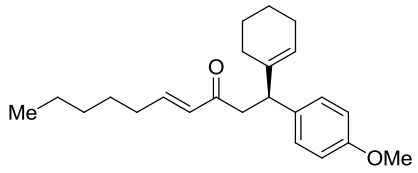
Prepared according to General Procedure G, using **7a** (65 mg), 5-chloro-1-pentyne (35 μL) and 1,4-benzodioxane-6-boronic acid (81 mg). $[Rh(L2)Cl]_2$ (6.9 mg) was used instead of $[Rh(L1)Cl]_2$. Flash column chromatography (gradient petrol/Et_2O, 90:10 to 88:12) afforded *the title compound* (83 mg, 76% yield, 90% ee) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 6.79-6.70 (m, 2H, Ar-*H* and C*H*=CH-CO), 6.69-6.62 (m, 2H, Ar-*H*), 6.01 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.23 (br. s, 4H, O-CH_2-CH_2-O), 3.44 (t, *J* = 6.5 Hz, 2H, CH_2-Cl), 3.12-3.03 (m, 1H, Ar-C*H*), 2.80 (dd, *J* = 16.0, 6.5 Hz, 1H, CH_aH$_b$-CO), 2.74 (dd, *J* = 16.0, 7.5 Hz, 1H, CH$_a$$H_b$-CO), 2.19-2.12 (m, 2H, CH_2-CH=CH), 1.81-1.52 (m, 4H, CH_2-CH_2-CH$_2$-Cl), 1.46-1.36 (m, 2H, CH_2-CH$_2$-CH=CH), 1.36-1.21 (m, 4H, 2 × CH_2), 0.88 (t, *J* = 7.0 Hz, 3H, CH$_2$-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 199.2, 148.1, 143.5, 142.2, 137.5, 130.7, 120.6, 117.3, 116.0, 64.5, 64.4, 47.5, 45.1, 40.2, 33.6, 32.5, 31.4, 30.7, 27.9, 22.5, 14.1; **HRMS** (ESI^+) $C_{21}H_{30}{}^{35}ClO_3$ requires 365.1878 $[M+H]^+$, found 365.1875; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2955, 2928, 2858, 1693, 1668, 1626, 1590, 1505, 1459, 1433, 1360, 1307, 1285, 1256, 1203, 1126, 1069, 984, 886, 813; the **ee** was determined by HPLC using a Chiralpak IA-3 column (^{n}hexane/^{i}PrOH, 97:3); flow rate 1.0 mL/min; τ_{major} = 13.57 min, τ_{minor} = 16.70 min (90% ee); $\boldsymbol{[\alpha]_D^{25}}$: +1.8 (*c* = 1.0, $CHCl_3$).

(*R*,*E*)-1-(4-Methoxyphenyl)-1-(naphthalen-2-yl)dec-4-en-3-one, 8t



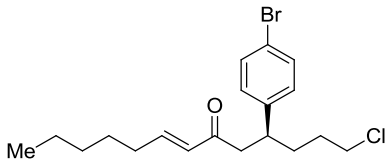
Prepared according to General Procedure G, on a 0.20 mmol scale, using **7a** (43 mg, 0.20 mmol), 4-ethynylanisole (29 μL) and 2-naphthylboronic acid (52 mg). Flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (63 mg, 81% yield, 87% ee) as a yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.81-7.72 (m, 3H, Ar-*H*), 7.68 (br. s, 1H, Ar-*H*), 7.44 (app. pd, *J* = 7.0, 1.5 Hz, 2H, Ar-*H*), 7.34 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-*H*), 7.20 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.88-6.79 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.10 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.81 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.77 (s, 3H, OCH_3), 3.44-3.31 (m, 2H, CH_2-CO), 2.21-2.13 (m, 2H, CH_2-CH=CH), 1.46-1.37 (m, 2H, CH_2-CH_2-CH=CH), 1.37-1.21 (m, 4H, 2 × CH_2), 0.90 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 198.6, 158.2, 148.2, 142.0, 136.2, 133.6, 132.3, 130.6, 129.0, 128.3, 127.9, 127.7, 126.8, 126.1, 125.7, 125.6, 114.0, 55.3, 46.2, 45.5, 32.6, 31.4, 27.8, 22.5, 14.1; **HRMS** (ESI^+) $C_{27}H_{30}O_2Na$ requires 409.2138 $[M+Na]^+$, found 409.2136; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2956, 2929, 2856, 1696, 1669, 1630, 1609, 1511, 1464, 1247, 1179, 1035, 815, 747; the **ee** was determined by HPLC using two Chiralpak AD-H columns in series (^{n}hexane/^{i}PrOH, 98:2); flow rate 0.8 mL/min; τ_{major} = 79.16 min, τ_{minor} = 84.52 min (87% ee); $\boldsymbol{[\alpha]_D^{25}}$: –34.2 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-(Cyclohex-1-en-1-yl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8u



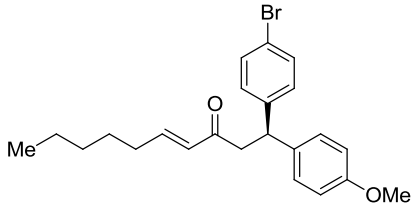
Prepared according to General Procedure G, on a 0.20 mmol scale, using **7a** (43 mg, 0.20 mmol), 4-ethynylanisole (29 μL) and 1-cyclohexen-1-yl-boronic acid (38 mg). $[Rh(L2)Cl]_2$ (4.6 mg) was used instead of $[Rh(L1)Cl]_2$. Flash column chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (30 mg, 44% yield, 94% ee) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.10 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82-6.71 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.03 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 5.55-5.50 (m, 1H, C=C*H*), 3.77 (s, 3H, OCH_3), 3.73 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.00 (dd, *J* = 15.5, 7.5 Hz, 1H, C$H_a$$H_b$-CO), 2.86 (dd, *J* = 15.5, 7.5 Hz, 1H, C$H_a$$H_b$-CO), 2.19-2.12 (m, 2H, CH_2-CH=CH), 2.06-1.98 (m, 2H, C=CH-CH_2), 1.82-1.75 (m, 2H, CH_2-C=CH), 1.58-1.47 (m, 4H, C=CH-CH_2-CH_2-CH_2), 1.46-1.37 (m, 2H, CH_2-CH_2-CH=CH), 1.36-1.21 (m, 4H, 2 × CH_2), 0.88 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 199.6, 158.1, 147.7, 139.6, 135.6, 130.7, 128.8, 121.1, 113.7, 55.3, 47.3, 44.4, 32.5, 31.4, 27.9, 27.5, 25.4, 23.0, 22.6, 22.5, 14.1; **HRMS** (ESI^+) $C_{23}H_{33}O_2$ requires 341.2475 $[M+H]^+$, found 341.2476; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2928, 2856, 1696, 1672, 1627, 1610, 1511, 1465, 1301, 1246, 1177, 1109, 1038, 983, 829; the **ee** was determined by HPLC using a Chiralpak IA-3 column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 12.41 min, τ_{minor} = 11.19 min (94% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –45.6 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-4-(4-Bromophenyl)-1-chlorotridec-7-en-6-one, 8v



Prepared according to General Procedure G, using **7a** (65 mg), 5-chloro-1-pentyne (35 μL) and 4-bromophenylboronic acid (90 mg). $[Rh(L2)Cl]_2$ (6.9 mg) was used instead of $[Rh(L1)Cl]_2$. Flash column chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (90 mg, 78% yield, 79% ee) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.40 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.07 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.74 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 6.00 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.45 (t, *J* = 6.0 Hz, 2H, CH_2-Cl), 3.22-3.13 (m, 1H, Ar-C*H*), 2.83 (dd, *J* = 15.0, 6.0 Hz, 1H, C$H_a$$H_b$-CO), 2.78 (dd, *J* = 15.0, 6.0 Hz, 1H, CH$_a$$H_b$-CO), 2.19-2.11 (m, 2H, CH_2-CH=CH), 1.86-1.48 (m, 4H, CH_2-CH_2-CH$_2$-Cl), 1.45-1.36 (m, 2H, CH_2-CH$_2$-CH=CH), 1.34-1.20 (m, 4H, 2 ×CH_2), 0.88 (t, *J* = 7.0 Hz, 3H, CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 198.7, 148.3, 143.2, 131.8, 130.5, 129.4, 120.3, 47.1, 45.0, 40.3, 33.4, 32.6, 31.4, 30.6, 27.8, 22.5, 14.1; **HRMS** (EI^+) $C_{19}H_{26}{}^{79}Br^{35}ClO$ requires 384.0856 $[M]^+$, found 384.0860; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2955, 2928, 2857, 1694, 1670, 1627, 1487, 1456, 1408, 1364, 1306, 1282, 1181, 1103, 1074, 1010, 983, 822, 718, 652; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 17.62 min, τ_{minor} = 20.42 min (79% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –3.4 (*c* = 1.0, $CHCl_3$).

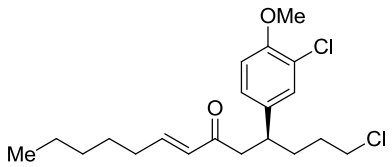
(*R*,*E*)-1-(4-Bromophenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8w



Prepared according to General Procedure G, on a 0.20 mmol scale, using **7a** (43 mg,

0.20 mmol), 4-ethynylanisole (29 μL) and 4-bromophenylboronic acid (60 mg). $[Rh(L2)Cl]_2$ (4.6 mg) was used instead of $[Rh(L1)Cl]_2$. Flash column chromatography (petrol/Et_2O, 93:7) afforded *the title compound* (59 mg, 71% yield, 78% ee) as a yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.38 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.13-7.06 (m, 4H, Ar-*H*), 6.85-6.76 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.06 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.58 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.76 (s, 3H, OCH_3), 3.23 (d, *J* = 7.5 Hz, 2H, CH_2-CO), 2.21-2.14 (m, 2H, CH_2-CH=CH), 1.47-1.38 (m, 2H, CH_2-CH_2-CH=CH), 1.35-1.21 (m, 4H, 2 × CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 198.2, 158.3, 148.4, 143.7, 135.8, 131.6, 130.4, 129.6, 128.8, 120.2, 114.1, 55.3, 46.1, 44.8, 32.6, 31.4, 27.8, 22.5, 14.1; **HRMS** (ESI^+) $C_{23}H_{27}{}^{79}BrO_2Na$ requires 437.1087 $[M+Na]^+$, found 437.1086; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2956, 2929, 2856, 1670, 1627, 1511, 1487, 1464, 1303, 1248, 1178, 1074, 1035, 1010, 984, 955, 818; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 24.16 min, τ_{minor} = 26.16 min (78% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –6.4 (*c* = 1.0, $CHCl_3$).

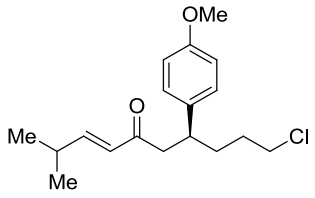
(*S*,*E*)-1-Chloro-4-(3-chloro-4-methoxyphenyl)tridec-7-en-6-one, 8x



Prepared according to General Procedure G, using **7a** (65 mg), 5-chloro-1-pentyne (35 μL) and 3-chloro-4-methoxyphenylboronic acid (84 mg). Flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (88 mg, 79% yield, 60% ee) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.18 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.04 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-*H*), 6.83 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 6.75 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-

CO), 6.00 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.86 (s, 3H, OCH_3), 3.45 (t, *J* = 6.5 Hz, 2H, CH_2-Cl), 3.17-3.08 (m, 1H, Ar-C*H*), 2.82 (dd, *J* = 15.5, 6.5 Hz, 1H, C$H_a$$H_b$-CO), 2.76 (dd, *J* = 15.5, 6.5 Hz, 1H, C$H_a$$H_b$-CO), 2.19-2.12 (m, 2H, CH_2-CH=CH), 1.83-1.53 (m, 4H, CH_2-CH_2-CH_2-Cl), 1.46-1.37 (m, 2H, CH_2-CH_2-CH=CH), 1.33-1.20 (m, 4H, 2 × CH_2), 0.88 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δC** (101 MHz, $CDCl_3$): 198.8, 153.6, 148.3, 137.3, 130.6, 129.0, 127.1, 122.5, 112.2, 56.2, 47.3, 45.0, 39.9, 33.5, 32.5, 31.4, 30.6, 27.8, 22.5, 14.1; **HRMS** (ESI$^+$) $C_{20}H_{28}{}^{35}Cl_2O_2Na$ requires 393.1359 $[M+Na]^+$, found 393.1358; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2956, 2929, 2858, 1693, 1668, 1627, 1503, 1461, 1442, 1412, 1363, 1281, 1257, 1183, 1065, 1024, 983, 882, 812, 722; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 15.34 min, τ_{minor} = 16.84 min (59% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +0.4 (*c* = 1.0, $CHCl_3$).

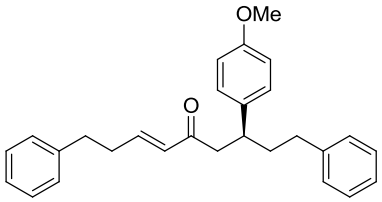
(*S*,*E*)-10-Chloro-7-(4-methoxyphenyl)-2-methyldec-3-en-5-one, 8aa



Prepared according to General Procedure G, using **7b** (56 mg), 5-chloro-1-pentyne (35 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (71 mg, 77% yield, 95% ee) as a colorless oil. **δH** (400 MHz, $CDCl_3$): 7.10 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.69 (dd, *J* = 16.0, 6.5 Hz, 1H, C*H*=CH-CO), 5.94 (dd, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.77 (s, 3H, OCH_3), 3.45 (t, *J* = 6.5 Hz, 2H, CH_2-Cl), 3.18-3.09 (m, 1H, Ar-C*H*), 2.87-2.73 (m, 2H, CH_2-CO), 2.45-2.34 (m, 1H, C*H*-CH=CH), 1.85-1.51 (m, 4H, 2 × CH_2), 1.01 (app. dd, *J* = 7.0, 2.0 Hz, 6H, CH(CH_3)$_2$); **δC** (101 MHz, $CDCl_3$): 199.7, 158.3, 153.9, 136.1,

128.5, 127.9, 114.0, 55.3, 47.7, 45.1, 40.2, 33.6, 31.2, 30.7, 21.40, 21.37; **HRMS** (ESI^+) $C_{18}H_{25}{}^{35}ClO_2Na$ requires 331.1435 $[M+Na]^+$, found 331.1437; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2960, 2932, 2870, 1693, 1668, 1625, 1612, 1583, 1512, 1462, 1365, 1301, 1246, 1178, 1110, 1035, 982, 830; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 16.51 min, τ_{minor} = 23.89 min (95% ee); $\boldsymbol{[\alpha]_D^{25}}$: +4.9 (*c* = 1.0, $CHCl_3$).

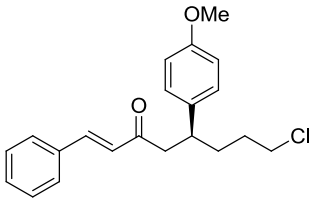
(*S*,*E*)-7-(4-Methoxyphenyl)-1,9-diphenylnon-3-en-5-one, 8ab



Prepared according to General Procedure G, on a 0.20 mmol scale, using **7c** (50 mg, 0.20 mmol), 4-phenyl-1-butyne (31 μL) and 4-methoxyphenylboronic acid (46 mg). Flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (53 mg, 66% yield, 93% ee) as a white solid. **M.p.** (Et_2O): 56-58 ℃; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.31-7.07 (m, 12H, Ar-*H*), 6.85 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.74 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 6.00 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.80 (s, 3H, OCH_3), 3.19-3.10 (m, 1H, Ar-C*H*), 2.84-2.68 (m, 4H, CH_2-CO and CH_2-CH_2-CH=CH), 2.50-2.41 (m, 4H, CH_2-CH=CH and Ar-CH-CH_2-CH_2), 2.02-1.91 (m, 1H, Ar-CH-C$H_a$$H_b$-$CH_2$), 1.91-1.79 (m, 1H, Ar-CH-$CH_a$$H_b$-$CH_2$); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 199.5, 158.2, 146.4, 142.3, 140.8, 136.3, 131.1, 128.65, 128.63, 128.5, 128.45, 128.41, 126.3, 125.8, 114.0, 55.4, 47.9, 40.6, 38.1, 34.5, 34.2, 33.8; **HRMS** (ESI^+) $C_{28}H_{30}O_2Na$ requires 421.2138 $[M+Na]^+$, found 421.2136; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 3027, 2930, 1693, 1667, 1626, 1611, 1512, 1496, 1454, 1363, 1301, 1247, 1178, 1033, 831, 749, 700; the **ee** was determined by HPLC using a Chiralpak AD-H column

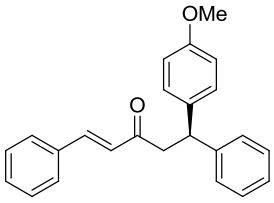
(^{n}hexane/^{i}PrOH, 97:3); flow rate 1.0 mL/min; τ_{major} = 20.23 min, τ_{minor} = 21.91 min (93% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +7.6 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-8-Chloro-5-(4-methoxyphenyl)-1-phenyloct-1-en-3-one, 8ac



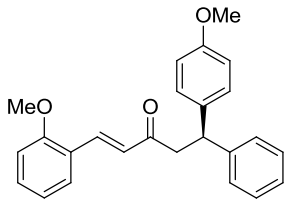
Prepared according to General Procedure G, using **7d** (67 mg), 5-chloro-1-pentyne (35 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (85 mg, 82% yield, 92% ee) as an off-white solid. **M.p.** (CH_2Cl_2): 83-86 ℃; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.51-7.43 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 7.40-7.35 (m, 3H, Ar-*H*), 7.14 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.84 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.64 (d, *J* = 16.0 Hz, 1H, CH=C*H*-CO), 3.77 (s, 3H, OCH_3), 3.47 (t, *J* = 6.5 Hz, 2H, CH_2-Cl), 3.26-3.17 (m, 1H, Ar-C*H*-CH_2), 3.00-2.87 (m, 2H, CH_2-CO), 1.91-1.54 (m, 4H, 2 ×CH_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 199.0, 158.3, 142.8, 136.0, 134.6, 130.6, 129.0, 128.5, 128.4, 126.5, 114.1, 55.3, 48.6, 45.1, 40.3, 33.6, 30.7; **HRMS** (ESI^+) $C_{21}H_{23}{}^{35}ClO_2Na$ requires 365.1279 $[M+Na]^+$, found 365.1282; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2954, 2934, 2835, 1687, 1659, 1609, 1576, 1512, 1449, 1301, 1246, 1178, 1096, 1034, 978, 830, 750, 690; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 96:4); flow rate 1.0 mL/min; τ_{major} = 23.75 min, τ_{minor} = 31.97 min (92% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –15.7 (*c* = 1.0, $CHCl_3$).

(*R*,*E*)-5-(4-Methoxyphenyl)-1,5-diphenylpent-1-en-3-one, 8ad



Prepared according to General Procedure G, using **7d** (67 mg), phenylacetylene (36 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (84 mg, 81% yield, 97% ee) as a white solid. **M.p.** (CH_2Cl_2): 125-128 ℃; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.55-7.48 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 7.41-7.36 (m, 3H, Ar-*H*), 7.32-7.24 (m, 4H, Ar-*H*), 7.21-7.15 (m, 3H, Ar-*H*), 6.83 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.71 (d, *J* = 16.0 Hz, 1H, CH=C*H*-CO), 4.70 (t, *J* = 7.5 Hz, 1H, Ar-C*H*-CH_2), 3.76 (s, 3H, OCH_3), 3.40 (d, *J* = 7.5 Hz, 2H, CH_2-CO); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 198.3, 158.2, 144.5, 142.9, 136.3, 134.6, 130.6, 129.1, 128.9, 128.7, 128.4, 127.8, 126.5, 126.4, 114.0, 55.3, 47.3, 45.5; **HRMS** (ESI^+) $C_{24}H_{22}O_2Na$ requires 365.1512 $[M+Na]^+$, found 365.1510; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 3059, 3027, 3001, 2955, 2933, 2906, 2835, 1688, 1663, 1609, 1576, 1510, 1495, 1450, 1331, 1302, 1249, 1178, 1093, 1034, 979, 834, 752, 699; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 96:4); flow rate 1.0 mL/min; τ_{major} = 32.10 min, τ_{minor} = 35.58 min (97% ee); $\boldsymbol{[\alpha]_D^{25}}$: −7.0 (*c* = 1.0, $CHCl_3$).

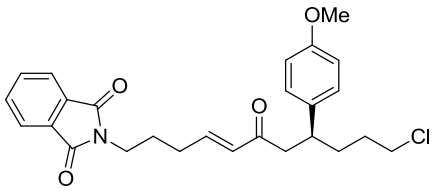
(*R*,*E*)-1-(2-Methoxyphenyl)-5-(4-methoxyphenyl)-5-phenylpent-1-en-3-one, 8ae



Prepared according to General Procedure G, on a 0.20 mmol scale, using **7e** (50 mg,

0.20 mmol), phenylacetylene (24 μL) and 4-methoxyphenylboronic acid (46 mg). Flash column chromatography (petrol/Et_2O, 7:3) afforded *the title compound* (60 mg, 81% yield, 96% ee) as a white solid. **M.p.** (petrol): 79-81 ℃; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.90 (d, *J* = 16.5 Hz, 1H, C*H*=CH-CO), 7.50 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.39-7.33 (m, 1H, Ar-*H*), 7.31-7.24 (m, 4H, Ar-*H*), 7.22-7.15 (m, 3H, Ar-*H*), 6.99-6.89 (m, 2H, Ar-*H*), 6.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.76 (d, *J* = 16.5 Hz, 1H, CH=C*H*-CO), 4.71 (t, *J* = 7.5 Hz, 1H, Ar-C*H*-CH_2), 3.89 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.47-3.36 (m, 2H, CH_2-CO); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 198.9, 158.5, 158.1, 144.7, 138.1, 136.4, 131.9, 128.9, 128.64, 128.62, 127.9, 127.1, 126.4, 123.5, 120.9, 114.0, 111.2, 55.6, 55.3, 46.8, 45.4; **HRMS** (ESI^+) $C_{25}H_{25}O_3$ requires 373.1798 $[M+H]^+$, found 373.1800; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2959, 2836, 1686, 1660, 1598, 1510, 1488, 1464, 1247, 1178, 1029, 754, 700; the **ee** was determined by HPLC using a Chiralpak IA-3 column (^{n}hexane/^{i}PrOH, 93:7); flow rate 1.0 mL/min; τ_{major} = 19.77 min, τ_{minor} = 20.90 min (96% ee); $\boldsymbol{[\alpha]_D^{25}}$: –9.4 (*c* = 1.0, $CHCl_3$).

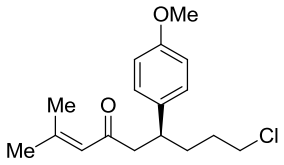
(*S*,*E*)-2-(11-Chloro-8-(4-methoxyphenyl)-6-oxoundec-4-en-1-yl)isoindoline-1,3-dione, 8af



Prepared according to General Procedure G, on a 0.20 mmol scale, using **7f** (67 mg, 0.20 mmol), 5-chloro-1-pentyne (23 μL) and 4-methoxyphenylboronic acid (46 mg). Flash column chromatography (gradient petrol/EtOAc, 4:1 to 3:1) afforded *the title compound* (70 mg, 77% yield, 85% ee) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.87-7.81 (m, 2H, Ar-*H*), 7.74-7.68 (m, 2H, Ar-*H*), 7.08 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H,

Ar-*H*), 6.71 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CH-CO), 6.04 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 3.75 (s, 3H, OCH_3), 3.68 (t, *J* = 7.0 Hz, 2H, CH_2-N), 3.44 (t, *J* = 6.5 Hz, 2H, CH_2-Cl), 3.16-3.06 (m, 1H, Ar-C*H*), 2.78 (dd, *J* = 16.0, 7.0 Hz, 1H, C$H_a$$H_b$-CO), 2.72 (dd, *J* = 16.0, 7.0 Hz, 1H, CH$_a$$H_b$-CO), 2.26-2.18 (m, 2H, CH_2-CH=CH), 1.86-1.50 (m, 6H, 3 × CH_2); **δC** (101 MHz, $CDCl_3$): 199.0, 168.5, 158.2, 145.7, 136.0, 134.2, 132.1, 131.1, 128.5, 123.4, 114.0, 55.3, 47.8, 45.1, 40.1, 37.4, 33.6, 30.7, 29.8, 27.0; **HRMS** (ESI^+) $C_{26}H_{28}{}^{35}ClO_4NNa$ requires 476.1599 $[M+Na]^+$, found 476.1599; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2937, 2836, 1771, 1709, 1670, 1626, 1612, 1512, 1466, 1438, 1396, 1369, 1246, 1179, 1111, 1034, 978, 831, 720; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*hexane/*i*PrOH, 88:12); flow rate 1.0 mL/min; τ_{major} = 40.16 min, τ_{minor} = 57.07 min (85% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +1.5 (*c* = 1.0, $CHCl_3$).

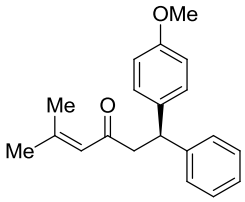
(*S*)-9-Chloro-6-(4-methoxyphenyl)-2-methylnon-2-en-4-one, 8ag



Prepared according to General Procedure G, using **7g** (52 mg), 5-chloro-1-pentyne (35 μL) and 4-methoxyphenylboronic acid (68 mg). Flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (67 mg, 76% yield, 85% ee) as a pale yellow oil. **δH** (400 MHz, $CDCl_3$): 7.09 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 5.97 (dt, *J* = 2.5, 1.0 Hz, 1H, C*H*-CO), 3.77 (s, 3H, OCH_3), 3.44 (t, *J* = 6.5 Hz, 2H, CH_2-Cl), 3.16-3.07 (m, 1H, Ar-C*H*), 2.68 (d, *J* = 7.0 Hz, 2H, CH_2-CO), 2.07 (d, *J* = 1.0 Hz, 3H, CH_3), 1.83 (d, *J* = 1.0 Hz, 3H, CH_3), 1.82-1.51 (m, 4H, 2 × CH_2); **δC** (101 MHz, $CDCl_3$): 199.6, 158.2, 155.5, 136.3, 128.5, 124.2, 114.0, 55.3, 51.7, 45.2, 40.1, 33.7, 30.7, 27.8, 20.8;

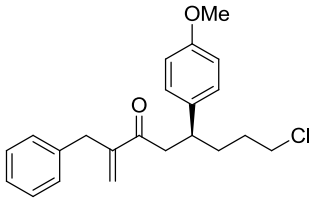
HRMS (ESI$^+$) $C_{17}H_{24}{}^{35}ClO_2$ requires 295.1459 $[M+H]^+$, found 295.1459; $\boldsymbol{\nu}_{\mathbf{max}}$ (film)/cm^{-1} 2935, 2912, 2836, 1685, 1614, 1512, 1444, 1379, 1301, 1246, 1178, 1105, 1034, 831; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 97:3); flow rate 1.0 mL/min; τ_{major} = 8.10 min, τ_{minor} = 9.35 min (85% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +32.8 (*c* = 1.0, $CHCl_3$).

(*R*)-1-(4-Methoxyphenyl)-5-methyl-1-phenylhex-4-en-3-one, 8ah



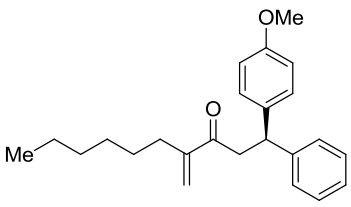
Prepared according to General Procedure G, on a 0.20 mmol scale, using **7g** (35 mg, 0.20 mmol), phenylacetylene (24 μL) and 4-methoxyphenylboronic acid (46 mg). Flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (41 mg, 70% yield, 88% ee) as an off-white solid. **M.p.** (Et_2O): 46-50 ℃; $\boldsymbol{\delta}_{\mathbf{H}}$ (400 MHz, $CDCl_3$): 7.31-7.14 (m, 7H, Ar-*H*), 6.83 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.10-6.07 (m, 1H, C*H*-CO), 4.61 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.78 (s, 3H, OCH_3), 3.16 (d, *J* = 7.5 Hz, 2H, CH_2-CO), 2.08 (d, *J* = 1.0 Hz, 3H, CH_3), 1.87 (d, *J* = 1.0 Hz, 3H, CH_3); $\boldsymbol{\delta}_{\mathbf{C}}$ (101 MHz, $CDCl_3$): 198.8, 158.0, 155.7, 144.8, 136.6, 128.9, 128.6, 127.8, 126.3, 124.1, 113.9, 55.3, 50.4, 45.4, 27.8, 20.9; **HRMS** (ESI$^+$) $C_{20}H_{23}O_2$ requires 295.1704 $[M+H]^+$, found 295.1693; $\boldsymbol{\nu}_{\mathbf{max}}$ (film)/cm^{-1} 2980, 2908, 2835, 1686, 1614, 1510, 1444, 1381, 1302, 1248, 1178, 1104, 1034, 952, 831, 700; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 18.17 min, τ_{minor} = 16.48 min (88% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: +5.1 (*c* = 1.0, $CHCl_3$).

(*S*)-2-Benzyl-8-chloro-5-(4-methoxyphenyl)oct-1-en-3-one, 8ai



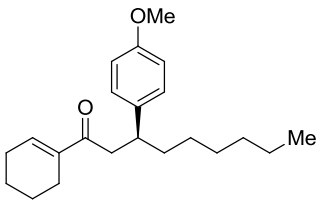
Prepared according to General Procedure G, using **7h** (71 mg), 5-chloro-1-pentyne (35 μL) and 4-methoxyphenylboronic acid (68 mg). After addition of DBU, the reaction mixture was stirred for 14 h before work-up. Flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (57 mg, 53% yield, 93% ee) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.28-7.14 (m, 3H, Ar-*H*), 7.10-7.02 (m, 4H, Ar-*H*), 6.80 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 5.97 (s, 1H, C*H*$_a$H$_b$=C-CO), 5.55 (t, *J* = 1.5 Hz, 1H, CH$_a$*H*$_b$=C-CO), 3.77 (s, 3H, OC*H*$_3$), 3.52 (app. s, 2H, Ar-C*H*$_2$), 3.39 (t, *J* = 6.5 Hz, 2H, C*H*$_2$-Cl), 3.16-3.06 (m, 1H, Ar-C*H*), 2.98 (dd, *J* = 16.0, 7.0 Hz, 1H, C*H*$_c$H$_d$-CO), 2.87 (dd, *J* = 16.0, 7.0 Hz, 1H, CH$_c$*H*$_d$-CO), 1.74-1.45 (m, 4H, 2 ×C*H*$_2$); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 200.3, 158.3, 148.8, 139.1, 136.0, 129.2, 128.51, 128.49, 126.3, 125.5, 114.0, 55.3, 45.5, 45.1, 40.4, 37.1, 33.5, 30.7; **HRMS** (CI^+) $C_{22}H_{26}{}^{35}ClO_2$ requires 357.1616 $[M+H]^+$, found 357.1607; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2954, 2933, 2835, 1675, 1610, 1512, 1454, 1367, 1301, 1247, 1178, 1078, 1033, 941, 830, 701; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 36.59 min, τ_{minor} = 42.40 min (93% ee); $\boldsymbol{[\alpha]_D^{25}}$: –1.0 (*c* = 1.0, $CHCl_3$).

(*R*)-1-(4-Methoxyphenyl)-4-methylene-1-phenyldecan-3-one, 8aj



Prepared according to General Procedure G, on a 0.20 mmol scale, using **7i** (46 mg, 0.20 mmol), phenylacetylene (24 μL) and 4-methoxyphenylboronic acid (46 mg). After addition of DBU, the reaction mixture was stirred for 14 h before work-up. Flash column chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (43 mg, 61% yield, 90% ee) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.30-7.19 (m, 4H, Ar-*H*), 7.19-7.11 (m, 3H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 5.98 (s, 1H, C*H*$_a$H$_b$=C-CO), 5.69 (s, 1H, CH$_a$*H*$_b$=C-CO), 4.63 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.76 (s, 3H, OC*H*$_3$), 3.46-3.34 (m, 2H, C*H*$_2$-CO), 2.19 (t, *J* = 7.0 Hz, 2H, C*H*$_2$-C-CO), 1.30-1.17 (m, 8H, 4 × C*H*$_2$), 0.87 (t, *J* = 7.0 Hz, 3H, CH$_2$-C*H*$_3$); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 200.2, 158.1, 149.6, 144.6, 136.4, 128.9, 128.6, 127.8, 126.4, 123.7, 114.0, 55.3, 45.7, 44.2, 31.8, 31.1, 29.1, 28.4, 22.7, 14.2; **HRMS** (ESI^+) $C_{24}H_{30}O_2Na$ requires 373.2138 $[M+Na]^+$, found 373.2138; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2954, 2928, 2856, 1678, 1611, 1511, 1454, 1249, 1179, 1036, 829, 699; the **ee** was determined by HPLC using a Chiralpak IA-3 column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 9.73 min, τ_{minor} = 11.01 min (90% ee); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$: –3.2 (*c* = 1.0, $CHCl_3$).

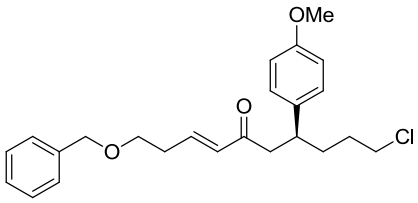
(*S*)-1-(Cyclohex-1-en-1-yl)-3-(4-methoxyphenyl)nonan-1-one, 8ak



Prepared according to General Procedure G, on a 0.20 mmol scale, using **7j** (40 mg, 0.20 mmol), 1-octyne (32 μL) and 4-methoxyphenylboronic acid (46 mg). Toluene was used instead of CH_2Cl_2 for the elimination step; after addition of DBU, the reaction mixture was refluxed at 120 ℃ for 1.5 h before work-up. Flash column chromatography (petrol/Et_2O, 96:4) afforded *the title compound* (33 mg, 50% yield, 96% ee) as a pale yellow

oil. **δ_H** (400 MHz, $CDCl_3$): 7.09 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.84-6.77 (m, 3H, 2 × Ar-*H* and C*H*=C-CO), 3.77 (s, 3H, OCH_3), 3.16-3.06 (m, 1H, Ar-C*H*), 2.92-2.79 (m, 2H, CH_2-CO), 2.23-2.10 (m, 4H, CH_2-CH=C-CH_2), 1.65-1.46 (m, 6H, 3 × CH_2), 1.30-1.02 (m, 8H, 4 × CH_2), 0.83 (t, *J* = 7.0 Hz, 3H, CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 200.7, 157.9, 139.8, 139.7, 137.4, 128.5, 113.8, 55.3, 44.8, 41.1, 36.5, 31.9, 29.4, 27.6, 26.2, 23.2, 22.7, 22.1, 21.6, 14.2; **HRMS** (ESI^+) $C_{22}H_{32}O_2Na$ requires 351.2295 $[M+Na]^+$, found 351.2295; **ν_{max}** (film)/cm^{-1} 2928, 2856, 1667, 1512, 1463, 1248, 1178, 1038, 829; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 10.31 min, τ_{minor} = 11.19 min (96% ee); $[\alpha]_D^{25}$: –12.0 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-(Benzyloxy)-10-chloro-7-(4-methoxyphenyl)dec-3-en-5-one, 8al

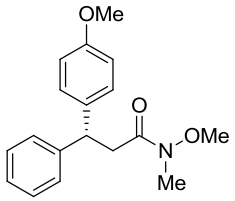


Prepared according to General Procedure G, on a 0.20 mmol scale, using **7k** (56 mg, 0.20 mmol), 5-chloro-1-pentyne (23 μL) and 4-methoxyphenylboronic acid (46 mg). Flash column chromatography (petrol/Et_2O, 4:1) afforded *the title compound* (63 mg, 78% yield, 77% ee) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.38-7.25 (m, 5H, Ar-*H*), 7.09 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.84-6.73 (m, 3H, 2 × Ar-*H* and C*H*=CH-CO), 6.08 (dt, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-CO), 4.51 (s, 2H, Ph-CH_2), 3.77 (s, 3H, OCH_3), 3.55 (t, *J* = 6.5 Hz, 2H, BnO-CH_2), 3.44 (t, *J* = 6.5 Hz, 2H, CH_2-Cl), 3.19-3.10 (m, 1H, Ar-C*H*), 2.87-2.74 (m, 2H, CH_2-CO), 2.51-2.44 (m, 2H, CH_2-CH=CH), 1.85-1.50 (m, 4H, 2 × CH_2); **δ_C** (101 MHz, $CDCl_3$): 199.1, 158.2, 144.1, 138.1, 136.0, 132.0, 128.6, 128.5, 127.9, 127.8, 114.0, 73.2, 68.4, 55.3, 47.7, 45.1, 40.0, 33.6, 33.0, 30.7; **HRMS** (ESI^+) $C_{24}H_{29}{}^{35}ClO_3Na$ requires 423.1697

[M+Na]$^+$, found 423.1696; ν_{max} (film)/cm^{-1} 2933, 2860, 1694, 1669, 1628, 1611, 1512, 1454, 1362, 1301, 1246, 1178, 1095, 1031, 976, 830, 737, 698; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 90:10); flow rate 1.0 mL/min; τ_{major} = 10.74 min, τ_{minor} = 13.32 min (77% ee); $[\alpha]_D^{25}$: +1.0 (*c* = 1.0, $CHCl_3$).

5.3.3 Determination of the absolute configuration

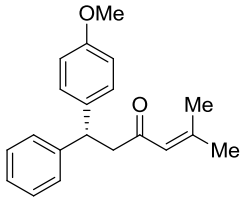
(*R*)-*N*-Methoxy-*N*-methyl-3-(4-methoxyphenyl)-3-phenylpropanamide, 9



Under N_2 atmosphere, 2.0 M aqueous solution of KOH (0.2 mL, 0.4 mmol) was added to a solution of $[Rh(L1)Cl]_2$ (7.5 mg, 0.008 mmol) in degassed 1,4-dioxane (1.0 mL) and the mixture stirred at 23 ℃ for 5 min. The solution was transferred to a N_2-purged reaction vial charged with *N*-methoxy-*N*-methylcinnamamide (76.5 mg, 0.4 mmol) and 4-methoxyphenylboronic acid (303.9 mg, 2.0 mmol) with additional 1,4-dioxane (1.0 mL) to rinse the remainder. The resulting mixture was stirred at 55 ℃ for 20 h, cooled to room temperature, filtered through a pad of SiO_2 and concentrated under reduced pressure. Flash column chromatography (CH_2Cl_2/Et_2O, 97:3) afforded the title compound (44.2 mg, 37% yield) as a white solid. δ_H (400 MHz, $CDCl_3$): 7.30-7.23 (m, 4H, Ar-*H*), 7.21-7.14 (m, 3H, Ar-*H*), 6.82 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 4.64 (t, *J* = 7.5 Hz, 1H, Ar-C*H*), 3.76 (s, 3H, ArOCH_3), 3.57 (s, 3H, N-OCH_3), 3.19-3.13 (m, 2H, CH_2-CO), 3.11 (s, 3H, N-CH_3); δ_C (101 MHz, $CDCl_3$): 172.6, 158.1, 144.7, 136.4, 128.9, 128.6, 127.9, 126.4, 114.0, 61.4, 55.3, 45.6, 38.1, 32.2; ν_{max} (film)/cm^{-1} 2936, 2836, 1660, 1611, 1511, 1453, 1418, 1385,

1303, 1249, 1178, 1115, 1033, 995, 830, 767, 700; $[\alpha]_D^{25}$: –4.4 (*c* = 1.0, $CHCl_3$); data consistent with literature.[85]

(*R*)-1-(4-Methoxyphenyl)-5-methyl-1-phenylhex-4-en-3-one, 10

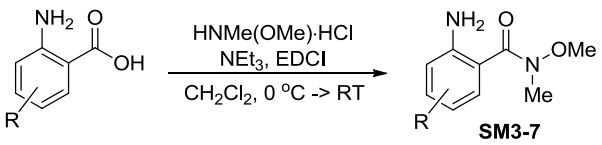


Under N_2 atmosphere, 2-methyl-1-propenylmagnesium bromide solution (0.5 M in THF, 0.30 mL, 0.15 mmol) was slowly added to a solution of **9** (30 mg, 0.10 mmol) in THF (1.0 mL) at 0 ℃. The reaction mixture was warmed to ambient temperature and stirred for 1 h. Saturated aqueous solution of NH_4Cl (2 mL) was added to quench the reaction and the mixture extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography (petrol/Et_2O, 92:8) afforded *the title compound* (16 mg, 54% yield, 80% ee) as an off-white solid. **Characterization data**: see compound **8ah**; the **ee** was determined by HPLC using a Chiralpak AD-H column (^{n}hexane/^{i}PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 18.21 min, τ_{minor} = 16.49 min (80% ee); $[\alpha]_D^{25}$: +3.5 (*c* = 1.0, $CHCl_3$).

5.4 Data for Chapter 4

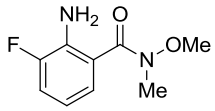
5.4.1 Preparation of starting aldehydes

General Procedure H: synthesis of 2-aminobenzamides.



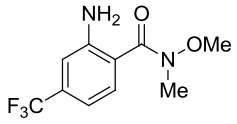
Triethylamine (1.1 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.1 equiv) were added to a suspension of anthranilic acid (1.0 equiv) in CH_2Cl_2 (0.1 M) at 0 ℃. *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDCI) (1.1 equiv) was then added to the reaction mixture in 4 portions, and it was stirred at 23 ℃ until all starting material was consumed. The reaction mixture was washed with saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography afforded the corresponding product.

2-Amino-3-fluoro-*N*-methoxy-*N*-methylbenzamide, SM3



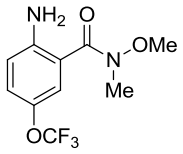
Prepared according to General Procedure H, using 2-amino-3-fluorobenzoic acid (1.55 g, 10 mmol), NEt_3 (1.5 mL, 11 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (1.07 g, 11 mmol), EDCI (2.11 g, 11 mmol) and CH_2Cl_2 (100 mL). Purification by flash column chromatography (CH_2Cl_2/Et_2O, 85:15) afforded *the title compound* (1.55 g, 78% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.20-7.14 (m, 1H, Ar-*H*), 7.05-6.97 (m, 1H, Ar-*H*), 6.64-6.56 (m, 1H, Ar-*H*), 4.73 (s, 2H, NH_2), 3.57 (s, 3H, OCH_3), 3.34 (s, 3H, NCH_3); **δ_C** (101 MHz, $CDCl_3$): 168.9, 151.9 (d, $J_{C\text{-}F}$ = 239.0 Hz), 136.0 (d, $J_{C\text{-}F}$ = 14.0 Hz), 124.6 (d, $J_{C\text{-}F}$ = 3.5 Hz), 119.1 (d, $J_{C\text{-}F}$ = 3.5 Hz), 116.7 (d, $J_{C\text{-}F}$ = 18.5 Hz), 116.1 (d, $J_{C\text{-}F}$ = 7.0 Hz), 61.3, 34.2; **δ_F** (377 MHz, $CDCl_3$): –134.8; **HRMS** (ESI^+) $C_9H_{12}FN_2O_2$ requires 199.0877 $[M+H]^+$, found 199.0878; **ν_{max}** (film)/cm^{-1} 3466, 3363, 2973, 2936, 1631, 1590, 1566, 1475, 1419, 1380, 1278, 1226, 1067, 984, 852, 786, 742.

2-Amino-*N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide, SM4



Prepared according to General Procedure H, using 2-amino-4-(trifluoromethyl)benzoic acid (3.08 g, 15 mmol), NEt_3 (2.3 mL, 16.5 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (1.61 g, 16.5 mmol), EDCI (3.16 g, 16.5 mmol) and CH_2Cl_2 (150 mL). Purification by flash column chromatography (gradient CH_2Cl_2/Et_2O, 95:5 to 90:10) afforded *the title compound* (3.16 g, 85% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.42 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.92-6.90 (m, 1H, Ar-*H*), 6.89-6.85 (m, 1H, Ar-*H*), 4.84 (s, 2H, N*H*$_2$), 3.53 (s, 3H, OC*H*$_3$), 3.32 (s, 3H, NC*H*$_3$); **δ_C** (101 MHz, $CDCl_3$): 168.7, 147.0, 133.0 (q, $J_{C\text{-}F}$ = 32.5 Hz), 129.8, 123.8 (q, $J_{C\text{-}F}$ = 272.5 Hz), 120.0, 113.3-112.9 (m, 2C), 61.3, 33.7; **δ_F** (377 MHz, $CDCl_3$): –63.4; **HRMS** (ESI^+) $C_{10}H_{12}F_3N_2O_2$ requires 249.0845 $[M+H]^+$, found 249.0845; ***ν*$_{max}$** (film)/cm^{-1} 3359, 1628, 1597, 1510, 1437, 1337, 1255, 1164, 1118, 1070, 978, 927, 870, 817, 696.

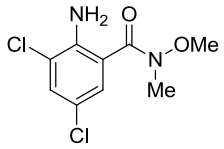
2-Amino-*N*-methoxy-*N*-methyl-5-(trifluoromethoxy)benzamide, SM5



Prepared according to General Procedure H, using 2-amino-5-(trifluoromethoxy) benzoic acid (885 mg, 4.0 mmol), NEt_3 (0.61 mL, 4.4 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (429 mg, 4.4 mmol), EDCI (844 mg, 4.4 mmol) and CH_2Cl_2 (40 mL). Purification by flash column chromatography (gradient CH_2Cl_2/Et_2O, 90:10 to 85:15) afforded *the title compound* (977 mg, 74% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.32-7.29 (m, 1H, Ar-*H*), 7.06-7.01 (m, 1H, Ar-*H*), 6.65 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 4.78 (s,

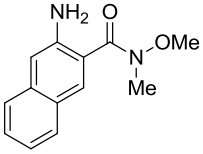
2H, NH_2), 3.55 (s, 3H, OCH_3), 3.32 (s, 3H, NCH_3); **δ_C** (101 MHz, $CDCl_3$): 168.6, 146.1, 139.3 (q, $J_{C\text{-}F}$ = 2.0 Hz), 125.0, 122.6, 120.8 (q, $J_{C\text{-}F}$ = 256.0 Hz), 117.3, 116.8, 61.3, 33.8; **δ_F** (377 MHz, $CDCl_3$): −58.8; **HRMS** (ESI^+) $C_{10}H_{12}F_3N_2O_3$ requires 265.0800 $[M+H]^+$, found 265.0805; ***ν*max** (film)/cm^{-1} 3360, 1631, 1593, 1499, 1434, 1383, 1252, 1208, 1147, 985, 957, 890, 825.

2-Amino-3,5-dichloro-*N*-methoxy-*N*-methylbenzamide, SM6



Prepared according to General Procedure H, using 2-amino-3,5-dichlorobenzoic acid (1.03 g, 5.0 mmol), NEt_3 (0.77 mL, 5.5 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (536 mg, 5.5 mmol), EDCI (1.05 g, 5.5 mmol) and CH_2Cl_2 (50 mL). Purification by flash column chromatography (gradient CH_2Cl_2/Et_2O, 95:5 to 90:10) afforded *the title compound* (584 mg, 47% yield) as a white solid. **M.p.** (Et_2O): 194-195 ℃; **δ_H** (400 MHz, $CDCl_3$): 7.30 (s, 2H, Ar-*H*), 5.08 (s, 2H, NH_2), 3.55 (s, 3H, OCH_3), 3.33 (s, 3H, NCH_3); **δ_C** (101 MHz, $CDCl_3$): 167.9, 142.2, 130.9, 127.6, 120.9, 120.8, 118.7, 61.5, 33.8; **HRMS** (ESI^+) $C_9H_{11}{}^{35}Cl_2N_2O_2$ requires 249.0198 $[M+H]^+$, found 249.0199; ***ν*max** (film)/cm^{-1} 3470, 3361, 2934, 1612, 1573, 1549, 1457, 1379, 1208, 1079, 981, 856, 777, 743, 640.

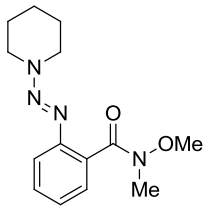
3-Amino-*N*-methoxy-*N*-methyl-2-naphthamide, SM7



Prepared according to General Procedure H, using 3-amino-2-naphthoic acid (936 mg, 5.0 mmol), NEt_3 (0.77 mL, 5.5 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride

(536 mg, 5.5 mmol), EDCI (1.05 g, 5.5 mmol) and CH_2Cl_2 (50 mL). Purification by flash column chromatography (CH_2Cl_2/Et_2O, 7:3) afforded *the title compound* (1.13 g, 98% yield) as a brown solid. **M.p.** (Et_2O): 216-218 ℃; **δ_H** (400 MHz, $CDCl_3$): 7.85 (s, 1H, Ar-*H*), 7.69 (dd, *J* = 8.0, 0.5 Hz, 1H, Ar-*H*), 7.54 (dd, *J* = 8.0, 0.5 Hz, 1H, Ar-*H*), 7.39 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar-*H*), 7.23 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar-*H*), 6.99 (s, 1H, Ar-*H*), 4.55 (s, 2H, NH_2), 3.57 (s, 3H, OCH_3), 3.38 (s, 3H, NCH_3); **δ_C** (101 MHz, $CDCl_3$): 169.3, 143.2, 135.5, 129.2, 128.4, 127.6, 126.6, 125.6, 122.9, 121.6, 110.3, 61.3, 34.1; **HRMS** (ESI^+) $C_{13}H_{15}N_2O_2$ requires 231.1134 $[M+H]^+$, found 231.1139; **ν_{max}** (film)/cm^{-1} 3446, 3355, 1634, 1610, 1580, 1507, 1457, 1381, 1184, 1150, 1118, 973, 906, 866, 728.

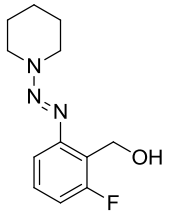
(*E*)-*N*-Methoxy-*N*-methyl-2-(piperidin-1-yldiazenyl)benzamide, SM8



A cold solution of sodium nitrite (4.14 g, 60 mmol) in water (5 mL) was slowly added to a suspension of 2-amino-*N*-methoxy-*N*-methylbenzamide[123] (5.40 g, 30 mmol) in conc. HCl (10 mL) at 0 ℃. The mixture was stirred for 10 min before it was poured into a solution of KOH (3.37 g, 60 mmol) and piperidine (5.9 mL, 60 mmol) in water (50 mL) at –20 ℃. It was then stirred for an additional 10 min, diluted in water and warmed to room temperature. The aqueous phase was extracted with Et_2O (2 ×), and the combined organic layers dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (8.23 g, 99% yield) as a yellow oil. **^{1}H NMR** and **^{13}C NMR** observed as a 7:5 mixture of rotamers. **δ_H**

(400 MHz, $CDCl_3$): 7.46-7.41 (m, 1H, Ar-*H*), 7.32-7.22 (m, 2H, Ar-*H*), 7.10 (td, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 3.81 (s, 3H, OCH_3, min. rot.), 3.70 (br. s, 4H, N(CH_2)$_2$), 3.33 (s, 3H, OCH_3, maj. rot.), 3.28 (s, 3H, NCH_3, maj. rot.), 2.98 (s, 3H, NCH_3, min. rot.), 1.62 (br. s, 6H, 3 ×CH_2); **δC** (101 MHz, $CDCl_3$): 171.8, 167.4, 147.1, 130.0, 126.6, 124.9, 118.2, 61.0, 52.7, 43.7, 32.4, 25.2 (2C), 24.2 (maj. rot.); 171.8, 167.4, 147.1, 129.4, 127.3, 125.4, 117.8, 60.4, 52.7, 43.7, 36.1, 25.2 (2C), 24.2 (min. rot.); **HRMS** (ESI^+) $C_{14}H_{21}N_4O_2$ requires 277.1659 $[M+H]^+$, found 277.1658; ν_{max} (film)/cm^{-1} 2937, 2856, 1650, 1422, 1356, 1295, 1182, 1098, 987, 915, 853, 759, 727, 645.

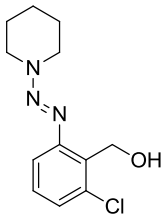
(*E*)-(2-Fluoro-6-(piperidin-1-yldiazenyl)phenyl)methanol, SM9



A cold solution of sodium nitrite (1.42 g, 20.6 mmol) in water (2 mL) was slowly added to a suspension of (2-amino-6-fluorophenyl)methanol[124] (1.46 g, 10.3 mmol) in conc. HCl (3.6 mL) at 0 ℃. The mixture was stirred for 10 min before it was poured into a solution of KOH (1.16 g, 20.6 mmol) and piperidine (2.0 mL, 20.6 mmol) in water (20 mL) at –20 ℃. It was then stirred for an additional 10 min, diluted in water and warmed to room temperature. The aqueous phase was extracted with Et_2O (2 ×), and the combined organic layers dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 3:2) afforded *the title compound* (2.39 g, 98% yield) as a yellow oil. **δH** (400 MHz, $CDCl_3$): 7.29 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.18 (dd, *J* = 14.5, 8.0 Hz, 1H, Ar-*H*), 6.84 (t, *J* = 8.5 Hz, 1H, Ar-*H*), 4.91 (d, *J* = 6.5 Hz, 2H, Ar-CH_2),

3.84-3.76 (m, 5H, N(C*H*$_2$)$_2$ and O*H*), 1.72 (br. s, 6H, 3 × C*H*$_2$); **δ$_C$** (101 MHz, $CDCl_3$): 160.4 (d, $J_{C\text{-}F}$ = 244.0 Hz), 150.7 (d, $J_{C\text{-}F}$ = 6.0 Hz), 128.8 (d, $J_{C\text{-}F}$ = 9.5 Hz), 121.7 (d, $J_{C\text{-}F}$ = 17.0 Hz), 112.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 112.1 (d, $J_{C\text{-}F}$ = 23.0 Hz), 55.9 (d, $J_{C\text{-}F}$ = 6.5 Hz), 53.1, 43.9, 26.0, 24.2, 24.1; **δ$_F$** (377 MHz, $CDCl_3$): −119.4; **HRMS** (ESI^+) $C_{12}H_{17}FN_3O$ requires 238.1350 $[M+H]^+$, found 238.1350; ***ν*$_{max}$** (film)/cm^{-1} 3433 (br.), 2940, 2857, 1609, 1579, 1419, 1355, 1294, 1242, 1183, 1110, 1011, 853, 835, 786, 745, 719.

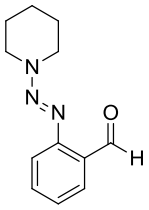
(*E*)-(2-Chloro-6-(piperidin-1-yldiazenyl)phenyl)methanol, SM10



A cold solution of sodium nitrite (1.46 g, 21.2 mmol) in water (2 mL) was slowly added to a suspension of (2-amino-6-chlorophenyl)methanol[125] (1.67 g, 10.6 mmol) in conc. HCl (3.7 mL) at 0 ℃. The mixture was stirred for 10 min before it was poured into a solution of KOH (1.19 g, 21.2 mmol) and piperidine (2.1 mL, 21.2 mmol) in water (18 mL) at −20 ℃. It was then stirred for an additional 10 min, diluted in water and warmed to room temperature. The aqueous phase was extracted with Et_2O (2 ×), and the combined organic layers dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 7:3) afforded *the title compound* (1.40 g, 52% yield) as a yellow oil. **δ$_H$** (400 MHz, $CDCl_3$): 7.44-7.37 (m, 1H, Ar-*H*), 7.18-7.11 (m, 2H, Ar-*H*), 5.03 (d, *J* = 6.5 Hz, 2H, Ar-C*H*$_2$), 3.84-3.76 (m, 5H, N(C*H*$_2$)$_2$ and O*H*), 1.72 (br. s, 6H, 3 × C*H*$_2$); **δ$_C$** (101 MHz, $CDCl_3$): 150.6, 133.6, 131.9, 128.8, 126.4, 115.4, 59.9, 53.2, 44.1, 26.0, 24.3, 24.1; **HRMS** (ESI^+) $C_{12}H_{17}{}^{35}ClN_3O$ requires 254.1055 $[M+H]^+$, found

254.1055; ν_{max} (film)/cm^{-1} 3442 (br.), 2939, 2856, 1570, 1417, 1355, 1291, 1259, 1188, 1106, 1013, 971, 853, 782, 737, 695.

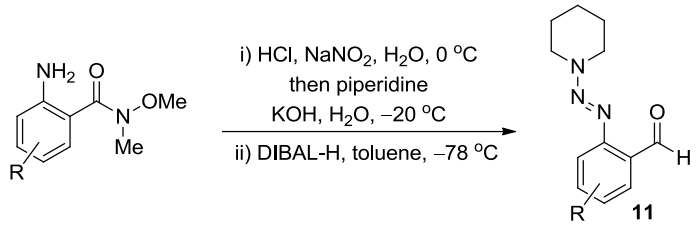
(*E*)-2-(Piperidin-1-yldiazenyl)benzaldehyde, 11b



Under N_2 atmosphere, a solution of DIBAL-H (1.0 M in toluene, 36 mL, 36 mmol) was added dropwise to a solution of **SM8** (8.23 g, 30 mmol) in toluene (300 mL) at −78 ℃. The reaction mixture was stirred at −78 ℃ for 3 h. EtOAc and saturated aqueous solution of sodium potassium tartrate were then added, and the mixture allowed to warm to room temperature. The organic phase was washed with saturated aqueous solution of sodium potassium tartrate and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (5.93 g, 92% yield) as a pale yellow solid. **M.p.** (petrol/Et_2O): 33-34 ℃; δ_H (400 MHz, $CDCl_3$): 10.83 (d, *J* = 1.0 Hz, 1H, C*H*O), 7.87-7.83 (m, 1H, Ar-*H*), 7.55-7.47 (m, 2H, Ar-*H*), 7.22-7.17 (m, 1H, Ar-*H*), 3.85 (br. s, 4H, N(CH_2)$_2$), 1.71 (br. s, 6H, 3 × CH_2); δ_C (101 MHz, $CDCl_3$): 192.6, 152.5, 134.7, 129.0, 127.0, 125.4, 117.6, 53.2, 44.0, 26.4, 24.4, 24.3; **HRMS** (ESI$^+$) $C_{12}H_{16}N_3O$ requires 218.1288 $[M+H]^+$, found 218.1289; ν_{max} (film)/cm^{-1} 2939, 2856, 1683, 1592, 1413, 1353, 1293, 1187, 1108, 1001, 761.

Aldehyde **11a** was synthesized in a similar manner; the procedure and characterization data can be found in Eva K. Paffenholz's thesis for her master degree.[94]

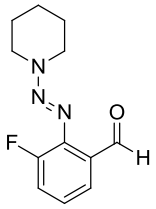
General Procedure I: synthesis of 2-triazenylbenzaldehydes.



A cold solution of sodium nitrite (2.0 equiv) in water was slowly added to a suspension of 2-aminobenzamide (1.0 equiv) in conc. HCl at 0 ℃. The mixture was stirred for 10 min before it was poured into a solution of KOH (2.0 equiv) and piperidine (2.0 equiv) in water at −20 ℃. It was then stirred for an additional 10 min, diluted in water and warmed to room temperature. The aqueous phase was extracted with Et_2O (2 ×), and the combined organic layers dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 2-(piperidin-1-yldiazenyl)benzamide, which was used in the reduction step without further purification.

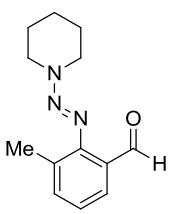
Under N_2 atmosphere, a solution of DIBAL-H (1.0 M in toluene, 1.1 or 1.2 equiv) was added dropwise to a solution of the benzamide (1.0 equiv) in toluene (0.1 M) at −78 ℃. The reaction mixture was stirred at −78 ℃ for 3 h. EtOAc and saturated aqueous solution of sodium potassium tartrate were then added, and the mixture allowed to warm to room temperature. The organic phase was washed with saturated aqueous solution of sodium potassium tartrate and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography afforded the corresponding 2-(piperidin-1-yldiazenyl)benzaldehyde.

(*E*)-3-Fluoro-2-(piperidin-1-yldiazenyl)benzaldehyde, 11c



Prepared according to General Procedure I, using: i) **SM3** (1.50 g, 7.6 mmol), conc. HCl (2.6 mL), sodium nitrite (1.05 g, 15.2 mmol, in 2 mL H_2O), KOH (853 mg, 15.2 mmol), piperidine (1.5 mL, 15.2 mmol) and H_2O (12 mL) to afford the corresponding 2-(piperidin-1-yldiazenyl)benzamide (1.98 g, 6.7 mmol) as a crude; ii) DIBAL-H (8.0 mL, 8.0 mmol) and toluene (67 mL). Purification by flash column chromatography (petrol/Et_2O, 9:1), followed by recrystallization (petrol/CH_2Cl_2), afforded *the title compound* (0.70 g, 39% yield) as a yellow solid. **M.p.** (petrol/CH_2Cl_2): 66-68 ℃; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 10.16 (d, *J* = 0.5 Hz, 1H, C*H*O), 7.65-7.60 (m, 1H, Ar-*H*), 7.34-7.28 (m, 1H, Ar-*H*), 7.17 (tdd, *J* = 8.0, 4.5, 0.5 Hz, 1H, Ar-*H*), 4.00-3.80 (2 × br. s, 4H, N(CH_2)$_2$), 1.75 (br. s, 6H, 3 × CH_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 190.8 (d, $J_{C\text{-}F}$ = 3.0 Hz), 155.4 (d, $J_{C\text{-}F}$ = 252.0 Hz), 141.8 (d, $J_{C\text{-}F}$ = 9.0 Hz), 131.1, 125.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 123.2 (d, $J_{C\text{-}F}$ = 4.0 Hz), 121.2 (d, $J_{C\text{-}F}$ = 20.5 Hz), 53.3, 43.9, 26.4, 24.3, 24.2; $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$): –126.3; **HRMS** (ESI^+) $C_{12}H_{15}FN_3O$ requires 236.1194 $[M+H]^+$, found 236.1193; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2941, 2858, 1684, 1601, 1573, 1415, 1354, 1286, 1250, 1182, 1108, 1014, 968, 853, 789, 765, 733.

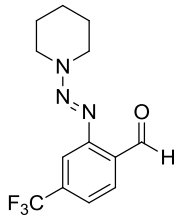
(*E*)-3-Methyl-2-(piperidin-1-yldiazenyl)benzaldehyde, 11d



Prepared according to General Procedure I, using: i) 2-amino-*N*-methoxy-*N*,3-

dimethylbenzamide[126] (692 mg, 3.6 mmol), conc. HCl (1.2 mL), sodium nitrite (492 mg, 7.1 mmol, in 1 mL H_2O), KOH (400 mg, 7.1 mmol), piperidine (0.70 mL, 7.1 mmol) and H_2O (6 mL) to afford the corresponding 2-(piperidin-1-yldiazenyl)benzamide (1.03 g, 3.6 mmol) as a crude; ii) DIBAL-H (3.9 mL, 3.9 mmol) and toluene (35 mL). Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (454 mg, 55% yield) as a pale yellow solid. **M.p.** (Et_2O): 58-60 ℃; **δ_H** (400 MHz, $CDCl_3$): 9.87 (s, 1H, C*H*O), 7.65 (dd, *J* = 7.5, 0.5 Hz, 1H, Ar-*H*), 7.37 (dd, *J* = 7.5, 0.5 Hz, 1H, Ar-*H*), 7.13 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 3.83 (br. s, 4H, N(C*H*$_2$)$_2$), 2.36 (s, 3H, C*H*$_3$), 1.71 (br. s, 6H, 3 × C*H*$_2$); **δ_C** (101 MHz, $CDCl_3$): 191.7, 151.9, 135.3, 133.0, 129.2, 125.7, 124.9, 52.6, 44.9, 25.3 (2C), 24.3, 18.0; **HRMS** (ESI^+) $C_{13}H_{18}N_3O$ requires 232.1450 $[M+H]^+$, found 232.1458; ***ν*$_{max}$** (film)/cm^{-1} 2940, 2855, 1679, 1588, 1420, 1355, 1286, 1238, 1179, 1106, 1083, 984, 853, 765.

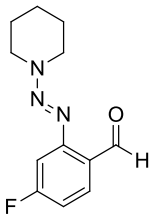
(*E*)-2-(Piperidin-1-yldiazenyl)-4-(trifluoromethyl)benzaldehyde, 11e



Prepared according to General Procedure I, using: i) **SM4** (3.06 g, 12.3 mmol), conc. HCl (4.1 mL), sodium nitrite (1.70 g, 24.6 mmol, in 3 mL H_2O), KOH (1.38 g, 24.6 mmol), piperidine (2.4 mL, 24.6 mmol) and H_2O (21 mL) to afford the corresponding 2-(piperidin-1-yldiazenyl)benzamide (3.43 g, 10.0 mmol) as a crude; ii) DIBAL-H (11.0 mL, 11.0 mmol) and toluene (110 mL). Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (1.43 g, 41% yield) as a pale yellow solid. **M.p.** (petrol/Et_2O):

108-110 ℃; **δ_H** (400 MHz, $CDCl_3$): 10.84 (d, *J* = 1.0 Hz, 1H, C*H*O), 7.94 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.85 (s, 1H, Ar-*H*), 7.41 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.98-3.86 (2 × br. s, 4H, N(CH_2)$_2$), 1.86-1.66 (m, 6H, 3 × CH_2); **δ_C** (101 MHz, $CDCl_3$): 191.8, 152.7, 135.8 (q, $J_{C\text{-}F}$ = 32.5 Hz), 130.8, 127.9, 123.8 (q, $J_{C\text{-}F}$ = 273.0 Hz), 121.3 (q, $J_{C\text{-}F}$ = 3.5 Hz), 115.0 (q, $J_{C\text{-}F}$ = 4.0 Hz), 53.6, 44.2, 26.6, 24.5, 24.2; **δ_F** (377 MHz, $CDCl_3$): –63.3; **HRMS** (ESI^+) $C_{13}H_{15}F_3N_3O$ requires 286.1162 $[M+H]^+$, found 286.1161; **ν_{max}** (film)/cm^{-1} 2946, 2863, 1680, 1394, 1327, 1159, 1122, 1065, 903, 832.

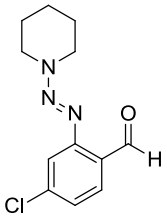
(*E*)-4-Fluoro-2-(piperidin-1-yldiazenyl)benzaldehyde, 11f



Prepared according to General Procedure I, using: i) 2-amino-4-fluoro-*N*-methoxy-*N*-methylbenzamide[127] (1.33 g, 6.7 mmol), conc. HCl (2.3 mL), sodium nitrite (925 mg, 13.4 mmol, in 2 mL H_2O), KOH (752 mg, 13.4 mmol), piperidine (1.3 mL, 13.4 mmol) and H_2O (10 mL) to afford the corresponding 2-(piperidin-1-yldiazenyl)benzamide (1.98 g, 6.7 mmol) as a crude; ii) DIBAL-H (8.0 mL, 8.0 mmol) and toluene (67 mL). Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (1.48 g, 94% yield) as a pale yellow solid. **M.p.** (petrol/Et_2O): 39-41 ℃; **δ_H** (400 MHz, $CDCl_3$): 10.73 (d, *J* = 0.5 Hz, 1H, C*H*O), 7.85 (dd, *J* = 8.5, 6.5 Hz, 1H, Ar-*H*), 7.22 (dd, *J* = 11.0, 2.5 Hz, 1H, Ar-*H*), 6.87-6.80 (m, 1H, Ar-*H*), 3.86 (br. s, 4H, N(CH_2)$_2$), 1.84-1.60 (m, 6H, 3 × CH_2); **δ_C** (101 MHz, $CDCl_3$): 191.0, 166.9 (d, $J_{C\text{-}F}$ = 255.0 Hz), 155.0 (d, $J_{C\text{-}F}$ = 8.5 Hz), 129.7 (d, $J_{C\text{-}F}$ = 10.5 Hz), 125.8 (d, $J_{C\text{-}F}$ = 2.5 Hz), 112.7 (d, $J_{C\text{-}F}$ = 23.0 Hz), 103.5 (d, $J_{C\text{-}F}$

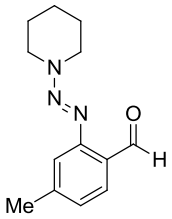
= 23.0 Hz), 53.4, 44.1, 26.5, 24.4, 24.2; **δ_F** (377 MHz, $CDCl_3$): −102.5; **HRMS** (ESI^+) $C_{12}H_{15}FN_3O$ requires 236.1194 $[M+H]^+$, found 236.1194; ***ν*max** (film)/cm^{-1} 2942, 2858, 1684, 1598, 1581, 1404, 1291, 1240, 1200, 1111, 1004, 864, 812, 656.

(*E*)-4-Chloro-2-(piperidin-1-yldiazenyl)benzaldehyde, 11g



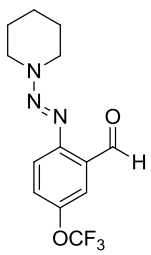
Prepared according to General Procedure I, using: i) 2-amino-4-chloro-*N*-methoxy-*N*-methylbenzamide[128] (1.25 g, 5.8 mmol), conc. HCl (2.0 mL), sodium nitrite (800 mg, 11.6 mmol, in 2 mL H_2O), KOH (651 mg, 11.6 mmol), piperidine (1.1 mL, 11.6 mmol) and H_2O (8.0 mL) to afford the corresponding 2-(piperidin-1-yldiazenyl)benzamide (1.62 g, 5.2 mmol) as a crude; ii) DIBAL-H (6.2 mL, 6.2 mmol) and toluene (52 mL). Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (1.20 g, 82% yield) as a pale yellow solid. **M.p.** (petrol/Et_2O): 46-47 ℃; **δ_H** (400 MHz, $CDCl_3$): 10.76 (d, *J* = 1.0 Hz, 1H, C*H*O), 7.78 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.56 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.13 (ddd, *J* = 8.5, 2.0, 1.0 Hz, 1H, Ar-*H*), 3.88 (br. s, 4H, N(CH_2)$_2$), 1.84-1.62 (m, 6H, 3 × CH_2); **δ_C** (101 MHz, $CDCl_3$): 191.5, 153.3, 141.0, 128.5, 127.3, 125.4, 117.4, 53.5, 44.1, 26.5, 24.5, 24.2; **HRMS** (ESI^+) $C_{12}H_{15}{}^{35}ClN_3O$ requires 252.0898 $[M+H]^+$, found 252.0898; ***ν*max** (film)/cm^{-1} 2941, 2857, 1683, 1585, 1421, 1394, 1375, 1354, 1339, 1184, 1111, 831.

(*E*)-4-Methyl-2-(piperidin-1-yldiazenyl)benzaldehyde, 11h



Prepared according to General Procedure I, using: i) 2-amino-*N*-methoxy-*N*,4-dimethylbenzamide[127] (1.88 g, 9.7 mmol), conc. HCl (3.3 mL), sodium nitrite (1.34 g, 19.4 mmol, in 2 mL H_2O), KOH (1.09 g, 19.4 mmol), piperidine (1.9 mL, 19.4 mmol) and H_2O (16 mL) to afford the corresponding 2-(piperidin-1-yldiazenyl)benzamide (2.80 g, 9.6 mmol) as a crude; ii) DIBAL-H (10.6 mL, 10.6 mmol) and toluene (100 mL). Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (2.06 g, 92% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 10.76 (d, *J* = 1.0 Hz, 1H, C*H*O), 7.76 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.31 (s, 1H, Ar-*H*), 7.03-6.98 (m, 1H, Ar-*H*), 3.83 (br. s, 4H, N(CH_2)$_2$), 2.36 (s, 3H, CH_3), 1.70 (br. s, 6H, 3 × CH_2); **δ_C** (101 MHz, $CDCl_3$): 192.2, 152.4, 145.7, 127.0, 126.9, 126.5, 117.7, 53.1, 44.0, 26.1, 24.4, 24.3, 22.1; **HRMS** (ESI$^+$) $C_{13}H_{18}N_3O$ requires 232.1444 $[M+H]^+$, found 232.1446; **ν_{max}** (film)/cm^{-1} 2939, 2854, 1679, 1600, 1422, 1353, 1291, 1190, 1096, 1001, 813, 648.

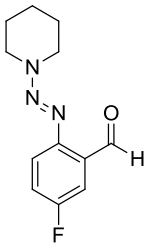
(*E*)-2-(Piperidin-1-yldiazenyl)-5-(trifluoromethoxy)benzaldehyde, 11i



Prepared according to General Procedure I, using: i) **SM5** (876 mg, 3.3 mmol), conc. HCl (1.1 mL), sodium nitrite (458 mg, 6.6 mmol, in 0.8 mL H_2O), KOH (372 mg,

6.6 mmol), piperidine (0.66 mL, 6.6 mmol) and H_2O (6.0 mL) to afford the corresponding 2-(piperidin-1-yldiazenyl)benzamide (1.07 g, 3.0 mmol) as a crude; ii) DIBAL-H (3.3 mL, 3.3 mmol) and toluene (30 mL). Purification by flash column chromatography (gradient petrol/Et_2O, 95:5 to 90:10) afforded *the title compound* (754 mg, 75% yield) as a pale orange solid. **M.p.** (petrol/Et_2O): 35-36 ℃; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 10.77 (s, 1H, C*H*O), 7.68-7.65 (m, 1H, Ar-*H*), 7.58 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.33-7.29 (m, 1H, Ar-*H*), 3.86 (br. s, 4H, N(CH_2)$_2$), 1.73 (br. s, 6H, 3 × CH_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 191.1, 151.1, 146.6 (q, *J* = 2.0 Hz), 129.6, 127.4, 120.6 (q, *J* = 257.5 Hz), 119.4, 118.8, 53.3, 44.1, 26.5, 24.4, 24.2; $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$): −58.1; **HRMS** (ESI^+) $C_{13}H_{15}F_3N_3O_2$ requires 302.1111 $[M+H]^+$, found 302.1110; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2944, 1686, 1410, 1244, 1212, 1175, 1141, 1108, 1002, 887, 834.

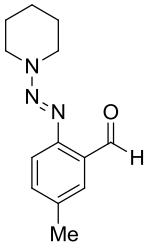
(*E*)-5-Fluoro-2-(piperidin-1-yldiazenyl)benzaldehyde, 11j



Prepared according to General Procedure I, using: i) 2-amino-5-fluoro-*N*-methoxy-*N*-methylbenzamide[127] (687 mg, 3.5 mmol), conc. HCl (1.2 mL), sodium nitrite (479 mg, 7.0 mmol, in 0.8 mL H_2O), KOH (389 mg, 7.0 mmol), piperidine (0.69 mL, 7.0 mmol) and H_2O (6.0 mL) to afford the corresponding 2-(piperidin-1-yldiazenyl)benzamide (725 mg, 2.5 mmol) as a crude; ii) DIBAL-H (2.7 mL, 2.7 mmol) and toluene (25 mL). Purification by flash column chromatography (gradient petrol/Et_2O, 95:5 to 90:10) afforded *the title compound* (458 mg, 56% yield) as an orange oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 10.76 (d, *J* = 3.5

Hz, 1H, C*H*O), 7.53 (dd, *J* = 9.0, 5.0 Hz, 1H, Ar-*H*), 7.48 (dd, *J* = 8.5, 3.0 Hz, 1H, Ar-*H*), 7.19 (ddd, *J* = 9.0, 8.0, 3.0 Hz, 1H, Ar-*H*), 3.82 (br. s, 4H, N(CH_2)$_2$), 1.71 (br. s, 6H, 3 × CH_2); **δC** (101 MHz, $CDCl_3$): 191.4, 160.6 (d, $J_{C\text{-}F}$ = 246.0 Hz), 149.1 (d, $J_{C\text{-}F}$ = 2.5 Hz), 130.0 (d, $J_{C\text{-}F}$ = 6.0 Hz), 122.0 (d, $J_{C\text{-}F}$ = 23.5 Hz), 119.6 (d, $J_{C\text{-}F}$ = 7.5 Hz), 112.4 (d, $J_{C\text{-}F}$ = 22.5 Hz), 53.1, 44.0, 26.3, 24.4, 24.2; **δF** (377 MHz, $CDCl_3$): −117.1; **HRMS** (ESI^+) $C_{12}H_{15}FN_3O$ requires 236.1194 $[M+H]^+$, found 236.1194; **ν_{max}** (film)/cm^{-1} 2941, 2858, 1681, 1478, 1411, 1254, 1106, 1002, 828, 736, 658.

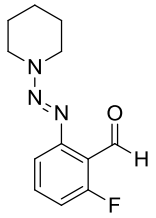
(*E*)-5-Methyl-2-(piperidin-1-yldiazenyl)benzaldehyde, 11k



Prepared according to General Procedure I, using: i) 2-amino-*N*-methoxy-*N*,5-dimethylbenzamide[129] (722 mg, 3.7 mmol), conc. HCl (1.3 mL), sodium nitrite (511 mg, 7.4 mmol, in 2 mL H_2O), KOH (415 mg, 7.4 mmol), piperidine (0.73 mL, 7.4 mmol) and H_2O (6.2 mL) to afford the corresponding 2-(piperidin-1-yldiazenyl)benzamide (909 mg, 3.1 mmol) as a crude; ii) DIBAL-H (3.7 mL, 3.7 mmol) and toluene (31 mL). Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (665 mg, 78% yield) as a pale yellow solid. **M.p.** (petrol/Et_2O): 50-51 ℃; **δH** (400 MHz, $CDCl_3$): 10.81 (s, 1H, C*H*O), 7.66 (d, *J* = 1.5 Hz, 1H, Ar-*H*), 7.45 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.33 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-*H*), 3.84 (br. s, 4H, N(CH_2)$_2$), 2.36 (s, 3H, CH_3), 1.73 (br. s, 6H, 3 ×CH_2); **δC** (126 MHz, $CDCl_3$): 192.7, 150.5, 135.7, 135.1, 128.8, 126.8, 117.5, 52.9, 44.0, 25.9, 24.8, 24.3, 20.9; **HRMS** (ESI^+) $C_{13}H_{18}N_3O$ requires 232.1444 $[M+H]^+$, found

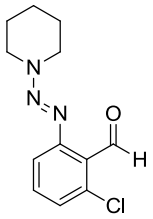
232.1445; ν_{max} (film)/cm^{-1} 2939, 2855, 1681, 1607, 1482, 1426, 1353, 1321, 1220, 1182, 1147, 1100, 1001, 827, 729, 662.

(*E*)-2-Fluoro-6-(piperidin-1-yldiazenyl)benzaldehyde, 11l



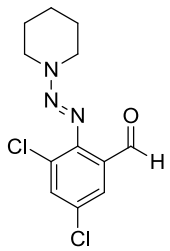
A solution of **SM9** (2.37 g, 10 mmol), Cu(MeCN)$_4$ OTf (188 mg, 0.5 mmol), 2,2'-bipyridine (78 mg, 0.5 mmol), TEMPO (78 mg, 0.5 mmol) and 1-methylimidazole (80 μL, 1.0 mmol) in acetonitrile (50 mL) was stirred under air for 2.5 h. The mixture was filtered through a pad of SiO_2 and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (2.11 g, 90% yield) as a yellow solid. **M.p.** (petrol/Et_2O): 36-38 ℃; δ_H (400 MHz, $CDCl_3$): 10.70 (s, 1H, C*H*O), 7.41 (td, *J* = 8.0, 6.0 Hz, 1H, Ar-*H*), 7.30 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.89-6.81 (m, 1H, Ar-*H*), 3.84 (br. s, 4H, N(C*H*$_2$)$_2$), 1.82-1.62 (m, 6H, 3 × C*H*$_2$); δ_C (101 MHz, $CDCl_3$): 190.3, 161.6 (d, $J_{C\text{-}F}$ = 261.0 Hz), 153.9 (d, $J_{C\text{-}F}$ = 3.5 Hz), 134.8 (d, $J_{C\text{-}F}$ = 11.0 Hz), 118.0 (d, $J_{C\text{-}F}$ = 8.5 Hz), 113.4 (d, $J_{C\text{-}F}$ = 3.5 Hz), 121.6 (d, $J_{C\text{-}F}$ = 21.5 Hz), 53.3, 44.1, 26.5, 24.4, 24.2; δ_F (377 MHz, $CDCl_3$): –116.2; **HRMS** (ESI$^+$) $C_{12}H_{15}FN_3O$ requires 236.1194 $[M+H]^+$, found 236.1193; ν_{max} (film)/cm^{-1} 2941, 2859, 1691, 1602, 1568, 1405, 1296, 1250, 1198, 1180, 1110, 1014, 868, 851, 791, 718.

(*E*)-2-Chloro-6-(piperidin-1-yldiazenyl)benzaldehyde, 11m



A solution of **SM10** (1.35 g, 5.3 mmol), $Cu(MeCN)_4$ OTf (100 mg, 0.27 mmol), 2,2'-bipyridine (41 mg, 0.27 mmol), TEMPO (41 mg, 0.27 mmol) and 1-methylimidazole (42 μL, 0.53 mmol) in acetonitrile (26 mL) was stirred under air for 2.5 h. The mixture was filtered through a pad of SiO_2 and concentrated under reduced pressure. Purification by flash column chromatography (petrol/CH_2Cl_2, 3:2) afforded *the title compound* (1.03 g, 77% yield) as a yellow solid. **M.p.** (Et_2O): 61-63 ℃; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 10.66 (s, 1H, C*H*O), 7.40 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.32 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.16 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.82 (br. s, 4H, N(CH_2)$_2$), 1.70 (br. s, 6H, 3 × CH_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 191.6, 153.8, 133.2, 133.1, 127.4, 126.9, 116.7, 53.2, 44.1, 26.4, 24.4, 24.2; **HRMS** (ESI^+) $C_{12}H_{15}{}^{35}ClN_3O$ requires 252.0898 $[M+H]^+$, found 252.0896; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2939, 2855, 1695, 1615, 1581, 1416, 1294, 1190, 1108, 1014, 945, 910, 787, 728.

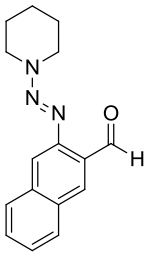
(*E*)-3,5-Dichloro-2-(piperidin-1-yldiazenyl)benzaldehyde, 11n



Prepared according to General Procedure I, using: i) **SM6** (510 mg, 2.0 mmol), conc. HCl (0.7 mL), sodium nitrite (284 mg, 4.1 mmol, in 1 mL H_2O), KOH (231 mg, 4.1 mmol), piperidine (0.41 mL, 4.1 mmol) and H_2O (3.4 mL) to afford the corresponding 2-(piperidin-

1-yldiazenyl)benzamide (618 mg, 1.8 mmol) as a crude; ii) DIBAL-H (2.0 mL, 2.0 mmol) and toluene (18 mL). Purification by flash column chromatography (gradient petrol/Et_2O, 95:5 to 90:10) afforded *the title compound* (517 mg, 88% yield) as a pale yellow solid. **M.p.** (Et_2O): 54-56 ℃; **δ_H** (400 MHz, $CDCl_3$): 9.74 (s, 1H, C*H*O), 7.63 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 7.56 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 4.01-3.76 (2 × br. s, 4H, N(CH_2)$_2$), 1.74 (br. s, 6H, 3 × CH_2); **δ_C** (101 MHz, $CDCl_3$): 189.0, 148.8, 133.9, 131.0, 130.6, 130.5, 126.6, 53.4, 44.6, 26.4, 24.3, 24.1; **HRMS** (ESI^+) $C_{12}H_{14}{}^{35}Cl_2N_3O$ requires 286.0514 $[M+H]^+$, found 286.0517; **ν_{max}** (film)/cm^{-1} 2941, 2857, 1685, 1415, 1374, 1184, 1108, 1001, 932, 872, 852, 820, 765, 687.

(*E*)-3-(Piperidin-1-yldiazenyl)-2-naphthaldehyde, 11o

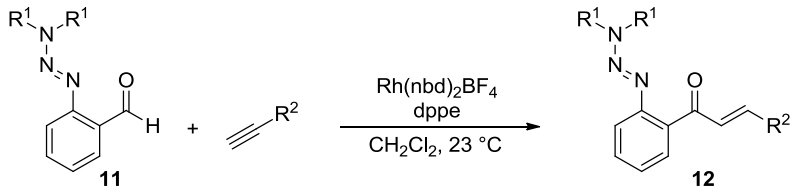


Prepared according to General Procedure I, using: i) **SM7** (839 mg, 3.7 mmol), conc. HCl (1.2 mL), sodium nitrite (504 mg, 7.4 mmol, in 1 mL H_2O), KOH (410 mg, 7.4 mmol), piperidine (0.72 mL, 7.4 mmol) and H_2O (6 mL) to afford the corresponding 2-(piperidin-1-yldiazenyl)benzamide (937 mg, 2.9 mmol) as a crude; ii) DIBAL-H (3.2 mL, 3.2 mmol) and toluene (29 mL). Purification by flash column chromatography (gradient petrol/Et_2O, 95:5 to 90:10) afforded *the title compound* (634 mg, 65% yield) as a yellow solid. **M.p.** (petrol/Et_2O): 93-95 ℃; **δ_H** (400 MHz, $CDCl_3$): 10.89 (s, 1H, C*H*O), 8.41 (s, 1H, Ar-*H*), 7.90 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.84 (s, 1H, Ar-*H*), 7.81 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.53-7.47 (m, 1H, Ar-*H*), 7.43-7.37 (m, 1H, Ar-*H*), 3.89 (br. s, 4H, N(CH_2)$_2$), 1.74 (br. s, 6H, 3

× C*H*$_2$); **δ$_C$** (101 MHz, $CDCl_3$): 192.8, 148.4, 137.0, 130.9, 129.9, 129.0, 128.9, 128.7, 128.1, 125.7, 114.4, 53.3, 44.0, 25.9, 25.0, 24.3; **HRMS** (ESI^+) $C_{16}H_{18}N_3O$ requires 268.1444 $[M+H]^+$, found 268.1444; ***ν*$_{max}$** (film)/cm^{-1} 2939, 2856, 1684, 1621, 1587, 1417, 1328, 1189, 1107, 1088, 1003, 886, 747.

5.4.2 Hydroacylation

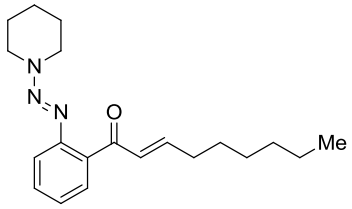
General Procedure J: hydroacylation using 2-(piperidin-1-yldiazenyl)benzaldehydes.



A microwave reaction vial charged with $Rh(nbd)_2BF_4$ (3.7 mg, 0.01 mmol, 5 mol%) and dppe (4.0 mg, 0.01 mmol, 5 mol%) was evacuated and back-filled with N_2 gas for 3 times. CH_2Cl_2 (0.25 mL) was added to dissolve the solids. The resulting solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until 0.1 mL of the solution was left. This solution was transferred to a N_2-purged microwave reaction vial containing aldehyde **11** (0.20 mmol, 1.0 equiv) with the aid of CH_2Cl_2 (0.1 mL) to rinse the remainder. Alkyne (0.30 mmol, 1.5 equiv) was added and the reaction mixture stirred at 23 ℃ for 16 h. The solution was diluted with Et_2O, filtered through a pad of SiO_2 and concentrated under reduced pressure. Purification by flash column chromatography afforded the corresponding hydroacylation adduct.

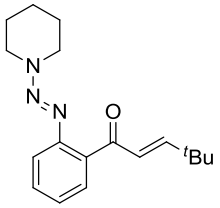
Details concerning the preparation of **12a** from **11a** can be found in the master thesis of Eva K. Paffenholz.[94]

(*E*)-1-(2-((*E*)-Piperidin-1-yldiazenyl)phenyl)non-2-en-1-one, 12b



Prepared according to General Procedure J, using **11b** (43 mg) and 1-octyne (44 μL). Purification by flash column chromatography (gradient petrol/Et_2O, 95:5 to 90:10) afforded *the title compound* (61 mg, 93% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.48-7.44 (m, 1H, Ar-*H*), 7.43-7.36 (m, 2H, Ar-*H*), 7.18 (td, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 6.70 (dt, *J* = 15.5, 7.0 Hz, 1H, CO-CH=C*H*), 6.45 (dt, *J* = 15.5, 1.5 Hz, 1H, CO-C*H*=CH), 3.74 (br. s, 4H, N(CH_2)$_2$), 2.21-2.14 (m, 2H, CH=CH-CH_2), 1.67 (br. s, 6H, 3 × CH_2), 1.46-1.37 (m, 2H, CH=CH-CH_2-CH_2), 1.34-1.20 (m, 6H, 3 × CH_2), 0.87 (t, *J* = 7.0 Hz, 3H, CH_3); **δ_C** (101 MHz, $CDCl_3$): 196.6, 149.0, 147.5, 134.8, 131.8, 130.9, 128.7, 125.3, 118.7, 52.4, 44.4, 32.6, 31.7, 29.0, 28.3, 25.5 (2C), 24.4, 22.6, 14.1; **HRMS** (ESI^+) $C_{20}H_{30}N_3O$ requires 328.2383 $[M+H]^+$, found 328.2379; ***ν_{max}*** (film)/cm^{-1} 2925, 2855, 1657, 1618, 1418, 1355, 1293, 1182, 1096, 970, 852, 758.

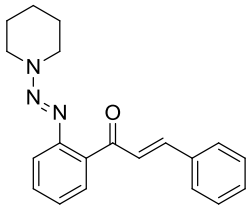
(*E*)-4,4-Dimethyl-1-(2-((*E*)-piperidin-1-yldiazenyl)phenyl)pent-2-en-1-one, 12c



Prepared according to General Procedure J, using **11b** (43 mg) and 3,3-dimethyl-1-butyne (37 μL). Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (58 mg, 97% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.48-7.36

(m, 3H, Ar-*H*), 7.17 (td, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 6.72 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.39 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.73 (br. s, 4H, N(CH_2)$_2$), 1.66 (br. s, 6H, 3 × CH_2), 1.04 (s, 9H, C(CH_3)$_3$); **δC** (101 MHz, $CDCl_3$): 197.0, 156.4, 149.0, 135.0, 131.0, 128.8, 126.8, 125.4, 118.8, 52.3, 44.1, 33.8, 28.9, 25.4 (2C), 24.3; **HRMS** (ESI$^+$) $C_{18}H_{26}N_3O$ requires 300.2070 $[M+H]^+$, found 300.2068; ν_{max} (film)/cm^{-1} 2957, 2860, 1656, 1614, 1421, 1357, 1297, 1182, 1096, 1018, 982, 852, 758.

(*E*)-3-Phenyl-1-(2-((*E*)-piperidin-1-yldiazenyl)phenyl)prop-2-en-1-one, 12d

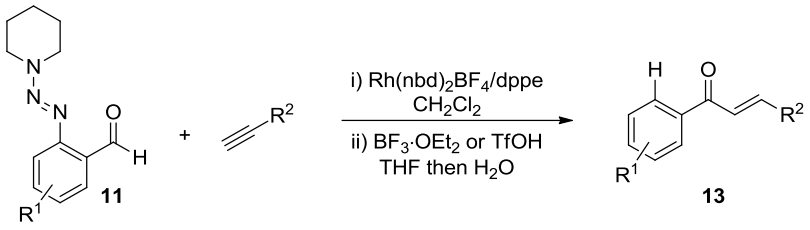


Prepared according to General Procedure J, using **11b** (43 mg) and phenylacetylene (33 μL). Purification by flash column chromatography (petrol/Et_2O, 4:1) afforded *the title compound* (57 mg, 89% yield) as a pale yellow solid. **M.p.** (Et_2O): 86-88 ℃; **δH** (400 MHz, $CDCl_3$): 7.57 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.54-7.42 (m, 5H, 4 × Ar-*H* and CO-CH=C*H*), 7.40-7.32 (m, 3H, Ar-*H*), 7.22 (td, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.15 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.74-3.66 (m, 4H, N(CH_2)$_2$), 1.55 (br. s, 6H, 3 × CH_2); **δC** (101 MHz, $CDCl_3$): 195.6, 149.4, 141.1, 135.3, 134.6, 131.5, 130.1, 129.1, 128.9, 128.5, 128.2, 125.4, 118.8, 52.8, 44.1, 26.2, 24.4, 24.2; **HRMS** (ESI$^+$) $C_{20}H_{22}N_3O$ requires 320.1757 $[M+H]^+$, found 320.1757; ν_{max} (film)/cm^{-1} 2940, 2856, 1664, 1600, 1415, 1354, 1329, 1295, 1182, 1095, 1017, 974, 759, 701.

3.0 mmol scale preparation: Rh(nbd)$_2$$BF_4$ (56 mg), dppe (60 mg), **11b** (652 mg), 1-octyne (0.66 mL) and acetone (3 mL) resulted in **12c** (776 mg) in 81% yield.

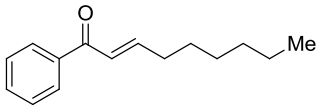
5.4.3 Sequential hydroacylation-triazene removal

General Procedure K: sequential hydroacylation-triazene removal.



A microwave reaction vial charged with $Rh(nbd)_2BF_4$ (3.7 mg, 0.01 mmol, 5 mol%) and dppe (4.0 mg, 0.01 mmol, 5 mol%) was evacuated and back-filled with N_2 gas for 3 times. CH_2Cl_2 (0.25 mL) was added to dissolve the solids. The resulting solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until 0.1 mL of the solution was left. This solution was transferred to a N_2-purged microwave reaction vial containing aldehyde **11** (0.20 mmol, 1.0 equiv) with the aid of CH_2Cl_2 (0.1 mL) to rinse the remainder. Alkyne (0.30 mmol, 1.5 equiv) was added and the reaction mixture stirred at 23 ℃ for 16 h. The solution was diluted with Et_2O, filtered through a pad of SiO_2 to a 25 mL round bottom flask and concentrated under reduced pressure. The remainder was dissolved in THF (4 mL, 0.05 M), followed by the addition of $BF_3 \cdot OEt_2$ (1.0 or 2.0 mmol, 5.0 or 10.0 equiv) or triflic acid (0.68 mmol, 3.4 equiv) at 0 ℃. It was then stirred at 23 ℃ until all hydroacylation product was consumed (5-60 min), and H_2O (50 μL) was added. The mixture was further stirred at 23 ℃ for 24 h, concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding product.

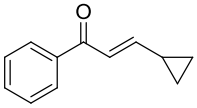
(*E*)-1-Phenylnon-2-en-1-one, 13a



Prepared according to General Procedure K, on a 0.15 mmol scale, using **11b** (33 mg,

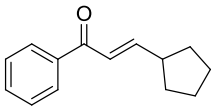
0.15 mmol), 1-octyne (33 μL) and $BF_3 OEt_2$ (0.19 mL). Purification by flash column chromatography (petrol/Et_2O, 95:5) afforded the title compound (28 mg, 86% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.95-7.90 (m, 2H, Ar-*H*), 7.58-7.52 (m, 1H, Ar-*H*), 7.50-7.43 (m, 2H, Ar-*H*), 7.07 (dt, *J* = 15.5, 7.0 Hz, 1H, CO-CH=C*H*), 6.87 (dt, *J* = 15.5, 1.5 Hz, 1H, CO-C*H*=CH), 2.36-2.28 (m, 2H, CH=CH-CH_2), 1.57-1.48 (m, 2H, CH=CH-CH_2-CH_2), 1.40-1.24 (m, 6H, 3 ×CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_3); **δ_C** (101 MHz, $CDCl_3$): 191.2, 150.3, 138.2, 132.7, 128.7, 128.6, 126.0, 33.0, 31.8, 29.1, 28.3, 22.7, 14.2; **ν_{max}** (film)/cm^{-1} 2927, 2856, 1671, 1621, 1448, 1286, 1225, 972, 693; data consistent with literature.[130]

(*E*)-3-Cyclopropyl-1-phenylprop-2-en-1-one, 13b



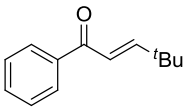
Prepared according to General Procedure K, using **11b** (43 mg), ethynylcyclopropane (25 μL) and $BF_3 OEt_2$ (0.12 mL). Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (22 mg, 64% yield) as a colorless oil. **δ_H** (400 MHz, $CDCl_3$): 7.96-7.90 (m, 2H, Ar-*H*), 7.58-7.51 (m, 1H, Ar-*H*), 7.50-7.43 (m, 2H, Ar-*H*), 7.02 (d, *J* = 15.0 Hz, 1H, CO-C*H*=CH), 6.56 (dd, *J* = 15.0, 10.5 Hz, 1H, CO-CH=C*H*), 1.76-1.66 (m, 1H, CH=CH-C*H*), 1.06-0.99 (m, 2H, C$H_a$$H_b$-C$H_c$$H_d$), 0.77-0.71 (m, 2H, $CH_a$$H_b$-$CH_c$$H_d$); **$\delta_C$** (101 MHz, $CDCl_3$): 190.1, 155.4, 138.3, 132.6, 128.6, 128.5, 123.0, 15.5, 9.4; **HRMS** (ESI^+) $C_{12}H_{13}O$ requires 173.0961 $[M+H]^+$, found 173.0962; **ν_{max}** (film)/cm^{-1} 2980, 2889, 1663, 1607, 1381, 1270, 1155, 1073, 938, 890, 696.

(*E*)-3-Cyclopentyl-1-phenylprop-2-en-1-one, 13c



Prepared according to General Procedure K, using **11b** (43 mg), ethynylcyclopentane (35 μL) and $BF_3 OEt_2$ (0.12 mL). Purification by flash column chromatography (petrol/CH_2Cl_2, 1:1) afforded *the title compound* (34 mg, 85% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.95-7.90 (m, 2H, Ar-*H*), 7.58-7.52 (m, 1H, Ar-*H*), 7.50-7.43 (m, 2H, Ar-*H*), 7.05 (dd, *J* = 15.5, 8.0 Hz, 1H, CO-CH=C*H*), 6.86 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 2.77-2.65 (m, 1H, CH=CH-C*H*), 1.94-1.85 (m, 2H, Cypent-*H*), 1.79-1.58 (m, 4H, Cypent-*H*), 1.53-1.42 (m, 2H, Cypent-*H*); **δ_C** (101 MHz, $CDCl_3$): 191.3, 154.4, 138.3, 132.7, 128.64, 128.62, 124.1, 43.6, 32.8, 25.5; **HRMS** (ESI^+) $C_{14}H_{17}O$ requires 201.1274 $[M+H]^+$, found 201.1274; **ν_{max}** (film)/cm^{-1} 2980, 2869, 1668, 1617, 1448, 1363, 1261, 1218, 1011, 984, 772, 697.

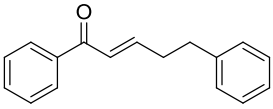
(*E*)-4,4-Dimethyl-1-phenylpent-2-en-1-one, 13d



Prepared according to General Procedure K, using **11b** (43 mg), 3,3-dimethyl-1-butyne (37 μL) and $BF_3 OEt_2$ (0.12 mL). Purification by flash column chromatography (petrol/Et_2O, 95:5) afforded the title compound (34 mg, 91% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.95-7.90 (m, 2H, Ar-*H*), 7.58-7.52 (m, 1H, Ar-*H*), 7.50-7.43 (m, 2H, Ar-*H*), 7.06 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 6.78 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 1.15 (s, 9H, $C(CH_3)_3$); **δ_C** (101 MHz, $CDCl_3$): 191.7, 159.8, 138.3, 132.7, 128.7, 128.6, 121.1, 34.3, 28.9; **ν_{max}** (film)/cm^{-1} 2961, 2868, 1668, 1618, 1448, 1301, 1224, 1018, 985, 841, 776,

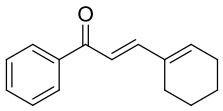
696, 656; data consistent with literature.[63]

(*E*)-1,5-Diphenylpent-2-en-1-one, 13e



Prepared according to General Procedure K, using **11b** (43 mg), but-3-yn-1-ylbenzene (42 μL) and $BF_3 OEt_2$ (0.12 mL). Purification by flash column chromatography (petrol/CH_2Cl_2, 1:1) afforded the title compound (33 mg, 70% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.91-7.87 (m, 2H, Ar-*H*), 7.59-7.53 (m, 1H, Ar-*H*), 7.49-7.43 (m, 2H, Ar-*H*), 7.35-7.29 (m, 2H, Ar-*H*), 7.25-7.19 (m, 3H, Ar-*H*), 7.09 (dt, *J* = 15.5, 7.0 Hz, 1H, CO-CH=C*H*), 6.88 (dt, *J* = 15.5, 1.5 Hz, 1H, CO-C*H*=CH), 2.89-2.83 (m, 2H, CH_2-Ph), 2.69-2.61 (m, 2H, CH=CH-CH_2); **δ_C** (101 MHz, $CDCl_3$): 191.0, 148.6, 140.9, 138.0, 132.8, 128.7, 128.6 (2C), 128.5, 126.7, 126.3, 34.7, 34.6; **ν_{max}** (film)/cm^{-1} 2981, 1669, 1619, 1448, 1283, 1224, 969, 695; data consistent with literature.[131]

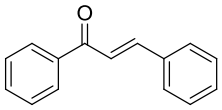
(*E*)-3-(Cyclohex-1-en-1-yl)-1-phenylprop-2-en-1-one, 13f



Prepared according to General Procedure K, using **11b** (43 mg), 1-ethynylcyclohex-1-ene (35 μL) and $BF_3 OEt_2$ (0.12 mL). Purification by flash column chromatography (petrol/CH_2Cl_2, 1:1) afforded the title compound (34 mg, 80% yield) as a pale yellow solid. **M.p.** (petrol/Et_2O): 70-71 ℃; **δ_H** (400 MHz, $CDCl_3$): 7.96-7.92 (m, 2H, Ar-*H*), 7.57-7.51 (m, 1H, Ar-*H*), 7.49-7.38 (m, 3H, 2 × Ar-*H* and CO-CH=C*H*), 6.84 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 6.29 (t, *J* = 3.5 Hz, 1H, C=C*H*), 2.30-2.21 (m, 4H, CH_2-C=CH-CH_2), 1.78-1.60 (m, 4H, 2 × CH_2); **δ_C** (101 MHz, $CDCl_3$): 191.4, 148.6, 140.9, 138.7, 135.7, 132.5,

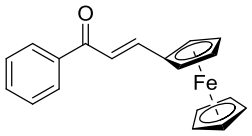
128.6, 128.5, 118.9, 26.8, 24.5, 22.2, 22.1; ν_{max} (film)/cm^{-1} 2981, 2930, 1660, 1586, 1447, 1291, 1210, 1017, 980, 763, 698, 623; data consistent with literature.[132]

(*E*)-Chalcone, 13g



Prepared according to General Procedure K, using **11b** (43 mg), phenylacetylene (33 μL) and $BF_3 \cdot OEt_2$ (0.25 mL). Purification by flash column chromatography (petrol/Et_2O, 95:5) afforded the title compound (35 mg, 83% yield) as a pale yellow solid. **M.p.** (petrol/Et_2O): 55-57 ℃; δ_H (400 MHz, $CDCl_3$): 8.05-8.01 (m, 2H, Ar-*H*), 7.82 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 7.68-7.63 (m, 2H, Ar-*H*), 7.62-7.57 (m, 1H, Ar-*H*), 7.57-7.48 (m, 3H, 2 × Ar-*H* and CO-C*H*=CH), 7.45-7.40 (m, 3H, Ar-*H*); δ_C (101 MHz, $CDCl_3$): 190.7, 145.0, 138.3, 135.0, 132.9, 130.7, 129.1, 128.8, 128.64, 128.58, 122.2; ν_{max} (film)/cm^{-1} 3059, 3027, 1662, 1604, 1575, 1449, 1335, 1214, 1016, 978, 745, 688; data consistent with literature.[133]

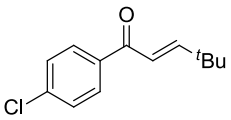
(*E*)-3-Ferrocenyl-1-phenylprop-2-en-1-one, 13h



Prepared according to General Procedure K, using **11b** (43 mg), ethynylferrocene (63 mg) and $BF_3 \cdot OEt_2$ (0.12 mL). Purification by flash column chromatography (petrol/Et_2O, 4:1) afforded *the title compound* (33 mg, 52% yield) as a purple solid. **M.p.** (petrol/Et_2O): 135-136 ℃; δ_H (400 MHz, $CDCl_3$): 8.00-7.96 (m, 2H, Ar-*H*), 7.76 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 7.60-7.54 (m, 1H, Ar-*H*), 7.52-7.47 (m, 2H, Ar-*H*), 7.13 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 4.60 (t, *J* = 2.0 Hz, 2H, Fc-*H*), 4.49 (t, *J* = 2.0 Hz, 2H, Fc-

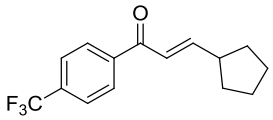
H), 4.18 (s, 5H, Fc-*H*); **δC** (101 MHz, $CDCl_3$): 190.0, 147.0, 138.7, 132.5, 128.7, 128.5, 119.3, 79.3, 71.5, 69.9, 69.2; **HRMS** (ESI^+) $C_{19}H_{17}{}^{54}FeO$ requires 315.0670 $[M+H]^+$, found 315.0667; ν_{max} (film)/cm^{-1} 3657, 2980, 2889, 1655, 1587, 1473, 1462, 1382, 1251, 1152, 1073, 954, 818.

(*E*)-1-(4-Chlorophenyl)-4,4-dimethylpent-2-en-1-one, 13i



Prepared according to General Procedure K, using **11g** (50 mg), 3,3-dimethyl-1-butyne (37 μL) and TfOH (0.06 mL). Purification by flash column chromatography (petrol/CH_2Cl_2, 3:2) afforded the title compound (32 mg, 72% yield) as a yellow oil. **δH** (400 MHz, $CDCl_3$): 7.86 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.43 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.06 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 6.73 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 1.15 (s, 9H, $C(CH_3)_3$); **δC** (101 MHz, $CDCl_3$): 190.3, 160.3, 139.1, 136.6, 130.1, 128.9, 120.6, 34.4, 28.8; **LRMS** (ESI^+) 223.1 ($[M+H]^+$, 100%); data consistent with literature.[134]

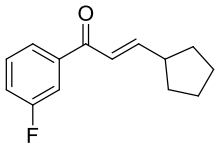
(*E*)-3-Cyclopentyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one, 13j



Prepared according to General Procedure K, using **11e** (57 mg), ethynylcyclopentane (35 μL) and TfOH (0.06 mL). Purification by flash column chromatography (petrol/CH_2Cl_2, 7:3) afforded *the title compound* (32 mg, 59% yield) as a yellow oil. **δH** (400 MHz, $CDCl_3$): 8.00 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.72 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.07 (dd, *J* = 15.5, 8.0 Hz, 1H, CO-CH=C*H*), 6.82 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 2.78-2.66 (m, 1H, CH=CH-C*H*), 1.96-1.86 (m, 2H, Cypent-*H*), 1.79-1.59 (m, 4H, Cypent-*H*), 1.53-1.42 (m, 2H, Cypent-*H*);

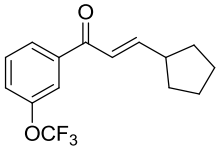
δ_C (101 MHz, $CDCl_3$): 190.4, 156.0, 141.1, 133.9 (q, J_{C-F} = 32.5 Hz), 128.9, 125.7 (q, J_{C-F} = 3.5 Hz), 123.84, 123.82 (q, J_{C-F} = 272.5 Hz), 43.7, 32.8, 25.5; **δ_F** (377 MHz, $CDCl_3$): −63.0; **HRMS** (ESI^+) $C_{15}H_{16}F_3O$ requires 269.1148 $[M+H]^+$, found 269.1149; ν_{max} (film)/cm^{-1} 2956, 2871, 1672, 1613, 1319, 1167, 1127, 1066, 1013, 830, 689.

(*E*)-3-Cyclopentyl-1-(3-fluorophenyl)prop-2-en-1-one, 13k



Prepared according to General Procedure K, using **11j** (47 mg), ethynylcyclopentane (35 μL) and TfOH (0.06 mL). Purification by flash column chromatography (petrol/CH_2Cl_2, 7:3) afforded *the title compound* (27 mg, 62% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.70 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.61 (d, *J* = 9.5 Hz, 1H, Ar-*H*), 7.44 (td, *J* = 8.0, 5.5 Hz, 1H, Ar-*H*), 7.28-7.21 (m, 1H, Ar-*H*), 7.07 (dd, *J* = 15.5, 8.0 Hz, 1H, CO-CH=C*H*), 6.81 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 2.77-2.65 (m, 1H, CH=CH-C*H*), 1.95-1.85 (m, 2H, Cypent-*H*), 1.79-1.59 (m, 4H, Cypent-*H*), 1.53-1.41 (m, 2H, Cypent-*H*); **δ_C** (101 MHz, $CDCl_3$): 189.8, 162.9 (d, J_{C-F} = 247.5 Hz), 155.3, 140.4 (d, J_{C-F} = 6.5 Hz), 130.3 (d, J_{C-F} = 7.5 Hz), 124.3 (d, J_{C-F} = 3.0 Hz), 123.6, 119.7 (d, J_{C-F} = 21.5 Hz), 115.4 (d, J_{C-F} = 22.5 Hz), 43.6, 32.7, 25.5; **δ_F** (377 MHz, $CDCl_3$): −112.0; **HRMS** (ESI^+) $C_{14}H_{16}FO$ requires 219.1180 $[M+H]^+$, found 219.1182; ν_{max} (film)/cm^{-1} 2954, 2869, 1670, 1620, 1586, 1484, 1441, 1361, 1300, 1265, 1151, 983, 894, 791, 723, 673.

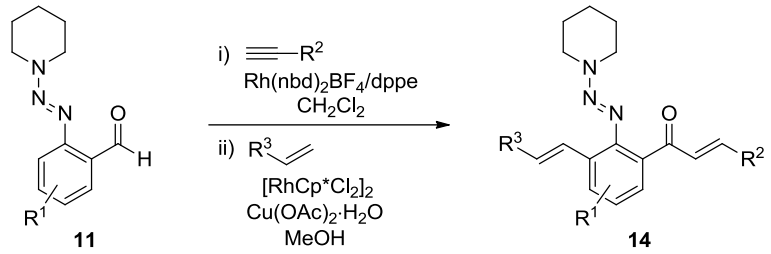
(*E*)-3-Cyclopentyl-1-(3-(trifluoromethoxy)phenyl)prop-2-en-1-one, 13l



Prepared according to General Procedure K, using **11i** (60 mg), ethynylcyclopentane (35 μL) and TfOH (0.06 mL). Purification by flash column chromatography (petrol/CH_2Cl_2, 3:1) afforded *the title compound* (34 mg, 60% yield) as a yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.84 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.75 (s, 1H, Ar-*H*), 7.50 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.39 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.07 (dd, *J* = 15.5, 8.0 Hz, 1H, CO-CH=C*H*), 6.80 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 2.78-2.66 (m, 1H, CH=CH-C*H*), 1.95-1.85 (m, 2H, Cypent-*H*), 1.79-1.59 (m, 4H, Cypent-*H*), 1.53-1.41 (m, 2H, Cypent-*H*); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 189.6, 155.7, 149.5, 140.1, 130.2, 126.9, 125.0, 123.6, 121.1, 120.6 (q, $J_{C\text{-}F}$ = 258.0 Hz), 43.7, 32.8, 25.5; $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$): –57.9; **HRMS** (ESI^+) $C_{15}H_{16}F_3O_2$ requires 285.1097 $[M+H]^+$, found 285.1098; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2957, 2871, 1672, 1619, 1585, 1442, 1251, 1212, 1160, 984.

5.4.4 Sequential hydroacylation-*ortho* C-H olefination

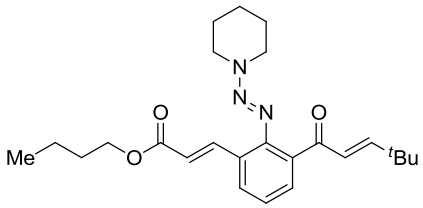
General Procedure L: sequential hydroacylation-*ortho* C-H olefination.



A microwave reaction vial charged with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 5 mol%) and dppe (6.0 mg, 0.015 mmol, 5 mol%) was evacuated and back-filled with N_2 gas for 3 times. CH_2Cl_2 (0.30 mL) was added to dissolve the solids. The resulting solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until 0.1 mL of the solution was left. This solution was transferred to a N_2-purged microwave reaction vial containing aldehyde **11** (0.30 mmol, 1.0 equiv) with the aid of CH_2Cl_2 (0.2 mL) to rinse the remainder. Alkyne

(0.45 mmol, 1.5 equiv) was added and the reaction mixture stirred at 23 ℃ for 16 h. The mixture was diluted with Et_2O, filtered through a pad of SiO_2 to a reaction vial, and concentrated under reduced pressure. To this was added MeOH (2.0 mL, 0.15 M), and the resulting solution transferred to a reaction vial containing $[RhCp^*Cl_2]_2$ (9.3 mg, 0.015 mmol, 5 mol%) and $Cu(OAc)_2 \cdot H_2O$ (120 mg, 0.60 mmol, 2.0 equiv), followed by the addition of alkene (0.75 mmol, 2.5 equiv). The reaction mixture was stirred at 70 ℃. Upon completion (6-16 h), it was cooled to room temperature, diluted with Et_2O, filtered through a pad of SiO_2 and concentrated under reduced pressure. Purification by flash column chromatography afforded the corresponding product.

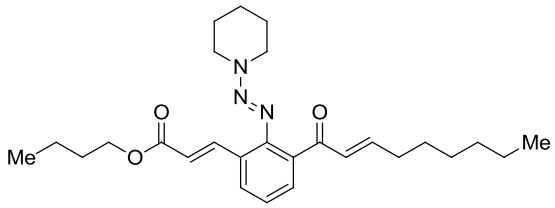
(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl) phenyl)acrylate, 14a



Prepared according to General Procedure L, using **11b** (65 mg), 3,3-dimethylbut-1-yne (55 μL) and *n*butyl acrylate (108 μL). Purification by flash column chromatography (petrol/Et_2O, 4:1) afforded *the title compound* (104 mg, 82% yield) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 8.32 (d, *J* = 16.0 Hz, 1H, CH=C*H*-Ar), 7.67 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.36 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.18 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.61 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.43 (d, *J* = 16.0 Hz, 1H, C*H*=CH-Ar), 5.90 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 4.18 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.90-3.60 (2 × br. s, 4H, $N(CH_2)_2$), 1.70-1.62 (m, 8H, 4 × CH_2), 1.47-1.37 (m, 2H, CH_2-CH_3), 0.99 (s, 9H, $C(CH_3)_3$), 0.93 (t, *J* = 7.5 Hz, 3H, CH_2-CH_3); δ_C (101 MHz, $CDCl_3$): 196.1, 167.3, 155.9, 148.2, 141.3, 133.7, 130.9,

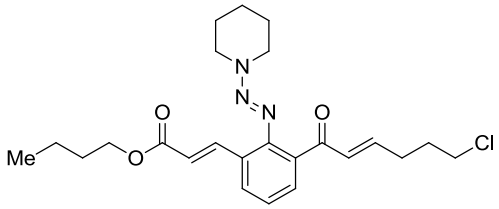
129.1, 128.6, 126.1, 125.1, 118.9, 64.3, 52.6, 44.3, 33.7, 30.8, 28.8, 26.4, 24.3, 24.1, 19.3, 13.8; **HRMS** (ESI$^+$) $C_{25}H_{36}N_3O_3$ requires 426.2751 $[M+H]^+$, found 426.2744; ν_{max} (film)/cm^{-1} 2957, 2864, 1710, 1676, 1656, 1622, 1413, 1356, 1315, 1255, 1165, 1108, 1059, 985, 755, 729.

(*E*)-Butyl 3-(3-((*E*)-non-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl)phenyl)acrylate, 14b



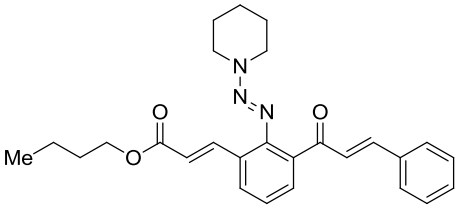
Prepared according to General Procedure L, using **11b** (65 mg), 1-octyne (66 μL) and ^{n}butyl acrylate (108 μL). Purification by flash column chromatography (gradient petrol/Et_2O, 8:2 to 7:3) afforded *the title compound* (101 mg, 74% yield) as a red oil. δ_H (400 MHz, $CDCl_3$): 8.31 (d, *J* = 16.0 Hz, 1H, CH=C*H*-Ar), 7.66 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.34 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.17 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.60 (dt, *J* = 15.5, 7.0 Hz, 1H, CO-CH=C*H*), 6.42 (d, *J* = 16.0 Hz, 1H, C*H*=CH-Ar), 6.01 (dt, *J* = 15.5, 1.5 Hz, 1H, CO-C*H*=CH), 4.18 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.90-3.60 (2 × br. s, 4H, $N(CH_2)_2$), 2.14-2.06 (m, 2H, CH=CH-CH_2), 1.72-1.61 (m, 8H, 4 × CH_2), 1.47-1.19 (m, 10H, 5 × CH_2), 0.93 (t, *J* = 7.5 Hz, 3H, CH_3), 0.84 (t, *J* = 7.0 Hz, 3H, CH_3); δ_C (101 MHz, $CDCl_3$): 195.8, 167.3, 148.2, 146.9, 141.3, 133.5, 131.0, 130.8, 129.1, 128.5, 125.0, 118.9, 64.3, 52.7, 44.0, 32.4, 31.6, 30.8, 28.9, 28.2, 26.5, 24.5, 24.2, 22.5, 19.3, 14.1, 13.8; **HRMS** (ESI$^+$) $C_{27}H_{40}N_3O_3$ requires 454.3064 $[M+H]^+$, found 454.3059; ν_{max} (film)/cm^{-1} 2980, 2889, 1710, 1675, 1627, 1463, 1382, 1314, 1254, 1164, 1109, 1071, 968, 754, 728.

(*E*)-Butyl 3-(3-((*E*)-6-chlorohex-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl)phenyl) acrylate, 14c



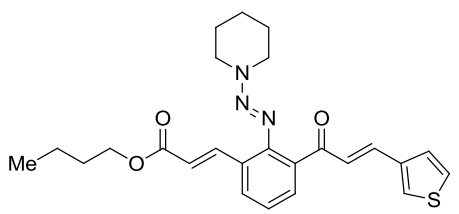
Prepared according to General Procedure L, using **11b** (65 mg), 5-chloropent-1-yne (48 μL) and ^{n}butyl acrylate (108 μL). Purification by flash column chromatography (petrol/Et_2O, 7:3) afforded *the title compound* (97 mg, 73% yield) as a brown oil. **δ_H** (400 MHz, $CDCl_3$): 8.30 (d, *J* = 16.0 Hz, 1H, CH=C*H*-Ar), 7.67 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 7.34 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.18 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.54 (dt, *J* = 15.5, 7.0 Hz, 1H, CO-CH=C*H*), 6.42 (d, *J* = 16.0 Hz, 1H, C*H*=CH-Ar), 6.05 (dt, *J* = 15.5, 1.5 Hz, 1H, CO-C*H*=CH), 4.17 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.92-3.60 (2 × br. s, 4H, $N(CH_2)_2$), 3.47 (t, *J* = 6.5 Hz, 2H, CH_2-Cl), 2.32-2.25 (m, 2H, CH=CH-CH_2), 1.88-1.80 (m, 2H, CH_2-CH_2-Cl), 1.72-1.61 (m, 8H, 4 × CH_2), 1.47-1.36 (m, 2H, CH_2-CH_3), 0.93 (t, *J* = 7.5 Hz, 3H, CH_3); **δ_C** (101 MHz, $CDCl_3$): 195.2, 167.2, 148.2, 143.9, 141.2, 133.2, 132.1, 130.8, 129.1, 128.7, 125.1, 119.0, 64.3, 52.7, 44.2, 44.0, 30.81, 30.80, 29.2, 26.5, 24.4, 24.1, 19.3, 13.8; **HRMS** (ESI^+) $C_{24}H_{33}{}^{35}ClN_3O_3$ requires 446.2216 $[M+H]^+$, found 446.2209; **ν_{max}** (film)/cm^{-1} 2939, 2860, 1708, 1676, 1627, 1574, 1411, 1355, 1313, 1256, 1167, 1108, 984, 755, 727.

(*E*)-Butyl 3-(3-cinnamoyl-2-((*E*)-piperidin-1-yldiazenyl)phenyl)acrylate, 14d



Prepared according to General Procedure L, using **11b** (65 mg), phenylacetylene (49 μL) and ^{n}butyl acrylate (108 μL). Purification by flash column chromatography (petrol/Et_2O, 7:3) afforded *the title compound* (108 mg, 81% yield) as a red oil. δ_H (400 MHz, $CDCl_3$): 8.33 (d, *J* = 16.0 Hz, 1H, CH=C*H*-Ar), 7.71 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.49 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.47-7.41 (m, 3H, CO-CH=C*H* and 2 × Ar-*H*), 7.35-7.30 (m, 3H, Ar-*H*), 7.22 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.59 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 6.47 (d, *J* = 16.0 Hz, 1H, C*H*=CH-Ar), 4.19 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.86-3.56 (2 × br. s, 4H, $N(CH_2)_2$), 1.71-1.63 (m, 2H, CH_2), 1.53-1.38 (m, 8H, 4 × CH_2), 0.94 (t, *J* = 7.5 Hz, 3H, CH_3); δ_C (101 MHz, $CDCl_3$): 194.6, 167.2, 148.7, 141.2, 140.9, 135.0, 133.8, 131.1, 130.1, 129.1, 129.0, 128.9, 127.9, 127.7, 125.1, 119.0, 64.3, 52.6, 44.0, 30.8, 26.3, 24.2, 23.9, 19.3, 13.8; **HRMS** (ESI^+) $C_{27}H_{32}N_3O_3$ requires 446.2438 $[M+H]^+$, found 446.2433; ν_{max} (film)/cm^{-1} 2980, 2889, 1707, 1669, 1631, 1607, 1575, 1462, 1383, 1315, 1253, 1165, 1110, 1071, 954, 762, 729, 699.

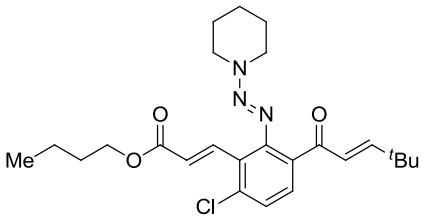
(*E*)-Butyl 3-(2-((*E*)-piperidin-1-yldiazenyl)-3-((*E*)-3-(thiophen-3-yl)acryloyl) phenyl)acrylate, 14e



Prepared according to General Procedure L, using **11b** (65 mg), 3-ethynylthiophene

(44 μL) and ^{n}butyl acrylate (108 μL). Purification by flash column chromatography (petrol/Et_2O, 7:3) afforded *the title compound* (76 mg, 56% yield) as a brown oil. **δ_H** (400 MHz, $CDCl_3$): 8.33 (d, *J* = 16.0 Hz, 1H, CH=C*H*-Ar), 7.72 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.48 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 7.46-7.39 (m, 2H, CO-CH=C*H* and Ar-*H*), 7.33-7.29 (m, 1H, Ar-*H*), 7.27-7.20 (m, 2H, Ar-*H*), 6.50-6.40 (m, 2H, C*H*=CH-Ar and CO-C*H*=CH), 4.21 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.88-3.59 (2 × br. s, 4H, $N(CH_2)_2$), 1.73-1.64 (m, 2H, CH_2), 1.58-1.39 (m, 8H, 4 × CH_2), 0.96 (t, *J* = 7.5 Hz, 3H, CH_3); **δ_C** (101 MHz, $CDCl_3$): 195.1, 167.4, 148.8, 141.3, 138.2, 134.9, 133.8, 131.2, 129.2, 129.0, 128.0, 127.7, 127.1, 125.1, 125.0, 119.1, 64.4, 52.7, 44.1, 30.9, 26.4, 24.4, 24.1, 19.3, 13.9; **HRMS** (ESI^+) $C_{25}H_{30}N_3O_3{}^{32}S$ requires 452.2002 $[M+H]^+$, found 452.2001; **ν_{max}** (film)/cm^{-1} 2939, 2859, 1707, 1667, 1631, 1602, 1409, 1315, 1290, 1254, 1168, 1111, 1051, 984, 867, 781, 755.

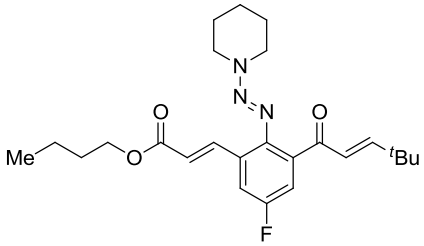
(*E*)-Butyl 3-(6-chloro-3-((*E*)-4,4-dimethylpent-2-enoyl)-2-((*E*)-piperidin-1-yl diazenyl)phenyl)acrylate, 14f



Prepared according to General Procedure L, using **11g** (75 mg), 3,3-dimethylbut-1-yne (55 μL) and ^{n}butyl acrylate (108 μL). Purification by flash column chromatography (petrol/Et_2O, 4:1) afforded *the title compound* (79 mg, 57% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 8.05 (d, *J* = 16.0 Hz, 1H, CH=C*H*-Ar), 7.26 (br. s, 2H, Ar-*H*), 6.64 (app. dd, *J* = 16.0, 7.0 Hz, 2H, CO-CH=C*H* and C*H*=CH-Ar), 5.85 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 4.20 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.87-3.63 (2 × br. s, 4H, $N(CH_2)_2$), 1.72-1.63 (m, 8H, 4

× CH_2), 1.47-1.37 (m, 2H, CH_2-CH_3), 1.00 (s, 9H, C(CH_3)$_3$), 0.95 (t, *J* = 7.5 Hz, 3H, CH_2-CH_3); **δC** (101 MHz, $CDCl_3$): 195.0, 167.1, 156.2, 150.3, 138.2, 136.6, 132.2, 130.1, 127.3, 126.4, 125.9, 125.8, 64.4, 52.7, 44.3, 33.7, 30.8, 28.7, 26.4, 24.4, 24.0, 19.2, 13.8; **HRMS** (ESI^+) $C_{25}H_{35}{}^{35}ClN_3O_3$ requires 460.2362 $[M+H]^+$, found 460.2356; ν_{max} (film)/cm^{-1} 2960, 1714, 1676, 1619, 1567, 1365, 1301, 1257, 1169, 1109, 1064, 982, 854, 814, 728.

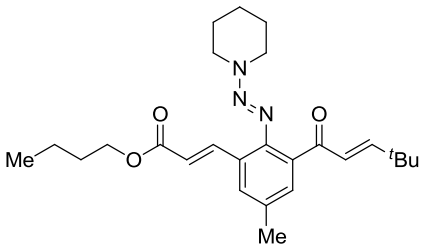
(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-5-fluoro-2-((*E*)-piperidin-1-yl diazenyl)phenyl)acrylate, 14g



Prepared according to General Procedure L, using **11j** (71 mg), 3,3-dimethylbut-1-yne (55 μL) and ^{n}butyl acrylate (108 μL). Purification by flash column chromatography (petrol/Et_2O, 4:1) afforded *the title compound* (82 mg, 62% yield) as a yellow oil. **δH** (400 MHz, $CDCl_3$): 8.27 (dd, *J* = 16.0, 1.5 Hz, 1H, CH=C*H*-Ar), 7.36 (dd, *J* = 9.0, 3.0 Hz, 1H, Ar-*H*), 7.08 (dd, *J* = 8.0, 3.0 Hz, 1H, Ar-*H*), 6.63 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.40 (d, *J* = 16.0 Hz, 1H, C*H*=CH-Ar), 5.89 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 4.19 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.88-3.59 (2 × br. s, 4H, N(CH_2)$_2$), 1.70-1.62 (m, 8H, 4 × CH_2), 1.47-1.37 (m, 2H, CH_2-CH_3), 1.00 (s, 9H, C(CH_3)$_3$), 0.94 (t, *J* = 7.5 Hz, 3H, CH_2-CH_3); **δC** (101 MHz, $CDCl_3$): 194.7, 167.0, 159.9 (d, $J_{C\text{-}F}$ = 246.0 Hz), 156.7, 144.7 (d, $J_{C\text{-}F}$ = 2.5 Hz), 140.3, 135.2 (d, $J_{C\text{-}F}$ = 6.5 Hz), 130.9 (d, $J_{C\text{-}F}$ = 7.5 Hz), 125.7, 120.0, 117.7 (d, $J_{C\text{-}F}$ = 24.0 Hz), 114.6 (d, $J_{C\text{-}F}$ = 23.0 Hz), 64.5, 52.6, 44.3, 33.8, 30.8, 28.8, 26.4, 24.3, 24.1, 19.3, 13.8; **δF** (377 MHz, $CDCl_3$): −117.2; **HRMS** (ESI^+) $C_{25}H_{35}FN_3O_3$ requires 444.2657 $[M+H]^+$,

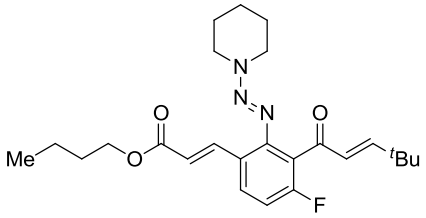
found 444.2655; ν_{max} (film)/cm^{-1} 2958, 2864, 1712, 1676, 1632, 1594, 1417, 1329, 1259, 1170, 1109, 983, 916, 857, 777, 731.

(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-5-methyl-2-((*E*)-piperidin-1-yl diazenyl)phenyl)acrylate, 14h



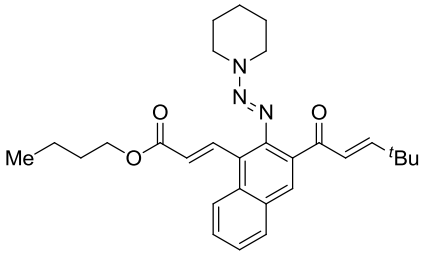
Prepared according to General Procedure L, using **11k** (69 mg), 3,3-dimethylbut-1-yne (55 μL) and ^{n}butyl acrylate (108 μL). Purification by flash column chromatography (petrol/Et_2O, 4:1) afforded *the title compound* (103 mg, 79% yield) as a brown oil. δ_H (400 MHz, $CDCl_3$): 8.30 (d, *J* = 16.0 Hz, 1H, CH=C*H*-Ar), 7.49 (d, *J* = 1.5 Hz, 1H, Ar-*H*), 7.17 (d, *J* = 1.5 Hz, 1H, Ar-*H*), 6.60 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.43 (d, *J* = 16.0 Hz, 1H, C*H*=CH-Ar), 5.89 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 4.17 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.90-3.56 (2 ×br. s, 4H, $N(CH_2)_2$), 2.33 (s, 3H, Ar-CH_3), 1.70-1.61 (m, 8H, 4 ×CH_2), 1.47-1.36 (m, 2H, CH_2-CH_3), 0.99 (s, 9H, $C(CH_3)_3$), 0.93 (t, *J* = 7.5 Hz, 3H, CH_2-CH_3); δ_C (101 MHz, $CDCl_3$): 196.2, 167.3, 155.6, 146.1, 141.4, 134.9, 133.6, 131.6, 129.1, 128.9, 126.2, 118.7, 64.3, 52.5, 44.2, 33.6, 30.8, 28.8, 26.3, 24.3, 24.1, 20.9, 19.3, 13.8; **HRMS** (ESI$^+$) $C_{26}H_{38}N_3O_3$ requires 440.2908 $[M+H]^+$, found 440.2900; ν_{max} (film)/cm^{-1} 2957, 2863, 1710, 1675, 1655, 1628, 1421, 1329, 1255, 1171, 1107, 983, 918, 855, 730.

(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-4-fluoro-2-((*E*)-piperidin-1-yl diazenyl)phenyl)acrylate, 14i



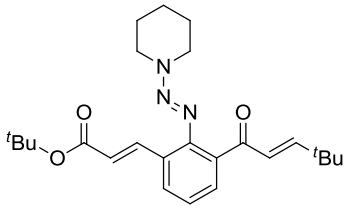
Prepared according to General Procedure L, on a 3.0 mmol scale, using **11l** (706 mg, 3.0 mmol), 3,3-dimethylbut-1-yne (0.55 mL) and ^{n}butyl acrylate (1.1 mL). Purification by flash column chromatography (petrol/Et_2O, 85:15) afforded *the title compound* (1.18 g, 89% yield) as an off-white solid. **M.p.** (petrol): 92-94 ℃; **δ_H** (400 MHz, $CDCl_3$): 8.27 (d, *J* = 16.0 Hz, 1H, CH=C*H*-Ar), 7.61 (dd, *J* = 8.5, 6.0 Hz, 1H, Ar-*H*), 6.89 (t, *J* = 8.5 Hz, 1H, Ar-*H*), 6.54 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.36 (d, *J* = 16.0 Hz, 1H, C*H*=CH-Ar), 6.06 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 4.18 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.88-3.58 (2 × br. s, 4H, $N(CH_2)_2$), 1.71-1.61 (m, 8H, 4 × CH_2), 1.47-1.36 (m, 2H, CH_2-CH_3), 1.01 (s, 9H, $C(CH_3)_3$), 0.94 (t, *J* = 7.5 Hz, 3H, CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 192.8, 167.3, 160.8 (d, $J_{C\text{-}F}$ = 253.0 Hz), 158.1, 148.7 (d, $J_{C\text{-}F}$ = 4.0 Hz), 140.9, 128.9 (d, $J_{C\text{-}F}$ = 10.0 Hz), 127.1, 125.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 120.3 (d, $J_{C\text{-}F}$ = 18.0 Hz), 118.2, 112.7 (d, $J_{C\text{-}F}$ = 23.5 Hz), 64.3, 52.7, 44.1, 33.8, 30.9, 28.7, 26.5, 24.4, 24.1, 19.3, 13.8; **δ_F** (377 MHz, $CDCl_3$): –113.1; **HRMS** (ESI^+) $C_{25}H_{35}FN_3O_3$ requires 444.2657 $[M+H]^+$, found 444.2654; **ν_{max}** (film)/cm^{-1} 2957, 2864, 1710, 1664, 1627, 1578, 1465, 1429, 1380, 1315, 1247, 1162, 1113, 1066, 1026, 983, 853, 814, 730.

(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl) naphthalen-1-yl)acrylate, 14j



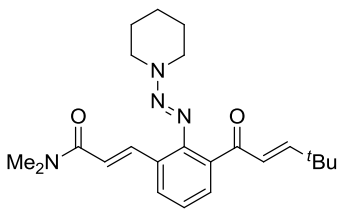
Prepared according to General Procedure L, using **11o** (80 mg), 3,3-dimethylbut-1-yne (55 μL) and ^{n}butyl acrylate (108 μL). Purification by flash column chromatography (gradient petrol/Et_2O, 4:1 to 3:1) afforded *the title compound* (70 mg, 49% yield) as a brown oil. **δ_H** (400 MHz, $CDCl_3$): 8.45 (d, *J* = 16.5 Hz, 1H, CH=C*H*-Ar), 8.25 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.87-7.83 (m, 2H, Ar-*H*), 7.56 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Ar-*H*), 7.46 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar-*H*), 6.64 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.45 (d, *J* = 16.5 Hz, 1H, C*H*=CH-Ar), 6.03 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 4.25 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.95-3.59 (m, 4H, $N(CH_2)_2$), 1.76-1.66 (m, 8H, 4 × CH_2), 1.52-1.41 (m, 2H, CH_2-CH_3), 1.02 (s, 9H, $C(CH_3)_3$), 0.98 (t, *J* = 7.5 Hz, 3H, CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 196.2, 167.3, 156.4, 145.5, 140.6, 133.2, 132.6, 131.1, 130.4, 129.4, 128.1, 126.5, 125.8, 125.4, 125.2, 124.8, 64.5, 52.7, 44.2, 33.8, 30.9, 28.9, 26.5, 24.4, 24.3, 19.4, 13.9; **HRMS** (ESI^+) $C_{29}H_{38}N_3O_3$ requires 476.2908 $[M+H]^+$, found 476.2914; **ν_{max}** (film)/cm^{-1} 2980, 1712, 1677, 1656, 1623, 1444, 1384, 1359, 1303, 1259, 1170, 1110, 1073, 977, 852, 752.

(*E*)-*tert*-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl) phenyl)acrylate, 14k



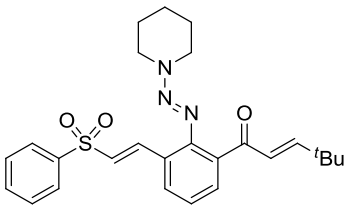
Prepared according to General Procedure L, using **11b** (65 mg), 3,3-dimethylbut-1-yne (55 μL) and ^{t}butyl acrylate (110 μL). Purification by flash column chromatography (petrol/Et_2O, 85:15) afforded *the title compound* (98 mg, 77% yield) as a white solid. **M.p.** (Et_2O): 126-128 ℃; **δ_H** (400 MHz, $CDCl_3$): 8.24 (d, *J* = 16.0 Hz, 1H, CH=C*H*-Ar), 7.67 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.34 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.17 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.61 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.37 (d, *J* = 16.0 Hz, 1H, C*H*=CH-Ar), 5.89 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.90-3.60 (2 ×br. s, 4H, N(CH_2)$_2$), 1.66 (br. s, 6H, 3 ×CH_2), 1.50 (s, 9H, C(CH_3)$_3$), 0.98 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 196.1, 166.5, 155.8, 148.1, 140.1, 133.7, 130.7, 129.2, 128.4, 126.1, 125.1, 120.7, 80.3, 52.6, 44.2, 33.7, 28.8, 28.3, 26.4, 24.3, 24.1; **HRMS** (ESI^+) $C_{25}H_{36}N_3O_3$ requires 426.2751 $[M+H]^+$, found 426.2743; **ν_{max}** (film)/cm^{-1} 2961, 2862, 1705, 1676, 1626, 1413, 1366, 1320, 1292, 1255, 1148, 1108, 983, 917, 852, 729.

(*E*)-3-(3-((*E*)-4,4-Dimethylpent-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-*N*,*N*-dimethylacrylamide, 14l



Prepared according to General Procedure L, using **11b** (65 mg), 3,3-dimethylbut-1-yne (55 μL) and *N*,*N*-dimethylacrylamide (77 μL). Purification by flash column chromatography (CH_2Cl_2/Et_2O, 4:1) afforded *the title compound* (72 mg, 61% yield) as a pale yellow solid. **M.p.** (Et_2O): 177-178 ℃; **δ_H** (400 MHz, $CDCl_3$): 8.27 (d, *J* = 15.5 Hz, 1H, CH=C*H*-Ar), 7.68 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 7.35 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.19 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.90 (d, *J* = 15.5 Hz, 1H, C*H*=CH-Ar), 6.62 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 5.91 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.90-3.60 (2 × br. s, 4H, N(CH_2)$_2$), 3.17 (s, 3H, N-CH_3), 3.06 (s, 3H, N-CH_3), 1.66 (br. s, 6H, 3 × CH_2), 1.00 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 196.4, 167.1, 155.9, 148.2, 139.2, 133.8, 130.3, 130.2, 128.6, 126.2, 125.1, 118.5, 52.7, 44.4, 37.6, 36.0, 33.7, 28.9, 26.4, 24.4, 24.2; **HRMS** (ESI^+) $C_{23}H_{33}N_4O_2$ requires 397.2598 $[M+H]^+$, found 397.2596; **ν_{max}** (film)/cm^{-1} 2950, 2862, 1647, 1608, 1392, 1298, 1259, 1184, 1140, 1108, 983, 921, 727.

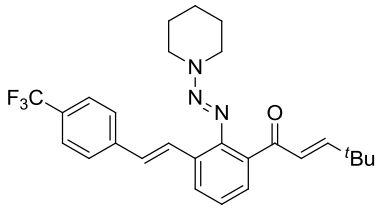
(*E*)-4,4-Dimethyl-1-(3-((*E*)-2-(phenylsulfonyl)vinyl)-2-((*E*)-piperidin-1-yldiazenyl) phenyl)pent-2-en-1-one, 14m



Prepared according to General Procedure L, using **11b** (65 mg), 3,3-dimethylbut-1-yne (55 μL) and (vinylsulfonyl)benzene (126 mg). Purification by flash column chromatography (petrol/Et_2O, 1:1) afforded *the title compound* (95 mg, 68% yield) as a pale yellow solid. **M.p.** (Et_2O): 161-164 ℃; **δ_H** (400 MHz, $CDCl_3$): 8.23 (d, *J* = 15.5 Hz, 1H, CH=C*H*-Ar), 7.95-7.90 (m, 2H, Ar-*H*), 7.62-7.49 (m, 4H, Ar-*H*), 7.37 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.16 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.93 (d, *J* = 15.5 Hz, 1H, C*H*=CH-Ar), 6.61

(d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 5.91 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.85-3.62 (2 × br. s, 4H, N(CH_2)$_2$), 1.67 (br. s, 6H, 3 × CH_2), 0.99 (s, 9H, C(CH_3)$_3$); **δC** (101 MHz, $CDCl_3$): 195.8, 156.4, 148.6, 140.9, 139.6, 133.9, 133.3, 131.7, 129.7, 129.3, 128.1, 127.7, 126.8, 126.0, 125.1, 52.7, 44.3, 33.7, 28.8, 26.4, 24.3, 24.0; **HRMS** (ESI^+) $C_{26}H_{32}N_3O_3{}^{32}S$ requires 466.2159 $[M+H]^+$, found 466.2156; ***ν*max** (film)/cm^{-1} 2952, 2861, 1673, 1654, 1613, 1408, 1305, 1185, 1145, 1110, 1085, 984, 913, 847, 727, 687, 647.

