

***Copper Inner-Sphere in Photocatalysis: Mechanisms
Elucidation and Reactions Design***

Dissertation

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‘... if you gaze into the abyss, the abyss gazes also into you’

Friedrich Nietzsche

‘Sometimes your gaze can be forcefully directed towards the abyss, and then you are traumatized. If it’s involuntary and accidental, it can kill you. The more it’s voluntary, the more transformative it is’

Jordan B. Peterson

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Abbreviations:

Ac	Acetyl	DCM	Dichloromethane
AIBN	2,2'-azobis(isobutyronitrile)	DE	Diethyl ether
Ampl.	Amplitude	DFT	Density functional theory
anh.	Anhydrous	DIPEA	<i>N,N</i> -diisopropylethylamine
APCI	Atmospheric pressure chemical ionization	DMAP	4-Dimethylaminopyridine
aq.	Aqueous	DCM	Dichloromethane
Ar	Aryl	DE	Diethyl ether
AT	Atom transfer	DFT	Density functional theory
ATRA	Atom transfer radical addition	DMF	<i>N,N</i> -dimethylformamide
BET	Back electron transfer	dmp	2,9-Dimethyl-1,10-phenanthroline
BINAP	2,2'-bis(diphenyl- phosphonio)-1,1'- binaphthyl	d.r.	Diastereomeric ratio
BINOL	1,1'-bi-2-naphthol	dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-bipyridine
Bn	Benzyl	E/E1/2/Ered	Standard reduction potential
Boc	<i>tert</i> -Butyloxycarbonyl	ϵ	Extinction coefficient
bpy	2,2'-bipyridine	EDG	Electron donating group
bpz	2,2'-bipyrazine	<i>e.g.</i>	<i>Exempli gratia</i>
<i>tBu</i>	<i>tert</i> -Butyl	EI	Electric ionization
°C	Degree Celsius	EPR	Electron paramagnetic resonance
c	centi / speed of light	equiv	Equivalents
CDCl ₃	Chloroform	ESI	Electrospray ionization
CFL	Compact fluorescence lamp	<i>etc.</i>	<i>Et cetera</i>
CF ₃	Trifluoromethyl	Et	Ethyl
cm	Centimeter	ET	Energy transfer
CN	Cyano	EtOAc	Ethyl acetate
conc.	Concentrated	EWG	Electron-withdrawing group
crm	Complex reaction mixture	fmoc	Fluorenylmethoxycarbonyl
CT	Charge transfer	FT-IR	Fourier-transformation infrared spectroscopy
CW	Continuous wave	LA	Lewis acid
4-CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6- Dicyanobenzene	LMCT	Ligand-to-metal charge transfer
δ	Chemical shift	MeCN	Acetonitrile
dap	2,9-Bis(para-anisyl)-1,10-phenanthroline	MeOH	Methanol
dba	Dibenzylideneacetone	MeO	Methoxy
DBU	1,8-Diazabicyclo-[5.4.0]undec-7-ene	mg	Milligram
DCC	Dicyclohexylcarbodiimide	MHz	Mega hertz

min	Minutes	Q-TOF	Quadrupole time-of-flight
mL	Milli liter	RLT	Radical ligand transfer
μL	Micro liter	<i>rac</i>	Racemic
MLCT	Metal-to-ligand charge transfer	redox	Reduction-oxidation
mM	Milli molar	ref.	Reference
mmol	Milli mole	rt	Room temperature (25 °C)
μmol	Micro mole	s	Second
mol	Mole	SCS	Spin center shift
mol%	Mole percent	SCE	Saturated calomel electrode
mp	Melting point	SET	Single electron transfer
μs	Microseconds	T	Temperature
mT	Megatesla	TBAF	Tetra- <i>n</i> -butylammonium fluoride
mW	Milli Watt	TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
m/z	Mass-to-charge ratio	THF	Tetrahydrofuran
N ₃	Azide	TLC	Thin layer chromatography
n.d.	Not detected	TM	Transition metal
NFTPT	1-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate	TMS	Trimethyl silyl
NFSI	<i>N</i> -fluorobenzene-sulfonimide	Ts	Tosyl
NIS	<i>N</i> -iodosuccinimide	UV	Ultraviolet
nm	Nano meter	V	Volt
NMR	Nuclear magnetic resonance	VLIH	Visible light-induced homolysis
NO ₂	Nitro	<i>vs.</i>	<i>Versus</i>
nr	No reaction	W	Watt
ns	Nanoseconds	X	Arbitrary halogen
Nu	Nucleophile		
<i>o</i>	<i>Ortho</i>		
<i>p</i>	<i>Para</i>		
PBN	C-phenyl- <i>N</i> - <i>tert</i> -butylnitrone		
PC	Photocatalyst		
Ph	Phenyl		
pH	Potential of hydrogen		
phen	Phenanthroline		
phth	Phthalimide		
ppm	Parts per million		
<i>iPr</i>	<i>Iso</i> -propyl		

Chapter I:

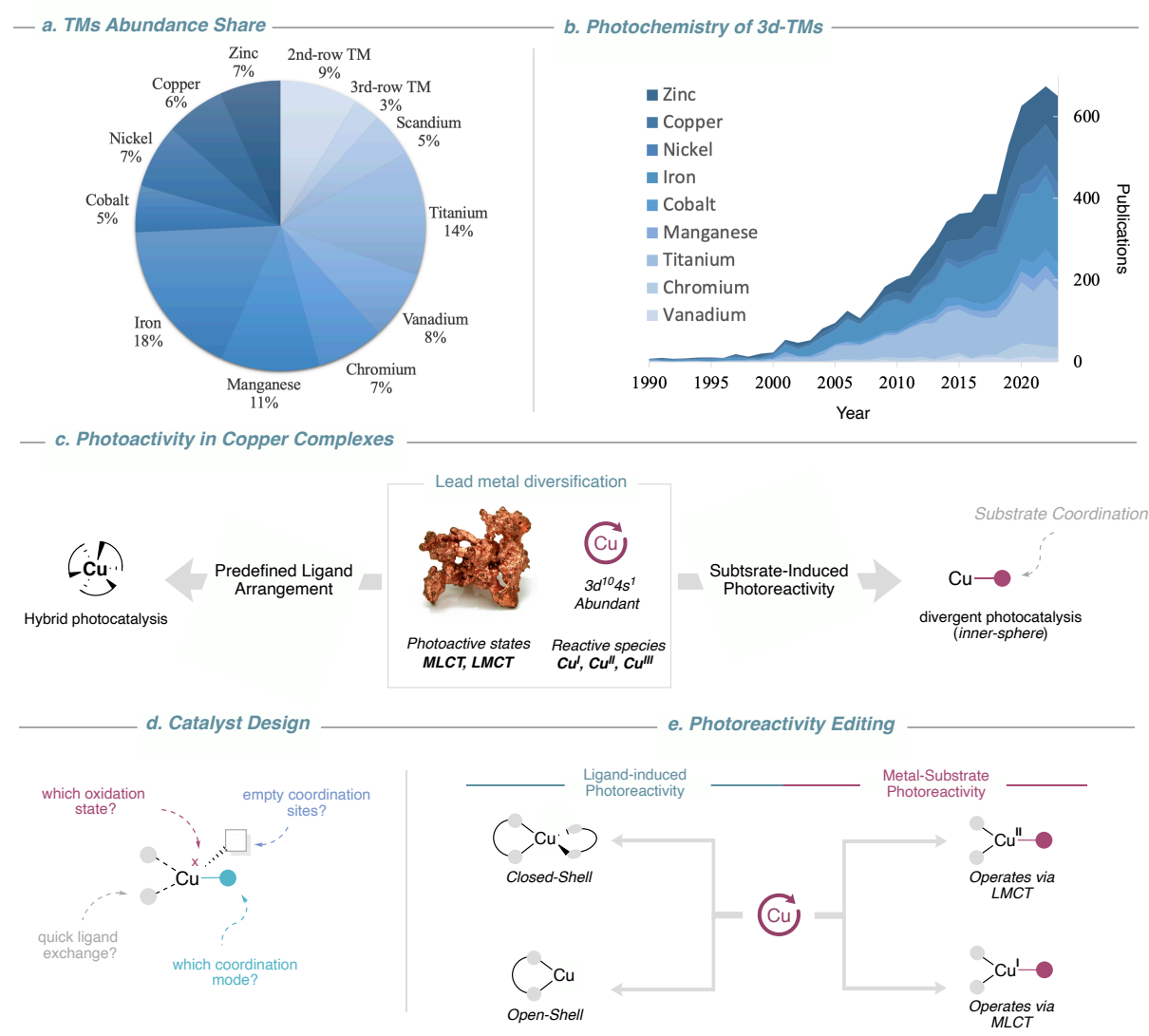
Inner-sphere paradigms in copper photocatalysis

1. Overview

Transition-metal catalysis (TM-catalysis) has long been a powerful synthetic method allowing the incorporation of simple chemical precursors into the synthesis of highly relevant entities. The engineering of bond breaking and forming using TM-catalysis operates through distinct mechanistic patterns relying mainly on scarce and expensive second- and third-row transition metals^{1–10} (Scheme 1a). Although this field embraces a rich array of synthetic versatility, the methods used to control metals' reactivity have remained relatively consistent over the last century. Predominant approaches to facilitate reactivity relied on adjusting the metal's ligand field, lowering the catalyst loading, and expanding its scope.

Over the past 15 years, transition-metal complexes were implemented as photocatalytic mediators serving as a potent platform for facilitating elusive syntheses.^{11–13} In these reactions, the photocatalyst is photonically irradiated to its excited state permitting the activation of substrates through single-electron transfer (SET) or energy-transfer (ET) mechanisms. Recent development consisted of shifting from heavy rare metals to first-row transition metals. Over the past few years, multiple discoveries of photoactive metal complexes have been achieved, focusing mainly on abundant elements pushing towards straightforward, economic, and sustainable photochemistry (Scheme 1b).^{14,15} Nevertheless, several complications arise in the design of first-row transition metal complexes since they are, unlike their heavy-metal counterparts, (i) more susceptible to fast ligand exchange compromising their structural stability, (ii) have a weaker ligand field allowing non-radiative decay of their excited-state back to their ground-state, and (iii) have considerably lower excited state lifetimes hence lowering their catalytic efficiency. Although typical ruthenium- and iridium-based photoredox catalysts are the choice by default when conceiving a chemical reaction, there is growing interest in the utilization of copper-based systems being considerably cheap and sustainable alternatives. In addition, copper shows a higher versatility in terms of photoactivity compared to other metals as it interacts with a wide array of functionalities as well as transient intermediates within its

first-coordination sphere. Two main photoreactivity patterns can be distinguished in which copper photoactivity can be engendered either through the coordination with exogenous ligands or with organic substrates (Scheme 1c). Depending on copper's oxidation state and the nature of the ligand/substrate coordinated, upon excitation, the copper complex undergoes either a



Scheme 1: a) Transition-metal abundance (for a better representation, the data was plotted in logarithmic scale), b) research evolution on 3d-metals photochemistry according to PubMed (number of papers vs year), photoactivity in copper complexes, d) copper complexes design for the application in catalysis, e) different types of photoactivity encountered when using copper.

metal-to-ligand charge transfer (MLCT), favoring an oxidative quenching mechanism, or a ligand-to-metal charge transfer (LMCT) which favors a reductive quenching pathway. The planning of a chemical transformation using copper as a catalyst requires careful design

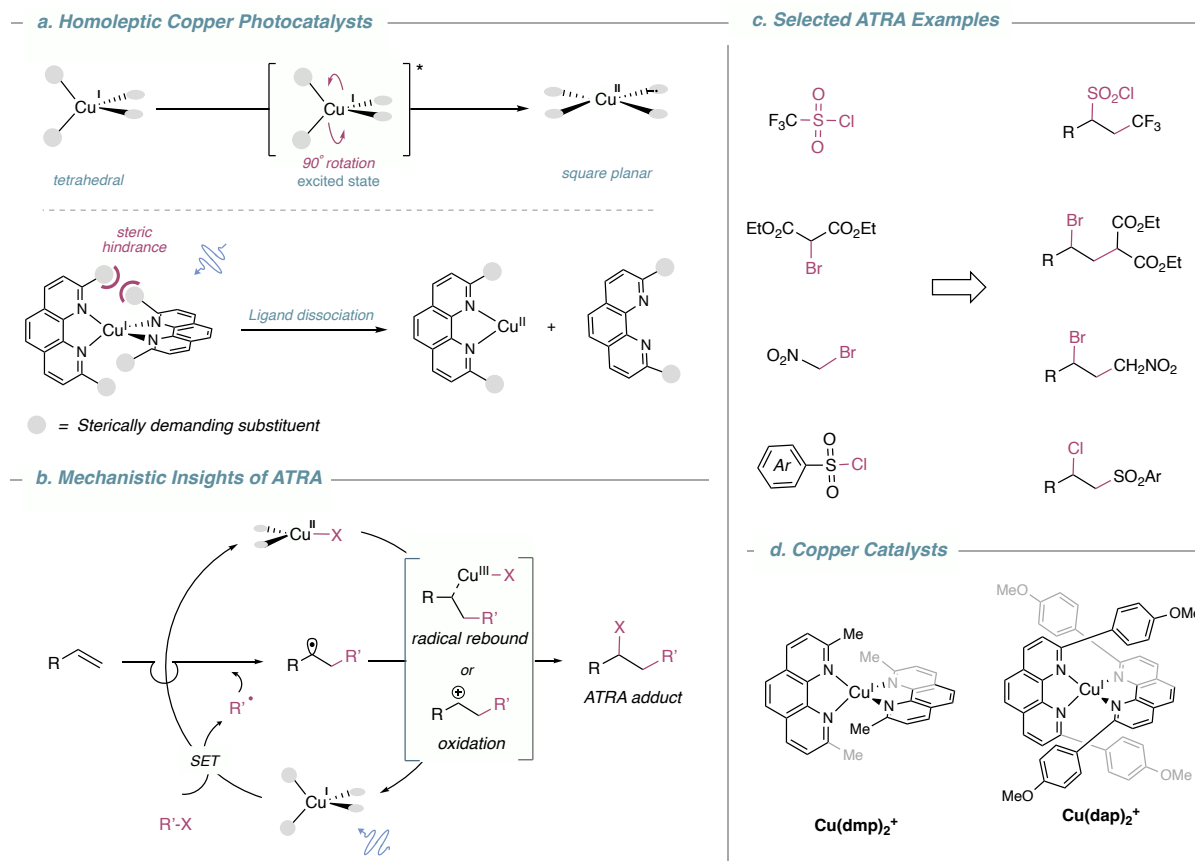
especially since copper complexes, in addition to their photoactivity features, are able to engage with transient intermediates hence performing dual photoredox-transition metal (metallaphotoredox) type reactivity. Consequently, considerable approaches were developed and implemented in catalysis. In this chapter, we outline the recent advances in the inclusion of copper complexes as photocatalysts and consider the advantages and disadvantages of each catalytic class. We will mainly discuss four mechanistic patterns: (i) the use of coordinatively saturated copper complexes (closed-shell), (ii) the use of open-shell copper complexes, and (iii) the use of substrates as photoactivity inductors in Cu^I and Cu^{II} complexes. The aim of this chapter is to focus on the different catalytic patterns involving copper's inner sphere and include their design and recent applications.

2. Copper-Ligand photocatalysis

2.1. Closed-Shell Cu^I-complexes

Homoleptic bis(diimine) Cu^I-complexes are well known for their visible absorption and highly reducing excited states as they have been extensively studied due to their alluring photophysical features.¹⁶ Beside their economic benefits vis-à-vis the extensively used ruthenium- and iridium-based photocatalysts, the dynamic nature of copper complexes and their capability to engage with entities within copper's first coordination sphere opened new mechanistic perspectives in catalytic design.

Upon light excitation, homoleptic copper complexes undergo a MLCT resulting in the electronic transfer from Cu^I to the ligand leading to the oxidation of the metal center to Cu^{II} which engenders a geometrical flattening from tetrahedral to square-planar (scheme 2a, top).^{17,18} Following the seminal discovery of copper-phenanthroline complexes, their application in catalysis only came later with Sauvage capitalizing on Cu(dap)₂Cl (dap = 2,9- (*p*-anisyl) -1,10-phenanthroline) to promote the homo-coupling of nitrobenzyl bromide.¹⁹ While the flattening mechanism is photochemically unproductive due to the rapid excited state quenching, the excited state's lifetime in Cu(dap)₂Cl is much higher since the implementation of bulky substituents in the 2- and 9- positions hinders the easy flattening.²⁰ Instead, ligand dissociation is commonly observed upon quenching resulting in an open-shell transient Cu^{II}-species with vacant coordination sites able to intercept incipient radicals (scheme 2a, bottom).



Scheme 2: a) Geometrical flattening of photoexcited copper-phenanthroline complexes, b) mechanism of copper catalyzed atom-transfer radical addition reactions, c) selected ATRA reactions using copper phenanthroline complexes, d) common copper catalysts for ATRA reactions.

Homoleptic copper-phenanthroline complexes are mostly employed in the difunctionalization of olefins allowing the access to more complex chemical space from simple commodities.^{21,22} Although various functionalization processes were achieved,²² well-established processes are the copper-catalyzed Atom-Transfer Radical Addition (ATRA) reactions.²¹ Pioneered by Kharasch,^{23,24} these reactions are initiated by the reduction of an ATRA reagent ($R'-X$) giving rise to a radical that adds across an olefin generating a transient radical which is then bonded to the anion issued from the reduction of the ATRA reagent to afford the ATRA adduct. While conventional photocatalysts close the cycle through the oxidation of the radical intermediate, enabling an ionic mechanism,^{25,26} copper catalysts benefit from the geometrical flattening facilitating the interception of radicals followed by a reductive elimination mediated by the transient Cu^{III} -species (Scheme 2b). Multiple reagents were compatible with such catalysis mode employing mainly $Cu(dmp)_2Cl$ and $Cu(dap)_2Cl$ as catalysts (Schemes 2c and 2d).^{21,27–32}

Further progress in ligand design led to the development of photostable and well-defined heteroleptic copper complexes³³ containing diimine and diphosphine ligands which are extensively applied as conventional photoredox catalysts.³⁴ Although they are mostly used as a presynthesized entities, they are also able to assemble *in-situ* upon addition of copper salts and the correspondent ligands with no homo-coordination.³³ Since these complexes operate similarly to conventional photoredox catalysts, allowing electrons shuttle with no direct interactions with substrates or intermediates within the copper's first coordination sphere, their application in catalysis will not be discussed here.

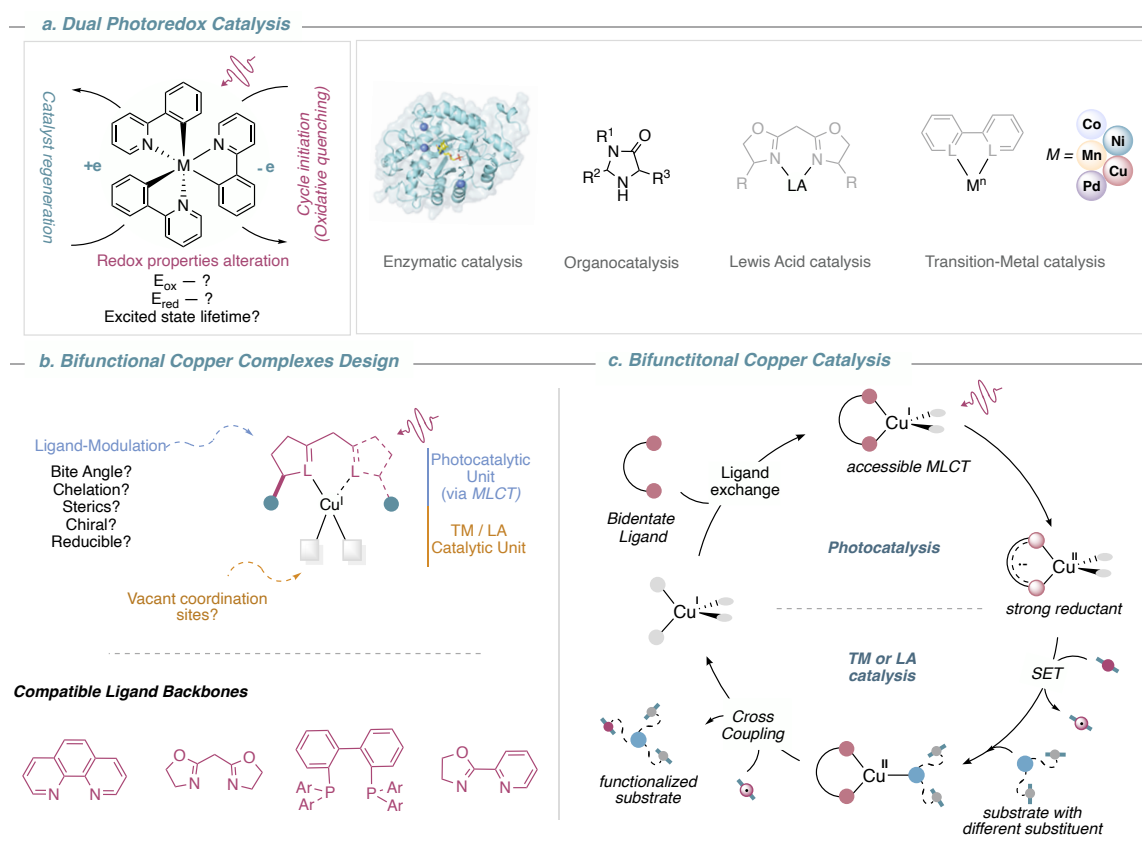
2.2. Open-Shell Cu^I-complexes

Dual catalytic approaches^{35,36,45–47,37–44} found application in photochemical processes, serving as a powerful predictable tool to facilitate intricate transformations.⁴⁸ The predominant class of dual catalysis in recent years necessitates the utilization of a photoredox catalyst in conjunction either with a metal- or an organic-based catalyst.^{49–51} While these catalysts combinations serve as potent platform in catalytic design, they concurrently offer the opportunity to forge new chemical bonds with specific stereo- and chemoselectivity.

The implementation of chiral scaffolds, whether in the form of ligands or catalysts, into photocatalytic processes has unveiled new avenues in asymmetric synthesis.^{52–54} Asymmetric photocatalysis is contingent on the synergy between an achiral photocatalyst and a chiral catalyst (organocatalyst,⁵⁵ transition metal catalyst,^{56–58} Lewis acid^{53,59,60} or enzyme^{61–68}) enabling stereoselective bonds formation (Scheme 3a). Ideally, advantageous approaches rely on a single catalyst to execute dual roles – photoactivation and chirality induction – thereby unveiling new mechanistic paradigms. While the conception of a singular catalyst to perform dual roles is challenging, a handful of organic⁶⁹ as well as metal-based⁷⁰ bifunctional chiral catalysts with photochemical properties were developed. Notably, the use of chiral Lewis acids^{71–73} or the rhodium^{74–78} and iridium⁷⁹ complexes with helical chirality.

Advancement in deciphering the mechanistic pattern in copper-phenanthroline photocatalysts has driven the expansion towards catalytic systems in which copper complexes with non-saturated coordination sphere are used enabling the metallic center to act whether as a Lewis acid, permitting the activation of certain classes of substrates, or as a TM-catalyst, allowing the capture of transient radical species and forging new chemical bonds through the transient Cu^{III}-intermediates (Scheme 3b). Within these lines, several copper-based catalytic

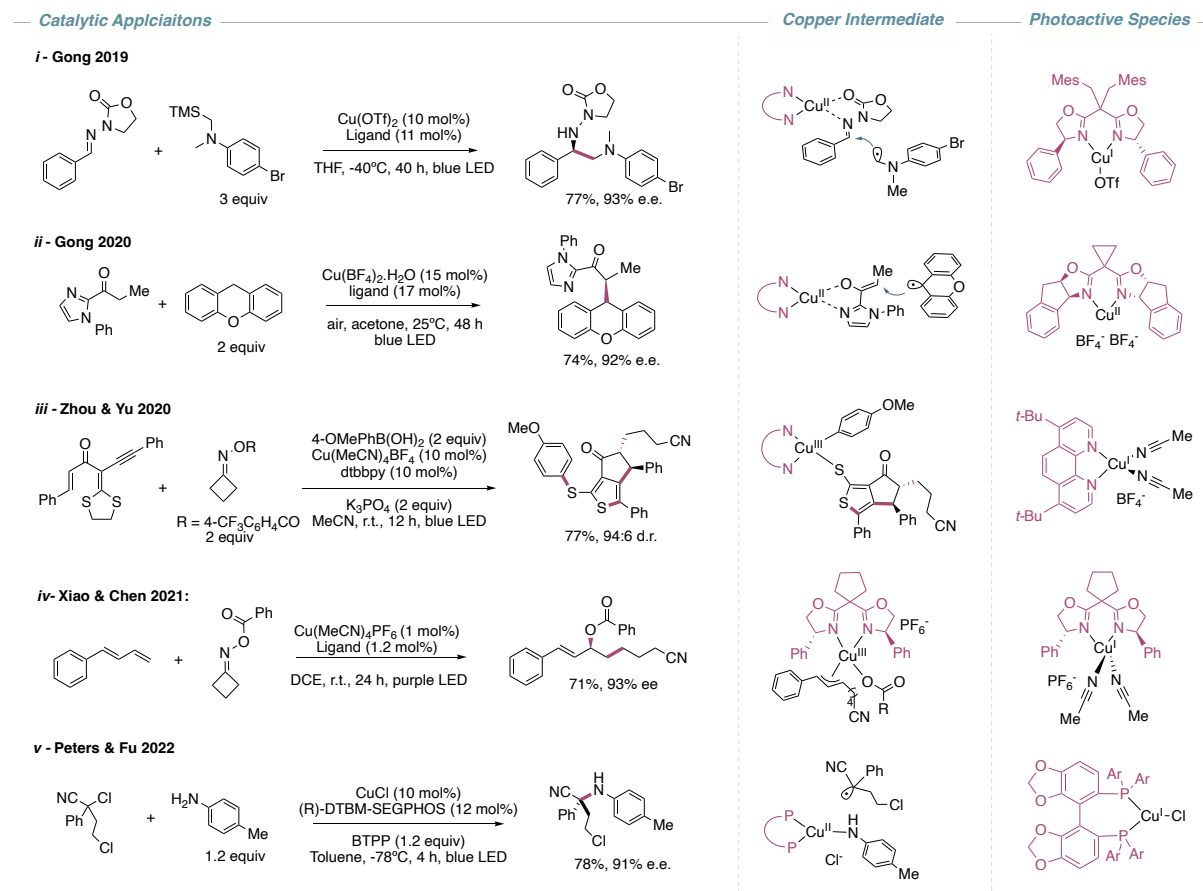
methodologies were designed using copper entities with half-filled coordination sphere. The architecture of the copper species used requires careful manipulation of the ligand field (ligand and counter-anions) since many hurdles can be imposed including (i) the necessity of high-frequency light irradiation, (ii) the short excited-state lifetime, (iii) the tediousness of trapping and stabilizing transient radical species and (iv) the possible reactivity divergence given the high ligand exchange rates at the copper center (Scheme 3b).



Scheme 3: a) Photoredox catalysis in dual catalytic approaches, b) design of open-shell copper complexes for the application as bifunctional catalysts, c) mechanistic picture of bifunctional catalysis using open-shell copper species.

This open-shell catalysis maneuver is usually initiated by the *in-situ* coordination of copper with a ligand, giving rise to a complex endowed with distinguished photochemical attributes. Upon exposure to photonic irradiation, this latter accesses its MLCT state generating an excited complex with potent reductive properties able to donate an electron to a given electrophile causing its reduction to the corresponding radical. Simultaneously, the formed Cu^{II} -species act

either as a LA or as a TM and coordinate with a given substrate before orchestrating the cross-coupling to yield the desired product (Scheme 3c).



Scheme 4: Catalytic applications of open-shell copper species displaying the photoactive species and the TM/LA interactions.

In 2019, Gong group initiated such catalysis-type where they reported the employment of a Cu^{II}-Box ligand as a dual catalyst for the asymmetric aminoalkylation of imines using α -silylamines as radical precursors (Scheme 4, eq. i).⁸⁰ In this framework, Cu^{II}-species engage in two distinct cycles: one involving LA-type reactivity promoting the imine activation, while the other entails the oxidation of the α -silylamine resulting in the photoactive Cu^I-Box complex and the α -amino radical. In turn, these radicals add across the activated Cu^{II}(Box)(imine) complex yielding a transient N-centered radical that gets subsequently photo-reduced by Cu^I-Box. In a similar fashion, Gong group reported the asymmetric cross dehydrogenative coupling between carbonyl compounds and xanthene derivatives using Cu^{II}-Box as a dual photo-oxidant and Lewis Acid (Scheme 4, eq. ii).⁸¹ Zhou and Yu groups reported the use of Cu^I-phenanthroline-based complex for the annulation of *gem*-dialkylthioethers enynes using

oxime esters and arylboronic acids (Scheme 4, eq. iii).⁸² The catalytic cycle commences with the reduction of the oxime ester through the photoexcited Cu^I-complex yielding an iminyl radical that undergoes a consecutive β -scission to lead to a C-centered alkyl radical. This latter in turn adds across the dialkylthioenynone causing an internal domino rearrangement engendering a thio-radical formation that gets captured by the simultaneously formed Cu^{II}(dtbphen)(Ar) and further delivers the cross-coupled product. Chen group reported the asymmetric carboxygenation of dienes employing *in-situ* formed Cu^I-Box to furnish functionalized allylic compounds (Scheme 4, eq. iv).⁸³ This process is initiated with the reduction of the oxime ester by the photoexcited [Cu^I-Box]* followed by a β -scission of the formed iminyl giving rise to a C-centered alkyl radical. This latter adds then across the diene forming a transient allylic radical that gets subsequently trapped by Cu^{II}(Box)(O₂CAr) to afford the C-O cross coupled product through a Cu^{III}-mediated reductive elimination.

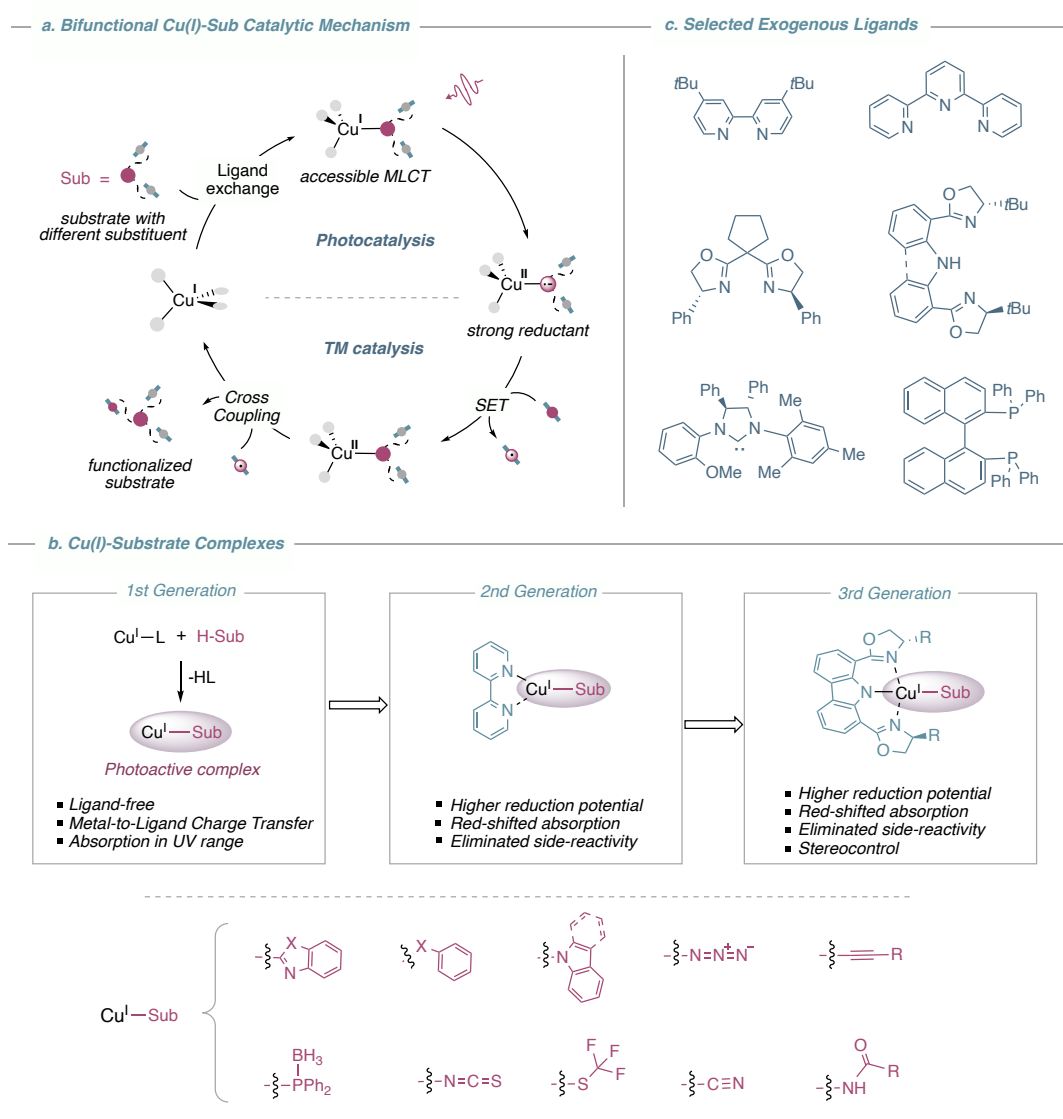
In 2022, Peters and Fu devised the enantioselective amination of tertiary electrophiles using aniline derivatives (Scheme 4, eq. v).⁸⁴ The transformation is inaugurated with the photoexcitation of Cu^I-(P[^]P), inducing the reduction of the electrophile to give rise to a C-centered radical. The parallelly generated Cu^{II}-species undergo a subsequent ligand exchange with the aniline resulting in a Cu^{II}-N complex that combines with the transient radical yielding chiral tertiary amines alongside the regenerated Cu^I catalyst.

3. Copper-Substrate photocatalysis

3.1. Cu^I-Substrate in photocatalysis

Copper offers unique reactivity features consisting of the exploitation of organic substrates as ligands to generate photoactive Copper-Substrate (Cu-Sub) complexes with distinct catalytic activity. Photoexcited Cu^I-Sub type complexes, with characteristic MLCT states, are known for their tendency to act as reductant especially when the substrate's architecture allows charge delocalization within its core which helps extending the excited state's lifetime and red-shifting the absorption frequency. Upon photoexcitation, these complexes reduce electrophiles *via* SET which results in organic radicals alongside Cu^{II}-Sub species that further act as TM-catalysts and orchestrate cross-coupling between the formed transient radicals and the precoordinated substrate (Scheme 5a).

The Cu^I-Sub catalysts can be classified into three generations in which Gen.1 complexes consist of the coordination between copper and a substrate in the absence of exogenous ligands; these complexes require high excitation energy with short wavelengths especially in the case of small non-conjugated substrates (Scheme 5b). Gen.2 complexes possess an exogenous ligand backbone that red-shifts the absorption wavelength helping in the prevention of undesirable photoreactivity of light-sensitive moieties as well as protecting the [Cu-Sub] fragment from agglomeration and/or substrate dimerization. In addition, the presence of external ligands increases the complex' reduction potential expanding the range of redox-compatible functionalities. On the other hand, Gen.3 complexes offer, in addition to the features mentioned in Gen.2, an asymmetric environment in which stereoselective reactions can be performed (Scheme 5c).



Scheme 5: a) Mechanism of bifunctional Cu^I-Substrate in catalysis, b) classification of Cu^I-Substrate complexes, c) compatible ligand scaffolds.

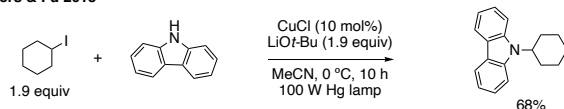
Initial breakthrough using photoactive Cu^I-Substrates in catalysis was achieved in the Ullman coupling reaction by Fu & Peters.⁸⁵ Classic Ullman-type coupling consists of forging a Nuc-Aryl (Nuc = nucleophile) bond starting from a nucleophile and an aryl halide, however, many limitations are imposed such as the requirement of strong bases, stoichiometric amounts of copper reagents, and elevated temperatures (>180°C) narrowing its application in organic synthesis. These drawbacks were faced through the design of radical pathways capitalizing on the photoactivity of the *in-situ* made Cu^I-Nuc complexes.⁸⁵ These are believed to reduce the Aryl-X bond forming the radical Ar• that, in the vicinity of the first coordination sphere of copper, bonds to the nucleophile. Several nucleophiles (i.e. -N(Het),⁸⁶ -OR,⁸⁷ -SR,^{88,89} CN,⁹⁰ Aryl^{91,92}) were successfully implemented with a high tolerance of various reactive functionalities. Nevertheless, these reactions necessitated harsh ultra-violet irradiations (254 nm) requiring further improvements. Peters & Fu introduced carbazoles as nucleophile partners in the copper-catalyzed cross-coupling with tertiary alkyl halides (Scheme 6, eq. i).⁹³ The *in-situ* generated photoactive [Cu^I(carb)₂]⁻ complex absorbs in the blue region lowering the energy requirement compared to saturated amine complexes. In a later report, mechanistic investigations performed by the same group revealed a parallel mechanism in which the free carbazole can absorb light and reduce the organohalides while Cu^{II}-species were still the entities responsible for the forging of the C-N bond.⁹⁴ In 2016, Peters & Fu introduced the use of chiral phosphine ligands alongside the Cu-carbazoles for the enantioselective coupling of amines with tertiary alkyl chlorides under visible light (Scheme 6, eq. ii).⁹⁵ The reaction is initiated by the formation of a complex between copper, carbazole and a chiral phosphine ligand that, owing to the carbazole's extended π -system, absorbs in the visible range of the light spectrum and is able to reduce the tertiary C-Cl bonds. The reaction delivered quaternary aminated carbon centers with high yields and enantioselectivity overcoming the steric limitations encountered in classical S_N-type reactions.⁹⁶ Nevertheless, the reaction was limited to heterocyclic amines with conjugated systems (carbazole and indole derivatives) rendering the incorporation of small amines challenging. To overcome this, Peters and Fu introduced in 2017 the concept of supporting the desired Cu-amines complexes with external tridentate carbazole-based (P[^]N[^]P) pincer ligands in order to shift their absorption to the visible region and avoid carbazole functionalization side-reaction.⁹⁷ This protocol was applied for the functionalization of carbamate derivatives with secondary alkyl halides extending the scope of their previously

reported copper-photocatalyzed amidation protocol under harsh 254 nm irradiations.⁹⁸ Nonetheless, unlike their amidation reaction, the reaction mechanism supported a metallaphotoredox-type system⁹⁹ where the formed Cu^I(P[^]N[^]P) photoredox complex acts only as an electron shuttle while the effective amine delivery is performed by a parallel Cu^{II}-complex.

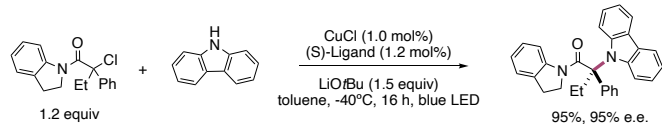
In 2019, Zhang group applied the Cu-carbazole system in the carboamination of olefins using alkyl halide precursors (Scheme 6, eq. iii).¹⁰⁰ The reaction was initiated by the formation of a Cu^I-carbazole complex that, upon visible light irradiation, is excited and reduces the substrates' carbon-halogen bonds. The carbon radical formed adds then across styrene generating a transient benzylic radical that gets further aminated through a rebound mechanism. The reaction had a broad functional group tolerance. Moreover, the introduction of an external ligand with a large π -system such as *rac*-BINOL led to the successful inclusion of amines with small or no conjugated systems owing to the absorption properties of the transient complex Cu-Amine-BINOL in the visible region, hence overcoming the limitation to substrates with extended π -systems. Capitalizing on the same strategy, valuable amines were synthesized by the same group through hydroamination of alkenes using the photoactive Cu-carbazole or Cu-amine-BINOL complexes.¹⁰¹

In addition to Peters and Fu's seminal work, Hwang group have simultaneously developed various reactions involving alkynes using the long-lived and high-reducing photoexcited Cu^I-acetylide complexes.^{102,103} The *in-situ* generated Cu^I-acetylide facilitated a myriad of transformations^{104–110} including several C-C bonds cross-coupling reactions.^{111–113} A compelling illustration of this approach was reported by Lalic group and involved the coupling between alkyl iodides and terminal alkynes in the presence of catalytic amounts of CuCl (Scheme 6, eq. iv). The proposed reaction mechanism is initiated by the formation of a terpyridine-supported Cu-acetylide complex that, upon irradiation, reduces the alkyl iodide through SET to generate a L-Cu^{II}-acetylide species and an alkyl radical that gets intercepted within the first coordination sphere of copper to generate internal alkynes.¹¹⁴ The use of the terpyridine ligand was to suppress the photoinduced dimerization of acetylenes. The same three-component complex was later used for the cross coupling between strained oxime esters and terminal alkynes.¹¹⁵

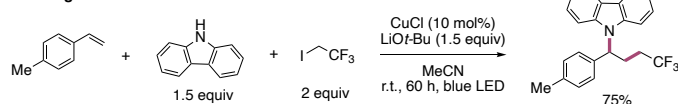
i - Peters & Fu 2013



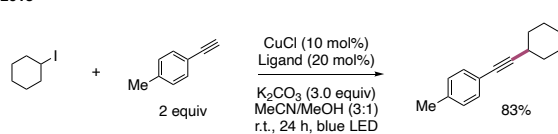
ii - Peters & Fu 2016



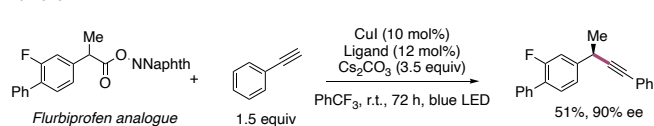
iii - Zhang 2019



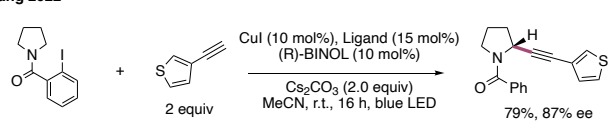
iv - Lalic 2018



v - Liu 2020



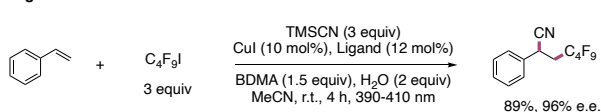
vi - Zhang 2022



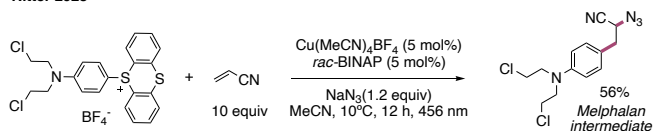
vii - Xiao & Chen 2021:



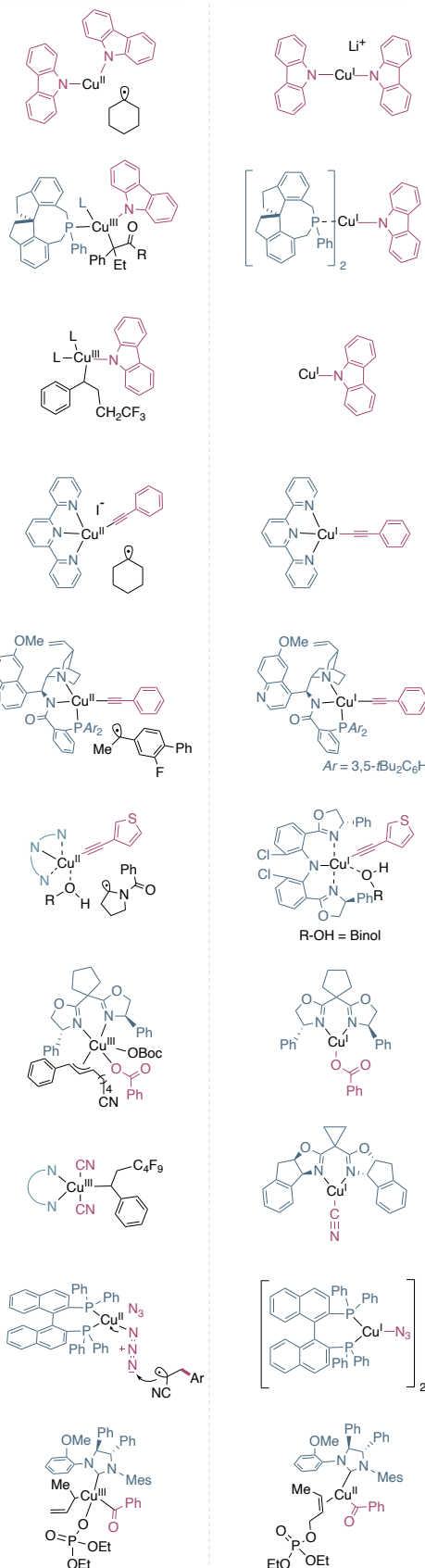
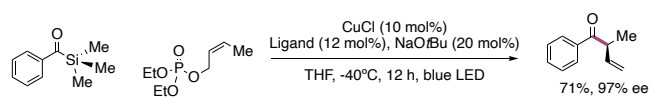
viii - Wang & Xu 2019



ix - Ritter 2023



x - Sawamura 2021:

Scheme 6: Application of Cu^I-Substrate in catalysis

In 2020, Liu group demonstrated that, in the presence of an exogenous chiral N,N,P-ligand, asymmetric decarboxylative alkynylation between phthalimide esters and terminal alkynes can be achieved (Scheme 6, eq. v).¹¹⁶ In a similar fashion, the reaction operates through an initial formation of (L)Cu-acetylide that, upon photo-excitation, reduces the phthalimide esters issuing C-centered radicals upon CO₂ extrusion. These radicals get trapped by the simultaneously formed L-Cu^{II}-acetylide species forging the asymmetric C(sp³)-C(sp) bond. Zhang group introduced the use of chiral pincer ligand BOPA for the enantioselective difunctionalization of alkenes using acetylenes and alkyl iodides.¹¹⁷ In a later report the same group applied their chiral catalytic system for the α -alkynylation of cyclic amines through intramolecular hydrogen-atom transfer (HAT) using catalytic amounts of CuI and BINOL as an additive (Scheme 6, eq. vi).¹¹⁸ The proposed mechanism involves the photoexcited Cu^I-acetylide complex assisted-SET promoting α -aminoradical through a consecutive C(sp²)-I bond reduction and 1,5-HAT. The Cu^{II}-acetylide subsequently captures the α -aminoradical and yields the cross-coupled product. Notably, the additional coordination of BOPA ligand and BINOL with Cu-acetylide increased the complex excited state reduction potential to E_{1/2} = – 3.18 V vs SCE.

A recent report by Xiao and Chen disclosed the enantioselective three-component reaction between dienes, oxime esters, and carboxylic acids in the presence of a simple copper salt to access value-added enantioselective allylic esters (Scheme 6, eq. vii).¹¹⁹ The key mechanistic steps of the reaction involves the ability of Cu^I-carboxylate, in the presence of a chiral Box-ligand, to act as a photoreductant allowing the cleavage and opening of the oxime esters. The transient copper (I) species formed rebound to the allylic radicals leading to C-O coupling products. The method successfully addressed the ability of carboxylates to be implemented as coupling partners in the absence of visible light-induced homolysis (VLH) even when secondary and tertiary acids were used.

In addition, small functional groups could also serve for photoactivity induction in visible light region in the form of Gen.2 or Gen.3 complexes (*vide supra*). Wang and Xu groups devised a cyanofluoroalkylation protocol for the enantioselective functionalization of olefins using a Gen.3 bifunctional Cu^I-CN based catalyst¹²⁰ (Scheme 6, eq viii). Similarly, the reaction proceeds through the initial reduction of the electrophile followed by an addition and transient radical trapping by Cu^{II}-species, the resulting Cu^{III}-complex performs a reductive elimination forging the chiral stereoselective C-CN bond. In 2023, Ritter group conceived an alkene azidoarylation process using arylthianthrenium salts and a photoactive Cu^I-N₃-based catalyst¹²¹

(Scheme 6, eq ix). Interestingly, the reaction termination operates through a radical-ligand transfer mechanism. Moreover, other pseudo-halogens were also compatible with such photoactivation mode including -SeCN,¹²² -SCF₃,¹²³ and -PPh₂BH₃.¹²⁴

In 2021, the phenacyl moiety was introduced as a coordinating partner of copper to achieve the enantioselective allylic functionalization of allyl phosphates. (Scheme 6, eq x).¹²⁵ The reaction involves two distinct light-dependent steps in which the acyl silane is first photoisomerized to the correspondent carbene before coordinating to the chiral copper complex. The resulting complex is excited which results in the reduction of the allylic phosphate and the formation of a Cu^{III}-species upon inter-system crossing (ISC). A follow-up reductive elimination delivers the chiral allylic product with good yields and selectivity.

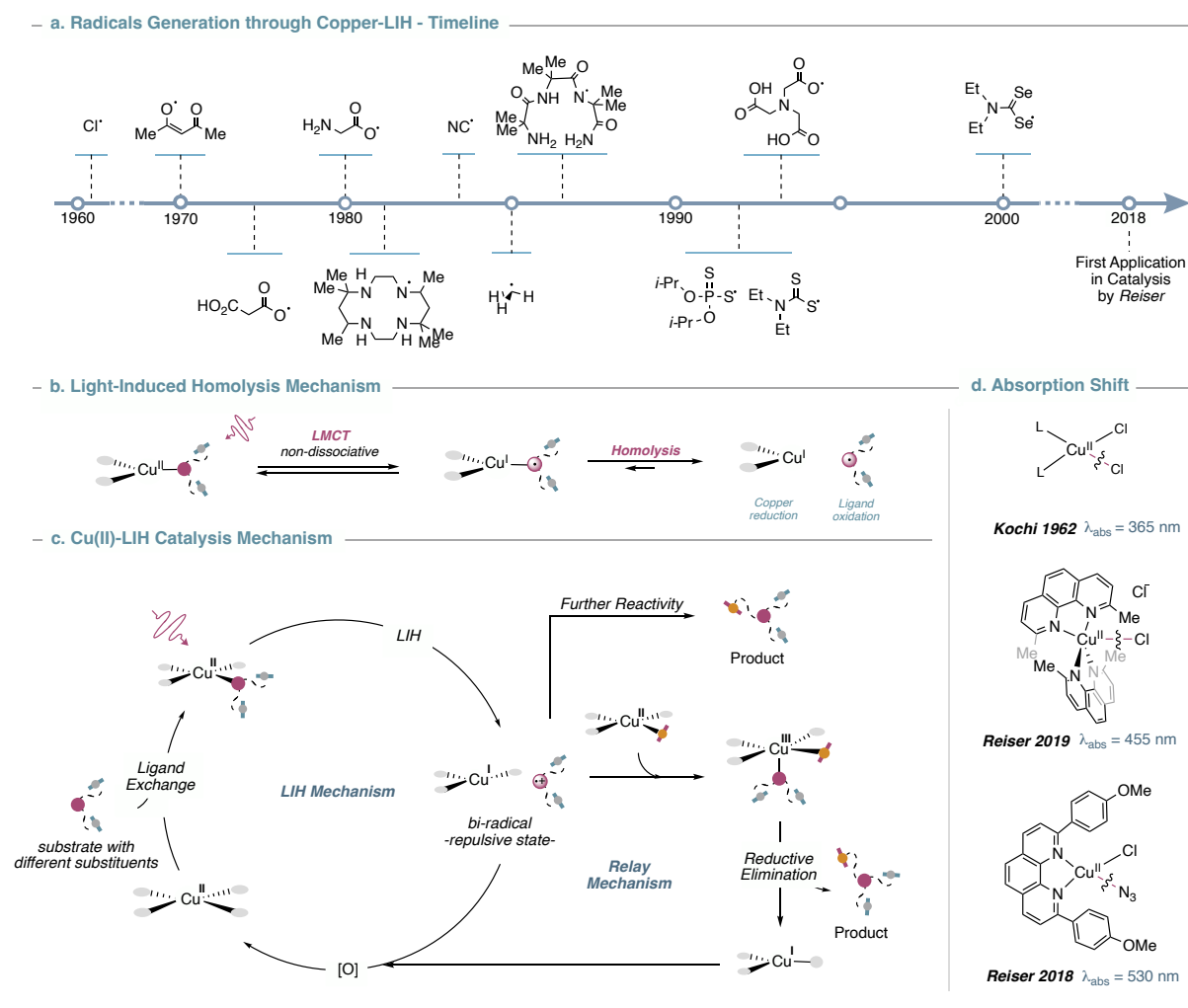
3.2. Cu^{II}-Substrate in photocatalysis

Catalysis by means of (visible) light-induced homolysis (V)LIH has been established recently as a straightforward strategy that mainly operates using first-row transition metals harnessing their high ligand exchange rate compared to their heavier congeners.^{126–128} Light-induced homolysis in a copper-ligand complex is referred to the process where a Cu^{II}-L bond dissociates upon exposure to light irradiation generating Cu^I and the radical L[•]. The pioneering illustration of the LIH concept was reported by Kochi with the photolysis of Cu^{II}Cl₂ to Cu^ICl and a chlorine radical.¹²⁹ Since, various studies in which the oxidation of nucleophiles using copper were reported (Scheme 7a).^{130,131,140–144,132–139}

In terms of reactivity, the binding of the ligand to the electron-deficient copper results in the formation of charge transfer bands that can be photonically attained. The irradiation of such complexes leads to the transfer of electron density from the ligand to the metal center resulting in its partial reduction. In reality, this electronic shift, mostly ligand-to-metal charge transfer, obeys the LIH catalysis only when the excited state is dissociative in its nature (Scheme 7b). Given the propensity of certain conventional photoredox catalysts to operate through LMCT transitions with no observable ligand dissociation or radical pair formation,^{14,15,145} describing LIH processes as ‘LMCT photochemistry’ can be misleading.

Copper-based LIH transformations proceed mechanistically through an initial formation of a copper-substrate complex [Cu^{II}-Sub] issued from a copper source in its electronical ground state and a substrate. The photolysis of Cu^{II}-Sub complex results in Cu^I and a substrate radical

that can either get directly functionalized (addition across unsaturated systems, hydrogen-atom-transfer, etc.) or get incorporated in a subsequent relay mechanism involving Cu^{II} that traps the substrate radical and delivers cross-coupling products through a Cu^{III} -mediated reductive elimination (Scheme 7c).



Scheme 7: a) Timeline of photooxidized ligands via inner-sphere mechanisms using copper, b) mechanism of the light-induced homolysis process, c) mechanism of copper-LIH in catalysis, d) influence of exogenous ligands on the absorption wavelength.

The pre-coordination requirement between copper and the substrate, before engaging in a photoinduced inner-sphere electron transfer, makes it very efficient as an oxidation process irrespective of the complex' excited state's lifetime. This proves to be very advantageous compared to classical photoredox processes as many prerequisites are implicated such as (i) the redox-match between the photocatalyst and the substrate, (ii) the diffusion rate in the solvent for successful encounter with the photocatalyst, and (iii) the requirement of long-lived

excited state lifetime to ensure an efficient bimolecular quenching mandating strenuous ligand design. On the other hand, the LIH process faces challenges due to the requirement of high-frequency light irradiations (365-400 nm) when copper salts are used as well as other 3d-metals.^{126,127} This limitation can be addressed through the introduction of exogenous ligands that red-shift the absorption to visible light. This was showcased by the Reiser group when $\text{Cu}^{\text{II}}(\text{dmp})_2\text{Cl}_2$ was used as a precatalyst.^{146,147} Moreover, the same group recorded larger absorption shifts with the incorporation of ligands with higher conjugated systems such as ‘dap’ in $\text{Cu}^{\text{II}}(\text{dap})\text{Cl}_2$ that was applied for the oxoazidation of vinyl arenes (Scheme 7d).¹⁴⁸

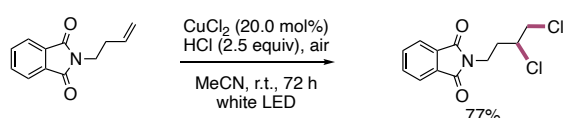
Following Kochi’s proposal and the utilization of stoichiometric amounts of CuCl_2 for dichlorination, oxidation and functionalization reactions,¹²⁹ the umpolung approach for the inversion of chlorine’s nucleophilic property was only recently leveraged in catalysis where generated chlorine radicals were either added across unsaturated systems or used as HAT agents for the activation of inert $\text{C}(\text{sp}^3)\text{-H}$ bonds to promote further functionalization. In 2020, the Wan group reported the vicinal dichlorination of alkenes using catalytic amounts of copper and air as the terminal oxidant (Scheme 8, eq. i).¹⁴⁹ In line with Kochi’s proposal, the reaction is initiated by a LIH of CuCl_2 to generate $\text{Cl}^\bullet$ which adds across the terminal olefin. The issued C-centered radical is chlorinated through another equivalent of CuCl_2 . The catalyst regeneration is performed by the action of oxygen and HCl . Furthermore, chlorine radicals originating from the LIH of $\text{Cu}^{\text{II}}\text{-Cl}$ were successfully trapped using diverse unsaturated systems including alkynes,¹⁵⁰ coumarins,¹⁵¹ and cinnamates.¹⁵²

The Rovis group demonstrated that chlorine radicals issued from LIH of $\text{Cu}^{\text{II}}\text{-Cl}$ can be leveraged as HAT reagents for the activation of inert $\text{C}(\text{sp}^3)\text{-H}$ bonds and applied the concept on the Giese-type hydroalkylation of alkenes (Scheme 8, eq. ii).¹⁵³ In agreement with the LIH proposal, photolysis of $\text{Cu}^{\text{II}}\text{-Cl}$ bond generates chlorine radicals that serve as hydrogen-atom-transfer (HAT) species enabling the generation of C-centered radicals from the corresponding alkanes. The issued alkane radical adds across a Michael acceptor forming a radical intermediate that regenerates Cu^{II} through a metalation-protodemetalation sequence facilitated by the HCl byproduct. Notably, the formed chlorine radical does not react with the Michael acceptor due to polarity mismatch. In a similar fashion, CuCl_2 has been successfully used by Aggarwal for the borylation of non-activated alkanes using B_2cat_2 in an oxidant-free protocol (Scheme 8, eq. iii).¹⁵⁴ The copper catalyst plays a dual role as it initially forms bisboryloxide ($\text{O}(\text{Bcat})_2$) from B_2cat_2 and water before engaging in the photocatalytic LIH process. Unlike Rovis proposal, the direct hydrogen atom abstraction by the formed $\text{Cl}^\bullet$ from the alkane is

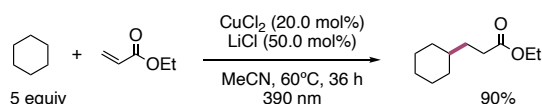
unproductive since it results in chlorination products. Instead, the chlorine radical adds to $O(Bcat)_2$ forming a transient boron ‘ate’ complex that is responsible for the HAT from the alkane. The resulting C-centered radical is borylated through the reaction with $O(Bcat)_2$ and Cu^I species.

– Cu-LIH Application in Catalysis

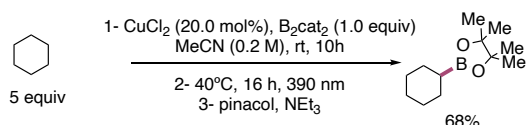
i - Wan 2020



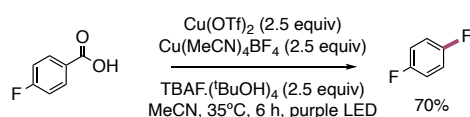
ii - Rovis 2021



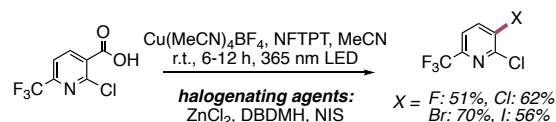
iii - Aggarwal 2023



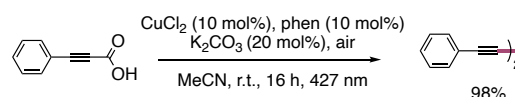
iv - Ritter 2021



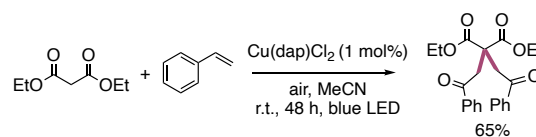
v - Macmillan 2022



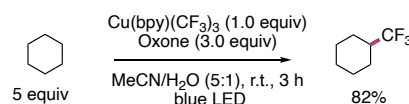
vi - Roy 2023



vii - Reiser 2022



viii - Hong 2021



Scheme 8: Applications of copper LIH in catalysis.

Following the LIH concept, the decarboxylation of carboxylic acids with of Cu^{II} -species was only achieved recently. Although the decarboxylation of aliphatic acids through LIH was performed using different 3d-metals^{126,127} including copper,¹⁵⁵ the engagement of more challenging acids could only be achieved *via* Cu^{II} salts. Cognizant of the challenges related to the decarboxylation of aryl carboxylic acids, the Ritter group devised a decarboxylative fluorination approach employing stoichiometric copper amounts in a dual LIH-Relay type mechanism (Scheme 8, eq. iv).¹⁵⁶ The transformation proceeds through the LIH of Cu^{II} - $OCOAr$ complex, leading to Cu^I and $ArCO_2^\bullet$ that further decarboxylates forming $Ar^\bullet$. This latter rebounds on copper yielding $LCu^{II}(F)(Ar)$. Subsequent oxidation to Cu^{III} by free Cu^{II} -species enables the formation of the fluoroaryl product through a reductive elimination. Relying on the

same dual LIH-Relay strategy, decarboxylative hydroxylation¹⁵⁷ and sulfoximation¹⁵⁸ of arylcarboxylic acids were successfully achieved.

In 2022, Macmillan group reported a unified halo decarboxylation protocol for aryl carboxylic acids using a simple copper salt and N-fluorotrimethylpyridinium triflate (NFTPT) as the terminal oxidant (Scheme 8, eq. v).¹⁵⁹ The process begins with the LIH of $\text{Cu}^{\text{II}}\text{-OCOAr}$, followed by the decarboxylation of the carboxylate radical to yield $\text{Ar}^\bullet$. Treatment with a halogenation reagent results in the halo-product. The halogen delivery mechanism varied, with a radical-relay mechanism traversing Cu^{III} -intermediate for the fluorination and chlorination, while an atom-transfer event takes place for the bromination and iodination. In later reports, the same catalytic system was employed for the decarboxylative borylation¹⁶⁰ and sulfonylation¹⁶¹ of carboxylic acids utilizing B_2Pin_2 and sulfur dioxide as the borylation and sulfonylation reagents respectively. The Roy group showcased the ability of copper to produce $\text{C}(\text{sp})$ radicals through the decarboxylation of arylpropionic acids (Scheme 8, eq. vi).¹⁶² In a similar fashion, the reaction takes off with the LIH of the copper carboxylate complex, forming Cu^{I} and alkynyl radicals upon decarboxylation. The $\text{C}(\text{sp})$ -radical gets captured by copper forming Cu^{II} -acetylide complex that orchestrates a homo Glaser-coupling through bimolecular Cu^{II} -acetylide interaction.

The exploration of copper's propensity to yield C-centered radicals from a $\text{Cu}^{\text{II}}\text{-R}$ complex was first applied by Gong group for the asymmetric alkylation of sulfonylimines, employing benzyltrifluoroborate salts as precursors.¹⁶³ Further investigations by Reiser group unveiled an umpolung strategy for the addition of malonate esters to electron-rich alkenes using copper in the presence of oxygen (Scheme 8, eq. vii).¹⁶⁴ This process unfolds through the VLIH of Cu^{II} -malonate complex, instigating the generation of a polarity-reversed malonyl radical that adds across the styrene. Atmospheric oxygen captures the transient benzylic radical forming peroxo-complex that delivers the oxoalkylation product while concurrently regenerating the Cu^{II} -catalyst. Hong group expanded the scope of copper LIH processes and demonstrated the potential of Cu^{III} -complexes to homolyze using bench-stable $\text{Cu}(\text{bpy})(\text{CF}_3)_3$ for the trifluoromethylation of inert $\text{C}(\text{sp}^3)\text{-H}$ bonds (Scheme 8, eq. viii).¹⁶⁵ The reaction is initiated with the VLIH of the $\text{Cu}^{\text{III}}\text{-CF}_3$ bond generating Cu^{II} -species and $\text{CF}_3^\bullet$ radicals which perform HAT from cyclohexane. The resulting cyclohexyl radical is then oxidized to a cation by Cu^{III} , and undergoes trifluoromethylation through a Cu-mediated radical-polar cross over mechanism.

4. Conclusion

In this chapter, we highlighted the mechanistic versatility copper offers in photocatalytic approaches for the construction of a wide array of chemical bonds that are highly valuable in synthetic chemistry. While the summarized protocols display a wide variety of photoactivated functionalities, we believe that copper's full potential in photochemical transformation is still underexplored. In addition to the development of robust and general strategies for the structural diversification of certain scaffolds (heterocyclic amines, alkynes, carboxylic acids, ...) under mild conditions, the improvement and generalization of copper catalytic approaches is highly dependent on the advancement of ligand design, especially in the case of bifunctional Cu^{I} -chemistry where the ligand is a crucial parameter affecting the compatibility between the photoactivation and the transition-metal catalytic steps. In addition, the LIH-Relay bicatalytic approach constitutes a very appealing platform for coupling reactions. Since such a strategy permits the access to radicals difficultly accessed in other ways, the interception of those in a chiral copper scaffold holds the potential to drive enantioselective cross-couplings. As described in this chapter, the area of copper photocatalysis is exponentially growing and is considered to be an indispensable approach in every chemist's toolbox.

Chapter II

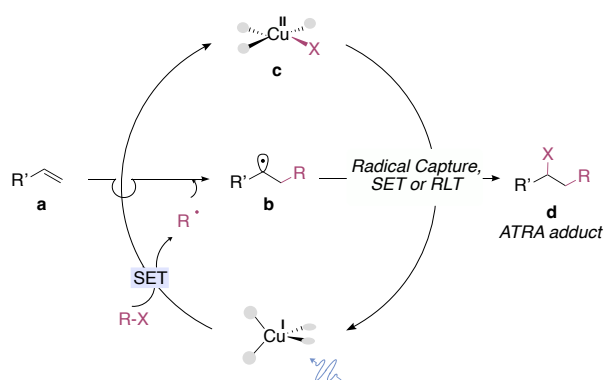
Copper-Photocatalyzed Benzylthio- and isothiocyanation

1. Introduction

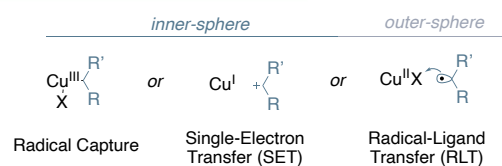
Recent years have witnessed increasing efforts to improve the sustainability of photocatalytic approaches by using inexpensive and readily available metals (Fe, Co, Ni, Cu, etc.) as well as appending atom-economical stratagems.^{14,15,30,126,166} Within this context, the selective difunctionalization of olefins has gained high attention as it represents a practical way to increase molecular complexity and access valuable molecules through the facile conversion of available feedstock chemicals. Atom-transfer radical additions (ATRA), pioneered by Kharasch,^{23,24} represent a unique way to trigger olefins reactivity as it allows the difunctionalization of unsaturated moieties with high atom- and step-economy. Nevertheless, despite the significant progress in this area, reagents compatible with ATRA processes are mainly limited to organic halides.^{21,27,28,30} Among the various photocatalysts that were discovered to promote ATRA processes, copper(I)-phenanthroline complexes are especially suitable given their ability to act beyond single-electron transfer (SET) reagents by engaging with substrates and thus promoting the forging of new chemical bonds with great efficiency.^{21,22,28,29,31,167,168} Cu(I)-complexes initiate such transformations through the reduction of a substrate R-X, yielding a radical R•, which subsequently engages with an olefin (**a**). The simultaneously formed Cu(II)-complex **c** interacts with the transient radical **b**, orchestrating the desired ATRA adduct **d** formation (Scheme 9a).

Nonetheless, the intricacies of the interaction between the radical entity **b** and the Cu(II)-complex **c** remain enigmatic, given the existence of three conceivable routes where **b** may either (i) rebind onto the Cu(II)-complex, traversing a Cu(III)-intermediate, (ii) execute a SET with the Cu(II)-complex, regenerating the Cu(I)-catalyst alongside a carbocation intermediate, or (iii) abstract the counter-anion through a Radical-Ligand Transfer (RLT) mechanism^{169,170} (Scheme 9b).

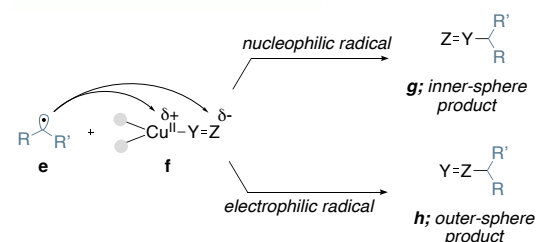
a. General Mechanism of ATRA Reactions



b. Cu-Radicals Possible Interactions



c. Case of Ambident Nucleophiles



Scheme 9: a) General mechanism of ATRA reactions, b) Potential interactions between Cu(II) and transient radicals, c) Reactivity of Cu(II) bearing ambident nucleophiles with organic radicals.

In pursuit of a more profound comprehension of the mechanism, we posited that the presence of an ambident nucleophile ($\text{Y}=\text{Z}$), with a defined coordination pattern at Cu(II) could serve as a discerning factor between inner-sphere and outer-sphere products. This differentiation is contingent upon the isomeric outcome obtained upon interaction with the radical species **e** (Scheme 9c). We reasoned that the product outcome will comply with the philicity of the formed radical adding either onto the Cu(II)-center of the complex **f** or on its Z-end.¹⁷¹ This dictates that electron-rich radicals, hence nucleophilic, will selectively engage with the electron deficient Cu(II)-center allowing the inner sphere product **g** to form, while electron-deficient radicals, that tend to be electrophilic, will associate with the Z-end of the complex leading to **h**.

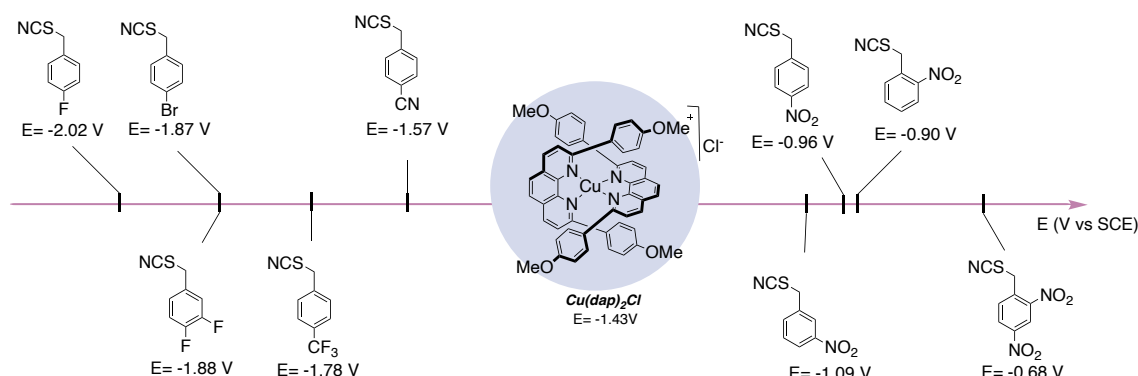
Organic thiocyanates and isothiocyanates constitute important classes of molecules. They are seen as valuable synthetic precursors that can readily interconvert into various functional groups, such as thioureas, disulfides and thiols.¹⁷² Consequently, they have attracted much interest in the pharmaceutical domain as well as other areas.^{172–175} In the many ways to incorporate thiocyanate moieties into molecules, nucleophilic addition/substitutions or addition of thiocyanate radicals to alkenes, alkynes or aromatic systems represent the main routes.^{175–}
¹⁸¹ Based on Houmam's report on the selective cleavage of benzylic thiocyanates,¹⁸² we envisioned that benzylthiocyanates can be amenable to current photocatalytic ATRA

approaches due to their accessible reduction potentials and their ability to release the ambident thiocyanate anion. We, therefore, set out to investigate benzyl thiocyanates as a new class of ATRA reagents for the benzylthiocyanation of olefins using the unique features that copper photocatalysts offer.

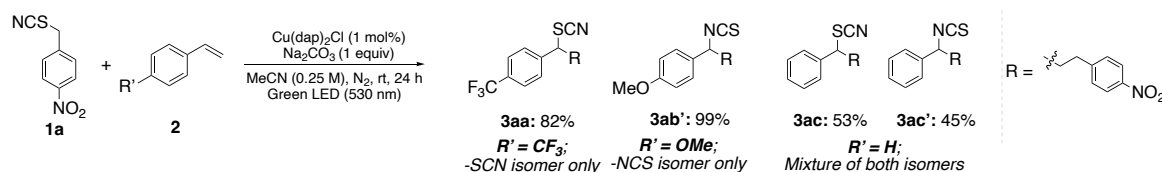
2. Preliminary studies

Having determined the reduction potential of a series of benzyl thiocyanates (Scheme 10a), we settled on 4-nitrobenzyl thiocyanate (**1a**) as a model substrate being in the right range ($E_{\text{red}}(\mathbf{1a}) = -0.96 \text{ V vs SCE}$) for reduction by many reported copper-based photocatalysts. We began our investigations with the exposure of 4-nitrobenzyl thiocyanate (**1a**), olefin (**2**), and Na_2CO_3 in the presence of catalytic amounts of $\text{Cu}(\text{dap})_2\text{Cl}$ (dap = 2,9-bis(4-methoxyphenyl)-1,10-phenanthroline) under green LED irradiation. Indeed, reacting 4-substituted styrene with a strong electron-withdrawing group such as the trifluoromethyl moiety led exclusively to the thiocyanate **3aa** while using a strong electron-donor such as the methoxy group selectively afforded the isothiocyanate **3ab'** in quantitative yield (Scheme 10b). However, subjecting the relatively electron-neutral styrene (**2c**) to the aforementioned conditions delivered both thiocyanate **3ac** and isothiocyanate **3ac'** products with a 1.2:1 ratio. We hypothesized that the low chemoselectivity is due to the involvement of multiple mechanistic pathways.¹⁸³ Thus, we assumed that the presence of thiocyanate source can help to drive the reaction's outcome towards a selective formation of one isomer over the other.

a. Reduction Potential of Substituted Benzylthiocyanates

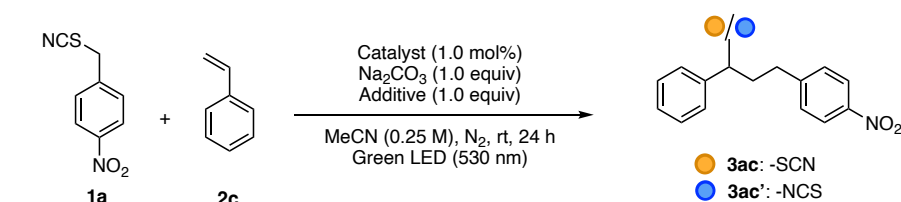


b. Application as an ATRA Reagent



Scheme 10: a) Reduction potential of benzylthiocyanates, b) The use of 4-nitrobenzylthiocyanate as an ATRA reagent with 4-trifluoromethylstyrene (**2a**), 4-methoxystyrene (**2b**) and styrene (**2c**).

Indeed, incorporation of a stoichiometric amount (for optimization details see the experimental part of chapter II) of sodium thiocyanate (entry 2) or related thiocyanates permitted access to thiocyanate **3ac** with much improved chemoselectivity. Alternatively, the Cu(II)-complex Cu(dap)Cl₂ (entry 3) that has been shown to form in situ Cu(I) by Cu–Cl homolysis,¹⁴⁶ or Cu(dmp)₂Cl (dmp = 2,9-dimethyl-1,10-phenanthroline, entry 4) as a more economical alternative¹⁴⁷ gave good, albeit somewhat inferior results. Changing the catalyst to the more reducing Ir(ppy)₃ (E_{1/2} = – 1.73 V vs SCE) or the less reducing Ru(bpy)₃Cl₂ (E_{1/2} = – 0.81 V vs SCE) diminished the selectivity but also the overall yield (entries 5 and 6). The absence of the base had a strongly negative impact on the efficiency even when the reaction time was prolonged to 48 h (entry 7). Attempting to initiate a radical chain using AIBN under thermal conditions resulted in a complete shut-down of the reaction, suggesting that a radical chain pathway for this transformation is not probable (entry 8). Control experiments revealed that the copper catalyst and the light source are necessary components (entries 9 and 10).



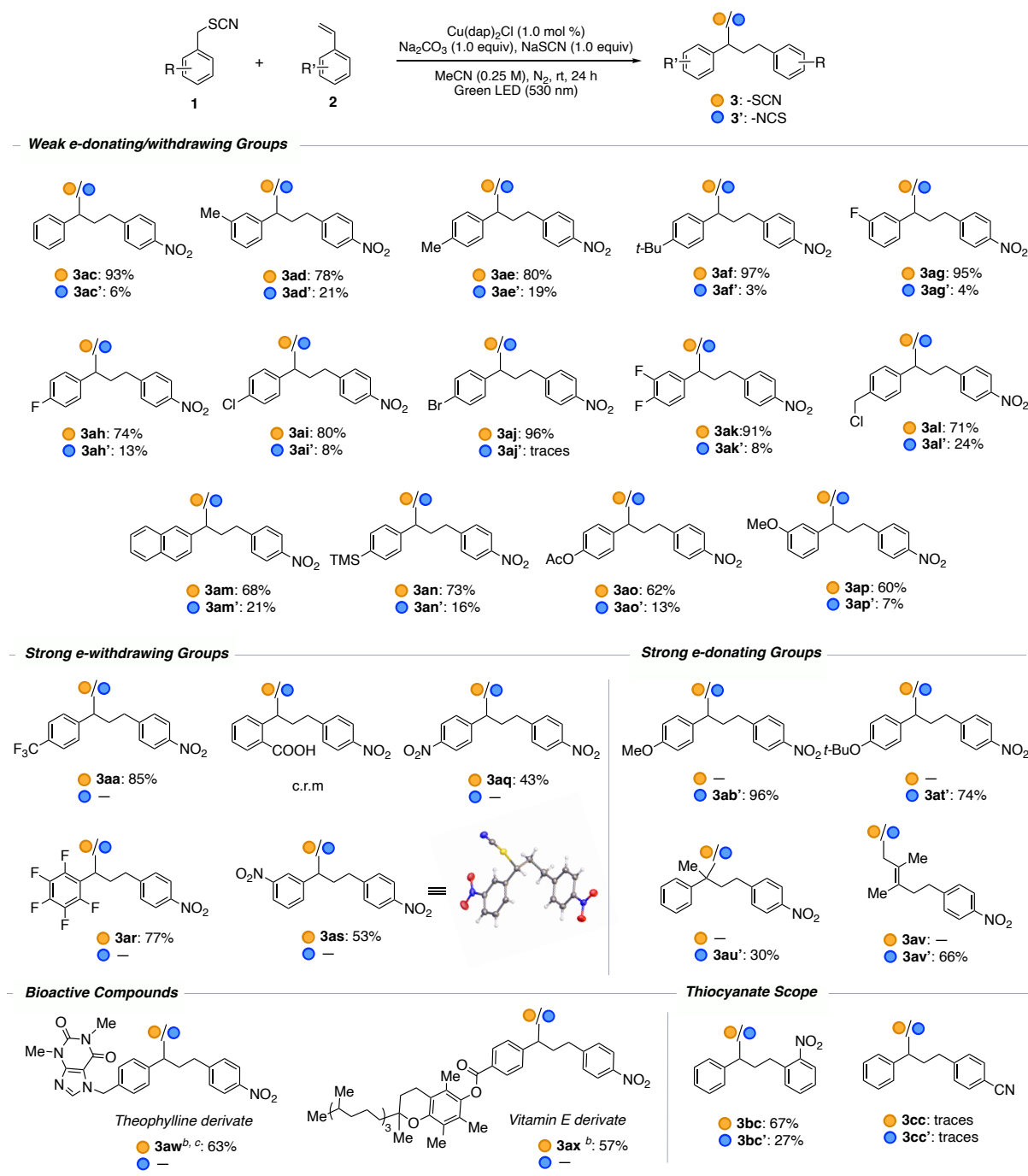
Entry	Catalyst	Additive (equiv)	3ac ^a (%)	3ac' ^a (%)
1	Cu(dap) ₂ Cl	—	53	45
2	Cu(dap) ₂ Cl	NaSCN (1.0 equiv)	93	7
3	Cu(dap)Cl ₂	NaSCN (1.0 equiv)	84	16
4 ^b	Cu(dmp) ₂ Cl	NaSCN (1.0 equiv)	81	6
5 ^b	Ir(ppy) ₃	NaSCN (1.0 equiv)	56	12
6 ^b	Ru(bpy) ₃ Cl ₂	NaSCN (1.0 equiv)	26	6
7 ^c	Cu(dap) ₂ Cl	—	10 (40) ^d	11 (40) ^d
8 ^e	AIBN	NaSCN (1.0 equiv)	n.r.	n.r.
9	—	NaSCN (1.0 equiv)	n.r.	n.r.
10 ^f	Cu(dap) ₂ Cl	NaSCN (1.0 equiv)	n.r.	n.r.

Table 1: Optimization of the reaction's conditions. ^a Yields determined by ¹H-NMR using tetrachloroethane as an internal standard, ^b irradiated by a 455 nm blue LED, ^c in the absence of the base, ^d after 48 h, ^e reaction performed at 80 °C, ^f in the absence of the light source.

3. Substrate scope

With the optimal conditions in hand (Table 1, entry 2), we evaluated the scope of the transformation (Scheme 11). Styrenes with weak electron-withdrawing or donating substituents generally gave the products with a marked preference for the thiocyanates (**3ac-3ap**). Good functional group tolerance was observed, i.e. alkyl, halide, naphthyl, trimethylsilyl and certain oxygen-based substituents in the arene moiety. The use of styrenes with much stronger electron-withdrawing groups, such as trifluoromethyl-, nitro- or pentafluorostyrene, selectively afforded the thiocyanates (**3aa**, **3aq-3as**) with no observable isothiocyanate isomer. In contrast, styrenes with a strong electron-donating alkoxy group resulted in a complete reversal of selectivity, furnishing exclusively the isothiocyanate products **3ab'** and **3at'**. This selectivity trend was also observed when α -methylstyrene and 2,3-dimethylbutadiene were employed leading solely to the isothiocyanates **3au'** and **3av'**.

Scope of the Reaction ^a

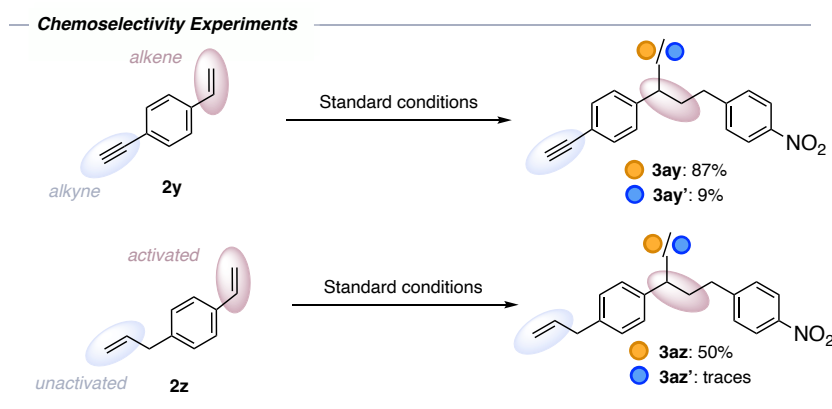


Scheme 11: Thiocyanate scope, ^a isolated yields.

The thiocyanation protocol could also be demonstrated for the late-stage functionalization of some biologically active molecules. Subjecting theophylline- and vitamin E-derived substrates to the optimal conditions delivered the corresponding ATRA adducts (**3aw**, **3ax**) with good yields. Nevertheless, the protocol was inefficient towards non-activated olefins, electron-deficient olefins, and alkynes reflecting the electrophilic character of the presumably

formed 4-nitrobenzyl radical.¹⁷¹ Trying to incorporate other benzyl thiocyanates was only successful in the case of 2-nitrobenzyl thiocyanate (**3bc/3bc'**) while other moieties such as *p*-cyanobenzylthiocyanate gave only trace amounts of product due to the higher reduction barrier ($E_{\text{red}} = -1.57 \text{ V vs SCE}$) being out of reach for the copper photocatalysts employed (see the experimental part).

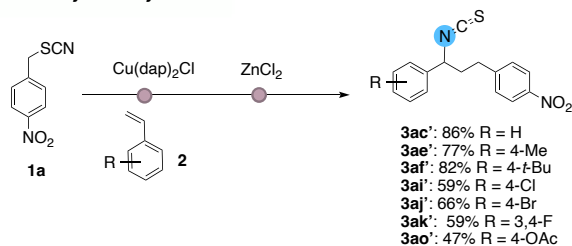
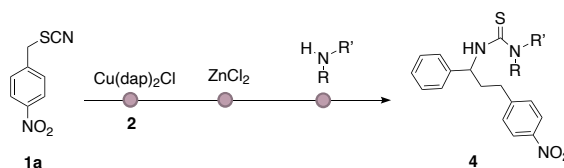
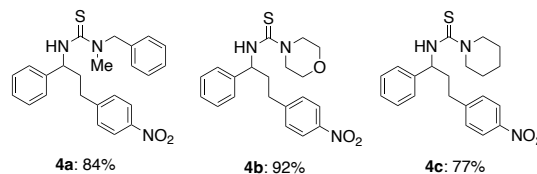
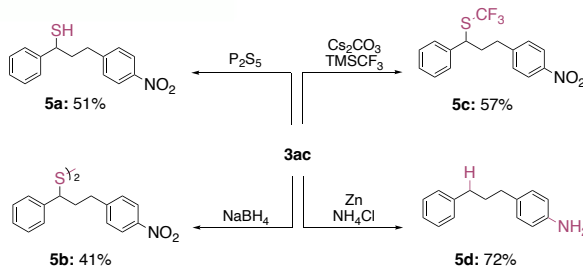
The chemoselectivity of the title transformation was assessed by incorporating competitive C-C unsaturated motifs within the same substrate. When both vinyl and ethynyl moieties were present, the vinyl group was selectively functionalized affording the products **3ay** and **3ay'**. Furthermore, the simultaneous presence of the vinyl and allyl groups gave rise to **3az** with the allyl moiety remaining intact (Scheme 12).



Scheme 12: Chemoselectivity experiments.

4. Applications

To broaden the scope of this ATRA reaction, we sought to develop of a protocol to selectively access isothiocyanates in a subsequent reaction. Given the frequent presence of benzyl isothiocyanates in bioactive molecules and their importance as synthetic intermediates,^{172,184} we targeted the design of a one-pot procedure encompassing sequential ATRA followed by a zinc mediated isomerization.¹⁸⁵ Gratifyingly, zinc chloride was proven to be an efficient isomerization mediator promoting the one-pot access to isothiocyanates with good overall yields (Scheme 13a). Expanding this one-pot protocol by adding secondary amines gave direct access to thioureas **4a-4c**, representing common structural motifs with high relevance in many domains^{186,187} (scheme 13b).

a. Isothiocyanate Synthesis**b. Thiourea Synthesis****c. Further Diversifications**

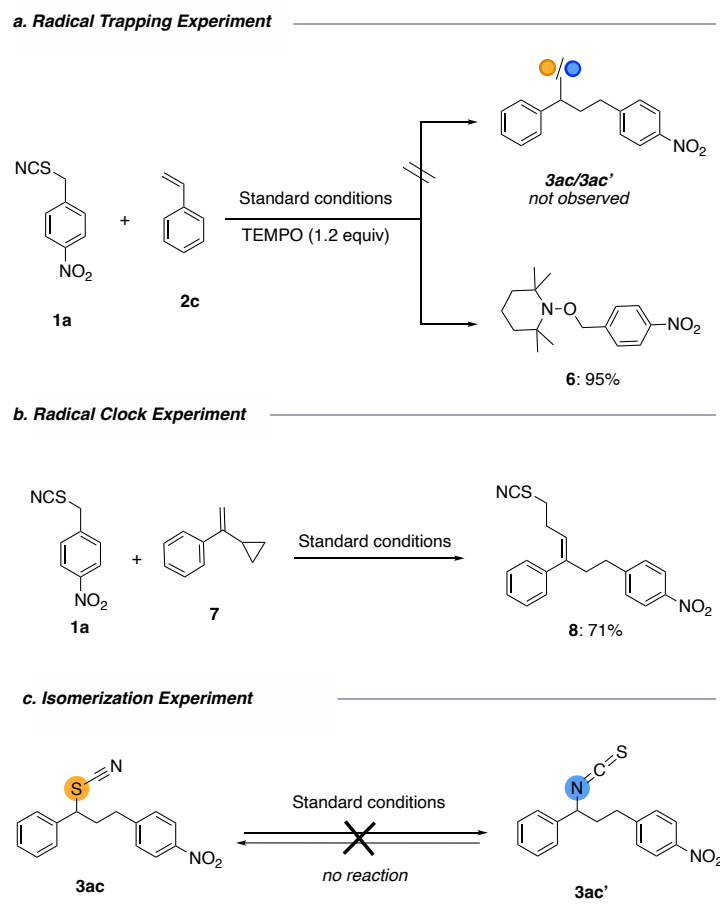
Scheme 13: Thiocyanate diversification: (a) access to isothiocyanates, (b) access to thioureas, (c) Further diversifications.

In addition, the thiocyanates **3** provide a robust synthetic platform to access different functionalities (Scheme 13c). For instance, the thiol **5a** was obtained by treatment of **3ac** with phosphorus pentasulfide while the reduction of **3ac** using NaBH₄ delivered the disulfide **5b** through the correspondent S-CN cleavage followed by S-S homocoupling. Furthermore, trifluoromethylthioether **5c**, an attractive building block in medicinal chemistry due to its typical lipophilicity,^{188,189} could be obtained by exposing **3ac** to trifluoromethyltrimethylsilane in the presence of cesium carbonate. Notably, upon the reduction of the nitro group in **3ac** with zinc the thiocyanate moiety is removed yielding the aniline derivate **5d** in 72% yield. Thus, the thiocyanate can serve as a traceless directing group, allowing overall a formal hydrobenzylation of styrenes.

5. Mechanistic studies

Several experiments were carried out to gain deeper insights into the mechanism of this reaction. Upon addition of stoichiometric amount of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to a reaction mixture of **1a** and **2c**, a complete shut-down of the benzylthiocyanation was observed. Instead, the TEMPO adduct **6** was isolated confirming the generation of the 4-nitrobenzyl radical upon the reductive cleavage of **1a** (Scheme 14a). The employment of a radical clock reagent **7** under the standard conditions exclusively led to the

formation of **8** through radical-initiated ring opening followed by a subsequent thiocyanation confirming the intermediacy of a benzylic radical (Scheme 14b).

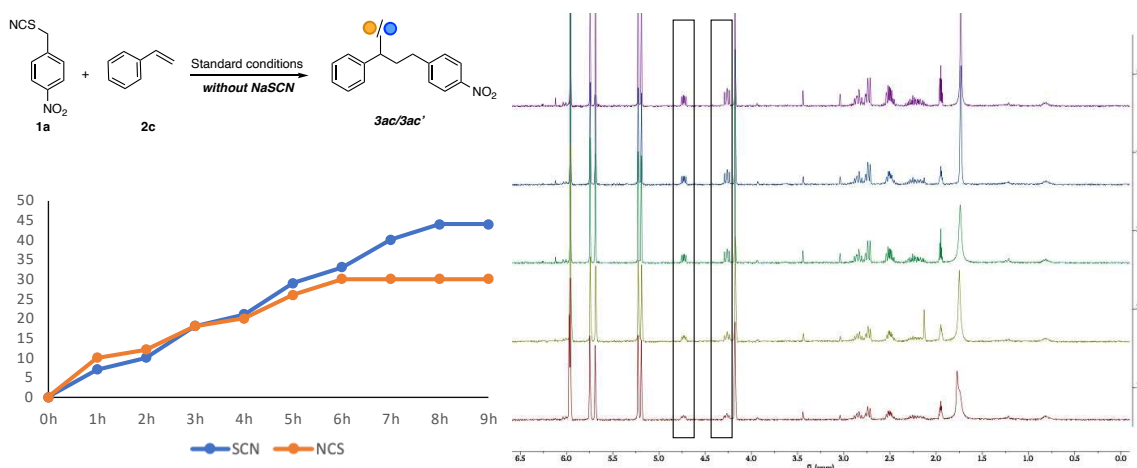


Scheme 14: Mechanistic investigations, (a) radical trapping experiment, (b) radical clock experiment, (c) isomerization experiments.

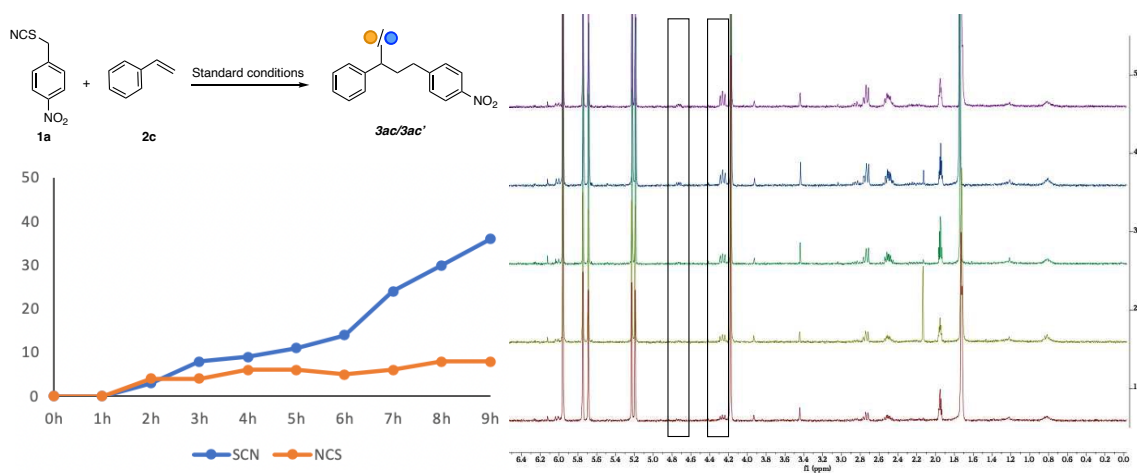
In order to gain a deeper understanding of the formation of the -SCN/-NCS isomers, we exposed **3ac** or **3ac'** to the reaction conditions and ruled out the potential photomediated isomerization (Scheme 14c).¹⁷⁹

Moreover, following the evolution of **3ac** and **3ac'** over time revealed their steady, independent development in the presence and absence of sodium thiocyanate as an additive (Scheme 15).

a. Concentration vs Time Profile in the Absence of NaSCN



b. Concentration vs Time Profile in the Presence of NaSCN

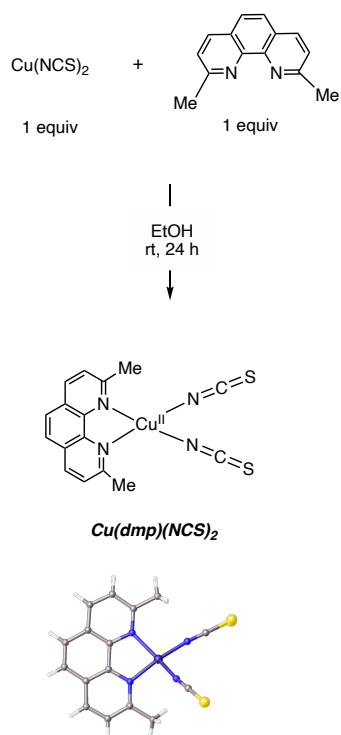


Scheme 15: Concentration versus time profiles of the formation of the -SCN and -NCS isomers, a) without NaSCN, b) in the presence of NaSCN.

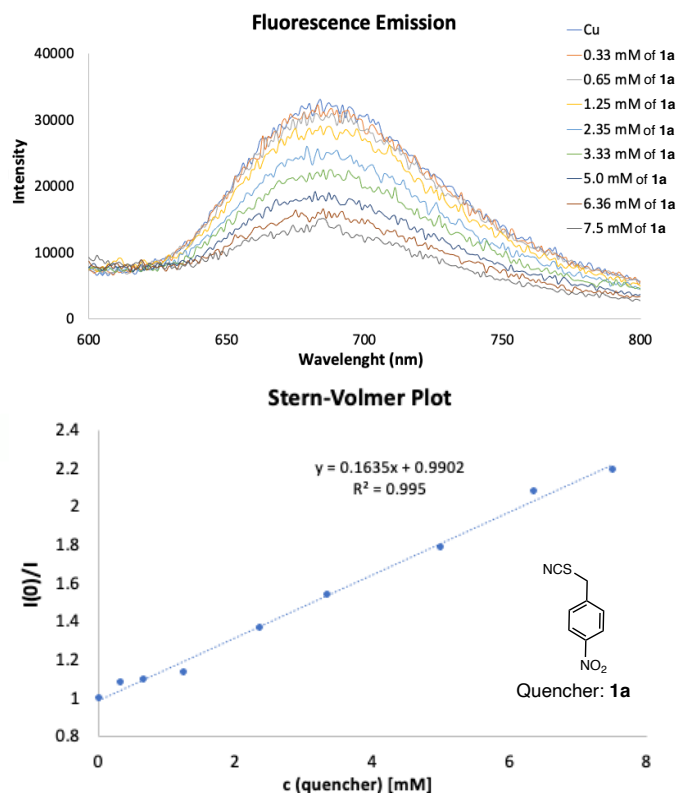
To probe the role of Cu(II) for the thiocyanate delivery to the products, attempts to obtain a crystal structure of a Cu(II)(dap)-thiocyanate complex failed but we were successful with the structurally more simple ‘dmp’ ligand which confirmed that Cu(II) coordinates to the N-end of the thiocyanate anion (Scheme 16a) in line with literature precedents.^{190–194} The decrease of the fluorescence intensity of the excited-state Cu(dap)₂Cl* in the presence of **1a** proved its interaction with the copper catalyst (Scheme 16b). Reacting Cu(dap)₂Cl with **1a** under green LED irradiation at room temperature resulted in the formation of the C-C coupled dimer **9** derived from the corresponding benzylic radicals along with Cu(dap)(NCS)₂ (Scheme 17, black spectra), which was confirmed by its independent synthesis (Scheme 17, red spectra). It is to note however that Cu(dap)(NCS)₂ is the predominant, but not the sole, paramagnetic species after 24 h of irradiation. Due to the very poor solubility of Cu(dap)(NCS)₂ in most organic

solvents, recrystallization in DMSO led to the decomposition and the formation of $[\text{Cu}(\text{dap})_2][\text{Cu}_2(\text{NCS})_3]$ accompanied with the release of $(\text{SCN})_2$.

a. Cu-SCN Coordination

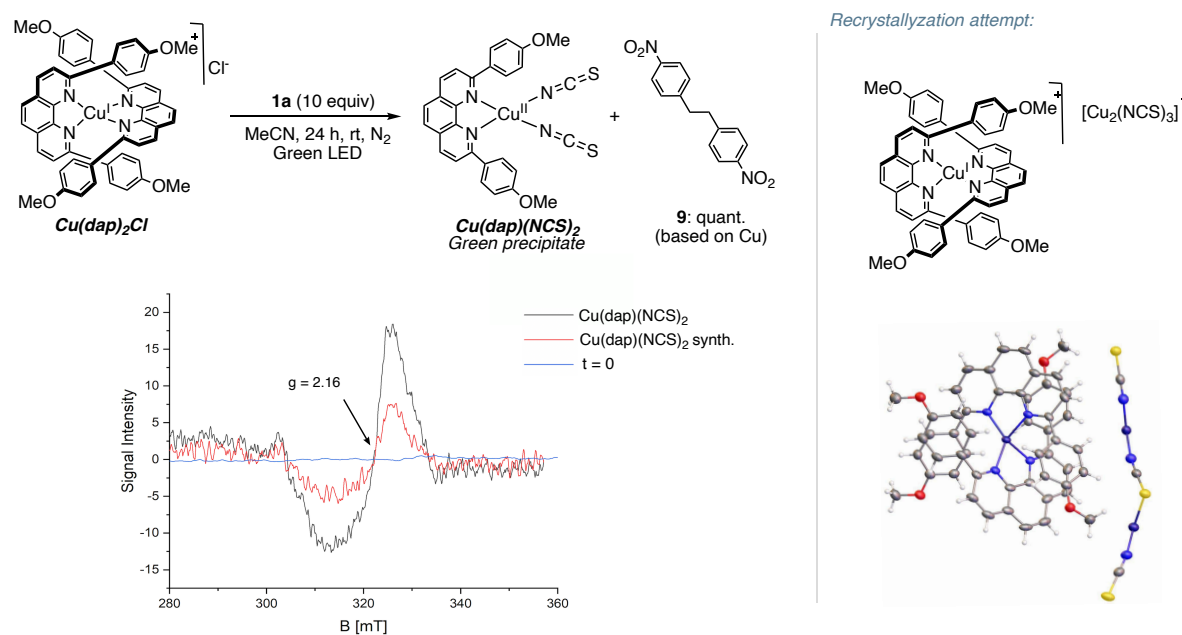


b. Stern-Volmer plot of $\text{Cu}(\text{dap})_2\text{Cl}$



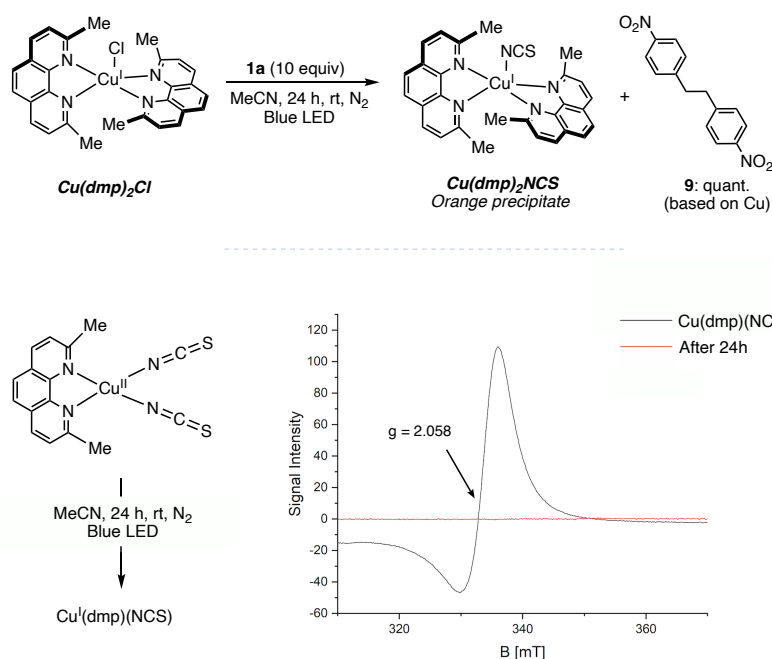
Scheme 16: a) Coordination mode between copper and thiocyanate, b) fluorescence quenching and Stern-Volmer plot of $\text{Cu}(\text{dap})_2\text{Cl}$ by 1a.

Moreover, the $\text{Cu}(\text{dap})_2\text{Cl}$ and the resulting $\text{Cu}(\text{dap})(\text{NCS})_2$ could be differentiated through UV-vis spectra especially since $\text{Cu}^{\text{II}}(\text{dap})$ complexes are known to have a lower absorption intensity in the 500-600 nm region (see the experimental section).



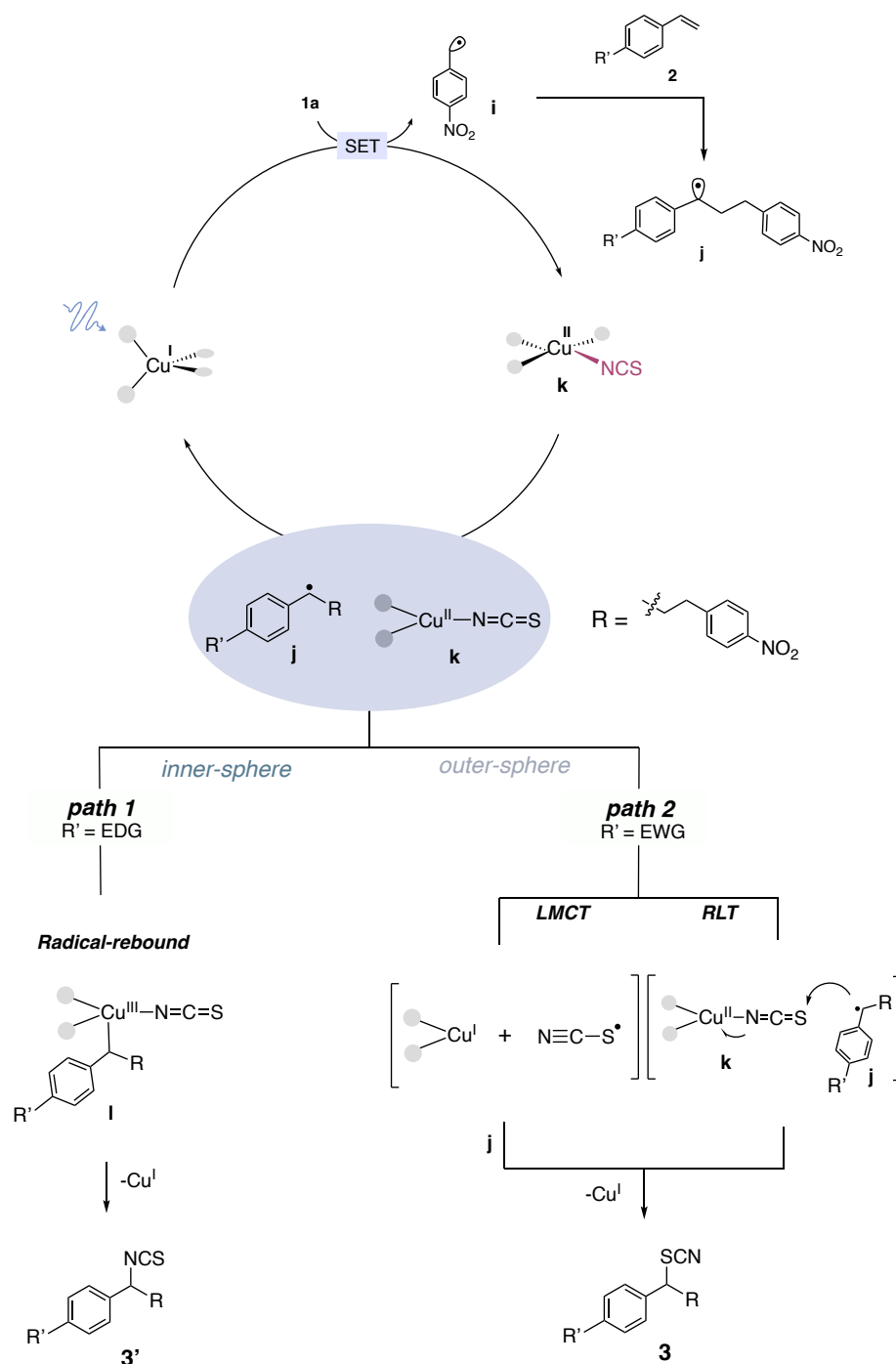
Scheme 17: Attempts to trap copper thiocyanate intermediate.

On the other hand, mixing **1a** with $\text{Cu(dmp)}_2\text{Cl}$ led to no reaction at room temperature in the dark, as confirmed by $^1\text{H-NMR}$ spectroscopy. However, when this mixture was subjected to blue light irradiation, the reddish solution turned into orange accompanied by the formation of an orange precipitate, which was identified as $\text{Cu(dmp)}_2\text{NCS}$ (Scheme 18, top). Surprisingly, we were not able to detect any Cu(II) -species using EPR spectroscopy. To understand the obtention of $\text{Cu(dmp)}_2\text{NCS}$, we have attempted to probe a potential visible-light-induced homolysis mechanism as we assumed that a Cu(II) -complex is transiently formed.¹⁹⁵ The irradiation of Cu(dmp)(NCS)_2 for 24 h led to the loss of the paramagnetic signal in the EPR spectra suggesting the formal reduction to Cu(I) -species through a ligand-to-metal charge transfer (LMCT) process accompanied by a release of a thiocyanate radical (Scheme 18, bottom). The reactivity of the thiocyanate radical in the photoreduction reaction was not further examined. Notably, during our optimization studies we observed the 1,2-dithiocyanated styrene as a side-product (see experimental part). The formation of this latter can only be initiated through a $\text{SCN}^\bullet$ addition to the styrene.^{196,197}



Scheme 18: Photolysis of Cu(dmp)(NCS)₂ and confirmation of a VLIH pathway.

On the basis of the mechanistic evidence, the reactivity pathway of the reaction is initiated by the formation of the 4-nitrobenzyl radical **i** and the Cu(II)-NCS species **k**, obtained from the reductive cleavage of **1a** by the photoexcited copper catalyst. The radical **i** adds to the olefin **2** forming a transient benzylic radical **j** that interacts with **k**. The interaction between these is dependent on the philicity of the C-centered radical. In the case of strong electron-donating substituent, where only the isothiocyanate isomer is observed (path 1), the NCS-moiety is transferred via an inner-sphere radical rebound mechanism initiated by a radical capture generating transient Cu(III)-complex **l** that forges the C-N bond in **3'** through a reductive elimination. On the other hand, electron-deficient radicals, where only S-end compounds **3** are formed, react in an outer-sphere fashion via two probable mechanisms (path 2) in which **j** can whether (i) perform a radical-coupling with SCN[•] issued from a LMCT in the Cu(II)-NCS bond¹⁹⁵ or (ii) abstract the -SCN ligand from the nucleophilic S-end¹⁹⁸ of **k** via a RLT mechanism (Scheme 19).¹⁹⁹

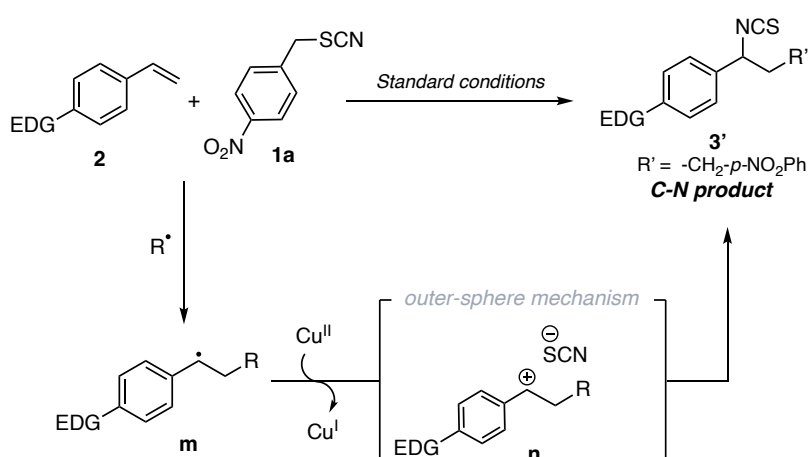


Scheme 19: Proposed reaction mechanism

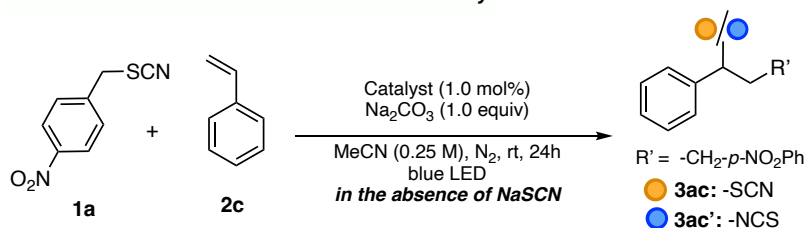
The path in which Cu(I) is regenerated through a SET is unlikely since the oxidation of the radical **m** would form the correspondent cation **n** that is relatively soft and is expected, following the HSAB theory, to lead to the C-S product instead of **3'** (Scheme 20a).^{180,185,200,201} To further probe the possibility of a redox-cycle, we decided to investigate the influence of the

catalyst's oxidation potential on the chemoselectivity outcome of our reaction. Since Cu(II)-species are weaker oxidants compared to other commonly used photoredox catalysts, we expected that implementing catalysts able to convert the radical **m** to **n** will display a distinct selectivity towards the obtention of one major isomer. Reacting **1a** and **2c** in the absence of an exogenous thiocyanate source with a variety of catalysts with different oxidation potentials was less efficient in the case of outer-sphere photoredox catalysts (entries 2, 3, and 4, Scheme 20b) highlighting that an ionic mechanism is not optimal. Moreover, the **3ac**/**3ac'** ratio could be correlated with the increase of the catalysts' oxidation potential suggesting that the passage through cationic intermediates favors the obtention of the C-S product.

a. Alternative Proposal of an Ionic Mechanism



b. Oxidation Potential Effect on the Selectivity



Entry	Catalyst	3ac ^a	3ac' ^a	Ratio
1	Cu(dap) ₂ Cl	53%	45%	1.17
2	Ir(ppy) ₃	16%	12%	1.33
3	Ru(bpy) ₃ Cl ₂	42%	8%	5.25
4	Ir(dFCF ₃ ppy) ₂ (dtbbpy)PF ₆	18%	5%	3.6

^a yield determined by ¹H-NMR using tetrachloroethane as an internal standard

Cu(dap) ₂ Cl	Ir(ppy) ₃	Ru(bpy) ₃ Cl ₂	Ir(dFCF ₃ ppy) ₂ (dtbbpy)PF ₆
Cu(II) ⁺ /Cu(II) = -1.43 V Cu(II)/Cu(I) = 0.61 V	Ir(III) ⁺ /Ir(IV) = -1.73 V Ir(IV)/Ir(III) = 0.77 V	Ru(II) ⁺ /Ru(III) = -0.81 V Ru(III)/Ru(II) = 1.29 V	Ir(III) ⁺ /Ir(IV) = -0.89 V Ir(IV)/Ir(III) = 1.69 V

Scheme 20: a) Benzylic isothiocyanation following an ionic mechanism b) correlation between the catalysts' oxidation potential and the -SCN/-NCS ratio

6. Summary

In summary, we have developed a copper-photocatalyzed benzylthiocyanation strategy using substituted-benzylthiocyanates as novel ATRA reagents. This protocol permits the access to thiocyanate and isothiocyanate derivatives in a highly chemo- and regioselective manner. The transformation was substrate dependent and selectively delivered the -SCN and -NCS isomers depending on the electronical properties of the substituted olefins. Mechanistical studies suggested that the reaction proceeds through distinct mechanistic pathways depending on the type of substrates. The incorporated thiocyanate and isothiocyanate functionalities were shown to be easily converted to various moieties of high interest in the synthetic and pharmaceutical fields.

Chapter III:

Palladium-free Wacker Oxidation using Copper as a site-selective sequential photooxidant-photoreductant

1. Introduction

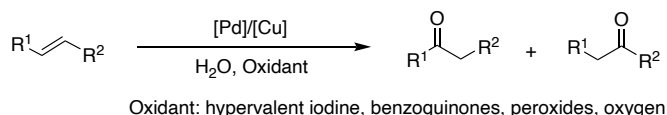
The ubiquity of the carbonyl scaffold in pharmaceutical and agrochemical compound libraries has spurred a heightened interest in developing more efficient and sustainable protocols for converting olefins into their corresponding carbonyl derivatives.^{202–205} The initial breakthrough was achieved through the Wacker process,^{206,207} leveraging the synergistic interplay between copper and palladium for the effective conversion of alkenes into aldehydes or ketones (Scheme 21).^{208,209,218,210–217} However, the Wacker-type reaction is afflicted with significant drawbacks: (i) the catalyst system proves less efficient for activated olefins, (ii) it necessitates high temperatures and pressures, (iii) it suffers from non-sustainability due to the reliance on palladium.²¹⁸ Besides, a major hurdle is faced when oxygen is used as the oxidant since it promotes the oxidative C-C cleavage of the olefin and is especially problematic for styrenes.^{219,220}

The substitution of palladium with an abundant and cost-effective metal holds the promise of transforming the Wacker-type reaction into a more sustainable and economically viable platform for olefin oxidation. Recent advancements, confining the catalytic system to a single metal, have introduced alternative strategies for oxidizing activated olefins, thereby redefining the paradigm of Wacker-type reactions.^{221–224} By comparison, procedures relying solely on 3d-metals are relatively scarce,^{220,225–227} spurring a quest for such methodologies. In 2016, the Lei group reported the use of a dual photoredox-cobalt system for the Wacker oxidation of

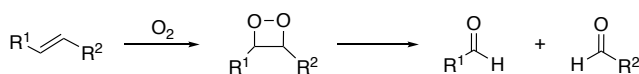
olefins with a distinct anti-Markovnikov selectivity (Scheme 21).²²⁵ In their approach, the olefin is oxidized to the correspondent radical cation followed by a hydration before getting converted by the cobalt catalyst to the ketone product. Another mechanistically different methodology to achieve Wacker oxidation was performed by Han's group using hydrosilane alongside iron under aerobic conditions in which the *in-situ* formed iron hydride species add across the olefin generating transient C-centered radicals that get further trapped with oxygen.²²⁰ With this in mind, we endeavored to design a Wacker-type oxidation of styrenes, capitalizing on the absorbance properties of phenacyl intermediates.

Reported Wacker-Tsuji Oxidation

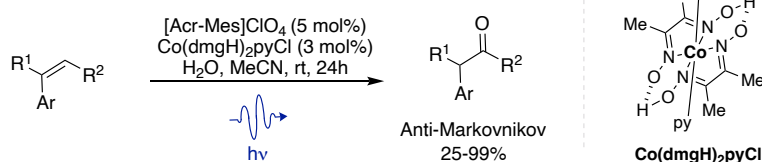
Classical Wacker-Tsuji oxidation:



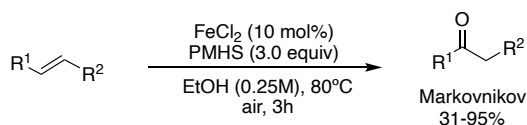
Use of oxygen as an oxidant



Lei (2016)



Han (2017)



Drawbacks

- Stoichiometric copper amounts
- Stoichiometric oxidant amounts
- Limited TON of Pd
- C-C cleavage when O_2 present

- Only Anti-Markovnikov product
- Highly oxidative conditions

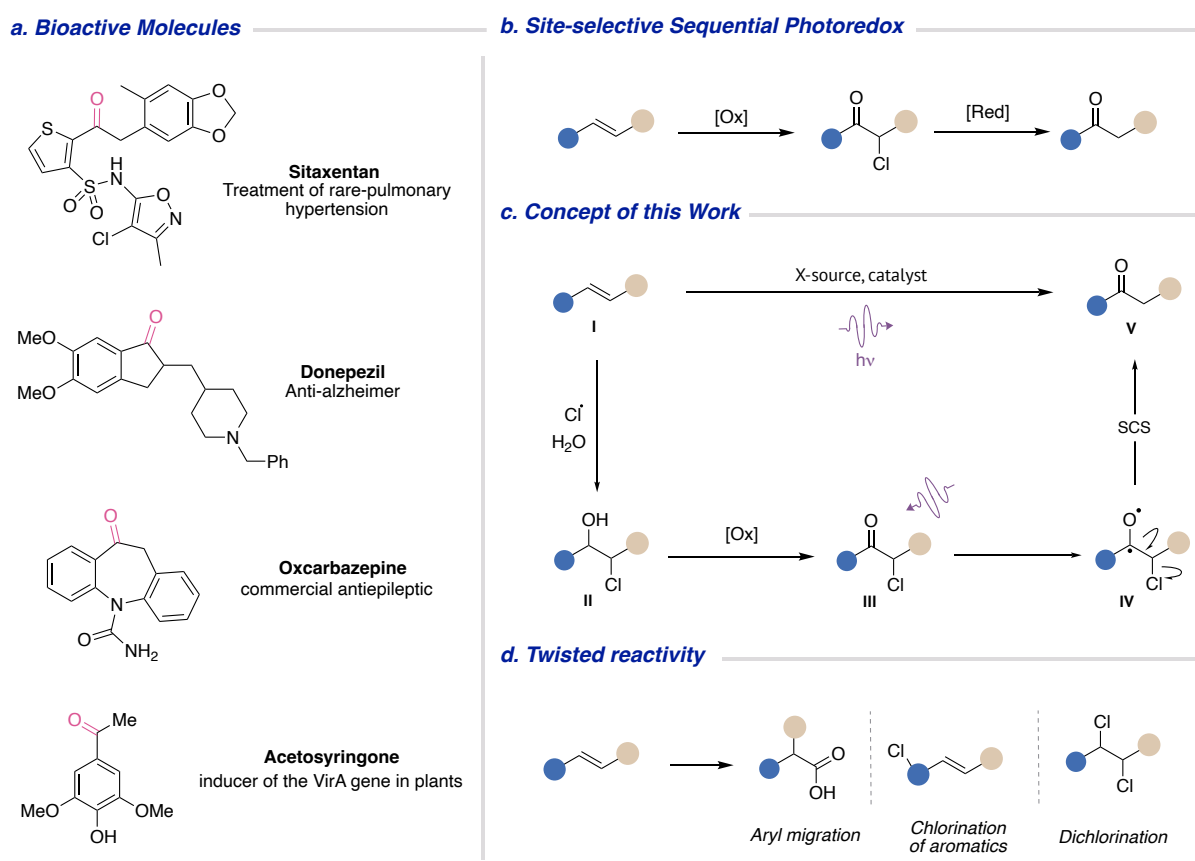
- Use of hydrosilanes
- Presence of O_2

Scheme 21: Wacker-Tsuji reaction precedents.

2. Study concept

Given the prevalence of the phenacyl moiety in bioactive compounds as well as molecules with therapeutic benefits (Scheme 22a), our objective was to forge a complementary and mechanistically distinct approach for synthesizing acetophenones. In this study, we unveil the

combination of a light-mediated oxidation and reduction of styrene derivatives, culminating in the production of acetophenone scaffolds with copper as the sole catalyst. We were inspired by an intriguing transformation wherein α -halo acetophenones underwent reductive dehalogenation under photolysis conditions.²²⁸ If in turn a photocatalytic oxidation of styrenes to α -halo acetophenones would be compatible with the subsequent reductive dehalogenation, the overall process would convert styrenes to acetophenones (Scheme 22b).



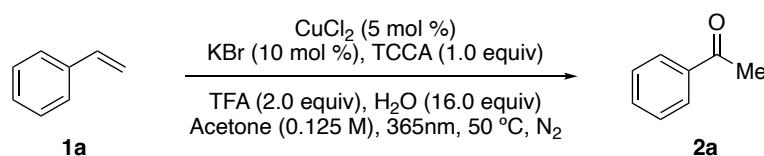
Scheme 22: a) Representative examples of bioactive molecules containing the phenacyl-motif, b) site-selective sequential photooxidation-photoreduction of olefins, c) hypothesized mechanistic pathway in this work, d) divergent reactivity encountered.

We initiated our investigation by focusing on the oxidation of vinylic arenes. We hypothesized that with the introduction of a chlorination reagent in the presence of an oxygen source, the olefin **I** would undergo a conventional oxochlorination, yielding α -chloroacetophenone **III** (Scheme 22c). We surmised that the latter compound would subsequently undergo excitation and intersystem crossing, resulting in **IV** in the triplet state. A subsequent homolysis of the C-Cl bond through a Spin-Center Shift (SCS),^{229,230} followed by protonation, would yield the

corresponding acetophenone **V**. However, under photoirradiation, we also discerned the potential for a divergent reactivity of the triplet **IV**, particularly a rearrangement leading to the formation of carboxylic acids through an aryl migration.²³¹ Additionally, other photochemical processes could potentially compromise the desired olefin oxidation reaction (Scheme 22d). For instance, the generated chlorine radicals can directly add onto the aromatic systems present.²³² Another complication could arise from benzylic chlorination, resulting in a dichlorination product that could not readily convert into any other intermediate.²³³ Thus, the prosperity of the whole process should depend on the compatibility of the two sequential site-selective modifications, the olefin's photooxidation and the photoreductive dehalogenation respectively, with the catalytic system used.

3. Preliminary study

After screening (see the ES for optimization details) we identified conditions using catalytic amounts of copper (II) chloride, commercially available trichloroisocyanuric acid (TCCA), and potassium bromide in acidic media at 50 °C under inert gas conditions (Table 2, entry 1). Running the reaction under air to promote a parallel oxochlorination path²³⁴ proved to be less efficacious (entry 2). The Wacker oxidation exhibited optimal efficiency under irradiation at a wavelength of 365 nm, while employing longer wavelengths (400 nm) resulted in a lower conversion, and the utilization of an even lower energy light source (455 nm) yielded no discernible product. Substituting trichloroisocyanuric acid with alternative halogen sources such as tribromoisocyanuric acid (TBCA) led to comparative yields, while N-chlorosuccinimide (NCS) proved to be inefficient (entries 3 and 4). Similarly, the application of other commonly employed halogen sources proved less efficacious (see experimental section). The replacement of copper (II) chloride with iron salts, such as FeCl₃, resulted in a significant reduction in yield, reaching only 40% (entry 5). The reaction predominantly exhibited reactivity in polar solvents; besides acetone (entry 1) acetonitrile promoted the desired transformation albeit with lower yields (entry 6), while attempts with alternative solvents such as toluene or dichloromethane yielded a complex reaction mixture. Notably, in the absence of the copper salt, a residual 25% yield of the desired product was observed (entry 7). However, upon the removal of TCCA, no conversion of the starting material was evident (entry 8). Furthermore, conducting the reaction in the dark resulted in no formation of the desired oxidation product (entry 9).



Entry	Variations from initial Conditions	2a (%) ^a
1	None	89 %
2	Under O ₂	74%
3	TBCA instead of TCCA	75 %
4	NCS instead of TCCA	5 %
5	FeCl ₃ instead of CuCl ₂	40 %
6	MeCN instead of acetone	60 %
7	No CuCl ₂	25 %
8	No TCCA	0 %
9	No light	0 %

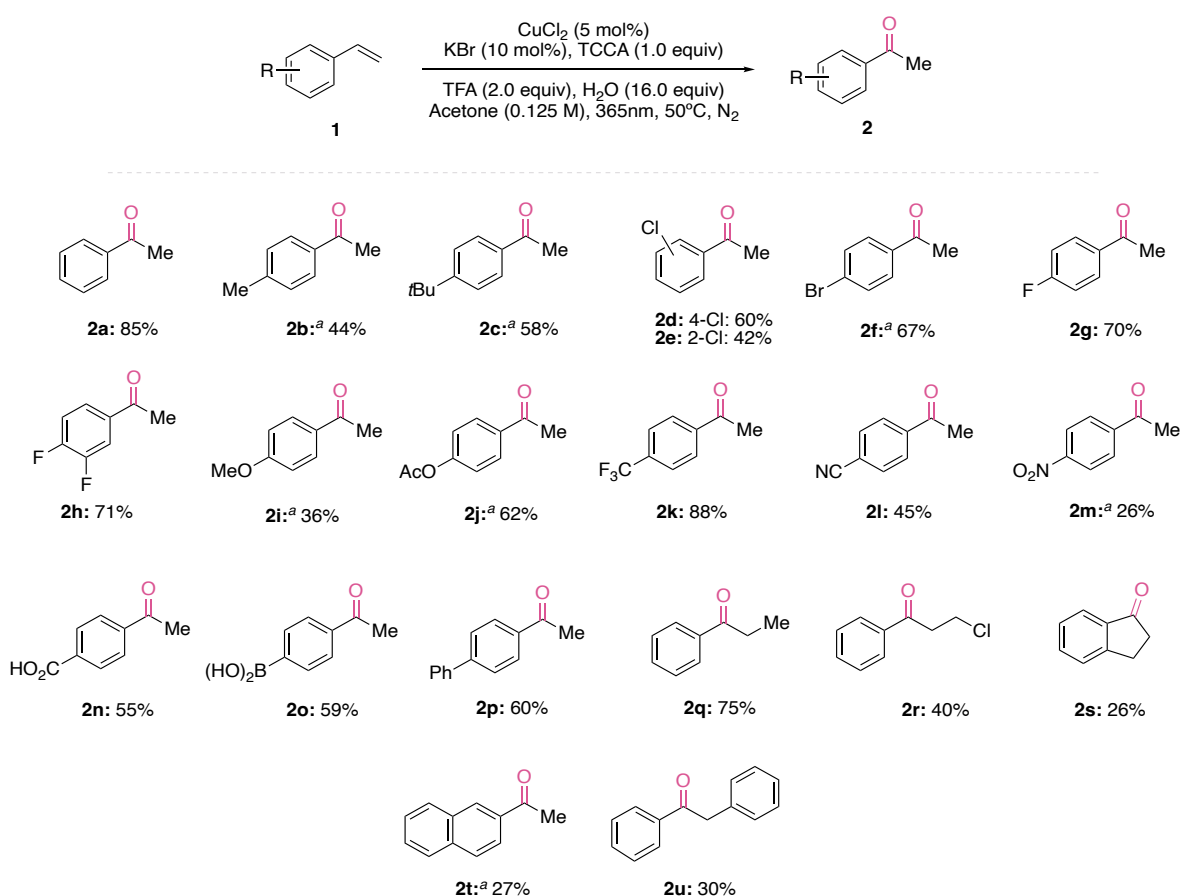
Table 2: Reaction optimization. Standard conditions: styrene (**1a**) (0.5 mmol, 1 equiv), TCCA (0.5 mmol, 1 equiv), CuCl₂ (25 μmol, 5 mol %), potassium bromide (50 μmol, 10 mol %), trifluoroacetic acid (1.0 mmol, 2 equiv), H₂O (8.0 mmol, 16 equiv), in 4mL of acetone under nitrogen atmosphere irradiated by a 365nm LED for 16h at 50 °C, ^a NMR-yield using 1,1,2,2-tetrachloroethane as internal standard.

4. Substrate scope

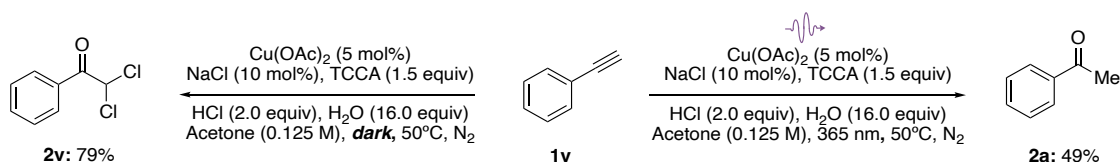
Once the optimal conditions were established, we investigated the Wacker oxidation on a representative series of substrates (Scheme 23a). Styrenes featuring weakly electron-donating substituents at the *para*-position such as methyl (**1b**) or *tert*-butyl (**1c**) moieties were fully converted but led to moderate yields of **2b** and **2c**. We were able to isolate the residual starting material as chlorohydrin in both cases. On the other hand, *ortho*- and *meta*-methyl substituted styrenes failed to deliver the corresponding acetophenone irrespective of the halogen-source used mainly due to the non-reproductive Norrish-Yang reaction.²³⁵ The inclusion of halogens within the molecular framework of the phenyl ring led to **2d-2h** with good yields. Unlike the methyl variants, the presence of halogen substituents in *ortho*-position was tolerated suggesting that the success of this transformation is not strictly dependent on the steric environment. We next investigated strongly electron-rich substrates such as 4-methoxystyrene (**1i**). When TCCA as the halogenating reagent was used, we did not obtain at all the corresponding acetophenone. Instead, we observed the formation of 4-methoxy phenylacetic acid in 34% yield. Nevertheless, switching to TBCA yielded the corresponding acetophenone **2i** albeit in low yield, indicating

that the nature of the halogen in the oxohalogenated intermediate is a relevant factor. Further experiments helped to understand the different outcome (*vide infra*). On the other hand, 4-acetoxystyrene (**1j**) with a mild O-donor was a better substrate in comparison yielding 62% of the corresponding acetophenone **2j**. 4-Substituted styrenes with electron acceptors, i.e., trifluoromethyl, cyano, nitro, and carboxyl groups worked moderately well, giving rise to **2k-2o** in good yields. In addition, 4-vinylbiphenyl was also compatible leading to **2p** with 60% yield. Substituted olefins with alkyl functionalities were tolerated, affording **2q-2s** in moderate yields with no observed Norrish-Yang type reactivity.^{235,236}

a. Reaction Scope



b. Case of acetylenes



Scheme 23: a) Reaction scope (isolated yields): styrene (**1**) (0.5 mmol, 1 equiv), TCCA (0.25 mmol, 1 equiv), CuCl_2 (25 μmol , 5 mol%), potassium bromide (50 μmol , 10 mol%), trifluoroacetic acid (1.0 mmol, 2 equiv), H_2O (8.0 mmol, 16 equiv), in 4mL of acetone under 365nm irradiation for 16h at 50°C. b) Case of phenylacetylene.

Other aromatic olefins were also examined. For instance, extended aromatic systems such as 2-naphthylstyrene (**1t**) performed poorly due to its ability to absorb light within the same frequency range as the copper catalyst, resulting in undesired reactivity.²³⁷ Similarly, stilbene performed poorly, furnishing only 30% yield of the desired product **2u**.

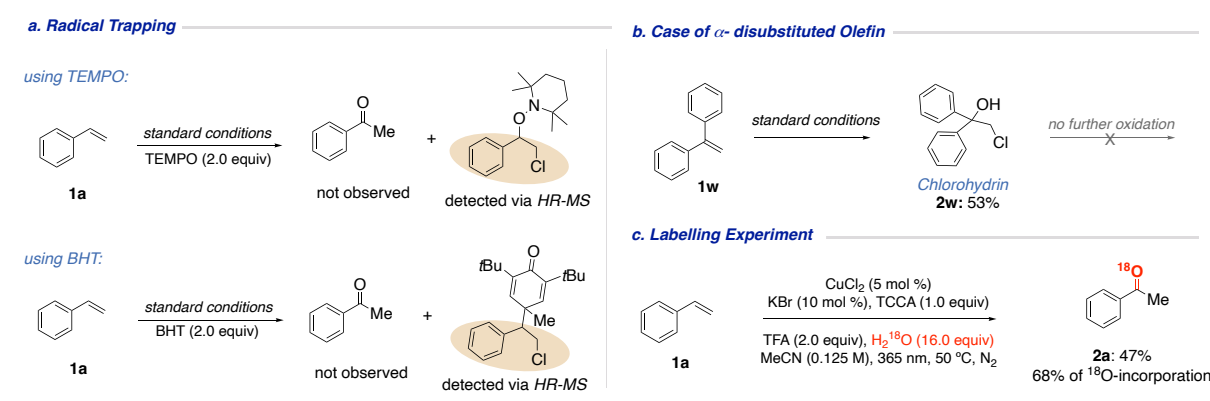
We then shifted our attention to acetylenes as they are more prone to oxidation and can easily trap chlorine radicals. Unexpectedly, we were only able to obtain 49% of **2a** and a sequential dark-light reaction performed comparably (Scheme 23b). Moreover, in contrast to olefins, the main intermediate observed in the dark was 2,2-dichloroacetophenone (**2v**) which should require two sequential dehalogenations, hence crossing two potential barriers, to afford the Wacker-type product (see ES for detailed conditions). Further analysis revealed that the intermediate **2v** could also be accessed in the absence of light and copper²³⁸ (see ES).

5. Mechanistic investigations

To gain deeper insights into the mechanism, we subjected the envisioned intermediates **IIa** and **IIIa** (derived from **1a**) to the standard conditions: in both cases, we were able to obtain the corresponding oxidation product **2a** in decent yields (see ES for details). We hypothesized that the introduction of chlorine radicals to the olefinic moiety constitutes the inaugural step leading to the formation of the oxochlorinated intermediate **IIa**. The inclusion of radical scavengers such as TEMPO and BHT not only validated the presence of the benzylic radical stemming from the aforementioned step but also completely halted the reaction (Scheme 24a). Furthermore, to corroborate the involvement of an alcohol intermediate, we observed that the reaction of 1,1-diphenyl ethylene (**1w**) yielded the corresponding chlorohydrin product (**2w**), with no detectable traces of dehalogenation products underscoring the indispensability of a carbonyl moiety in this process (Scheme 24b).

Running the reaction using H₂¹⁸O afforded **2a** with 68% ¹⁸O-incorporation, which is in agreement with water addition onto the benzylic position (Scheme 24c). We then probed the source of hydrogen in the final reduction step (**III** to **V**) through deuterium labelling. Running the reaction using D₂O under standard conditions resulted in 54% D-incorporation. However, due to the ability of the acetophenone to enolize, multiple D-labelled compounds were observed (see the experimental section).

To shed light on the role of copper and light in this transformation, UV absorption profiles indicated that CuCl_2 and KBr are the sole light-absorbing species in the 365 nm region. The impact of TFA on the copper complex revealed that optimal absorption is achieved in the presence of two equivalents of potassium bromide and TFA (see ES). Fluorescence quenching experiments further indicated the interaction of copper and TCCA, underscoring its role in facilitating the initial chlorination step. In the absence of light, the reaction did not proceed to the ketone and we were only able to isolate the correspondent chlorohydrin **IIa** (see ES), which was further converted to **2a** in the presence of copper and TCCA. Attempts to isolate the 2-chloroacetophenone intermediate **IIIa** failed, and we were only able to detect traces using GC-MS.