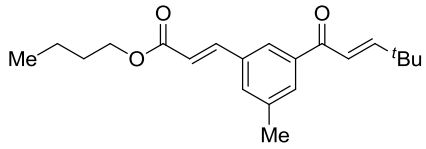
(*E*)-4,4-Dimethyl-1-(2-((*E*)-piperidin-1-yldiazenyl)-3-((*E*)-4-(trifluoromethyl) styryl)phenyl)pent-2-en-1-one, 14n



Prepared according to General Procedure L, using **11b** (65 mg), 3,3-dimethylbut-1-yne (55 μL) and 1-(trifluoromethyl)-4-vinylbenzene (110 μL). Purification by flash column chromatography (petrol/Et_2O, 4:1) afforded *the title compound* (81 mg, 58% yield) as a yellow oil. **δH** (400 MHz, $CDCl_3$): 7.86 (d, *J* = 16.5 Hz, 1H, CH=C*H*-Ar), 7.77 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 7.60 (s, 4H, Ar-*H*), 7.33 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.23 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.12 (d, *J* = 16.5 Hz, 1H, C*H*=CH-Ar), 6.69 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 5.95 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.78 (br. s, 4H, N(CH_2)$_2$), 1.70 (br. s, 6H, 3 × CH_2), 1.03 (s, 9H, C(CH_3)$_3$); **δC** (101 MHz, $CDCl_3$): 196.4, 155.8, 147.3, 141.4, 133.8, 131.4, 129.2 (q, $J_{C\text{-}F}$ = 32.5 Hz), 129.1, 127.9, 127.8, 127.5, 126.7, 126.3, 125.7 (q, $J_{C\text{-}F}$ = 3.5 Hz), 125.3, 124.4 (q, $J_{C\text{-}F}$ = 271.5 Hz), 52.4, 44.2, 33.7, 28.9, 26.2, 24.5, 24.2; **δF** (377 MHz, $CDCl_3$): −62.4; **HRMS** (ESI^+) $C_{27}H_{31}F_3N_3O$ requires 470.2414 $[M+H]^+$, found

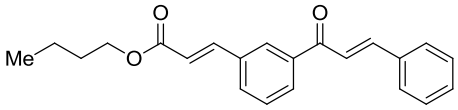
470.2408; ν_{max} (film)/cm^{-1} 2954, 2862, 1674, 1655, 1613, 1416, 1321, 1184, 1163, 1109, 1067, 1015, 979, 913, 826, 752, 734, 681.

(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-5-methylphenyl)acrylate, 15a



Under N_2 atmosphere, triflic acid (20 μL, 0.23 mmol) was added to a solution of **14h** (44 mg, 0.1 mmol) in THF (2 mL) at 0 ℃. The reaction mixture was stirred at 23 ℃ for 1 h, followed by the addition of H_2O (25 μL). It was then further stirred at 23 ℃ for 24 h and concentrated under reduced pressure. Purification by flash column chromatography (gradient petrol/CH_2Cl_2, 7:3 to 5:5) afforded *the title compound* (24 mg, 76% yield) as a colorless oil. δ_H (400 MHz, $CDCl_3$): 7.84 (s, 1H, Ar-*H*), 7.74-7.67 (m, 2H, Ar-*H* and CH=C*H*-Ar), 7.52 (s, 1H, Ar-*H*), 7.08 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 6.75 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 6.50 (d, *J* = 16.0 Hz, 1H, C*H*=CH-Ar), 4.22 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 2.44 (s, 3H, Ar-CH_3), 1.74-1.65 (m, 2H, CH_2), 1.50-1.39 (m, 2H, CH_2-CH_3), 1.17 (s, 9H, $C(CH_3)_3$), 0.97 (t, *J* = 7.5 Hz, 3H, CH_2-CH_3); δ_C (101 MHz, $CDCl_3$): 191.2, 167.0, 160.4, 143.8, 139.2, 139.1, 134.9, 132.5, 130.9, 125.6, 120.9, 119.4, 64.7, 34.4, 30.9, 28.9, 21.5, 19.3, 13.9; **HRMS** (ESI^+) $C_{21}H_{29}O_3$ requires 329.2111 $[M+H]^+$, found 329.2125; ν_{max} (film)/cm^{-1} 2959, 2871, 1713, 1671, 1640, 1620, 1334, 1272, 1172, 982, 848.

(*E*)-Butyl 3-(3-cinnamoylphenyl)acrylate, 15b

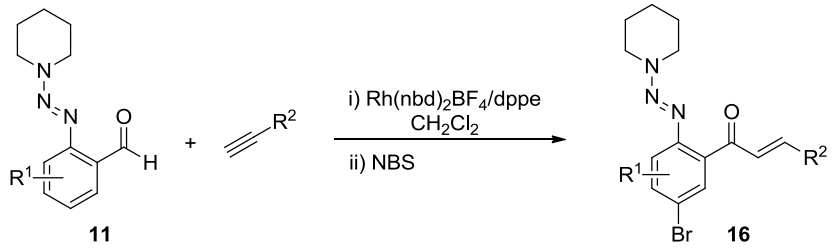


Under N_2 atmosphere, triflic acid (20 μL, 0.23 mmol) was added to a solution of **14d** (45 mg, 0.1 mmol) in THF (2 mL) at 0 ℃. The reaction mixture was stirred at 23 ℃ for 1 h,

followed by the addition of H_2O (25 μL). It was then further stirred at 23 ℃ for 24 h and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (29 mg, 87% yield) as a pale yellow solid. **M.p.** (Et_2O): 80-81 ℃; **δ_H** (400 MHz, $CDCl_3$): 8.15 (s, 1H, Ar-*H*), 8.02 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.84 (d, *J* = 15.5 Hz, 1H, CH=C*H*-Ar), 7.78-7.71 (m, 2H, CO-CH=C*H* and Ar-*H*), 7.69-7.64 (m, 2H, Ar-*H*), 7.56-7.50 (m, 2H, Ar-*H* and C*H*=CH-Ar), 7.47-7.41 (m, 3H, Ar-*H*), 6.55 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 4.23 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 1.75-1.66 (m, 2H, CH_2), 1.50-1.39 (m, 2H, CH_2-CH_3), 0.97 (t, *J* = 7.5 Hz, 3H, CH_3); **δ_C** (101 MHz, $CDCl_3$): 190.0, 166.9, 145.6, 143.5, 139.0, 135.2, 134.8, 132.0, 130.9, 130.1, 129.4, 129.1, 128.7, 128.1, 121.8, 119.8, 64.7, 30.9, 19.3, 13.9; **HRMS** (ESI^+) $C_{22}H_{23}O_3$ requires 335.1642 $[M+H]^+$, found 335.1641; **ν_{max}** (film)/cm^{-1} 2959, 2873, 1709, 1665, 1639, 1606, 1575, 1450, 1305, 1162, 1055, 1033, 979, 863, 805, 761, 687.

5.4.5 Sequential hydroacylation-electrophilic substitution-triazene removal

General Procedure M: sequential hydroacylation-electrophilic aromatic bromination.

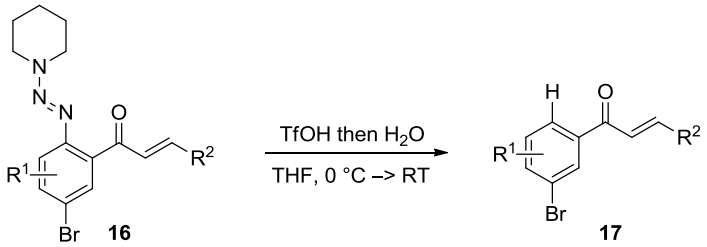


11 16

A microwave reaction vial charged with $Rh(nbd)_2BF_4$ (3.7 mg, 0.01 mmol, 5 mol%) and dppe (4.0 mg, 0.01 mmol, 5 mol%) was evacuated and back-filled with N_2 gas for 3 times. CH_2Cl_2 (0.25 mL) was added to dissolve the solids. The resulting solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until 0.1 mL of the solution was left.

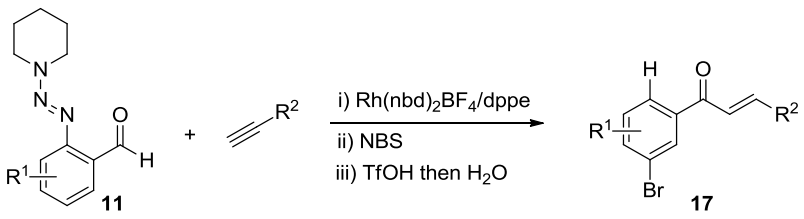
This solution was transferred to a N_2-purged microwave reaction vial containing aldehyde **11** (0.20 mmol, 1.0 equiv) with the aid of CH_2Cl_2 (0.1 mL) to rinse the remainder. Alkyne (0.30 mmol, 1.5 equiv) was added and the reaction mixture stirred at 23 ℃ for 16 h. CH_2Cl_2 (0.80 mL) and NBS (53.4 mg, 0.30 mmol, 1.5 equiv) were added and the resulting mixture stirred at 23 ℃. Upon completion (1-1.5 h), the mixture was concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding enone.

General Procedure N: removal of the triazene unit.



Triflic acid (3.4 equiv) was added to a solution of **16** in THF (0.05 M) at 0 ℃. It was then stirred at 23 ℃ until all initial enone was consumed (normally 60 min), and H_2O (50 μL/0.2 mmol) was added. The mixture was further stirred at 23 ℃ for 24 h, concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding product.

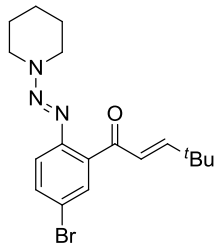
General Procedure O: sequential hydroacylation-bromination-triazene removal.



A microwave reaction vial charged with $Rh(nbd)_2BF_4$ (3.7 mg, 0.01 mmol, 5 mol%) and dppe (4.0 mg, 0.01 mmol, 5 mol%) was evacuated and back-filled with N_2 gas for 3 times. CH_2Cl_2 (0.25 mL) was added to dissolve the solids. The resulting solution was

bubbled with H_2 gas for 2 min, followed by N_2 gas until 0.1 mL of the solution was left. This solution was transferred to a N_2-purged microwave reaction vial containing aldehyde **11** (0.20 mmol, 1.0 equiv) with the aid of CH_2Cl_2 (0.1 mL) to rinse the remainder. Alkyne (0.30 mmol, 1.5 equiv) was added and the reaction mixture stirred at 23 ℃ for 16 h. CH_2Cl_2 (0.80 mL) and NBS (53.4 mg, 0.30 mmol, 1.5 equiv) were added and the resulting mixture stirred at 23 ℃. Upon completion (1-1.5 h), the mixture was diluted with Et_2O, filtered through a pad of SiO_2 to a 25 mL round bottom flask and concentrated under reduced. The reminder was dissolved in THF (4 mL, 0.05 M), followed by the addition of triflic acid (0.06 mL, 0.68 mmol, 3.4 equiv) at 0 ℃. It was then stirred at 23 ℃ until all brominated product was consumed (5-60 min), and H_2O (50 μL) was added. The mixture was further stirred at 23 ℃ for 24 h, concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding product.

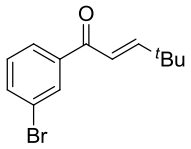
(*E*)-1-(5-Bromo-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-4,4-dimethylpent-2-en-1-one, 16a



Prepared according to General Procedure M, using **11b** (43 mg) and 3,3-dimethyl-1-butyne (37 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 1:1) afforded *the title compound* (72 mg, 95% yield) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 7.53-7.45 (m, 2H, Ar-*H*), 7.36 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 6.72 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.36 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.73 (br. s, 4H, N(CH_2)$_2$), 1.67 (br. s, 6H, 3 × CH_2), 1.04

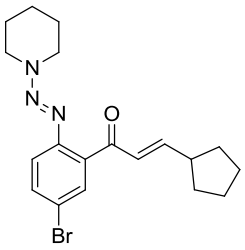
(s, 9H, C(C*H*$_3$)$_3$); **δ$_C$** (101 MHz, $CDCl_3$): 195.4, 157.4, 147.9, 136.4, 133.8, 131.4, 126.4, 120.3, 118.5, 52.9, 44.0, 33.9, 28.9, 26.2, 24.4, 24.3; **HRMS** (ESI$^+$) $C_{18}H_{25}{}^{79}BrN_3O$ requires 378.1176 $[M+H]^+$, found 378.1172; ***ν*$_{max}$** (film)/cm^{-1} 2941, 2859, 1663, 1614, 1422, 1391, 1355, 1297, 1184, 1105, 983, 853, 825.

(*E*)-1-(3-Bromophenyl)-4,4-dimethylpent-2-en-1-one, 17a



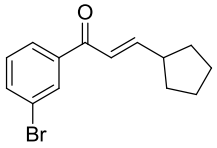
Prepared according to General Procedure N, using **16a** (72 mg, 0.19 mmol), TfOH (0.06 mL, 0.65 mmol), THF (3.8 mL) and H_2O (48 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 7:3) afforded *the title compound* (41 mg, 80% yield) as a yellow oil. Alternatively, prepared according to General Procedure O, using **11b** (43 mg) and 3,3-dimethyl-1-butyne (37 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 7:3) afforded *the title compound* (41 mg, 77% yield) as a yellow oil. **δ$_H$** (400 MHz, $CDCl_3$): 8.04 (s, 1H, Ar-*H*), 7.83 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.67 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.35 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.08 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 6.71 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 1.15 (s, 9H, C(C*H*$_3$)$_3$); **δ$_C$** (101 MHz, $CDCl_3$): 190.1, 160.8, 140.1, 135.5, 131.6, 130.2, 127.2, 123.0, 120.6, 34.4, 28.8; **HRMS** (ESI$^+$) $C_{13}H_{16}{}^{79}BrO$ requires 267.0379 $[M+H]^+$, found 267.0380; ***ν*$_{max}$** (film)/cm^{-1} 2961, 1670, 1617, 1565, 1302, 1216, 984, 790, 718, 687.

(*E*)-1-(5-Bromo-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-3-cyclopentylprop-2-en-1-one, 16b



Prepared according to General Procedure M, using **11b** (43 mg) and ethynyl cyclopentane (35 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 1:1) afforded *the title compound* (68 mg, 87% yield) as a yellow solid. **M.p.** (petrol): 67-69 ℃; **δ_H** (400 MHz, $CDCl_3$): 7.53-7.44 (m, 2H, Ar-*H*), 7.35 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 6.67 (dd, *J* = 15.5, 8.0 Hz, 1H, CO-CH=C*H*), 6.40 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 3.73 (br. s, 4H, N(CH_2)$_2$), 2.63-2.51 (m, 1H, CH=CH-C*H*), 1.83-1.52 (m, 12H, 6 ×CH_2), 1.40-1.30 (m, 2H, Cypent-*H*); **δc** (101 MHz, $CDCl_3$): 195.1, 152.3, 147.9, 136.2, 133.8, 131.4, 129.4, 120.2, 118.4, 53.0, 44.2, 43.2, 32.6, 26.4, 25.4, 24.4, 24.3; **HRMS** (ESI^+) $C_{19}H_{25}{}^{79}BrN_3O$ requires 390.1176 $[M+H]^+$, found 390.1173; **ν_{max}** (film)/cm^{-1} 2942, 2859, 1662, 1615, 1423, 1393, 1355, 1297, 1260, 1184, 1106, 981.

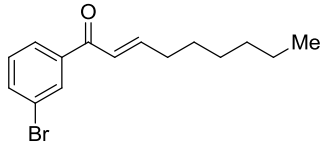
(*E*)-1-(3-Bromophenyl)-3-cyclopentylprop-2-en-1-one, 17b



Prepared according to General Procedure N, using **16b** (66 mg, 0.17 mmol), TfOH (0.05 mL, 0.58 mmol), THF (3.4 mL) and H_2O (43 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 3:2) afforded *the title compound* (36 mg, 77% yield) as a yellow oil. Alternatively, prepared according to General Procedure O, using **11b** (43 mg)

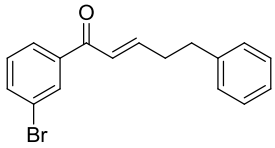
and ethynylcyclopentane (35 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 3:2) afforded *the title compound* (34 mg, 61% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 8.03 (s, 1H, Ar-*H*), 7.83 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.66 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.33 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.06 (dd, *J* = 15.5, 8.0 Hz, 1H, CO-CH=C*H*), 6.79 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 2.76-2.64 (m, 1H, CH=CH-C*H*), 1.94-1.84 (m, 2H, Cypent-*H*), 1.78-1.58 (m, 4H, Cypent-*H*), 1.51-1.41 (m, 2H, Cypent-*H*); **δ_C** (101 MHz, $CDCl_3$): 189.7, 155.4, 140.0, 135.5, 131.6, 130.2, 127.1, 123.5, 122.9, 43.6, 32.7, 25.5; **HRMS** (ESI^+) $C_{14}H_{16}{}^{79}BrO$ requires 279.0379 $[M+H]^+$, found 279.0381; **ν_{max}** (film)/cm^{-1} 2952, 2867, 1669, 1616, 1563, 1421, 1360, 1300, 1254, 1212, 983, 789, 719, 703.

(*E*)-1-(3-Bromophenyl)non-2-en-1-one, 17c



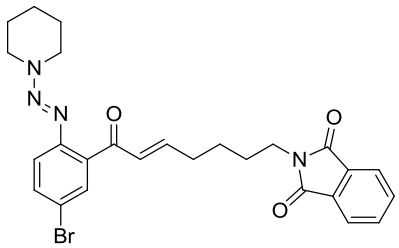
Prepared according to General Procedure O, using **11b** (43 mg) and 1-octyne (44 μL). Purification by flash column chromatography (petrol/Et_2O, 98:2) afforded *the title compound* (38 mg, 65% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 8.04 (t, *J* = 2.0 Hz, 1H, Ar-*H*), 7.85-7.81 (m, 1H, Ar-*H*), 7.66 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar-*H*), 7.34 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.08 (dt, *J* = 15.5, 7.0 Hz, 1H, CO-CH=C*H*), 6.81 (dt, *J* = 15.5, 1.5 Hz, 1H, CO-C*H*=CH), 2.35-2.28 (m, 2H, CH=CH-CH_2), 1.56-1.46 (m, 2H, CH=CH-CH_2-CH_2), 1.39-1.26 (m, 6H, 3 × CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_3); **δ_C** (101 MHz, $CDCl_3$): 189.5, 151.4, 139.9, 135.5, 131.7, 130.2, 127.1, 125.5, 122.9, 33.0, 31.7, 29.0, 28.2, 22.7, 14.2; **HRMS** (ESI^+) $C_{15}H_{20}{}^{79}BrO$ requires 295.0692 $[M+H]^+$, found 295.0692; **ν_{max}** (film)/cm^{-1} 2926, 2855, 1671, 1619, 1564, 1466, 1420, 1289, 1214, 971, 783, 700.

(*E*)-1-(3-Bromophenyl)-5-phenylpent-2-en-1-one, 17d



Prepared according to General Procedure O, using **11b** (43 mg) and 4-phenyl-1-butyne (42 μL). Purification by flash column chromatography (petrol/Et_2O, 98:2) afforded *the title compound* (32 mg, 51% yield) as a yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.99 (s, 1H, Ar-*H*), 7.78 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.67 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.36-7.29 (m, 3H, Ar-*H*), 7.26-7.19 (m, 3H, Ar-*H*), 7.09 (dt, *J* = 15.5, 7.0 Hz, 1H, CO-CH=C*H*), 6.79 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 2.86 (t, *J* = 7.5 Hz, 2H, CH_2-Ph), 2.66 (q, *J* = 7.5 Hz, 2H, CH=CH-CH_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 189.5, 149.6, 140.8, 139.8, 135.6, 131.7, 130.2, 128.7, 128.5, 127.2, 126.4, 126.3, 122.9, 34.7, 34.5; **HRMS** (ESI^+) $C_{17}H_{16}{}^{79}BrO$ requires 315.0379 $[M+H]^+$, found 315.0380; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 3062, 3026, 2924, 2853, 1670, 1619, 1563, 1420, 1299, 1213, 1068, 1030, 981, 789, 748, 698.

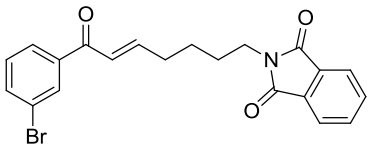
2-((*E*)-7-(5-Bromo-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-7-oxohept-5-en-1-yl) isoindoline-1,3-dione, 16e



Prepared according to General Procedure M, using **11b** (43 mg) and 2-(hex-5-yn-1-yl)isoindoline-1,3-dione (68 mg). Purification by flash column chromatography (gradient petrol/Et_2O, 7:3 to 6:4) afforded *the title compound* (83 mg, 79% yield) as a thick yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.83-7.76 (m, 2H, Ar-*H*), 7.71-7.65 (m, 2H, Ar-*H*), 7.49-7.41

(m, 2H, Ar-*H*), 7.33 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 6.70-6.60 (m, 1H, CO-CH=C*H*), 6.42 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 3.73-3.61 (m, 6H, N(CH_2)$_2$ and CH_2-N), 2.26-2.18 (m, 2H, CH=CH-CH_2), 1.72-1.40 (m, 10H, 5 × CH_2); **δC** (101 MHz, $CDCl_3$): 194.6, 168.4, 147.9, 146.9, 135.9, 134.0, 133.8, 132.0, 131.6, 131.2, 123.2, 120.2, 118.3, 52.9, 44.0, 37.6, 32.0, 28.3, 26.3, 25.4, 24.3, 24.2; **HRMS** (ESI^+) $C_{26}H_{28}{}^{79}BrN_4O_3$ requires 523.1339 $[M+H]^+$, found 523.1340; **ν_{max}** (film)/cm^{-1} 2940, 2857, 1708, 1660, 1616, 1394, 1296, 1184, 1106, 1043, 911, 826, 718.

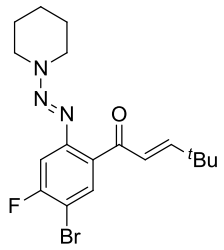
(*E*)-2-(7-(3-Bromophenyl)-7-oxohept-5-en-1-yl)isoindoline-1,3-dione, 17e



Prepared according to General Procedure N, using **16e** (80 mg, 0.15 mmol), TfOH (0.05 mL, 0.51 mmol), THF (3.0 mL) and H_2O (38 μL). Purification by flash column chromatography (petrol/Et_2O, 7:3) afforded *the title compound* (41 mg, 65% yield) as a thick yellow oil. Alternatively, prepared according to General Procedure O, using **11b** (43 mg) and 2-(hex-5-yn-1-yl)isoindoline-1,3-dione (68 mg). Purification by flash column chromatography (petrol/Et_2O, 7:3) afforded *the title compound* (41 mg, 50% yield) as a thick yellow oil. **δH** (400 MHz, $CDCl_3$): 8.04 (t, *J* = 1.5 Hz, 1H, Ar-*H*), 7.87-7.81 (m, 3H, Ar-*H*), 7.74-7.64 (m, 3H, Ar-*H*), 7.34 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.04 (dt, *J* = 15.5, 7.0 Hz, 1H, CO-CH=C*H*), 6.83 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 3.72 (t, *J* = 7.0 Hz, 2H, CH_2-N), 2.42-2.34 (m, 2H, CH=CH-CH_2), 1.80-1.71 (m, 2H, CH_2-CH_2-N), 1.63-1.54 (m, 2H, CH_2); **δC** (101 MHz, $CDCl_3$): 189.3, 168.5, 150.0, 139.8, 135.6, 134.1, 132.2, 131.6, 130.2, 127.2, 125.9, 123.3, 123.0, 37.6, 32.4, 28.2, 25.4; **HRMS** (ESI^+) $C_{21}H_{19}{}^{79}BrNO_3$ requires

412.0543 $[M+H]^+$, found 412.0541; ν_{max} (film)/cm^{-1} 2938, 2861, 1707, 1670, 1619, 1396, 1370, 1216, 1041, 719.

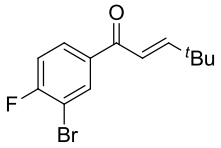
(*E*)-1-(5-Bromo-4-fluoro-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-4,4-dimethylpent-2-en-1-one, 16f



Prepared according to General Procedure M, using **11f** (47 mg) and 3,3-dimethyl-1-butyne (37 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 1:1) afforded *the title compound* (73 mg, 92% yield) as a thick yellow oil. δ_H (400 MHz, $CDCl_3$): 7.62 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.27 (d, *J* = 10.5 Hz, 1H, Ar-*H*), 6.76 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.44 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.76 (br. s, 4H, N(CH_2)$_2$), 1.78-1.56 (m, 6H, 3 × CH_2), 1.04 (s, 9H, C(CH_3)$_3$); δ_C (101 MHz, $CDCl_3$): 194.1, 160.6 (d, J_{C-F} = 251.0 Hz), 157.2, 150.2 (d, J_{C-F} = 7.0 Hz), 133.8 (d, J_{C-F} = 1.5 Hz), 132.3 (d, J_{C-F} = 3.0 Hz), 126.4, 105.4 (d, J_{C-F} = 24.0 Hz), 105.0 (d, J_{C-F} = 22.5 Hz), 53.2, 44.2, 34.0, 28.9, 26.4, 24.5, 24.2; δ_F (377 MHz, $CDCl_3$): –113.4; **HRMS** (ESI^+) $C_{18}H_{24}{}^{79}BrFN_3O$ requires 396.1081 $[M+H]^+$, found 396.1077; ν_{max} (film)/cm^{-1} 2948, 2860, 1663, 1613, 1418, 1381, 1340, 1292, 1249, 1202, 1146, 1108, 983, 853.

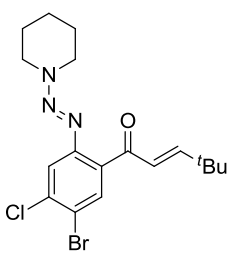
2.0 mmol scale synthesis: i) **11f** (471 mg, 2.0 mmol), 3,3-dimethyl-1-butyne (0.37 mL), $Rh(nbd)_2BF_4$ (37 mg), dppe (40 mg) and CH_2Cl_2 (2 mL); ii) NBS (534 mg) and CH_2Cl_2 (8 mL), 3 h resulted in **16f** (782 mg) in 99% yield.

(*E*)-1-(3-Bromo-4-fluorophenyl)-4,4-dimethylpent-2-en-1-one, 17f



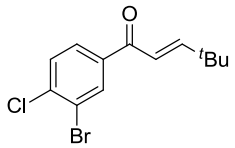
Prepared according to General Procedure N, using **16f** (70 mg, 0.18 mmol), TfOH (0.05 mL, 0.61 mmol), THF (3.6 mL) and H_2O (44 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 4:1) afforded *the title compound* (42 mg, 82% yield) as a yellow oil. Alternatively, prepared according to General Procedure O, using **11f** (47 mg) and 3,3-dimethyl-1-butyne (37 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 4:1) afforded *the title compound* (41 mg, 73% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 8.14 (d, *J* = 6.5 Hz, 1H, Ar-*H*), 7.91-7.85 (m, 1H, Ar-*H*), 7.20 (t, *J* = 8.5 Hz, 1H, Ar-*H*), 7.09 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 6.70 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 1.15 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 188.6, 161.8 (d, $J_{C\text{-}F}$ = 255.0 Hz), 160.9, 135.8 (d, $J_{C\text{-}F}$ = 3.5 Hz), 134.4 (d, $J_{C\text{-}F}$ = 1.0 Hz), 129.8 (d, $J_{C\text{-}F}$ = 8.5 Hz), 120.1, 116.7 (d, $J_{C\text{-}F}$ = 23.0 Hz), 109.7 (d, $J_{C\text{-}F}$ = 21.5 Hz), 34.5, 28.8; **δ_F** (377 MHz, $CDCl_3$): −100.4; **HRMS** (ESI$^+$) $C_{13}H_{15}{}^{79}BrFO$ requires 285.0285 $[M+H]^+$, found 285.0286; **ν_{max}** (film)/cm^{-1} 2962, 2904, 2868, 1672, 1618, 1590, 1491, 1396, 1303, 1260, 1244, 1207, 1049, 984, 826, 732, 671, 615.

(*E*)-1-(5-Bromo-4-chloro-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-4,4-dimethylpent-2-en-1-one, 16g



Prepared according to General Procedure M, using **11g** (50 mg) and 3,3-dimethyl-1-butyne (37 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 1:1) afforded *the title compound* (74 mg, 90% yield) as an off-white solid. **M.p.** (Et_2O): 102-104 ℃; **δ_H** (400 MHz, $CDCl_3$): 7.65 (s, 1H, Ar-*H*), 7.60 (s, 1H, Ar-*H*), 6.74 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.40 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.78-3.74 (m, 4H, N(CH_2)$_2$), 1.78-1.56 (m, 6H, 3 ×CH_2), 1.05 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 194.3, 157.7, 148.8, 136.9, 134.5, 133.6, 126.3, 119.7, 118.1, 53.1, 44.1, 34.0, 28.8, 26.4, 24.4, 24.2; **HRMS** (ESI^+) $C_{18}H_{24}{}^{79}Br^{35}ClN_3O$ requires 412.0786 $[M+H]^+$, found 412.0782; ***ν*max** (film)/cm^{-1} 2941, 2858, 1724, 1666, 1614, 1573, 1416, 1354, 1339, 1293, 1265, 1203, 1108, 729.

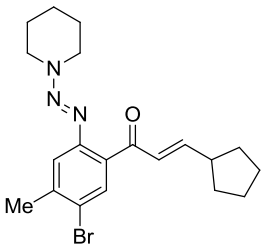
(*E*)-1-(3-Bromo-4-chlorophenyl)-4,4-dimethylpent-2-en-1-one, 17g



Prepared according to General Procedure N, using **16g** (70 mg, 0.17 mmol), TfOH (0.05 mL, 0.58 mmol), THF (3.4 mL) and H_2O (43 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 4:1) afforded *the title compound* (41 mg, 79% yield) as a yellow oil. Alternatively, prepared according to General Procedure O, using **11g** (50 mg) and 3,3-dimethyl-1-butyne (37 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 4:1) afforded *the title compound* (42 mg, 71% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 8.15 (s, 1H, Ar-*H*), 7.79 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.54 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.09 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 6.69 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 1.15 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 189.0, 161.2, 139.1, 137.9, 133.9, 130.6, 128.4, 123.1, 120.1, 34.5, 28.8; **HRMS** (ESI^+) $C_{13}H_{15}{}^{79}Br^{35}ClO$ requires 300.9989 $[M+H]^+$,

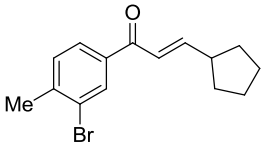
found 300.9991; ν_{max} (film)/cm^{-1} 2962, 2904, 2867, 1671, 1617, 1583, 1552, 1462, 1369, 1302, 1273, 1212, 1125, 1022, 984, 860, 825, 728, 712, 661.

(*E*)-1-(5-Bromo-4-methyl-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-3-cyclopentyl prop-2-en-1-one, 16h



Prepared according to General Procedure M, using **11h** (46 mg) and ethynyl cyclopentane (35 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 1:1) afforded *the title compound* (66 mg, 81% yield) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 7.59 (s, 1H, Ar-*H*), 7.33 (s, 1H, Ar-*H*), 6.68 (dd, *J* = 15.5, 8.0 Hz, 1H, CO-CH=C*H*), 6.43 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 3.73 (br. s, 4H, N(CH_2)$_2$), 2.62-2.50 (m, 1H, CH=CH-C*H*), 2.39 (s, 3H, CH_3), 1.84-1.51 (m, 12H, 6 × CH_2), 1.41-1.30 (m, 2H, Cypent-*H*); δ_C (101 MHz, $CDCl_3$): 194.6, 151.6, 148.1, 140.9, 133.8, 132.4, 129.5, 121.2, 120.6, 52.7, 44.2, 43.2, 32.6, 26.3, 25.4, 24.5, 24.3, 23.2; **HRMS** (ESI$^+$) $C_{20}H_{27}{}^{79}BrN_3O$ requires 404.1332 [M+H]$^+$, found 404.1327; ν_{max} (film)/cm^{-1} 2941, 2858, 1661, 1614, 1418, 1353, 1292, 1255, 1191, 1149, 1105, 981, 892, 852.

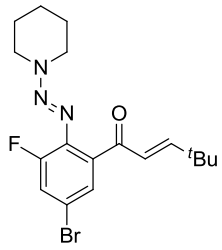
(*E*)-1-(3-Bromo-4-methylphenyl)-3-cyclopentylprop-2-en-1-one, 17h



Prepared according to General Procedure N, using **16h** (66 mg, 0.16 mmol), TfOH (0.05 mL, 0.54 mmol), THF (3.2 mL) and H_2O (40 μL). Purification by flash column

chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (33 mg, 70% yield) as a yellow oil. Alternatively, prepared according to General Procedure O, using **11h** (46 mg) and ethynylcyclopentane (35 μL). Purification by flash column chromatography (petrol/Et_2O, 95:5) afforded *the title compound* (31 mg, 53% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 8.08 (d, *J* = 1.5 Hz, 1H, Ar-*H*), 7.76 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.31 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.05 (dd, *J* = 15.5, 8.0 Hz, 1H, CO-CH=C*H*), 6.80 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 2.76-2.65 (m, 1H, CH=CH-C*H*), 2.45 (s, 3H, CH_3), 1.94-1.85 (m, 2H, Cypent-*H*), 1.78-1.58 (m, 4H, Cypent-*H*), 1.52-1.41 (m, 2H, Cypent-*H*); **δ_C** (101 MHz, $CDCl_3$): 189.3, 154.9, 143.1, 137.6, 132.6, 130.9, 127.4, 125.3, 123.5, 43.6, 32.8, 25.5, 23.3; **HRMS** (ESI^+) $C_{15}H_{18}{}^{79}BrO$ requires 293.0536 $[M+H]^+$, found 293.0536; ***ν*max** (film)/cm^{-1} 2953, 2867, 1668, 1617, 1554, 1450, 1381, 1296, 1255, 1208, 1038, 983, 821, 723, 674.

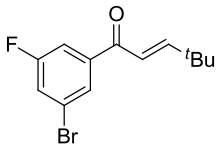
(*E*)-1-(5-Bromo-3-fluoro-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-4,4-dimethylpent-2-en-1-one, 16i



Prepared according to General Procedure M, using **11c** (47 mg) and 3,3-dimethyl-1-butyne (37 μL). The bromination step was carried out at 39 ℃. Purification by flash column chromatography (petrol/CH_2Cl_2, 1:1) afforded *the title compound* (63 mg, 80% yield) as a yellow solid. **M.p.** (Et_2O): 53-55 ℃; **δ_H** (400 MHz, $CDCl_3$): 7.32 (d, *J* = 10.0 Hz, 1H, Ar-*H*), 7.24 (s, 1H, Ar-*H*), 6.62 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 5.97 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.86-3.60 (2 × br. s, 4H, N(CH_2)$_2$), 1.67 (br. s, 6H, 3 × CH_2), 1.01 (s, 9H,

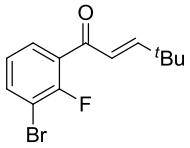
C(C*H*$_3$)$_3$); **δ$_C$** (101 MHz, $CDCl_3$): 194.0 (d, $J_{C\text{-}F}$ = 2.5 Hz), 157.4, 155.6 (d, $J_{C\text{-}F}$ = 255.5 Hz), 137.5 (d, $J_{C\text{-}F}$ = 9.0 Hz), 136.0, 127.2 (d, $J_{C\text{-}F}$ = 3.5 Hz), 125.6, 121.1 (d, $J_{C\text{-}F}$ = 23.5 Hz), 117.4 (d, $J_{C\text{-}F}$ = 9.0 Hz), 52.8, 44.0, 33.9, 28.8, 26.4, 24.4, 24.1; **δ$_F$** (377 MHz, $CDCl_3$): −123.1; **HRMS** (ESI$^+$) $C_{18}H_{24}{}^{79}BrFN_3O$ requires 396.1081 $[M+H]^+$, found 396.1086; ***ν*$_{max}$** (film)/cm^{-1} 2945, 2861, 1662, 1620, 1565, 1420, 1339, 1297, 1255, 1183, 1108, 985, 954, 922, 891, 853, 756, 732, 690.

(*E*)-1-(3-Bromo-5-fluorophenyl)-4,4-dimethylpent-2-en-1-one, 17i



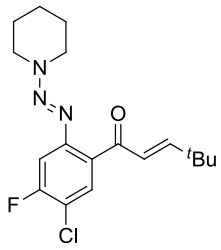
Prepared according to General Procedure N, using **16i** (52 mg, 0.13 mmol), TfOH (0.04 mL, 0.44 mmol), THF (2.6 mL) and H_2O (33 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 4:1) afforded *the title compound* (10 mg, 26% yield) as a yellow oil. **δ$_H$** (400 MHz, $CDCl_3$): 7.82 (s, 1H, Ar-*H*), 7.54 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.43 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.11 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 6.67 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 1.16 (s, 9H, C(C*H*$_3$)$_3$); **δ$_C$** (101 MHz, $CDCl_3$): 188.7 (d, $J_{C\text{-}F}$ = 2.0 Hz), 162.7 (d, $J_{C\text{-}F}$ = 253.0 Hz), 161.7, 141.4 (d, $J_{C\text{-}F}$ = 6.5 Hz), 127.6 (d, $J_{C\text{-}F}$ = 3.0 Hz), 123.09 (d, $J_{C\text{-}F}$ = 9.0 Hz), 123.08 (d, $J_{C\text{-}F}$ = 24.5 Hz), 120.1, 114.5 (d, $J_{C\text{-}F}$ = 22.0 Hz), 34.6, 28.8; **δ$_F$** (377 MHz, $CDCl_3$): −109.4; **HRMS** (ESI$^+$) $C_{13}H_{15}{}^{79}BrFO$ requires 285.0285 $[M+H]^+$, found 285.0286; ***ν*$_{max}$** (film)/cm^{-1} 2963, 2869, 1674, 1619, 1578, 1427, 1303, 1162, 984, 925, 839, 694.

(*E*)-1-(3-Bromo-2-fluorophenyl)-4,4-dimethylpent-2-en-1-one, 17j



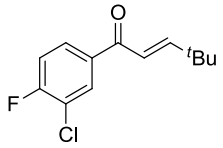
General Procedure M was first followed, using **11l** (47 mg) and 3,3-dimethyl-1-butyne (37 μL). The bromination step was carried out at 35 ℃. Purification by flash column chromatography (petrol/CH_2Cl_2, 2:3) afforded *5-brominated enone* (68 mg, 86% yield) as a yellow oil, isolated as an inseparable 5:1 mixture with 3-brominated product. This mixture was subjected to General Procedure N, using TfOH (0.05 mL, 0.58 mmol), THF (3.4 mL) and H_2O (43 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 7:3) afforded *the title compound* (33 mg, 81% yield based on 5-brominated enone) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.72-7.67 (m, 1H, Ar-*H*), 7.63-7.58 (m, 1H, Ar-*H*), 7.11 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 6.97 (dd, *J* = 16.0, 1.5 Hz, 1H, CO-CH=C*H*), 6.59 (dd, *J* = 16.0, 3.0 Hz, 1H, CO-C*H*=CH), 1.13 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 189.5, 161.0, 157.2 (d, $J_{C\text{-}F}$ = 253.0 Hz), 136.9, 130.0 (d, $J_{C\text{-}F}$ = 2.5 Hz), 128.8 (d, $J_{C\text{-}F}$ = 15.0 Hz), 125.4 (d, $J_{C\text{-}F}$ = 4.5 Hz), 124.6 (d, $J_{C\text{-}F}$ = 5.5 Hz), 110.3 (d, $J_{C\text{-}F}$ = 22.5 Hz), 34.4, 28.7; **δ_F** (377 MHz, $CDCl_3$): −105.1; **HRMS** (ESI^+) $C_{13}H_{15}{}^{79}BrFO$ requires 285.0285 $[M+H]^+$, found 285.0286; **ν_{max}** (film)/cm^{-1} 2962, 2868, 1671, 1616, 1445, 1302, 1243, 1135, 986, 737.

(*E*)-1-(5-Chloro-4-fluoro-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-4,4-dimethylpent-2-en-1-one, 18



A microwave reaction vial charged with $Rh(nbd)_2BF_4$ (3.7 mg, 0.01 mmol) and dppe (4.0 mg, 0.01 mmol) was evacuated and back-filled with N_2 gas for 3 times. CH_2Cl_2 (0.25 mL) was added to dissolve the solids. The resulting solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until 0.1 mL of the solution was left. This solution was transferred to a N_2-purged microwave reaction vial containing **11f** (47.1 mg, 0.20 mmol) with the aid of CH_2Cl_2 (0.1 mL) to rinse the remainder. 3,3-Dimethyl-1-butyne (37 μL, 0.30 mmol) was added and the reaction mixture stirred at 23 ℃ for 16 h. DMF (0.80 mL) and 1-chloro-1,2-benziodoxol-3-one (113.0 mg, 0.40 mmol) were added and the resulting mixture stirred at 39 ℃ for 16 h. The mixture was diluted with 5% aqueous solution of LiCl and extracted with CH_2Cl_2 (3×). The combined organic layers were concentrated under reduced pressure and purified by flash column chromatography (petrol/CH_2Cl_2, 3:2) to afford *the title compound* (56 mg, 79% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.49 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.31 (d, *J* = 10.5 Hz, 1H, Ar-*H*), 6.77 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 6.45 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.77 (br. s, 4H, $N(CH_2)_2$), 1.82-1.56 (m, 6H, 3 × CH_2), 1.06 (s, 9H, $C(CH_3)_3$); **δ_C** (101 MHz, $CDCl_3$): 194.2, 159.6 (d, $J_{C\text{-}F}$ = 252.5 Hz), 157.3, 149.4 (d, $J_{C\text{-}F}$ = 6.5 Hz), 131.9 (d, $J_{C\text{-}F}$ = 3.0 Hz), 131.0, 126.4, 117.4 (d, $J_{C\text{-}F}$ = 19.0 Hz), 105.6 (d, $J_{C\text{-}F}$ = 23.0 Hz), 53.2, 44.3, 34.0, 28.9, 26.5, 24.5, 24.2; **δ_F** (377 MHz, $CDCl_3$): −111.3; **HRMS** (ESI^+) $C_{18}H_{24}{}^{35}ClFN_3O$ requires 352.1586 $[M+H]^+$, found 352.1588; **ν_{max}** (film)/cm^{-1} 2943, 2860, 1664, 1613, 1478, 1420, 1384, 1295, 1252, 1202, 1147, 1108, 1065, 983, 853, 743, 693.

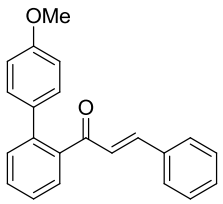
(*E*)-1-(3-Chloro-4-fluorophenyl)-4,4-dimethylpent-2-en-1-one, 19



Prepared according to General Procedure N, using **18** (56 mg, 0.16 mmol), TfOH (0.05 mL, 0.54 mmol), THF (3.2 mL) and H_2O (40 μL). Purification by flash column chromatography (petrol/CH_2Cl_2, 7:3) afforded *the title compound* (24 mg, 63% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 8.00 (dd, *J* = 7.0, 1.5 Hz, 1H, Ar-*H*), 7.86-7.81 (m, 1H, Ar-*H*), 7.22 (t, *J* = 8.5 Hz, 1H, Ar-*H*), 7.09 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 6.71 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 1.16 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 188.7, 160.89, 160.88 (d, $J_{C\text{-}F}$ = 256.5 Hz), 135.4 (d, $J_{C\text{-}F}$ = 3.5 Hz), 131.5, 129.0 (d, $J_{C\text{-}F}$ = 8.5 Hz), 121.8 (d, $J_{C\text{-}F}$ = 18.0 Hz), 120.1, 116.8 (d, $J_{C\text{-}F}$ = 21.5 Hz), 34.5, 28.8; **δ_F** (377 MHz, $CDCl_3$): –108.4; **HRMS** (ESI$^+$) $C_{13}H_{15}{}^{35}ClFO$ requires 241.0790 $[M+H]^+$, found 241.0792; **ν_{max}** (film)/cm^{-1} 2963, 2869, 1715, 1673, 1617, 1592, 1496, 1397, 1365, 1304, 1264, 1246, 1221, 1208, 1064, 984, 826, 732, 694, 616.

5.4.6 Other transformations

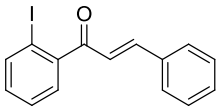
(*E*)-1-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-3-phenylprop-2-en-1-one, 20



A microwave reaction vial charged with **12d** (47.9 mg, 0.15 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol) and 4-methoxyphenylboronic acid (45.6 mg, 0.30 mmol) was evacuated and back-filled with N_2 gas for 3 times. 1,4-Dioxane (1.5 mL) and $BF_3{\cdot}OEt_2$ (0.02 mL,

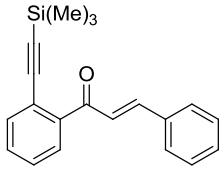
0.15 mmol) were added and the reaction mixture stirred at 23 ℃ for 24 h. It was concentrated under reduced pressure and purified by flash column chromatography (petrol/Et_2O, 9:1) to afford *the title compound* (42 mg, 88% yield) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 7.55 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.49-7.43 (m, 1H, Ar-*H*), 7.39-7.32 (m, 2H, Ar-*H*), 7.29 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 7.25-7.14 (m, 7H, Ar-*H*), 6.81 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.47 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.67 (s, 3H, CH_3); δ_C (101 MHz, $CDCl_3$): 196.6, 159.5, 143.5, 140.7, 139.8, 134.9, 132.9, 130.8, 130.5, 130.4, 130.2, 128.9, 128.8, 128.3, 127.1, 127.0, 114.2, 55.4; **HRMS** (ESI^+) $C_{22}H_{19}O_2$ requires 315.1380 $[M+H]^+$, found 315.1381; ν_{max} (film)/cm^{-1} 3059, 2836, 1664, 1643, 1607, 1575, 1516, 1475, 1448, 1330, 1298, 1245, 1206, 1178, 1034, 978, 834, 763.

(*E*)-1-(2-Iodophenyl)-3-phenylprop-2-en-1-one, 21



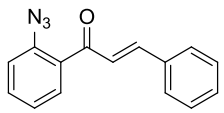
In a sealed microwave reaction vial under N_2 atmosphere, a solution of **12d** (31.9 mg, 0.1 mmol) in MeI (1 mL) was refluxed at 100 ℃ for 16 h. The mixture was concentrated under reduced pressure and purified by flash column chromatography (petrol/Et_2O, 92:8) to afford the title compound (25 mg, 75% yield) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 7.94 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.59-7.54 (m, 2H, Ar-*H*), 7.48-7.36 (m, 6H, 5 × Ar-*H* and CO-CH=C*H*), 7.17 (td, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.08 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH); δ_C (101 MHz, $CDCl_3$): 196.2, 147.2, 144.8, 140.1, 134.5, 131.4, 131.1, 129.1, 128.7, 128.6, 128.1, 125.7, 92.3; ν_{max} (film)/cm^{-1} 3058, 2981, 1644, 1602, 1449, 1331, 1285, 1210, 1011, 753; data consistent with literature.[135]

(*E*)-3-Phenyl-1-(2-((trimethylsilyl)ethynyl)phenyl)prop-2-en-1-one, 22



In a sealed microwave reaction vial under N_2 atmosphere, a solution of **12d** (31.9 mg, 0.1 mmol) in MeI (1 mL) was refluxed at 100 ℃ for 16 h. The mixture was concentrated under reduced pressure and back-filled with N_2 gas. To this was added $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol), ethynyltrimethylsilane (28 μL, 0.2 mmol) and NEt_3 (0.5 mL) and the mixture stirred at 23 ℃ for 24 h. It was then concentrated under reduced pressure and purified by flash column chromatography (petrol/CH_2Cl_2, 3:2) to afford *the title compound* (22 mg, 73% yield) as a yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.65-7.56 (m, 5H, 4 × Ar-*H* and CO-CH=C*H*), 7.49-7.37 (m, 6H, 5 × Ar-*H* and CO-C*H*=CH), 0.08 (s, 9H, Si(CH_3)$_3$); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 194.1, 144.3, 142.7, 135.0, 133.7, 130.8, 130.7, 129.0, 128.8, 128.7 (2C), 126.0, 121.4, 103.1, 101.5, –0.2; **HRMS** (ESI^+) $C_{20}H_{21}OSi$ requires 305.1356 $[M+H]^+$, found 305.1356; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 3060, 2981, 2159, 1643, 1607, 1575, 1478, 1448, 1331, 1287, 1206, 1178, 1034, 690.

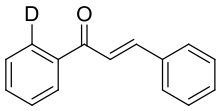
(*E*)-1-(2-Azidophenyl)-3-phenylprop-2-en-1-one, 23



Under N_2 atmosphere, azidotrimethylsilane (66 μL, 0.5 mmol) and trifluoroacetic acid (0.06 mL, 0.8 mmol) were added to a solution of **12d** (31.9 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) at 0 ℃. The reaction mixture was stirred at 23 ℃ for 1 h and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 92:8)

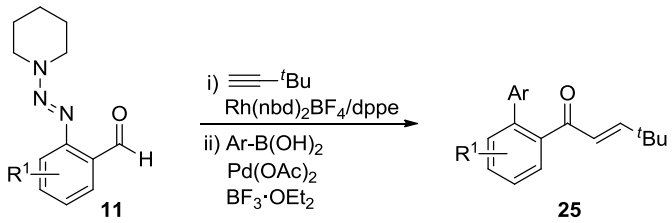
afforded *the title compound* (24 mg, 96% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.56-7.44 (m, 5H, 4 ×Ar-*H* and CO-CH=C*H*), 7.37-7.31 (m, 3H, Ar-*H*), 7.22-7.14 (m, 3H, 2 ×Ar-*H* and CO-C*H*=CH); **δ_C** (101 MHz, $CDCl_3$): 192.8, 145.2, 138.4, 134.7, 132.4, 132.0, 130.8, 130.2, 129.1, 128.7, 126.4, 124.9, 119.2; **HRMS** (ESI^+) $C_{15}H_{11}N_3ONa$ requires 272.0794 $[M+Na]^+$, found 272.0795; **ν_{max}** (film)/cm^{-1} 3060, 2981, 2123, 1661, 1646, 1599, 1575, 1480, 1448, 1332, 1287, 1207, 1021, 978, 754, 705.

(*E*)-1-(2-Deuteriophenyl)-3-phenylprop-2-en-1-one, 24



Trifluoroacetic acid-d (0.10 mL) was added to a solution of **12d** (31.9 mg, 0.10 mmol) in THF-d_8 (2 mL) and the mixture stirred at 40 ℃ for 16 h. It was then concentrated under reduced pressure and purified by flash column chromatography (petrol/Et_2O, 92:8) to afford *the title compound* (8 mg, 40% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 8.03 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.82 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 7.69-7.63 (m, 2H, Ar-*H*), 7.62-7.48 (m, 4H, 3 ×Ar-*H* and CO-C*H*=CH), 7.46-7.39 (m, 3H, Ar-*H*); **δ_C** (101 MHz, $CDCl_3$): 190.7, 145.0, 138.2, 135.0, 132.9, 130.7, 129.1, 128.8, 128.7, 128.63, 128.60 (2C), 122.2; **HRMS** (ESI^+) $C_{15}H_{12}DO$ requires 210.1024 $[M+H]^+$, found 210.1024; **ν_{max}** (film)/cm^{-1} 3060, 2921, 1663, 1604, 1575, 1449, 1334, 1214, 1018, 745.

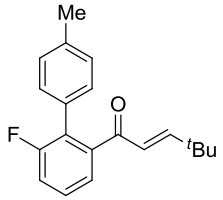
General Procedure P: sequential hydroacylation-Suzuki coupling



A microwave reaction vial charged with $Rh(nbd)_2BF_4$ (3.7 mg, 0.01 mmol, 5 mol%)

and dppe (4.0 mg, 0.01 mmol, 5 mol%) was evacuated and back-filled with N_2 gas for 3 times. CH_2Cl_2 (0.25 mL) was added to dissolve the solids. The resulting solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until 0.1 mL of the solution was left. This solution was transferred to a N_2-purged microwave reaction vial containing aldehyde **11** (0.20 mmol, 1.0 equiv) with the aid of CH_2Cl_2 (0.1 mL) to rinse the remainder. Alkyne (0.30 mmol, 1.5 equiv) was added and the reaction mixture stirred at 23 ℃ for 16 h. The solution was diluted with Et_2O, filtered through a pad of SiO_2 to a 25 mL round bottom flask and concentrated under reduced pressure. To this was added arylboronic acid (0.40 mmol, 2.0 equiv) and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol%). The flask was then evacuated and back-filled with N_2 gas, followed by the addition of 1,4-dioxane (2 mL, 0.1 M) and BF_3 OEt_2 (0.05 mL, 0.40 mmol, 2.0 equiv). The reaction mixture was stirred at 23 ℃ for 24 h, filtered through a pad of SiO_2 and concentrated under reduced pressure. Purification by flash column chromatography afforded the corresponding product.

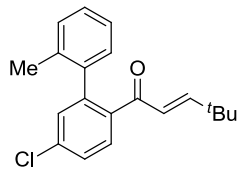
(*E*)-1-(6-Fluoro-4'-methyl-[1,1'-biphenyl]-2-yl)-4,4-dimethylpent-2-en-1-one, 25a



Prepared according to General Procedure P, using **11c** (47 mg), 3,3-dimethyl-1-butyne (37 μL) and *p*-tolylboronic acid (54 mg). Purification by flash column chromatography (gradient petrol/CH_2Cl_2, 7:3 to 6:4) afforded *the title compound* (47 mg, 79% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.44-7.34 (m, 2H, Ar-*H*), 7.31-7.24 (m, 1H, Ar-*H*), 7.21 (app. s, 4H, Ar-*H*), 6.55 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 5.76 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 2.39 (s, 3H, Ar-CH_3), 0.83 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 196.2 (d,

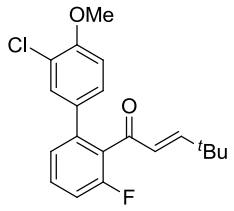
$J_{C\text{-}F}$ = 3.0 Hz), 159.4 (d, $J_{C\text{-}F}$ = 247.5 Hz), 158.8, 142.7 (d, $J_{C\text{-}F}$ = 2.0 Hz), 138.3, 130.5, 130.3 (d, $J_{C\text{-}F}$ = 1.5 Hz), 129.1, 128.9 (d, $J_{C\text{-}F}$ = 8.5 Hz), 128.1 (d, $J_{C\text{-}F}$ = 16.5 Hz), 125.6, 124.3 (d, $J_{C\text{-}F}$ = 3.5 Hz), 117.9 (d, $J_{C\text{-}F}$ = 23.5 Hz), 33.8, 28.5, 21.3; **δ_F** (377 MHz, $CDCl_3$): –116.7; **HRMS** (ESI^+) $C_{20}H_{22}FO$ requires 297.1649 $[M+H]^+$, found 297.1651; **ν_{max}** (film)/cm^{-1} 2961, 2867, 1672, 1654, 1616, 1451, 1300, 1244, 1060, 983, 817, 748.

(*E*)-1-(5-Chloro-2'-methyl-[1,1'-biphenyl]-2-yl)-4,4-dimethylpent-2-en-1-one, 25b



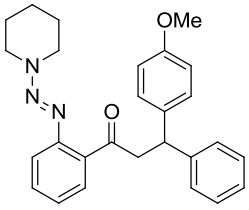
Prepared according to General Procedure P, using **11g** (50 mg), 3,3-dimethyl-1-butyne (37 μL) and *o*-tolylboronic acid (54 mg). Purification by flash column chromatography (petrol/Et_2O, 94:6) afforded *the title compound* (55 mg, 88% yield) as a yellow oil. **δ_H** (400 MHz, $CDCl_3$): 7.58 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.39 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-*H*), 7.27-7.21 (m, 2H, Ar-*H*), 7.20-7.13 (m, 2H, Ar-*H*), 7.07 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 6.59 (d, *J* = 15.5 Hz, 1H, CO-CH=C*H*), 5.74 (d, *J* = 15.5 Hz, 1H, CO-C*H*=CH), 2.11 (s, 3H, Ar-CH_3), 0.78 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$): 195.0, 158.0, 142.3, 139.3, 138.8, 136.6, 135.8, 130.6, 130.5, 130.4, 130.0, 128.5, 127.7, 126.0, 124.6, 33.7, 28.5, 20.2; **HRMS** (ESI^+) $C_{20}H_{22}{}^{35}ClO$ requires 313.1354 $[M+H]^+$, found 313.1354; **ν_{max}** (film)/cm^{-1} 2961, 2867, 1669, 1617, 1587, 1554, 1463, 1389, 1365, 1297, 1094, 1017, 983, 851, 826, 766, 730.

(*E*)-1-(3'-Chloro-3-fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)-4,4-dimethylpent-2-en-1-one, 25c



Prepared according to General Procedure P, using **11l** (47 mg), 3,3-dimethyl-1-butyne (37 μL) and 3-chloro-4-methoxyphenylboronic acid (75 mg). Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (68 mg, 98% yield) as a colorless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.46-7.39 (m, 1H, Ar-*H*), 7.31 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.17-7.08 (m, 3H, Ar-*H*), 6.88 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 6.43 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 5.97 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 3.89 (s, 3H, OCH_3), 0.90 (s, 9H, C(CH_3)$_3$); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 194.6, 162.2, 159.4 (d, $J_{C\text{-}F}$ = 249.0 Hz), 154.9, 140.7 (d, $J_{C\text{-}F}$ = 4.0 Hz), 132.5 (d, $J_{C\text{-}F}$ = 2.5 Hz), 130.9 (d, $J_{C\text{-}F}$ = 9.0 Hz), 130.6, 128.5, 127.5 (d, $J_{C\text{-}F}$ = 17.5 Hz), 127.3, 125.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 122.6, 114.9 (d, $J_{C\text{-}F}$ = 22.0 Hz), 111.9, 56.3, 34.1, 28.5; $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$): −115.7; **HRMS** (ESI^+) $C_{20}H_{21}{}^{35}ClFO_2$ requires 347.1209 $[M+H]^+$, found 347.1208; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2962, 1657, 1608, 1508, 1460, 1290, 1253, 1236, 1105, 1066, 1023, 984, 925, 800, 755, 705.

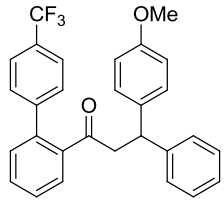
(*E*)-3-(4-Methoxyphenyl)-3-phenyl-1-(2-(piperidin-1-yldiazenyl)phenyl)propan-1-one, 26



A microwave reaction vial charged with $Rh(nbd)_2BF_4$ (7.5 mg, 0.02 mmol) and dppe

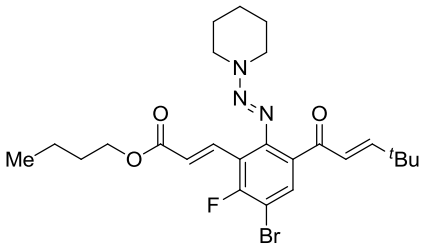
(8.0 mg, 0.02 mmol) was evacuated and back-filled with N_2 gas for 3 times. CH_2Cl_2 (0.35 mL) was added to dissolve the solids. The resulting solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until 0.1 mL of the solution was left. This solution was transferred to a N_2-purged microwave reaction vial containing **11b** (43.5 mg, 0.20 mmol) with the aid of CH_2Cl_2 (0.1 mL) to rinse the remainder. Phenylacetylene (33 μL, 0.30 mmol) was added and the reaction mixture stirred at 23 ℃ for 16 h. The solution was transferred to a N_2-purged microwave reaction vial containing 4-methoxyphenylboronic acid (60.8 mg, 0.40 mmol) and K_2CO_3 (27.6 mg, 0.20 mmol). Acetone (1.8 mL) and MeOH (0.2 mL) were added and the mixture stirred in a sealed tube at 55 ℃ for 24 h. It was then diluted with Et_2O, filtered through a pad of SiO_2 and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 4:1) afforded *the title compound* (68 mg, 80% yield) as a thick yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.37 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.28 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.16-6.96 (m, 9H, Ar-*H*), 6.67 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.53 (t, *J* = 7.5 Hz, 1H, C*H*), 3.70-3.56 (m, 9H, CH-CH_2, N(CH_2)$_2$ and OCH_3), 1.54 (br. s, 6H, 3 ×CH_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 204.2, 158.0, 148.7, 144.8, 136.5, 134.8, 131.6, 128.9, 128.7, 128.4, 127.9, 126.2, 125.4, 117.7, 113.8, 55.3, 53.0, 51.3, 45.9, 44.1, 26.3, 24.5, 24.3; **HRMS** (ESI^+) $C_{27}H_{30}N_3O_2$ requires 428.2332 $[M+H]^+$, found 428.2325; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 2939, 2856, 1674, 1610, 1591, 1510, 1418, 1355, 1295, 1247, 1181, 1110, 1096, 1033, 987, 909, 829, 761, 729, 699.

3-(4-Methoxyphenyl)-3-phenyl-1-(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl) propan-1-one, 27



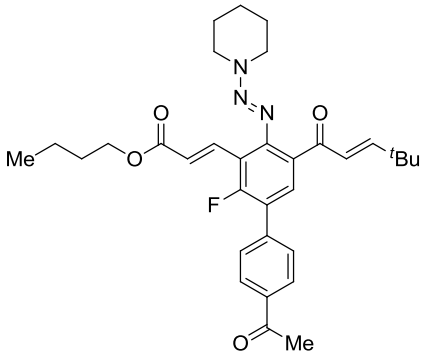
Under N_2 atmosphere, $BF_3{\cdot}OEt_2$ (0.03 mL, 0.20 mmol) was added to a solution of **26** (85.5 mg, 0.20 mmol), 4-(trifluoromethyl)phenylboronic acid (76.0 mg, 0.40 mmol) and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) in 1,4-dioxane (2 mL) and the mixture stirred at 23 ℃ for 24 h. It was then diluted with Et_2O, filtered through a pad of SiO_2 and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 9:1) afforded *the title compound* (92 mg, 99% yield) as a thick yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 7.58-7.51 (m, 3H, Ar-*H*), 7.47-7.41 (m, 2H, Ar-*H*), 7.37 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.30-7.18 (m, 5H, Ar-*H*), 7.13 (d, *J* = 7.5 Hz, 2H, Ar-*H*), 7.06 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.58 (t, *J* = 7.5 Hz, 1H, C*H*), 3.80 (s, 3H, OCH_3), 3.31 (d, *J* = 7.5 Hz, 2H, CH_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$): 203.8, 158.2, 144.3, 144.0, 140.3, 139.1, 135.7, 130.9, 130.6, 129.6 (q, $J_{C\text{-}F}$ = 32.5 Hz), 129.2, 128.9, 128.6, 128.1, 128.0, 127.8, 126.5, 125.5 (q, $J_{C\text{-}F}$ = 3.5 Hz), 124.3 (q, $J_{C\text{-}F}$ = 272.0 Hz), 114.0, 55.3, 49.0, 45.5; $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$): –62.3; **HRMS** (ESI^+) $C_{29}H_{23}F_3O_2Na$ requires 483.1542 $[M+Na]^+$, found 483.1540; $\boldsymbol{\nu_{max}}$ (film)/cm^{-1} 3061, 3029, 2934, 2837, 1692, 1613, 1511, 1324, 1248, 1164, 1122, 1069, 1033, 844, 766, 735, 699.

(*E*)-Butyl 3-(3-bromo-5-((*E*)-4,4-dimethylpent-2-enoyl)-2-fluoro-6-((*E*)-piperidin-1-yldiazenyl)phenyl)acrylate, 28



Under N_2 atmosphere, ^{n}butyl acrylate (0.72 mL, 5.0 mmol) was added to a suspension of **16f** (782 mg, 2.0 mmol), $[RhCp^*Cl_2]_2$ (62 mg, 0.10 mmol) and $Cu(OAc)_2 \cdot H_2O$ (799 mg, 4.0 mmol) in MeOH (13 mL) and the reaction mixture stirred at 70 ℃ for 20 h. It was then diluted with Et_2O, filtered through a pad of SiO_2 and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 85:15) afforded *the title compound* (695 mg, 67% yield) as a yellow solid. **M.p.** (petrol): 67-69 ℃; δ_H (400 MHz, $CDCl_3$): 8.10 (d, *J* = 16.5 Hz, 1H, CH=C*H*-Ar), 7.53 (d, *J* = 7.0 Hz, 1H, Ar-*H*), 6.71 (d, *J* = 16.5 Hz, 1H, C*H*=CH-Ar), 6.63 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 5.84 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 4.19 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.90-3.64 (2 × br. s, 4H, $N(CH_2)_2$), 1.73-1.63 (m, 8H, 4 × CH_2), 1.48-1.37 (m, 2H, CH_2-CH_3), 1.00 (s, 9H, $C(CH_3)_3$), 0.94 (t, *J* = 7.5 Hz, 3H, CH_2-CH_3); δ_C (101 MHz, $CDCl_3$): 193.7, 167.4, 158.7 (d, $J_{C\text{-}F}$ = 256.0 Hz), 156.6, 149.5 (d, $J_{C\text{-}F}$ = 5.0 Hz), 134.4, 134.1 (d, $J_{C\text{-}F}$ = 2.0 Hz), 130.3 (d, $J_{C\text{-}F}$ = 3.5 Hz), 125.6, 124.4 (d, $J_{C\text{-}F}$ = 13.5 Hz), 118.3 (d, $J_{C\text{-}F}$ = 13.5 Hz), 105.7 (d, $J_{C\text{-}F}$ = 23.0 Hz), 64.6, 52.9, 44.6, 33.8, 30.8, 28.8, 26.5, 24.4, 24.0, 19.3, 13.9; δ_F (377 MHz, $CDCl_3$): −101.3; **HRMS** (ESI^+) $C_{25}H_{34}{}^{79}BrFN_3O_3$ requires 522.1762 $[M+H]^+$, found 522.1764; ν_{max} (film)/cm^{-1} 2957, 2864, 1714, 1674, 1622, 1563, 1417, 1398, 1366, 1302, 1253, 1176, 1109, 986, 874, 851, 726, 653.

(*E*)-Butyl 3-(4'-acetyl-5-((*E*)-4,4-dimethylpent-2-enoyl)-2-fluoro-4-((*E*)-piperidin-1-yldiazenyl)-[1,1'-biphenyl]-3-yl)acrylate, 29



Under N_2 atmosphere, a suspension of **28** (52.2 mg, 0.10 mmol), 4-acetylphenyl boronic acid (32.8 mg, 0.20 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), DavePhos (3.9 mg, 0.01 mmol) and KF (14.5 mg, 0.25 mmol) in THF (0.5 mL) was stirred at 60 ℃ for 16 h. It was then diluted with H_2O and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et_2O, 3:2) afforded *the title compound* (47 mg, 84% yield) as a yellow solid. **M.p.** (petrol): 153-155 ℃; **δ_H** (400 MHz, $CDCl_3$): 8.20 (d, *J* = 16.5 Hz, 1H, CH=C*H*-Ar), 8.02 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.65 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.48 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.76 (d, *J* = 16.5 Hz, 1H, C*H*=CH-Ar), 6.69 (d, *J* = 16.0 Hz, 1H, CO-CH=C*H*), 5.90 (d, *J* = 16.0 Hz, 1H, CO-C*H*=CH), 4.20 (t, *J* = 6.5 Hz, 2H, CO_2CH_2), 3.94-3.68 (2 × br. s, 4H, $N(CH_2)_2$), 2.63 (s, 3H, CO-CH_3), 1.77-1.63 (m, 8H, 4 × CH_2), 1.49-1.37 (m, 2H, CH_2-CH_3), 1.02 (s, 9H, $C(CH_3)_3$), 0.95 (t, *J* = 7.5 Hz, 3H, CH_2-CH_3); **δ_C** (101 MHz, $CDCl_3$): 197.7, 194.7, 167.6, 159.6 (d, $J_{C\text{-}F}$ = 259.0 Hz), 156.2, 150.2 (d, $J_{C\text{-}F}$ = 5.5 Hz), 139.7, 136.4, 135.0, 132.0 (d, $J_{C\text{-}F}$ = 6.0 Hz), 129.9 (d, $J_{C\text{-}F}$ = 3.5 Hz), 129.3 (d, $J_{C\text{-}F}$ = 3.0 Hz), 128.6, 125.9, 124.9 (d, $J_{C\text{-}F}$ = 15.5 Hz), 124.1 (d, $J_{C\text{-}F}$ = 13.5 Hz), 117.7 (d, $J_{C\text{-}F}$ = 13.5 Hz), 64.5, 53.0, 44.6, 33.8, 30.9, 28.9, 26.8, 26.5, 24.4, 24.0, 19.3, 13.9; **δ_F** (377

MHz, $CDCl_3$): −112.2; **HRMS** (ESI^+) $C_{33}H_{41}FN_3O_4$ requires 562.3076 $[M+H]^+$, found 562.3074; $\boldsymbol{\nu}_{\mathbf{max}}$ (film)/cm^{-1} 2957, 2917, 2849, 1721, 1683, 1606, 1409, 1267, 1191, 1154, 1091, 732.

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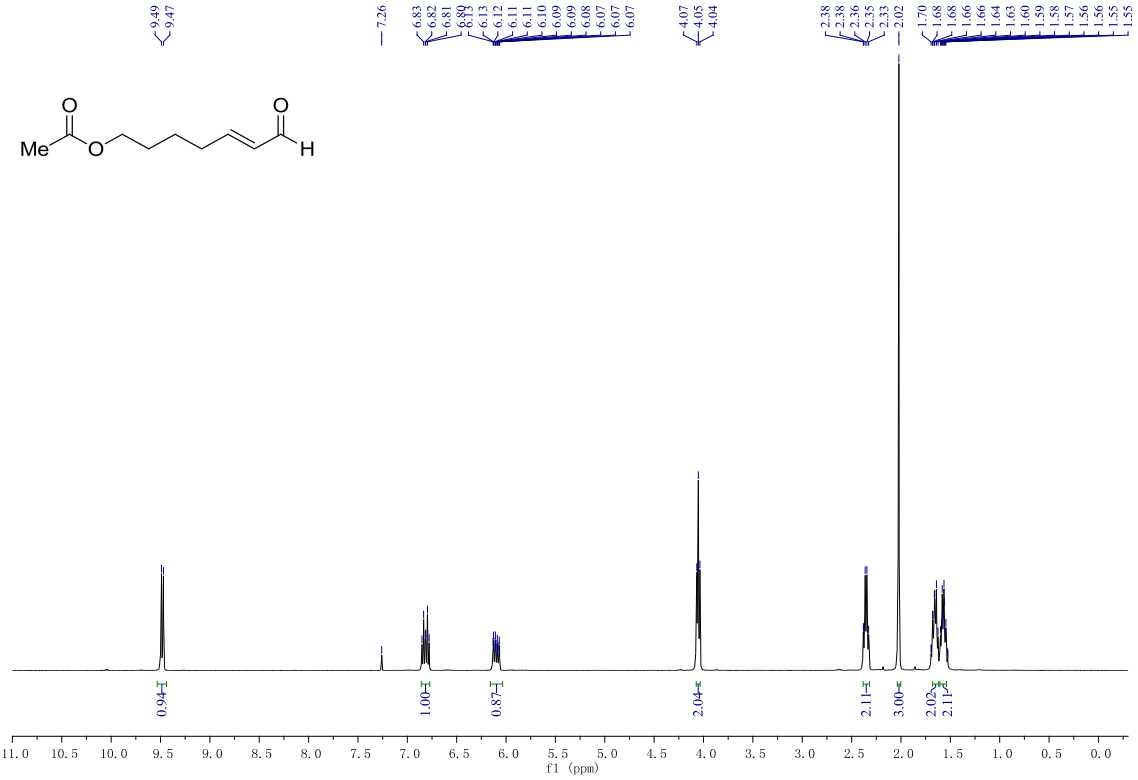
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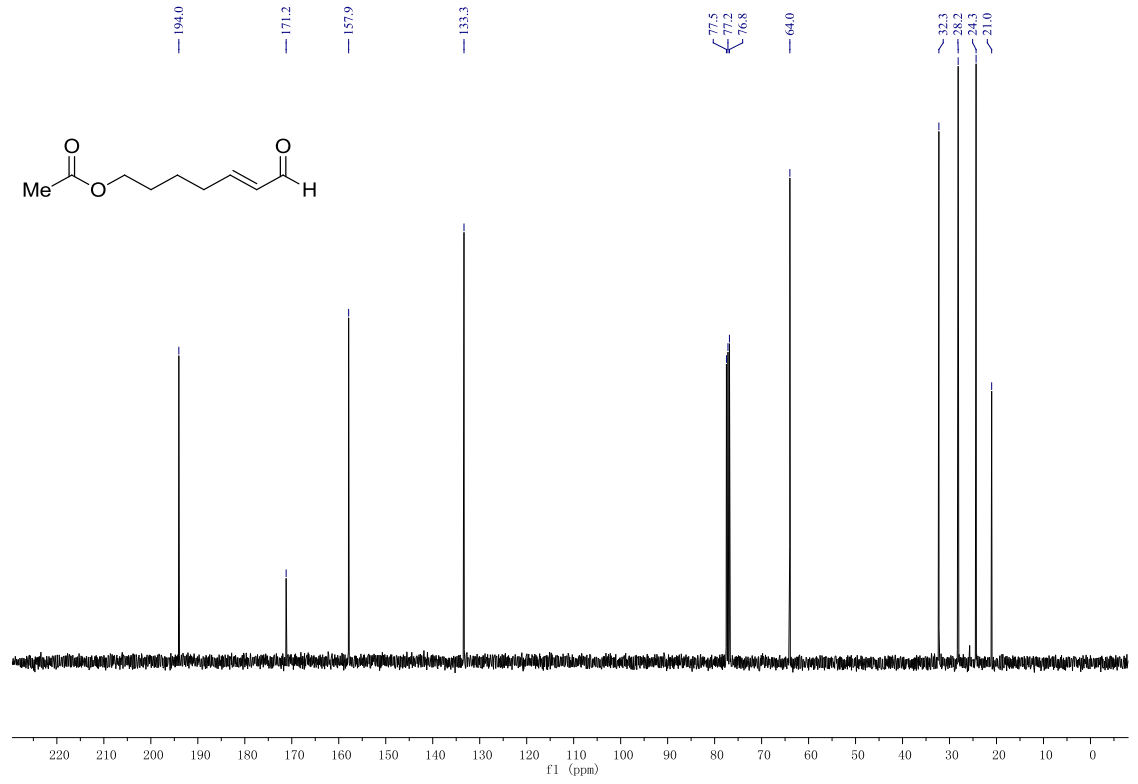
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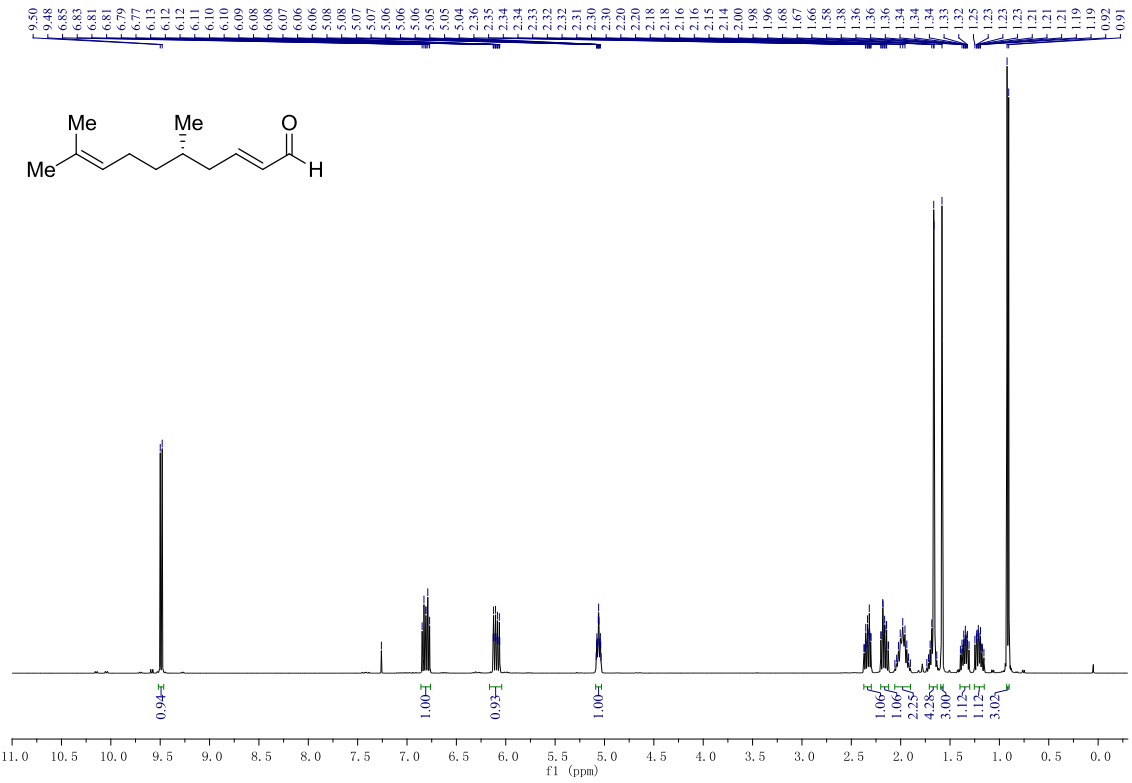
Spectra of novel compounds

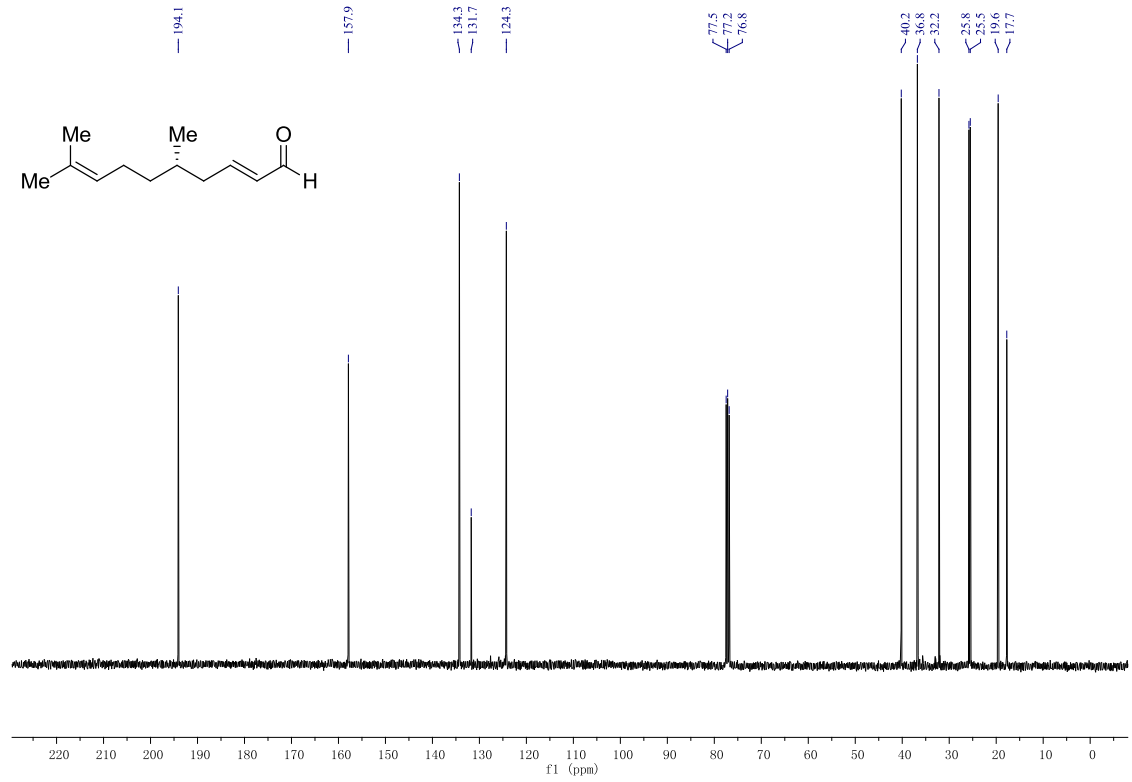
(*E*)-7-Oxohept-5-en-1-yl acetate, SM1



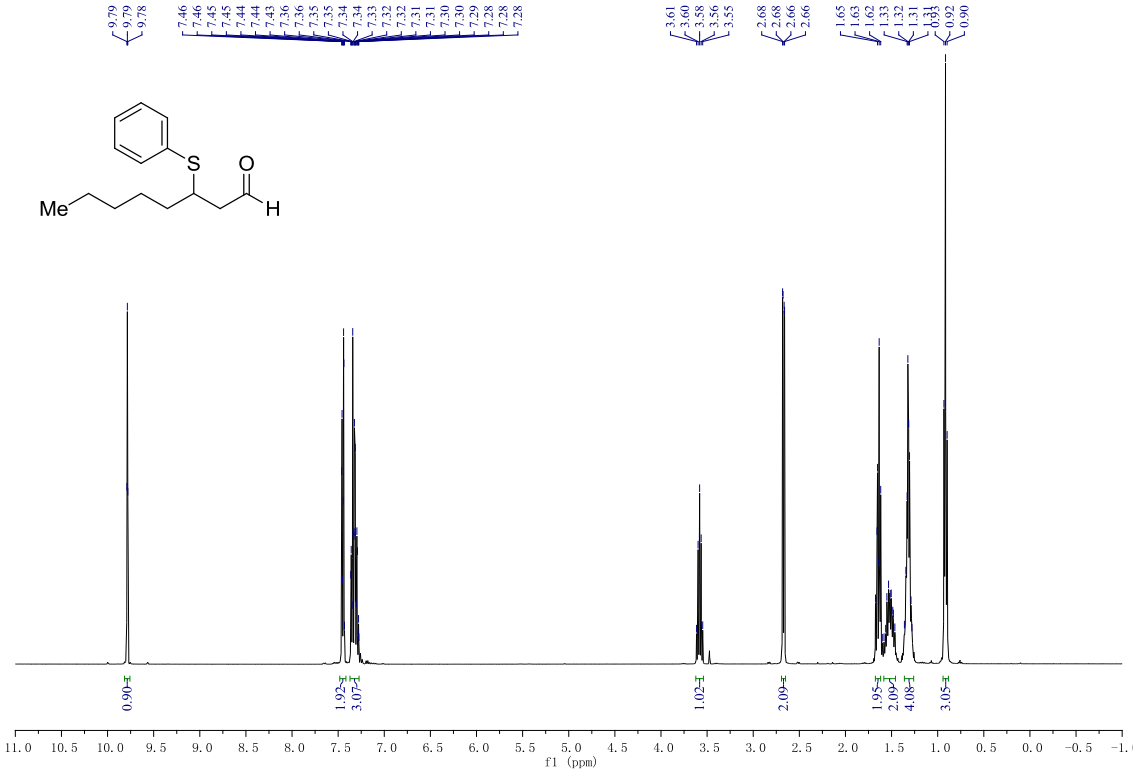


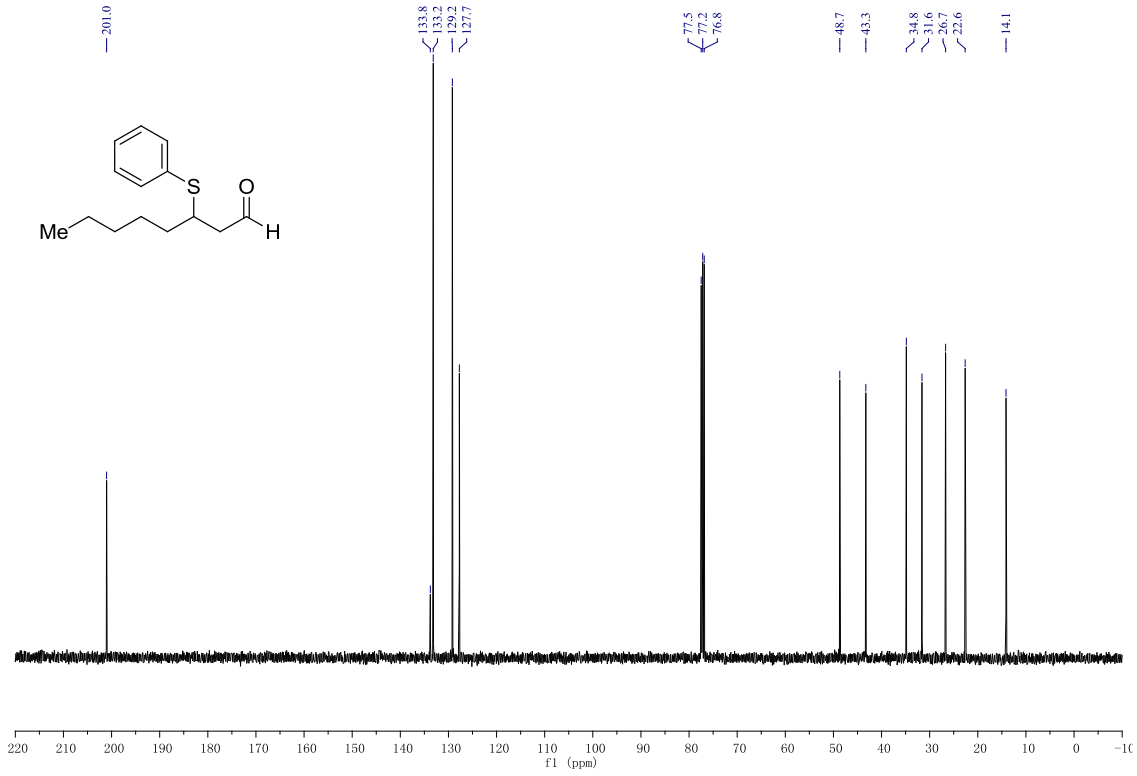
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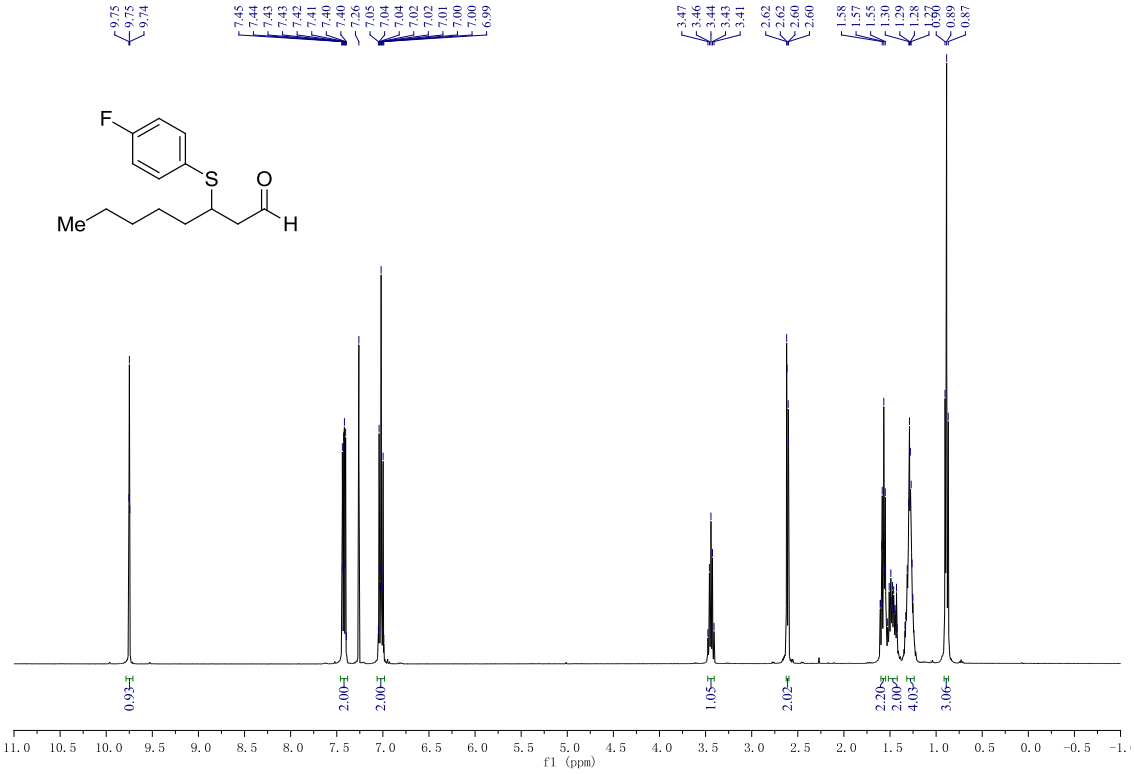


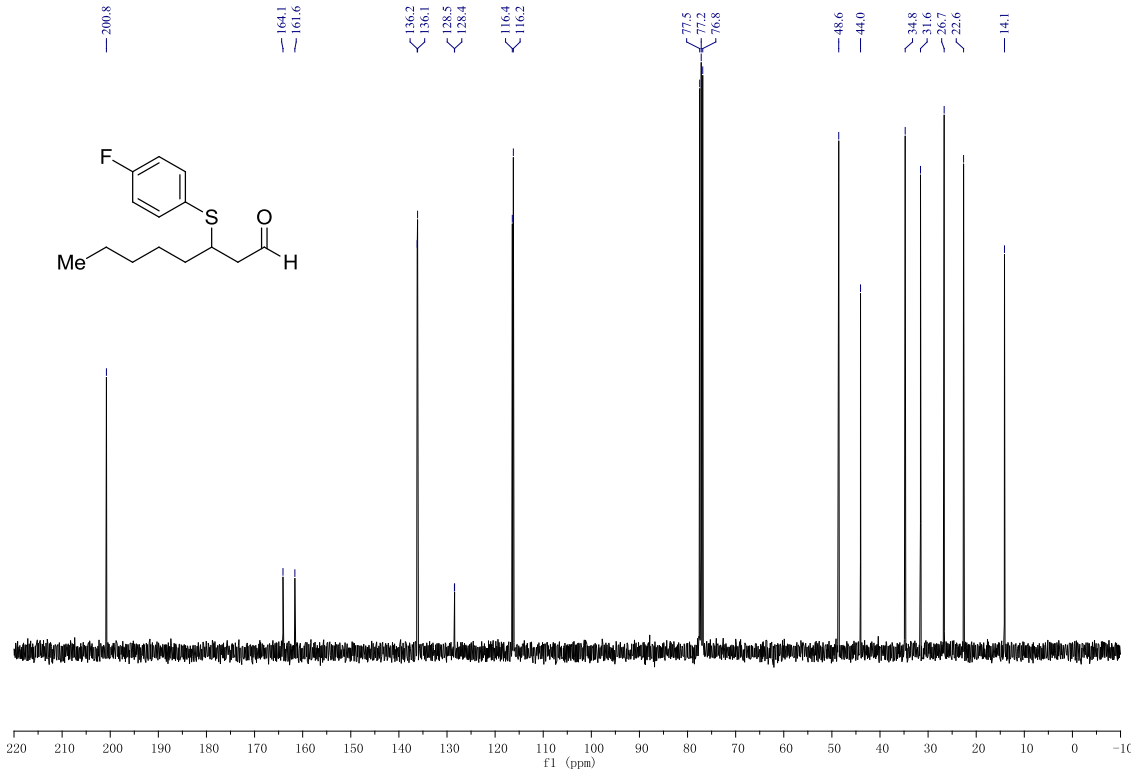
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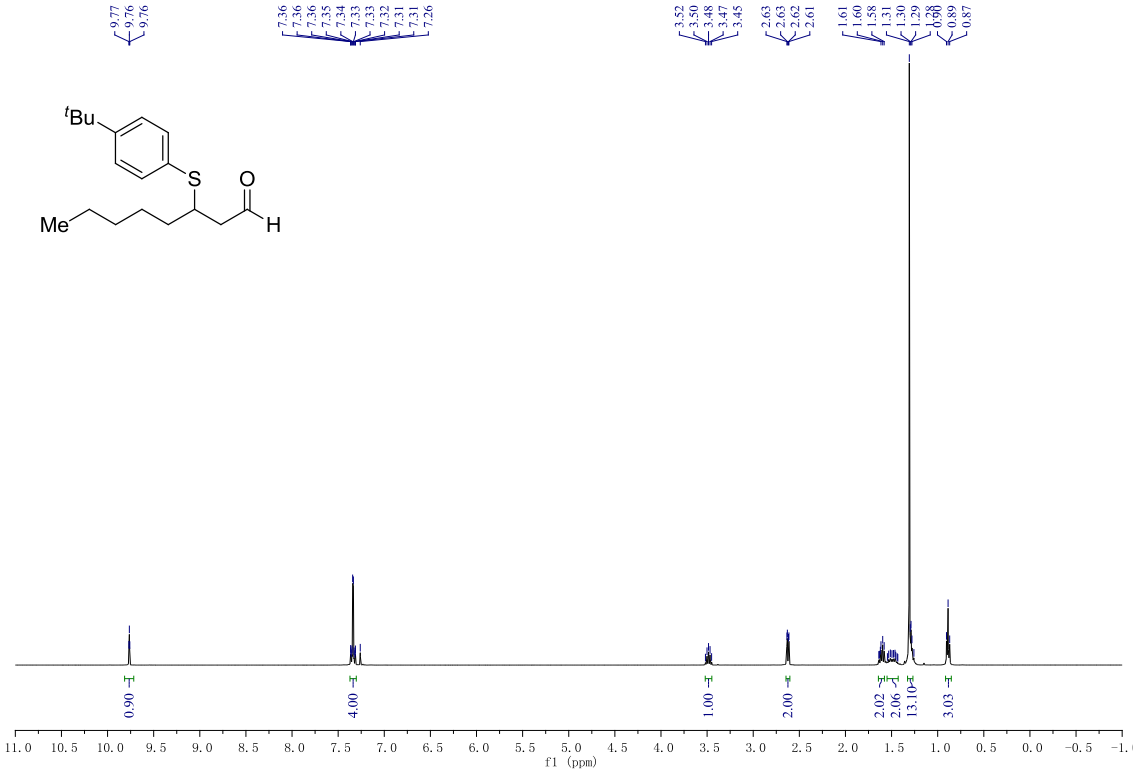


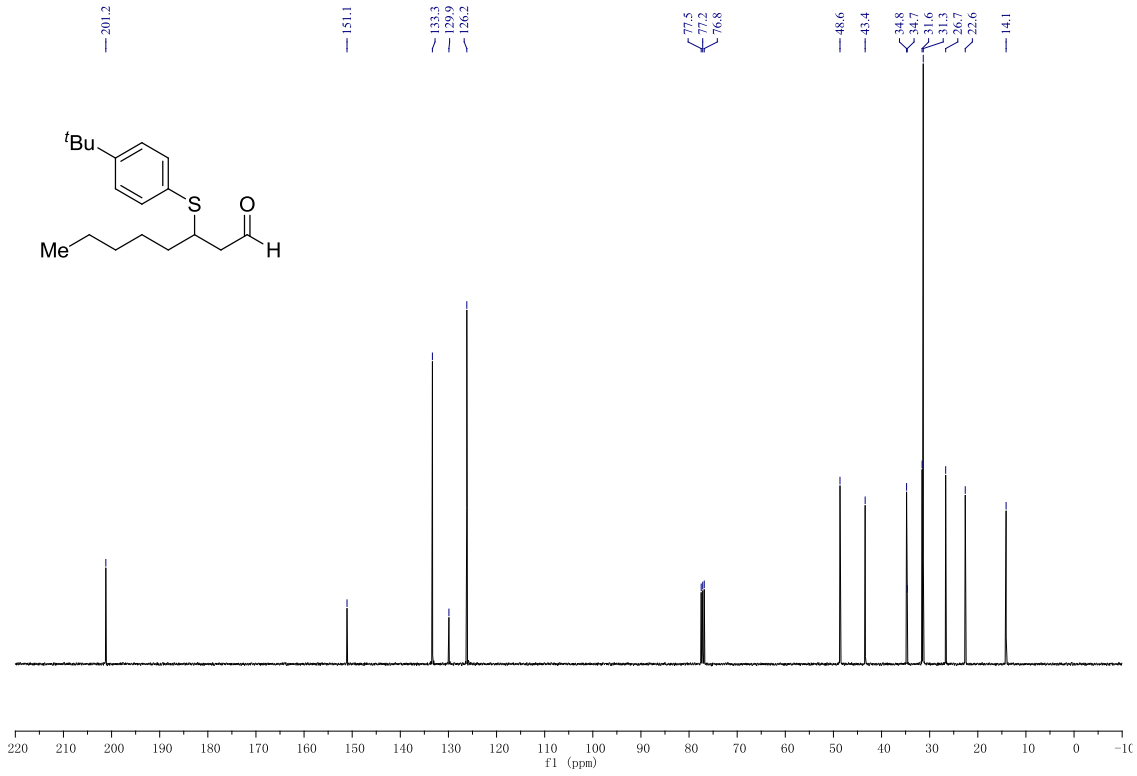
3-((4-Fluorophenyl)thio)octanal, 1c



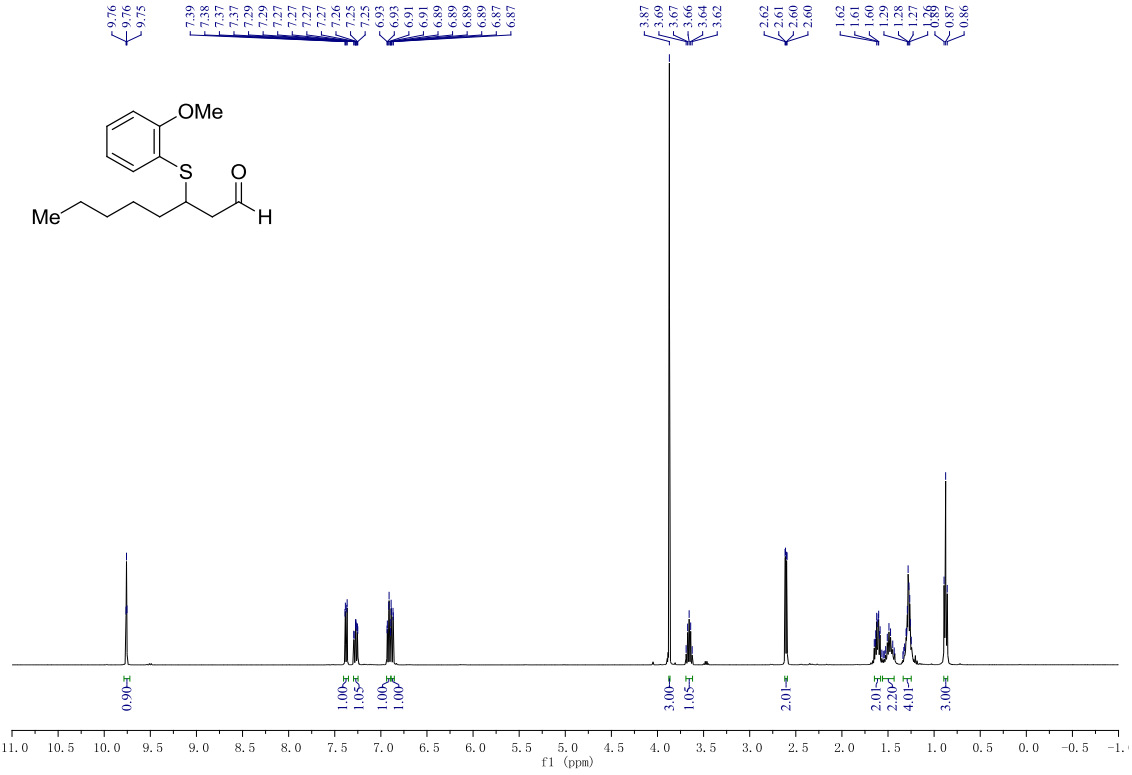


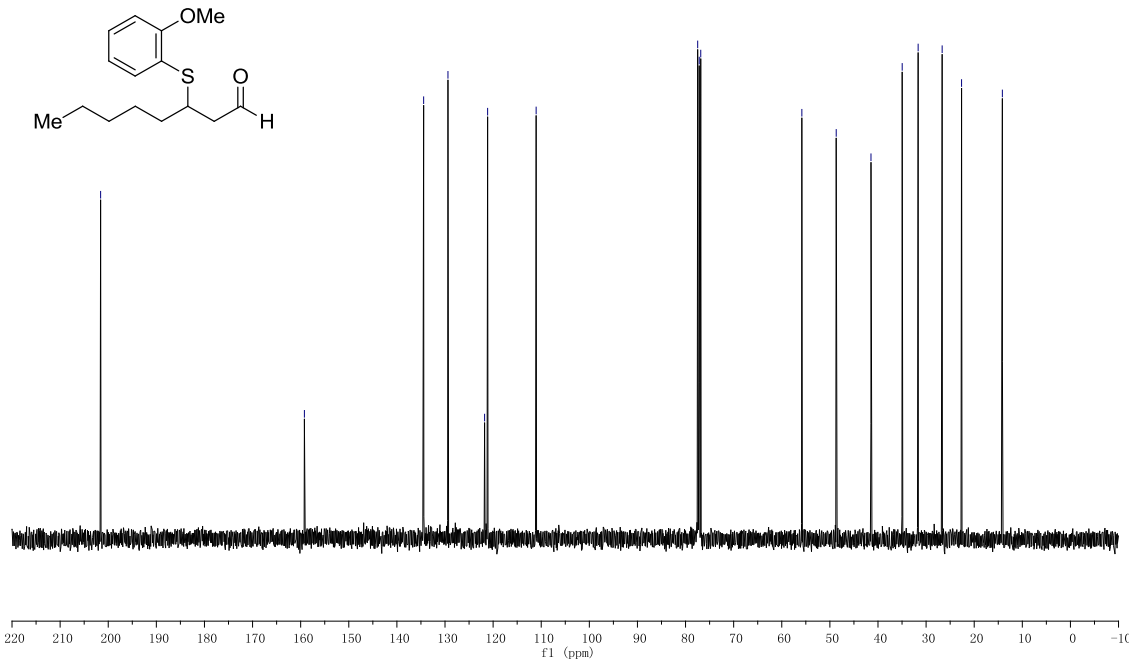
3-((4-(*tert*-Butyl)phenyl)thio)octanal, 1d



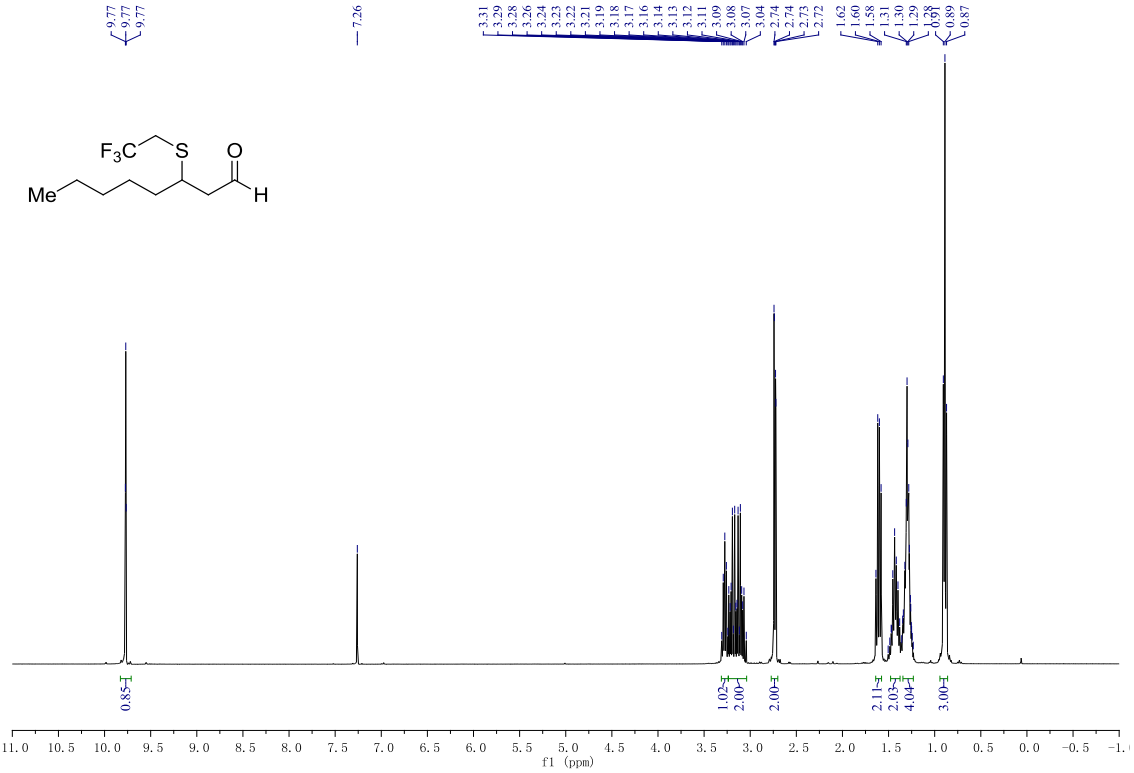


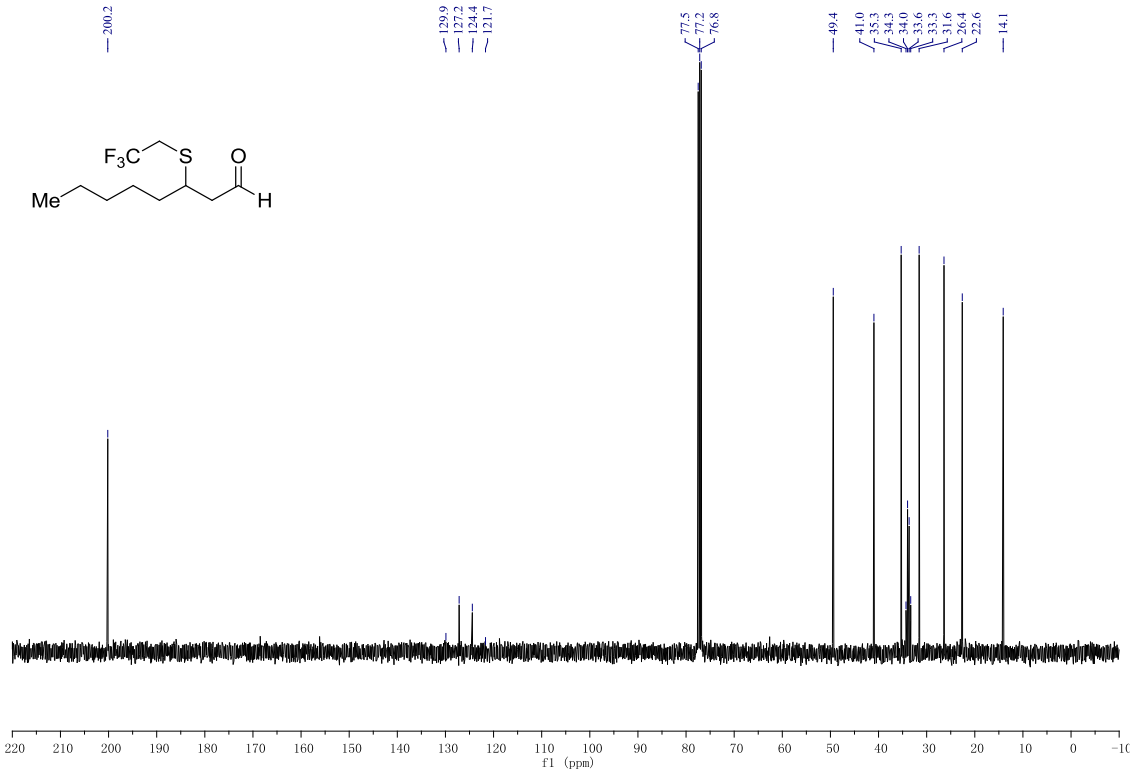
3-((2-Methoxyphenyl)thio)octanal, 1e



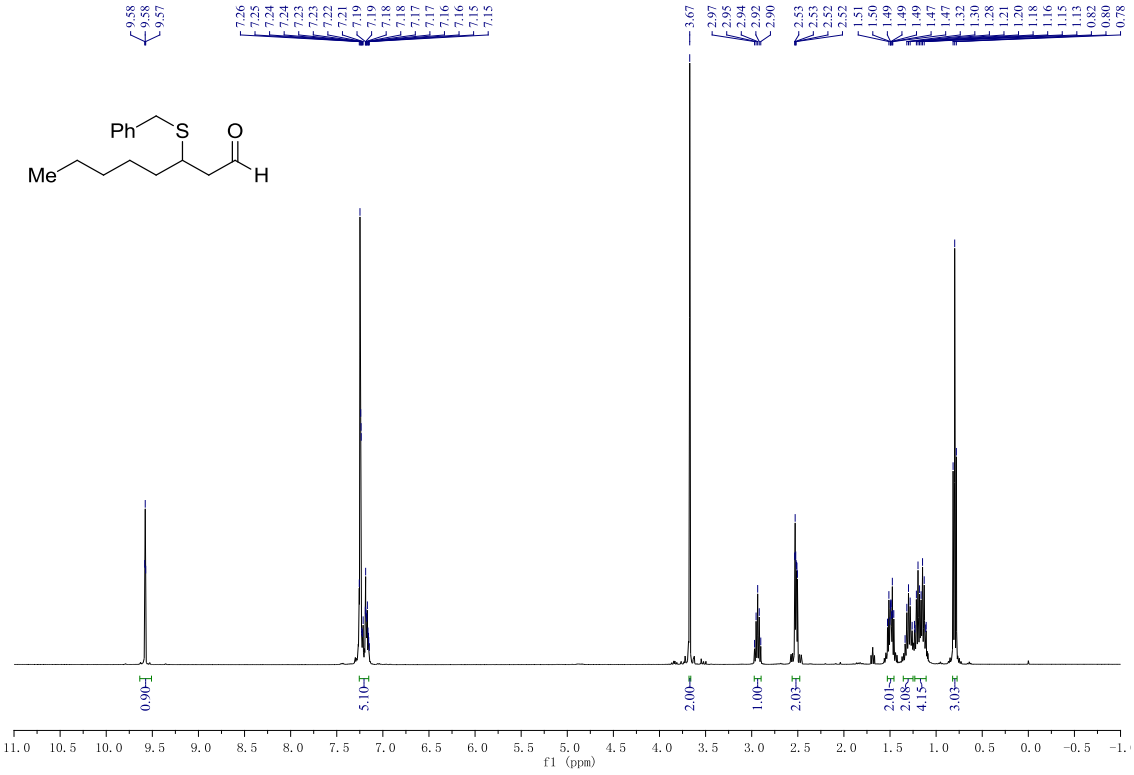


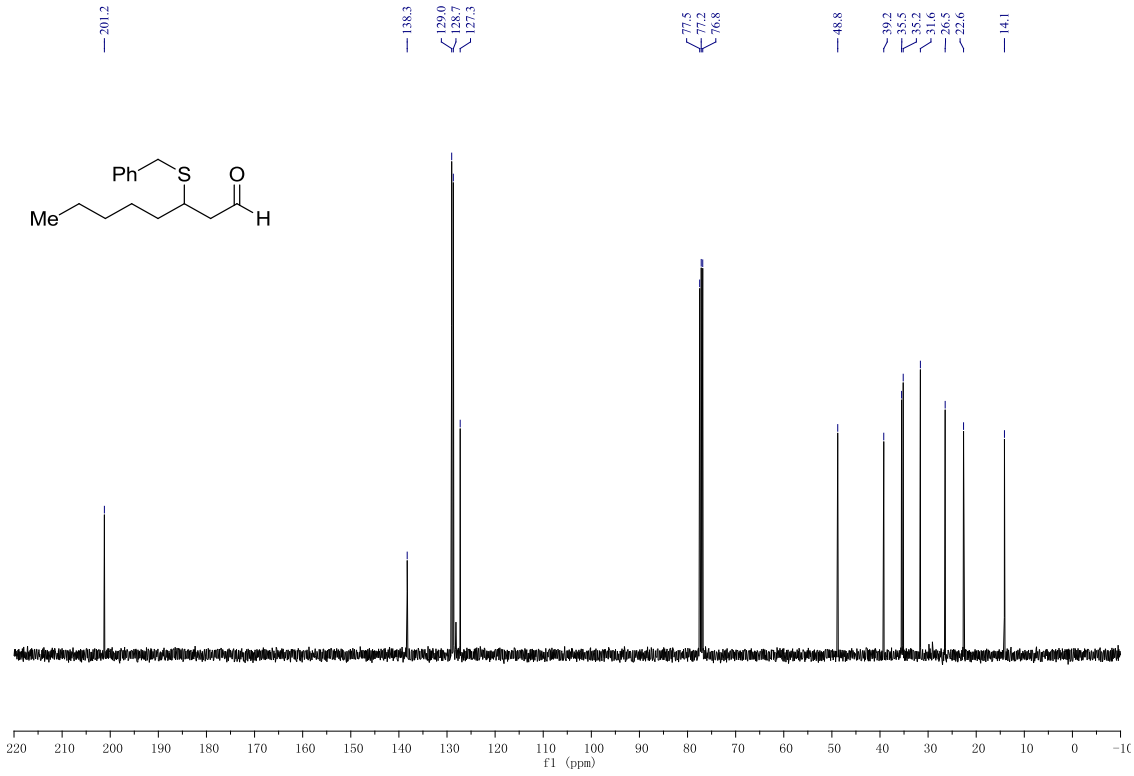
3-((2,2,2-Trifluoroethyl)thio)octanal, 1f



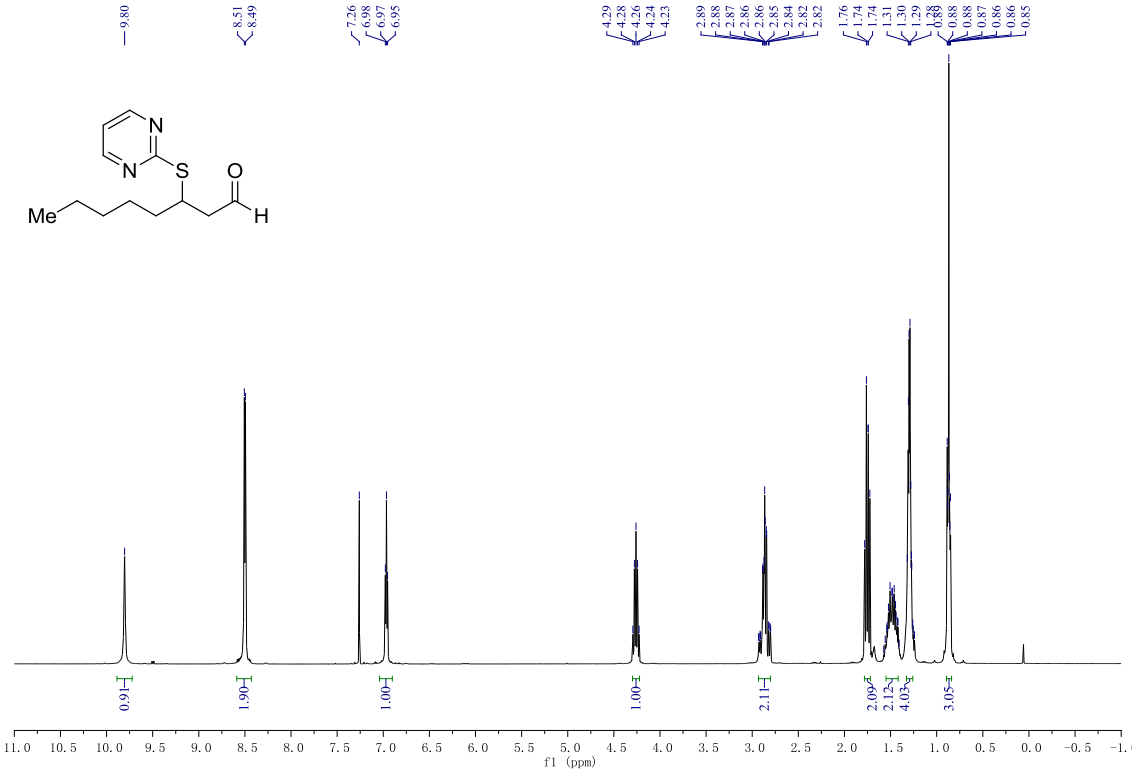


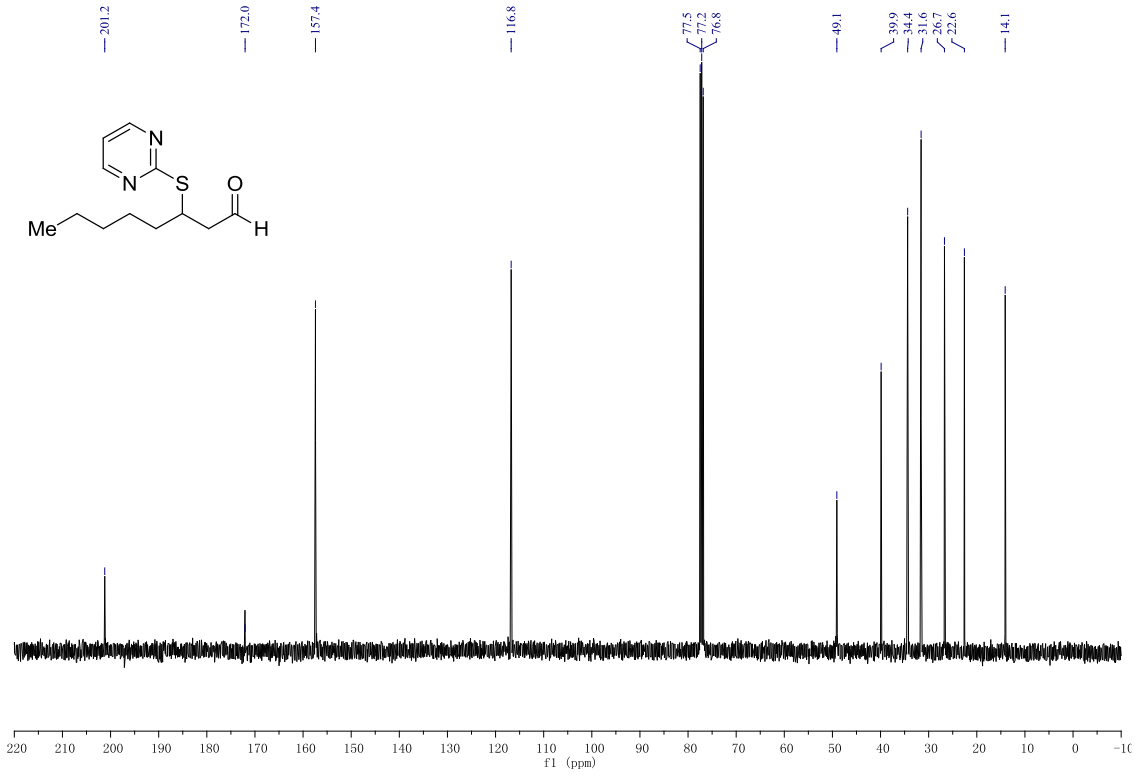
3-(Benzylthio)octanal, 1g



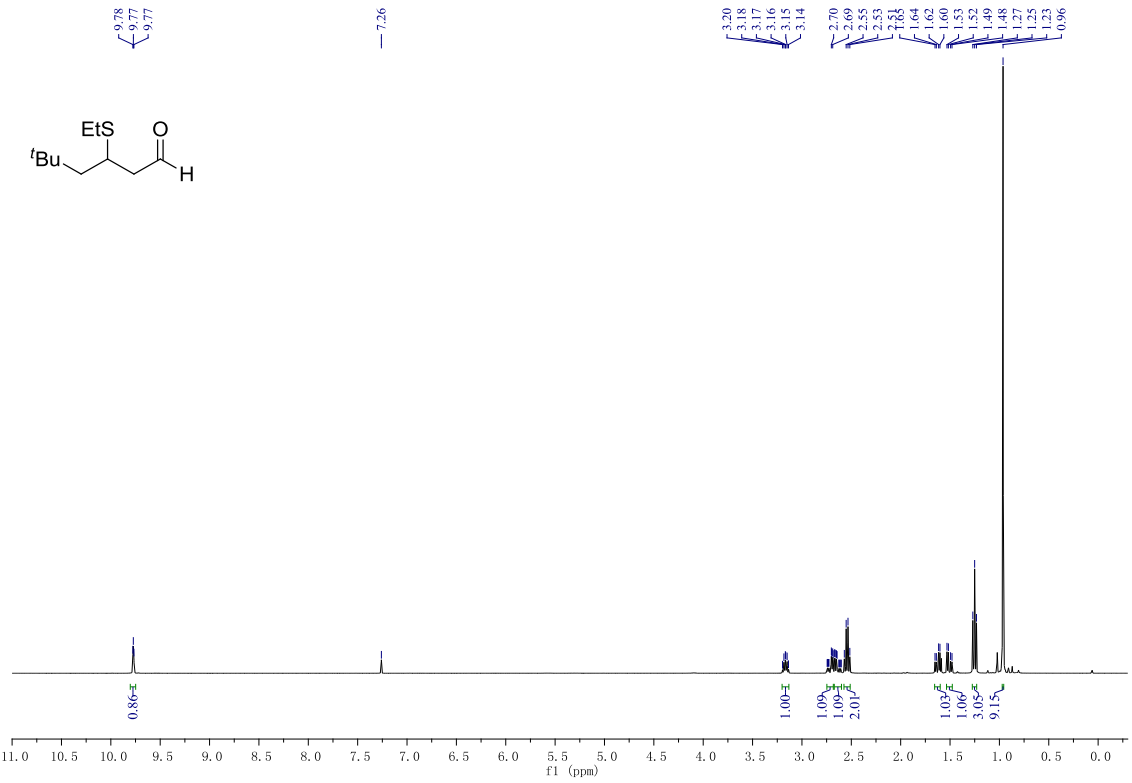


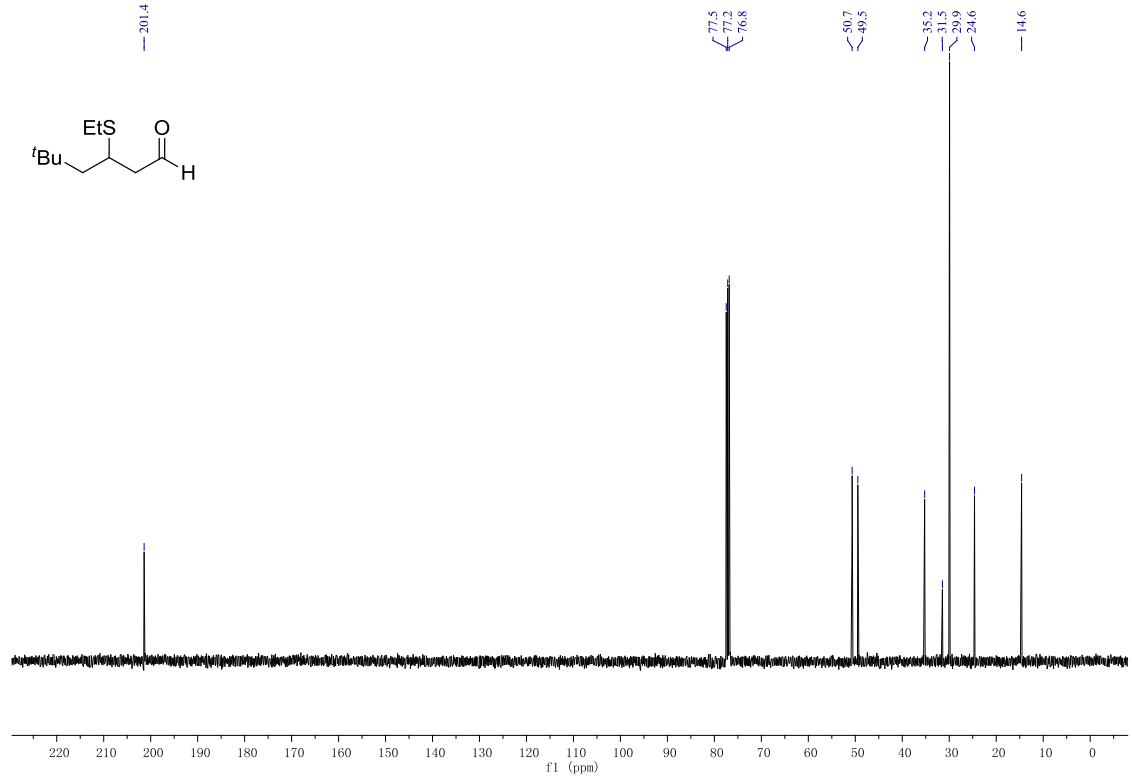
3-(Pyrimidin-2-ylthio)octanal, 1h



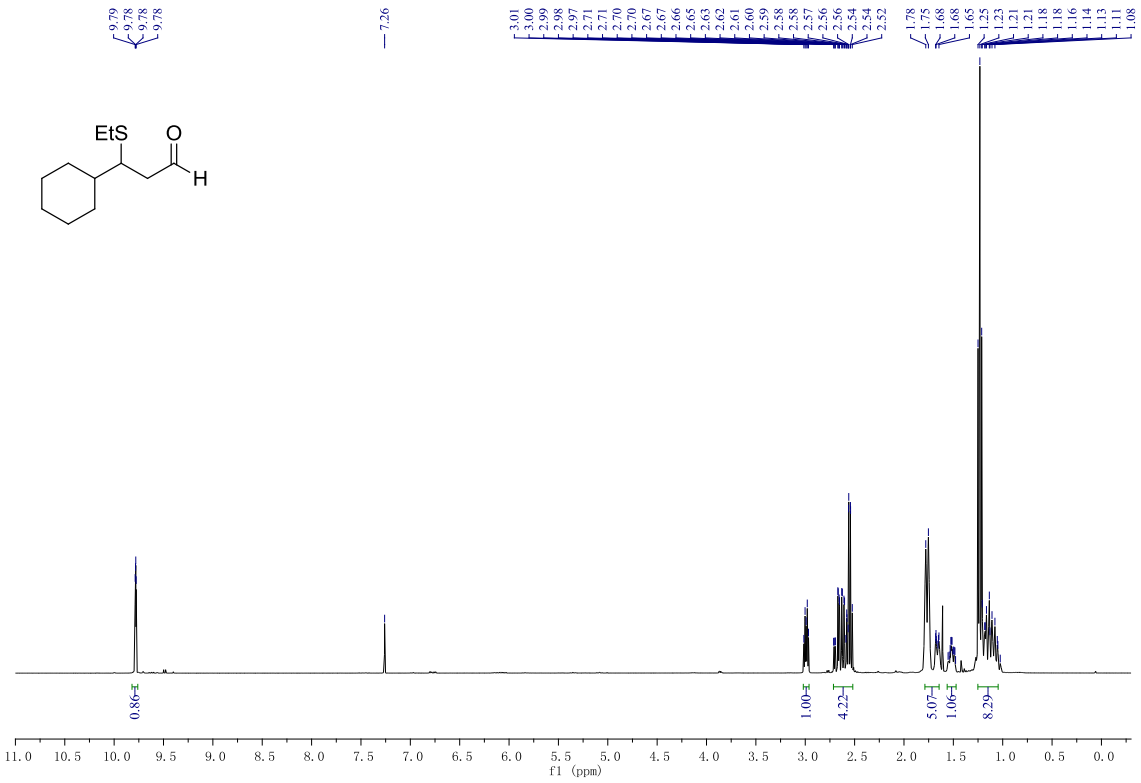


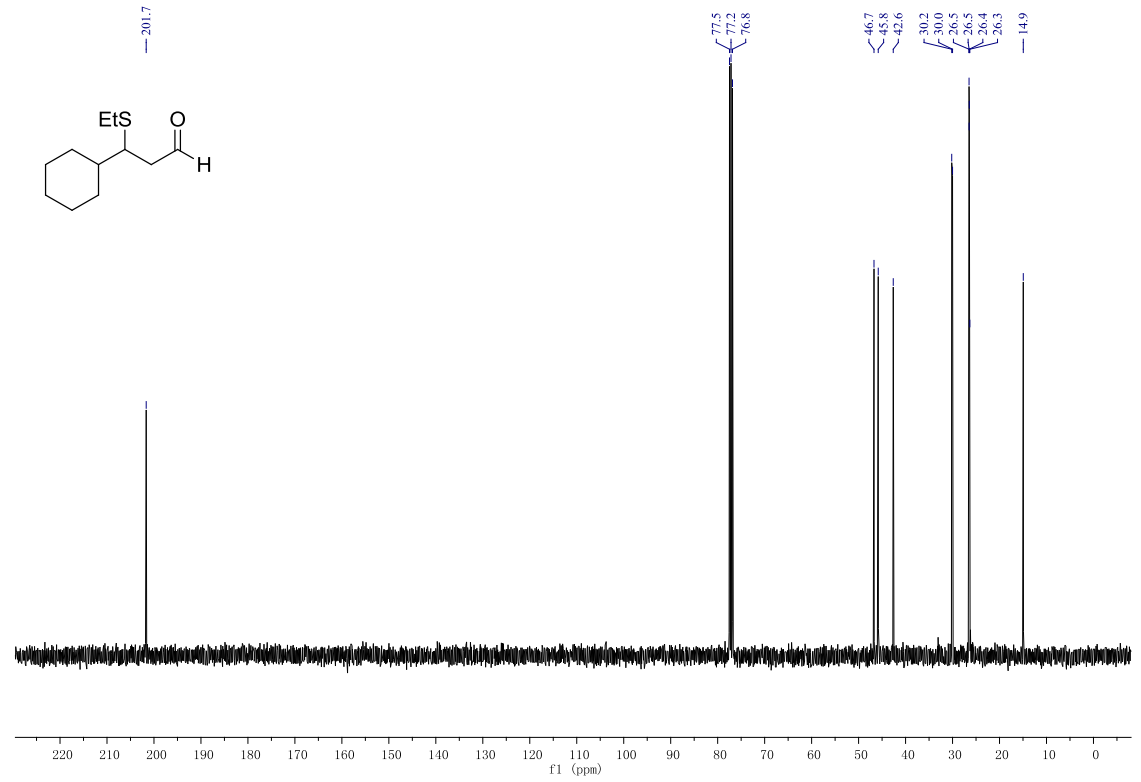
3-(Ethylthio)-5,5-dimethylhexanal, 1j



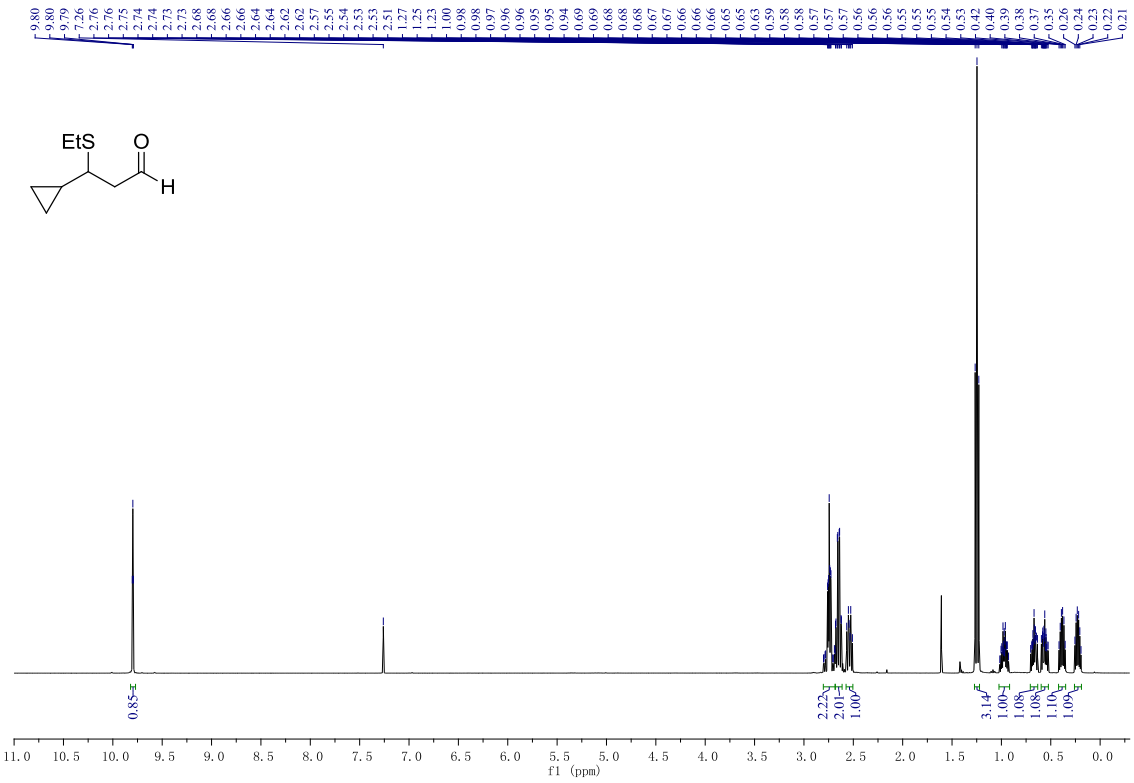


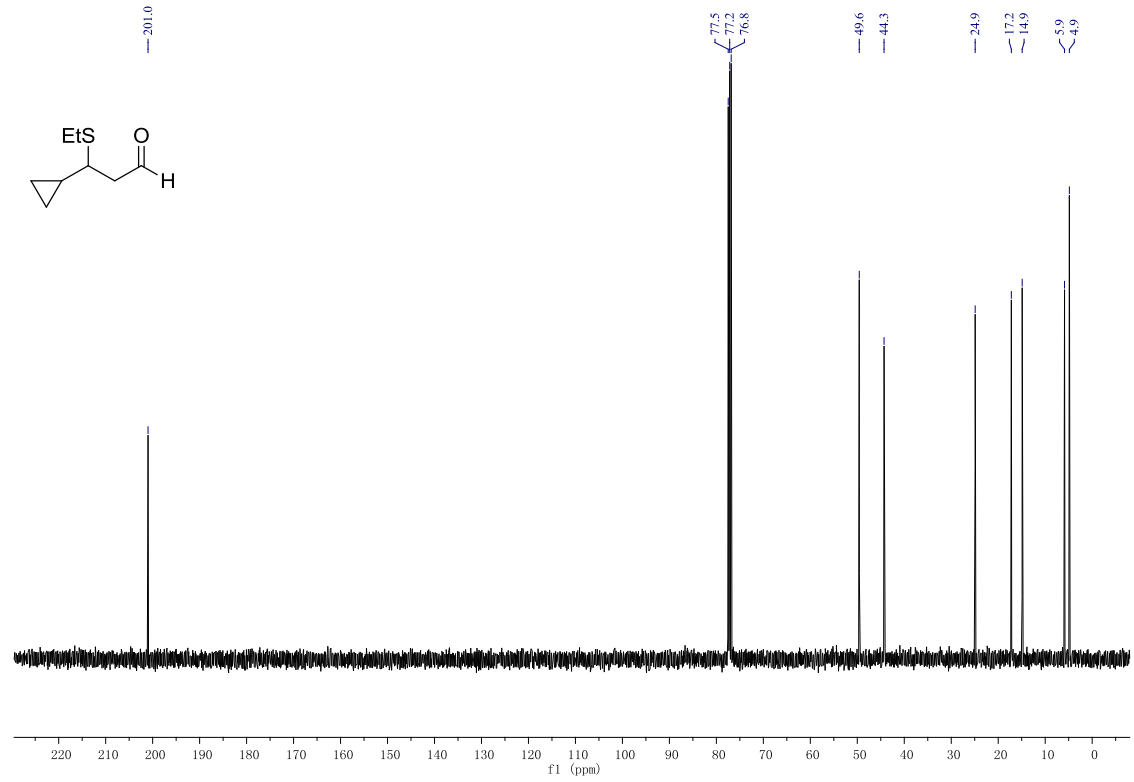
3-Cyclohexyl-3-(ethylthio)propanal, 1k



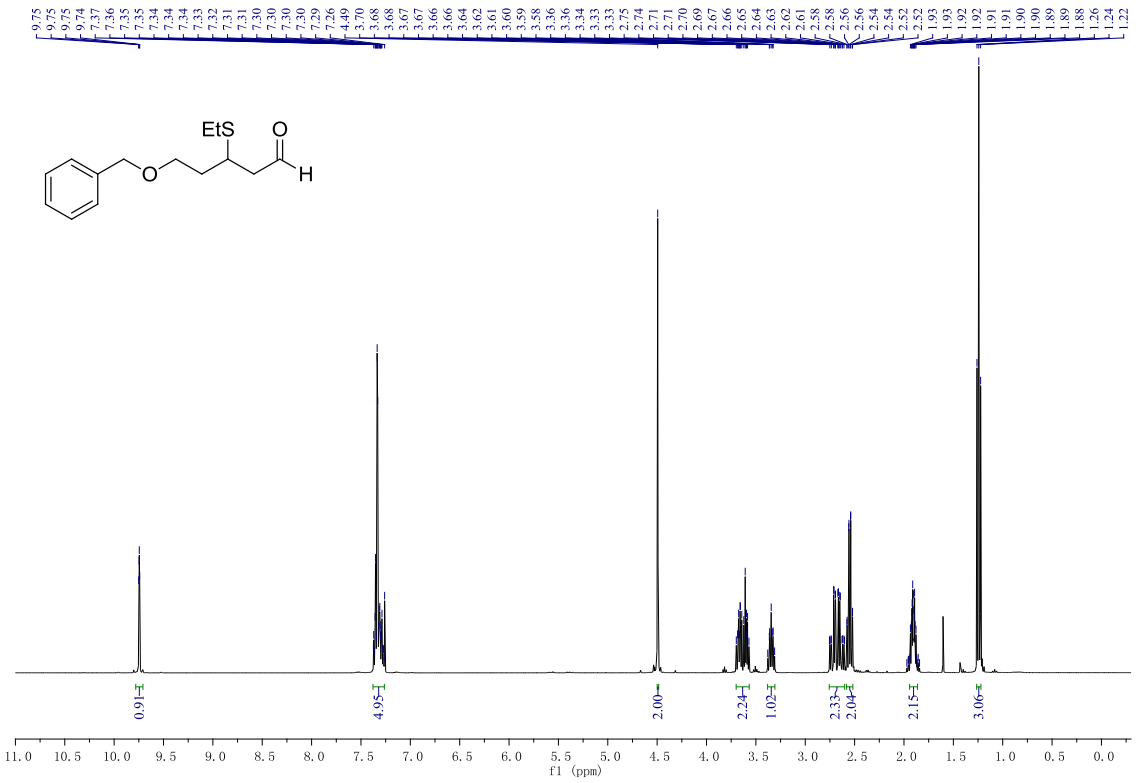


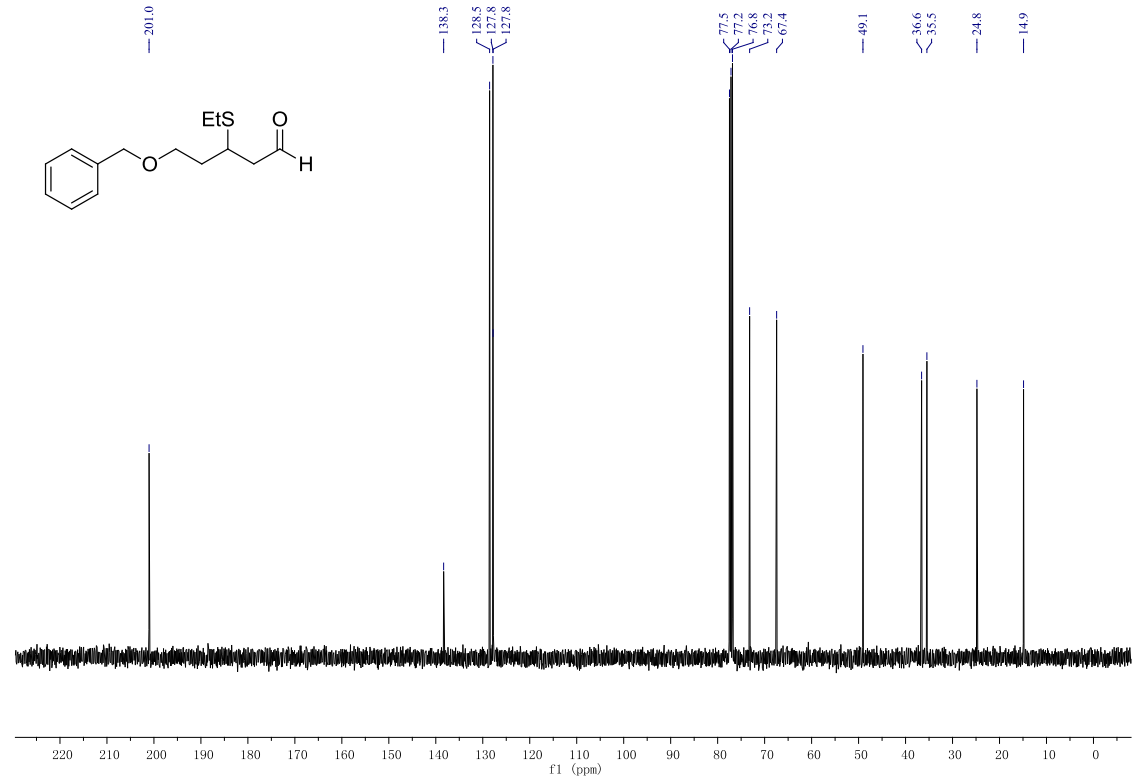
3-Cyclopropyl-3-(ethylthio)propanal, 1l



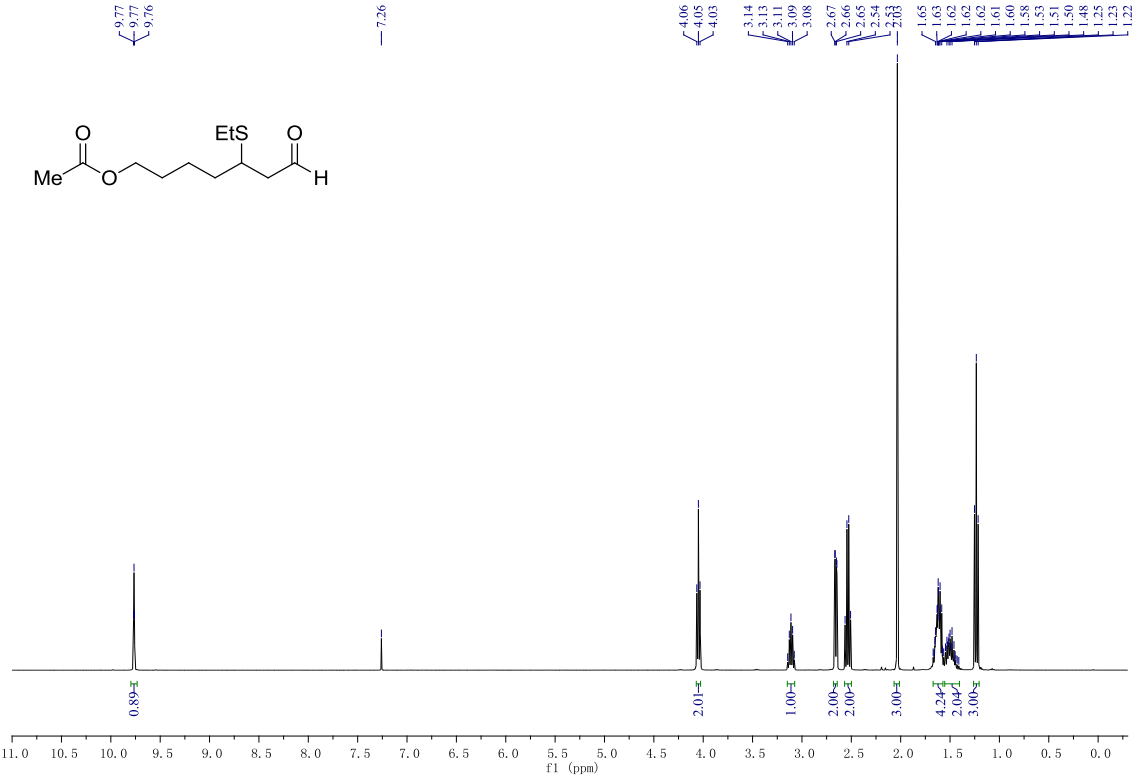


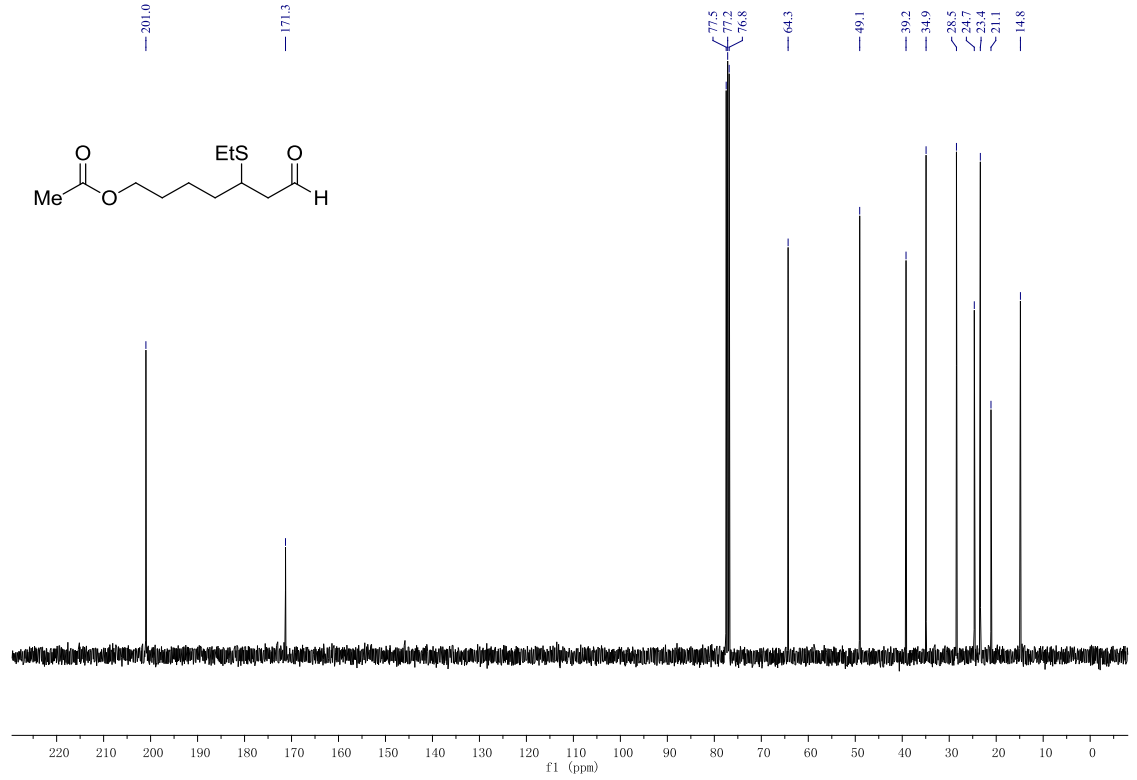
5-(Benzyloxy)-3-(ethylthio)pentanal, 1q



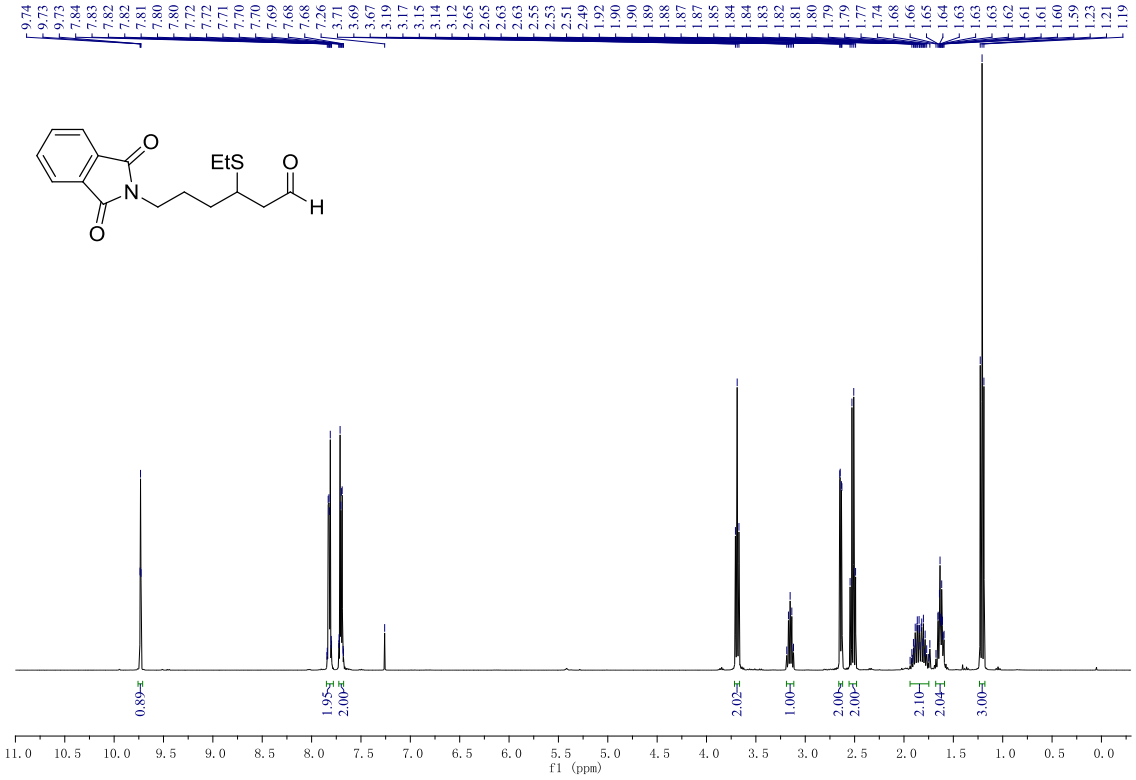


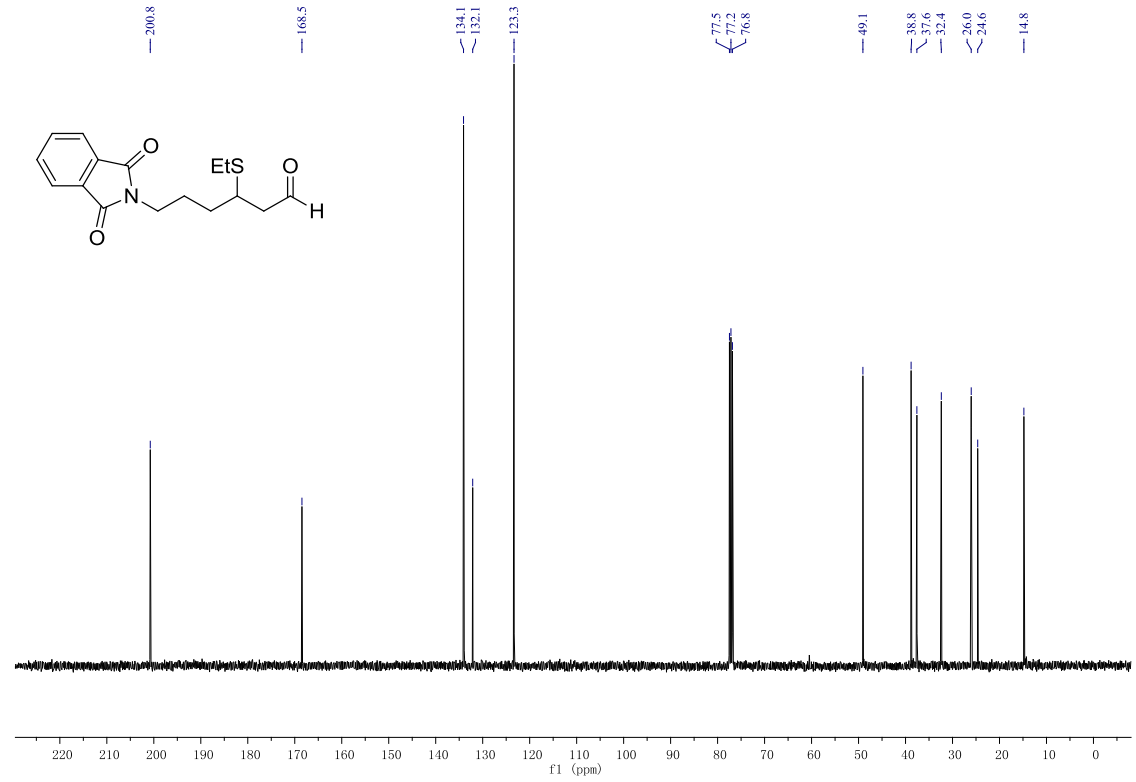
5-(Ethylthio)-7-oxoheptyl acetate, 1r



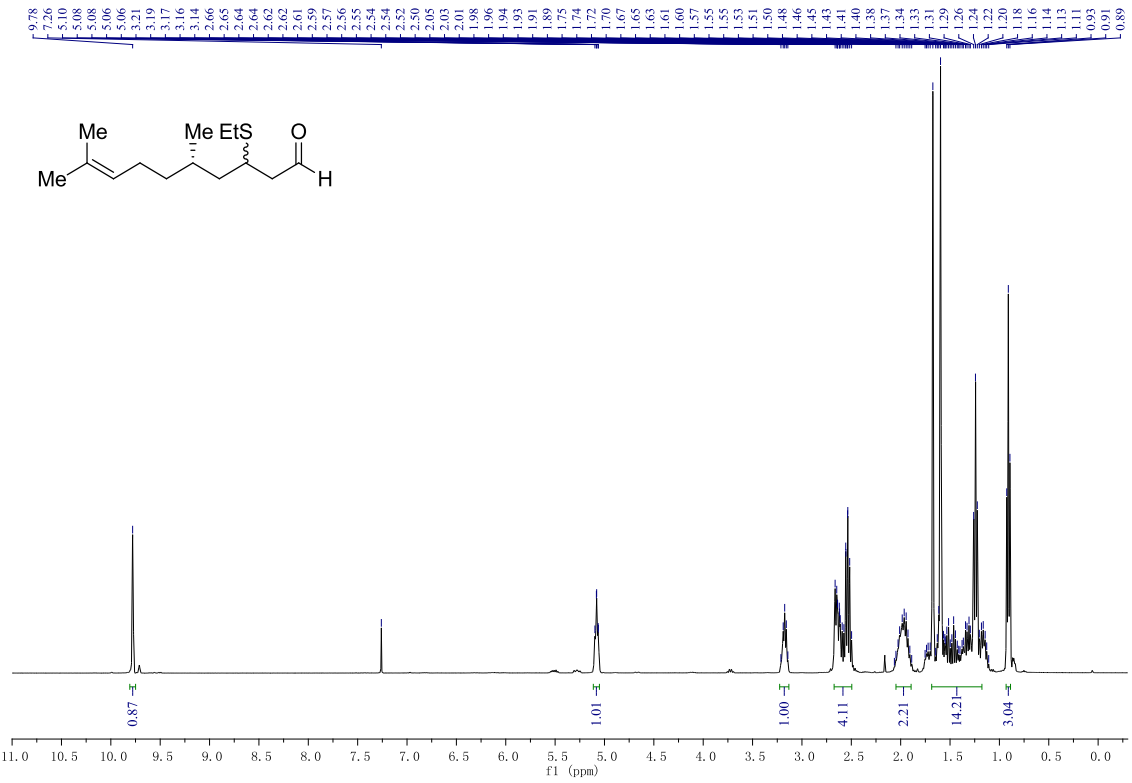


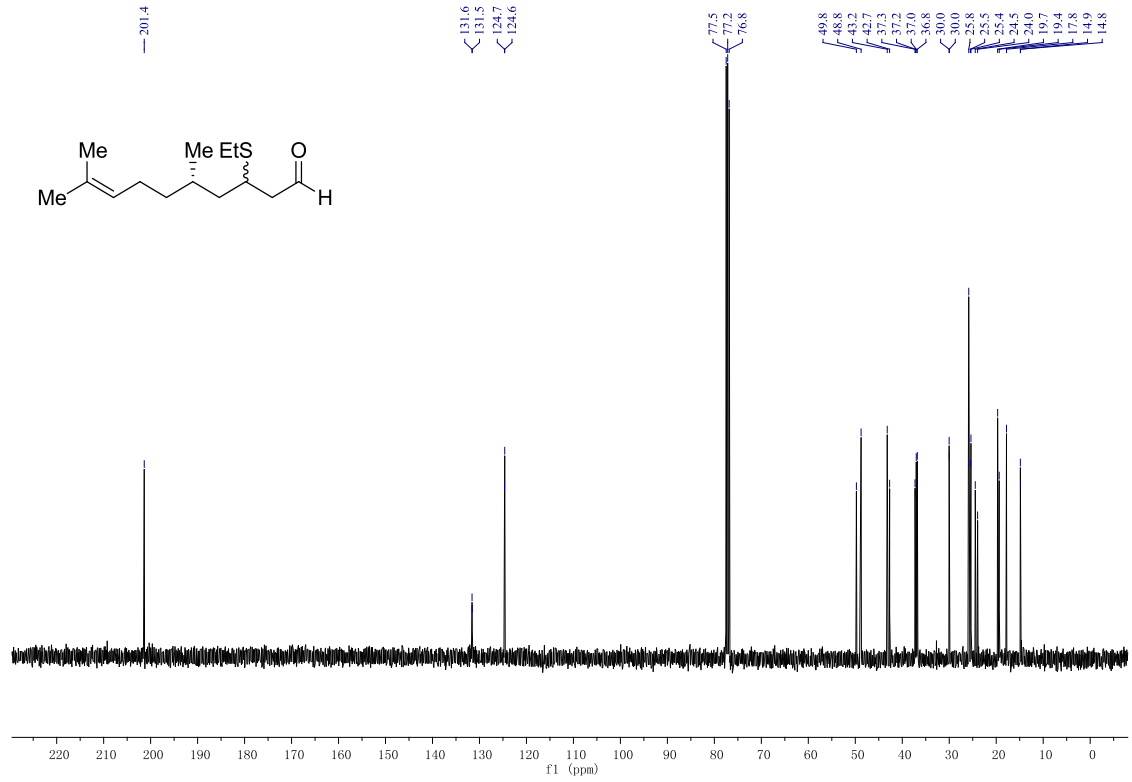
6-(1,3-Dioxoisoindolin-2-yl)-3-(ethylthio)hexanal, 1s