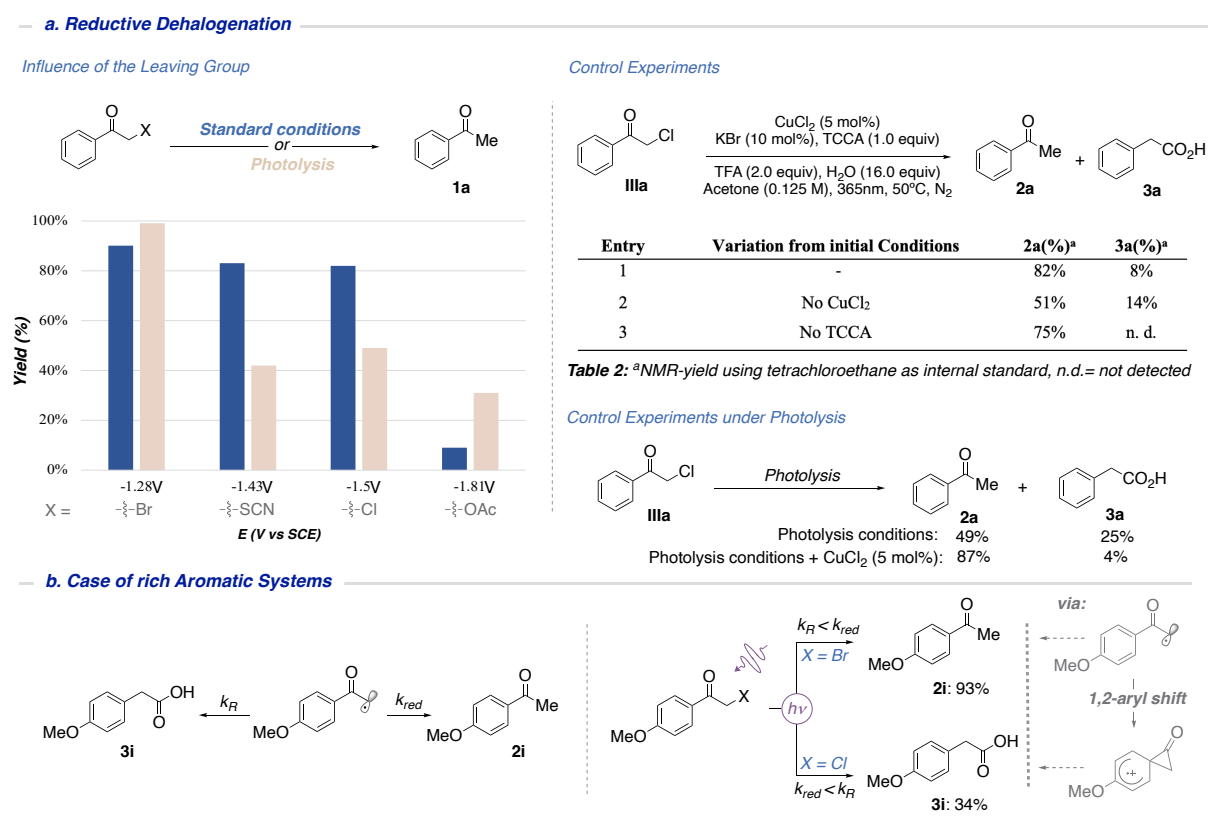


Scheme 24: a) Radical trapping experiments using TEMPO and BHT, b) reaction using 1,1-diphenyl ethylene, c) labelling experiment using H_2^{18}O .

The observation of the oxochlorination intermediate **IIIa** is unexpected, especially as it has not been commonly invoked in Wacker-type reactions. To assess the generality of this observation, we have studied the influence of the substituent on the α -position to the carbonyl moiety. Several halogen and pseudo-halogen substituted acetophenones were tested using the standard conditions (Table 2, entry 1) and under photolysis conditions (sole 365 nm irradiation, Scheme 25a). The defunctionalization yield pattern correlates with the reduction potentials of the corresponding substrates suggesting that the higher the potential barrier imposed the lower the SCS tendency. Similar pattern was observed in the case of **2v** (see ES). Attempts to unveil the promoting factors of the SCS dehalogenation of **IIIa** suggested that copper helps driving this reaction as indicated by the higher yields observed under photolysis conditions in the presence

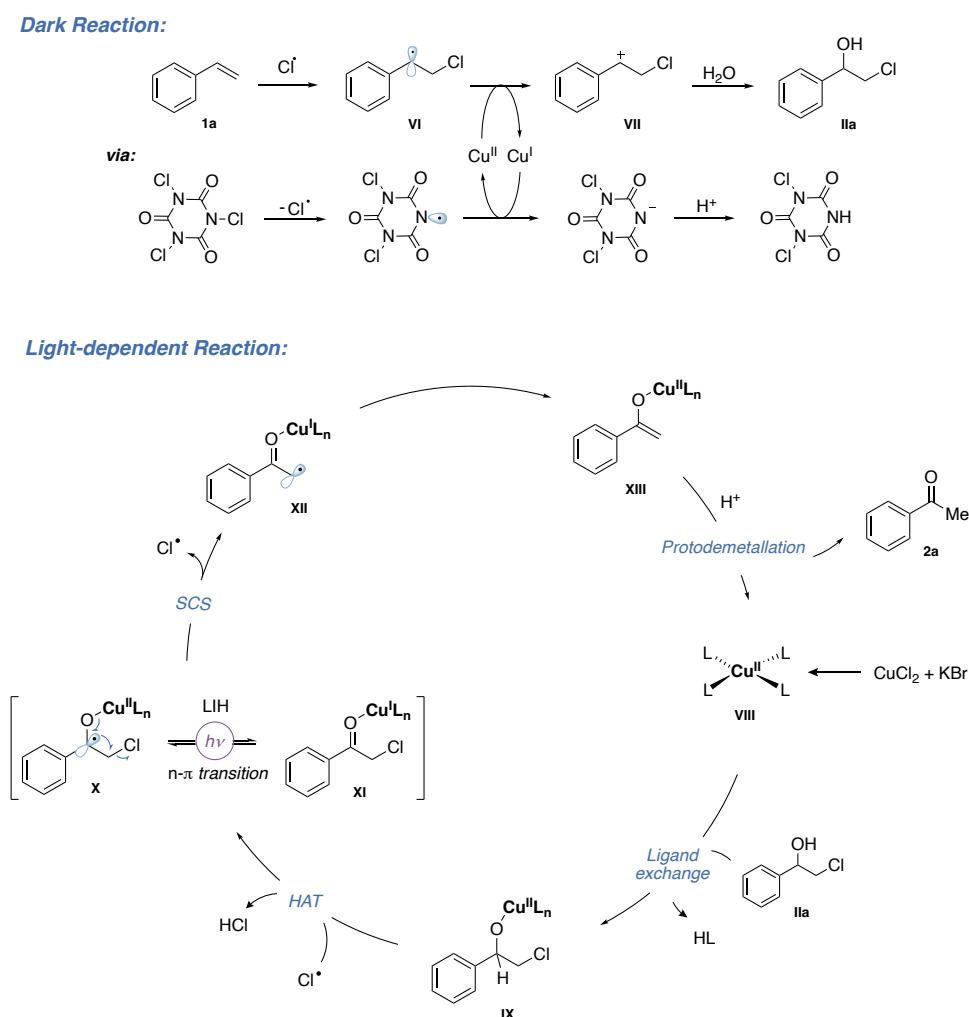
of CuCl₂ (87%). Furthermore, UV-vis measurements highlighted the potential coordination between CuCl₂ and 2-chloroacetophenone (see the experimental section).

Additionally, we evaluated the influence of the presence of strong-electron donor substituents on the phenyl ring (Scheme 25b). In the case of 4-methoxystyrene where the acetophenone (**2i**) could only be accessed when TBCA was used, we set up to understand the implication of the nature of the halogen source present. We presumed that the divergent reaction outcome when Cl⁻ or Br⁻ are involved is dependent on the passage from **III** to **V**.²³⁹ Indeed, photolysis experiments of 4-methoxy- α -haloacetophenone supported a halogen-dependent pathway as upon the homolysis of the C-X bond, the correspondent C-centered radical, in the case where X = Br, is promptly reduced resulting in the correspondent 4-methoxyacetophenone (**2i**), while in the case where X = Cl, the 1,2-aryl shift rearrangement becomes the predominant pathway affording the acid **3i**.



Scheme 25: a) Reductive dehalogenation of α -substituted acetophenone experiments under standard conditions (*vide-supra*) or under photolysis conditions: α -substituted acetophenone (0.5 mmol) in acetone (0.125 M) under N₂ irradiated by 365 nm for 16h at 50°C, b) divergent reactivity of electron-rich α -substituted acetophenone derivate (k_R : rearrangement rate, k_{red} : reduction rate).

Based on the mechanistic investigations and supported by existing literature,^{126,228–230} a plausible mechanism emerges, unfolding in two distinct stages (Scheme 26). The initial phase involves a copper-promoted dark reaction in which TCCA fragments, generating a chlorine radical. This radical subsequently adds onto the olefin **1a**, giving rise to the intermediate **VI** that undergoes oxidation via Cu^{II} and a hydration to ultimately yield the chlorohydrin **IIa**. The subsequent stage operates through a photochemical process that is initiated by a coordination between the copper complex **VIII** and **IIa** affording **IX** that, facilitated by a chlorine radical acting as a hydrogen-atom transfer agent, forms **X**. This species is able to interconvert, either proceeding towards the corresponding 2-chloroacetophenone **XI** through a copper-mediated light-induced homolysis (LIH),^{126,128} or alternatively undergoing a spin-center shift (SCS), leading to the formation of **XII**. This, in turn, leads to the production of **2a** through an initial copper-mediated reduction forming **XIII** followed by a protodemetalation.

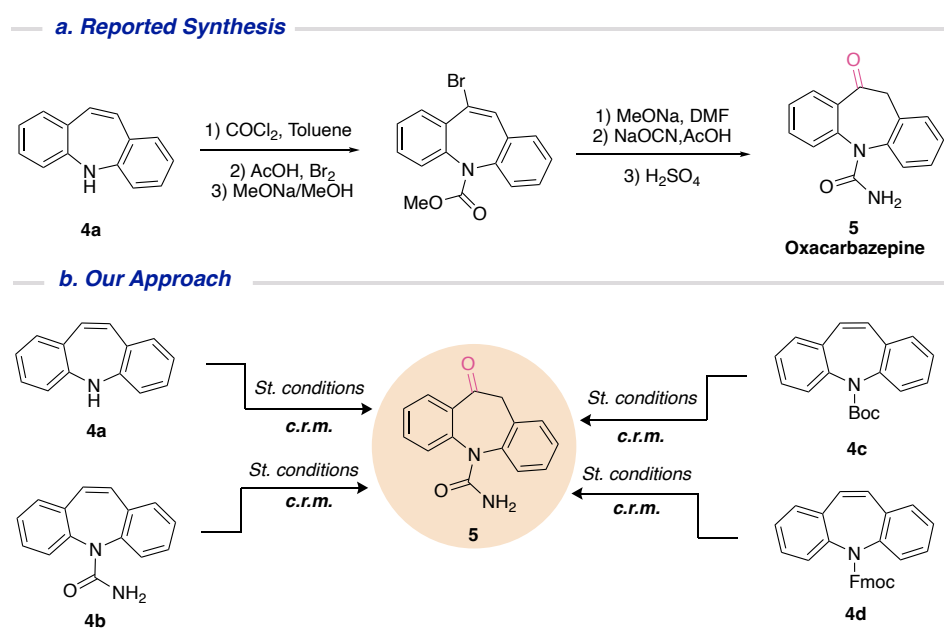


Scheme 26: Proposed reaction mechanism.

6. Application

In order to showcase the synthetic utility of the conceptualized oxidation protocol, we decided to target the synthesis of Oxacarbazepine, an antiepileptic drug and one of the most prescribed drugs in the United States in 2021.

The industrial synthesis of Oxacarbazepine drug is reported to be multistep starting either from iminostilbene or from indole derivatives.²⁴⁰ For instance, the Sun Pharma's synthetic protocol relies on the bromination of the olefinic moiety through a *N*-protection, debromination, and elimination sequence followed by an etherification through a nucleophilic substitution of the bromine with a methoxy group (Scheme 27a). This latter gets then oxidized delivering the desired oxidation product. Based on this, we assumed that a direct Wacker-type oxidation of the olefin would yield the desired drug in a much higher step-economical process. Indeed, we initiated our efforts by subjecting non-protected iminostilbene to our standard conditions (Scheme 27b). Running the reaction for 16 hours afforded no discernible product and we obtained a mixture of products that could not be analyzed. Similar reactivity pattern was observed when using iminostilbene carboxamide. This was potentially justified by the ability of TCCA to chlorinate non-protected N-H bonds, resulting in N-Cl scaffolds that, under photochemical conditions, are able to homolyze and disturb our desired reaction pathway.



Scheme 27: a) Reported synthesis of oxacarbazepine by Sun Pharma, b) approaches used relying on Wacker type oxidation

The implementation of a different functional group as a protecting agent was fruitless in the case of Boc since, under acidic conditions, the hydrolysis of the N-Boc group is highly probable. On the other hand, the use of Fmoc, a stable protecting group under acidic conditions, also lead to no desirable product probably given the propensity of chlorine radicals to abstract hydrogen atoms from the benzylic position of the Fmoc group.

7. Summary

In summary, our study showcases the promising potential of copper, in conjunction with a halogenation agent, in mediating the Wacker-type oxidation of olefins in the presence of water. The reaction showed a good tolerance for diverse functional groups, relying solely on copper as the catalyst while eliminating the need of external stoichiometric oxidants highlighting a potential avenue for environmentally friendly olefins oxidation processes. Furthermore, intriguing mechanistic investigations have elucidated that water functions as the oxygen source, and light plays an indispensable role in driving the reaction to completion.

Chapter IV:

Light-Induced Homolysis of Copper-Acid Complexes for the Functionalization of Ethers C(sp³)-H bonds

1. Introduction

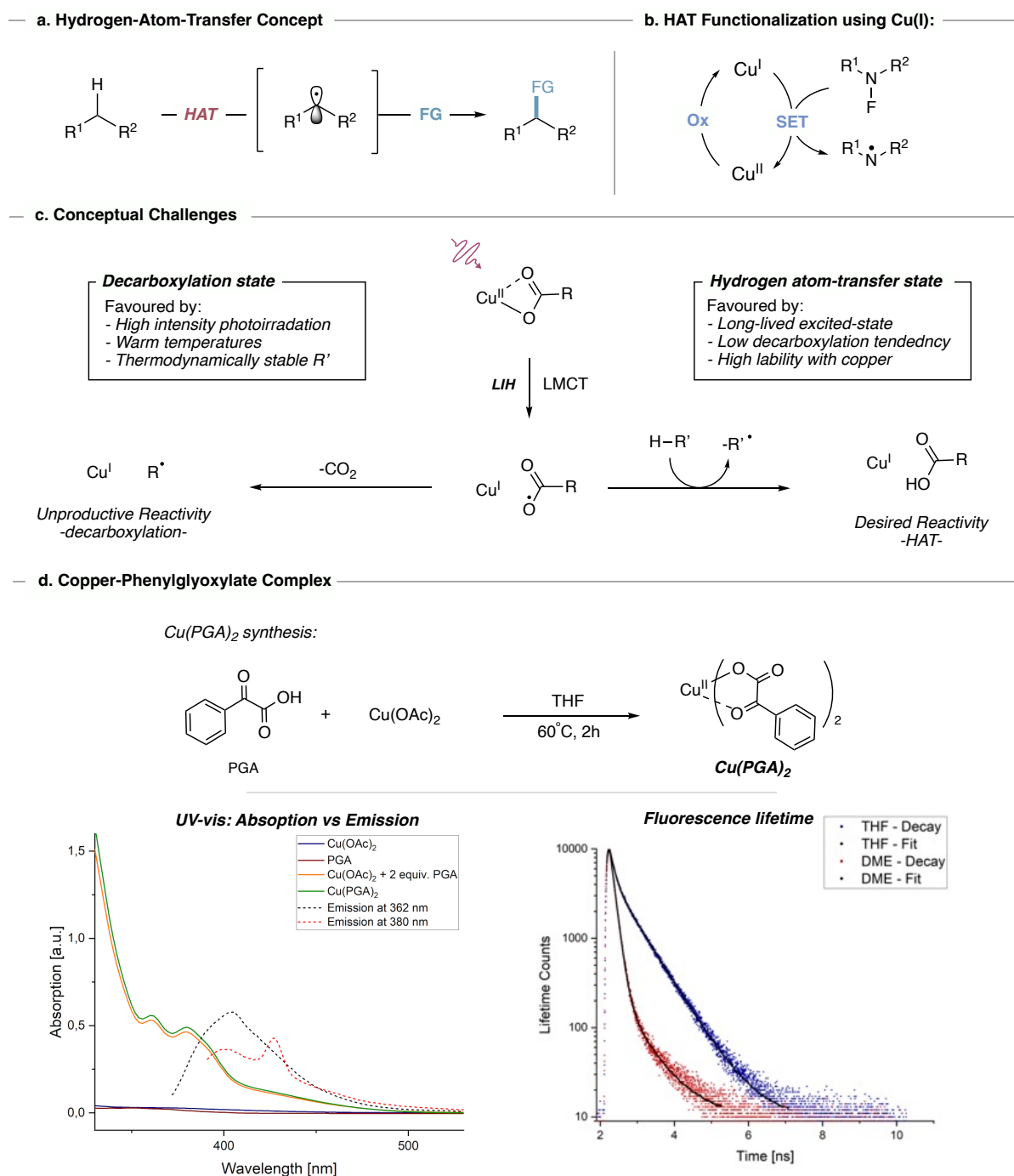
The construction of C-C bonds *via* reductive radical addition onto electrophilic olefins - also known as Giese reaction²⁴¹ - has been a very prolific approach for constructing complex molecules.^{242–246} Although many protocols were developed focusing mainly on the modulation of the radical sources, avoiding prefunctionalized substrates and using lesser hazardous additives, the hydrogen-atom transfer (HAT) concept has emerged as a powerful tool for the activation of chemically inert C(sp³)-H bonds for further functionalization (Scheme 28a).²⁴⁷

Several factors are involved in a HAT mechanism especially since the feasibility and selectivity of a HAT event relies, among other factors, on the bond dissociation energies²⁴⁸ (BDEs) as well as the polarity-match between the HAT reagent and the substrate.²⁴⁹ Progress made in this area has mainly relied on photochemical techniques for the activation of HAT reagents through oxidative/reductive single-electron transfer (SET) mechanisms mediated by photoredox catalysts which are usually ruthenium- and iridium-based.^{250–254} While other strategies capitalized on the employment of organic or metal-based HAT catalysts able to be photonically activated, these usually required a high catalyst loading spurring the quest for further improvement.^{255–261} Recent advancement was confined into the implementation of economical approaches making use of first-row transition metals given their abundance and propensity to efficiently activate HAT reagents. The functionalization of inert C(sp³)-H bonds using copper catalysis is majorly performed using Cu(I)-complexes and requires either the use of stoichiometric amounts of N-Fluorinated compounds serving as HAT precursors^{185,262–268} or

prefunctionalized substrates especially in the case of intramolecular HAT (Scheme 28b).^{269–271} Although these reagents offer a great compatibility with copper catalytic systems, they are majorly successful for the functionalization of benzylic C(sp³)-H positions. Moreover, a main drawback of such reagents is their high cost and reactivity making large-scale reactions economically and environmentally arduous.

Recently, the catalysis trend by means of VLIH opened new venues for the activation of a wide array of inert C(sp³)-H bonds.¹²⁶ Given the aptitude of copper-ligand (Cu(II)-L) complexes to undergo a homolysis through photoexcitation to ligand-to-metal charge transfer (LMCT) states generating Cu(I)-species alongside radical ligands (L•) (see section 3.3),^{128,272} chlorine salts could be easily converted to the corresponding radicals and were exploited as HAT catalysts for the Giese-type addition as demonstrated by the Rovis group in 2021 (Scheme 8, eq. ii).¹⁵³ Still, despite their high accessibility, the high reactivity of the chlorine radicals and the high bond dissociation energy of their protonated form (103 kcal.mol⁻¹ for H-Cl) makes the functionalization unselective.²⁷³ In addition, chlorine radicals possess a high oxidation potential ($E(\text{Cl}^\bullet/\text{Cl}^-) = +2.03 \text{ V vs SCE}$) rendering their likelihood to undergo redox mechanisms with oxidant-prone moieties very probable which limits their substrate compatibility.²⁷⁴ In addition, the employment of chlorine radicals as generic HAT-catalysts is substrate unspecific, and is moderately efficient for the functionalization of ethers spurring the quest for the development and design of efficient substrate-specific catalytic strategies.¹⁵³

To address these challenges, capitalizing on the LIH catalysis using copper, we reasoned that the incorporation of a HAT reagent having a lower bond dissociation energy compared to H-Cl, can serve as a mild H-abstractor for selective site functionalization of C(sp³)-H bonds. We were then interested in investigating carboxylic acids as HAT precursors given their tendency to easily coordinate with copper and to form the correspondent O-centered radicals upon photo-mediated LMCT.²⁷⁵ The engineering of such system is faced with sundry hurdles especially since the decarboxylation of carboxylate radicals is an established process to access C-centered radicals (Scheme 28c).^{157,158,275} Moreover, the light-induced homolysis process is reversible and requires high energy irradiation for cage-escape and prolonging the radical's lifetime which enhances the process efficiency.¹²⁷ On the other hand, under high-intensity irradiations, the CO₂ extrusion becomes predominant. We therefore hypothesized that acids with a high charge delocalization and a large chromophoric backbone serving as an energy repository hence prolonging the excited state's lifetime may be optimal under low-intensity irradiation and can efficiently promote the HAT mechanism.

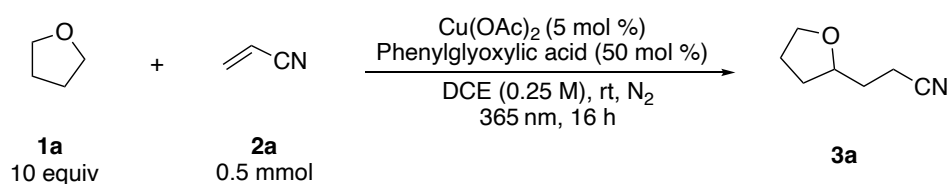


Scheme 28: a) Hydrogen-atom transfer general mechanism, b) functionalization using Cu(I) catalysis following a HAT mechanism, c) conceptual challenges in the design HAT catalytic system using carboxylic acids, d) Copper-phenylglyoxylate synthesis and spectroscopic characterization.

We started our investigations with the synthesis of several copper carboxylate complexes ($\text{Cu}^{\text{II}}(\text{OCOR})_2$) and measured their absorbance and excited state lifetime. To our delight, copper (II) phenylglyoxylate $\text{Cu}(\text{PGA})_2$, prepared from $\text{Cu}(\text{OAc})_2$ and phenylglyoxylic acid (PGA), displayed high absorption intensity with two maxima at 362 and 380 nm which is characteristic for LMCT bands in copper complexes (Scheme 28d). Upon irradiation of a THF solution of

Cu(PGA)₂ in both wavelengths, 362 and 380 nm, high energy emission was displayed. In addition, Cu(PGA)₂ exhibited high fluorescence lifetimes especially in tetrahydrofuran and dimethoxymethane (DMM) as solvents with 2.87 and 1.22 ns respectively which is much superior compared to the LMCT lifetime in other complexes ¹⁴⁶ (see ES for lifetime in other solvents). Moreover, mixing Cu(OAc)₂ and PGA in 1:2 ratio displayed a similar UV profile as the pre-synthesized complex reflecting its facile complexation in solution.

2. Giese-type reaction optimization



Entry	Variation from Initial Conditions	Yield ^a (%)
1	none	99%
2	THF as solvent	99 % (78 %) ^b
3	MeCN as solvent	56 %
4	CHCl ₃ as solvent	60%
5	5.0 equiv of THF	75%
6	20% of acid	33%
7	(R)(-)-Mandelic acid	25%
8	Pyruvic acid	7 %
9	N,N-dimethyl oxamic acid	n.r.
10 ^c	No copper	n.r.
11 ^d	No light	n.r.

Table 3: Optimization of the reaction conditions. *Standard conditions:* tetrahydrofuran (**1a**) (5 mmol, 10.0 equiv), acrylonitrile (**2a**) (0.5 mmol, 1.0 equiv), Cu(OAc)₂ (25 μmol, 5.0 mol %), phenylglyoxylic acid (0.25 mmol, 0.5 equiv) in DCE (anh. degassed, 2 mL, 0.25 M) for 16 h under nitrogen atmosphere at room temperature. ^a NMR yields using 1,1,2,2-tetrachloroethane as internal standard, ^b using 1.0 mol % of Cu(OAc)₂, ^c in the absence of copper, ^d in the dark.

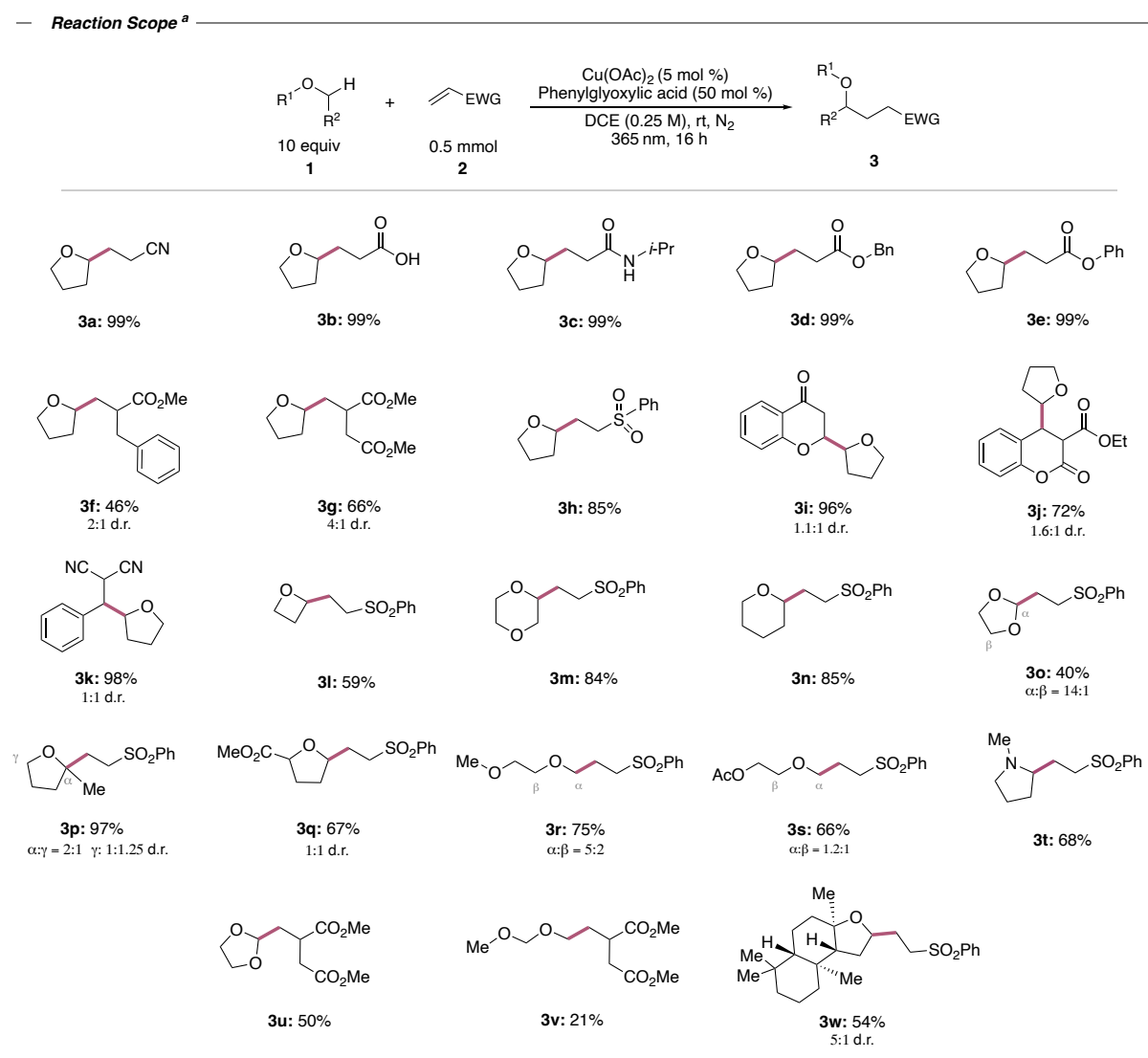
We therefore decided to probe the catalytic efficiency of the *in-situ* formed complex using catalytic amounts of phenylglyoxylic acid alongside copper acetate while employing tetrahydrofuran **1a** and acrylonitrile **2a** as model substrates under 365 nm LED irradiation in

an inert nitrogen atmosphere using 1,2-dichloroethane (DCE) as solvent (table 3, entry 1). Changing the solvent to THF resulted in the same efficiency (entry 2) while employing other solvents such as acetonitrile or chloroform reduced the reaction's performance (entries 3 and 4). Given the high volatility of **1a** and the propensity of the product **3a** to get activated and added across **2a**, optimal yields are achieved with an excess up to 10 equivalents of **1a**. Reducing the amount of this latter had a negative impact on the reaction's outcome (entry 5). The reduction of the acid loading resulted in a decreased yield (entry 6). The employment of other acids to promote the initial C(sp³)-H activation was fruitless in most cases giving traces of the product or completely halting the reaction (see experimental section). On the other hand, structurally similar acids such as mandelic and pyruvic acid were able to promote the obtention of the desired product albeit with sharp yields drop (entries 7 and 8) while *N,N*-dimethyloxamic acid led to no reactivity (entry 9). Control experiments indicated that copper and light were indeed necessary components for the reaction (entries 10 and 11).

3. Substrate scope of the Giese reaction

With the optimal conditions in hand (table 3, entry 1), we explored the scope of the electrophilic acceptors compatible with our transformation (Scheme 29). A handful of electron-deficient Michael acceptors were evaluated including acrylates and acrylamide (**2a-2e**) affording the alkylated products (**3a-3e**) with quantitative yields with no observable trace of side reactivity. Moreover, α -substituted acrylates with electronically diverse substituents were compatible with our process delivering **3f** and **3g**. In addition, vinyl sulfone (**3h**) and other acceptors including cyclic olefins (**3i-3k**) were also very well tolerated yielding **3h-3k**. We then sought to evaluate the compatibility with various ethers. Unfunctionalized cyclic ethers were proven to be effective partners for the Giese-type addition giving rise to alkylated products **3l-3o** with good yields and α -selectivity. On the other hand, when non-symmetric ethers were used, a mixture of regioisomers was observed. For instance, in the case of **3p** issued from 2-methyltetrahydrofuran, a regioselectivity profile of 2:1 with preferential alkylation at the tertiary carbon was observed, potentially owing to the additional stabilization offered to the transiently formed radical by the methyl group. On the other hand, the use of a carboxylate substituted tetrahydrofuran to get **3q** was selective owing to the unlikeliness of HAT in the α -position of the ester moiety due to polarity mismatch. Dimethoxyethane and ethyleneglycol

monomethyl ether acetate were successful coupling partners yielding **3r** and **3s** with good yields. In addition, C(sp³)-H bonds adjacent to a nitrogen atom could also be functionalized yielding **3t**. Interestingly, a distinct selectivity trend was observed when comparing dioxolane to dimethoxymethane in **3u** and **3v**. This selectivity divergence may be assigned to the instability of the *gem*-C-centered radical in dimethoxymethane given the rotational freedom compared to dioxolane which may be a destabilizing factor. Moreover, (-)-ambroxide was efficiently functionalized yielding **3w** using only 1 equivalent of the ether.



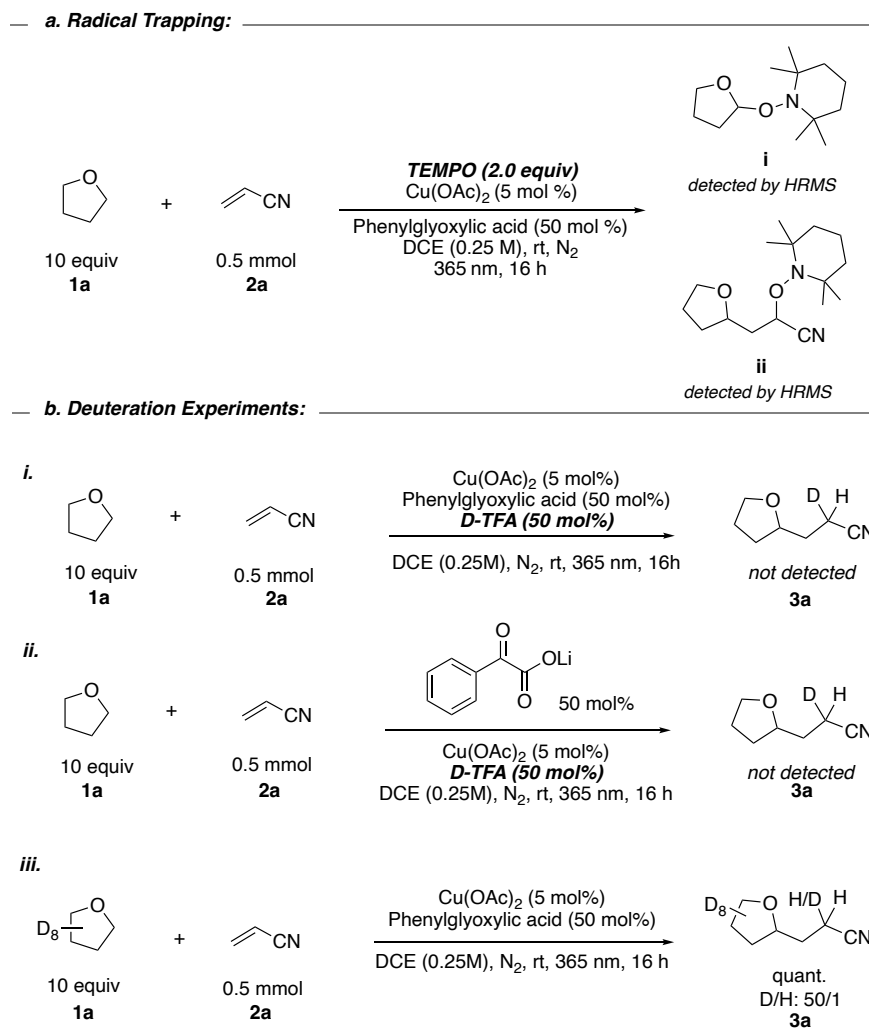
Scheme 29: Substrate scope: ^a isolated yields, *Standard conditions:* ether (**1**) (5 mmol, 10.0 equiv), olefin (**2**) (0.5 mmol, 1.0 equiv), Cu(OAc)₂ (25 mmol, 5.0 mol %), phenylglyoxylic acid (0.25 mmol, 0.5 equiv) in DCE (anh., degassed, 2 mL, 0.25 M) for 16 h under nitrogen atmosphere at room temperature.

4. Mechanism elucidation

Multiple experiments were conducted to elucidate the reaction mechanism. Upon the addition of stoichiometric quantity of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the reaction mixture between **1a** and **2a**, a complete cessation of the hydroalkylation was observed, and we were able to detect the TEMPO adducts **i** and **ii** confirming a radical pathway (Scheme 30a). To further investigate the catalyst regeneration step and product delivery from **ii**, deuteration experiments were employed. The neutralization of such intermediates has been documented to occur via two pathways: (i) a radical path involving reverse HAT or (ii) an ionic path that includes protodemetalation when metal species are present. The reverse HAT pathway is typically performed either from the catalyst or from another substrate which is characteristic for a chain reaction. However, this path can be disregarded since α -(CH)-CN radical (BDE of 94.0 kcal.mol⁻¹) is thermodynamically unable to perform a reverse HAT from the acid (ca. 102 kcal.mol⁻¹, 102.7 kcal.mol⁻¹ for benzoic acid).²⁷³ On the other hand, a reverse HAT from the ether substrate can only be feasible in some cases including tetrahydrofuran (92.1 kcal.mol⁻¹) unlike others (96.0 and 97.0 kcal.mol⁻¹ for tetrahydropyran and dioxane respectively).

Given that ionic species are potentially implicated in the protodemetalation termination mechanism, labelling experiments were conducted to investigate deuterium incorporation within the final product's core (Scheme 30b). Addition of exogenous deuterated trifluoroacetic acid (D-TFA) to the reaction's standard condition did not yield noticeable deuteration products, indicating that the protonation likely occurs faster than the deuteration (Scheme 3b, eq.i). We hypothesized that the incorporated proton in the final product may originate either from the acetic acid, obtained from the ligand exchange between phenylglyoxylic acid and Cu(OAc)₂, or from the hydrogen atom initially abstracted from the substrate. Indeed, utilizing lithium phenylglyoxylate in the presence of D-TFA, forming *in-situ* deuterated phenylglyoxylic acid, afforded no deuterated product suggesting that the hydrogen incorporated in **3a** likely derives from the substrate (Scheme 3b, eq.ii). Notably, in the absence of any acid while using lithium phenylglyoxylate, a complete shutdown of the reaction was observed. Moreover, when tetrahydrofuran-d₈ was subjected to the standard reaction conditions, we obtained the deuterated product with a D/H ratio of 50/1 which indicates that the deuteration performed by

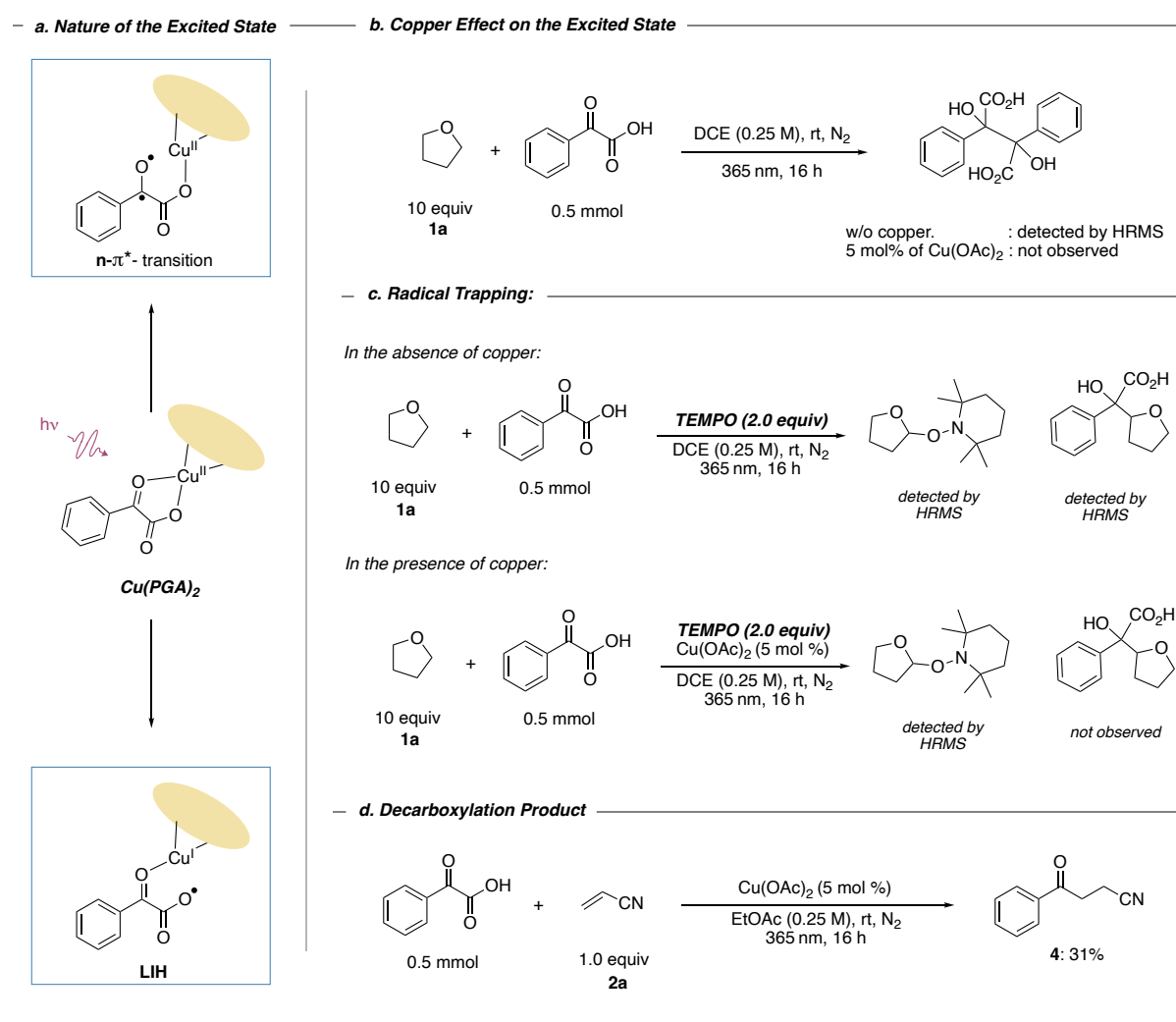
the deuterated HAT catalyst occurs in a confined environment within copper's first coordination sphere.



Scheme 30: a) Radical trapping experiment, b) labelling experiments using deuterated compounds.

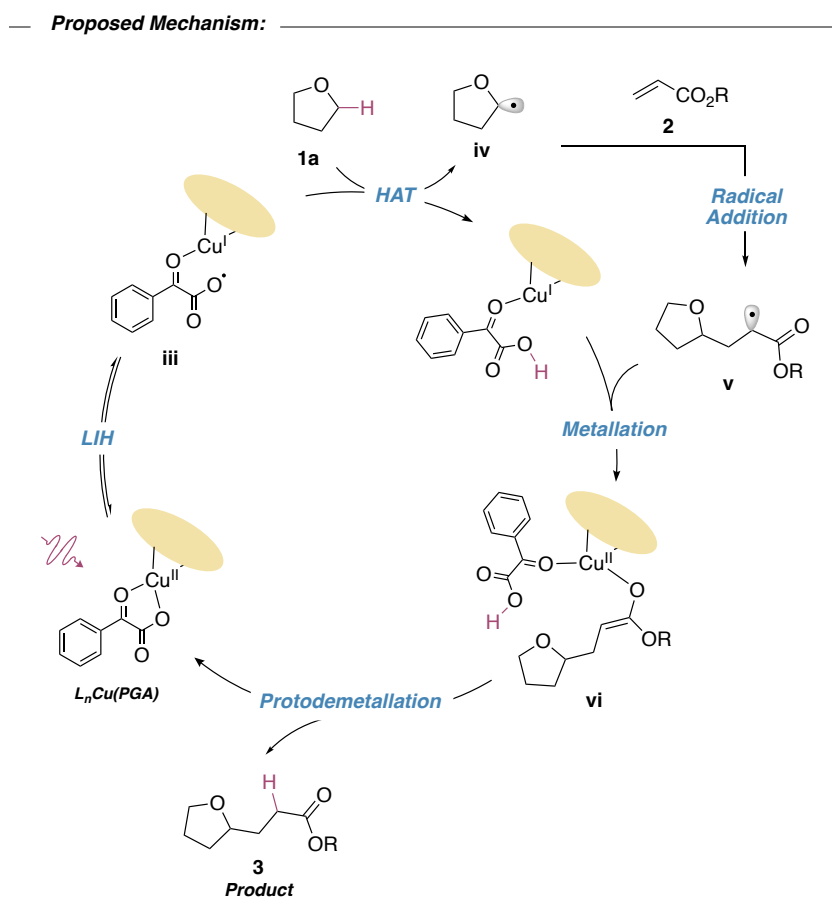
We then sought to probe the excited state's nature in our presumably formed Cu(PGA)_2 complex. Given the possibility of the phenacyl moiety to get photoexcited, undergoing a $n\text{-}\pi^*$ transition,²⁷⁶ we assumed that the differentiation between the two excited states, namely $n\text{-}\pi^*$ transition and LIH (Scheme 31a), can be distinguished capitalizing on the reactivity features of the generated radical intermediates – the carboxylate and C-centered radicals respectively. The irradiation of a mixture of phenylglyoxylic acid and **1a** yielded, in the absence of copper, traces of the PGA-derived dimerization product potentially issued from $n\text{-}\pi^*$ transitions (Scheme 31b). On the other hand, the presence of copper completely inhibited the reaction suggesting

that the passage through a triplet biradical is in this case unlikely. Furthermore, in the presence of the radical trap TEMPO, we were able to detect the coupling product between the tetrahydrofuryl radical and C-centered PGA radical (Scheme 31c). Nevertheless, in the presence of copper, we were able to trap the tetrahydrofuryl radical while no sign of PGA side product was identified with correlates with the activation through LIH pathway via LMCT. Moreover, in the absence of any electrophilic acceptor, the decarboxylation-addition product **4** was isolated confirming the passage through a carboxylate radical as commonly observed in oxidative processes involving α -oxoacids (Scheme 31d).^{277–280}



Scheme 31: a) Potential excited states responsible for HAT, b) copper's influence on the excited state, c) excited state radical trapping, d) copper LMCT issued product.

Based on our mechanistic analysis and literature precedents,^{126,153} we propose the mechanism depicted in scheme 32. The catalytic cycle is initiated by the excitation of the *in-situ* formed Cu(PGA)_2 complex which undergoes a light-induced homolysis process giving rise to the *O*-centered radical in **iii**. Subsequent hydrogen atom abstraction from the substrate **1a** affords the radical **iv**. The resultant nucleophilic radical **iv** adds onto the olefin **2** forming a new C-C bond alongside a transient radical **v** which subsequently recombines with copper and delivers the desired product **3** after an inner-sphere protodemetalation within **vi**.

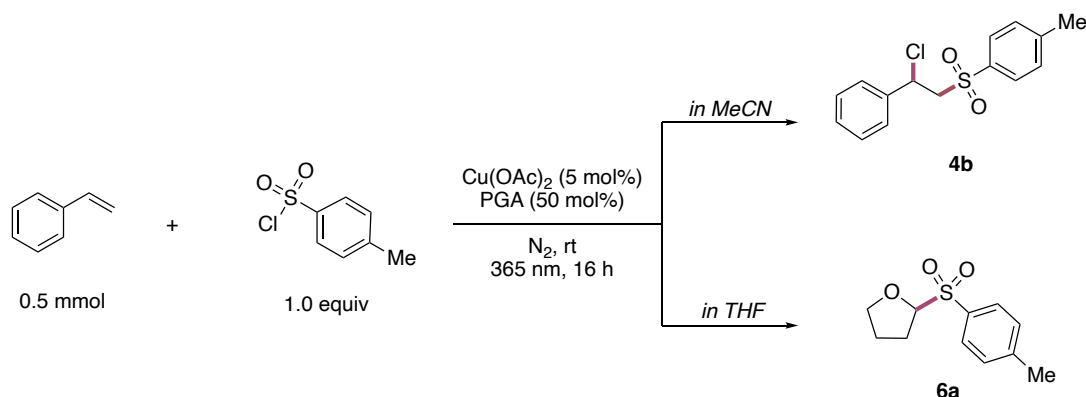


Scheme 32: Proposed reaction mechanism of the Giese-type addition

5. Ethers sulfonylation

Given the propensity of copper complexes to easily undergo redox reactions and the high measured lifetime of Cu(PGA)_2 , we surmised that Cu(PGA)_2 can also catalyze other type of transformations. To our delight, subjecting sulfonyl chloride alongside styrene and catalytic amount of the copper complex in acetonitrile afforded the correspondent chlorosulfonylation

product **4b**.²⁸ On the other hand, running the reaction in THF resulted, to our surprise, in a completely different outcome and afforded tosylated THF **6a** (Scheme 33). We have then queried the reduction properties of our copper complex, especially since such ATRA reaction are initiated through Cu(I)-mediated reduction of the ATRA reagent.



Scheme 33: Solvent-dependent outcome of the copper-catalyzed sulfonylation.

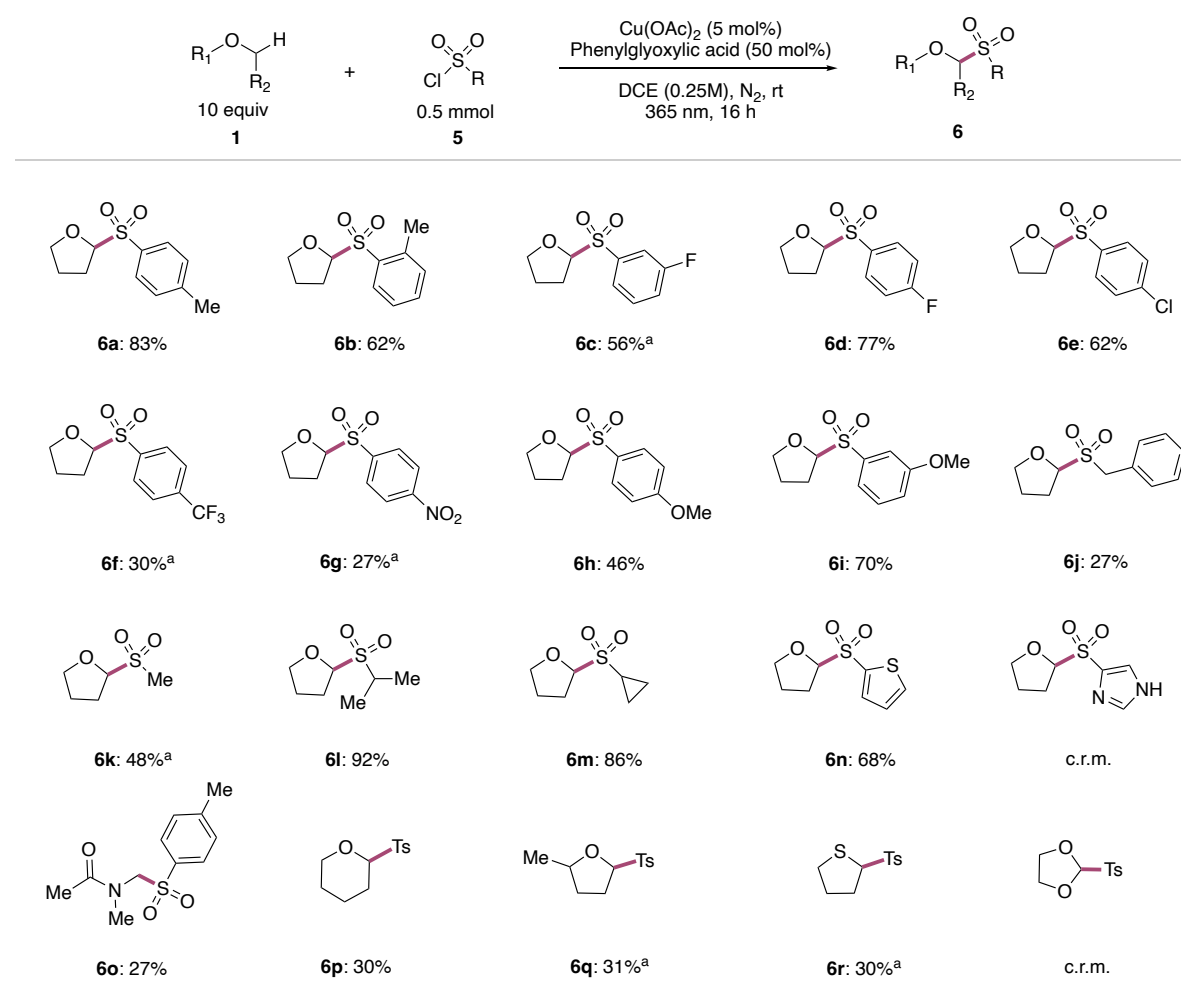
Sulfones represent a key motif of fundamental importance in synthetic chemistry.^{281,282} Given their propensity to be used as synthetic precursors, many methods have been developed for the implementation of sulfur functionalities in organic compounds. Among these, the design of photochemical thiolation and sulfinylation methods has gained high attention due to the ease of generating S-centered radicals.^{283,284} Despite the popularity of such methods, the main route consists of S-centered radical addition across unsaturated motifs limiting the scope of compatible substrates. Accompanying the development of C-centered radical generation through photocatalyzed HAT or SET processes, few S-incorporation protocols were developed in which photochemically generated organic radicals are intercepted by prefunctionalized oxidizable S-compounds (S^{II} or S^{IV}) delivering the correspondent thioether or sulfoxide.^{283,284} Despite the aforementioned advances, the implementation of sulfonyl moiety was performed either through multistep synthesis²⁸⁵ or through the use of stoichiometric amounts of sensitizer,²⁵⁹ metal source,²⁸⁶ or bicatalytic systems.^{287,288}

6. Sulfonylation scope

In light of the ease of manipulation of sulfonyl moieties for synthetic purposes as well as the prevalence of ethers in bioactive compounds,^{289–294} we have then applied our preconceived

optimal conditions (table 3, entry 1) onto the sulfonylation of ethers in the α -position. We initiated our scope evaluation by subjecting tetrahydrofuran (**1a**) to different sulfonyl chloride derivatives (Scheme 34). The use of methyl substituted sulfonyl chlorides delivered **6b** and **6c** in good yields. The implementation of halogens within the sulfonyl moiety did not have a strong influence on the reaction's outcome and delivered **6c-6e** with good yields. The presence of strong electron-withdrawing groups such as trifluoromethyl and nitro sharply diminished the reaction efficiency in **6f** and **6g**.

— **Reaction Scope** —



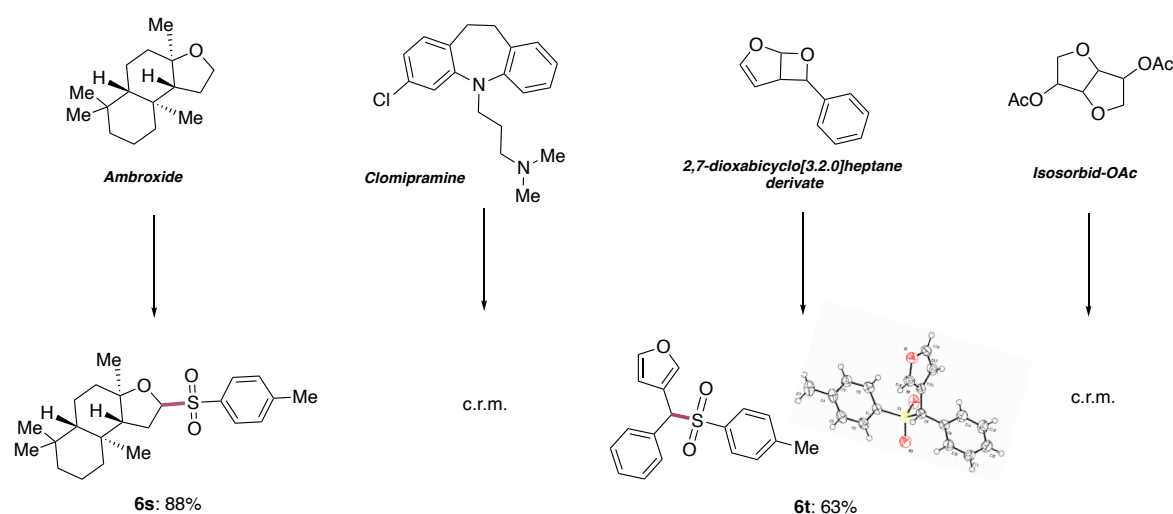
Scheme 34: Substrate scope (isolated yields unless otherwise noted), *Standard conditions*: ether (**1**) (5 mmol, 10.0 equiv), sulfonyl chloride (**5**) (0.5 mmol, 1.0 equiv), Cu(OAc)₂ (25 mmol, 5.0 mol %), phenylglyoxylic acid (0.25 mmol, 0.5 equiv) in DCE (anh., degassed, 2 mL, 0.25 M) for 16 h under nitrogen atmosphere at room temperature. ^aSubstrate not isolated and yield determined *via* quantitative NMR using 1,1,2,2-tetrachloroethane as internal standard.

Conversely, the use of an electron rich sulfonyl group bearing the methoxy group in the para-position diminished the yield to 46% for **6h**. On the other hand, when *m*-methoxysulfonyl chloride was used, we could isolate 70% of **6i**. The developed protocol was compatible with alkyl sulfonyl chlorides (*i.e.*, benzyl, methyl, isopropyl, and cyclopropyl) and afforded **6j-6m** with good to excellent yields. We have then probed other heterocyclic sulfonyl chlorides. The use of thiophenesulfonyl chloride afforded **6n** in good yield. On the other hand, the employment of imidazole-substituted reagent led to complex reaction mixture due to the potential coordination between the imidazole and copper which poisons its catalytic activity.

We have then shifted our attention to test other substrates. To our surprise, the employment of N,N-dimethylacetamide or structurally similar heterocycles to tetrahydrofuran yielded the corresponding tosylation products **6o-6r** in low yields which may be attributed to the radical lifetimes, since, based on our mechanism (*vide-infra*), the final product delivery step requires the coupling between the C-centered radical issued from **1** with the tosyl radical. Moreover, the employment of dioxolan led to a complex reaction mixture potentially due to the relatively higher acidity of the C-H bond.

7. Applications

We have then sought to apply our protocol on complex molecules with biological relevance (Scheme 35). Subjecting (-)-Ambroxide to the standard reaction conditions delivered the correspondent tosylation product **6s** with excellent yield. The use of Clomipramine, a commercial antidepressant, with the aim to functionalize amine's α -position, led to no desirable product and we could only isolate decomposed structural fragments of the starting material. Given the propensity of this drug to absorb light within the same region, running the reaction in a lower energy wavelength such as 400 nm was still inefficient.

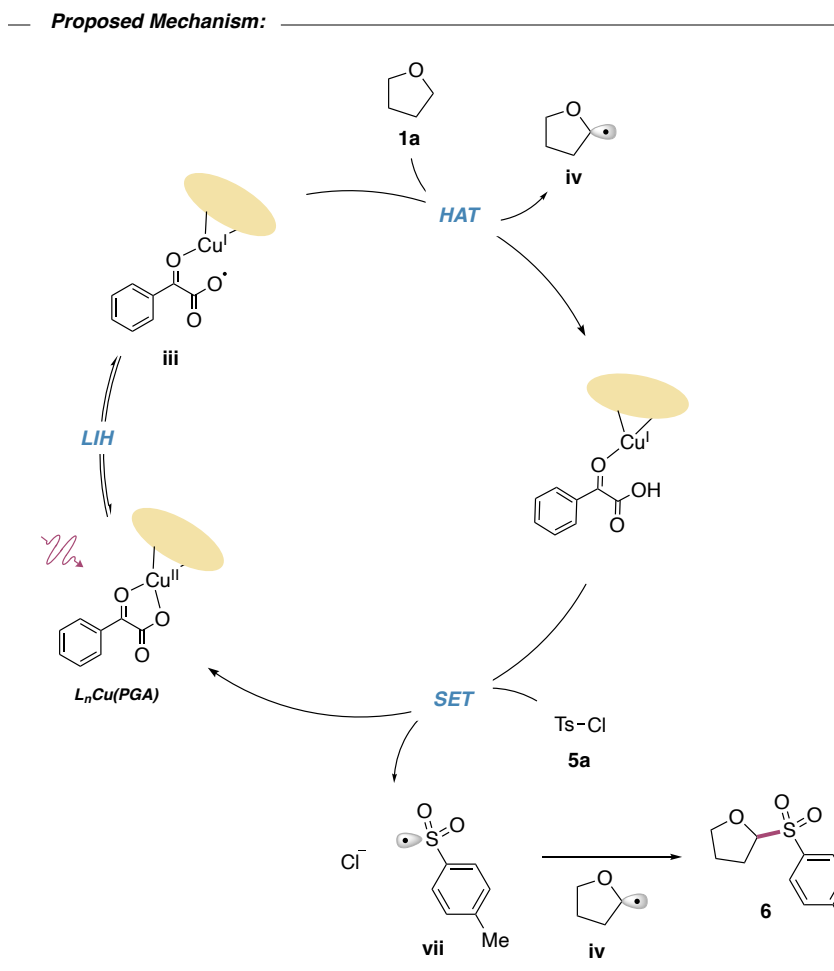


Scheme 35: Sulfonylation of biologically relevant scaffolds using 1 equivalent of the substrate

We were then interested in the functionalization of bicyclic ethers as they are present as a core motif in many bioactive compounds.²⁹⁵ The subsection of the bicyclic derivative, issued from a Paterno-Büchi reaction between furane and benzaldehyde, delivered to our surprise the product **6t** through a potential rearrangement and water elimination. It is to note however that the mechanism of this reaction is still unclear. Moreover, when we subjected isosorbide to our standard conditions, no desired product was detected, potentially due to the presence of the acetate moiety in the vicinity of the C-H bond to be functionalized, which may diverge from the desired reactivity especially due to its redox sensitiveness.

8. Sulfonylation mechanism

Based on our reaction analysis, we propose the mechanism in scheme 36. The reaction is initiated with the light-induced homolysis of Cu(PGA)_2 affording **iii** that undergoes a HAT with **1a** to deliver the radical **iv**. The simultaneously formed Cu(I) complex undergoes a single-electron transfer event with the sulfonyl chloride **5a** leading to the formation of the radical **vii** and the regeneration of the Cu(II) complex. A radical-radical cross coupling between **iv** and **vii** takes place to finally afford the product **6**.



Scheme 36: Proposed reaction mechanism of ethers sulfonylation

9. Summary

In summary, we have developed a mild protocol for the selective α -functionalization of feedstock ethers relying on the light-induced homolysis concept using copper salts and phenylglyoxylic acid as a HAT catalyst. This alkylation and sulfonylation processes gave good overall yields and selectivity. Current efforts are underway for this catalytic system expansion for the functionalization of other substrate classes.

Summary/Zusammenfassung:

Summary:

Synthetic chemistry has long been focused on the development of predictable catalytic approaches for the engineering of chemical reactivity in response to the challenges associated with the molecular complexity in pharmaceuticals and natural products. Visible light photocatalysis has experienced a resurgence as a potent platform in chemical synthesis allowing the realization of previously elusive transformations. Copper has emerged as a robust alternative to classical ruthenium/iridium photo-complexes serving as a hybrid catalytic platform capable of performing inner-/outer-sphere photoredox reactions and engaging in dual catalytic endeavors rendering it the passepartout metal in photocatalysis. The first chapter of this thesis provides an overview of copper's different photocatalytic patterns, covering both the pioneering and the recent approaches applied in synthesis, focusing on the inner-sphere interactions while showcasing the benefits and limitations of each.

The second chapter discloses a novel chemical labelling method to unveil the mechanism involved in atom-transfer radical addition reactions using benzylthiocyanates. The developed copper-photocatalyzed strategy enables the selective access to organic thiocyanates and isothiocyanates. The electronic nature of the aromatic system was revealed to be a crucial factor defining the outcome of the reaction for forging either the kinetic C-S or the thermodynamic C-N bonds. Mechanistic investigations support a radical pathway initiated by a reductive C-S bond cleavage of the substrates followed by a divergent inner-/outer-sphere interaction with copper depending on the electronic density of the formed intermediates. The developed protocol proceeds with high regio- and chemoselectivity and was also applied for late-stage functionalization of bioactive molecules. The utility of the products is highlighted by their facile conversion to several building blocks relevant to organic synthesis.

The chapter three reveals a novel alternative protocol to accomplish Wacker-type oxidation of olefins using copper as the sole catalyst and trichloroisocyanuric acid as the halogenating agent in the absence of palladium and oxidants. The reaction protocol was proven to be compatible with diverse functional groups affording selectively the oxidation products. The mechanistic analysis revealed that a site-selective sequential photooxidation/photoreduction of the intermediary chlorohydrin is the key to the success of this transformation.

The fourth chapter probes the influence of the incorporation of phenylglyoxylic acid alongside copper for the functionalization of C(sp³)-H bonds. Capitalizing light-induced homolysis principle using copper, we could efficiently perform the alkylation of inert C(sp³)-H bonds in a Giese-type addition protocol. Moreover, the *in-situ* formed complex could also serve as a reductant and catalyze the α -sulfonylation of ethers. Mechanistic investigations indicate the distinct role of copper in shifting the nature of the excited state which helps enhancing the process' efficiency and the excited state's lifetime.

Zusammenfassung:

Die synthetische Chemie konzentriert sich seit langem auf die Entwicklung vorhersagbarer katalytischer Ansätze zur Entwicklung chemischer Reaktivität als Antwort auf die Herausforderungen, die mit der molekularen Komplexität von Arzneimitteln und Naturprodukten verbunden sind. Die Photokatalyse mit sichtbarem Licht erlebt als leistungsfähige Plattform in der chemischen Synthese eine Renaissance, da sie die Realisierung bisher schwer fassbarer Transformationen ermöglicht. Kupfer hat sich als robuste Alternative zu klassischen Ruthenium/Iridium-Photokomplexen erwiesen, da es als hybride katalytische Plattform dient, die Photoredoxreaktionen in der inneren und äußeren Sphäre durchführen und sich an dualen katalytischen Aufgaben beteiligen kann, was es zum Passepartout-Metall in der Photokatalyse macht. Das erste Kapitel dieser Arbeit bietet einen Überblick über die verschiedenen photokatalytischen Muster von Kupfer und behandelt sowohl die bahnbrechenden als auch die jüngsten Ansätze, die in der Synthese angewendet werden. Dabei liegt der Schwerpunkt auf den Wechselwirkungen in der inneren Sphäre, wobei die Vorteile und Grenzen der einzelnen Ansätze aufgezeigt werden.

Das zweite Kapitel beschreibt eine neuartige chemische Markierungsmethode, um den Mechanismus von Atomtransfer-Radikaladditionsreaktionen unter Verwendung von Benzylthiocyanaten aufzudecken. Die entwickelte kupferphotokatalytische Strategie ermöglicht den selektiven Zugang zu organischen Thiocyanaten und Isothiocyanaten. Die elektronische Natur des aromatischen Systems erwies sich als entscheidender Faktor, der das Ergebnis der Reaktion zur Bildung entweder der kinetischen C-S- oder der thermodynamischen C-N-Bindungen bestimmt. Mechanistische Untersuchungen unterstützen einen radikalischen Reaktionsweg, der durch eine reduktive C-S-Bindungsspaltung der Substrate eingeleitet wird, gefolgt von einer divergierenden Innen-/Außensphärenwechselwirkung mit Kupfer, abhängig von der elektronischen Dichte der gebildeten Zwischenprodukte. Das entwickelte Protokoll verläuft mit hoher Regio- und Chemoselektivität und wurde auch für die Funktionalisierung bioaktiver Moleküle im Spätstadium angewendet. Die Nützlichkeit der Produkte wird durch ihre einfache Umwandlung in mehrere für die organische Synthese relevante Bausteine hervorgehoben.

Kapitel drei enthüllt ein neuartiges alternatives Protokoll zur Durchführung einer Wacker-artigen Oxidation von Olefinen unter Verwendung von Kupfer als einzigem Katalysator und Trichlorisocyanursäure als Halogenierungsmittel in Abwesenheit von Palladium und Oxidationsmitteln. Das Reaktionsprotokoll erwies sich als kompatibel mit verschiedenen funktionellen Gruppen und liefert selektiv die Oxidationsprodukte. Die mechanistische Analyse ergab, dass eine ortsselektive sequentielle Photooxidation/Photoreduktion des intermediären Chlorhydrins der Schlüssel zum Erfolg dieser Transformation ist.

Das vierte Kapitel untersucht den Einfluss der Einbindung von Phenylglyoxylsäure neben Kupfer zur Funktionalisierung von C(sp³)-H-Bindungen. Durch Nutzung des Prinzips der lichtinduzierten Homolyse unter Verwendung von Kupfer konnten wir die Alkylierung inerter C(sp³)-H-Bindungen in einem Giese-artigen Additionsprotokoll effizient durchführen. Darüber hinaus könnte der in situ gebildete Komplex auch als Reduktionsmittel dienen und die α -Sulfonylierung von Ethern katalysieren. Mechanistische Untersuchungen weisen auf die besondere Rolle von Kupfer bei der Veränderung der Art des angeregten Zustands hin, was dazu beiträgt, die Effizienz des Prozesses und die Lebensdauer des angeregten Zustands zu verbessern.

Experimental part:

Experimental section of chapter 2

1. General Information

Commercial reagents were purchased in high quality and further used without prior purification. Solvents for chromatography were distilled prior to use. Chromatographic purification was carried out on 0.062-0.200 mm silica gel or 0.040-0.063 mm flash silica. Thin-layer chromatography (TLC) was performed on precoated aluminum sheets (Merck) Silica gel 60 F254, 0.2 mm layer thickness. Visualization of the developed chromatogram was performed by a UV lamp ($\lambda = 254$ or 366 nm), cerium ammonium molybdate or potassium permanganate stain. ^1H -NMR spectra were recorded on Bruker Avance 300 (300 MHz), Bruker Avance 400 (376 MHz) or Bruker Avance III 400 ‘Nanobay’ (400 MHz) instruments. ^1H -NMR data was reported relative to the signal of CDCl_3 at 7.26 ppm as follow: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), integration, and coupling constant (Hz). ^{13}C -NMR spectra were recorded on Bruker Avance 300 (75 MHz), Bruker Avance 400 (101 MHz) or Bruker Avance III 400 ‘Nanobay’ (101 MHz) instruments. ^{13}C -NMR data was reported in terms of chemical shift (δ ppm) relative to the signal of CDCl_3 triplet at 77.2 ppm. ^{19}F -NMR spectra were recorded on Bruker Avance 400 (282 MHz) or Bruker Avance III 400 “Nanobay” (282 MHz) Spectrometer. IR-spetra were recorded on a Cary 630 FT-IR Spectrometer and reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectroscopy was performed by the Central Analytic Department of the University of Regensburg using Joel AccuTOF GCX and Agilent Q-TOF 6540 UHD Spectrometers using atmospheric pressure chemical ionization (APCI), electrospray ionization (ESI) or electron ionization (EI) methods. X-ray analysis was carried out by the Central Analytic Department of the University of Regensburg using Agilent Technologies SuperNova, Agilent Technologies Gemini R Ultra, Agilent GV 50 or Rigaku GV 50 diffractometers. The structures were solved with the ShelXT (Scheldrick 2015) structure solution program using the Intrinsic Phasing solution method and by using Olex2 as the graphical interface. The model was refined with ShelXL using Least Squares minimization. Cyclic Voltammetry measurements were recorded using Autolab PGSTAT302N Metrohm. All photochemical

reactions were performed in a flame-dried Schlenk tube using LED as light source based on the setup on Figure S1. Blue light irradiation was carried out by OSLO SSL 80 (3 W, 700 mA, $\lambda_{\text{max}} = 455 \text{ nm}$). Green light irradiation was performed using an OSLO SSL 80 (3 W, 700 mA, $\lambda_{\text{max}} = 530 \text{ nm}$).

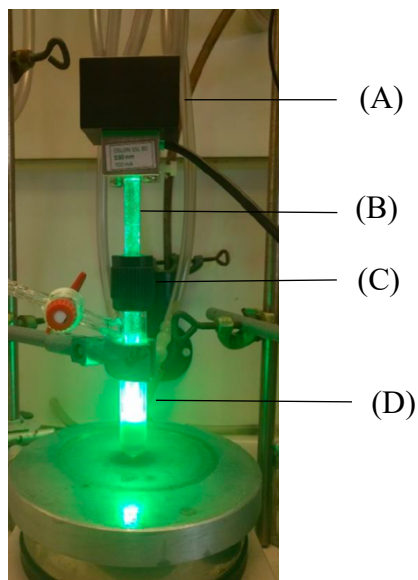


Figure 1: Photochemical setup: (A) Light source, (B) Glass rod, (C) Teflon adapter, (D) 10.0 mL Schlenk tube

2. Cyclic voltammetry measurements:

The cyclic voltammetry measurements were performed using Glassy Carbon as the working-electrode and Platinum wire as the counter-electrode. A silver wire was used as a pseudo-reference electrode. Tetrabutylammonium tetrafluoroborate (0.1 M) was the supporting electrolyte in all measurements.

Prior to the measurement, the solvent is degassed with argon. All experiments are performed under argon atmosphere. Ferrocene is used as an internal reference for determining the reduction and oxidation potentials. Potentials vs SCE were calculated using the formula: $E_{\text{SCE}} = E_{\text{Fc/Fc}^+} + 0.38 \text{ V}$.

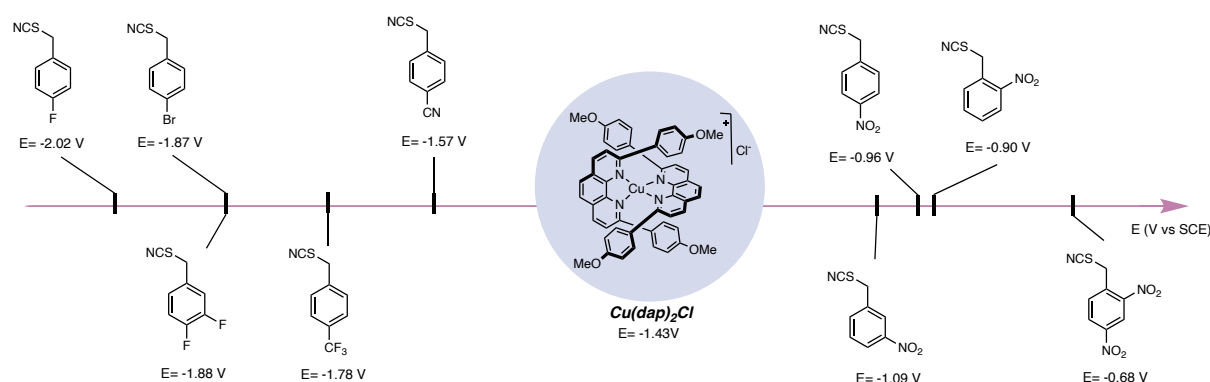
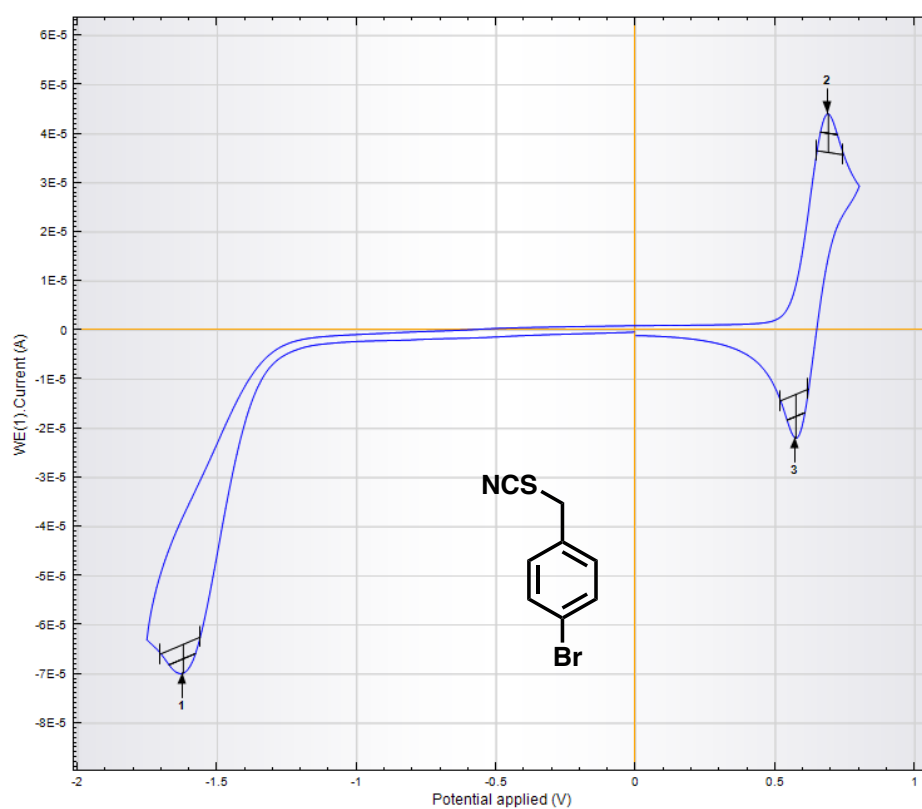


Figure 2: Reduction potential of a series of substituted benzyl thiocyanates

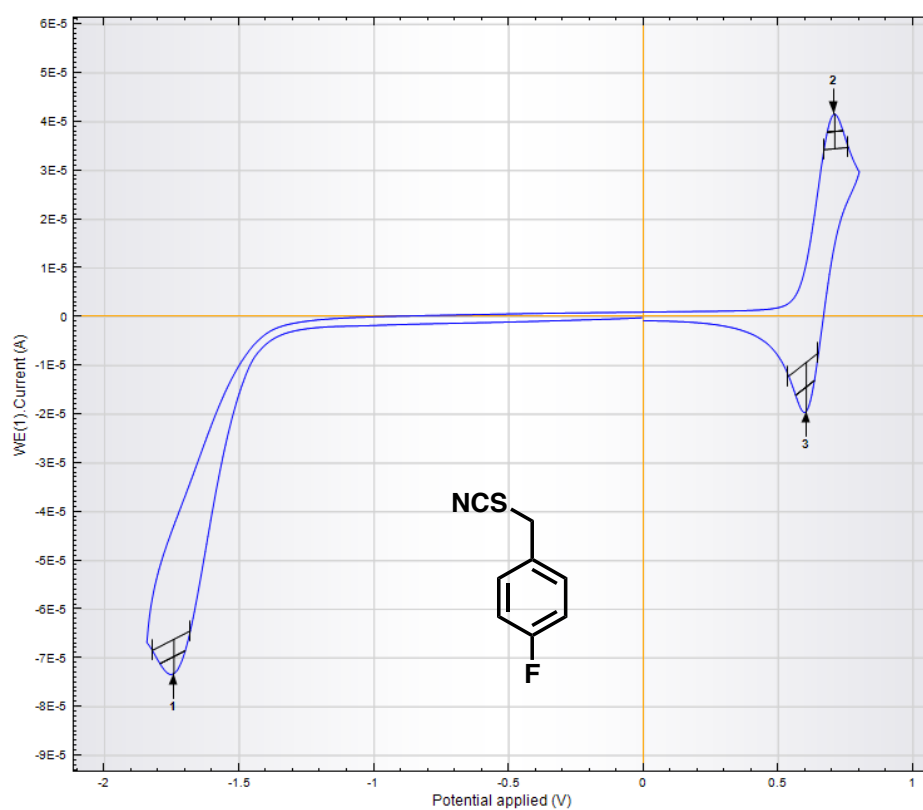
1-bromo-4-(thiocyanatomethyl)benzene



$E_{\text{red}} = -1.87 \text{ V vs SCE}$

Index	Peak position
1	-1.6214
2	0.68985
3	0.57404

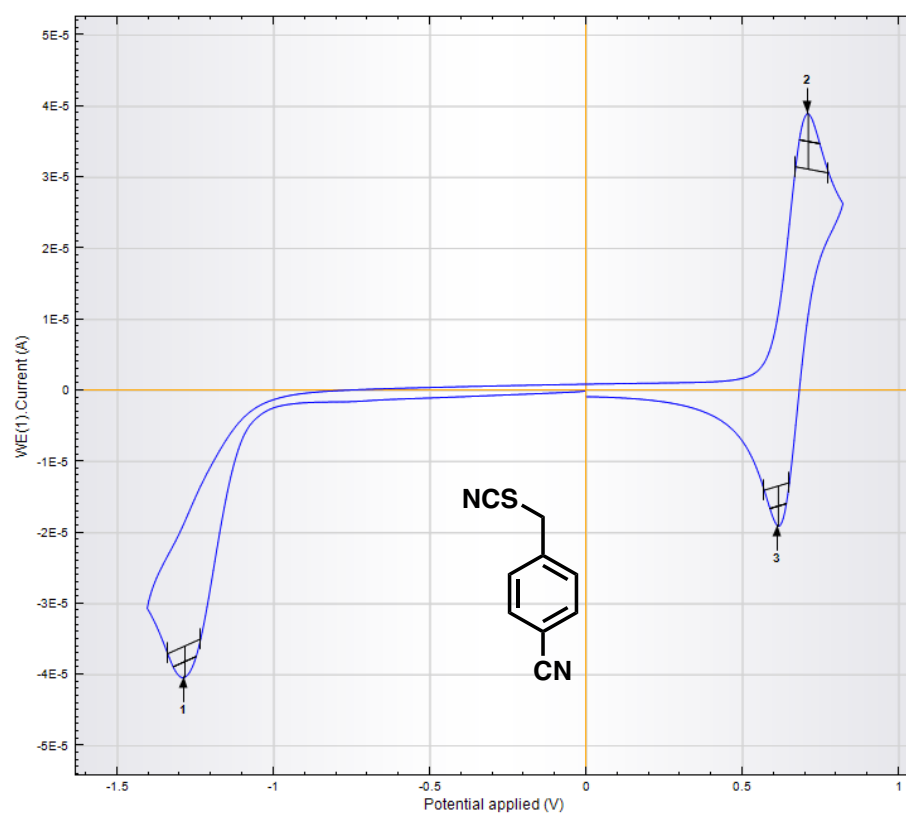
1-fluoro-4-(thiocyanatomethyl)benzene



$E_{\text{red}} = -2.02 \text{ V vs SCE}$

Index	Peak position
1	-1.7422
2	0.70999
3	0.60425

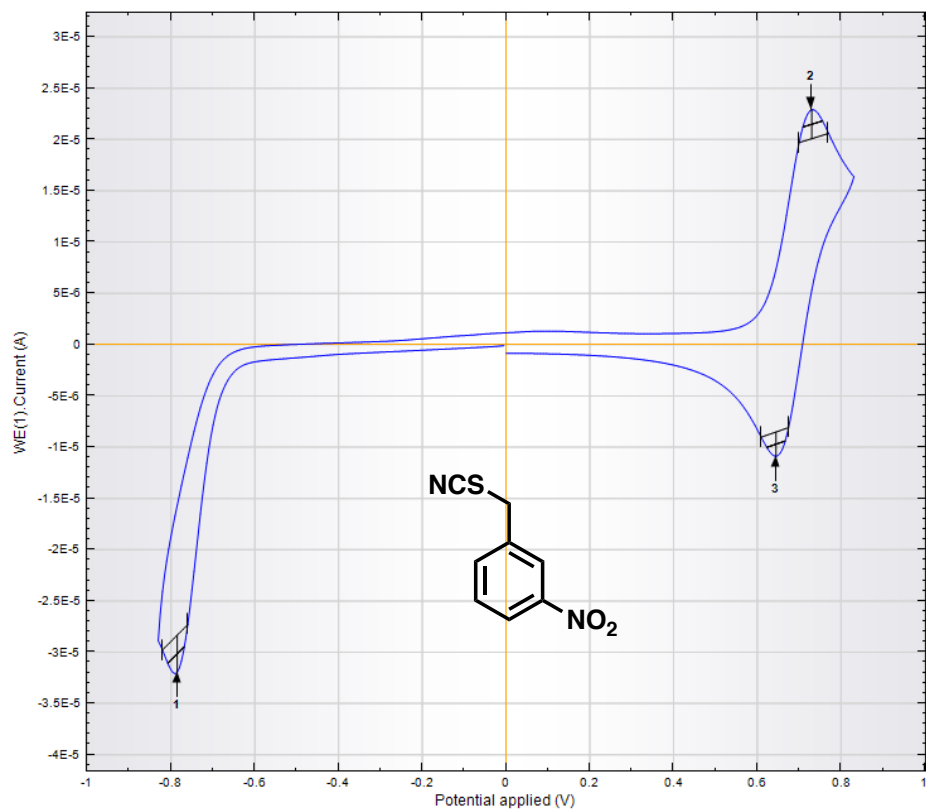
4-(thiocyanatomethyl)benzonitrile



$$E_{\text{red}} = -1.57 \text{ V vs SCE}$$

Index	Peak position
1	-1.284
2	0.70999
3	0.61432

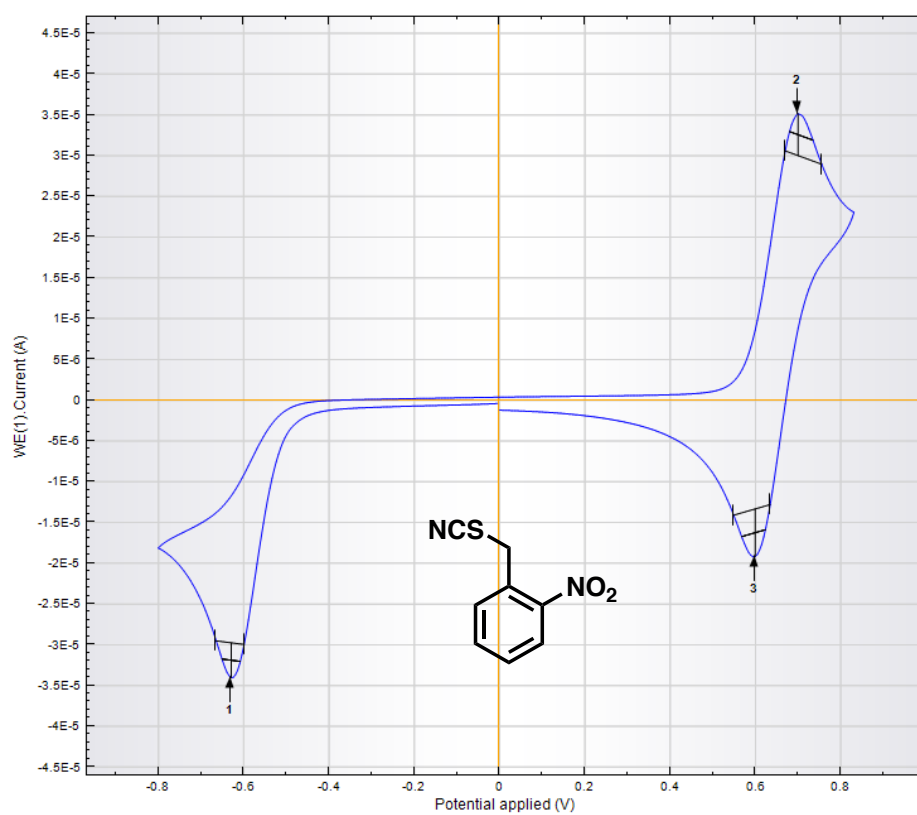
1-nitro-3-(thiocyanatomethyl)benzene



$E_{\text{red}} = -1.09 \text{ V vs SCE}$

Index	Peak position
1	-0.78552
2	0.73013
3	0.64453

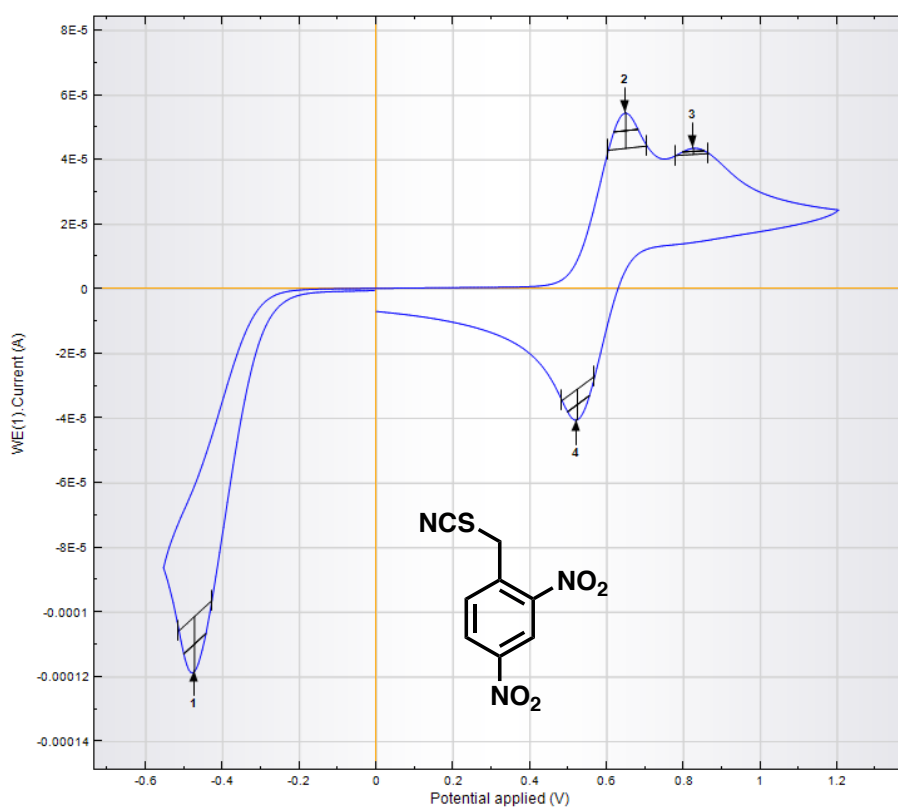
1-nitro-2-(thiocyanatomethyl)benzene



$$E_{\text{red}} = -0.9 \text{ V vs SCE}$$

Index	Peak position
1	-0.62943
2	0.69992
3	0.59921

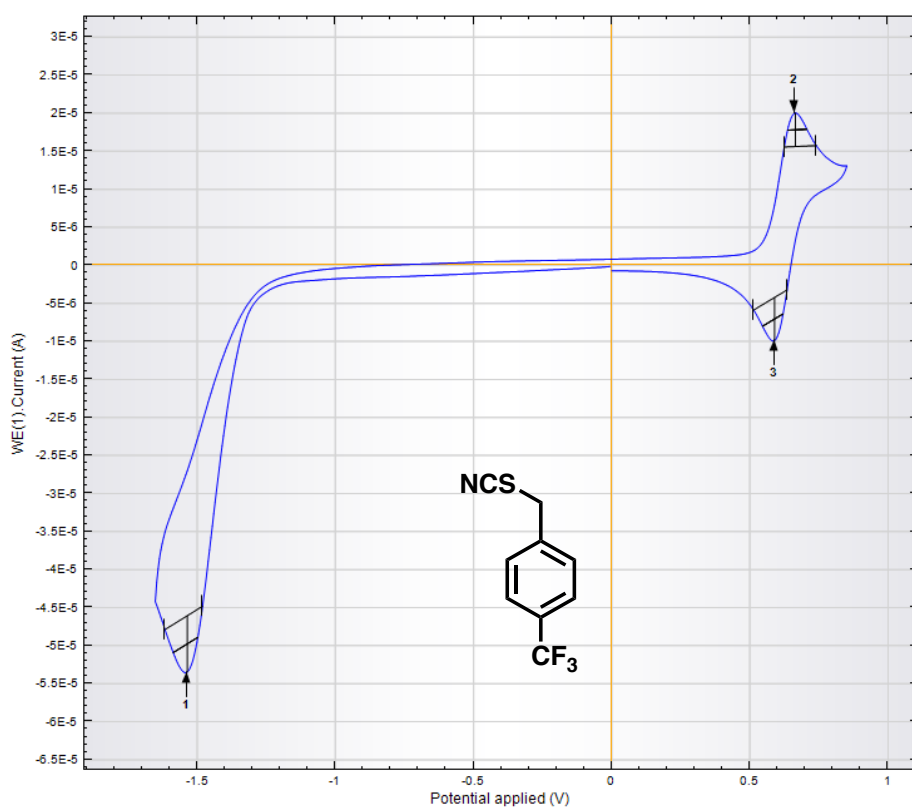
2,4-dinitro-1-(thiocyanatomethyl)benzene



$$E_{\text{red}} = -0.68 \text{ V vs SCE}$$

Index	Peak position
1	-0.47333
2	0.64957
3	0.82581
4	0.52368

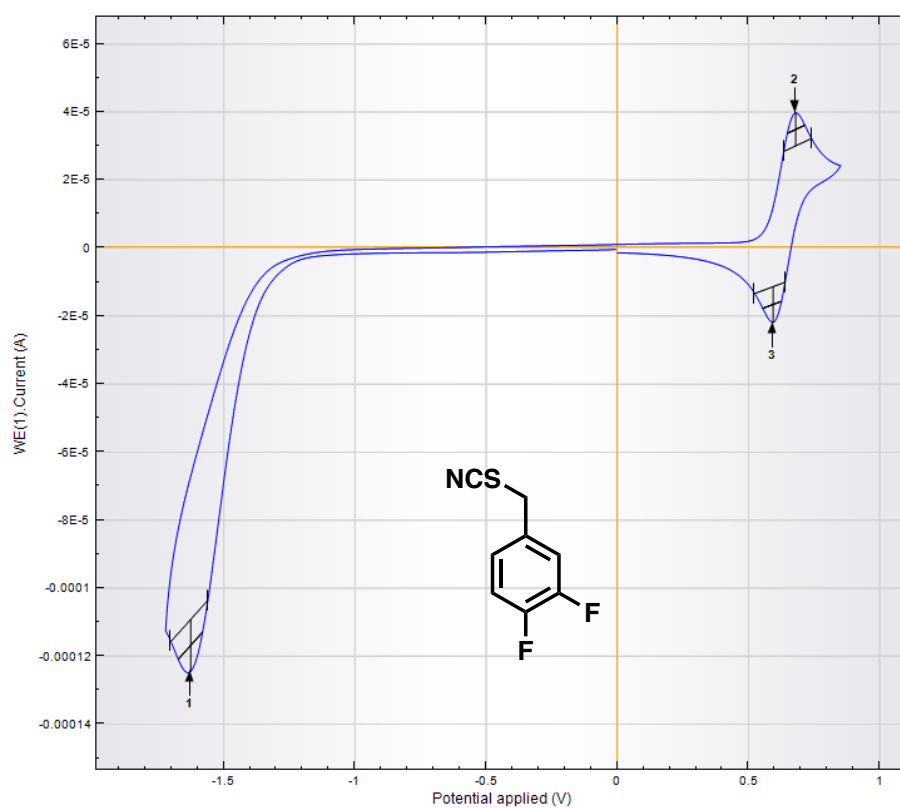
1-(thiocyanatomethyl)-4-(trifluoromethyl)benzene



$$E_{\text{red}} = -1.78 \text{ V vs SCE}$$

Index	Peak position
1	-1.5358
2	0.66467
3	0.58914

1,2-difluoro-4-(thiocyanatomethyl)benzene

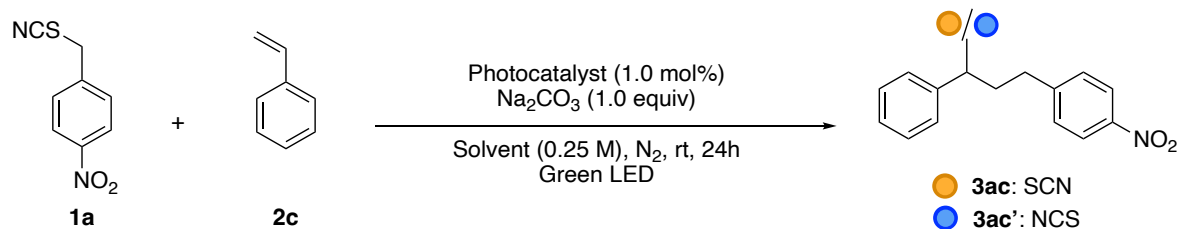


$E_{\text{red}} = -1.88 \text{ V vs SCE}$

Index	Peak position
1	-1.6264
2	0.67978
3	0.59418

3. Reaction optimization:

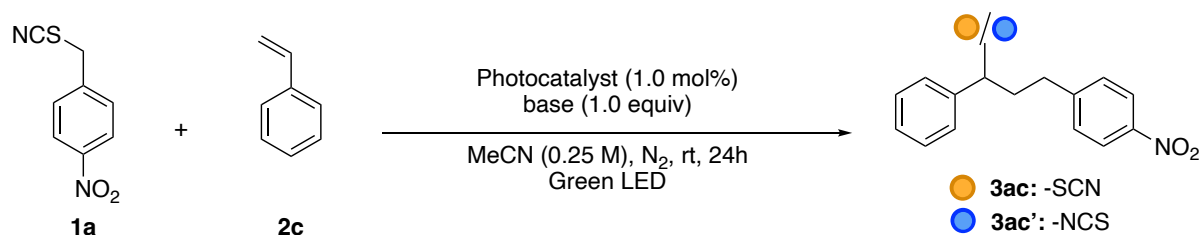
Solvent screening:



Entry	Solvent	3ac ^a	3ac' ^a	Total yield
1	MeCN	53%	45%	98%
2	MeOH	c.r.m.	c.r.m.	—
3	DMF	46%	14%	60%
4	DCM	62%	26%	88%
5	DMC	30%	6%	36%

Standard conditions: 4-nitrobenzylthiocyanate (**1a**) (0.25 mmol, 1.0 equiv), styrene (**2c**) (0.5 mmol, 2.0 equiv), Cu(dap)₂Cl (2.5 μmol, 1.0 mol%), Na₂CO₃ (0.25 mmol, 1.0 equiv) in solvent (anh., degassed, 1.0 mL, 0.25 M), irradiated by 530nm LED for 24 h under N₂ atmosphere at room temperature. ^aYields determined by ¹H-NMR using tetrachloroethane as an internal standard. c.r.m. = complex reaction mixture.

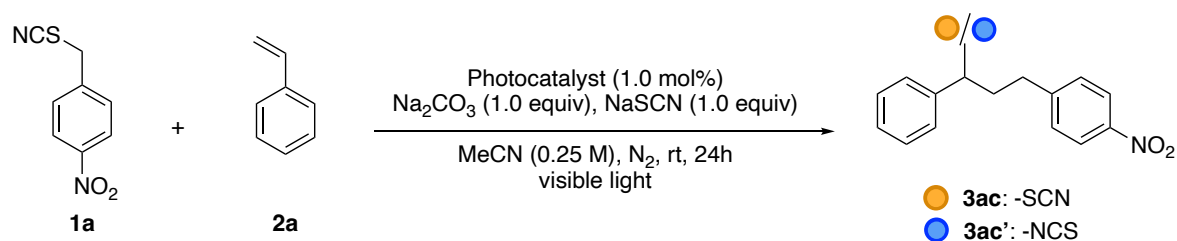
Base screening:



Entry	Base	Additive (equiv)	3ac ^a	3ac' ^a	Total yield
1	Na ₂ CO ₃	—	53%	45%	98%
2	K ₂ CO ₃	—	54%	31%	85%
3	NaHCO ₃	—	47%	46%	93%
4	Na ₂ HPO ₄	—	48%	42%	90%
5	2,6-Lutidine	—	50%	40%	90%
6	DMAP	—	12%	—	12%
7	Na ₂ CO ₃	NaSCN (1.0 equiv.)	93%	7%	>99%
8	Na ₂ CO ₃	NaSCN (0.2 equiv.)	26%	12%	38%
9	Na ₂ CO ₃	KSCN (1.0 equiv.)	82%	4%	86%
10	Na ₂ CO ₃	NH ₄ SCN (1.0 equiv.)	76%	—	76%
11	Na ₂ CO ₃	TMSNCS (1.0 equiv.)	88%	12%	>99%
12	Na ₂ HPO ₄	NaSCN (1.0 equiv.)	48%	10%	58%

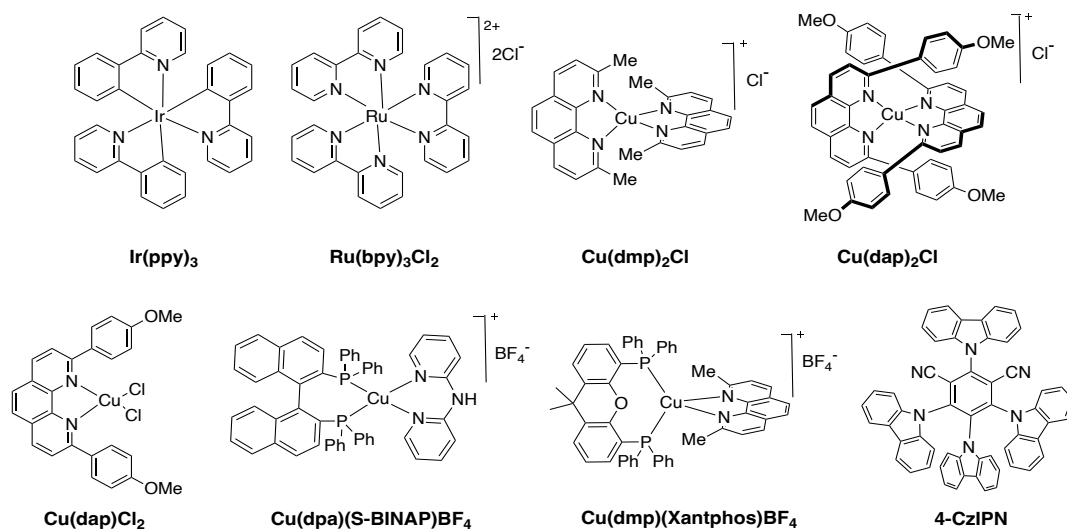
Standard conditions: 4-nitrobenzylthiocyanate (**1a**) (0.25 mmol, 1.0 equiv), styrene (**2c**) (0.5 mmol, 2.0 equiv), Cu(dap)₂Cl (2.5 μmol, 1.0 mol%), base (0.25 mmol, 1.0 equiv) in MeCN (anh., degassed, 1.0 mL, 0.25 M), irradiated for 24 h under N₂ atmosphere at room temperature. ^aYields determined by ¹H-NMR using tetrachloroethane as an internal standard. DMAP = 4-(dimethylamino)pyridin.

Photocatalyst screening

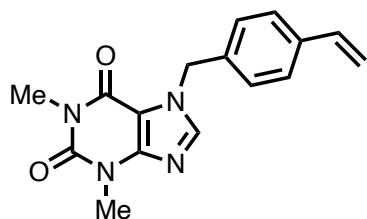


Entry	Catalyst	λ_{vis}	3ac ^a	3ac' ^a	Total yield
1	$\text{Ir}(\text{ppy})_3$	455 nm	56%	12%	68%
2	$\text{Ru}(\text{bpy})_3\text{Cl}_2$	455 nm	26%	6%	32%
3	$\text{Cu}(\text{dmp})_2\text{Cl}$	455nm	81%	6%	87%
4 ^b	$\text{Cu}(\text{dap})_2\text{Cl}$	530nm	93%	7%	>99%
5	$\text{Cu}(\text{dap})\text{Cl}_2$	530nm	84%	16%	>99%
6	$\text{Cu}(\text{dpa})(\text{S-BINAP})\text{BF}_4$	455nm	19%	6 %	25%
7	$\text{Cu}(\text{dmp})(\text{Xantphos})\text{BF}_4$	455nm	64%	4%	68%
8	4-CzIPN	455nm	24%	—	24%

Standard conditions: 4-nitrobenzylthiocyanate (**1a**) (0.25 mmol, 1.0 equiv), styrene (**2c**) (0.5 mmol, 2.0 equiv), photocatalyst (2.5 μmol , 1.0 mol%), sodium carbonate (0.25 mmol, 1.0 equiv.), sodium thiocyanate (0.25 mmol, 1.0 equiv) in MeCN (anh., degassed, 1.0 mL, 0.25 M) for 24 h under N_2 atmosphere at room temperature. ^aYields determined by $^1\text{H-NMR}$ using tetrachloroethane as an internal standard. ^bReaction conducted for 48h. ppy = 2-phenylpyridine, bpy = 2,2'-bipyridine, dmp = 2,9-dimethyl-1,10-phenanthroline, dap = 2,9-bis(4-methoxyphenyl)-1,10-phenanthroline, dpa = 2,2'-dipyridylamine, S-BINAP= ([1,1'-Binaphthalene]-2,2'-diyl)bis(diphenylphosphane), Xantphos = (9,9-Dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane), 4-CzIPN = 2,4,5,6-Tetra(9H-carbazol-9-yl)isophthalonitrile.



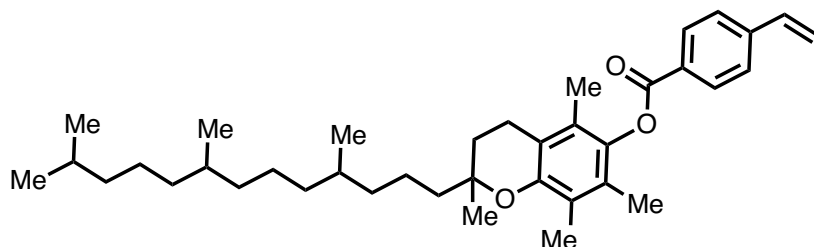
4. Synthesis of literature known compounds:



1,3-dimethyl-7-(4-vinylbenzyl)-3,7-dihydro-1H-purine-2,6-dione (**2w**)

The synthesis of **2w** was based on the literature procedure.²⁹⁶ To a flame dried flask was added Theophylline (1.8 g, 10.0 mmol, 1.0 equiv), 4-vinylbenzyl chloride (3.0 g, 20.0 mmol, 2.0 equiv) and DMSO (36.0 mL), then the mixture was cooled to 0°C. Afterwards, NaH (959.6 mg, 40.0 mmol, 4.0 equiv) was added slowly and the mixture was stirred for 30 min at 0°C. The reaction was allowed to warm up to room temperature, stirred for an additional 3h and monitored by TLC. After stopping the reaction, the mixture was added to water which led to the formation of a precipitate that was purified using flash column chromatography on silica gel to yield 1.6 g (5.5 mmol, 55%) of 1,3-dimethyl-7-(4-vinylbenzyl)-3,7-dihydro-1H-purine-2,6-dione (**2w**) as a white solid. Spectral data were in accordance with literature.

¹H-NMR (400 MHz, DMSO-*d*₆): 8.27 (s, 1H), 7.43 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8Hz, 2H), 6.85 (dd, 1H, (dd, 1H, ³*J* = 18 Hz (trans), ³*J* = 10 Hz (cis), CH=CH₂). 5.80 (dd, 1H, ¹*J* = 1 Hz, ³*J* = 18 Hz), 5.25 (dd, 1H, ¹*J* = 1 Hz, ³*J* = 18 Hz), 3.41 (s, 3H), 3.20 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃): 154.3, 150.9, 148.3, 142.5, 136.7, 136.4, 136.0, 127.8, 126.3, 114.6, 105.7, 48.7, 29.4, 27.5.

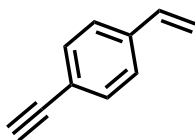


2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl 4-vinylbenzoate (**2x**)

The synthesis of **2x** was based on the literature procedure.²⁹⁷ Rac. Vitamin-E (1.3 g, 3.0 mmol, 1.0 equiv), 4-vinylbenzoic acid (445.0 mg, 3.0 mmol, 1.0 equiv), DCC (745.0 mg, 3.6 mmol, 1.2 equiv), DMAP (440.0 mg, 3.6 mmol, 1.2 equiv) and anhydrous DCM (30.0 mL, 0.1 M)

were charged in a flame dried 3-neck round bottom flask and stirred for 44h at room temperature. The reaction was monitored by TLC. The reaction mixture was then concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to yield 1.3 g (2.4 mmol, 80%) of 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl 4-vinylbenzoate (**2x**) as an orange sticky oil. Spectral data were in accordance with literature.

¹H-NMR (400 MHz, CDCl₃): 8.24 (dd, 2H), 7.56 (d, 2H), 6.82 (dd, 1H), 5.93 (d, 1H), 5.45 (d, 1H), 2.66, (t, 2H), 2.17 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 1.93-1.77 (m, 2H), 1.64-1.12 (m, 24H), 0.94-0.87 (m, 12H). ¹³C-NMR (101 MHz, CDCl₃): 165.0, 149.6, 142.6, 140.8, 136.1, 130.6, 128.9, 127.0, 126.4, 125.2, 123.2, 117.6, 116.9, 75.2, 39.5, 37.7, 37.6, 37.5, 37.4, 32.9, 32.9, 32.8, 28.1, 25.0, 25.0, 24.6, 22.9, 22.8, 21.2, 20.8, 19.9, 19.8, 19.8, 13.2, 12.3, 12.0.

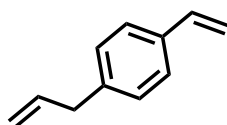


1-ethynyl-4-vinylbenzene (**2y**)

The synthesis of **2y** was based on the literature procedure.²⁷ [PdCl₂(PPh₃)₂] (139.4 mg, 0.2 mmol, 2.0 mol%) was dissolved in anhydrous triethylamine (20.0 mL, 0.25 M) and charged in a flame-dried Schlenk flask. The mixture was degassed by three consecutive freeze-pump-thaw cycles. Then, 4-bromostyrene (915.0 mg, 5.0 mmol, 1.0 equiv) and ethynyltrimethylsilane (1.13 g, 11.5 mmol, 2.3 equiv) were added under a positive nitrogen overpressure. The reaction mixture was stirred for 10 min at 50°C. CuI (28.6 mg, 0.15 mmol, 3.0 mol%) was then added under a positive nitrogen overpressure; the resulting mixture was allowed to magnetically stir for 24h at 50°C while being monitored by TLC. Later, the reaction was cooled down to room temperature and was subsequently quenched using saturated aqueous NH₄Cl solution and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo affording ((4-vinylphenyl)ethynyl)silane as crude product. The latter was directly used in the following step without further purification. The latter product was charged in a round-bottom flask and dissolved in methanol (10 mL, 0.25 M), then, K₂CO₃ (1.38 g, 10.0 mmol, 2.0 equiv) was added and the mixture was stirred for 24h at room temperature. After completion, the reaction mixture was quenched with saturated aqueous NH₄Cl and extracted three times with diethyl ether. The combined organic layers were

washed with water and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified using flash column chromatography on silica gel yielding to 440 mg (3.4 mmol, 68%) of 1-ethynyl-4-vinylbenzene (**2y**) as a clear colorless liquid. Spectral data were in accordance with literature.

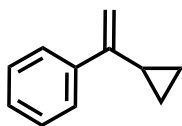
¹H-NMR (400 MHz, CDCl₃): 7.46 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 6.71 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.78 (dd, *J* = 17.6, 0.7 Hz, 1H), 5.31 (dd, *J* = 10.9, 0.7 Hz, 1H), 3.12 (s, 1H). ¹³C-NMR (101 MHz, CDCl₃): 138.1, 136.3, 132.4, 126.2, 121.5, 115.2, 83.8, 77.9.



1-allyl-4-vinylbenzene (**2z**)

The synthesis of **2z** was based on the literature procedure.²⁷ [Pd(dba)₂] (69.0 mg, 0.12 mmol, 3.0 mol%), tricyclohexylphosphonium tetrafluoroborate (88.4 mg, 0.24 mmol, 0.06 equiv), and CsF (1.34 g, 8.8 mmol, 2.2 equiv) were charged in a flame dried Schlenk flask and dissolved in anhydrous dioxane (8.0 mL, 1.0 M). The Schlenk flask was then sealed with a screw cap and degassed by three consecutive freeze-pump-thaw cycles. Then, 2-bromostyrene (730 mg, 4.0 mmol, 1.0 equiv) and allytributyltin (1.39 g, 4.2 mmol, 1.05 equiv) were added under a positive nitrogen overpressure. The reaction mixture was then stirred for 72h at 101°C and monitored by TLC. After completion, the reaction was quenched using saturated aqueous NH₄Cl solution and then extracted three times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was then purified by flash column chromatography on silica gel to yield 363.8 mg (2.53 mmol, 63%) of 1-allyl-4-vinylbenzene (**2z**) as a clear colorless liquid. Spectral data were in accordance with literature.

¹H-NMR (300 MHz, CDCl₃): 7.38 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.73 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.09 – 5.89 (m, 1H), 5.75 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.24 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.16 – 5.11 (m, 1H), 5.09 (t, *J* = 1.5 Hz, 1H), 3.41 (d, *J* = 6.7 Hz, 2H). ¹³C-NMR (75 MHz, CDCl₃): 139.9, 137.4, 136.8, 135.6, 128.9, 126.4, 116.0, 113.3, 40.1.



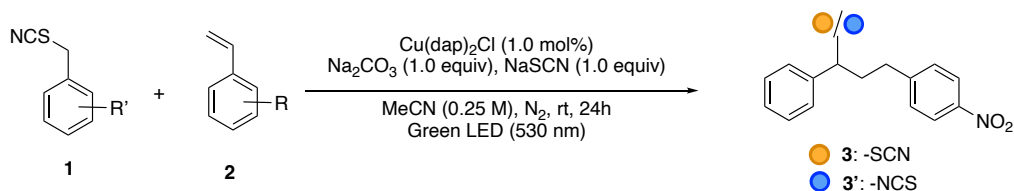
(1-cyclopropylvinyl) benzene (7)

The synthesis of **7** was based on the literature procedure.²⁹⁸ Methyltriphenylphosphonium bromide (3.5 g, 10.0 mmol, 2.0 equiv) and anhydrous THF (30.0 mL) were charged in a flame dried round-bottom flask. The mixture was cooled to 0°C then *n*-butyllithium (6.2 mL, 1.6 M in hexanes, 10.0 mmol, 2.0 equiv) was slowly added. The mixture was stirred at room temperature for 1h. Afterwards, cyclopropyl(phenyl)methanone (0.7 mL, 0.7 g, 5.0 mmol, 1.0 equiv) in anhydrous THF (3.0 mL) was added dropwise to the solution. The reaction was then stirred for 12h at 40°C. The reaction mixture was quenched with brine and extracted 3 times with hexanes. The combined organic layers were washed three times with water, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography to yield 0.65 g (4.5 mmol, 90%) of (1-cyclopropylvinyl) benzene (**7**) as a colorless oil. Spectral data were in accordance with literature.

¹H-NMR (300 MHz, CDCl₃): 7.69 – 7.58 (m, 2H), 7.43 – 7.27 (m, 3H), 5.31 (d, *J* = 1.1 Hz, 1H), 4.96 (t, *J* = 1.2 Hz, 1H), 1.68 (ttt, *J* = 8.3, 5.4, 1.2 Hz, 1H), 0.92 – 0.82 (m, 2H), 0.67 – 0.58 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 149.5, 141.8, 128.3, 127.6, 126.3, 109.1, 15.8, 6.8.

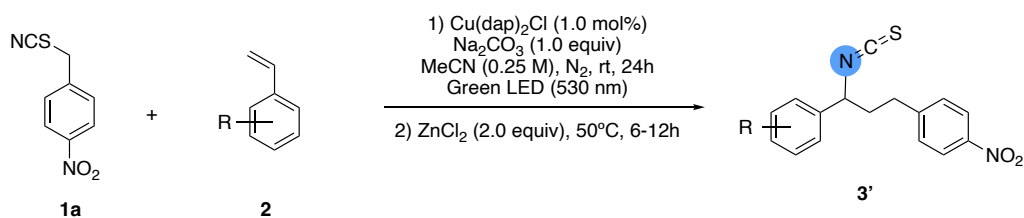
5. Synthesis procedures:

General procedure for the benzylthiocyanation reactions (GPI):



To a flame-dried Schlenk tube equipped with a stirring bar was added benzylthiocyanate (**1**) (97.0 mg, 0.5 mmol, 1.0 equiv), sodium carbonate (53.0 mg, 0.5 mmol, 1.0 equiv), sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) and $\text{Cu(dap)}_2\text{Cl}$ (4.4mg, 5.0 μmol , 1.0 mol%). Then a mixture of styrene **2** (104.0 mg, 1.0 mmol, 2.0 equiv) in anhydrous acetonitrile (degassed, 2.0 mL, 0.25 M) was added. The tube was sealed with a screw-cap and subsequently degassed by three consecutive freeze-pump-thaw cycles. The screw-cap was, under a positive nitrogen pressure, replaced by a Teflon inlet with a glass rod that transmits the light irradiations (530nm LED). The Schlenk tube was placed in an aluminum block and stirred at room temperature for 24h. The reaction was monitored by TLC. After completion, the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel to deliver a mixture of thiocyanated (**3**) and isothiocyanated (**3'**) products.

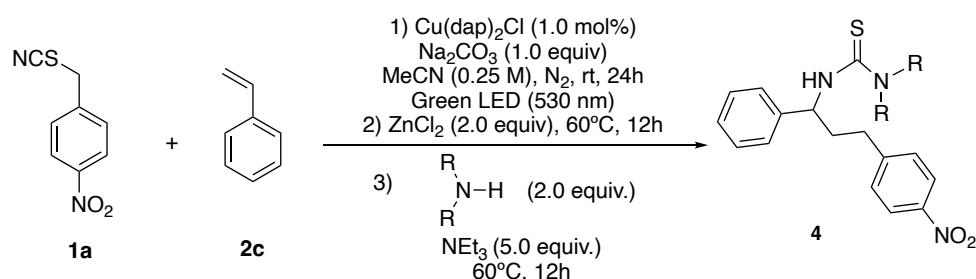
General procedure for isothiocyanation (GPII):



To a flame-dried Schlenk tube equipped with a stirring bar was added 4-nitrobenzyl thiocyanate (**1a**) (97.0 mg, 0.5 mmol, 1.0 equiv), sodium carbonate (53.0 mg, 0.5 mmol, 1.0 equiv) and $\text{Cu(dap)}_2\text{Cl}$ (4.4mg, 5.0 μmol , 1.0 mol%). Then a mixture of styrene (**2**) (104.0 mg, 1.0 mmol, 2.0 equiv) in anhydrous acetonitrile (degassed, 2.0 mL, 0.25 M) was added. The tube was

sealed with a screw-cap and subsequently degassed by three consecutive freeze-pump-thaw cycles. The screw-cap was, under a positive nitrogen pressure, replaced by a Teflon inlet with a glass rod that transmits the light irradiations (530nm LED). The Schlenk tube was placed in an aluminum block and stirred at room temperature for 24h. The reaction was monitored by TLC. After completion, zinc chloride (136.3 mg, 1.0 mmol, 2.0 equiv) was added under a positive nitrogen overpressure. The reaction was allowed to stir for 12h while being monitored by TLC. Afterwards, the reaction mixture was quenched with water and extracted three times using DCM. The organic layers were collected, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude mixture was then purified using flash column chromatography on silica gel to yield to the corresponding isothiocyanate compound **3'**.

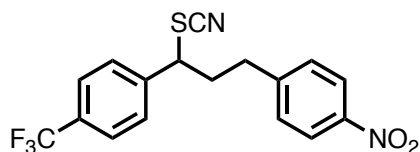
General procedure for the synthesis of thioureas (GPIII):



To a flame-dried Schlenk tube equipped with a stirring bar was added 4-nitrobenzyl thiocyanate (**1a**) (97.0 mg, 0.5 mmol, 1.0 equiv), sodium carbonate (53.0 mg, 0.5 mmol, 1.0 equiv) and Cu(dap)₂Cl (4.4mg, 5.0 μmol, 1.0 mol%). Then a mixture of styrene (**2c**) (104.0 mg, 1.0 mmol, 2.0 equiv) in anhydrous acetonitrile (degassed, 2.0 mL, 0.25 M) was added. The tube was sealed with a screw-cap and subsequently degassed by three consecutive freeze-pump-thaw cycles. The screw-cap was, under a positive nitrogen pressure, replaced by a Teflon inlet with a glass rod that transmits the light irradiations (530nm LED). The Schlenk tube was placed in an aluminum block and stirred at room temperature for 24h. The reaction was monitored by TLC. After completion, zinc chloride (136.3 mg, 1.0 mmol, 2.0 equiv) was added under a positive nitrogen overpressure. The reaction was allowed to stir for 12h while being monitored by TLC. After completion, NEt₃ (253.0 mg, 2.5 mol, 5 equiv) and amine (1.0 mmol, 2.0 equiv) were added under a positive nitrogen overpressure. The reaction was stirred for 6-12h and was monitored by TLC. Afterwards, the reaction mixture was quenched with water and extracted

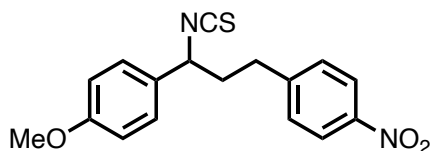
three times using DCM. The organic layers were collected, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude mixture was then purified using flash column chromatography on silica gel to yield to the corresponding thioureas (**4**).

6. Spectral data



1-nitro-4-(3-thiocyanato-3-(4-(trifluoromethyl)phenyl)propyl)benzene (**3aa**)

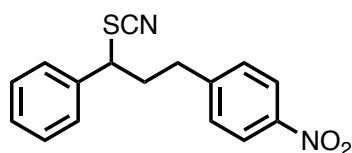
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-trifluoromethyl styrene (**2a**) (176.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 85% (155.6 mg, 425.0 μmol) of **3aa** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.14 (d, 2H), 7.68 (d, 2H), 7.48 (d, 2H), 7.30 (d, 2H), 4.30 (t, 1H), 2.89-2.72 (m, 2H), 2.63-2.42 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 147.16, 146.86, 141.84, 131.59, 131.15, 129.32, 127.94, 126.44, 126.39, 125.51, 124.02, 121.91, 110.50, 51.43, 36.18, 33.15. ¹⁹F-NMR (282 MHz, CDCl₃): -63.29 (s, 3F). IR (neat, cm⁻¹): 3078, 2940, 2855, 2154, 1602, 1517, 1345, 1162, 1110, 1066, 1017, 849, 749, 697. HRMS m/z calculated for C₁₇H₁₃F₃N₂O₂S ([M+Na]⁺) 389.0547 found 389.0541.



1-(3-isothiocyanato-3-(4-methoxyphenyl)propyl)-4-nitrobenzene (**3ab'**)

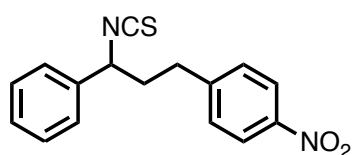
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-methoxystyrene (**2b**) (134.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol,

1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 96% (157.5 mg, 480.0 mmol) of **3ab'** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.13 (d, 2H), 7.33 (d, 2H), 7.21 (d, 2H), 6.90 (d, 2H), 4.68 (q, 1H), 3.79 (s, 3H), 2.93-2.75 (m, 2H), 2.35-2.09 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 159.70, 148.11, 146.68, 130.47, 129.35, 127.19, 123.91, 114.39, 60.53, 55.41, 39.82, 32.23. IR (neat, cm⁻¹): 2929, 2840, 2076, 1707, 1602, 1513, 1461, 1341, 1248, 1177, 1110, 1028, 831, 745, 697. HRMS m/z calculated for C₁₇H₁₆N₂O₃S ([M+Na]⁺) 351.0779 found 351.0777.



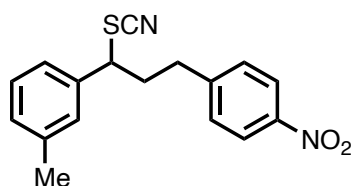
1-nitro-4-(3-phenyl-3-thiocyanatopropyl)benzene (**3ac**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), styrene (**2c**) (104.15 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 93% (138 mg, 465.0 mmol) of **3ac** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.15 (d, 2H), 7.46-4.37 (m, 3H), 7.37-7.32 (m, 2H), 7.29 (d, 2H), 4.28 (q, 1H), 2.78 (t, 2H), 2.64-2.46 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 147.55, 146.80, 137.34, 129.45, 129.41, 129.31, 127.49, 123.97, 111.22, 52.35, 36.63, 33.22. IR (neat, cm⁻¹): 3075, 2929, 2855, 2150, 1602, 1513, 1453, 1341, 1252, 1177, 1110, 1013, 849, 745, 697. HRMS m/z calculated for C₁₆H₁₄N₂O₂S ([M+NH₄]⁺) 316.1119 found 316.1116.



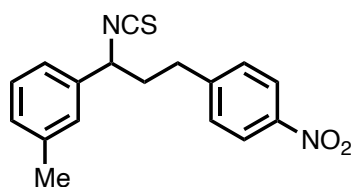
1-(3-isothiocyanato-3-phenylpropyl)-4-nitrobenzene (**3ac'**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), styrene (**2c**) (104.15 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 7% (8.94 mg, 35.0 μmol) of **3ac'** as a light-yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.06 (d, 2H), 7.33-7.21 (m, 5H), 7.20-7.16 (m, 2H), 4.64 (q, 1H), 2.86-2.70 (m, 2H), 2.25-2.04 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 147.91, 146.76, 138.41, 129.30, 129.07, 128.60, 125.84, 123.95, 60.94, 39.92, 32.19. IR (neat, cm⁻¹): 3063, 2929, 2855, 2079, 1602, 1513, 1453, 1241, 1110, 1013, 849, 745, 697. HRMS m/z calculated for C₁₆H₁₄N₂O₂S ([M+Na]⁺) 321.0673 found 321.0670.



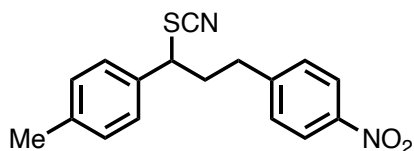
1-methyl-3-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3ad**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 3-methylstyrene (**2d**) (118.08 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 78% (121 mg, 390.0 μmol) of **3ad** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.14 (d, 2H), 7.33-7.26 (m, 3H), 7.18 (d, 1H), 7.13 (s, 2H), 4.26 (t, 1H), 2.81-2.71 (m, 2H), 2.62-2.45 (m, 2H), 2.37 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 147.70, 146.76, 139.28, 137.23, 130.18, 129.32, 129.30, 128.12, 124.51, 123.93, 111.38, 52.47, 36.69, 33.25, 21.50. IR (neat, cm⁻¹): 3078, 2922, 2855, 2150, 1602, 1513, 1453, 1341, 1177, 1110, 849, 790, 745, 700. HRMS m/z calculated for C₁₇H₁₆N₂O₂S ([M+Na]⁺) 335.0830 found 335.0831.



1-(1-isothiocyanato-3-(4-nitrophenyl)propyl)-3-methylbenzene (**3ad'**)

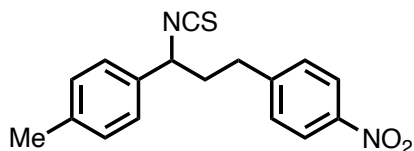
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 3-methylstyrene (**2d**) (118.08 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 21% (33 mg, 105.0 μmol) of **3ad'** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.17 (d, 2H), 7.35(d, 2H), 7.29-7.24 (m, 1H), 7.15 (d, 1H), 7.08 (s, 2H), 4.70 (q, 1H), 2.97-2.78 (m, 2H), 2.37 (s, 3H), 2.34-2.12 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 148.00, 146.74, 138.92, 138.33, 129.33, 128.96, 126.52, 123.95, 122.92, 60.94, 39.92, 32.24, 21.50. IR (neat, cm⁻¹): 3019, 2922, 2855, 2072, 1602, 1513, 1453, 1341, 1177, 1110, 849, 782, 745, 697. HRMS m/z calculated for C₁₇H₁₆N₂O₂S ([M+Na]⁺) 335.0830 found 335.0829.



1-methyl-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3ae**)

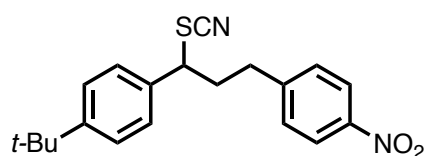
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-methylstyrene (**2e**) (118.08 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 80% (124.8 mg, 400.0 μmol) of **3ae** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.14 (d, 2H), 7.33-7.17 (m, 6H), 4.27 (q, 1H), 2.76 (t, 2H), 2.59-2.45 (m, 2H), 2.37 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 147.72, 146.75, 139.44, 134.21, 130.10, 129.33, 127.42, 123.93, 111.44, 52.30, 36.66, 33.23, 21.27. IR (neat, cm⁻¹):

3026, 2926, 2855, 2150, 1602, 1513, 1449, 1341, 1181, 1110, 849, 820, 745, 697. HRMS m/z calculated for $C_{17}H_{16}N_2O_2S$ ($[M+Na]^+$) 335.0830 found 335.0830.



1-(1-isothiocyanato-3-(4-nitrophenyl)propyl)-4-methylbenzene (**3ae'**)

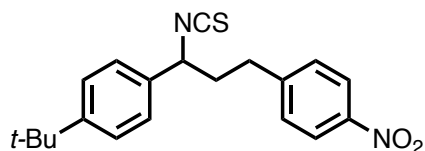
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-methylstyrene (**2e**) (118.08 mg, 1.0 mmol, 2.0 equiv), $Cu(dap)_2Cl$ (4.4 mg, 5.0 μ mol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 19% (30 mg, 95.0 μ mol) of **3ae'** as a yellow sticky oil. 1H -NMR (300 MHz, $CDCl_3$): 8.16 (d, 2H), 7.34 (d, 2H), 7.22-7.13 (m, 4H), 4.71 (q, 1H), 2.96-2.76 (m, 2H), 2.36 (s, 3H), 2.33-2.10 (m, 2H). ^{13}C -NMR (75 MHz, $CDCl_3$): 148.04, 146.72, 138.50, 135.44, 129.71, 129.32, 125.79, 123.94, 60.76, 39.86, 32.20, 21.15. IR (neat, cm^{-1}): 3026, 2922, 2855, 2076, 1602, 1513, 1449, 1341, 1181, 1110, 1017, 849, 812, 745, 697. HRMS m/z calculated for $C_{17}H_{16}N_2O_2S$ ($[M+Na]^+$) 335.0830 found 335.0830.



1-(tert-butyl)-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3af**)

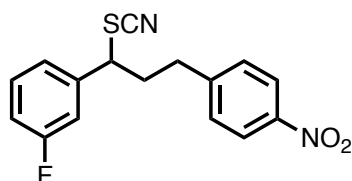
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-*tert*-butylstyrene (**2f**) (160.13 mg, 1.0 mmol, 2.0 equiv), $Cu(dap)_2Cl$ (4.4 mg, 5.0 μ mol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 97% (171 mg, 485.0 μ mol) of **3af** as a yellow sticky oil. 1H -NMR (300 MHz, $CDCl_3$): 8.13 (d, 2H), 7.41 (d, 2H), 7.28 (t, 4H), 4.30

(t, 1H), 2.82-2.74 (m, 2H), 2.62-2.47 (m, 2H), 1.32 (s, 9H). ^{13}C -NMR (75 MHz, CDCl_3): 152.51, 147.83, 146.72, 134.18, 129.37, 127.21, 126.33, 123.90, 111.53, 52.27, 36.69, 34.76, 33.28, 31.27. IR (neat, cm^{-1}): 2959, 2866, 2150, 1602, 1513, 1341, 1267, 1110, 1013, 849, 745, 697. HRMS m/z calculated for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ ($[\text{M}+\text{Na}]^+$) 377.1299 found 377.1299.



1-(*tert*-butyl)-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (**3af'**)

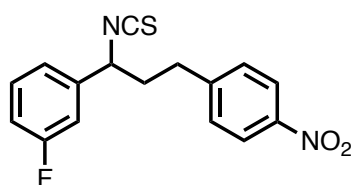
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-*tert*-butylstyrene (**2f**) (160.13 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μmol , 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 $^\circ\text{C}$) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 3% (5.5 mg, 15.0 μmol) of **3af'** as a yellow sticky oil. ^1H -NMR (300 MHz, CDCl_3): 8.16 (d, 2H), 7.38 (q, 4H), 7.22 (d, 2H), 4.72 (q, 1H), 2.98-2.79 (m, 2H), 2.37-2.12 (m, 2H), 1.31 (s, 9H). ^{13}C -NMR (75 MHz, CDCl_3): 151.72, 148.07, 146.71, 135.39, 129.34, 125.98, 125.60, 123.93, 60.72, 39.82, 34.67, 32.26, 31.31. IR (neat, cm^{-1}): 2959, 2866, 2076, 1602, 1517, 1408, 1341, 1110, 1013, 849, 745, 697. HRMS m/z calculated for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ ($[\text{M}+\text{Na}]^+$) 377.1299 found 377.1299.



1-fluoro-3-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3ag**)

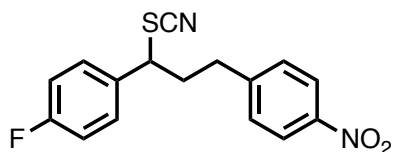
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 3-fluorostyrene (**2g**) (122.05 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μmol , 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 $^\circ\text{C}$) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column

chromatography (*hexanes* : *EtOAc*) to yield 95% (142.5 mg, 475.0 μ mol) of **3ag** as a yellow sticky oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.13 (d, 2H), 7.43-7.34 (m, 1H), 7.30 (d, 2H), 7.13 (d, 1H), 7.11-7.03 (m, 2H), 4.26 (t, 1H), 2.86-2.70 (m, 2H), 2.56-2.42 (m, 2H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 164.67, 161.38, 147.38, 146.81, 140.17, 140.07, 131.16, 131.05, 129.34, 123.99, 123.35, 123.31, 116.56, 116.28, 114.60, 114.30, 110.78, 51.64, 51.61, 36.38, 33.17. $^{19}\text{F-NMR}$ (282 MHz, CDCl_3): -111.23 (s, 1F). IR (neat, cm^{-1}): 3078, 2929, 2855, 2154, 1591, 1513, 1449, 1341, 1252, 1140, 1110, 849, 790, 749, 693. HRMS m/z calculated for $\text{C}_{16}\text{H}_{13}\text{FN}_2\text{O}_2\text{S}$ ($[\text{M}+\text{Na}]^+$) 339.0579 found 339.0577.



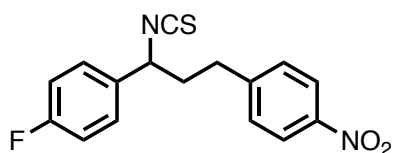
1-fluoro-3-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (**3ag'**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 3-fluorostyrene (**2g**) (122.05 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μ mol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 $^\circ\text{C}$) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 4% (6 mg, 20.0 μ mol) of **3ag'** as a yellow sticky oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.18 (d, 2H), 7.39-7.32 (m, 3H), 7.10-6.98 (m, 3H), 4.76 (q, 1H), 2.98-2.80 (m, 2H), 2.36-2.13 (m, 2H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 147.62, 130.79, 130.71, 129.30, 124.01, 121.52, 115.70, 113.18, 112.96, 60.36, 39.84, 32.10, 29.72. $^{19}\text{F-NMR}$ (282 MHz, CDCl_3): -111.75 (s, 1F). IR (neat, cm^{-1}): 2922, 2855, 2087, 1736, 1599, 1520, 1449, 1345, 1252, 1110, 1017, 861, 790, 752, 700. HRMS m/z calculated for $\text{C}_{16}\text{H}_{13}\text{FN}_2\text{O}_2\text{S}$ ($[\text{M}+\text{Na}]^+$) 339.0579 found 339.0571.



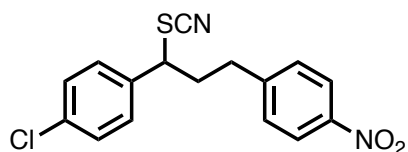
1-fluoro-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3ah**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-fluorostyrene (**2h**) (122.05 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 74% (117 mg, 370.0 μmol) of **3ah** as a yellow sticky oil. ¹H-NMR (400 MHz, CDCl₃): 8.09 (d, 2H), 7.32-7.20 (m, 4H), 7.05 (t, 2H), 4.23 (q, 1H), 2.73 (t, 2H), 2.56-2.36 (m, 2H). ¹³C-NMR (101 MHz, CDCl₃): 164.22, 161.74, 147.30, 146.85, 133.38, 133.35, 129.36, 129.28, 124.00, 123.81, 116.59, 116.37, 110.90, 51.61, 36.58, 33.19. ¹⁹F-NMR (282 MHz, CDCl₃): -111.78 (s, 1F). IR (neat, cm⁻¹): 3078, 2987, 2855, 2150, 1602, 1509, 1457, 1341, 1226, 1159, 1107, 1013, 842, 749, 433. HRMS m/z calculated for C₁₆H₁₃FN₂O₂S ([M+Na]⁺) 339.0579 found 339.0574.



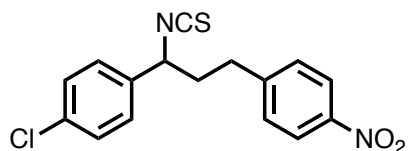
1-fluoro-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (**3ah'**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-fluorostyrene (**2h**) (122.05 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 13% (20.5 mg, 65.0 μmol) of **3ah'** as a yellow sticky oil. ¹H-NMR (400 MHz, CDCl₃): 8.34 (d, 2H), 7.59 (d, 2H), 7.47-7.41 (m, 2H), 7.25 (t, 2H), 4.90 (q, 1H), 3.13-2.97 (m, 2H), 2.51-2.40 (m, 1H), 2.39-2.29 (m, 1H). ¹³C-NMR (101 MHz, CDCl₃): 163.84, 161.37, 147.72, 146.80, 134.33, 134.30, 129.30, 127.68, 127.60, 123.98, 116.17, 115.95, 60.29, 39.97, 32.17. ¹⁹F-NMR (282 MHz, CDCl₃): -113.45 (s, 1F). IR (neat, cm⁻¹): 3078, 2929, 2855, 2072, 1602, 1509, 1341, 1222, 1159, 1110, 1013, 834, 745, 697. HRMS m/z calculated for C₁₆H₁₃FN₂O₂S ([M+Na]⁺) 339.0579 found 339.0573.