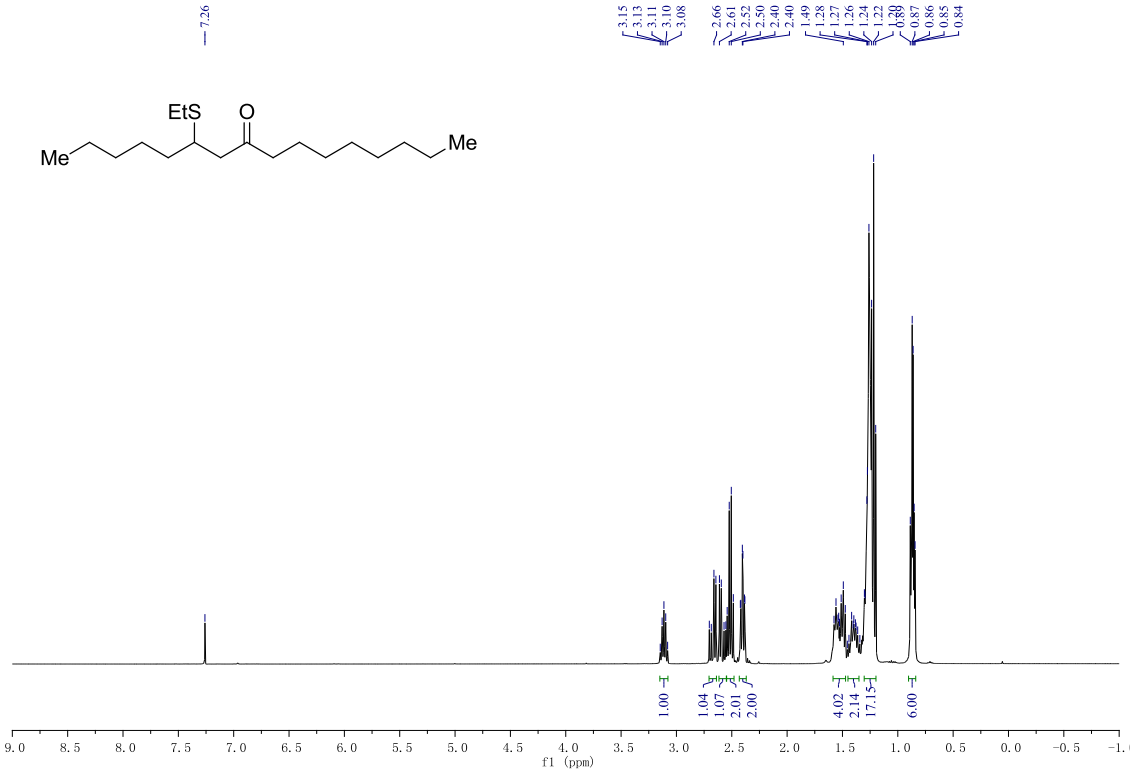


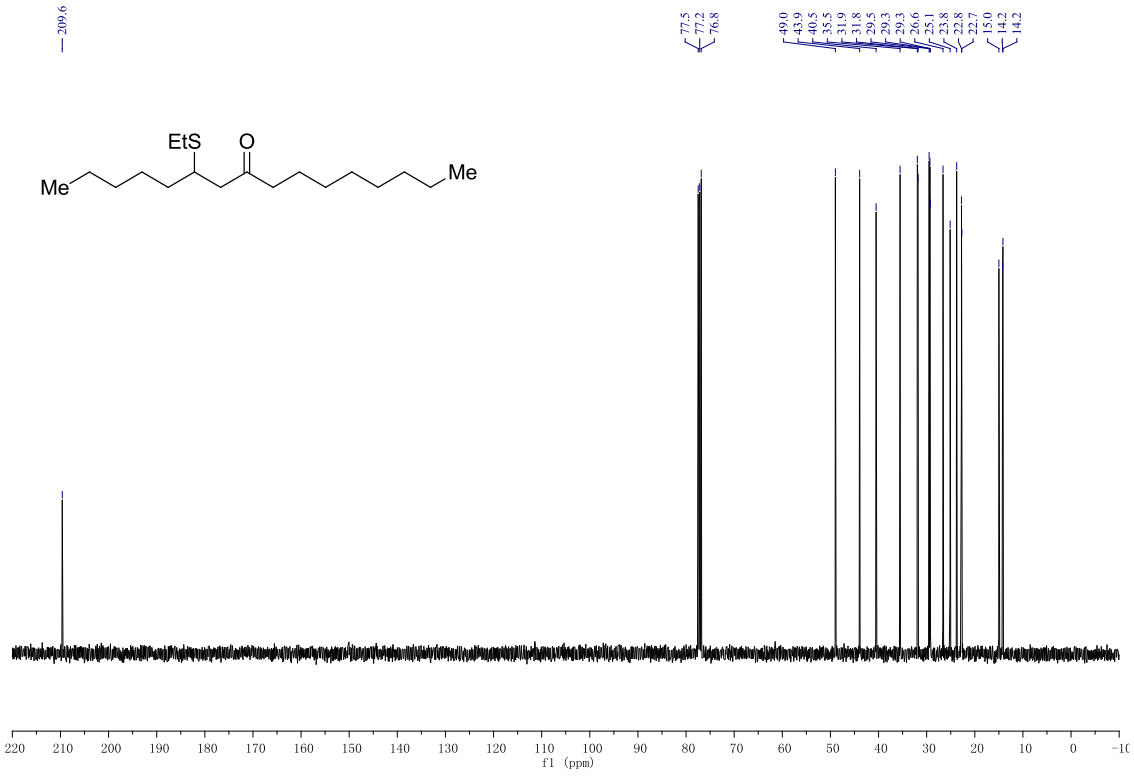
(5*S*)-3-(Ethylthio)-5,9-dimethyldec-8-enal, 1t



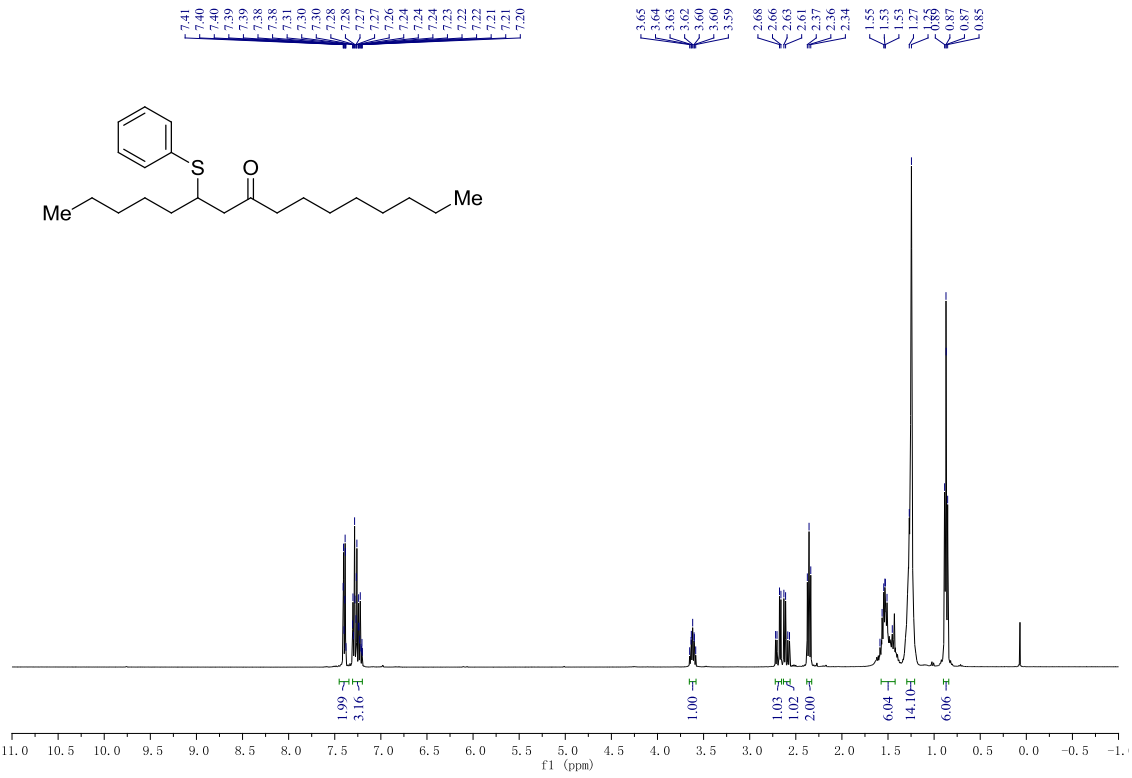


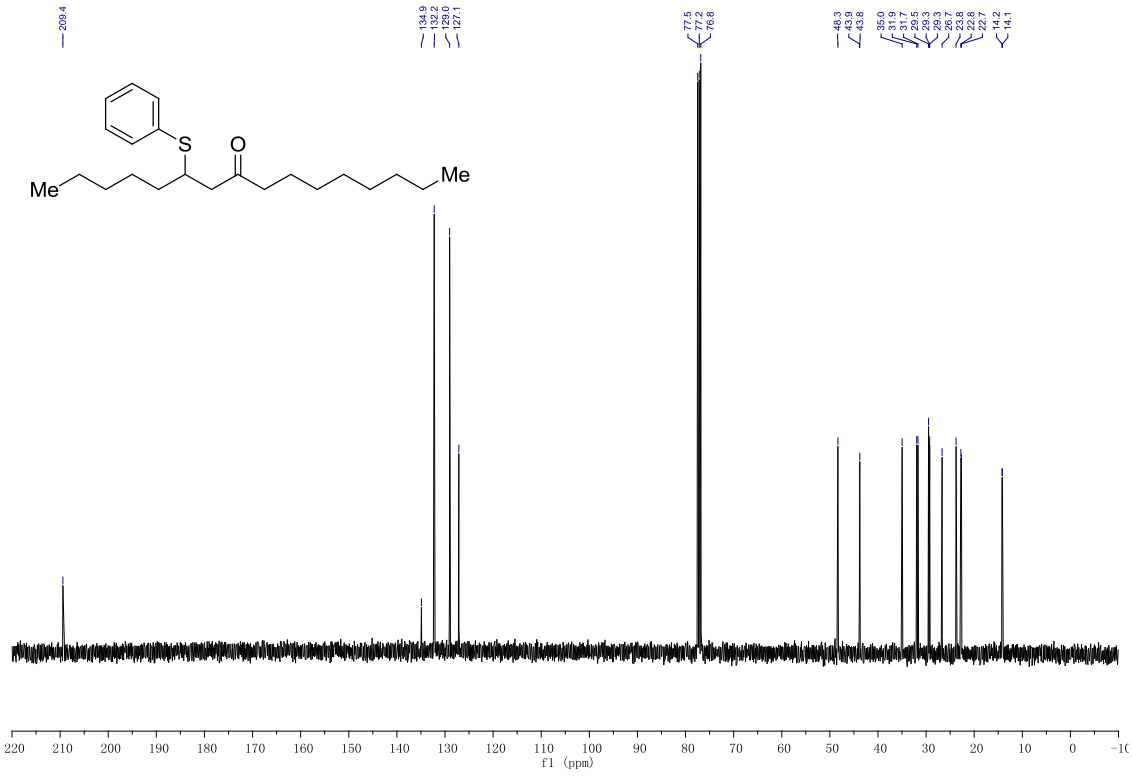
6-(Ethylthio)hexadecan-8-one, 2a



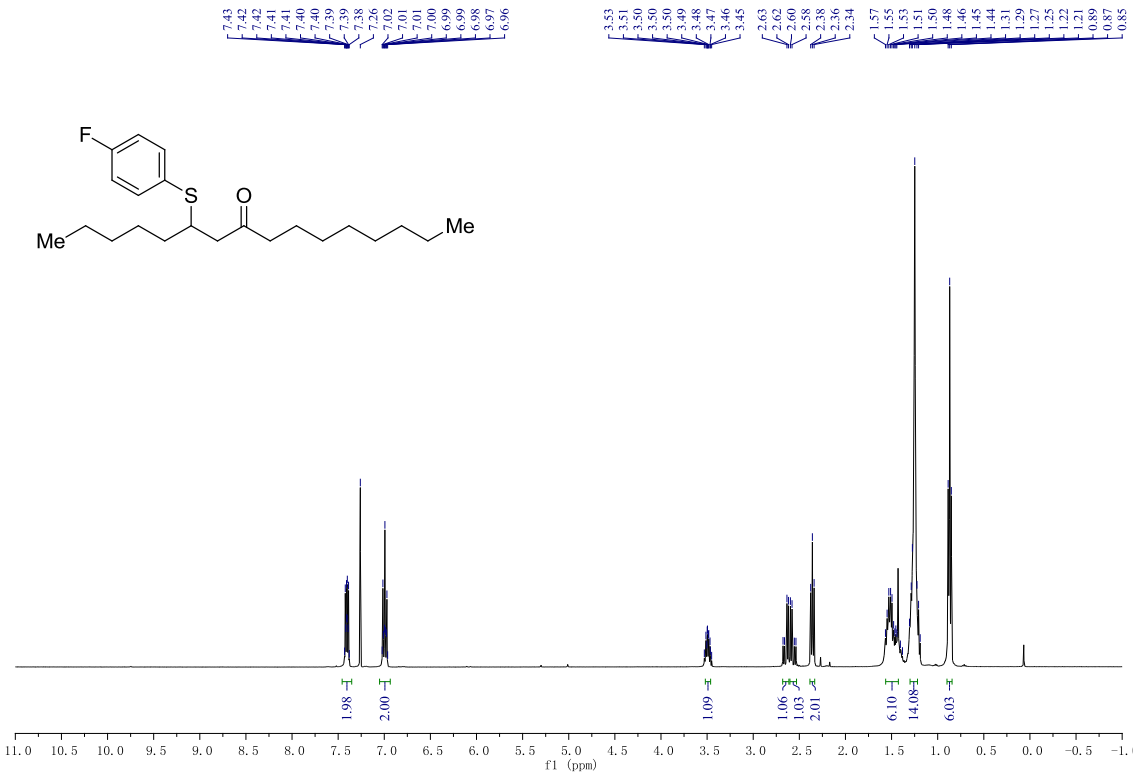


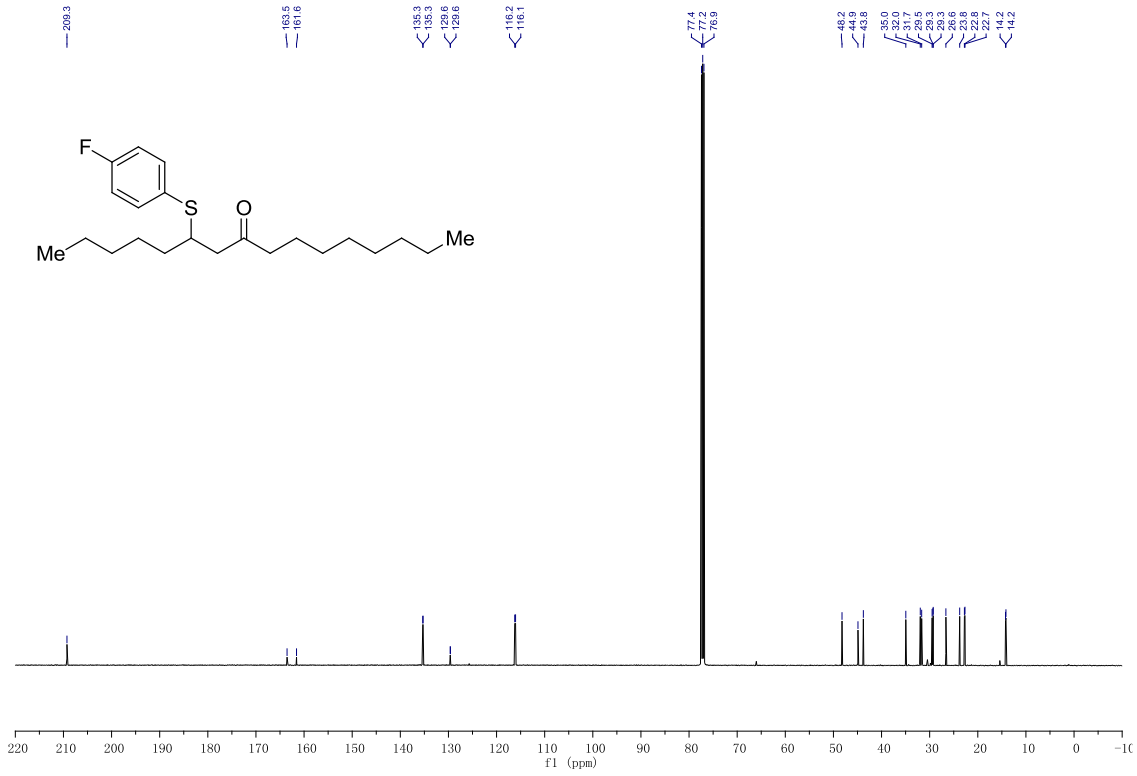
6-(Phenylthio)hexadecan-8-one, 2b



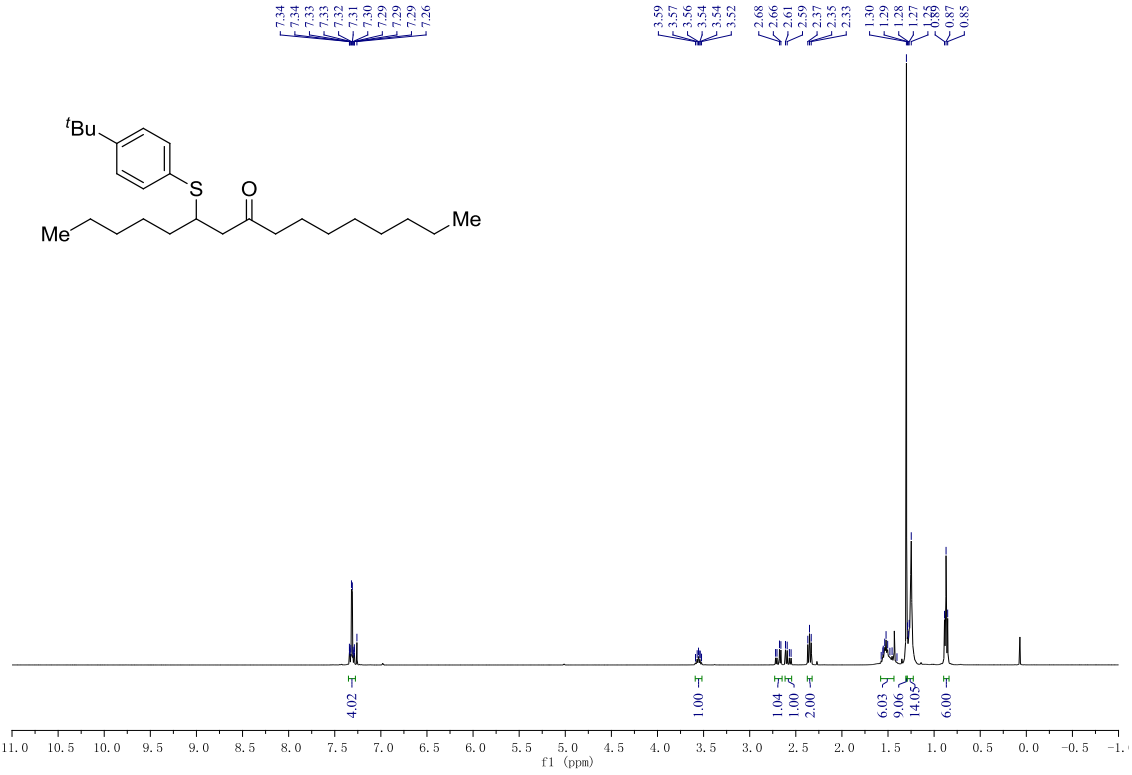


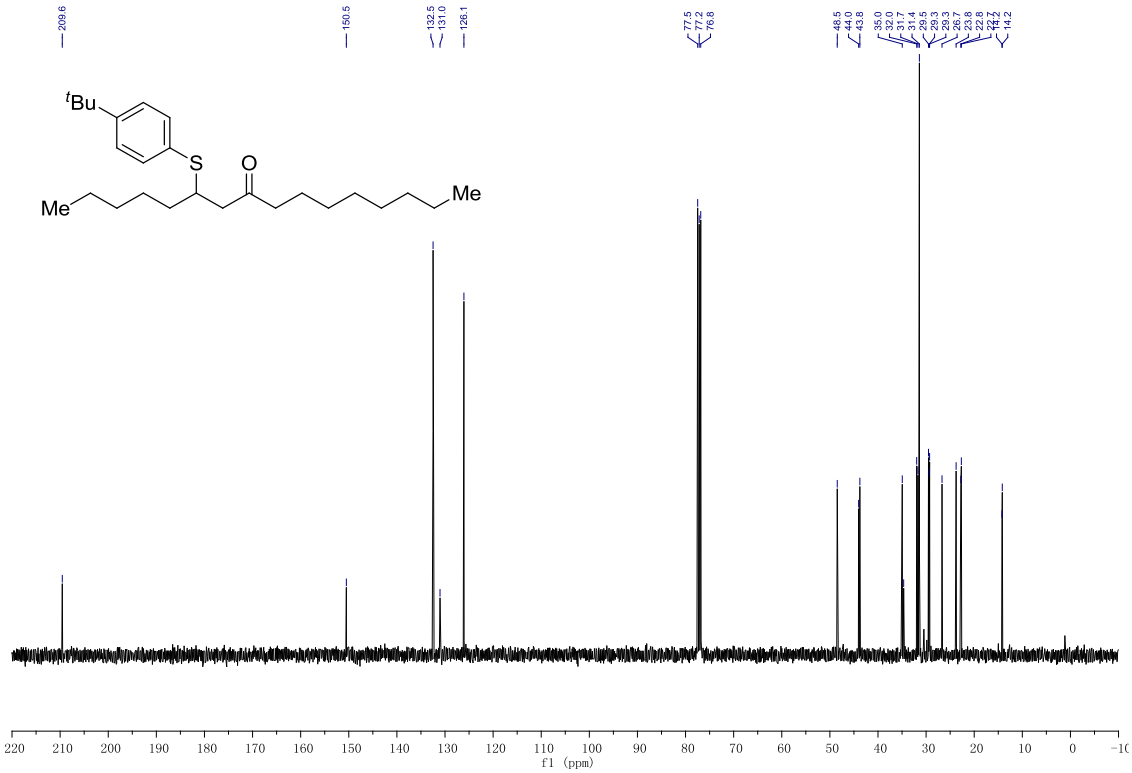
6-((4-Fluorophenyl)thio)hexadecan-8-one, 2c



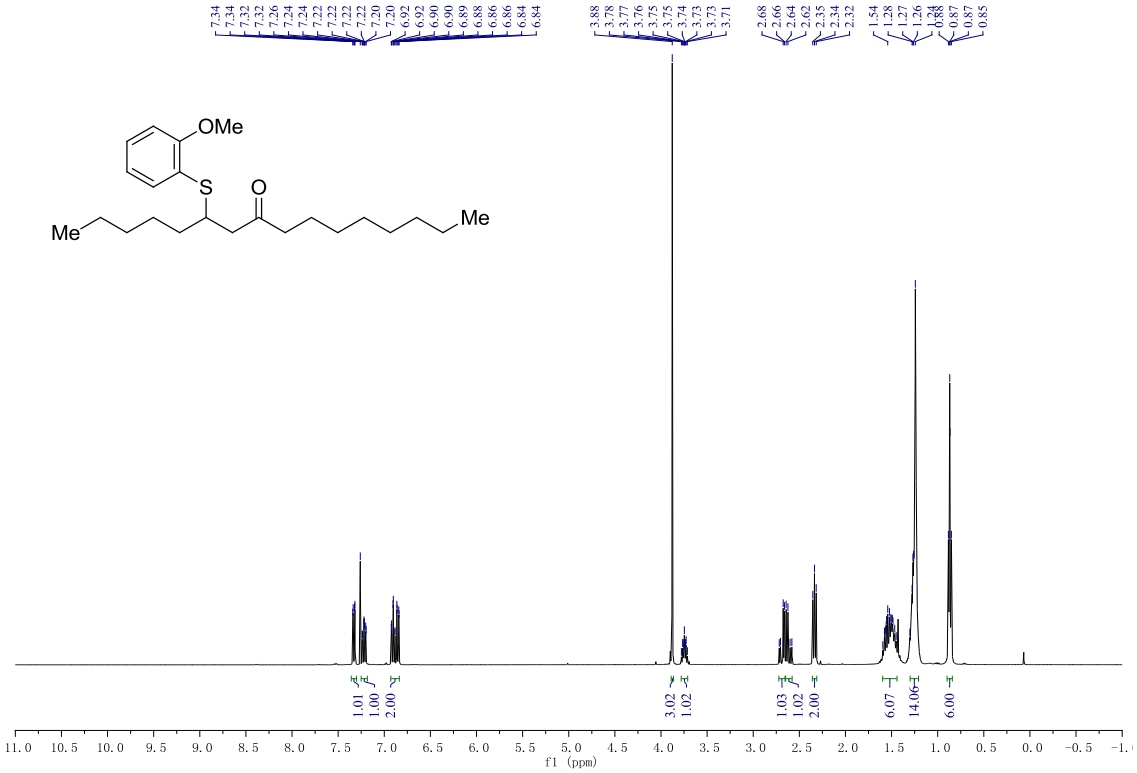


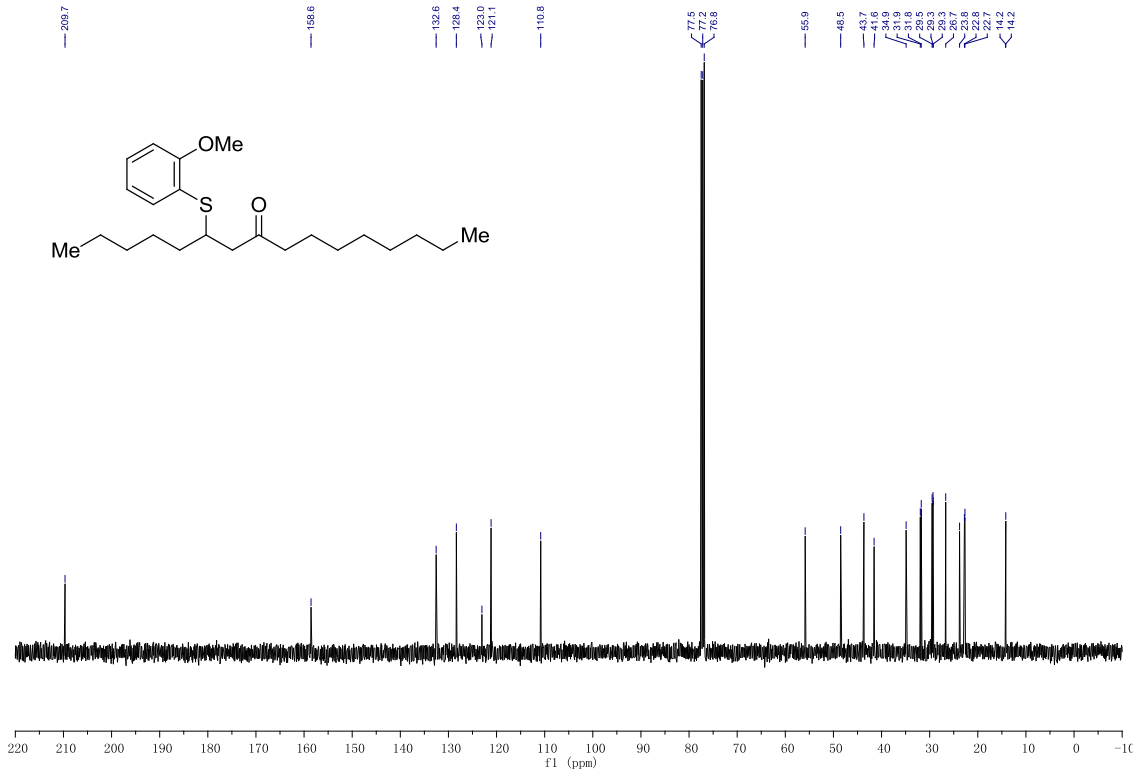
6-((4-(*tert*-Butyl)phenyl)thio)hexadecan-8-one, 2d



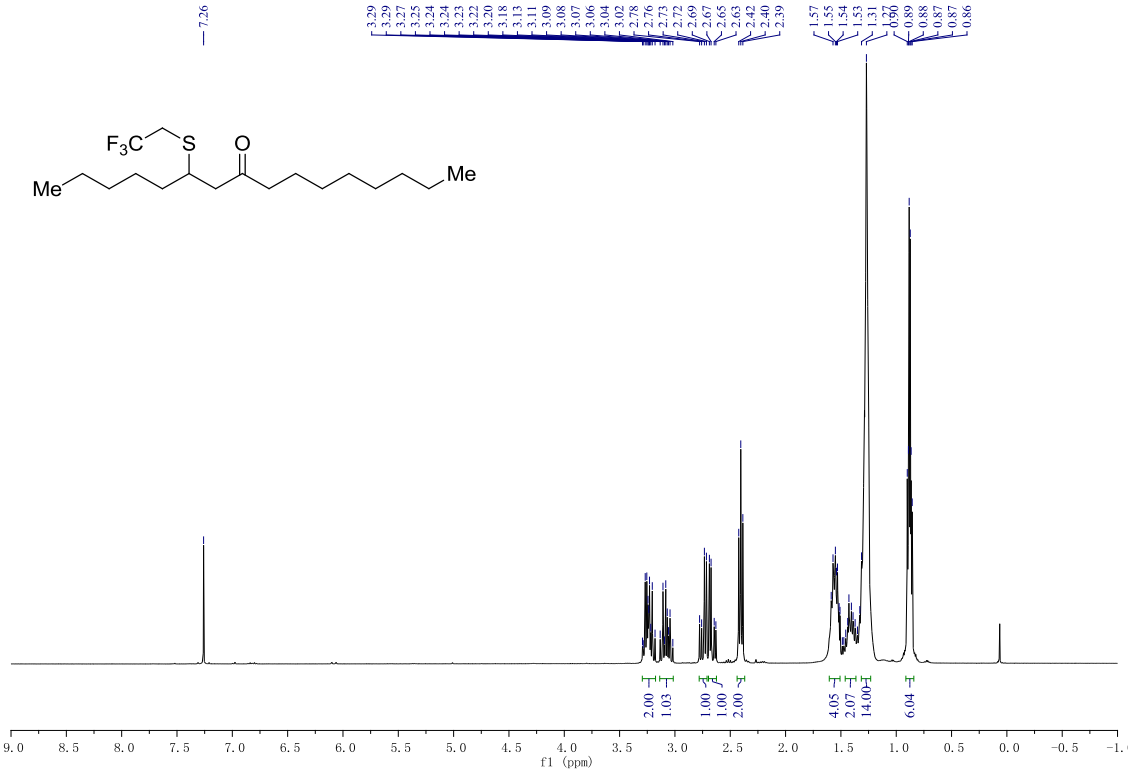


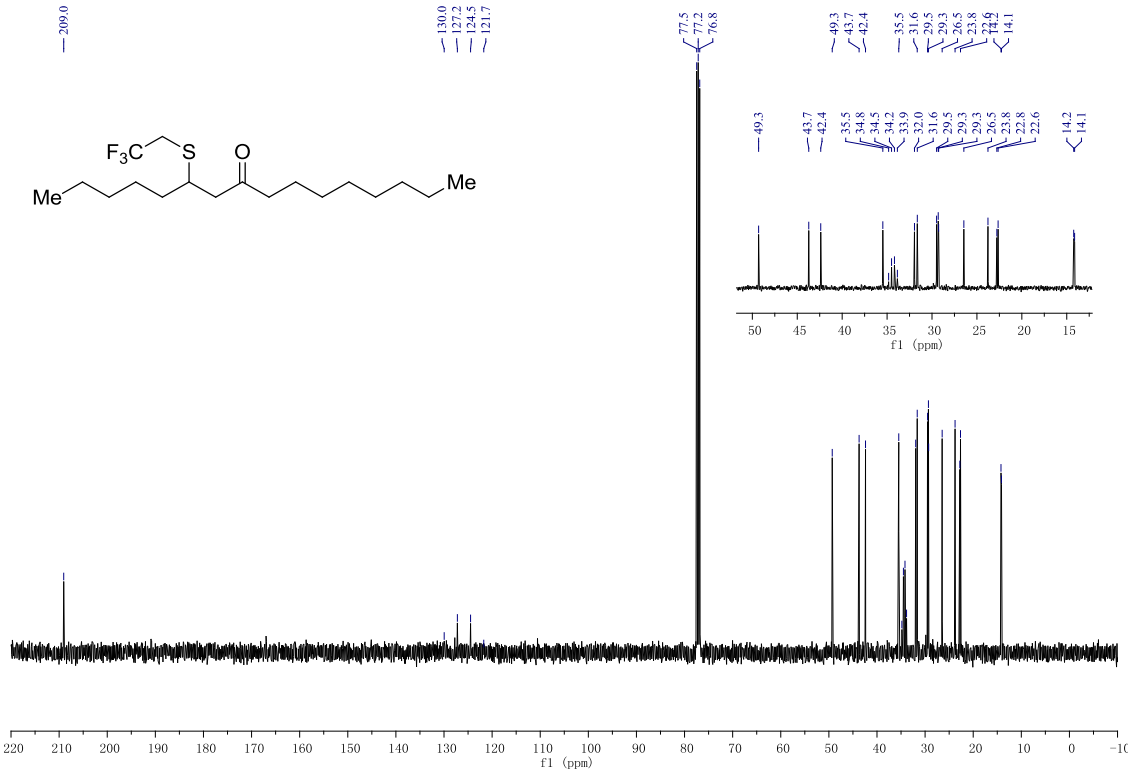
6-((2-Methoxyphenyl)thio)hexadecan-8-one, 2e



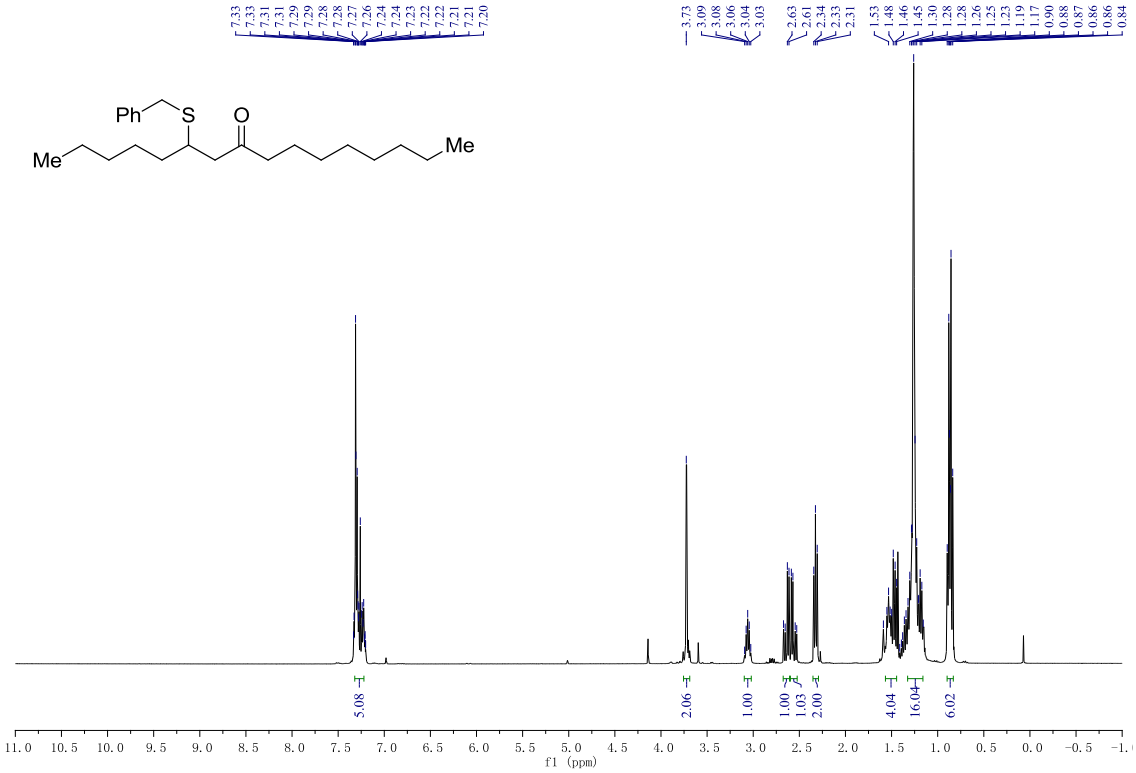


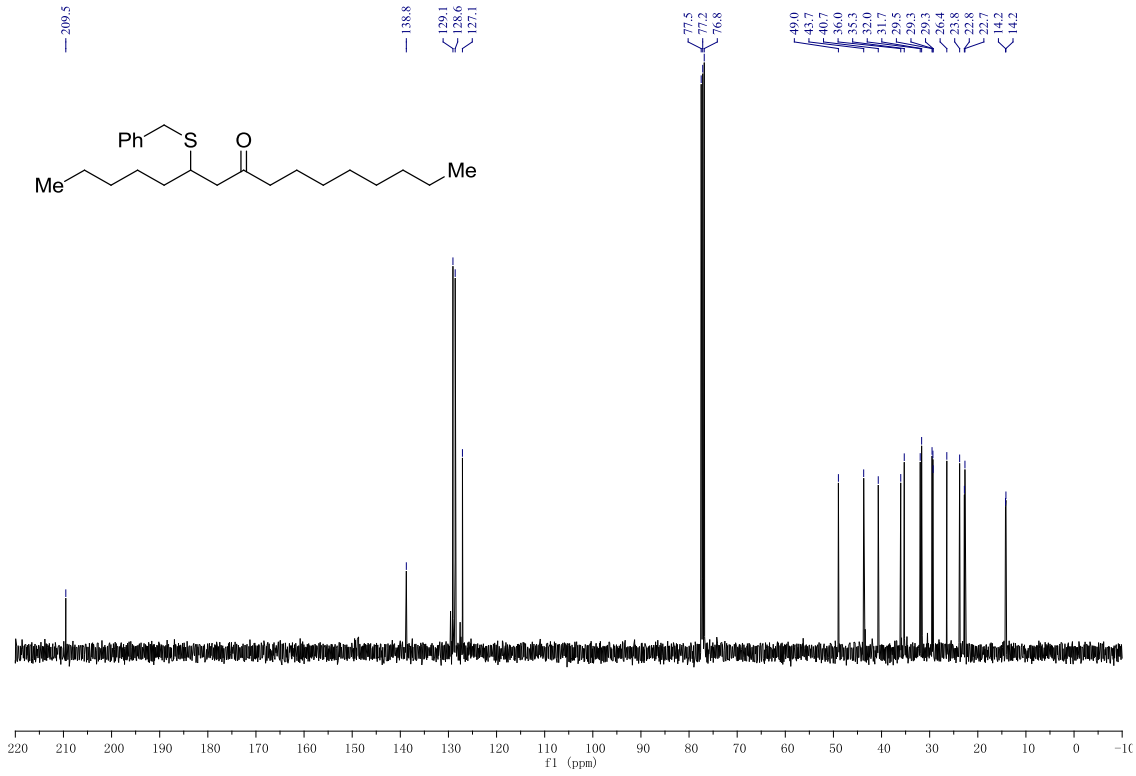
6-((2,2,2-Trifluoroethyl)thio)hexadecan-8-one, 2f



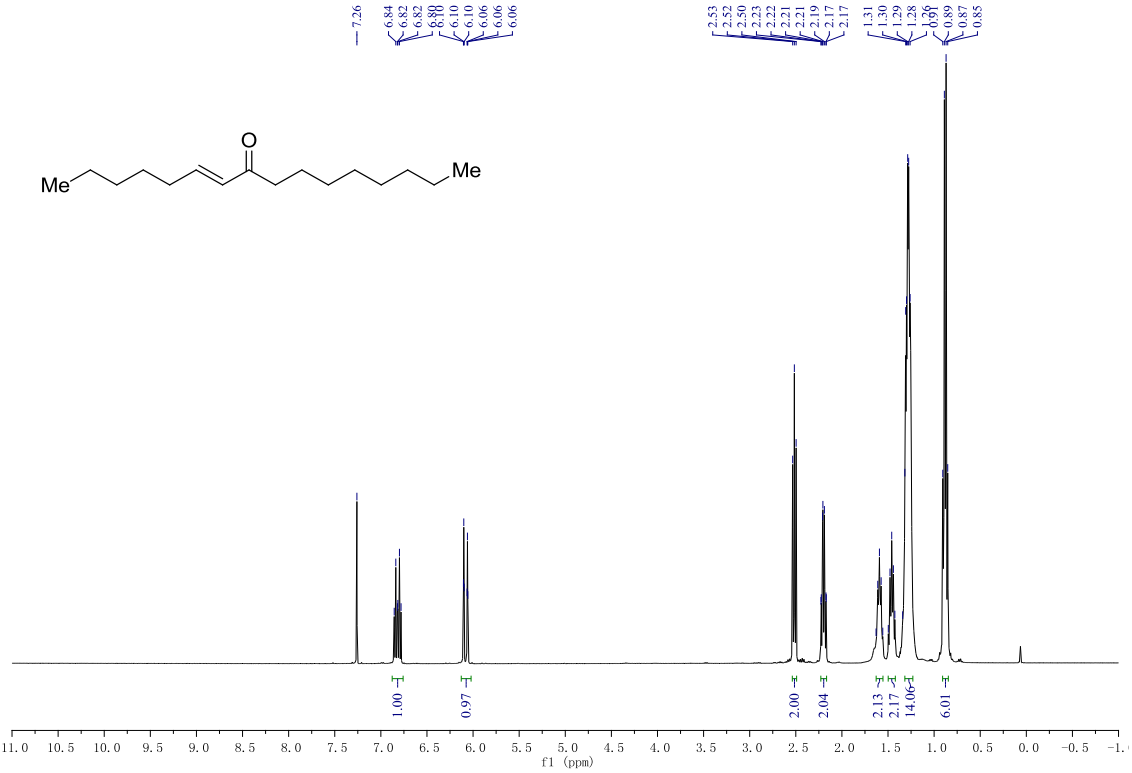


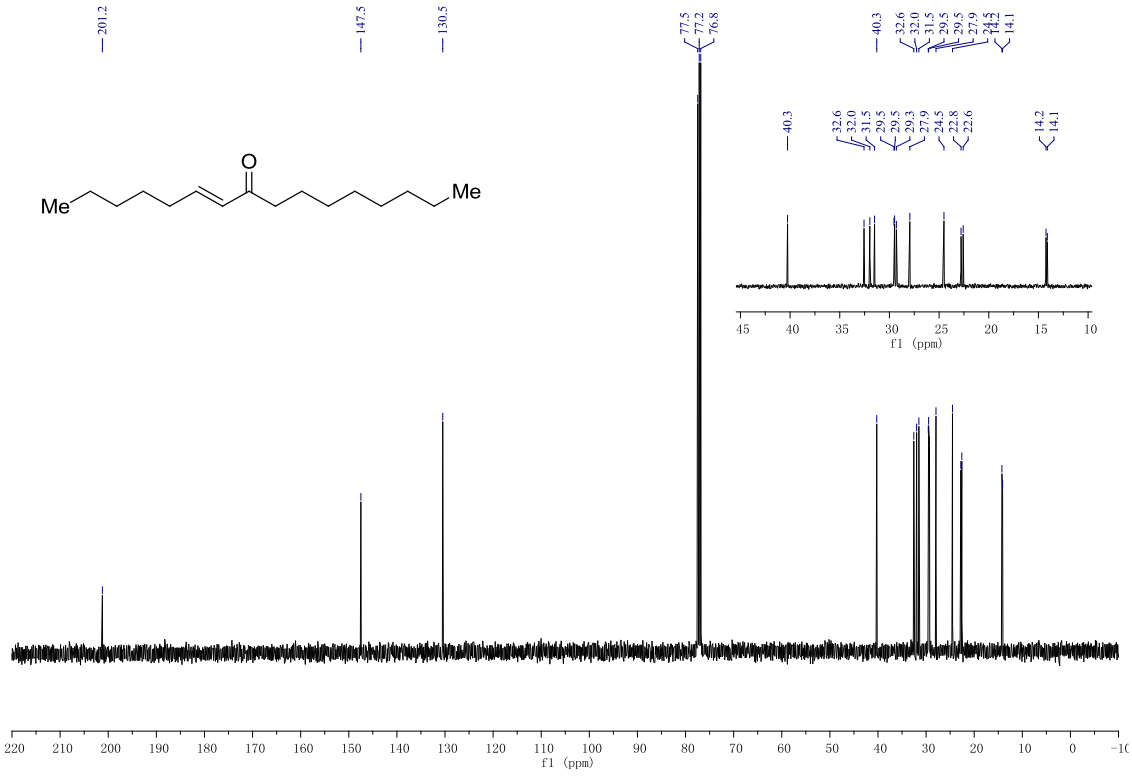
6-(Benzylthio)hexadecan-8-one, 2g



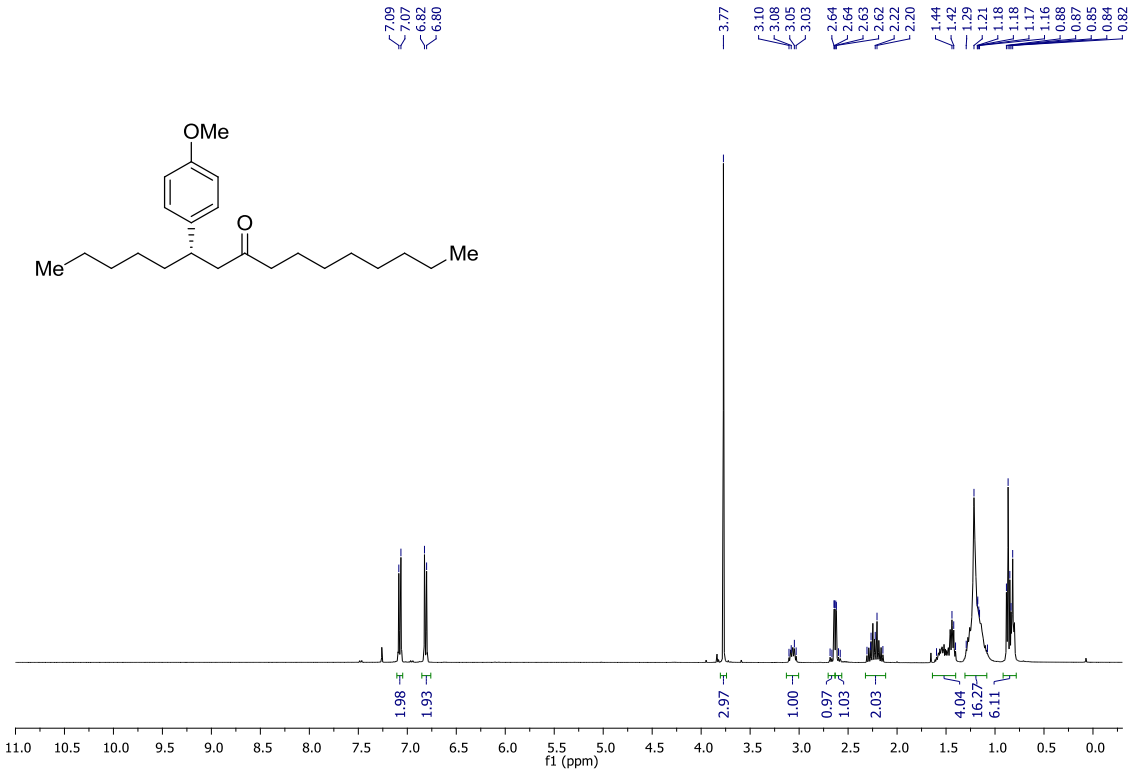


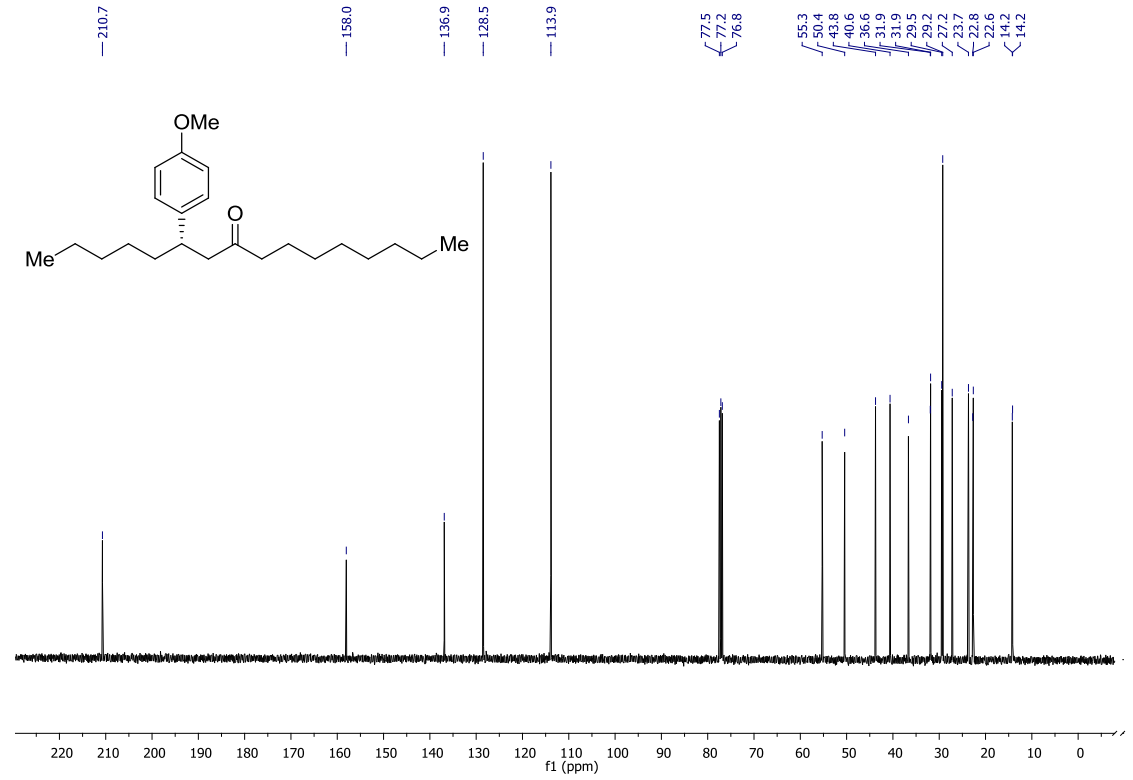
(*E*)-Hexadec-6-en-8-one, 3



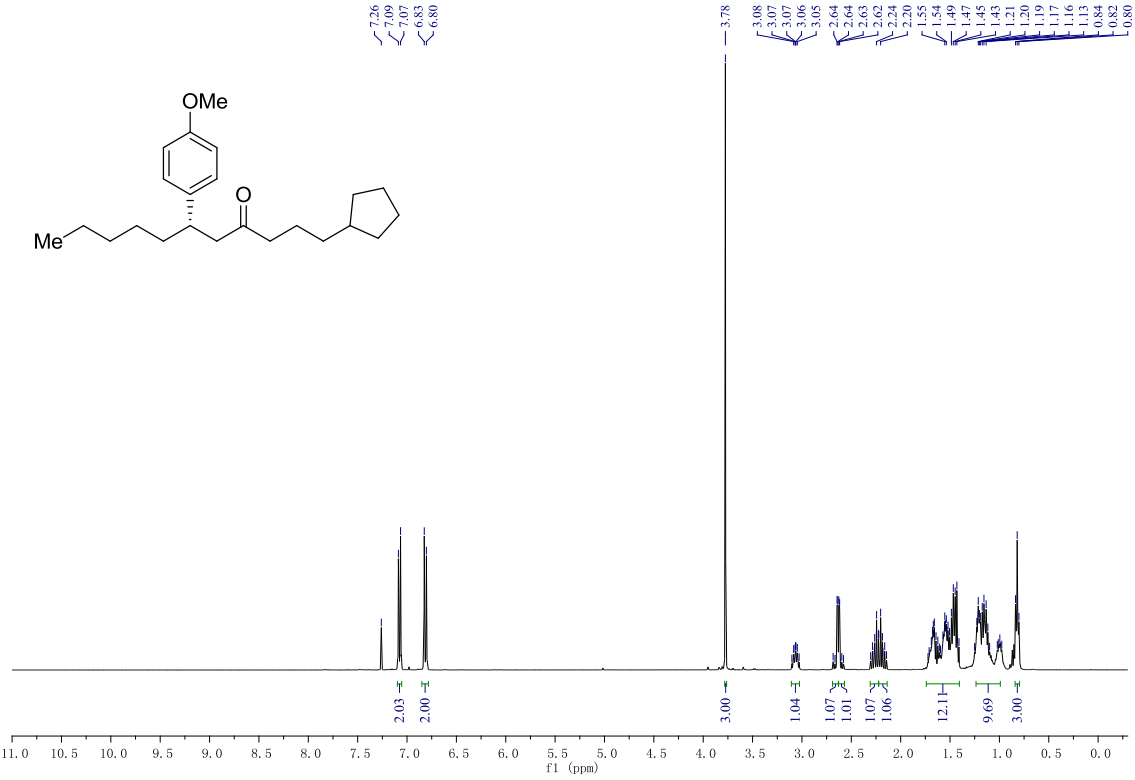


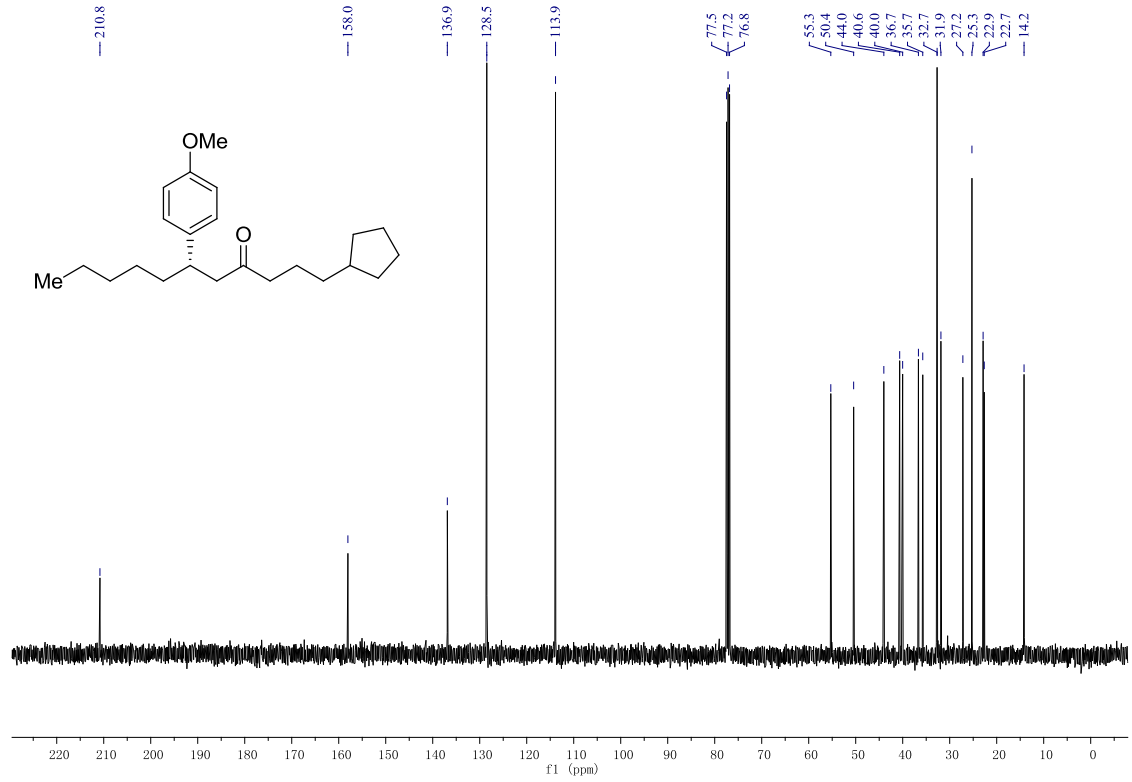
(*S*)-6-(4-Methoxyphenyl)hexadecan-8-one, 4a



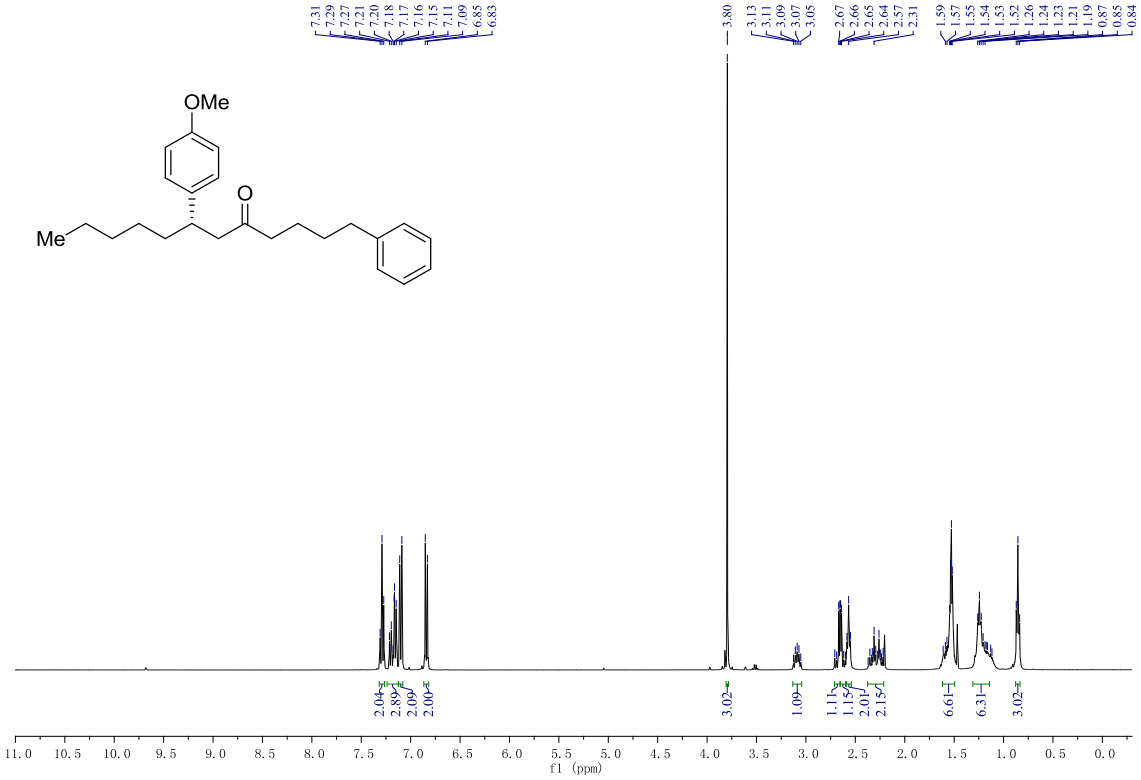


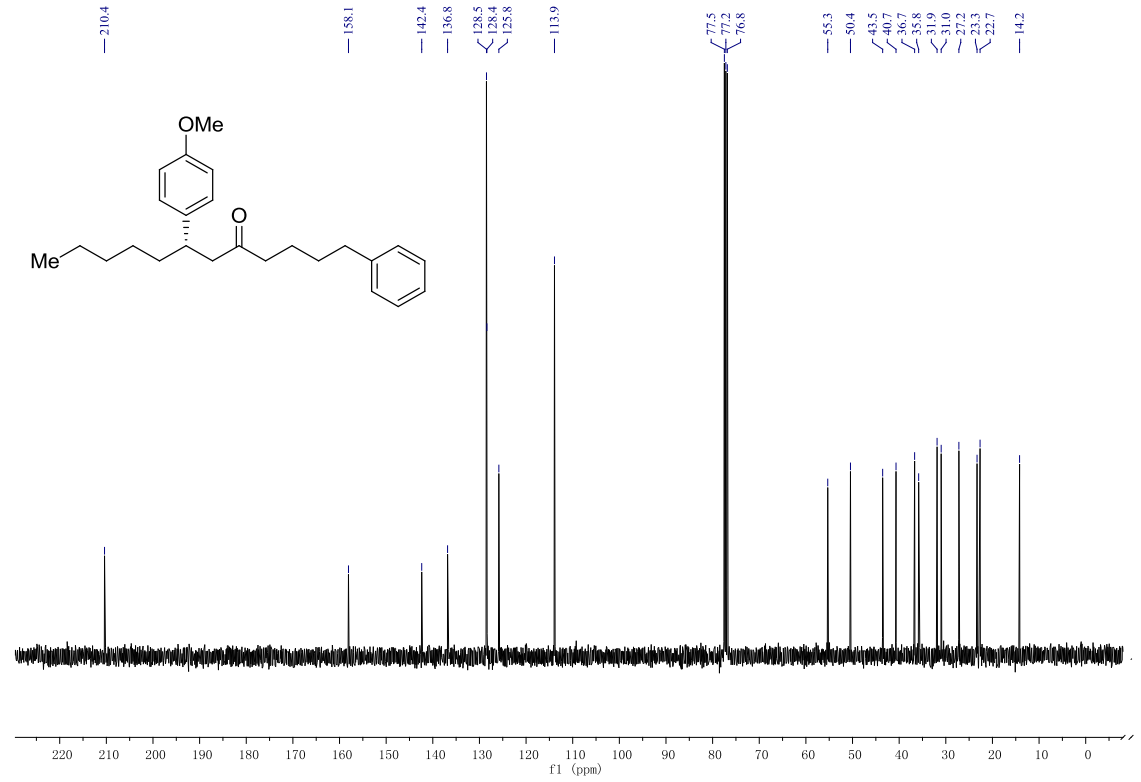
(*S*)-1-Cyclopentyl-6-(4-methoxyphenyl)undecan-4-one, 4b



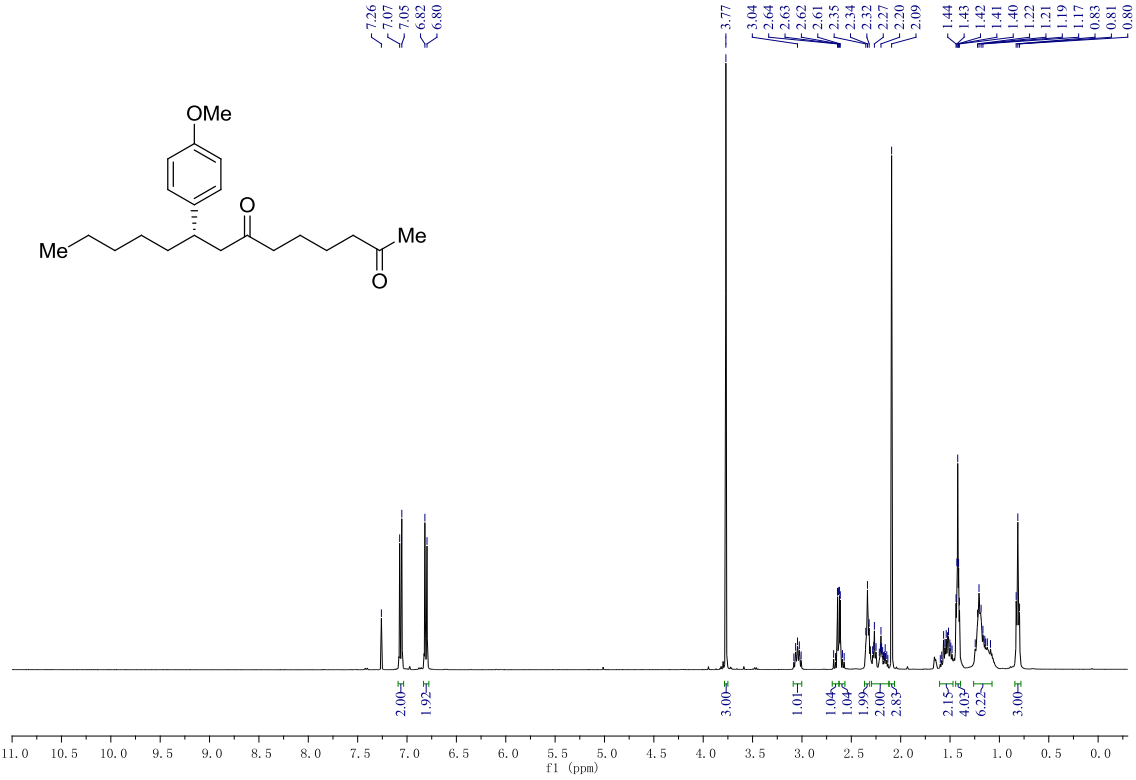


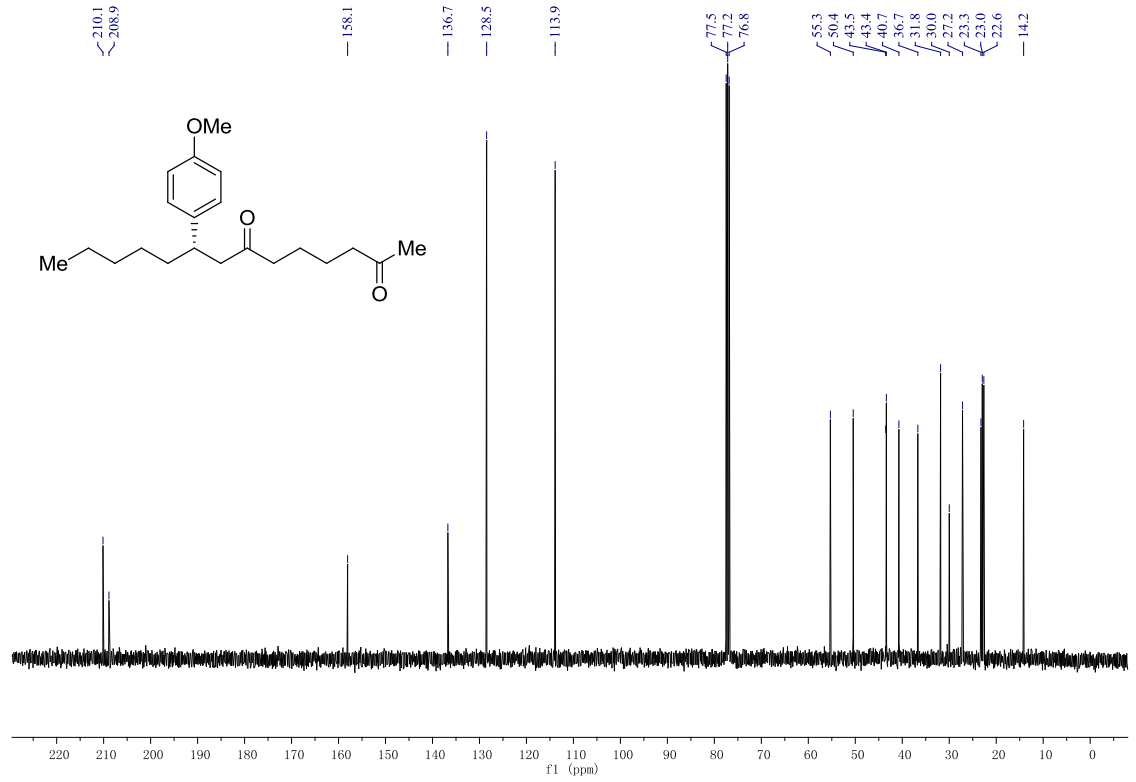
(*S*)-7-(4-Methoxyphenyl)-1-phenyldodecan-5-one, 4c



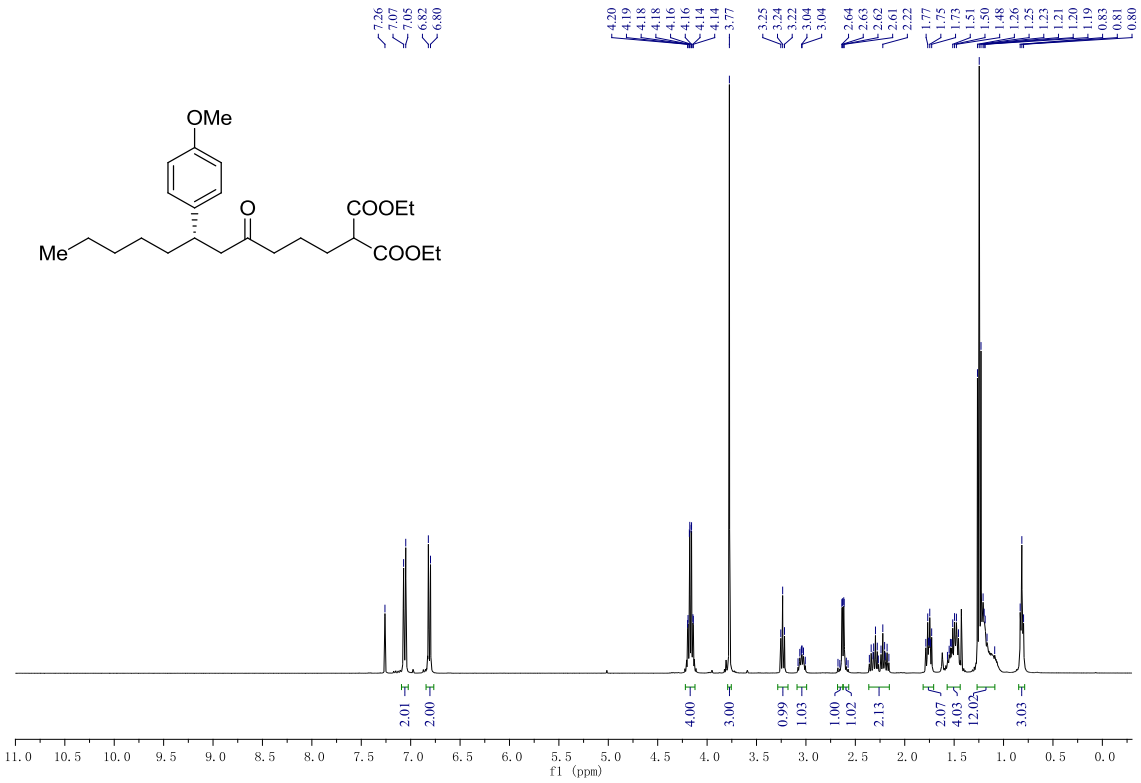


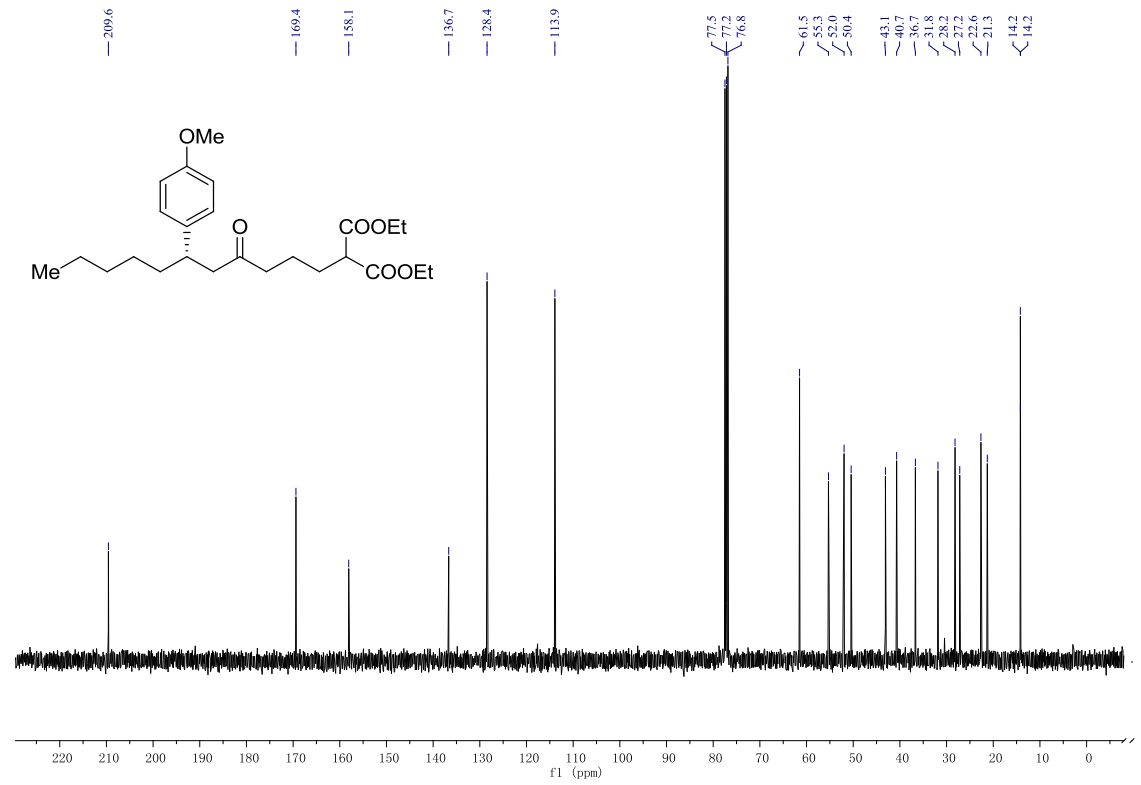
(*S*)-9-(4-Methoxyphenyl)tetradecane-2,7-dione, 4d



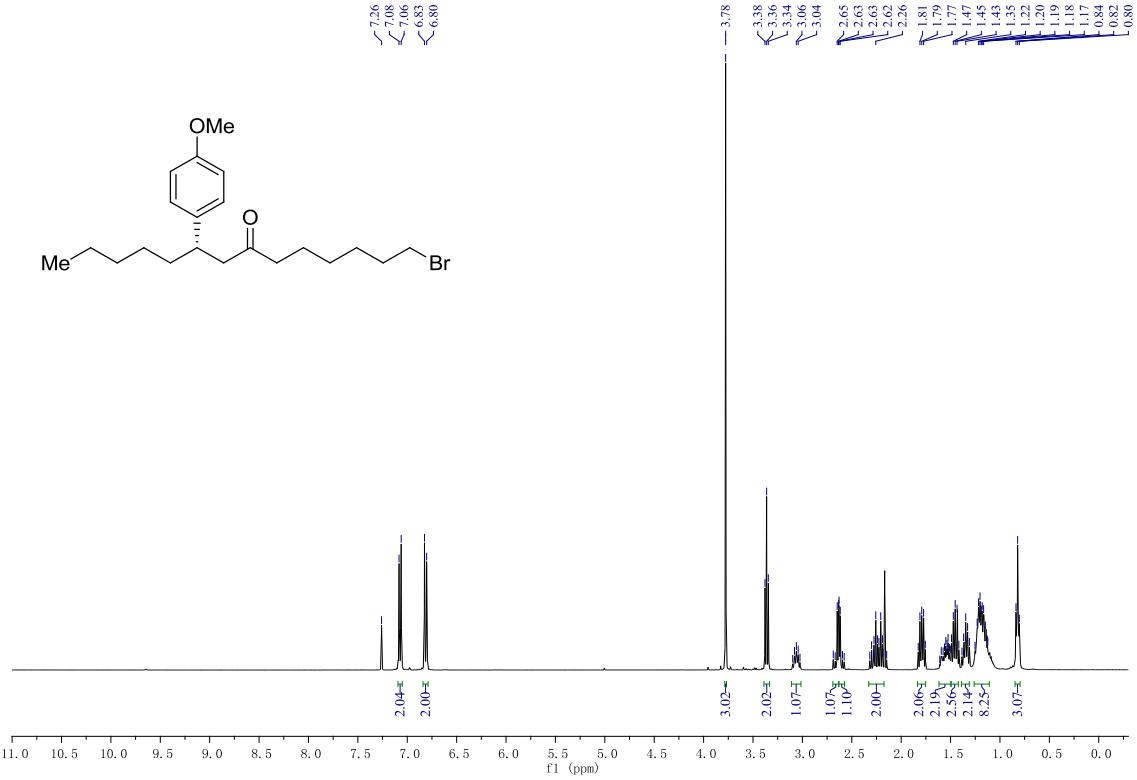


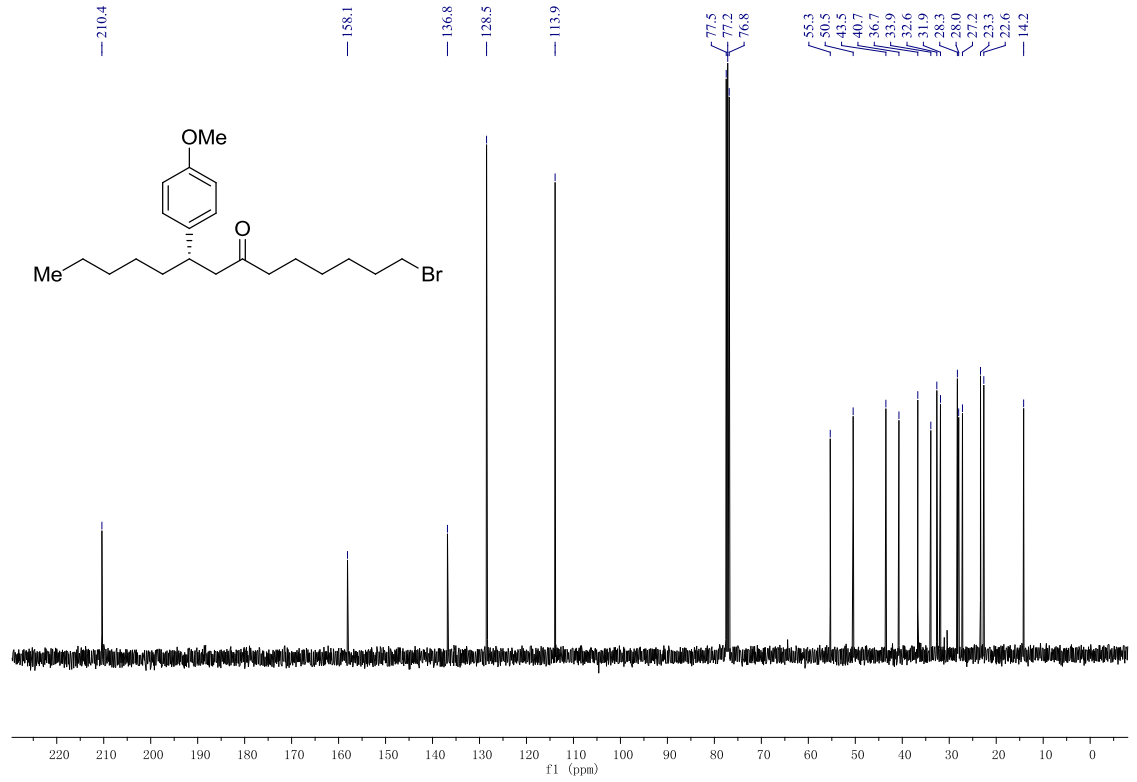
(*S*)-Diethyl 2-(6-(4-methoxyphenyl)-4-oxoundecyl)malonate, 4e



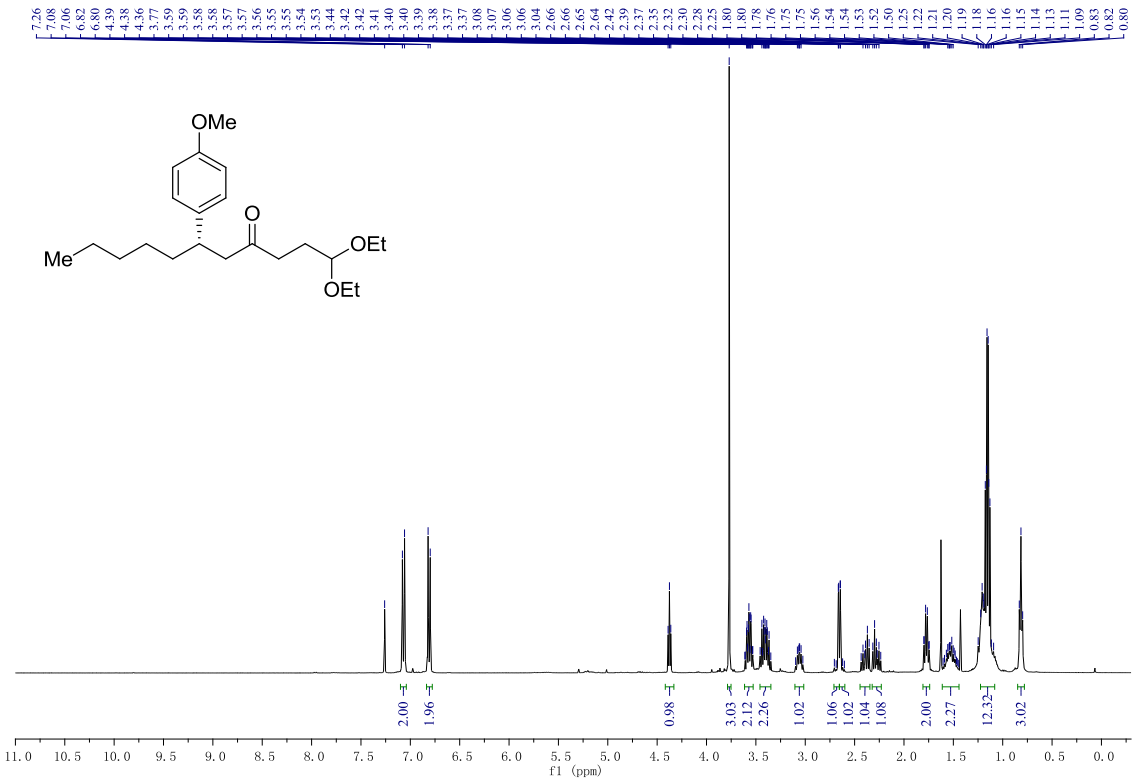


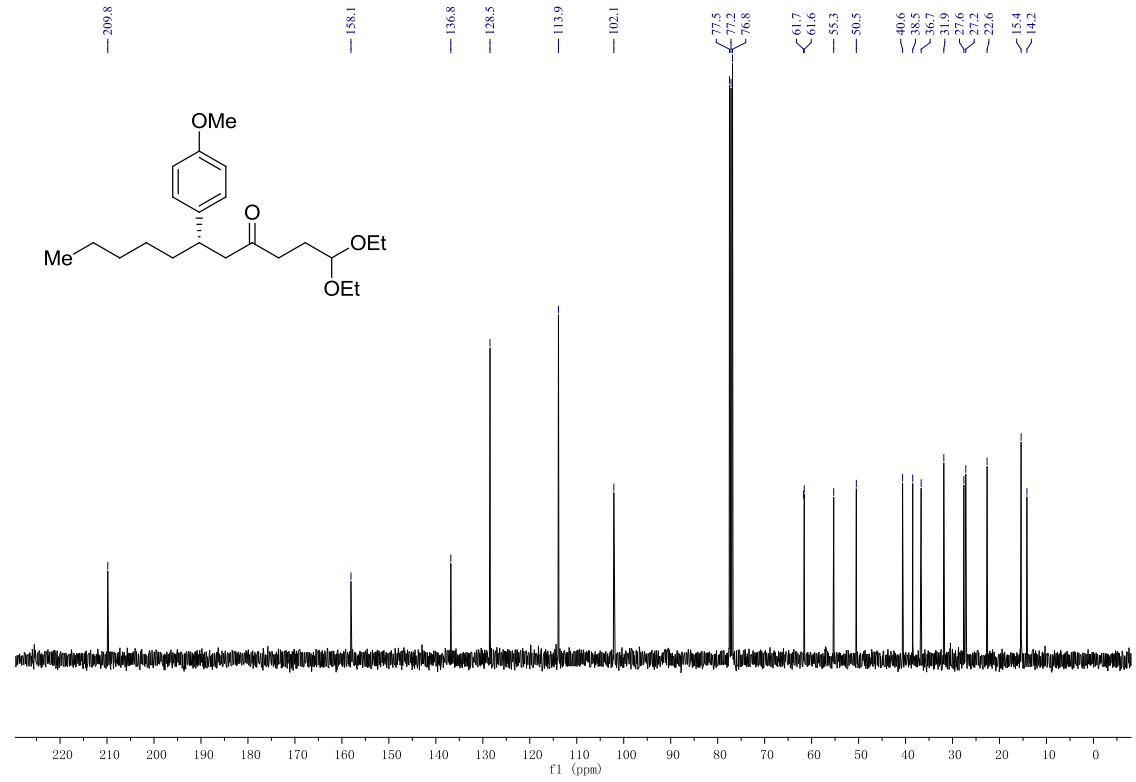
(*S*)-1-Bromo-9-(4-methoxyphenyl)tetradecan-7-one, 4f



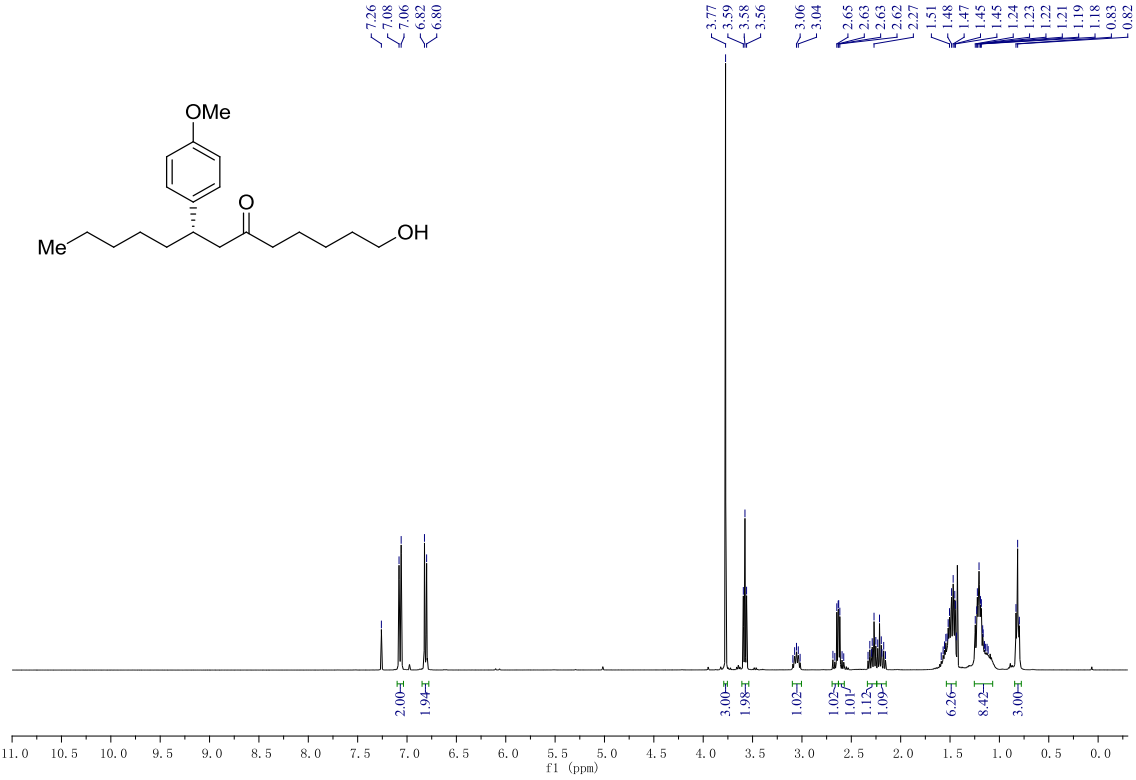


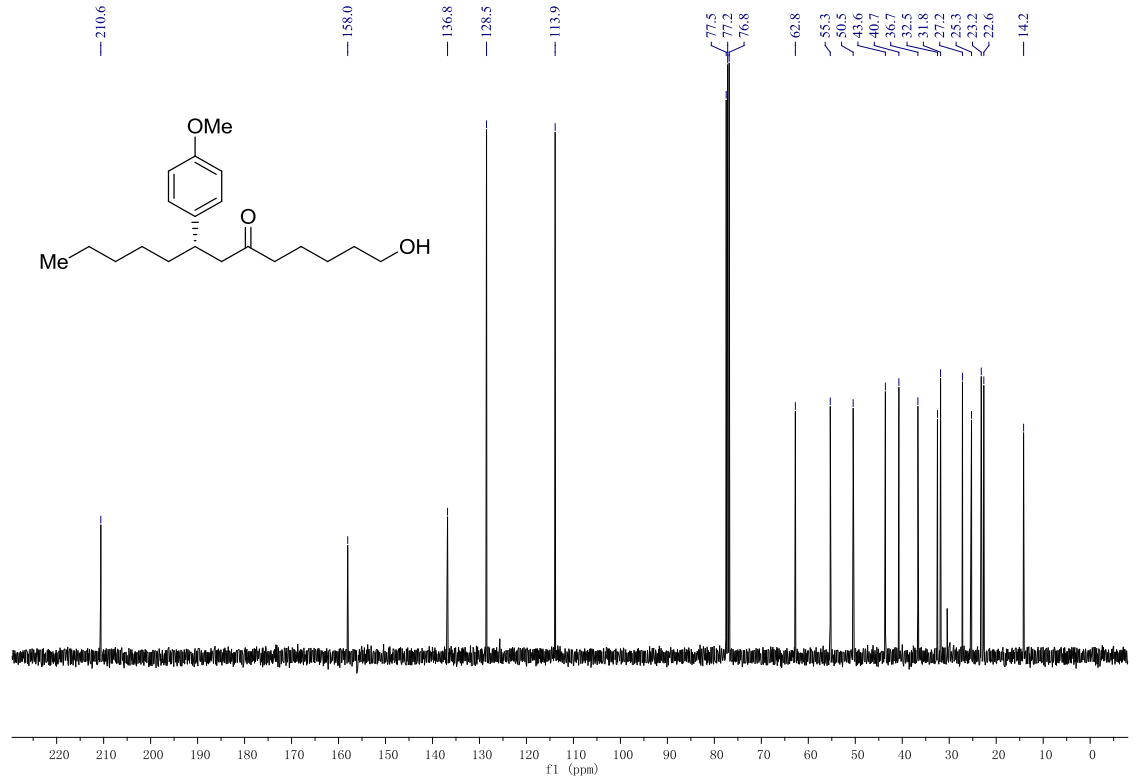
(*S*)-1,1-Diethoxy-6-(4-methoxyphenyl)undecan-4-one, 4g



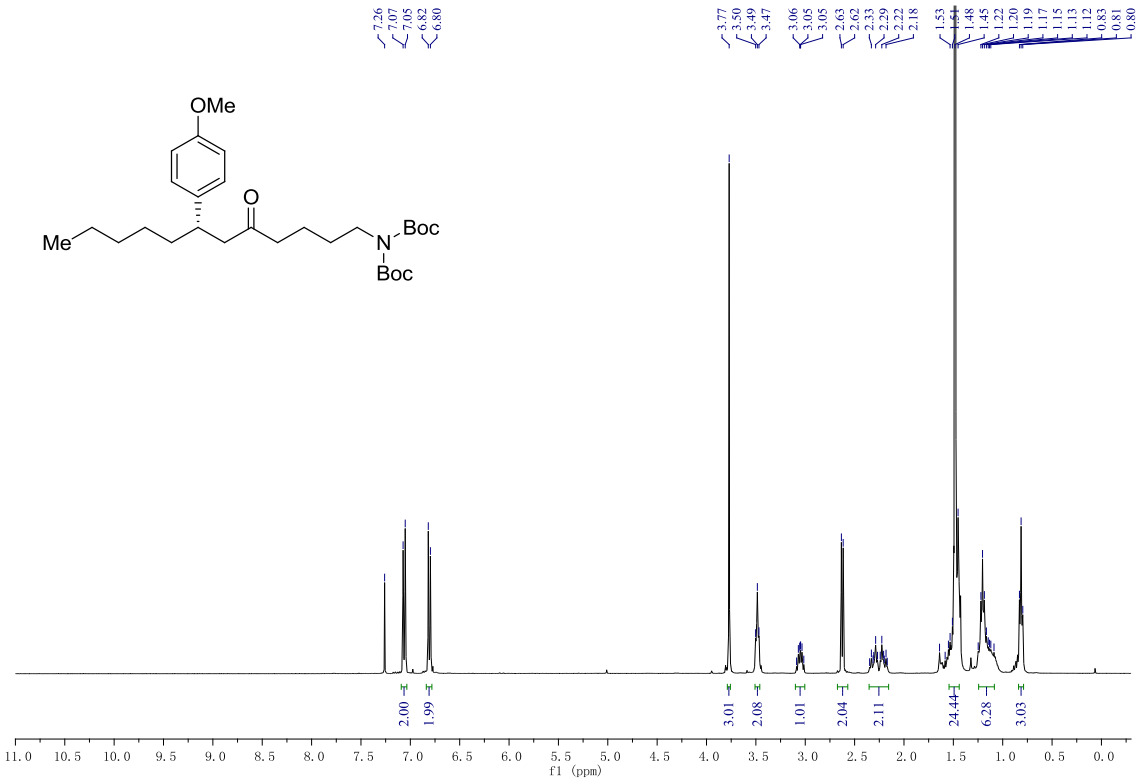


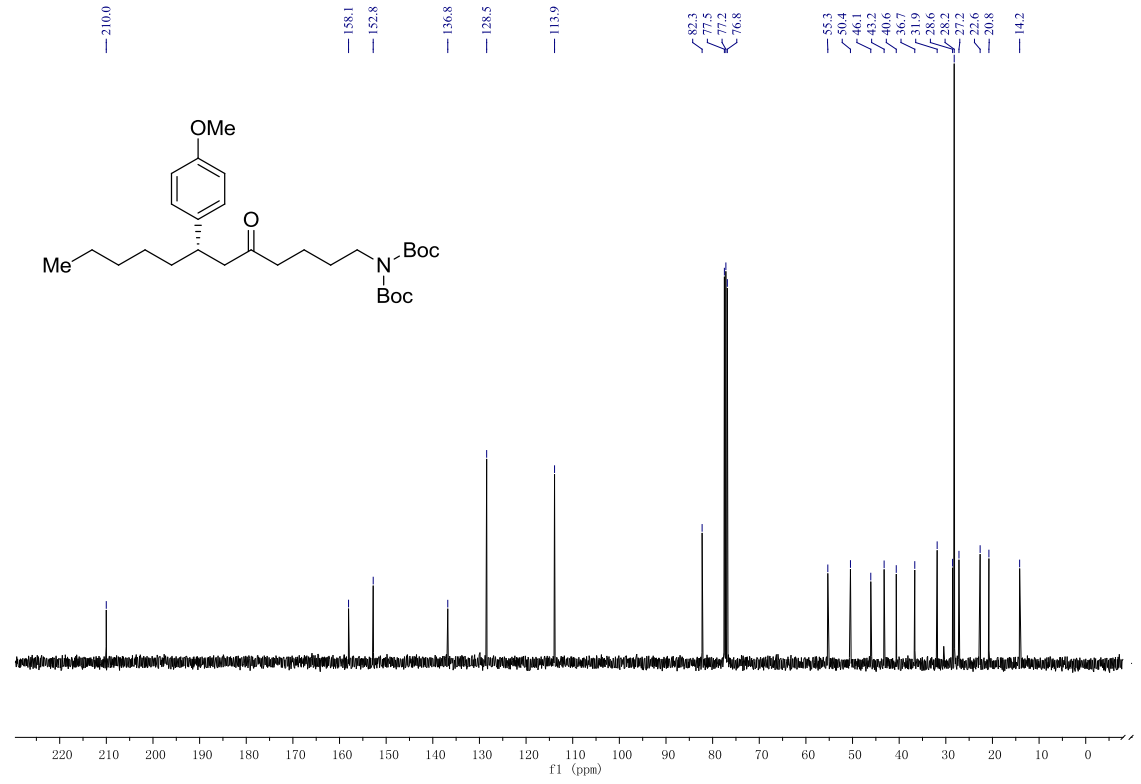
(*S*)-1-Hydroxy-8-(4-methoxyphenyl)tridecan-6-one, 4h



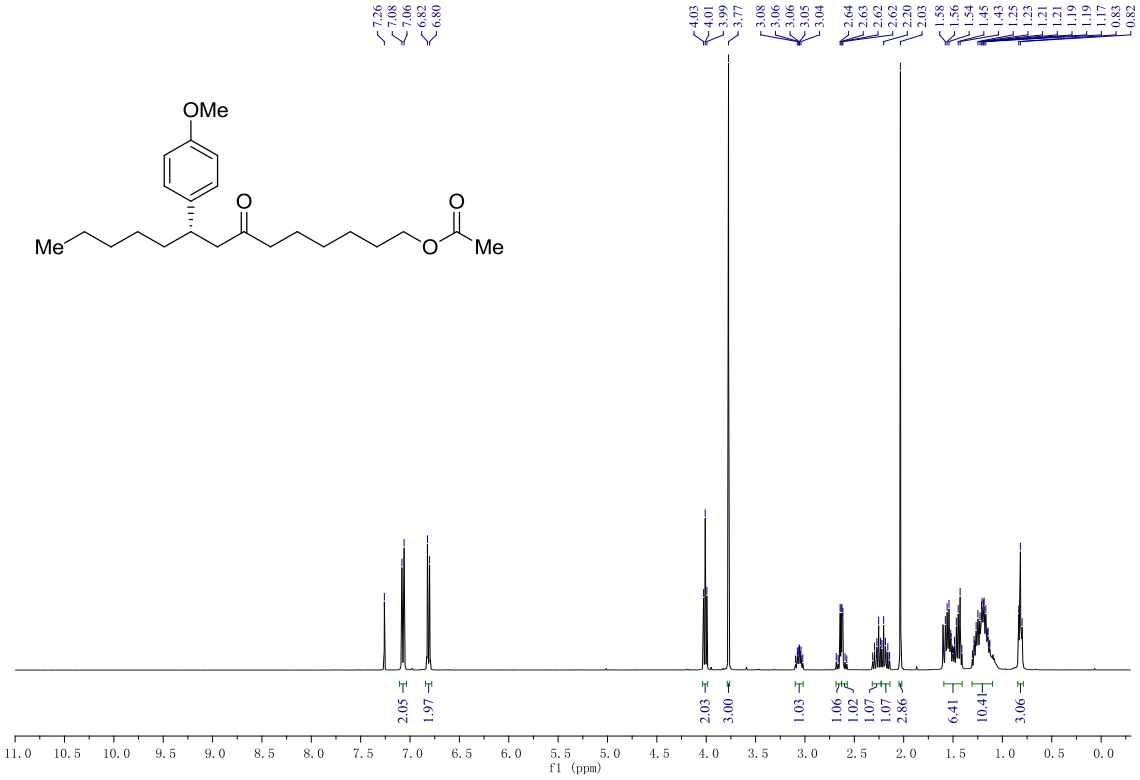


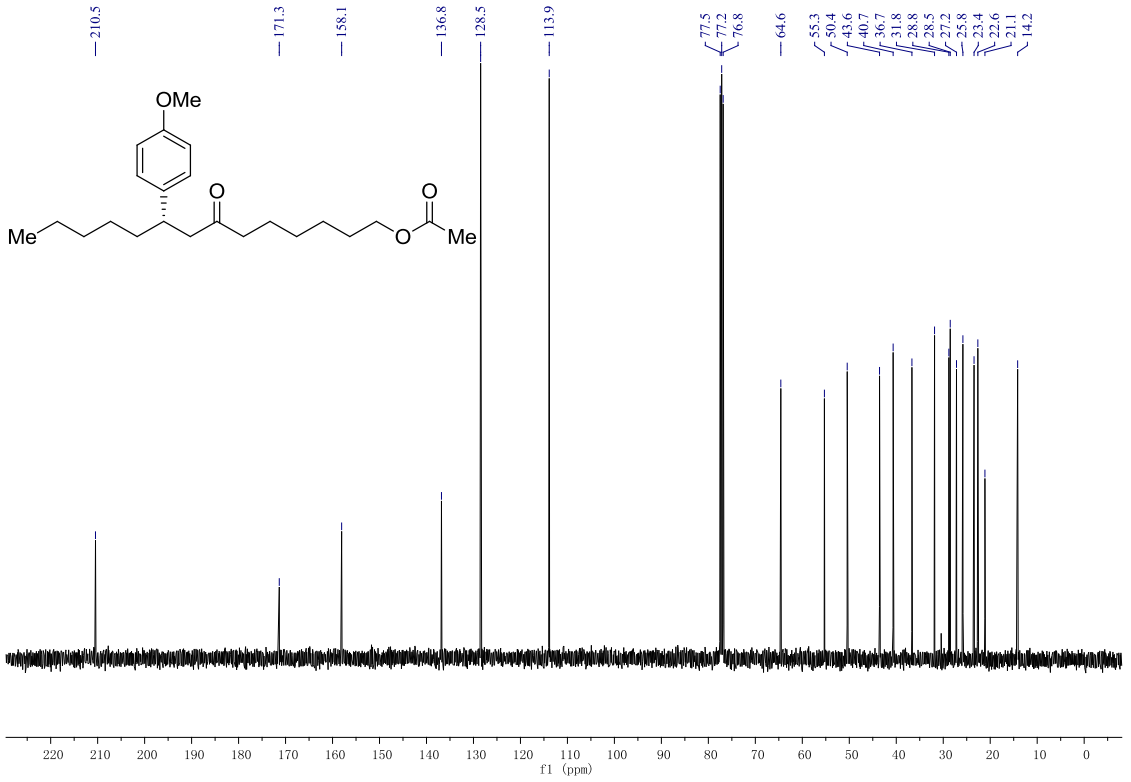
(*S*)-*N*,*N*-Di-Boc-1-amino-7-(4-methoxyphenyl)dodecan-5-one, 4i



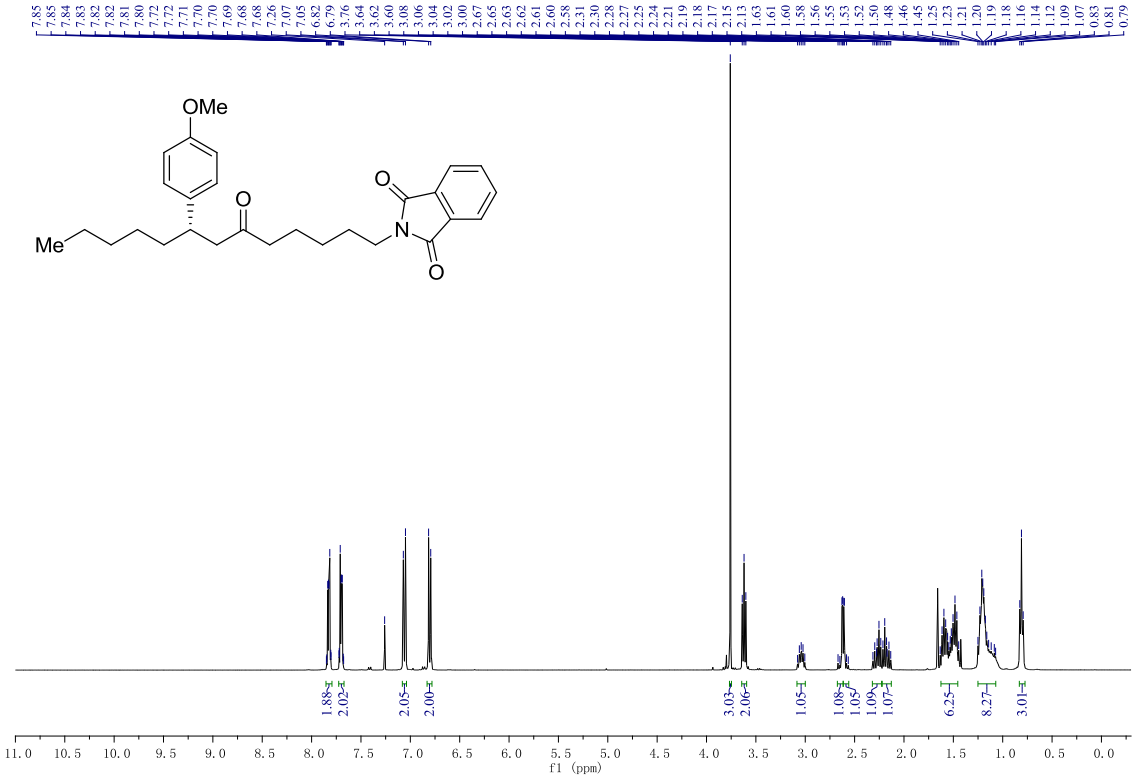


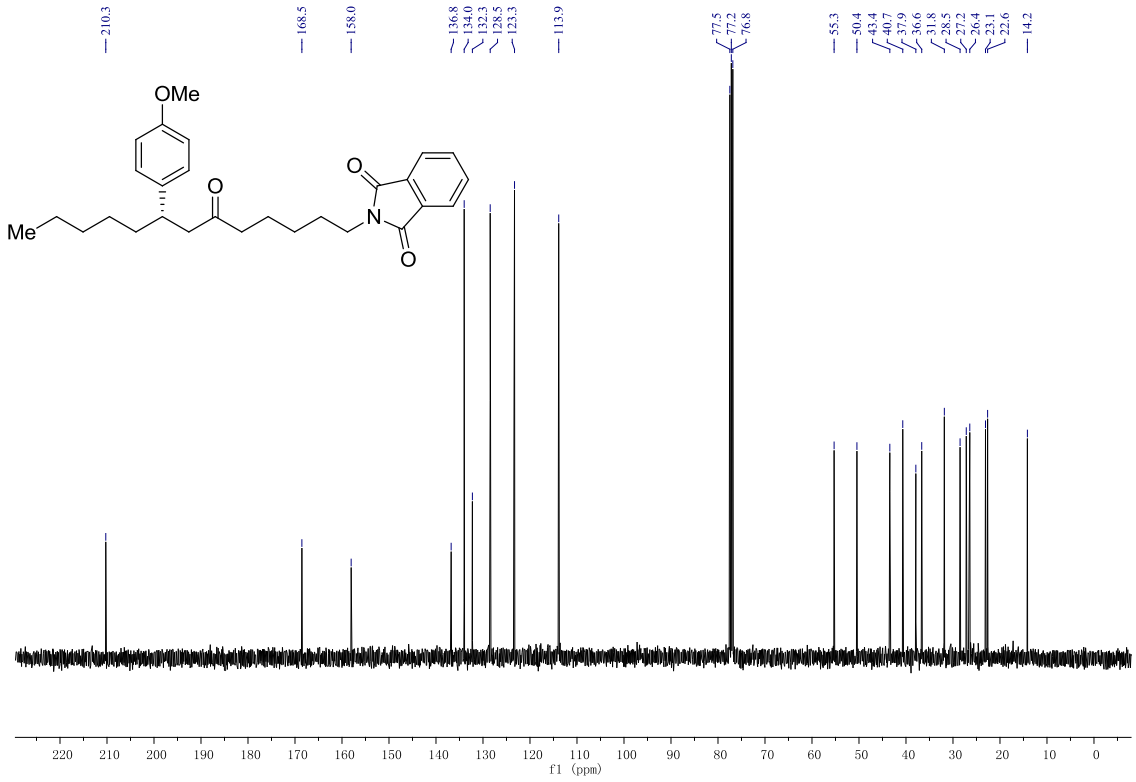
(*S*)-9-(4-Methoxyphenyl)-7-oxotetradecyl acetate, 4j



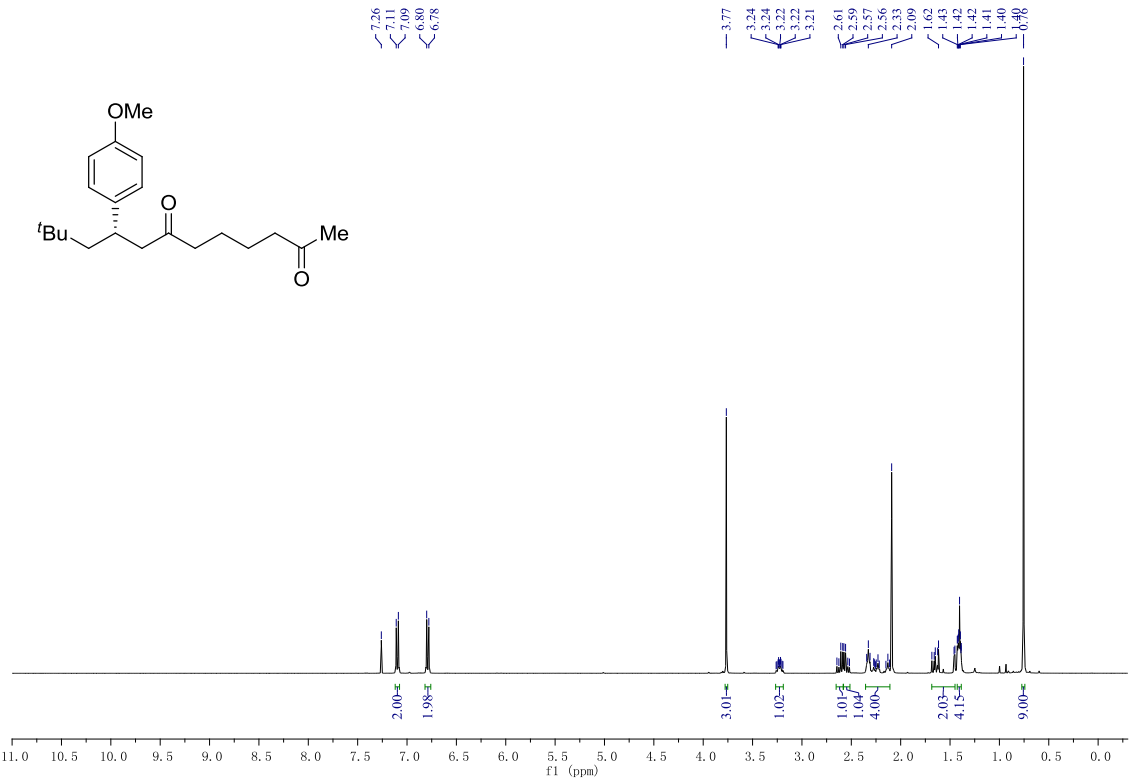


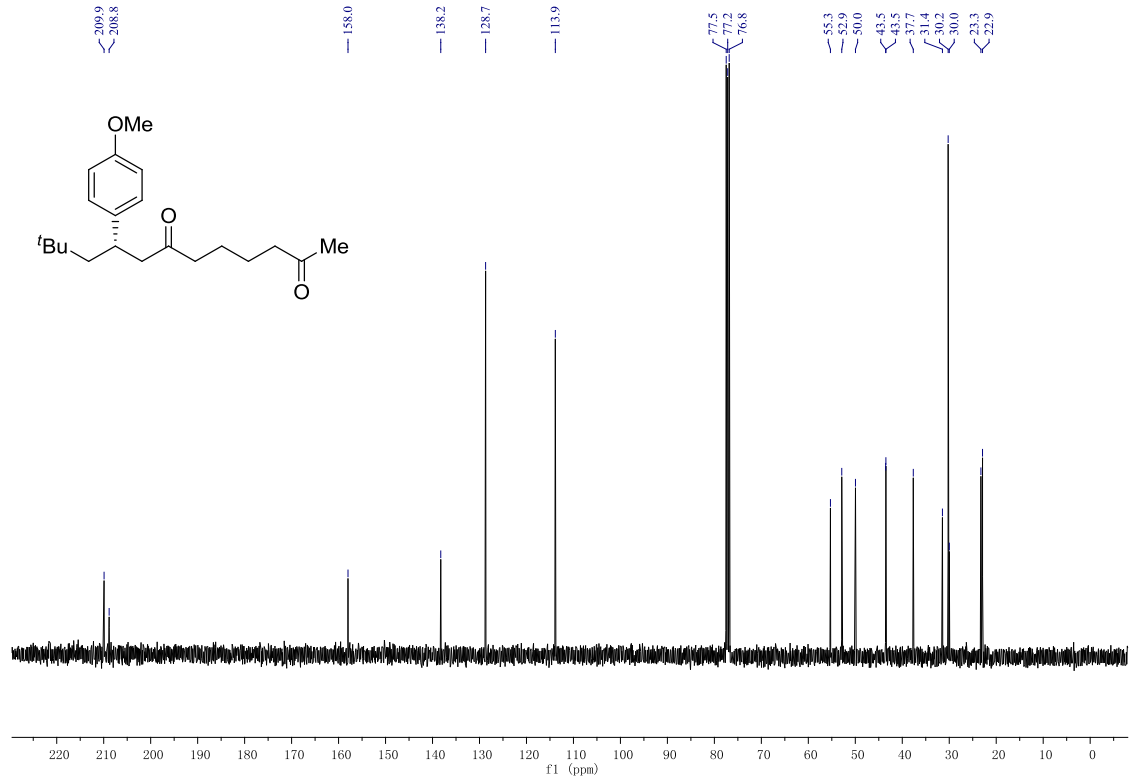
(*S*)-2-(8-(4-Methoxyphenyl)-6-oxotridecyl)isoindoline-1,3-dione, 4k



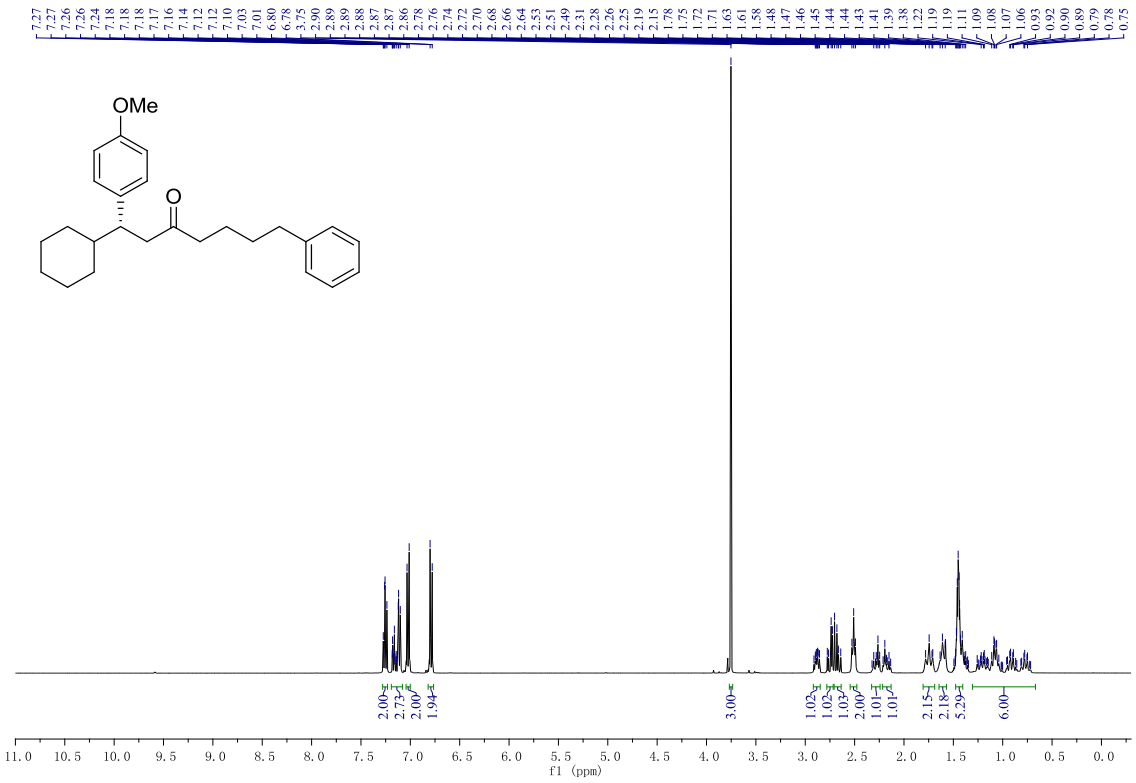


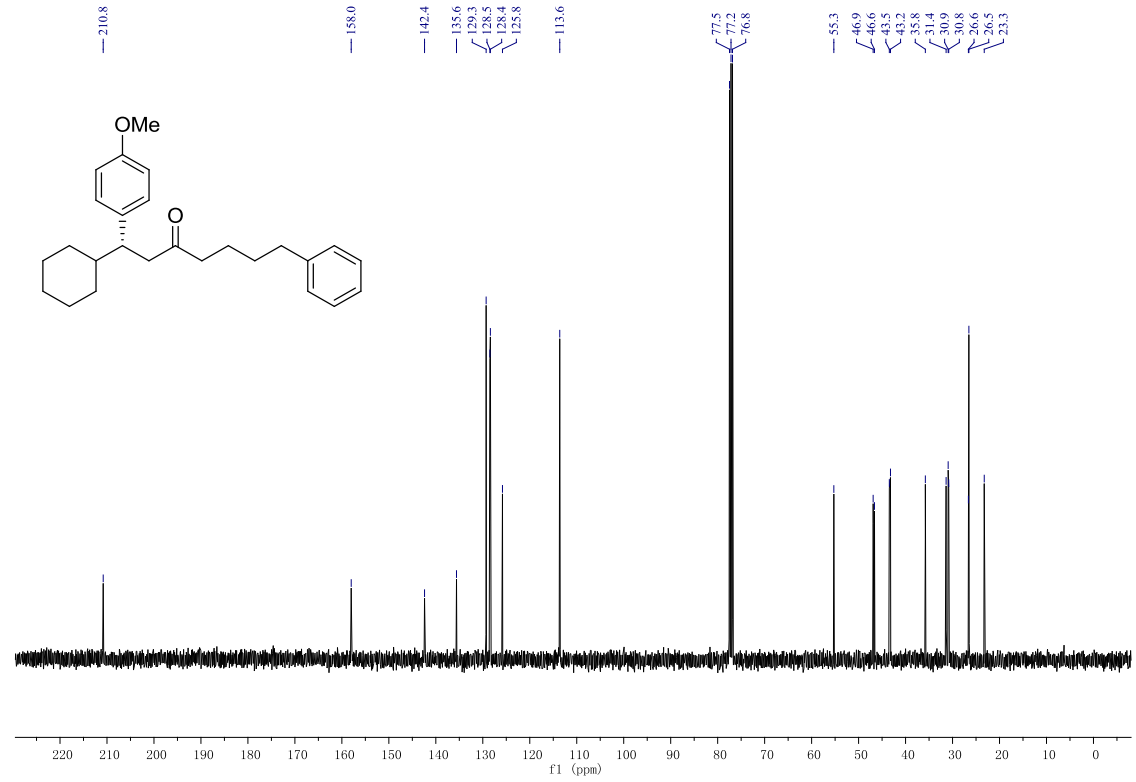
(*S*)-9-(4-Methoxyphenyl)-11,11-dimethyldodecane-2,7-dione, 4ab



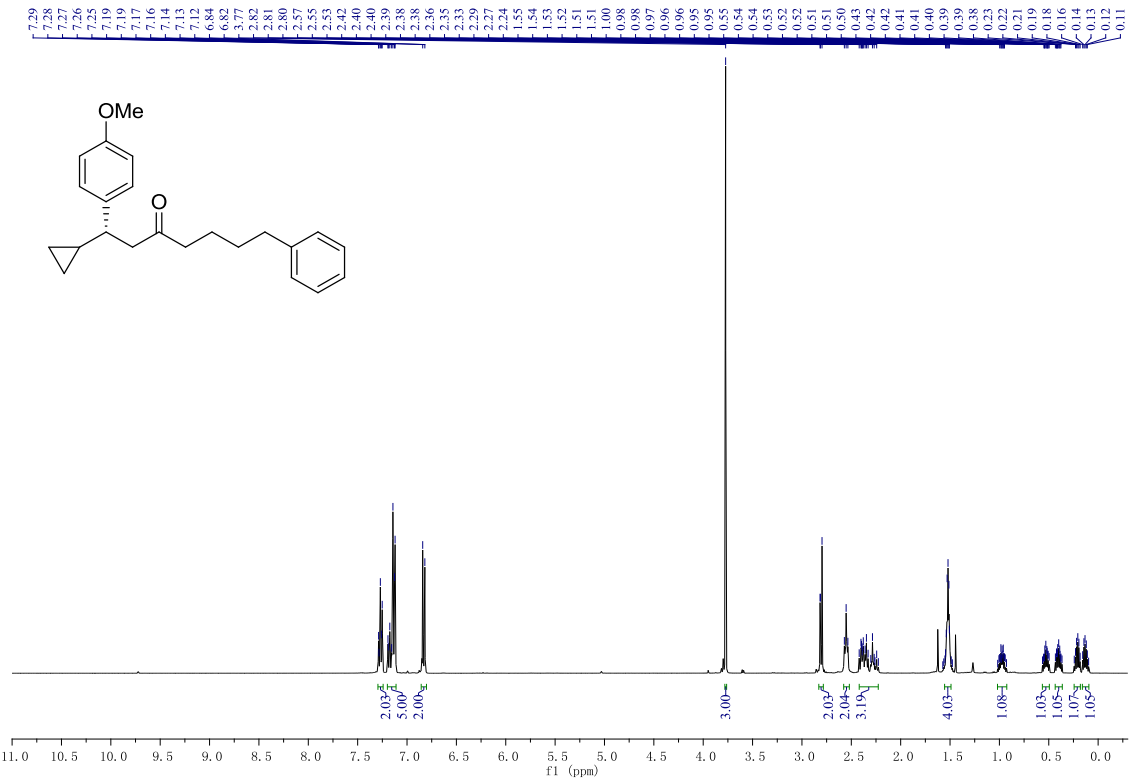


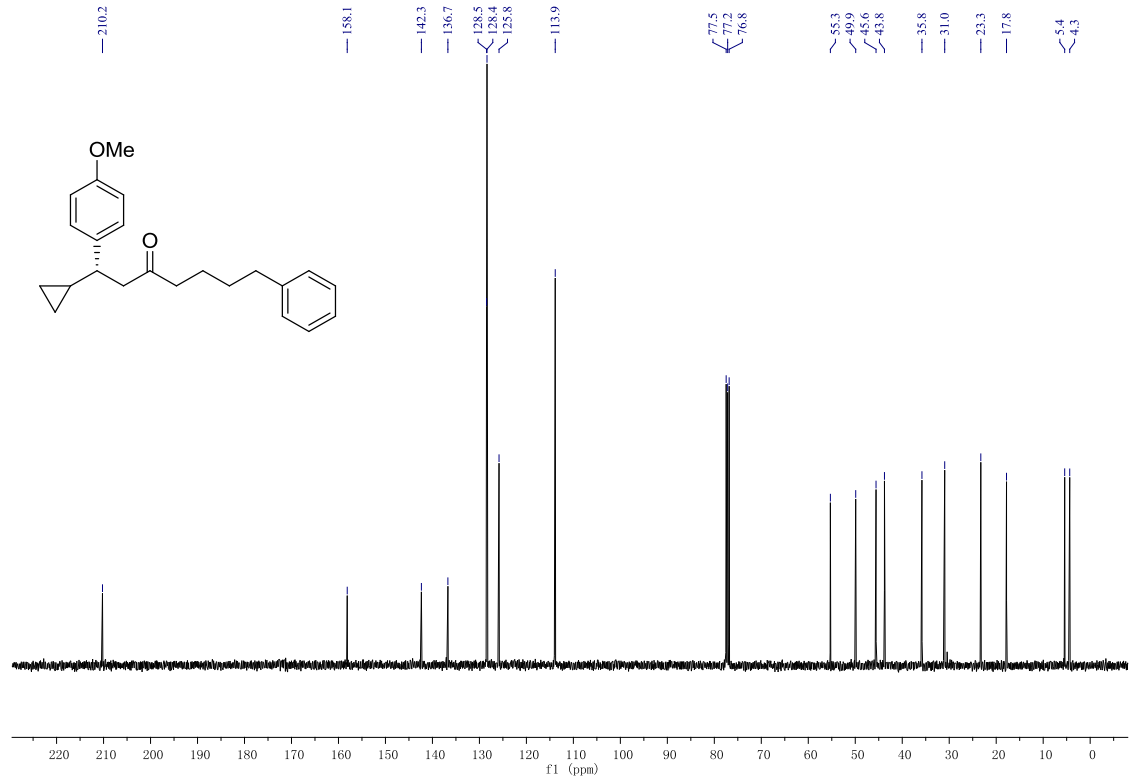
(*R*)-1-Cyclohexyl-1-(4-methoxyphenyl)-7-phenylheptan-3-one, 4ac