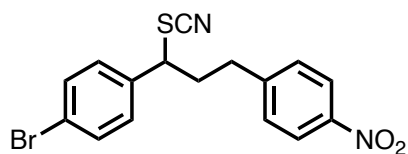
1-chloro-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3ai**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-chlorostyrene (**2i**) (138.02 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 80% (133.0 mg, 400.0 μmol) of **3ai** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.13 (d, 2H), 7.41-2.35 (m, 2H), 7.32-2.25 (d, 4H), 4.25 (q, 1H), 2.83-2.69 (m, 2H), 2.60-2.38 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 147.27, 146.84, 136.10, 135.28, 129.66, 129.30, 128.84, 124.02, 110.80, 51.57, 36.38, 33.8. IR (neat, cm⁻¹): 3078, 2937, 2855, 2150, 1599, 1513, 1341, 1181, 1092, 842, 734, 697. HRMS m/z calculated for C₁₆H₁₃ClN₂O₂S ([M+Na]⁺) 355.0283 found 355.0277.



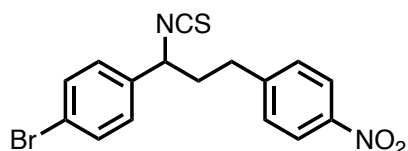
1-chloro-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (**3ai'**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-chlorostyrene (**2i**) (138.02 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 8% (13.3 mg, 40.0 μmol) of **3ai'** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.17 (d, 2H), 7.40-7.32 (m, 4H), 7.23 (d, 2H), 4.73 (q, 1H), 2.97-2.78 (m, 2H), 2.34-2.09 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 147.65, 136.98, 134.50, 129.32, 129.29, 127.26, 124.02, 60.32, 39.89, 32.12. IR (neat, cm⁻¹): 3078, 2929, 2858, 2191, 2120, 1595, 1509, 1334, 1088, 961, 853, 820, 745. HRMS m/z calculated for C₁₆H₁₃ClN₂O₂S ([M+Na]⁺) 355.0283 found 355.0279.



1-bromo-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3aj**)

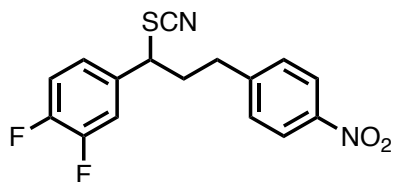
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-bromostyrene (**2j**) (182.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 96% (180.5.0 mg, 480.0 μmol) of **3aj** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.14 (d, 2H), 7.54 (d, 2H), 7.29 (d, 2H), 7.22 (d, 2H), 4.23 (t, 1H), 2.82-2.72 (m, 2H), 2.60-2.38 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 147.30, 146.82, 136.67, 132.61, 129.32, 129.13, 124.02, 123.43, 110.81, 51.61, 36.30, 33.17. IR (neat, cm⁻¹): 3078, 2929, 2855, 2150, 1599, 1513, 1487, 1341, 1181, 1110, 1073, 1010, 827, 730, 697. HRMS m/z calculated for C₁₆H₁₃BrN₂O₂S ([M+Na]⁺) 398.9778 found 398.9777.



1-bromo-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (**3aj'**)

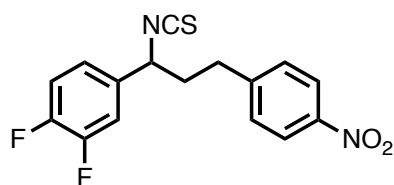
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-bromostyrene (**2j**) (182.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield traces of **3aj'** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.18 (d, 2H), 7.52 (d, 2H), 7.35 (d, 2H), 7.16 (d, 2H), 4.72 (q, 1H), 2.97-2.79 (m, 2H), 2.33-2.09 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 147.64, 146.81, 137.50, 132.25, 129.32, 127.56, 124.02, 122.57, 60.38, 39.84, 32.11. IR (neat, cm⁻¹): 3075, 2926, 2855, 2184,

2120, 1595, 1509, 1301, 1334, 1103, 1010, 849, 816, 745, 700. HRMS m/z calculated for $C_{16}H_{13}BrN_2O_2S$ ($[M+Na]^+$) 398.9778 found 398.9773.



1,2-difluoro-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3ak**)

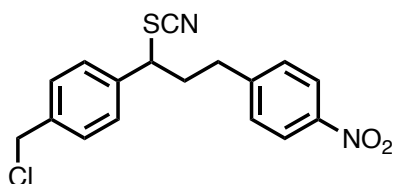
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 3,4-difluorostyrene (**2k**) (140.0 mg, 1.0 mmol, 2.0 equiv), $Cu(dap)_2Cl$ (4.4 mg, 5.0 μ mol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 91% (152.0 mg, 455.0 μ mol) of **3ak** as a yellow sticky oil. 1H -NMR (300 MHz, $CDCl_3$): 8.10(d, 2H), 7.24 (d, 2H), 7.18-7.08 (m, 2H), 7.06-7.00 (m, 1H), 4.16 (t, 1H), 2.81-7.68 (m, 2H), 2.51-2.32 (m, 2H). ^{13}C -NMR (75 MHz, $CDCl_3$): 152.01, 151.96, 151.89, 151.84, 149.51, 149.39, 149.35, 147.00, 146.91, 134.82, 134.78, 134.73, 129.26, 124.05, 123.94, 123.90, 123.88, 123.84, 118.40, 118.23, 116.62, 116.44, 110.40, 51.19, 51.17, 36.36, 33.14. ^{19}F -NMR (282 MHz, $CDCl_3$): -135.52 (d, 1F), -136.29 (d, 1F). IR (neat, cm^{-1}): 3078, 2937, 2855, 2154, 1602, 1513, 1435, 1341, 1282, 1211, 1118, 1013, 931, 853, 820, 775, 749, 697. HRMS m/z calculated $C_{16}H_{12}F_2N_2O_2S$ ($[M+Na]^+$) 357.0485 found 357.048.



1,2-difluoro-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (**3ak'**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 3,4-difluorostyrene (**2k**) (140.0 mg, 1.0 mmol, 2.0 equiv), $Cu(dap)_2Cl$ (4.4 mg, 5.0 μ mol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate

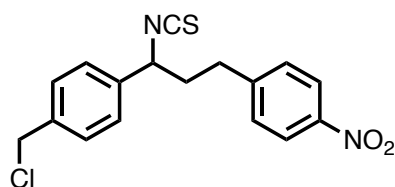
(40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 8% (13.5 mg, 40.0 mmol) of **3ak'** as a yellow sticky oil. ¹H-NMR (400 MHz, CDCl₃): 8.18 (d, 2H), 7.36 (d, 2H), 7.23-7.10 (m, 2H), 7.05-7.00 (m, 1H), 4.72 (q, 1H), 2.97-2.81 (m, 2H), 2.32-2.11 (m, 2H). ¹³C-NMR (101 MHz, CDCl₃): 147.45, 129.31, 124.05, 122.03, 118.10, 117.92, 115.29, 115.10, 59.94, 39.91, 32.10. ¹⁹F-NMR (282 MHz, CDCl₃): -135.92 (d, 1F), -137.67 (d, 1F). IR (neat, cm⁻¹): 2926, 2855, 2079, 1602, 1520, 1435, 1345, 1282, 1215, 1114, 1017, 861, 820, 752, 700. HRMS *m/z* calculated C₁₆H₁₂F₂N₂O₂S ([M]⁺) 334.0587 found 334.0588.



1-(chloromethyl)-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3al**)

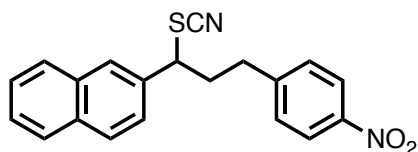
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-vinylbenzyl chloride (**2l**) (152.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 71% (122.83 mg, 355.0 mmol) of **3al** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.10 (d, 2H), 7.40 (d, 2H), 7.32-7.22 (m, 4H), 4.54 (s, 2H), 4.22 (q, 1H), 2.79-2.68 (m, 2H), 2.58-2.37 (m, 2H).

¹³C-NMR (75 MHz, CDCl₃): 146.32, 145.77, 137.66, 136.61, 128.53, 128.24, 126.82, 122.94, 109.91, 50.84, 44.39, 35.40, 32.15. IR (neat, cm⁻¹): 3078, 2937, 2855, 2150, 1602, 1513, 1446, 1341, 1267, 1181, 1110, 1013, 849, 745, 697. HRMS *m/z* calculated C₁₇H₁₅ClN₂O₂S ([M+Na]⁺) 369.0440 found 369.0442.



1-(chloromethyl)-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (**3al'**)

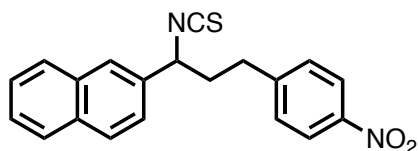
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-vinylbenzyl chloride (**2l**) (152.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 24% (41.5 mg, 120.0 μmol) of **3al'** as a yellow sticky oil. ¹H-NMR (400 MHz, CDCl₃): 8.13 (d, 2H), 7.38 (d, 2H), 7.31 (d, 2H), 7.24 (t, 3H), 4.72 (q, 1H), 4.55 (s, 2H), 2.93-2.77 (m, 2H), 2.30-2.09 (m, 2H). ¹³C-NMR (101 MHz, CDCl₃): 147.75, 146.80, 138.66, 137.97, 129.30, 129.28, 126.28, 123.98, 60.61, 45.50, 39.85, 32.14. IR (neat, cm⁻¹): 3078, 2929, 2855, 2079, 1707, 1602, 1513, 1446, 1341, 1267, 1196, 1110, 1013, 849, 812, 738, 678. HRMS *m/z* calculated C₁₇H₁₅ClN₂O₂S ([M+Na]⁺) 369.0440 found 369.0439.



2-(3-(4-nitrophenyl)-1-thiocyanatopropyl)naphthalene (**3am**)

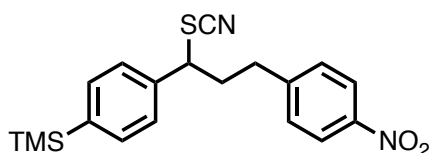
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 2-vinyl naphthalene (**2m**) (154.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 68% (118.4 mg, 340.0 μmol) of **3am** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.14 (d, 2H), 7.92 (d, 1H), 7.89-7.82 (m, 2H), 7.79 (s, 1H), 7.58-7.51 (m, 2H), 7.46 (dd, 1H), 7.28 (d, 2H), 4.47 (t, 1H), 2.85-2.74 (m, 2H), 2.68-2.56 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 147.58, 146.78, 134.60, 133.51, 133.16,

129.68, 129.67, 129.33, 128.17, 127.89, 127.24, 127.14, 127.04, 124.30, 123.96, 111.25, 52.77, 36.52, 33.29. IR (neat, cm^{-1}): 3056, 2933, 2851, 2150, 1599, 1513, 1341, 1177, 1110, 1017, 853, 816, 749, 697. HRMS m/z calculated for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ ($[\text{M}+\text{Na}]^+$) 371.0830 found 371.0828.



2-(1-isothiocyanato-3-(4-nitrophenyl)propyl)naphthalene (**3am'**)

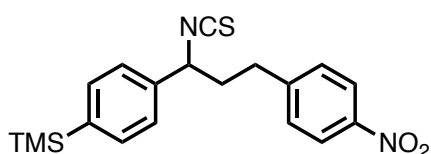
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 2-vinyl naphthalene (**2m**) (154.0 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μmol , 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 $^\circ\text{C}$) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 21% (36.5 mg, 105.0 μmol) of **3am'** as a yellow sticky oil. ^1H -NMR (400 MHz, CDCl_3): 8.06 (d, 2H), 7.78 (d, 1H), 7.75 (q, 2H), 7.63 (s, 1H), 7.46-7.39 (m, 2H), 7.28 (dd, $J = 9$ Hz, 1H), 7.24 (d, 2H), 4.81 (q, 1H), 2.87-2.73 (m, 2H), 2.34-2.23 (m, 1H), 7.23-7.13 (m, 1H). ^{13}C -NMR (101 MHz, CDCl_3): 147.91, 146.75, 135.64, 134.01, 133.15, 133.13, 129.32, 129.20, 128.00, 127.81, 126.85, 126.69, 125.14, 123.95, 123.25, 61.11, 39.73, 32.18. IR (neat, cm^{-1}): 3056, 2926, 2855, 2072, 1688, 1599, 1513, 1341, 1177, 1110, 853, 816, 749, 697. HRMS m/z calculated for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ ($[\text{M}+\text{Na}]^+$) 371.0830 found 371.0817.



trimethyl(4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)phenyl)silane (**3an**)

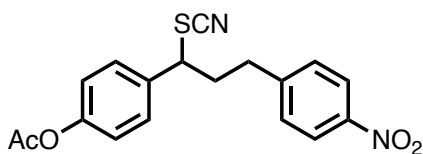
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), trimethyl(4-vinylphenyl)silane (**2n**) (176.0 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μmol , 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium

thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 73% (135.0 mg, 365.0 mmol) of **3an** as a yellow sticky oil. ¹H-NMR (400 MHz, CDCl₃): 8.09 (d, 2H), 7.49 (d, 2H), 7.24 (q, 4H), 4.21 (q, 1H), 2.72 (t, 2H), 2.56-2.41 (m, 2H), 0.22 (s, 9H). ¹³C-NMR (101 MHz, CDCl₃): 148.78, 147.99, 143.58, 138.81, 135.54, 130.50, 127.88, 125.13, 112.44, 53.60, 37.78, 34.42. IR (neat, cm⁻¹): 3071, 3019, 2952, 2855, 2150, 1602, 1517, 1397, 1341, 1248, 1110, 834, 730, 697. HRMS m/z calculated for C₁₉H₂₂N₂O₂SSi ([M+Na]⁺) 393.1068 found 393.1063.



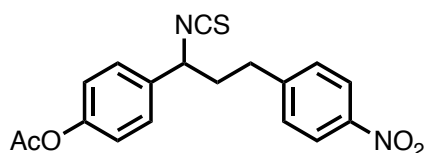
4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)phenyltrimethylsilane (3an')

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), trimethyl(4-vinylphenyl)silane (**2n**) (176.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 16% (29.6 mg, 80.0 mmol) of **3an'** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.12 (d, 2H), 7.50 (d, 2H), 7.31 (d, 2H), 7.22 (d, 2H), 4.69 (q, 1H), 2.97-2.78 (m, 2H), 2.32-2.09 (m, 2H), 0.25 (s, 9H). ¹³C-NMR (75 MHz, CDCl₃): 149.13, 147.90, 142.48, 139.99, 135.21, 130.49, 126.34, 125.12, 62.11, 40.98, 33.37. IR (neat, cm⁻¹): 3071, 3019, 2952, 2855, 2076, 1602, 1517, 1394, 1341, 1248, 1110, 834, 745, 693. HRMS m/z calculated for C₁₉H₂₂N₂O₂SSi ([M+Na]⁺) 393.1068 found 393.1065.



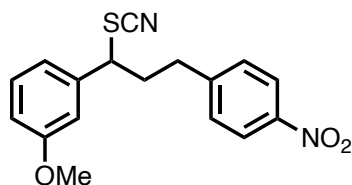
4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)phenyl acetate (3ao)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-acetoxystyrene (**2o**) (162.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 62% (110.0 mg, 310.0 μmol) of **3ao** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.14 (d, 2H), 7.35 (d, 2H), 7.29 (d, 2H), 7.14 (d, 2H), 4.27 (t, 1H), 2.78 (t, 2H), 2.63-2.44 (m, 2H), 2.31 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 169.20, 151.21, 147.41, 146.81, 134.91, 129.31, 128.61, 123.99, 122.63, 111.01, 51.71, 36.59, 33.18, 21.18. IR (neat, cm⁻¹): 3071, 2940, 2847, 2154, 1763, 1599, 1513, 1457, 1341, 1285, 1203, 1170, 1110, 1043, 1017, 950, 909, 853, 734, 700. HRMS m/z calculated C₁₈H₁₆N₂O₄S ([M+Na]⁺) 379.0728 found 379.0723.



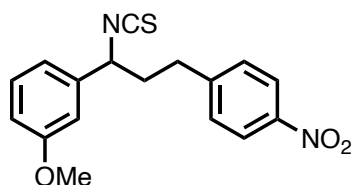
4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)phenyl acetate (**3ao'**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-acetoxystyrene (**2o**) (162.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 13% (23.0 mg, 65.0 μmol) of **3ao'** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.17 (d, 2H), 7.33 (q, 4H), 7.11 (d, 2H), 4.75 (q, 1H), 2.98-2.79 (m, 2H), 2.30 (s, 3H), 2.29-2.09 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 169.35, 150.67, 147.80, 146.76, 135.95, 129.33, 127.02, 123.99, 122.28, 60.41, 39.92, 32.17, 21.16. IR (neat, cm⁻¹): 3078, 2929, 2855, 2079, 1759, 1602, 1513, 1420, 1341, 1192, 1110, 1013, 909, 849, 730, 697. HRMS m/z calculated C₁₈H₁₆N₂O₄S ([M+Na]⁺) 379.0728 found 379.0722.



1-methoxy-3-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3ap**)

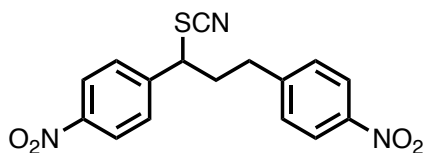
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 3-methoxystyrene (**2p**) (134.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 60% (98.4 mg, 300.0 μmol) of **3ap** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.14 (d, 2H), 7.36-7.25 (m, 3H), 6.94-6.84 (m, 3H), 4.25 (t, 1H), 3.82 (s, 3H), 2.77 (t, 2H), 2.60-2.42 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 160.21, 147.65, 146.76, 138.83, 130.52, 129.33, 123.93, 119.64, 114.47, 113.35, 111.29, 55.41, 52.31, 36.66, 33.20. IR (neat, cm⁻¹): 3078, 2926, 2855, 2150, 1599, 1513, 1453, 1341, 1259, 1151, 1036, 849, 745, 697. HRMS *m/z* calculated for C₁₇H₁₆N₂O₃S ([M+Na]⁺) 351.0779 found 351.0776.



1-(1-isothiocyanato-3-(4-nitrophenyl)propyl)-3-methoxybenzene (**3ap'**)

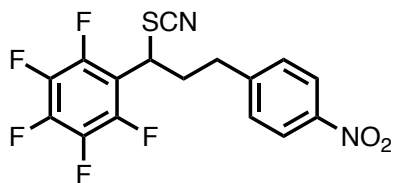
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 3-methoxystyrene (**2p**) (134.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 7% (11.5 mg, 35.0 μmol) of **3ap'** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.17 (d, 2H), 7.37-7.27 (m, 3H), 6.89-6.83 (m, 2H), 6.82 (t, 1H), 4.71 (q, 1H), 3.82 (s, 3H), 2.93-2.81 (m, 2H), 2.32-2.18 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 160.07, 147.94, 139.96, 130.17, 129.32, 123.95, 118.08, 113.66, 111.82, 60.86,

55.39, 39.83, 32.18. IR (neat, cm^{-1}): 3078, 2926, 2855, 2076, 1707, 1602, 1513, 1453, 1341, 1259, 1148, 1110, 1036, 849, 782, 749, 693. HRMS m/z calculated for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ ($[\text{M}+\text{Na}]^+$) 351.0779 found 351.0775.



4,4'-(1-isothiocyanatopropyl)bis(nitrobenzene) (**3aq**)

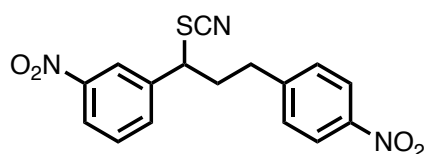
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-nitrostyrene (**2q**) (149.0 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μmol , 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 $^{\circ}\text{C}$) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 43% (73.7 mg, 215.0 μmol) of **3aq** as a yellow sticky oil. ^1H -NMR (300 MHz, CDCl_3): 8.30 (d, 2H), 8.19 (d, 2H), 7.54 (d, 2H), 7.32 (d, 2H), 4.29 (t, 1H), 2.94-2.75 (m, 2H), 2.65-2.42 (m, 2H). ^{13}C -NMR (75 MHz, CDCl_3): 146.61, 144.93, 129.25, 128.44, 124.67, 124.17, 51.03, 36.01, 33.14. IR (neat, cm^{-1}): 3078, 2929, 2855, 2452, 2154, 2079, 1692, 1599, 1513, 1341, 1181, 1110, 1013, 853, 745, 697. HRMS m/z calculated for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 366.0524 found 366.0517.



1,2,3,4,5-pentafluoro-6-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3ar**)

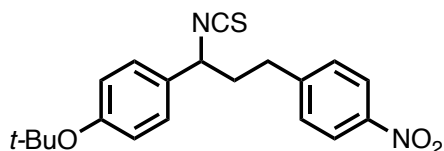
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 2,3,4,5,6-pentafluorostyrene (**2r**) (194.0 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μmol , 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 $^{\circ}\text{C}$) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 77% (149.4 mg, 385.0 μmol) of **3ar** as a

yellow sticky oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.17 (d, 2H), 7.33 (d, 2H), 4.73 (t, 1H), 2.96-2.75 (m, 2H), 2.56 (q, 2H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 147.02, 146.30, 143.44, 129.22, 124.10, 112.05, 109.71, 42.05, 34.54, 34.50, 34.46, 33.58. $^{19}\text{F-NMR}$ (282 MHz, CDCl_3): -140.07 (d, 2F), -151.23 (t, 1F), -159.84 (m, 2F). IR (neat, cm^{-1}): 3082, 2944, 2855, 2154, 1654, 1602, 1498, 1341, 1125, 976, 853, 745, 697. HRMS m/z calculated for $\text{C}_{16}\text{H}_9\text{F}_5\text{N}_2\text{O}_2\text{S}$ ($[\text{M}+\text{Na}]^+$) 411.0202 found 411.0200.



1-nitro-3-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3as**)

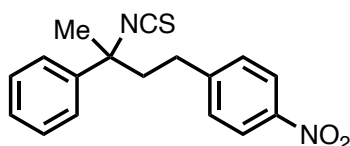
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 3-nitrostyrene (**2s**) (149.0 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μmol , 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 $^\circ\text{C}$) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 53% (90.9 mg, 265.0 μmol) of **3as** as a yellow solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.28-8.12 (m, 4H), 7.75-7.60 (m, 2H), 7.32 (d, 2H), 4.36 (t, 1H), 2.96-2.76 (m, 2H), 2.65-2.45 (m, 2H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 148.69, 146.97, 146.76, 140.20, 133.44, 130.62, 129.30, 124.24, 124.13, 122.47, 110.03, 51.22, 36.03, 33.19. IR (neat, cm^{-1}): 3078, 2922, 2851, 2150, 1599, 1513, 1446, 1341, 1103, 1013, 872, 797, 715. HRMS m/z calculated for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 366.0524 found 366.0516.



1-(*tert*-butoxy)-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (**3at'**)

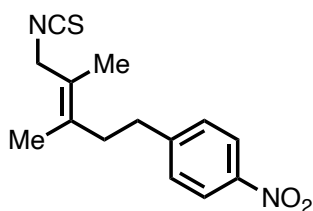
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 4-*tert*-butoxystyrene (**2t**) (176.0 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μmol , 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate

(40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 74% (137 mg, 370.0 mmol) of **3at'** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.13 (d, 2H), 7.33 (d, 2H), 7.12 (d, 2H), 4.70 (q, 1H), 2.94-2.74 (m, 2H), 2.35-2.08 (m, 2H), 1.33 (s, 9H). ¹³C-NMR (75 MHz, CDCl₃): 155.69, 148.09, 146.66, 133.11, 133.00, 129.36, 126.53, 124.37, 123.90, 78.93, 60.59, 39.89, 32.27, 28.86. IR (neat, cm⁻¹): 3075, 2974, 2933, 2866, 2076, 1736, 1602, 1509, 1341, 1237, 1159, 1110, 1013, 894, 849, 745, 697. HRMS m/z calculated C₂₀H₂₂N₂O₃S ([M+Na]⁺) 393.1248 found 393.1244.



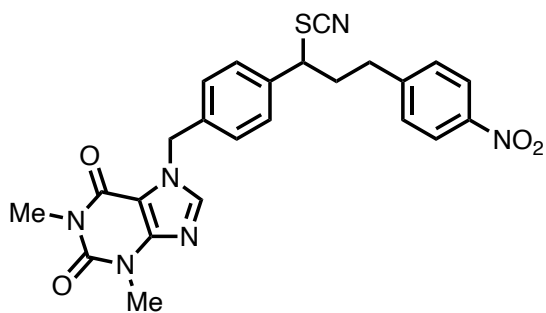
1-(3-isothiocyanato-3-phenylbutyl)-4-nitrobenzene (**3au'**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), *a*-methylstyrene (**2u**) (118.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 30% (46.8 mg, 150.0 mmol) of **3au'** as a yellow sticky oil. ¹H-NMR (400 MHz, CDCl₃): 8.11 (d, 2H), 7.44-7.37 (m, 4H), 7.36-7.30 (m, 1H), 7.26 (d, 2H), 2.86-2.76 (m, 1H), 2.58-2.47 (m, 1H), 2.36-2.23 (m, 2H), 1.84 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃): 148.66, 146.58, 141.94, 133.77, 129.20, 128.95, 127.95, 124.61, 123.82, 67.40, 45.84, 31.11, 31.06. IR (neat, cm⁻¹): 3060, 2981, 2933, 2855, 2057, 1602, 1513, 1446, 1379, 1341, 1177, 1110, 1077, 1028, 976, 849, 745, 697. HRMS m/z calculated for C₁₇H₁₆N₂O₂S ([M+Na]⁺) 335.0830 found 335.0826.



1-(5-isothiocyanato-3,4-dimethylpent-3-en-1-yl)-4-nitrobenzene (**3av'**)

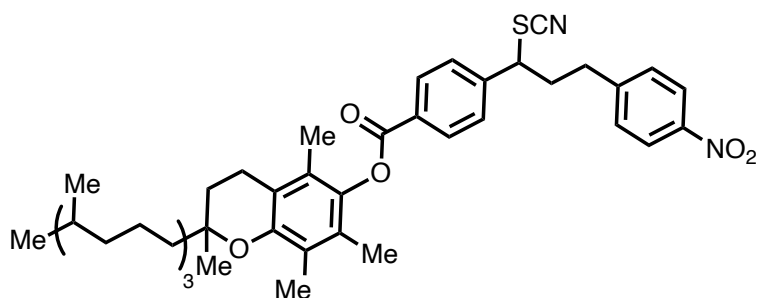
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 2,3-dimethylbutadiene (**2v**) (82.1 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 66% (91.0 mg, 330.0 μmol) of **3av'** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.15 (d, 2H), 7.34 (d, 2H), 5.16 (s, 1H), 5.01 (s, 1H), 2.86-2.63 (m, 2H), 2.11-1.97 (m, 2H), 1.80 (s, 3H), 1.58 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 148.81, 146.62, 144.11, 129.23, 123.88, 113.08, 67.88, 41.76, 30.92, 27.85, 18.73. IR (neat, cm⁻¹): 3078, 2940, 2858, 2061, 1602, 1517, 1446, 1341, 1162, 1110, 905, 849, 749, 697. HRMS m/z calculated C₁₄H₁₆N₂O₂S ([M+NH₄]⁺) 294.1276 found 294.1272



1,3-dimethyl-7-(4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzyl)-3,7-dihydro-1H-purine-2,6-dione (**3aw**)

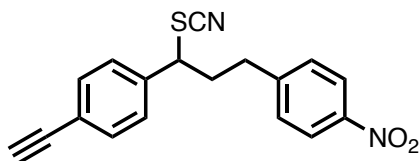
Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 1,3-dimethyl-7-(4-vinylbenzyl)-3,7-dihydro-1H-purine-2,6-dione (**2w**) (296.1 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield

63% (154.0 mg, 315.0 μ mol) of **3aw** as a yellow sticky oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 8.06 (d, 2H), 7.54 (s, 1H), 7.27 (q, 4H), 7.19 (d, 2H), 5.43 (s, 2H), 4.15 (t, 1H), 3.50 (s, 3H), 3.31 (s, 3H), 2.74-2.62 (m, 2H), 2.50-2.32 (m, 2H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): 155.29, 151.62, 148.96, 147.21, 146.86, 140.91, 138.06, 136.85, 129.28, 129.24, 128.79, 128.54, 128.17, 126.62, 123.99, 110.77, 106.91, 51.80, 49.65, 36.36, 33.18, 29.83, 28.05. IR (neat, cm^{-1}): 3112, 2948, 2251, 2150, 2087, 1699, 1651, 1546, 1513, 1453, 1375, 1341, 1289, 1230, 1185, 1110, 1025, 909, 853, 723. HRMS m/z calculated $\text{C}_{24}\text{H}_{22}\text{N}_6\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 491.1501 found 491.1498.



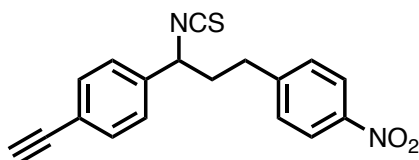
2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl 4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzoate (3ax**)**

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl-4-vinylbenzoate (**2x**) (560.4 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μ mol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 $^\circ\text{C}$) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 57% (215.0 mg, 285.0 μ mol) of **3ax** as a yellow sticky oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 8.22 (d, 2H), 8.09 (d, 2H), 7.43 (d, 2H), 7.27 (d, 2H), 4.27 (t, 2H), 2.80-2.69 (m, 2H), 2.57-2.46 (m, 4H), 2.05 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H), 1.80-1.66 (m, 2H), 1.56-0.96 (m, 24H), 0.81-0.76 (m, 12H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): 164.34, 149.65, 147.20, 146.90, 143.11, 140.55, 131.19, 130.57, 129.32, 127.78, 126.80, 125.07, 124.03, 123.26, 117.61, 110.56, 75.19, 51.71, 39.41, 37.61, 37.58, 37.50, 37.46, 37.43, 37.40, 37.33, 36.29, 33.20, 32.83, 32.81, 32.76, 28.02, 24.86, 24.85, 24.49, 22.78, 22.69, 21.09, 20.69, 19.82, 19.75, 13.15, 12.30, 11.93. IR (neat, cm^{-1}): 3075, 2926, 2866, 2154, 1729, 1606, 1520, 1461, 1379, 1345, 1274, 1233, 1181, 1092, 1017, 913, 853, 734. HRMS m/z calculated $\text{C}_{46}\text{H}_{62}\text{N}_2\text{O}_5\text{S}$ ($[\text{M}+\text{Na}]^+$) 777.4277 found 777.4274.



1-ethynyl-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3ay**)

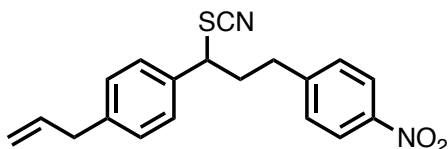
Following general procedure **GPI** using 2-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 1-ethynyl-4-vinylbenzene (**2y**) (128.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 87% (140.07 mg, 435.0 μmol) of **3ay** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.10 (d, 2H), 7.48 (d, 2H), 7.24 (q, 4H), 4.19 (q, 1H), 3.09 (s, 1H), 2.76-2.67 (m, 2H), 2.54-2.37 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 147.22, 146.87, 138.04, 133.09, 129.27, 124.01, 123.36, 110.73, 82.61, 78.78, 51.90, 36.32, 33.16. IR (neat, cm⁻¹): 3283, 3078, 2922, 2855, 2150, 1599, 1513, 1461, 1341, 1177, 1110, 1013, 842, 745, 697. HRMS *m/z* calculated C₁₈H₁₄N₂O₂S ([M+Na]⁺) 345.0673 found 345.0669.



1-ethynyl-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3ay'**)

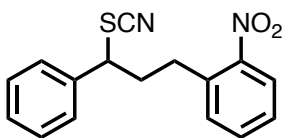
Following general procedure **GPI** using 2-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 1-ethynyl-4-vinylbenzene (**2y**) (128.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 9% (14.5 mg, 45.0 μmol) of **3ay'** as a yellow sticky oil. ¹H-NMR (400 MHz, CDCl₃): 8.17 (d, 2H), 7.52 (d, 2H), 7.35 (d, 2H), 7.25 (d, 2H), 4.75 (q, 1H), 3.11 (s, 1H), 2.94-2.80 (m, 2H), 2.33-2.12 (m, 2H). ¹³C-NMR (101 MHz,

CDCl₃): 147.67, 146.81, 138.98, 132.79, 129.30, 125.86, 124.00, 122.56, 82.74, 78.20, 60.62, 39.81, 32.09. IR (neat, cm⁻¹): 3283, 3078, 2929, 2855, 2076, 1684, 1602, 1513, 1341, 1203, 1110, 1013, 834, 749, 697. HRMS m/z calculated C₁₈H₁₄N₂O₂S ([M+Na]⁺) 345.0673 found 345.0663.



1-allyl-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (**3az**)

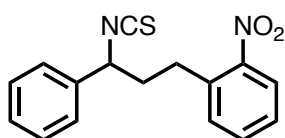
Following general procedure **GPI** using 2-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), 1-allyl-4-vinylbenzene (**2z**) (144.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 50% (84.5 mg, 250.0 μmol) of **3az** as a yellow sticky oil. ¹H-NMR (400 MHz, CDCl₃): 8.15 (d, 2H), 7.33-7.23 (m, 7H), 6.04-5.87 (m, 1H), 5.13 (d, 1H), 5.10-5.05 (m, 1H), 4.27 (q, 1H), 3.41 (d, 2H), 2.76 (t, 2H), 2.63-2.45 (m, 2H). ¹³C-NMR (101 MHz, CDCl₃): 148.06, 147.54, 146.80, 141.59, 136.63, 134.93, 129.59, 129.27, 127.55, 123.95, 123.83, 116.50, 111.26, 52.23, 39.86, 36.65, 33.23. IR (neat, cm⁻¹): 3078, 2929, 2855, 2150, 1602, 1517, 1423, 1345, 1181, 1110, 1017, 916, 853, 749, 700. HRMS m/z calculated C₁₉H₁₈N₂O₂S ([M]⁺) 338.1089 found 338.1083.



1-nitro-2-(3-phenyl-3-thiocyanatopropyl)benzene (**3bc**)

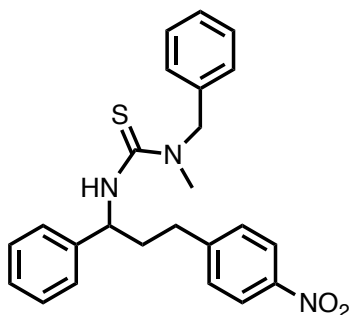
Following general procedure **GPI** using 2-nitrobenzyl thiocyanate (**1b**) (97 mg, 0.5 mmol, 1.0 equiv), styrene (**2c**) (104.0 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation

for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 67% (99.85 mg, 335.0 μ mol) of **3bc** as a yellow sticky oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.80 (dd, 1H, $J = 8$ Hz), 7.39 (td, 1H, $^1J = 8$ Hz, $^3J = 15$ Hz), 7.30-7.19 (m, 6H), 7.16 (dd, 1H, $J = 8$ Hz), 4.27 (t, 1H), 2.85-2.70 (m, 2H), 2.50-2.34 (m, 2H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 149.00, 137.62, 135.29, 133.46, 132.13, 129.31, 129.26, 127.84, 127.56, 125.15, 111.34, 53.09, 36.38, 31.36. IR (neat, cm^{-1}): 3034, 2937, 2866, 2150, 1610, 1576, 1520, 1453, 1341, 1198, 1077, 913, 864, 786, 741, 697. HRMS m/z calculated for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ ($[\text{M}+\text{Na}]^+$) 321.0673 found 321.0675.



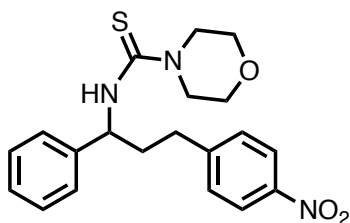
1-(3-isothiocyanato-3-phenylpropyl)-2-nitrobenzene (**3bc'**)

Following general procedure **GPI** using 2-nitrobenzyl thiocyanate (**1b**) (97 mg, 0.5 mmol, 1.0 equiv), styrene (**2c**) (104.0 mg, 1.0 mmol, 2.0 equiv), $\text{Cu}(\text{dap})_2\text{Cl}$ (4.4 mg, 5.0 μ mol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 $^\circ\text{C}$) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 27% (40.2 mg, 135.0 μ mol) of **3bc'** as a yellow sticky oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.91 (dd, $J = 9$ Hz, 1H), 7.50 (td, 1H, $^1J = 8$ Hz, $^3J = 15$ Hz), 7.38-7.24 (m, 7H), 4.78 (q, 1H), 3.10-2.88 (m, 2H), 2.29-2.14 (m, 2H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 138.49, 135.58, 133.42, 132.28, 129.01, 128.50, 127.74, 125.90, 125.18, 61.50, 39.65, 30.39. IR (neat, cm^{-1}): 3063, 3034, 2870, 2076, 1722, 1610, 1576, 1520, 1453, 1341, 1200, 1162, 1073, 1028, 957, 861, 786, 738, 697. HRMS m/z calculated for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ ($[\text{M}+\text{Na}]^+$) 321.0673 found 321.0671.



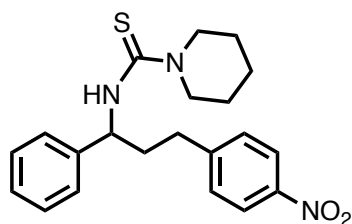
1-benzyl-1-methyl-3-(3-(4-nitrophenyl)-1-phenylpropyl)thiourea (**4a**)

Following general procedure **GPIII** on a 0.5 mmol scale using N-benzylmethylamine (121.1 mg, 1.0 mmol, 2.0 equiv) for 8h. After completion, the crude mixture was extracted, dried in vacuo and purified using flash column chromatography to yield 84% (176.0 g, 420.0 mmol) of **4a** as a yellow oil. ¹H-NMR (400 MHz, CDCl₃): 8.09 (d, 2H), 7.36-7.20 (m, 12H), 5.73-5.60 (m, 2H), 4.97 (t, 2H), 3.20 (s, 3H), 2.72-2.56 (m, 2H), 2.41-2.31 (m, 1H), 2.02-2.12 (m, 1H). ¹³C-NMR (101 MHz, CDCl₃): 181.69, 149.47, 146.38, 141.28, 136.32, 129.26, 129.04, 128.96, 127.92, 127.83, 127.00, 126.79, 123.65, 59.35, 56.55, 38.61, 37.18, 32.50. IR (neat, cm⁻¹): 3391, 3063, 3030, 2922, 2855, 1599, 1513, 1453, 1341, 1203, 1107, 909, 849, 730, 697. HRMS m/z calculated C₂₄H₂₅N₃O₂S ([M+H]⁺) 420.1745 found 420.1743.



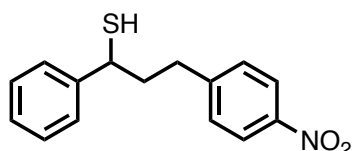
N-(3-(4-nitrophenyl)-1-phenylpropyl)morpholine-4-carbothioamide (**4b**)

Following general procedure **GPIII** on a 0.5 mmol scale using morpholine (87.1 mg, 1.0 mmol, 2.0 equiv) for 8h. After completion, the crude mixture was extracted, dried in vacuo and purified using flash column chromatography to yield 92% (177.1 g, 460.0 mmol) of **4b** as a yellow oil. ¹H-NMR (400 MHz, CDCl₃): 8.01 (d, 2H), 7.32-7.19 (m, 7H), 5.65-5.53 (m, 2H), 3.63 (d, 8H), 2.71-2.62 (m, 1H), 2.61-2.52 (m, 1H), 2.48-2.38 (m, 1H), 2.11-2.01 (m, 1H). ¹³C-NMR (101 MHz, CDCl₃): 182.03, 149.42, 146.37, 140.86, 129.27, 129.13, 128.12, 127.06, 123.67, 66.10, 59.26, 47.53, 36.70, 32.54. IR (neat, cm⁻¹): 3388, 3030, 2922, 2855, 1599, 1513, 1453, 1338, 1267, 1207, 1110, 1066, 1017, 909, 853, 726, 697. HRMS m/z calculated C₂₀H₂₃N₃O₃S ([M+H]⁺) 386.1538 found 386.1533.



***N*-(3-(4-nitrophenyl)-1-phenylpropyl)piperidine-1-carbothioamide (**4c**)**

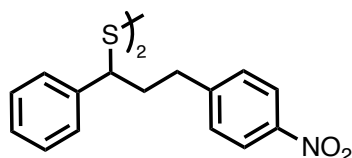
Following general procedure **GPIII** on a 0.5 mmol scale using piperidine (85.1 mg, 1.0 mmol, 2.0 equiv) for 8h. After completion, the crude mixture was extracted, dried in vacuo and purified using flash column chromatography to yield 77% (147.5 g, 385.0 mmol) of **4c** as a yellow oil. ¹H-NMR (400 MHz, CDCl₃): 8.01 (d, 2H), 7.31-7.21 (m, 7H), 5.65 (q, 1H), 5.49 (d, 1H), 3.63 (t, 4H), 2.73-2.64 (m, 1H), 2.62-2.54 (m, 1H), 2.45-2.35 (m, 1H), 2.11-2.01 (m, 1H). ¹³C-NMR (101 MHz, CDCl₃): 180.72, 149.53, 146.40, 141.31, 129.26, 129.03, 127.90, 126.96, 123.64, 59.11, 48.88, 36.97, 32.58, 25.40, 24.19. IR (neat, cm⁻¹): 3384, 3082, 2926, 2855, 2202, 1602, 1517, 1408, 1341, 1282, 1237, 1107, 1021, 998, 916, 849, 767, 697. HRMS *m/z* calculated C₂₁H₂₅N₃O₂S ([M+H]⁺) 384.1745 found 384.1741.



3-(4-nitrophenyl)-1-phenylpropane-1-thiol (5a**)**

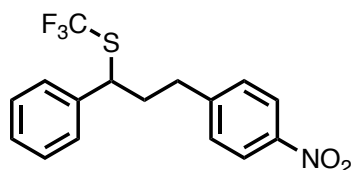
Based on the literature procedure,²⁹⁹ a two-necked round bottom flask equipped with a magnetic stirring bar was charged with the thiocyanate (**3ac**) (89.4 mg, 0.3 mmol, 1.0 equiv) in toluene (1 mL). Then P₂S₅ (133.66 mg, 0.3 mmol, 1.0 equiv) was added and the resulting suspension was refluxed for 3 hours. The reaction was monitored by TLC. After consumption of the starting material, the reaction was quenched with water and extracted three times by EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude was then purified by flash column chromatography on silica gel to yield 51% (39.0 mg, 153.0 mmol) of **5a** as yellow oil. ¹H-NMR (300 MHz, CDCl₃): 8.09 (d, 2H), 7.33-7.19 (m, 7H), 3.88 (q, 1H), 2.81-2.61 (m, 2H), 2.32-2.15 (m, 2H), 1.91 (d, 1H). ¹³C-NMR (75 MHz, CDCl₃): 148.98, 146.54, 143.94, 129.28, 128.91, 127.57, 126.86, 123.78,

43.23, 40.64, 33.90, 29.75. IR (neat, cm^{-1}): 3063, 3026, 2926, 2855, 2568, 2452, 2366, 2083, 1599, 1513, 1453, 1341, 1177, 1110, 1013, 849, 745, 697. HRMS m/z calculated $\text{C}_{15}\text{H}_{15}\text{NO}_2\text{S}$ $[\text{M}^+]$ 273.0823 found 273.0810.



1,2-bis(3-(4-nitrophenyl)-1-phenylpropyl)disulfane (**5b**)

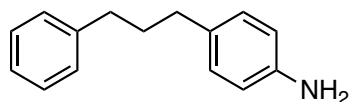
Based on a literature procedure,¹⁸⁵ sodium borohydride (17 mg, 0.45 mmol, 1.5 equiv) was added to a solution of **3ac** (149 mg, 0.5 mmol, 1 equiv) in 3 mL of MeCN at 0°C and let to stir for 12h. The reaction was then quenched with 20 mL of saturated aqueous NaHCO_3 solution and extracted three times with EtOAc. The combined organic layers were collected, washed with brine, dried over Na_2SO_4 then concentrated. The residue was purified by column chromatography on silica gel to afford 41% (66.0 mg 205.0 mmol) of **5b** as a yellow oil. ^1H -NMR (400 MHz, CDCl_3): 8.11 (q, 4H), 7.35-7.27 (m, 6H), 7.21-7.05 (m, 8H), 3.27-3.15 (m, 2H), 2.64-2.41 (m, 4H), 2.36-2.01 (m, 4H). ^{13}C -NMR (101 MHz, CDCl_3): 148.93, 146.48, 140.32, 140.16, 129.22, 128.72, 128.66, 128.18, 128.14, 127.96, 127.85, 123.71, 54.21, 53.97, 35.49, 35.39, 33.46, 33.42. IR (neat, cm^{-1}): 3060, 3026, 2929, 2855, 2452, 1599, 1513, 1453, 1341, 1177, 1110, 1077, 1013, 849, 745, 693. HRMS m/z calculated $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}_4\text{S}_2$ ($[\text{M}+\text{Na}]^+$) 567.1388 found 567.1384.



(3-(4-nitrophenyl)-1-phenylpropyl)(trifluoromethyl)sulfane (**5c**)

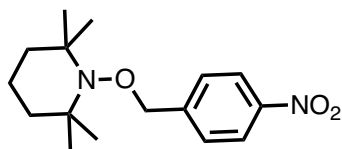
Based on a literature procedure,¹⁹⁶ thiocyanate **3ac** (89.4 mg, 0.3 mmol, 1.0 equiv), Cs_2CO_3 (391.0 mg, 1.2 mmol, 4.0 equiv) and MeCN (3 mL) were added to a flame-dried Schlenk tube with a positive nitrogen overpressure. After the mixture dissolved, the system was cooled to 0°C and trifluoromethyltrimethylsilane (170.6 mg, 1.2 mmol, 4.0 equiv) was added afterwards under a positive nitrogen pressure. The reaction was stirred for 16h. After completion

(monitored by TLC), the reaction was quenched with water and extracted three times by DCM. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude was then purified by flash column chromatography on silica gel to yield 54% (58.3 mg, 162.0 μ mol) of **5c** as a yellow oil. ¹H-NMR (400 MHz, CDCl₃): 8.14 (d, 2H), 7.41-7.26 (m, 7H), 4.24 (q, 1H), 2.76-2.67 (m, 2H), 2.42-2.25 (m, 2H). ¹³C-NMR (101 MHz, CDCl₃): 148.13, 146.69, 139.60, 129.20, 129.06, 128.34, 127.40, 123.85, 48.71, 37.46, 33.17. ¹⁹F-NMR (282 MHz, CDCl₃): -40.22 (s, 3F). IR (neat, cm⁻¹): 3067, 3034, 2926, 2855, 1602, 1520, 1453, 1345, 1110, 853, 760, 700. HRMS m/z calculated C₁₆H₁₄F₃NO₂S ([M+H]⁺) 342.0775 found 342.0774.



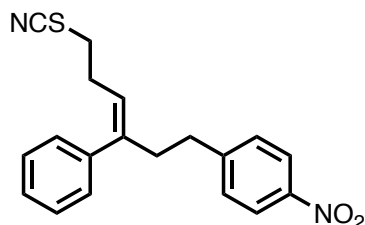
4-(3-phenylpropyl)aniline (**5d**)

Thiocyanate **3ac** (75 mg, 0.25 mmol, 1.0 equiv) was dissolved in MeOH (6 mL). The tube was sealed with a screw-cap and subsequently degassed by three consecutive freeze-pump-thaw cycles. The solution was cooled in an ice-bath to 0°C. Zinc dust (82.5 mg, 1.25 mmol, 5.0 equiv) and NH₄Cl (100.3 mg, 1.875 mmol, 7.5 equiv) were added to the reaction mixture under a positive nitrogen overpressure. The reaction was stirred for 12h. After completion (monitored by TLC), the reaction was quenched with water and extracted three times by DCM. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude was then purified by flash column chromatography on silica gel to yield 72% (38.0 mg, 180.0 μ mol) of **5d** as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): 7.31-7.26 (m, 2H), 7.22-7.15 (m, 3H), 7.00 (d, 2H), 6.68 (d, 2H), 3.67 (s, 2H), 2.64 (t, 2H), 2.56 (t, 2H), 1.91 (q, 2H). ¹³C-NMR (75 MHz, CDCl₃): 143.16, 142.48, 133.10, 129.26, 128.46, 128.34, 128.28, 125.67, 115.75, 35.40, 34.59, 33.23. IR (neat, cm⁻¹): 3444, 3362, 3026, 2929, 2855, 1621, 1513, 1453, 1274, 1177, 823, 745, 700. HRMS m/z calculated C₁₅H₁₇N (M⁺) 211.1360 found 211.1355



2,2,6,6-tetramethyl-1-((4-nitrobenzyl)oxy)piperidine (**6**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), styrene (**2c**) (104.15 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv), sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) and TEMPO (94 mg, 0.6 mmol, 1.2 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 95% (139 mg, 475.0 μmol) of **6** as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): 8.20 (d, 2H), 7.50 (d, 2H), 4.93 (s, 2H), 1.58-1.43 (m, 6H), 1.90 (d, 12H). ¹³C-NMR (75 MHz, CDCl₃): 147.08, 146.00, 128.51, 127.38, 123.56, 84.24, 60.17, 40.31, 39.69, 33.02, 20.32, 17.06. IR (neat, cm⁻¹): 2974, 2929, 1520, 1468, 1341, 1133, 1058, 842, 738, 697. HRMS *m/z* calculated for C₁₆H₂₄N₂O₃ ([M+H]⁺) 293.1865 found 293.1863.



1-nitro-4-(3-phenyl-6-thiocyanatohex-3-en-1-yl)benzene (**8**)

Following general procedure **GPI** using 4-nitrobenzyl thiocyanate (**1a**) (97 mg, 0.5 mmol, 1.0 equiv), (1-cyclopropylvinyl) benzene (**7**) (144.1 mg, 1.0 mmol, 2.0 equiv), Cu(dap)₂Cl (4.4 mg, 5.0 μmol, 1.0 mol%), sodium carbonate (53 mg, 0.5 mmol, 1.0 equiv) and sodium thiocyanate (40.5 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.25 M) at room temperature (25 °C) under 530 nm irradiation for 24 h. The crude mixture was dried in vacuo and purified using flash column chromatography (*hexanes* : *EtOAc*) to yield 71% (120.0 mg, 355.0 μmol) of **8** as a yellow sticky oil. ¹H-NMR (300 MHz, CDCl₃): 8.12 (d, 2H), 7.40-7.24 (m, 7H), 5.58 (t, 1H), 2.93-2.82 (m, 4H), 2.75 (t, 2H), 2.53 (q, 2H). ¹³C-NMR (75 MHz, CDCl₃): 149.29, 146.49, 142.38, 141.49, 129.28, 127.68, 126.59, 124.89, 123.65, 112.14, 34.28, 33.65, 31.41, 28.93. IR (neat, cm⁻¹): 3056, 3026, 2929, 2855, 2452, 2370, 2154, 1599, 1513, 1336, 1341,

1110, 1013, 849, 760, 693. HRMS m/z calculated $C_{19}H_{18}N_2O_2S$ ($[M+Na]^+$) 361.0986 found 361.0979.

7. Benzyl thiocyanates scope:

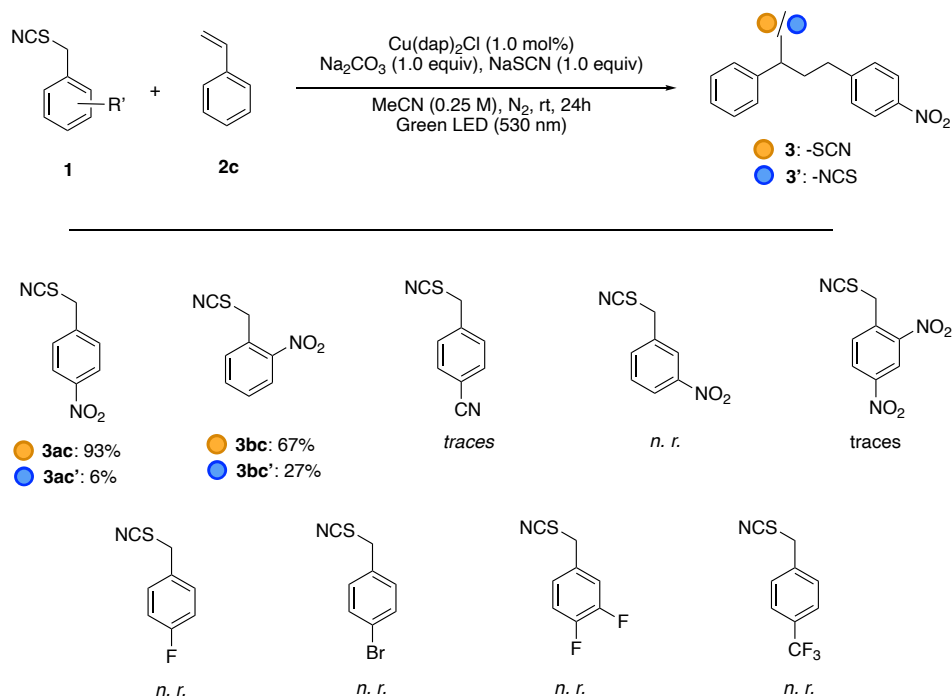
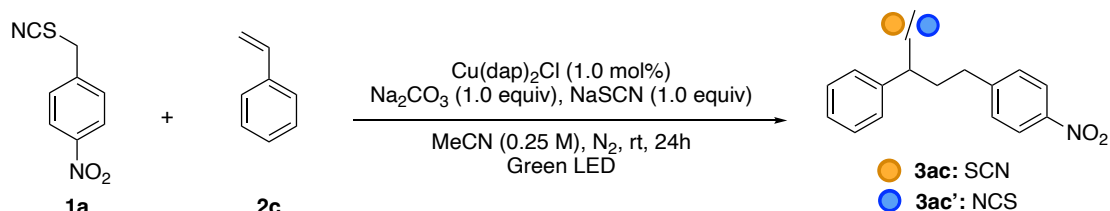


Figure 3: Scope of the various benzyl thiocyanates

Besides the compounds out of reach for the used copper catalyst in terms of redox potential, the nitro-substituted benzyl thiocyanate substrates are supposed to be successful reactive partners. However, depending on the substitution site, kinetics of the decomposition of the benzylthiocyanate may vary. Literature report on the decomposition rate of nitro-substituted benzyl halides suggests that m-nitro compounds have a relatively slower decomposition rate which may serve as an explanation for their inability to add across the styrene.³⁰⁰ On the other hand, the use of 2,4-dinitro benzyl thiocyanate as precursor fails mainly due to the high instability of the generated correspondent radical.

8. Mechanistic investigations:

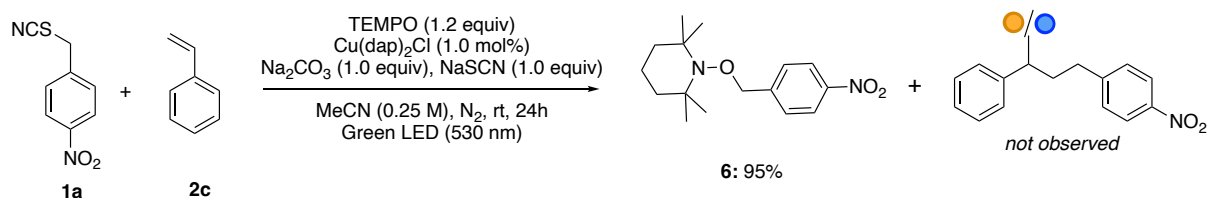
Control experiments:



Entry	Conditions	3ac ^a	3ac' ^a
1	—	93%	7%
2	AIBN	n. r.	n. r.
3	No catalyst	n. r.	n. r.
4	No light	n. r.	n. r.

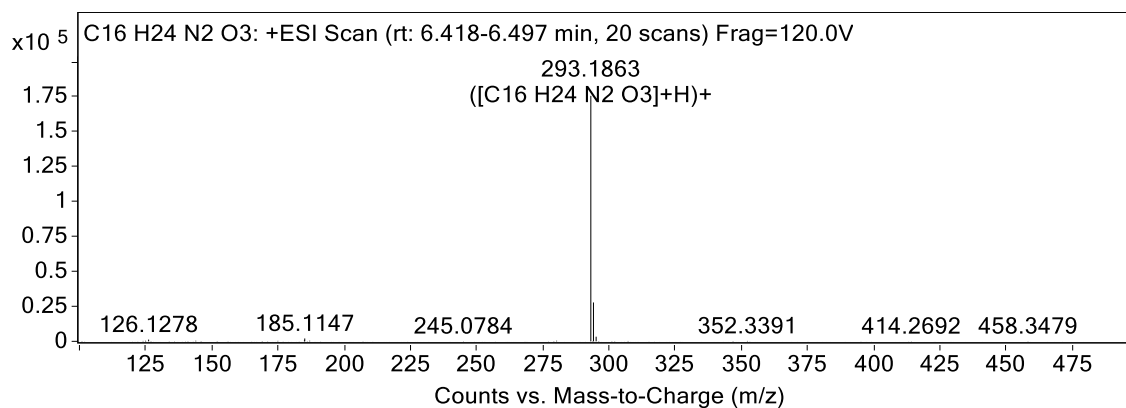
Standard conditions: 4-nitrobenzylthiocyanate (**1a**) (0.25 mmol, 1.0 equiv), styrene (**2c**) (0.5 mmol, 2.0 equiv), photocatalyst (2.5 μmol , 1.0 mol%), sodium carbonate (0.25 mmol, 1.0 equiv), sodium thiocyanate (0.25 mmol, 1.0 equiv.) in MeCN (anh., degassed, 1.0 mL, 0.25 M) for 24h under N_2 atmosphere at room temperature. ^aYields determined by $^1\text{H-NMR}$ using tetrachloroethane as an internal standard. n. r.= no reaction.

Radical trapping:

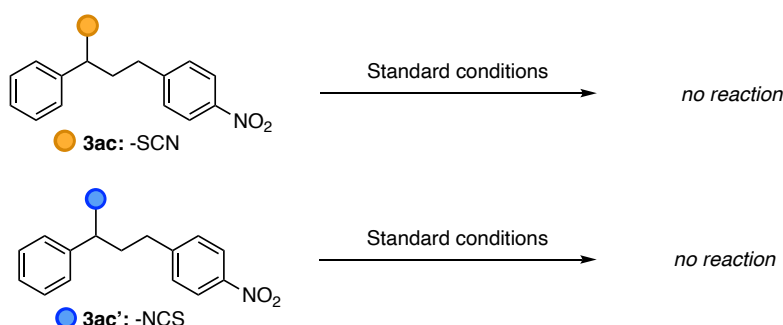


The reaction was set up following the general procedure (G.P.1) on 0.25 mmol scale. Subsequently, TEMPO (46.8 mg, 0.3 mmol, 1.2 equiv) was added and the reaction was run for 24 hours. Fortunately, we were able to isolate the TEMPO-adduct using flash column

chromatography on silica gel. Moreover, the standard reaction products (**3ac** & **3ac'**) were not observed.



Isomerization experiments:



The isomerization reaction was set up by subjecting the products **3ac** or **3ac'** to the standard conditions. The reaction was run for 24h, afterwards, the reaction mixture was analyzed using ^1H -NMR and HR-MS. No traces of the other isomer were observed indicating the improbability of an internal isomerization.

We have also followed the concentration profile of **3ac** and **3ac'** over time in the cases where no additive was present and when NaSCN was added to the solution. The curves obtained show no major formation of one isomer and its consumption, however, a steady increase of the concentration of both isomers suggests their independent promotion.

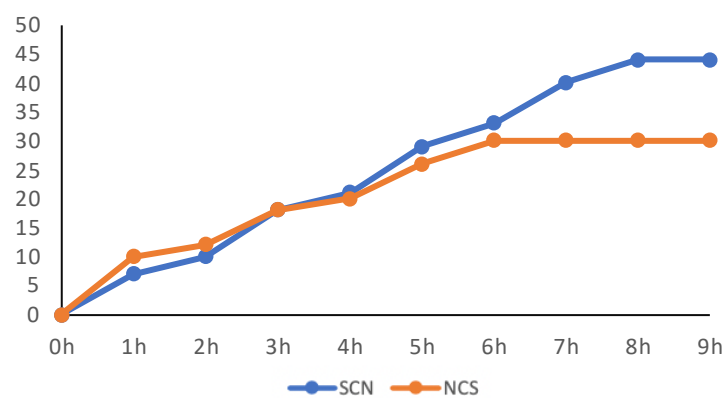


Figure 4: Concentration profile in the absence of NaSCN

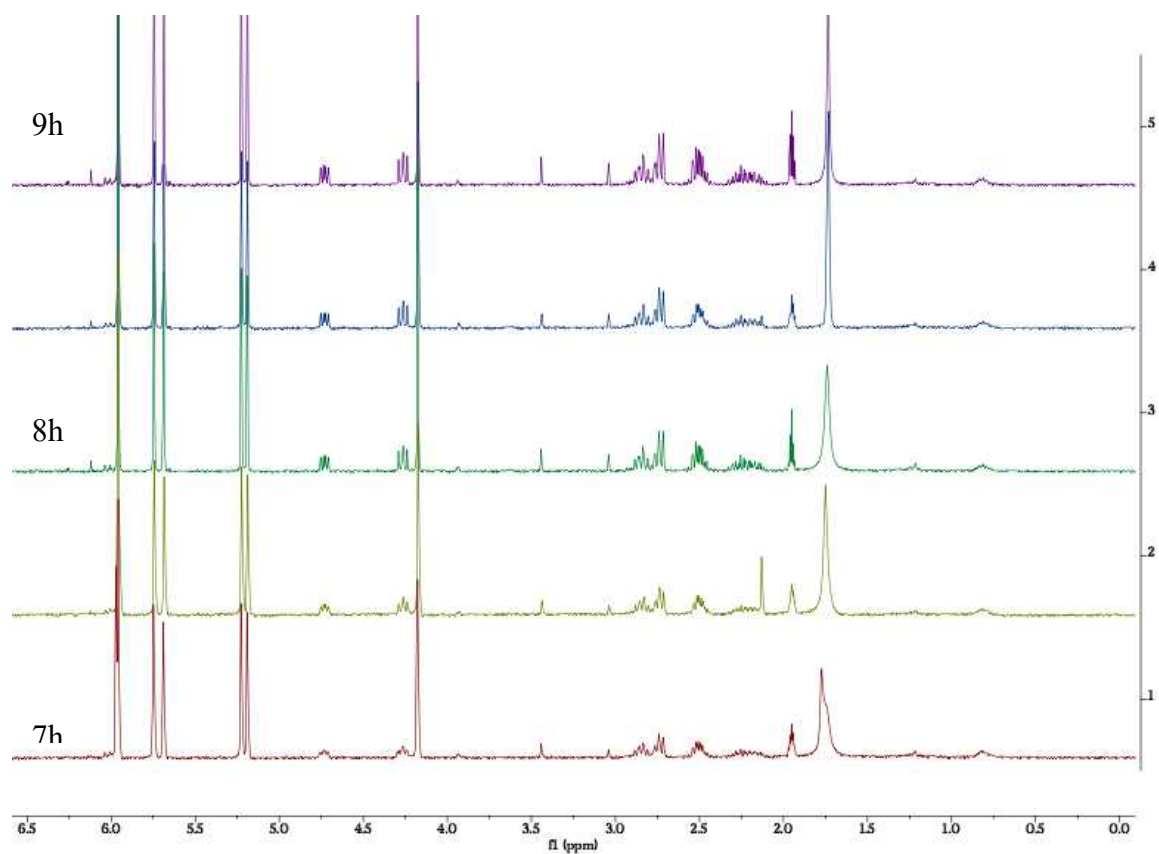


Figure 5: Evolution of the concentrations in the absence of NaSCN followed by ¹H-NMR

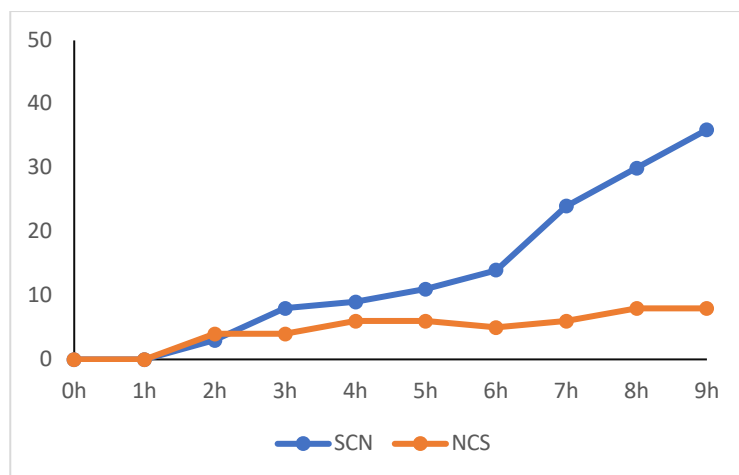


Figure 6: Concentration profile in the presence of NaSCN

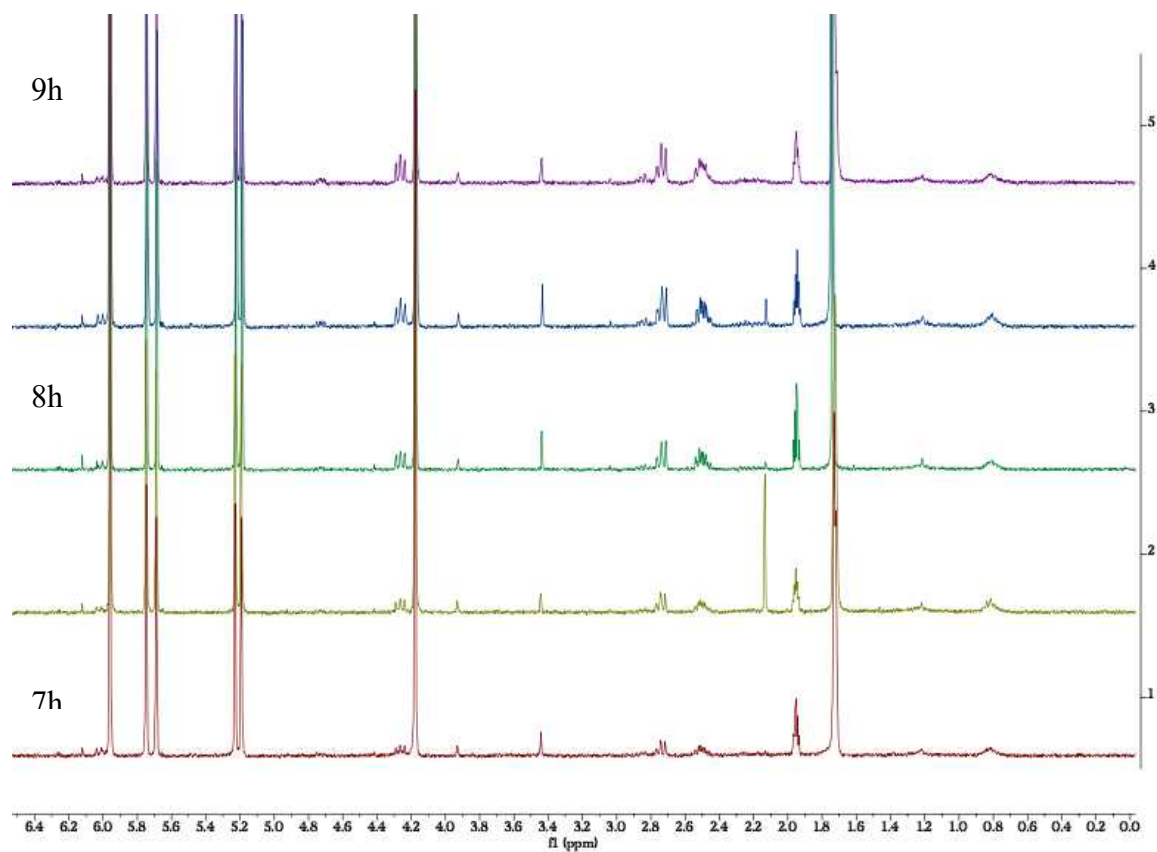
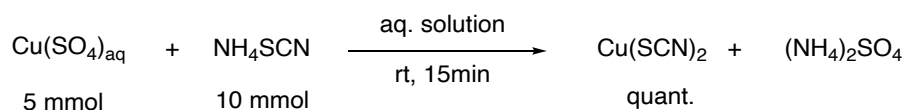
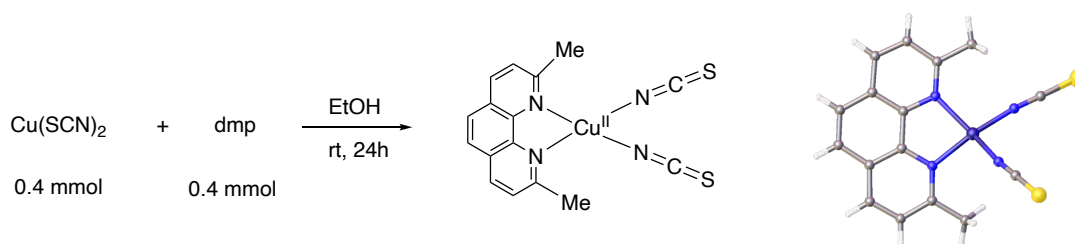


Figure 7: Evolution of the concentrations in the presence of NaSCN followed by ^1H -NMR

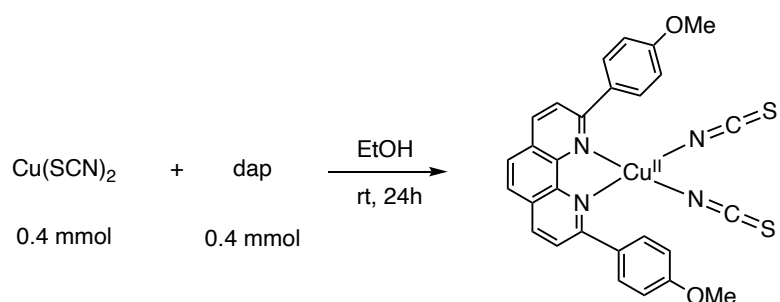
9. Synthesis of Copper-Thiocyanate Complexes:



$\text{Cu}(\text{NCS})_2$ was prepared following a reported procedure.³⁰¹ To an aqueous solution of copper sulfate pentahydrate (1.24 g, 5 mmol, 1 equiv) in 10 mL of water was added a solution of ammonium thiocyanate (761.2 mg, 10 mmol, 2 equiv) in 10 mL of water. The mixture was stirred for 15 minutes using a magnetic stirrer at room temperature. A black precipitate was formed and was filtered using a fritted glass filter and washed with ice-cold water. The $\text{Cu}(\text{NCS})_2$ obtained was dried in a desiccator overnight.