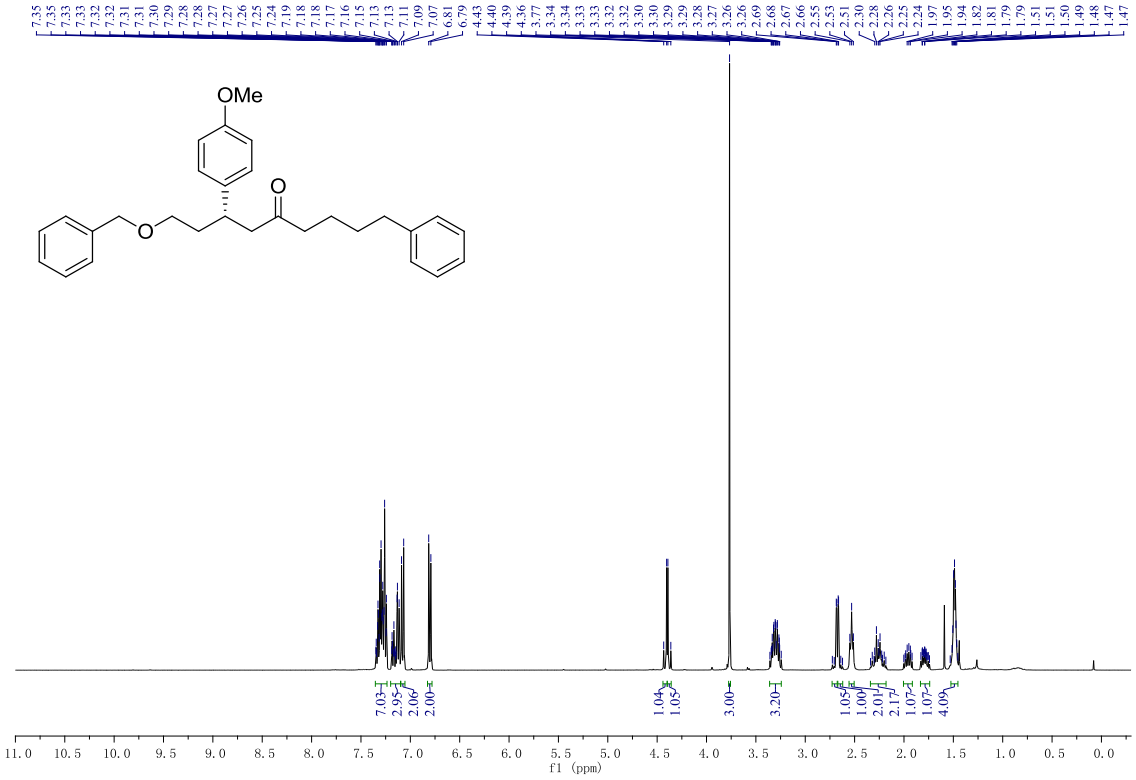


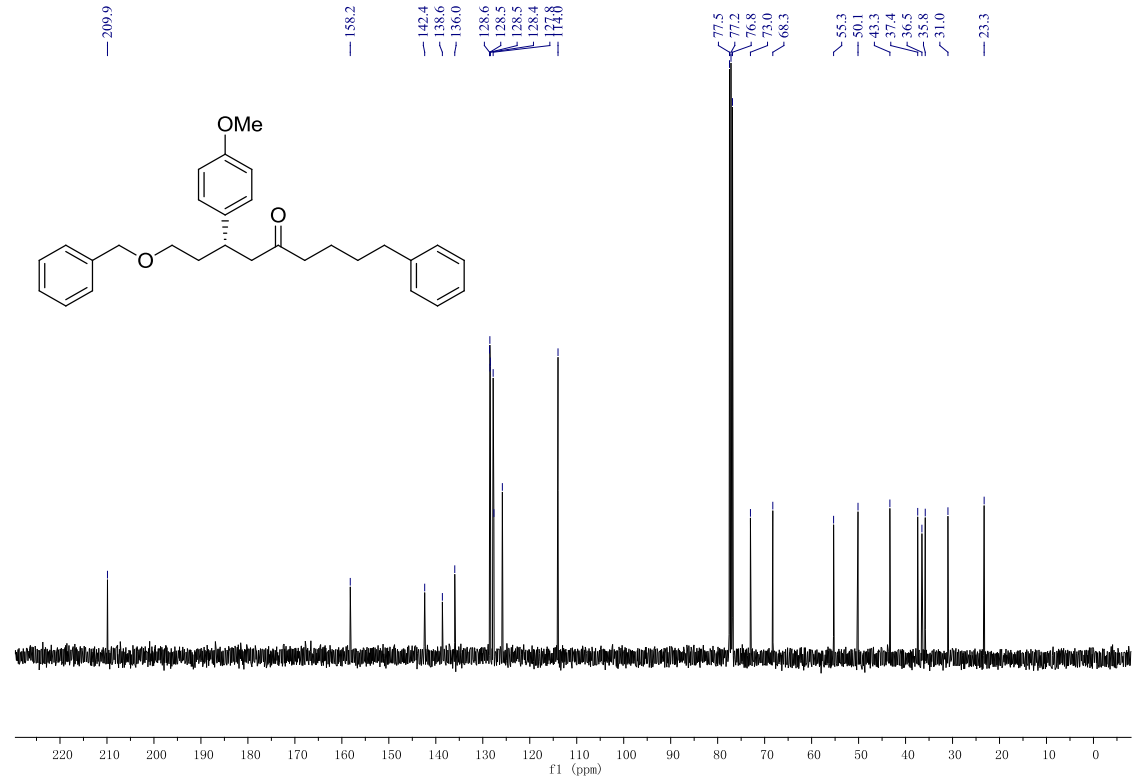
(*R*)-1-Cyclopropyl-1-(4-methoxyphenyl)-7-phenylheptan-3-one, 4ad



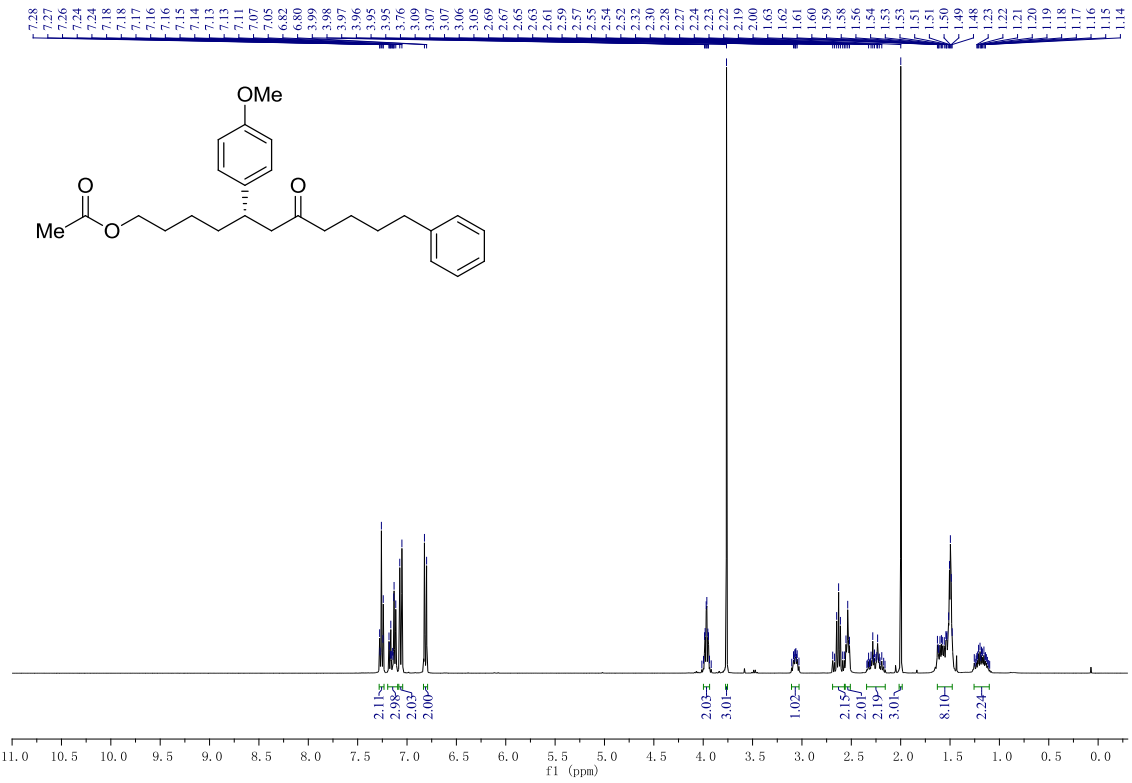


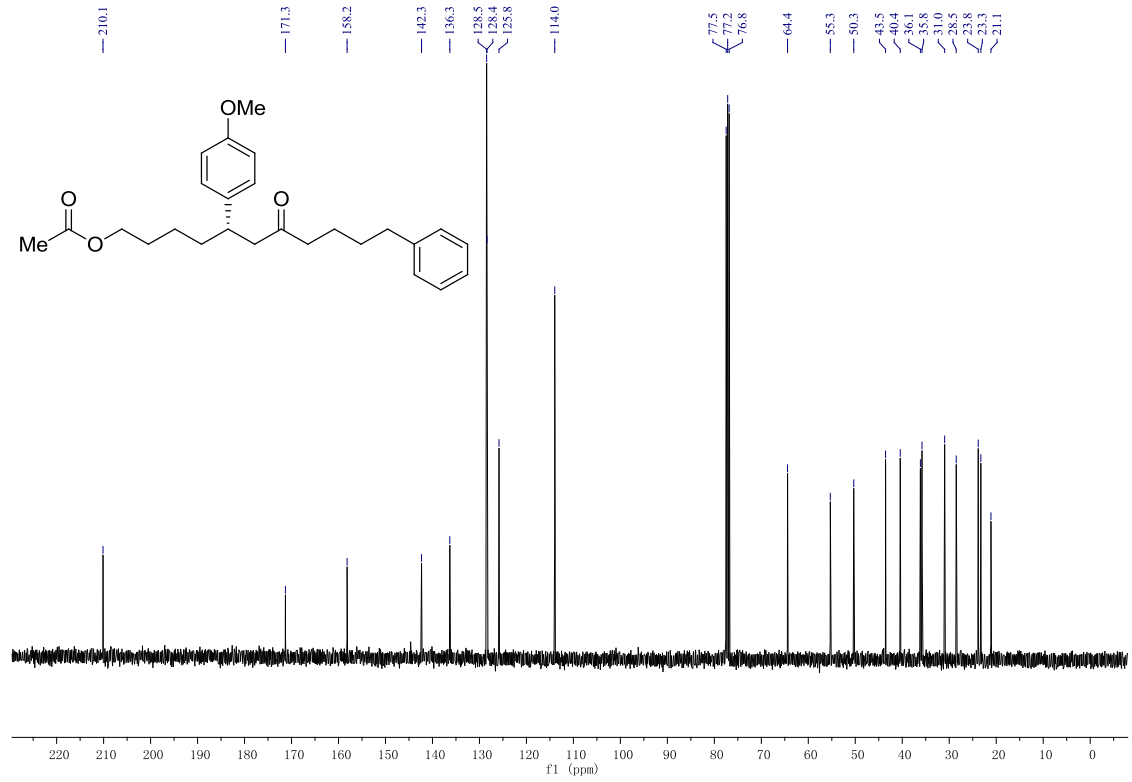
(*S*)-1-(Benzyloxy)-3-(4-methoxyphenyl)-9-phenylnonan-5-one, 4ai



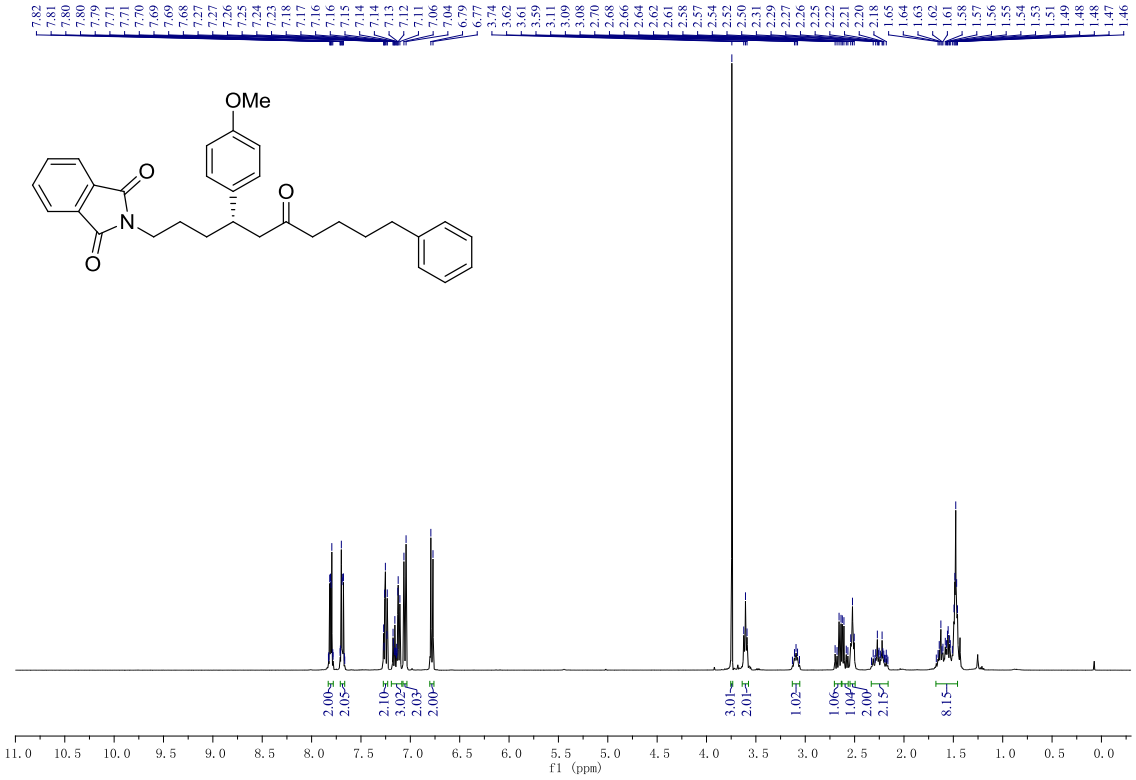


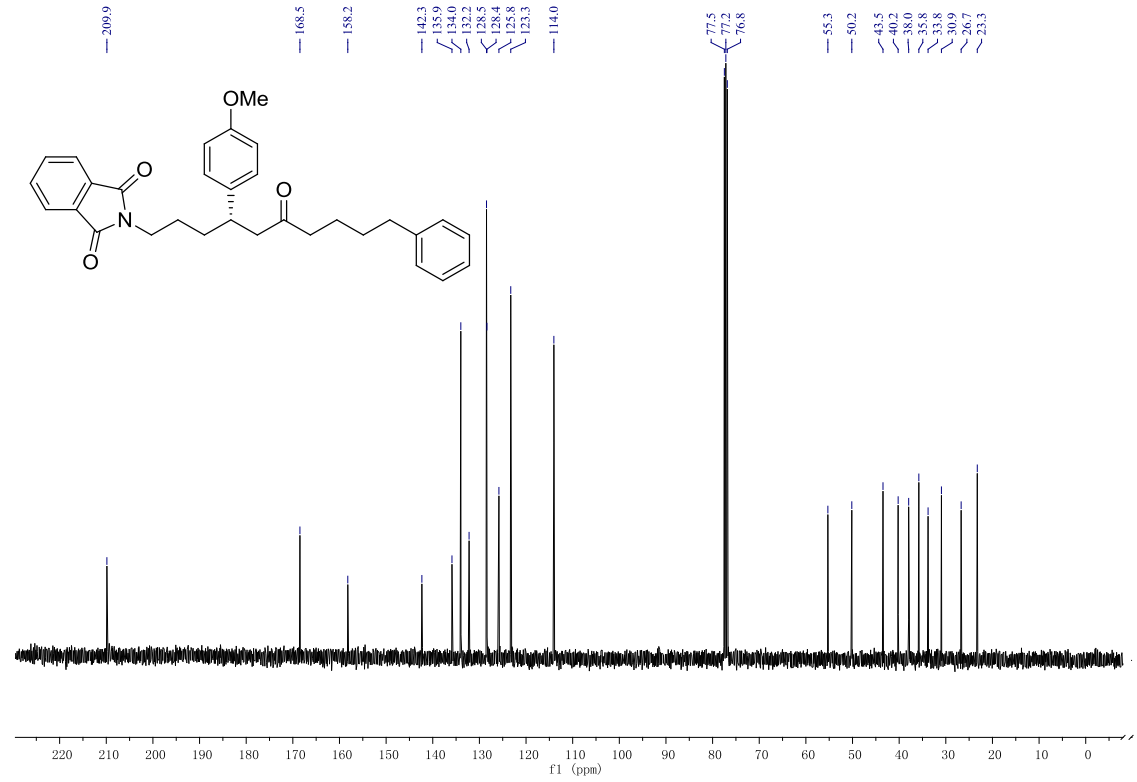
(*S*)-5-(4-Methoxyphenyl)-7-oxo-11-phenylundecyl acetate, 4aj



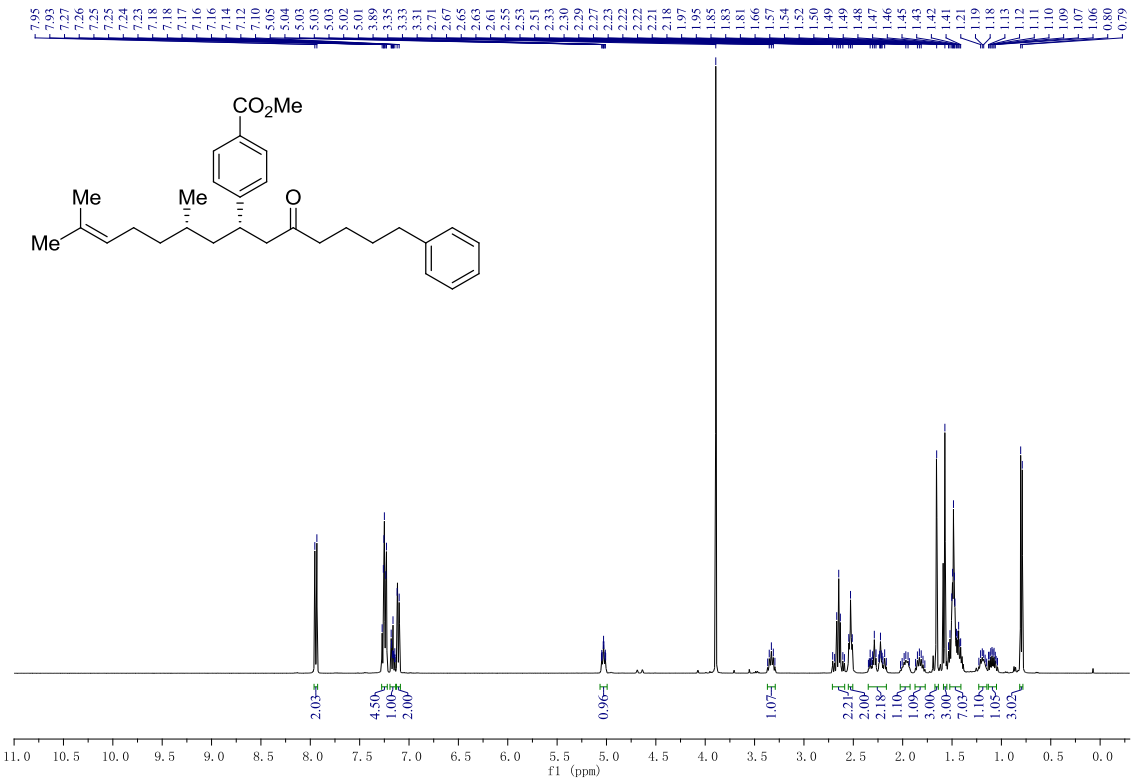


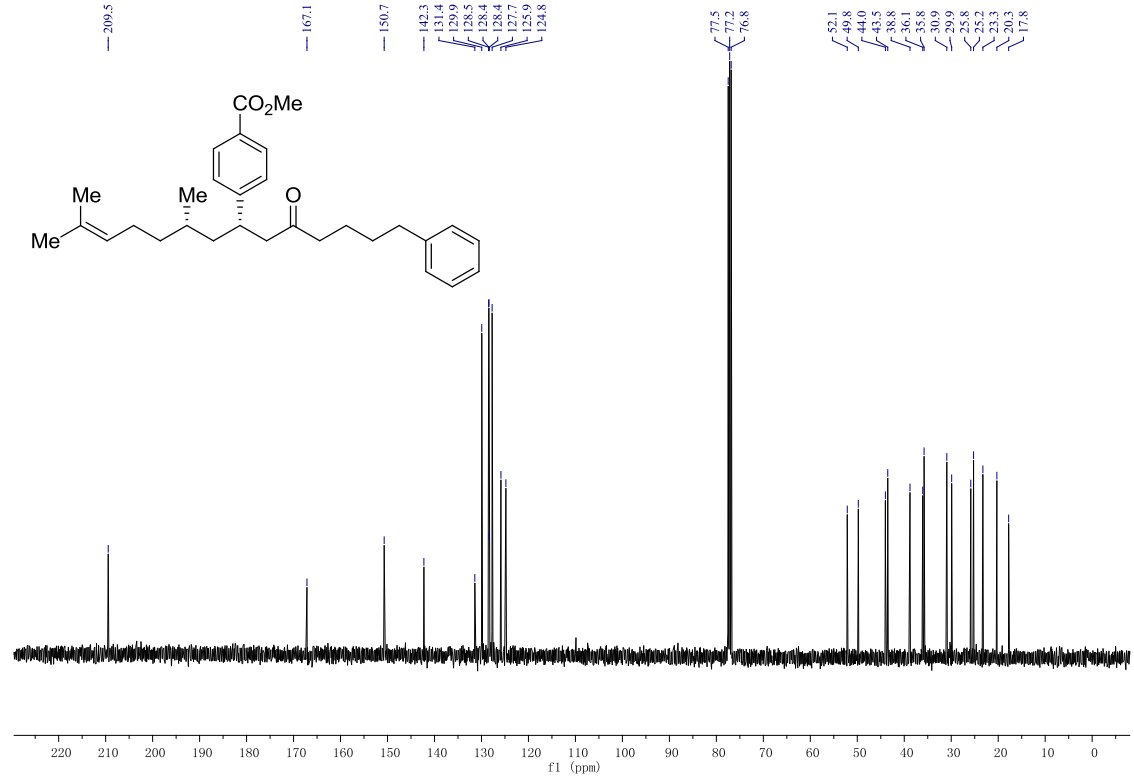
(*S*)-2-(4-(4-Methoxyphenyl)-6-oxo-10-phenyldecyl)isoindoline-1,3-dione, 4ak



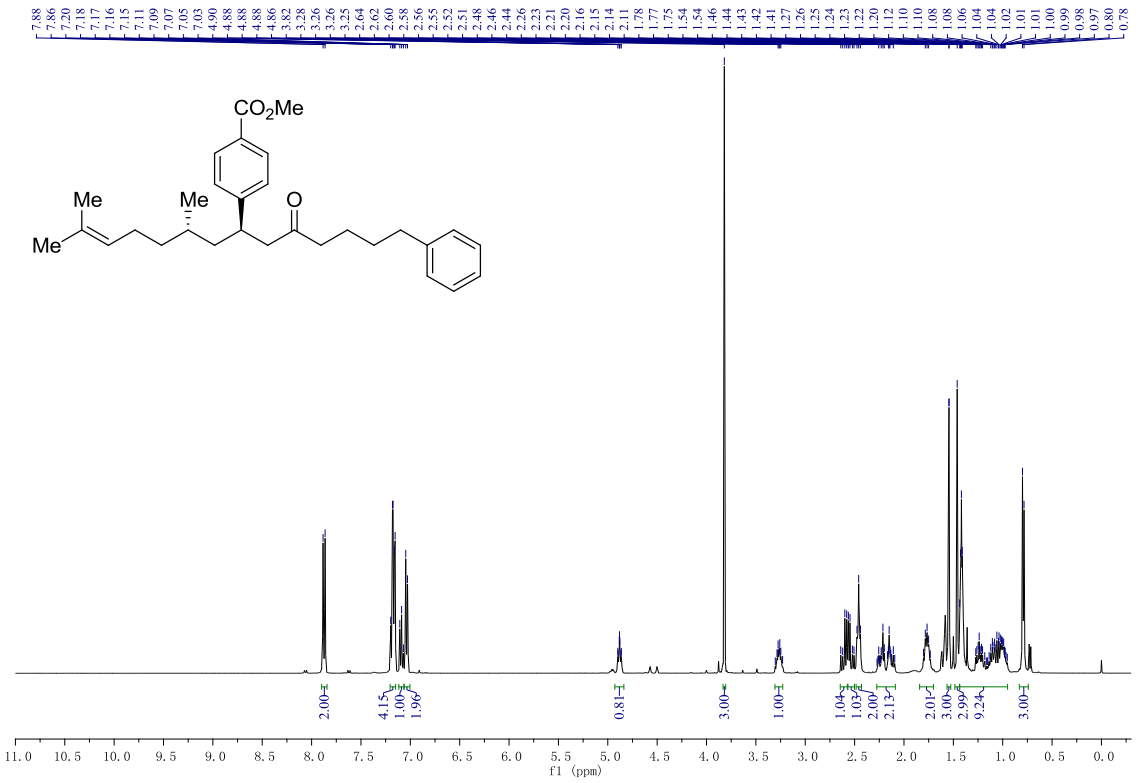


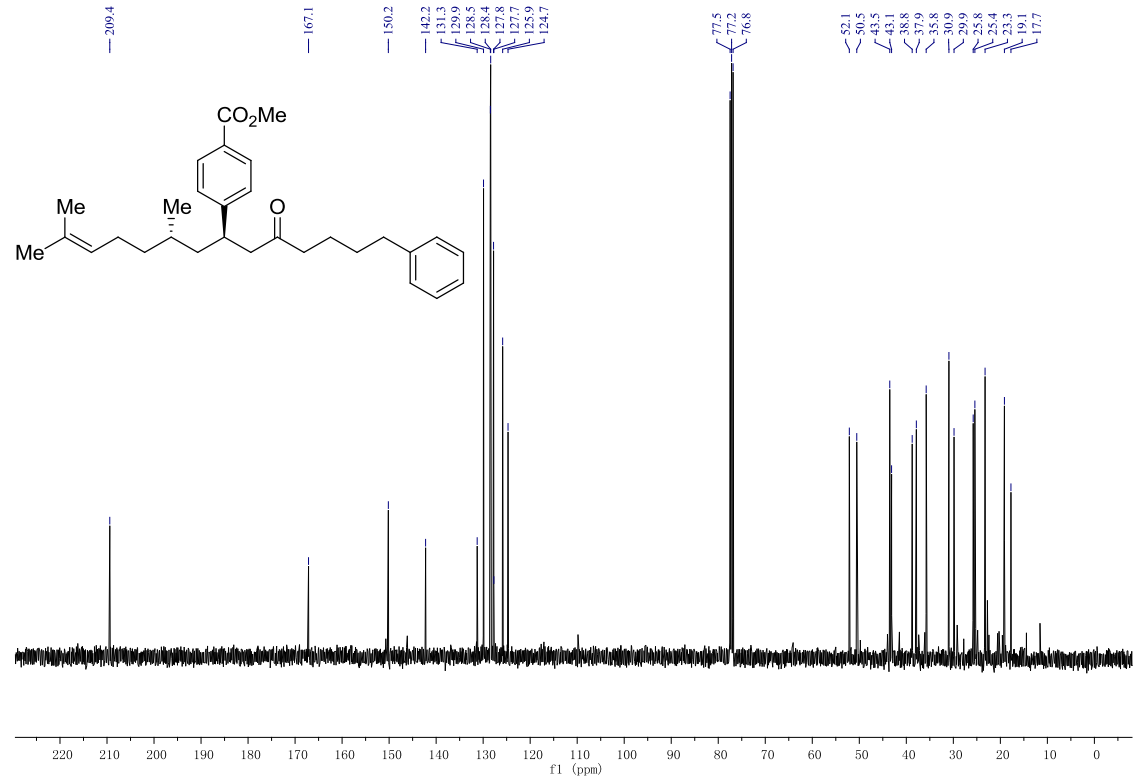
Methyl 4-((7*S*,9*S*)-9,13-dimethyl-5-oxo-1-phenyltetradec-12-en-7-yl)benzoate, 4al



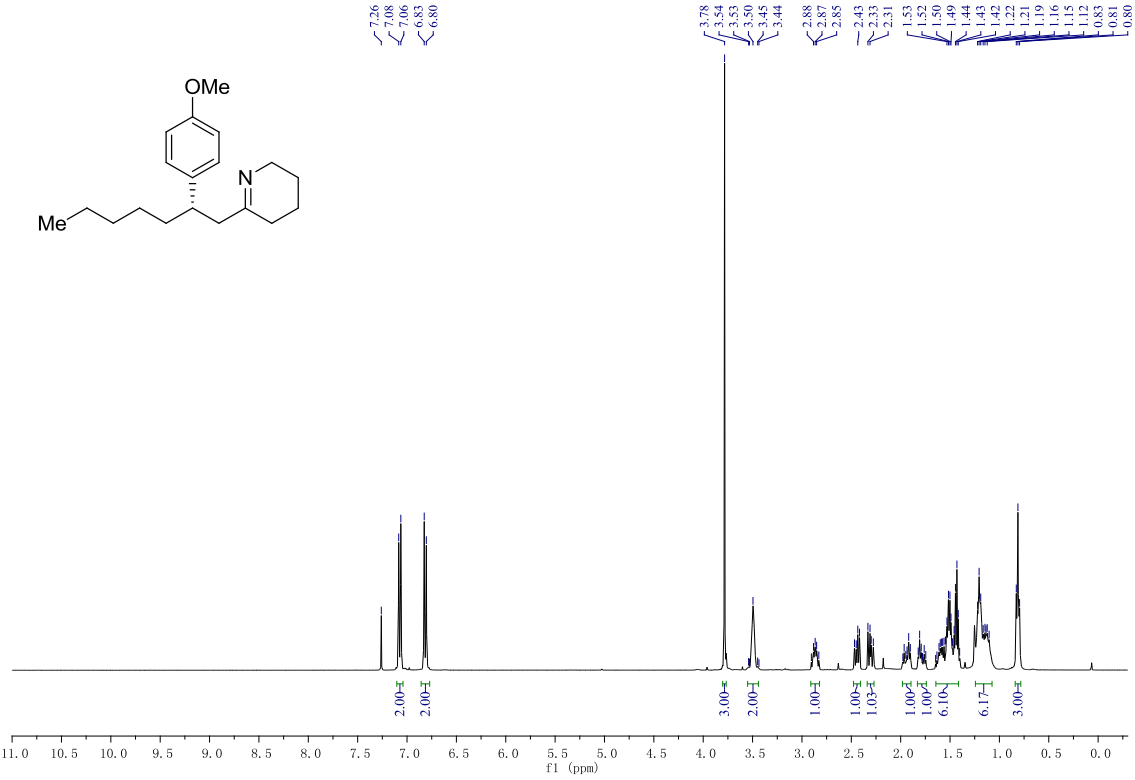


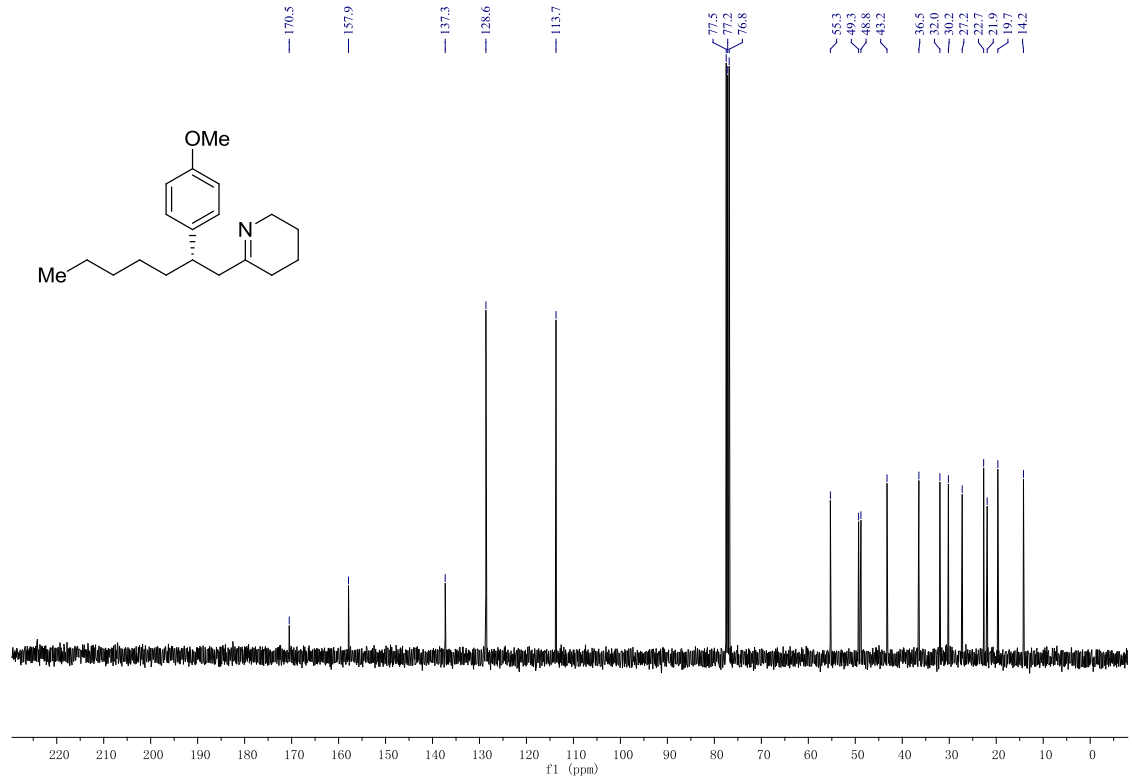
Methyl 4-((7*R*,9*S*)-9,13-dimethyl-5-oxo-1-phenyltetradec-12-en-7-yl)benzoate, 4am



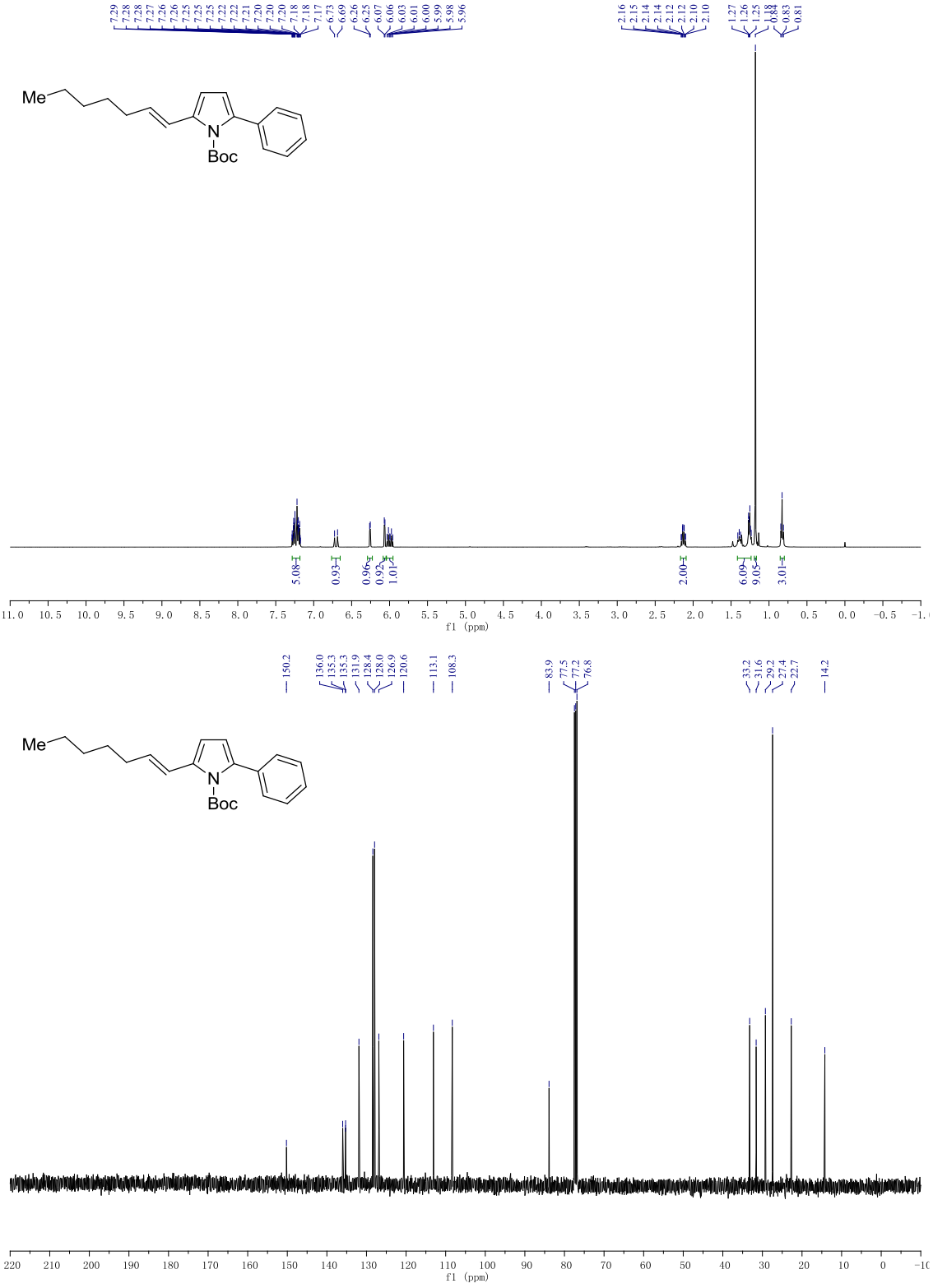


(*S*)-6-(2-(4-Methoxyphenyl)heptyl)-2,3,4,5-tetrahydropyridine, 5a

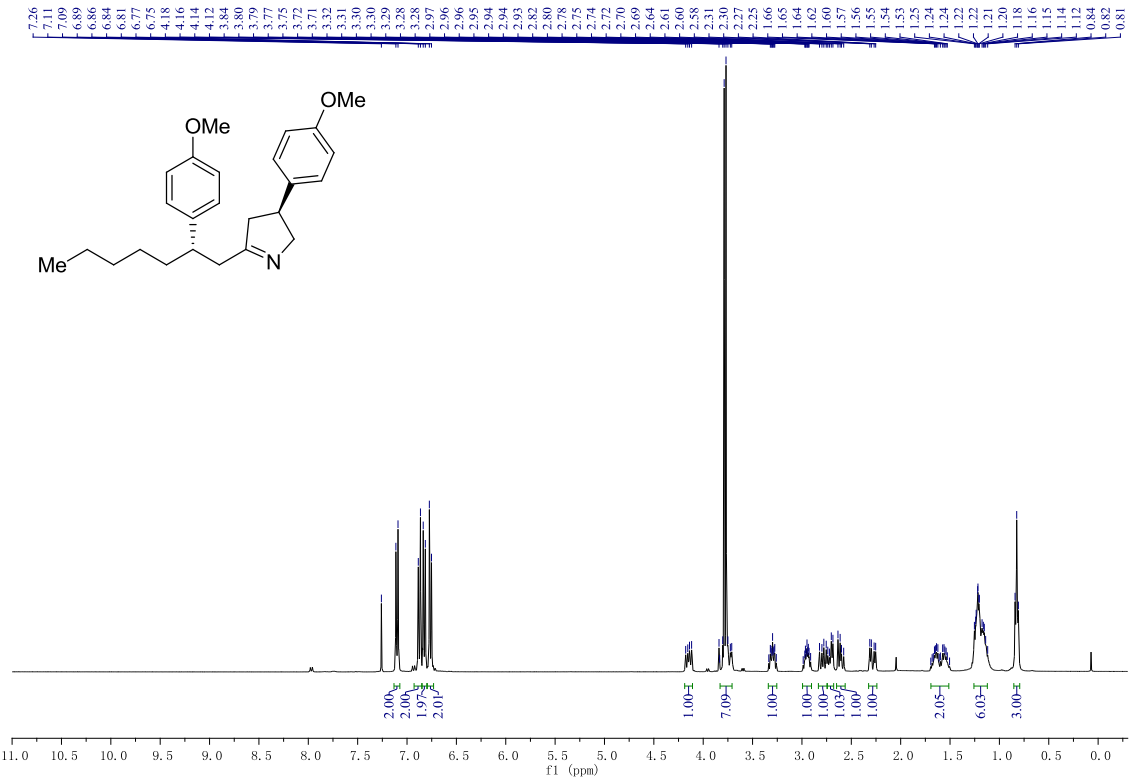


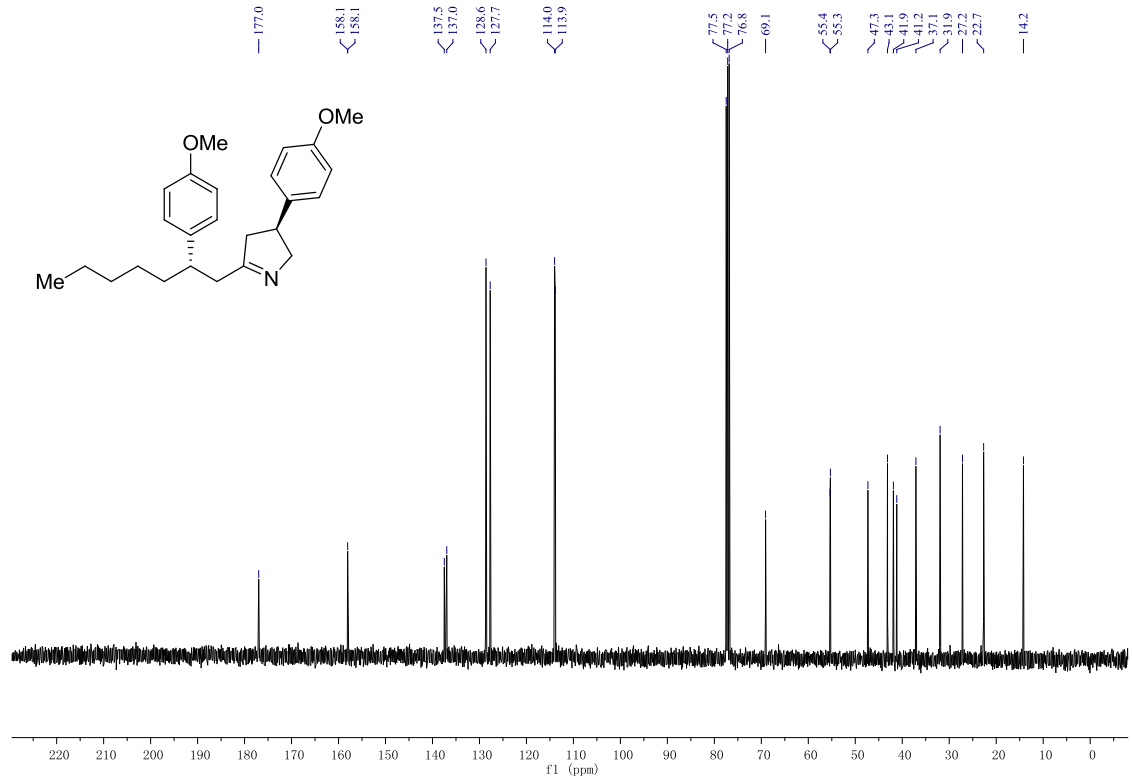


(*E*)-*tert*-Butyl 2-(hept-1-en-1-yl)-5-phenyl-1*H*-pyrrole-1-carboxylate, 5b

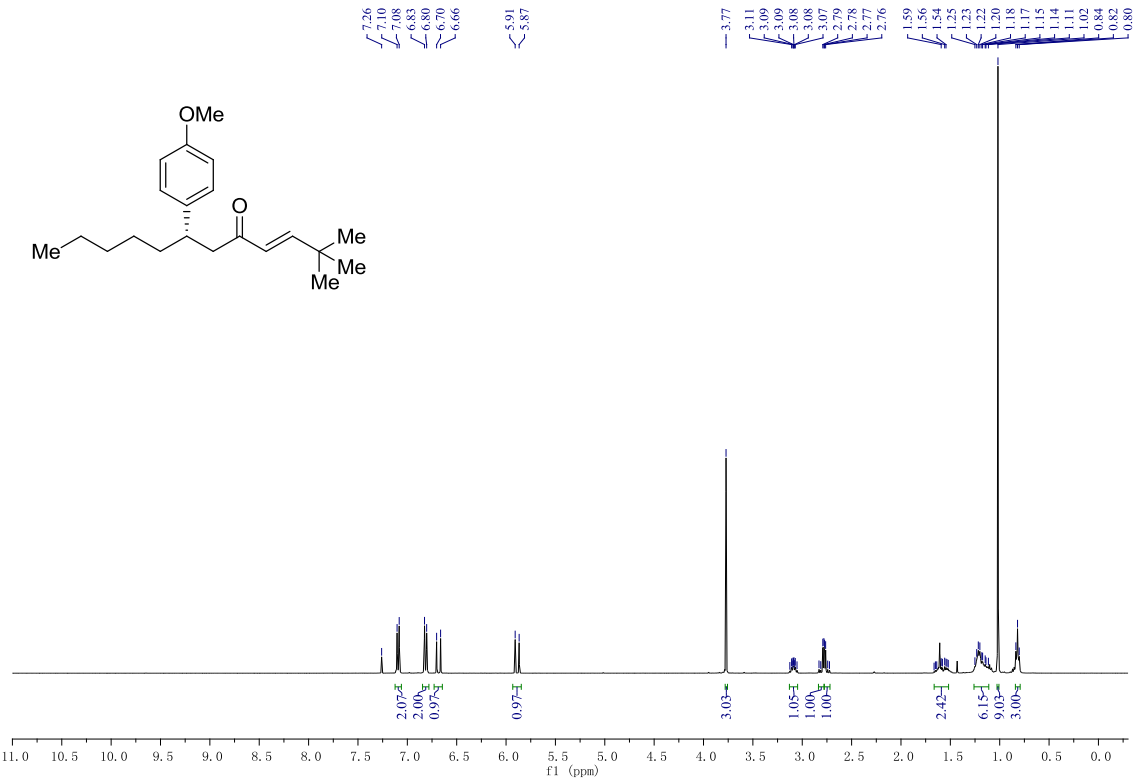


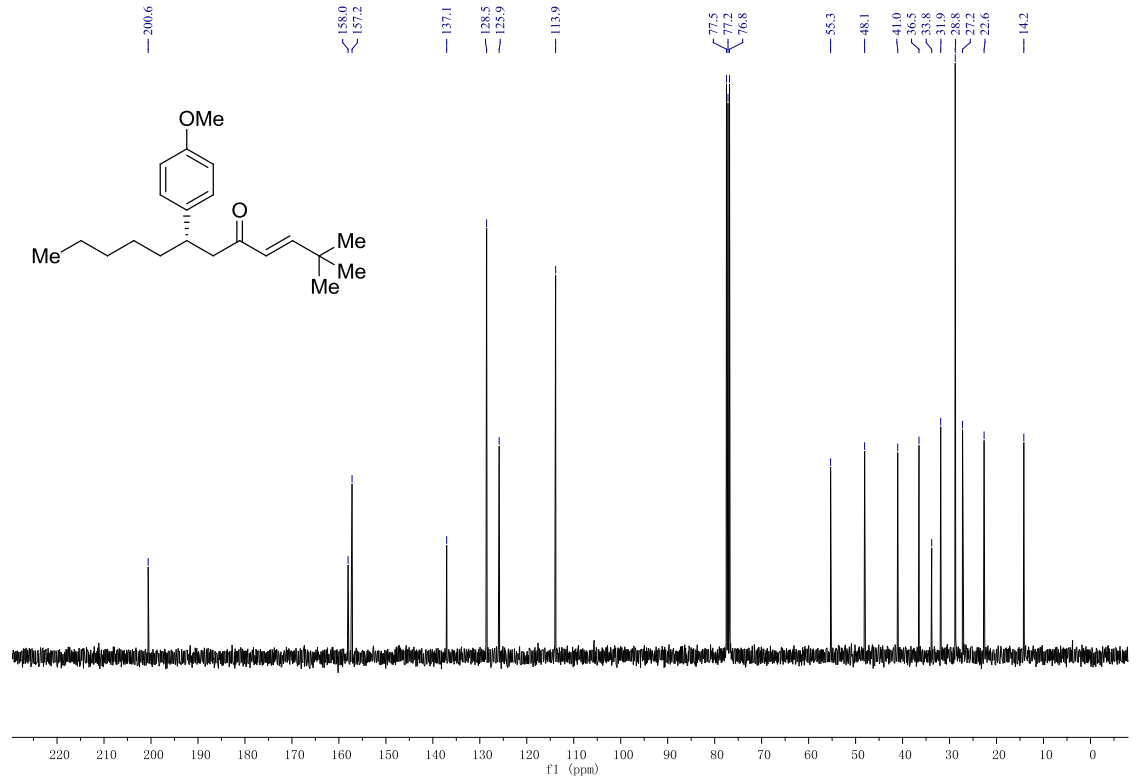
(*S*)-3-(4-Methoxyphenyl)-5-((*S*)-2-(4-methoxyphenyl)heptyl)-3,4-dihydro-2*H*-pyrrole, 5c



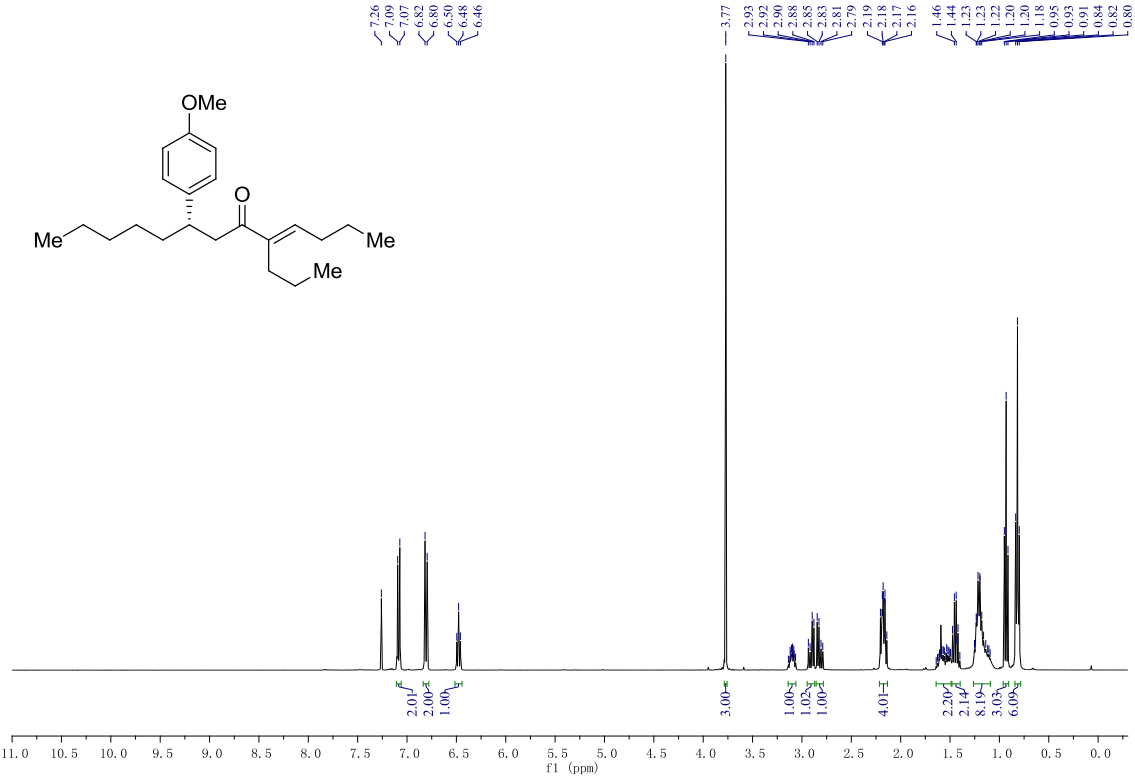


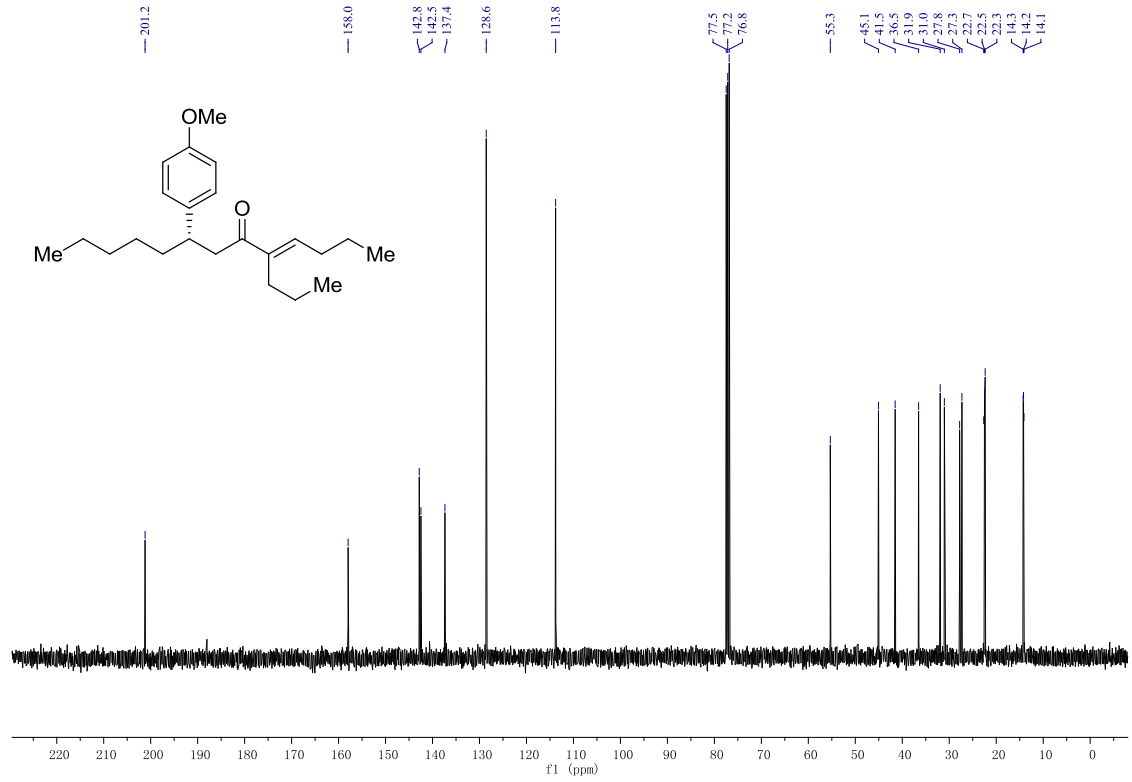
(*S*,*E*)-7-(4-Methoxyphenyl)-2,2-dimethyldodec-3-en-5-one, 6a



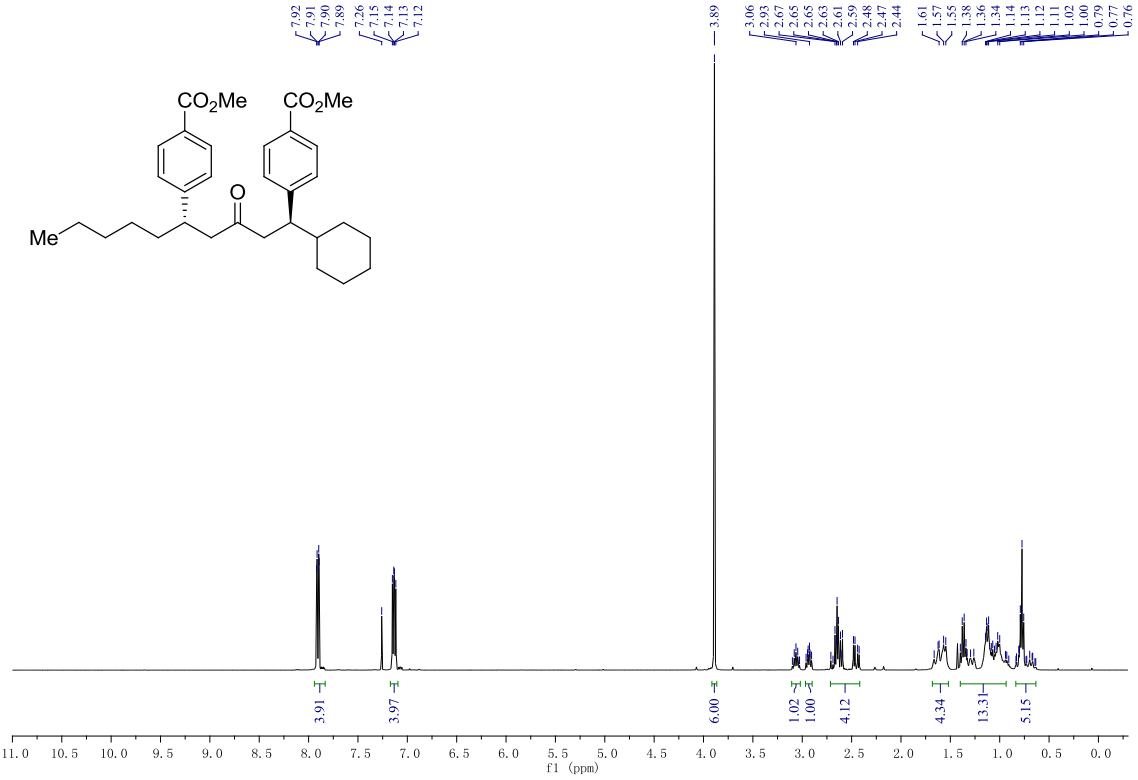


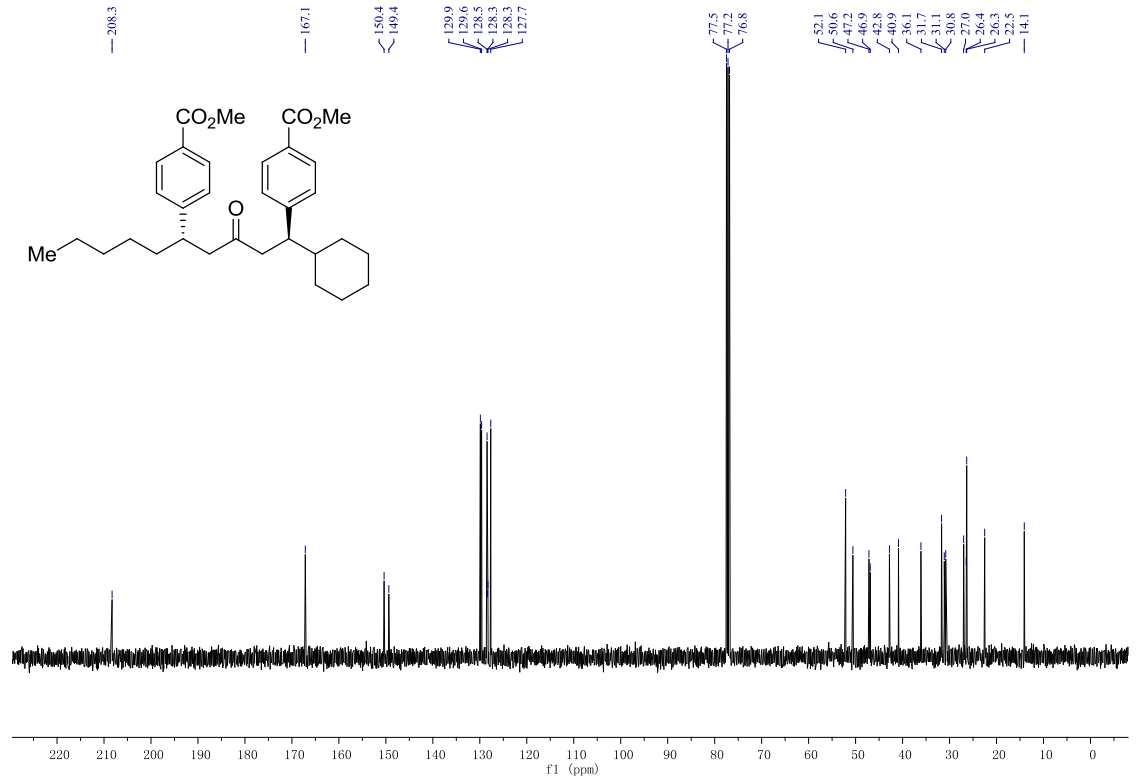
(*S*,*E*)-8-(4-Methoxyphenyl)-5-propyltridec-4-en-6-one, 6b



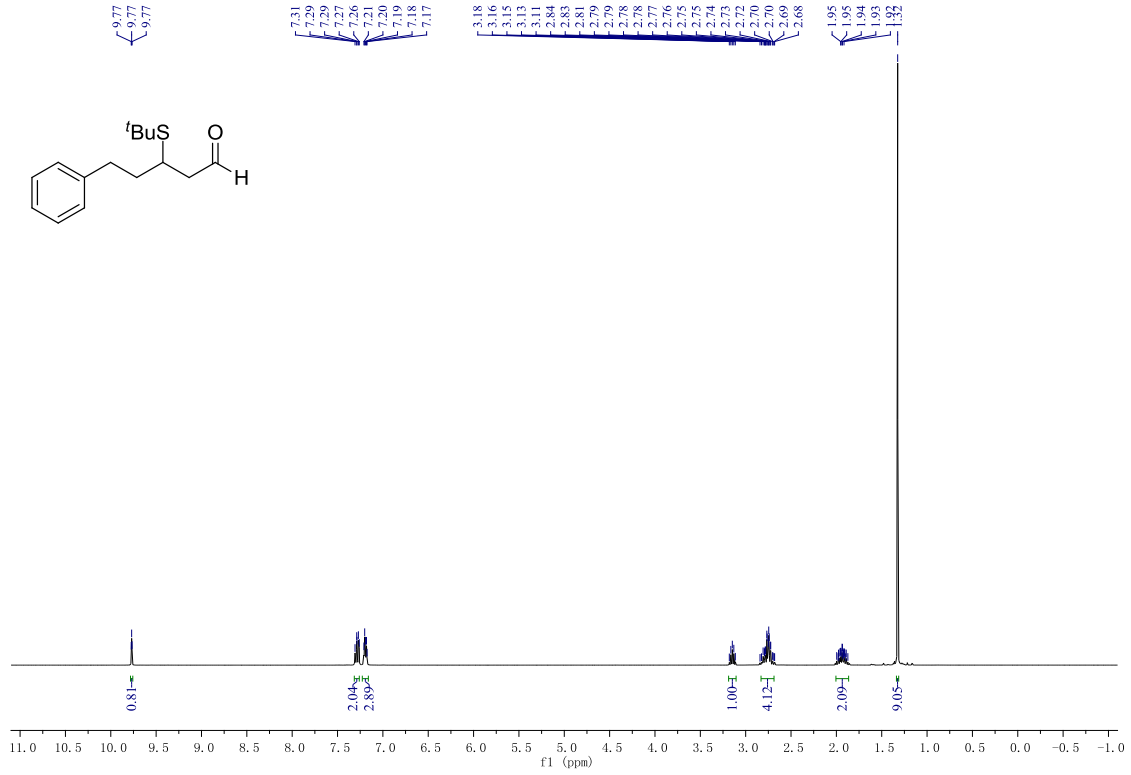


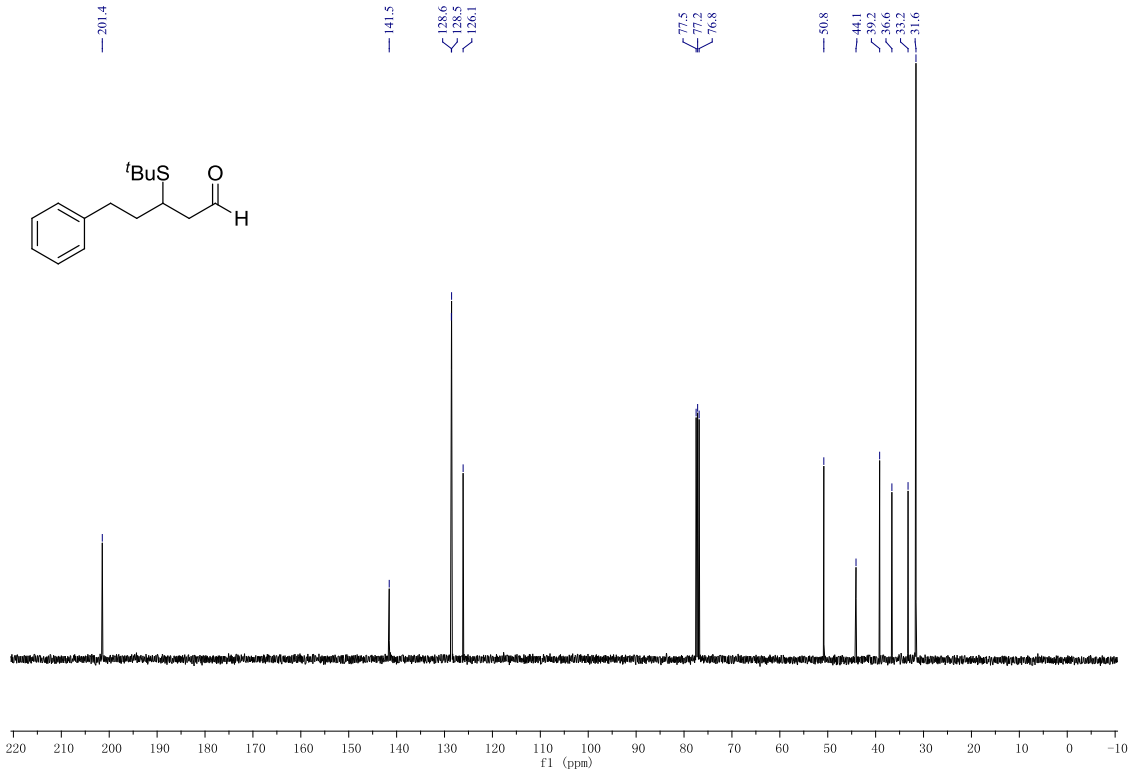
Dimethyl 4,4'-((1*R*,5*S*)-1-cyclohexyl-3-oxodecane-1,5-diyl)dibenzoate, 6c



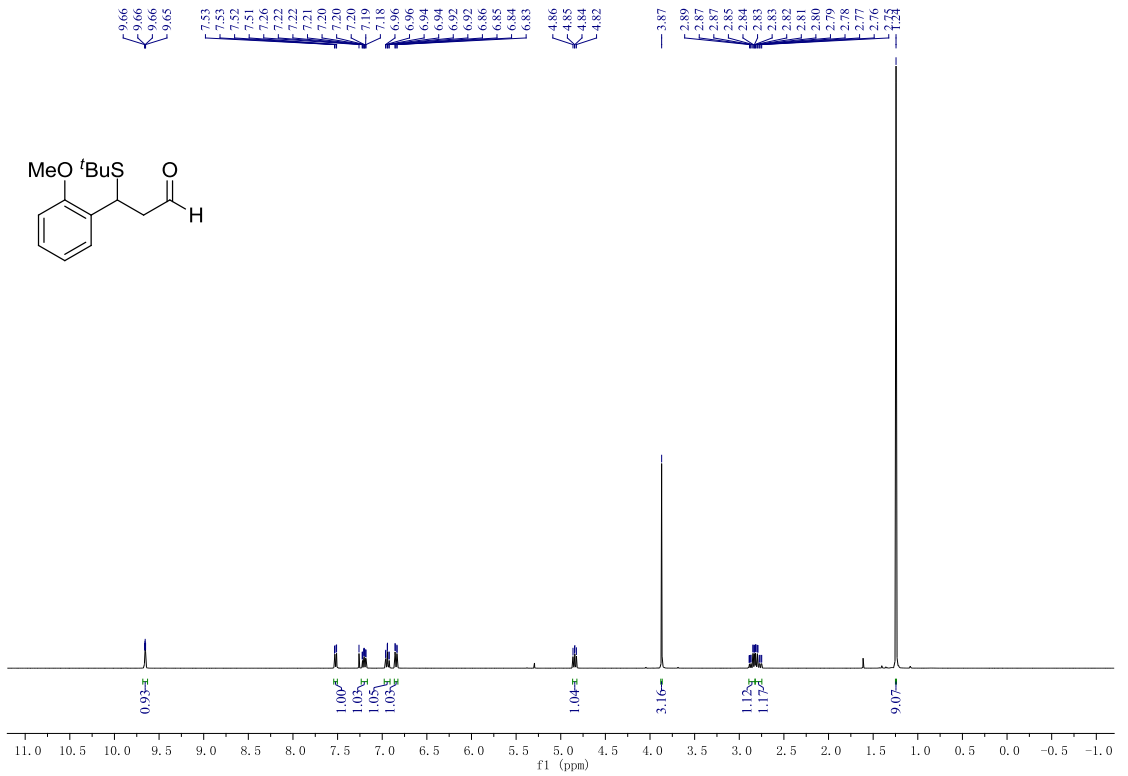


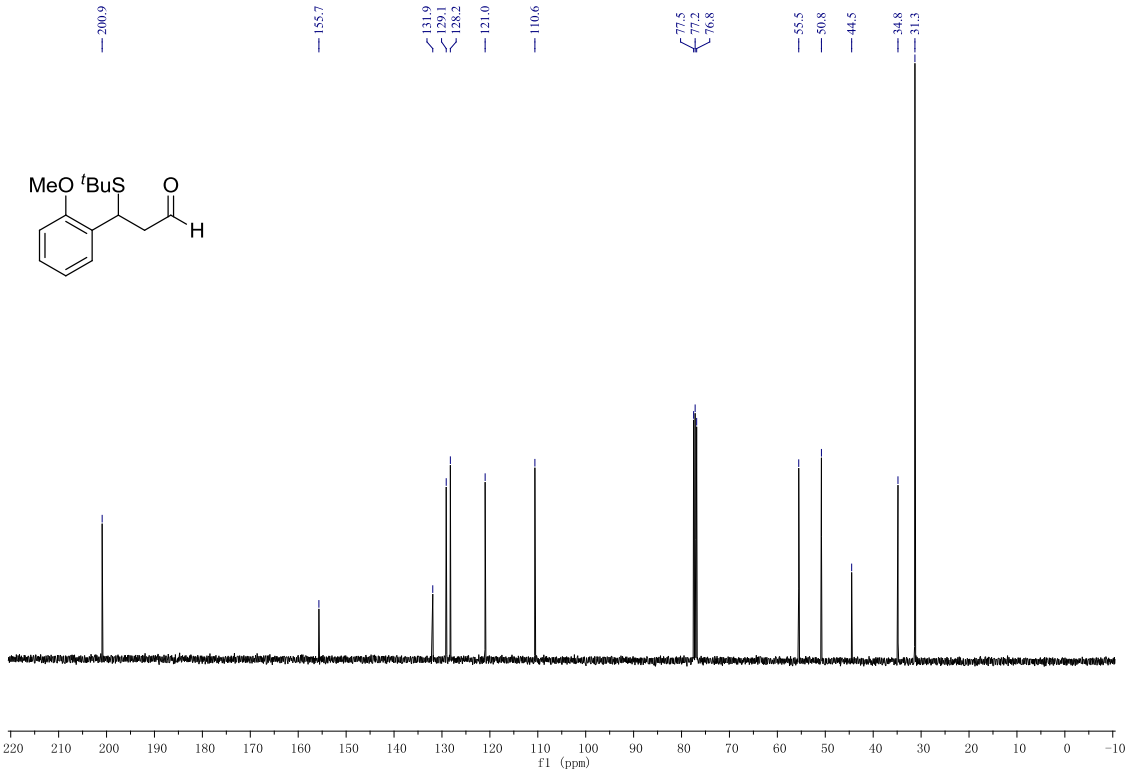
3-(*tert*-Butylthio)-5-phenylpentanal, 7c



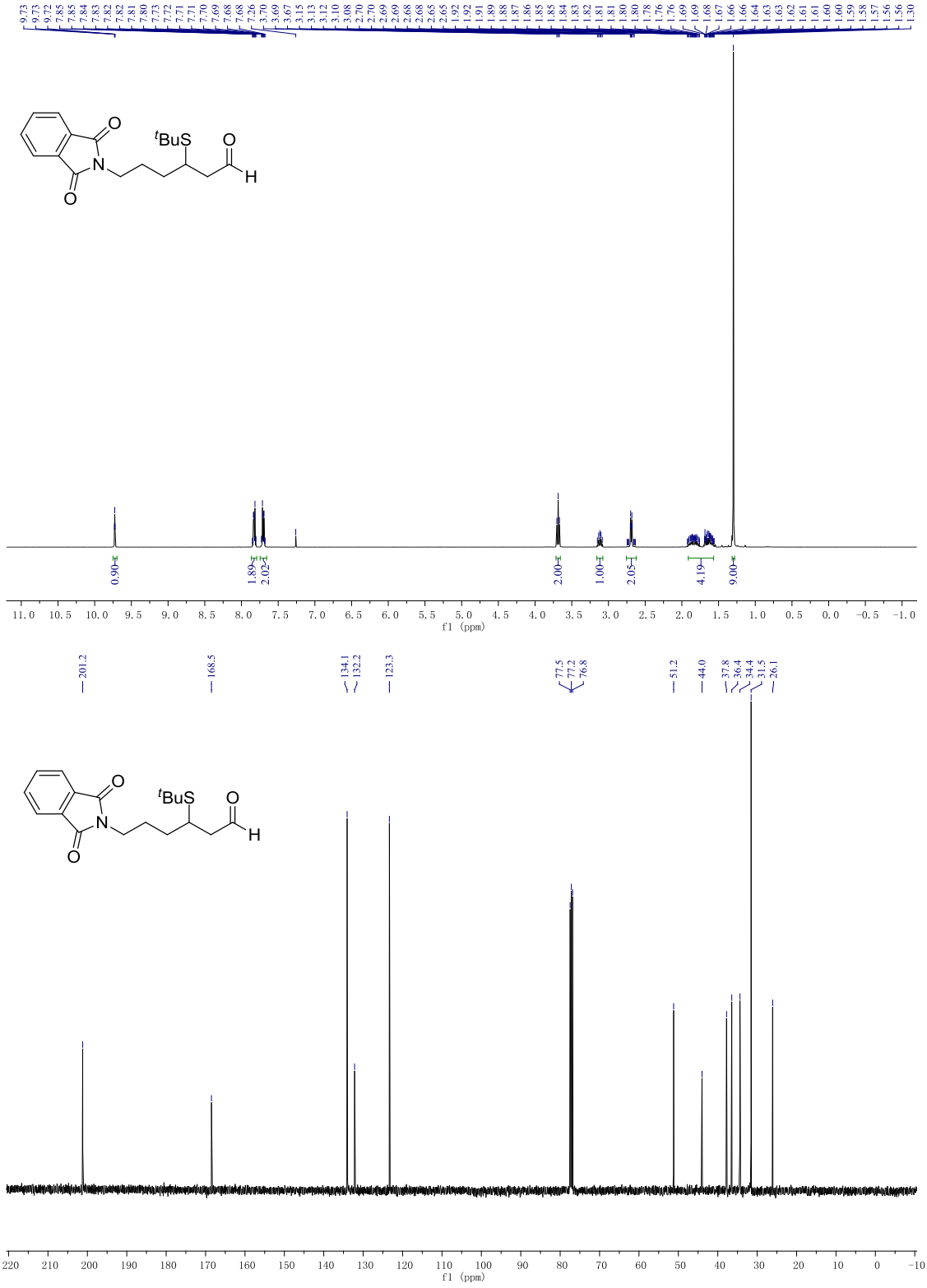


3-(*tert*-Butylthio)-3-(2-methoxyphenyl)propanal, 7e

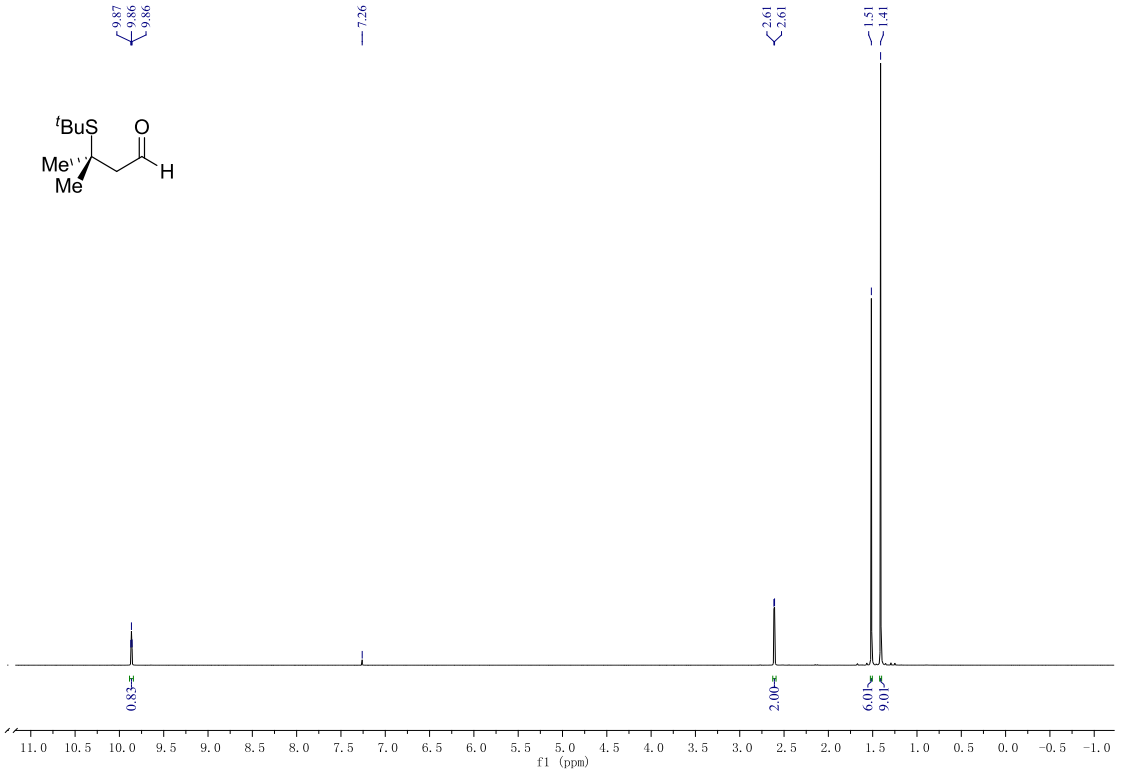


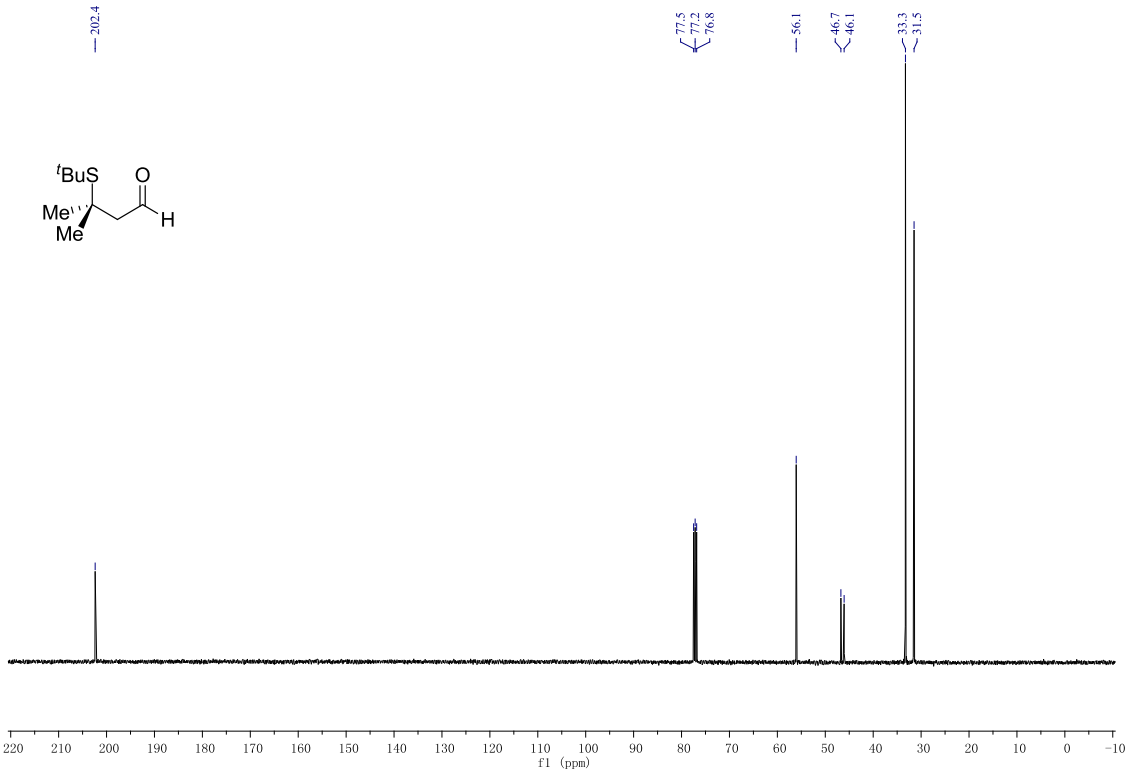


3-(*tert*-Butylthio)-6-(1,3-dioxoisoindolin-2-yl)hexanal, 7f

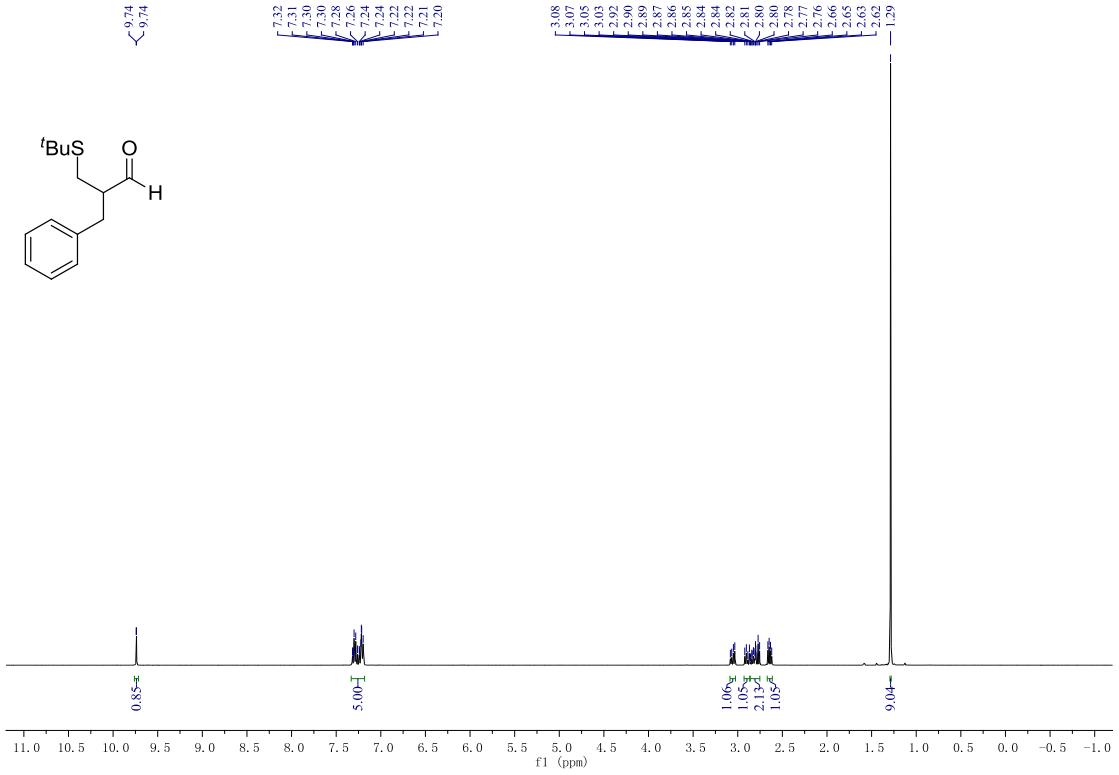


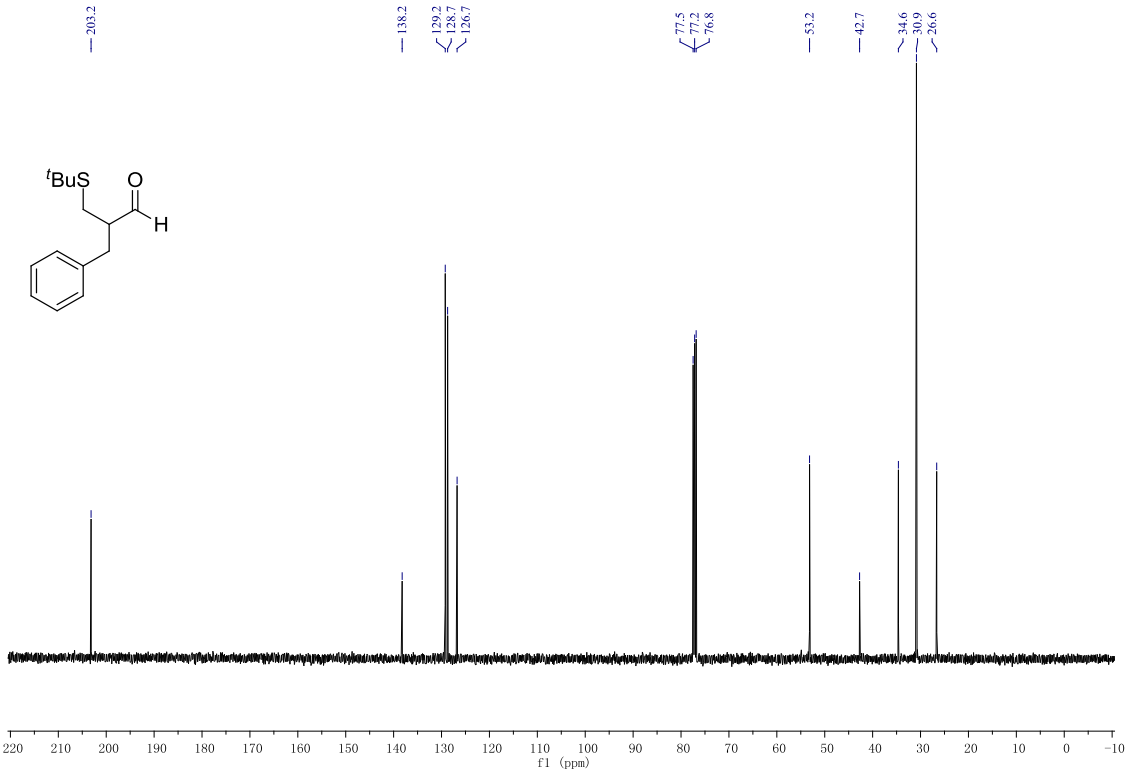
3-(*tert*-Butylthio)-3-methylbutanal, 7g



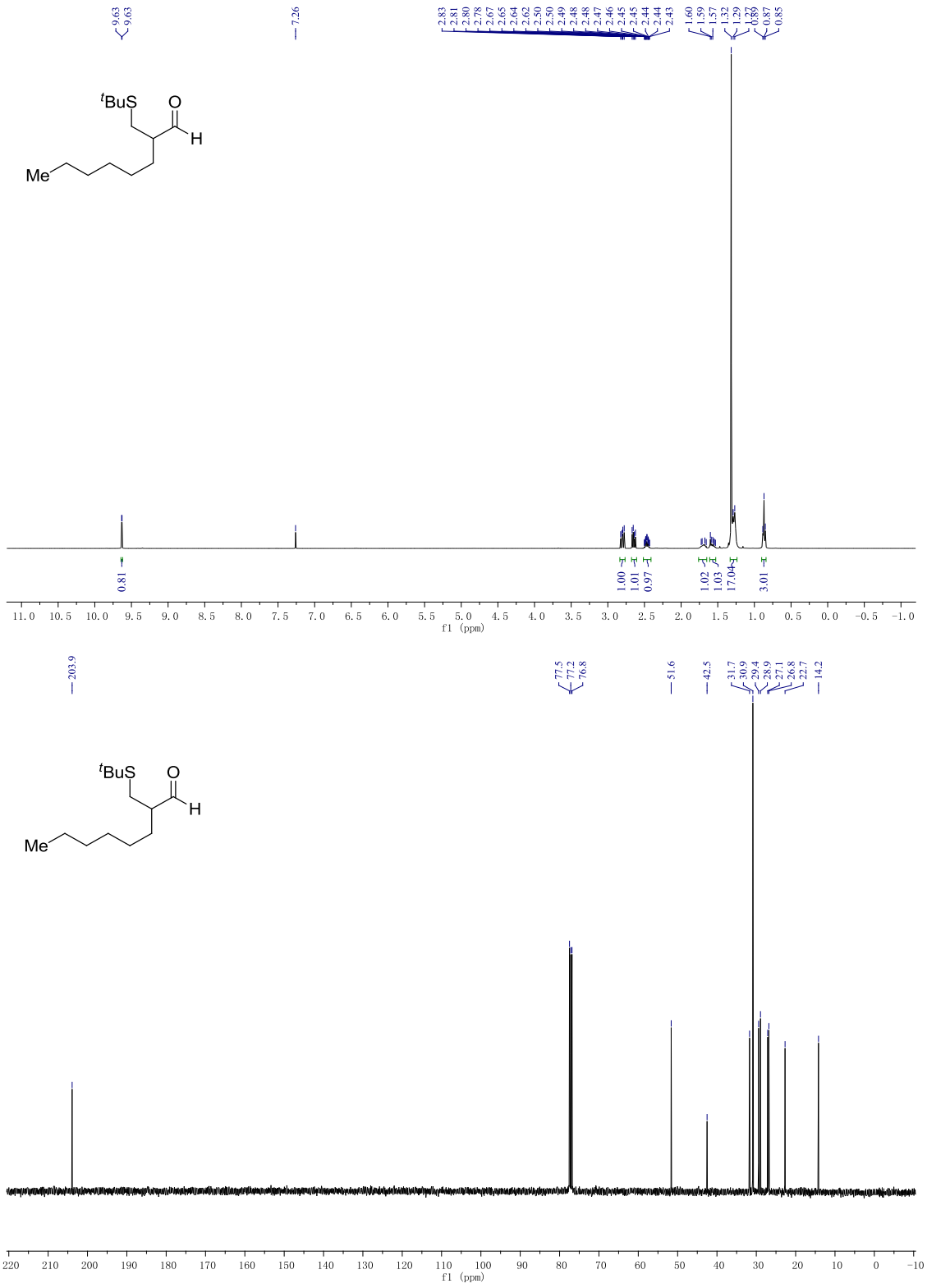


2-Benzyl-3-(*tert*-butylthio)propanal, 7h

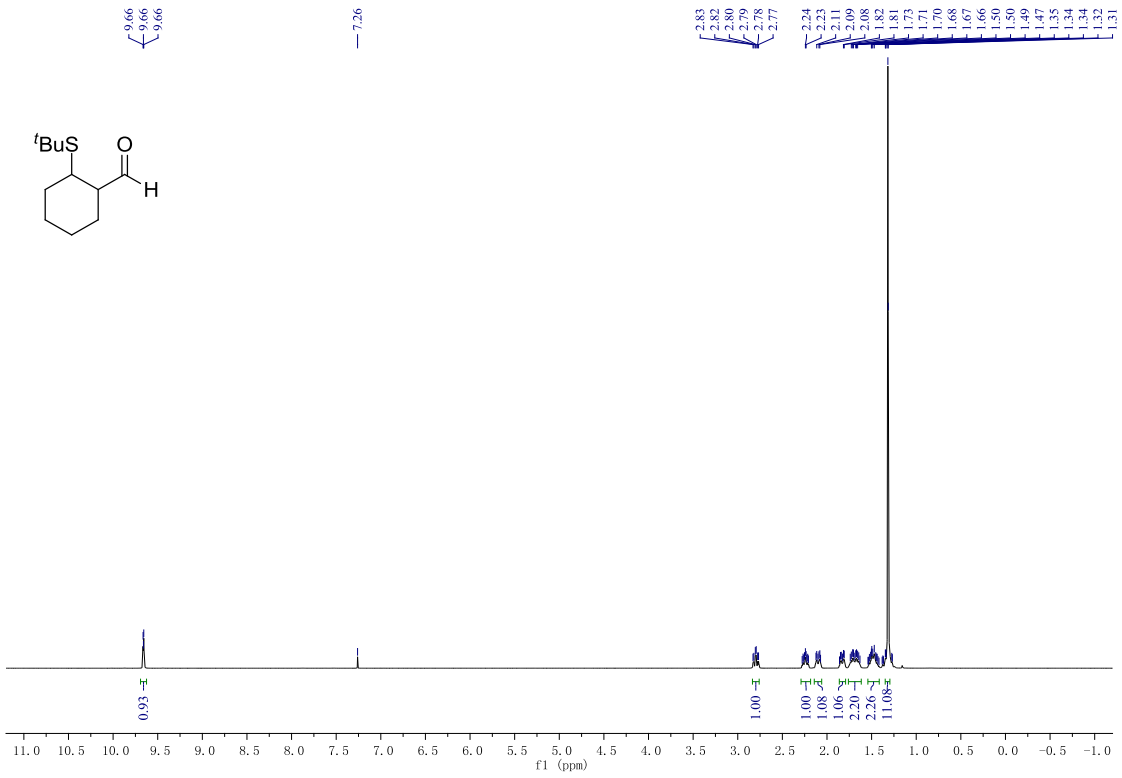


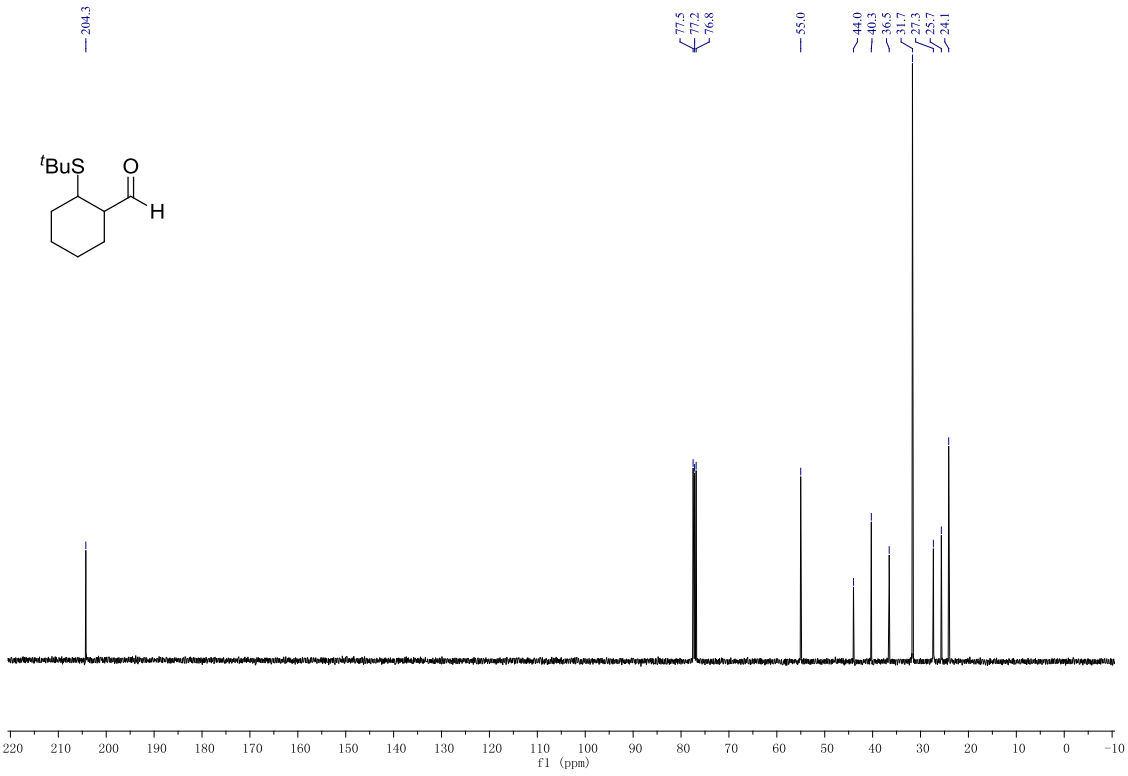


2-((*tert*-Butylthio)methyl)octanal, 7i

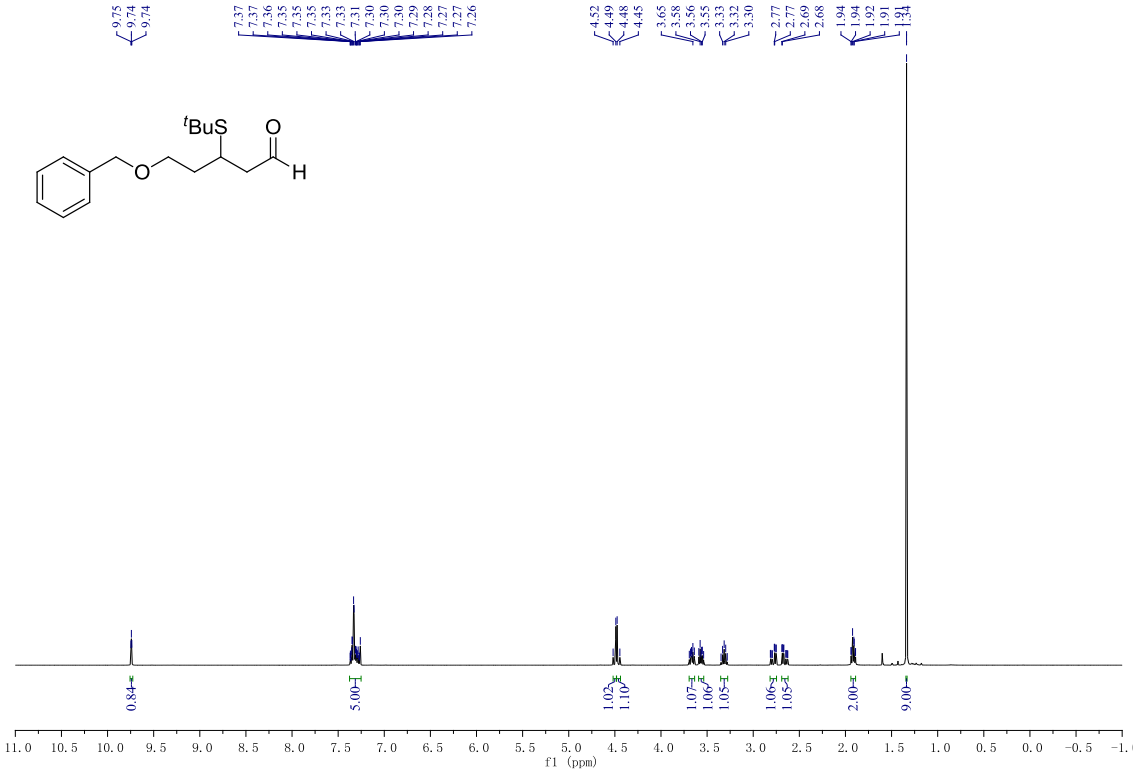


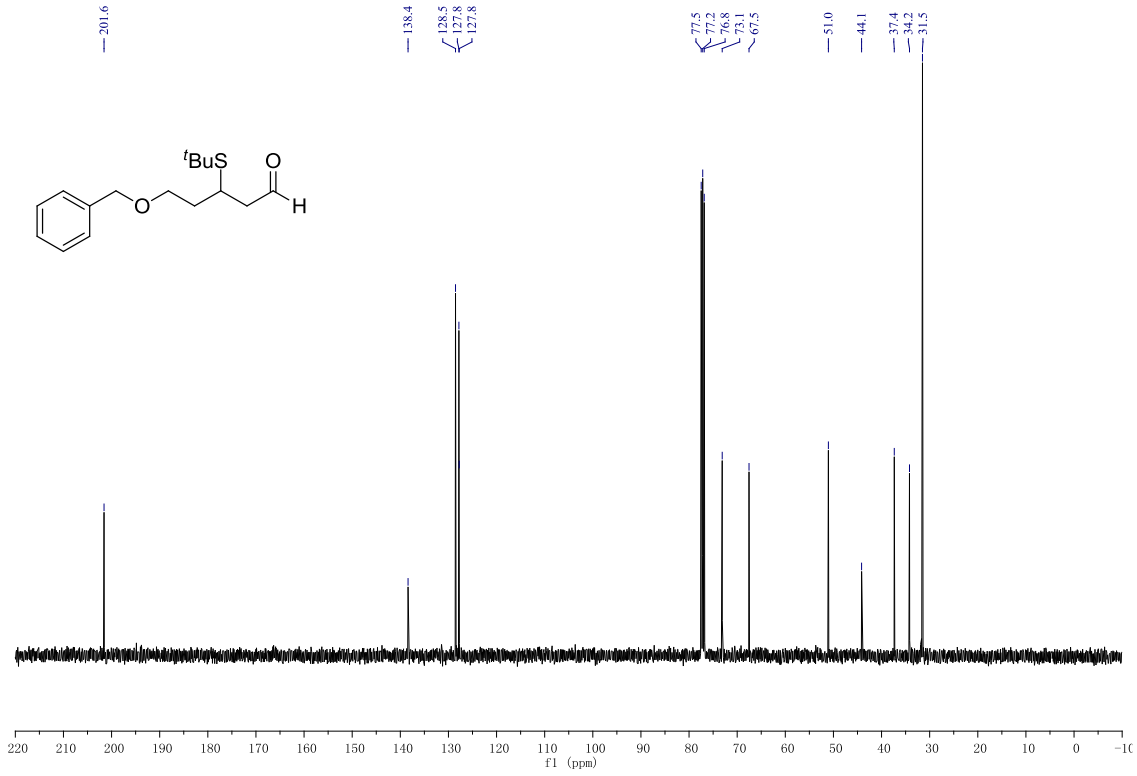
2-(*tert*-Butylthio)cyclohexanecarbaldehyde, 7j



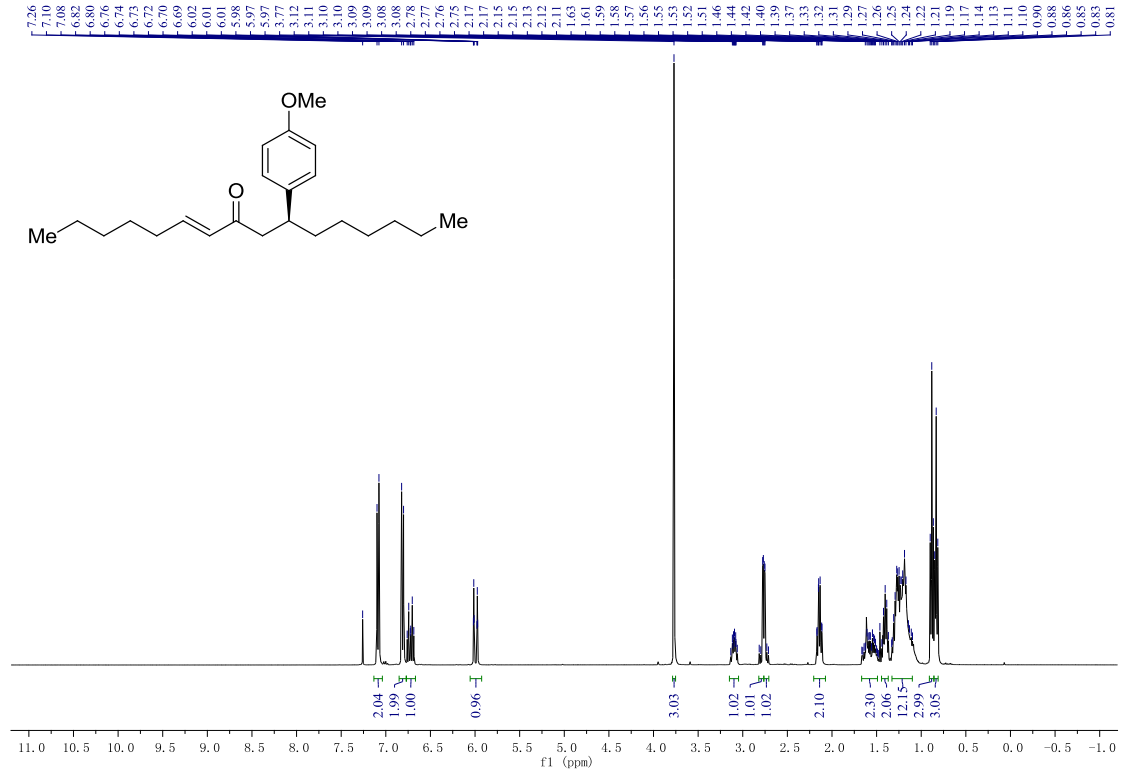


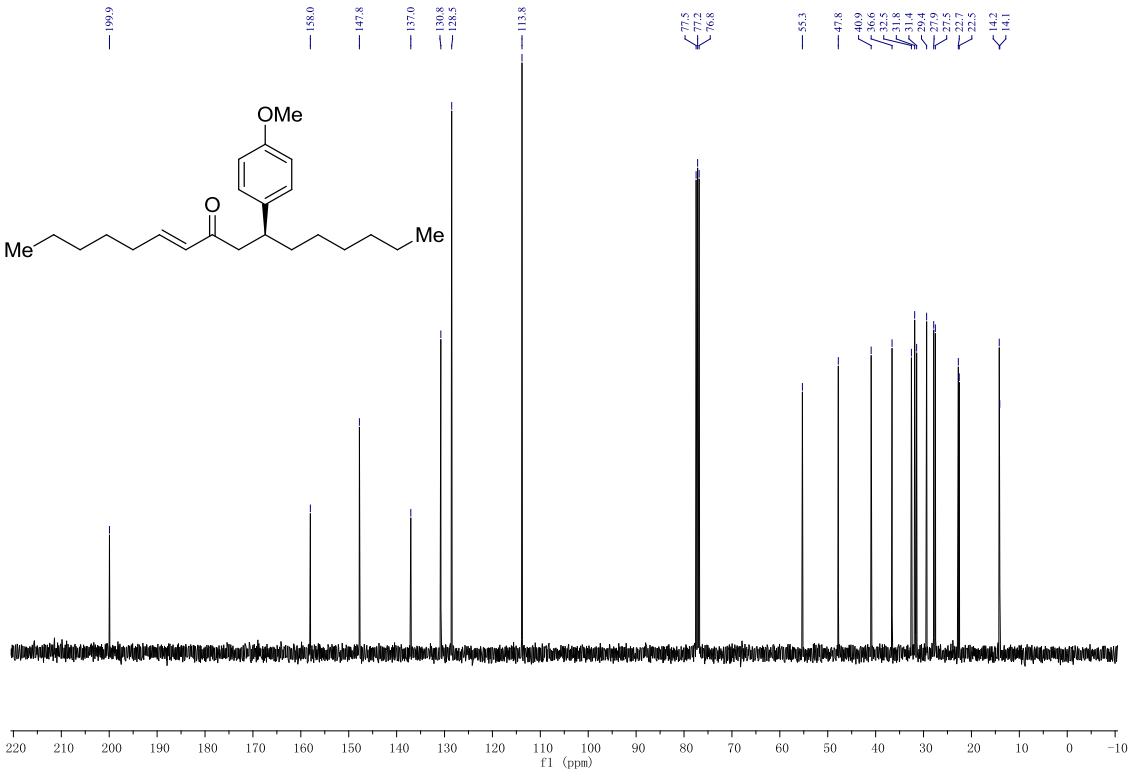
5-(Benzyloxy)-3-(*tert*-butylthio)pentanal, 7k



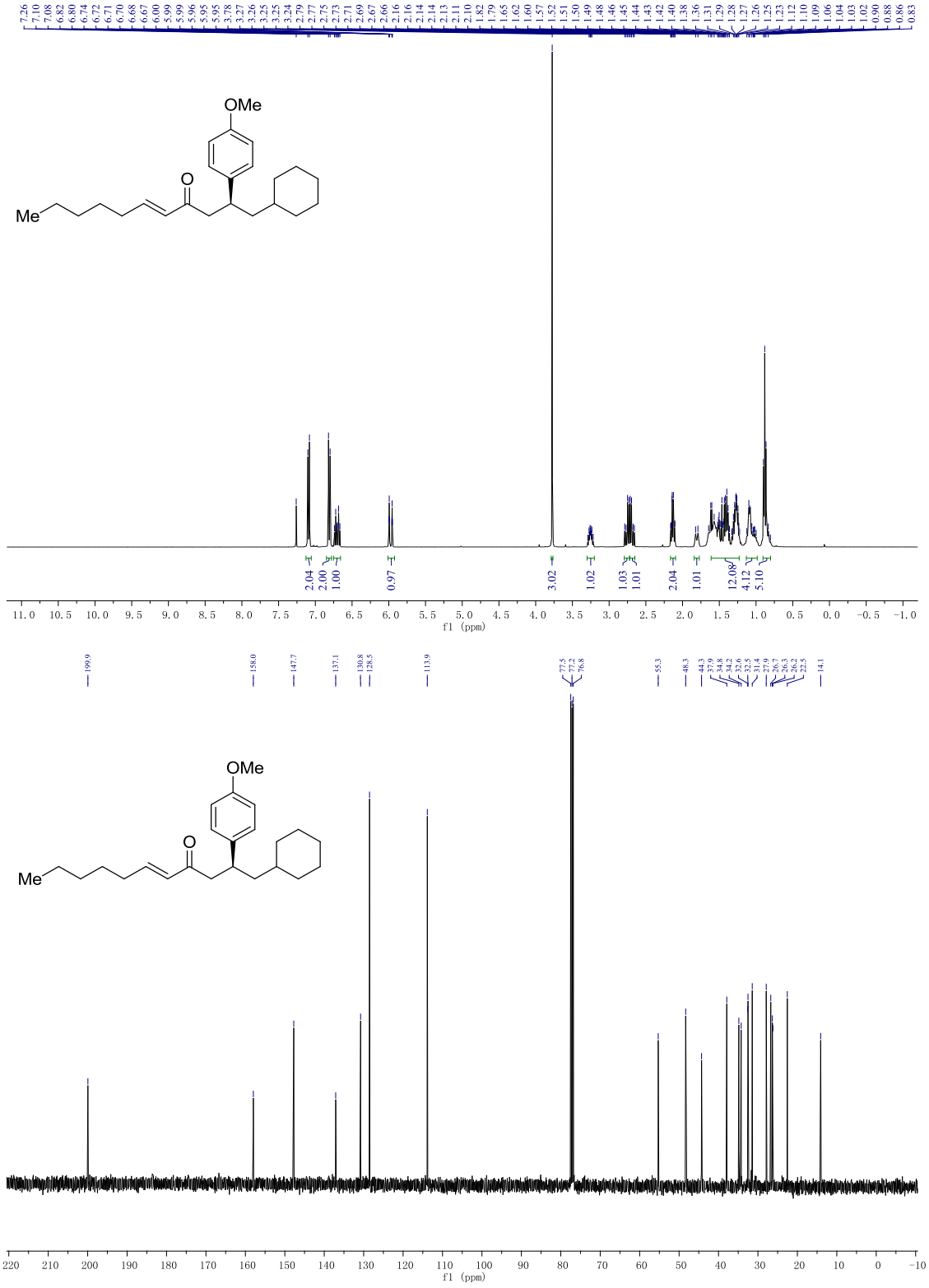


(*S*,*E*)-10-(4-Methoxyphenyl)hexadec-6-en-8-one, 8a

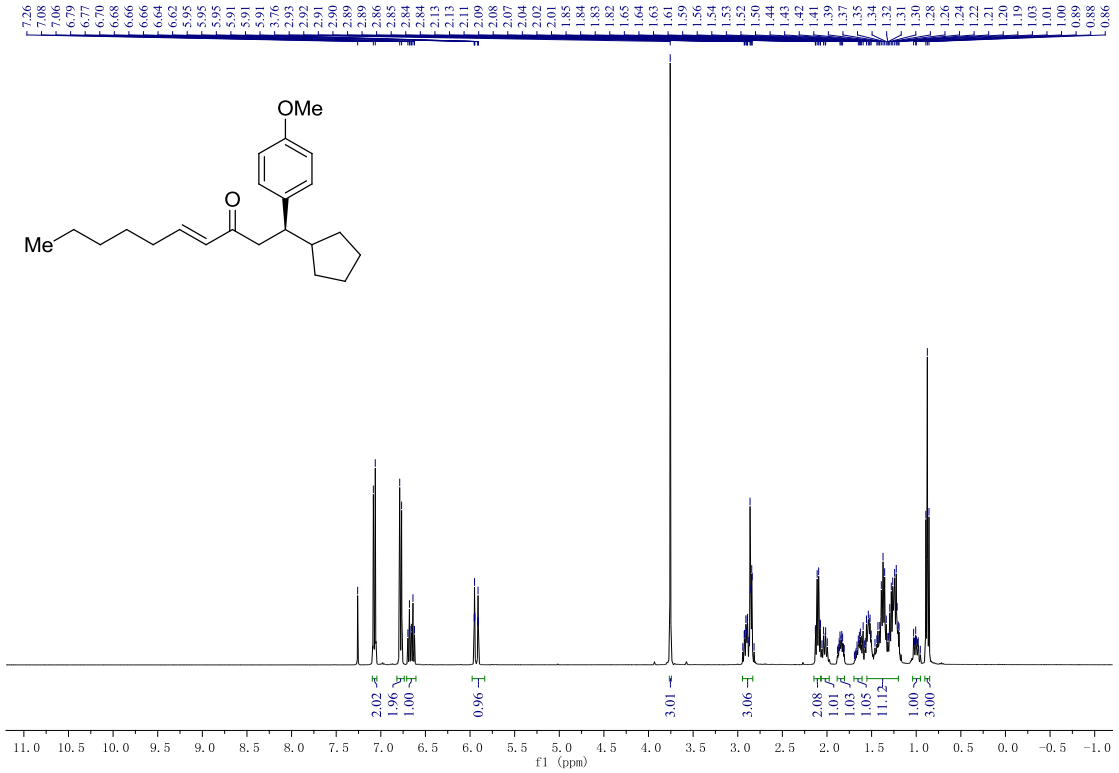


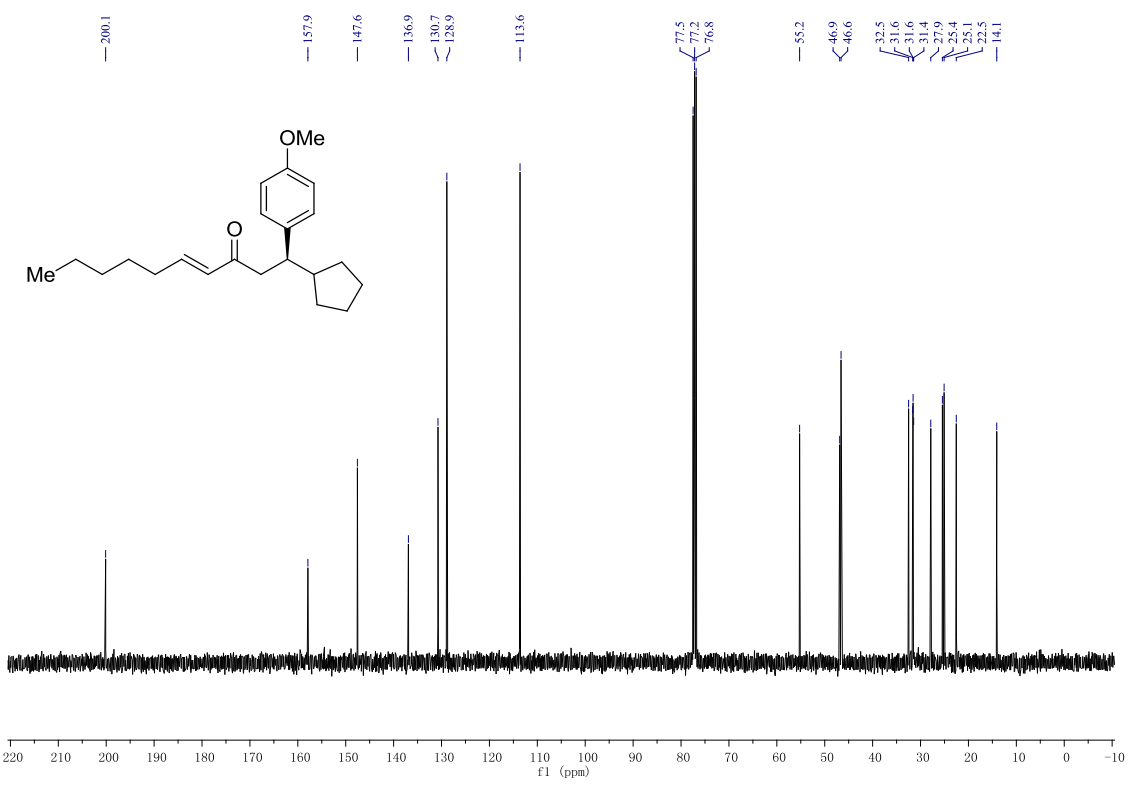


(*S*,*E*)-1-Cyclohexyl-2-(4-methoxyphenyl)undec-5-en-4-one, 8b

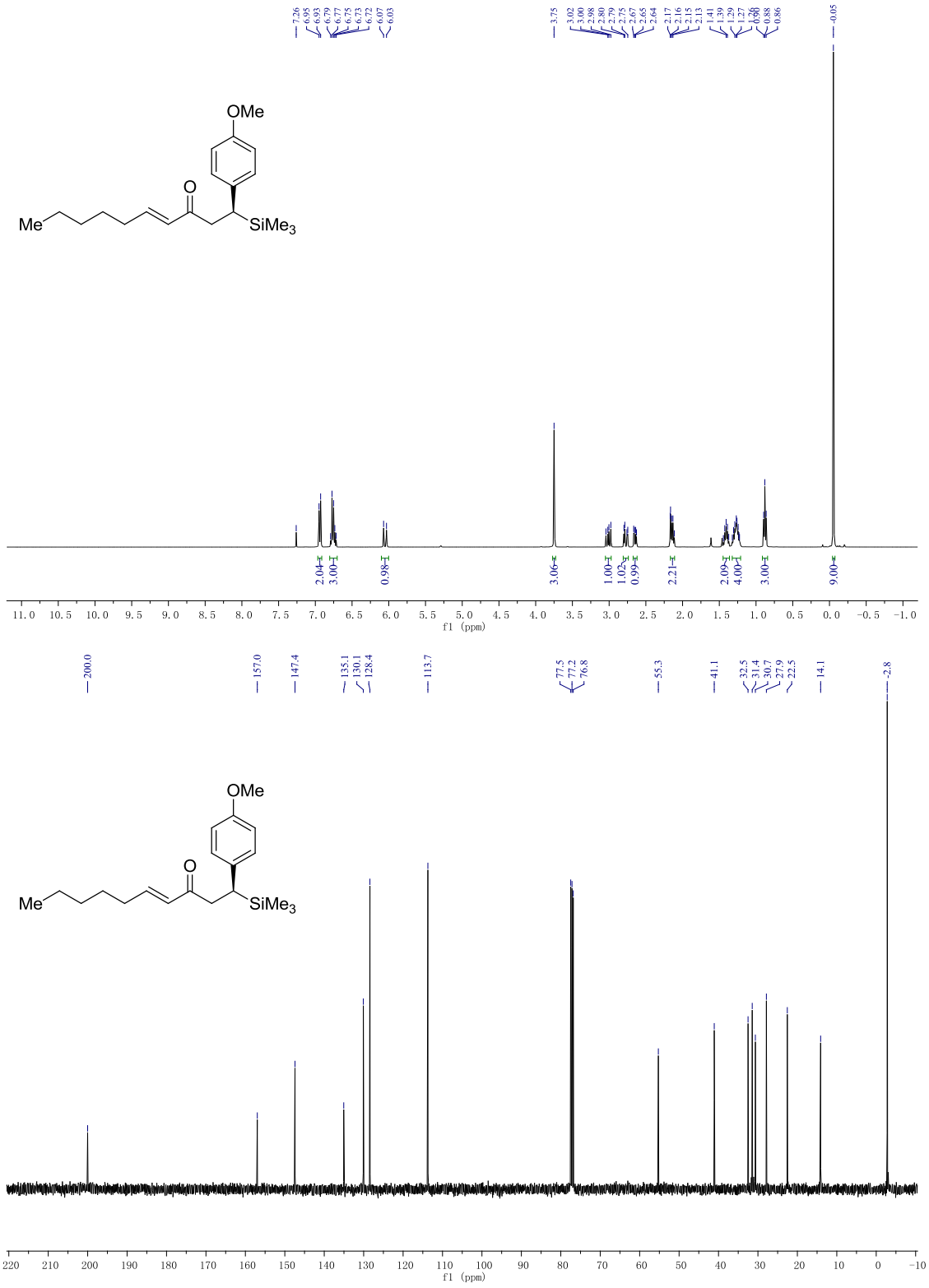


(*R*,*E*)-1-Cyclopentyl-1-(4-methoxyphenyl)dec-4-en-3-one, 8c

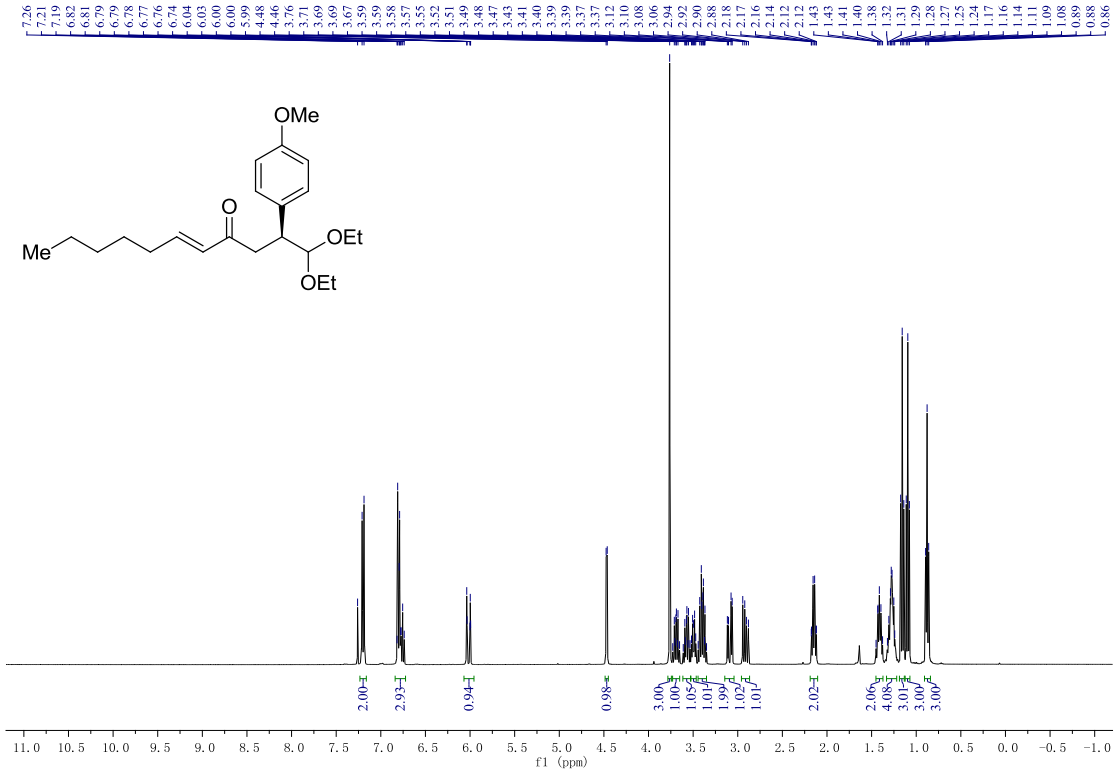


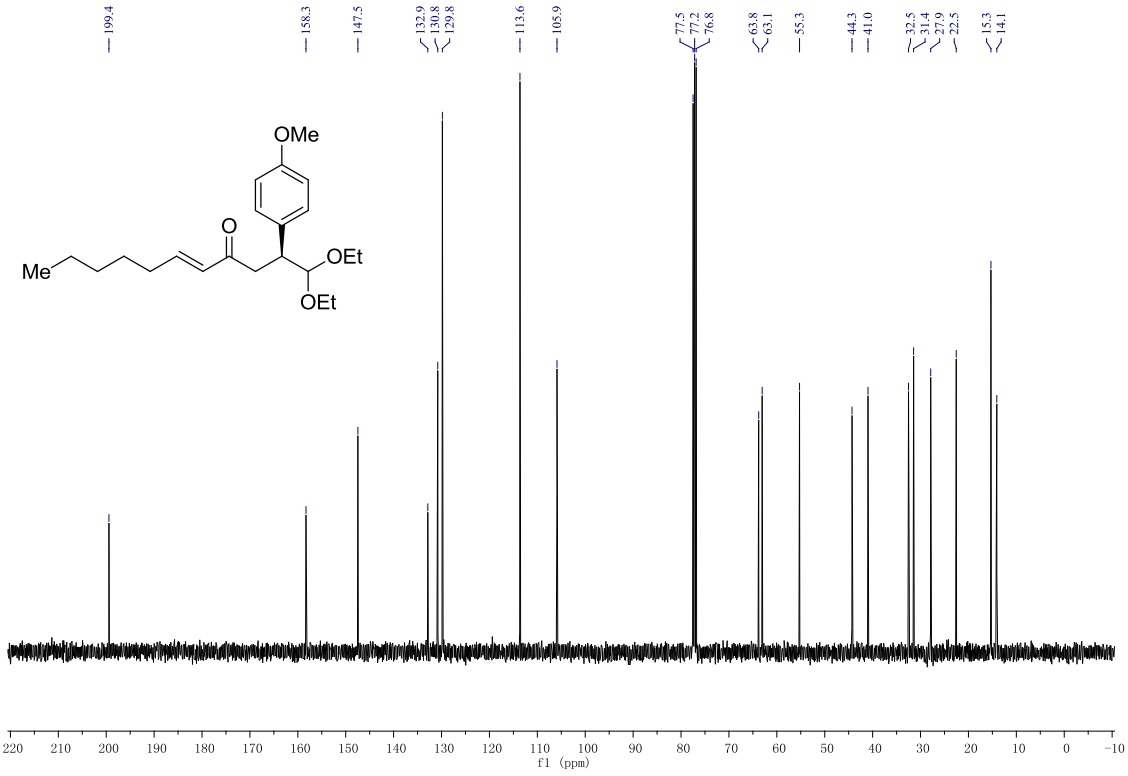


(*S*,*E*)-1-(4-Methoxyphenyl)-1-(trimethylsilyl)dec-4-en-3-one, 8d

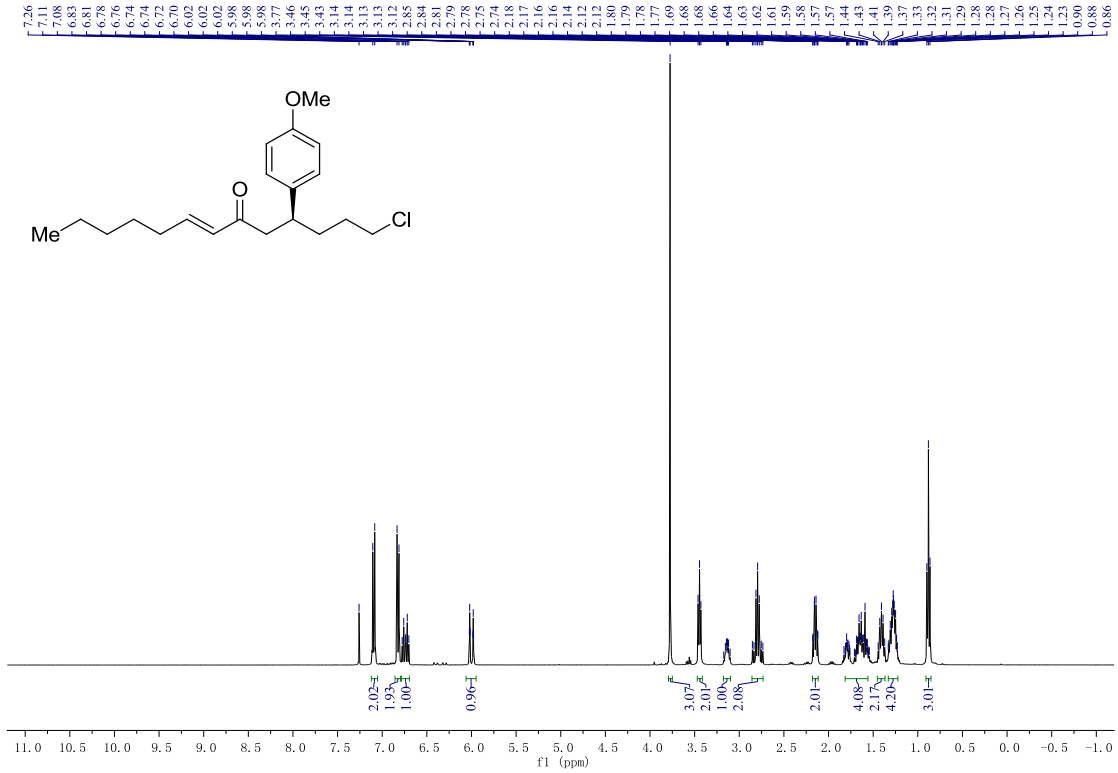


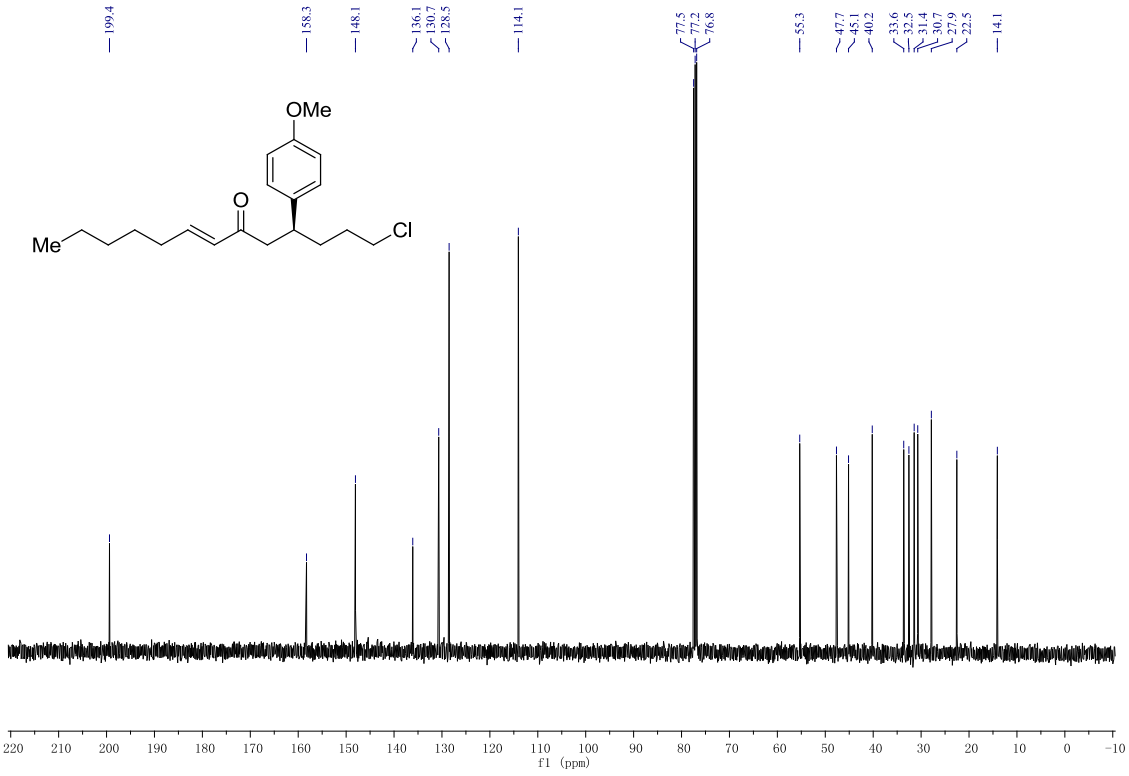
(*S*,*E*)-1,1-Diethoxy-2-(4-methoxyphenyl)undec-5-en-4-one, 8e



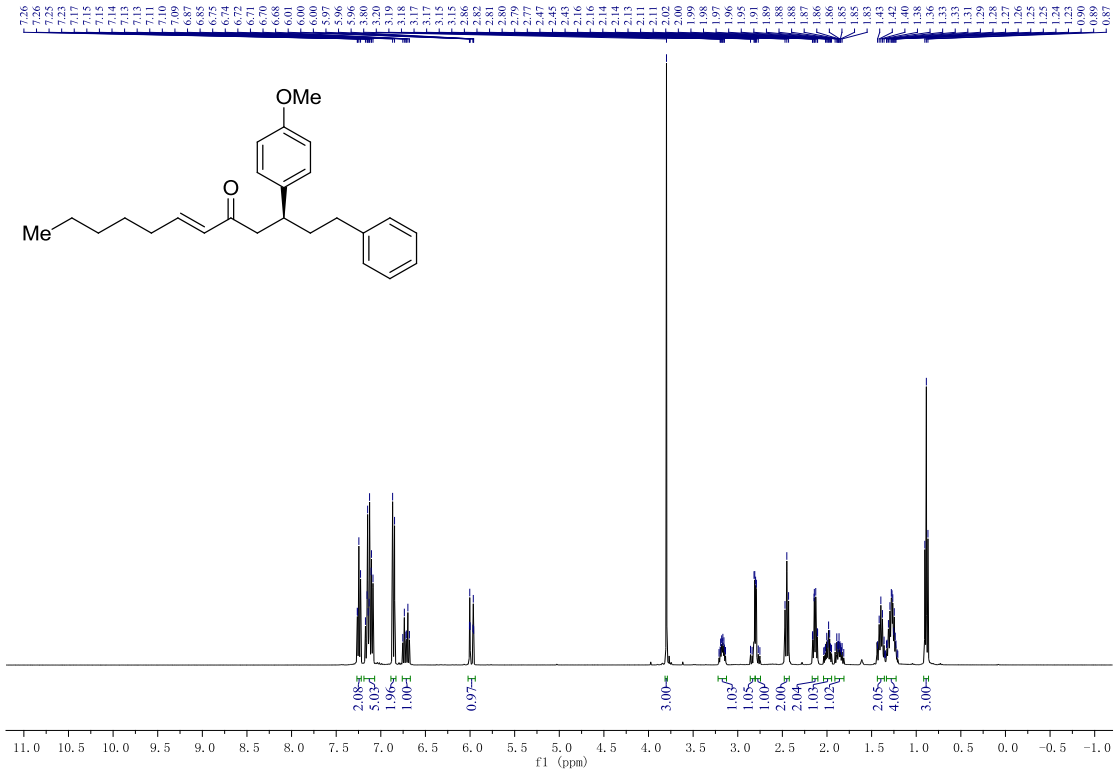


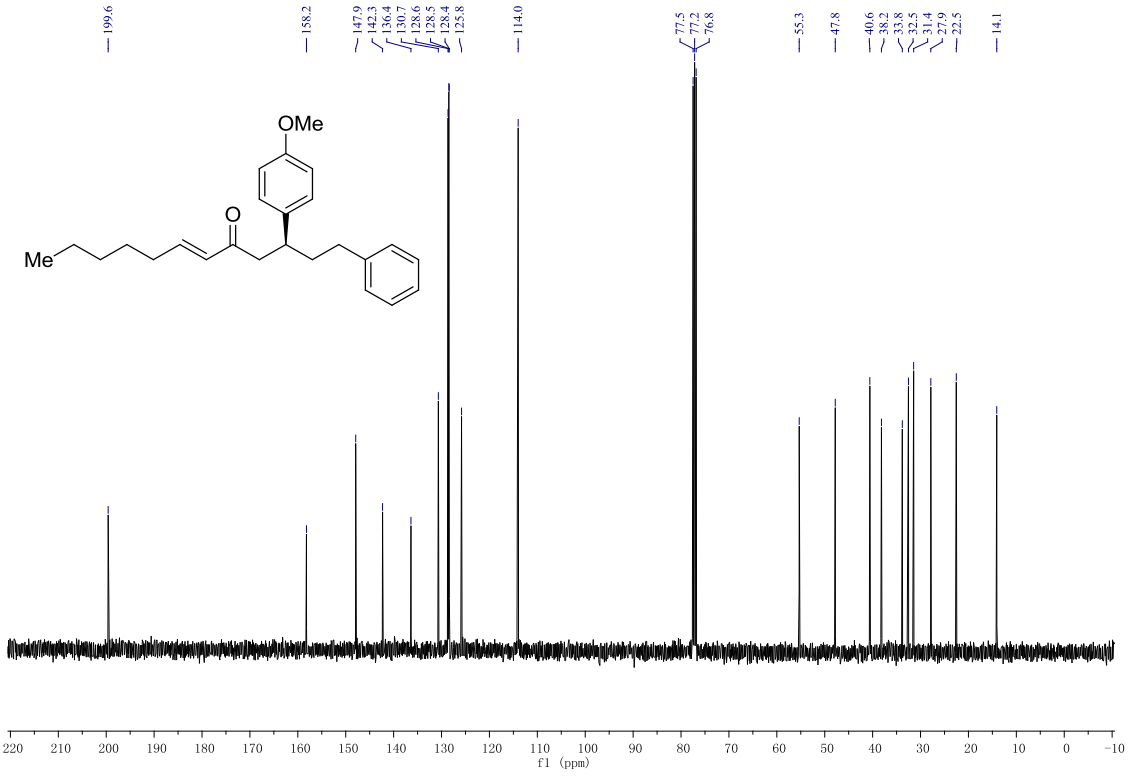
(*S*,*E*)-1-Chloro-4-(4-methoxyphenyl)tridec-7-en-6-one, 8f



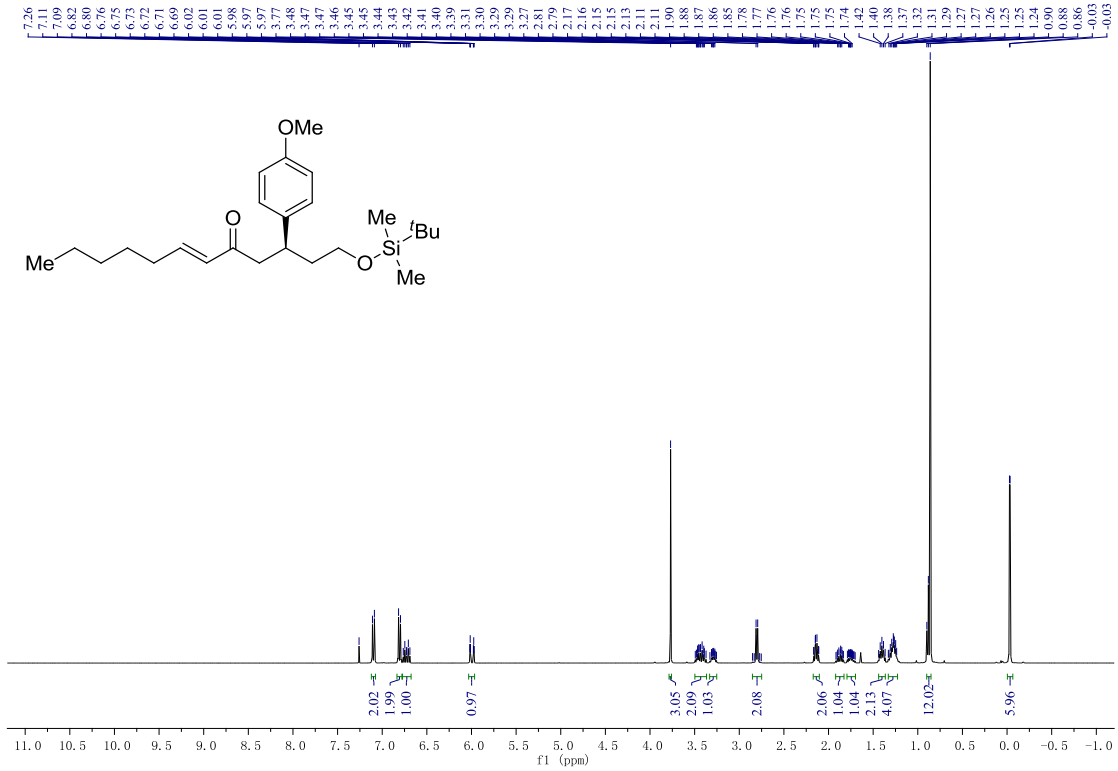


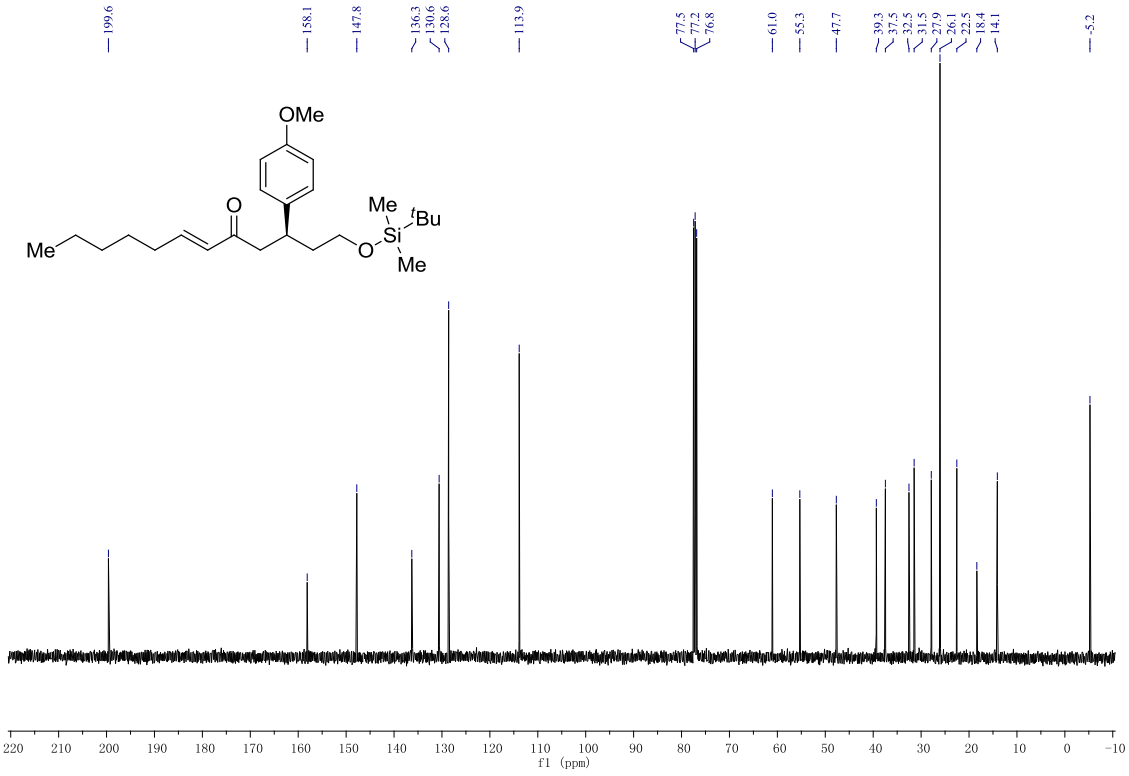
(*S*,*E*)-3-(4-Methoxyphenyl)-1-phenyldodec-6-en-5-one, 8g