A 100 mL round-bottom flask was charged with $\text{Cu}(\text{NCS})_2$ (71.23 mg, 0.4 mmol, 1 equiv) in ethanol (20 mL) and was stirred at room temperature for 20 min. 2,9-dimethylphenanthroline (dmp) (83.3mg, 0.4 mmol, 1 equiv) dissolved in ethanol (20 mL) was slowly added with a flow rate of 1mL/h under magnetic stirring at room temperature. After the addition is complete, the dark green precipitate formed was filtered using a fritted glass filter and washed with cold ethanol. The solid obtained was recrystallized in acetone to give brown crystals. It is to note that the color of the precipitate before recrystallization immediately changed to brown immediately after adding acetone. IR (neat, cm^{-1}): 2068, 1736, 1595, 1565, 1498, 1423, 1364, 1293, 1215, 1151, 1036, 857, 812, 726, 682.



A 100 mL round-bottom flask was charged with Cu(NCS)_2 (71.23 mg, 0.4 mmol, 1 equiv) in ethanol (20 mL) and was stirred at room temperature for 20 min. 2,9-bis(4-methoxyphenyl)-1,10-phenanthroline (dap) (156.8 mg, 0.4 mmol, 1 equiv) dissolved in acetonitrile (20 mL) was slowly added with a flow rate of 1 mL/h under magnetic stirring at room temperature. After the addition is complete, the green precipitate formed was separated using a centrifuge and washed with acetonitrile and dichloromethane. IR (neat, cm^{-1}): 2083, 1736, 1595, 1490, 1457, 1364, 1252, 1177, 1036, 864, 838, 805, 745.

10. Fluorescence quenching:

The interaction between the photocatalyst $\text{Cu(dap)}_2\text{Cl}$ and the ATRA-reagent 4-nitrobenzylthiocyanate (**1a**) was assessed by recording fluorescence emission spectra. These measurements were conducted using a HORIBA Fluoromax-4 from Horiba Scientific, employing a High Precision Cell 117100F-10-40 quartz cuvette with a screw cap (Hellma Analytics quartz cuvette, dimensions: 10×10 mm, capacity: 3.5 mL)

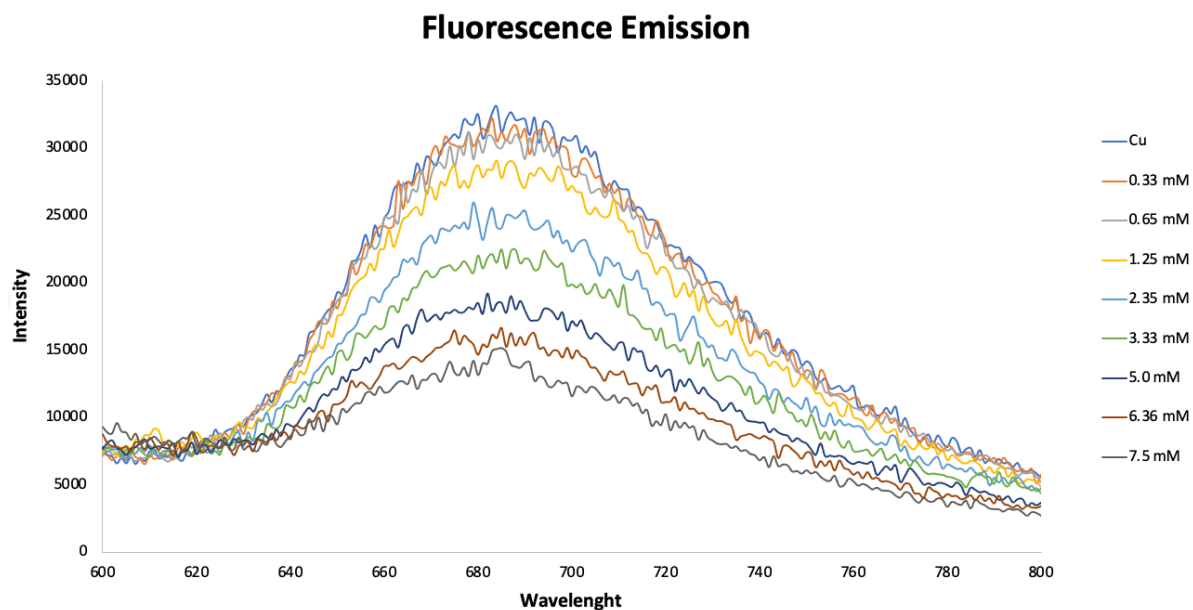


Figure 8: Cu(dap)₂Cl emission quenching using **1a** as quencher

4-nitrobenzyl thiocyanate (**1a**) was proven to quench the photocatalyst. The Stern-Volmer plot and quenching constants were calculated. Solutions under nitrogen atmosphere were freshly prepared prior to the measurements. The mixtures were irradiated at 465nm and the data for the plot was collected from the maximum emission wavelength (684 nm).

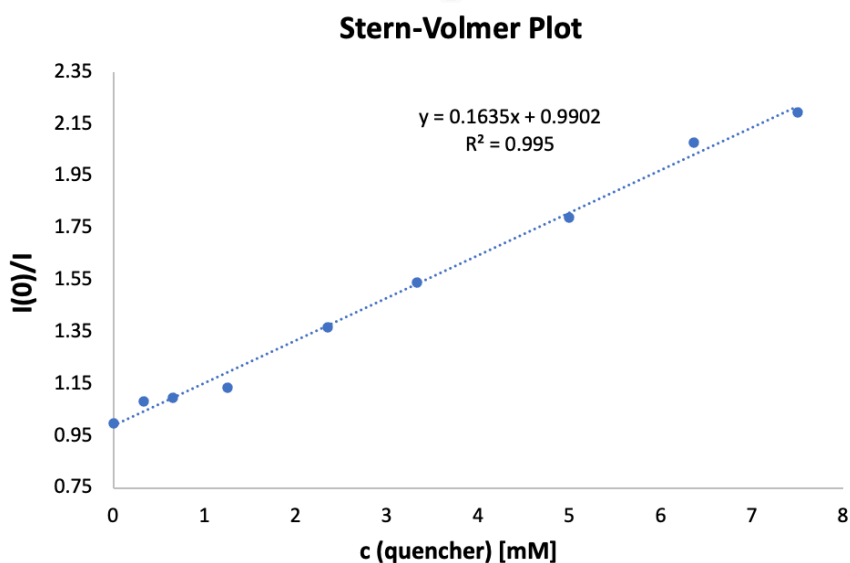


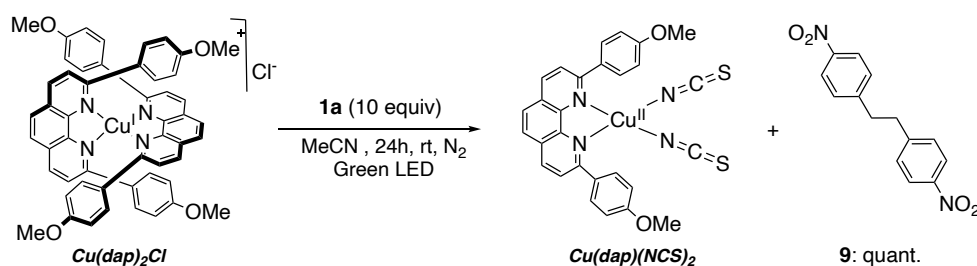
Figure 9: Stern-Volmer quenching plot of Cu(dap)₂Cl using **1a** as quencher

11. EPR Measurements:

Electron Paramagnetic Resonance (EPR) experiments were conducted using a Magnettech Miniscope MS 400 spectrometer (X-Band, 9-10 GHz). Glass pipettes, evacuated and purged with dry nitrogen multiple times, were filled with 0.3 mL of the specified solutions. Solvents, along with solid reactants, underwent degassing through three freeze-pump-thaw cycles.

EPR spectra were acquired in the form of a first-order derivative plot. All spectra underwent baseline correction; to minimize noise, each spectrum was subtracted by the correspondent solvent spectra.

Stoichiometric reaction of $\text{Cu(dap)}_2\text{Cl}$ and **1a**:



To a flame-dried Schlenk tube with a stirring bar was added $\text{Cu(dap)}_2\text{Cl}$ (8.9 mg, 0.01 mmol, 1.0 equiv), **1a** (19.4 mg, 0.1 mmol, 10.0 equiv), and 1 mL of anhydrous acetonitrile. The tube was sealed with a screw-cap and subsequently degassed by three consecutive freeze-pump-thaw cycles. The screw-cap was, under a positive nitrogen pressure, replaced by a Teflon inlet with a glass rod that transmits the light irradiations (530 nm LED). The reaction was irradiated for 24 h. After completion, we observed the deposit of a green precipitate (fine powder). This latter was separated using a centrifuge and was later revealed to be **c**. In the reaction solution we also detected the dimerization product.

1,2-bis(4-nitrophenyl)ethane (9): Data was in accordance with literature.³⁰² $^1\text{H-NMR}$ (400 MHz, CDCl_3): 3.08 (s, 4H), 7.28 (d, 4H, $J = 8.5$ Hz), 8.14 (d, 4H, $J = 8.5$ Hz); $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): 148.0, 146.8, 129.3, 123.8, 36.9.

Cu(dap)(NCS)₂: IR (neat, cm⁻¹): 2083, 1595, 1490, 1457, 1256, 1177, 1114, 1013, 834, 752;
 Elemental Analysis: 59.28 %C, 3.88 %H, 9.54 %N, 10.76 %S.

Notably, recrystallization attempts of Cu(dap)(NCS)₂ in DMSO were unsuccessful and led to its decomposition forming [Cu(dap)₂][Cu₂(NCS)₃] alongside the (SCN)₂.¹⁹⁵

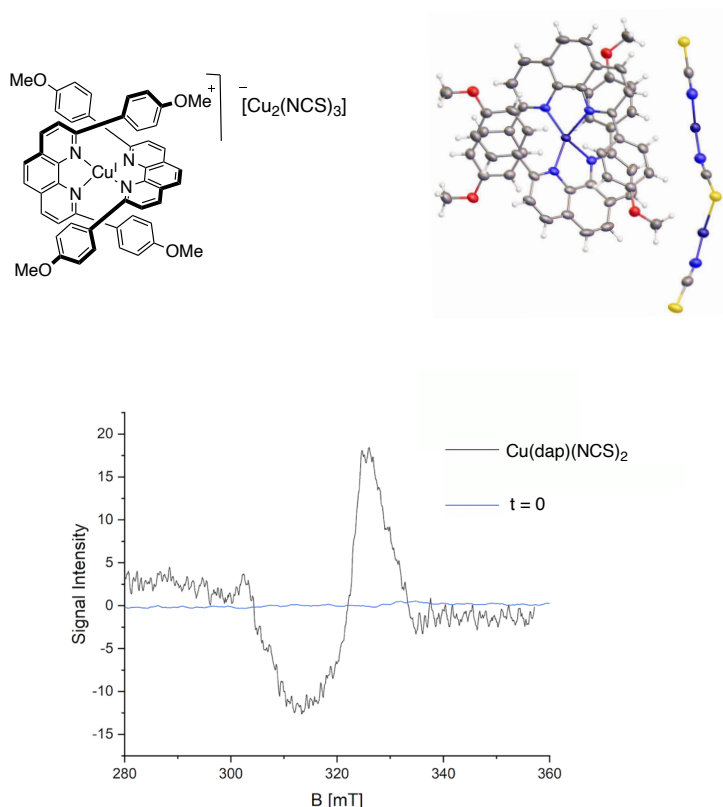


Figure 10: EPR spectra of the reaction mixture at $t = 0$ and Cu(dap)(NCS)₂ solution in dimethylsulfoxide (DMSO). Frequency: 9.6509 GHz; B₀-Sweep = 80 mT; Sweep- Time = 60 s.

After having synthesized Cu(dap)(NCS)₂, we compared its signature to Cu(dap)(NCS)₂ obtained from the reaction between Cu(dap)₂Cl and **1a** which was identical with a g-value of 2.16.

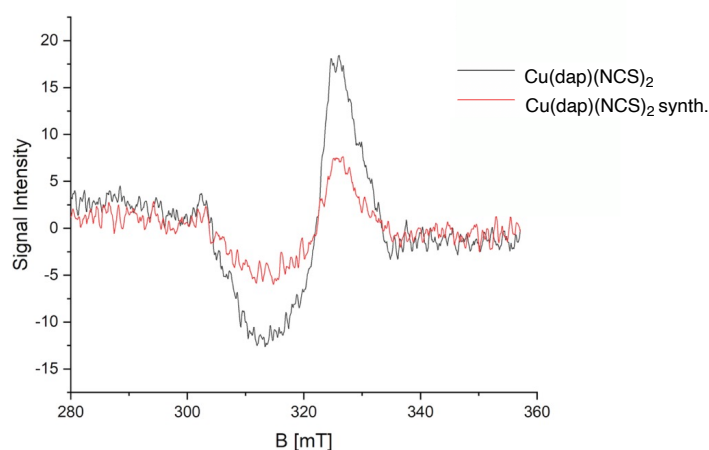
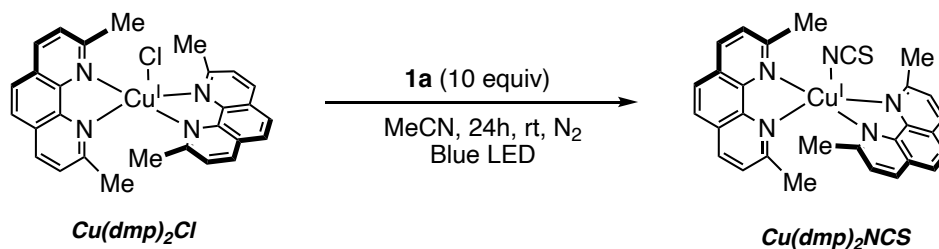


Figure 11: EPR spectra of obtained Cu(dap)(NCS)_2 from the reaction between $\text{Cu(dap)}_2\text{Cl}$ and **1a** and the independently synthesized Cu(dap)(NCS)_2 in dimethylsulfoxide (DMSO). Frequency: 9.6509 GHz; B_0 -Sweep = 80 mT; Sweep-Time = 60 s.

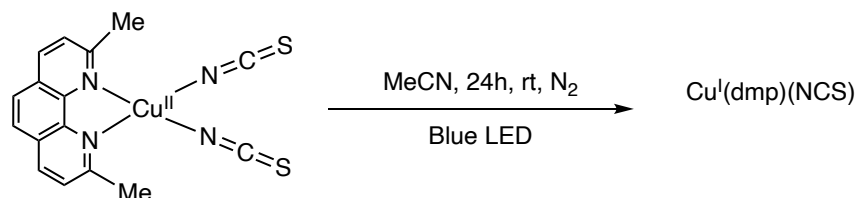
12. Probing thiocyanate radicals



To a flame-dried Schlenk tube with a stirring bar was added $\text{Cu(dmp)}_2\text{Cl}$ (5.2 mg, 0.01 mmol, 1.0 equiv), **1a** (19.4 mg, 0.1 mmol, 10.0 equiv), and 1 mL of anhydrous acetonitrile. The tube was sealed with a screw-cap and subsequently degassed by three consecutive freeze-pump-thaw cycles. The screw-cap was, under a positive nitrogen pressure, replaced by a Teflon inlet with a glass rod that transmits the light irradiations (530 nm LED). The reaction was irradiated for 24h. After completion, we observed the deposit of an orange precipitate (very fine powder). This latter was separated using a centrifuge and was later revealed to be a Cu(I)-species via EPR.

$\text{Cu(dmp)}_2(\text{NCS})$: IR(neat, cm^{-1}): 2102, 1740, 1587, 1498, 1423, 1356, 1148, 1013, 853, 775, 730. HRMS m/z calculated for $\text{C}_{29}\text{H}_{24}\text{CuN}_5\text{S}$ ([M-SCN]) 537.1048 found 537.1053.

Photodecomposition of Cu(dmp)(NCS)₂:



To a flame-dried Schlenk tube with a stirring bar was added Cu(dmp)(NCS)₂ (3.9 mg, 0.01 mmol, 1.0 equiv) and 1mL of anhydrous acetonitrile. The tube was sealed with a screw-cap and subsequently degassed by three consecutive freeze-pump-thaw cycles. The screw-cap was, under a positive nitrogen pressure, replaced by a Teflon inlet with a glass rod that transmits the light irradiations (455nm LED). The reaction was irradiated for 24h. After completion, EPR revealed no presence of paramagnetic copper species in the solution indicating its photodecomposition and reduction to Cu(I) accompanied with the release of a SCN-radical.

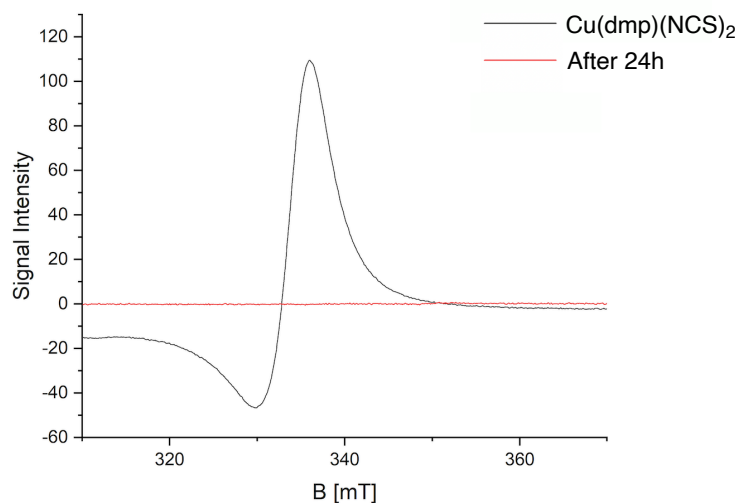


Figure 12: EPR spectra of Cu(dmp)(NCS)₂ in solid state ($g = 2.058$), reaction mixture in dimethylsulfoxide (DMSO). Frequency: 9.6515 GHz; B₀-Sweep = 80 mT; Sweep-Time = 60s.

Presence of dithiocyanation product:^{196,197}

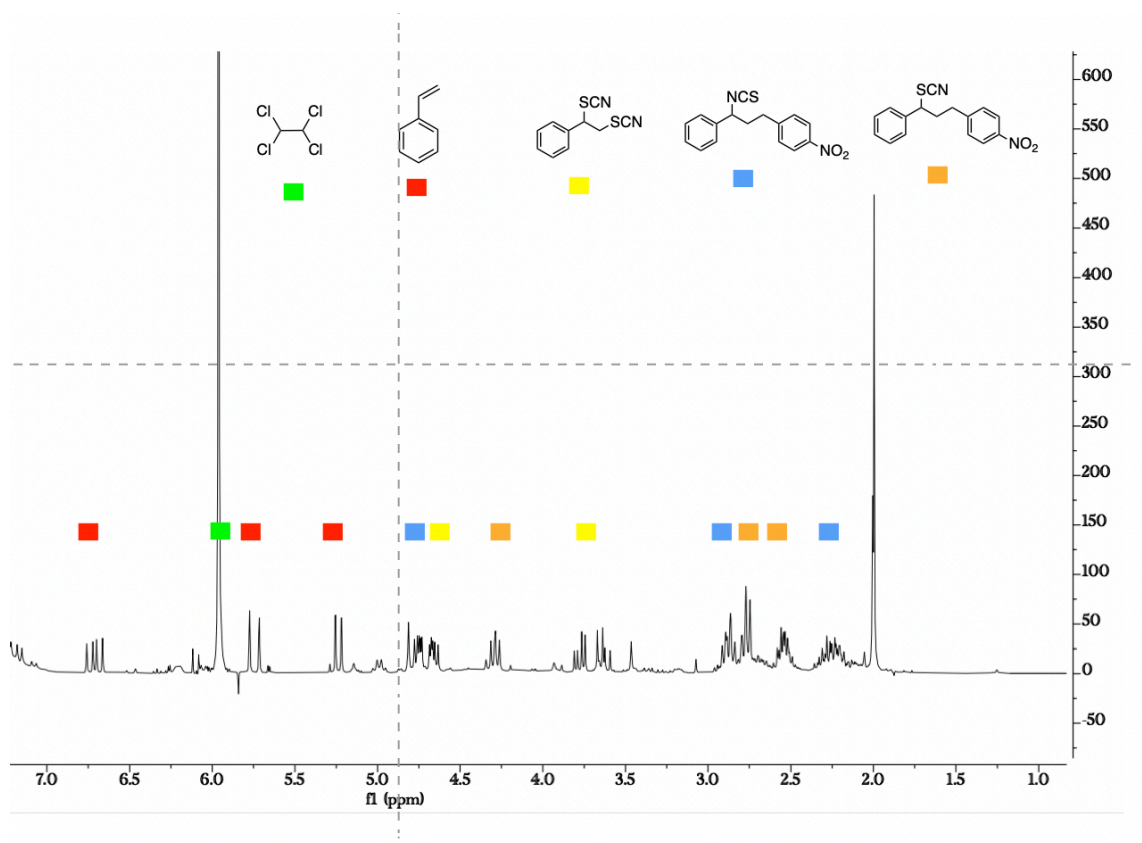


Figure 13: Presence of the dithiocyanation product as viewed in ^1H -NMR

Dithiocyanation mechanism:

Based on reported precedent in literature,^{196,197} the reaction is initiated by the oxidation of the thiocyanate anion by the photocatalyst generating SCN-radical that adds to an olefin. The transient C-centered radical formed is then oxidized and coupled to a thiocyanate anion leading to the dithiocyanation product.

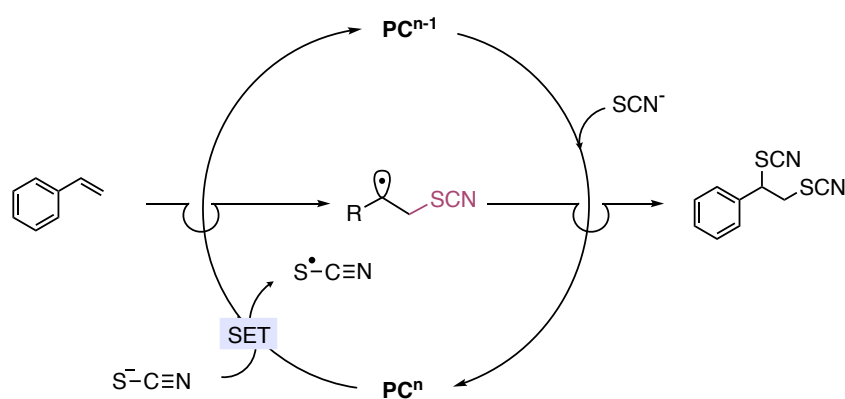


Figure 14: Proposed mechanism for the dithiocyanation side-product

13. UV-vis Absorption Measurements:

All UV-Vis measurements were conducted using a SPECTRORECORD 200 PLUS spectrophotometer by analytikjena, employing a Macro cell type 110-QS quartz cuvette with a PTFE stopper (Hellma Analytics quartz cuvette, 10×10 mm, 3.5 mL).

The measurements were recorded using dry DMSO as a solvent.

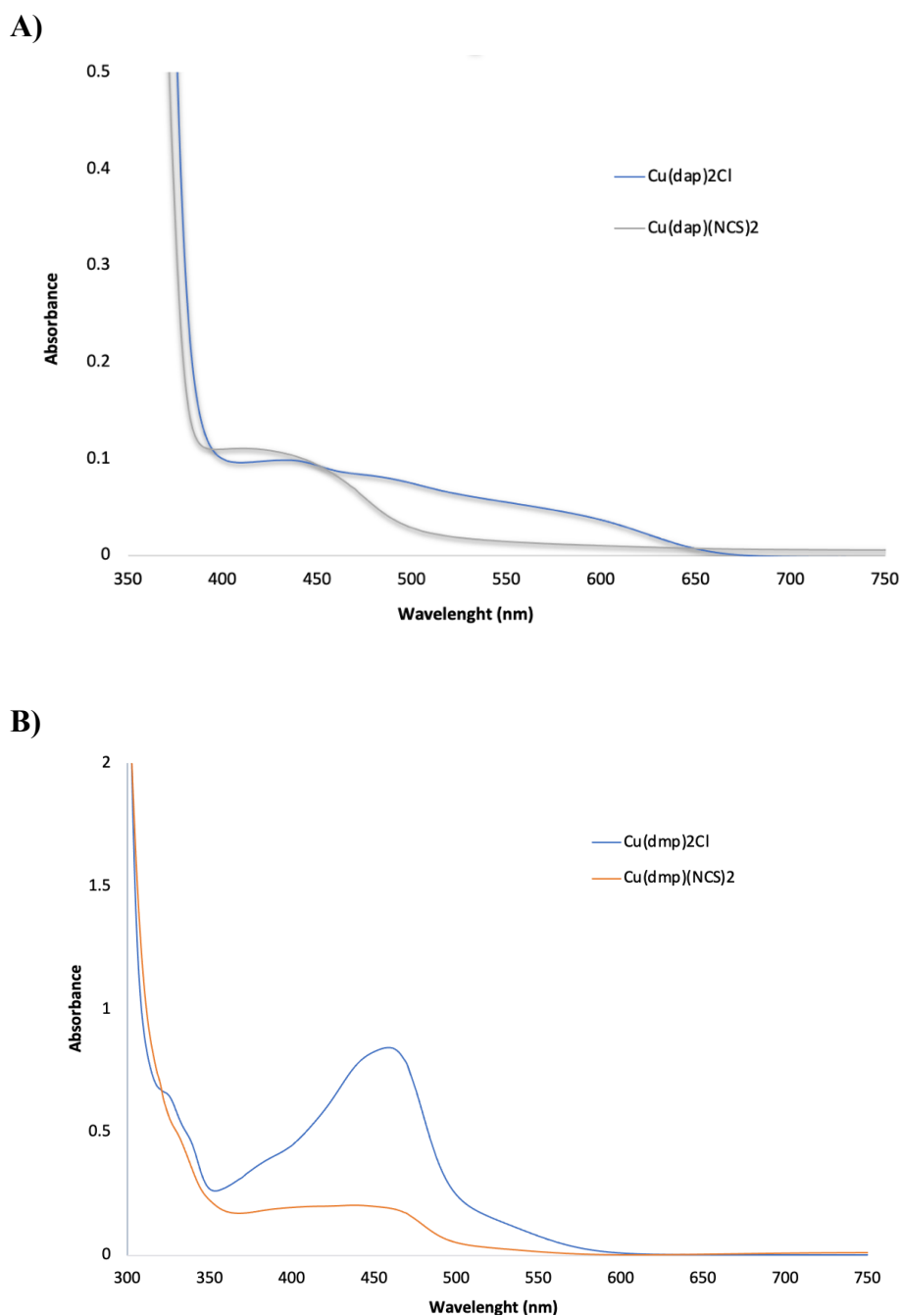


Figure 15: (A) Change in the absorption between $\text{Cu(dap)}_2\text{Cl}$ and $\text{Cu(dap)}(\text{NCS})_2$; (B) Change in the absorption between $\text{Cu(dmp)}_2\text{Cl}$ and $\text{Cu(dmp)}(\text{NCS})_2$

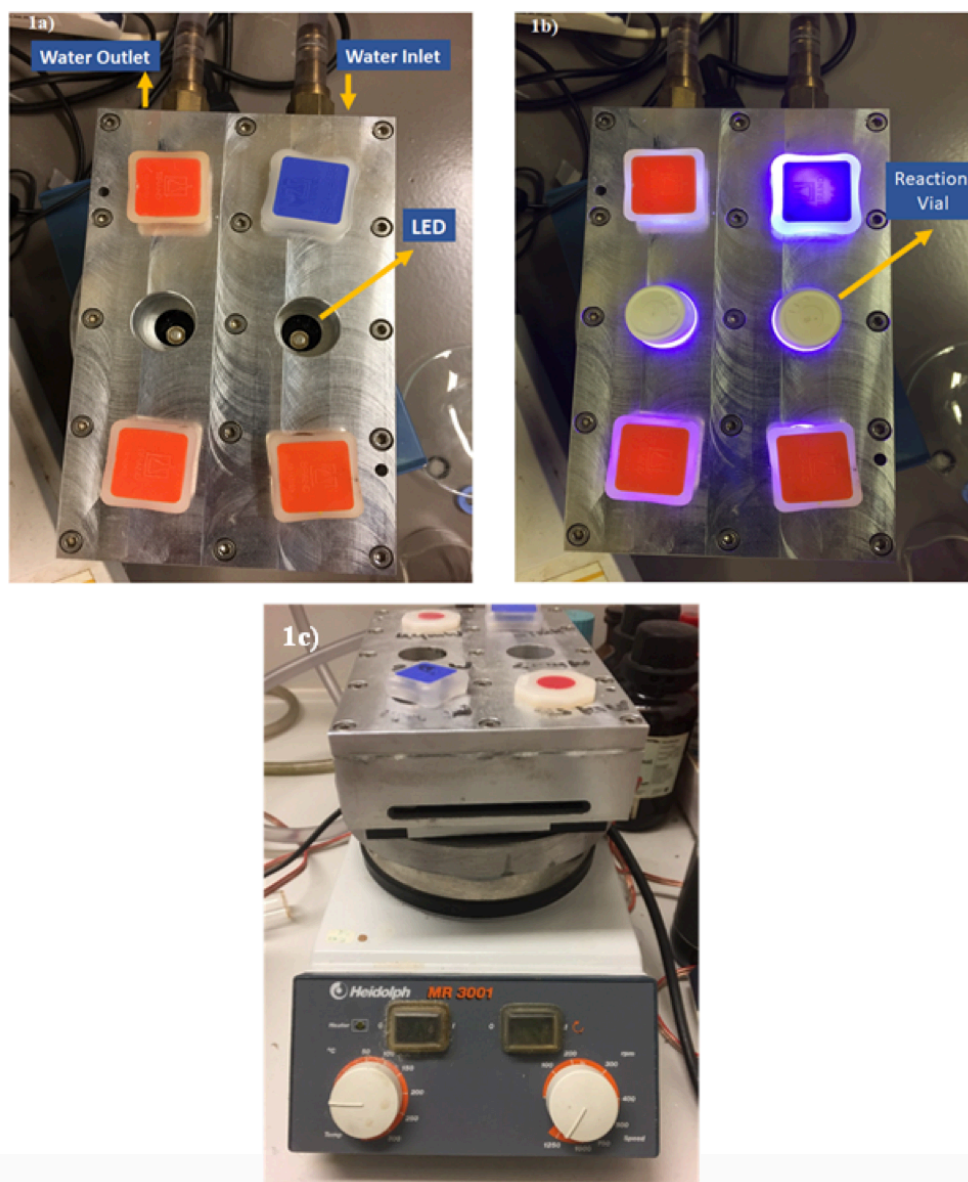
Experimental section of chapter 3

1. General information

We employed commercially available chemicals without further purification. The synthesized compounds underwent purification following standard procedures. All photochemical reactions took place in oven-dried glassware under atmospheric conditions unless otherwise specified. Reaction mixtures underwent degassing through three freeze-pump-thaw cycles. Prior to use, petroleum ether (hexanes) and ethyl acetate (EtOAc) were distilled. Yields reported refer to isolated compounds, unless specified otherwise. For thin-layer chromatography (TLC), we utilized precoated aluminum sheets (Merck silica gel 60 F254). Visualization was achieved using UV light ($\lambda = 254$ nm). Staining was performed with vanillin (6.0 g vanillin, 100.0 mL ethanol (95%), and 1.0 mL conc. sulfuric acid), potassium permanganate (1.0 g KMnO_4 , 2.0 g Na_2CO_3 , and 100.0 mL distilled water), or Seebach's stain (0.5 g cer. ammonium molybdate, 12.0 g ammonium molybdate, 15.0 mL conc. sulfuric acid, and 235 mL water) followed by heating. Column chromatography involved silica gel (Merck, Geduran 80, 0.063 – 0.200 mm particle size) and flash silica gel (Merck, 0.040 – 0.200 mm particle size). ^1H -NMR and ^{13}C -NMR spectra³⁰³ were recorded on Avance III Systems from Bruker, Rheinstetten: (i) Bruker Avance 300 FT-NMR (for 300 MHz ^1H -NMR and 75 MHz ^{13}C -NMR) (ii) Bruker Avance 400 FT-NMR (for 400 MHz ^1H -NMR and 101 MHz ^{13}C -NMR and 377 MHz ^{19}F -NMR). Field strengths are expressed in MHz, and chemical shifts are reported relative to the solvent residual peak of commercially available NMR solvents CDCl_3 : δ ppm = 7.26; D_2O : δ ppm = 4.79, and $\text{DMSO}-d_6$: δ ppm = 2.5. Peak multiplicities are designated as follows: s–singlet, d–doublet, dd–doublet of doublet, ddd–doublet of doublet of doublet, dt–doublet of triplet, dtd–doublet of triplet of doublet, t–triplet, td–triplet of doublet, q–quartet, p–pentet, m–multiplet. FTIR spectroscopy was performed on a Cary 630 FTIR spectrometer. Solid and liquid compounds were measured neatly, and the wave numbers are reported as cm^{-1} . Mass spectra were recorded by the Central Analytical Laboratory at the Department of Chemistry of the University of Regensburg on a Varian MAT311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000, or Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS. High-resolution mass spectra were performed using electrospray ionization (ESI) or electron ionization (EI) with a quadrupole time-of-flight (Q-TOF) detector."

The irradiation was done using Inolux IN-C68QABTMU2 – UV LED (3.08 W electric power @700mA, $\lambda = 365$ nm).

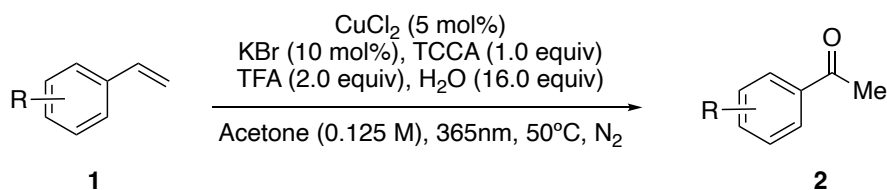
Photochemical setup:



Safety Statement:

Ultra-violet LEDs is harmful for skin and eyes. Caution must be taken during the handling of the LEDs and safety equipment should be worn before switching the LEDs on.

2. Experimental procedures:



General procedure 1 (G.P.1)

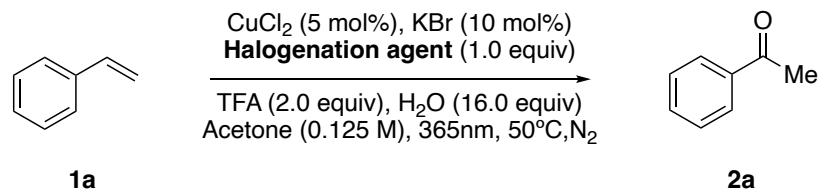
A glass vial was loaded with trichloroisocyanuric acid (TCCA) (0.5 mmol, 1.0 equiv), copper (II) chloride (0.025 mmol, 5 mol%) and potassium bromide (0.05 mmol, 10 mol%) in 4 mL of acetone. A stirring bar was added and the vial was capped with a rubber septum. The reaction mixture was then degassed by nitrogen. Afterwards, water (8.0 mmol, 16.0 equiv), trifluoroacetic acid (1.0 mmol, 2.0 equiv) and the olefin (0.5 mmol, 1.0 equiv) were consecutively injected into the mixture. The vial was then placed in a cooling block and irradiated from the bottom side by a 365 nm LED (3W electrical power) for 16 hours at 50°C. After completion, the solvent was removed in *vacuo*. The crude mixture was then dissolved in 2 mL of dichloromethane and 2 mL of H_2O and transferred into a separatory funnel. The aqueous layer was extracted two times with 4 mL of DCM. The combined organic layers were dried over MgSO_4 , filtered and evaporated under reduced pressure. Purification by flash column chromatography furnished the desired products.

General procedure 2 (G.P.2)

G.P.2 is identical to G.P.1 except tribromoisocyanuric acid (TBCA) (0.5 mmol, 1.0 equiv) was used instead of TCCA and the reaction was conducted at room temperature instead of 50°C.

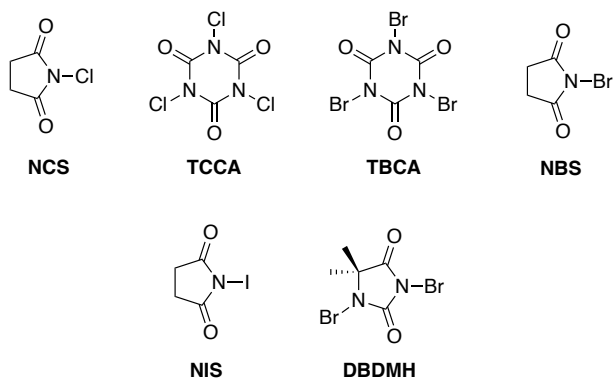
3. Reaction optimization:

Halogenation agent screening:

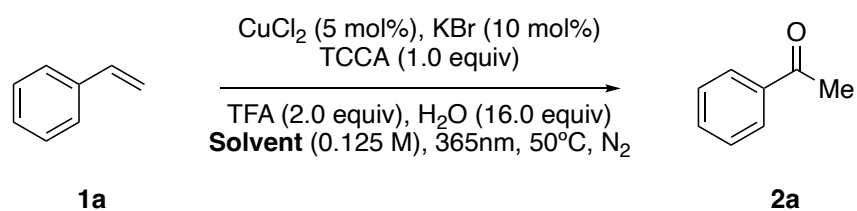


Entry	Halogenation agent	Yield ^a (%)
1	NCS	5%
2	NBS	24%
3	NIS	16%
4	TCCA	89%
5	TBCA	75% (56%) ^b
6	DBDMH	37%

^a ¹H-NMR yield using tetrachloroethane as internal standard, ^b reaction under 400 nm



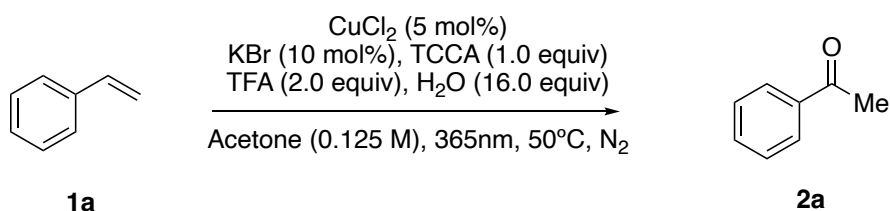
Solvent screening:



Entry	Solvent	Yield ^a (%)
1	Acetone	89%
2	MeCN	60%
3	DCM	c.r.m.
4	CHCl ₃	c.r.m.
5	MeOH	c.r.m.
6	Benzene	c.r.m.

^a ¹H-NMR yield using tetrachloroethane as internal standard

Control experiments:



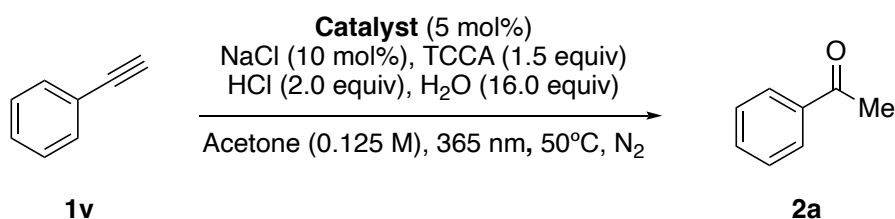
Entry	Conditions	Yield ^a (%)
1	-	89%
2	No light	-
3	No CuCl ₂	25 %

^a ¹H-NMR-yield using tetrachloroethane as internal standard

4. Optimization using phenylacetylene:

A glass vial was loaded with trichloroisocyanuric acid (TCCA) (174.3 mg, 0.75 mmol, 1.5 equiv), copper (II) acetate (4.54 mg, 0.025 mmol, 5 mol%) and sodium chloride (2.9 mg, 0.05 mmol, 10 mol%) in 4 mL of acetone. A stirring bar was added and the vial was capped with a rubber septum. The reaction mixture was then degassed by nitrogen. Afterwards, water (144 mg, 8.0 mmol, 16.0 equiv), hydrochloric acid (1.0 mmol, 2.0 equiv) and phenylacetylene **1v** (51.1 mg, 0.5 mmol, 1.0 equiv) were consecutively injected into the mixture. The vial was then placed in a cooling block and irradiated from the bottom side by a 365 nm LED (3W electrical power) for 16 hours at 50°C. After completion, the solvent was removed in *vacuo*. The crude mixture was then dissolved in 2 mL of dichloromethane and 2 mL of H₂O and transferred into a separatory funnel. The aqueous layer was extracted two times with 4 mL of DCM. The combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The crude mixture was analyzed via ¹H-NMR using tetrachloroethane as an internal standard.

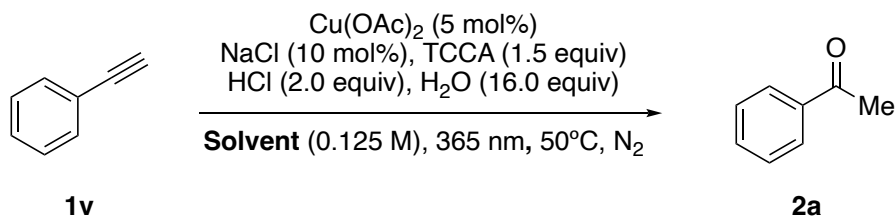
Catalyst screening:



Entry	Catalyst	Yield ^a (%)
1	FeCl ₃	49 %
2	CeCl ₃	24 %
3	Fe(acac) ₃	48 %
4	Cu(acac) ₂	49 %
5	CuCl ₂	42 %
6	Cu(OAc) ₂	45% (45%) ^b

^a ¹H-NMR-yield using tetrachloroethane as internal standard, ^b 10 mol% of Cu(OAc)₂

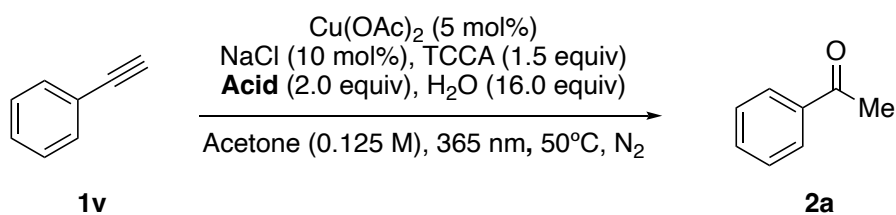
Solvent screening:



Entry	Solvent	Yield ^a (%)
1	Acetone	49%
2	MeCN	44 %
3	EtOAc	35 %
4	DCE	c.r.m.
5	MeOH	c.r.m.
6	DMF	c.r.m.

^a ¹H-NMR-yield using tetrachloroethane as internal standard

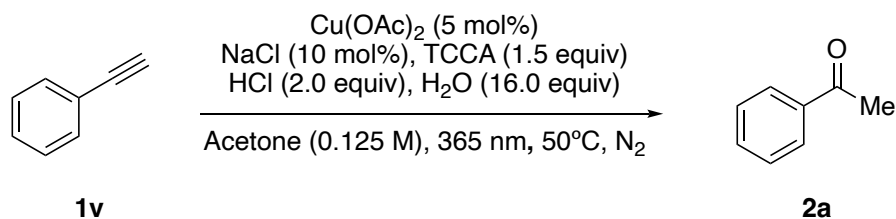
Acid screening:



Entry	Acid	Yield ^a (%)
1	TFA	45%
2	TFAA	16%
3	H_2SO_4	36%
4	PTSA	n.r.
5	MeCO_2H	26%

^a ¹H-NMR-yield using tetrachloroethane as internal standard

Control experiments:



Entry	Conditions	Yield ^a (%)
1	No $\text{Cu}(\text{OAc})_2$	14 %
2	No TCCA	n.r.
3	No HCl	18 %
4	No NaCl	48 %
5	400 nm irradiation	31 %
6	No Light	0 %

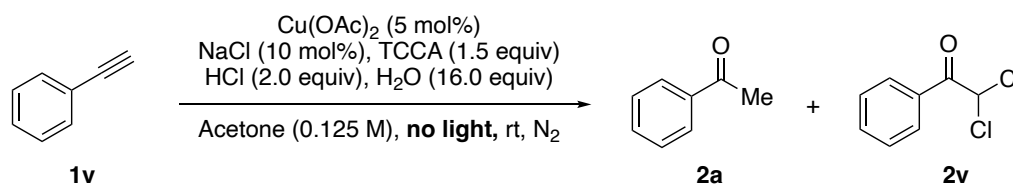
^a ^1H -NMR-yield using tetrachloroethane as internal standard

Phenylacetylene: Dark experiments

A glass vial was loaded with trichloroisocyanuric acid (TCCA) (174.3 mg, 0.75 mmol, 1.5 equiv), copper (II) acetate (4.54 mg, 0.025 mmol, 5 mol%) and sodium chloride (2.9 mg, 0.05 mmol, 10 mol%) in 4 mL of acetone. A stirring bar was added and the vial was capped with a rubber septum. The reaction mixture was then degassed by nitrogen. Afterwards, water (144 mg, 8.0 mmol, 16.0 equiv), hydrochloric acid (1.0 mmol, 2.0 equiv) and phenylacetylene **1v** (51.1 mg, 0.5 mmol, 1.0 equiv) were consecutively injected into the mixture. The vial was then covered with an aluminum foil and stirred for 24h. After completion, the solvent was removed *in vacuo*. The crude mixture was then dissolved in 2 mL of dichloromethane and 2 mL of H_2O and transferred into a separatory funnel. The aqueous layer was extracted two times with 4 mL of DCM. The combined organic layers were dried over MgSO_4 , filtered and evaporated under reduced pressure. The crude mixture was analyzed via ^1H -NMR using tetrachloroethane as an internal standard.

2,2-dichloro-1-phenylethan-1-one (2v)

$^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.08 (d, 2H), 7.65 (t, 2H), 7.51 (t, 2H), 6.70 (s, 1H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 185.94, 134.62, 131.35, 129.77, 128.97, 67.82. HRMS (EI) m/z calculated for $\text{C}_8\text{H}_6\text{Cl}_2\text{O}$ (M^+) 187.9797 found 187.9799. IR (neat, cm^{-1}): 1704, 1595, 1450, 1278, 1220, 812, 776, 687, 654.



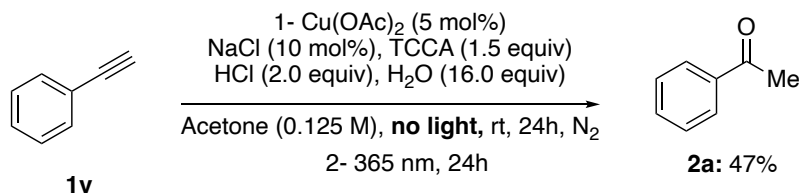
Entry	Conditions	2a ^a (%)	2v ^a (%)
1	-	-	79%
2	Under air	-	86 %
3	No NaCl	-	86 %
4	1.0 equiv of TCCA	-	79 %
5	No $\text{Cu}(\text{OAc})_2$	-	88 %

^a $^1\text{H-NMR}$ -yield using tetrachloroethane as internal standard

Dark-light experiment:

A glass vial was loaded with trichloroisocyanuric acid (TCCA) (174.3 mg, 0.75 mmol, 1.5 equiv), copper (II) acetate (4.54 mg, 0.025 mmol, 5 mol%) and sodium chloride (2.9 mg, 0.05 mmol, 10 mol%) in 4 mL of acetone. A stirring bar was added and the vial was capped with a rubber septum. The reaction mixture was then degassed by nitrogen. Afterwards, water (144 g, 8.0 mmol, 16.0 equiv), hydrochloric acid (1.0 mmol, 2.0 equiv) and phenylacetylene **1v** (51.1 mg, 0.5 mmol, 1.0 equiv) were consecutively injected into the mixture. The vial was then covered with an aluminum foil and stirred for 24h. After completion, the vial was placed in a cooling block and irradiated from the bottom side by a 365 nm LED (3W electrical power) for 24 hours at 50°C. The solvent was then removed in *vacuo*. The crude mixture was then dissolved in 2 mL of dichloromethane and 2 mL of H_2O and transferred into a separatory funnel. The aqueous layer was extracted two times with 4 mL of DCM. The combined organic

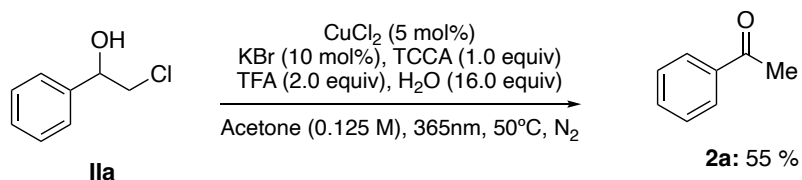
layers were dried over MgSO_4 , filtered and evaporated under reduced pressure. The crude mixture was analyzed via $^1\text{H-NMR}$ using tetrachloroethane as an internal standard.



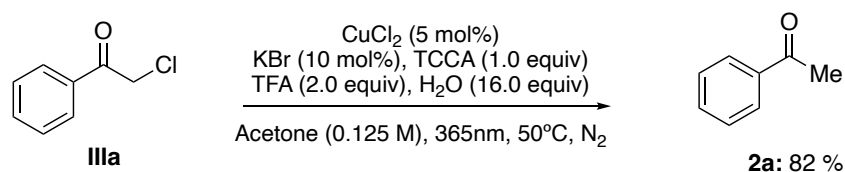
5. Testing intermediates:

In order to prove the validity of our proposed reaction pathway, we have subjected both conceptualized intermediates **IIa** and **IIIa** to our standard conditions following GP1.

Starting from chlorohydrin:



Starting from 2-Chloroacetophenon:

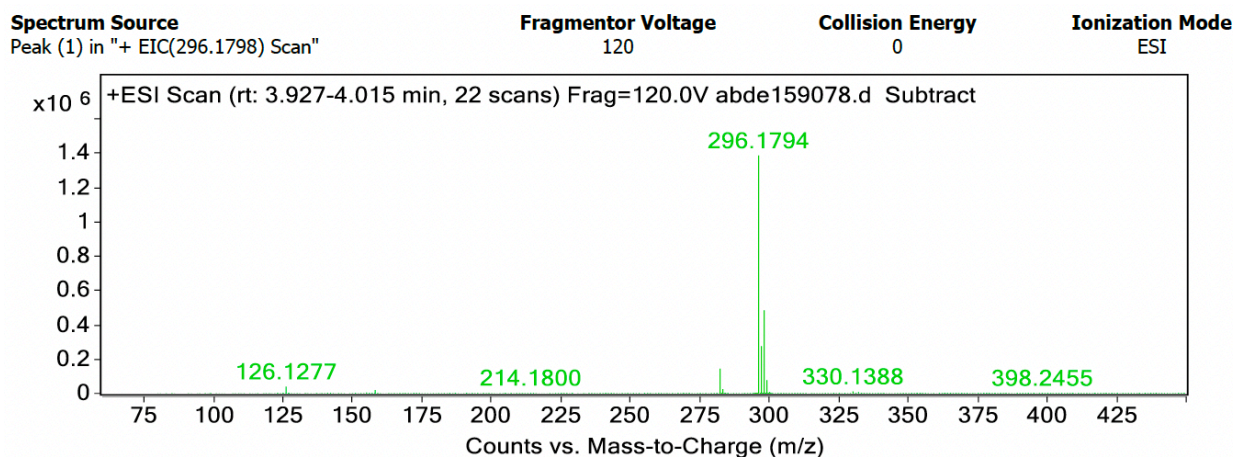
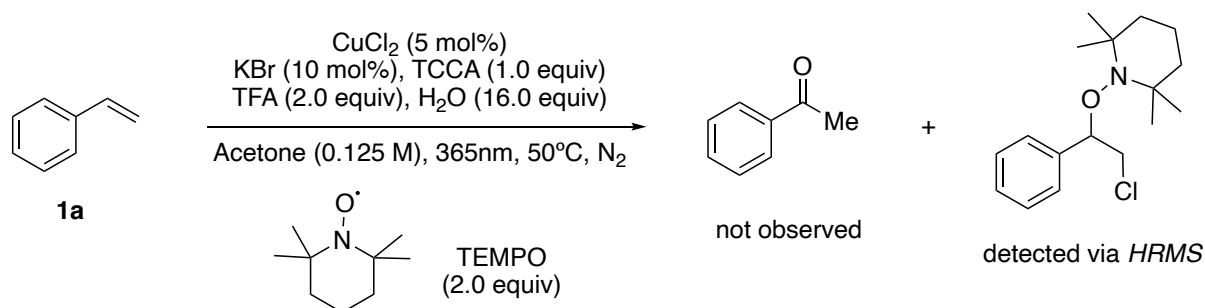


6. Radical trapping experiments:

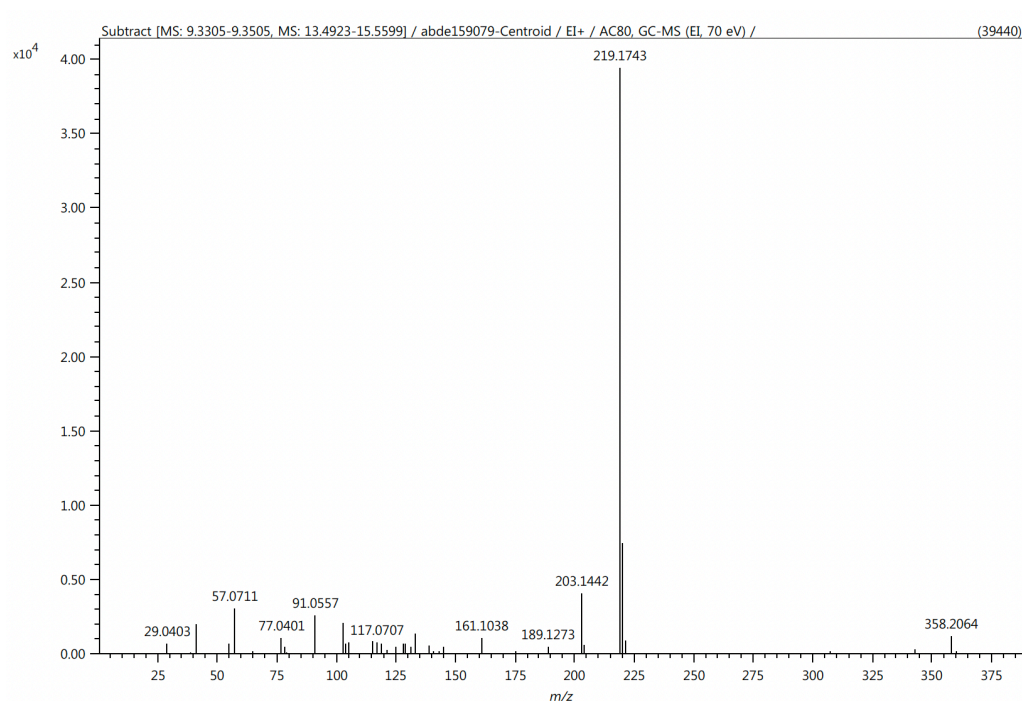
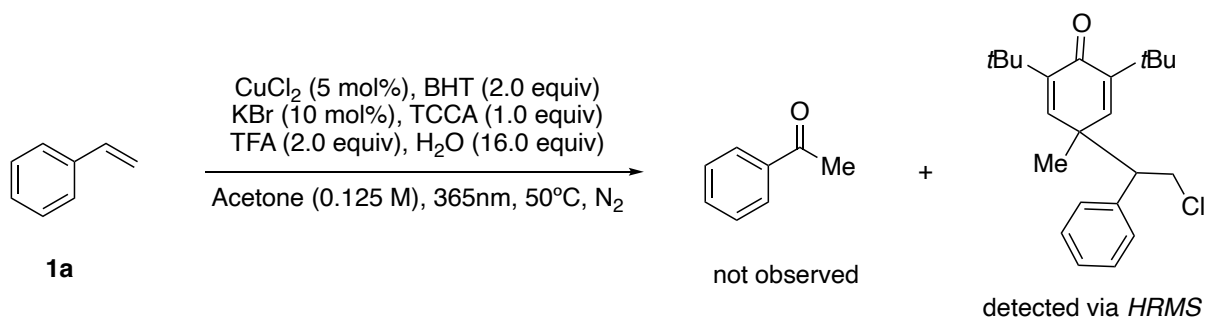
Experimental procedure:

A glass vial was loaded with trichloroisocyanuric acid (58.0 mg, 0.25 mmol, 1.0 equiv), copper (II) chloride (1.68 mg, 0.0125 mmol, 5 mol%), potassium bromide (2.98 mg, 0.025 mmol, 10 mol%) and the radical trapping reagent (0.5 mmol, 2 equiv) in 2 mL of acetone. A stirring bar was added and the vial was capped with a rubber septum. The reaction mixture was then degassed using nitrogen. Afterwards, water (72.0 mg, 4.0 mmol, 16.0 equiv), trifluoroacetic acid (57 mg, 0.5 mmol, 2.0 equiv) and styrene (26.1 mg, 0.25 mmol, 1.0 equiv) were consecutively injected into the reaction mixture. The vial was then irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C. After completion, an aliquot (100 μ L) was taken, diluted with DCM (500 μ L), dried over MgSO_4 and filtered. The remaining solution was passed through a syringe filter for further GC-MS analysis.

TEMPO trapping:



BHT trapping:



7. ^{18}O -labelling experiment:

An oven dried vial was equipped with trichloroisocyanuric acid (58.0 mg, 0.25 mmol, 1.0 equiv), copper (II) chloride (1.68 mg, 0.0125 mmol, 5 mol%) and potassium bromide (2.98 mg, 0.025 mmol, 10 mol%) in 2 mL of solvent. A stirring bar was added and the vial was capped with a rubber septum. The reaction mixture was then degassed by nitrogen. Afterwards, H_2^{18}O (80.1 mg, 4.0 mmol, 16.0 equiv), trifluoroacetic acid (57.0 mg, 0.5 mmol, 2.0 equiv) and styrene (26.1 mg, 0.25 mmol, 1.0 equiv) were consecutively injected into the mixture. The reaction was irradiated for 16h at 50°C. After completion, the reaction mixture was allowed to cool down to room temperature and charged with trimethoxybenzene as ^1H NMR internal standard. An aliquot (100 μL) was taken, diluted with DCM (500 μL), dried over MgSO_4 and

filtered. The remaining solution was passed through a syringe filter for further GC-MS analysis. The ^{18}O enrichment percentage was determined according to literature³⁰⁴ using the following formula.

^{18}O enrichment equation:

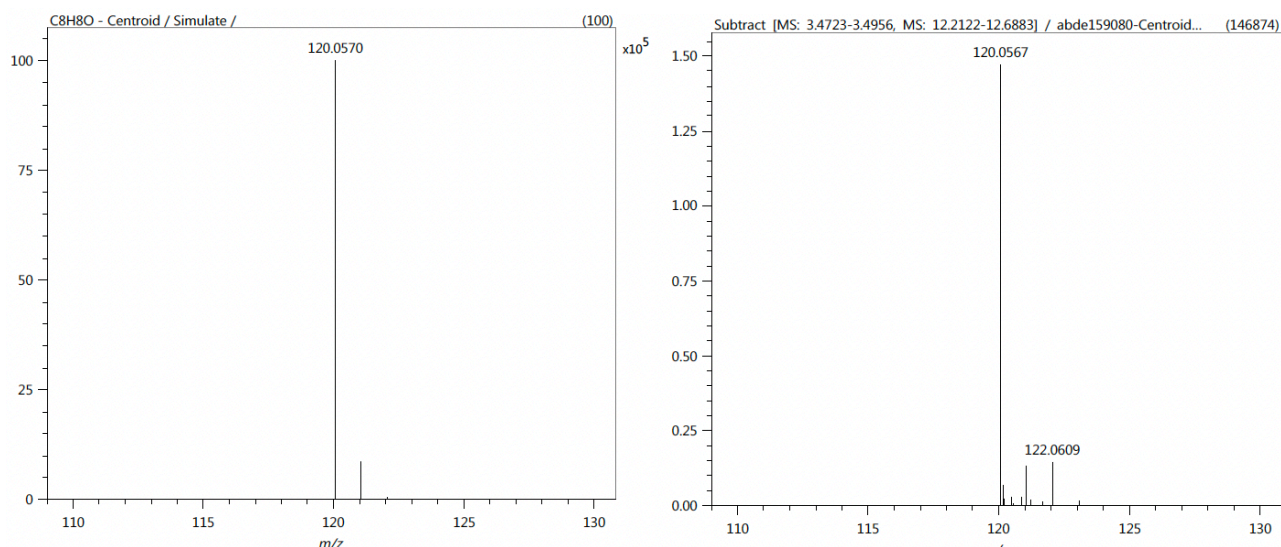
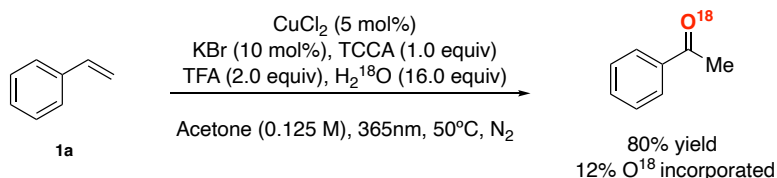
$$100 \cdot \frac{Rx - Ro}{1 + (Rx - Ro)} ; \quad R = \frac{m/z + 2}{m/z + 0}$$

Rx = experimental

Ro = formula isotopic distribution

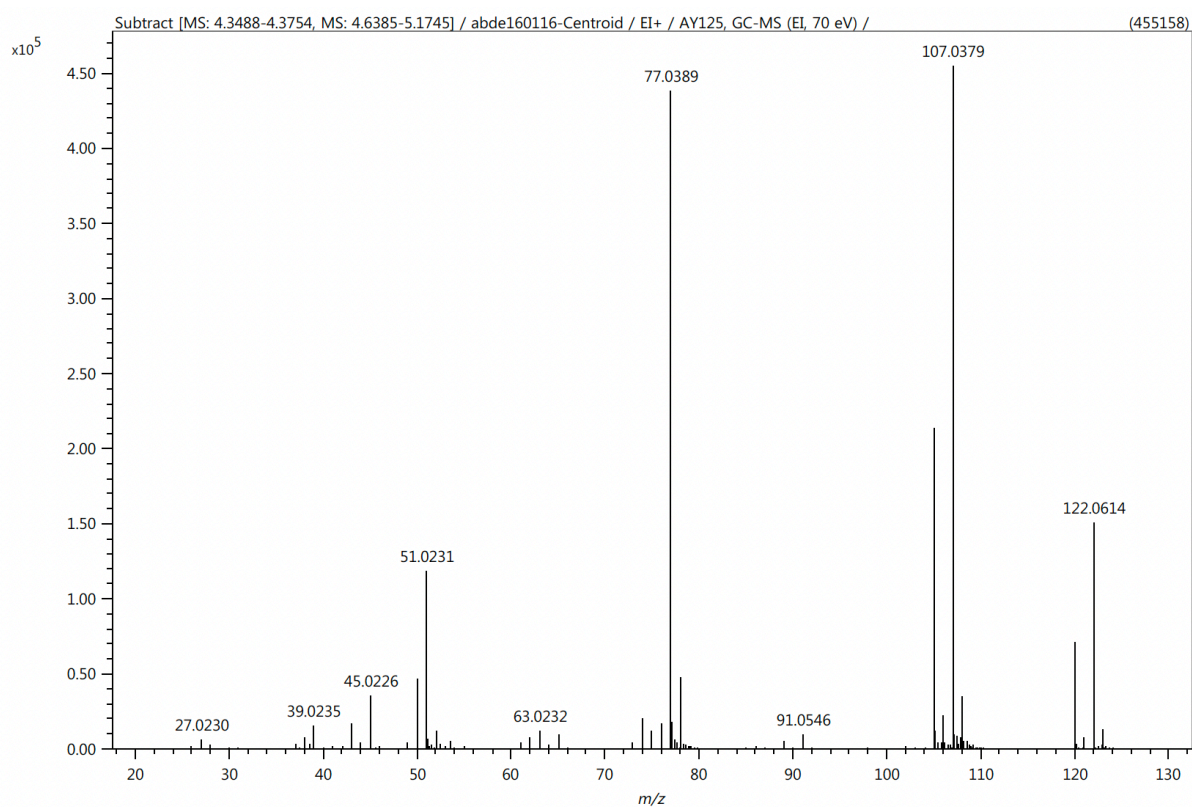
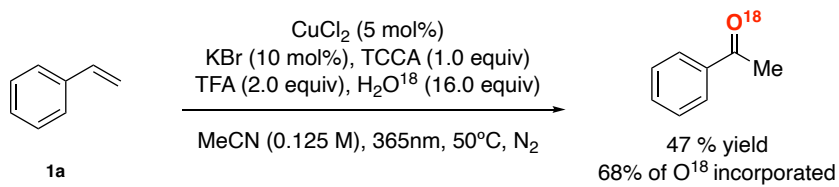
The ^{18}O labelling was conducted in acetone and in MeCN as solvents. This was due to the low enrichment we obtained in acetone caused by self-condensation (catalyzed by TFA) present which released an extra amount of H_2^{16}O and perturbed the experiment. However, in MeCN, 68% incorporation was observed.

In acetone:

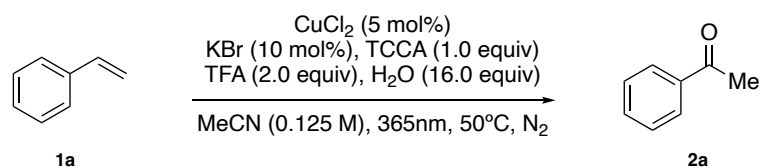


Acetophenone: Simulated spectra (left) vs measured spectra (right)

In MeCN:



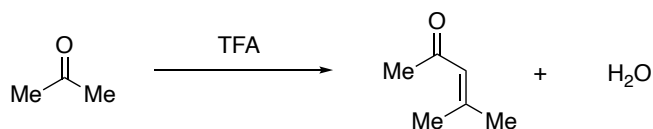
Formation of water through acetone:



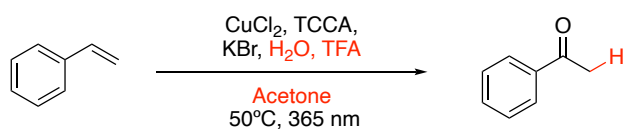
Entry	Conditions	Yield ^a (%)
1	-	60 %
2	No H ₂ O, 16 equiv of acetone	50 %
3	No H ₂ O, no acetone	0 %

^a ¹H-NMR-yield using tetrachloroethane as internal standard

Formation of water (side-reaction)



8. D-labelling experiments



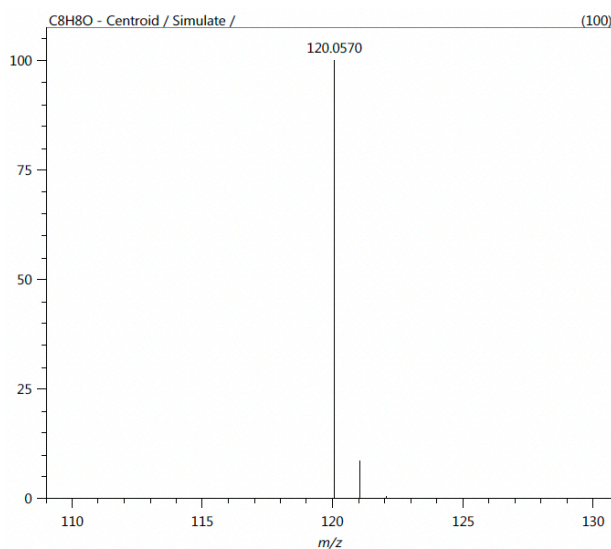
From a general point of view, the reaction consists of the addition of a hydrogen and oxygen atoms over an unsaturated olefin. Looking at the standard conditions, the source of the hydrogen atom can whether be H₂O, TFA or acetone. We have decided to perform deuteration labelling experiments to determine the nature of the H-donor for our system.