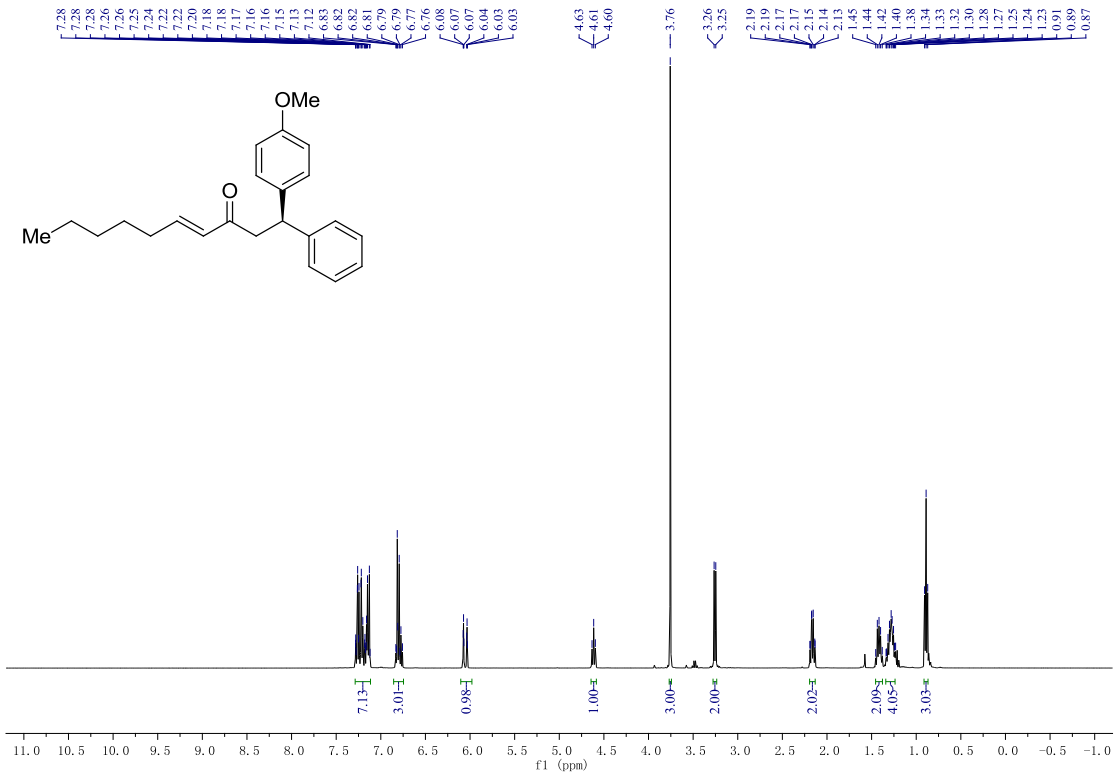


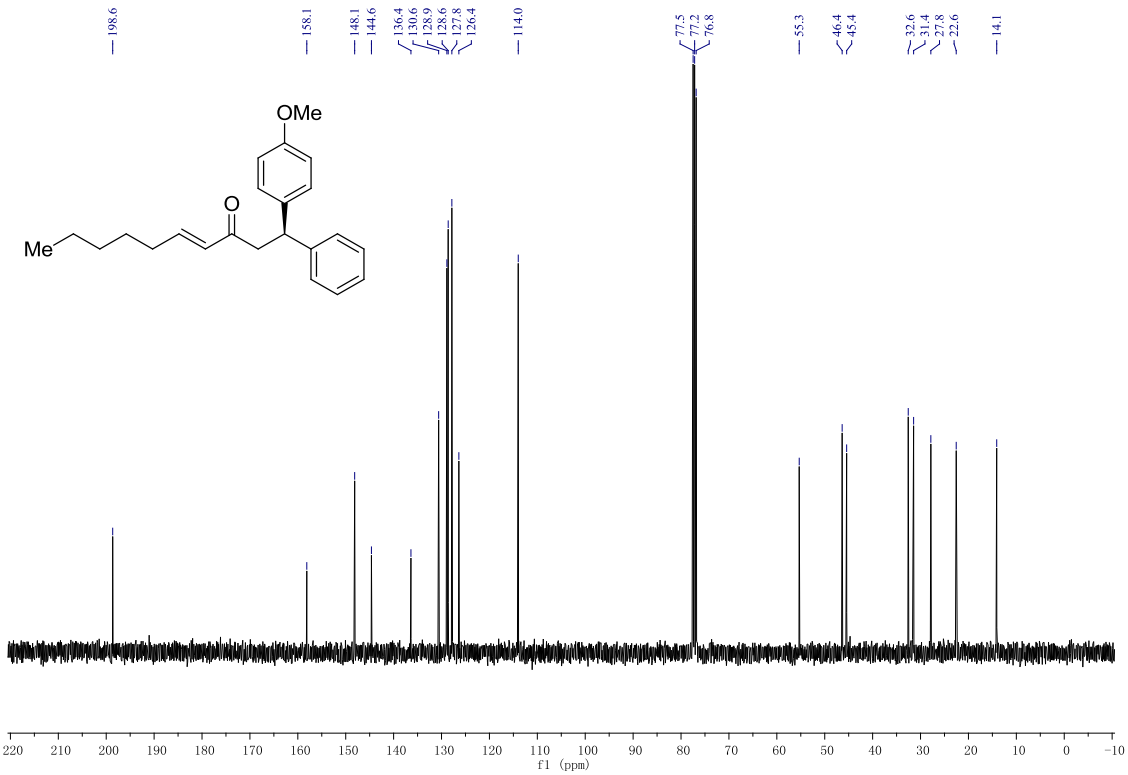
(*S*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(4-methoxyphenyl)dodec-6-en-5-one, 8h



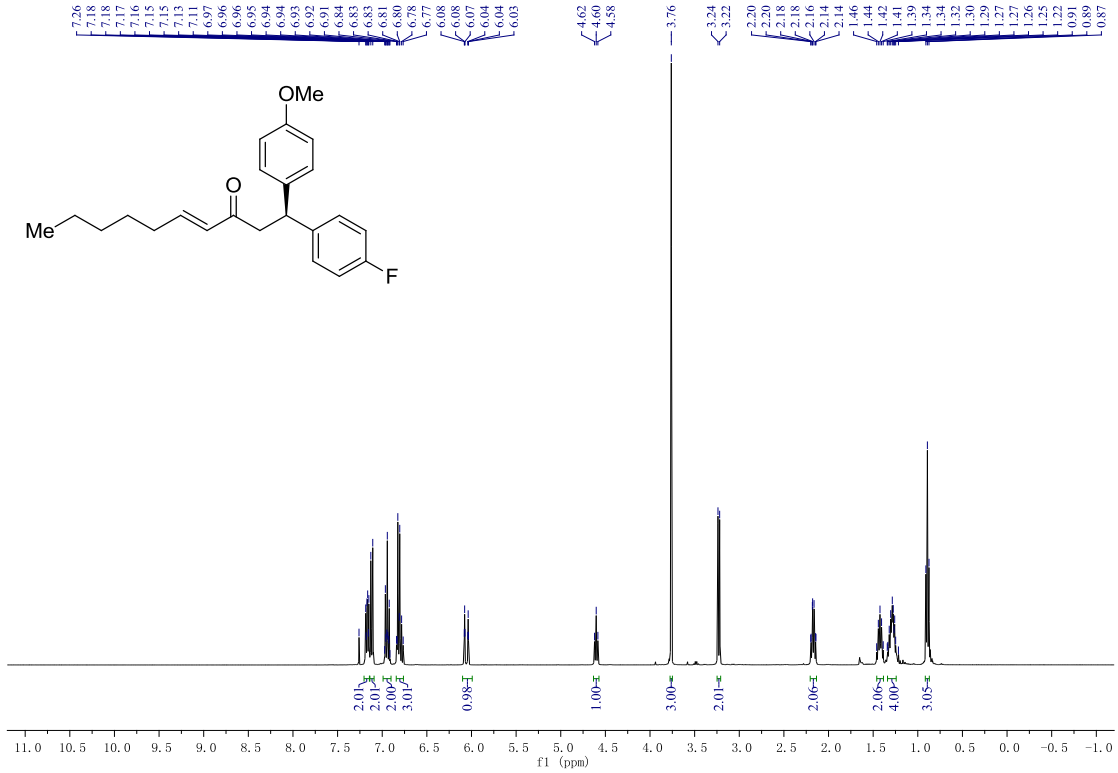


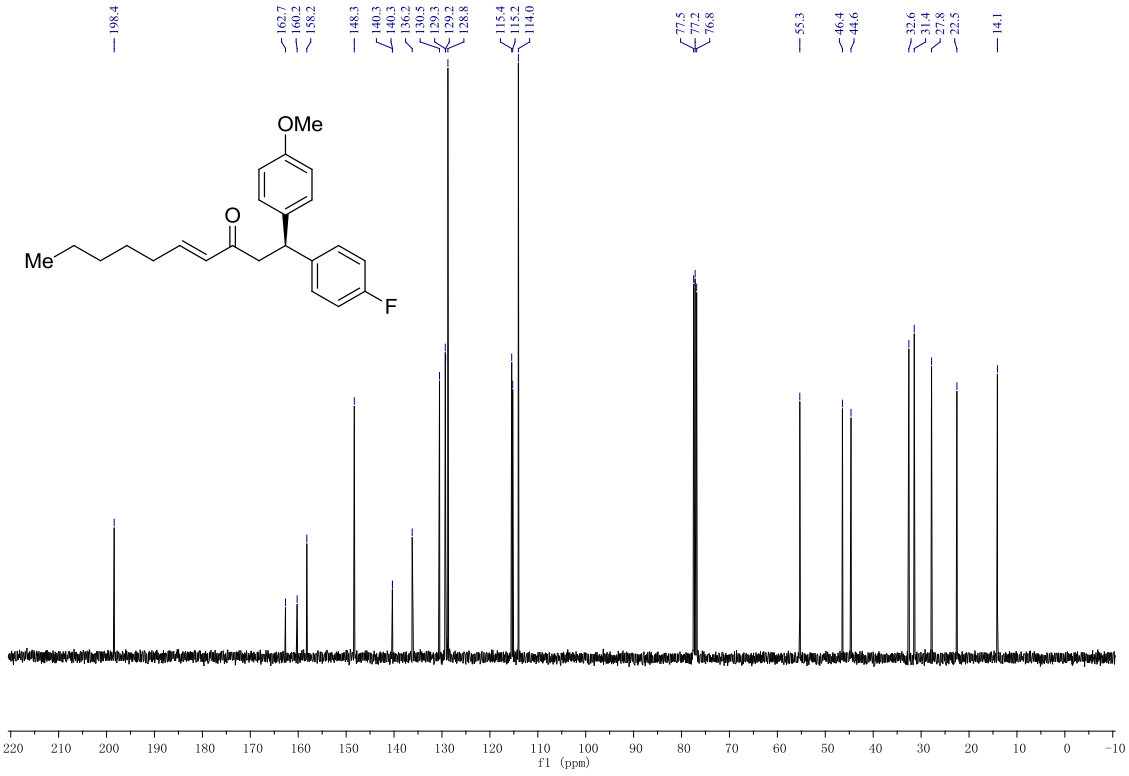
(*R*,*E*)-1-(4-Methoxyphenyl)-1-phenyldec-4-en-3-one, 8i



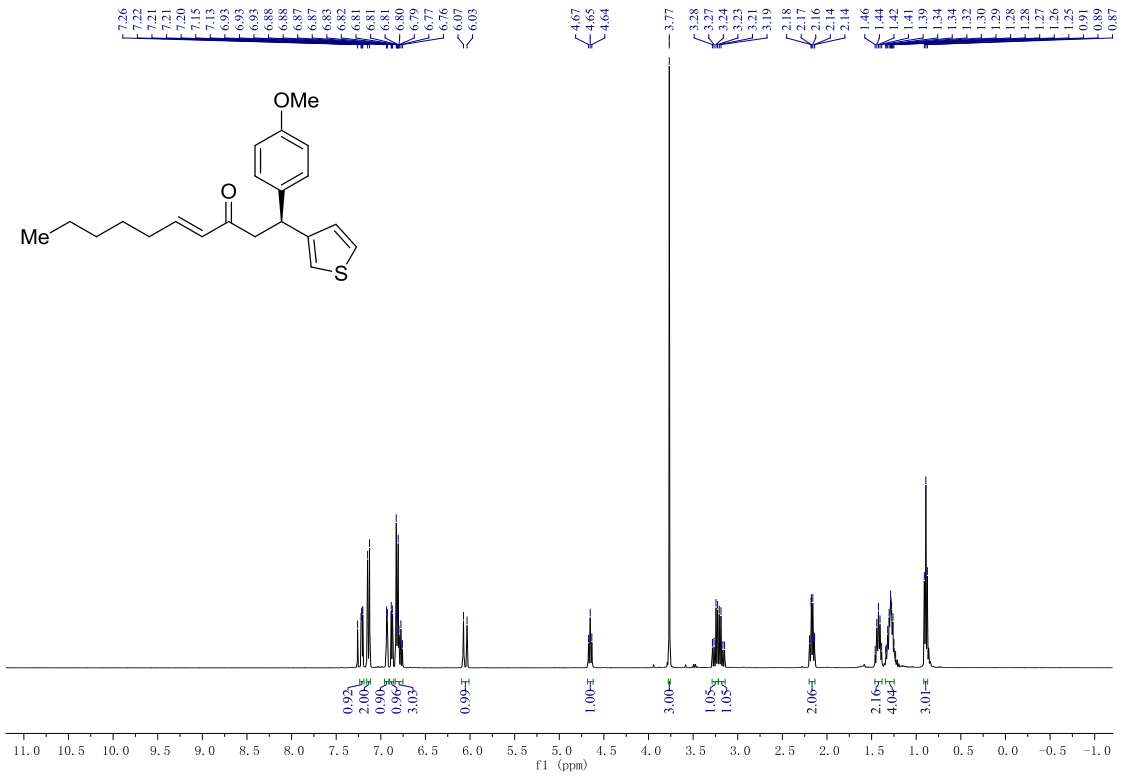


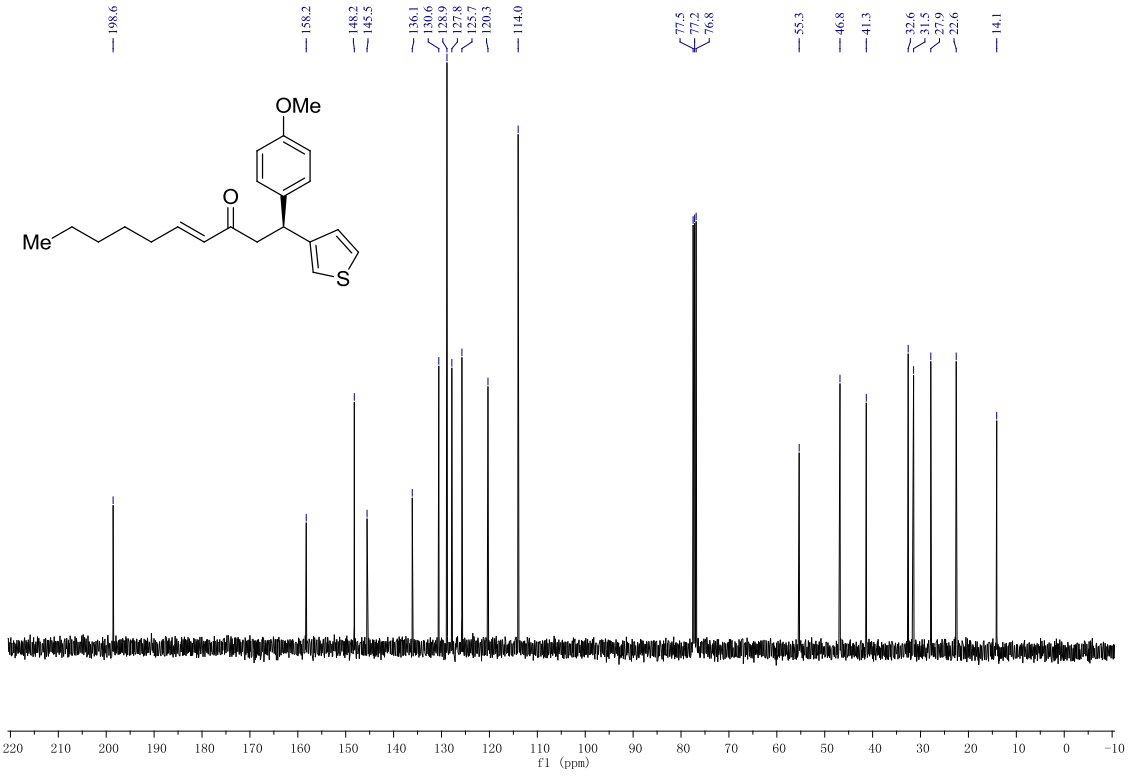
(*S*,*E*)-1-(4-Fluorophenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8j



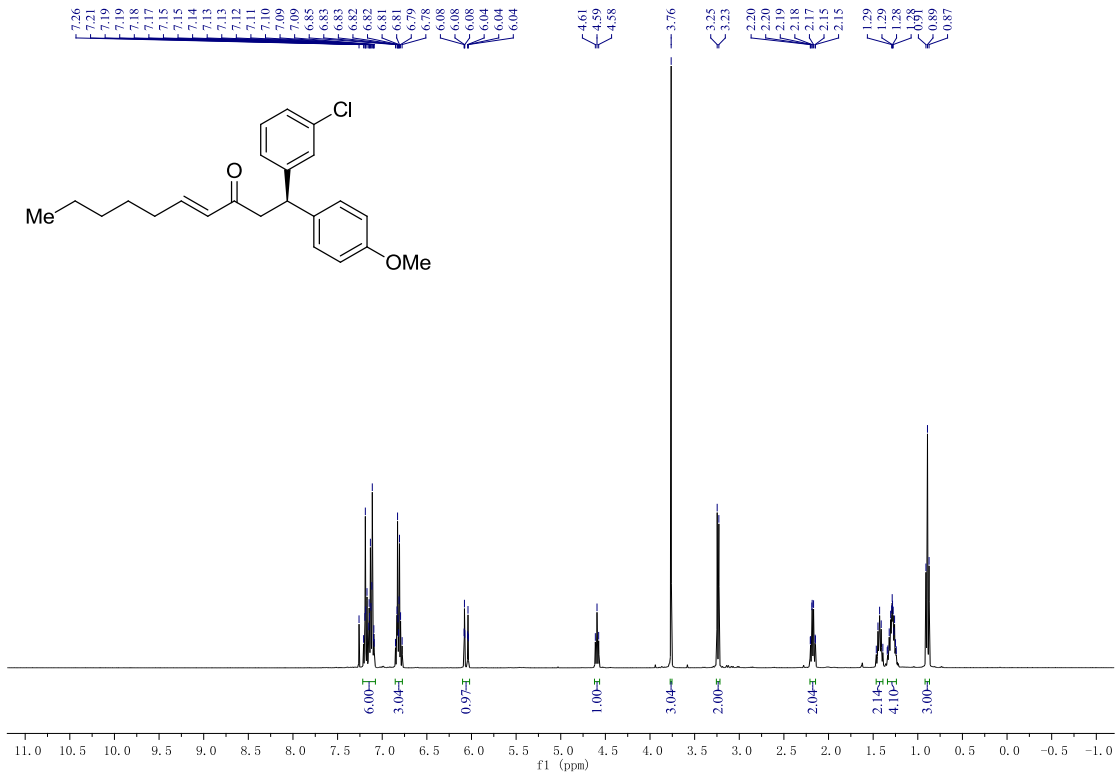


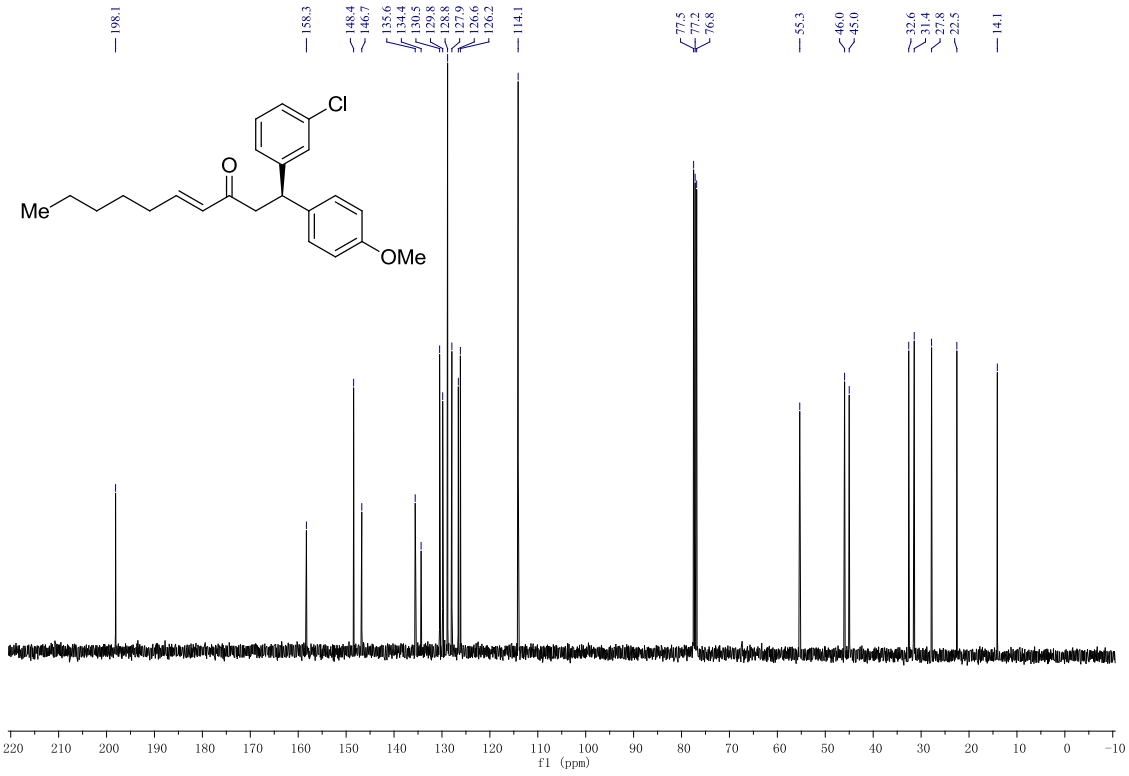
(*S*,*E*)-1-(4-Methoxyphenyl)-1-(thiophen-3-yl)dec-4-en-3-one, 8k



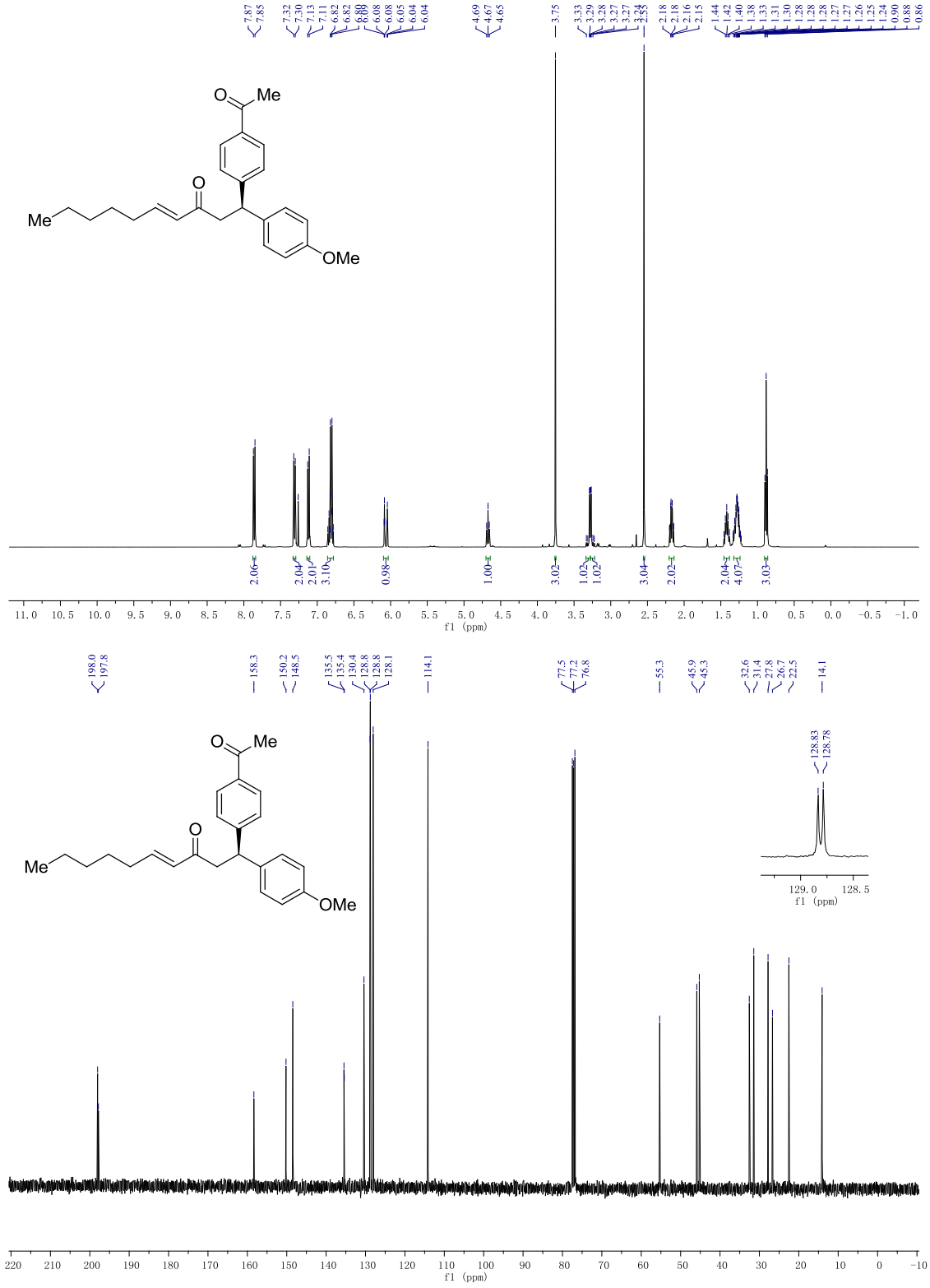


(*R*,*E*)-1-(3-Chlorophenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8m

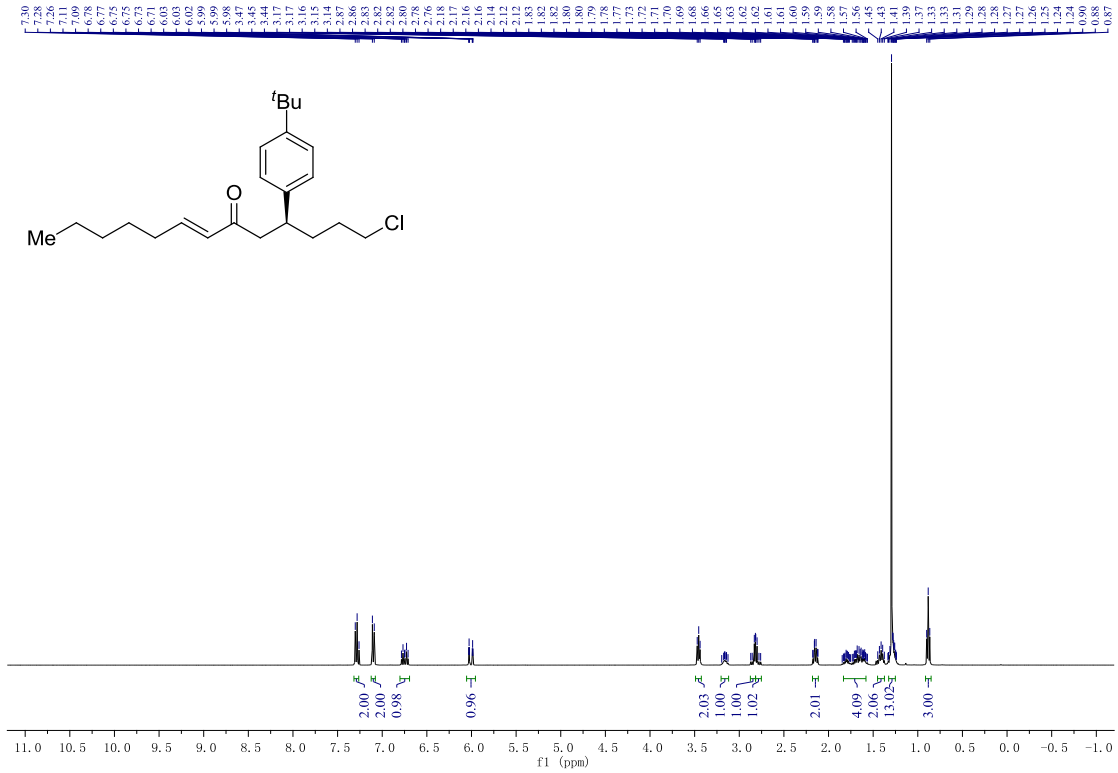


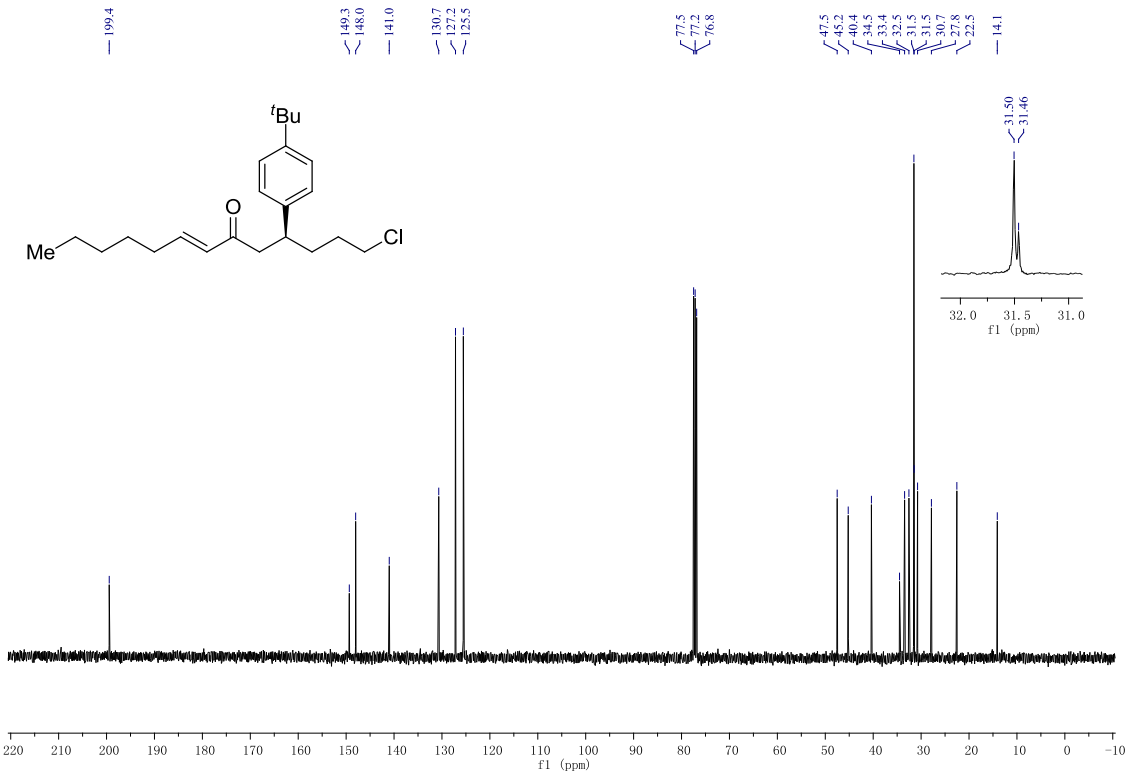


(*S*,*E*)-1-(4-Acetylphenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8n

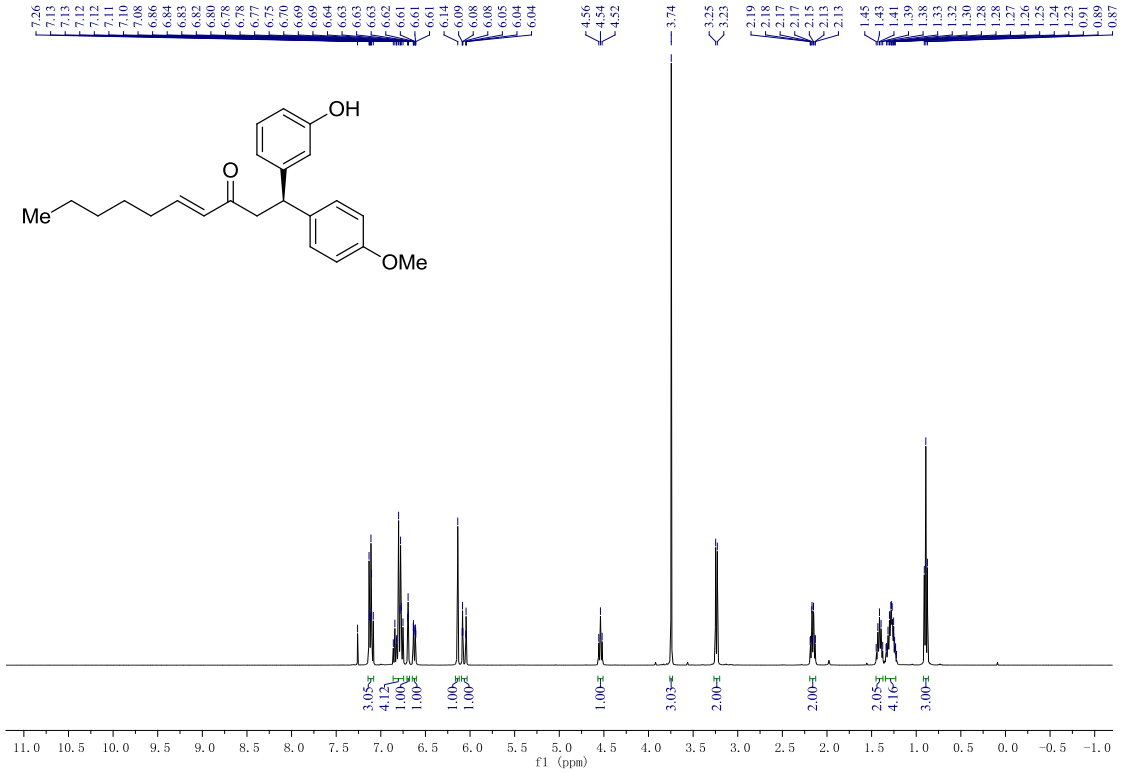


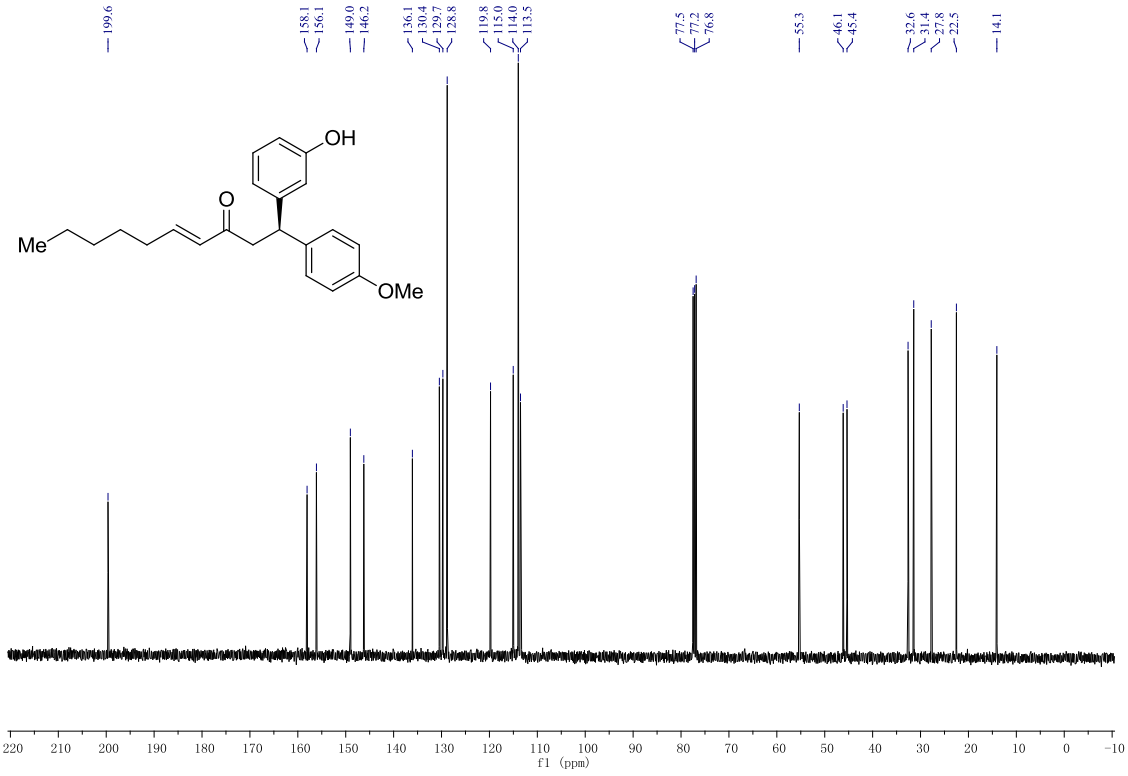
(*S*,*E*)-4-(4-(*tert*-Butyl)phenyl)-1-chlorotridec-7-en-6-one, 8p



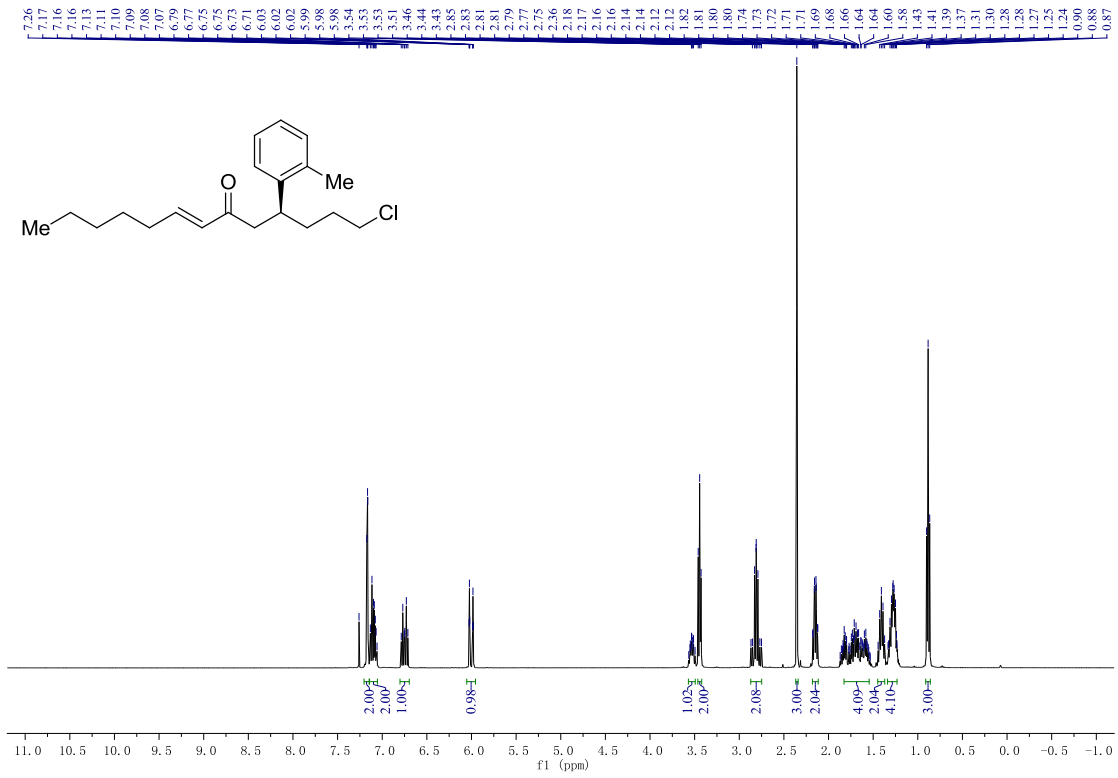


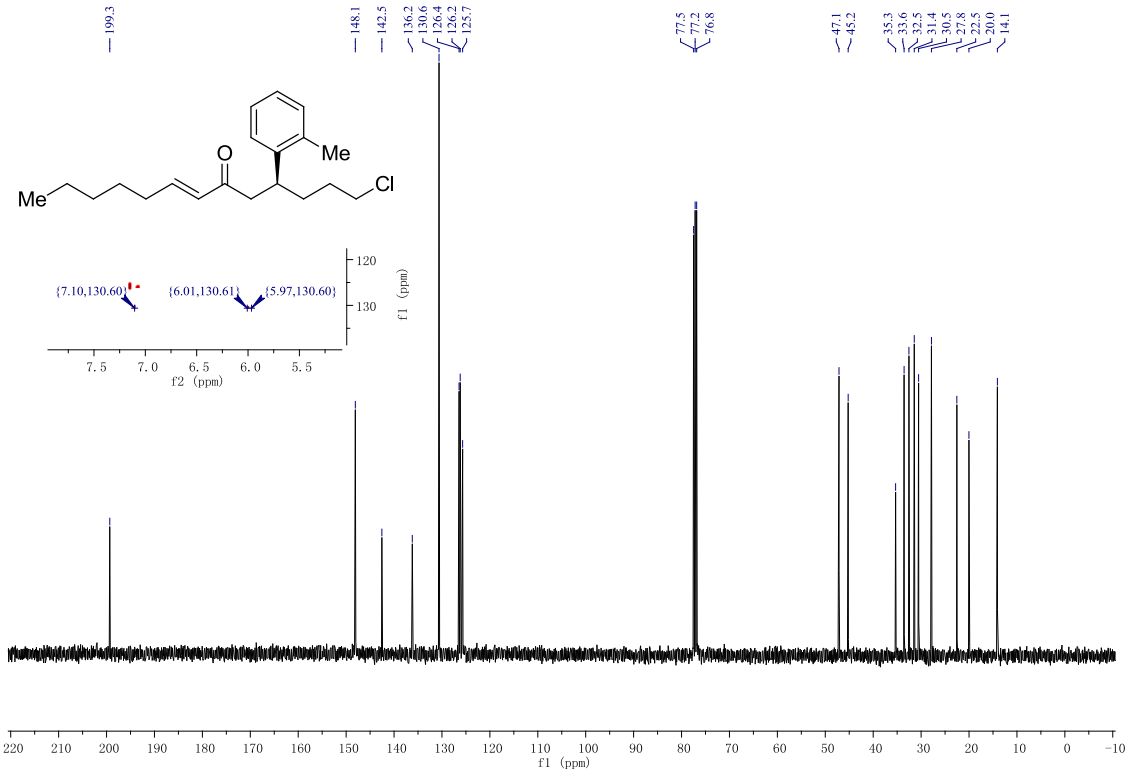
(*R*,*E*)-1-(3-Hydroxyphenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8q



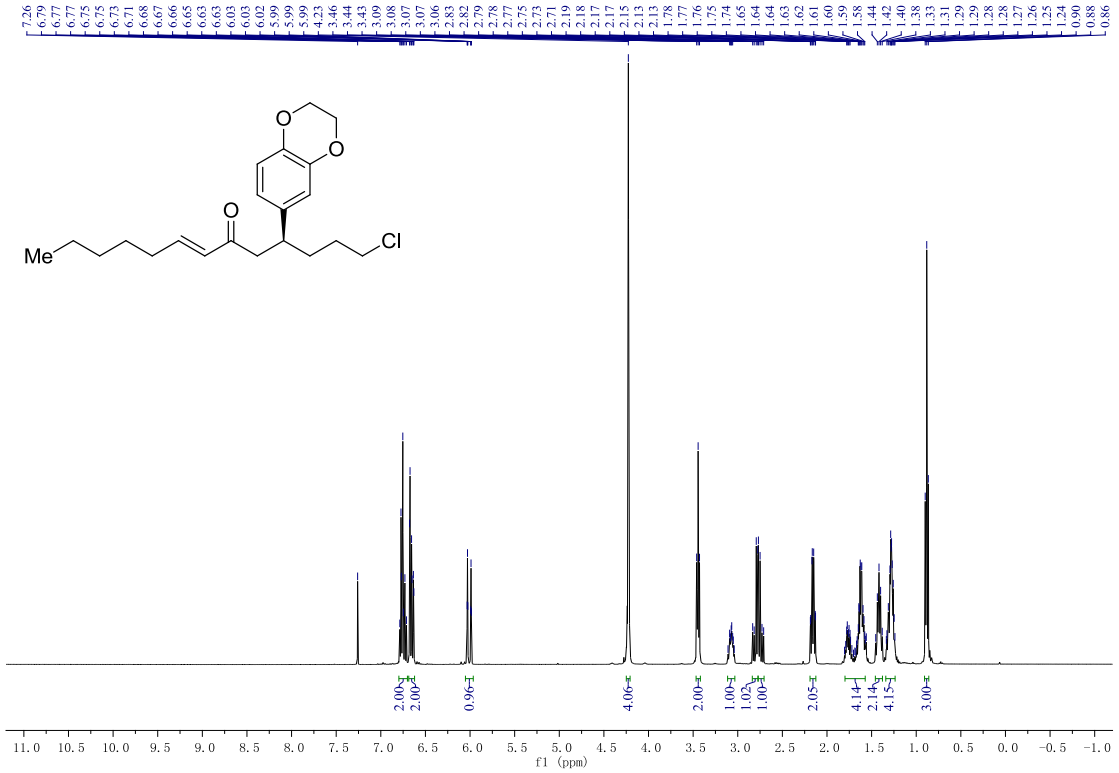


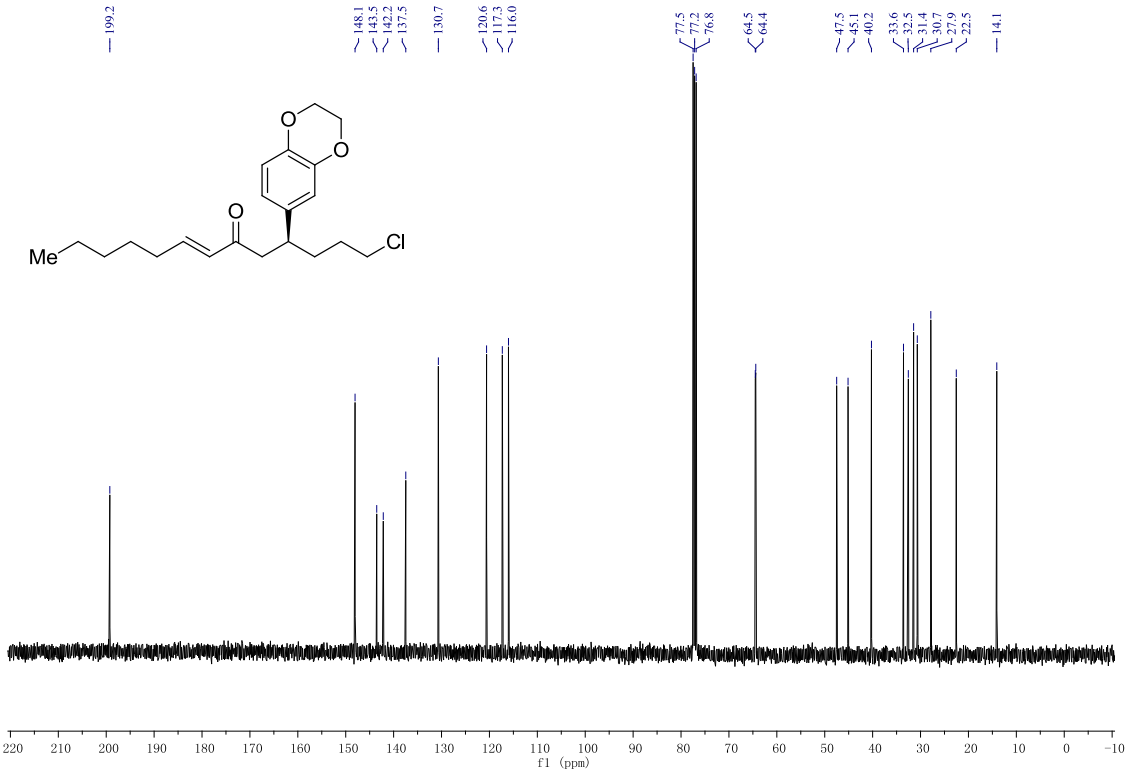
(*S*,*E*)-1-Chloro-4-(*o*-tolyl)tridec-7-en-6-one, 8r



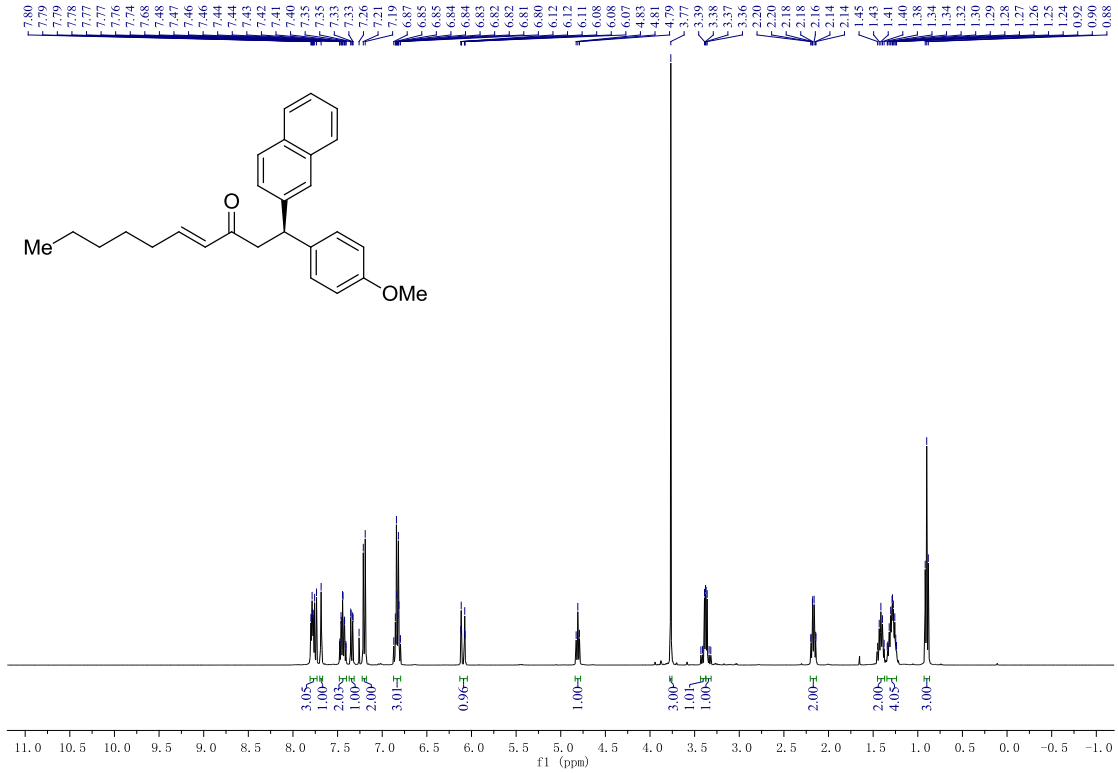


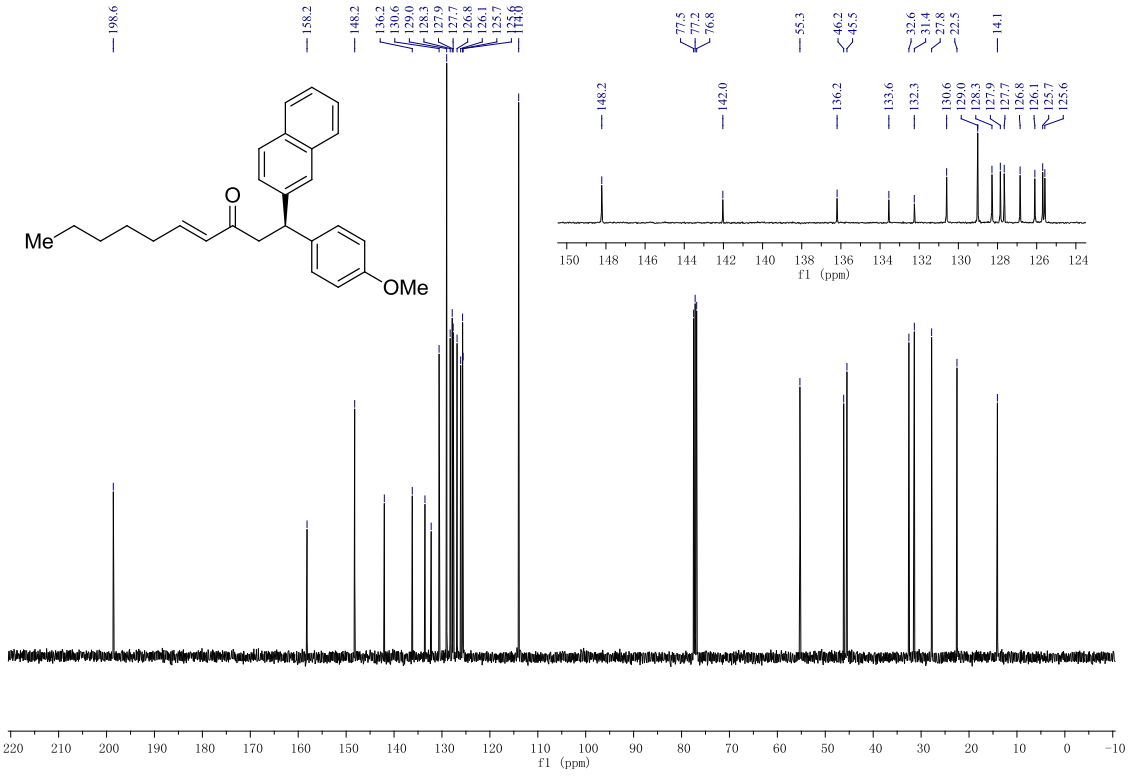
(*S*,*E*)-1-Chloro-4-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)tridec-7-en-6-one, 8s



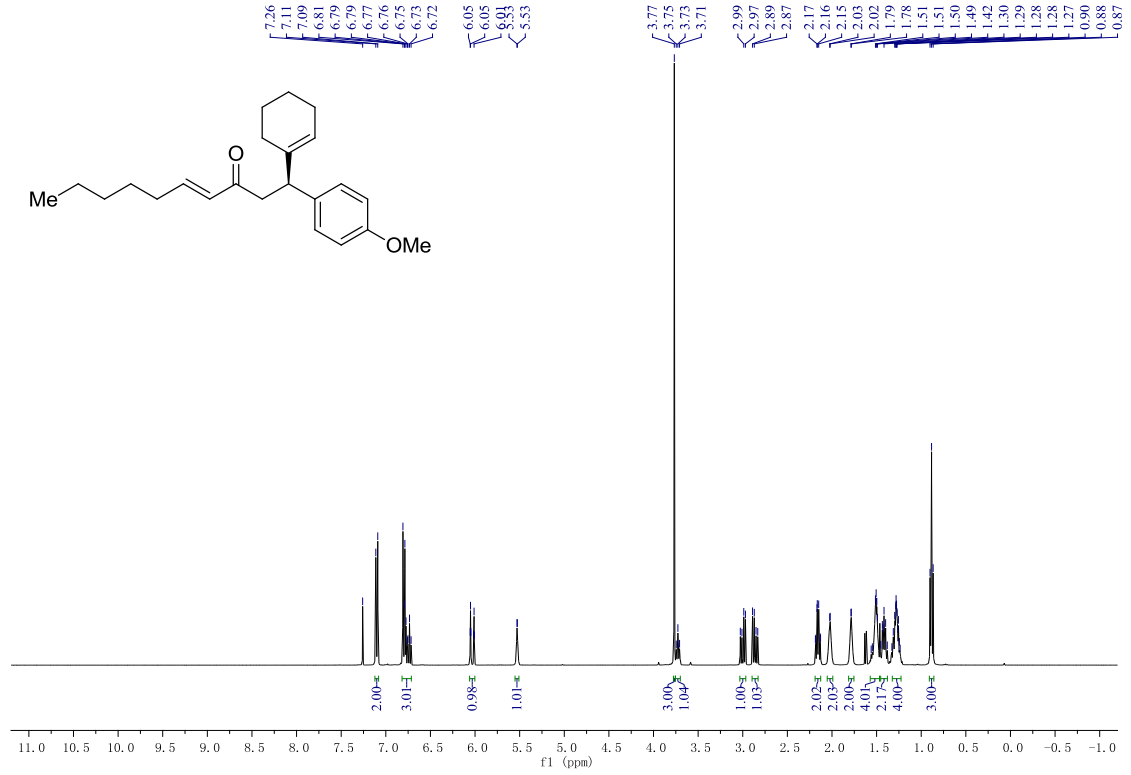


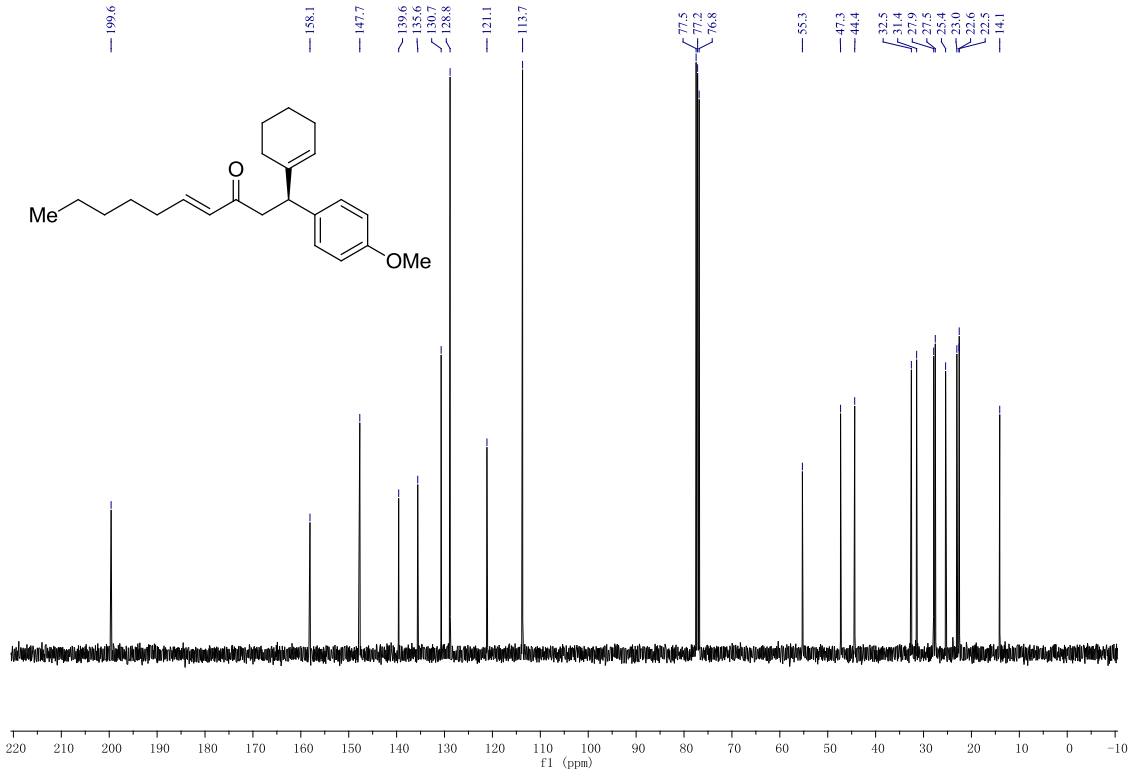
(*R*,*E*)-1-(4-Methoxyphenyl)-1-(naphthalen-2-yl)dec-4-en-3-one, 8t



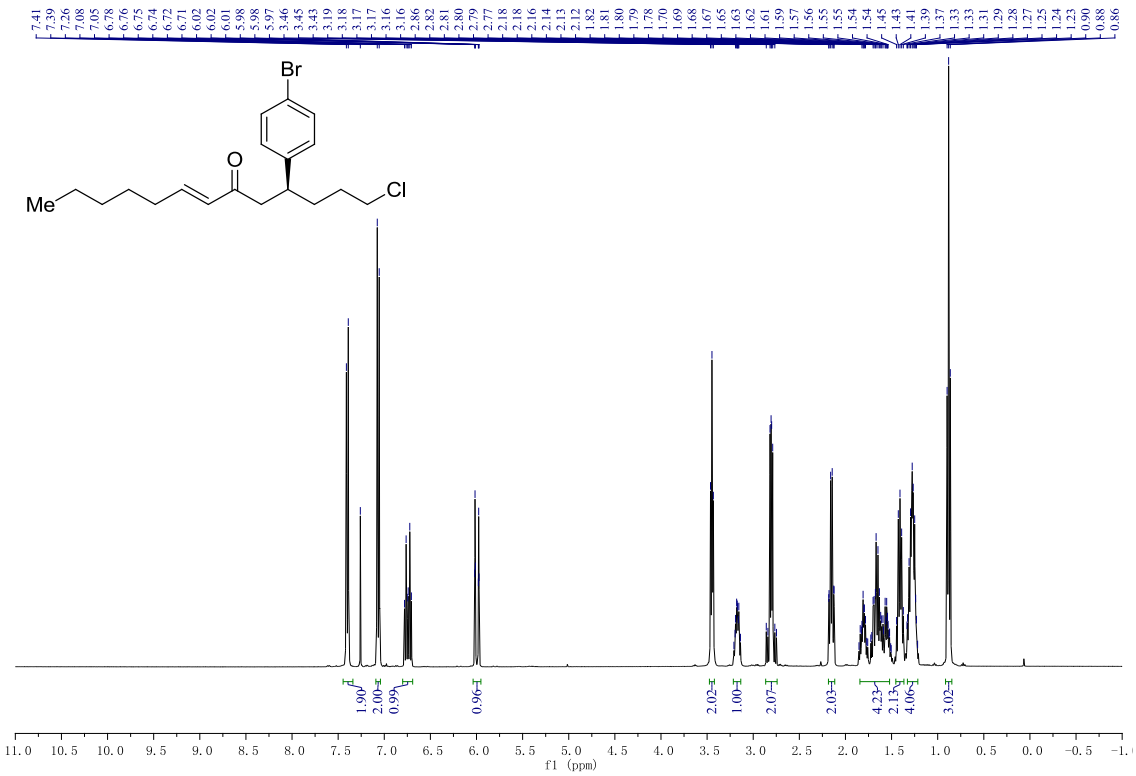


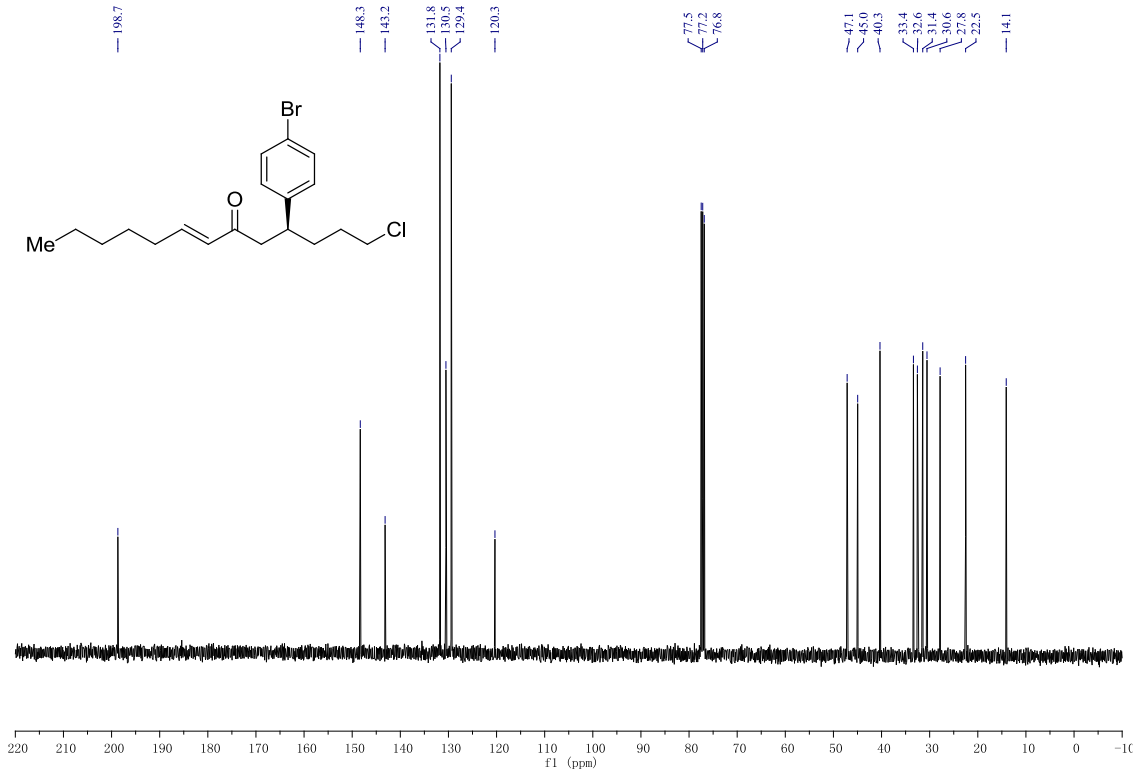
(*S*,*E*)-1-(Cyclohex-1-en-1-yl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8u



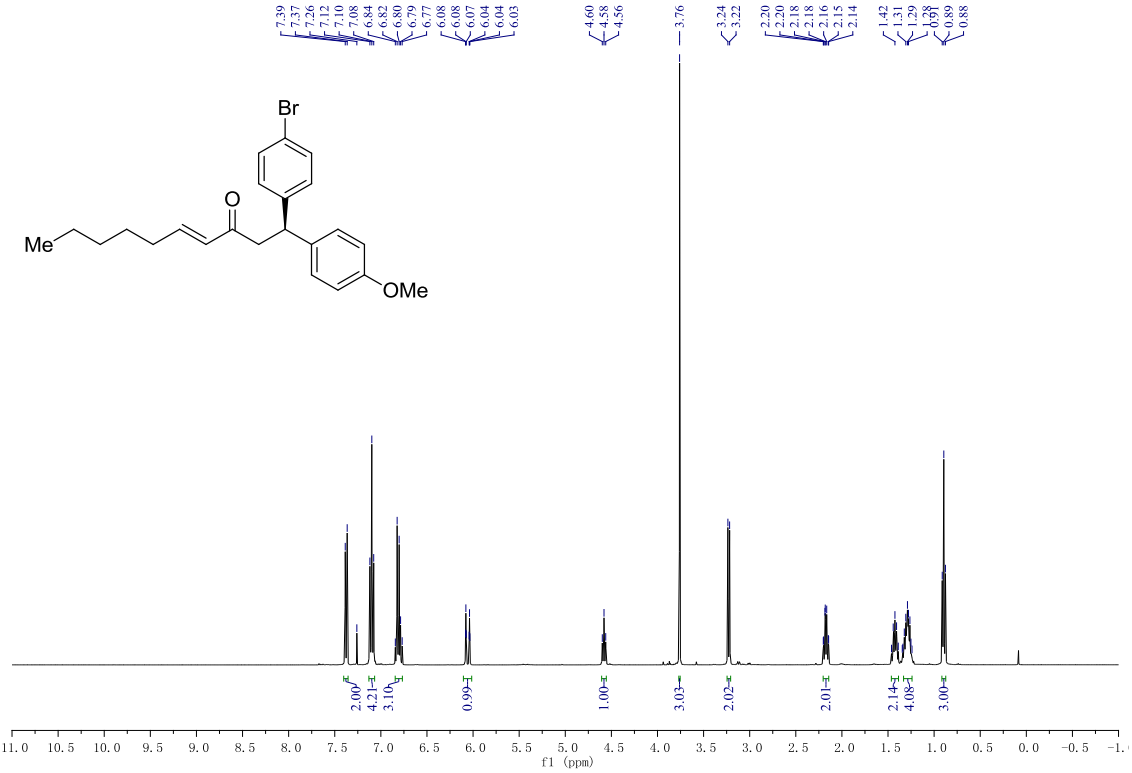


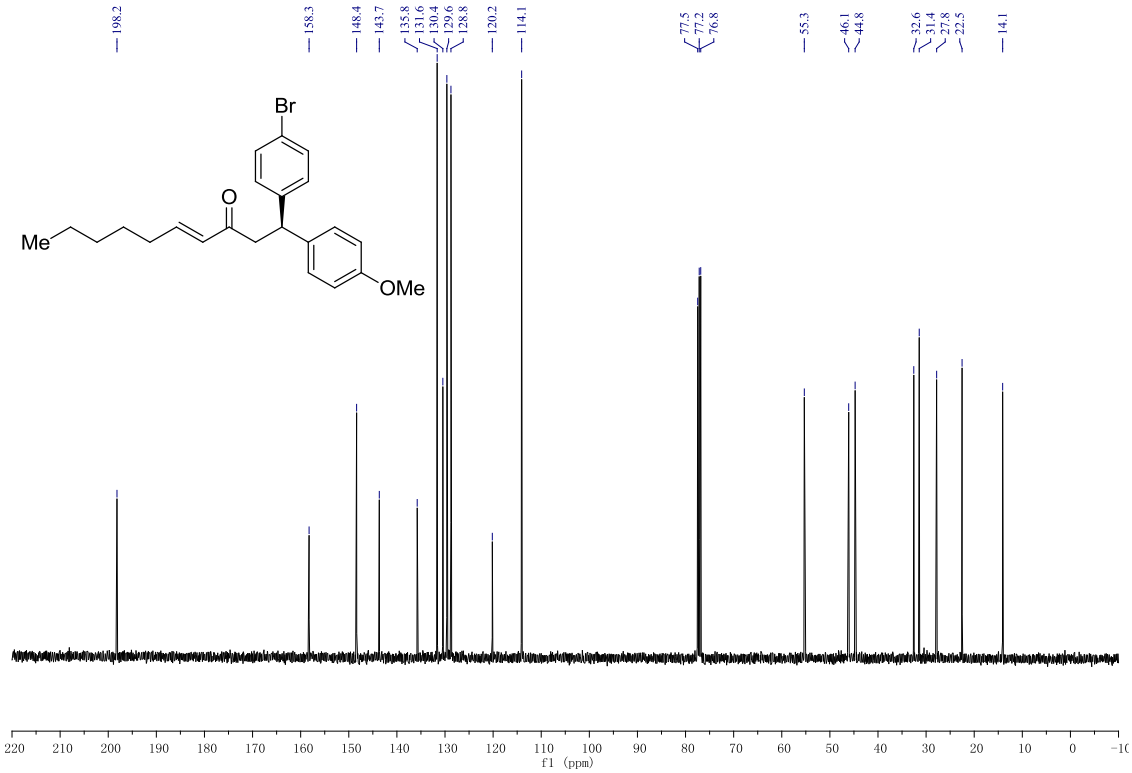
(*S*,*E*)-4-(4-Bromophenyl)-1-chlorotridec-7-en-6-one, 8v



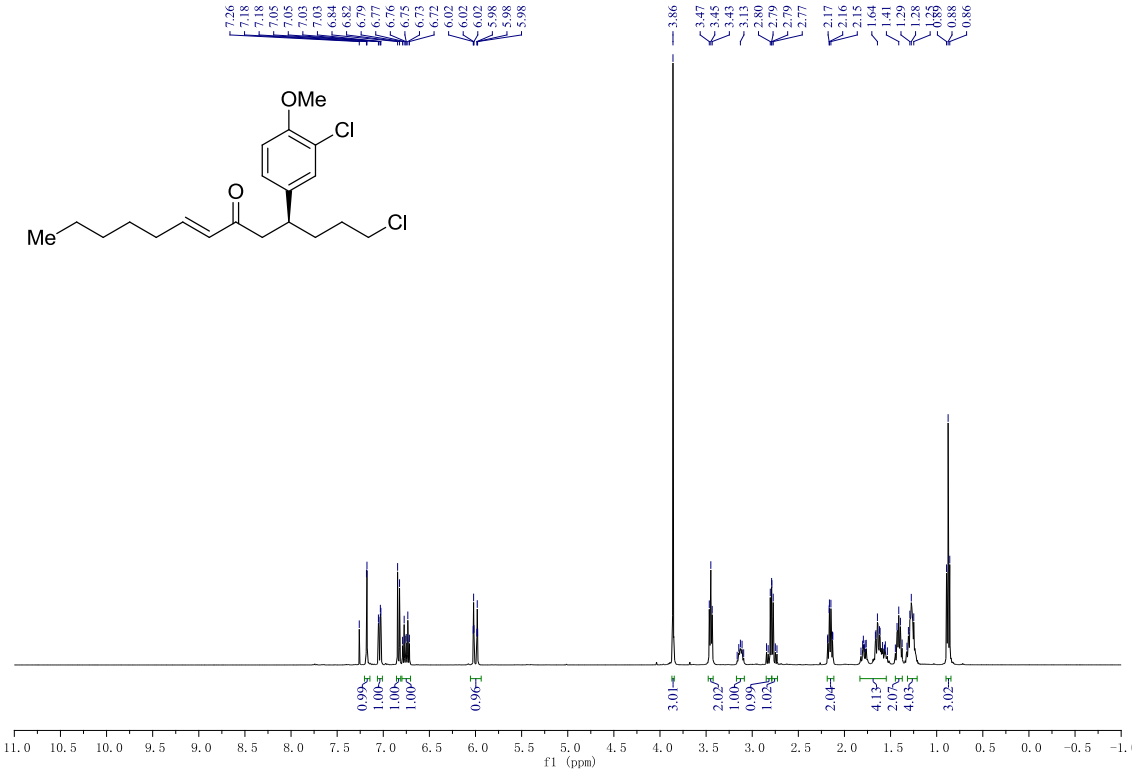


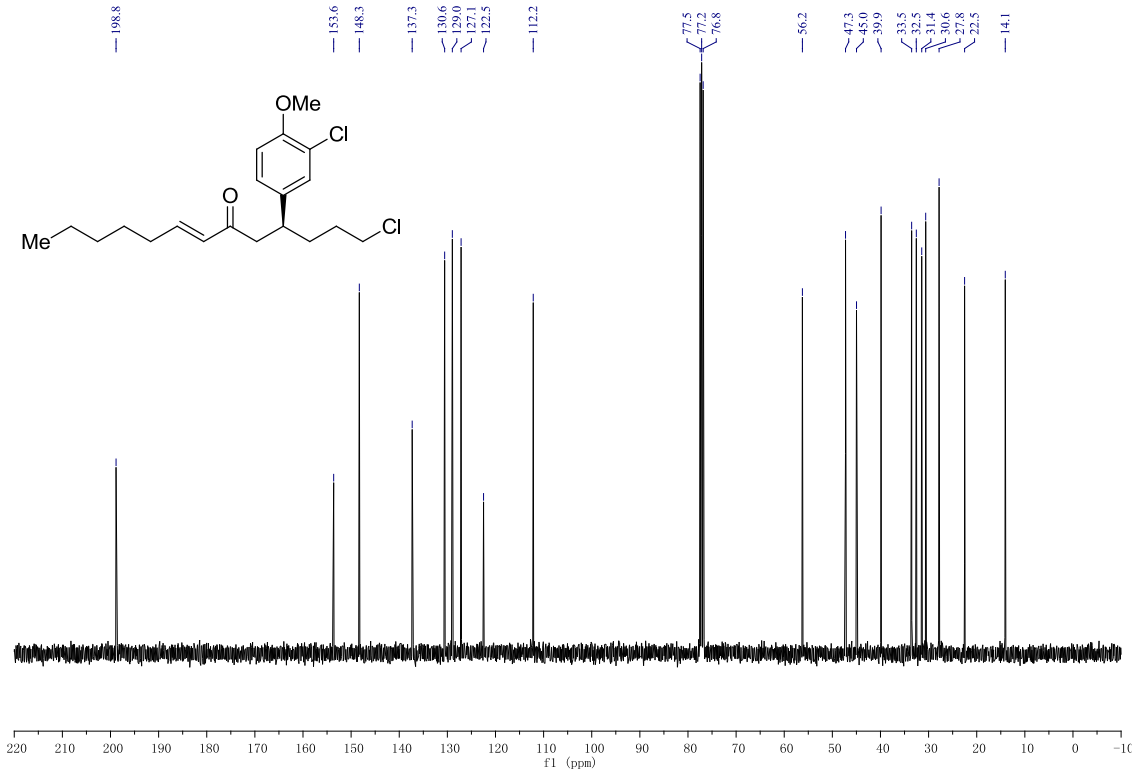
(*R*,*E*)-1-(4-Bromophenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8w



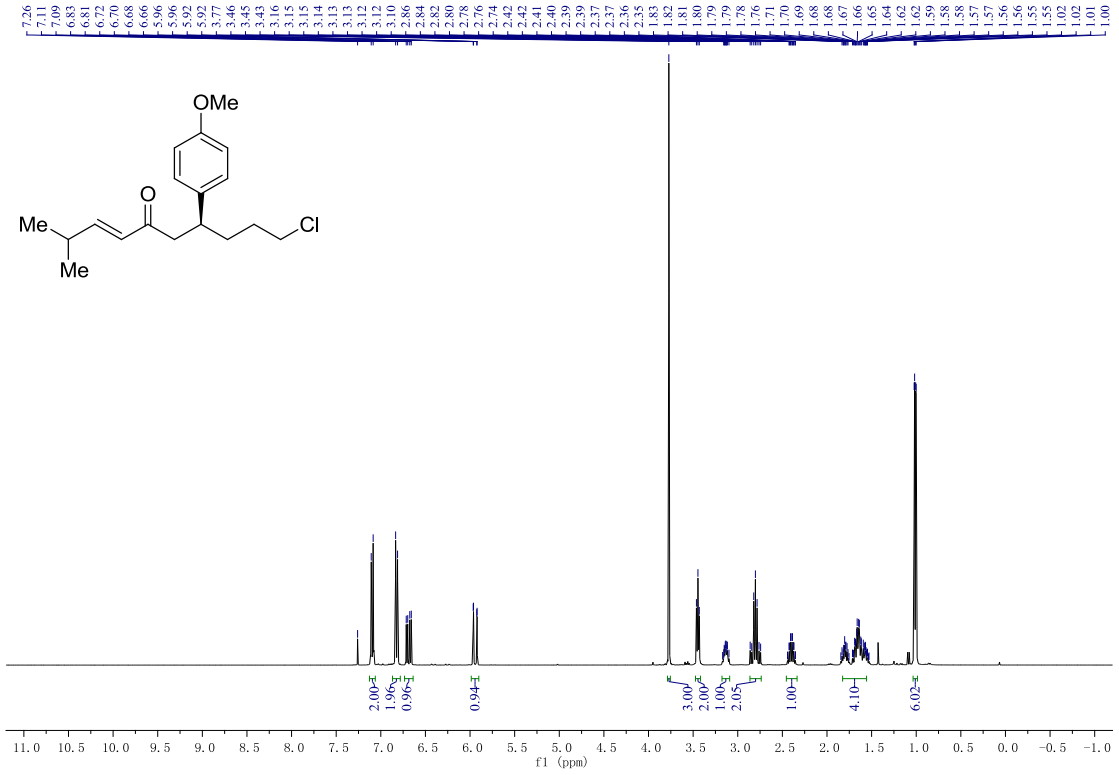


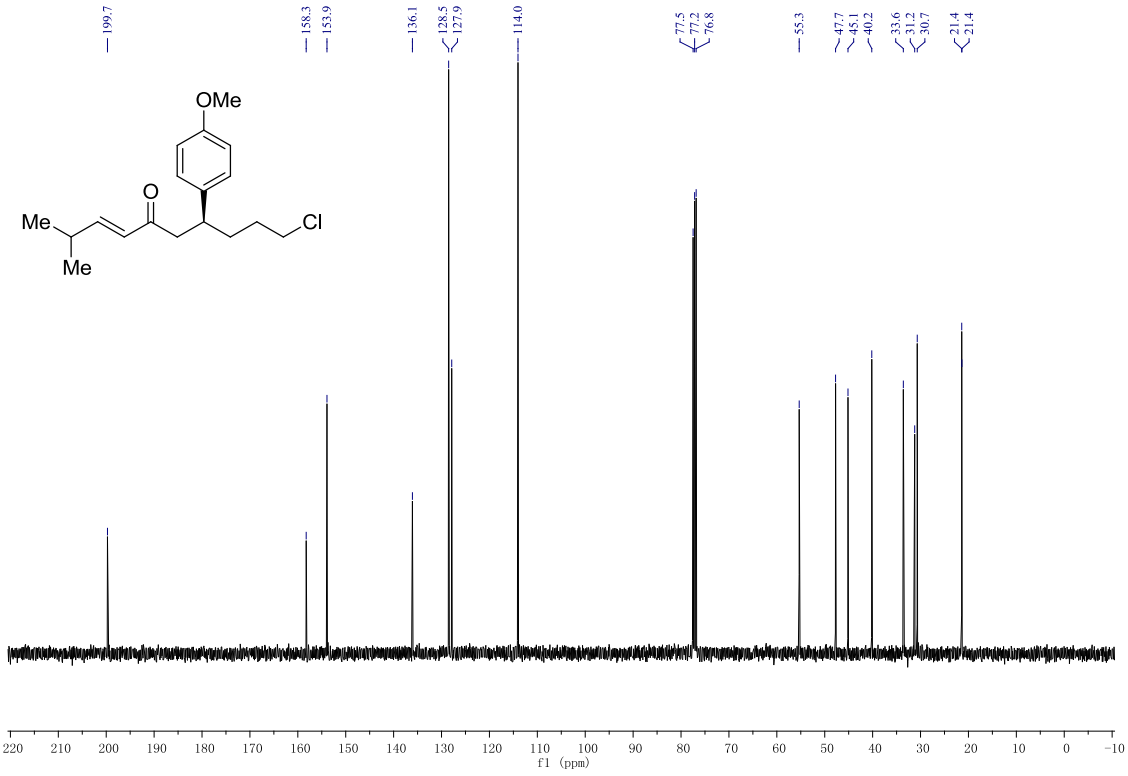
(*S*,*E*)-1-Chloro-4-(3-chloro-4-methoxyphenyl)tridec-7-en-6-one, 8x



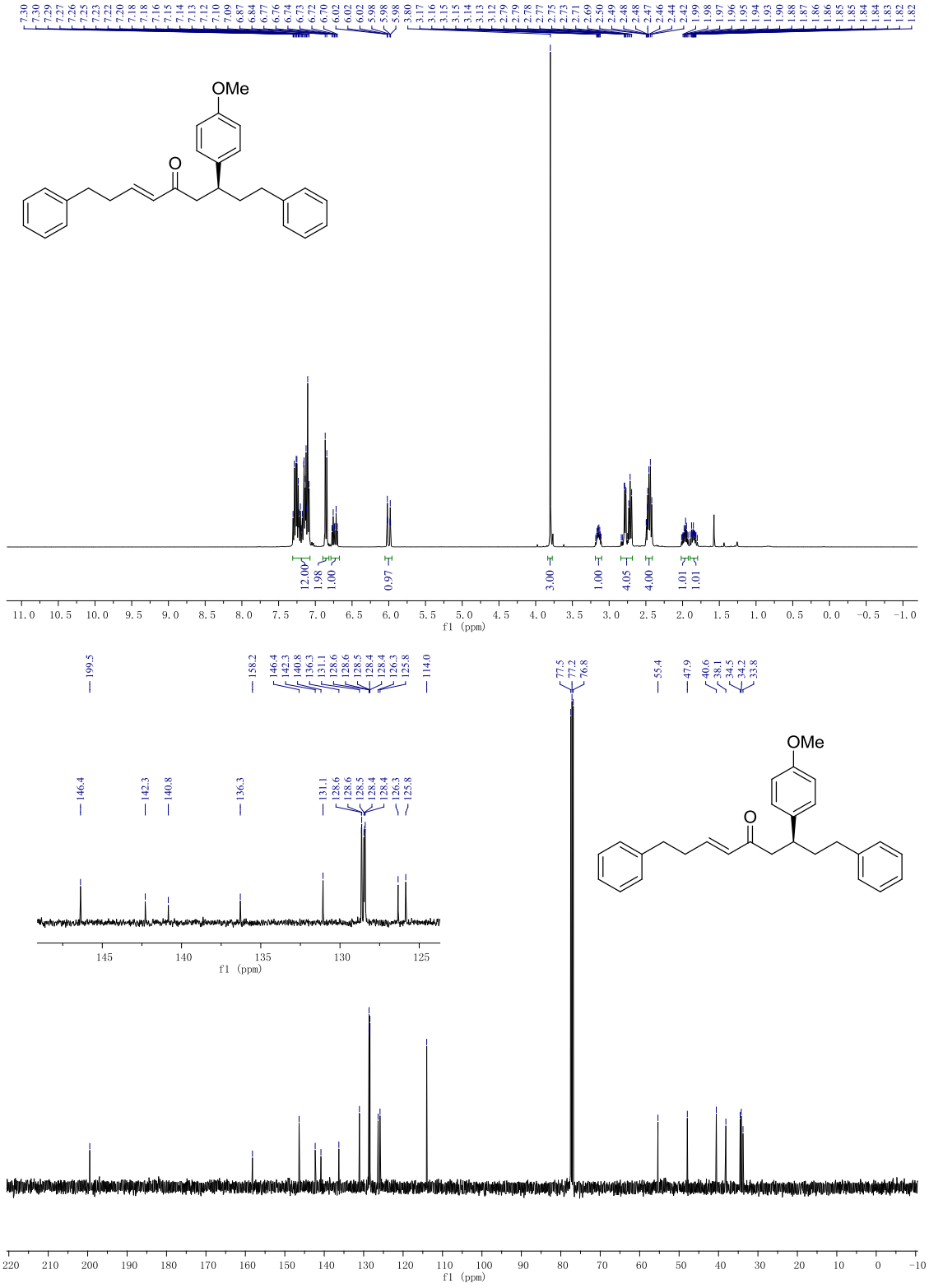


(*S*,*E*)-10-Chloro-7-(4-methoxyphenyl)-2-methyldec-3-en-5-one, 8aa

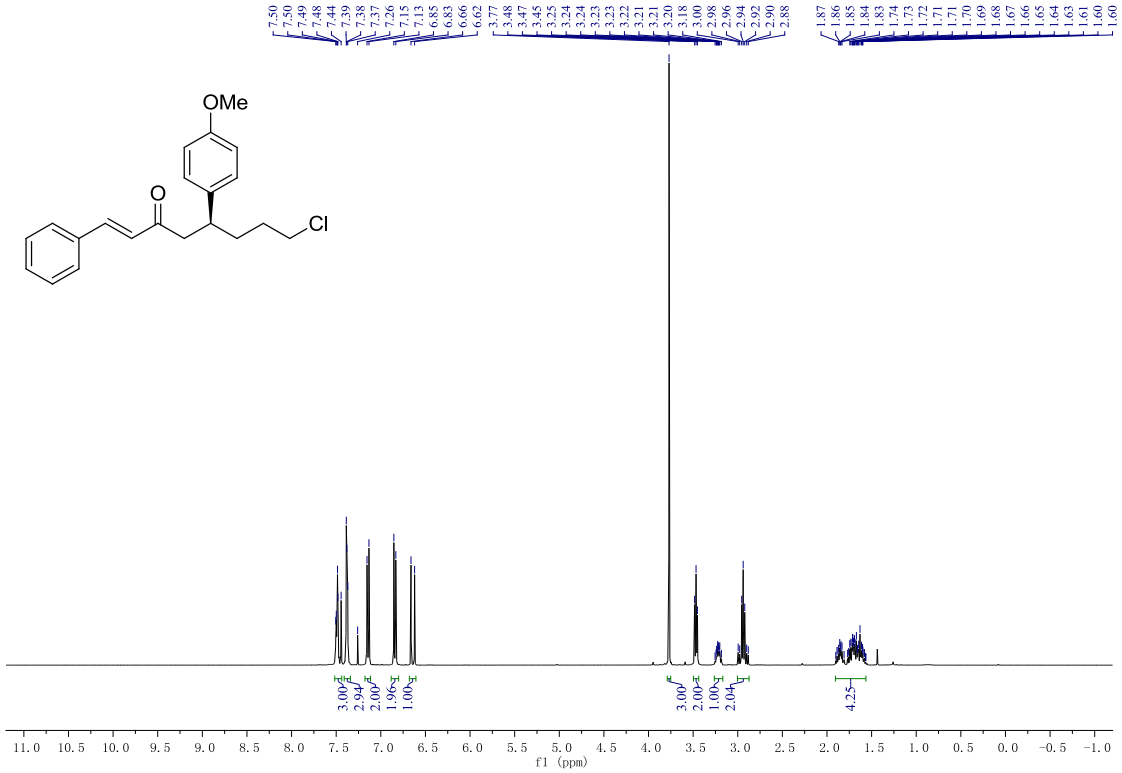


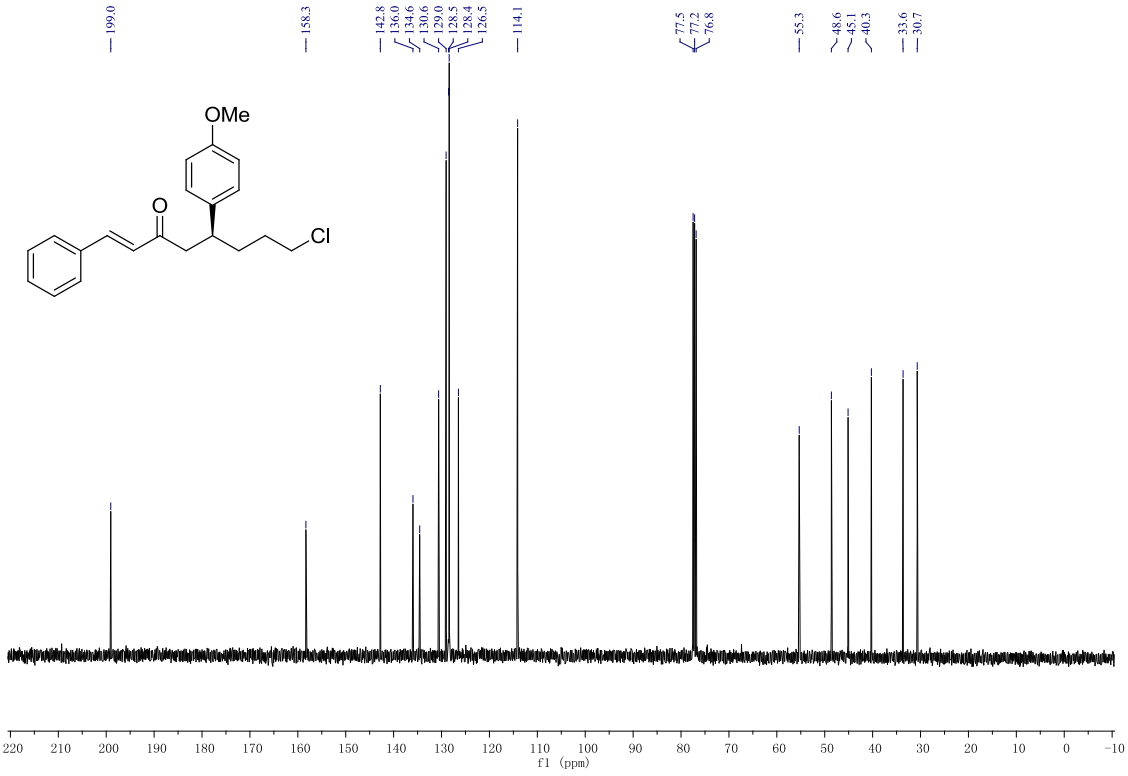


(*S*,*E*)-7-(4-Methoxyphenyl)-1,9-diphenylnon-3-en-5-one, 8ab

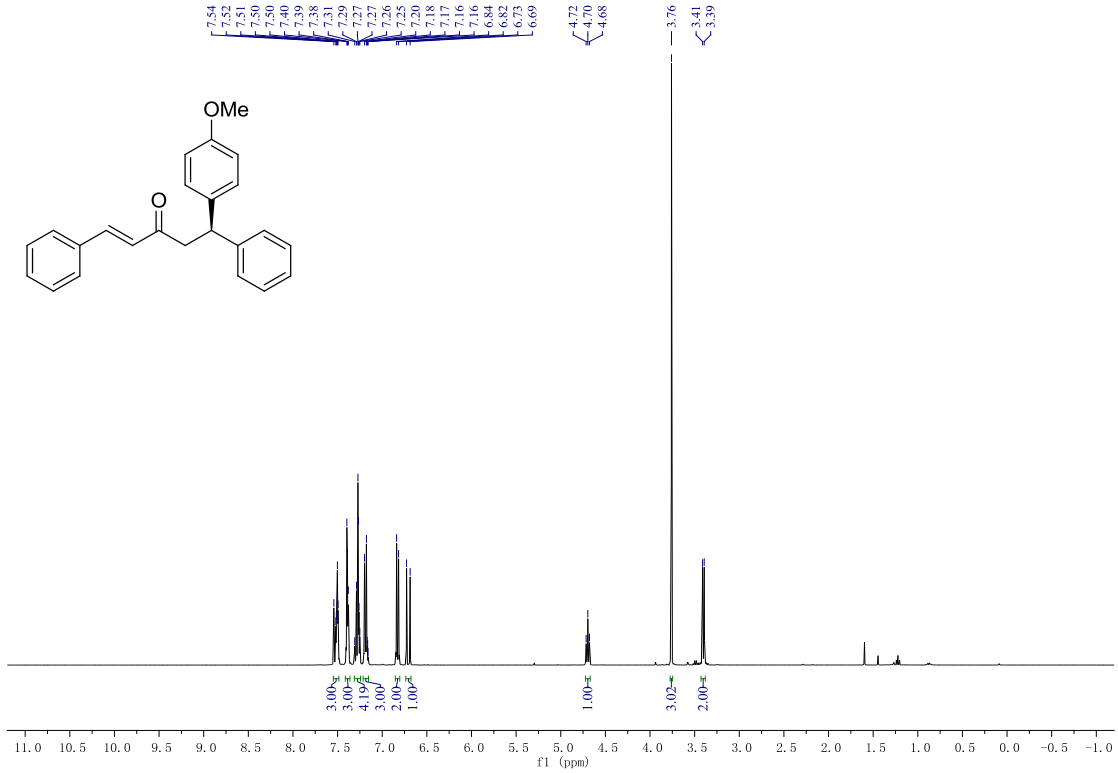


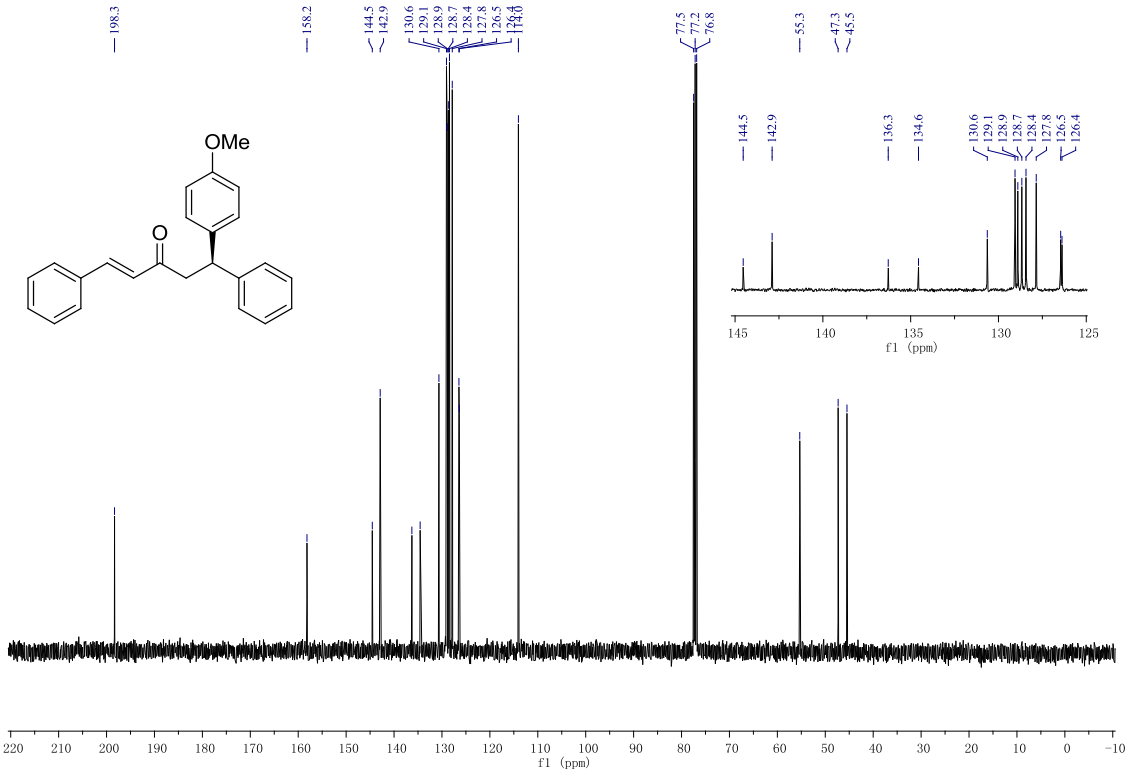
(*S*,*E*)-8-Chloro-5-(4-methoxyphenyl)-1-phenyloct-1-en-3-one, 8ac



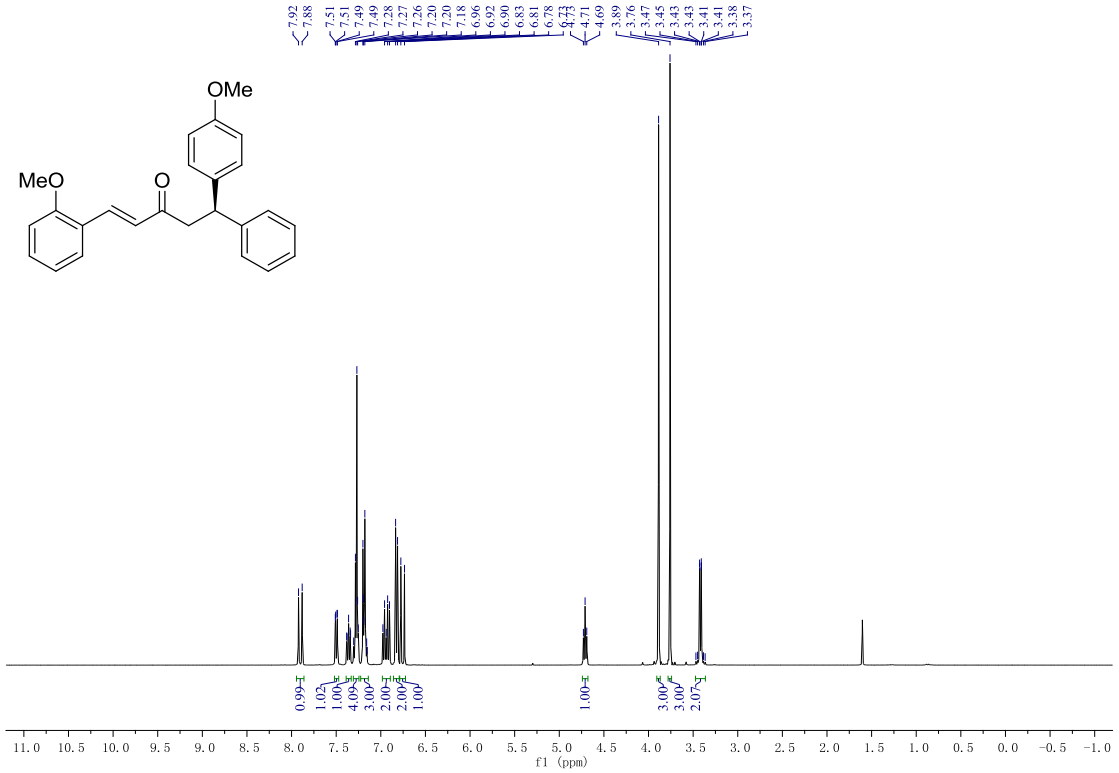


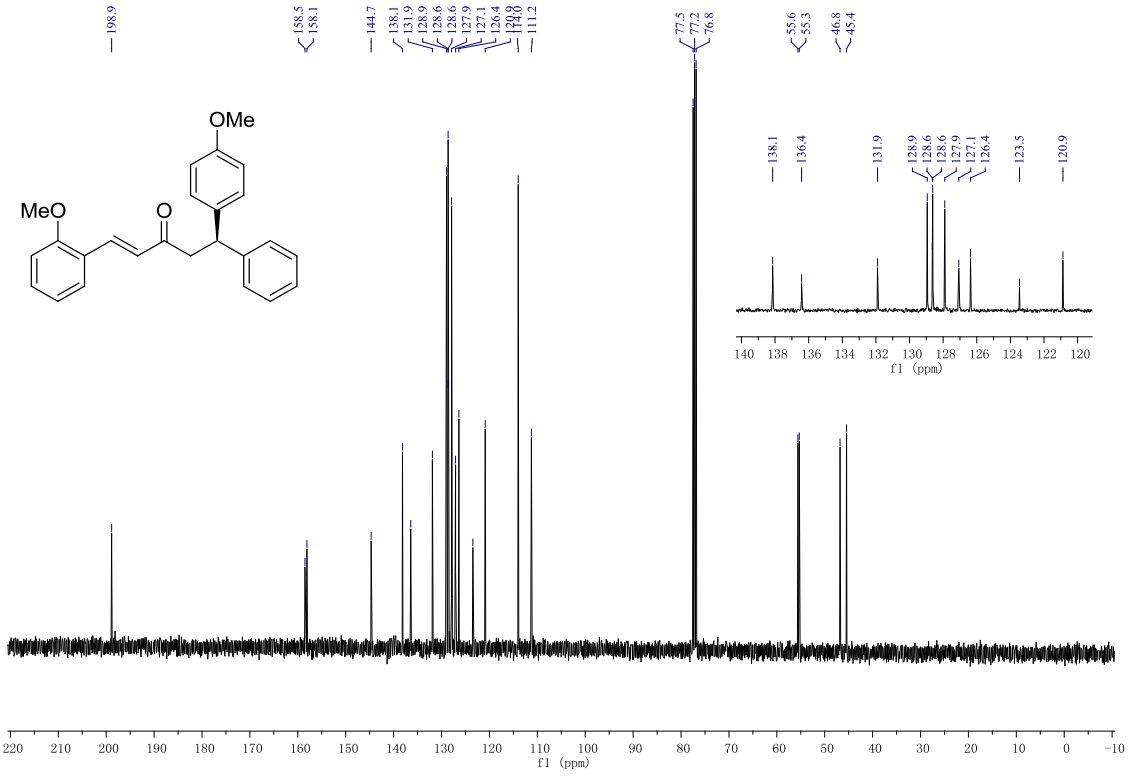
(*R*,*E*)-5-(4-Methoxyphenyl)-1,5-diphenylpent-1-en-3-one, 8ad



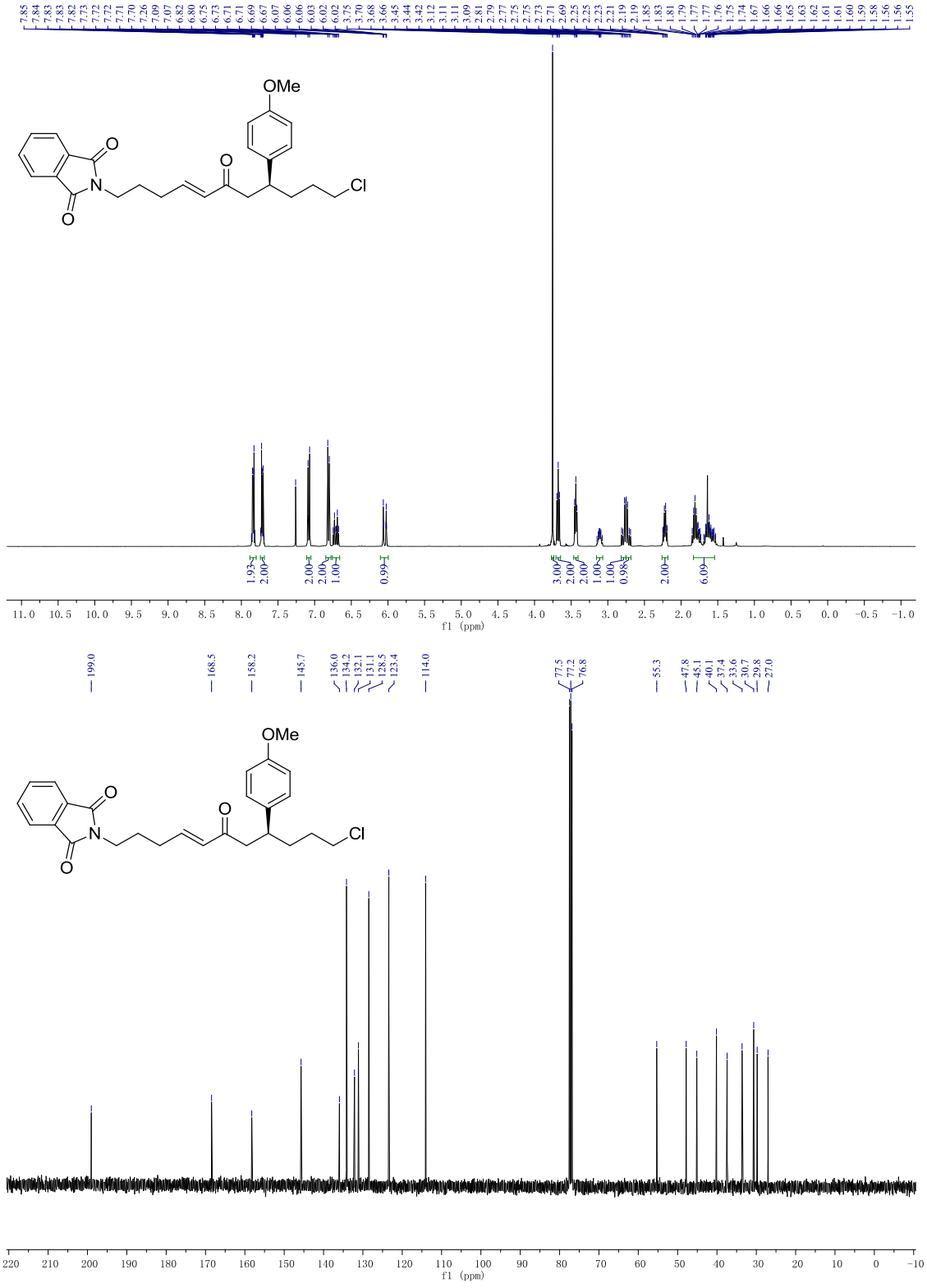


(*R*,*E*)-1-(2-Methoxyphenyl)-5-(4-methoxyphenyl)-5-phenylpent-1-en-3-one, 8ae

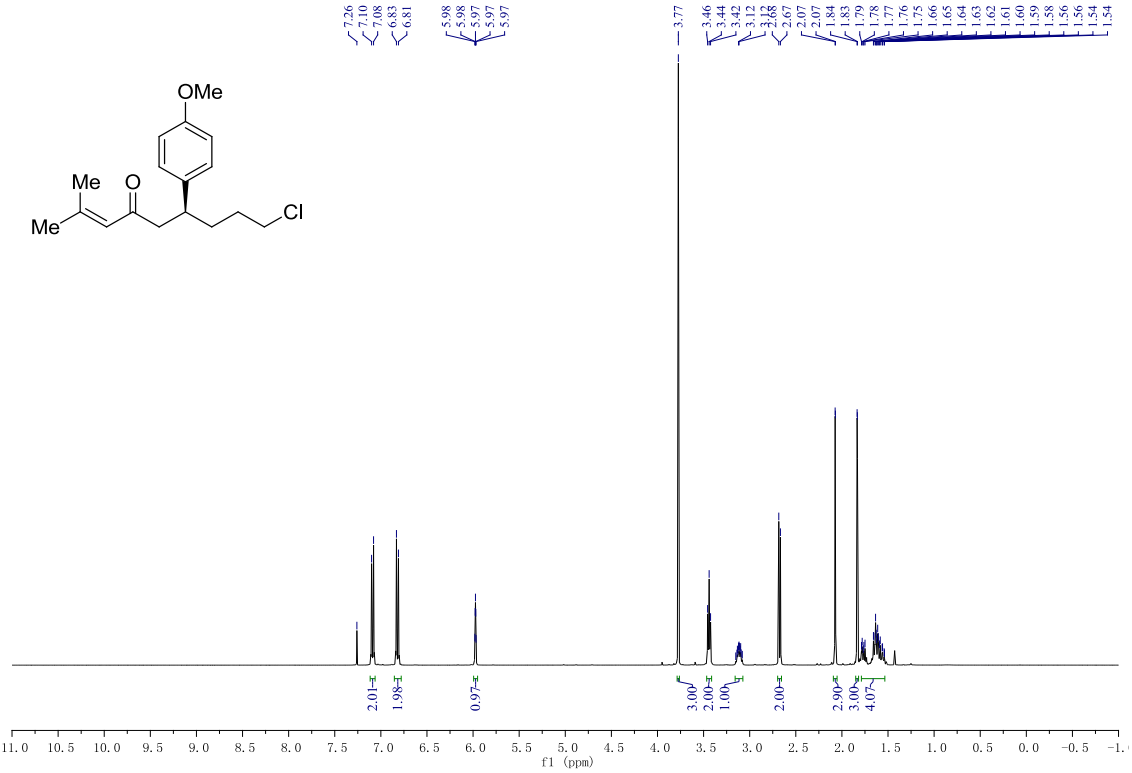


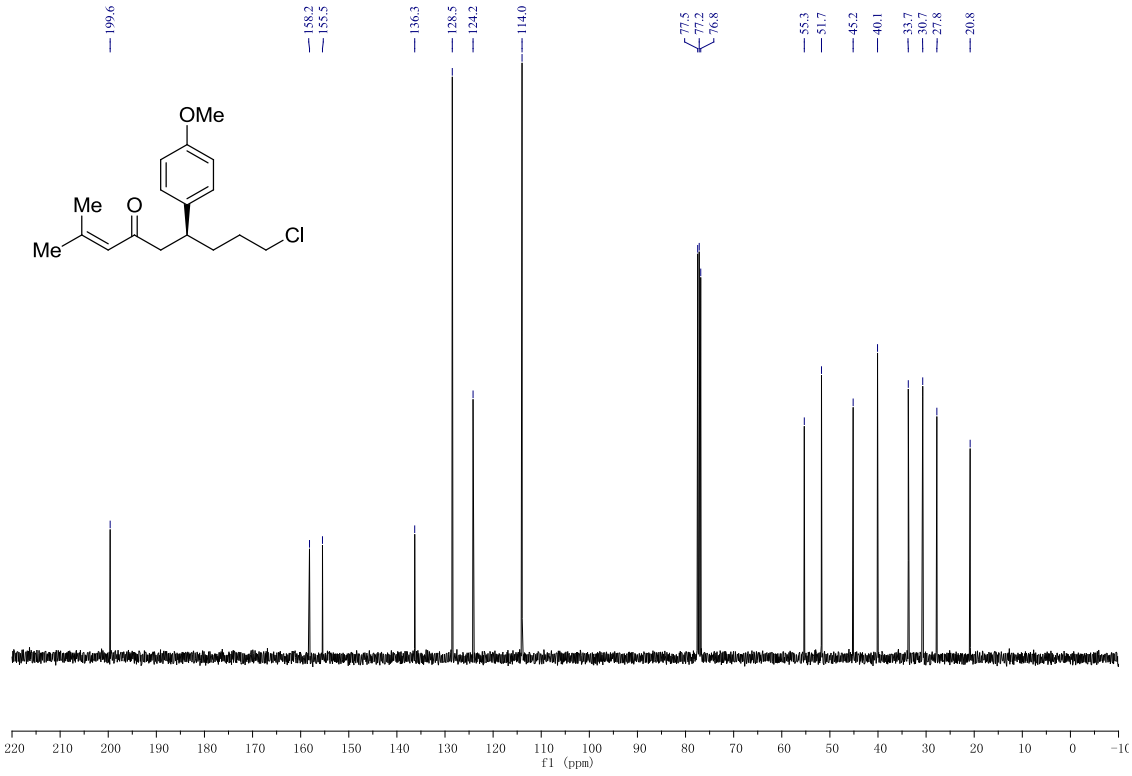


(*S*,*E*)-2-(11-Chloro-8-(4-methoxyphenyl)-6-oxoundec-4-en-1-yl)isoindoline-1,3-dione, 8af

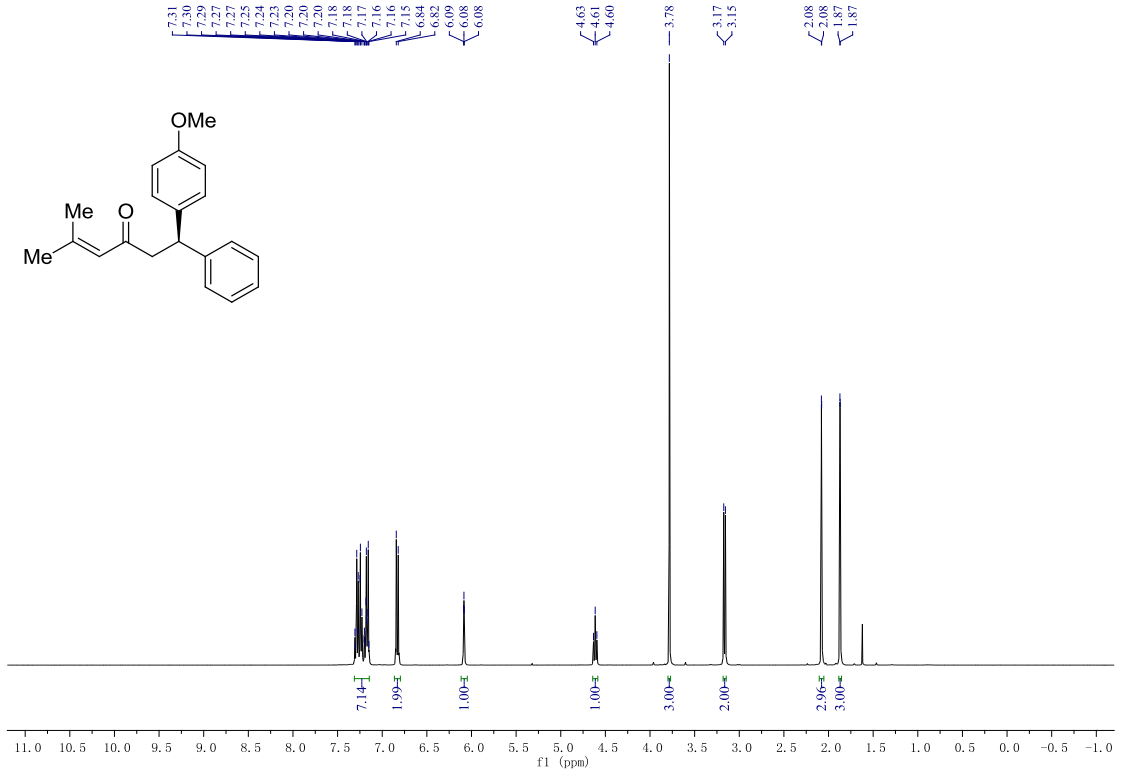


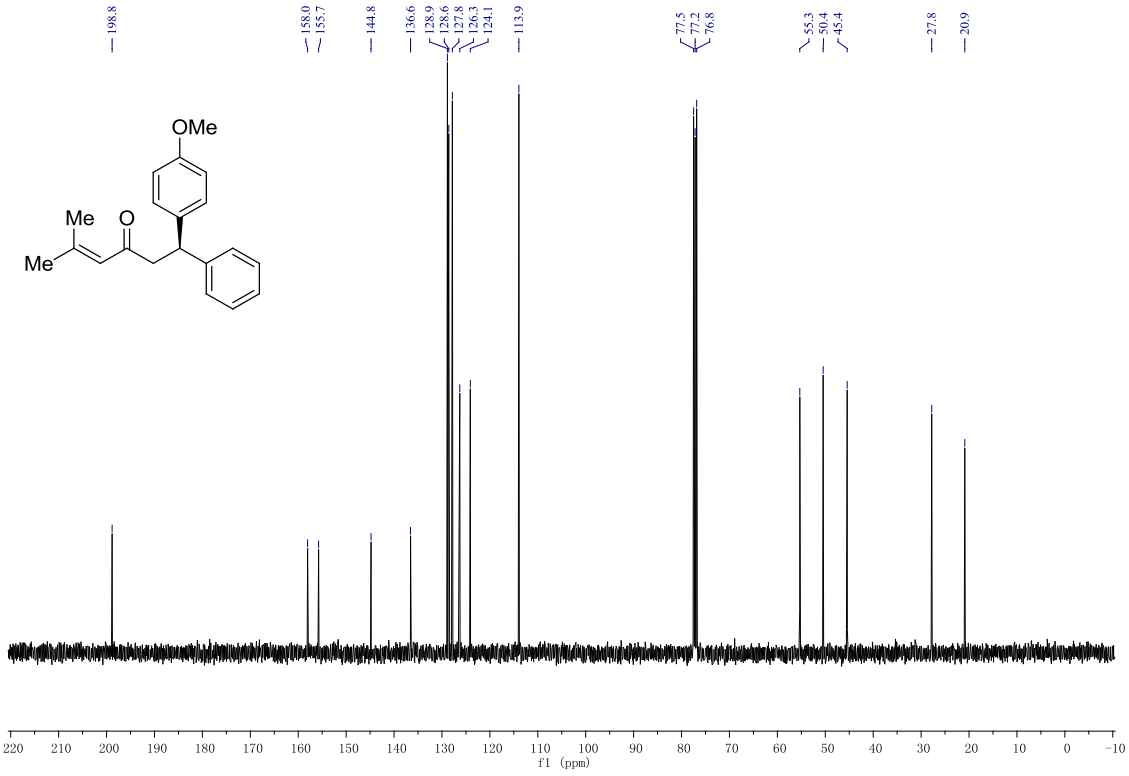
(*S*)-9-Chloro-6-(4-methoxyphenyl)-2-methylnon-2-en-4-one, 8ag



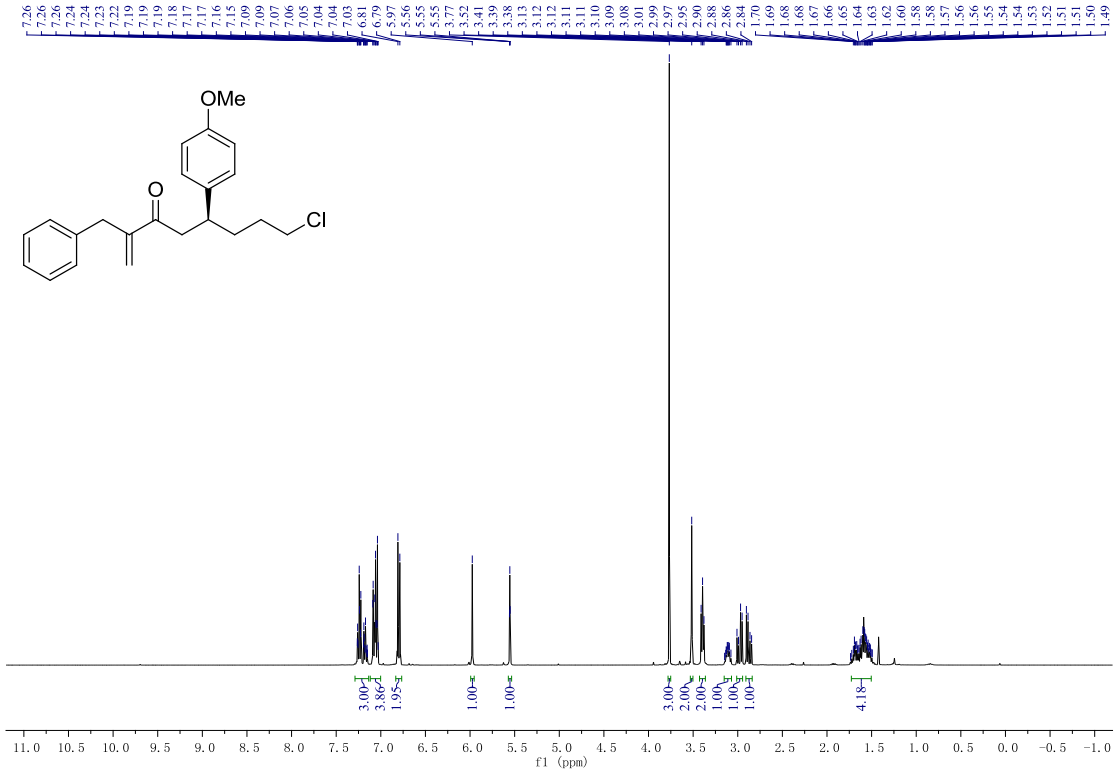


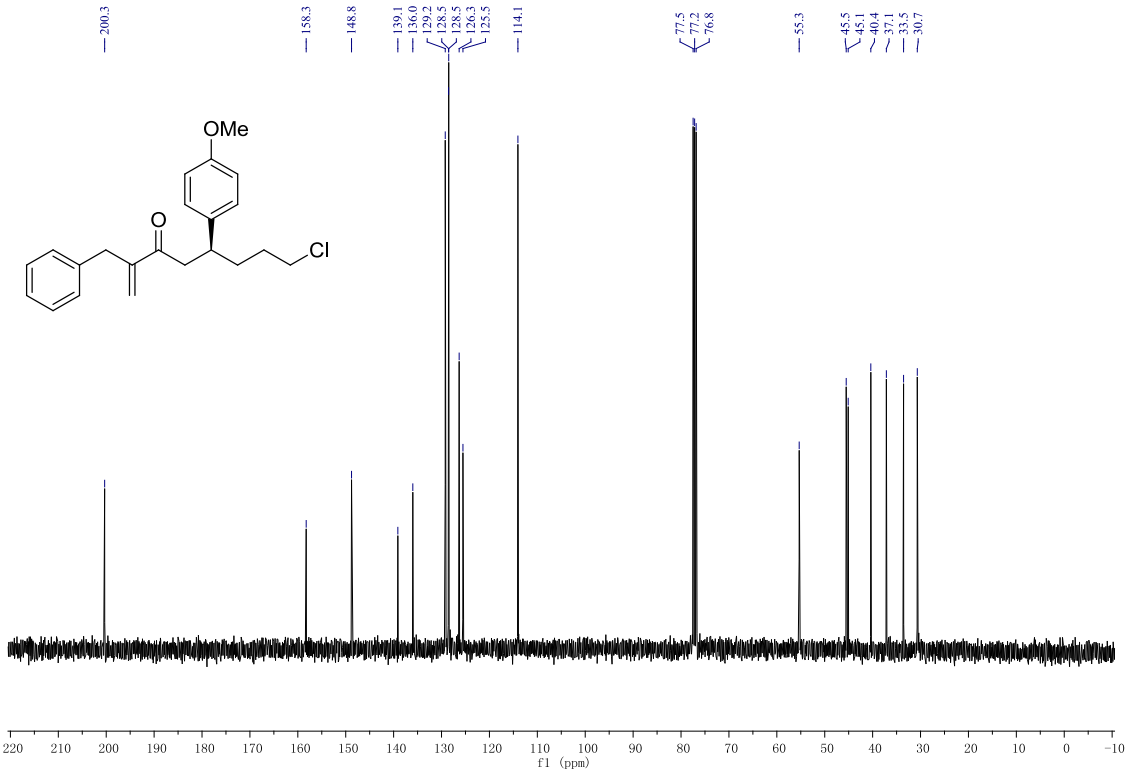
(*R*)-1-(4-Methoxyphenyl)-5-methyl-1-phenylhex-4-en-3-one, 8ah



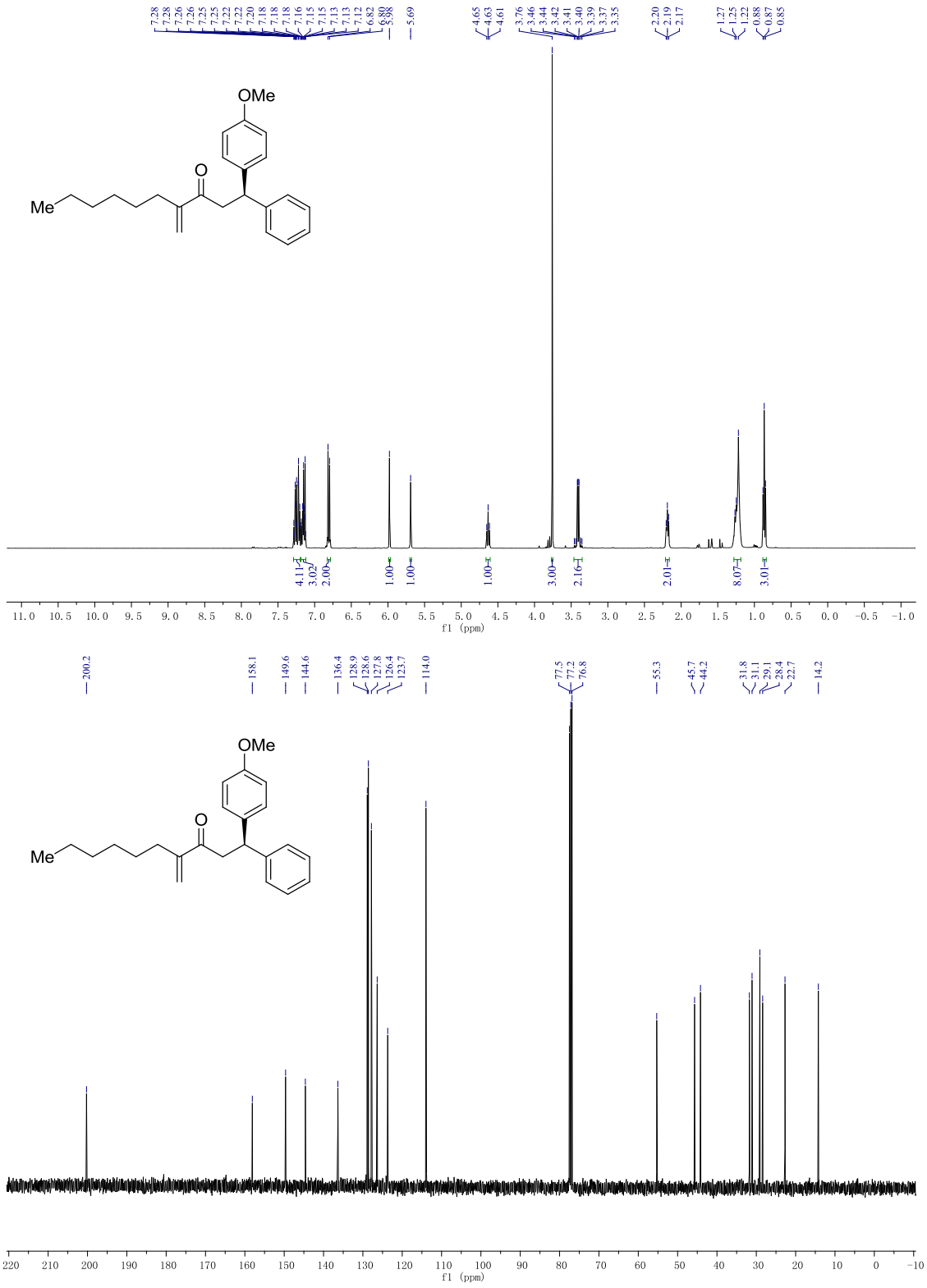


(*S*)-2-Benzyl-8-chloro-5-(4-methoxyphenyl)oct-1-en-3-one, 8ai

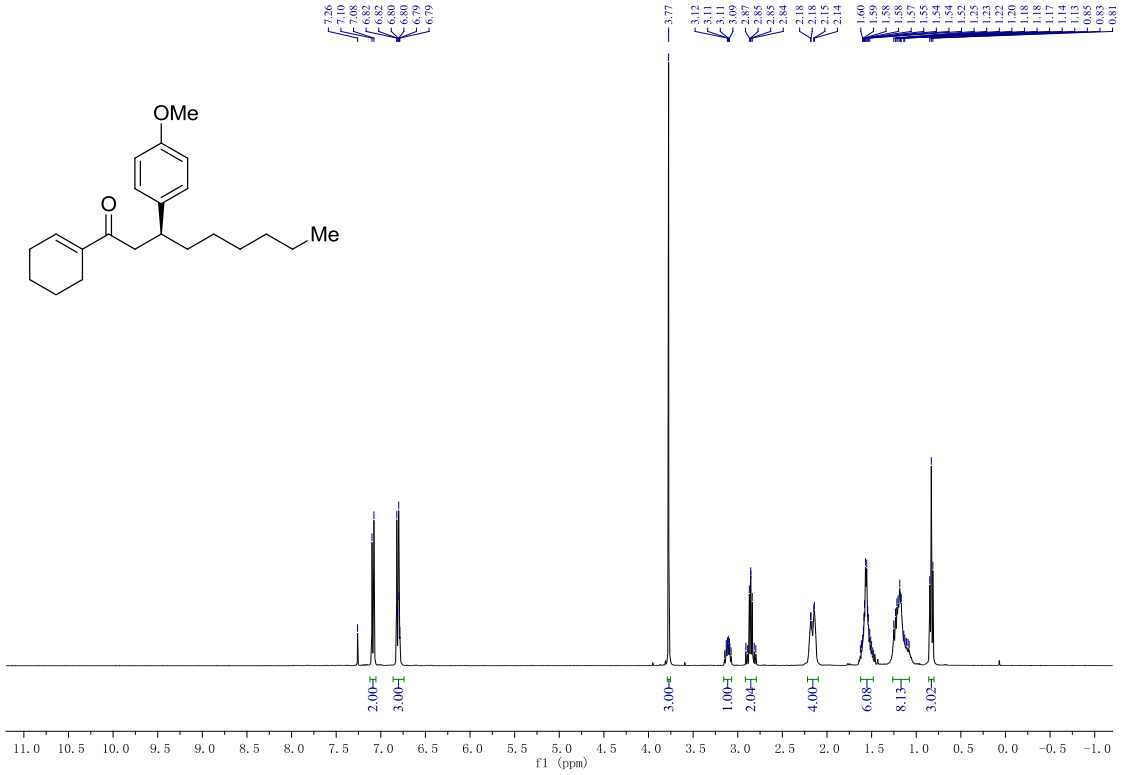


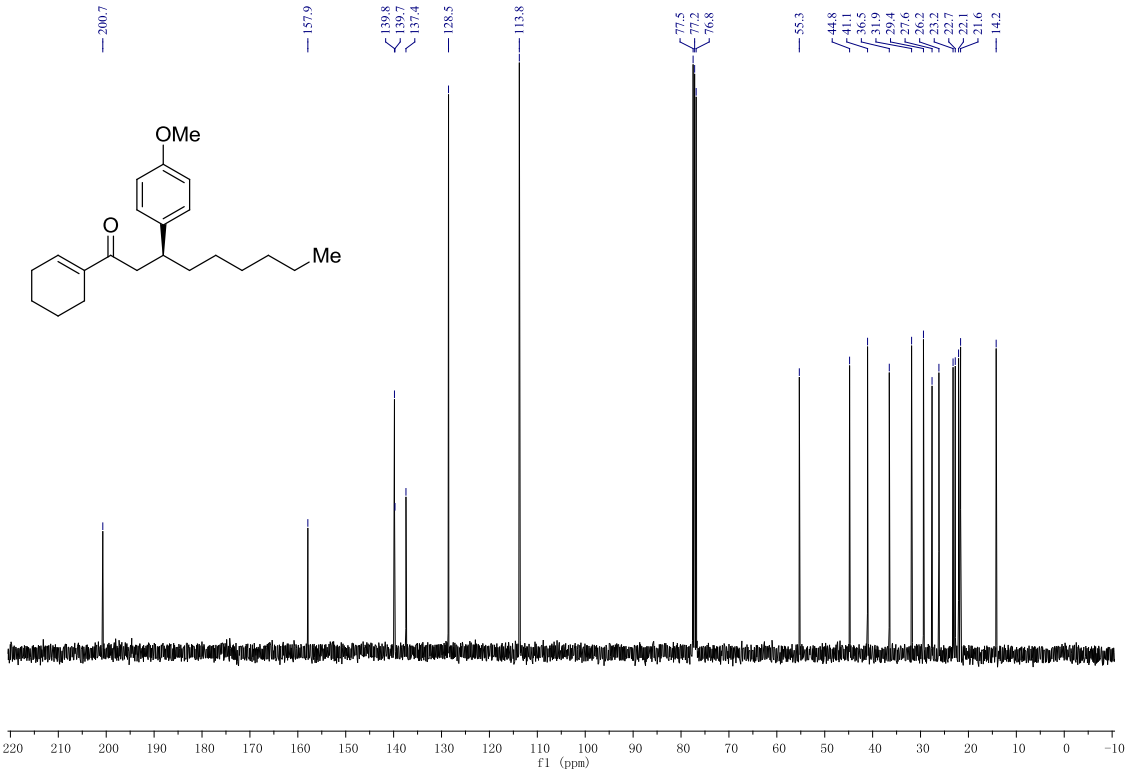


(*R*)-1-(4-Methoxyphenyl)-4-methylene-1-phenyldecan-3-one, 8aj

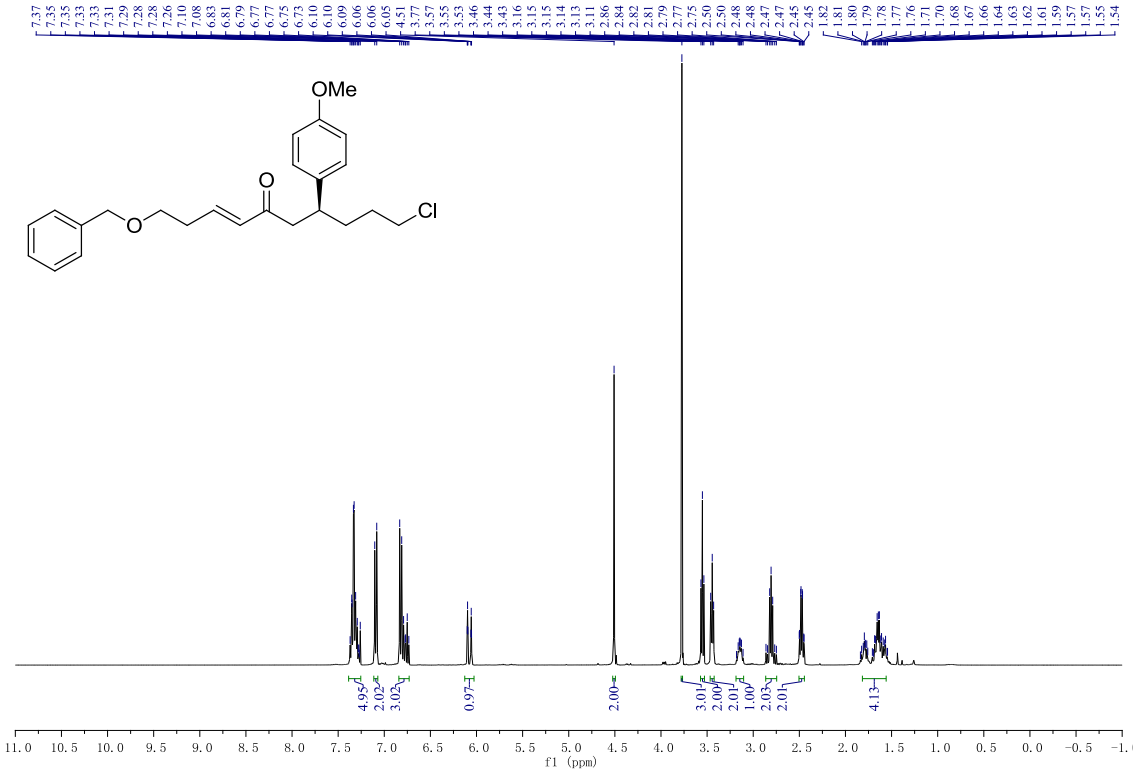


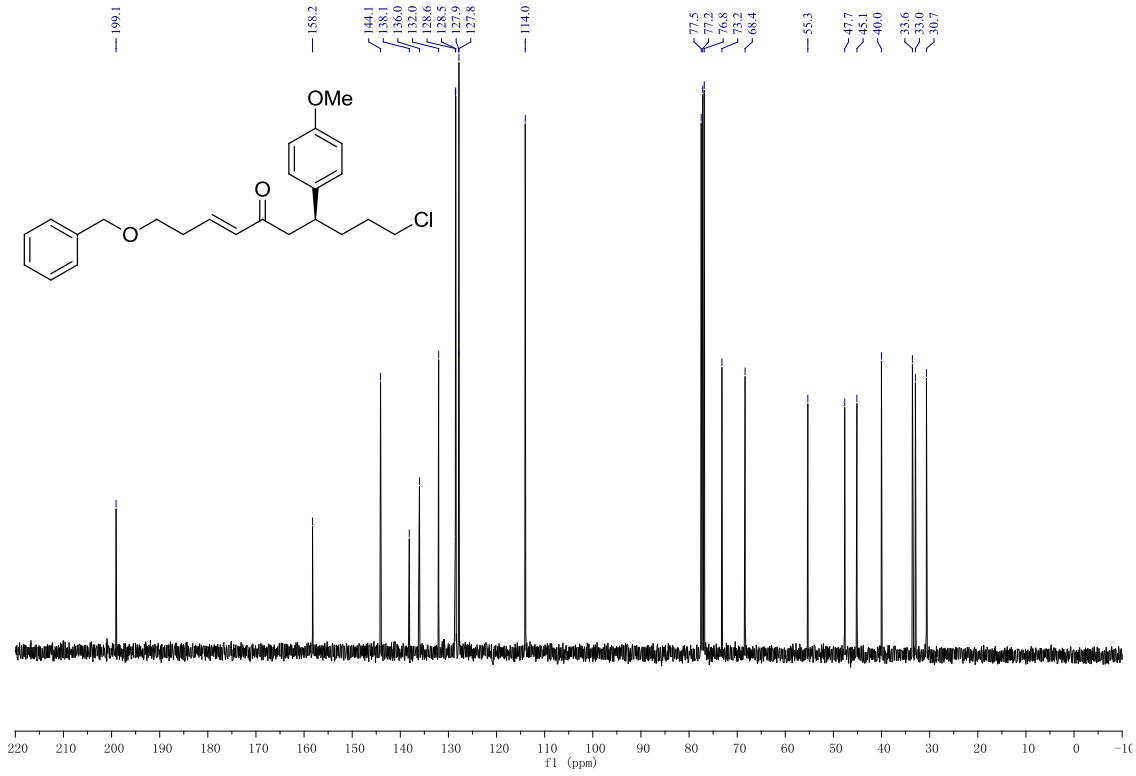
(*S*)-1-(Cyclohex-1-en-1-yl)-3-(4-methoxyphenyl)nonan-1-one, 8ak



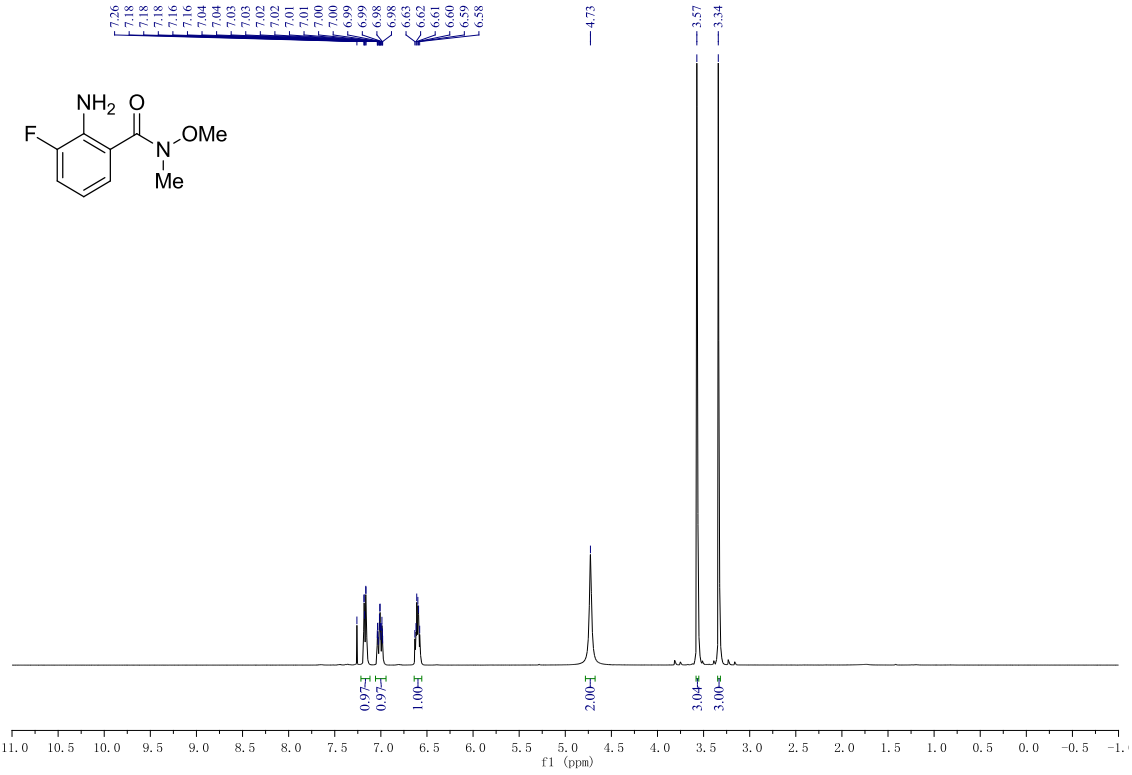


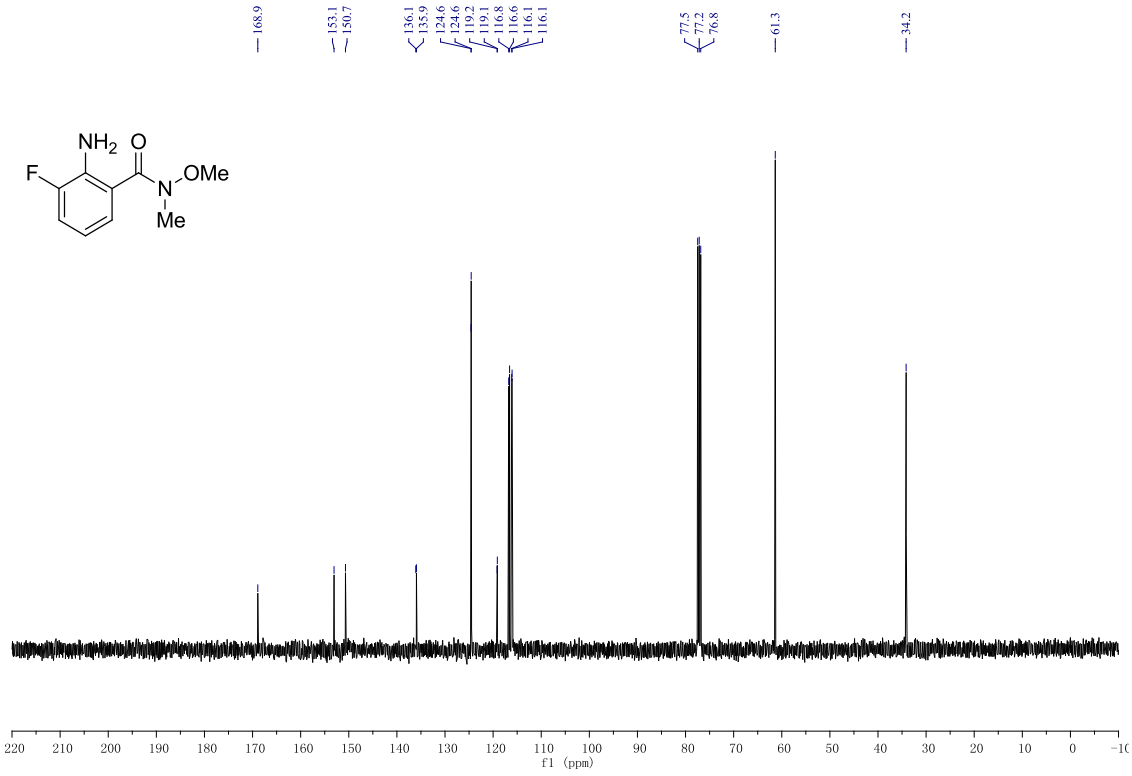
(*S*,*E*)-1-(Benzyloxy)-10-chloro-7-(4-methoxyphenyl)dec-3-en-5-one, 8al



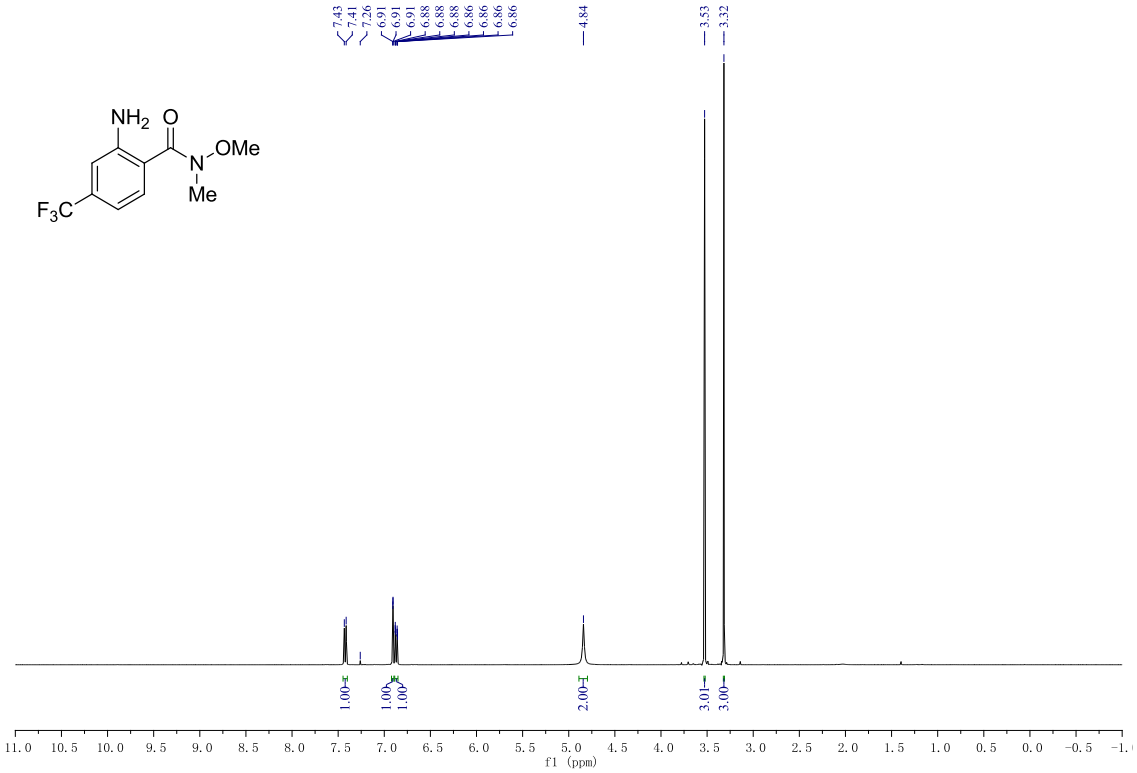


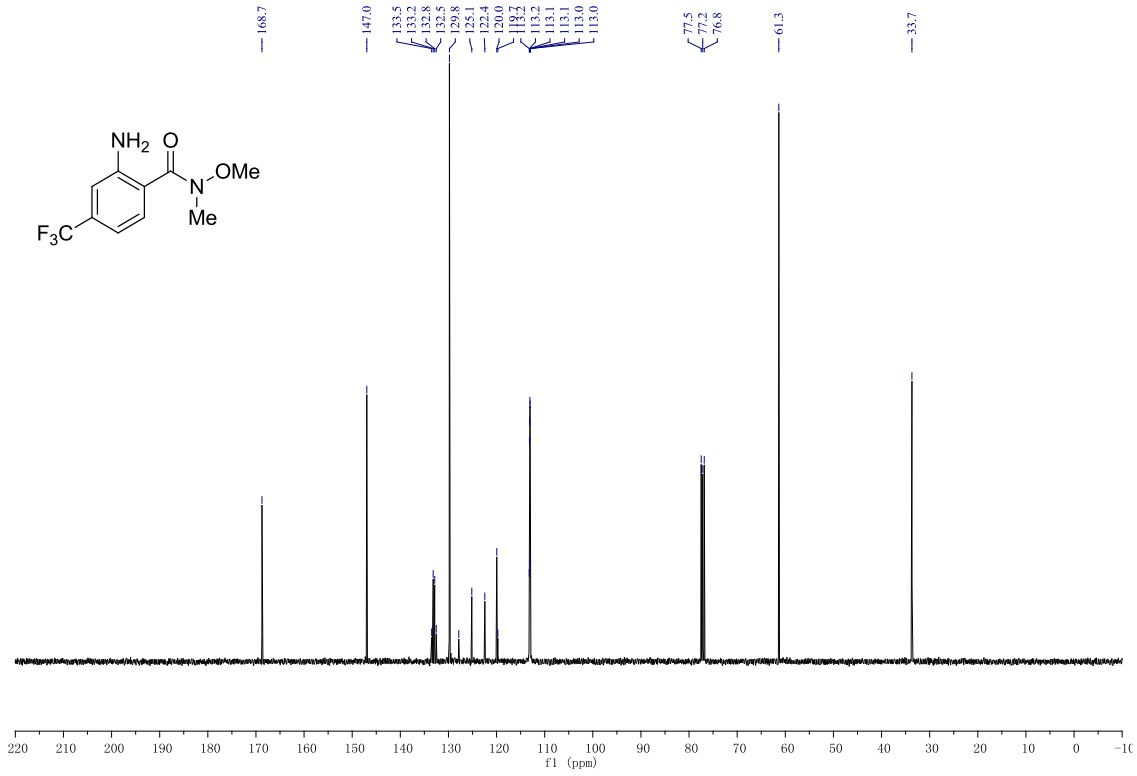
2-Amino-3-fluoro-*N*-methoxy-*N*-methylbenzamide, SM3



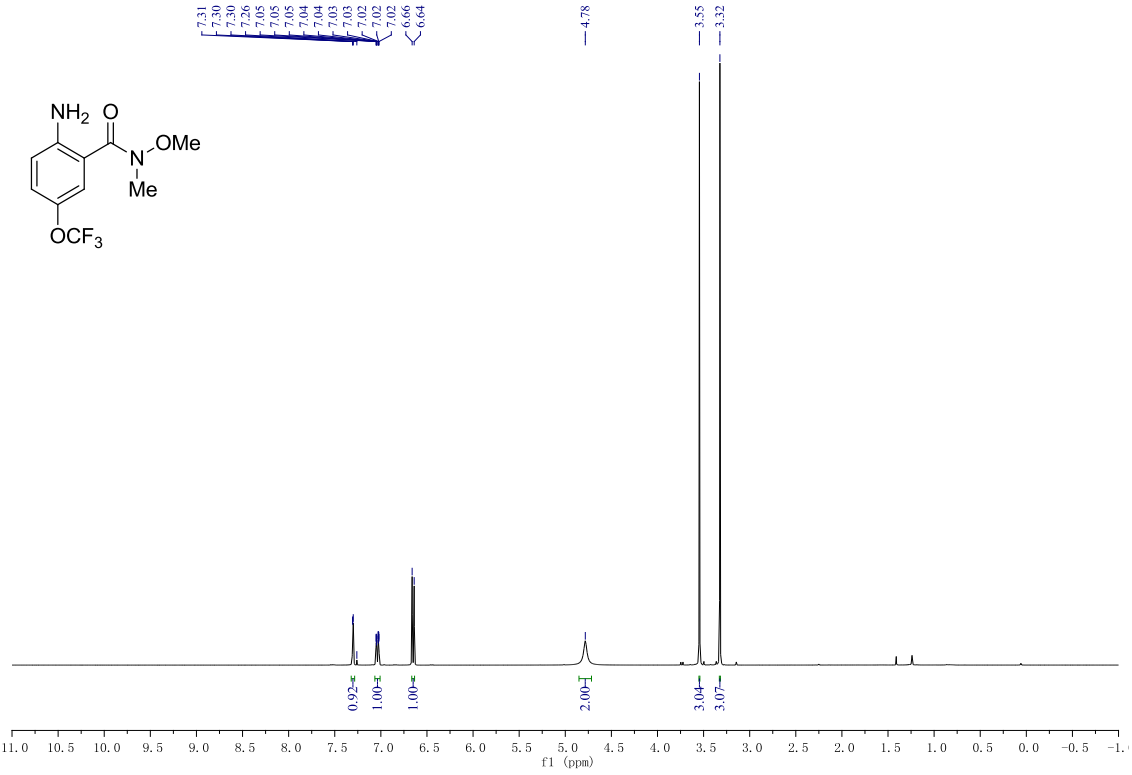


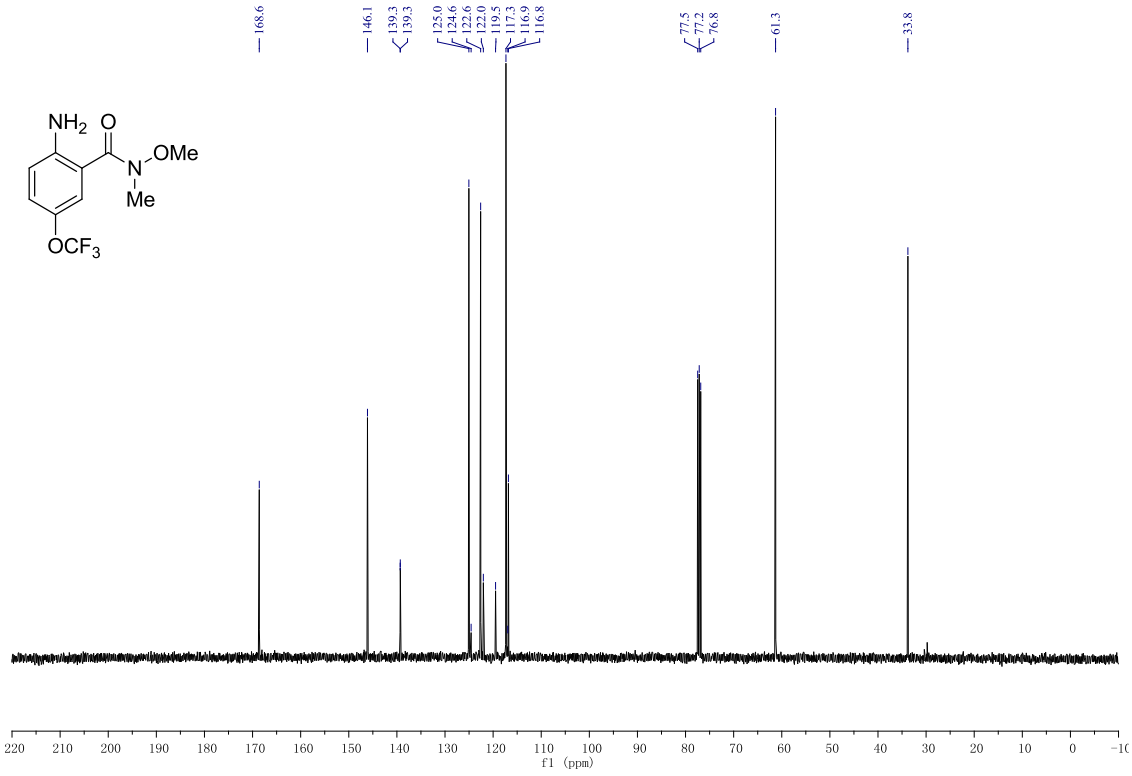
2-Amino-*N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide, SM4



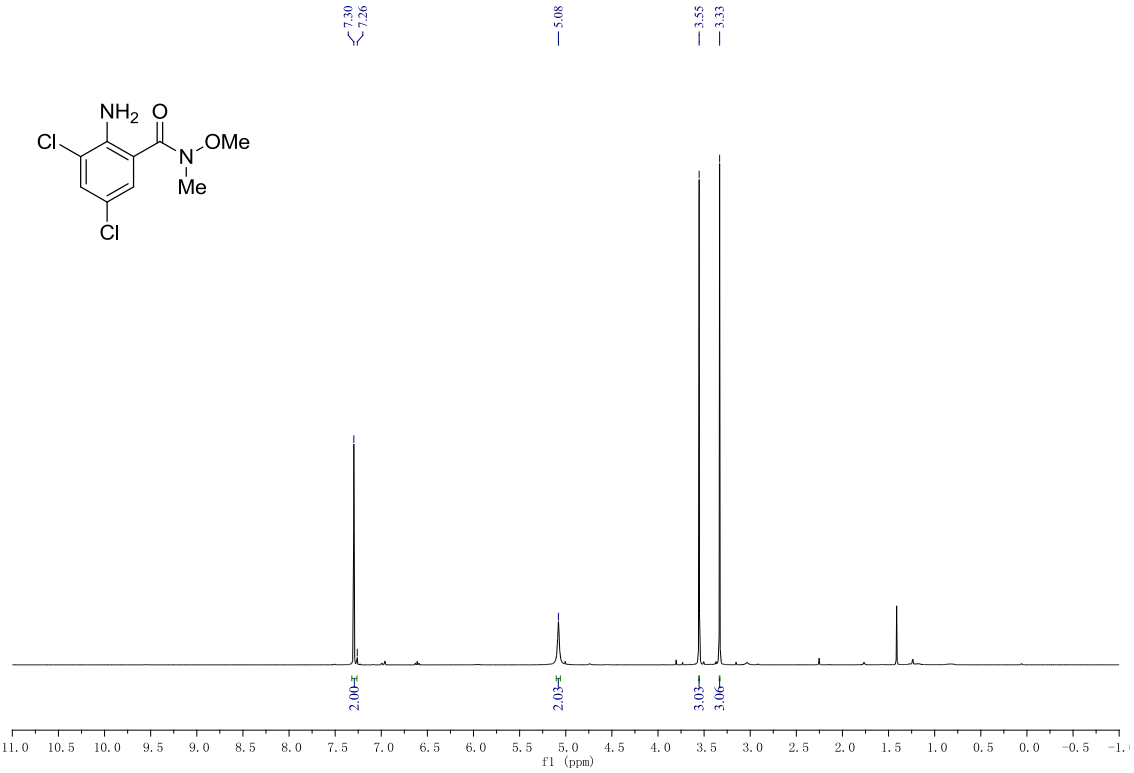


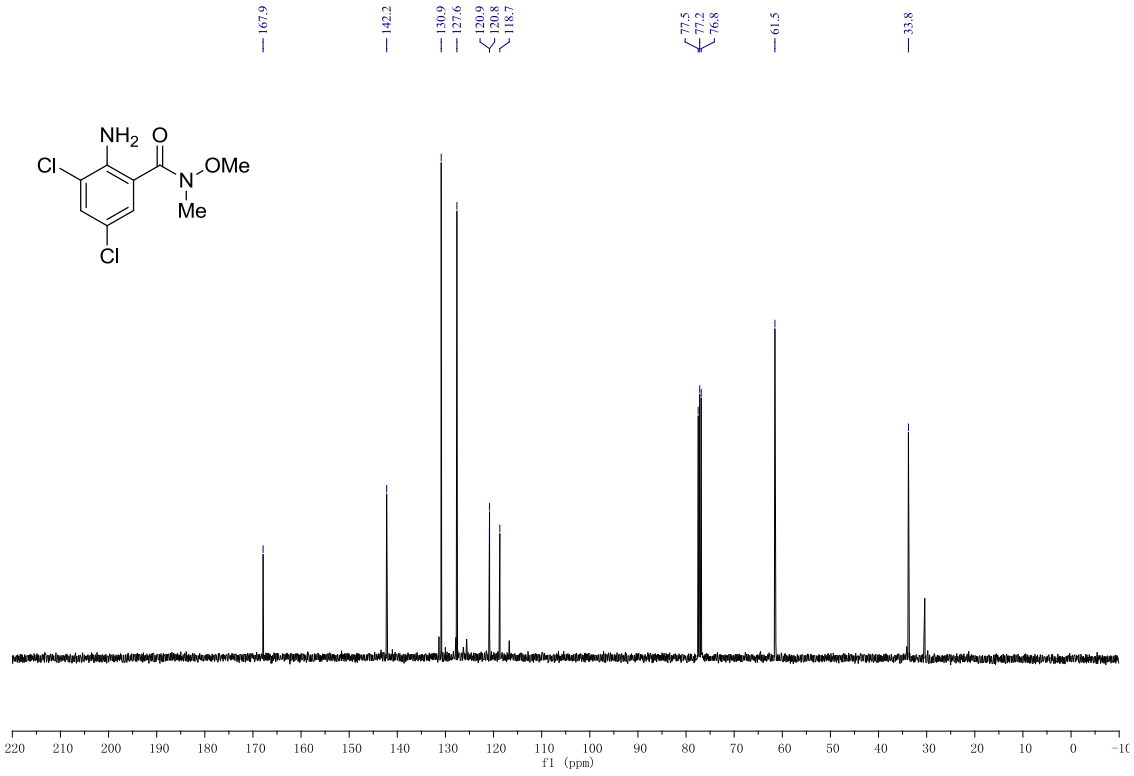
2-Amino-*N*-methoxy-*N*-methyl-5-(trifluoromethoxy)benzamide, SM5



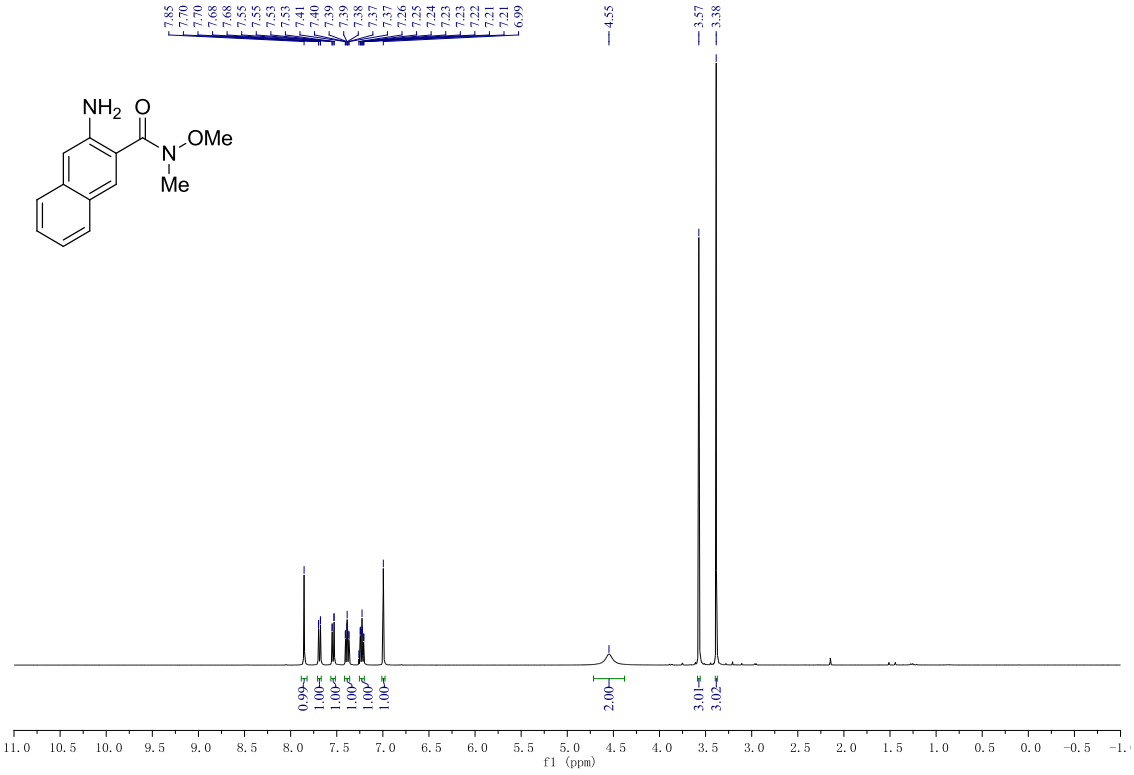


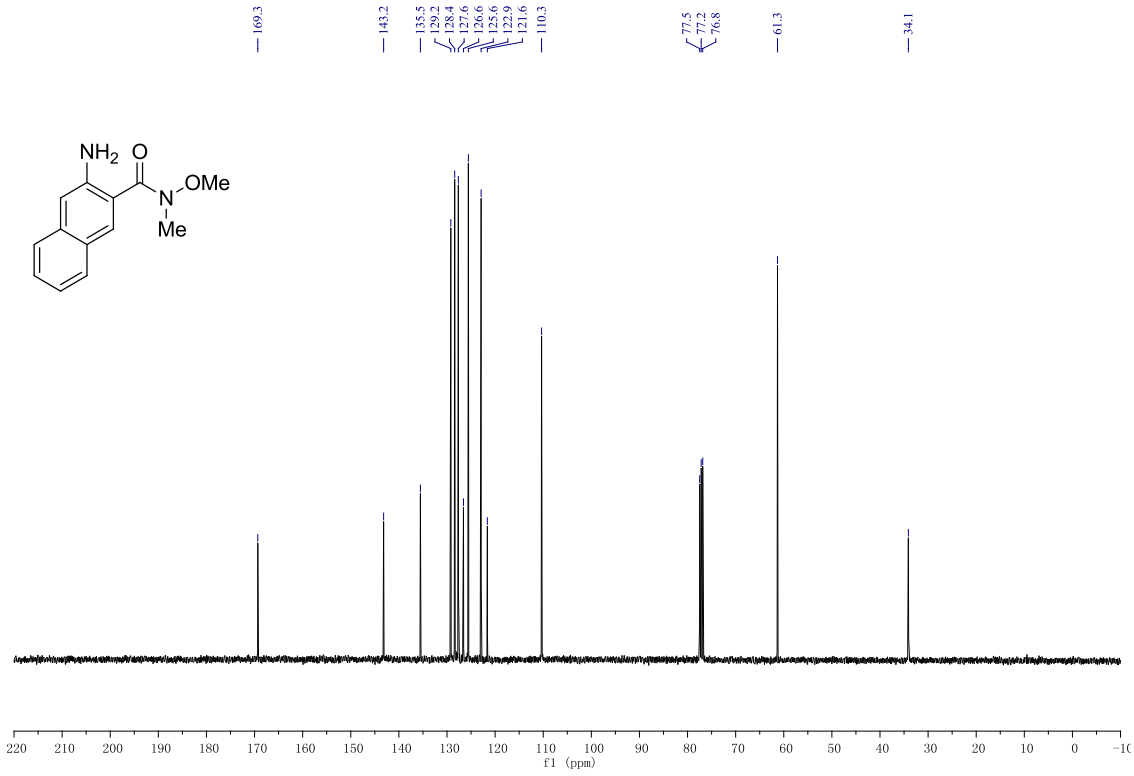
2-Amino-3,5-dichloro-*N*-methoxy-*N*-methylbenzamide, SM6



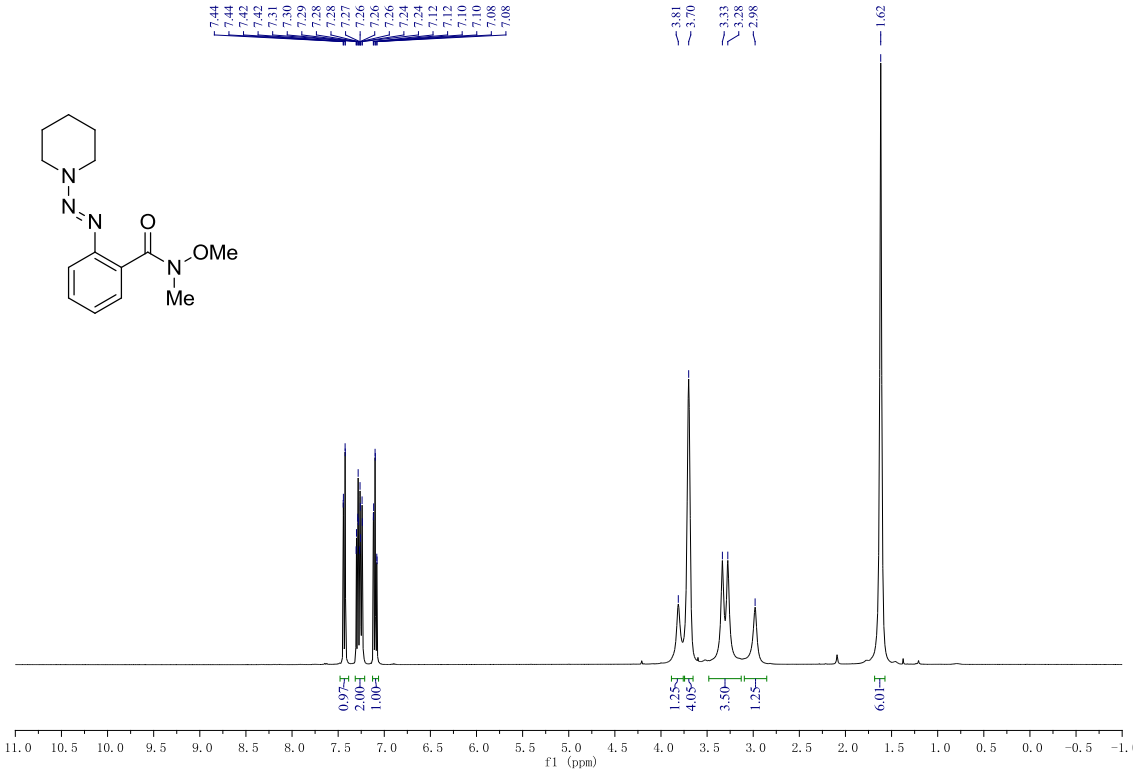


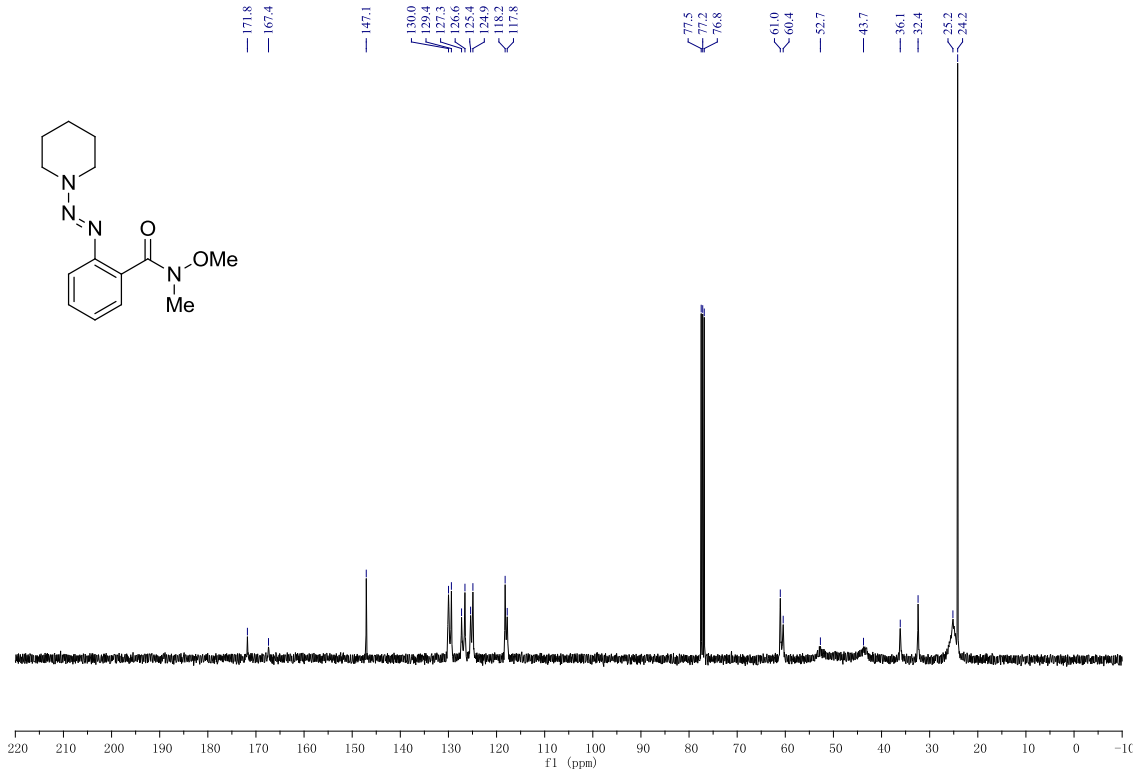
3-Amino-*N*-methoxy-*N*-methyl-2-naphthamide, SM7



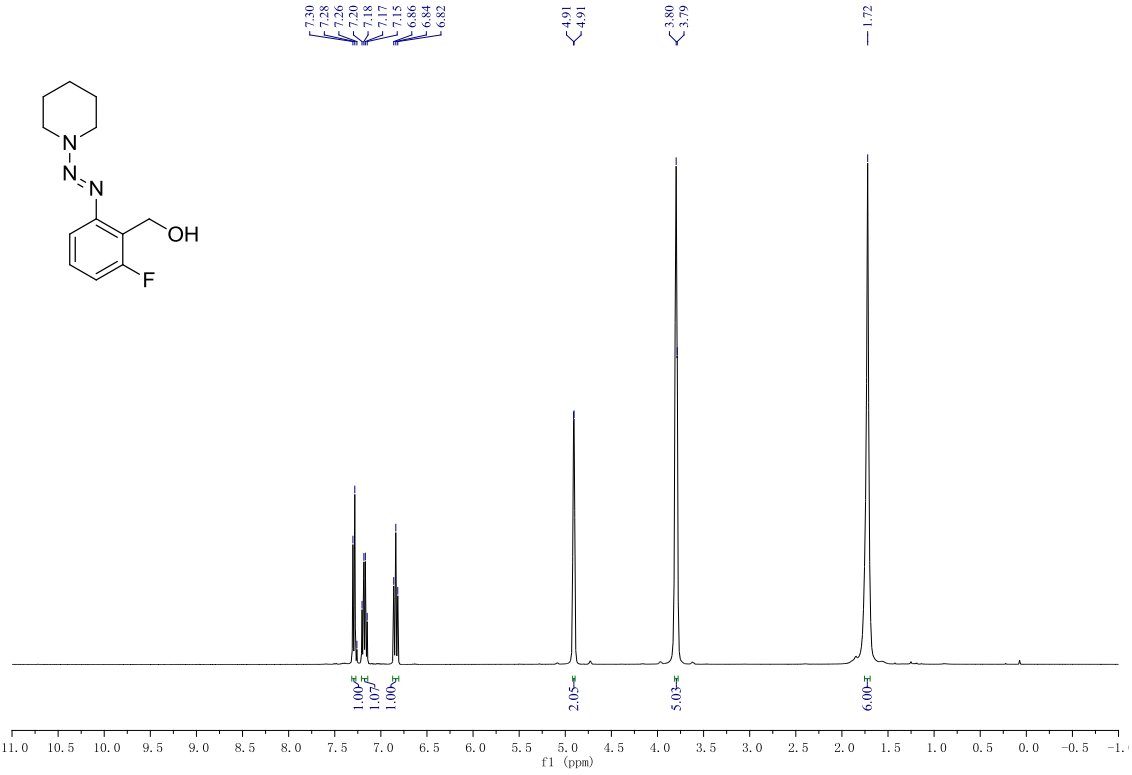


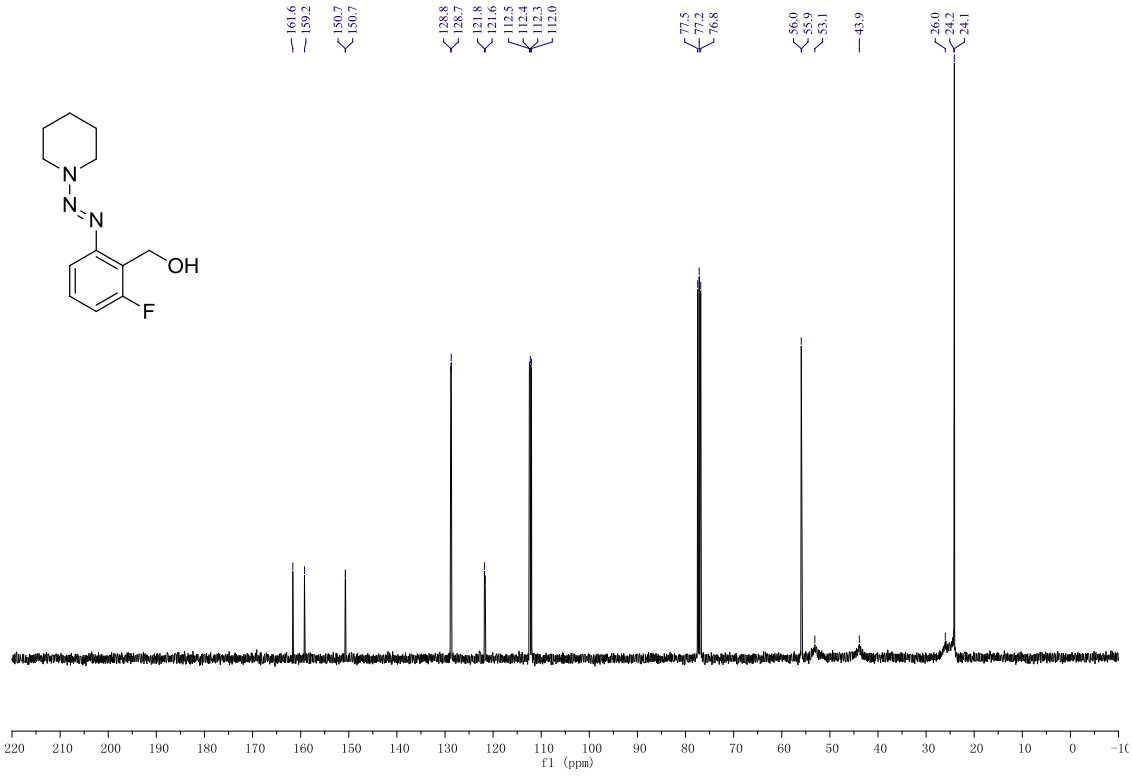
(*E*)-*N*-Methoxy-*N*-methyl-2-(piperidin-1-yldiazenyl)benzamide, SM8



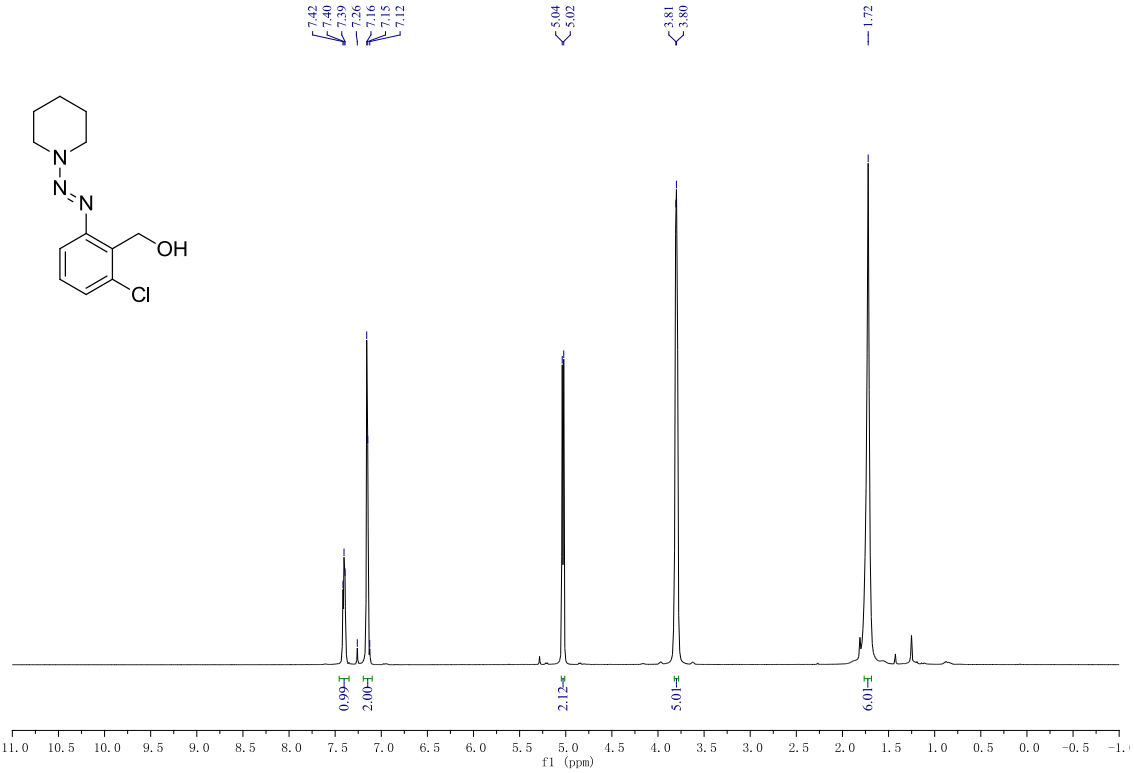


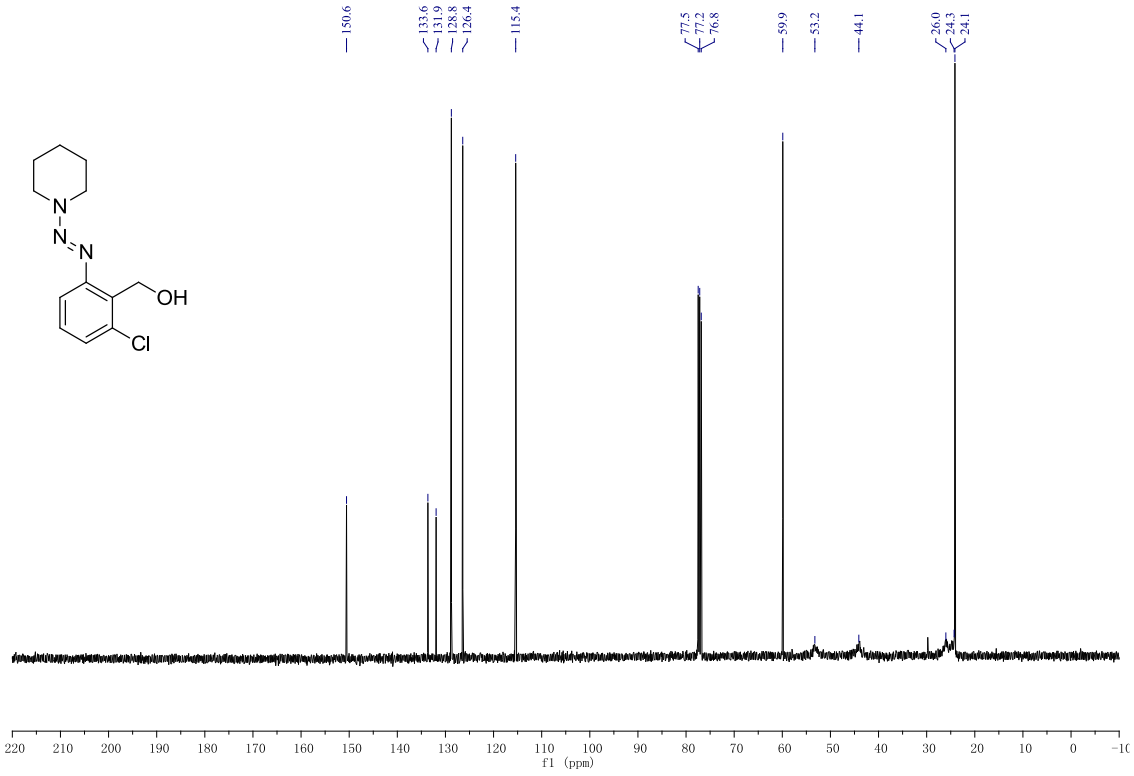
(*E*)-(2-Fluoro-6-(piperidin-1-yldiazenyl)phenyl)methanol, SM9



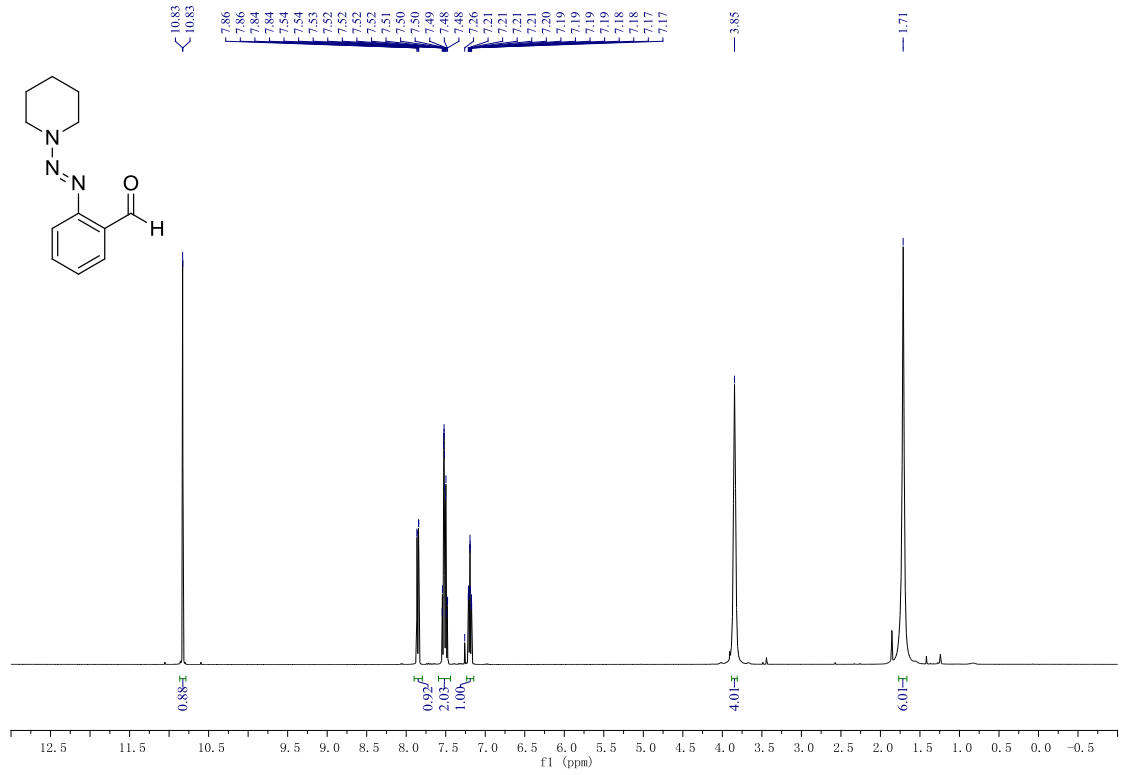


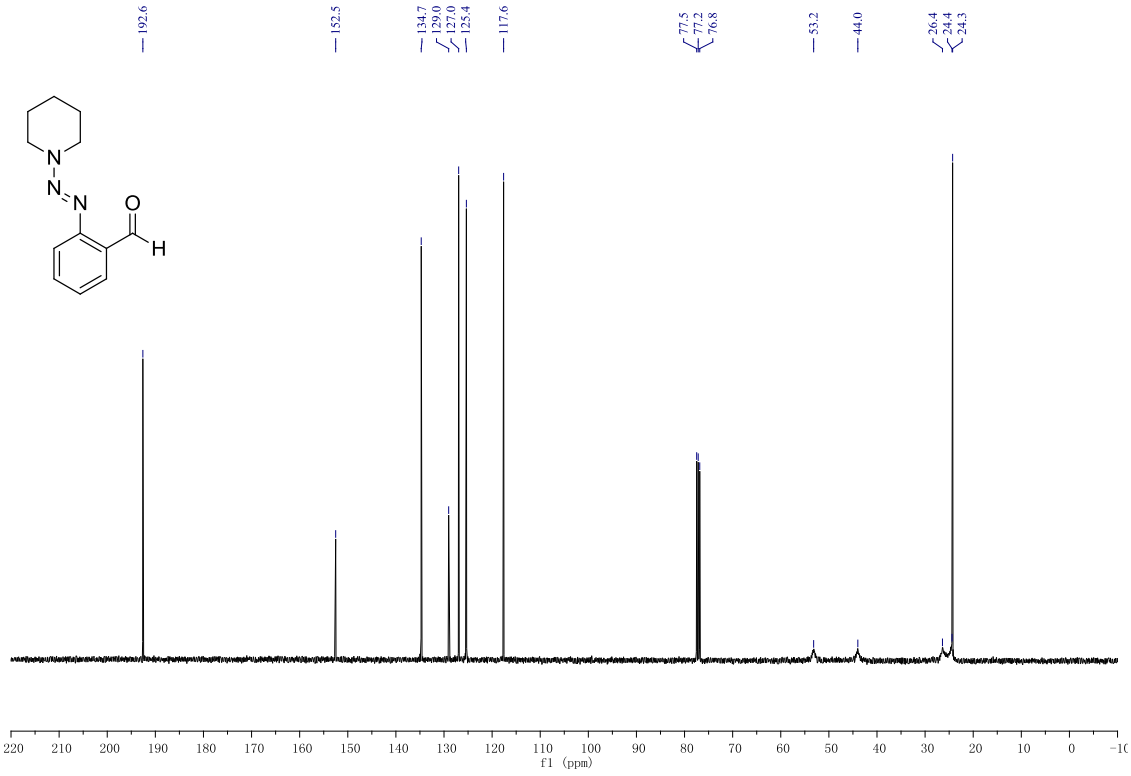
(*E*)-(2-Chloro-6-(piperidin-1-yldiazenyl)phenyl)methanol, SM10



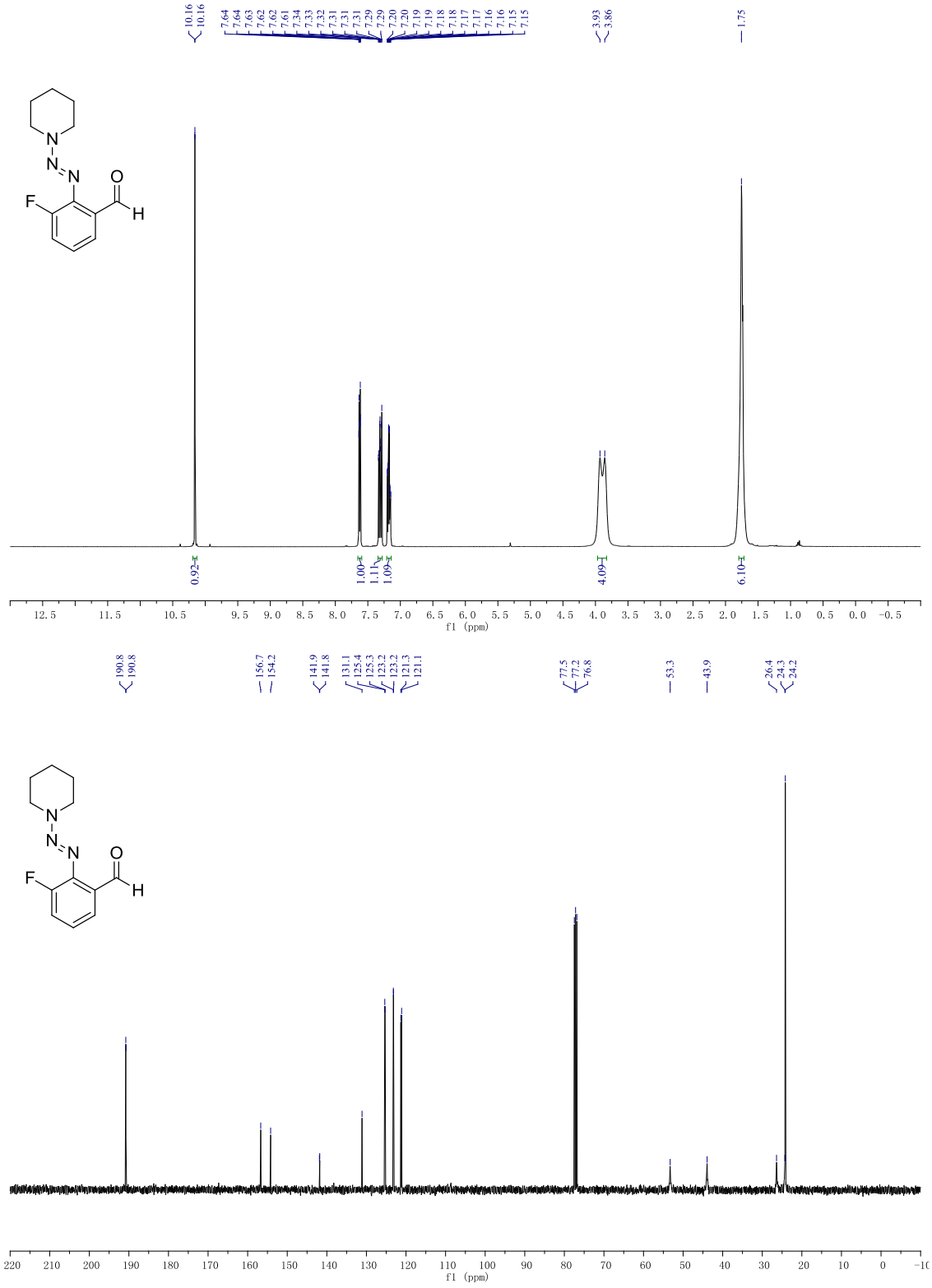


(*E*)-2-(Piperidin-1-yldiazenyl)benzaldehyde, 11b

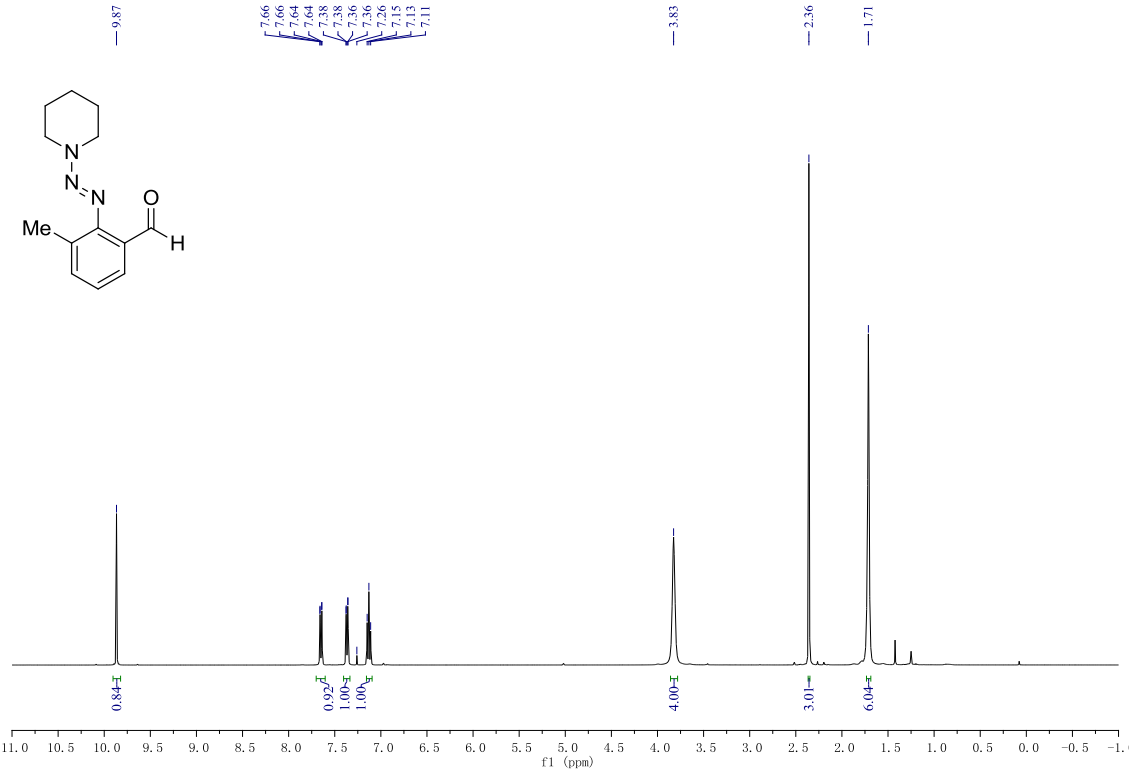


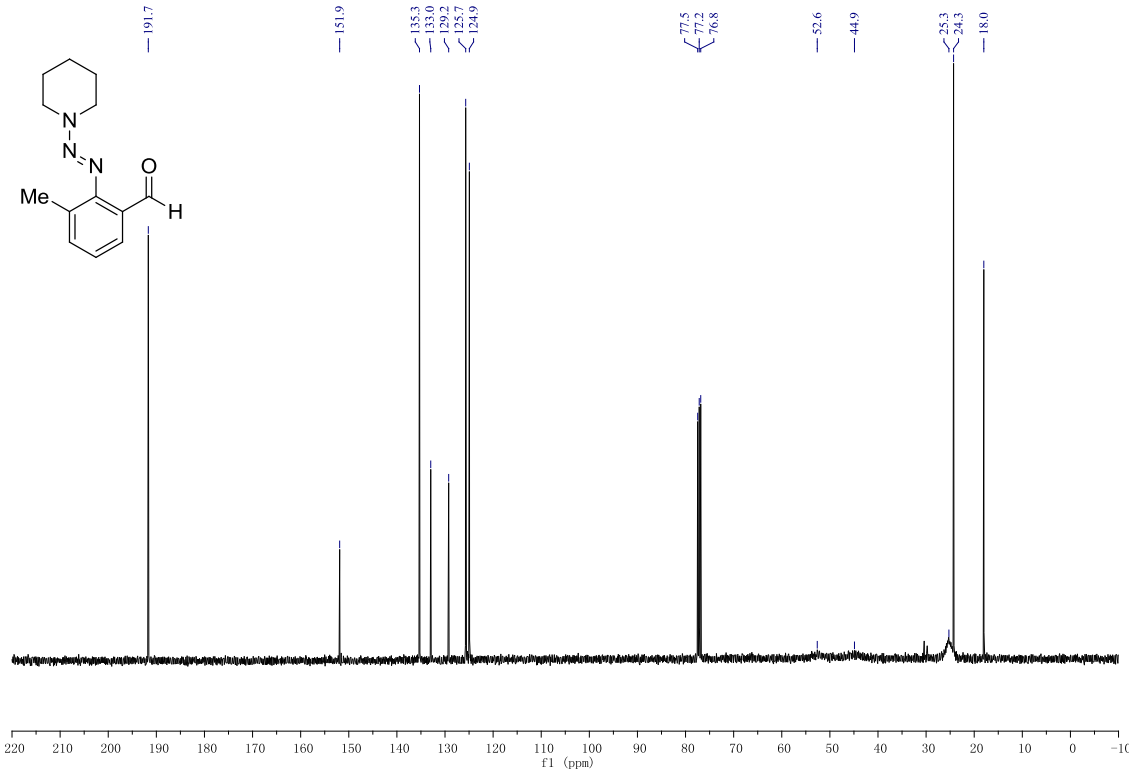


(*E*)-3-Fluoro-2-(piperidin-1-yldiazenyl)benzaldehyde, 11c

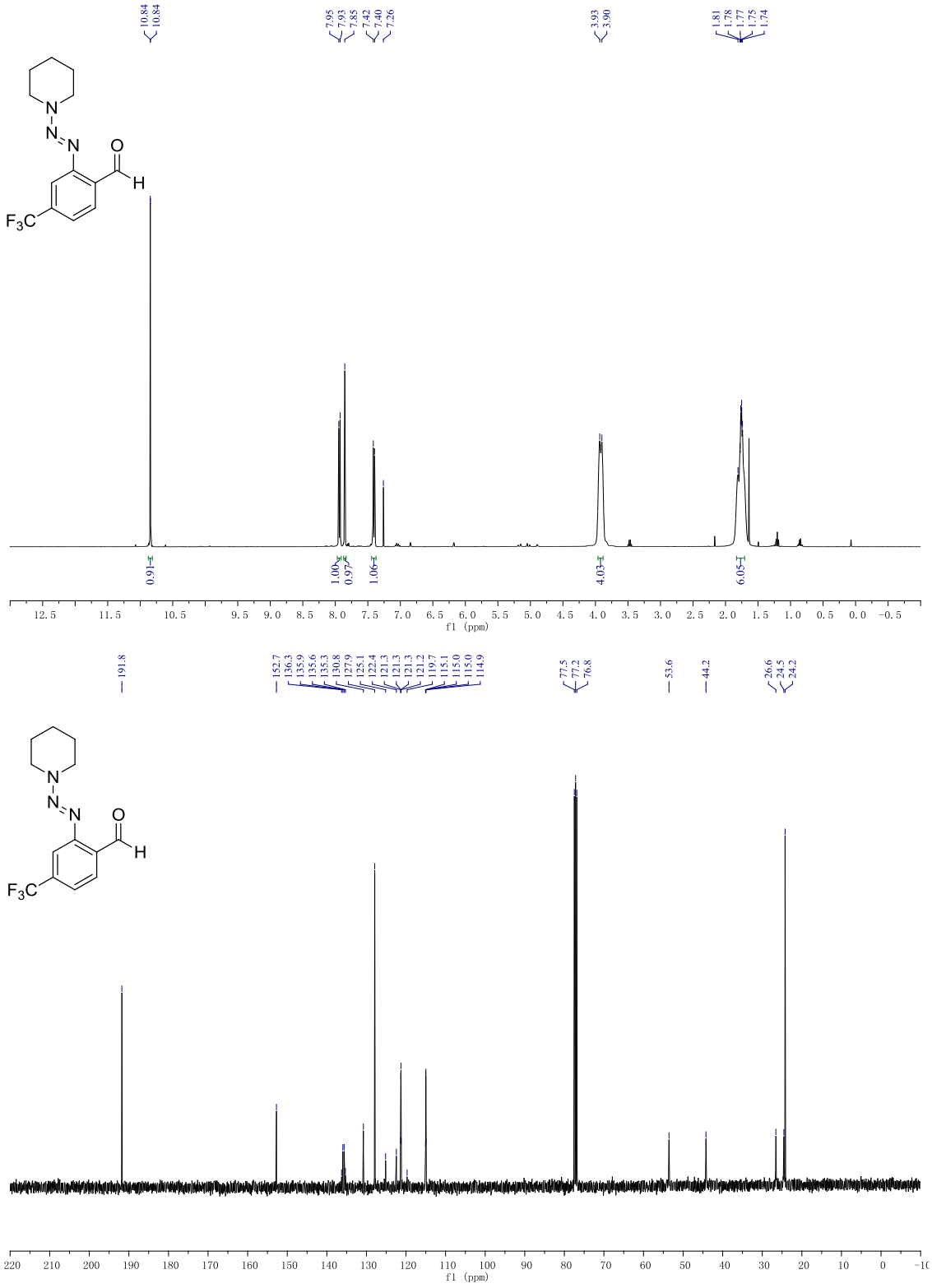


(*E*)-3-Methyl-2-(piperidin-1-yldiazenyl)benzaldehyde, 11d

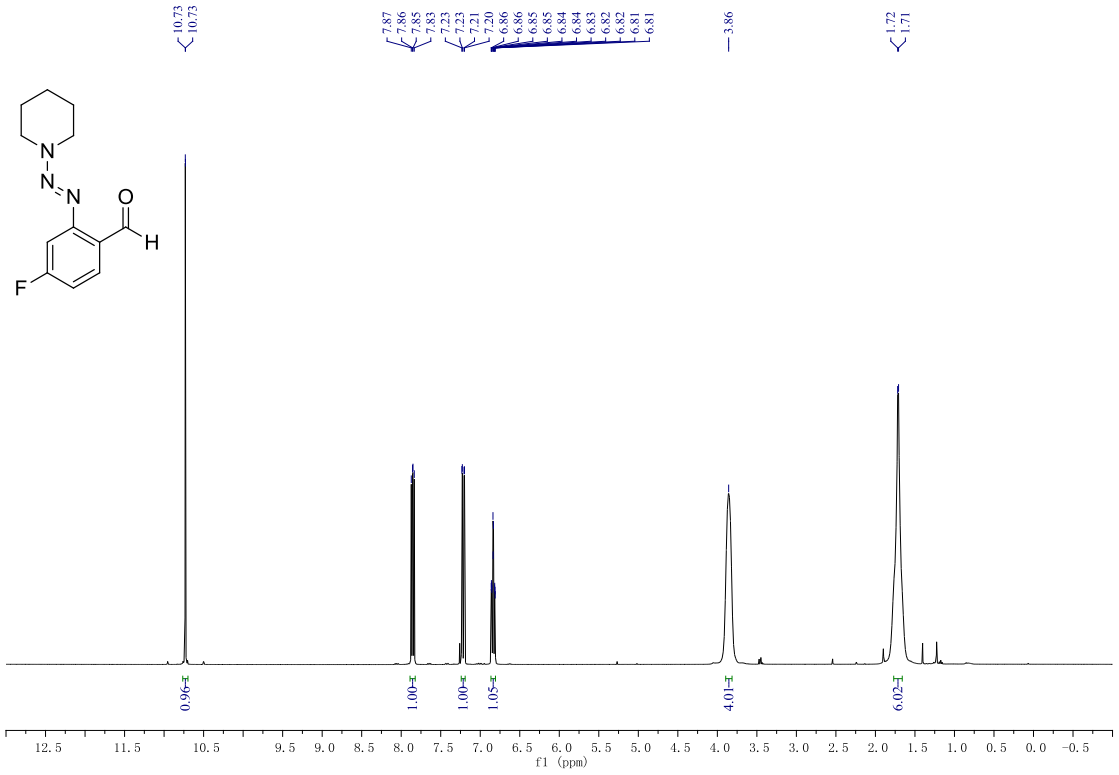


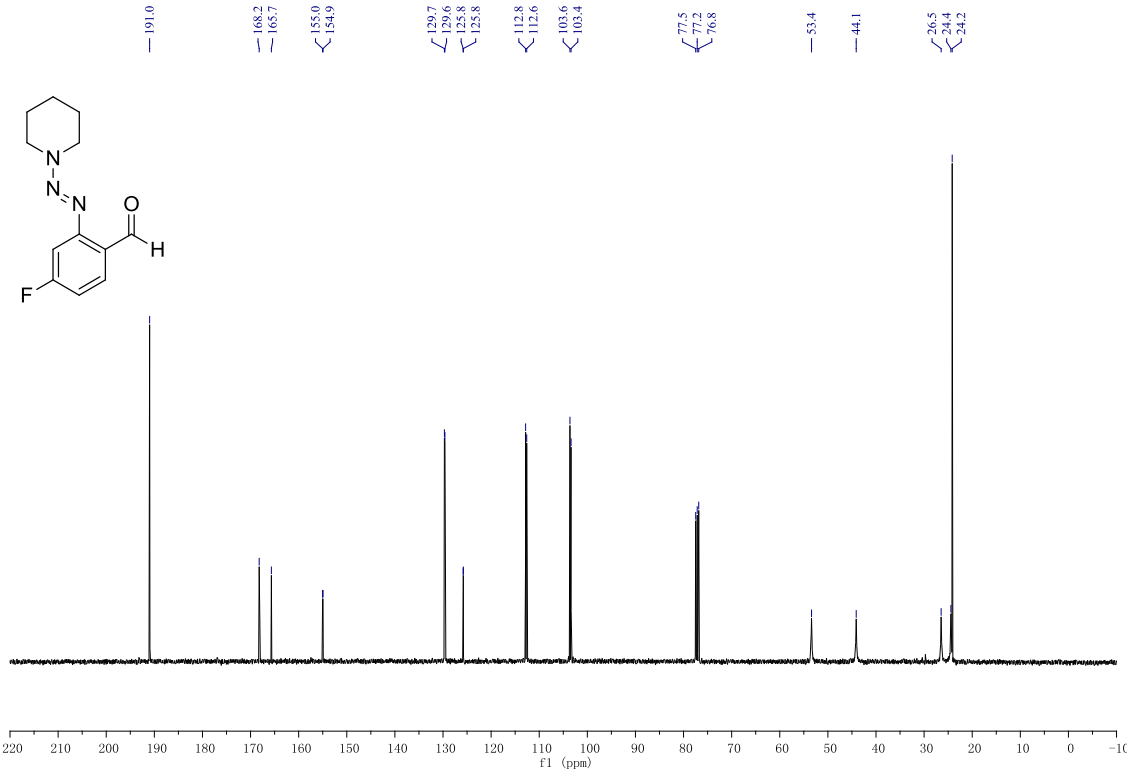


(*E*)-2-(Piperidin-1-yldiazenyl)-4-(trifluoromethyl)benzaldehyde, 11e

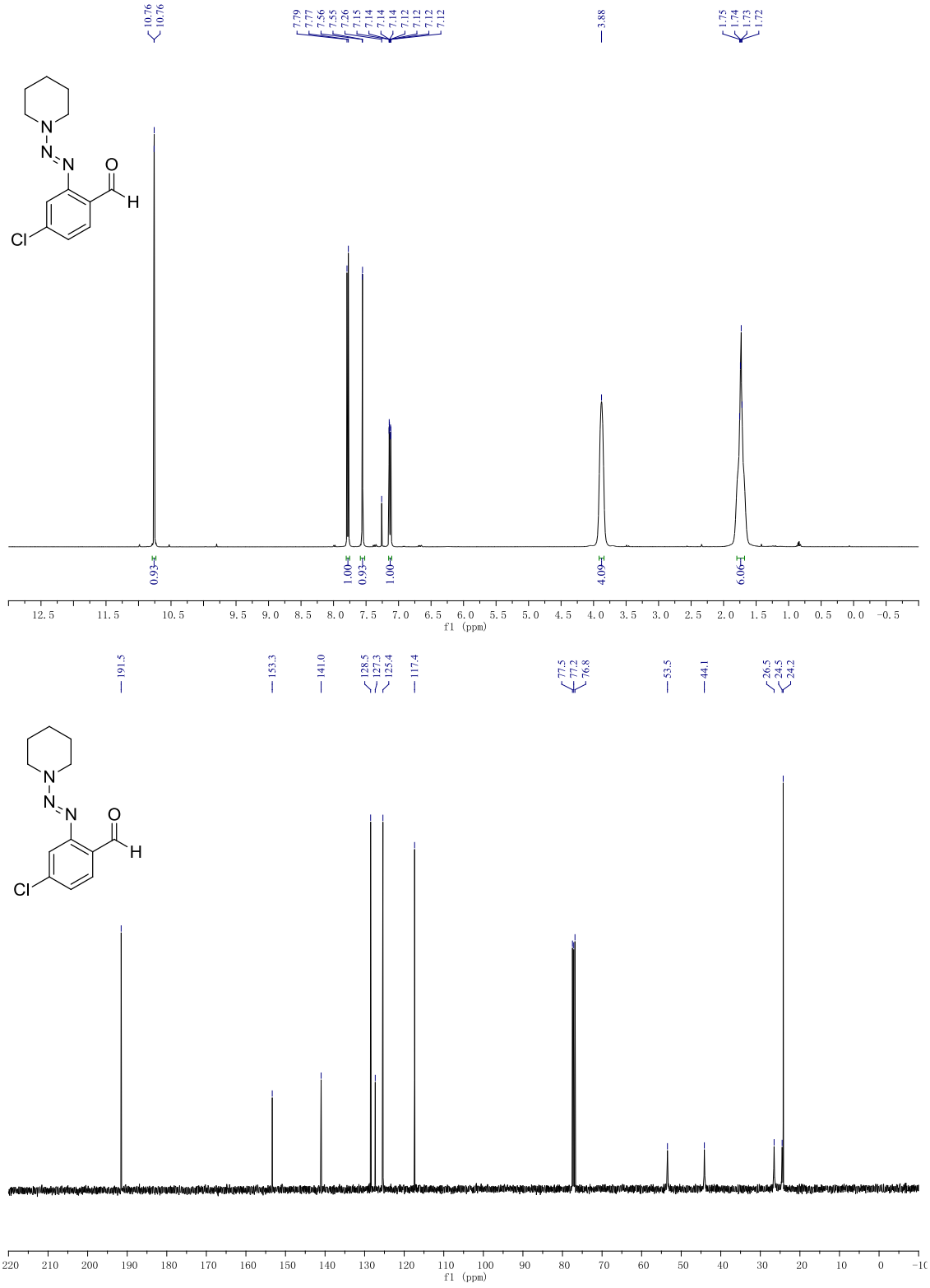


(*E*)-4-Fluoro-2-(piperidin-1-yldiazenyl)benzaldehyde, 11f

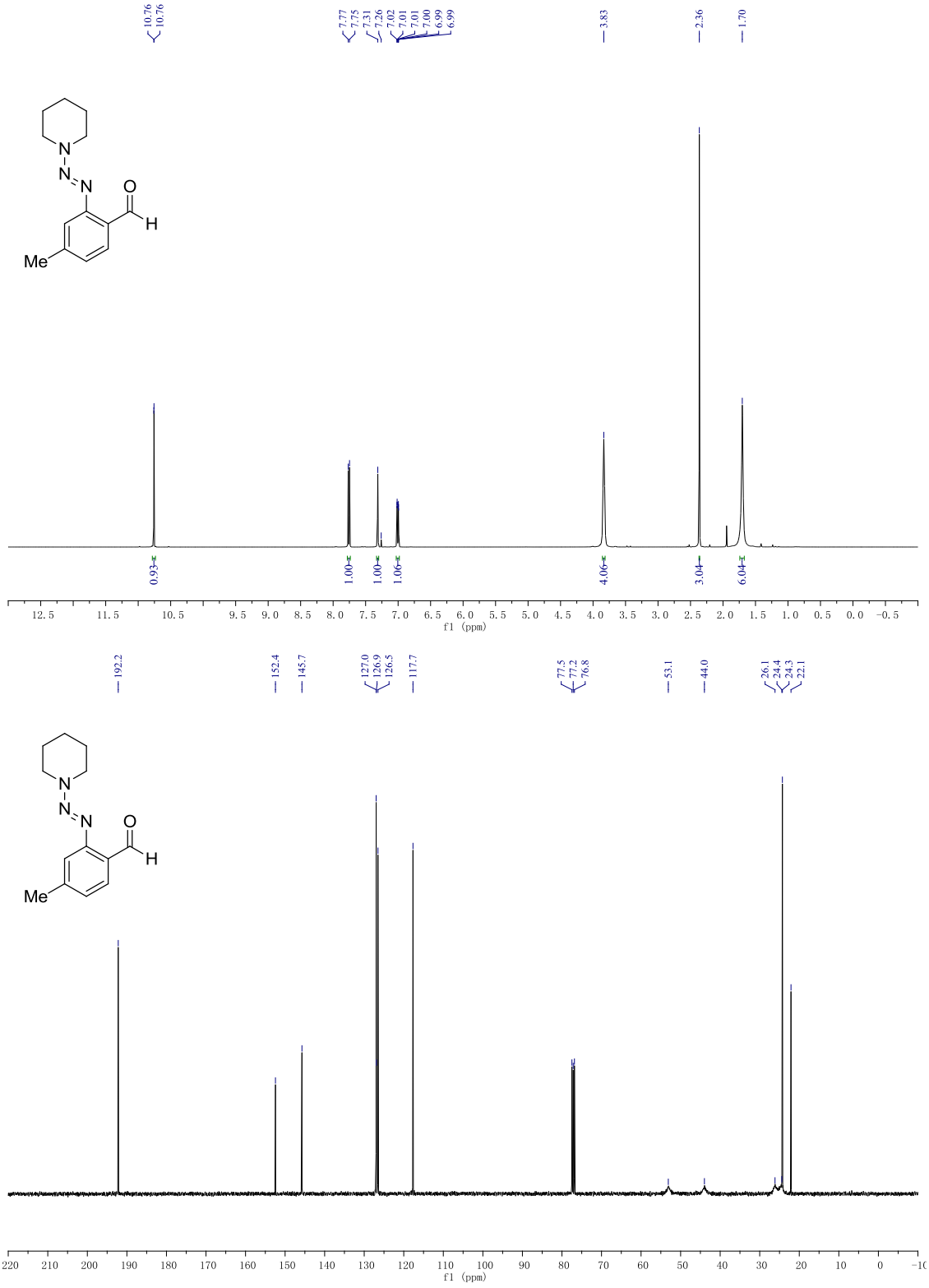




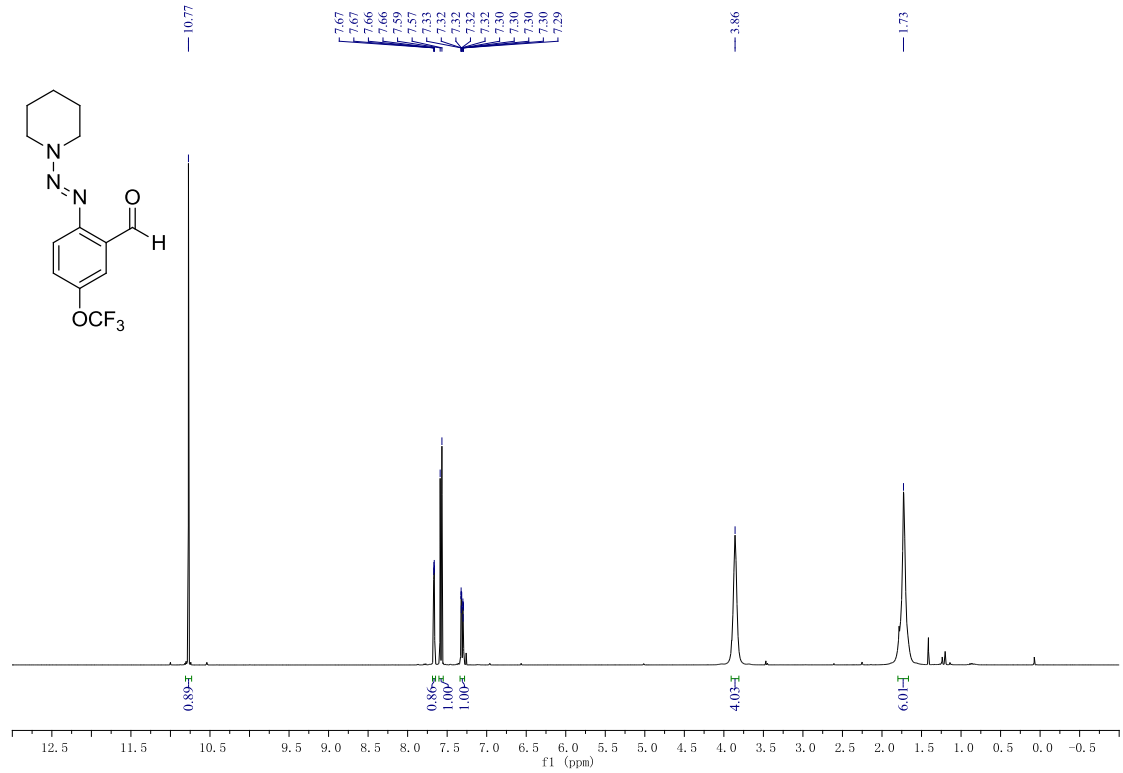
(*E*)-4-Chloro-2-(piperidin-1-yldiazenyl)benzaldehyde, 11g

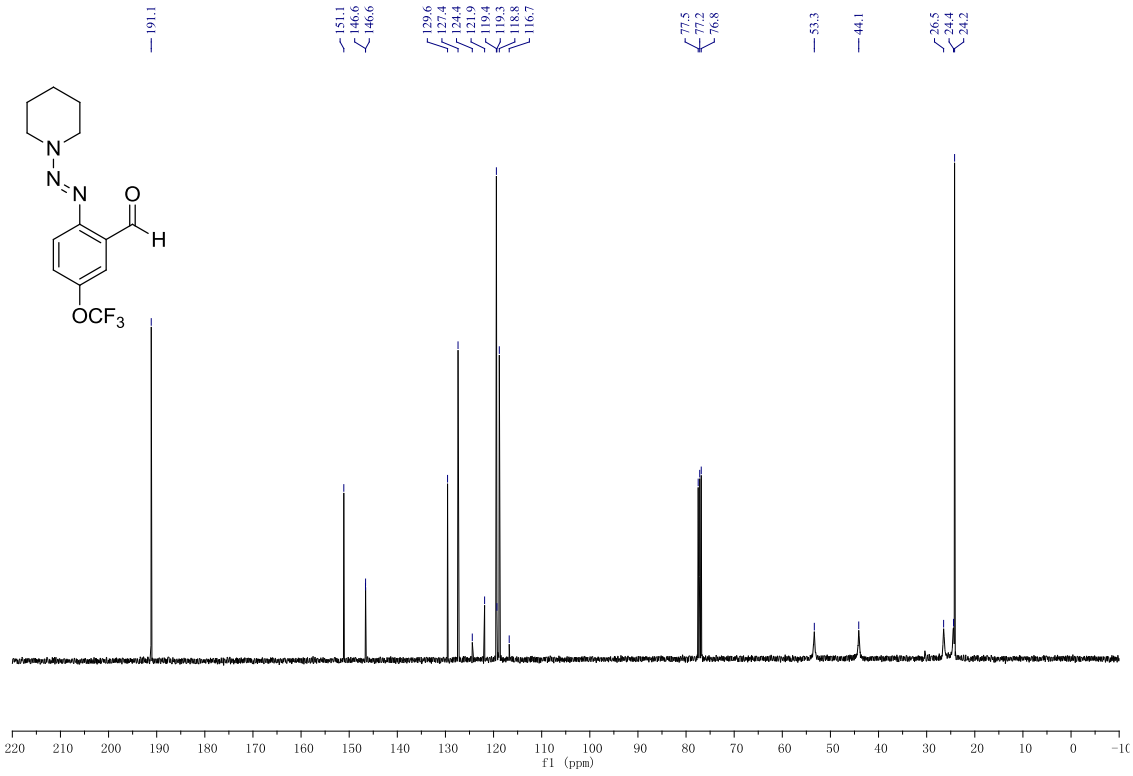


(*E*)-4-Methyl-2-(piperidin-1-yldiazenyl)benzaldehyde, 11h

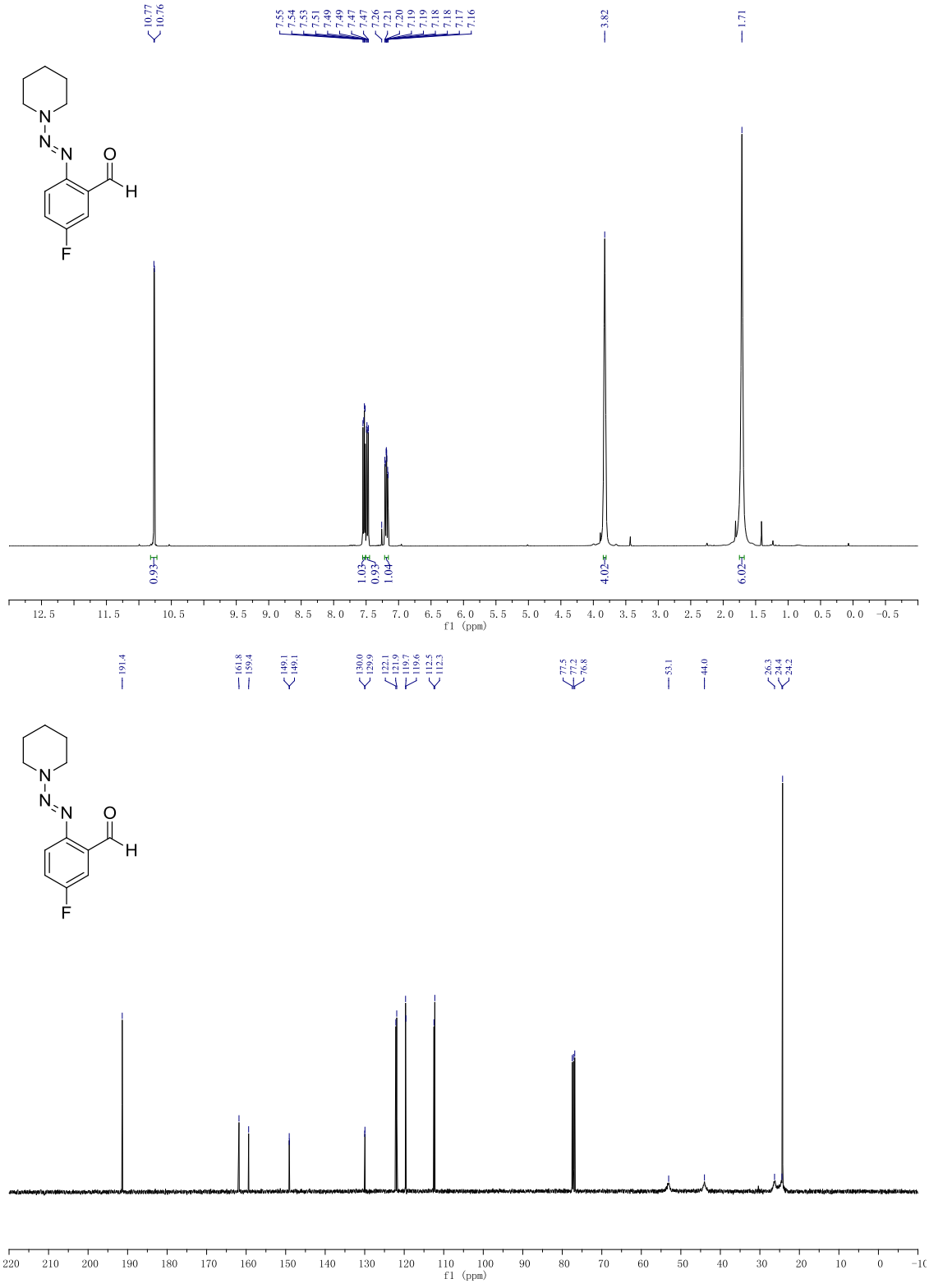


(*E*)-2-(Piperidin-1-yldiazenyl)-5-(trifluoromethoxy)benzaldehyde, 11i

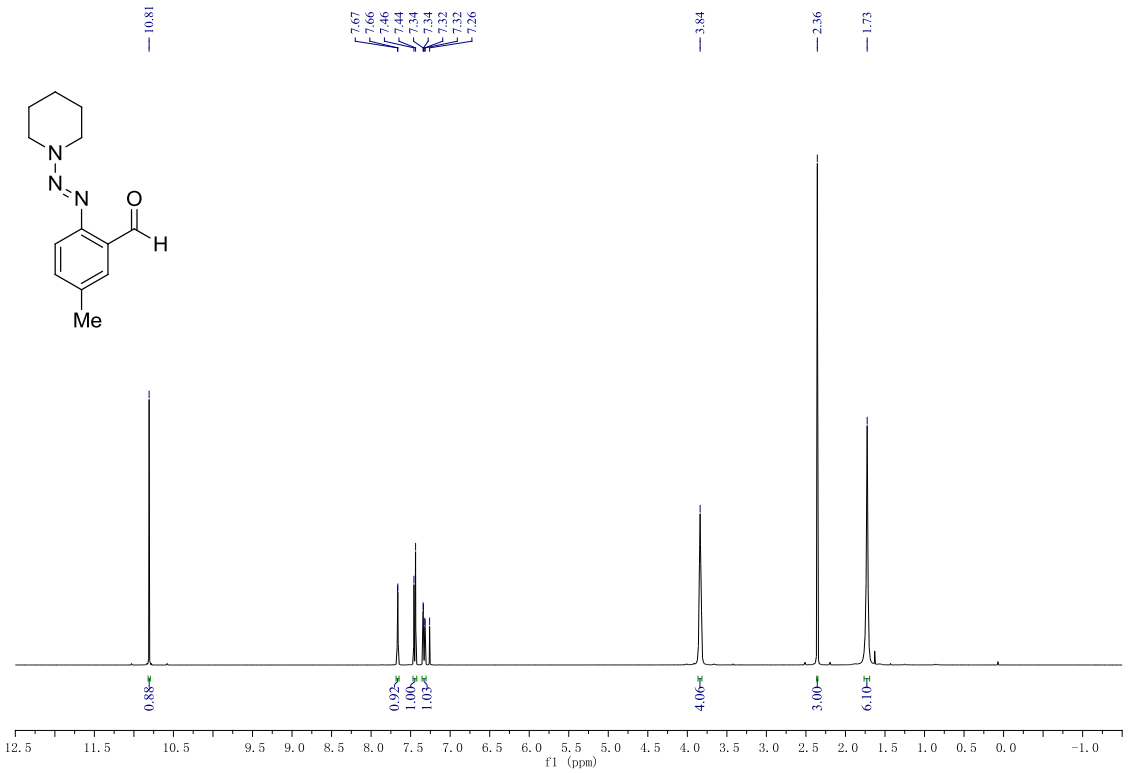


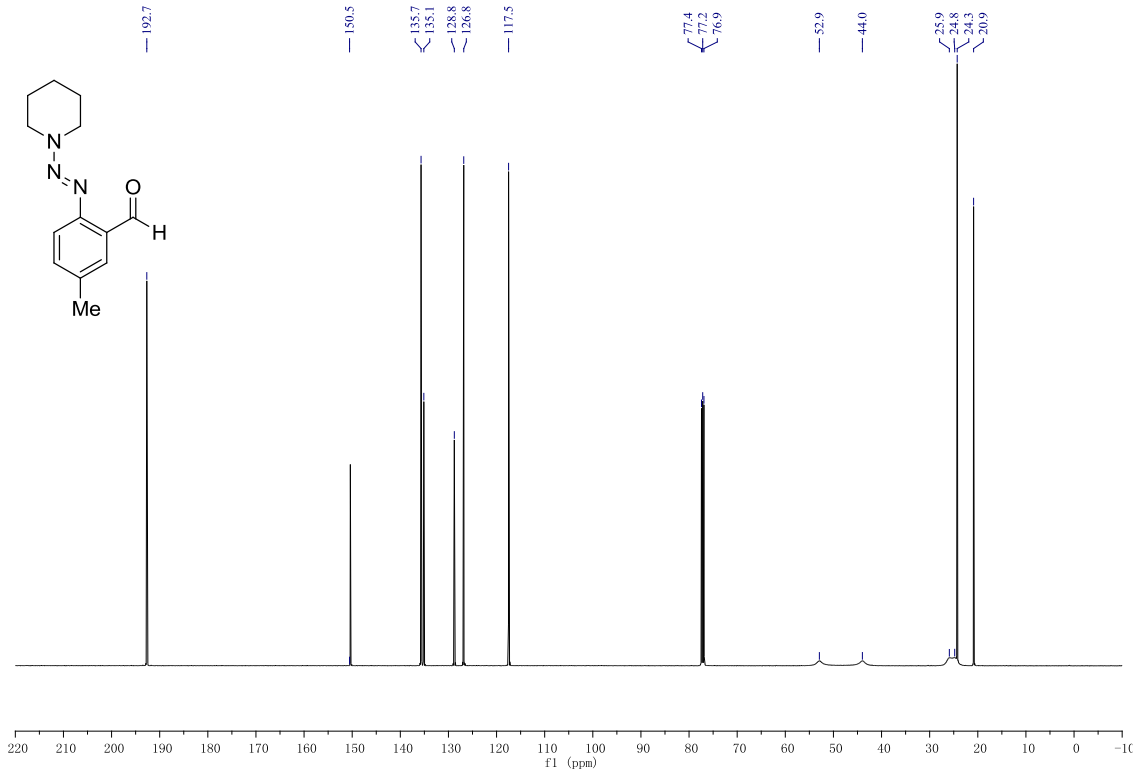


(*E*)-5-Fluoro-2-(piperidin-1-yldiazenyl)benzaldehyde, 11j

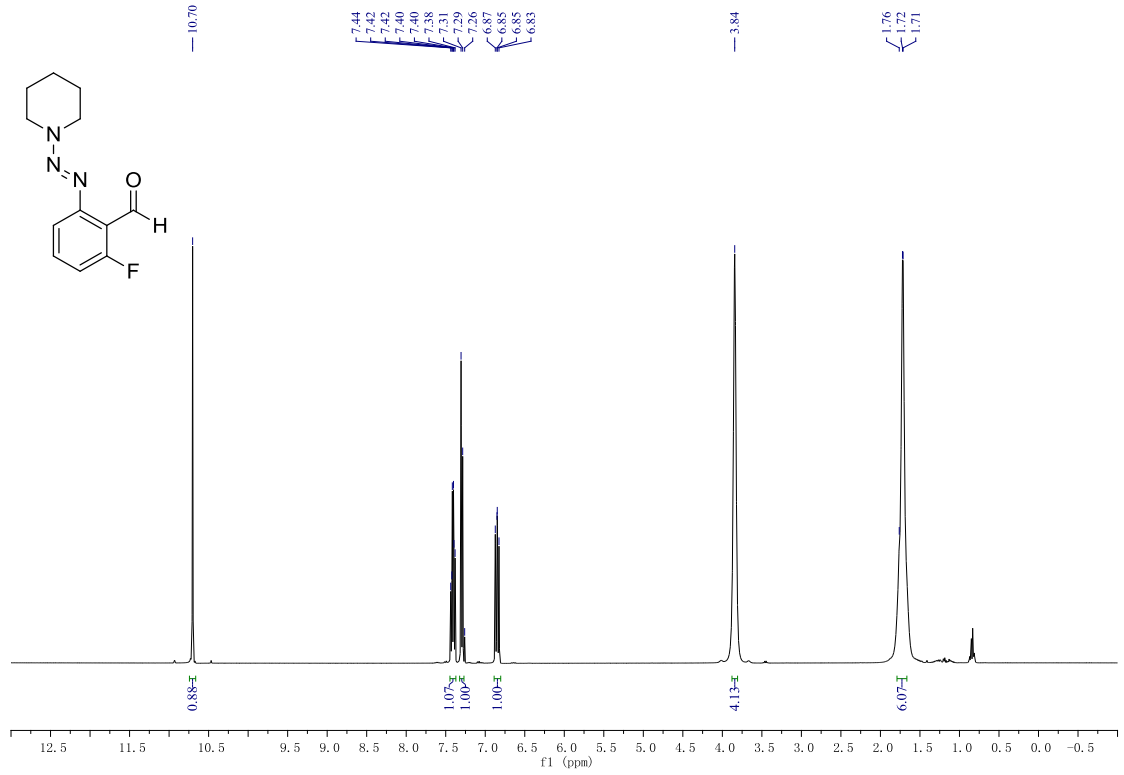


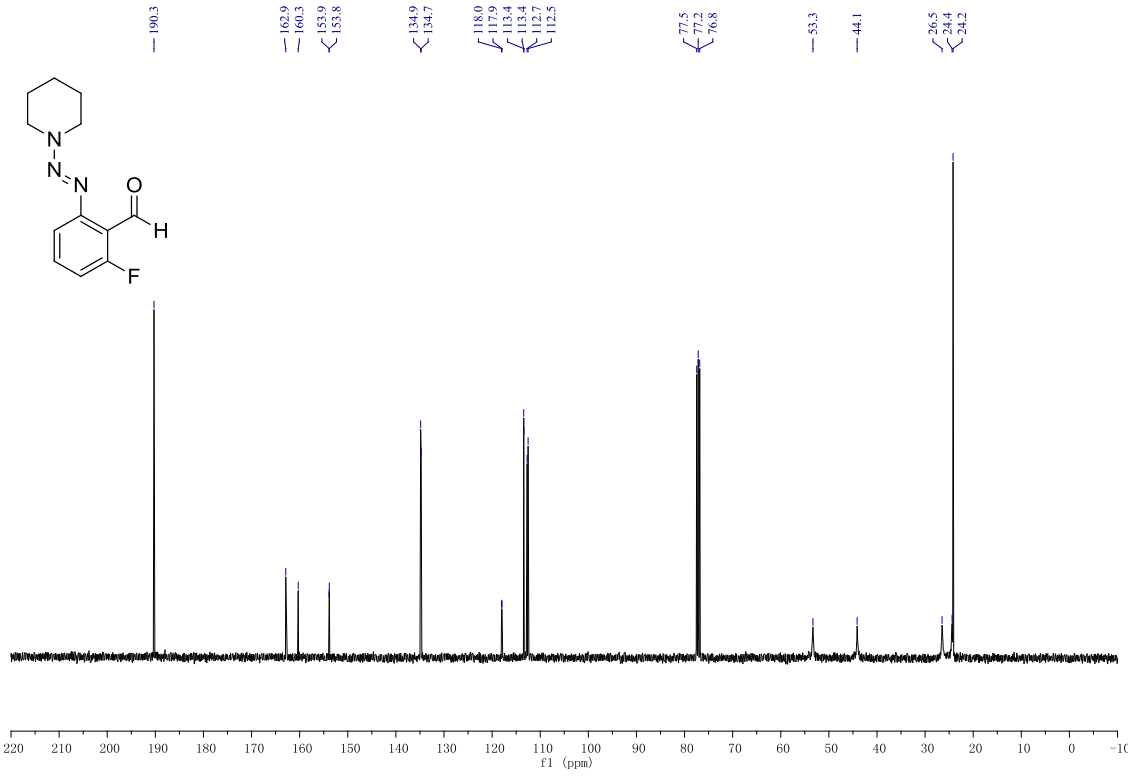
(*E*)-5-Methyl-2-(piperidin-1-yldiazenyl)benzaldehyde, 11k



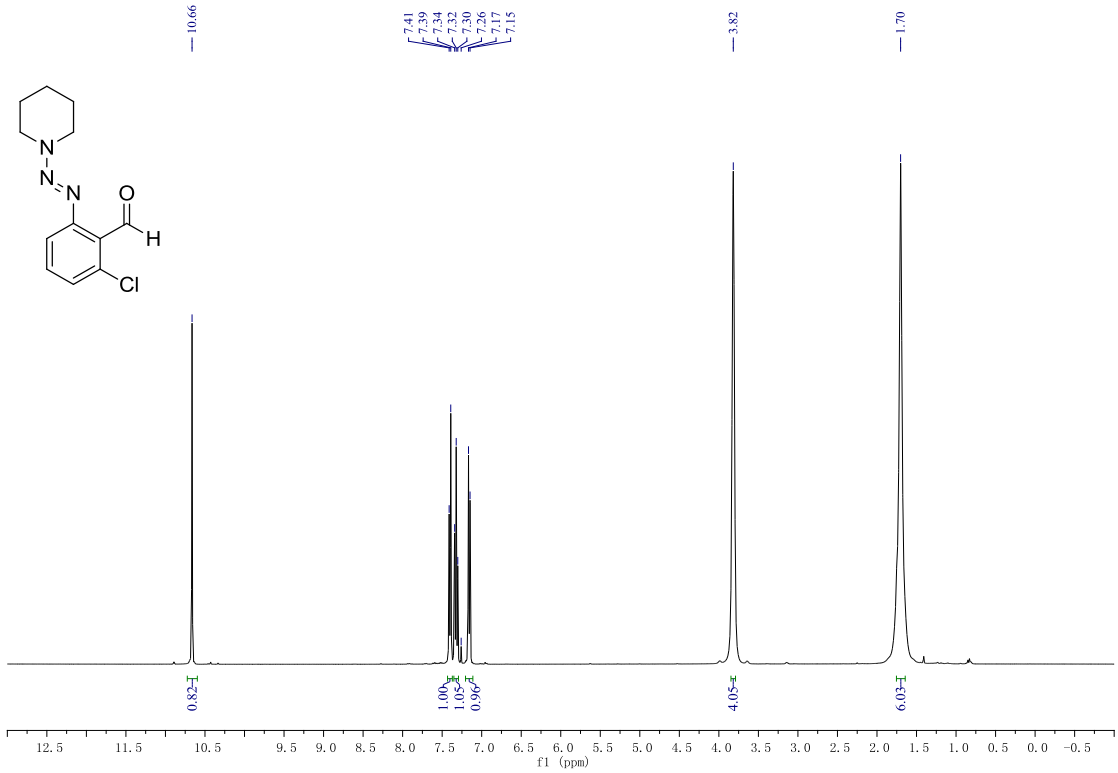


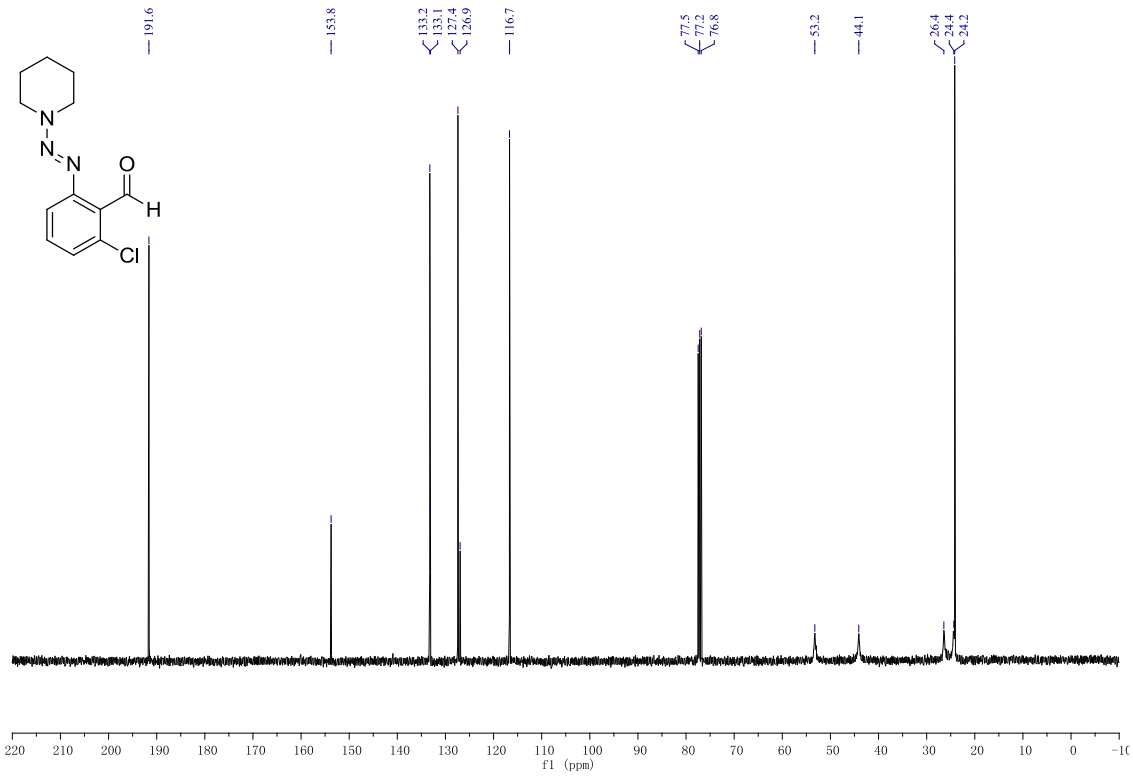
(*E*)-2-Fluoro-6-(piperidin-1-yldiazenyl)benzaldehyde, 11l



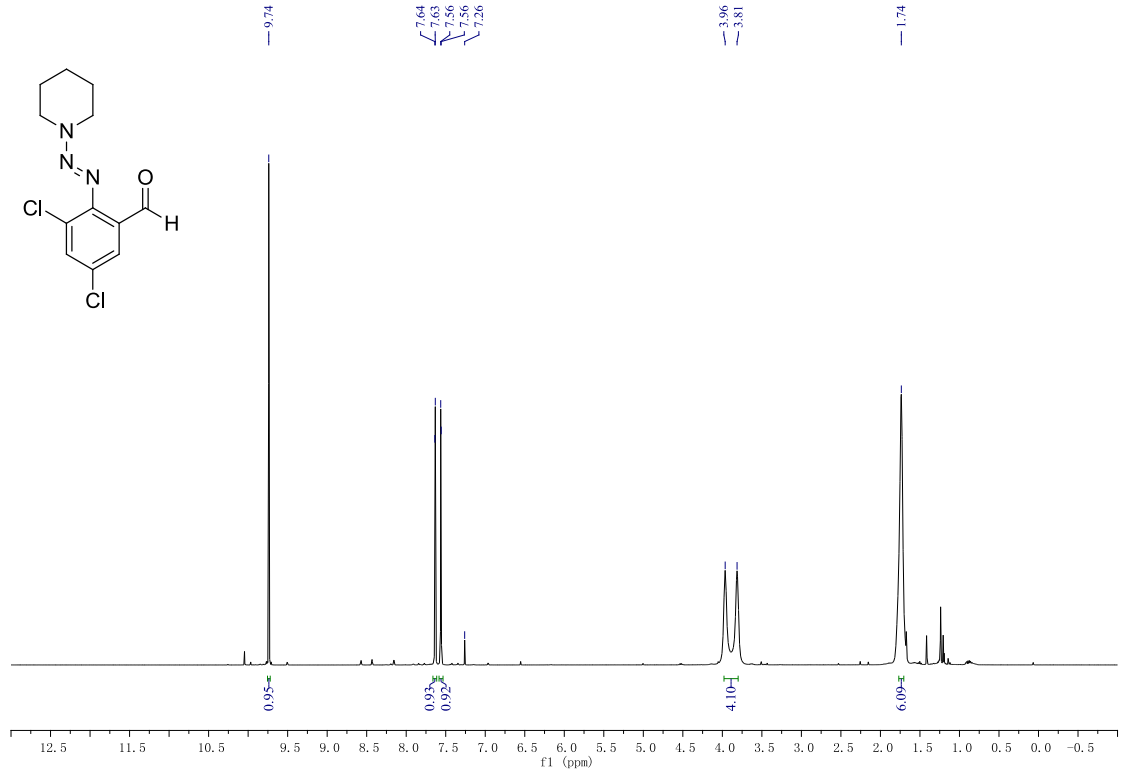


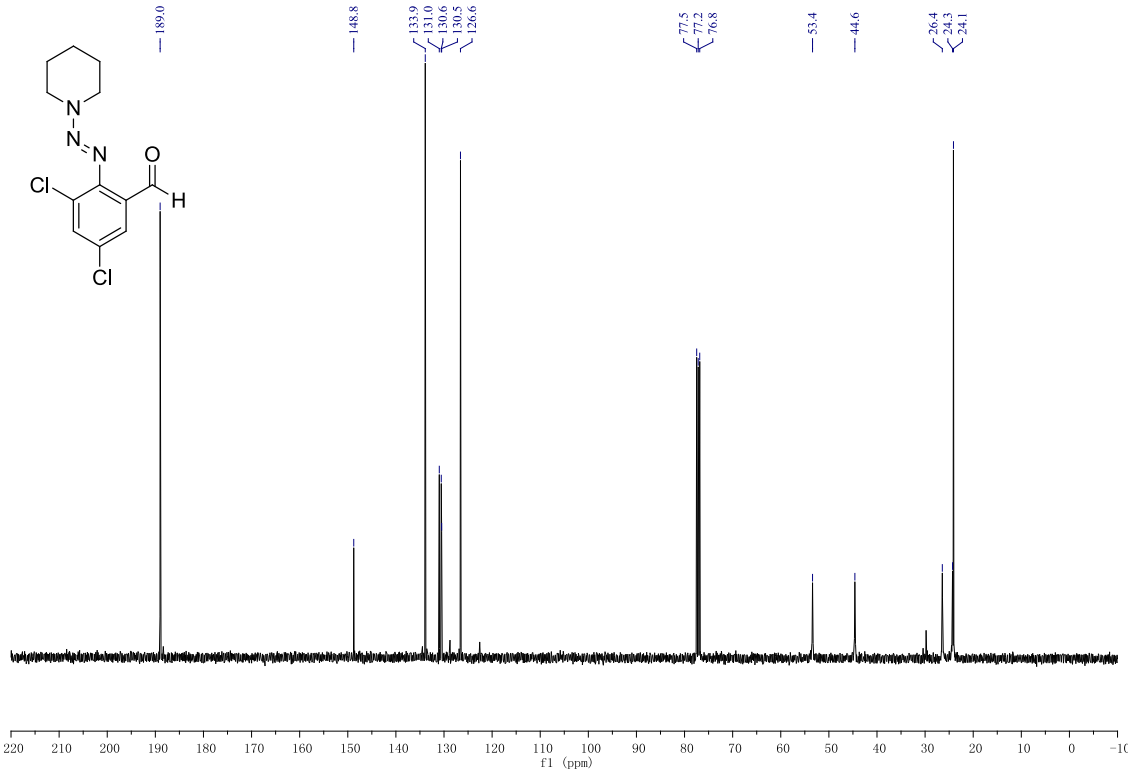
(*E*)-2-Chloro-6-(piperidin-1-yldiazenyl)benzaldehyde, 11m



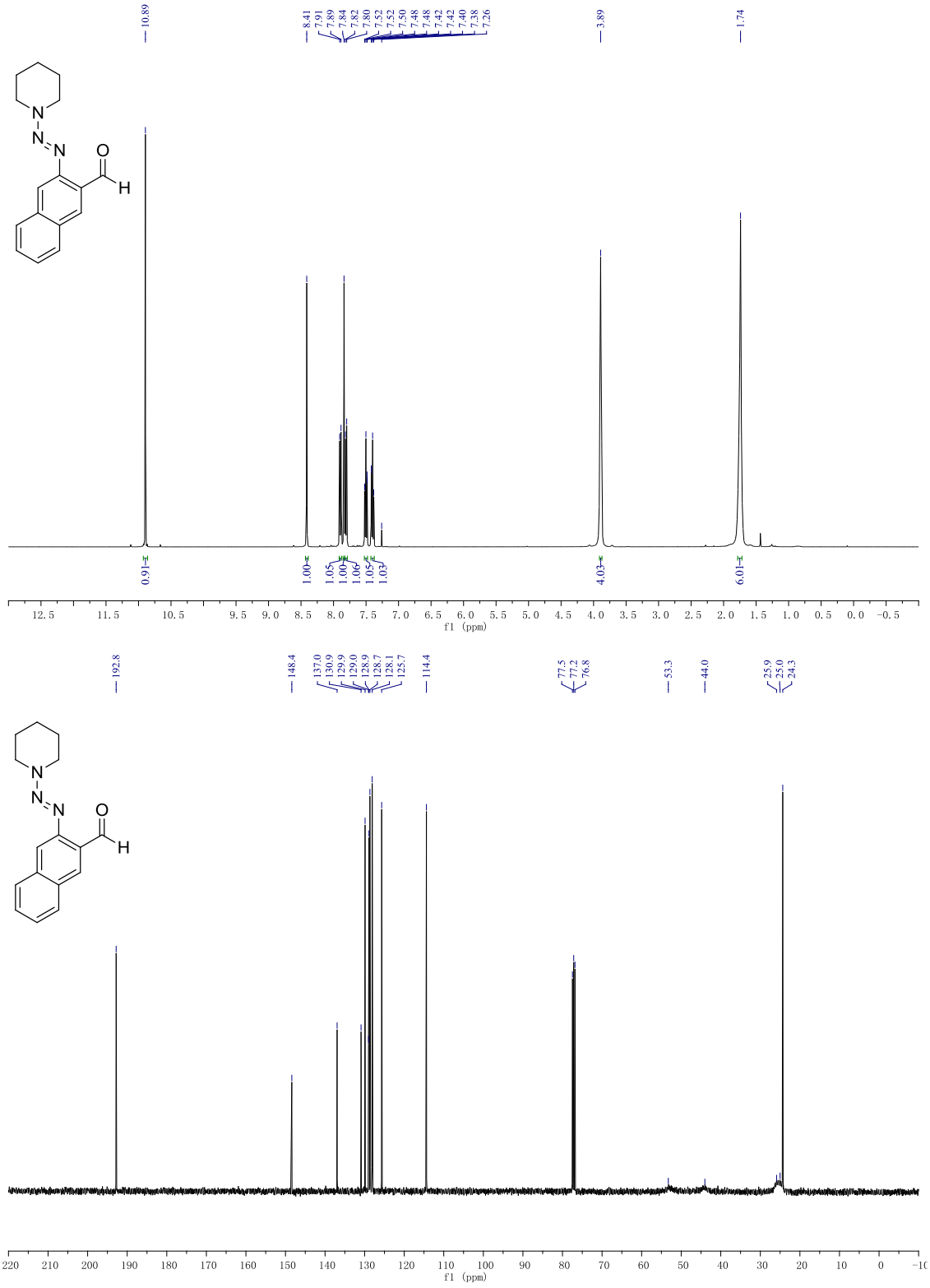


(*E*)-3,5-Dichloro-2-(piperidin-1-yldiazenyl)benzaldehyde, 11n

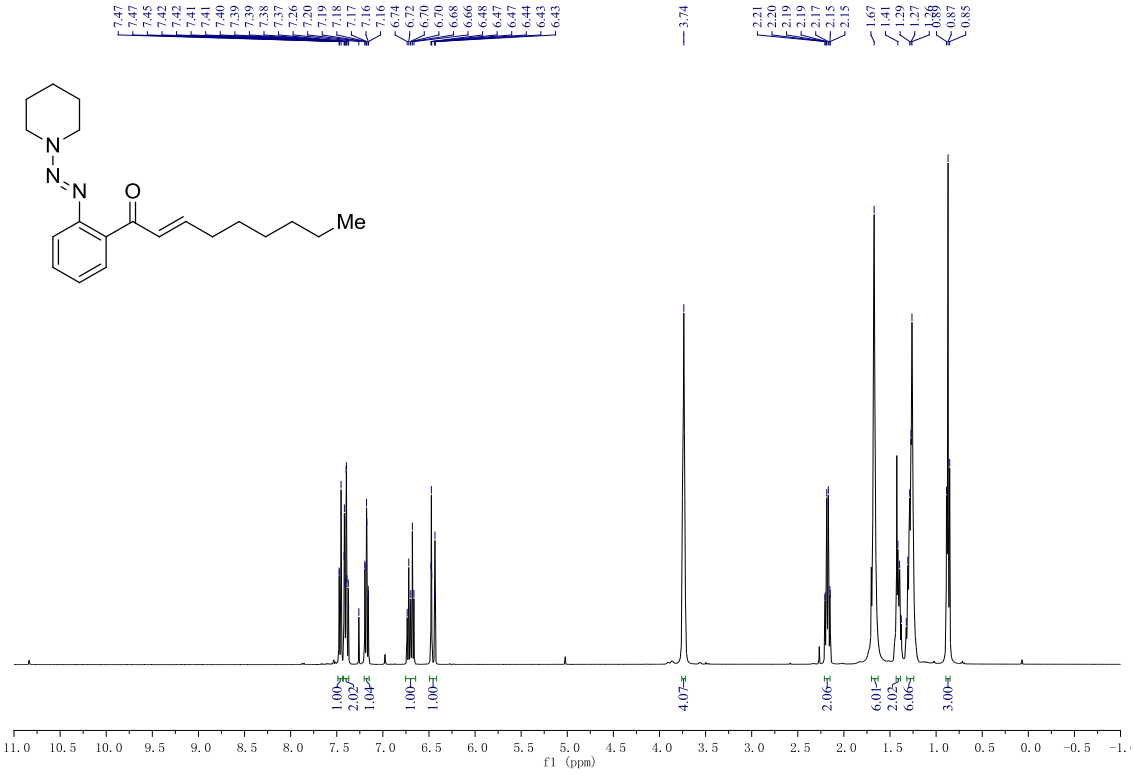


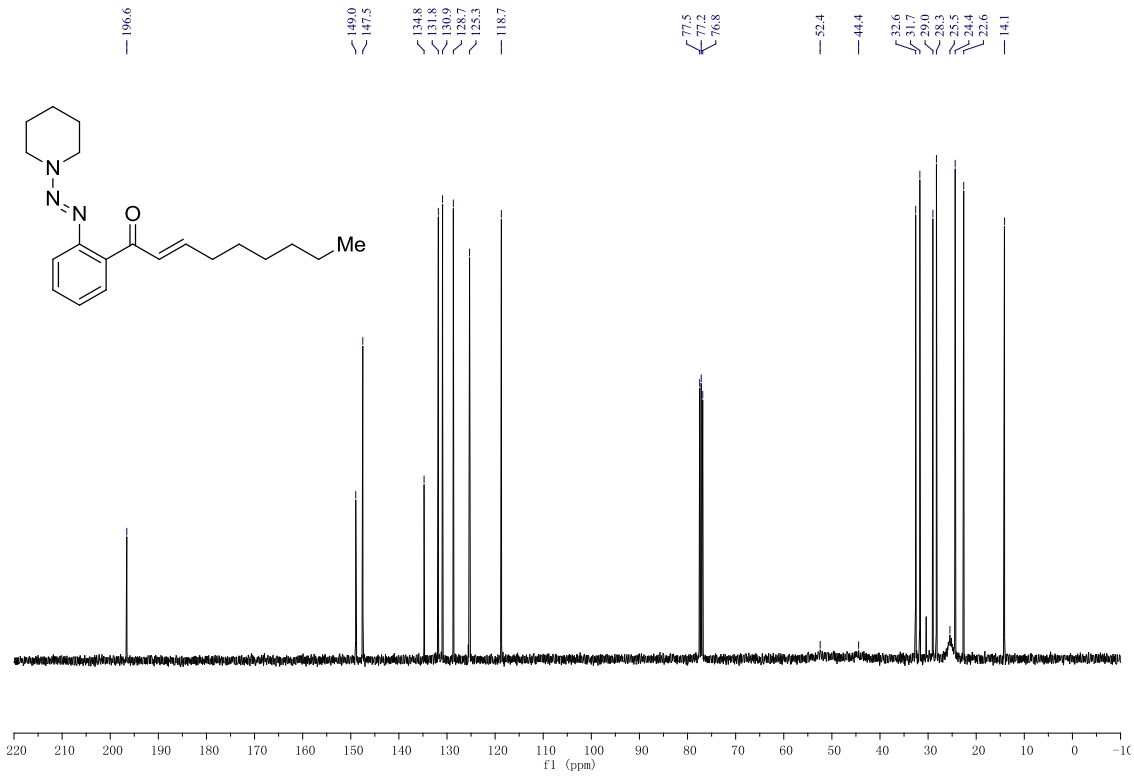


(*E*)-3-(Piperidin-1-yldiazenyl)-2-naphthaldehyde, 11o

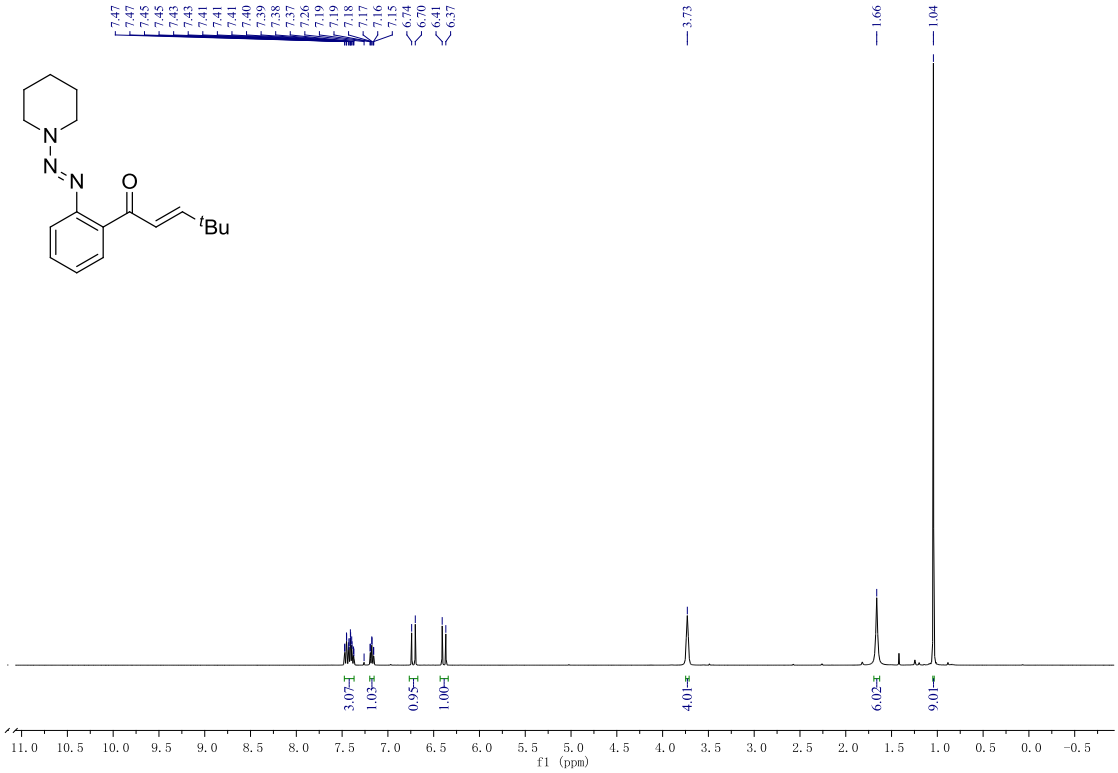


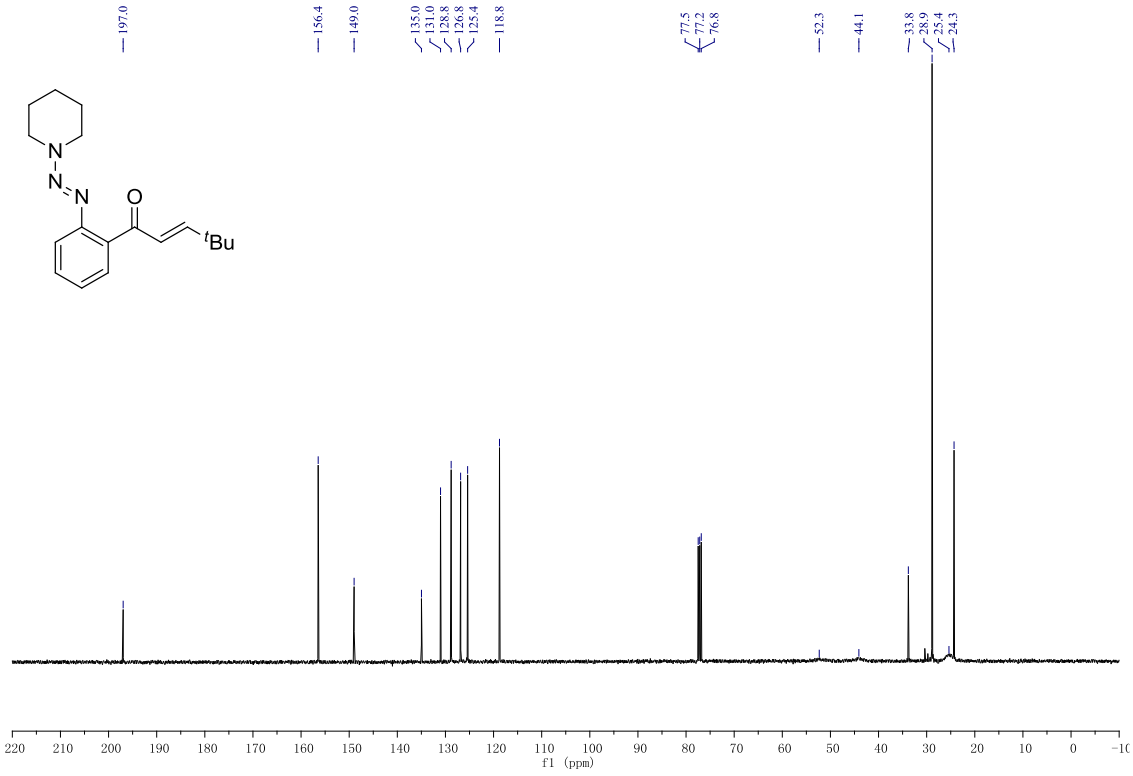
(*E*)-1-(2-((*E*)-Piperidin-1-yldiazenyl)phenyl)non-2-en-1-one, 12b



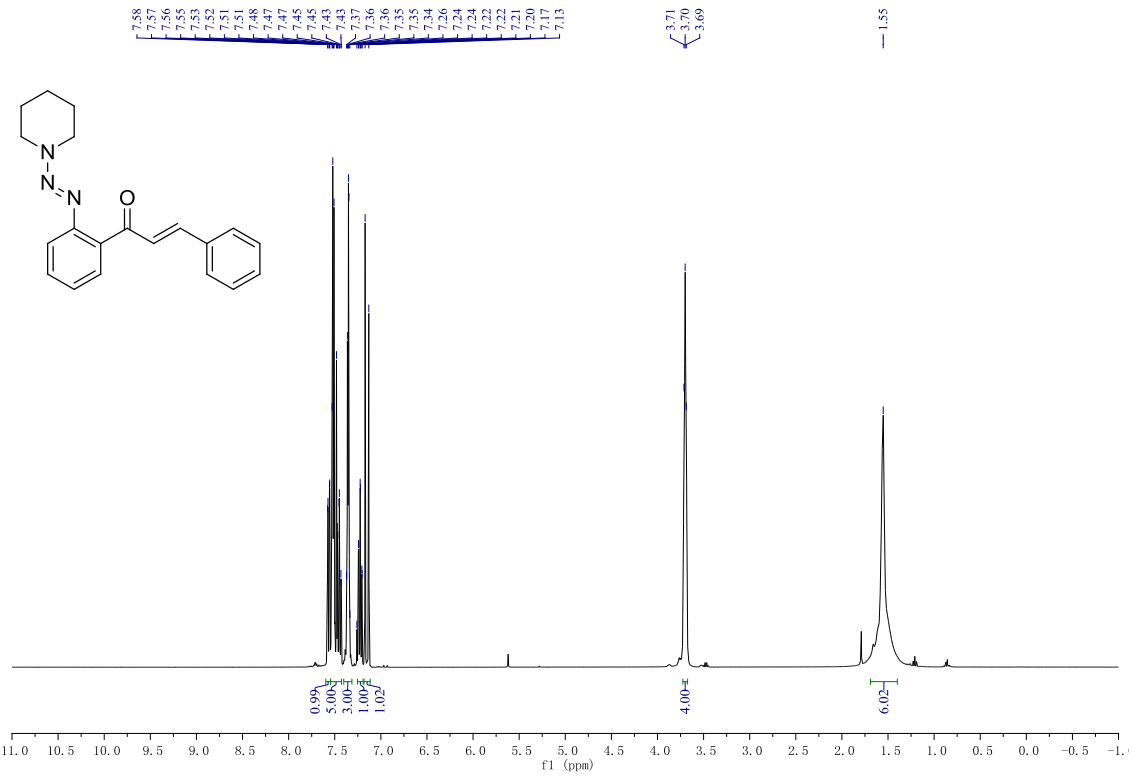


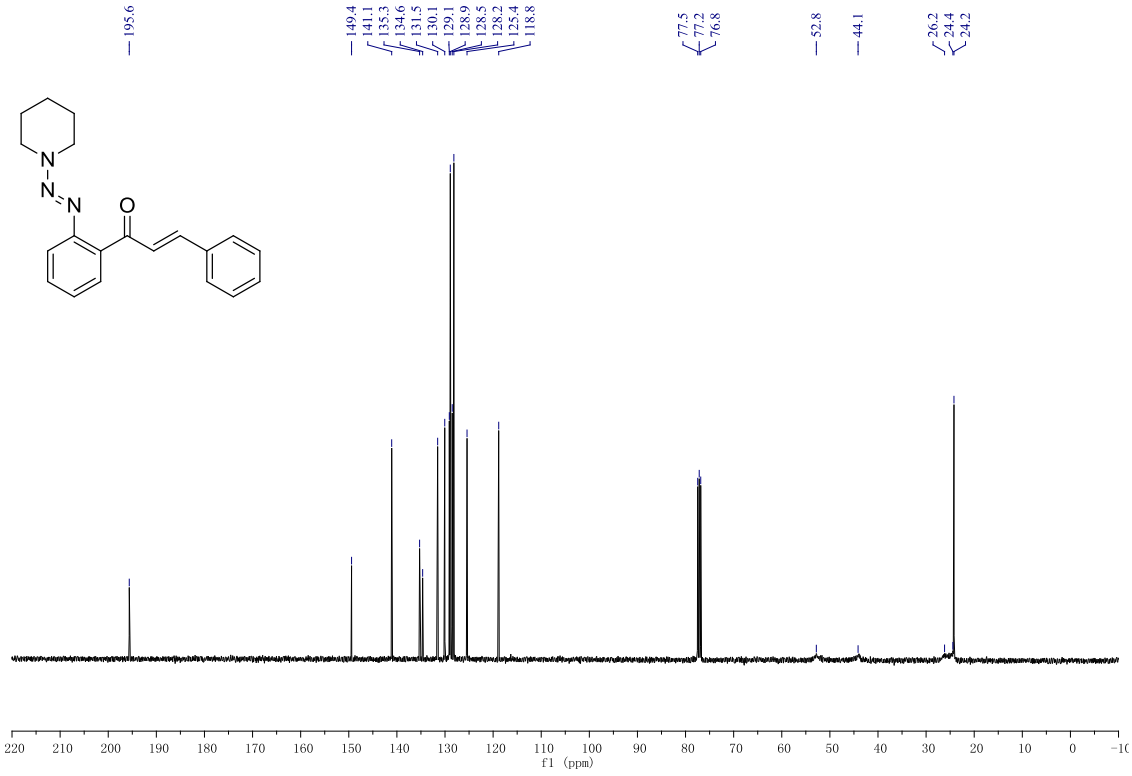
(*E*)-4,4-Dimethyl-1-(2-((*E*)-piperidin-1-yldiazenyl)phenyl)pent-2-en-1-one, 12c



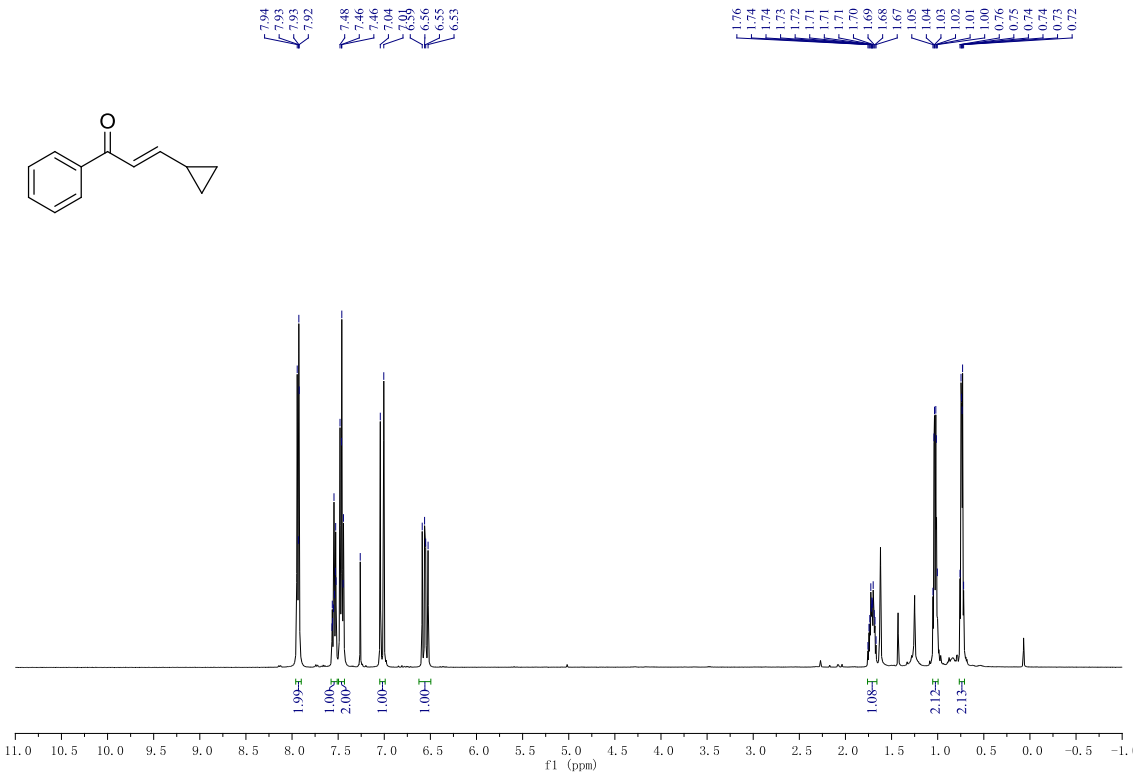


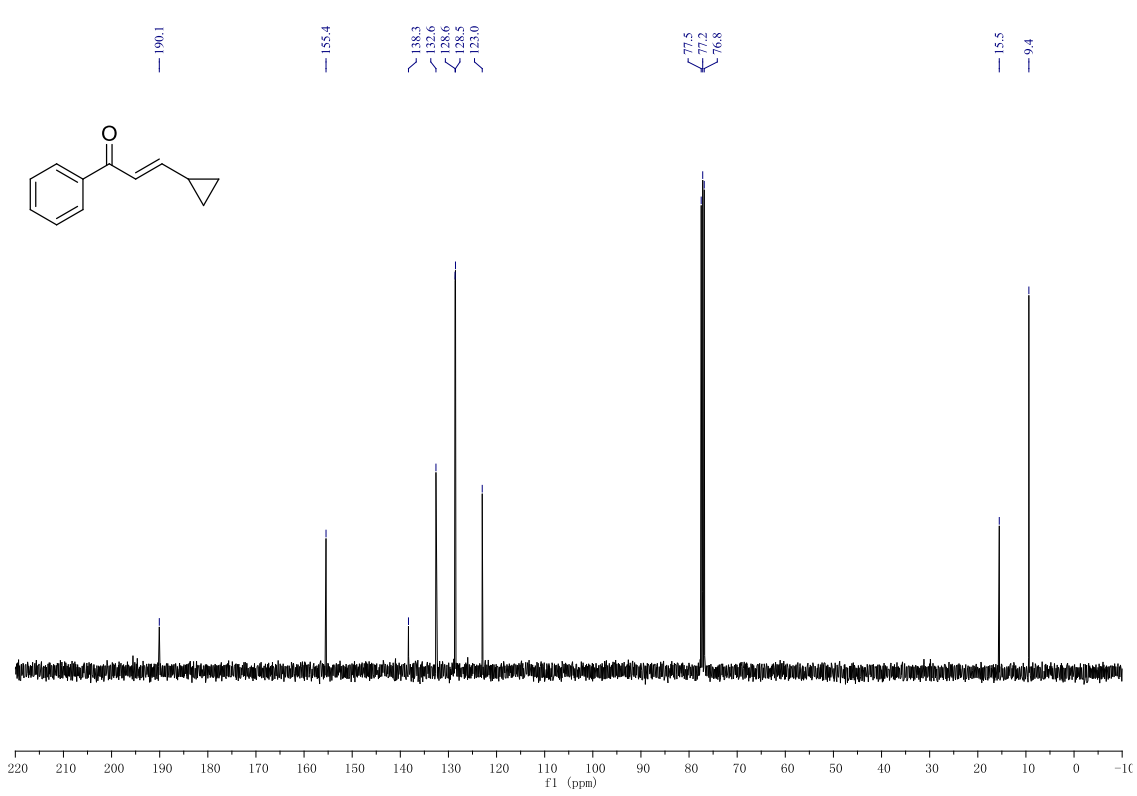
(*E*)-3-Phenyl-1-(2-((*E*)-piperidin-1-yldiazenyl)phenyl)prop-2-en-1-one, 12d



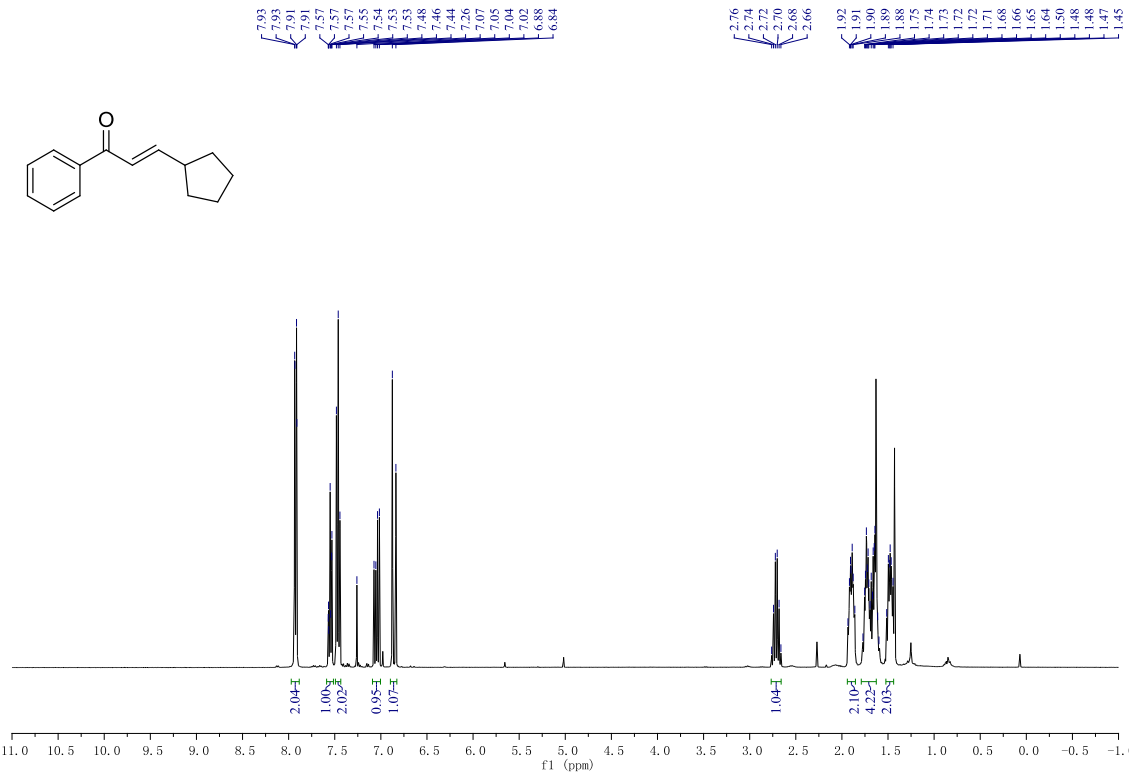


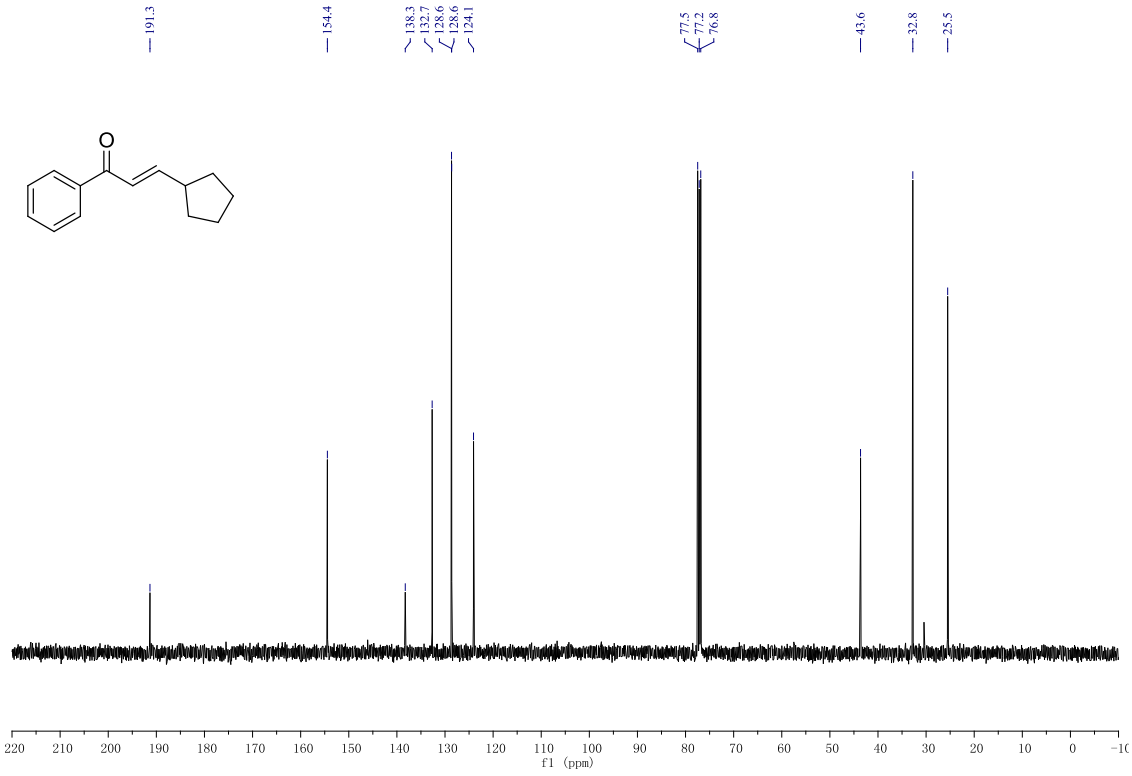
(*E*)-3-Cyclopropyl-1-phenylprop-2-en-1-one, 13b



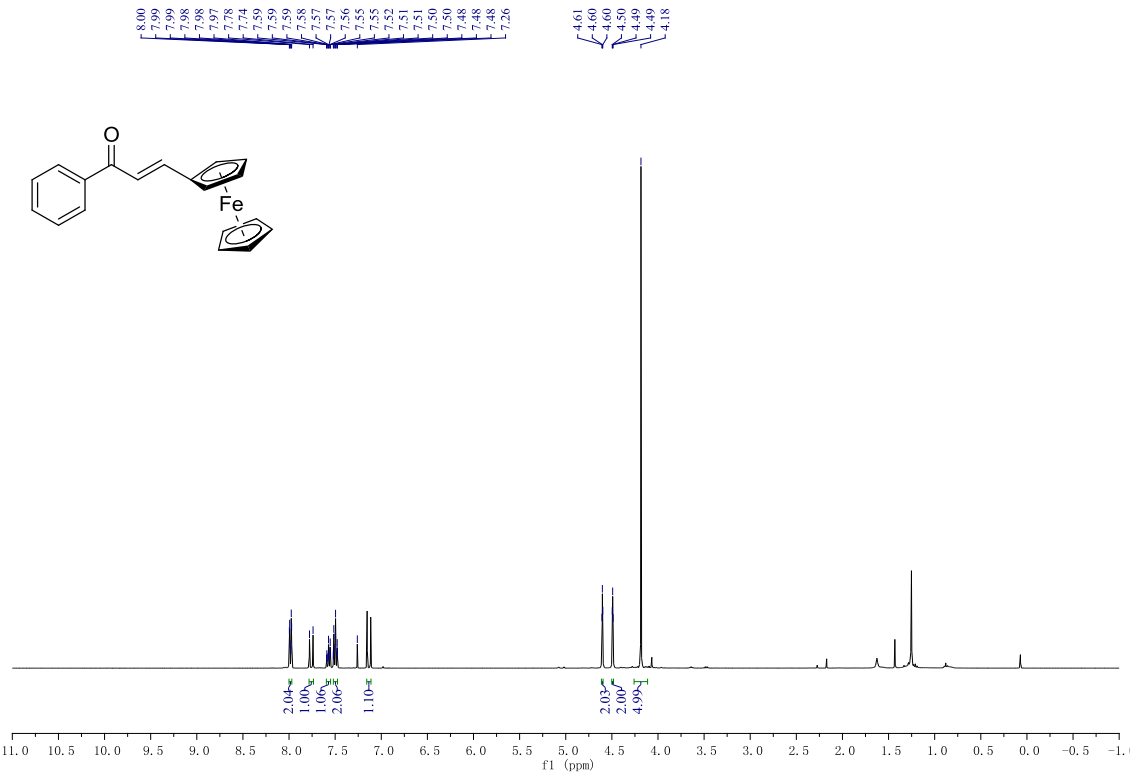


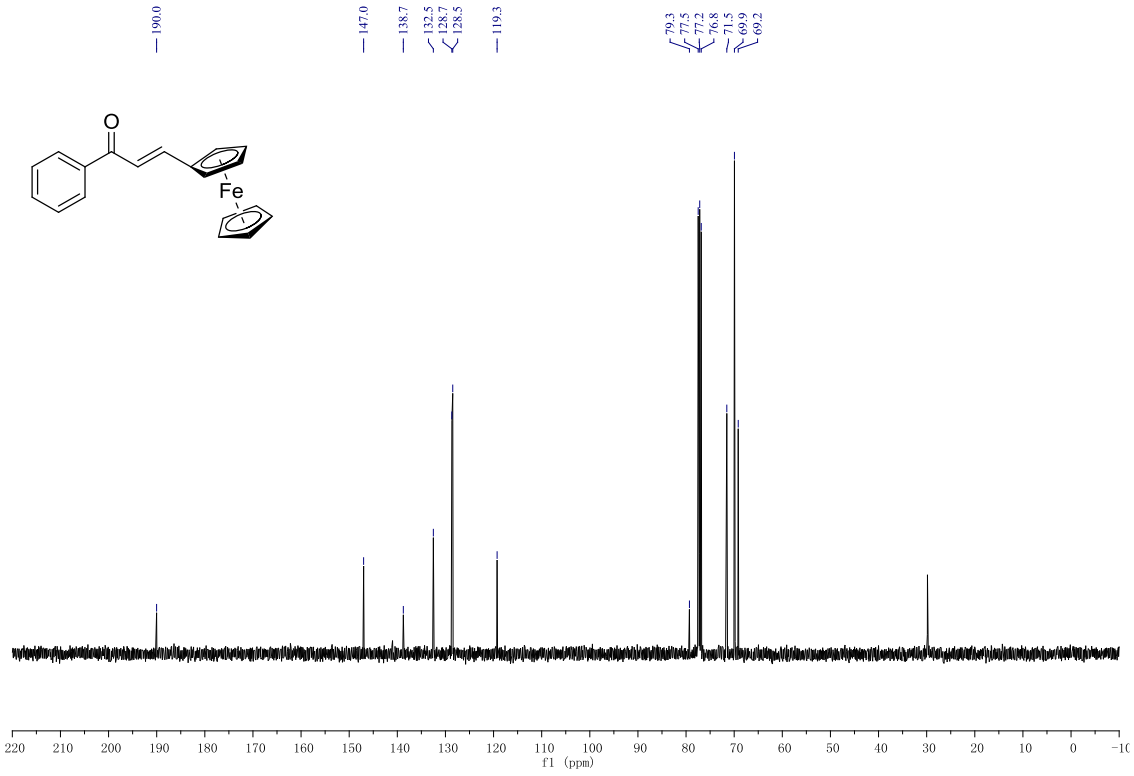
(*E*)-3-Cyclopentyl-1-phenylprop-2-en-1-one, 13c