Procedure:

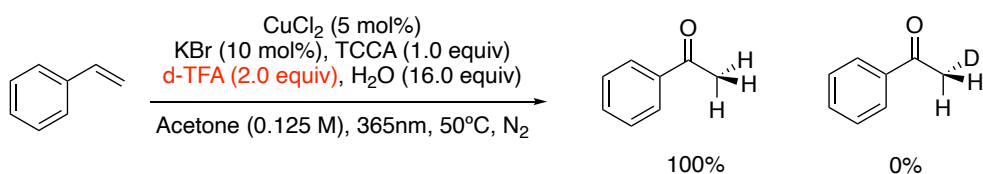
The reaction was set-up using the general procedure (G.P.1) while using the correspondent deuterated reagent. After completion, the reaction was allowed to cool to room temperature. An aliquot (100 μ L) was taken, diluted with DCM (500 μ L), dried over MgSO_4 and filtered. The remaining solution was passed through a syringe filter for further GC-MS analysis. The Deuterium incorporation was calculated using the formula:

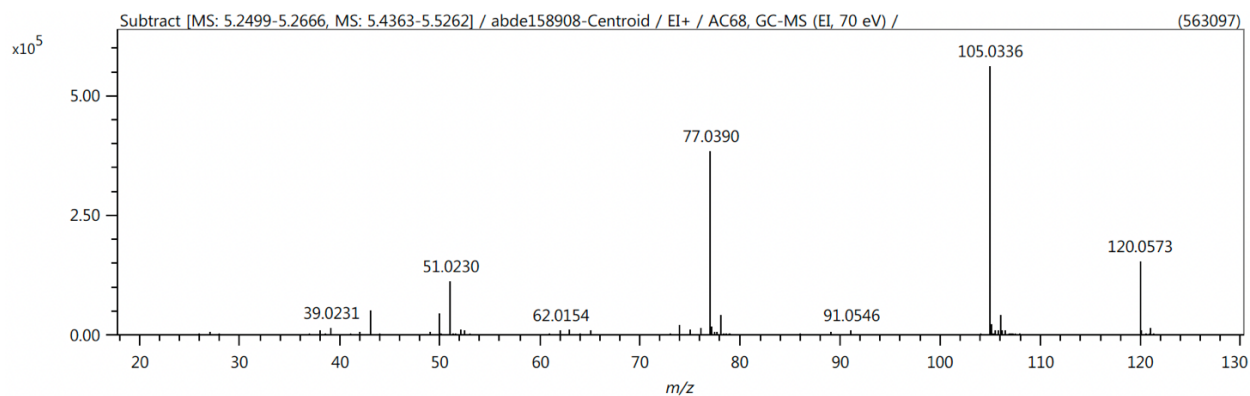
$$R = 100 \cdot \frac{m/z + x}{\sum m/z + x}$$

Simulated Mass spectra of acetophenone:

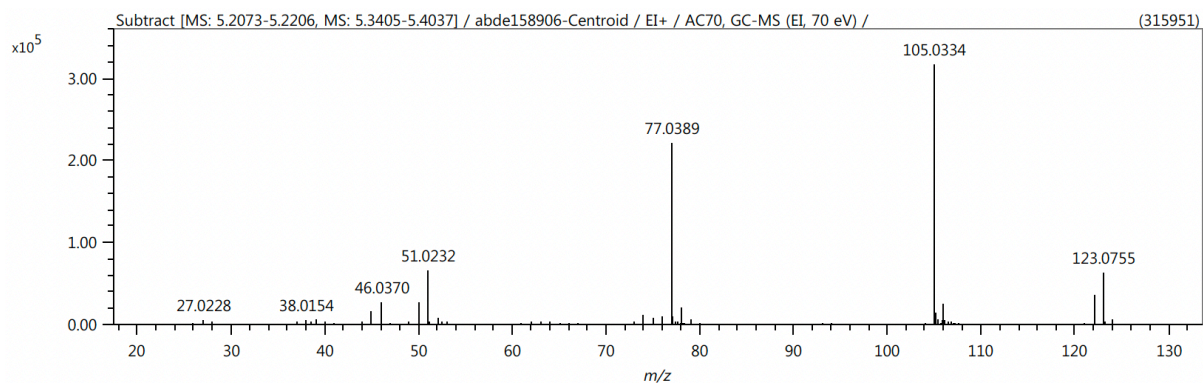
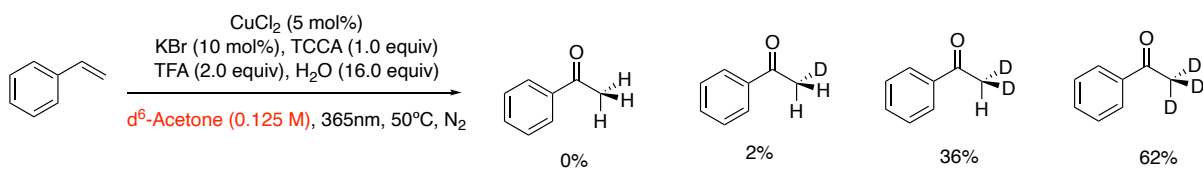


Using d-TFA:

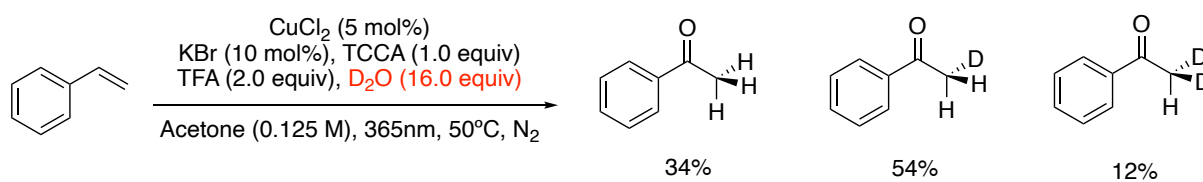


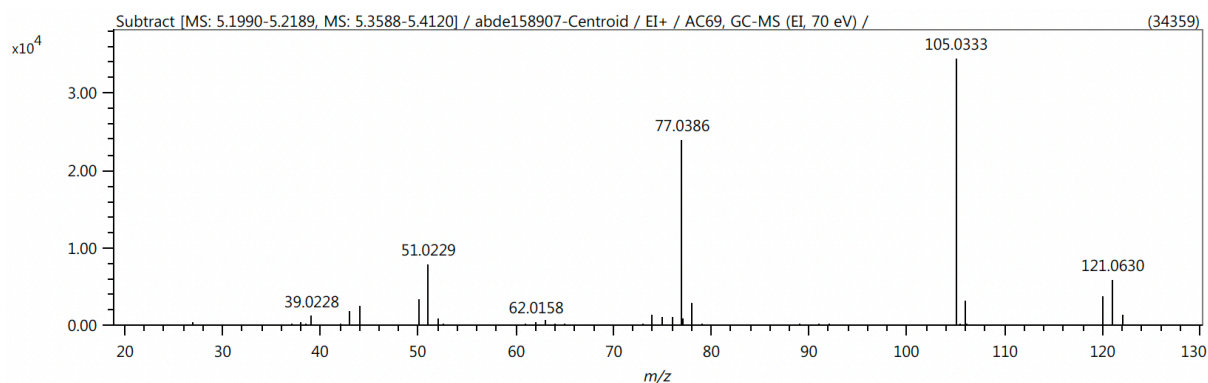


Using d^6 -acetone:



Using D_2O :





9. UV-vis measurements:

UV-vis measurements were recorded using a SPECTRORECORD 200 PLUS spectrophotometer by analytikjena, while employing a Macro cell type 110-QS quartz cuvette with a PTFE stopper (Hellma Analytics quartz cuvette, 10 × 10 mm, 3.5 mL).

The measurements were recorded using acetone as a solvent.

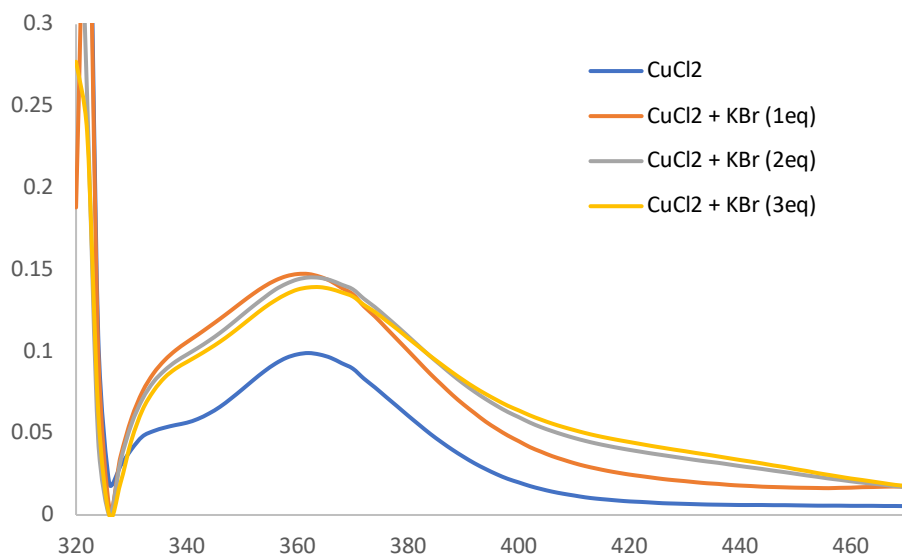


Figure 16: Absorption profile of CuCl₂ and KBr mixtures

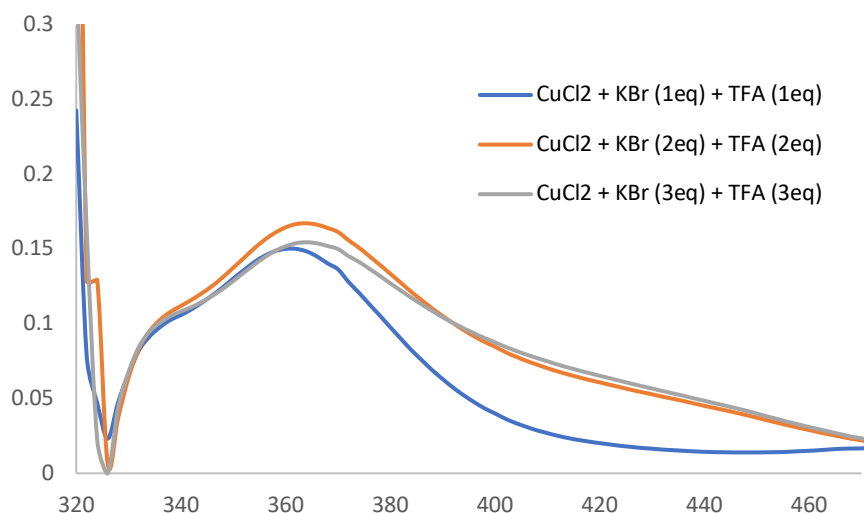


Figure 17: Absorption profile of CuCl_2 , KBr and TFA mixtures

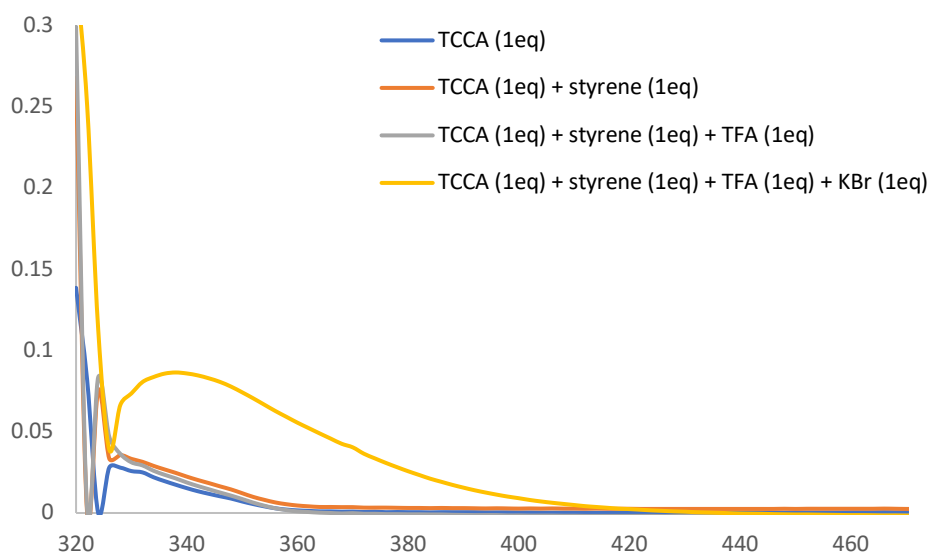


Figure 18: Absorption profile of other reaction components

10. Role of Copper:

Copper-TCCA fluorescence quenching

The interaction between the catalyst CuCl_2 and TCCA was assessed by recording fluorescence emission spectra through irradiation at 365 nm. These measurements were conducted using a HORIBA Fluoromax-4 from Horbia Scientific, employing a High Precision Cell 117100F-10-40 quartz cuvette with a screw cap (Hellma Analytics quartz cuvette, dimensions: 10×10 mm, capacity: 3.5 mL)

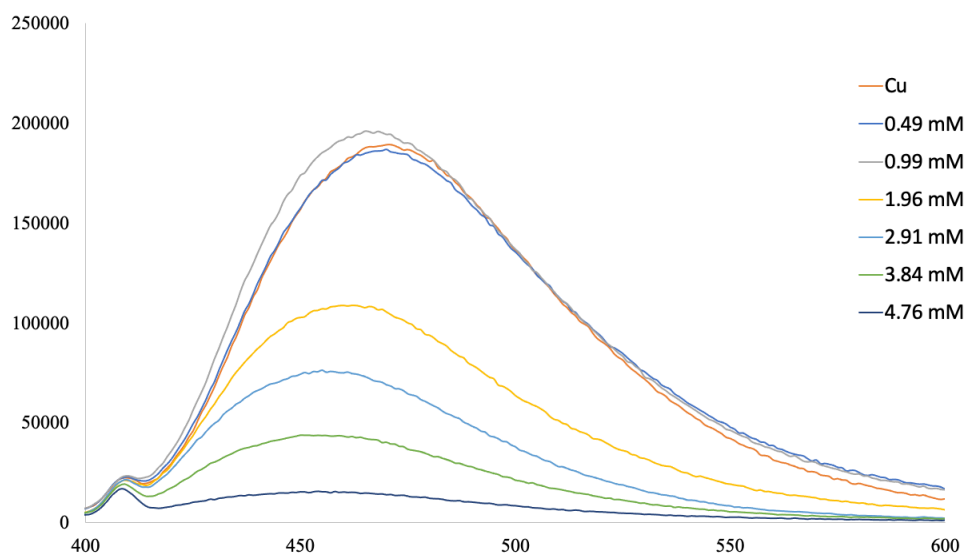


Figure 19: CuCl₂ emission quenching using TCCA as quencher

TCCA was proven to quench the photocatalyst. The Stern-Volmer plot and quenching constants were calculated. solutions under nitrogen atmosphere were freshly prepared prior to the measurements. The mixtures were irradiated at 365nm and the data for the plot was collected from the maximum emission wavelength (466 nm).



Figure 19: Stern-Volmer quenching plot of CuCl₂ using TCCA as quencher

Copper interaction with intermediates:

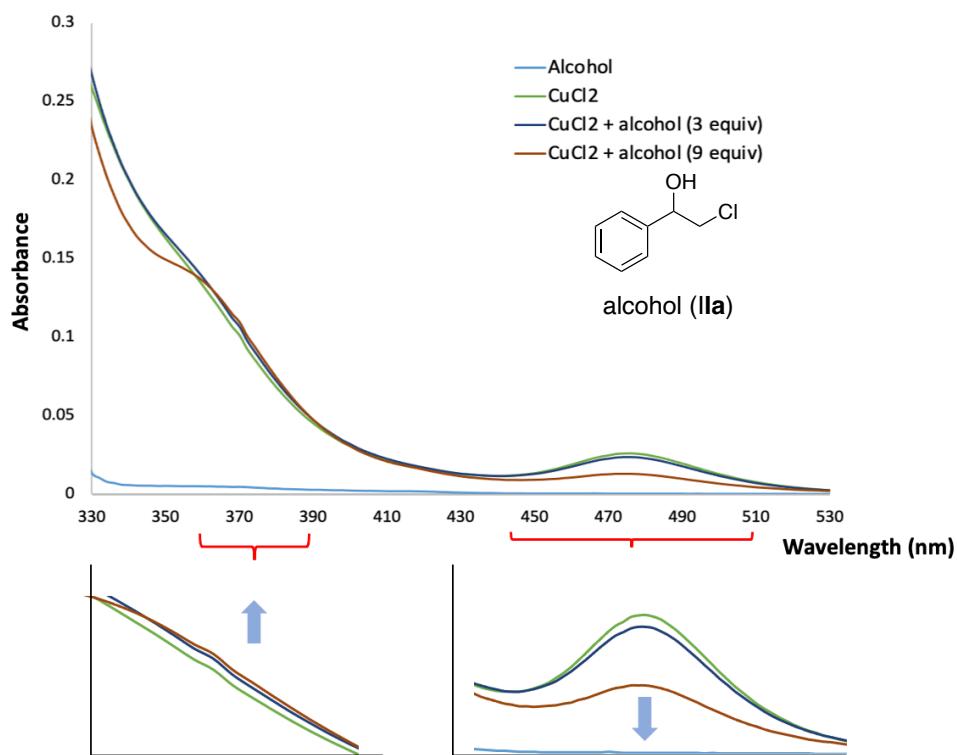


Figure 20: Absorbance variation of copper-alcohol complex

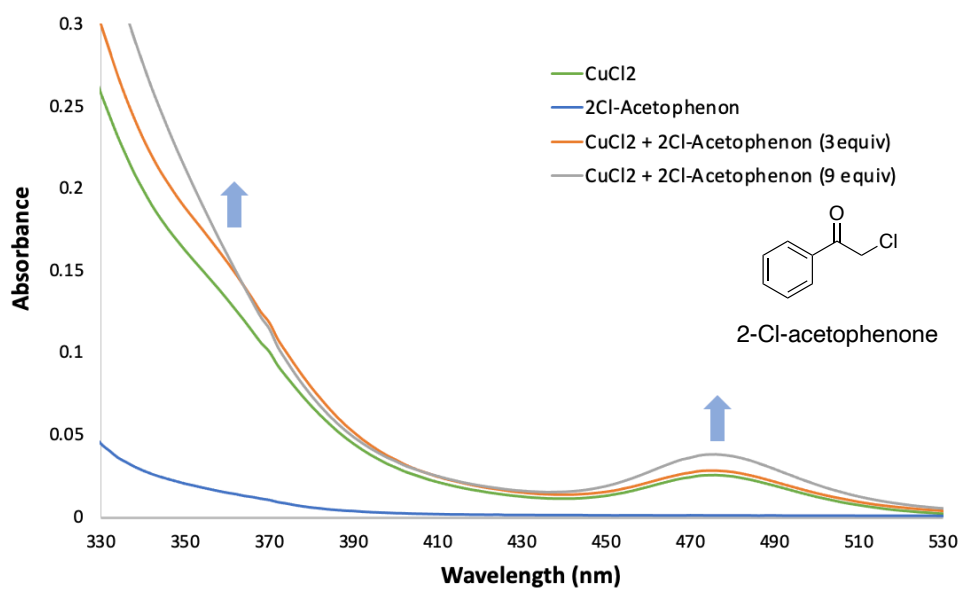
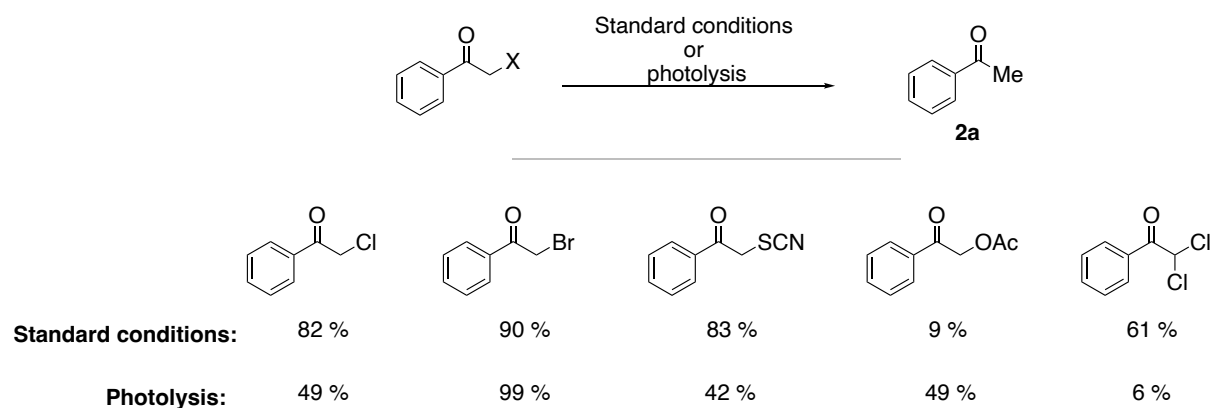


Figure 21: Absorbance variation of copper-2-chloroacetophenone complex

11. Reductive dehalogenation:

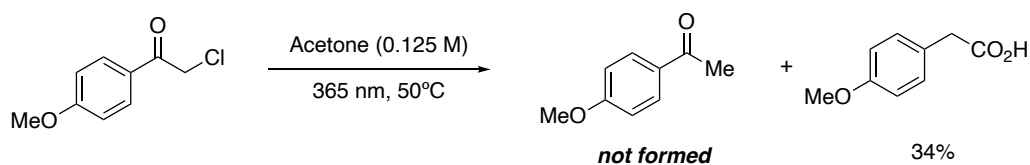
Procedure under standard conditions: The reaction was performed following G.P.1 using α -substituted acetophenone instead of styrene.

Procedure of the photolysis reactions: In an oven dried vial, 2-chloroacetophenone (0.25 mmol) was diluted in acetone (2 mL). The vial was charged with a stirring bar, capped with a rubber septum and bubbled with nitrogen. The reaction was then irradiated at 365 nm for 16 hours at 50°C. Afterwards, the reaction was concentrated in *vacuo*, charged with tetrachloroethane (^1H -NMR internal standard), dissolved in CDCl_3 and added directly to an NMR tube for quantitative analysis.

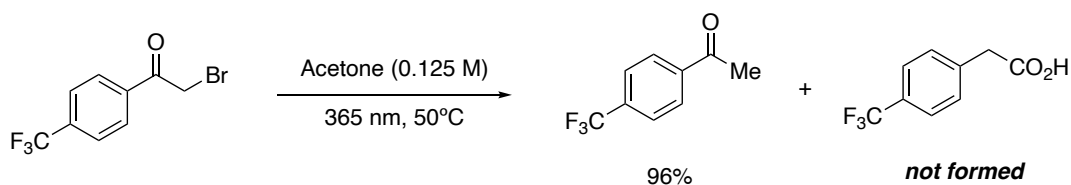
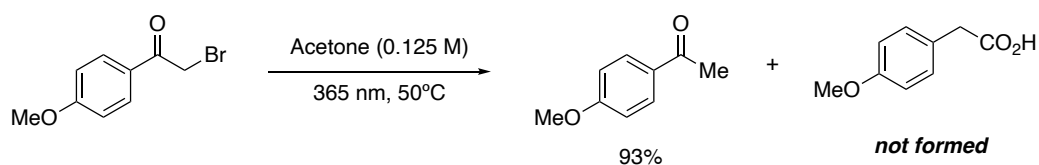


Reductive dehalogenation: case of substituted styrenes

We were interested to evaluate the substituents effects on the homolysis of 2-haloacetophenone derivatives to understand why certain electron rich styrenes do not afford the desired acetophenone when TCCA was used.

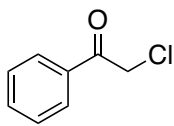


In the case of 2-bromoacetophenones, the outcome is independent of the electronics involved in the phenyl ring and let to the corresponding acetophenones selectively.



12. Cyclic voltammetry analysis:

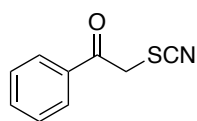
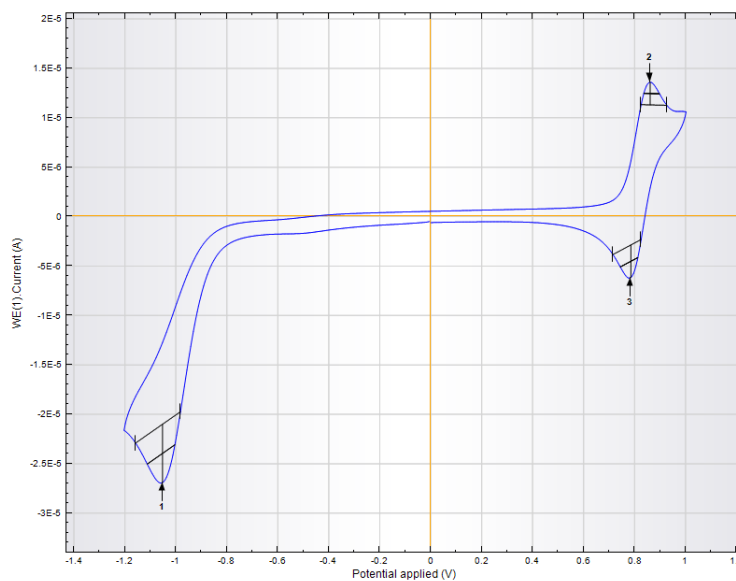
Cyclic voltammetry was measured on a three-electrode potentiostat galvanostat PGSTAT302N from Metrohm Autolab using a glassy carbon working electrode (3mm in diameter), a platinum wire as counter electrode and a silver wire as a reference electrode. The cyclic voltammograms were recorded in acetone with NBu_4BF_4 as electrolyte using ferrocene (Fc/Fc^+) as an internal standard. Measurements were carried out at room temperature with a scan rate of 50 mV/s. Potentials vs SCE were calculated using the formula: $E_{\text{SCE}} = E_{\text{Fc}/\text{Fc}^+} + 0.38 \text{ V}$.



2-chloro-1-phenylethan-1-one

$E_{\text{red}} = -1.50 \text{ V vs SCE}$

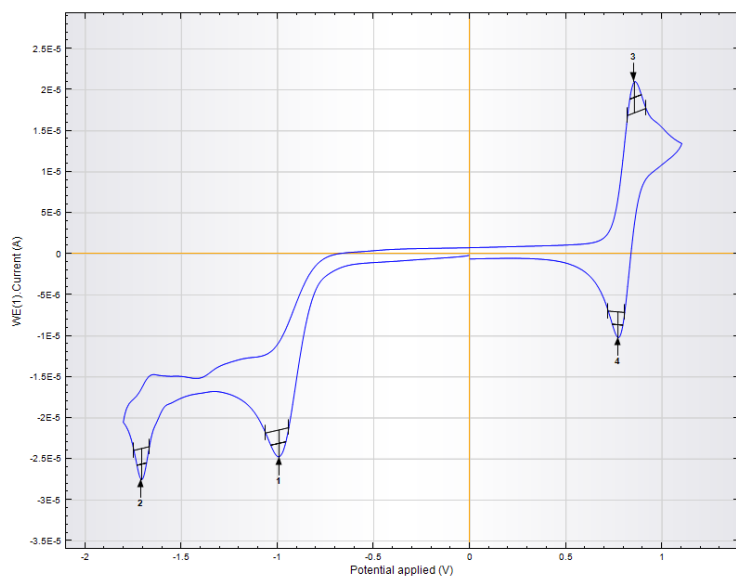
Index	Peak position vs Ferrocene
1	-1.0524
2	0.86105
3	0.78552

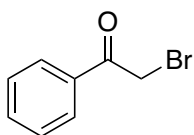


1-phenyl-2-thiocyanatoethan-1-one

$E_{\text{red}} = -1.43 \text{ V vs SCE}$

Index	Peak position vs Ferrocene
1	-0.99197
2	-1.707
3	0.85602
4	0.77042



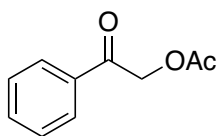
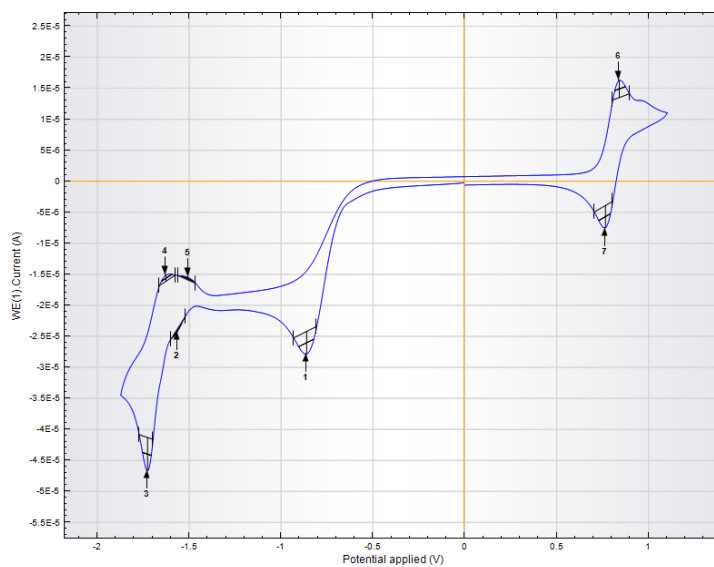


2-bromo-1-phenylethan-1-one

$E_{\text{red}} = -1.28 \text{ V vs SCE}$

Index **Peak position vs Ferrocene**

1	-0.86105
2	-1.566
3	-1.7271
4	-1.6264
5	-1.5056
6	0.84091
7	0.76538

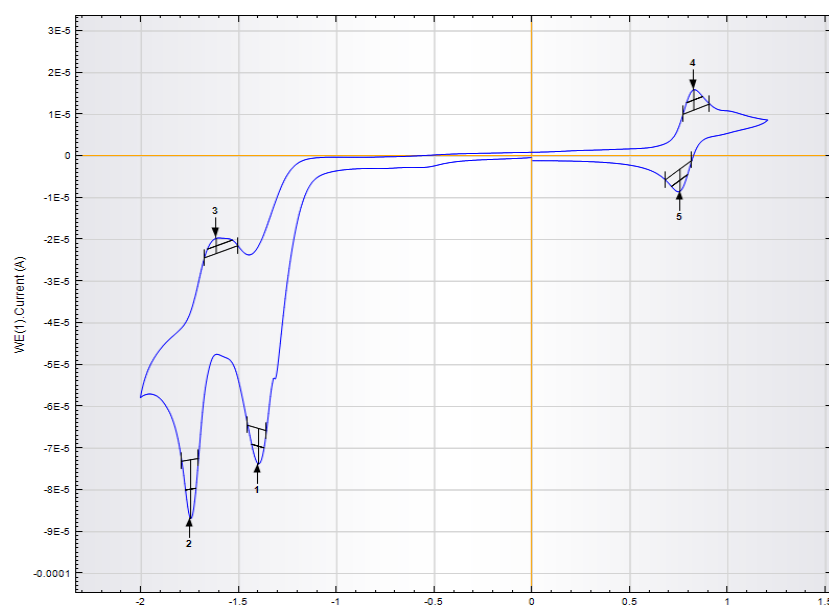


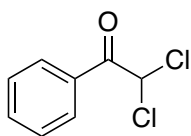
2-oxo-2-phenylethyl acetate

$E_{\text{red}} = -1.81 \text{ V vs SCE}$

Index **Peak position vs Ferrocene**

1	-1.3998
2	-1.7473
3	-1.6164
4	0.82581
5	0.75531



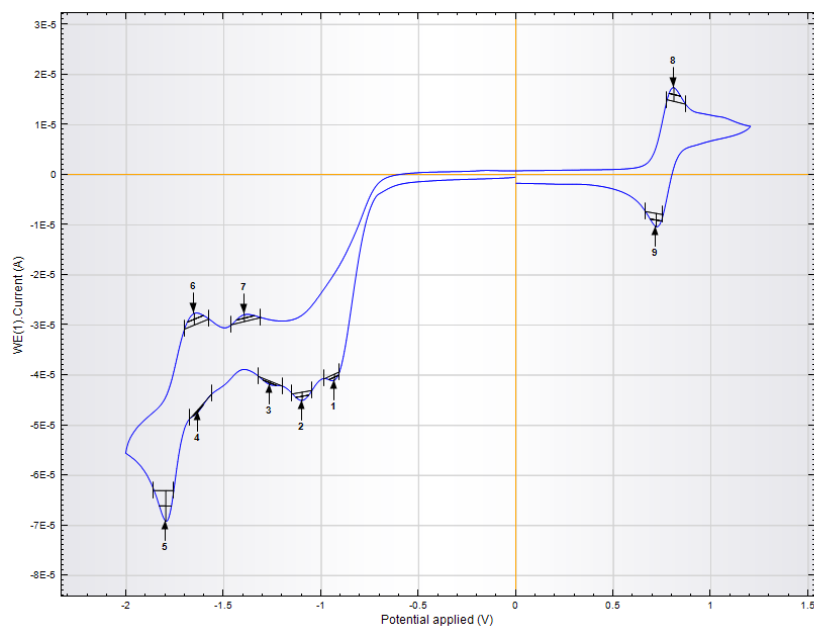


2,2-dichloro-1-phenylethan-1-one

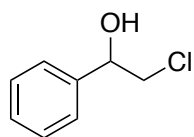
$E_{\text{red}} = -1.32 \text{ V vs SCE}$

Index Peak position vs Ferrocene

1	-0.93155
2	-1.0977
3	-1.2639
4	-1.6315
5	-1.7976
6	-1.6516
7	-1.3948
8	0.8107
9	0.72006

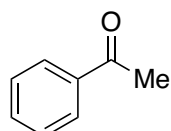


13. Spectral data:



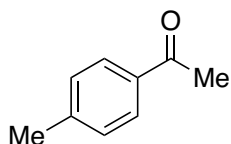
2-chloro-1-phenylethan-1-ol (**IIa**)

Following G.P.1 using styrene (**1a**) (52.1 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone in dark for 16 hours at room temperature yielded 75% of 2-chloro-1-phenylethan-1-ol (**IIa**) (58.5 mg, 0.375 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.41-7.29 (m, 5H), 4.88 (dd, *J*=8.61 Hz, 1H), 3.76-3.60 (m, 2H), 2.80 (s, 1H). ¹³C-NMR (75 MHz, CDCl₃): 140.03, 128.71, 128.50, 126.13, 74.10, 50.85. HRMS (EI) *m/z* calculated for C₈H₉ClONa (M⁺) 179.0239 found 179.0241. IR (neat, cm⁻¹): 3367, 2005, 2989, 1275, 1260, 767



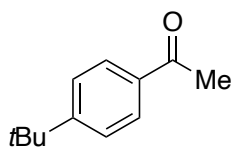
Acetophenone (**2a**)

Following G.P.1 using styrene (**1a**) (52.1 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom using a 365 nm LED for 16 hours at 50°C yielded 85% of acetophenone (**2a**) (51.1 mg, 0.425 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.90 (d, 2H), 7.50 (t, 1H), 7.39 (t, 2H), 2.53 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 197.97, 137.08, 133.06, 128.54, 128.26, 26.51. HRMS (EI) *m/z* calculated for C₈H₈O (M⁺) 120.0569 found 120.0572. IR (neat, cm⁻¹): 1681, 1599, 1449, 1356, 1263, 1177, 1077, 1025, 954, 760, 689.



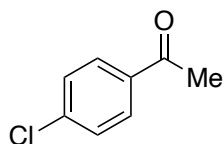
1-(*p*-tolyl)ethan-1-one (**2b**)

Following G.P.2 using 4-methylstyrene (**1b**) (59.1 mg, 0.5 mmol, 1 equiv), tribromoisocyanuric acid (TBICA) (183mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at room temperature yielded 44% of 1-(*p*-tolyl)ethan-1-one (**2b**) (29.5 mg, 0.22 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.82 (d, 2H), 7.21 (d, 2H), 2.53 (s, 3H), 2.37 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 197.79, 143.86, 134.70, 129.24, 128.44, 26.51, 21.62. HRMS (EI) *m/z* calculated for C₉H₁₀O (M⁺) 134.0726 found 134.0729. IR (neat, cm⁻¹): 1677, 1606, 1405, 1356, 1267, 1181, 1017, 954, 812, 711, 670.



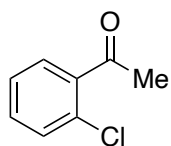
1-(4-(*tert*-butyl)phenyl)ethan-1-one (**2c**)

Following G.P.2 using 4-*tert*-butylstyrene (**1c**) (80.13 mg, 0.5 mmol, 1 equiv), tribromoisocyanuric acid (TBICA) (183mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at room temperature yielded 58% of 1-(4-(*tert*-butyl)phenyl)ethan-1-one (**2c**) (51.1 mg, 0.29 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.89 (d, 2H), 7.46 (d, 2H), 2.56 (s, 3H), 1.32 (s, 9H). ¹³C-NMR (75 MHz, CDCl₃): 197.81, 156.81, 134.63, 128.32, 125.52, 35.11, 31.11, 26.56. HRMS (EI) *m/z* calculated for C₁₂H₁₆O (M⁺) 176.1201 found 176.1195. IR (neat, cm⁻¹): 2963, 2870, 1681, 1606, 1405, 1356, 1267, 1192, 1110, 1013, 957, 834



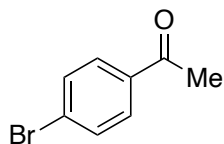
1-(4-chlorophenyl)ethan-1-one (2d)

Following G.P.1 using 4-chlorostyrene (**1d**) (69.3 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 60% of 1-(4-chlorophenyl)ethan-1-one (**2d**) (46.4 mg, 0.3 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.86 (d, 2H), 7.39 (d, 2H), 2.55 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 196.79, 139.54, 135.45, 129.73, 128.88, 26.55. HRMS (EI) m/z calculated for C₈H₇OCl (M⁺) 154.0179 found 154.0176. IR (neat, cm⁻¹): 1684, 1587, 1394, 1356, 1256, 1092, 1013, 954, 820, 760.



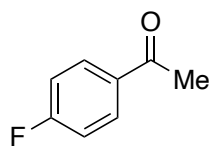
1-(2-chlorophenyl)ethan-1-one (2e)

Following G.P.1 using 2-chlorostyrene (**1e**) (69.3 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 42% of 1-(2-chlorophenyl)ethan-1-one (**2e**) (32.5 mg, 0.21 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.52 (d, 1H), 7.41-7.33 (m, 2H), 7.32-7.27 (m, 1H), 2.62 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 139.16, 132.01, 131.31, 130.66, 129.41, 126.96, 30.72. HRMS (EI) m/z calculated for C₈H₇OCl (M⁺) 154.0179 found 154.0184. IR (neat, cm⁻¹): 1692, 1591, 1468, 1431, 1356, 1274, 1237, 1095, 1043, 961, 752, 670.



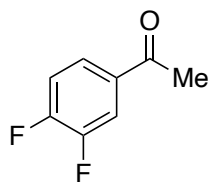
1-(4-bromophenyl)ethan-1-one (**2f**)

Following G.P.2 using 4-bromostyrene (**1f**) (91.6 mg, 0.5 mmol, 1 equiv), tribromoisocyanuric acid (TBICA) (183mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at room temperature yielded 67% of 1-(4-bromophenyl)ethan-1-one (**2f**) (66.7 mg, 0.335 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.81 (d, 2H), 7.60 (d, 2H), 2.58 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 197.03, 135.86, 131.92, 129.87, 128.33, 26.56. HRMS (EI) m/z calculated for C₈H₇OBr (M⁺) 197.9674 found 197.9678. IR (neat, cm⁻¹): 1677, 1584, 1479, 1423, 1394, 1356, 1263, 1078, 1006, 957, 820, 745



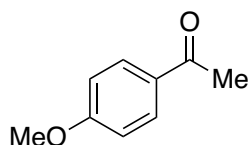
1-(4-fluorophenyl)ethan-1-one (**2g**)

Following G.P.1 using 4-fluorostyrene (**1g**) (61.1 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 70% of 1-(4-fluorophenyl)ethan-1-one (**2g**) (48.35 mg, 0.35 mg) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (400 MHz, CDCl₃): 7.91 (q, 2H), 7.05 (t, 2H), 2.52 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃): 196.38, 166.98, 164.45, 133.59 (d, *J*^I = 3Hz), 130.91 (d, *J*^I = 9Hz), 115.58 (d, *J*^I = 22Hz), 26.43. ¹⁹F (282 MHz, CDCl₃): -105.94 (s, 1F). HRMS (EI) m/z calculated for C₈H₇OF (M⁺) 138.0475 found 138.0477. IR (neat, cm⁻¹): 1681, 1595, 1505, 1408, 1356, 1263, 1226, 1155, 1103, 957, 834.



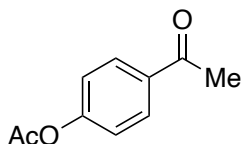
1-(3,4-difluorophenyl)ethan-1-one (2h)

Following G.P.1 using 3,4-difluorostyrene (**1h**) (70.1 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 71% of 1-(3,4-difluorophenyl)ethan-1-one (**2h**) (55.4 mg, 0.355 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (400 MHz, CDCl₃): 7.81-7.70 (m, 2H), 7.30-7.20 (m, 1H), 2.58 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃): 195.35, 153.22 (dd, *J*^I = 14Hz, *J*^B = 329Hz), 150.69 (dd, *J*^I = 14 Hz, *J*^B = 330Hz), 134.22 (t, *J*^I = 4Hz), 125.36 (q, *J*^I = 4Hz, *J*^B = 8Hz), 117.42 (d, *J*^I = 18Hz), 26.35. ¹⁹F (282 MHz, CDCl₃): -130.54 (s, 1F), -136.79 (s, 1F). HRMS (EI) *m/z* calculated for C₈H₆OF₂ (M⁺) 156.0381 found 156.0377. IR (neat, cm⁻¹): 1688, 1610, 1513, 1423, 1360, 1282, 1185, 1114, 898, 820, 775.



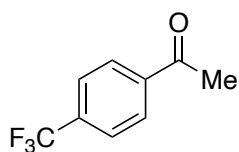
1-(4-methoxyphenyl)ethan-1-one (2i)

Following G.P.2 using 4-methoxystyrene (**1i**) (67.1 mg, 0.5 mmol, 1 equiv), tribromoisocyanuric acid (TBCA) (183mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at room temperature yielded 36% of 1-(4-methoxyphenyl)ethan-1-one (**2i**) (27.0 mg, 0.18 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.93 (d, 2H), 6.93 (d, 2H), 3.87 (s, 3H), 2.56 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 196.80, 163.51, 130.62, 130.39, 113.71, 55.49, 26.37. HRMS (EI) *m/z* calculated for C₉H₁₀O₂ (M⁺) 150.0675 found 150.0676. IR (neat, cm⁻¹): 1666, 1595, 1505, 1416, 1356, 1244, 1174, 1110, 1021, 954, 831.



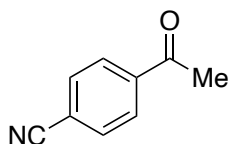
4-acetylphenyl acetate (**2j**)

Following G.P.1 using 4-acetoxystyrene (**1j**) (81.1 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 62% of 4-acetylphenyl acetate (**2j**) (55.2 mg, 0.31 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.99 (d, 2H), 7.19 (d, 2H), 2.59 (s, 3H), 2.32 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 196.84, 168.86, 154.36, 134.75, 129.95, 121.78, 26.60, 21.15. HRMS (EI) m/z calculated for C₁₀H₁₀O₃ (M⁺) 178.0624 found 178.0622. IR (neat, cm⁻¹): 1759, 1681, 1599, 1505, 1412, 1360, 1263, 1185, 1013, 849.



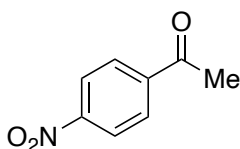
1-(4-(trifluoromethyl)phenyl)ethan-1-one (**2k**)

Following G.P.1 using 4-trifluoromethylstyrene (**1k**) (86.1 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 88% of 1-(4-(trifluoromethyl)phenyl)ethan-1-one (**2k**) (82.8 mg, 0.44 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (400 MHz, CDCl₃): 8.05 (d, 2H), 7.73 (d, 2H), 2.64 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃): 196.98, 139.71, 134.44 (q, *J*¹ = 33Hz, *J*³ = 68Hz), 128.64, 127.70 (q, *J*¹ = 4Hz, *J*³ = 7Hz), 124.97, 122.26, 26.79. ¹⁹F (282 MHz, CDCl₃): -63.63 (s, 3F). HRMS (EI) m/z calculated for C₉H₇OF₃ (M⁺) 188.0443 found 188.0447. IR (neat, cm⁻¹): 1692, 1513, 1408, 1323, 1263, 1166, 1125, 1058, 1013, 961, 834, 719.



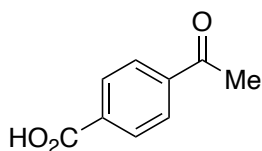
4-acetylbenzonitrile (**2l**)

Following G.P.1 using 4-cyanostyrene (**1l**) (64.6 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 45% of 4-acetylbenzonitrile (**2l**) (32.7 mg, 0.225 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 8.04 (d, 2H), 7.77 (d, 2H), 2.64 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 196.54, 139.96, 132.55, 128.73, 117.95, 116.46, 26.79. HRMS (EI) m/z calculated for C₉H₇NO (M⁺) 145.0522 found 145.0520. IR (neat, cm⁻¹): 2228, 1684, 1602, 1561, 1401, 1353, 1259, 954, 827.



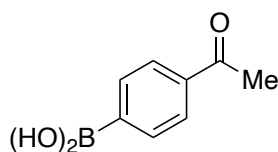
1-(4-nitrophenyl)ethan-1-one (**2m**)

Following G.P.2 using 4-nitrostyrene (**1m**) (74.6 mg, 0.5 mmol, 1 equiv), tribromoisocyanuric acid (TBICA) (183mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at room temperature yielded 26% of 1-(4-nitrophenyl)ethan-1-one (**2m**) (21.5 mg, 0.13 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 8.30 (d, 2H), 8.10 (d, 2H), 2.67 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 196.35, 150.38, 141.40, 129.34, 123.89, 27.03. HRMS (EI) m/z calculated for C₈H₇NO₃ (M⁺) 165.0420 found 165.0424. IR (neat, cm⁻¹): 3362, 3108, 1692, 1606, 1520, 1431, 1341, 1319, 1244, 1103, 1006, 961, 857, 745, 693.



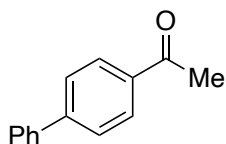
4-acetylbenzoic acid (**2n**)

Following G.P.1 using 4-vinylbenzoic acid (**1n**) (74.1 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 55% of 4-acetylbenzoic acid (**2n**) (45.1 mg, 0.275 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, DMSO-d₆): 13.31 (s, 1H), 8.04 (s, 4H), 2.61 (s, 3H). ¹³C-NMR (75 MHz, DMSO-d₆): 198.16, 167.11, 140.27, 134.96, 130.00, 128.77, 27.45. HRMS (EI) m/z calculated for C₉H₈O₃ (M⁺) 164.0468 found 164.0463. IR (neat, cm⁻¹): 2810, 2661, 2542, 1669, 1569, 1423, 1364, 1289, 1248, 1118, 931, 868, 771, 730, 693.



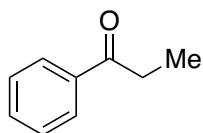
(4-acetylphenyl)boronic acid (**2o**)

Following G.P.1 using 4-vinylphenylboronic acid (**1o**) (74 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 59% of (4-acetylphenyl)boronic acid (**2o**) (48.4 mg, 0.295 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, DMSO-d₆): 8.28 (s, 2H), 7.90 (s, 4H), 2.58 (s, 3H). ¹³C-NMR (75 MHz, DMSO-d₆): 198.72, 138.30, 134.70, 127.42, 27.28. HRMS (ESI) m/z calculated for C₈H₉BO₃ (M+H⁺) 165.0722 found 165.0722. IR (neat, cm⁻¹): 3425, 3198, 1662, 1505, 1401, 1334, 1271, 1170, 1170, 1103, 1006, 834, 745, 700.



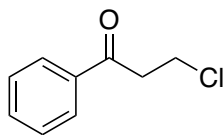
1-([1,1'-biphenyl]-4-yl)ethan-1-one (**2p**)

Following G.P.1 using 4-vinyl biphenyl (**1p**) (90.13 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 60% of 1-([1,1'-biphenyl]-4-yl)ethan-1-one (**2p**) (58.9 mg, 0.3 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 8.03 (d, 2H), 7.69 (d, 2H), 7.63 (d, 2H), 7.51-7.36 (m, 3H), 2.64 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 197.81, 145.82, 139.90, 135.87, 128.97 (d, *J'* = 3Hz), 128.27, 127.28 (d, *J'* = 3Hz), 26.72. HRMS (EI) *m/z* calculated for C₁₄H₁₂O (M⁺) 196.0882 found 196.0881. IR (neat, cm⁻¹): 1677, 1599, 1356, 1259, 957, 834, 764, 719, 689.



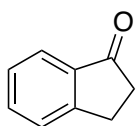
Propiophenone (**2q**)

Following G.P.1 using trans-β-methylstyrene (**1q**) (59.1 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 75% of propiophenone (**2q**) (50.31 mg, 0.375 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.92 (d, 2H), 7.50 (t, 1H), 7.40 (t, 1H), 2.94 (q, 2H), 1.18 (t, 3H). ¹³C-NMR (75 MHz, CDCl₃): 200.77, 136.89, 132.88, 128.55, 127.96, 31.75, 8.22. HRMS (EI) *m/z* calculated for C₉H₁₀O (M⁺) 134.0726 found 134.0729. IR (neat, cm⁻¹): 1684, 1595, 1449, 1349, 1218, 1077, 1013, 950, 745, 689.



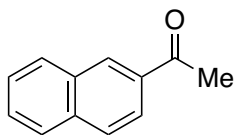
3-chloro-1-phenylpropan-1-one (**2r**)

Following G.P.1 using cinnamyl chloride (**1r**) (76.3 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 40% of 3-chloro-1-phenylpropan-1-one (**2r**) (33.7 mg, 0.2 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.96 (d, 2H), 7.59 (t, 1H), 7.48 (t, 2H), 3.93 (t, 2H), 3.46 (t, 2H). ¹³C-NMR (75 MHz, CDCl₃): 196.75, 136.38, 133.60, 128.79, 128.09, 41.31, 38.72. HRMS (EI) m/z calculated for C₉H₉OC₁ (M⁺) 168.0336 found 168.0335. IR (neat, cm⁻¹): 1677, 1595, 1446, 1353, 1267, 1200, 1066, 976, 741, 715.



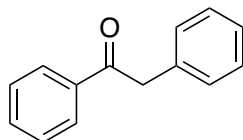
2,3-dihydro-1H-inden-1-one (**2s**)

Following G.P.1 using indene (**1s**) (58.1 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 26% of 2,3-dihydro-1H-inden-1-one (**2s**) (17.2 mg, 0.13 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.75 (d, 1H), 7.58 (t, 1H), 7.47 (d, 1H), 7.36 (t, 1H), 3.14 (t, 2H), 2.71-2.64 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): 207.13, 155.20, 137.11, 134.63, 127.31, 126.73, 123.74, 36.25, 25.83. HRMS (EI) m/z calculated for C₉H₈O (M⁺) 132.0569 found 132.0572. IR (neat, cm⁻¹): 1699, 1584, 1394, 1326, 1274, 1241, 1148, 1032, 823, 767.



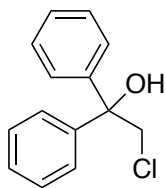
1-(naphthalen-2-yl)ethan-1-one (2t)

Following G.P.2 using 2-vinylnaphthalene (**1t**) (77.1 mg, 0.5 mmol, 1 equiv), tribromoisocyanuric acid (TBCA) (183mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at room temperature yielded 27% of 1-(naphthalen-2-yl)ethan-1-one (**2t**) (23.0 mg, 0.135 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 8.46 (s, 1H), 8.05-8.01 (m, 1H), 7.96 (d, 1H), 7.91-7.85 (m, 2H), 7.63-7.51 (m, 2H), 2.72 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): 198.16, 135.62, 134.51, 132.54, 130.24, 129.59, 128.51, 128.46, 127.82, 126.82, 123.93, 26.74. HRMS (EI) m/z calculated for C₁₂H₁₀O (M+H⁺) 171.0809 found 171.0804. IR (neat, cm⁻¹): 1669, 1364, 1267, 1222, 1189, 868, 834, 752



1,2-diphenylethan-1-one (2u)

Following G.P.1 using trans-stilbene (**1u**) (90.12 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 30% of 1,2-diphenylethan-1-one (**2u**) (29.4 mg, 0.15 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 8.02 (d, 2H), 7.56 (t, 1H), 7.46 (t, 2H), 7.37-7.22 (m, 5H), 4.29 (s, 2H). ¹³C-NMR (75 MHz, CDCl₃): 197.66, 136.63, 134.58, 133.21, 129.51, 128.69 (t, *J*^I = 4Hz), 126.94, 45.54. HRMS m/z calculated for C₁₄H₁₂O (M⁺) 198.0882 found 196.0882. IR (neat, cm⁻¹): 1740, 1681, 1580, 1446, 1334, 1215, 1073, 987, 752, 685.



2-chloro-1,1-diphenylethan-1-ol (2w):

Following G.P.1 using 1,1-diphenylethylene (**1w**) (90.12 mg, 0.5 mmol, 1 equiv), trichloroisocyanuric acid (TCCA) (116.2 mg, 0.5 mmol, 1.0 equiv), copper (II) chloride (3.36 mg, 0.025 mmol, 5 mol%) and potassium bromide (5.95 mg, 0.05 mmol, 10 mol%), water (144 mg, 8.0 mmol, 16.0 equiv) and trifluoroacetic acid (114 mg, 1.0 mmol, 2.0 equiv) in 4 mL of acetone irradiated from the bottom side by a 365 nm LED for 16 hours at 50°C yielded 53% of 2-chloro-1,1-diphenylethan-1-ol (**2w**) (61.67 mg, 0.265 mmol) after flash chromatography on silica (hexanes : EtOAc). ¹H-NMR (300 MHz, CDCl₃): 7.46 (d, 4H), 7.40-7.27 (m, 6H), 4.21 (s, 2H), 3.18 (s, 1H). ¹³C-NMR (75 MHz, CDCl₃): 143.28, 128.43, 127.77, 126.43, 126.11, 77.90, 53.26. HRMS (ESI) m/z calculated for C₁₄H₁₃ClO (M⁺) 232.0654 found 232.0660. IR (neat, cm⁻¹): 3548, 3060, 3026, 2963, 1599, 1490, 1446, 1334, 1267, 1166, 1062, 1010, 752, 723, 693.

Experimental section of Chapter 4

1. Absorption and emission measurements:

UV-Vis measurements were conducted using a SPECTRORECORD 200 PLUS spectrophotometer by analytikjena, employing a Macro cell type 110-QS quartz cuvette with a PTFE stopper (Hellma Analytics quartz cuvette, 10×10 mm, 3.5 mL).

The measurements were recorded using dry THF as a solvent.

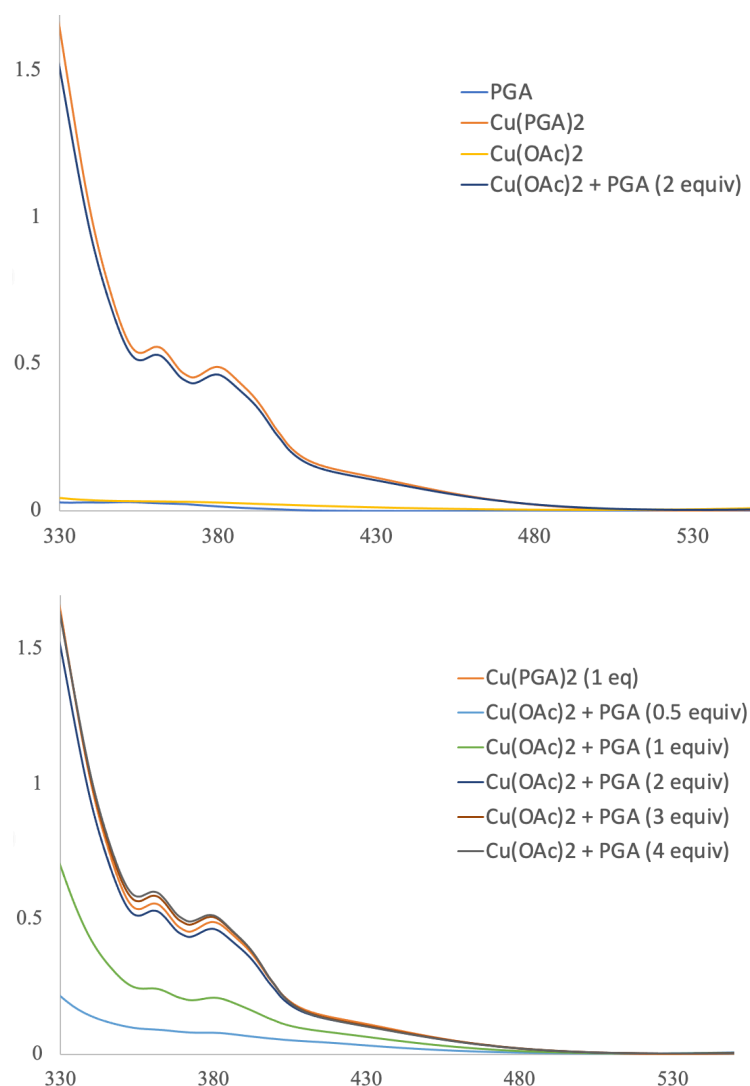


Figure 22: UV-vis spectra of Cu(PGA)₂ in different added amounts of phenylglyoxylic acid

The emission spectra of Cu(PGA)₂ was recorded using through irradiation at the two absorption maxima, 362 nm and 380 nm respectively. These measurements were conducted using a HORIBA Fluoromax-4 from Horiba Scientific, employing a High Precision Cell 117100F-10-

40 quartz cuvette with a screw cap (Hellma Analytics quartz cuvette, dimensions: 10×10 mm, capacity: 3.5 mL)

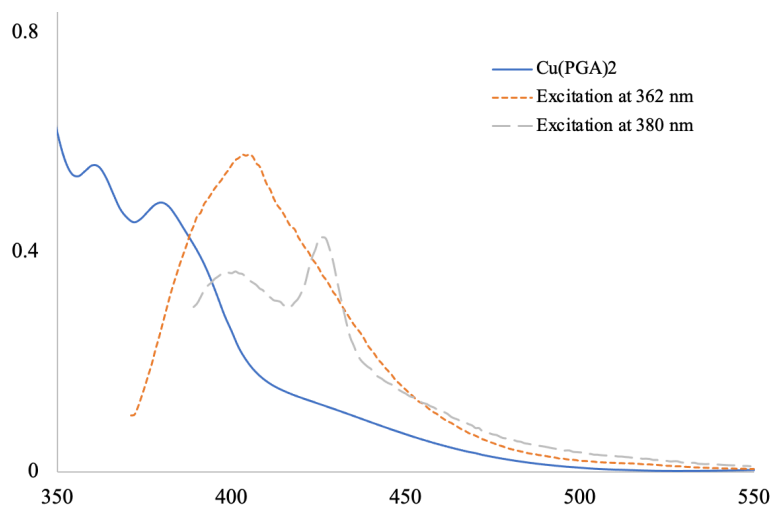


Figure 23: Emission spectra of the Cu(PGA)₂ complex

2. Fluorescence Lifetime measurement:

The luminescence lifetime was recorded in dry solvents using a quartz cuvette (1×1 cm) with septum screw cap. The cuvette was degassed *in vacuo* and filled with nitrogen before the stock solution of the copper complex was injected. For excitation of the sample, a 370 nm LED was used and an optical longpass filter (cut-on wavelength 399 nm) was installed before the detection unit. The measurement time range was set to 100 ns. The experimental data were fitted with a mono-exponential function.

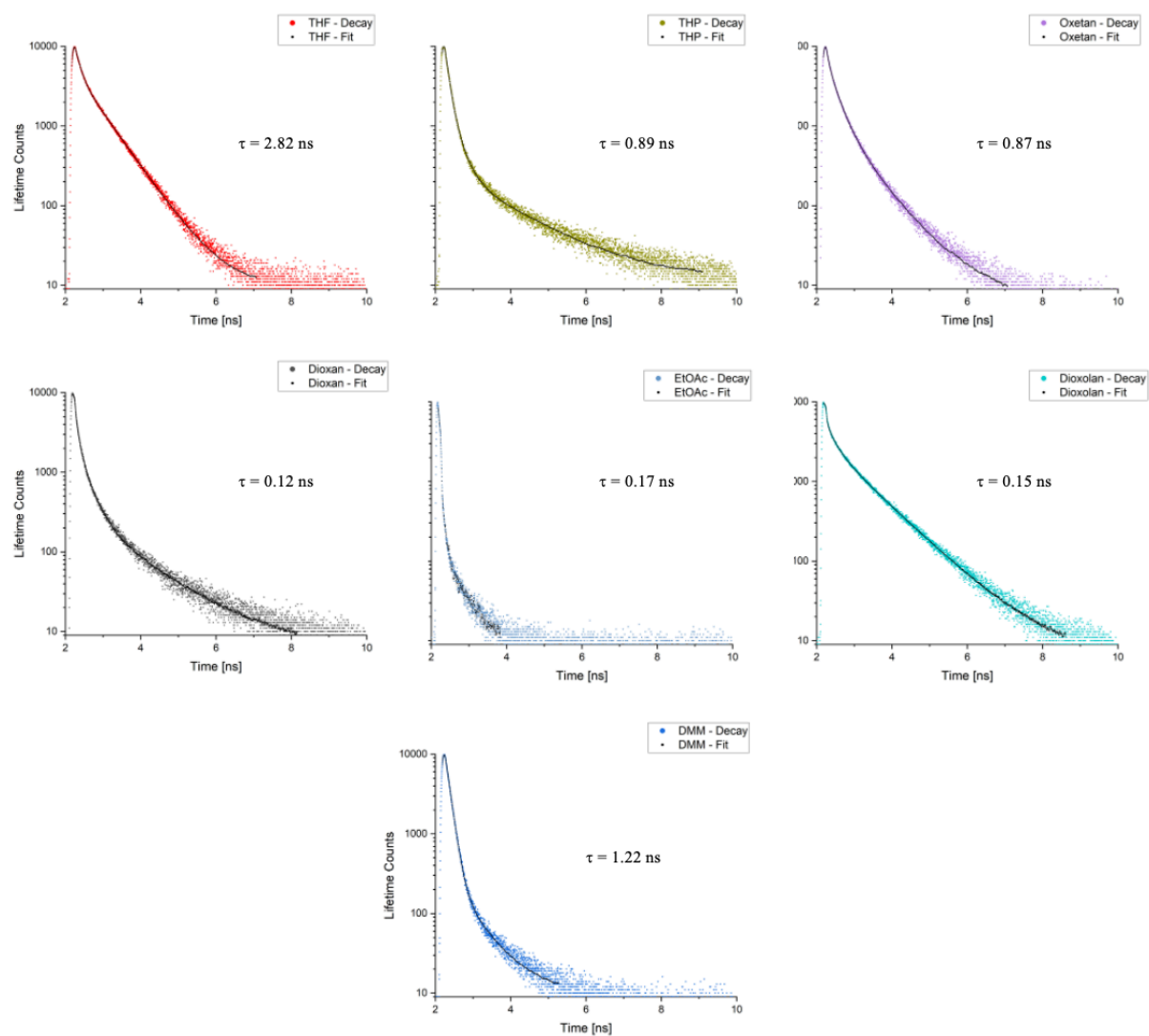
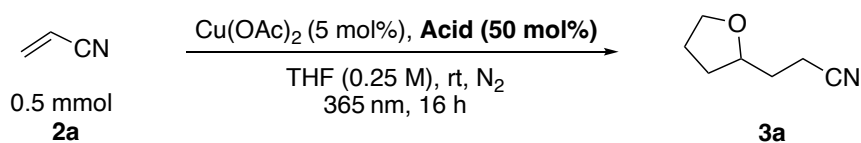


Figure 24: Fluorescence lifetime measurement of Cu(PGA)_2 in different solvents.

3. Reaction optimization:

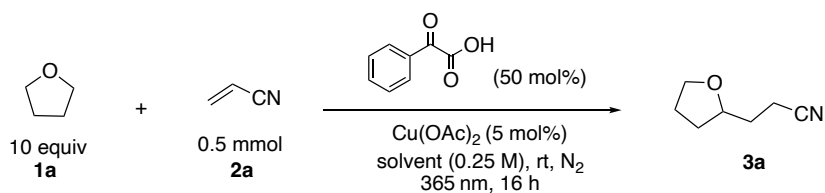
Acid screening:



Entry	Conditions	Yield ^a (%)
1	Benzoic acid	< 5 %
2	Acetic acid	traces
3	Phenylglyoxylic acid	99%
4	(R)(-)-Mandelic acid	25%
5	Pyruvic acid	7 %
6	N,N-dimethyl oxamic acid	n.r.
7	Oxalic acid	n.r.
8	Sodium oxalate	n.r.