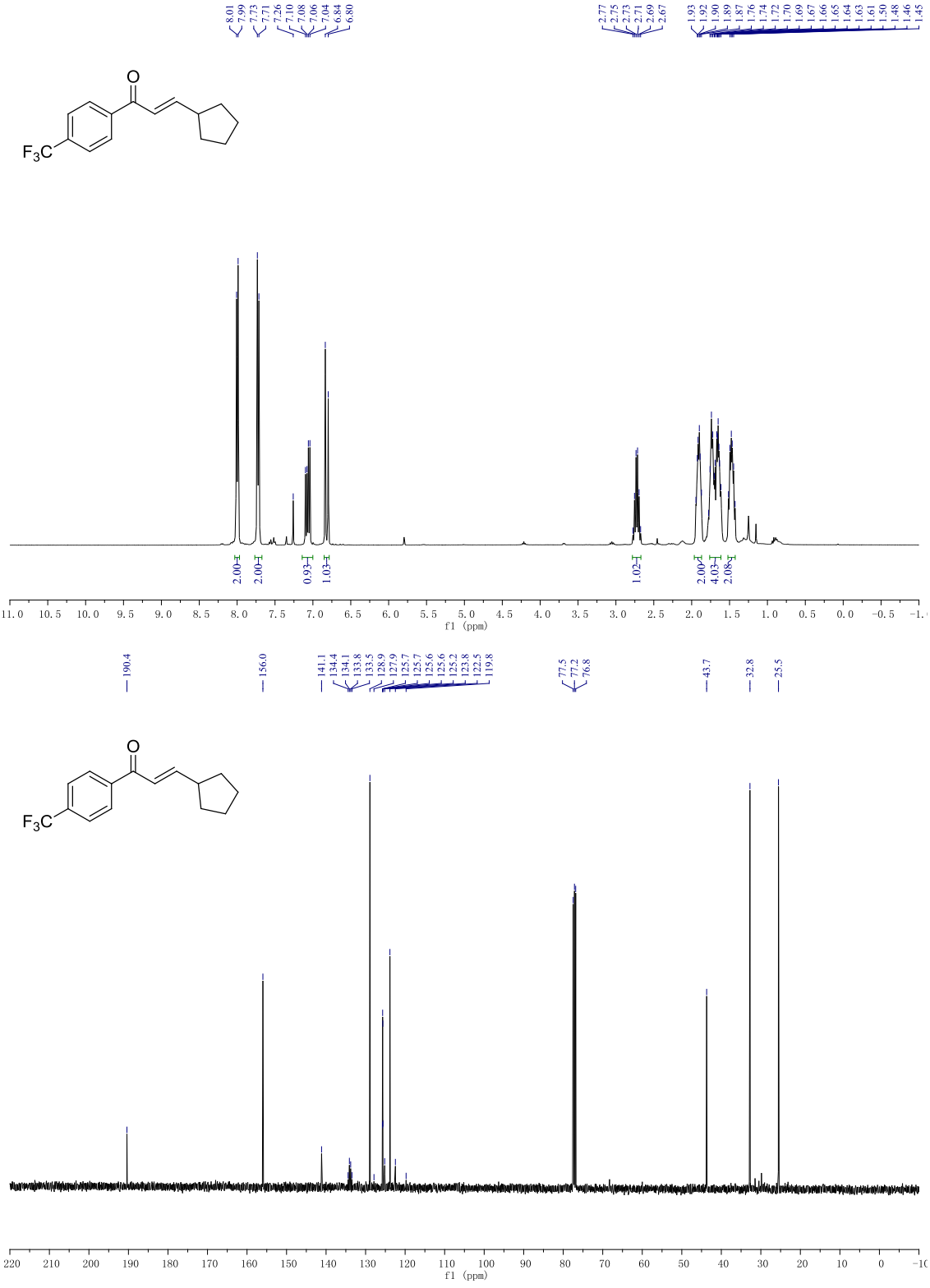


(*E*)-3-Ferrocenyl-1-phenylprop-2-en-1-one, 13h

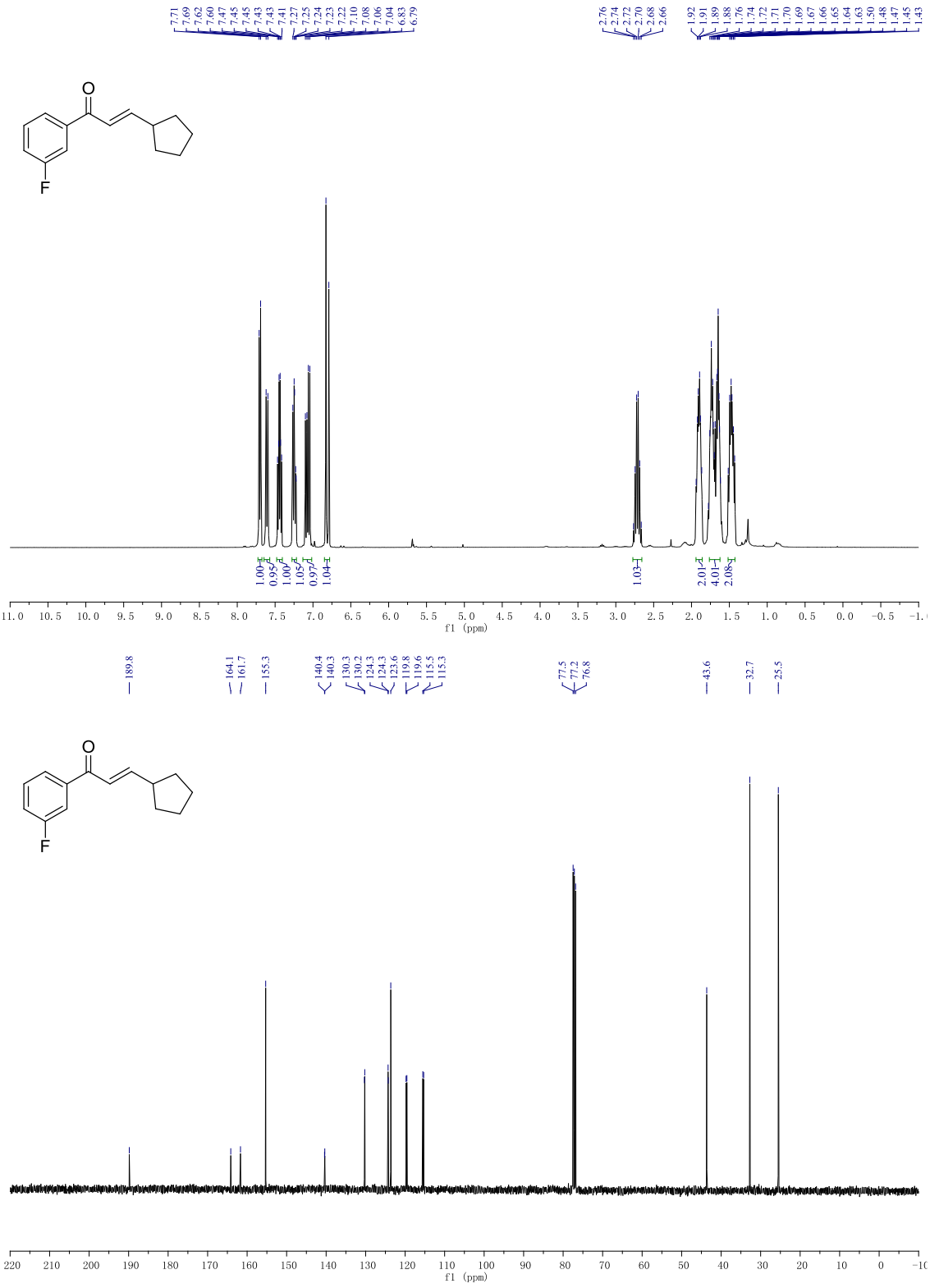




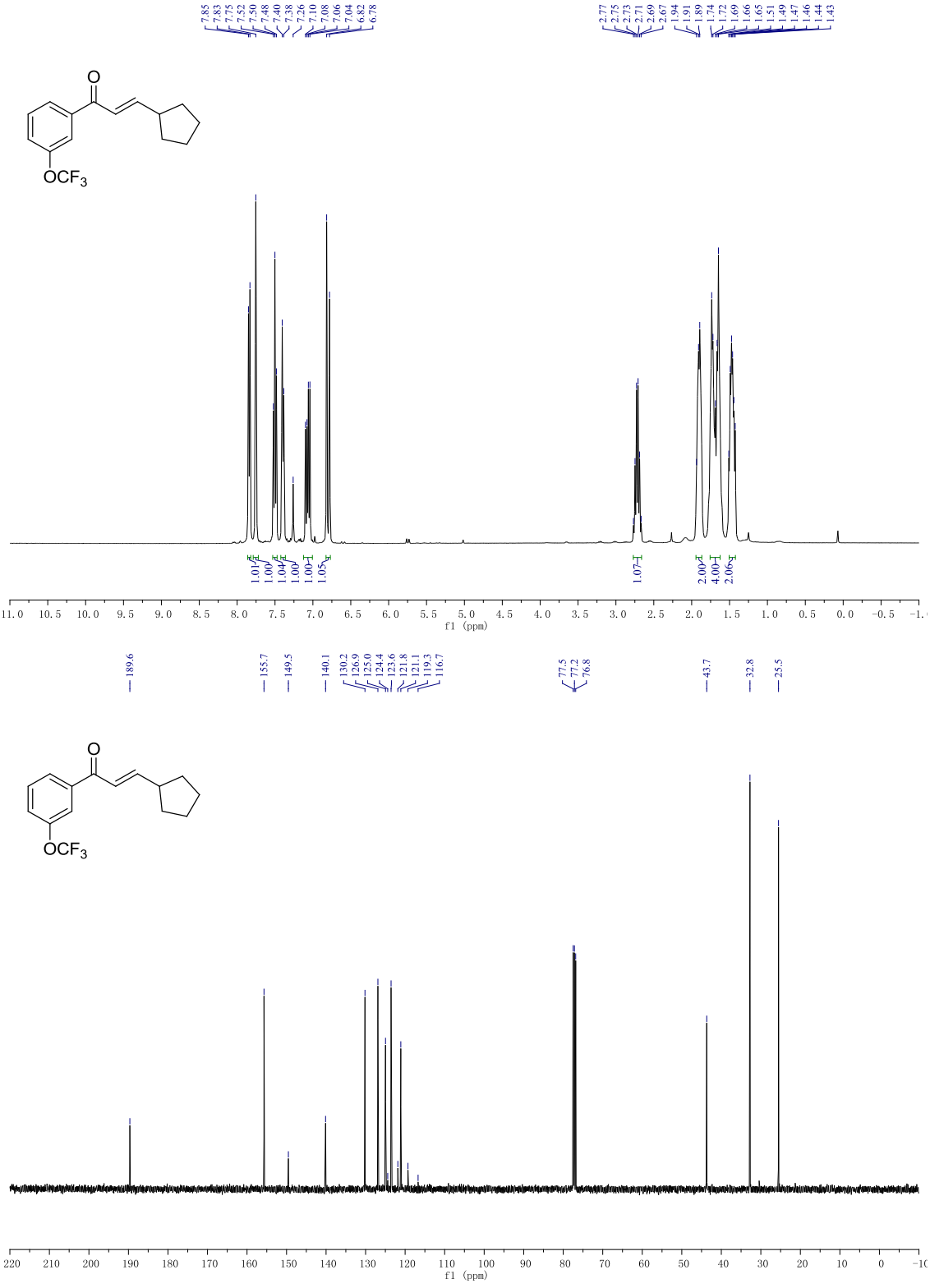
(*E*)-3-Cyclopentyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one, 13j



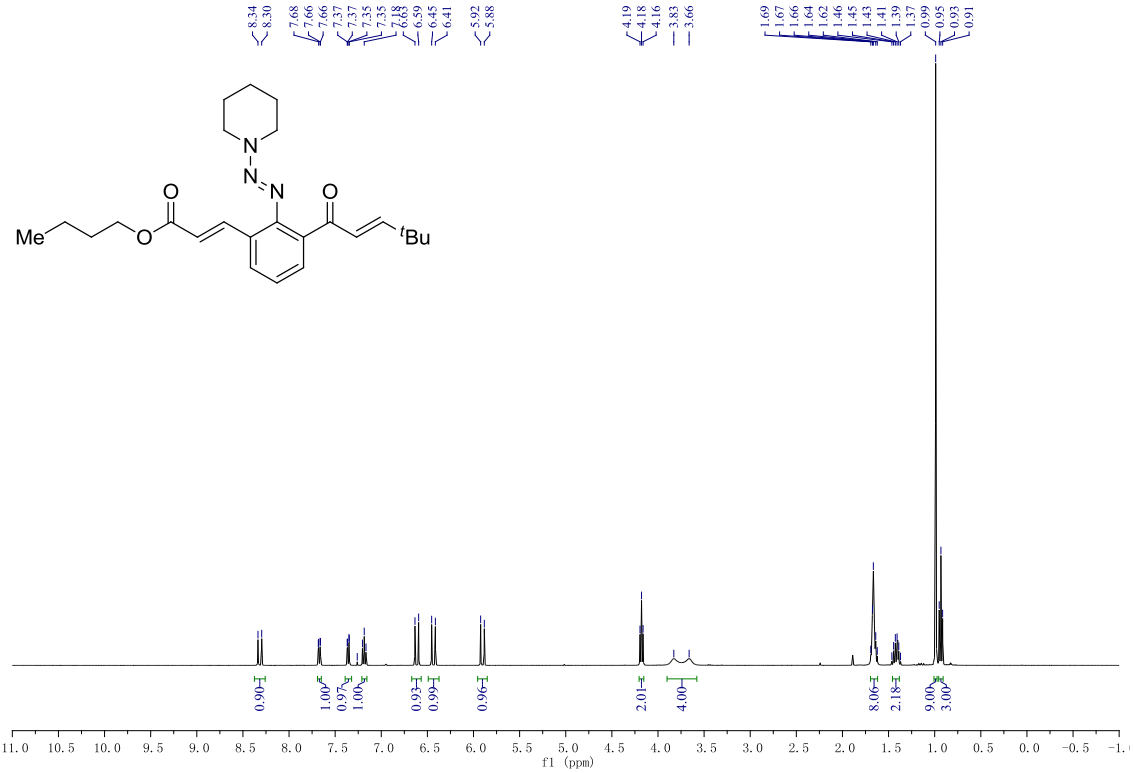
(*E*)-3-Cyclopentyl-1-(3-fluorophenyl)prop-2-en-1-one, 13k

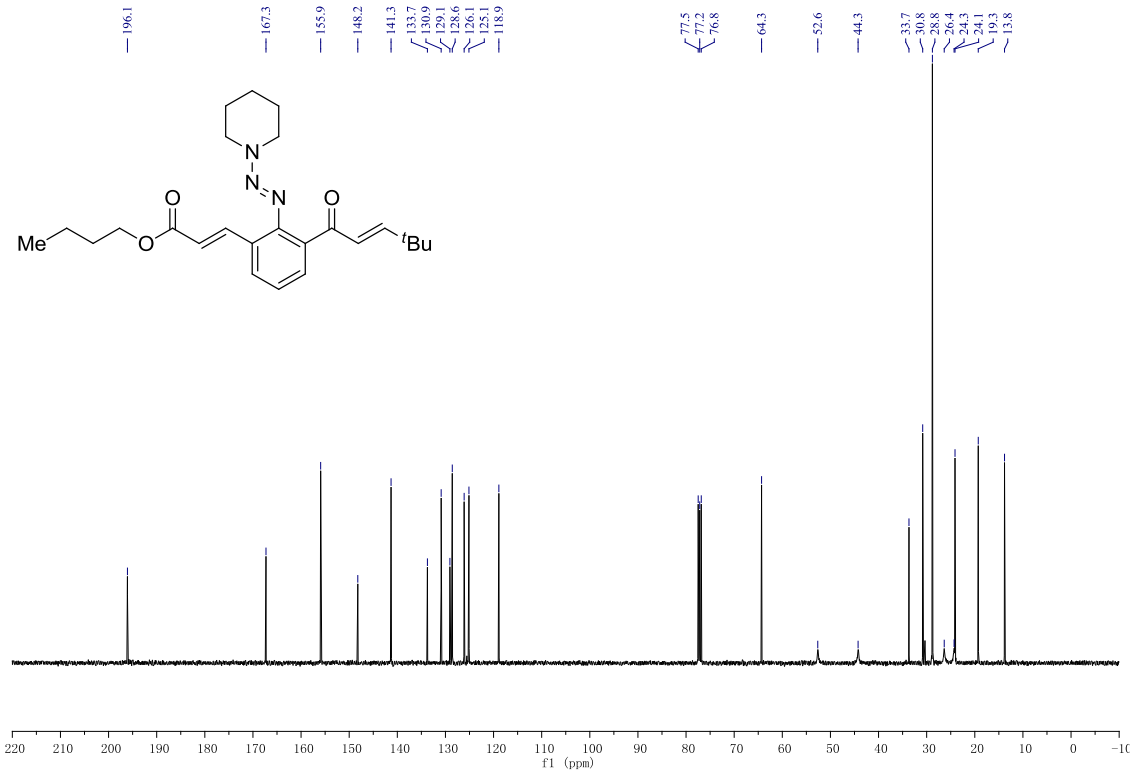


(*E*)-3-Cyclopentyl-1-(3-(trifluoromethoxy)phenyl)prop-2-en-1-one, 13l

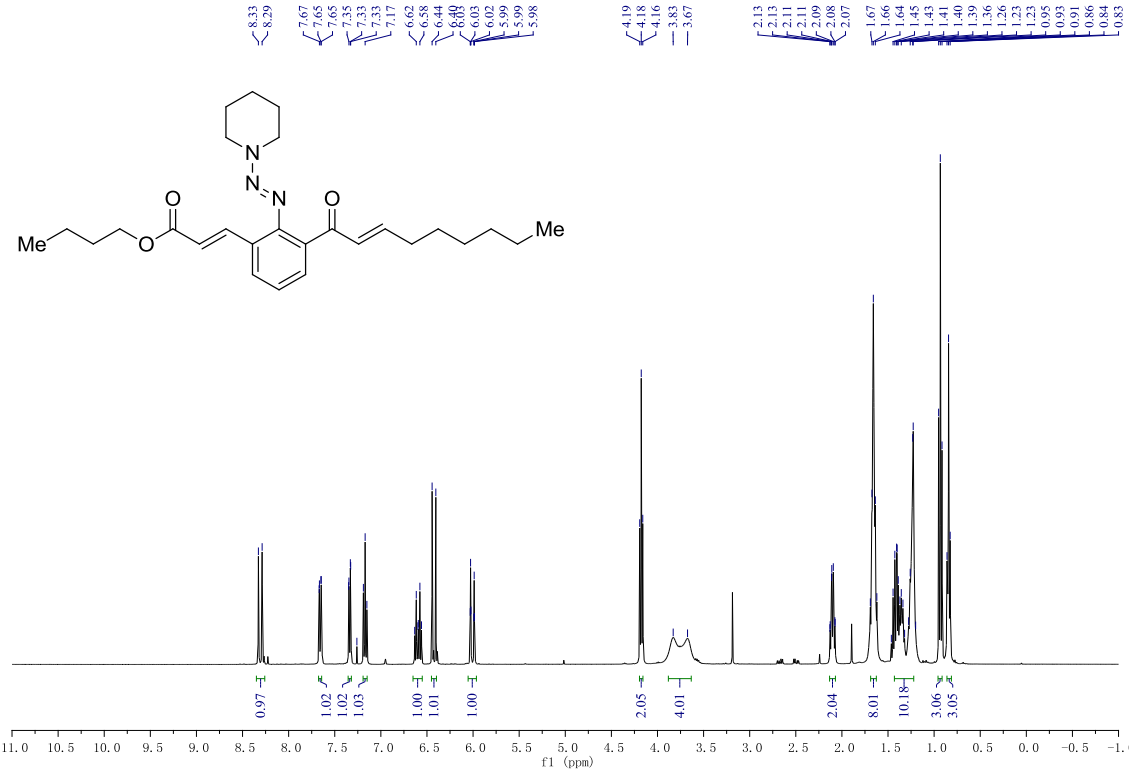


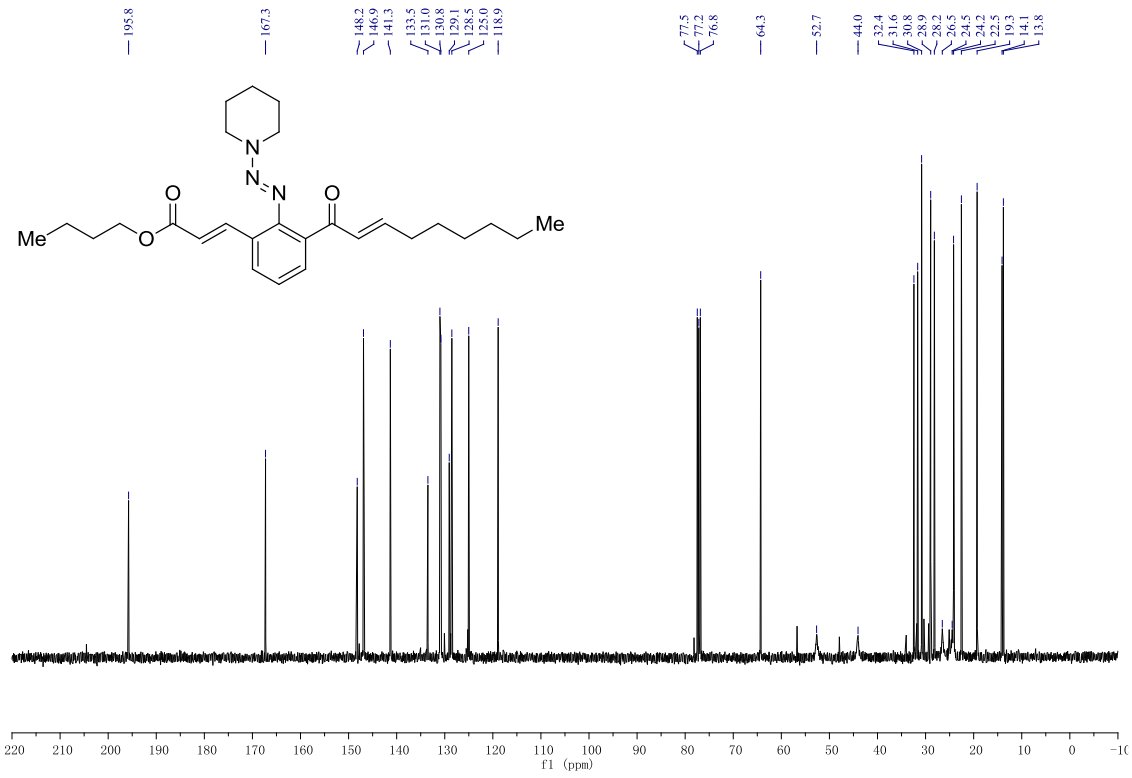
(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl)phenyl) acrylate, 14a



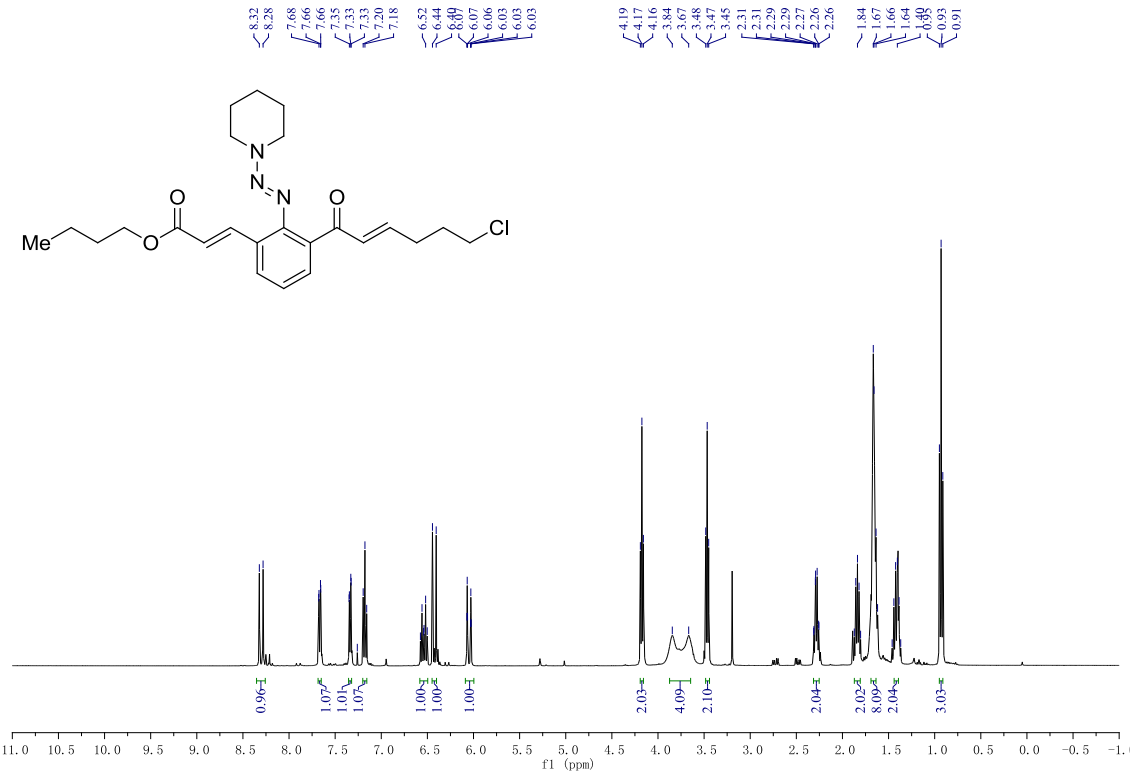


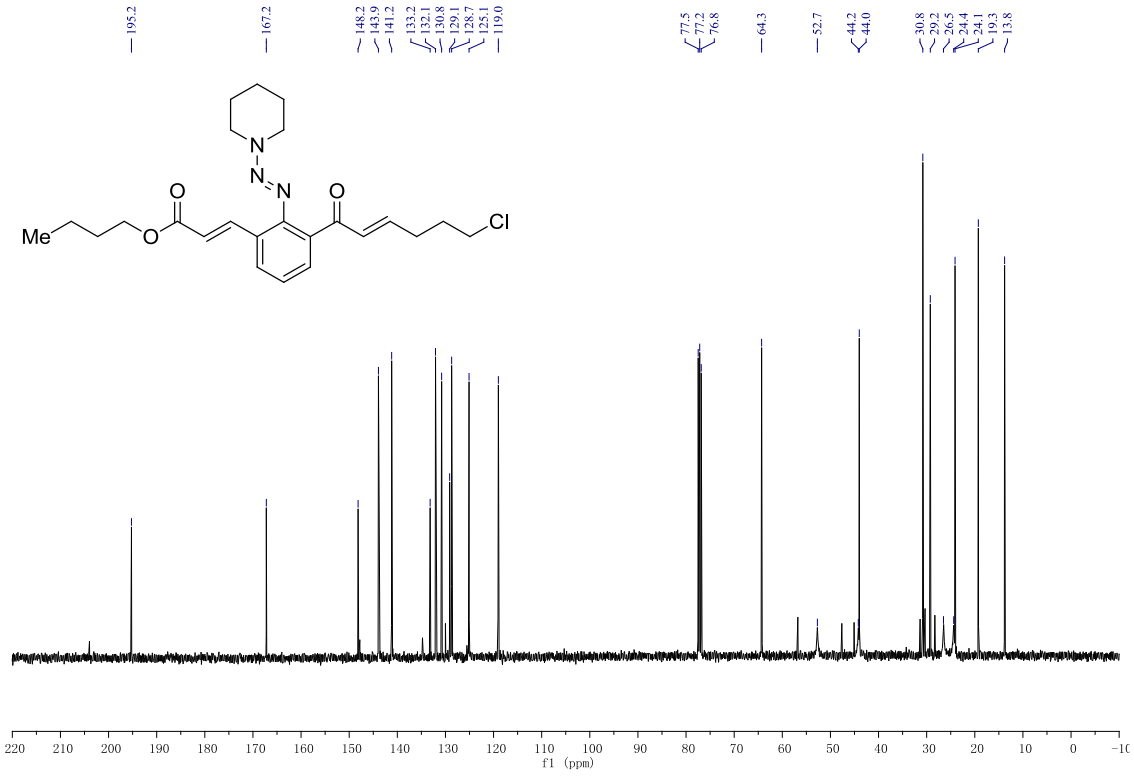
(*E*)-Butyl 3-(3-((*E*)-non-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl)phenyl)acrylate, 14b



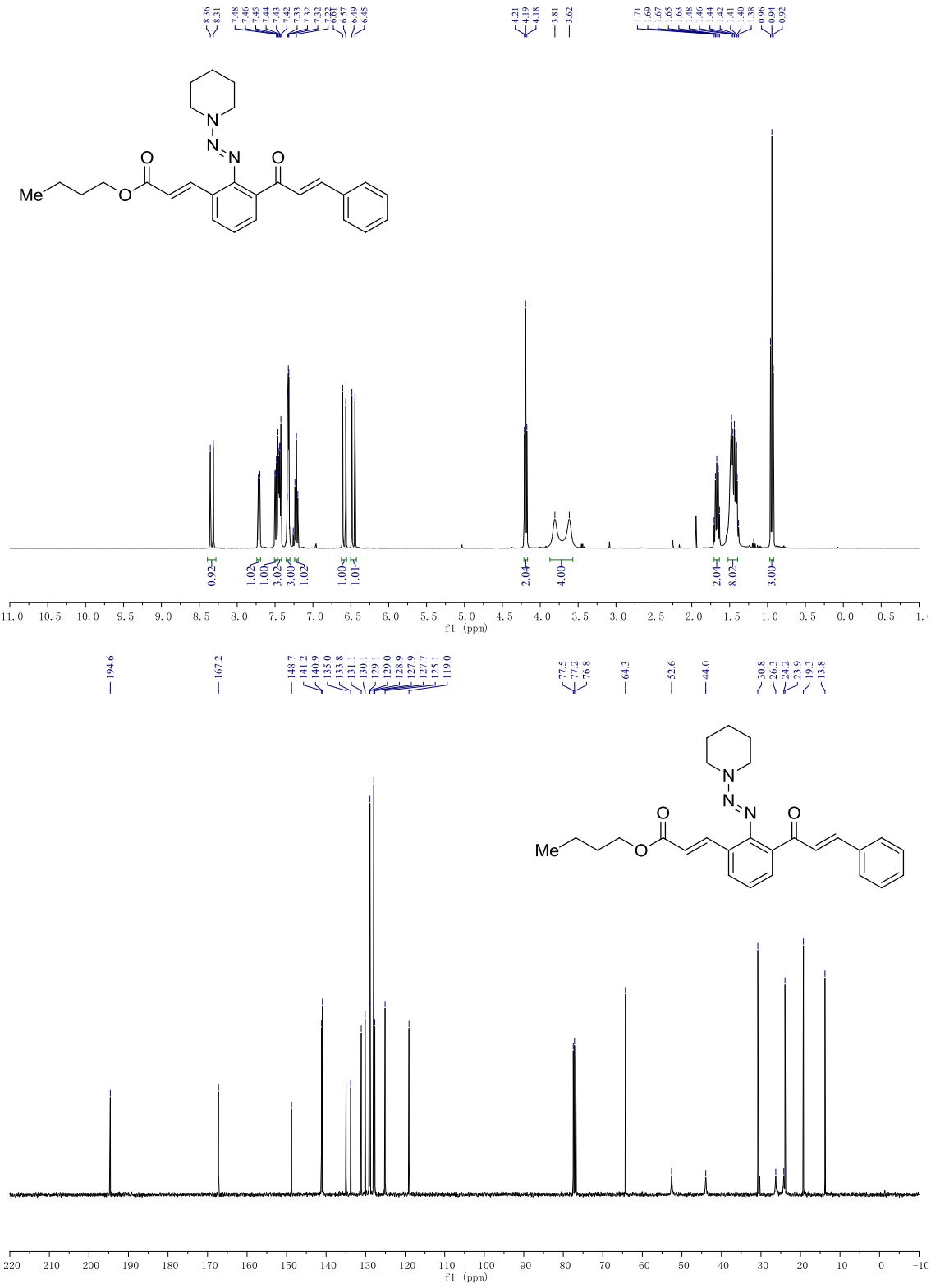


(*E*)-Butyl 3-(3-((*E*)-6-chlorohex-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl)phenyl) acrylate, 14c

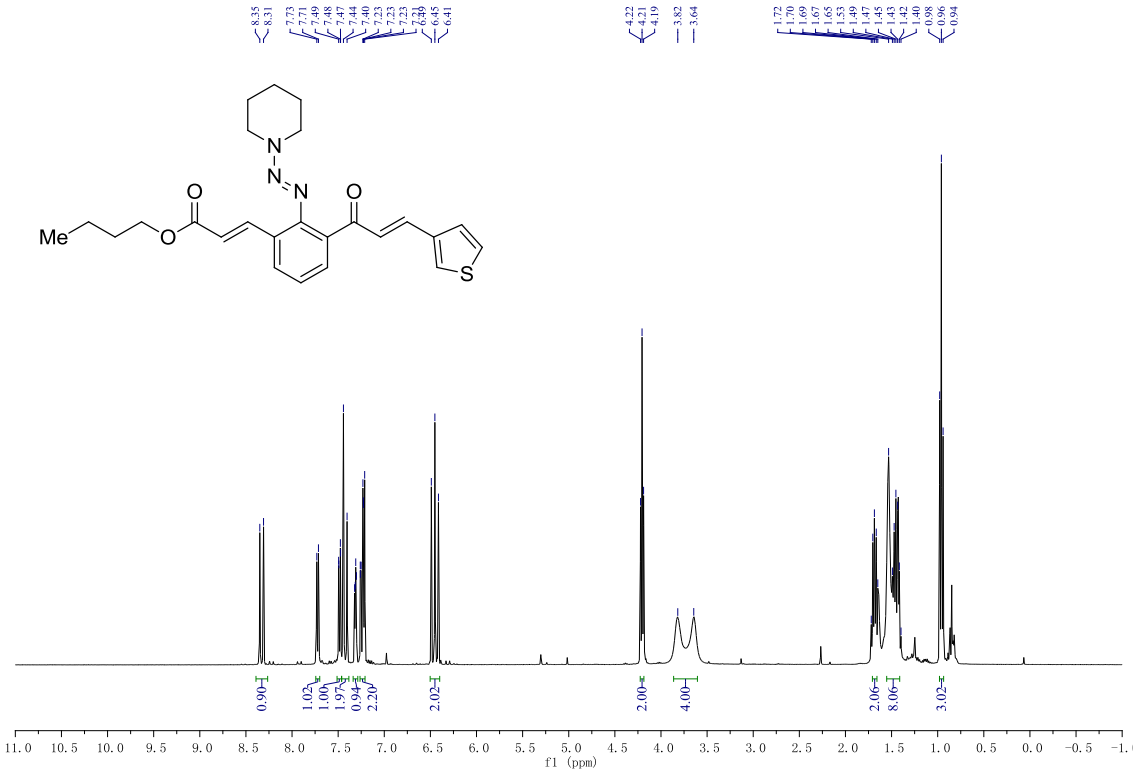


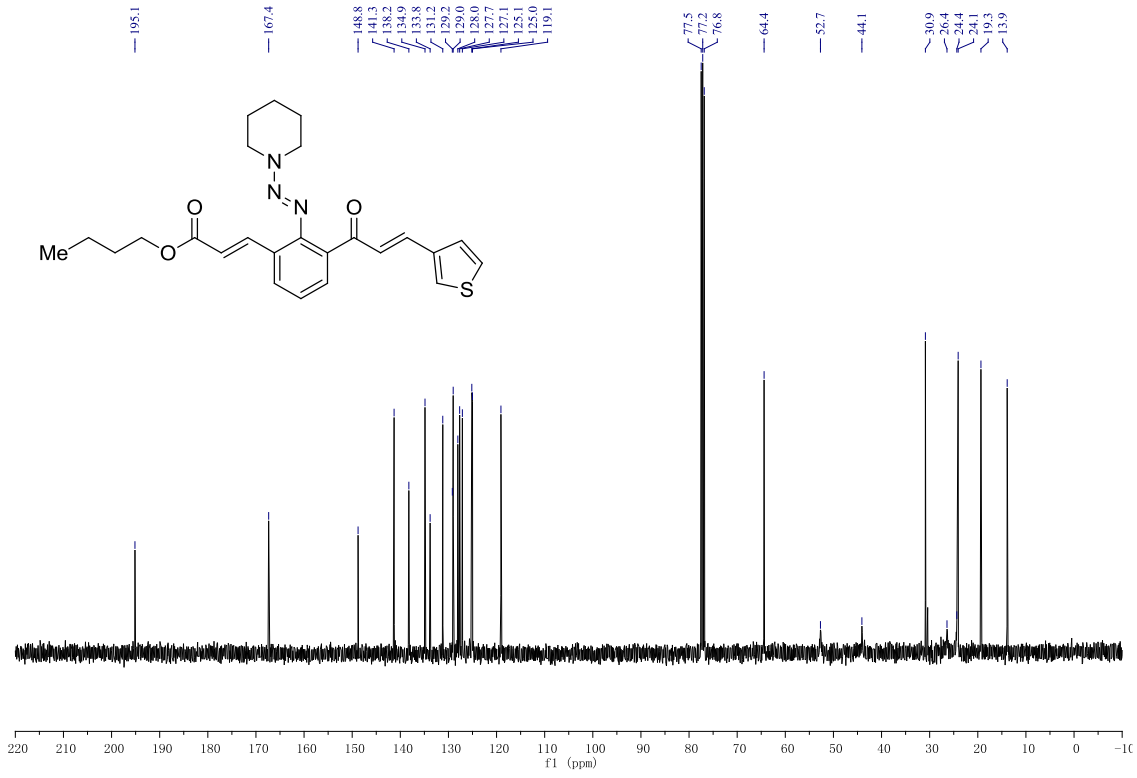


(*E*)-Butyl 3-(3-cinnamoyl-2-((*E*)-piperidin-1-yldiazenyl)phenyl)acrylate, 14d

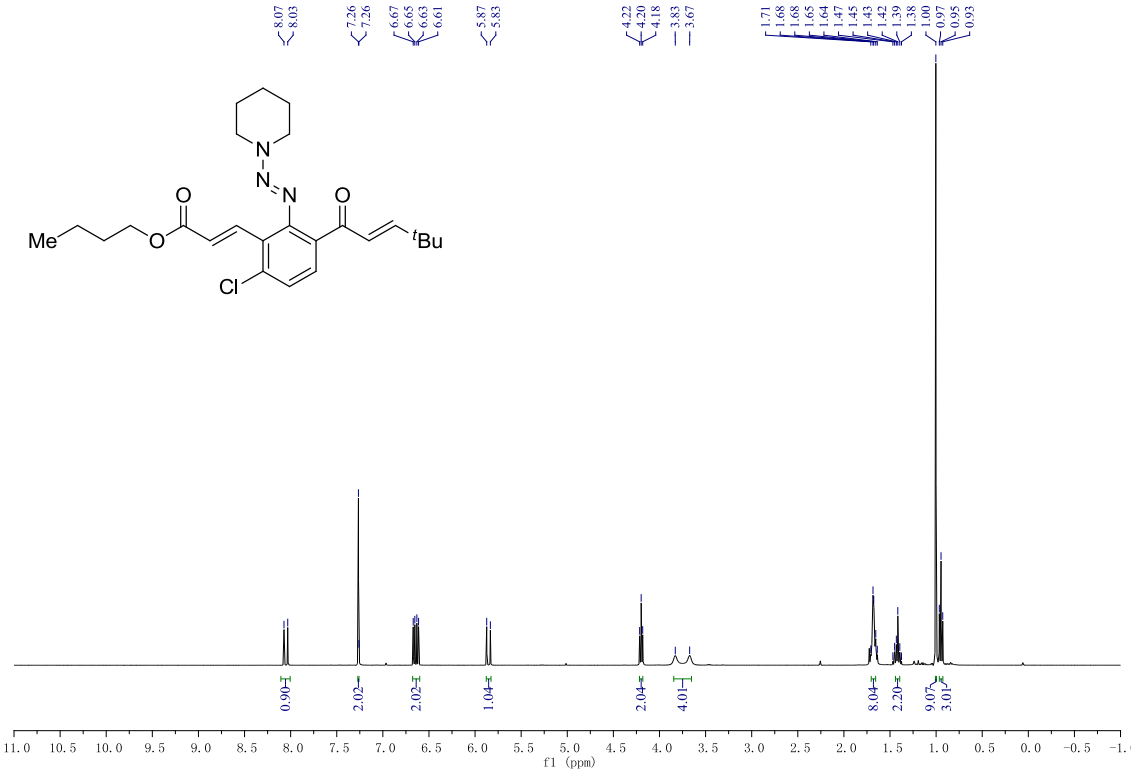


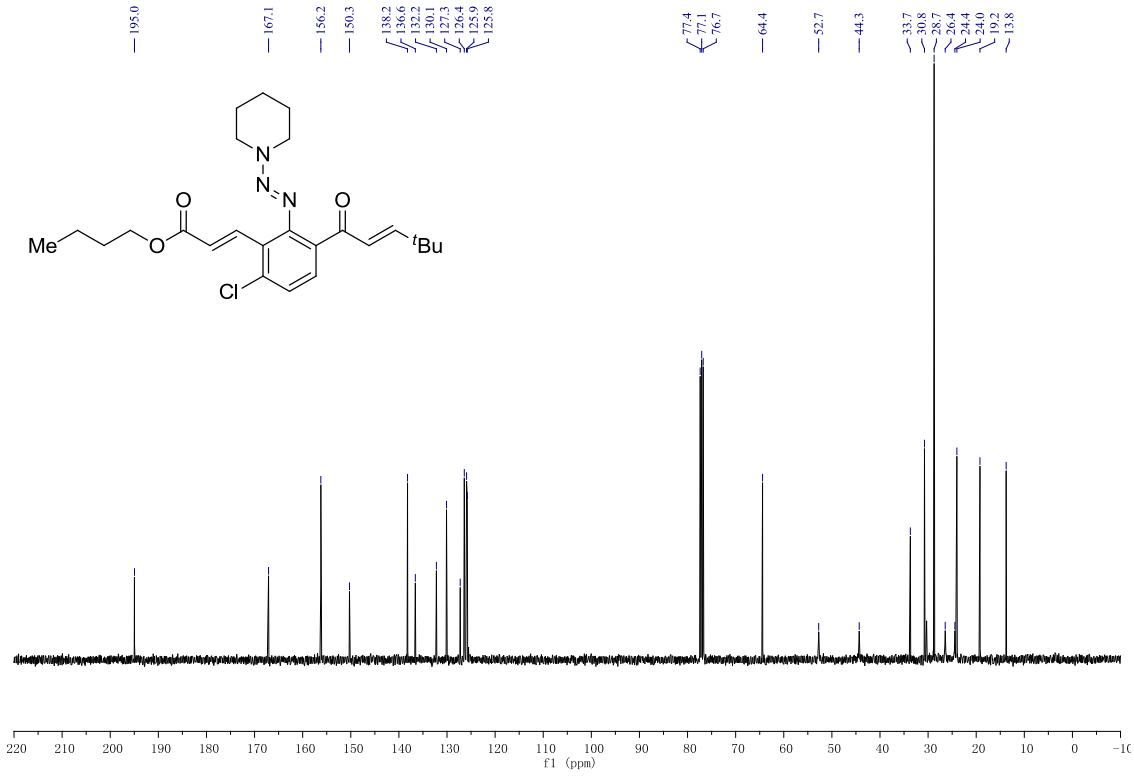
(*E*)-Butyl 3-(2-((*E*)-piperidin-1-yldiazenyl)-3-((*E*)-3-(thiophen-3-yl)acryloyl)phenyl) acrylate, 14e



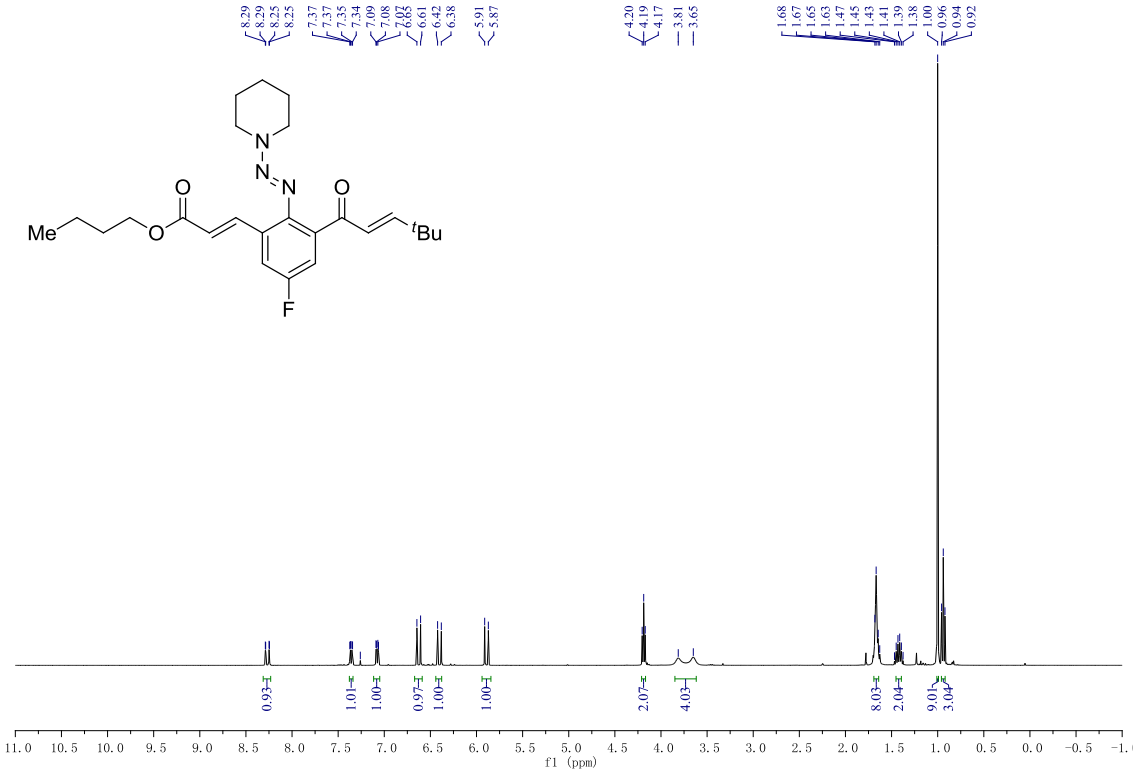


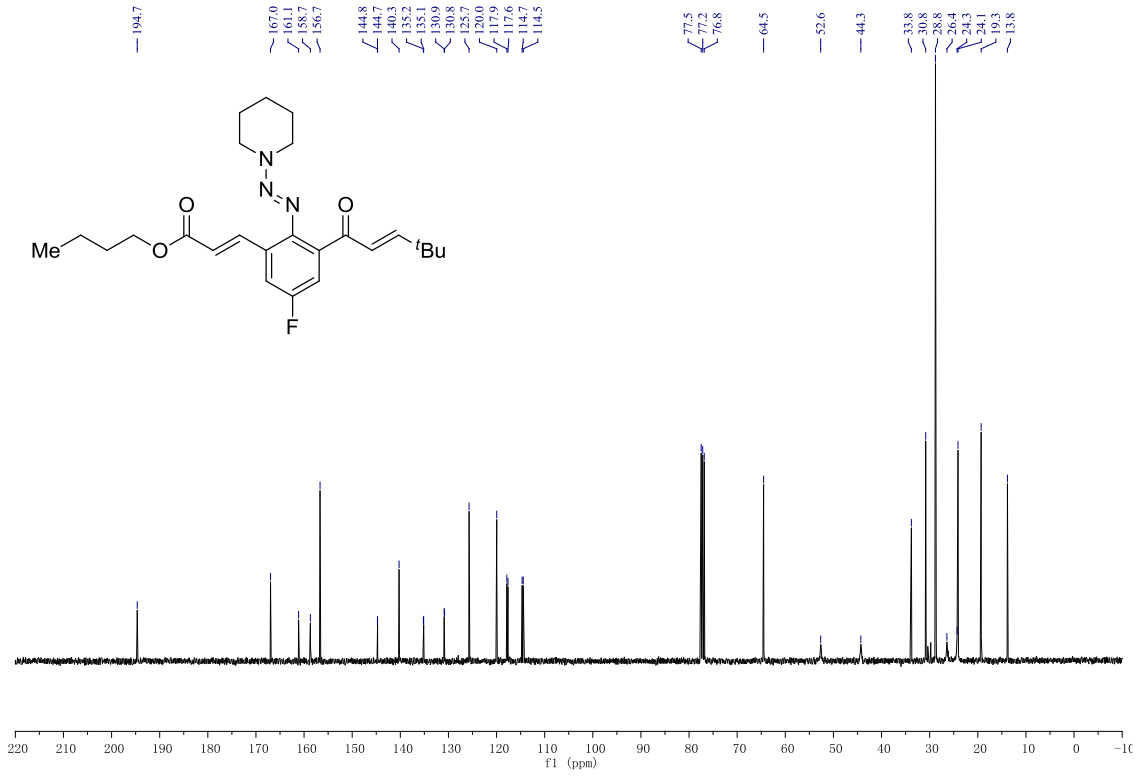
(*E*)-Butyl 3-(6-chloro-3-((*E*)-4,4-dimethylpent-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl) phenyl)acrylate, 14f



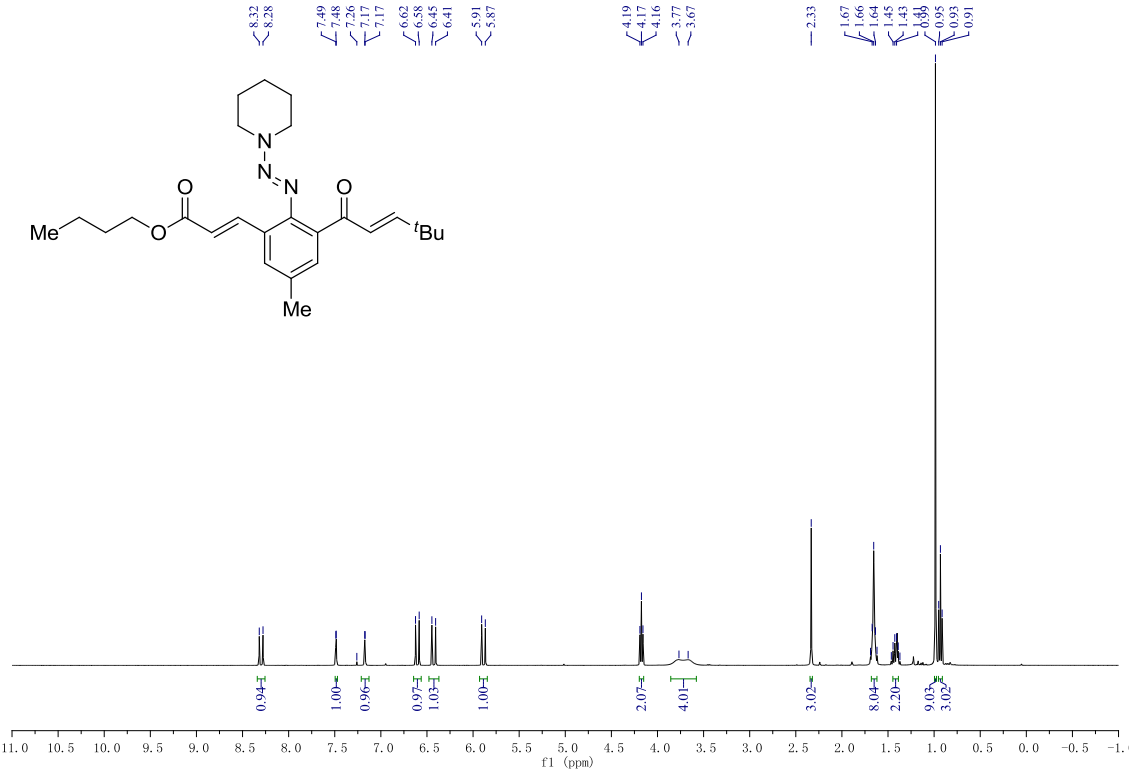


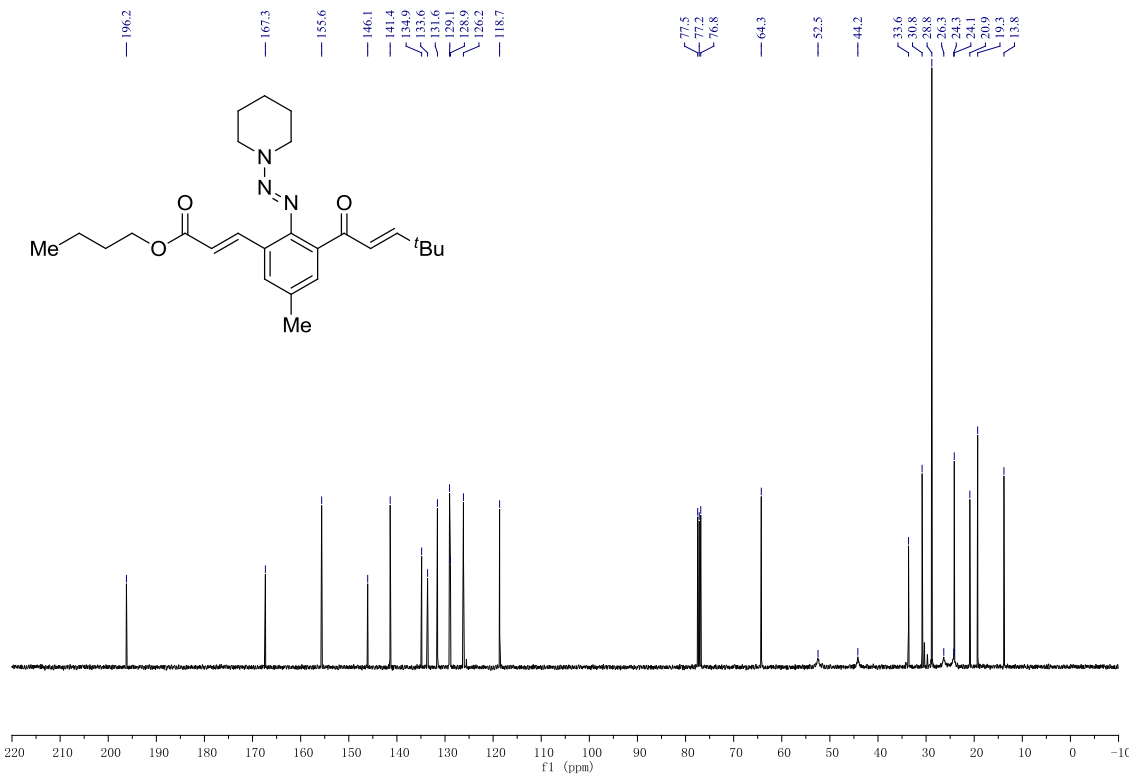
(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-5-fluoro-2-((*E*)-piperidin-1-yldiazenyl) phenyl)acrylate, 14g



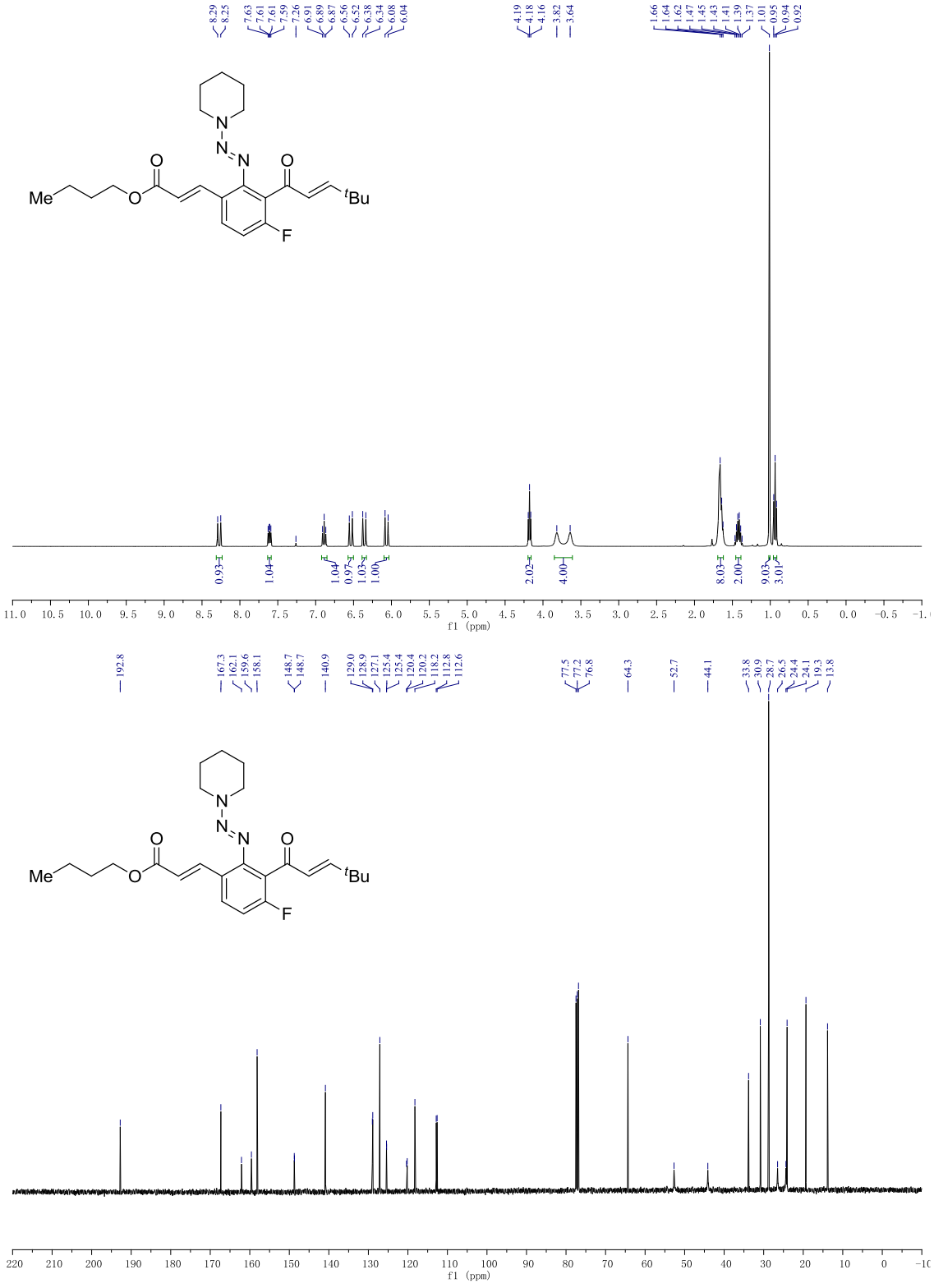


(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-5-methyl-2-((*E*)-piperidin-1-yl diazenyl)phenyl)acrylate, 14h

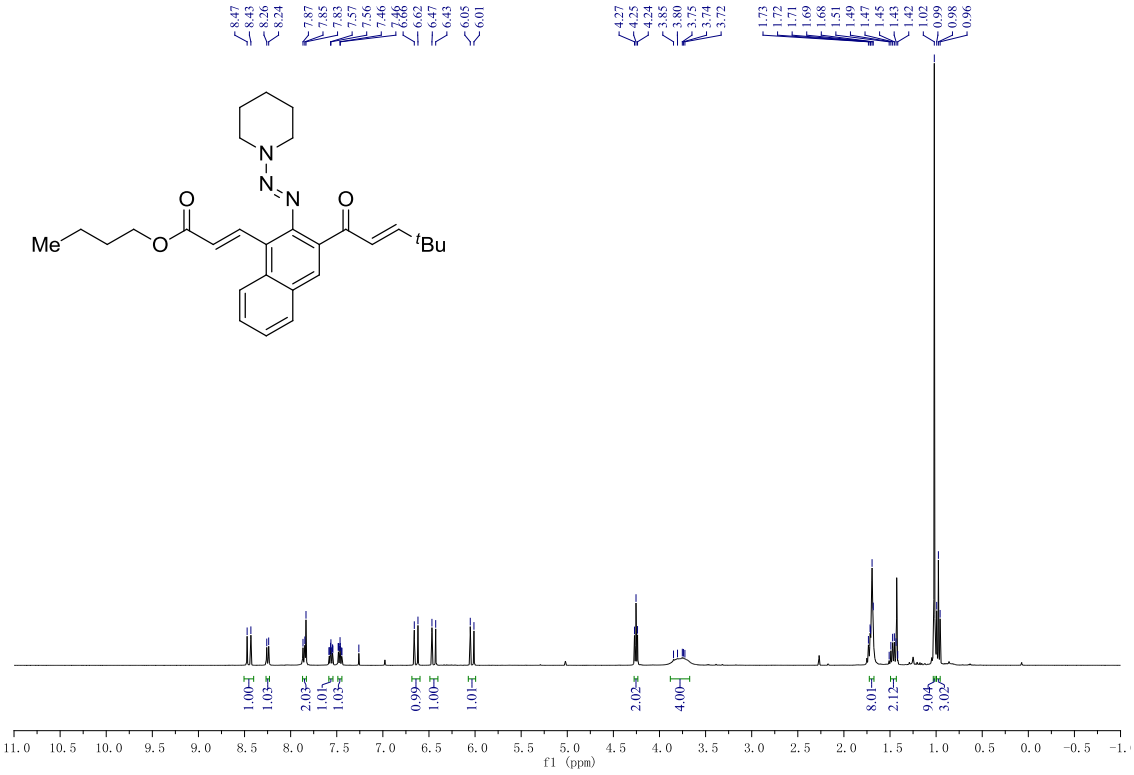


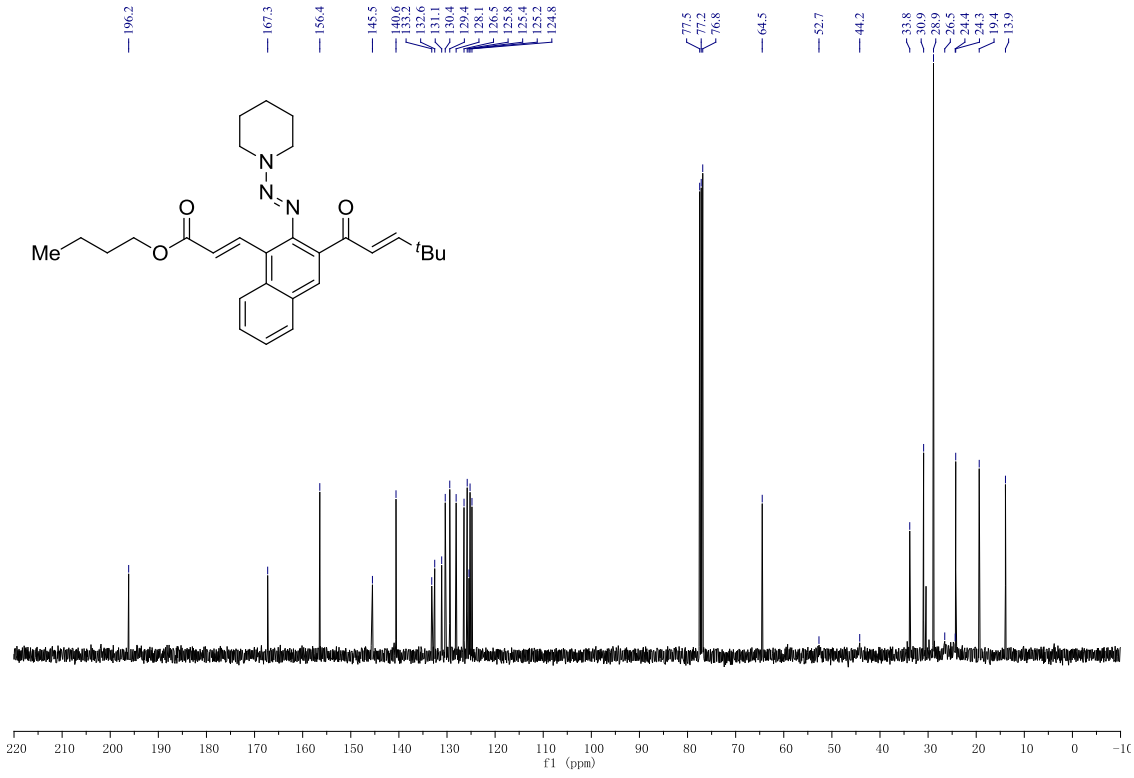


(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-4-fluoro-2-((*E*)-piperidin-1-yldiazenyl) phenyl)acrylate, 14i

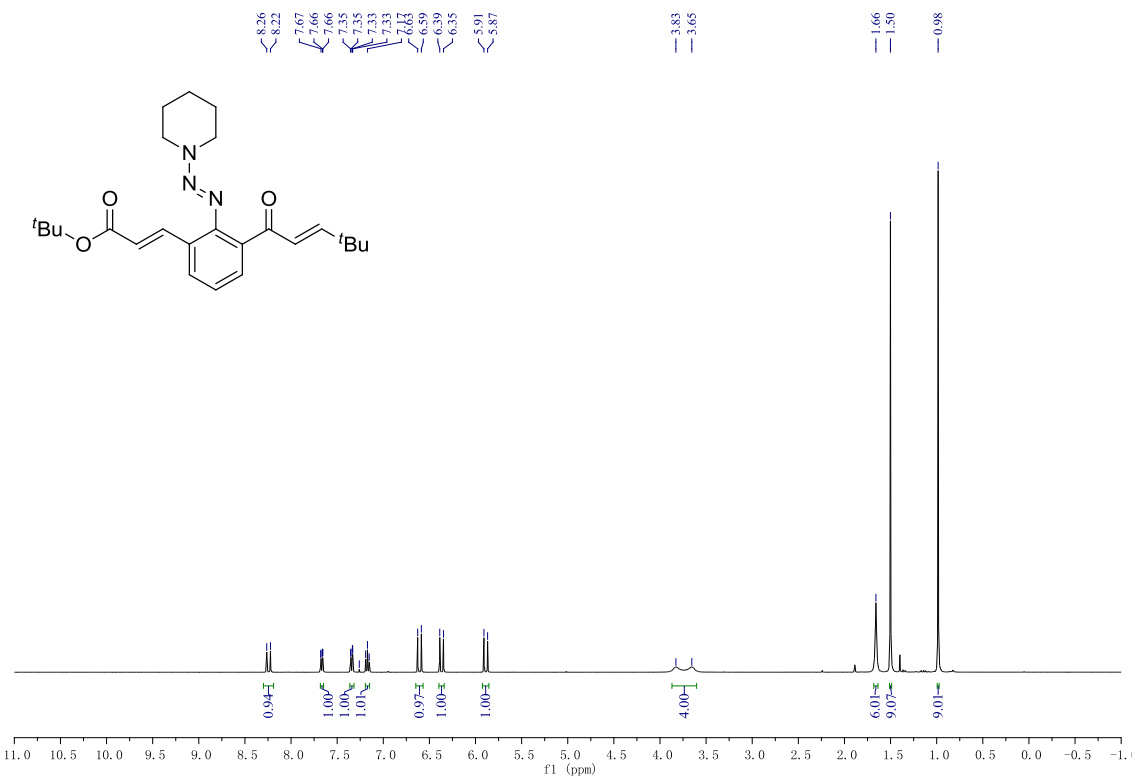


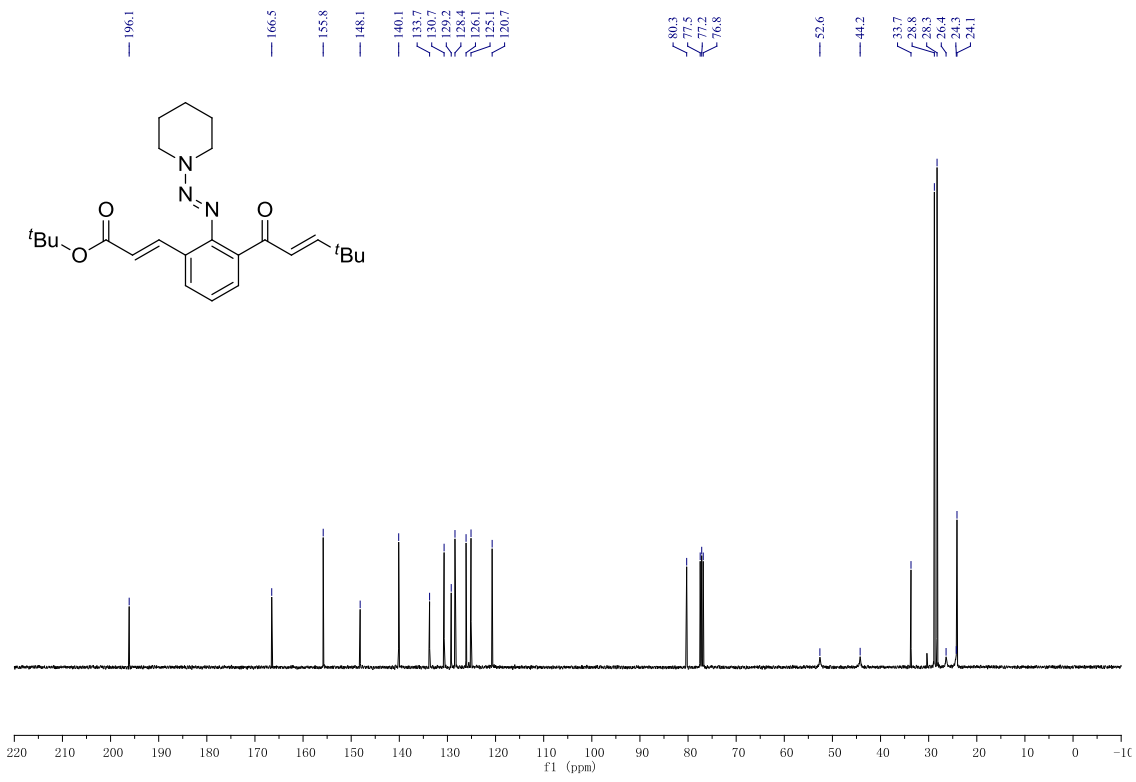
(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl) naphthalen-1-yl)acrylate, 14j



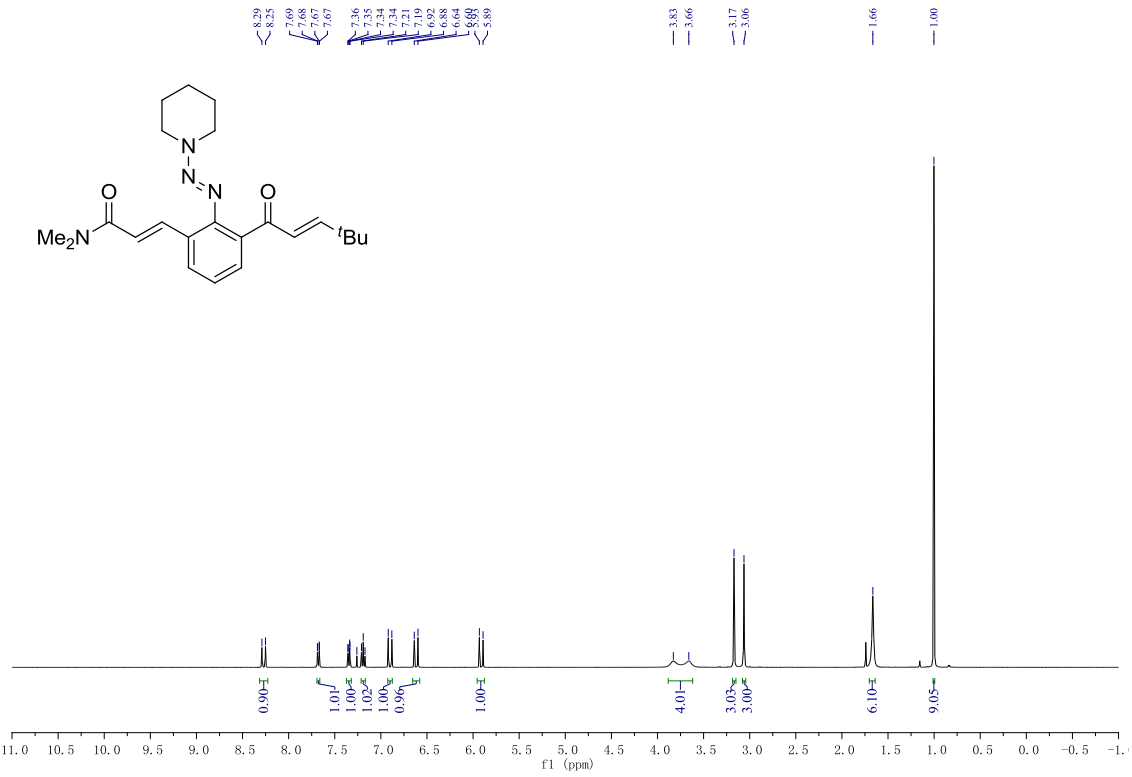


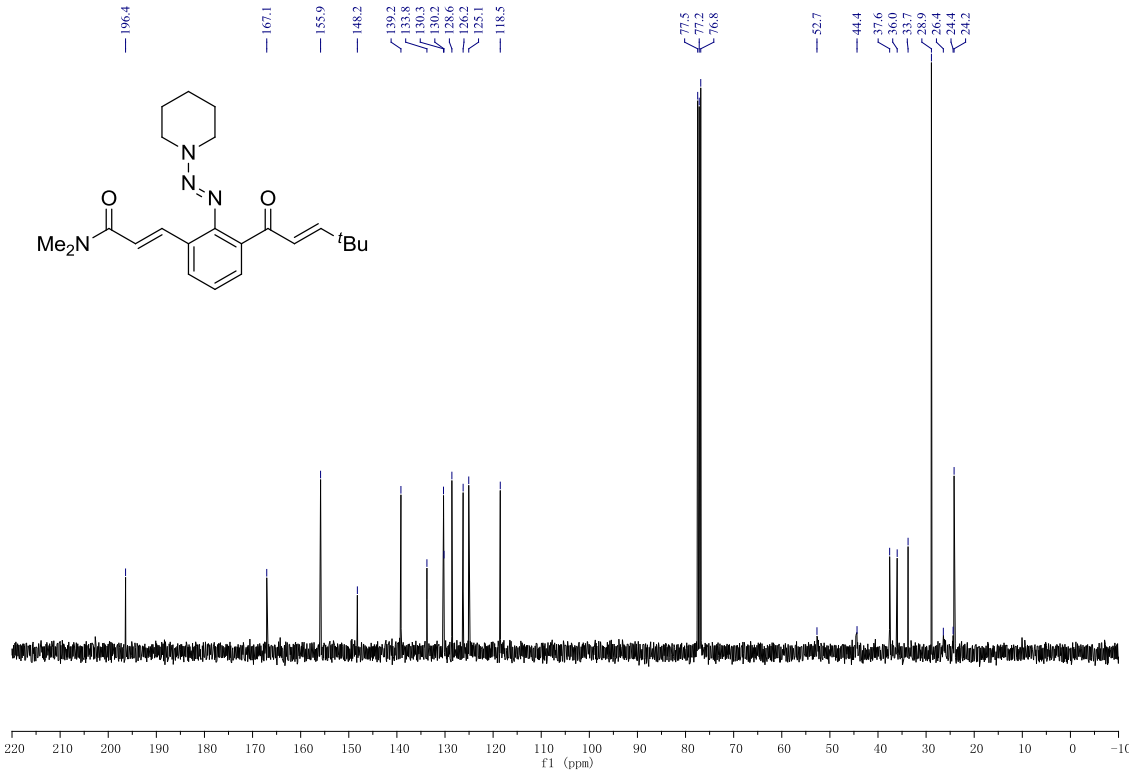
(*E*)-*tert*-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl) phenyl)acrylate, 14k



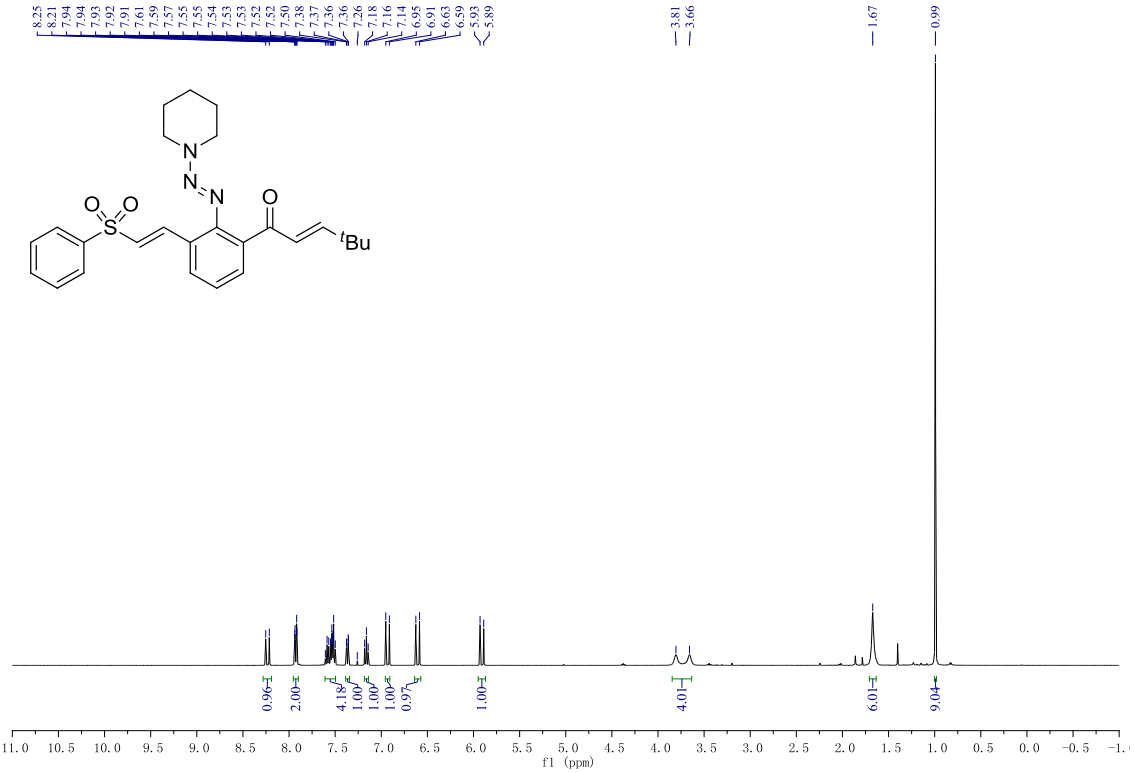


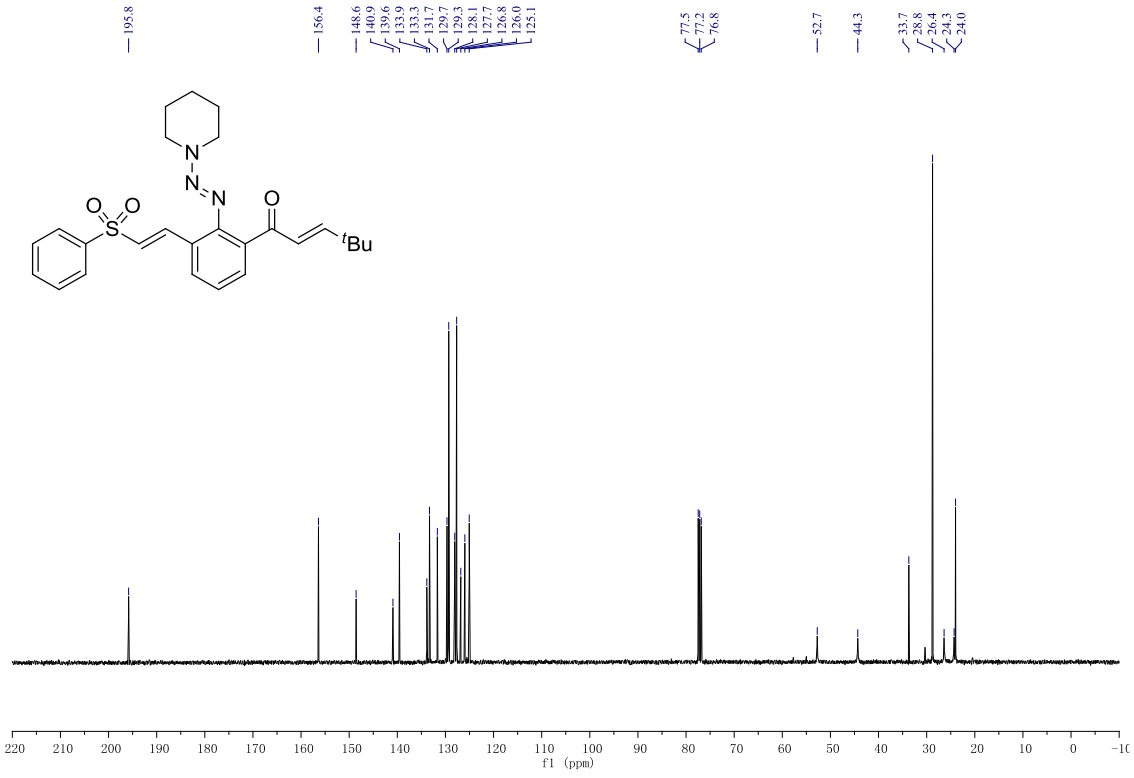
(*E*)-3-(3-((*E*)-4,4-Dimethylpent-2-enoyl)-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-*N*,*N*-dimethylacrylamide, 14l



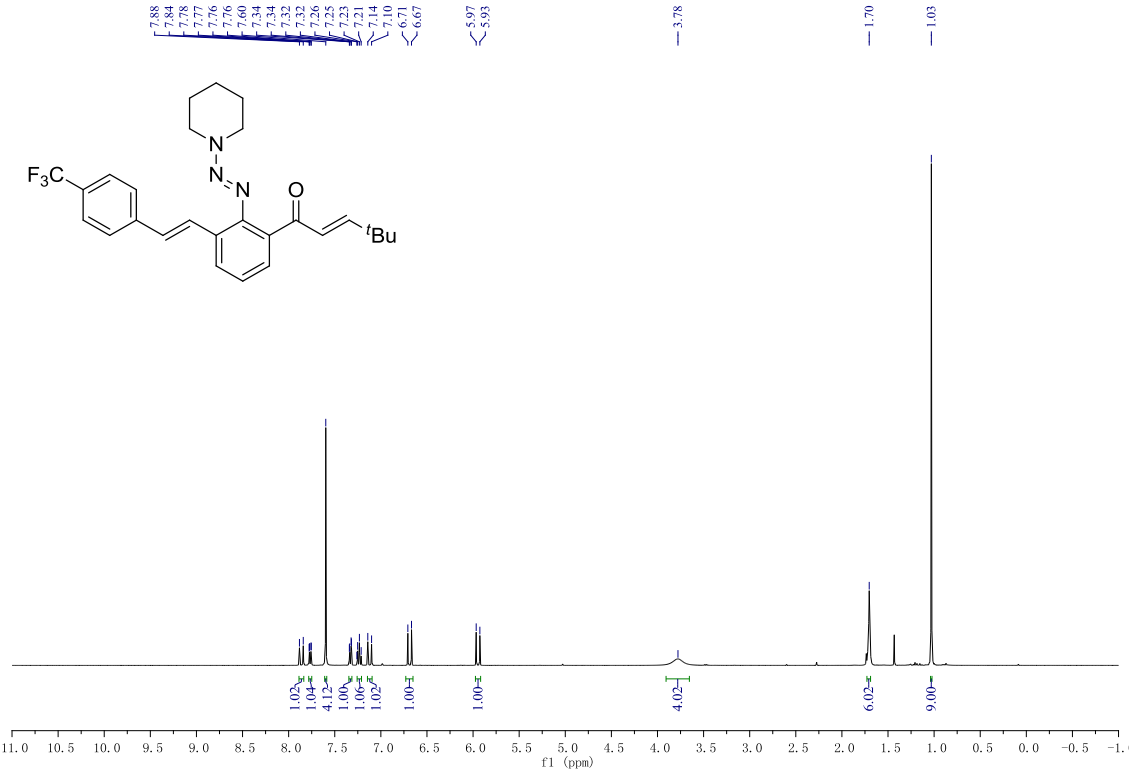


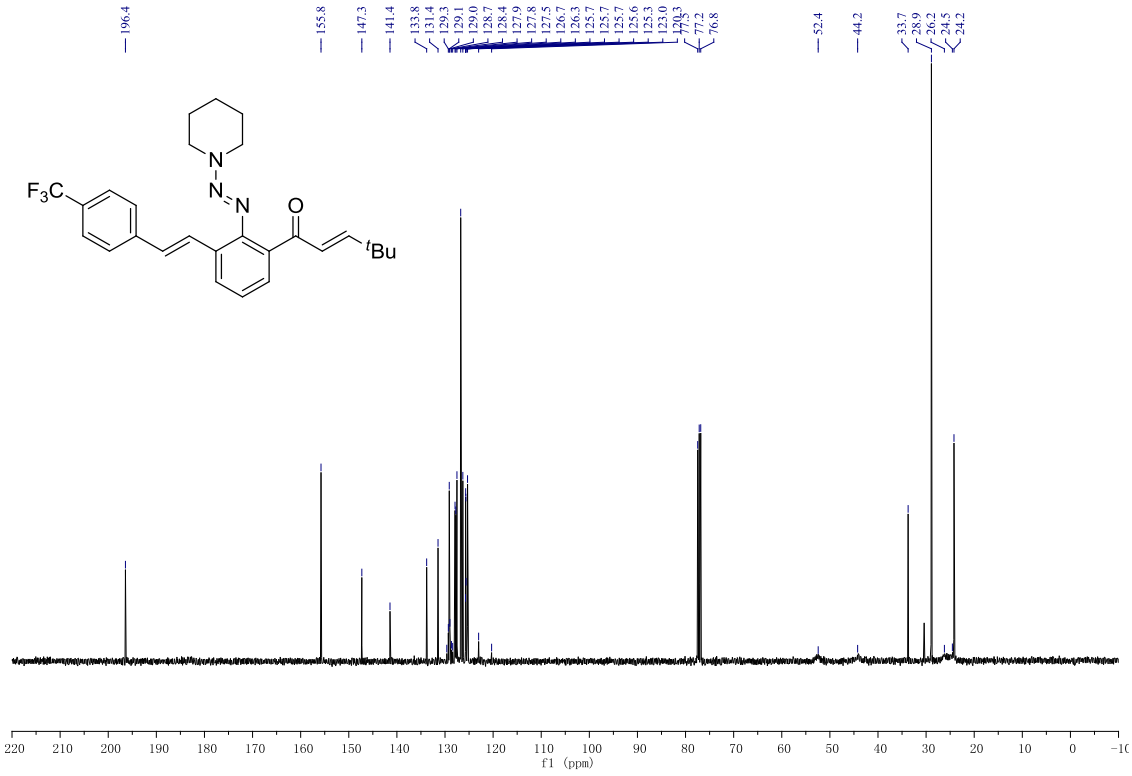
(*E*)-4,4-Dimethyl-1-(3-((*E*)-2-(phenylsulfonyl)vinyl)-2-((*E*)-piperidin-1-yldiazenyl) phenyl)pent-2-en-1-one, 14m



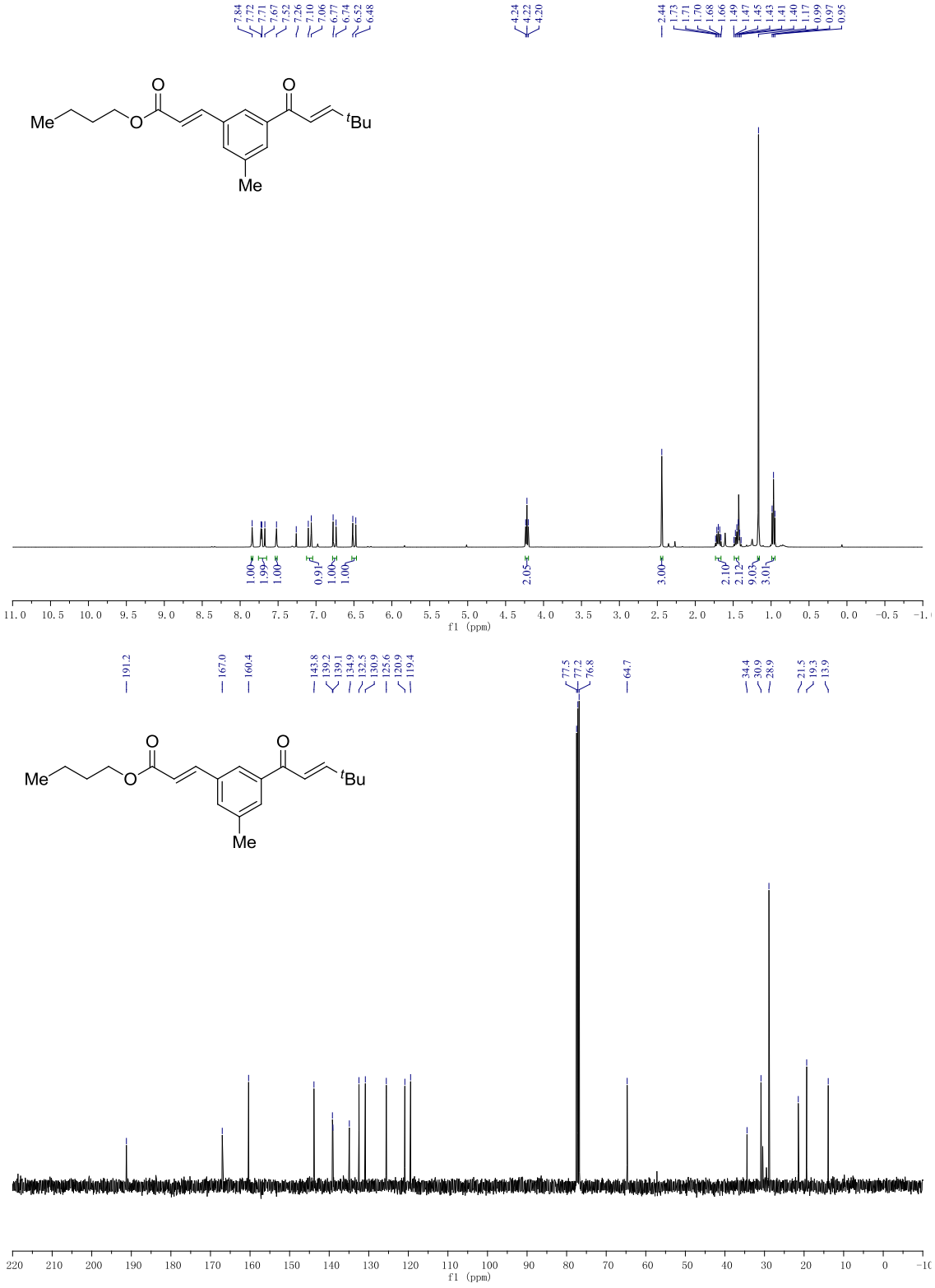


(*E*)-4,4-Dimethyl-1-(2-((*E*)-piperidin-1-yldiazenyl)-3-((*E*)-4-(trifluoromethyl)styryl) phenyl)pent-2-en-1-one, 14n

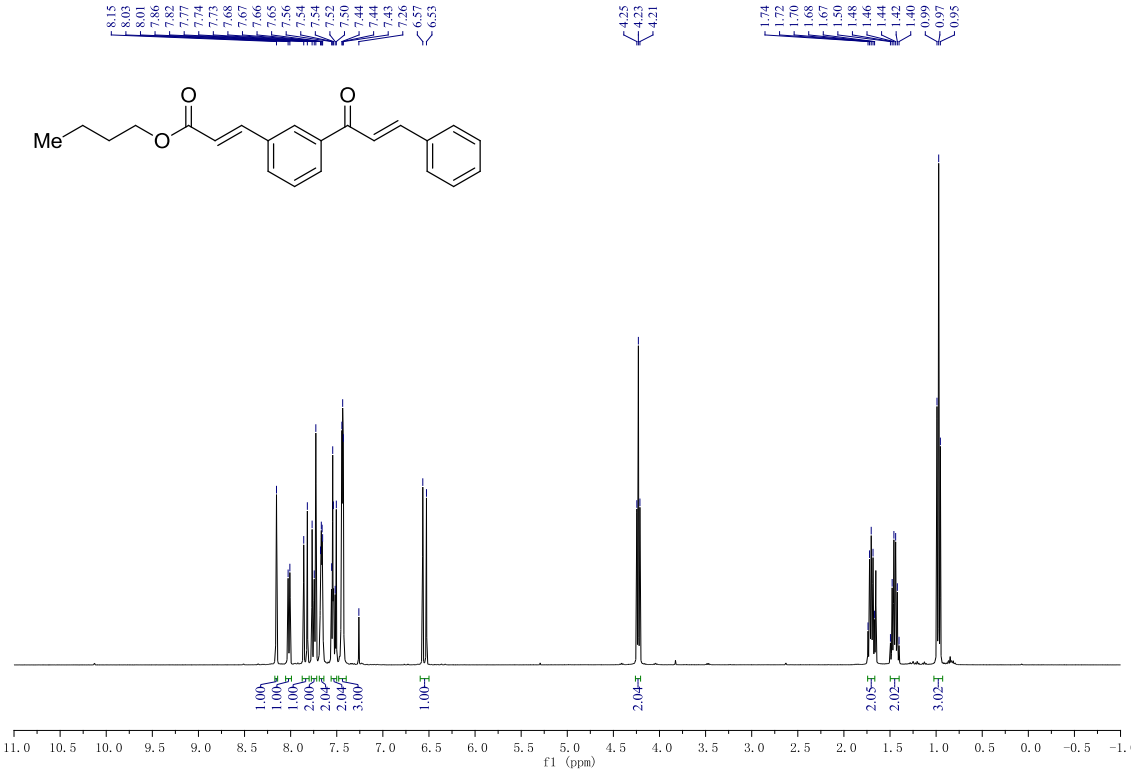


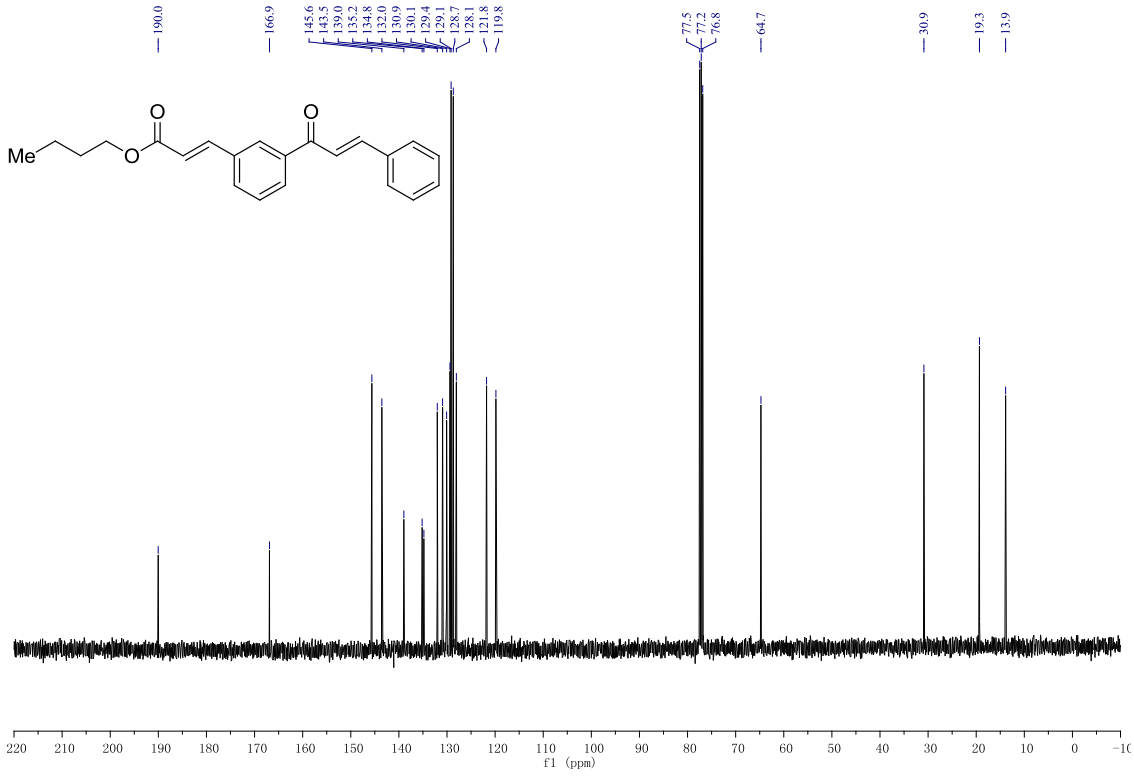


(*E*)-Butyl 3-(3-((*E*)-4,4-dimethylpent-2-enoyl)-5-methylphenyl)acrylate, 15a

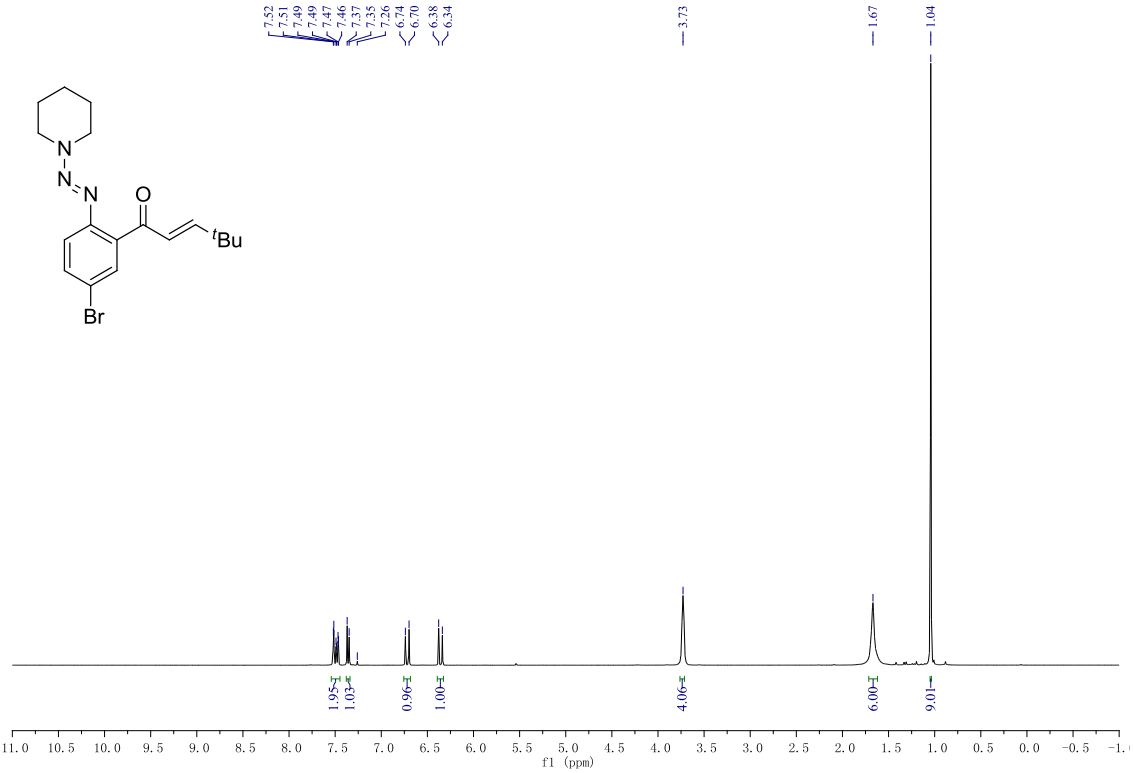


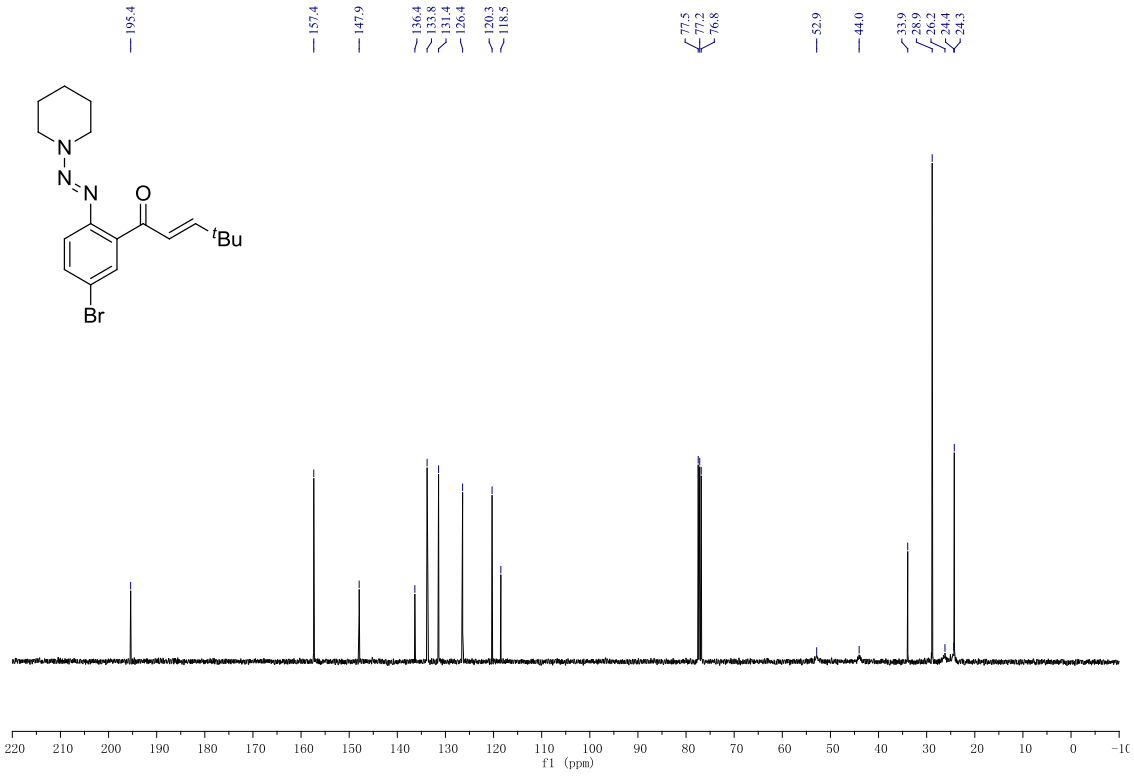
(*E*)-Butyl 3-(3-cinnamoylphenyl)acrylate, 15b



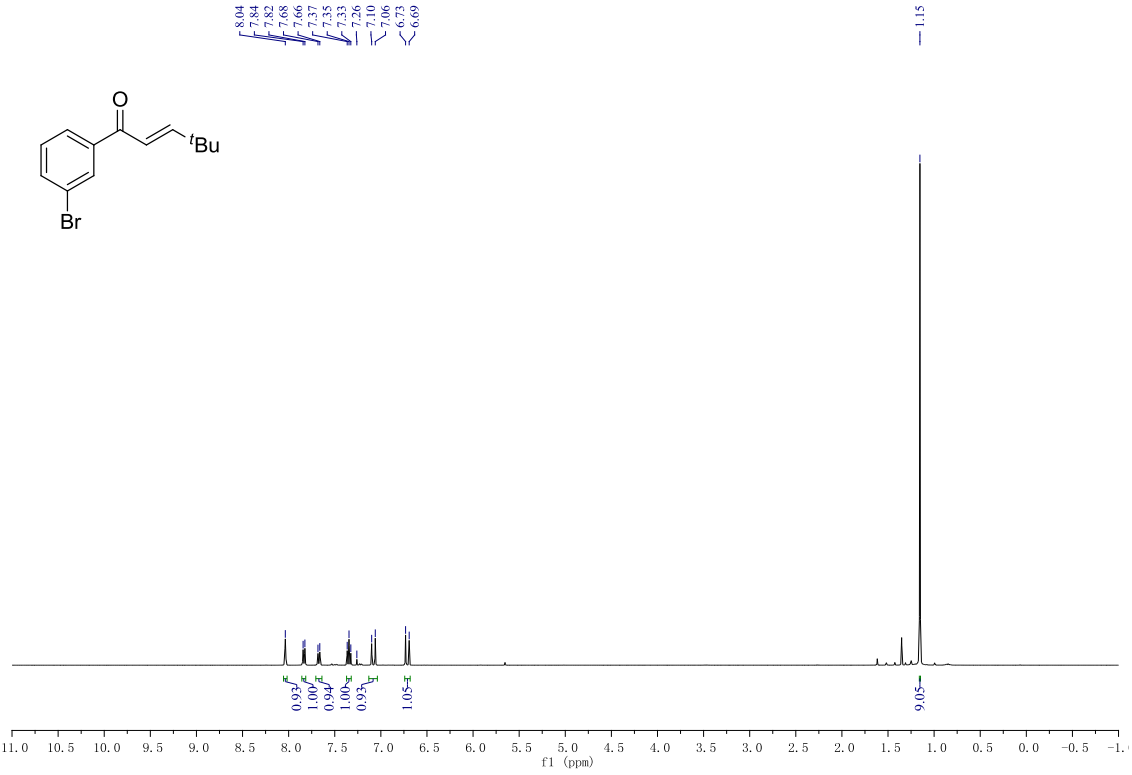


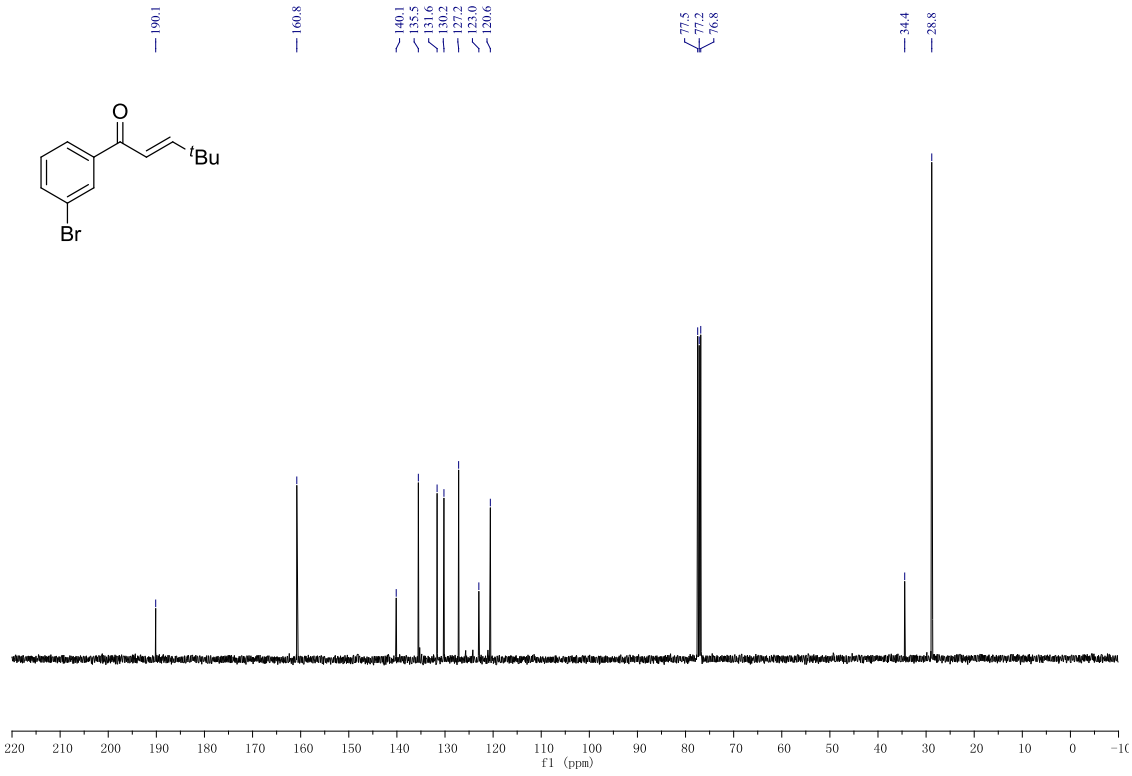
(*E*)-1-(5-Bromo-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-4,4-dimethylpent-2-en-1-one, 16a



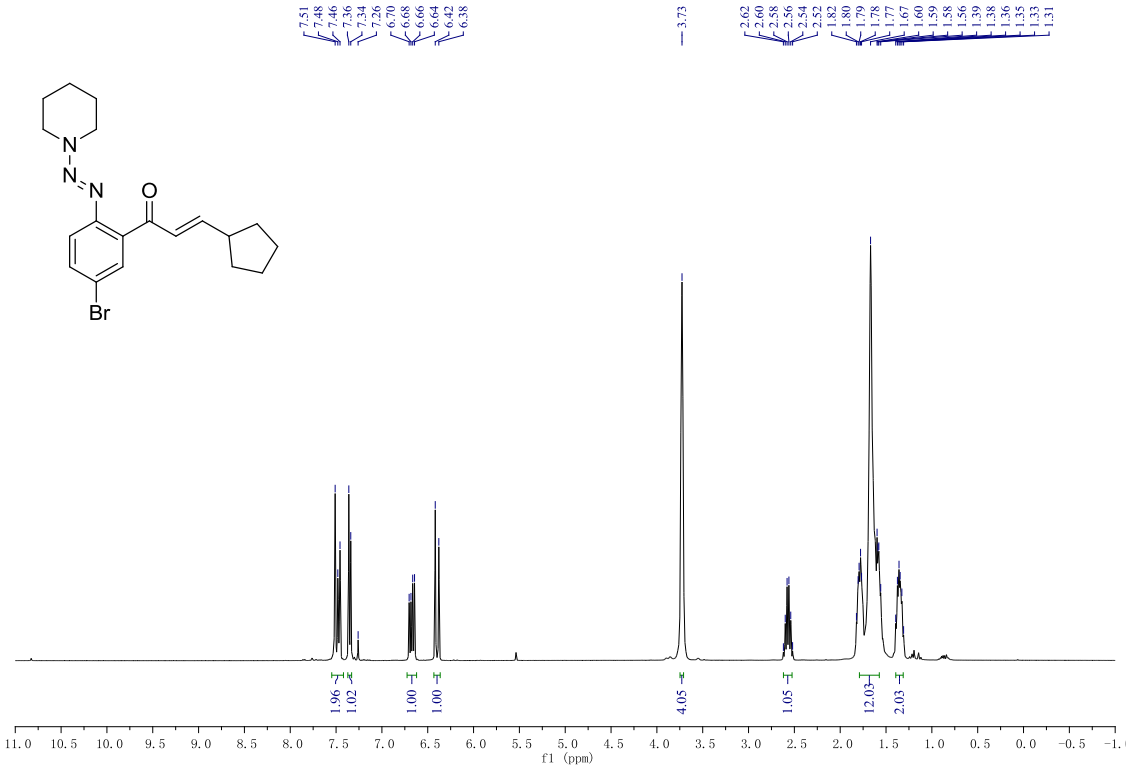


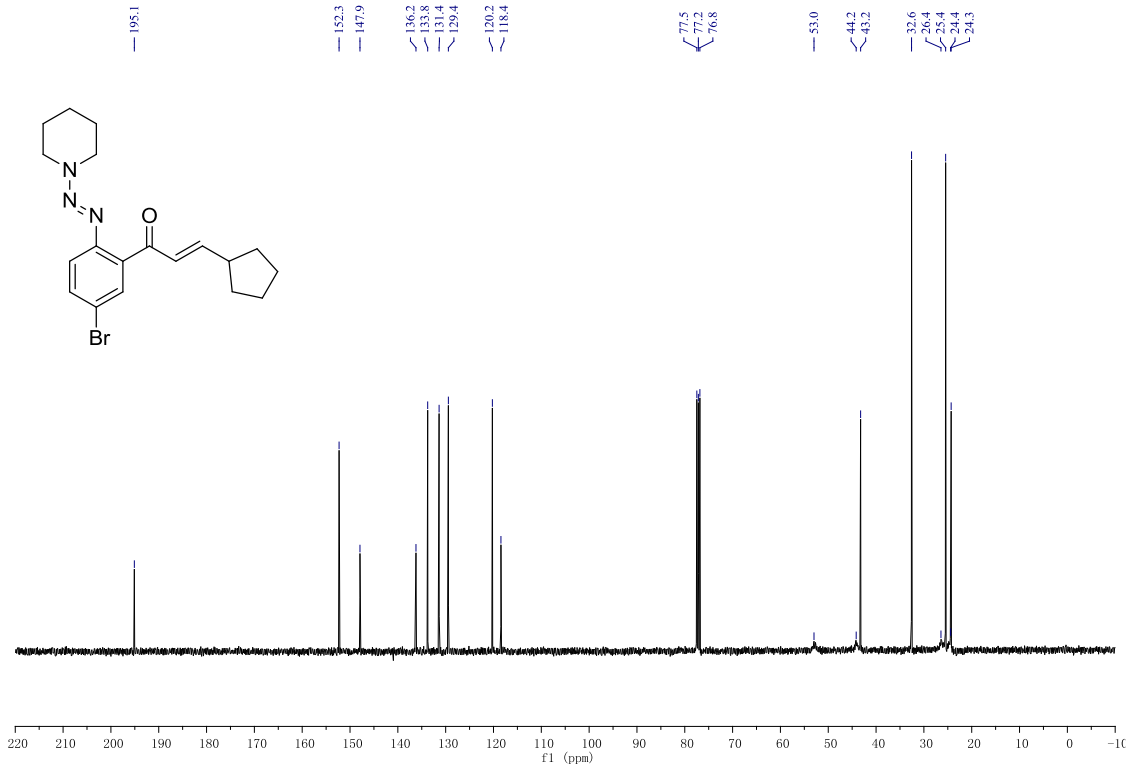
(*E*)-1-(3-Bromophenyl)-4,4-dimethylpent-2-en-1-one, 17a



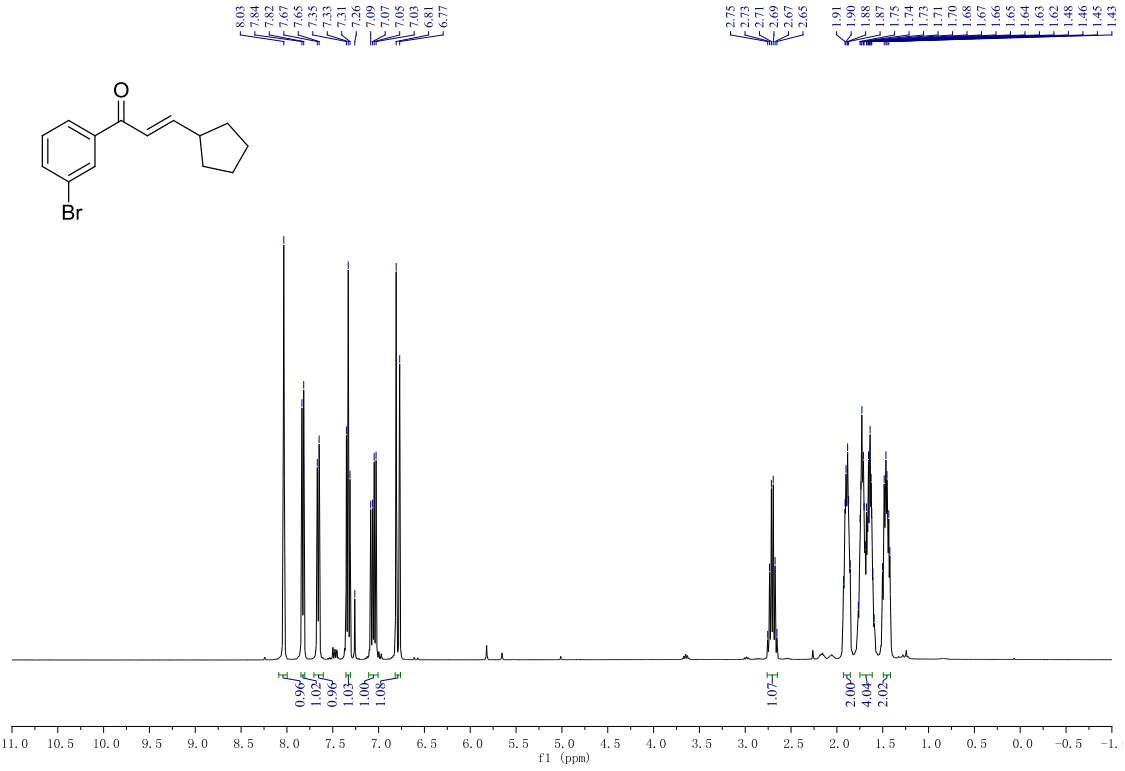


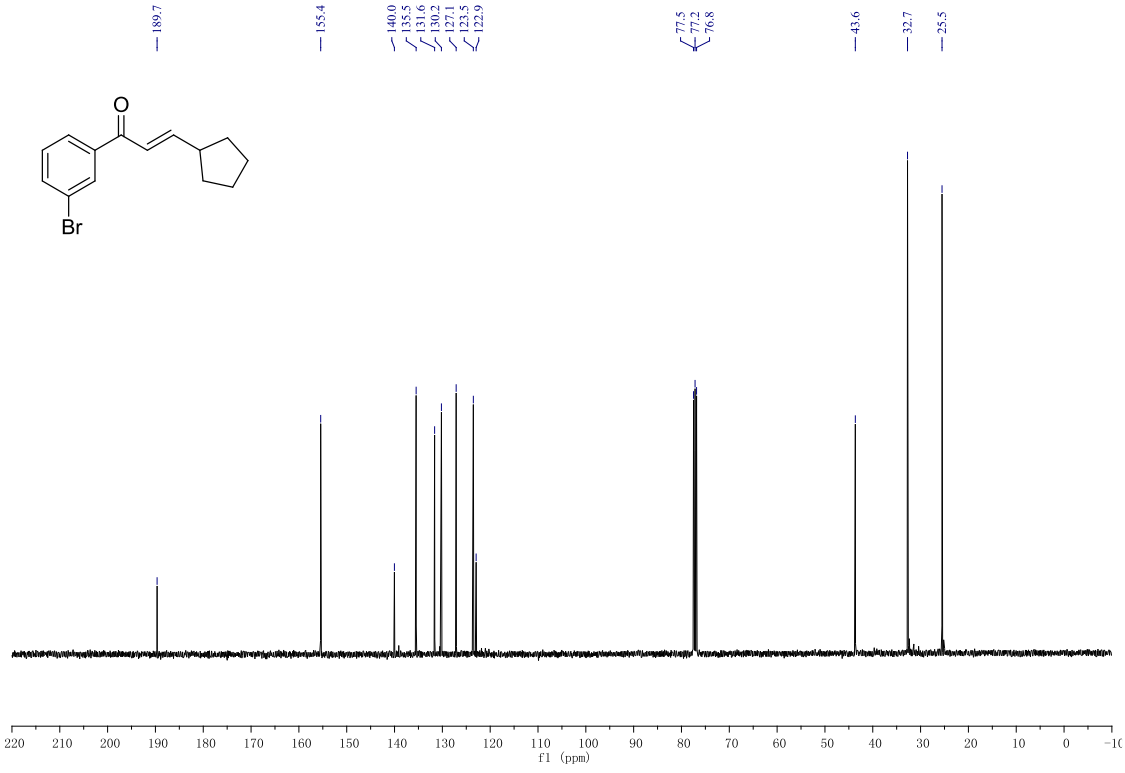
(*E*)-1-(5-Bromo-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-3-cyclopentylprop-2-en-1-one, 16b



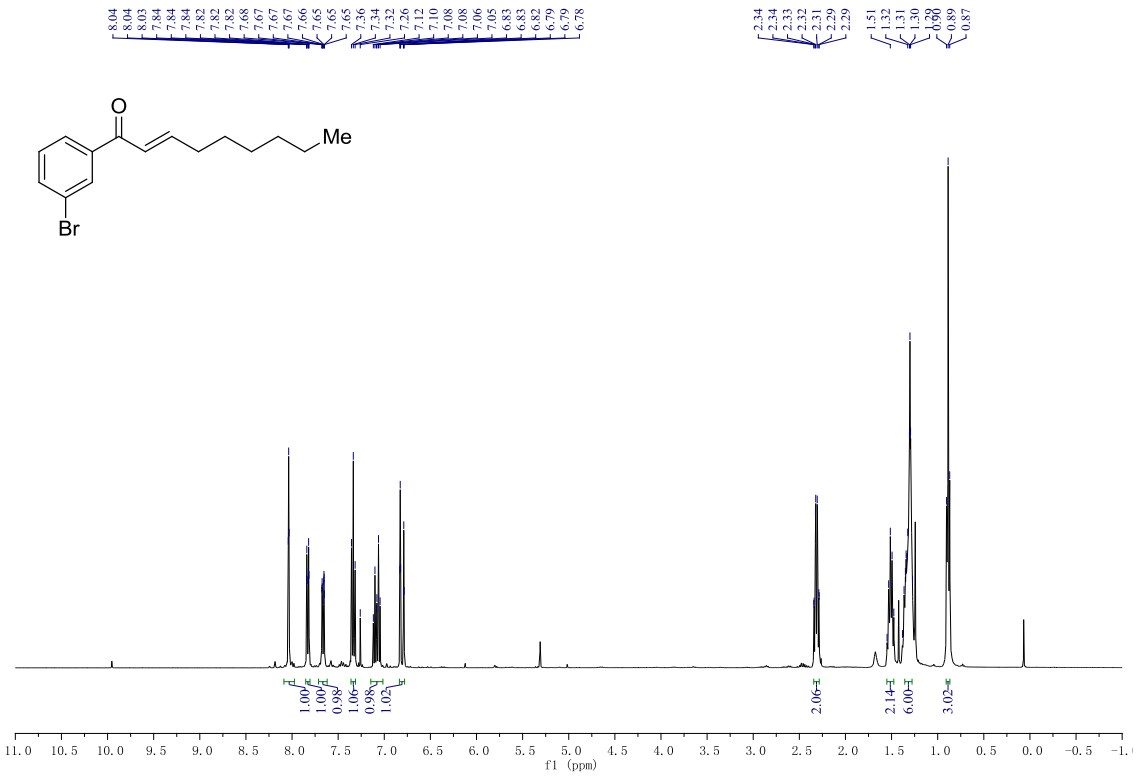


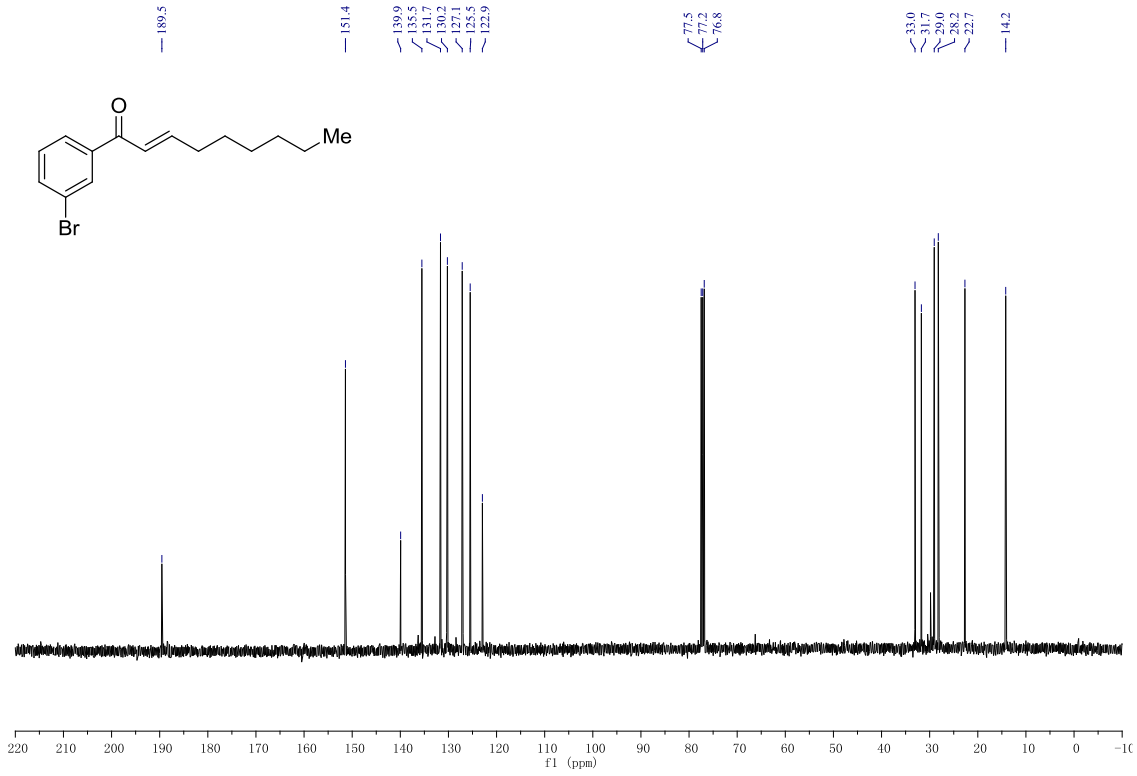
(*E*)-1-(3-Bromophenyl)-3-cyclopentylprop-2-en-1-one, 17b



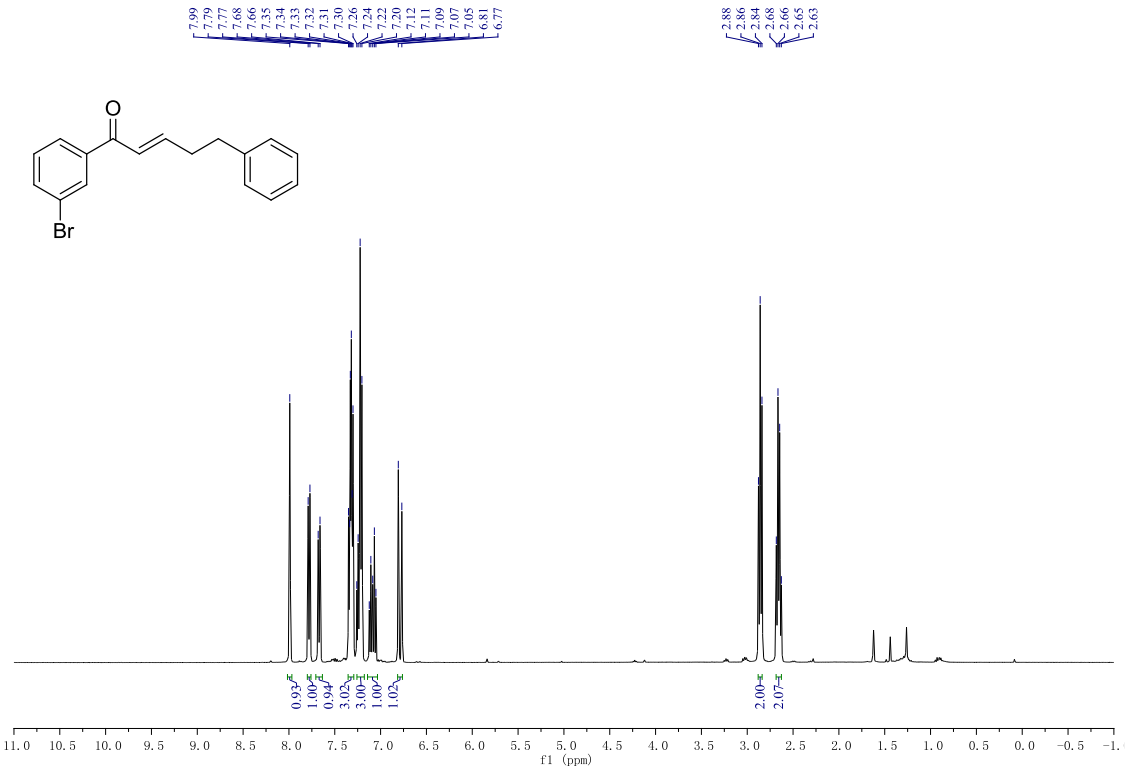


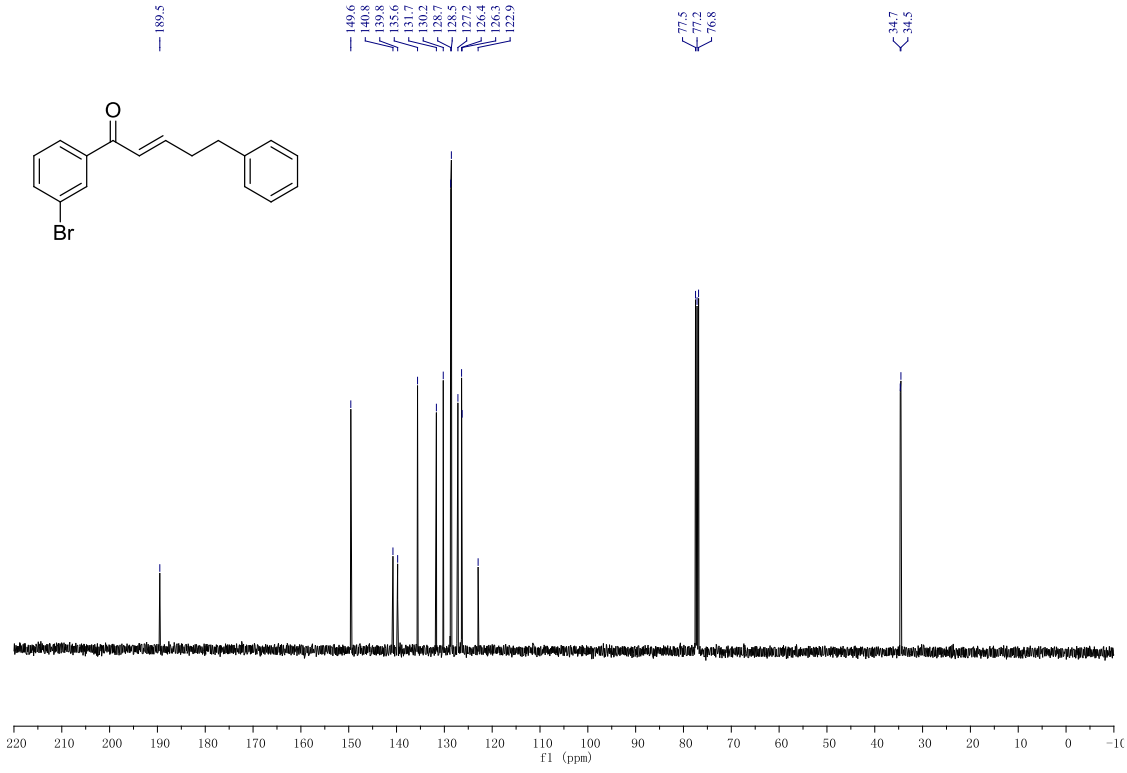
(*E*)-1-(3-Bromophenyl)non-2-en-1-one, 17c



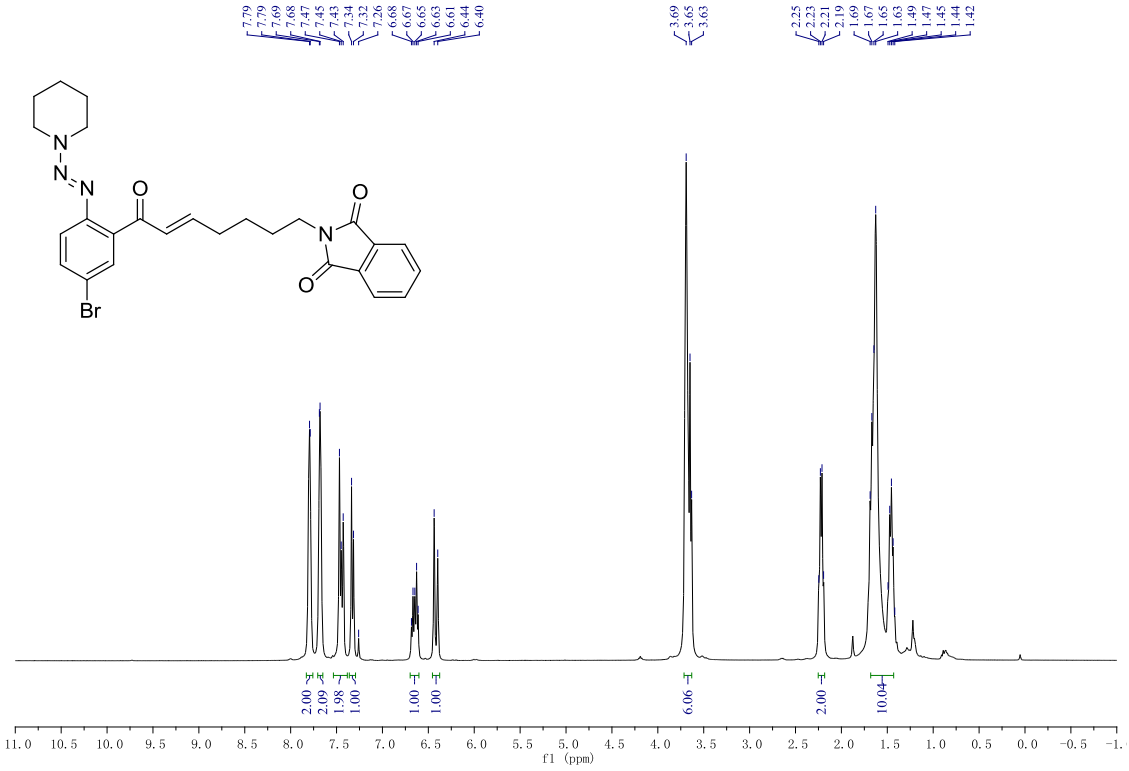


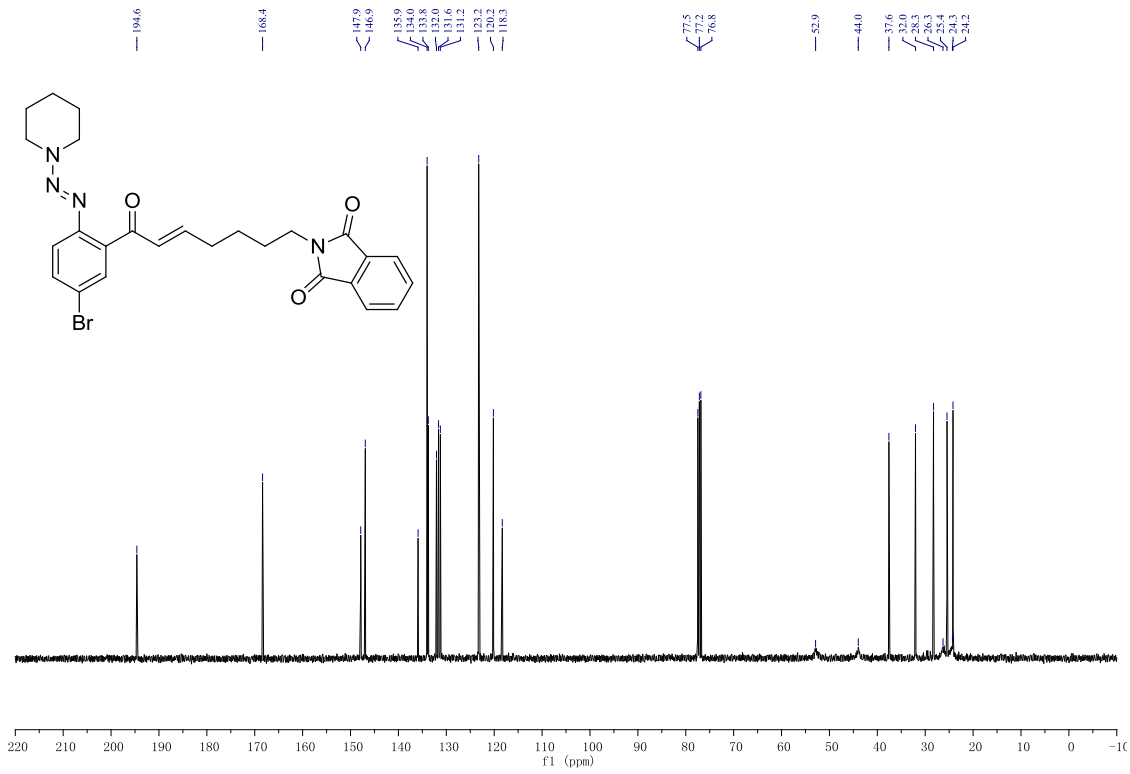
(*E*)-1-(3-Bromophenyl)-5-phenylpent-2-en-1-one, 17d



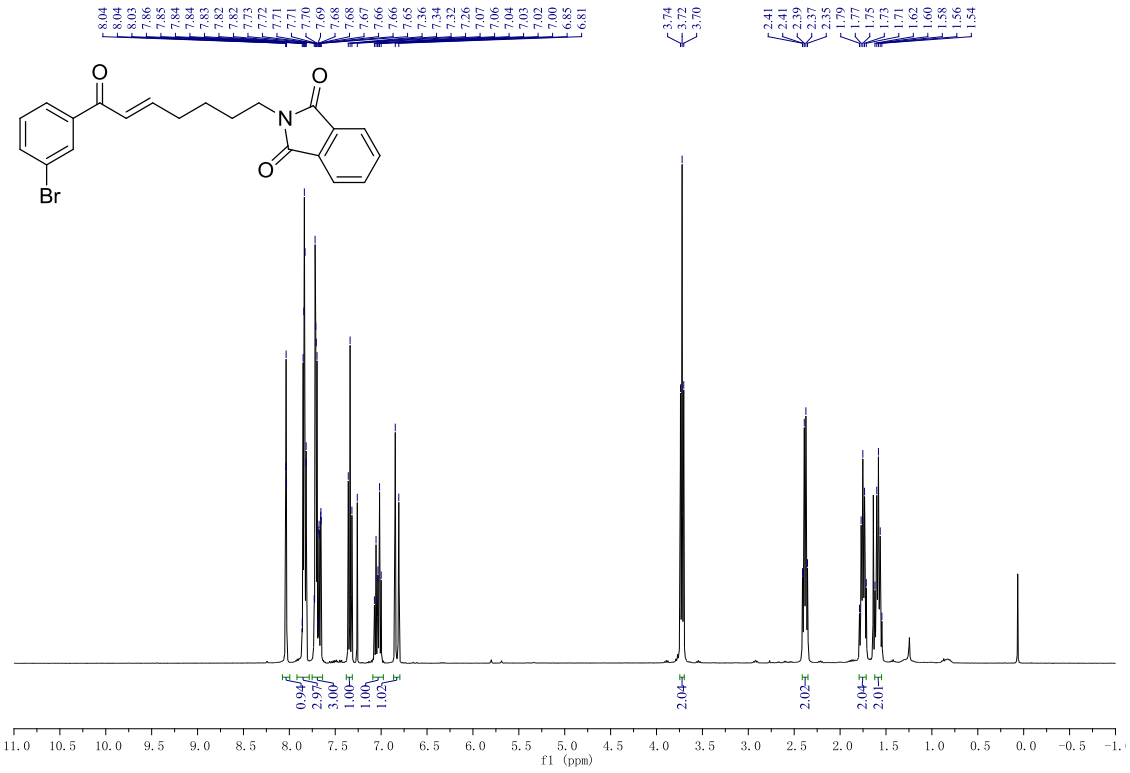


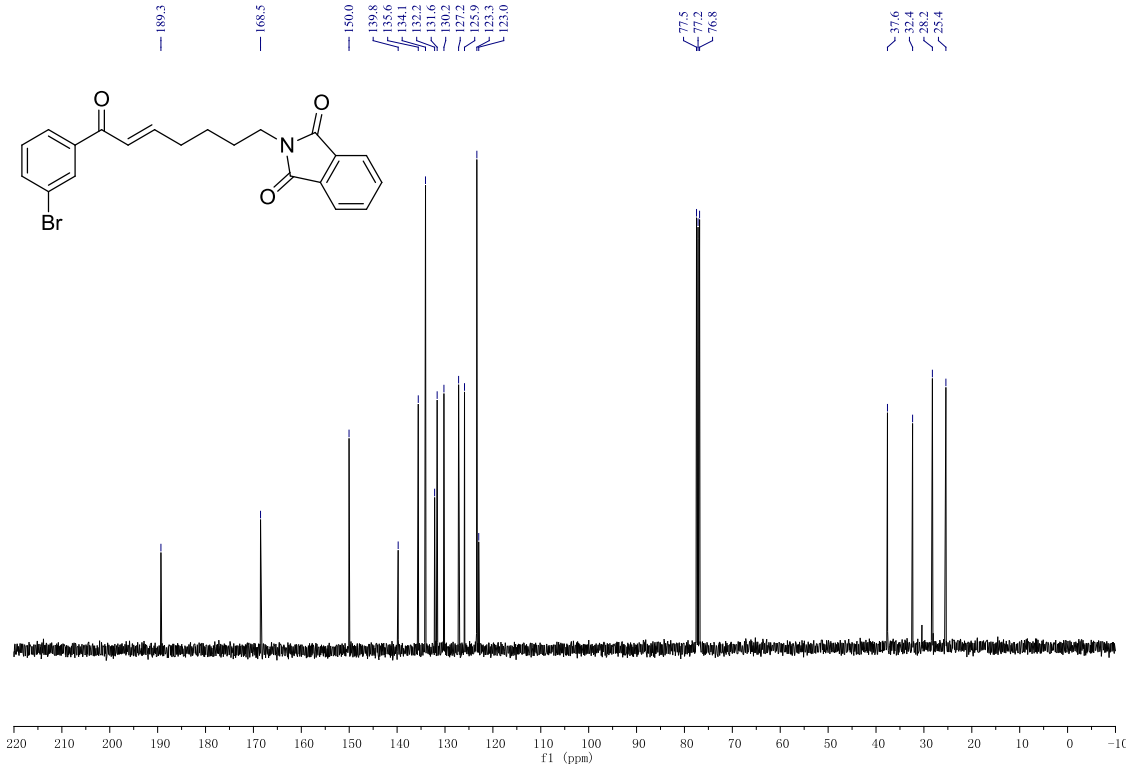
2-((*E*)-7-(5-Bromo-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-7-oxohept-5-en-1-yl) isoindoline-1,3-dione, 16e



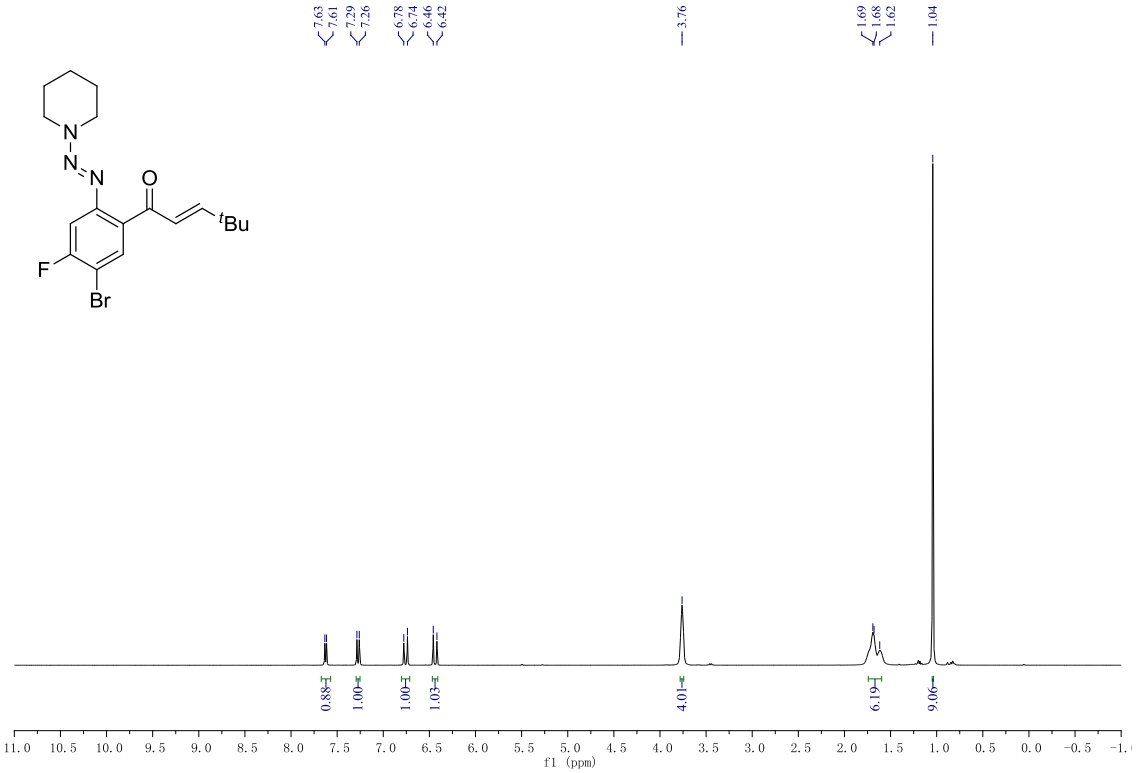


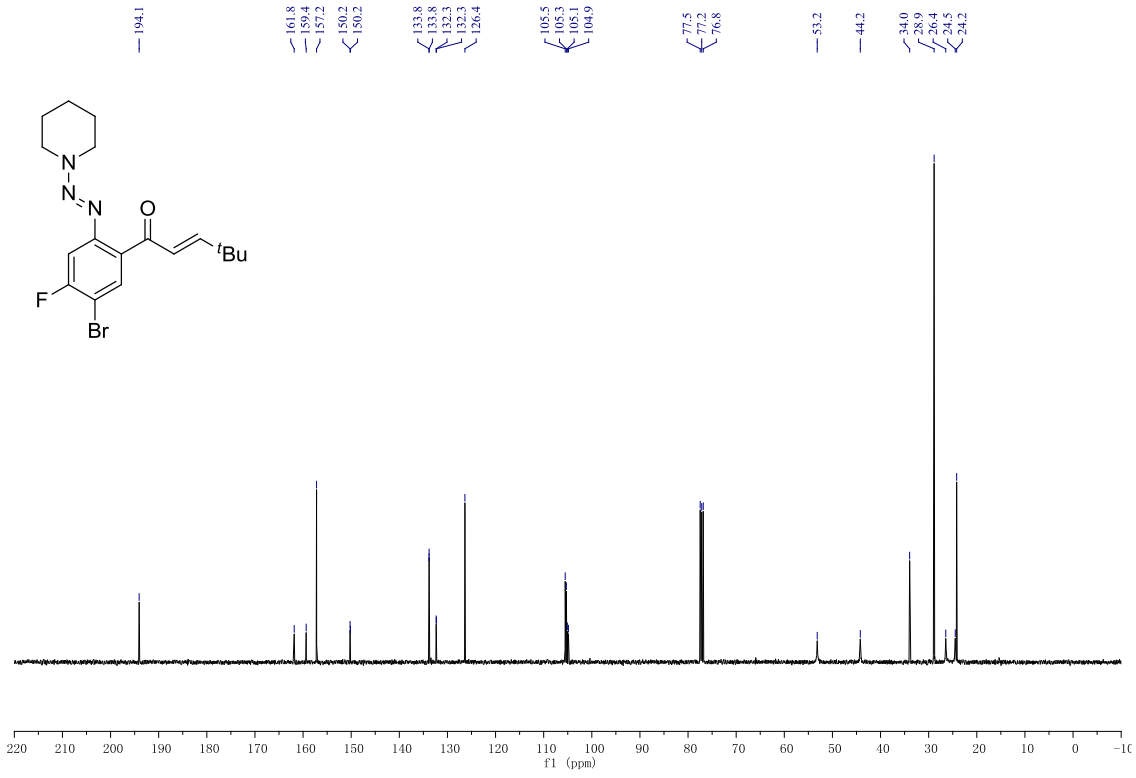
(*E*)-2-(7-(3-Bromophenyl)-7-oxohept-5-en-1-yl)isoindoline-1,3-dione, 17e



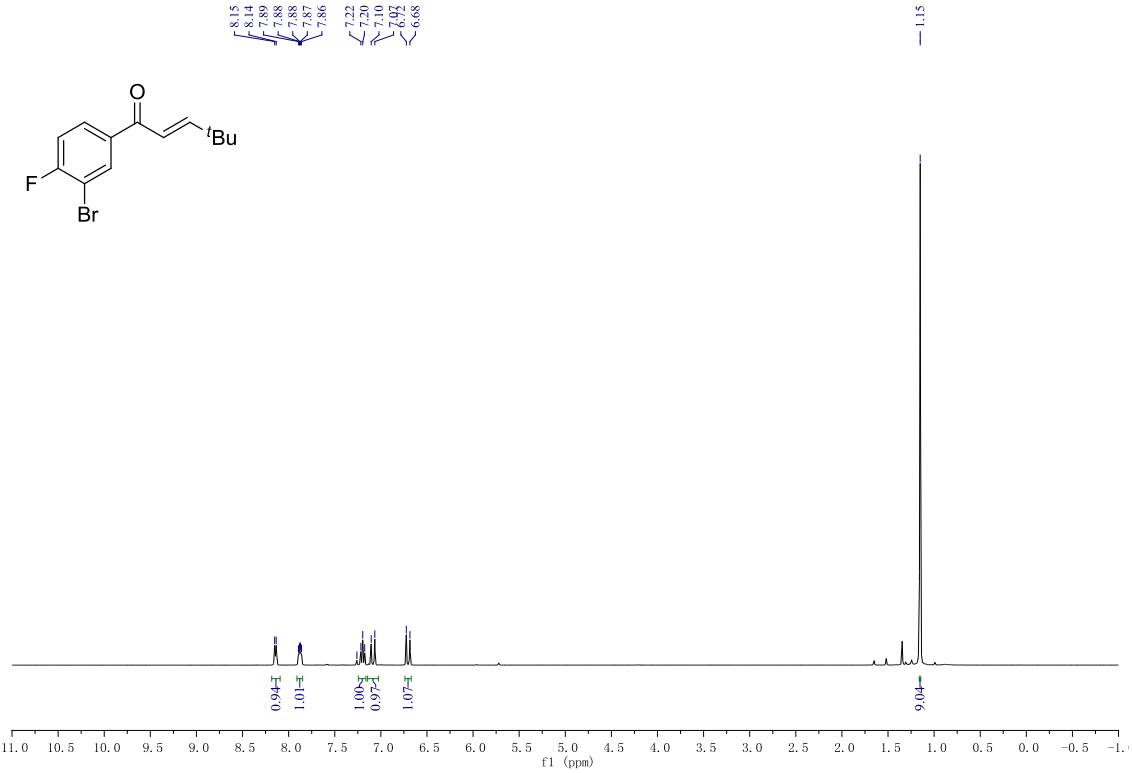


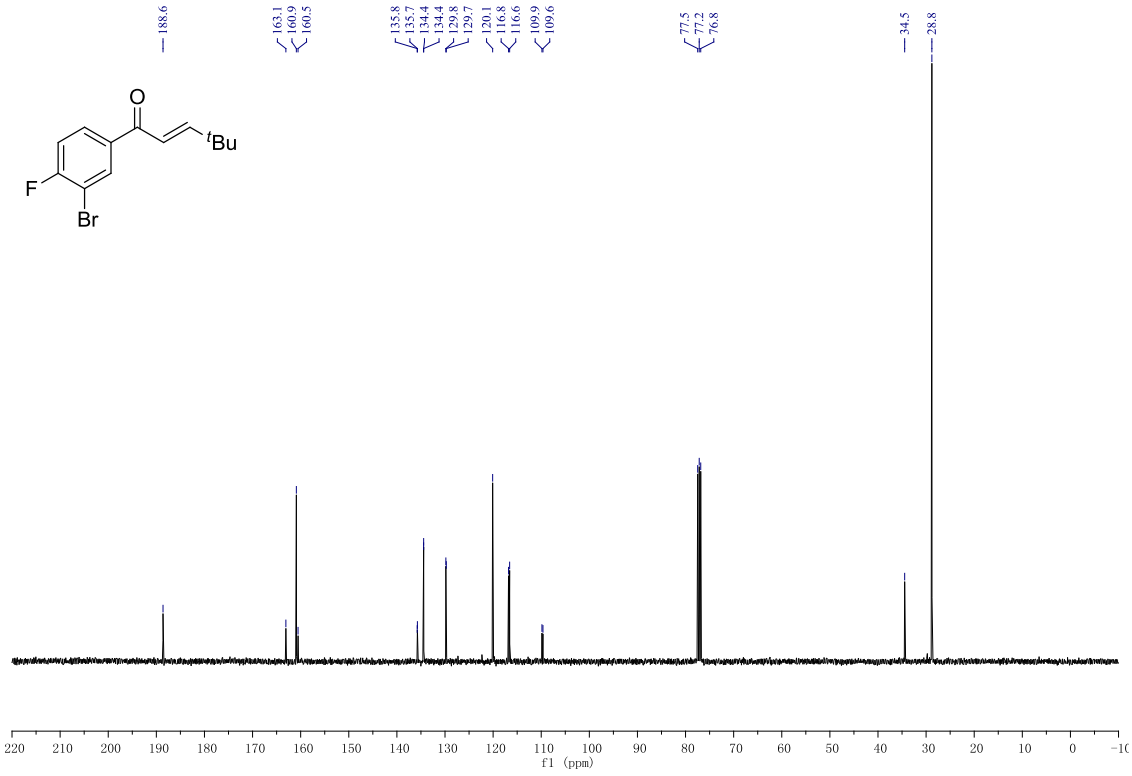
(*E*)-1-(5-Bromo-4-fluoro-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-4,4-dimethylpent-2-en-1-one, 16f



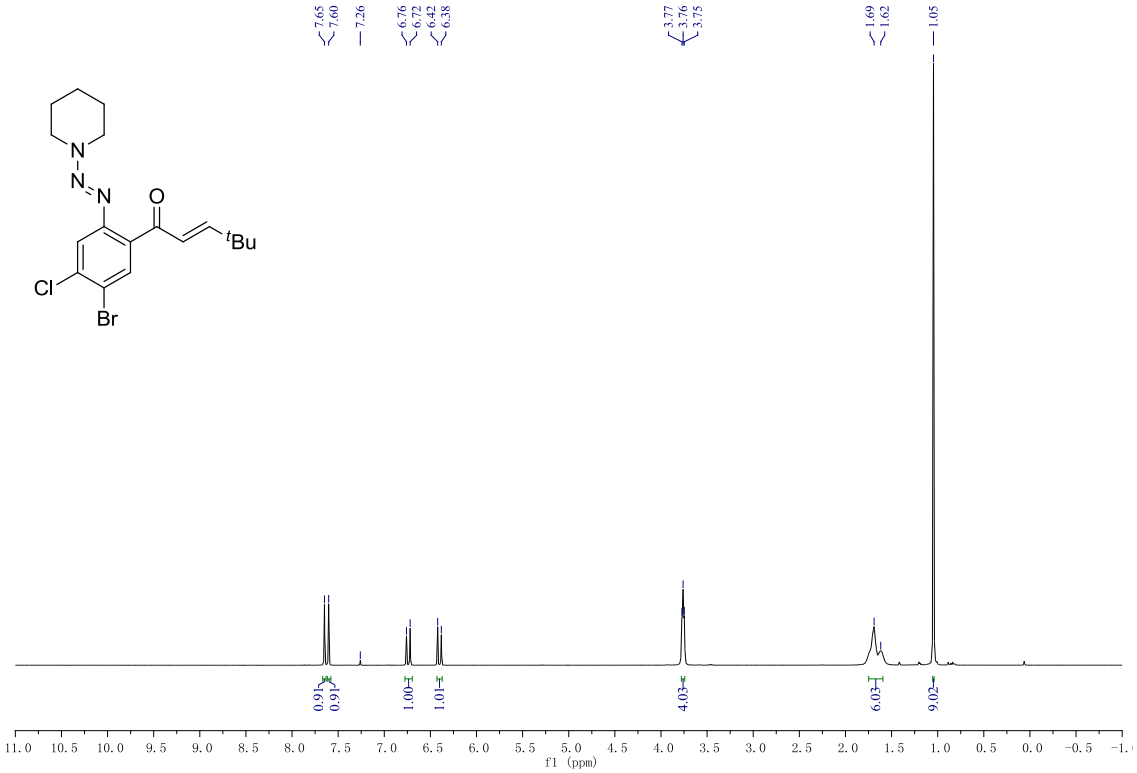


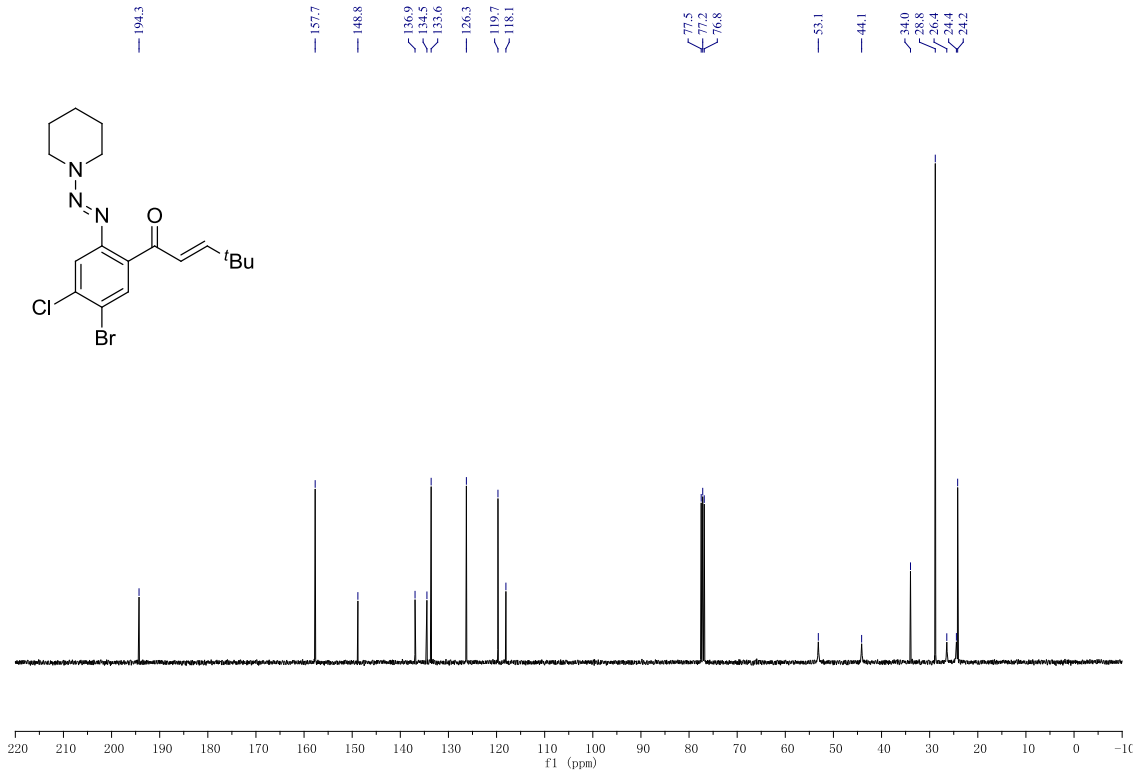
(*E*)-1-(3-Bromo-4-fluorophenyl)-4,4-dimethylpent-2-en-1-one, 17f



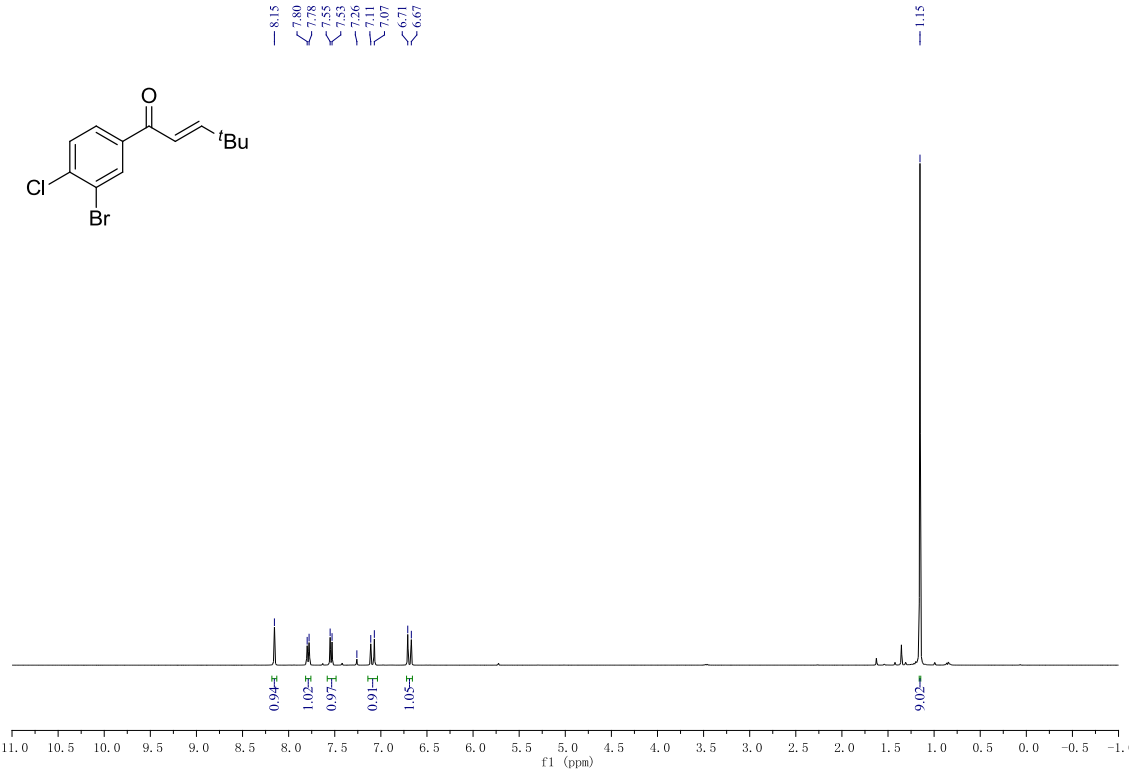


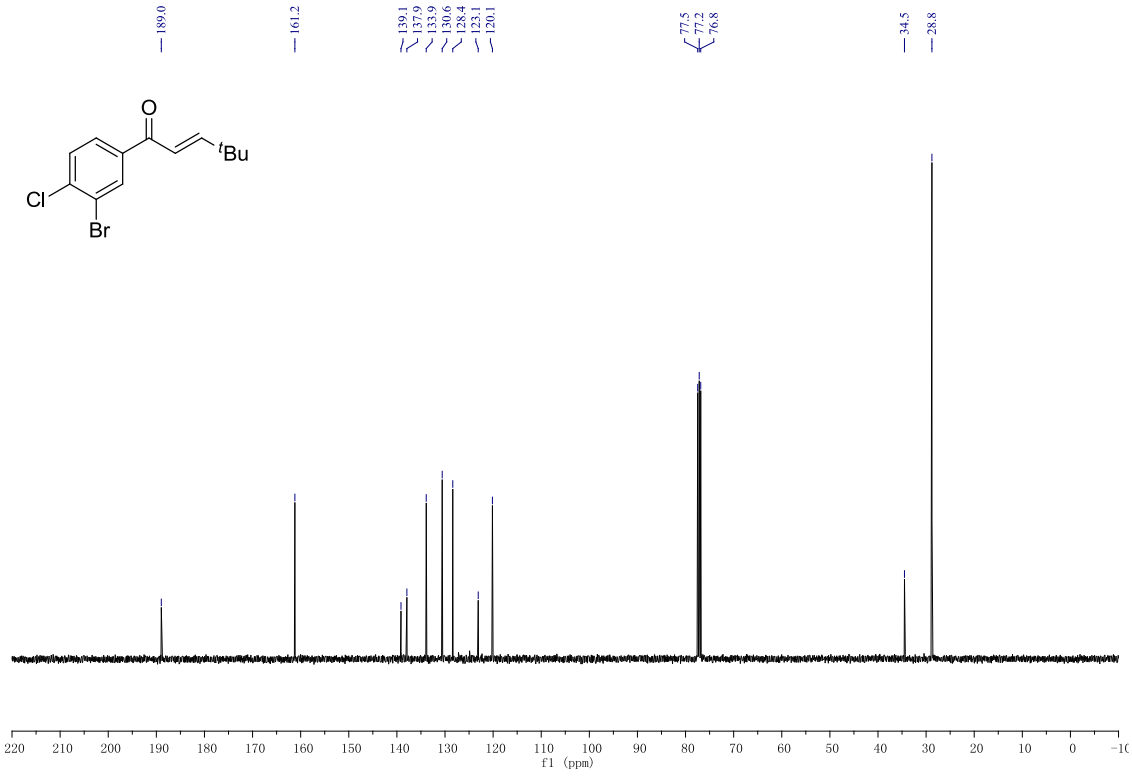
(*E*)-1-(5-Bromo-4-chloro-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-4,4-dimethylpent-2-en-1-one, 16g



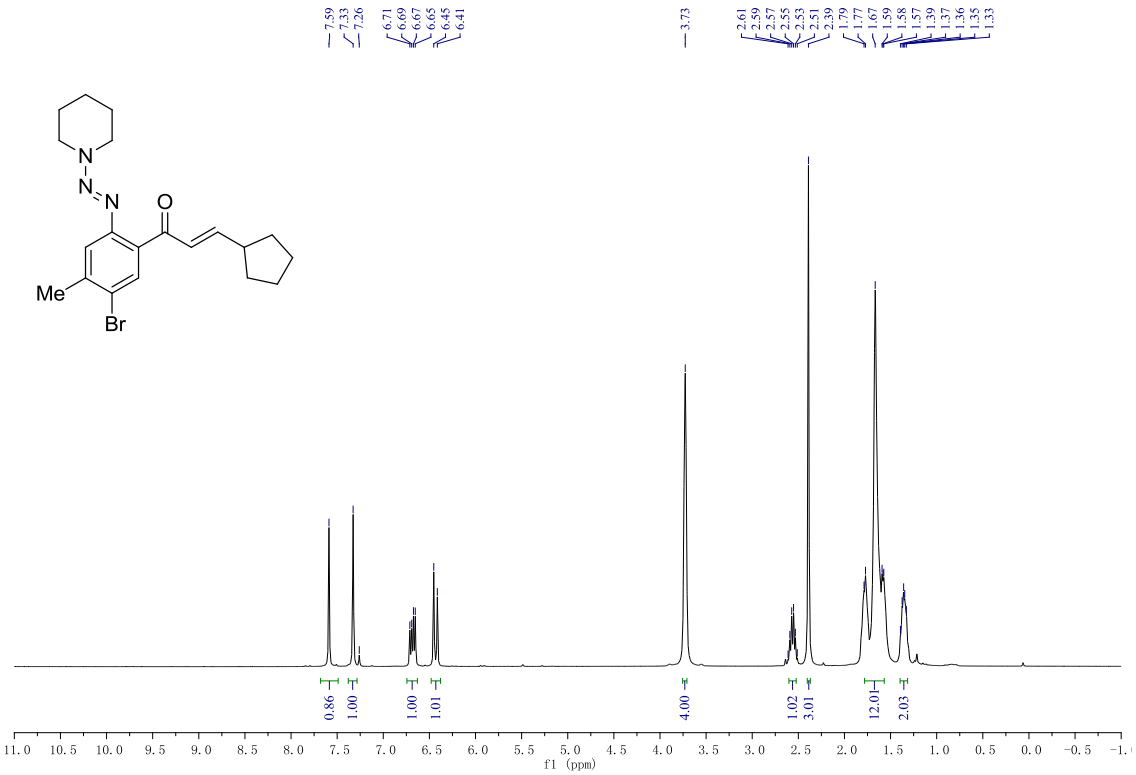


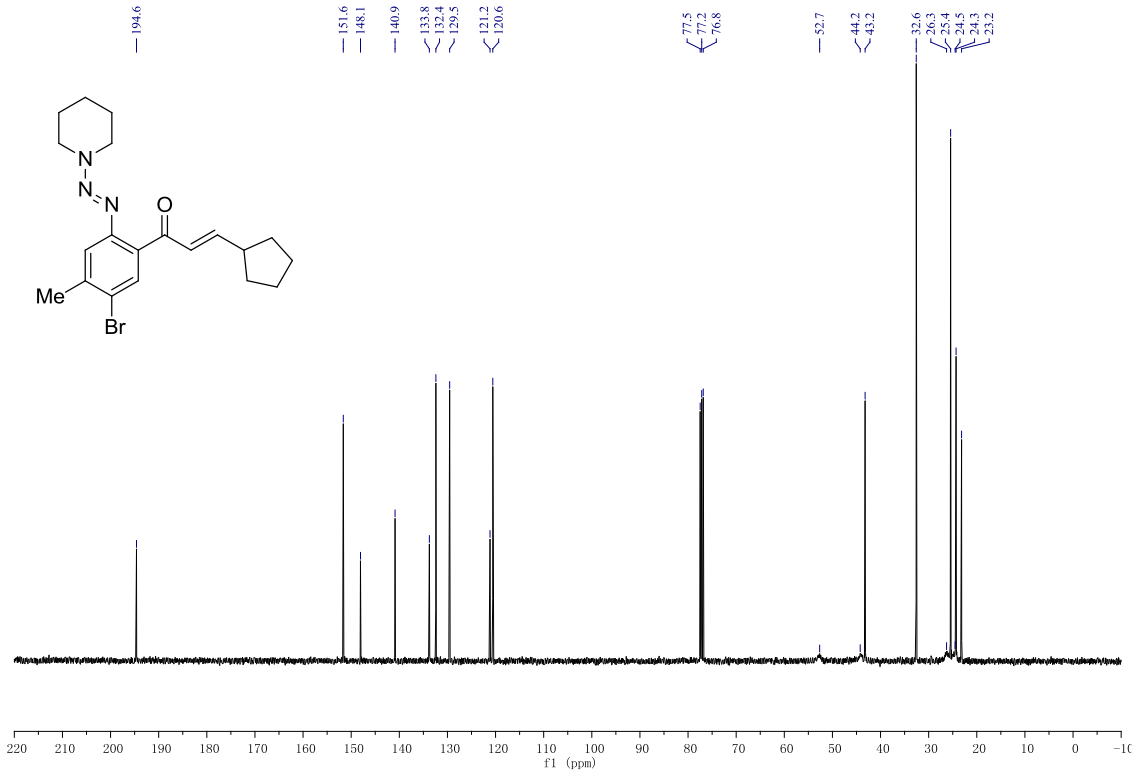
(*E*)-1-(3-Bromo-4-chlorophenyl)-4,4-dimethylpent-2-en-1-one, 17g



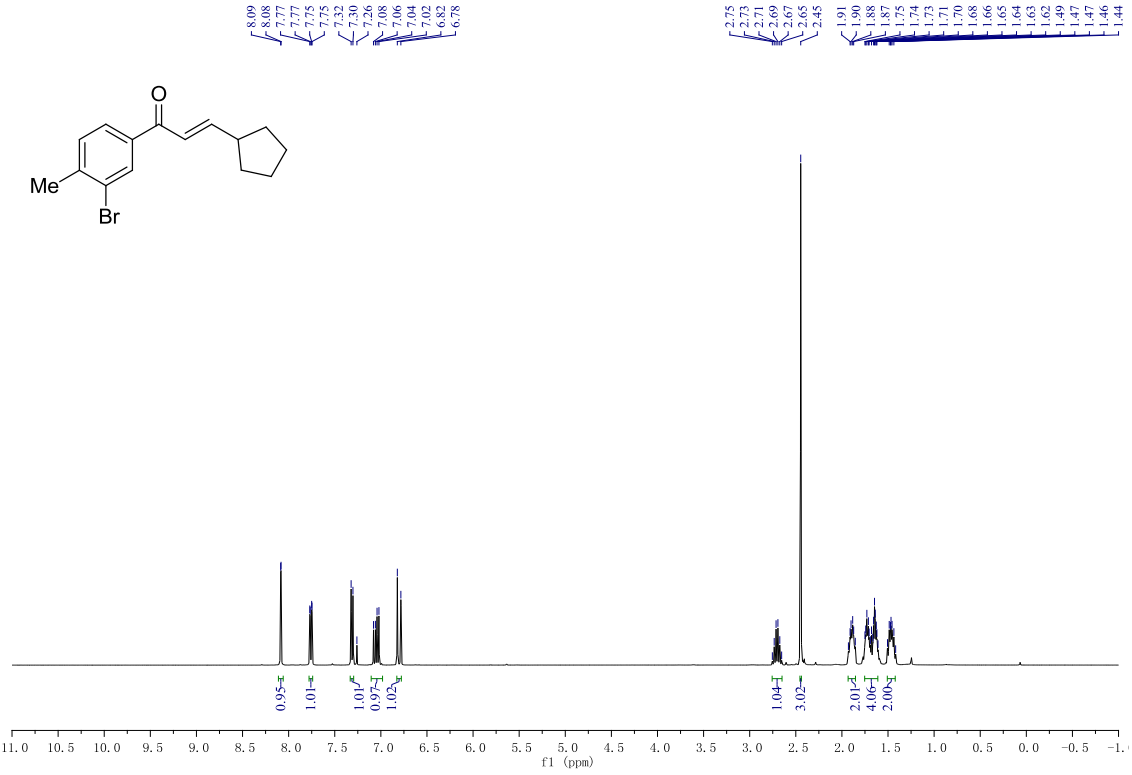


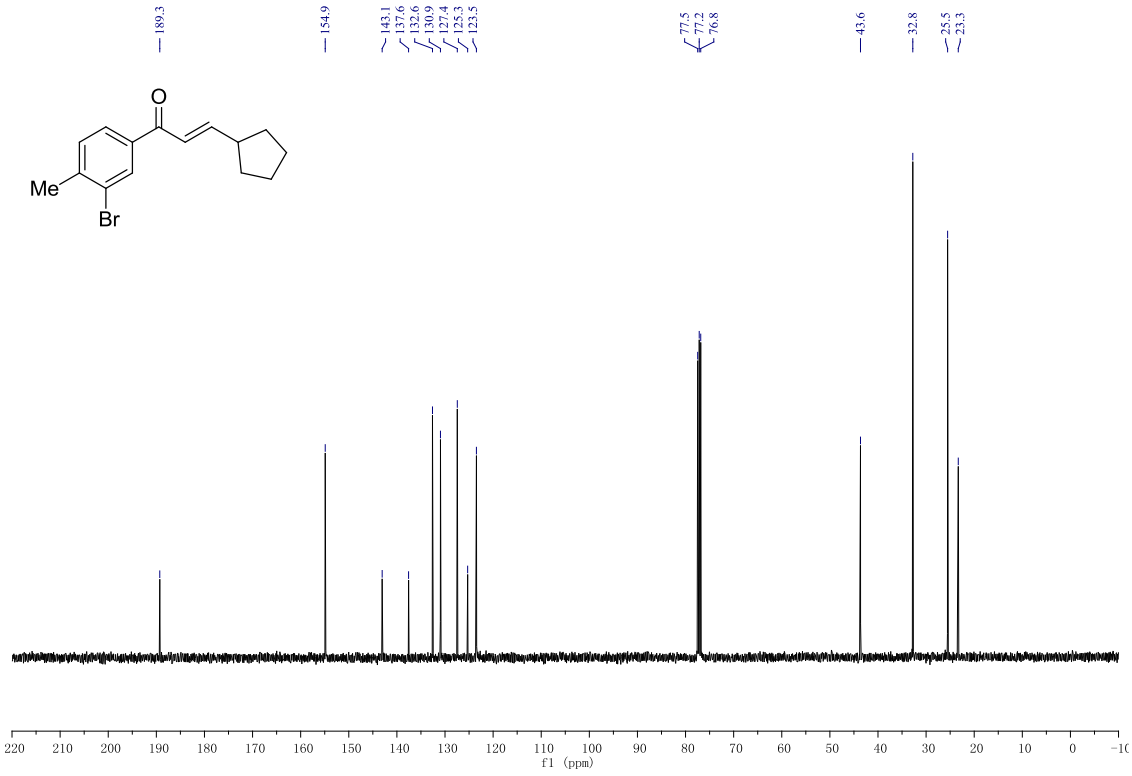
(*E*)-1-(5-Bromo-4-methyl-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-3-cyclopentyl prop-2-en-1-one, 16h



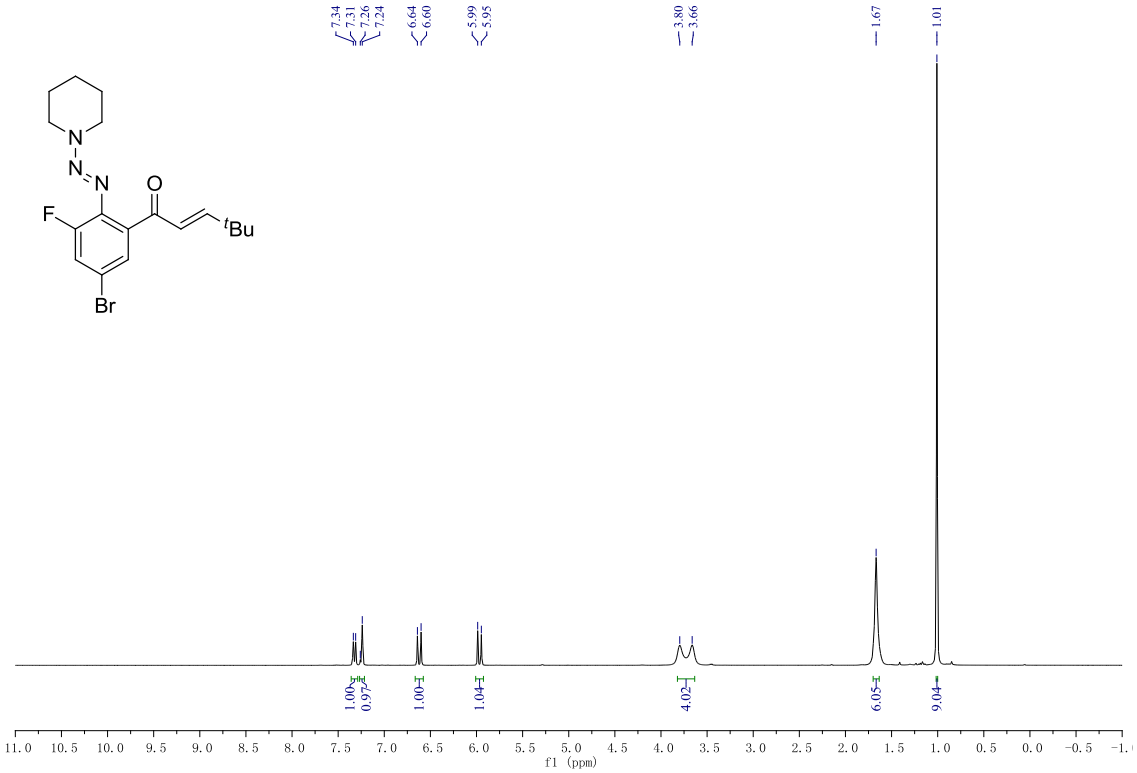


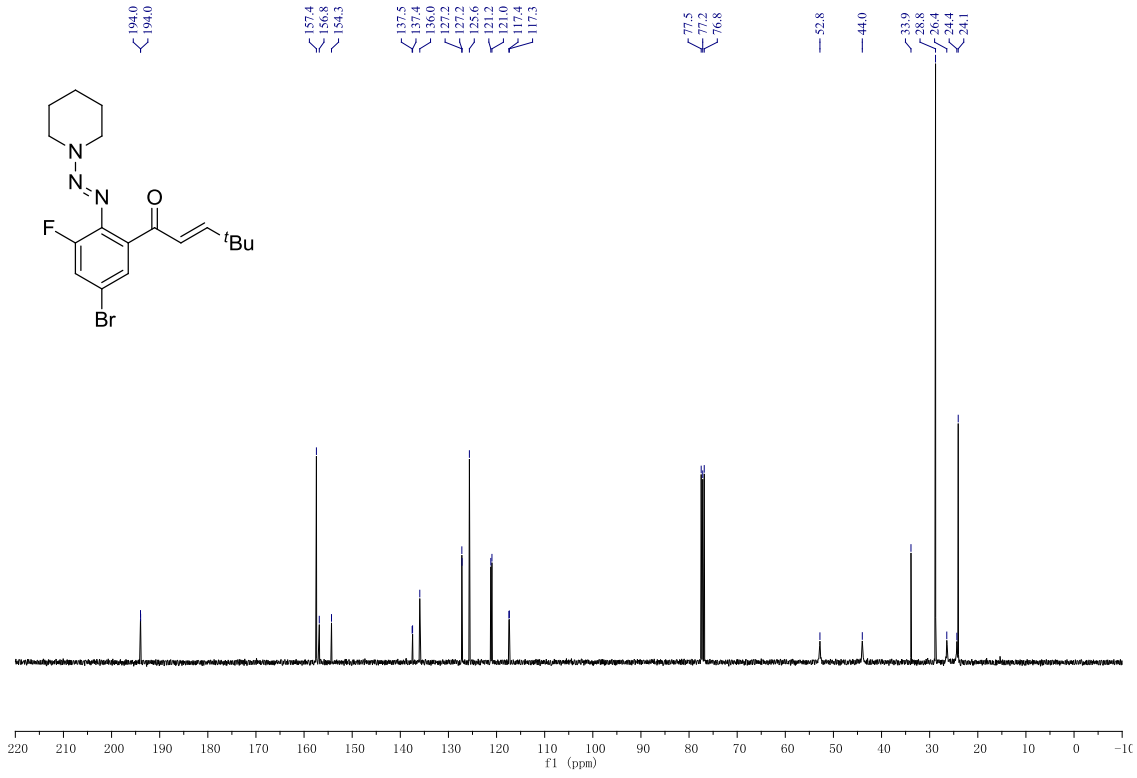
(*E*)-1-(3-Bromo-4-methylphenyl)-3-cyclopentylprop-2-en-1-one, 17h



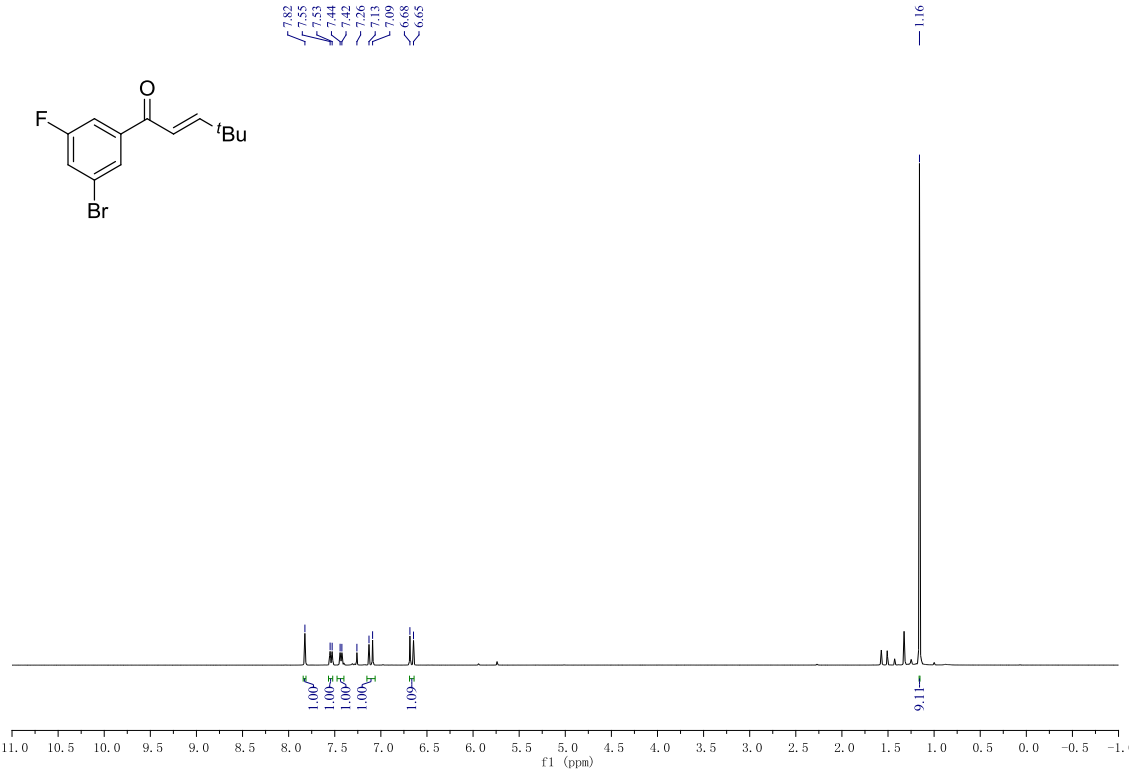


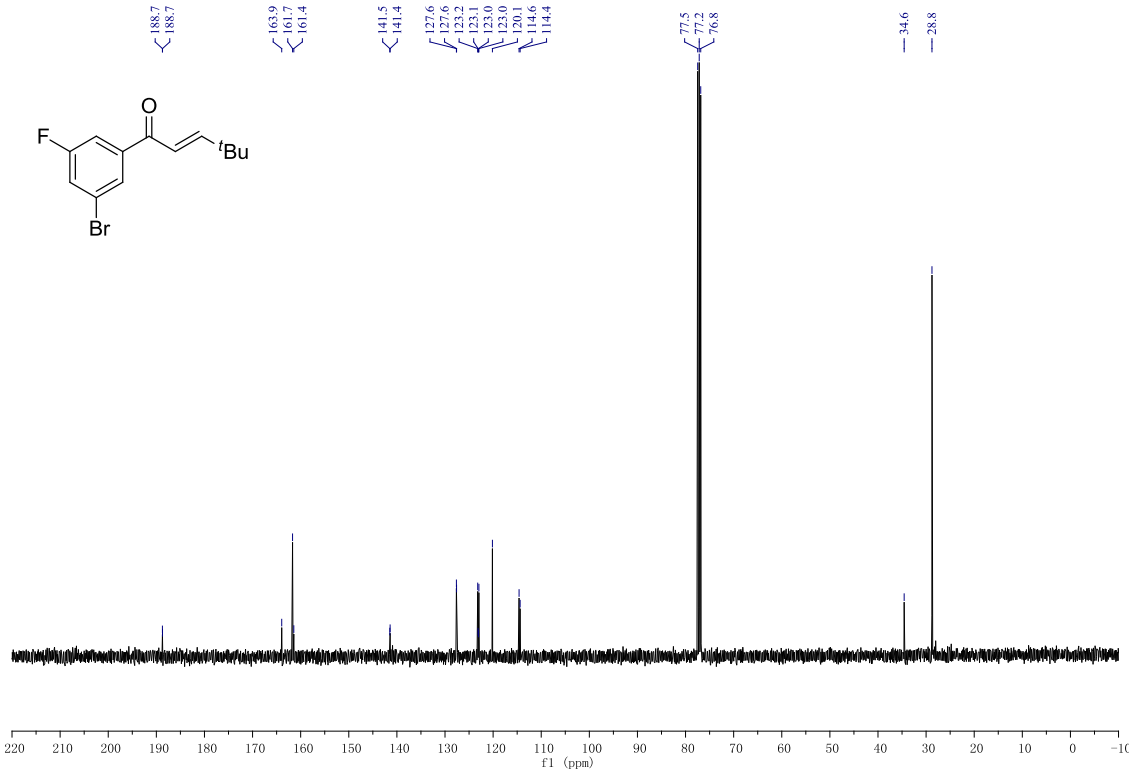
(*E*)-1-(5-Bromo-3-fluoro-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-4,4-dimethylpent-2-en-1-one, 16i



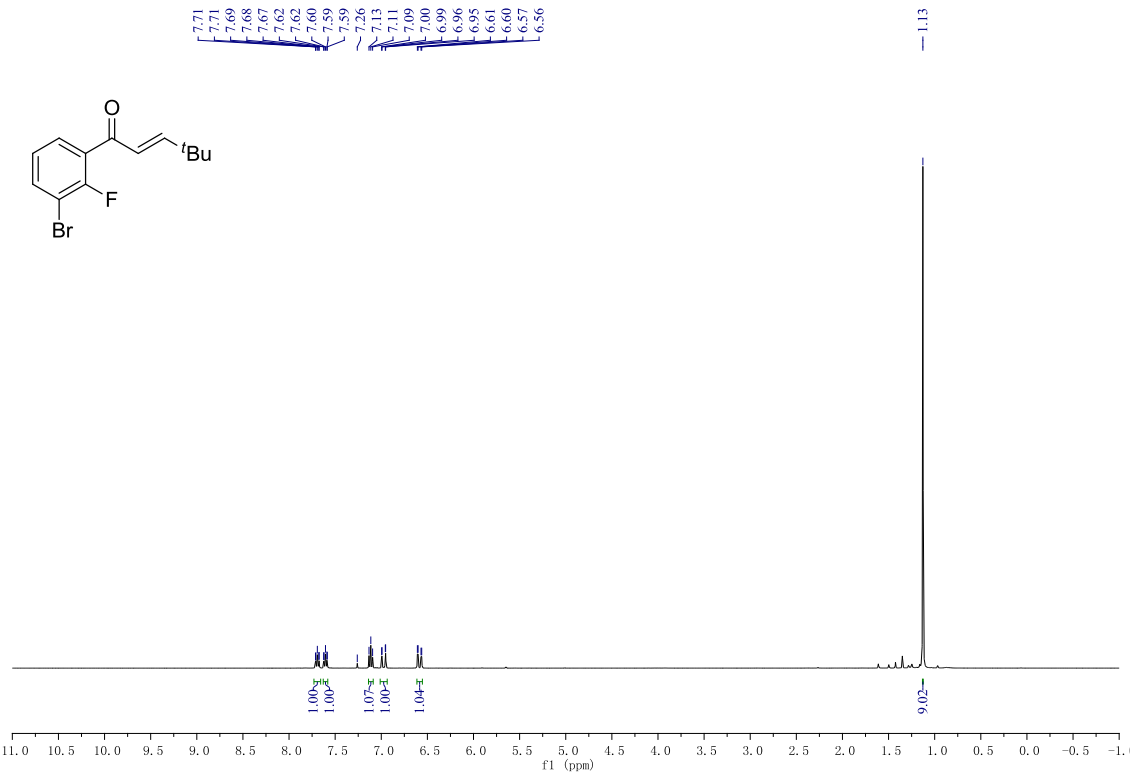


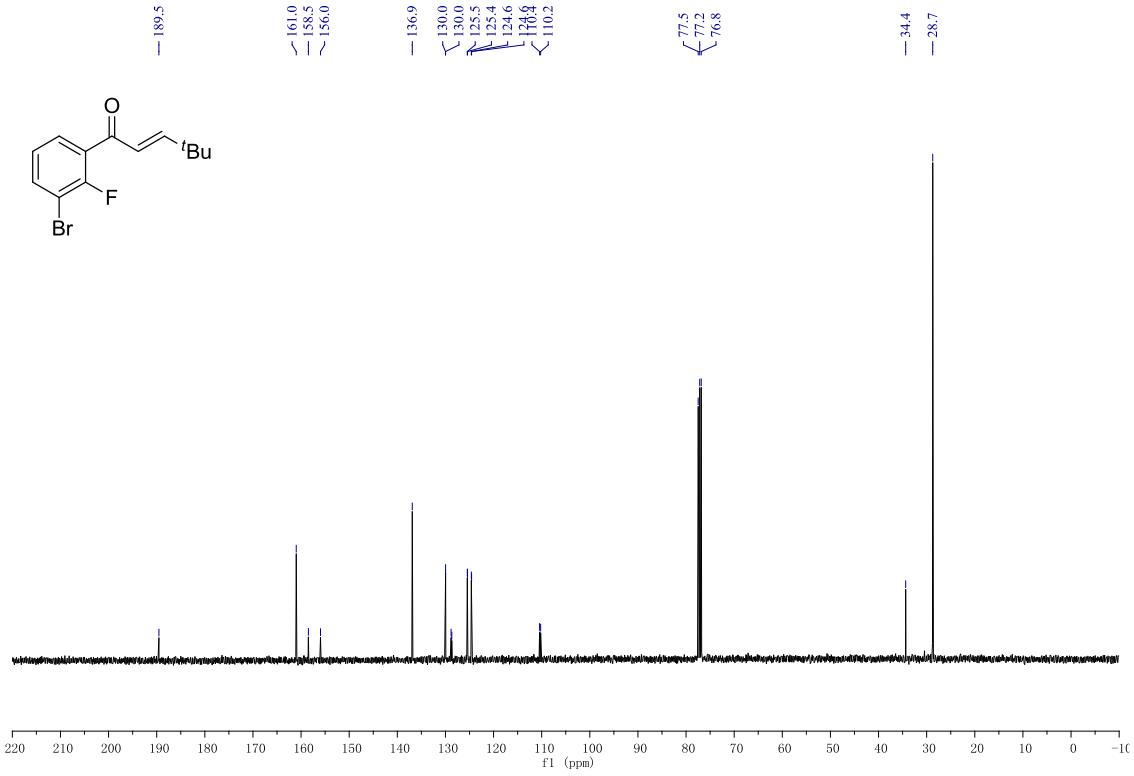
(*E*)-1-(3-Bromo-5-fluorophenyl)-4,4-dimethylpent-2-en-1-one, 17i



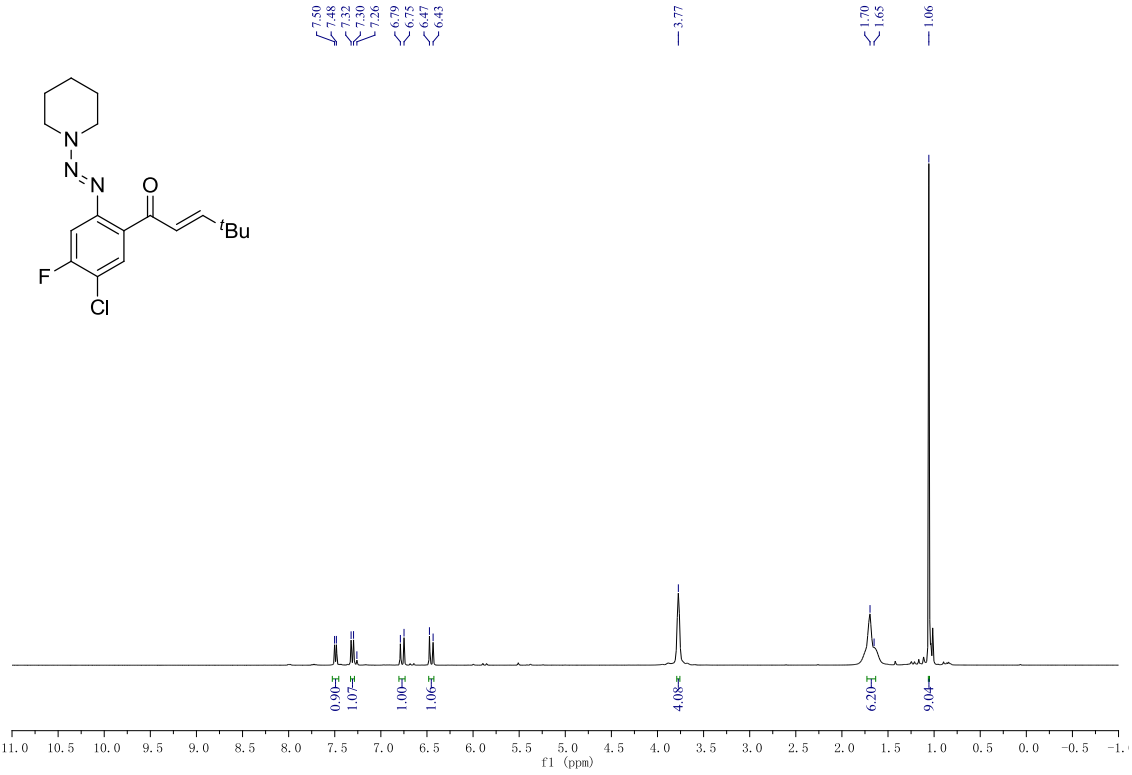


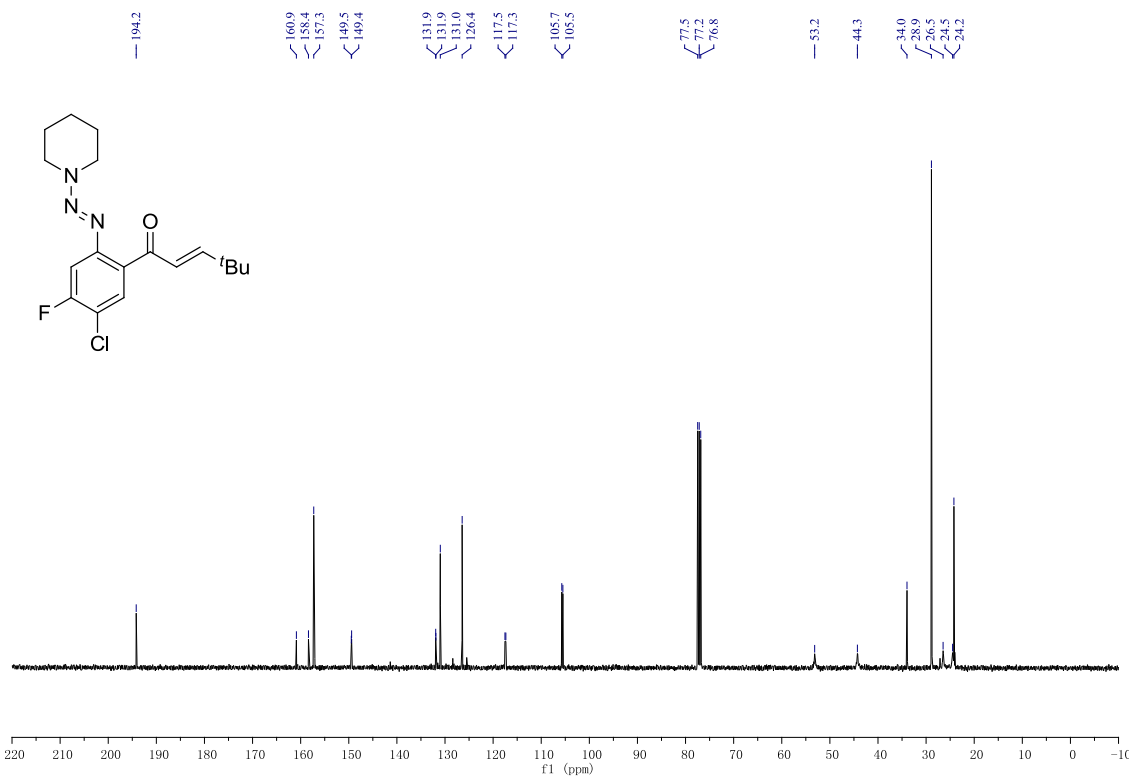
(*E*)-1-(3-Bromo-2-fluorophenyl)-4,4-dimethylpent-2-en-1-one, 17j



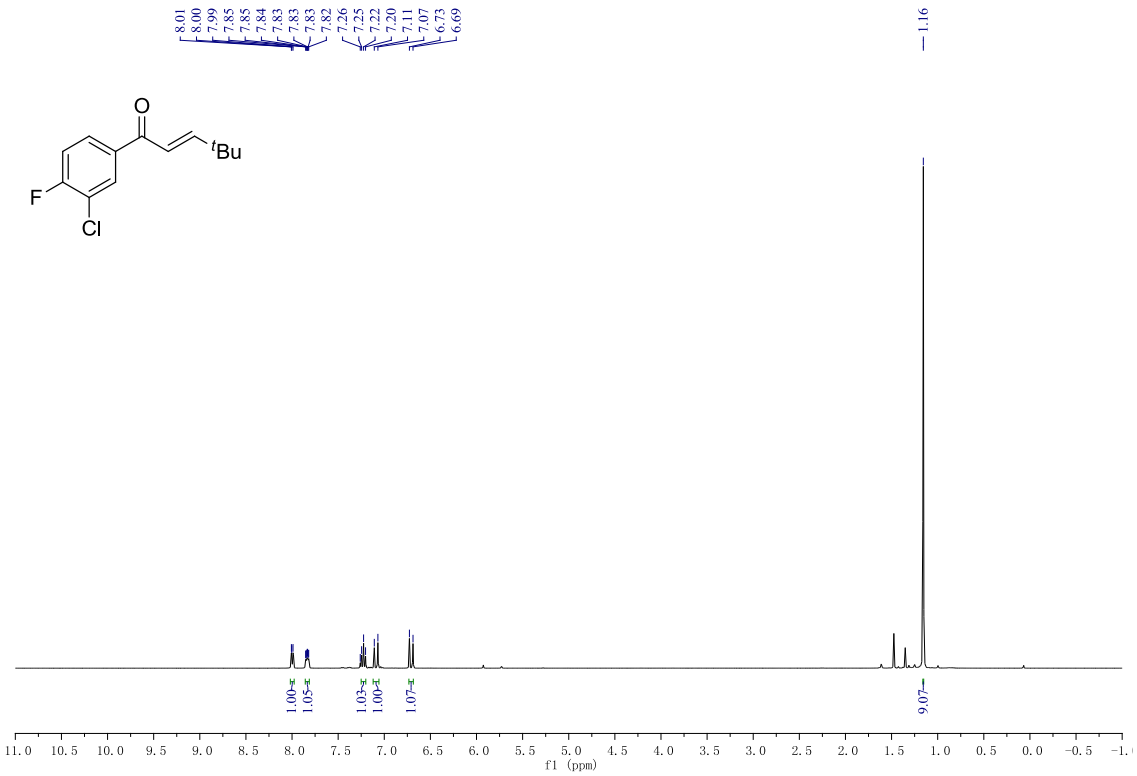


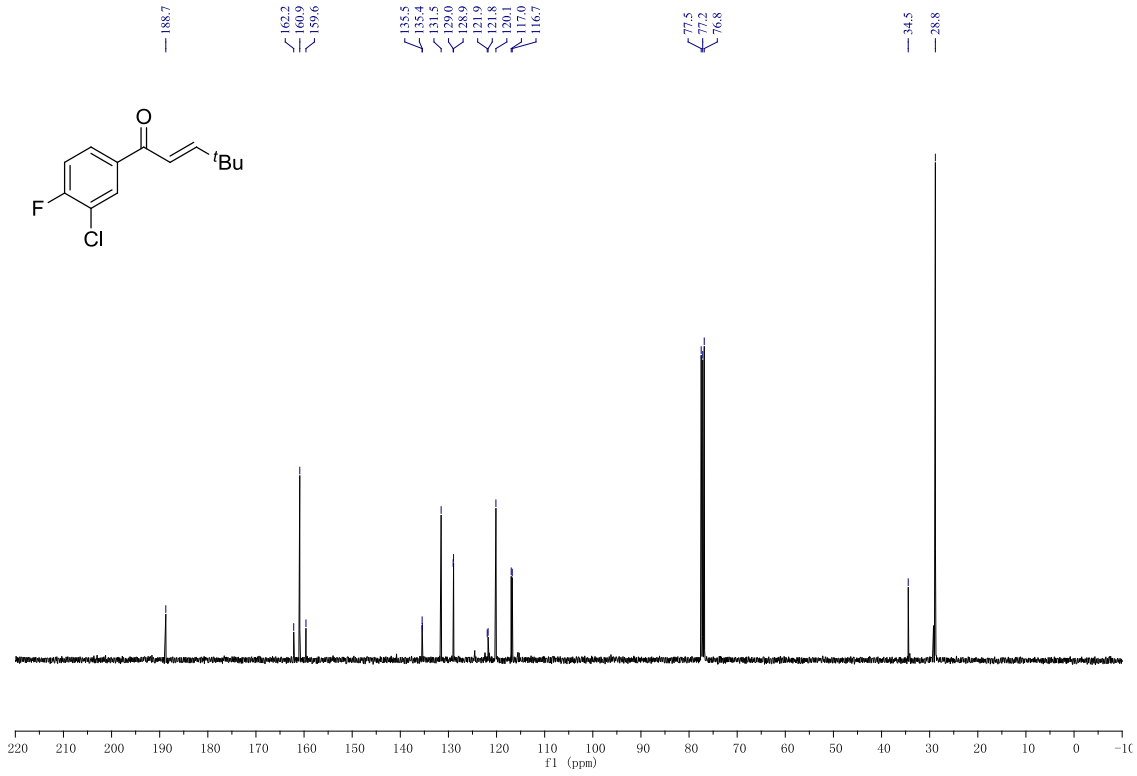
(*E*)-1-(5-Chloro-4-fluoro-2-((*E*)-piperidin-1-yldiazenyl)phenyl)-4,4-dimethylpent-2-en-1-one, 18



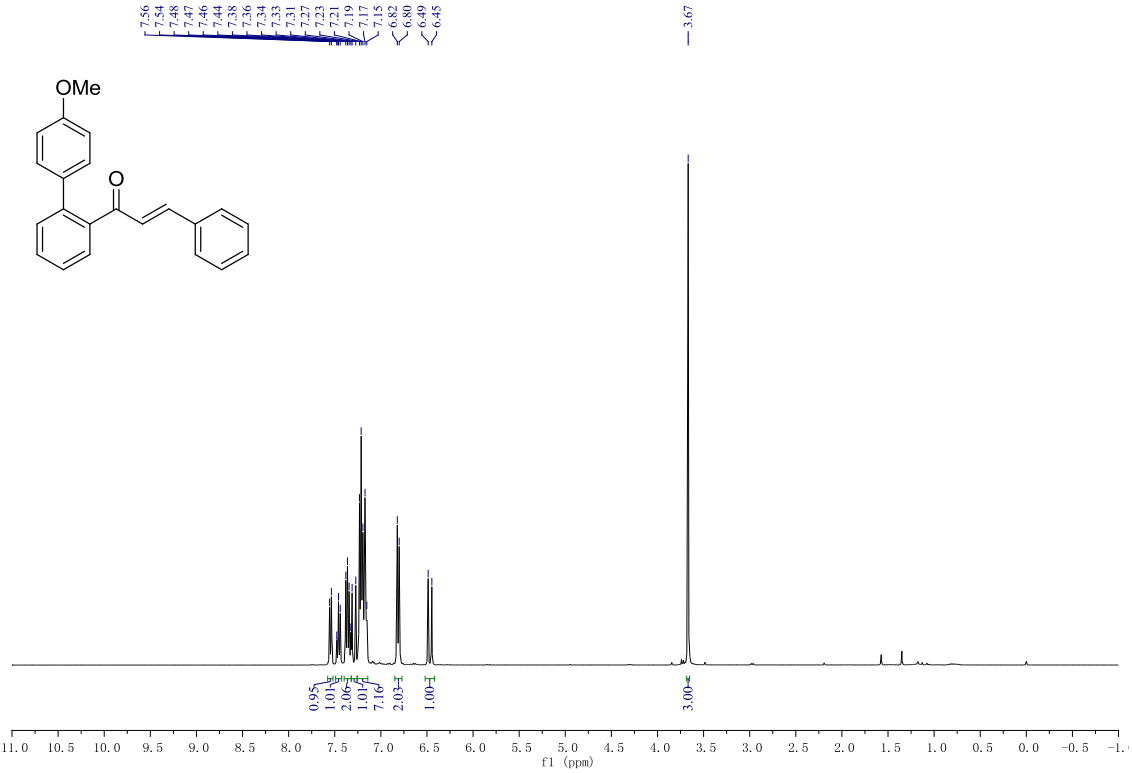


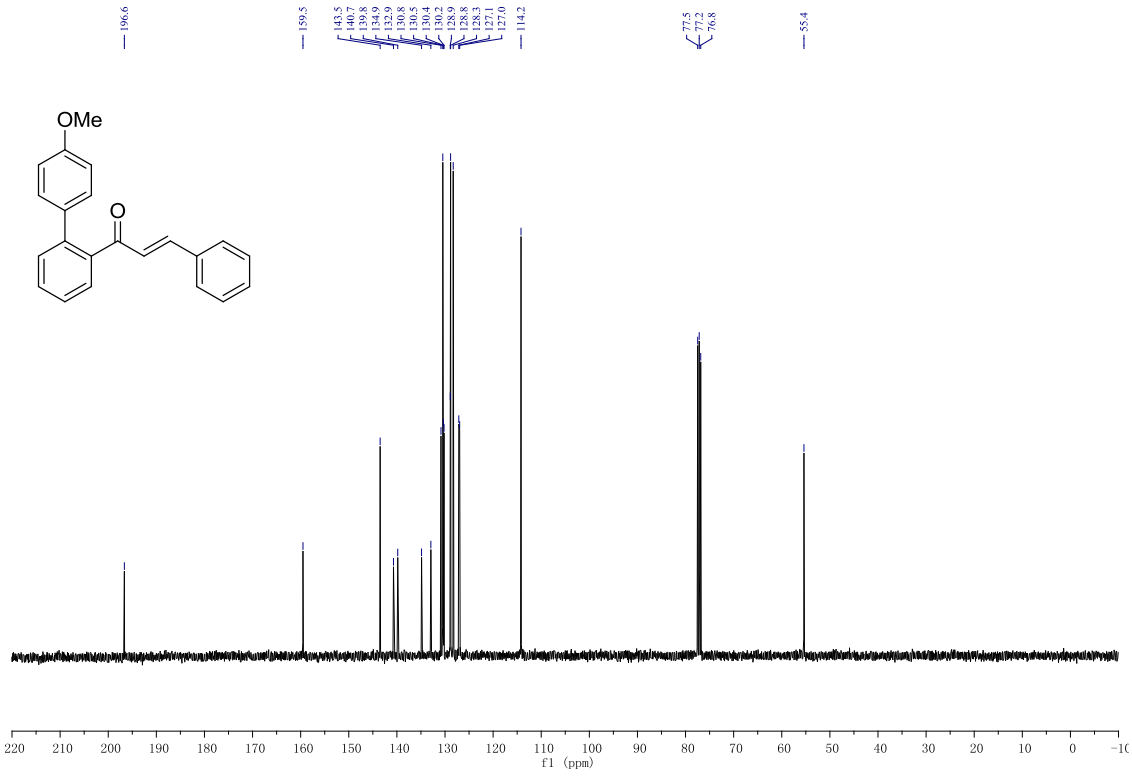
(*E*)-1-(3-Chloro-4-fluorophenyl)-4,4-dimethylpent-2-en-1-one, 19



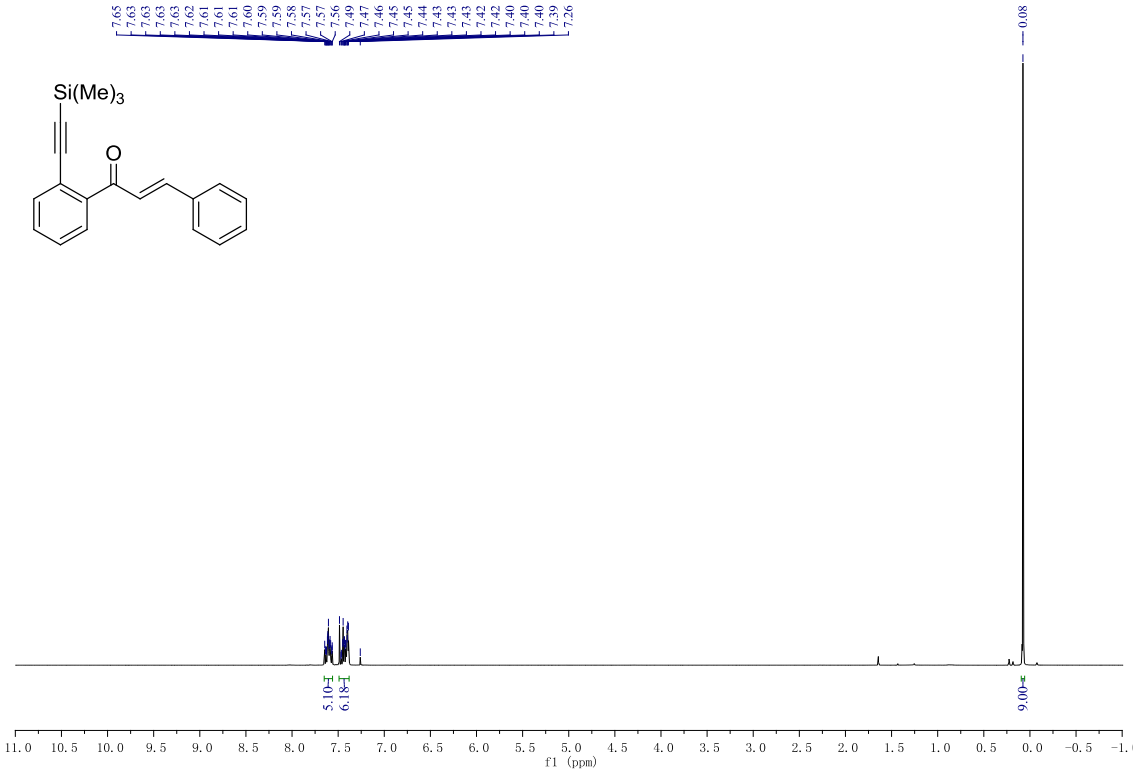


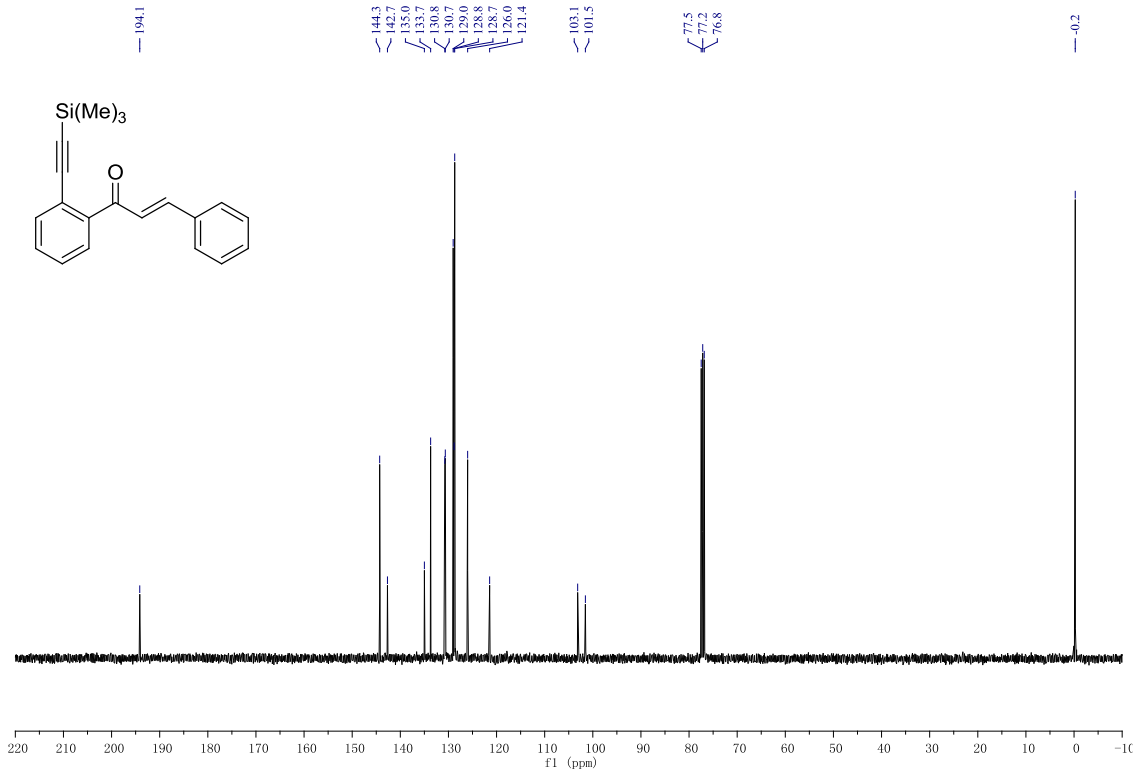
(*E*)-1-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-3-phenylprop-2-en-1-one, 20



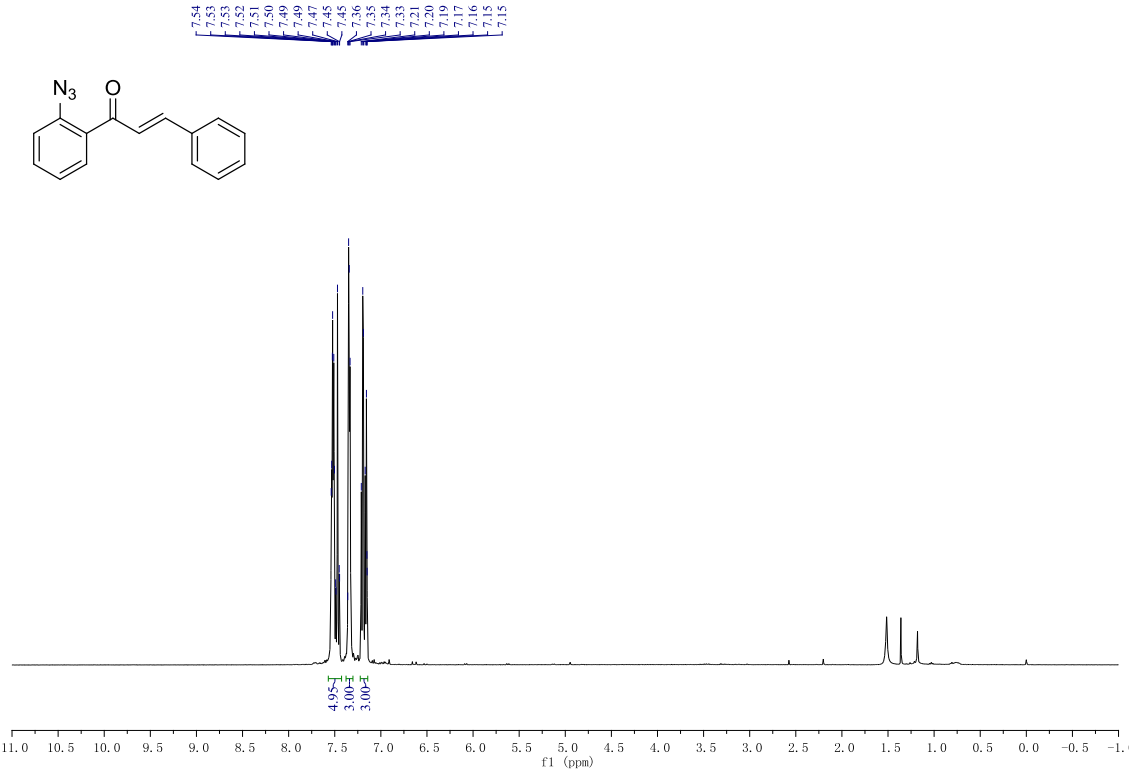


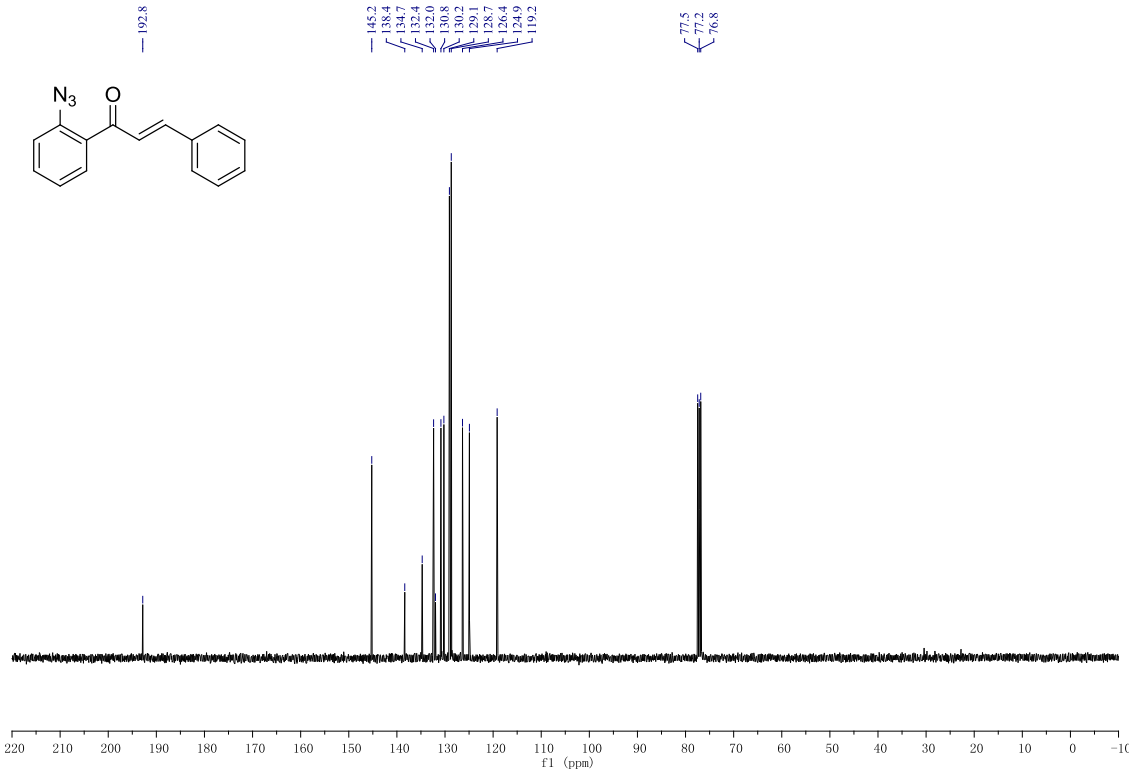
(*E*)-3-Phenyl-1-(2-((trimethylsilyl)ethynyl)phenyl)prop-2-en-1-one, 22



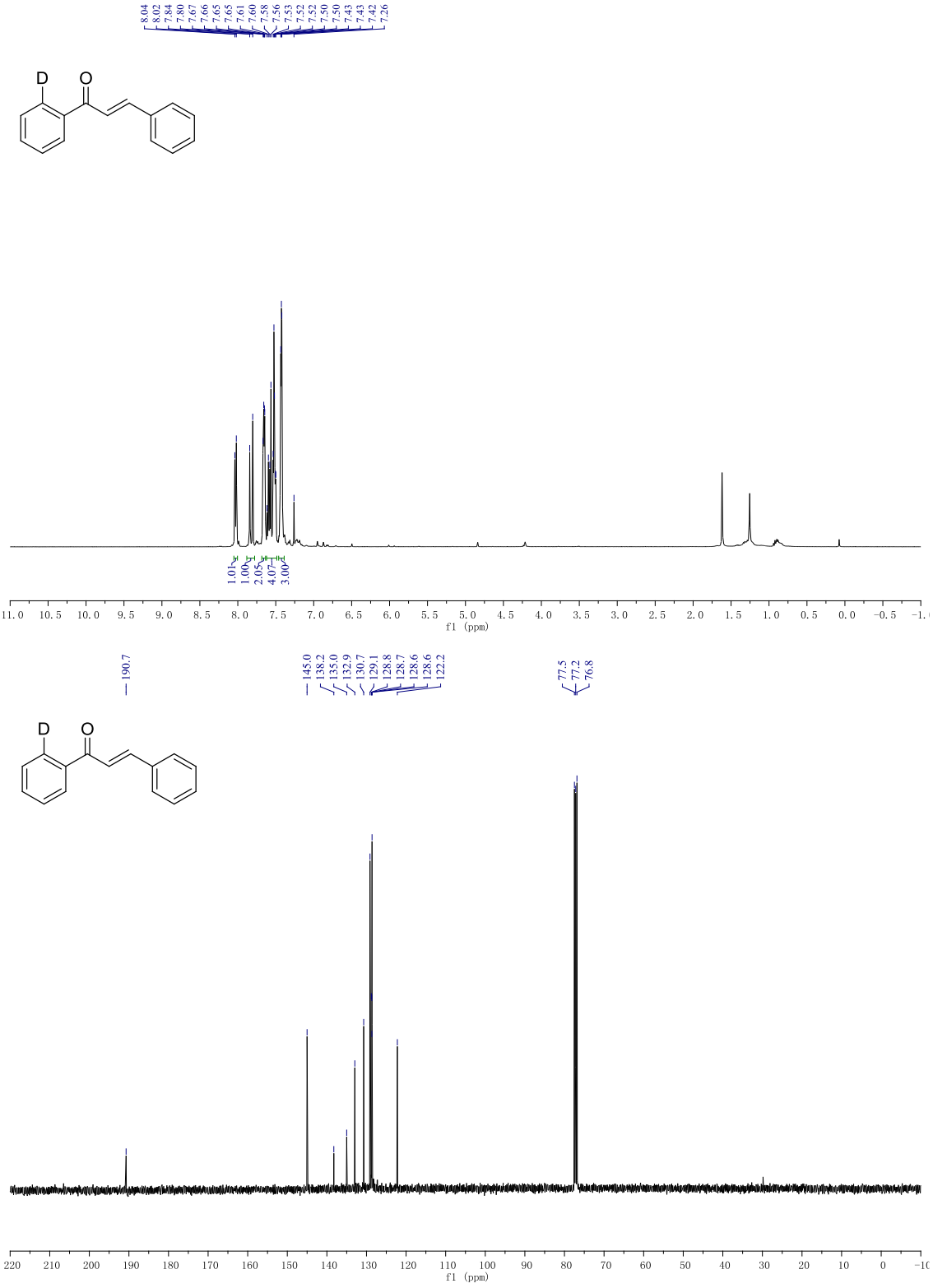


(*E*)-1-(2-Azidophenyl)-3-phenylprop-2-en-1-one, 23

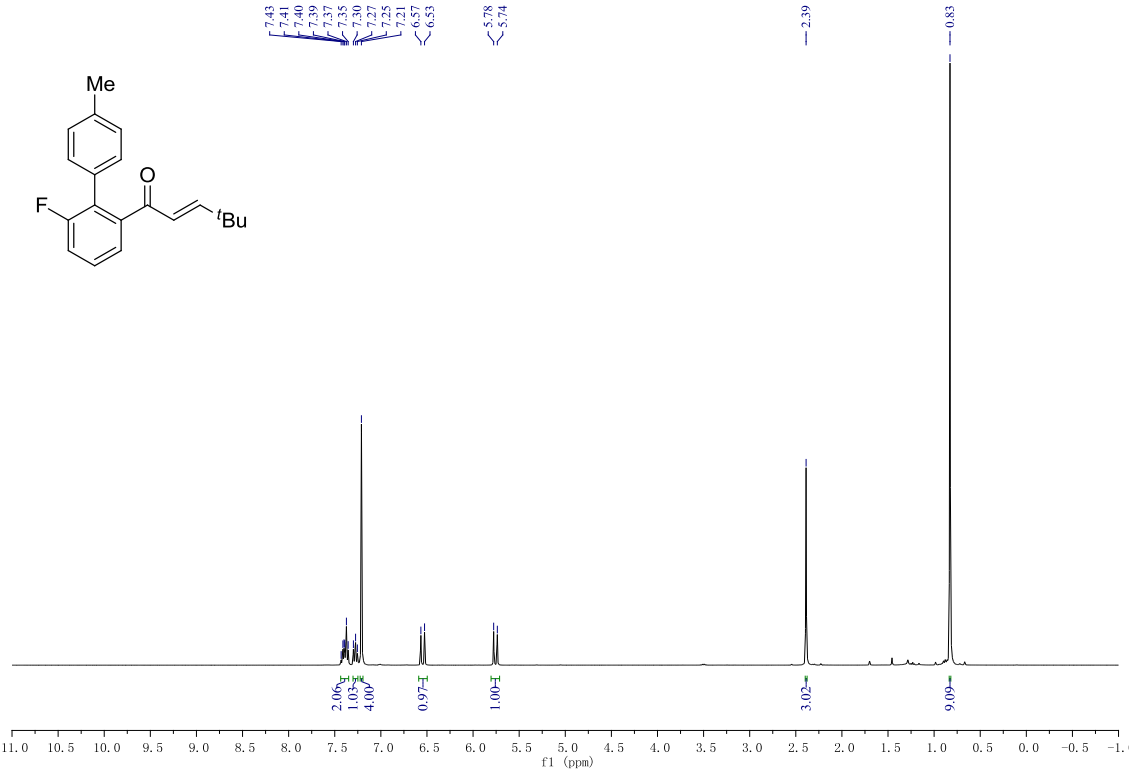


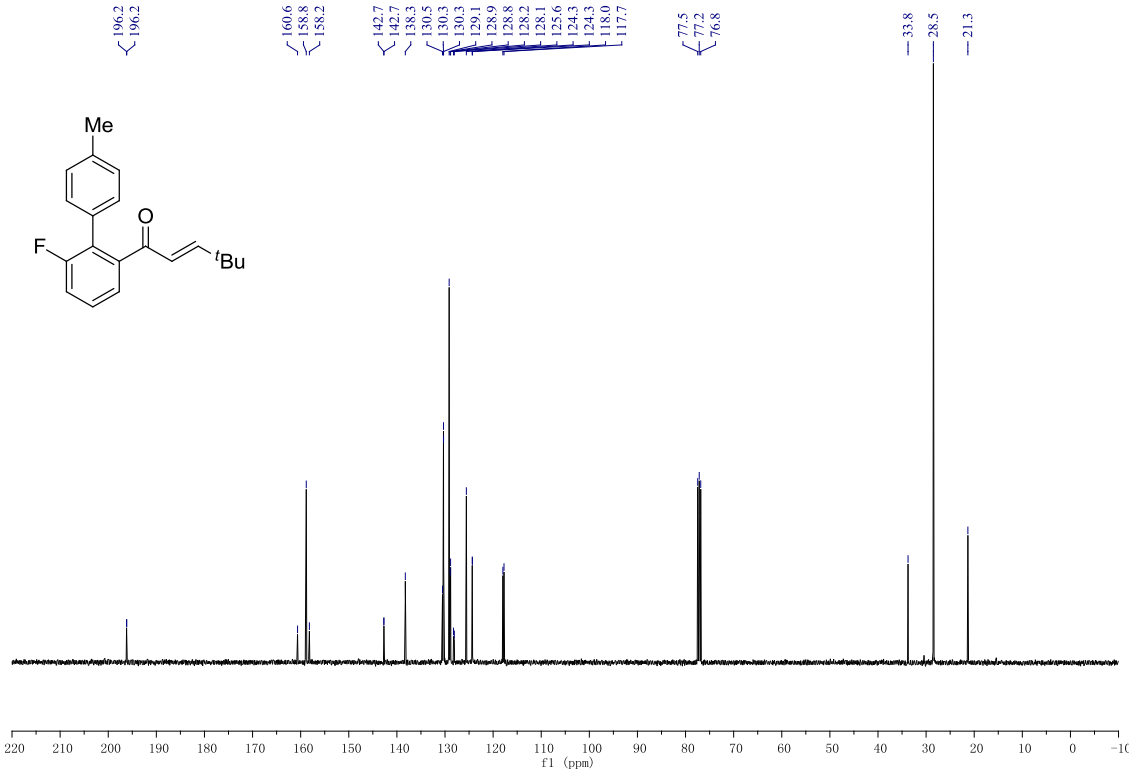


(*E*)-1-(2-Deuteriophenyl)-3-phenylprop-2-en-1-one, 24

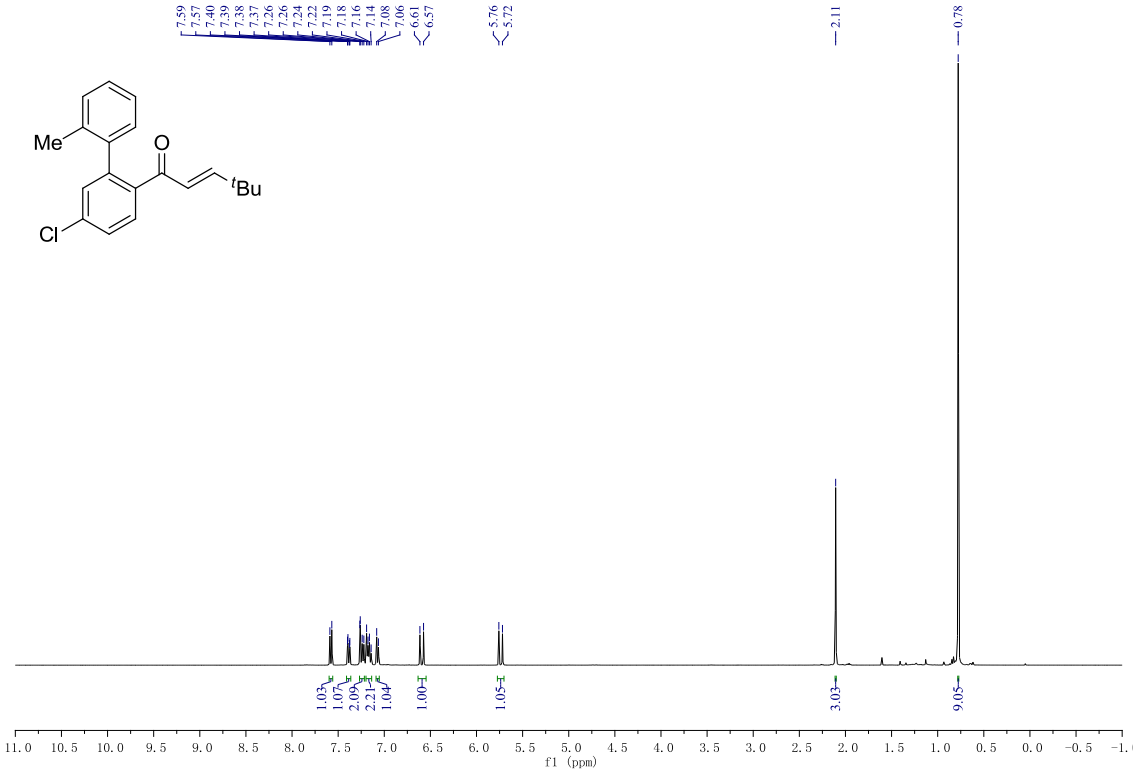


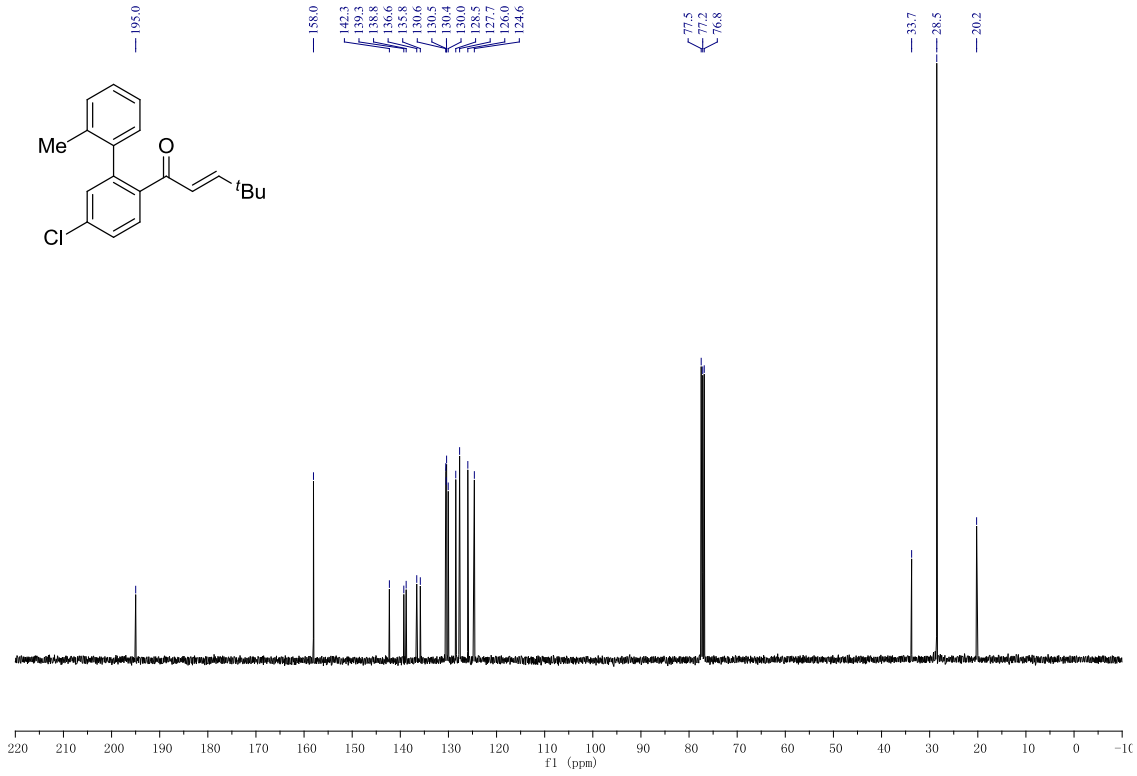
(*E*)-1-(6-Fluoro-4'-methyl-[1,1'-biphenyl]-2-yl)-4,4-dimethylpent-2-en-1-one, 25a



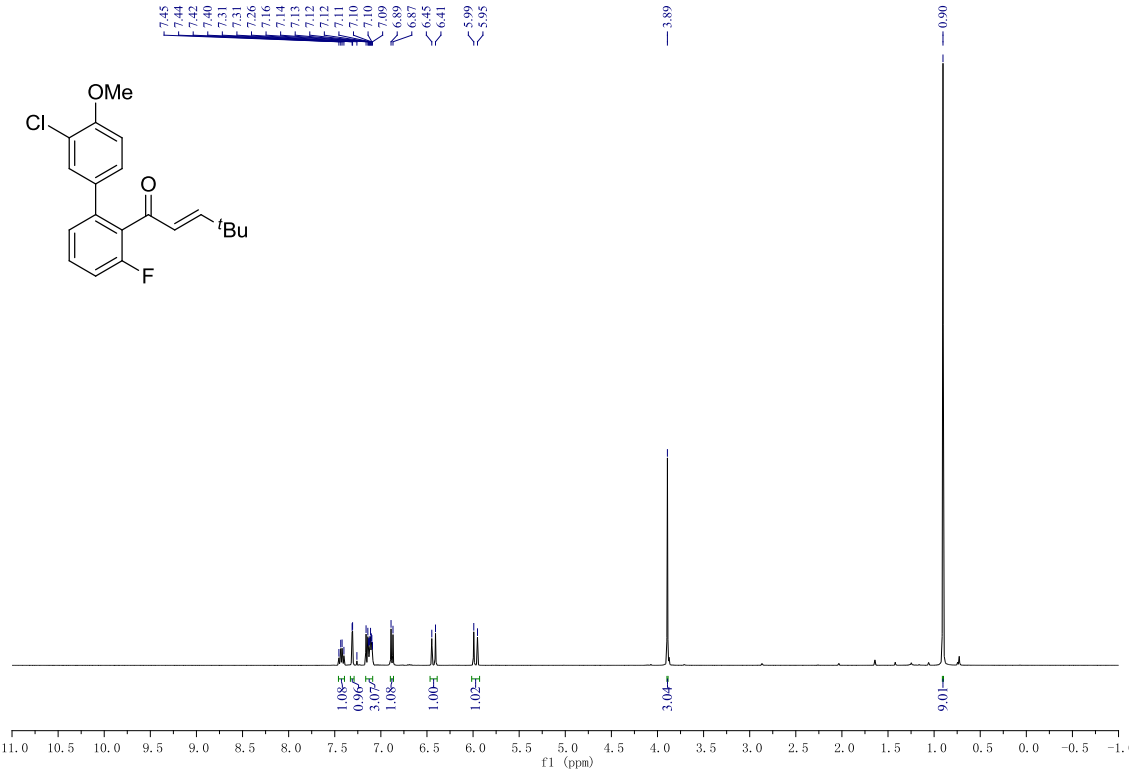


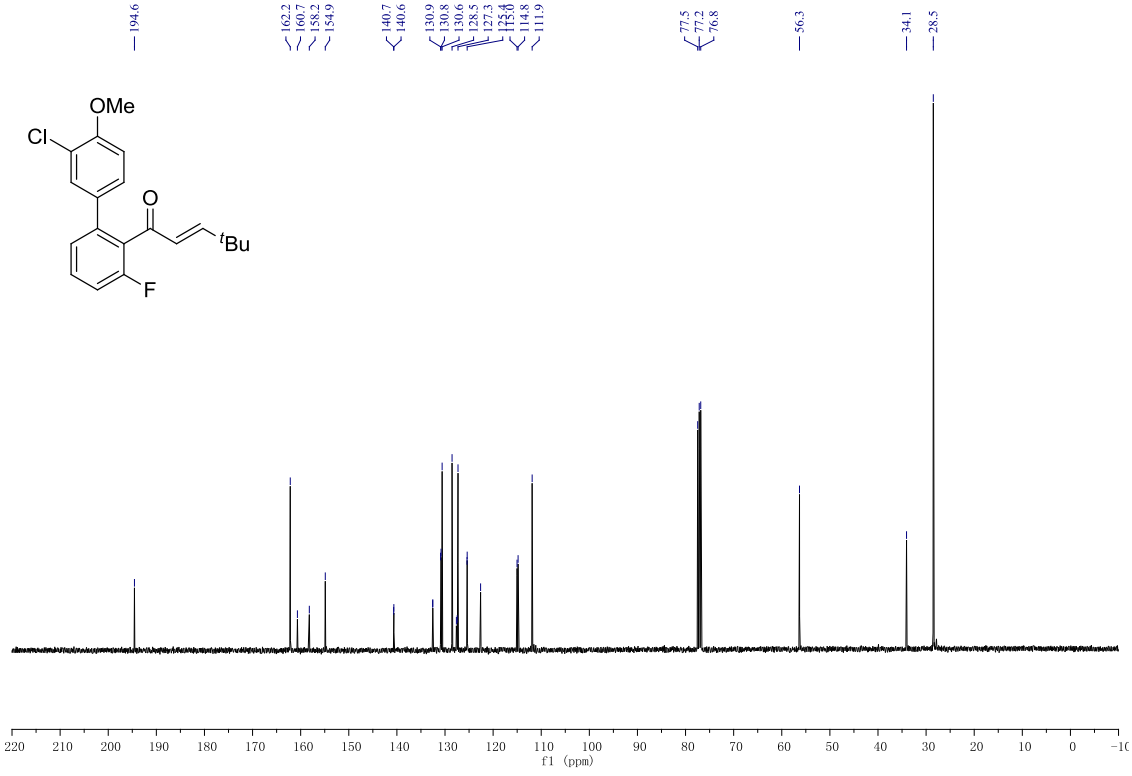
(*E*)-1-(5-Chloro-2'-methyl-[1,1'-biphenyl]-2-yl)-4,4-dimethylpent-2-en-1-one, 25b



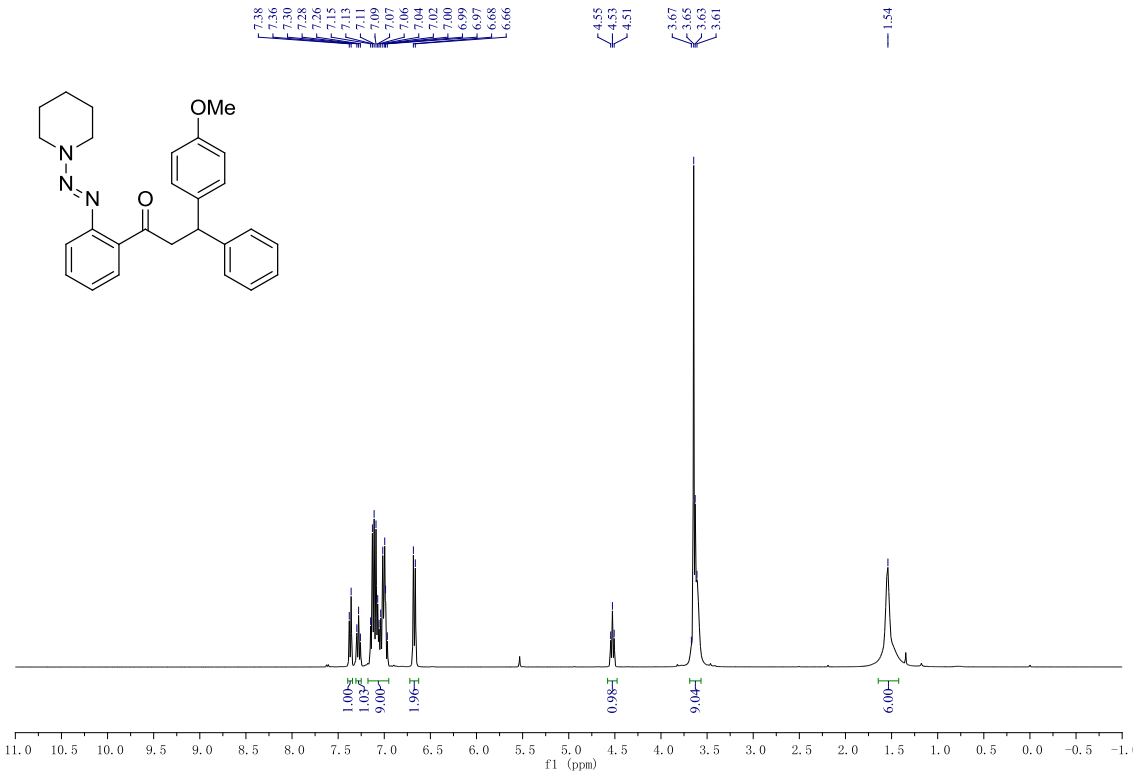


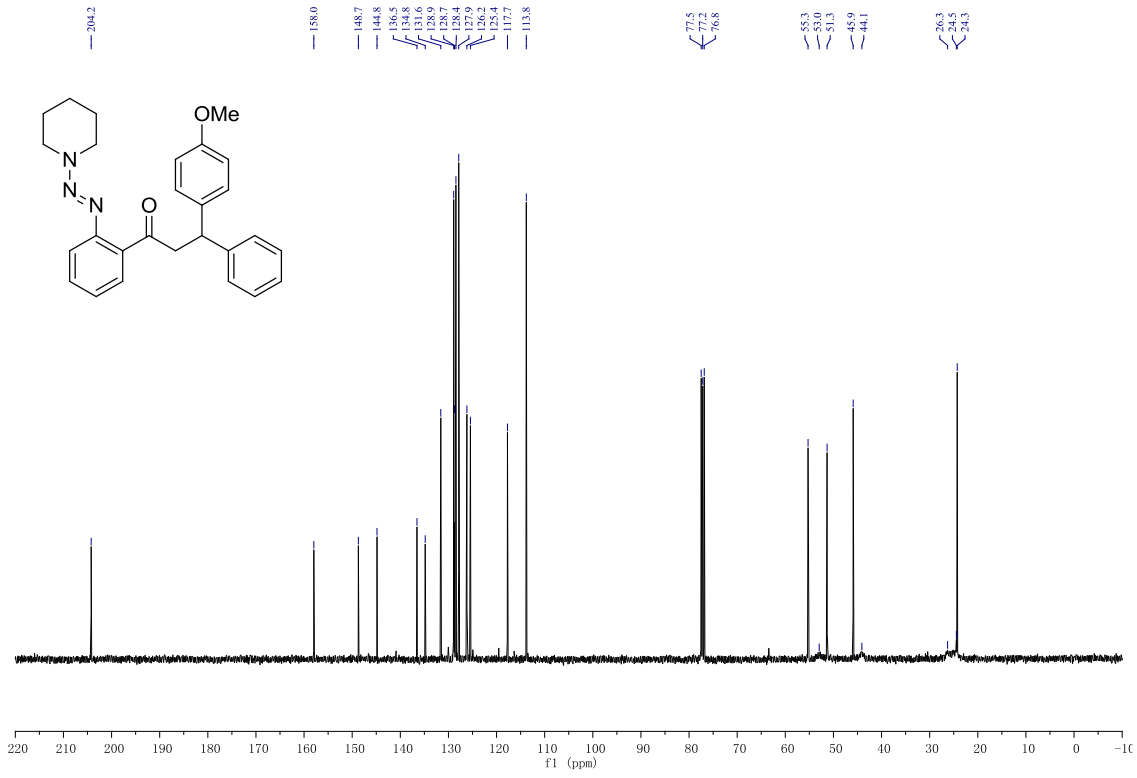
(*E*)-1-(3'-Chloro-3-fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)-4,4-dimethylpent-2-en-1-one, 25c



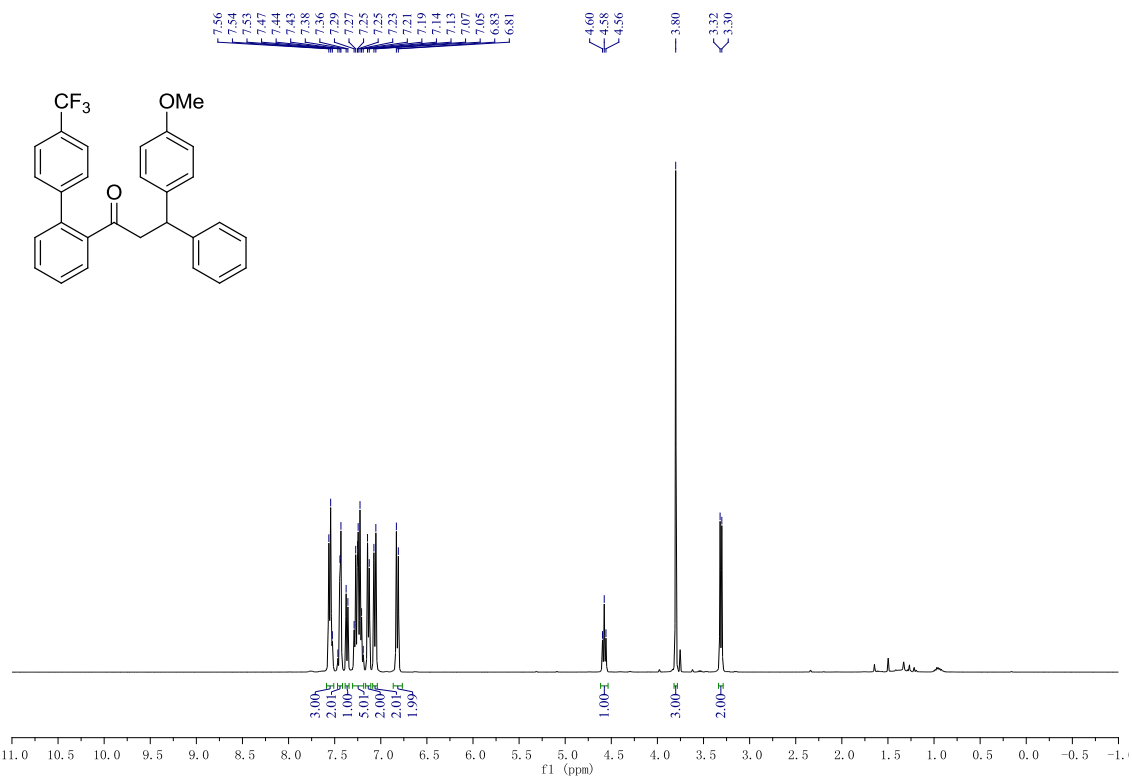


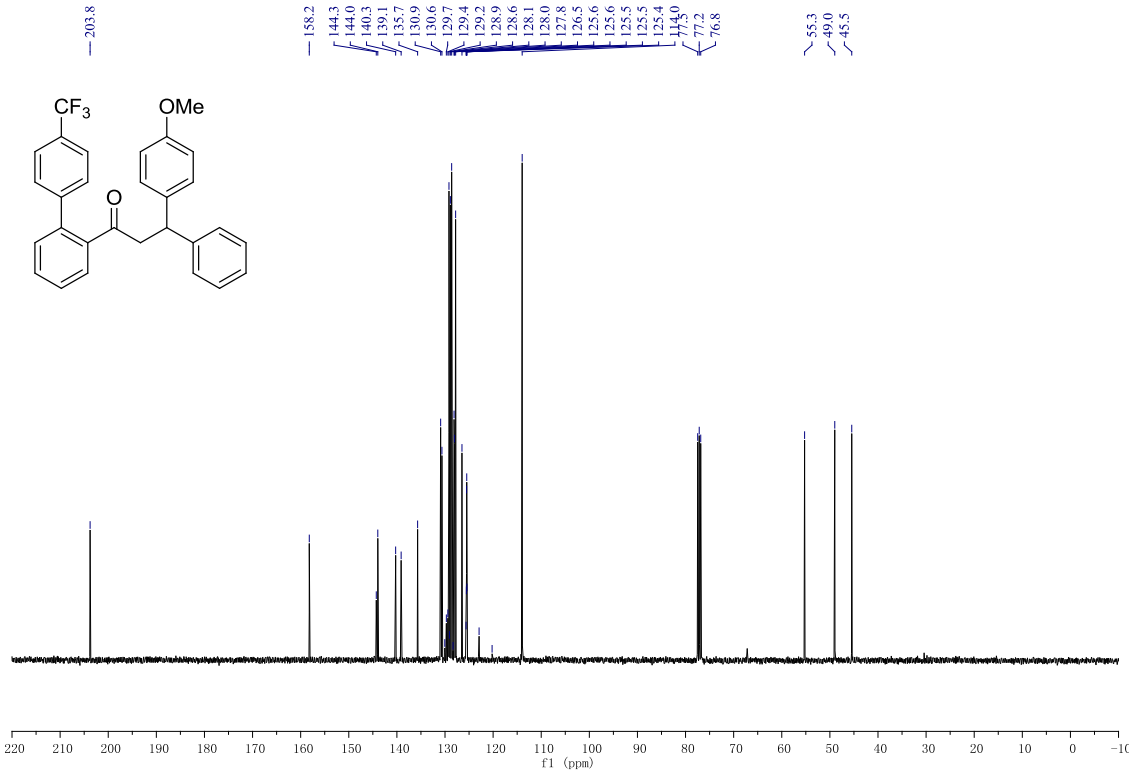
(*E*)-3-(4-Methoxyphenyl)-3-phenyl-1-(2-(piperidin-1-yldiazenyl)phenyl)propan-1-one, 26



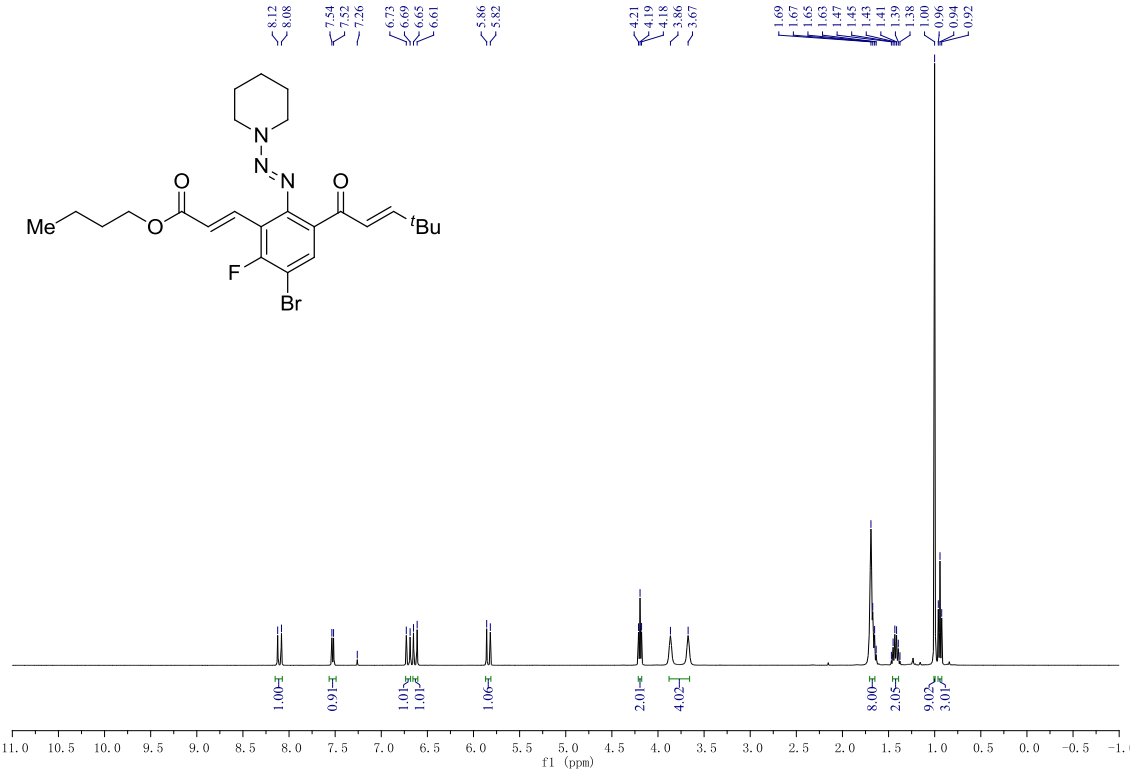


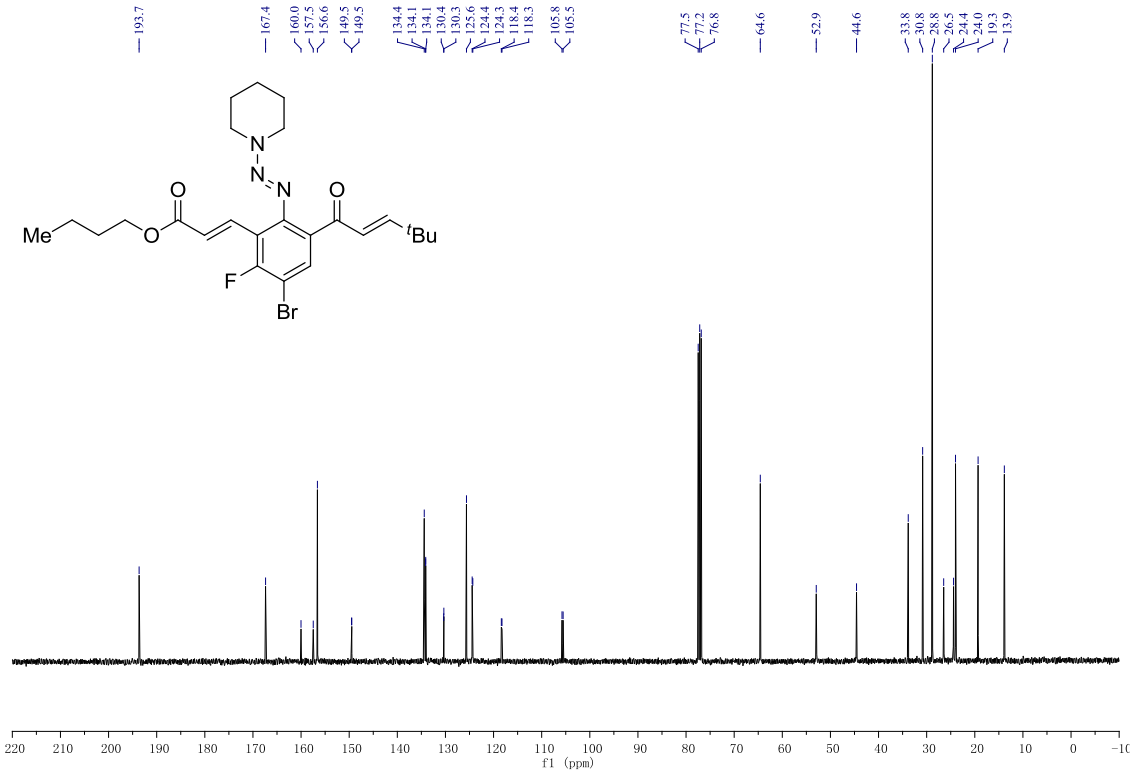
3-(4-Methoxyphenyl)-3-phenyl-1-(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl) propan-1-one, 27



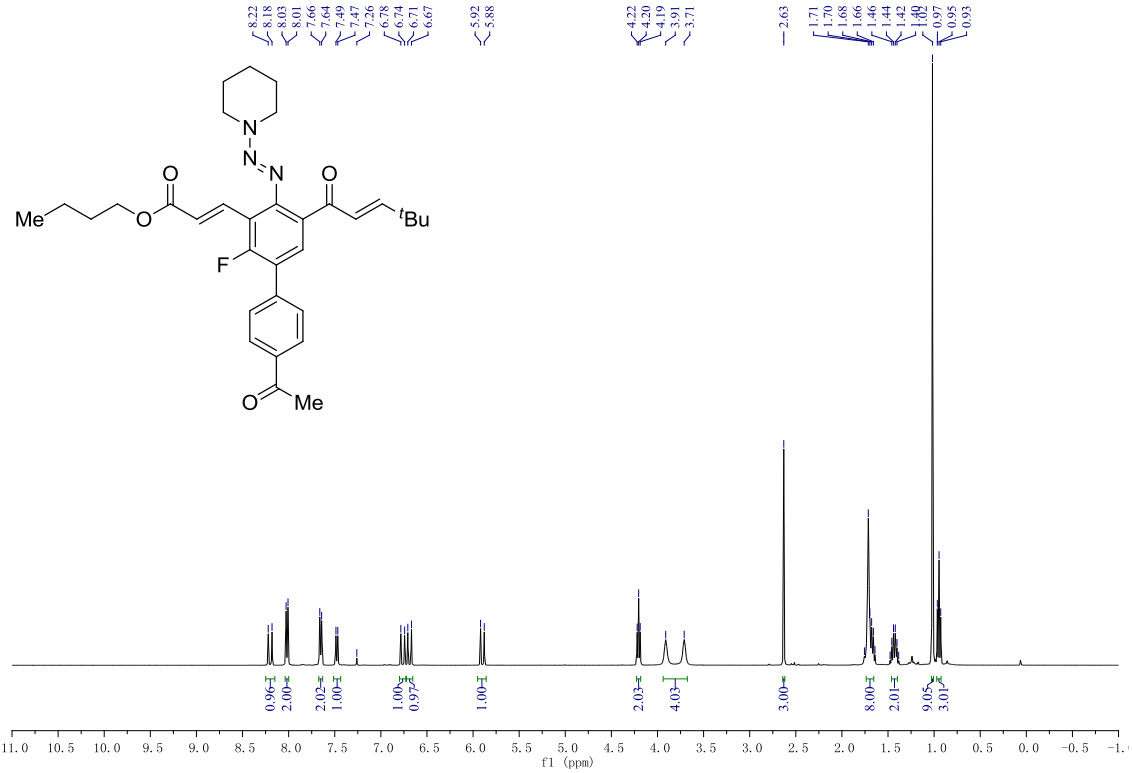


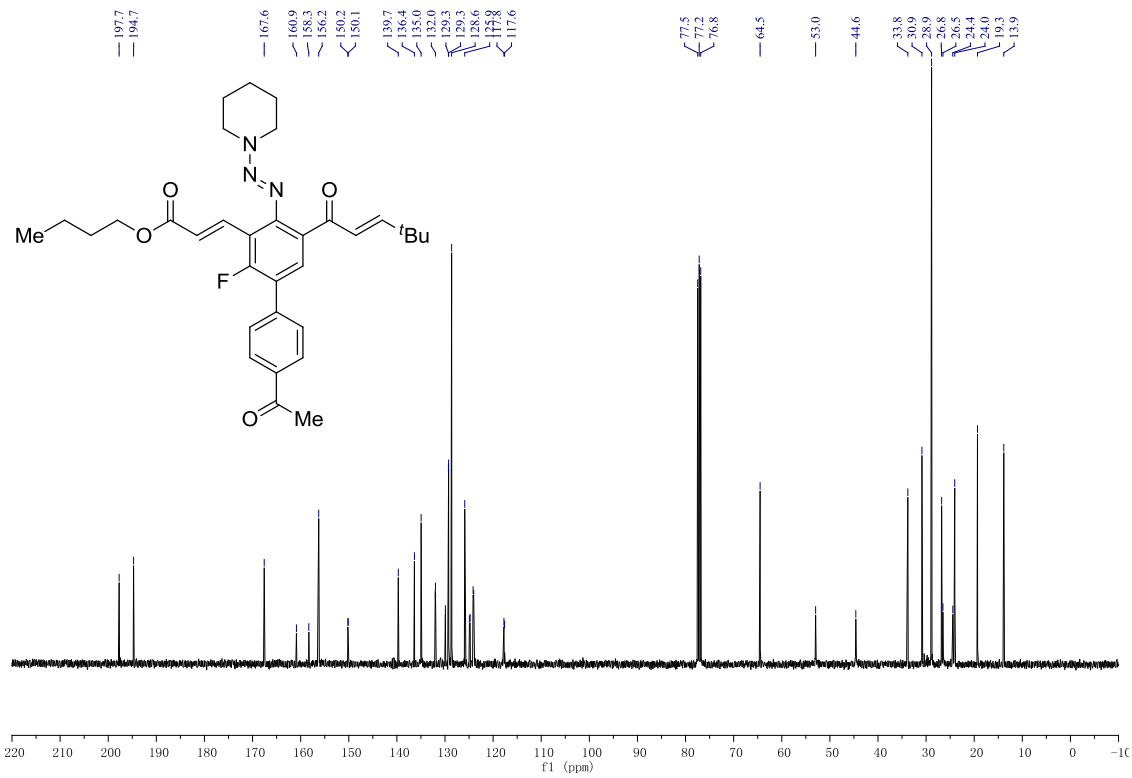
(*E*)-Butyl 3-(3-bromo-5-((*E*)-4,4-dimethylpent-2-enoyl)-2-fluoro-6-((*E*)-piperidin-1-yl diazenyl)phenyl)acrylate, 28





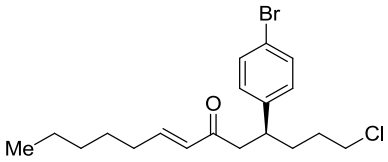
(*E*)-Butyl 3-(4'-acetyl-5-((*E*)-4,4-dimethylpent-2-enoyl)-2-fluoro-4-((*E*)-piperidin-1-yl diazenyl)-[1,1'-biphenyl]-3-yl)acrylate, 29

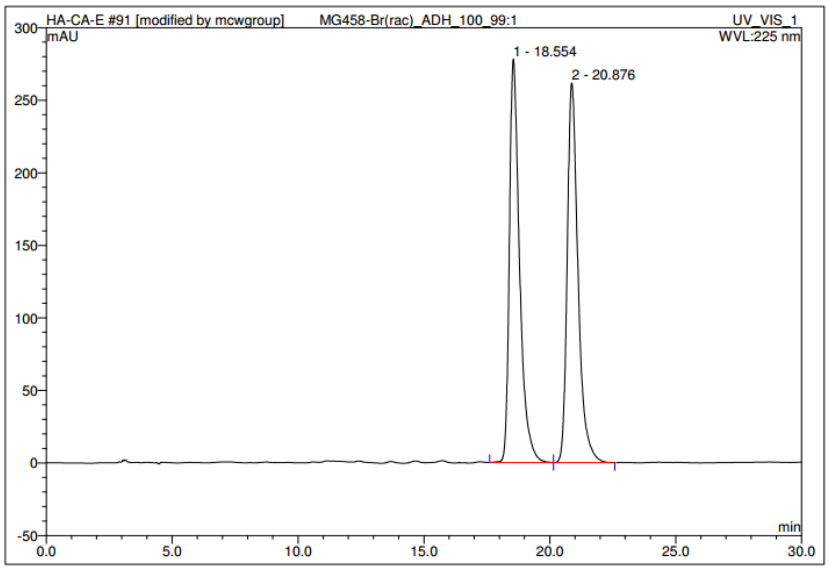




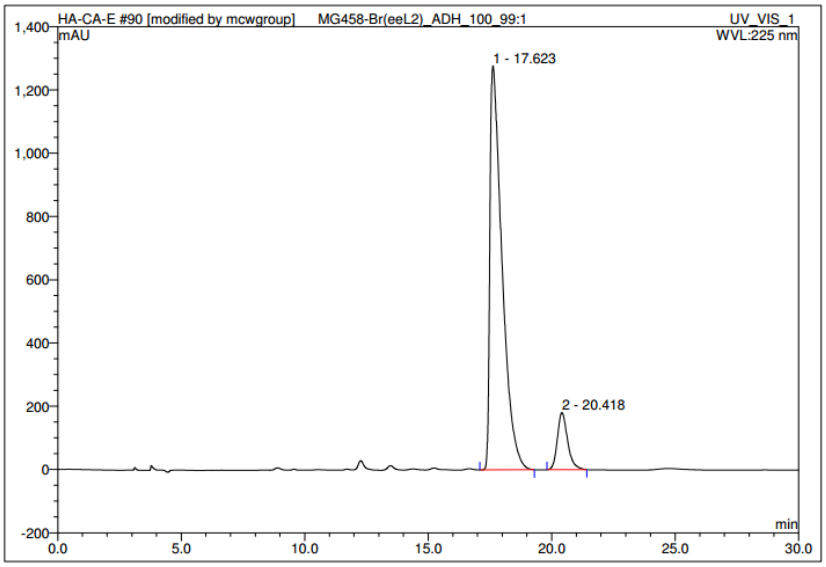
HPLC traces of unpublished compounds

(*S*,*E*)-4-(4-Bromophenyl)-1-chlorotridec-7-en-6-one, 8v



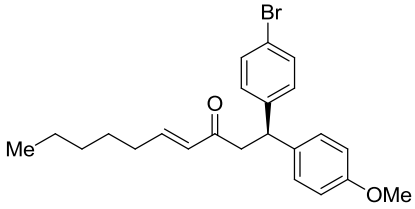


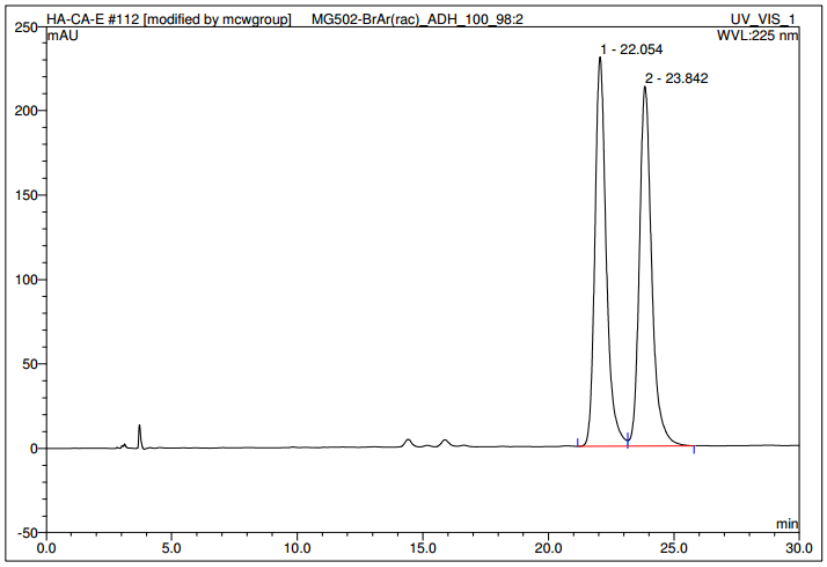
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18.55	n.a.	277.953	130.844	50.07	n.a.	BM *
2	20.88	n.a.	261.735	130.476	49.93	n.a.	MB*
Total:			539.688	261.320	100.00	0.000	



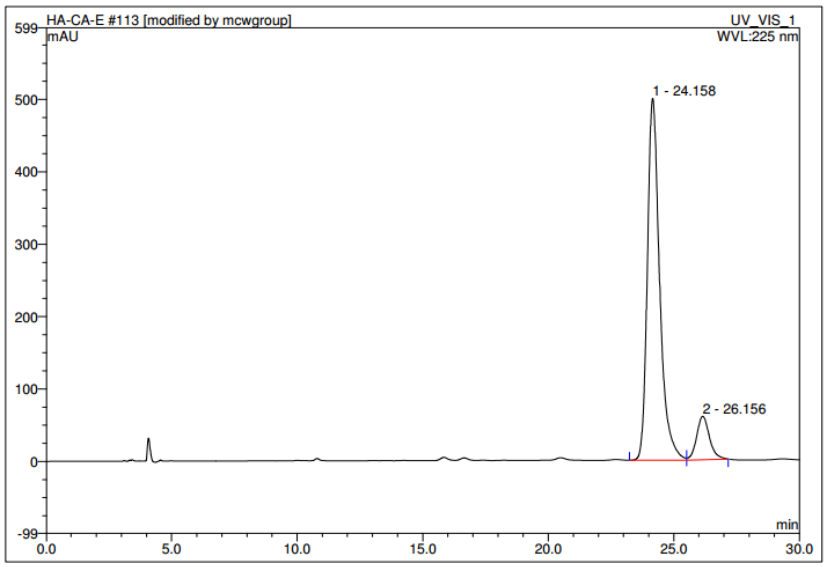
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17.62	n.a.	1276.706	727.353	89.35	n.a.	BMB*
2	20.42	n.a.	179.818	86.664	10.65	n.a.	BMB*
Total:			1456.524	814.017	100.00	0.000	

(*R*,*E*)-1-(4-Bromophenyl)-1-(4-methoxyphenyl)dec-4-en-3-one, 8w



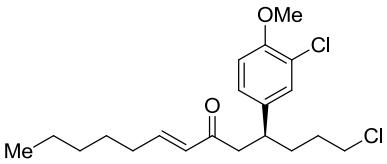


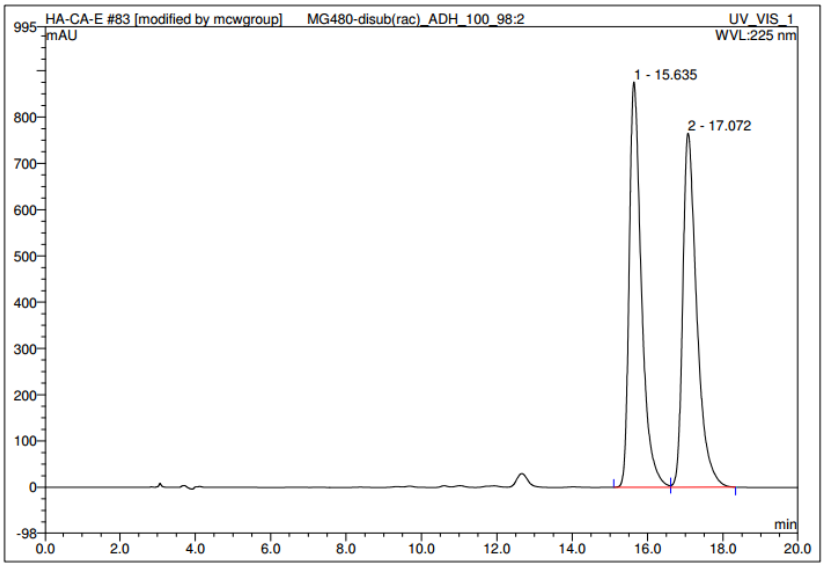
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	22.05	n.a.	230.437	120.753	49.87	n.a.	BM *
2	23.84	n.a.	212.882	121.381	50.13	n.a.	MB*
Total:			443.319	242.135	100.00	0.000	



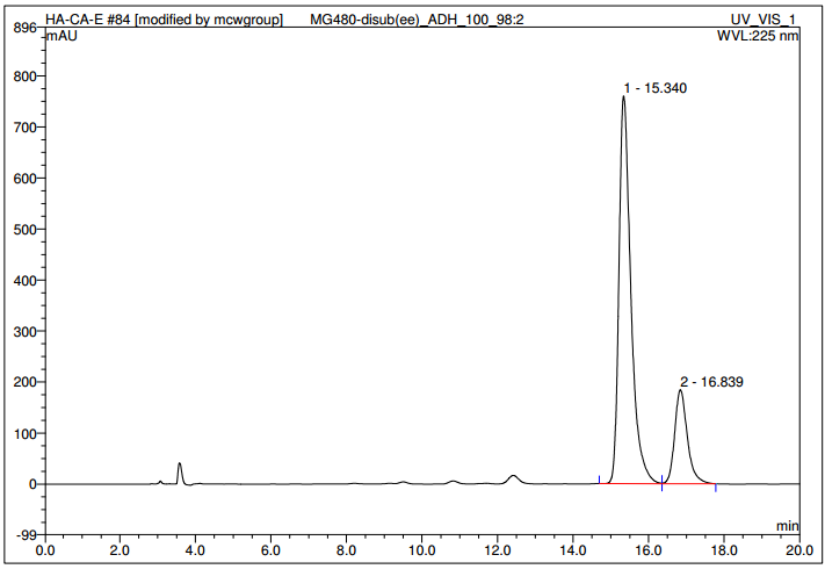
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24.16	n.a.	499.822	282.793	88.84	n.a.	BM *
2	26.16	n.a.	59.926	35.533	11.16	n.a.	MB*
Total:			559.748	318.326	100.00	0.000	

(*S*,*E*)-1-Chloro-4-(3-chloro-4-methoxyphenyl)tridec-7-en-6-one, 8x



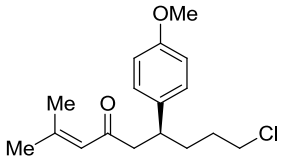


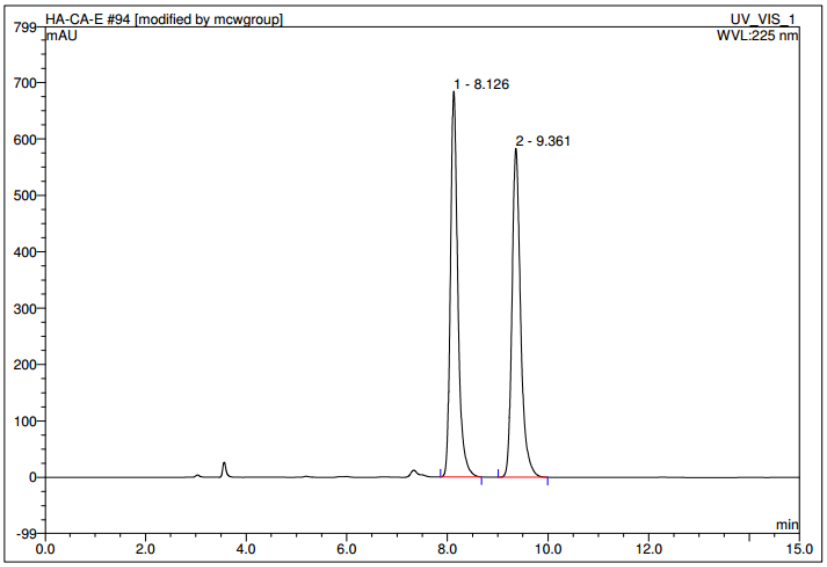
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.64	n.a.	875.590	329.107	49.95	n.a.	BM *
2	17.07	n.a.	764.700	329.794	50.05	n.a.	MB*
Total:			1640.289	658.901	100.00	0.000	



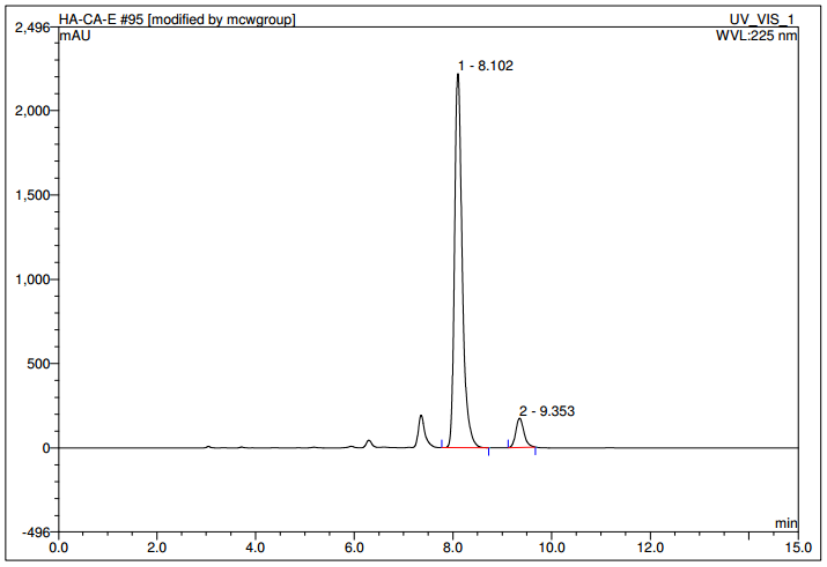
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.34	n.a.	759.937	278.232	79.53	n.a.	BM *
2	16.84	n.a.	183.994	71.608	20.47	n.a.	MB*
Total:			943.931	349.840	100.00	0.000	

(*S*)-9-Chloro-6-(4-methoxyphenyl)-2-methylnon-2-en-4-one, 8ag



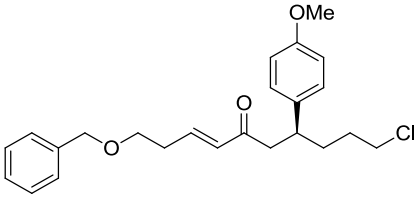


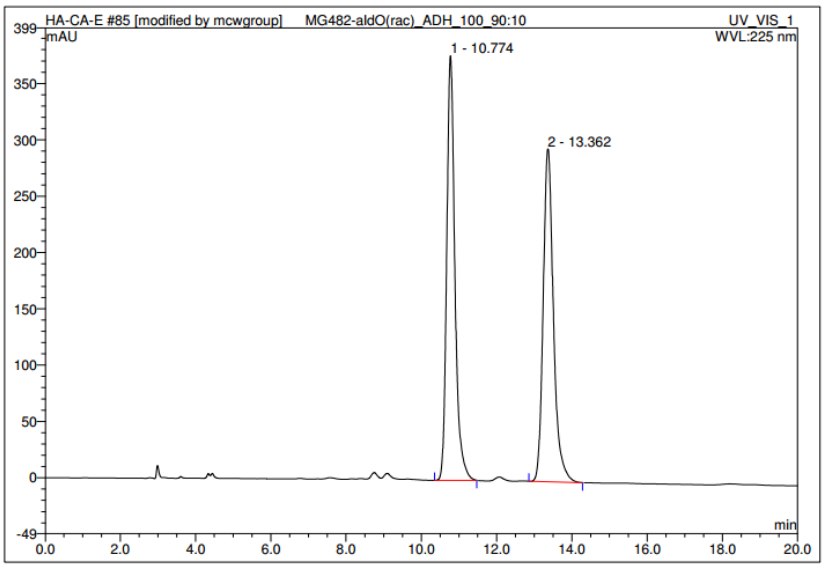
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.13	n.a.	683.806	116.421	50.07	n.a.	BMB*
2	9.36	n.a.	582.922	116.107	49.93	n.a.	BMB*
Total:			1266.728	232.528	100.00	0.000	



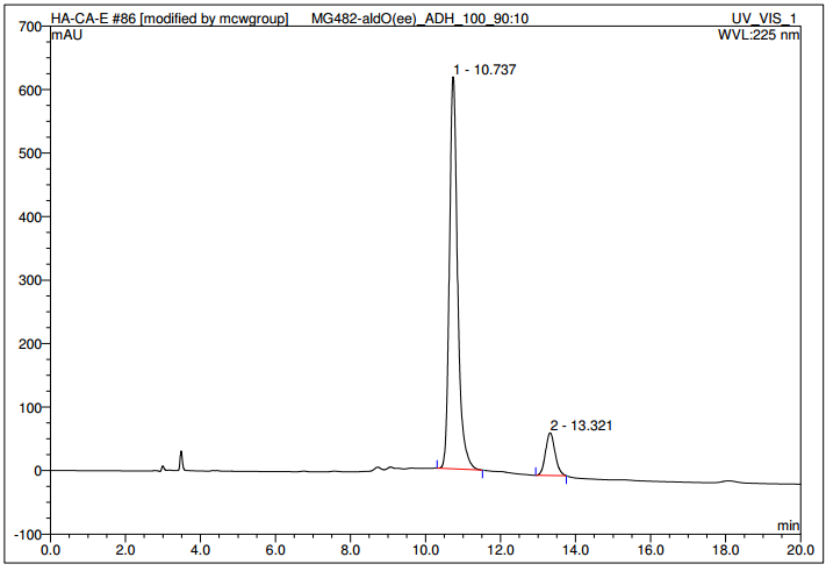
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.10	n.a.	2216.877	400.854	92.41	n.a.	BMB*
2	9.35	n.a.	173.587	32.937	7.59	n.a.	BMB*
Total:			2390.464	433.791	100.00	0.000	

(*S*,*E*)-1-(Benzyloxy)-10-chloro-7-(4-methoxyphenyl)dec-3-en-5-one, 8al





No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.77	n.a.	376.688	94.828	50.40	n.a.	BMB*
2	13.36	n.a.	295.458	93.311	49.60	n.a.	BMB*
Total:			672.147	188.139	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.74	n.a.	617.301	155.904	88.69	n.a.	BMB*
2	13.32	n.a.	67.158	19.886	11.31	n.a.	BMB*
Total:			684.459	175.790	100.00	0.000	