^aNMR yields using tetrachloroethane as internal standard, ^b using 20% of the acid

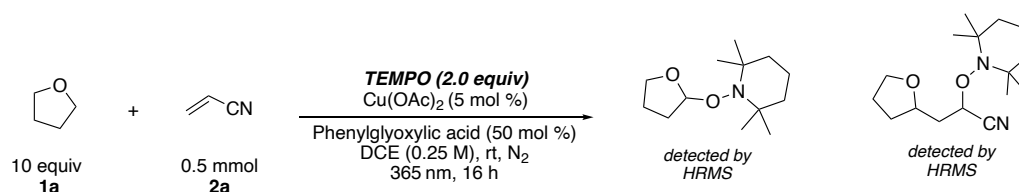
Solvent screening:



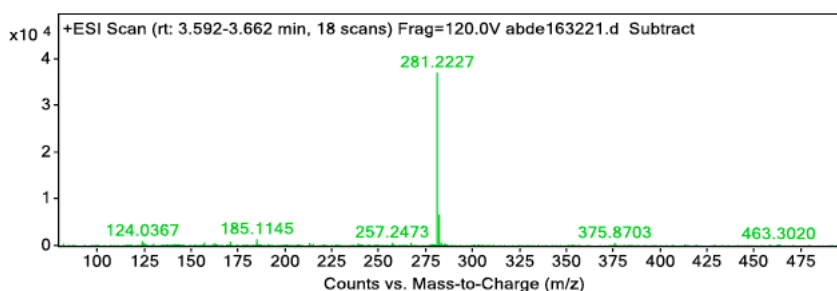
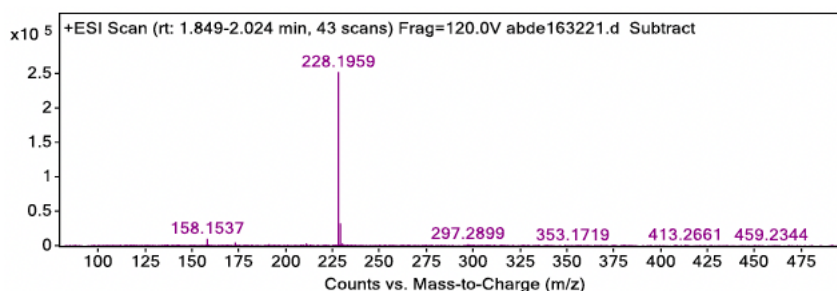
Entry	Conditions	Yield ^a (%)
1	MeCN	56 %
2	CHCl ₃	60%
3	DCE	99%
4	DCE, 5.0 equiv of THF	75%
5	DCE, 20% of acid	33%

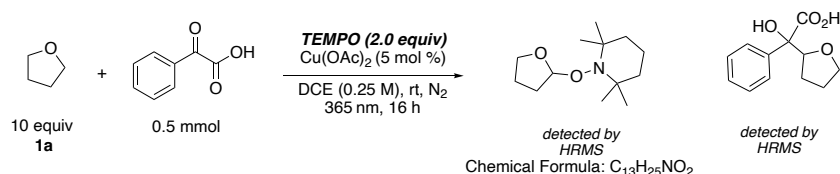
^aNMR yields using tetrachloroethane as internal standard

4. Radical trapping experiments:

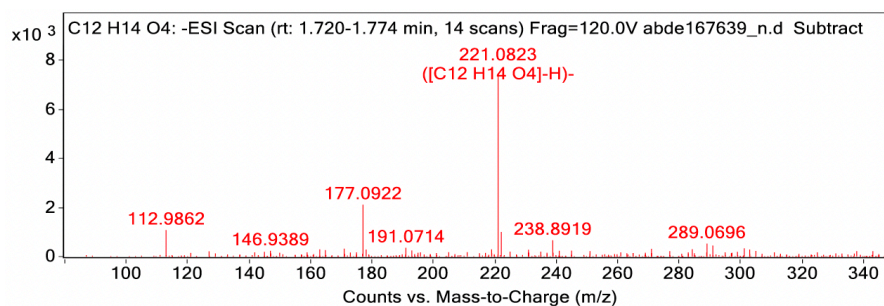
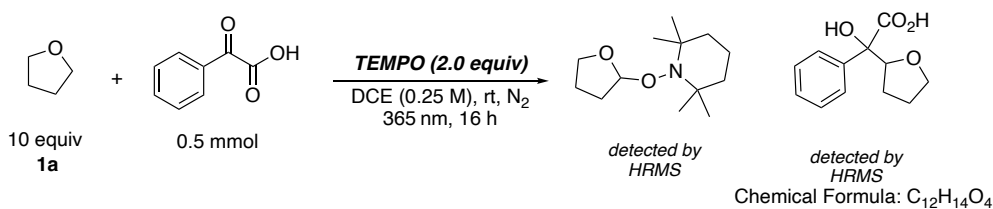
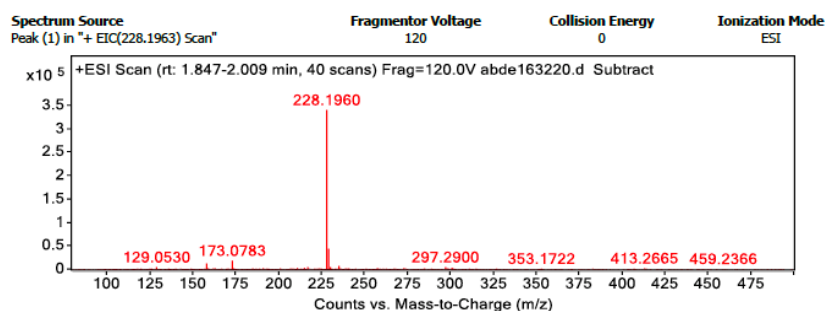


To a flame-dried glass vial equipped with a stirring bar was added copper (II) acetate (4.54 mg, 0.025 mmol, 0.05 equiv), phenylglyoxylic acid (75 mg, 0.5 mmol, 0.5 equiv), and TEMPO (156.5 mg, 1 mmol, 2.0 equiv) in 2 mL of DCE. The vial was capped with a rubber septum and the solution was degassed using nitrogen. Tetrahydrofuran (**1a**) (360.55 mg, 5 mmol, 10.0 equiv) and acrylonitrile (26.6 mg, 0.5 mmol, 1.0 equiv) were then injected into the mixture. The vial was then placed in a cooling block and irradiated from the bottom using a 365 nm LED (3W) for 16 hours at room temperature. After completion, an aliquot (100 μ L) was taken, diluted with DCM (500 μ L), dried over MgSO₄ and filtered. The remaining solution was passed through a syringe filter for further GC-MS analysis.

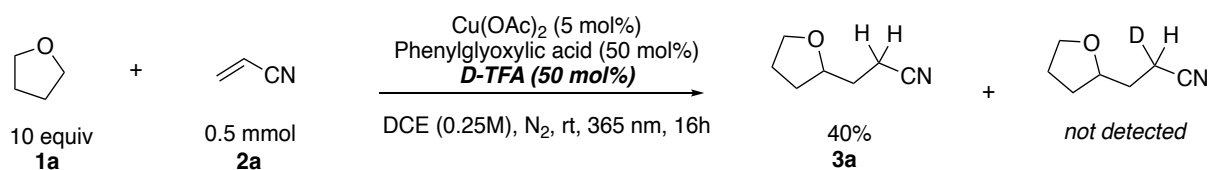




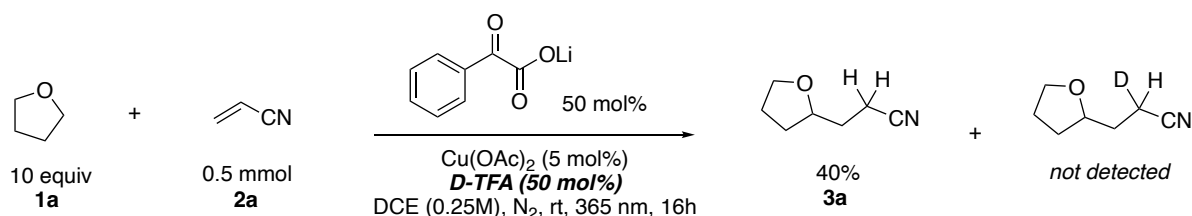
To a flame-dried glass vial equipped with a stirring bar was added copper (II) acetate (4.54 mg, 0.025 mmol, 0.05 equiv), phenylglyoxylic acid (75 mg, 0.5 mmol, 1.0 equiv), and TEMPO (156.5 mg, 1 mmol, 2.0 equiv) in 2 mL of DCE. The vial was capped with a rubber septum and the solution was degassed using nitrogen. Tetrahydrofuran (**1a**) (360.55 mg, 5 mmol, 10.0 equiv) was then injected into the mixture. The vial was then placed in a cooling block and irradiated from the bottom using a 365 nm LED (3W) for 16 hours at room temperature. After completion, an aliquot (100 μL) was taken, diluted with DCM (500 μL), dried over MgSO_4 and filtered. The remaining solution was passed through a syringe filter for further GC-MS analysis.



5. Labelling experiments:



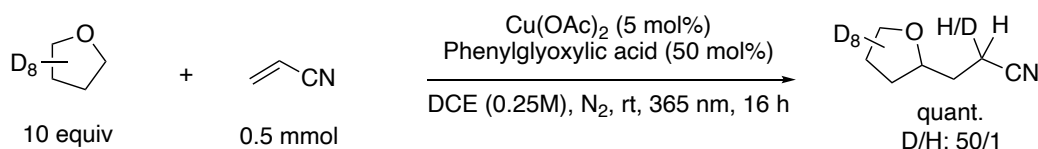
To a flame-dried glass vial equipped with a stirring bar was added copper (II) acetate (4.54 mg, 0.025 mmol, 0.05 equiv) and phenylglyoxylic acid (75 mg, 0.25 mmol, 0.5 equiv) in 2 mL of DCE. The vial was capped with a rubber septum and the solution was degassed using nitrogen. Tetrahydrofuran (**1a**) (360.55 mg, 5 mmol, 10.0 equiv), acrylonitrile (26.6 mg, 0.5 mmol, 1.0 equiv), and deuterated trifluoroacetic acid (29 mg, 0.25 mmol, 0.5 equiv) were then injected into the mixture. The vial was then placed in a cooling block and irradiated from the bottom using a 365 nm LED (3W) for 16 hours at room temperature. After completion, tetrachloroethane was added as an internal standard to the reaction mixture, an aliquot (100 μL) was taken, diluted with DCM (500 μL), dried over MgSO_4 and filtered. The remaining solution was passed through a syringe filter for further ^1H -NMR and GC-MS analyses.



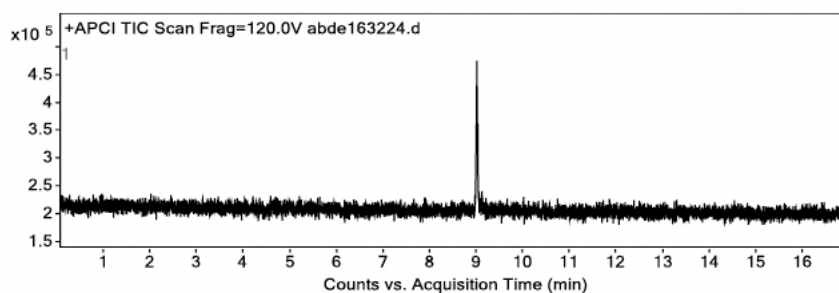
To a flame-dried glass vial equipped with a stirring bar was added copper (II) acetate (4.54 mg, 0.025 mmol, 0.05 equiv) and lithium phenylglyoxylate (78 mg, 0.25 mmol, 0.5 equiv) in 2 mL of DCE. The vial was capped with a rubber septum and the solution was degassed using nitrogen. Tetrahydrofuran (**1a**) (360.55 mg, 5 mmol, 10.0 equiv), acrylonitrile (26.6 mg, 0.5 mmol, 1.0 equiv), and deuterated trifluoroacetic acid (29 mg, 0.25 mmol, 0.5 equiv) were then injected into the mixture. The vial was then placed in a cooling block and irradiated from the bottom using a 365 nm LED (3W) for 16 hours at room temperature. After completion, tetrachloroethane was added as an internal standard to the reaction mixture, an aliquot (100

μL) was taken, diluted with DCM (500 μL), dried over MgSO_4 and filtered. The remaining solution was passed through a syringe filter for further ^1H -NMR and GC-MS analyses.

Note: In the absence of TFA, a complete shut-down of the reaction was observed.



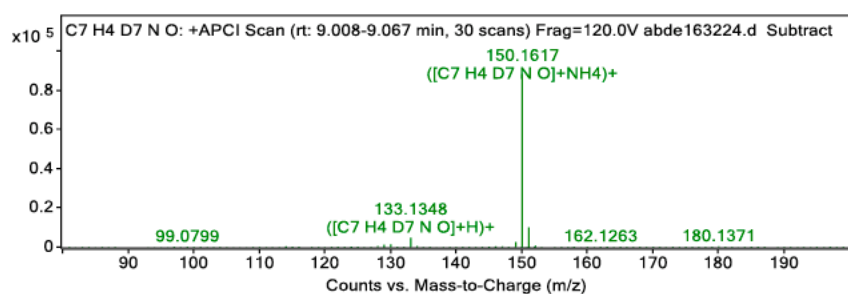
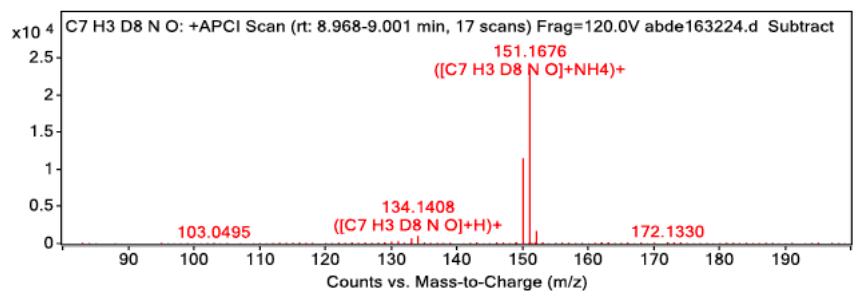
To a flame-dried glass vial equipped with a stirring bar was added copper (II) acetate (4.54 mg, 0.025 mmol, 0.05 equiv) and phenylglyoxylic acid (75 mg, 0.25 mmol, 0.5 equiv) in 2 mL of DCE. The vial was capped with a rubber septum and the solution was degassed using nitrogen. Tetrahydrofuran- D_8 (**1a**) (400.8 mg, 5 mmol, 10.0 equiv) and acrylonitrile (26.6 mg, 0.5 mmol, 1.0 equiv) were then injected into the mixture. The vial was then placed in a cooling block and irradiated from the bottom using a 365 nm LED (3W) for 16 hours at room temperature. After completion, tetrachloroethane was added as an internal standard to the reaction mixture, an aliquot (100 μL) was taken, diluted with DCM (500 μL), dried over MgSO_4 and filtered. The remaining solution was passed through a syringe filter for further ^1H -NMR and GC-MS analyses.



Integration Peak List

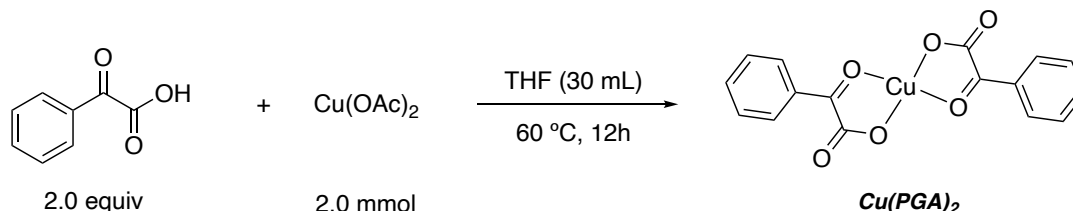
Peak	Start	RT	End	Height	Area	Area %
1	8.954	8.999	9.001	40327.11	47533.37	100
2	9.09	9.098	9.107	1516.69	875.22	1.84

Spectrum Source	Fragmentor Voltage	Collision Energy	Ionization Mode
Peak (1) in "+ EIC(151.1676) Scan"	120	0	APCI



6. Synthesis procedures:

Synthesis of Cu(PGA)₂:



A 100 mL round-bottom flask was charged with Cu(OAc)₂ (363.26 mg, 2 mmol, 1 equiv) in tetrahydrofuran (30 mL) and was sonicated in a water bath for 10 minutes then stirred at room temperature for 20 min. Phenylglyoxylic acid (601 mg, 4 mmol, 2 equiv) was then slowly added under magnetic stirring at room temperature. After the addition is complete, the solution turned dark green and was stirred for 2 hours at 60 °C. After completion, the solution was concentrated in a rotavap then dried in vacuo to afford a light-green powder in quantitative yield. HRMS (ESI) *m/z* calculated for C₁₆H₁₀CuO₆ [M]⁺ 360.9773 found 360.9790. IR (neat, cm⁻¹): 3067, 1677, 1617, 1412, 1230, 1181, 987, 846, 738, 678.

General procedure for the Giese addition:

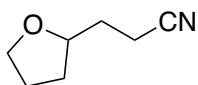
To a flame-dried glass vial equipped with a stirring bar was added copper (II) acetate (4.54 mg, 0.025 mmol, 0.05 equiv) and phenylglyoxylic acid (37.5 mg, 0.25 mmol, 0.5 equiv) in 2 mL of DCE. The vial was capped with a rubber septum and the solution was degassed using nitrogen. Ether (**1**) (5 mmol, 10.0 equiv), and the olefin (**2**) (0.5 mmol, 1.0 equiv) were consecutively injected into the mixture. The vial was then placed in a cooling block and irradiated from the bottom using a 365 nm LED (3W) for 16 hours at room temperature. The reaction was monitored by TLC; once the starting material consumed, the reaction mixture was diluted in DCM and was extracted three times using water. The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. The crude mixture was then purified by flash column chromatography of silica gel to deliver the product **3**.

General procedure for the sulfonylation:

To a flame-dried glass vial equipped with a stirring bar was added copper (II) acetate (4.54 mg, 0.025 mmol, 0.05 equiv), phenylglyoxylic acid (37.5 mg, 0.25 mmol, 0.5 equiv), and sulfonyl chloride (**5**) (0.5 mmol, 1.0 equiv) in 2 mL of DCE. The vial was capped with a rubber septum and the solution was degassed using nitrogen. Ether (**1**) (5 mmol, 10.0 equiv) was then injected into the mixture. The vial was placed in a cooling block and irradiated from the bottom using a 365 nm LED (3W) for 16 hours at room temperature. The reaction was monitored by TLC; once the starting material consumed, the reaction mixture was diluted in DCM and was extracted three times using water. The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. The crude mixture was then purified by flash column chromatography of silica gel to deliver the products **6**.

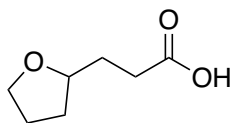
Note: For a better representation of the scope of this transformation, compounds (**6c**, **6f**, **6g**, **6k**, **6p**, **6q**, **6r**) were only detected in crude NMR and were not isolated.

7. Spectral data:



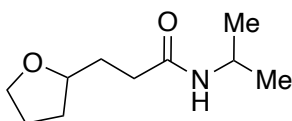
3-(Tetrahydrofuran-2-yl)propanenitrile (3a)

The compound **3a** was synthesized following the general procedure using tetrahydropyran (430.65 mg, 5.0 mmol, 10.0 equiv) and acrylonitrile (26.5 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 99% of **3a** (61.9 mg, 0.495 mmol) as a yellow oil. The characterization data was in accordance with literature.³⁰⁵ ¹H NMR (400 MHz, CDCl₃): 3.70-4.00 (m, 3H), 2.50 (m, 2H), 1.70-2.10 (m, 5H), 1.50 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 119.60, 77.00, 67.70, 31.10, 30.90, 25.60, 13.90.



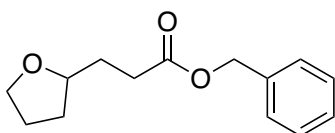
3-(tetrahydrofuran-2-yl)propanoic acid

The compound **3b** was synthesized following the general procedure using tetrahydropyran (430.65 mg, 5.0 mmol, 10.0 equiv) and acrylic acid (36.03 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 99% of **3b** (71.3 mg, 0.495 mmol) as a yellow oil. The characterization data was in accordance with literature.³⁰⁶ ¹H NMR (400 MHz, CDCl₃): 11.22 (s, 1H), 3.93-3.77 (m, 2H), 3.77-3.65 (m, 1H), 2.53-2.43 (m, 1H), 2.43-2.35 (m, 1H), 2.10-1.94 (m, 1H), 1.92-1.83 (m, 2H), 1.83-1.73 (m, 2H), 1.57-1.32 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 178.90, 78.10, 67.60, 31.10, 30.90, 30.20, 25.60.



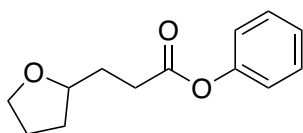
N-isopropyl-3-(tetrahydrofuran-2-yl)propanamide (3c)

The compound **3c** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and N-isopropylacrylamide (**2c**) (56.6 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 99% of **3c** (91.15 mg, 0.425 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): 5.89-5.69 (s, 1H), 4.06-3.96 (m, 1H), 3.83-3.74 (m, 2H), 3.70-3.63 (m, 1H), 2.30-2.11 (m, 2H), 1.99-1.90 (m, 1H), 1.88-1.78 (m, 3H), 1.73-1.63 (m, 1H), 1.49-1.39 (m, 1H), 1.10 (s, 3H), 1.08 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): 172.24, 78.60, 67.69, 67.52, 41.32, 33.80, 31.45, 31.33, 25.74, 22.79, 22.77. HRMS (EI) m/z calculated for C₁₀H₁₉NO₂ [M+H]⁺ 186.1494 found 186.1488. IR (neat, cm⁻¹): 3295, 2970, 2929, 2870, 1640, 1543, 1457, 1364, 1230, 1174, 1066, 916, 730, 700.



Benzyl 3-(tetrahydrofuran-2-yl)propanoate (**3d**)

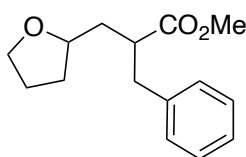
The compound **3d** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and benzyl acrylate (81.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 99% of **3d** (115.83 mg, 0.495 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃): 7.37-7.28 (m, 5H), 5.12 (s, 2H), 3.83 (m, 2H), 3.70 (q, 1H), 2.55-2.39 (m, 2H), 2.02-1.93 (m, 1H), 1.91-1.79 (m, 4H), 1.51-1.41 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 171.55, 136.21, 128.66, 128.31, 128.29, 78.28, 67.84, 66.31, 31.30, 30.81, 25.84. HRMS (EI) m/z calculated for C₁₄H₁₈O₃ [M]⁺ 234.1255 found 234.1250. IR (neat, cm⁻¹): 2952, 2873, 1736, 1453, 1349, 1259, 1159, 1073, 752, 700.



Phenyl 3-(tetrahydrofuran-2-yl)propanoate (**3e**)

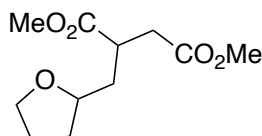
The compound **3e** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and phenylacrylate (74.1 mg, 0.5 mmol, 1.0 equiv). After

the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 99% of **3e** (108.95 mg, 0.495 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃): 7.39-7.34 (m, 2H), 7.23-7.19 (m, 1H), 7.10-7.06 (m, 2H), 3.97-3.84 (m, 2H), 3.78-3.71 (m, 1H), 2.76-2.59 (m, 2H), 2.08-2.00 (m, 1H), 2.00-2.86 (m, 4H), 1.57-1.49 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 172.27, 150.93, 129.52, 125.85, 121.72, 78.26, 67.92, 31.46, 31.38, 30.83, 25.90. HRMS (EI) m/z calculated for C₁₃H₁₆O₃ [M+H]⁺ 221.1177 found 221.1171. IR (neat, cm⁻¹): 2952, 2870, 1759, 1595, 1494, 1356, 1196, 1140, 1069, 924, 752, 693



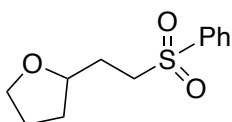
Methyl 2-benzyl-3-(tetrahydrofuran-2-yl)propanoate (**3f**)

The compound **3f** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and methyl 2-benzylacrylate (88.04 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 46% of **3f** (57.1 mg, 0.23 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): 7.22-7.16 (m, 2H), 7.14-7.06 (m, 3H), 3.78-3.68 (m, 2H), 3.61 (q, 1H), 3.51 (s, 3H), 2.90-2.82 (m, 1H), 2.76-2.66 (m, 2H), 1.95-1.84 (m, 2H), 2.82-2.72 (m, 2H), 1.58-1.48 (m, 1H), 1.37-1.27 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 176.16, 176.13, 139.23, 139.13, 129.07, 129.03, 128.50, 128.48, 126.50, 67.83, 67.69, 51.64, 51.58, 45.47, 44.79, 39.27, 38.72, 38.02, 37.86, 31.68, 31.58, 25.78, 25.69. HRMS (EI) m/z calculated for C₁₅H₂₀O₃ [M+H]⁺ 249.1490 found 249.1491. IR (neat, cm⁻¹): 2952, 2862, 1733, 1494, 1438, 1371, 1200, 1162, 1066, 745, 700.



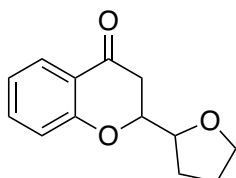
Dimethyl 2-((tetrahydrofuran-2-yl)methyl)succinate (**3g**)

The compound **3g** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and dimethyl itaconate (79.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 66% of **3g** (75.94 mg, 0.33 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): 3.87-3.75 (m, 2H), 3.69-3.64 (m, 4H), 3.64 (s, 3H), 3.01-2.91 (m, 1H), 2.76-2.66 (m, 1H), 2.59-2.50 (m, 1H), 2.03-1.94 (m, 1H), 1.93-1.78 (m, 3H), 1.67-1.59 (m, 1H), 1.48-1.38 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 175.42, 172.40, 76.56, 67.75, 52.00, 51.81, 38.97, 37.38, 35.60, 31.61, 25.64. HRMS (EI) m/z calculated for C₁₁H₁₈O₅ [M+H]⁺ 231.1232 found 231.1225. IR (neat, cm⁻¹): 2952, 2862, 1733, 1438, 1353, 1192, 1159, 1066, 1006, 924, 887, 846.



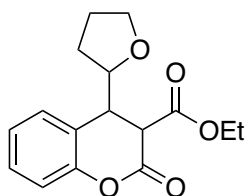
2-(2-(Phenylsulfonyl)ethyl)tetrahydrofuran (**3h**)

The compound **3h** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and phenyl vinyl sulfone (84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 85% of **3h** (102.03 mg, 0.425 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃): 7.90 (d, 2H), 7.64 (t, 1H), 7.55 (t, 2H), 3.86-3.80 (m, 1H), 3.80-3.73 (m, 1H), 3.69-3.62 (m, 1H), 3.33-3.24 (m, 1H), 3.17-3.08 (m, 1H), 2.02-1.90 (m, 2H), 1.88-1.77 (m, 3H), 1.50-1.39 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 139.29, 133.77, 129.39, 128.13, 67.96, 53.70, 31.32, 28.62, 25.70. HRMS (EI) m/z calculated for C₁₂H₁₆O₃S [M+H]⁺ 241.0898 found 241.0894. IR (neat, cm⁻¹): 2952, 2877, 1446, 1304, 1148, 1088, 760, 689.



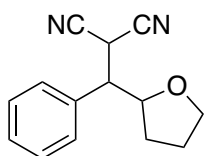
2-(Tetrahydrofuran-2-yl)chroman-4-one (**3i**)

The compound **3i** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv), chromone (73.1 mg, 0.5 mmol, 1.0 equiv), and perchloric acid (25 mg, 0.25 mmol, 0.5 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 96% of **3i** (104.64 mg, 0.48 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): 7.80 (d, 1H), 7.39 (t, 1H), 6.96-6.89 (m, 2H), 4.34-4.28 (m, 1H), 4.13-4.06 (m, 1H), 3.88-3.73 (m, 2H), 2.76-2.66 (m, 2H), 2.10-2.00 (m, 1H), 1.93-1.79 (m, 3H). ¹³C NMR (101 MHz, CDCl₃): 192.30, 161.51, 136.09, 127.04, 121.49, 121.23, 118.10, 79.81, 79.59, 69.12, 39.21, 27.72, 25.80. HRMS (EI) m/z calculated for C₁₃H₁₄O₃ [M]⁺ calculated 218.0937 found 218.0941. IR (neat, cm⁻¹): 2974, 2877, 1692, 1606, 1464, 1304, 1230, 1066, 767.



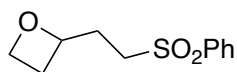
Ethyl 2-oxo-4-(tetrahydrofuran-2-yl)chromane-3-carboxylate (3j**)**

The compound **3j** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and ethyl coumarin-3-carboxylate (109.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 72% of **3j** (104.44 mg, 0.36 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): 7.30-7.26 (m, 1H), 7.19 (d, 1H), 7.13-7.04 (m, 2H), 4.13-3.98 (m, 3H), 3.94-3.82 (m, 2H), 3.75-3.69 (m, 1H), 3.39 (d, 1H), 1.99-1.83 (m, 3H), 1.79-1.68 (m, 1H), 1.04 (t, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.44, 164.20, 151.46, 129.19, 128.93, 124.69, 121.68, 117.02, 80.38, 68.57, 62.21, 48.20, 45.28, 29.45, 25.85, 13.80. HRMS (EI) m/z calculated for C₁₆H₁₈O₅ [M+H]⁺ 291.1232 found 291.1231. IR (neat, cm⁻¹): 2981, 2873, 1777, 1736, 1490, 1457, 1222, 1162, 1069, 1021, 760.



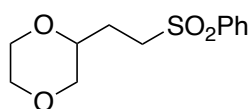
2-(Phenyl(tetrahydrofuran-2-yl)methyl)malononitrile (**3k**)

The compound **3k** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and benzylidenemalononitrile (77.0 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 98% of **3k** (110.8 mg, 0.49 mmol) as a white solid. ^1H NMR (300 MHz, CDCl_3): 7.44-7.34 (m, 8H), 7.34-7.28 (m, 2H), 4.54 (d, 1H), 4.49-4.42 (m, 1H), 4.42-4.36 (m, 2H), 3.99-3.82 (m, 2H), 3.74 (t, 2H), 3.28 (q, 1H), 3.04 (q, 1H), 2.00-1.85 (m, 4H), 1.84-1.71 (m, 1H), 1.53-1.33 (m, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 134.53, 134.03, 129.32, 129.27, 129.04, 129.00, 128.57, 112.45, 112.42, 112.40, 111.83, 78.10, 68.92, 68.79, 51.97, 50.64, 30.39, 28.96, 27.42, 27.07, 25.85. HRMS (EI) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$ $[\text{M}+\text{NH}_4]^+$ 244.1449 found 244.1447. IR (neat, cm^{-1}): 2978, 2907, 2877, 1498, 1453, 1185, 1066, 928, 879, 760, 704.



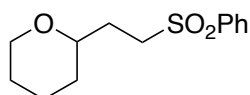
2-(2-(Phenylsulfonyl)ethyl)oxetane (**3l**)

The compound **3l** was synthesized following the general procedure using oxetane (290.4 mg, 5.0 mmol, 10.0 equiv) and phenyl vinyl sulfone (84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 59% of **3l** (66.7 mg, 0.295 mmol) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3): 7.93 (d, 2H), 7.67 (t, 1H), 7.58 (t, 2H), 4.88-4.80 (m, 1H), 4.63 (q, 1H), 4.51-4.43 (m, 1H), 3.30 (m, 1H), 3.14-3.05 (m, 1H), 2.76-2.66 (m, 1H), 2.38-2.28 (m, 1H), 2.23-2.04 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3): 139.05, 133.80, 129.35, 128.04, 80.06, 68.21, 51.66, 30.60, 26.94. HRMS (EI) m/z calculated for $\text{C}_{11}\text{H}_{14}\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 227.0741 found 227.0738. IR (neat, cm^{-1}): 2929, 2885, 2832, 1446, 1304, 1144, 1087, 745, 693.



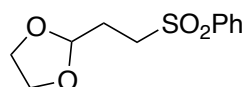
2-(2-(Phenylsulfonyl)ethyl)-1,4-dioxane (**3m**)

The compound **3m** was synthesized following the general procedure using dioxane (440.55 mg, 5.0 mmol, 10.0 equiv) and phenyl vinyl sulfone (84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 84% of **3m** (107.55 mg, 0.42 mmol) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): 7.95 – 7.85 (m, 2H), 7.71 – 7.59 (m, 1H), 7.65 – 7.50 (m, 2H), 3.77 – 3.43 (m, 6H), 3.38 – 3.05 (m, 3H), 1.89 – 1.62 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): 139.03, 133.82, 129.38, 128.04, 73.14, 70.73, 66.63, 66.38, 52.37, 24.66. HRMS (EI) m/z calculated for C₁₂H₁₆O₄S [M+H]⁺ 257.0847 found 257.0844. IR (neat, cm⁻¹): 2959, 2922, 2855, 1446, 1304, 1237, 1144, 1084, 954, 894, 741, 689.



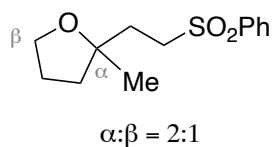
2-(2-(Phenylsulfonyl)ethyl)tetrahydro-2H-pyran (**3n**)

The compound **3n** was synthesized following the general procedure using tetrahydropyran (430.65 mg, 5.0 mmol, 10.0 equiv) and phenyl vinyl sulfone (84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 85% of **3n** (108.0 mg, 0.425 mmol) as a white solid. ¹H NMR (300 MHz, CDCl₃): 7.92-7.85 (m, 2H), 7.67-7.59 (m, 1H), 7.58-7.50 (m, 2H), 3.87 (d, 1H), 3.36-3.20 (m, 3H), 3.19-3.07 (m, 1H), 1.94-1.68 (m, 3H), 1.57-1.34 (m, 4H), 1.27-1.13 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): 139.26, 133.64, 129.28, 128.05, 75.68, 68.42, 53.06, 31.76, 29.35, 25.84, 23.24. HRMS (EI) m/z calculated for C₁₃H₁₈O₃S [M+H]⁺ 255.1054 found 255.1054. IR (neat, cm⁻¹): 2933, 2847, 1446, 1304, 1144, 1084, 1047, 879, 738, 689.



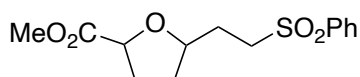
2-(2-(Phenylsulfonyl)ethyl)-1,3-dioxolane (**3o**)

The compound **3o** was synthesized following the general procedure using dioxolane (370.4 mg, 5.0 mmol, 10.0 equiv) and phenyl vinyl sulfone (84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 40% of **3o** (48.41 mg, 0.20 mmol) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): 7.94-7.87 (m, 2H), 7.69-7.62 (m, 1H), 7.61-7.52 (m, 2H), 4.97-4.91 (m, 1H), 3.98-3.77 (m, 4H), 3.26-3.16 (m, 2H), 2.11-2.02 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): 138.93, 133.79, 129.35, 128.11, 101.77, 65.18, 50.67, 27.07. HRMS (EI) m/z calculated for C₁₁H₁₄O₄S [M+H]⁺ 243.0691 found 243.0689. IR (neat, cm⁻¹): 2929, 2888, 1446, 1408, 1304, 1230, 1144, 1088, 1021, 946, 887, 797, 749, 689.



2-Methyl-2-(2-(phenylsulfonyl)ethyl)tetrahydrofuran (**3p**)

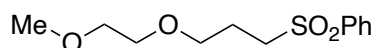
The compound **3p** was synthesized following the general procedure using 2-methyltetrahydrofuran (430.65 mg, 5.0 mmol, 10.0 equiv) and phenyl vinyl sulfone (84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 97% of **3p** (123.24 mg, 0.485 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): 7.89 (d, 2H), 7.67-7.59 (m, 1H), 7.58-7.50 (m, 2H), 4.04-3.61 (m, 2H), 3.34-3.04 (m, 2H), 2.08-1.75 (m, 4H), 1.71-1.63 (m, 1H), 1.56-1.30 (m, 1H), 1.16-1.07 (m, 3H). ¹³C NMR (101 MHz, CDCl₃): 139.23, 133.74, 129.36, 128.07, 80.83, 77.08, 76.62, 75.81, 74.90, 67.49, 53.74, 53.52, 52.41, 37.27, 33.67, 32.93, 32.78, 32.15, 31.19, 29.14, 28.90, 25.95, 25.78, 21.33, 21.15. HRMS (EI) m/z calculated for C₁₃H₁₈O₃S [M+H]⁺ 255.1054 found 255.1055. IR (neat, cm⁻¹): 2967, 2870, 1446, 1379, 1304, 1230, 1144, 1084, 1043, 943, 887, 805, 745, 689.



Methyl 5-(2-(phenylsulfonyl)ethyl)tetrahydrofuran-2-carboxylate (**3q**)

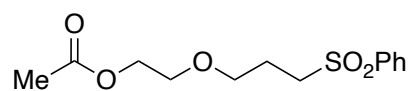
The compound **3q** was synthesized following the general procedure using methyl tetrahydrofuran-2-carboxylate (650.7 mg, 5.0 mmol, 10.0 equiv) and phenyl vinyl sulfone

(84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 67% of **3q** (99.86 mg, 0.335 mmol) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): 7.94 – 7.86 (m, 2H), 7.68 – 7.60 (m, 1H), 7.59 – 7.51 (m, 2H), 4.43 (ddd, *J* = 14.5, 8.4, 5.3 Hz, 1H), 4.21 – 4.03 (m, 1H), 3.69 (d, *J* = 7.3 Hz, 3H), 3.45 – 3.07 (m, 2H), 2.32 – 2.16 (m, 1H), 2.13 – 1.81 (m, 4H), 1.67 – 1.48 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): 173.63, 173.50, 139.29, 139.14, 133.85, 133.76, 129.42, 129.38, 128.12, 79.17, 78.52, 77.12, 76.77, 53.46, 53.31, 52.19, 52.17, 30.81, 30.54, 30.25, 29.94, 28.43, 28.36. HRMS (EI) *m/z* calculated for C₁₄H₁₈O₅S [M+H]⁺ 299.0953 found 299.0949. IR (neat, cm⁻¹): 2952, 2363, 1748, 1446, 1304, 1211, 1148, 1084, 745, 693.



((3-(2-Methoxyethoxy)propyl)sulfonyl)benzene (**3r**)

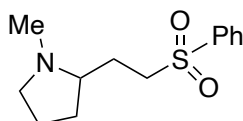
The compound **3r** was synthesized following the general procedure using ethyleneglycoldimethylether (450.6 mg, 5.0 mmol, 10.0 equiv) and phenyl vinyl sulfone (84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 75% of **3r** (96.78 mg, 0.375 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃): 7.90 (d, 2H), 7.67-7.62 (m, 1H), 7.56 (m, 2H), 3.54-3.49 (m, 4H), 3.49-3.46 (m, 2H), 3.34 (s, 3H), 3.23-3.18 (2H), 2.04-1.96 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): 139.17, 133.67, 129.28, 128.08, 71.81, 70.15, 68.83, 59.06, 53.46, 23.23. HRMS (EI) *m/z* calculated for C₁₂H₁₈O₄S [M+H]⁺ 259.1004 found 259.1002. IR (neat, cm⁻¹): 2926, 2877, 1446, 1308, 1144, 1110, 1087, 857, 734, 693.



2-(3-(Phenylsulfonyl)propoxy)ethyl acetate (**3s**)

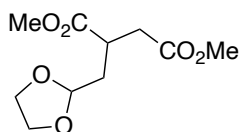
The compound **3s** was synthesized following the general procedure using 2-methoxyethyl acetate (590.65 mg, 5.0 mmol, 10.0 equiv) and phenyl vinyl sulfone (84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 66% of **3s** (94.41 mg, 0.33 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃): 7.84 (d, 2H), 7.62-7.56 (m, 1H), 7.53-7.47 (m, 2H),

4.10-3.92 (m, 2H), 3.51-3.26 (m, 4H), 3.22-3.06 (m, 2H), 1.98 (d, 3H), 1.95-1.77 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3): 170.95, 170.71, 139.15, 139.05, 133.80, 133.72, 129.36, 129.32, 128.03, 76.51, 68.73, 68.62, 64.22, 63.33, 57.68, 53.29, 52.25, 24.83, 23.19, 20.91, 20.80. HRMS (EI) m/z calculated for $\text{C}_{13}\text{H}_{18}\text{O}_5\text{S}$ $[\text{M}+\text{NH}_4]^+$ 304.1218 found 304.1219. IR (neat, cm^{-1}): 2937, 1736, 1446, 1371, 1304, 1233, 1144, 1088, 1047, 797, 738, 693.



1-methyl-2-(2-(phenylsulfonyl)ethyl)pyrrolidine (**3t**)

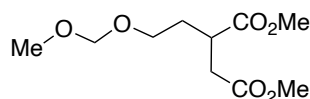
The compound **3t** was synthesized following the general procedure using N-methylpyrrolidine (425.75 mg, 5.0 mmol, 10.0 equiv) and phenyl vinyl sulfone (84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 68% of **3t** (86.05 mg, 0.34 mmol) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): 7.93-7.89 (m, 2H), 7.67-7.62 (m, 1H), 7.59-7.53 (m, 2H), 3.23-3.14 (m, 1H), 3.10-2.98 (m, 2H), 2.24-2.11 (m, 5H), 2.07-1.97 (m, 1H), 1.90-1.80 (m, 1H), 1.76-1.62 (m, 3H), 1.41-1.31 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3): 139.12, 133.66, 129.29, 128.07, 63.93, 57.07, 52.77, 40.24, 29.75, 25.64, 21.98. HRMS (EI) m/z calculated for $\text{C}_{13}\text{H}_{19}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 254.1214 found 254.1212. IR (neat, cm^{-1}): 2948, 2784, 1446, 1304, 1230, 1148, 1088, 741, 693.



Dimethyl 2-((1,3-dioxolan-2-yl)methyl)succinate (**3u**)

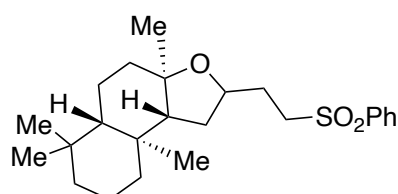
The compound **3u** was synthesized following the general procedure using dioxolane (370.4 mg, 5.0 mmol, 10.0 equiv) and dimethyl itaconate (79.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 50% of **3u** (58.02 mg, 0.25 mmol) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): 4.93 (t, 1H), 3.97-3.91 (m, 2H), 3.86-3.79 (m, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.10-2.99 (m, 1H), 2.81-2.54 (m, 2H), 2.16-2.06 (m, 1H), 1.91-1.80 (m, 1H). ^{13}C NMR (101

MHz, CDCl₃): 175.00, 172.29, 102.72, 65.09, 65.05, 52.15, 51.90, 36.93, 36.11, 35.40. HRMS (EI) *m/z* calculated for C₁₀H₁₆O₆ [M+H]⁺ 233.1025 found 233.1019. IR (neat, cm⁻¹): 2955, 2892, 1736, 1438, 1364, 1200, 1166, 1010, 946, 849.



Dimethyl 2-(2-(methoxymethoxy)ethyl)succinate (**3v**)

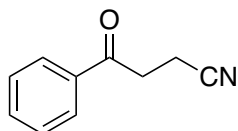
The compound **3v** was synthesized following the general procedure using dimethoxymethane (380.5 mg, 5.0 mmol, 10.0 equiv) and dimethyl itaconate (79.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 21% of **3v** (24.5 mg, 0.105 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): 4.58 (s, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 3.55 (s, 2H), 3.34 (s, 3H), 3.05-3.97 (m, 1H), 3.79-3.71 (m, 1H), 2.55-2.48 (m, 1H), 2.02-1.92 (m, 1H), 1.86-1.76 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 175.11, 172.14, 96.45, 64.99, 55.29, 51.93, 51.80, 38.45, 35.73, 31.69. HRMS (EI) *m/z* calculated for C₁₀H₁₈O₆ [M+H]⁺ 235.1181 found 235.1180. IR (neat, cm⁻¹): 2952, 2888, 1736, 1438, 1200, 1166, 1110, 1043.



(3aR,5aS,9aS,9bR)-3a,6,6,9a-tetramethyl-2-(2-(phenylsulfonyl)ethyl)dodecahydronaphtho[2,1-*b*]furan (**3w**)

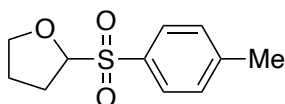
The compound **3w** was synthesized following the general procedure using (-)-ambroxide (118.2 mg, 0.5 mmol, 1.0 equiv) and phenyl vinyl sulfone (84.1 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 54% of **3w** (109.1 mg, 0.27 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃): 7.90 (d, 2H), 7.64 (t, 1H), 7.55 (t, 2H), 4.15-4.00 (m, 1H), 3.30-3.20 (m, 1H), 3.15-3.05 (m, 1H), 1.95-1.83 (m, 3H), 1.74-1.56 (m, 2H), 1.43-1.11 (m, 9H), 1.05 (s, 3H), 1.02-0.89 (m, 2H), 0.86 (s, 3H), 0.80 (s, 3H), 0.79 (s, 3H). ¹³C NMR (101 MHz, CDCl₃):

139.39, 133.73, 129.38, 128.20, 81.74, 73.75, 59.28, 57.34, 53.39, 47.36, 42.52, 40.02, 39.87, 36.25, 33.68, 33.20, 30.04, 28.50, 21.60, 21.22, 20.64, 18.47, 15.04. HRMS (EI) m/z calculated for $C_{24}H_{36}O_3S$ $[M+H]^+$ 405.2463 found 405.2465. IR (neat, cm^{-1}): 2929, 2363, 1446, 1379, 1308, 1222, 1148, 1088, 1013, 797, 745, 689.



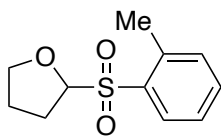
4-Oxo-4-phenylbutanenitrile (**4**)

The compound **4** was synthesized following the general procedure using acrylonitrile (**2a**) (26.5 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 31% of **4** (24.6 mg, 0.155 mmol) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$): 7.95 (d, 2H), 7.62 (t, 1H), 7.50 (t, 2H), 3.39 (t, 2H), 2.78 (t, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): 195.45, 135.74, 134.07, 129.03, 128.17, 119.34, 34.42, 29.84, 11.95. HRMS (EI) m/z calculated for $C_{10}H_9NO$ $[M]^+$ 159.0678 found 159.0683. IR (neat, cm^{-1}): 2922, 2855, 1688, 1599, 1449, 1416, 1364, 1285, 1252, 1211, 972, 913, 730, 689.



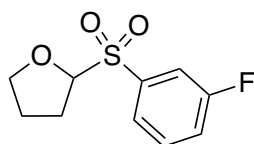
2-tosyltetrahydrofuran (**6a**)

The compound **6a** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and tosyl chloride (95.0 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 83% of **6a** (93.82 mg, 0.415 mmol) as a white solid. 1H NMR (300 MHz, $CDCl_3$): 7.80 (s, 2H), 7.36 (s, 2H), 4.86 (q, 1H), 4.12 (q, 1H), 4.02-3.93 (m, 1H), 2.72-2.60 (m, 1H), 2.44 (s, 3H), 2.36-2.22 (m, 1H), 2.20-2.07 (m, 1H), 2.01-1.88 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 145.04, 134.06, 129.88, 129.36, 94.31, 71.06, 26.10, 25.10, 21.83. HRMS (ESI) m/z calculated for $C_{11}H_{14}O_3S$ $[M+Na]^+$ 249.0561 found 249.0559. IR (neat, cm^{-1}): 2955, 2892, 1595, 1490, 1453, 1390, 1315, 1282, 1144, 1066, 913, 861, 816, 719.



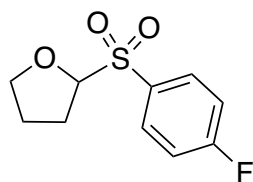
2-(*o*-tolylsulfonyl)tetrahydrofuran (**6b**)

The compound **6b** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and *o*-toluenesulfonyl chloride (95.0 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 62% of **6b** (70.10 mg, 0.310 mmol) as a white solid. ¹H NMR (400 MHz, CDCl₃): 7.73-7.69 (m, 2H), 7.46-7.42 (m, 2H), 4.88 (q, 1H), 4.12 (q, 1H), 3.97 (q, 1H), 2.70-2.61 (m, 1H), 2.43 (s, 3H), 2.34-2.23 (m, 1H), 2.19-2.08 (m, 1H), 1.98-1.88 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 139.37, 136.99, 134.77, 129.53, 129.02, 126.41, 94.23, 71.05, 26.06, 25.03, 21.42. HRMS (ESI) *m/z* calculated for C₁₁H₁₄O₃S [M+Na]⁺ 249.0561 found 249.0558 IR (neat, cm⁻¹): 2926, 2892, 1774, 1722, 1476, 1375, 1300, 1222, 1170, 1140, 1069, 928, 864, 790, 685.



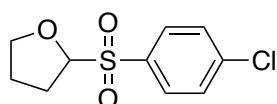
2-((3-fluorophenyl)sulfonyl)tetrahydrofuran (**6c**)

The compound **6c** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and 3-fluorobenzenesulfonyl chloride (97.3 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was analyzed through quantitative ¹H-NMR using tetrachloroethane as an internal standard.



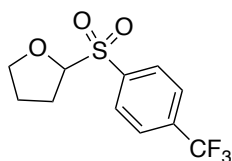
2-((4-fluorophenyl)sulfonyl)tetrahydrofuran (**6d**)

The compound **6d** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and 4-fluorobenzenesulfonyl chloride (97.3 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 77% of **6d** (88.70 mg, 0.385 mmol) as a clear oil. ^1H NMR (400 MHz, CDCl_3): 8.01 – 7.84 (m, 2H), 7.34 – 7.13 (m, 2H), 4.85 (dd, J = 8.1, 3.9 Hz, 1H), 4.13 (dt, J = 8.2, 7.2 Hz, 1H), 3.99 (td, J = 7.8, 5.5 Hz, 1H), 2.66 (dddd, J = 14.2, 8.5, 5.9, 4.0 Hz, 1H), 2.31 (dddd, J = 14.0, 9.0, 8.2, 6.7 Hz, 1H), 2.24 – 2.08 (m, 1H), 1.96 (ddtd, J = 12.1, 9.1, 7.2, 5.9 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3): 167.45, 164.91, 133.17, 133.14, 132.24, 132.14, 116.62, 116.39, 94.36, 71.11, 26.02, 25.08. HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{11}\text{FNaO}_3\text{S}$ $[\text{M}]^+$ 253.0311 found 253.0305. IR (neat): $\nu[\text{cm}^{-1}]$ = 3075.1, 3108.6, 2981.9, 2896.1, 2359.4, 1591.6, 1490.9, 1319.5, 1289.7, 1233.7, 1148.0, 1089.7, 842.4.



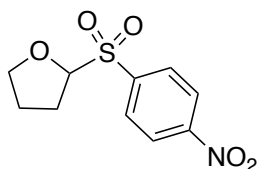
2-((4-chlorophenyl)sulfonyl)tetrahydrofuran (**6e**)

The compound **6e** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and 4-chlorobenzenesulfonyl chloride (105.6 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 62% of **6e** (76.26 mg, 0.310 mmol) as a clear oil. ^1H NMR (400 MHz, CDCl_3): 7.85 (d, 2H), 7.53 (d, 2H), 4.85 (q, 1H), 4.13 (q, 1H), 3.99 (q, 1H), 2.71-2.62 (m, 1H), 2.36-2.25 (m, 1H), 2.23-2.12 (m, 1H), 2.01-1.90 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3): 140.83, 135.66, 130.81, 129.52, 94.37, 71.15, 26.00, 25.09. HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{11}\text{ClO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 269.0015 found 269.0010. IR (neat, cm^{-1}): 2959, 2896, 1774, 1580, 1476, 1394, 1319, 1278, 1148, 1069, 928, 831, 760.



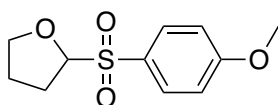
2-((4-(trifluoromethyl)phenyl)sulfonyl)tetrahydrofuran (**6f**)

The compound **6f** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and 4-trifluoromethylbenzenesulfonyl chloride (122.3 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was analyzed through quantitative ^1H -NMR using tetrachloroethane as an internal standard.



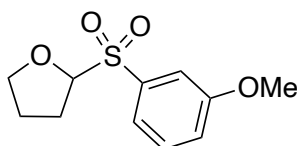
2-((4-nitrophenyl)sulfonyl)tetrahydrofuran (**6g**)

The compound **6g** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and 4-nitrobenzenesulfonyl chloride (110.8 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was analyzed through quantitative ^1H -NMR using tetrachloroethane as an internal standard.



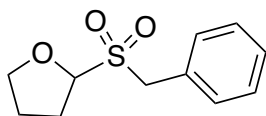
2-((4-methoxyphenyl)sulfonyl)tetrahydrofuran (**6h**)

The compound **6h** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and 4-methoxybenzenesulfonyl chloride (103.3 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 46% of **6h** (55.67 mg, 0.230 mmol) as a clear oil. ^1H NMR (400 MHz, CDCl_3): 7.83 (d, 2H), 7.01 (d, 2H), 4.83 (q, 1H), 4.09 (q, 1H), 3.96 (q, 1H), 3.86 (s, 3H), 2.67-2.57 (m, 1H), 2.33-2.22 (m, 1H), 2.17-2.06 (m, 1H), 1.98-1.86 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3): 164.09, 131.48, 128.44, 114.45, 94.39, 70.99, 55.76, 26.19, 25.08. HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{15}\text{O}_4\text{S}$ $[\text{M}+\text{Na}]^+$ 265.0510 found 265.0506. IR (neat, cm^{-1}): 2952, 2896, 1595, 1498, 1461, 1297, 1259, 1140, 1069, 1025, 928, 834, 805, 726, 663.



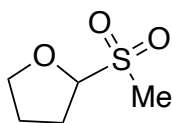
2-((3-methoxyphenyl)sulfonyl)tetrahydrofuran (**6i**)

The compound **6i** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and 3-methoxybenzenesulfonyl chloride (103.3 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 70% of **6i** (84.70 mg, 0.350 mmol) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): 7.54 – 7.38 (m, 3H), 7.17 (ddd, $J = 8.0, 2.7, 1.3$ Hz, 1H), 4.89 (dd, $J = 8.1, 3.9$ Hz, 1H), 4.13 (q, $J = 7.3$ Hz, 1H), 3.98 (td, $J = 7.8, 5.6$ Hz, 1H), 3.86 (s, 3H), 2.73 – 2.60 (m, 1H), 2.37 – 2.23 (m, 1H), 2.22 – 2.09 (m, 1H), 2.02 – 1.88 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3): 159.99, 138.28, 130.23, 121.48, 120.47, 113.74, 94.32, 71.10, 55.80, 26.12, 25.04. HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{15}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 243.0691 found 243.0685. IR (neat, cm^{-1}): 3075.1, 2959.5, 2892.4, 1595.3, 1479.8, 1431.3, 1304.6, 1241.2, 1140.6, 1066.0, 1032.5.



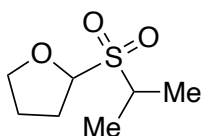
2-(benzylsulfonyl)tetrahydrofuran (**6j**)

The compound **6j** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and benzylsulfonyl chloride (95.3 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 27% of **6j** (30.50 mg, 0.135 mmol) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): 7.48 – 7.34 (m, 5H), 4.72 (dd, $J = 8.0, 4.0$ Hz, 1H), 4.51 (d, $J = 13.9$ Hz, 1H), 4.21 (dt, $J = 8.1, 7.2$ Hz, 1H), 4.16 (d, $J = 13.9$ Hz, 1H), 4.12 – 4.05 (m, 1H), 2.59 – 2.47 (m, 1H), 2.27 – 2.09 (m, 2H), 2.01 – 1.87 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3): 131.08, 129.06, 128.95, 128.05, 88.97, 71.22, 55.77, 25.22, 24.50. HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{15}\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 227.0742 found 227.0736. IR (neat, cm^{-1}): 2929.7, 2363.1, 1736.9, 1494.7, 1457.4, 1315.8, 1073.5.



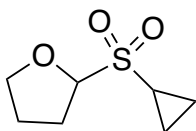
2-(methylsulfonyl)tetrahydrofuran (**6k**)

The compound **6k** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and methanesulfonyl chloride (57.3 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was analyzed through quantitative ^1H -NMR using tetrachloroethane as an internal standard.



2-(isopropylsulfonyl)tetrahydrofuran (**6l**)

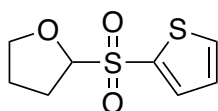
The compound **6l** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and 2-propanesulfonyl chloride (71.3 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 92% of **6l** (82.0 mg, 0.46 mmol) as a clear oil. ^1H NMR (400 MHz, CDCl_3): 4.98 (dd, $J = 8.0, 4.1$ Hz, 1H), 4.12 – 3.95 (m, 2H), 3.39 (p, $J = 6.9$ Hz, 1H), 2.61 – 2.51 (m, 1H), 2.28 – 2.10 (m, 2H), 1.92 (dddd, $J = 12.0, 10.7, 5.3, 3.2$ Hz, 1H), 1.36 (t, $J = 6.6$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3): 89.09, 71.06, 49.85, 25.06, 16.43, 13.67. HRMS (ESI) m/z calculated for $\text{C}_7\text{H}_{15}\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 179.0742 found 179.0737. IR (neat, cm^{-1}): 2981.9, 2363.1, 1464.8, 1304.6, 1252.4, 1133.1, 1069.7.



2-(cyclopropylsulfonyl)tetrahydrofuran (**6m**)

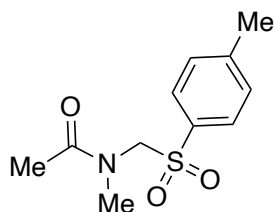
The compound **6m** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and cyclopropanesulfonyl chloride (70.3 mg, 0.5 mmol, 1.0

equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 86% of **6m** (75.70 mg, 0.43 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃): 4.88 (dd, *J* = 8.0, 4.1 Hz, 1H), 4.18 – 4.08 (m, 1H), 4.08 – 3.99 (m, 1H), 2.60 – 2.47 (m, 2H), 2.32 – 2.11 (m, 2H), 2.04 – 1.88 (m, 1H), 1.38 – 1.27 (m, 1H), 1.10 – 1.03 (m, 2H), 1.03 – 0.96 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 92.35, 70.98, 26.51, 25.37, 25.08, 4.65, 4.14. HRMS (ESI) *m/z* calculated for C₇H₁₃O₃S [M+H]⁺ 177.0585 found 177.0577. IR (neat, cm⁻¹): 2985.6, 2892.4, 2363.1, 1722.0, 1449.9, 1319.5, 1282.2, 1136.8, 1073.5.



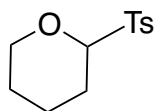
2-(thiophen-2-ylsulfonyl)tetrahydrofuran (**6n**)

The compound **6n** was synthesized following the general procedure using tetrahydrofuran (360.55 mg, 5.0 mmol, 10.0 equiv) and 2-thiophenesulfonyl chloride (91.4 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 68% of **6n** (74.12 mg, 0.340 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃): 7.75 (d, 1H), 7.71 (d, 1H), 7.17 (q, 1H), 4.93 (q, 1H), 4.14 (q, 1H), 4.01 (q, 1H), 2.68-2.59 (m, 1H), 2.37-2.26 (m, 1H), 2.17-2.06 (m, 1H), 2.01-1.90 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): 137.32, 135.35, 135.02, 127.97, 95.19, 71.21, 26.37, 24.99. HRMS (ESI) *m/z* calculated for C₈H₁₀O₃S₂ [M+Na]⁺ 240.9969 found 240.9964. IR (neat, cm⁻¹): 3097, 2959, 2892, 1505, 1457, 1401, 1315, 1226, 1140, 1066, 1013, 928, 857, 730, 663.



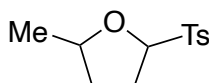
N-methyl-N-(tosylmethyl)acetamide (**6o**)

The compound **6o** was synthesized following the general procedure using *N,N*-dimethylacetamide (435.6 mg, 5.0 mmol, 10.0 equiv) and tosyl chloride (95.0 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 27% of **6o** (32.60 mg, 0.135 mmol) as a clear oil with a rotameric ratio of 3:1. ¹H NMR (400 MHz, CDCl₃): 7.76 (d, 2H), 7.33 (d, 2H), 4.79 (s, 3H), 3.26 (s, 3H), 2.43 (s, 3H), 1.97 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): 170.76, 145.39, 134.82, 129.92, 128.80, 67.84, 37.49, 35.67, 21.89, 21.32. HRMS (ESI) *m/z* calculated for C₁₁H₁₅NO₃S [M+H]⁺ 242.0850 found 242.0848. IR (neat, cm⁻¹): 3004, 2970, 2937, 2359, 2161, 1736, 1666, 1390, 1319, 1285, 1215, 1148, 1088, 1025, 894, 820, 749.



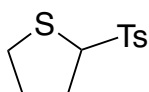
2-tosyltetrahydro-2*H*-pyran (**6p**)

The compound **6p** was synthesized following the general procedure using tetrahydropyran (430.65 mg, 5.0 mmol, 10.0 equiv) and tosyl chloride (95.0 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was analyzed through quantitative ¹H-NMR using tetrachloroethane as an internal standard.



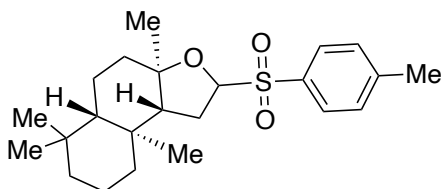
2-methyl-5-tosyltetrahydrofuran (**6q**)

The compound **6q** was synthesized following the general procedure using 2-methyltetrahydrofuran (430.65 mg, 5.0 mmol, 10.0 equiv) and tosyl chloride (95.0 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was analyzed through quantitative ¹H-NMR using tetrachloroethane as an internal standard.



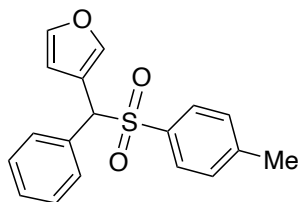
2-tosyltetrahydrothiophene (**6r**)

The compound **6r** was synthesized following the general procedure using tetrahydrothiophene (440.0 mg, 5.0 mmol, 10.0 equiv) and tosyl chloride (95.0 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was analyzed through quantitative ^1H -NMR using tetrachloroethane as an internal standard.



(3aR,5aS,9aS,9bR)-3a,6,6,9a-tetramethyl-2-tosyldodecahydronaphtho[2,1-b]furan (6s)

The compound **6s** was synthesized following the general procedure using (-)-ambroxide (118.2 mg, 0.5mmol, 1 equiv) and tosyl chloride (95.0 mg, 0.5 mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 88% of **6s** (171.7 mg, 0.440 mmol) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): 7.79 (s, 2H), 7.35 (d, 2H), 4.85 (dd, $J = 8.9$ Hz, 1H), 2.44 (s, 3H), 3.31 (ddd, $J = 13.3$, 6.6, 1.8 Hz, 1H), 2.09 (td, $J = 13.6$, 8.9 Hz, 1H), 1.92 (dt, $J = 11.7$, 3.3 Hz, 1H), 1.75-1.68 (m, 1H), 1.66-1.55 (m, 1H), 1.40 (tdd, $J = 11.4$, 5.4, 2.3 Hz, 4H), 1.33-1.12 (m, 3H), 1.07 (s, 3H), 0.95-0.84 (m, 2H), 0.82 (s, 3H), 0.77 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3): 144.97, 133.49, 130.01, 129.66, 92.02, 85.62, 57.72, 56.95, 42.45, 39.71, 39.34, 36.29, 33.62, 33.08, 25.29, 22.17, 21.80, 21.06, 20.72, 18.32, 15.09. HRMS (ESI) m/z calculated for $\text{C}_{23}\text{H}_{34}\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 413.2126 found 413.2126. IR (neat, cm^{-1}): 2926, 1595, 1461, 1386, 1319, 1285, 1148, 1073, 1051, 1006, 972, 916, 816, 734, 663.



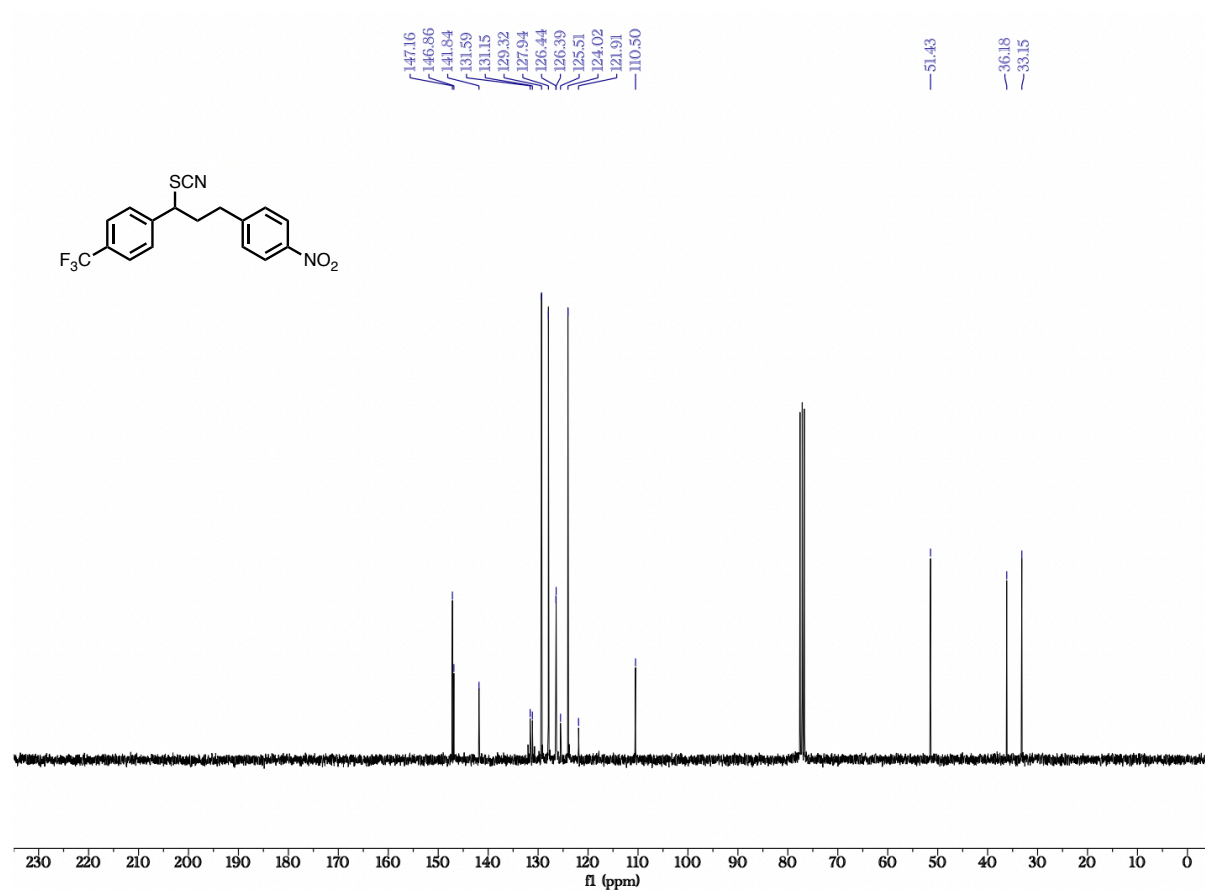
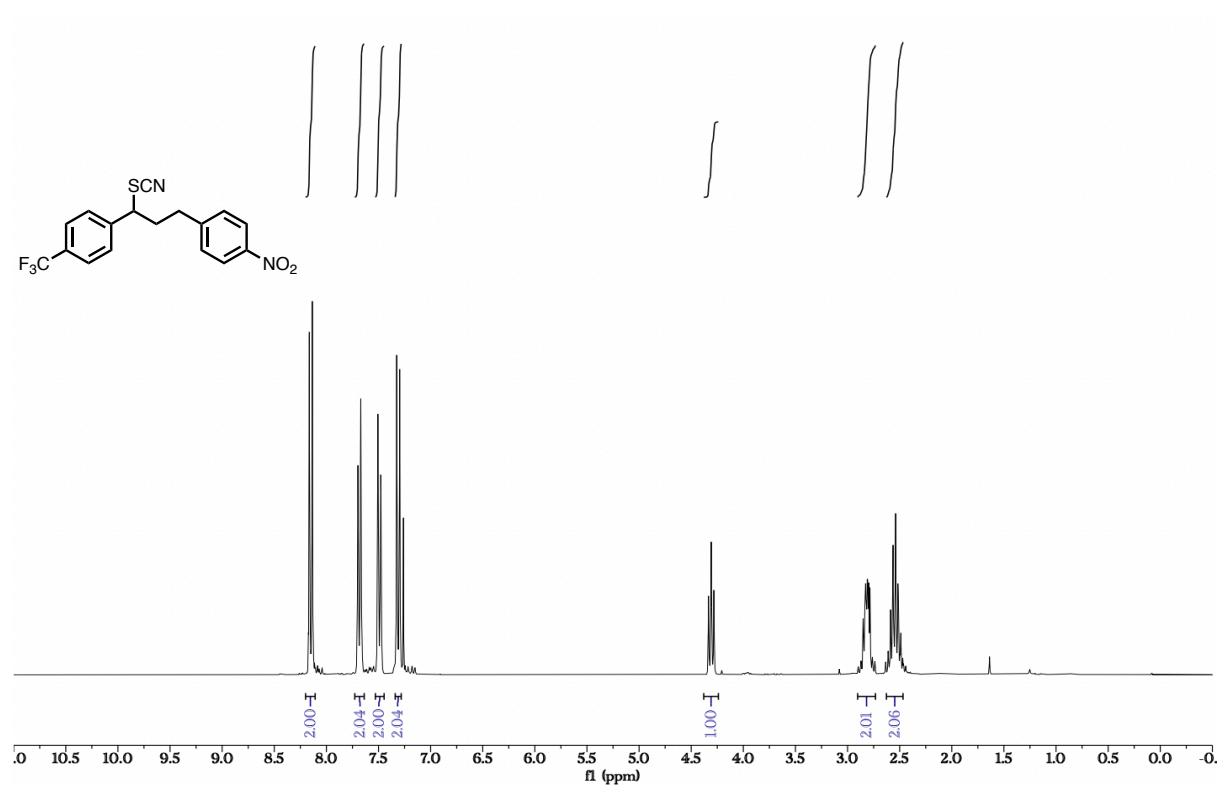
3-(phenyl(tosyl)methyl)furan (6t)

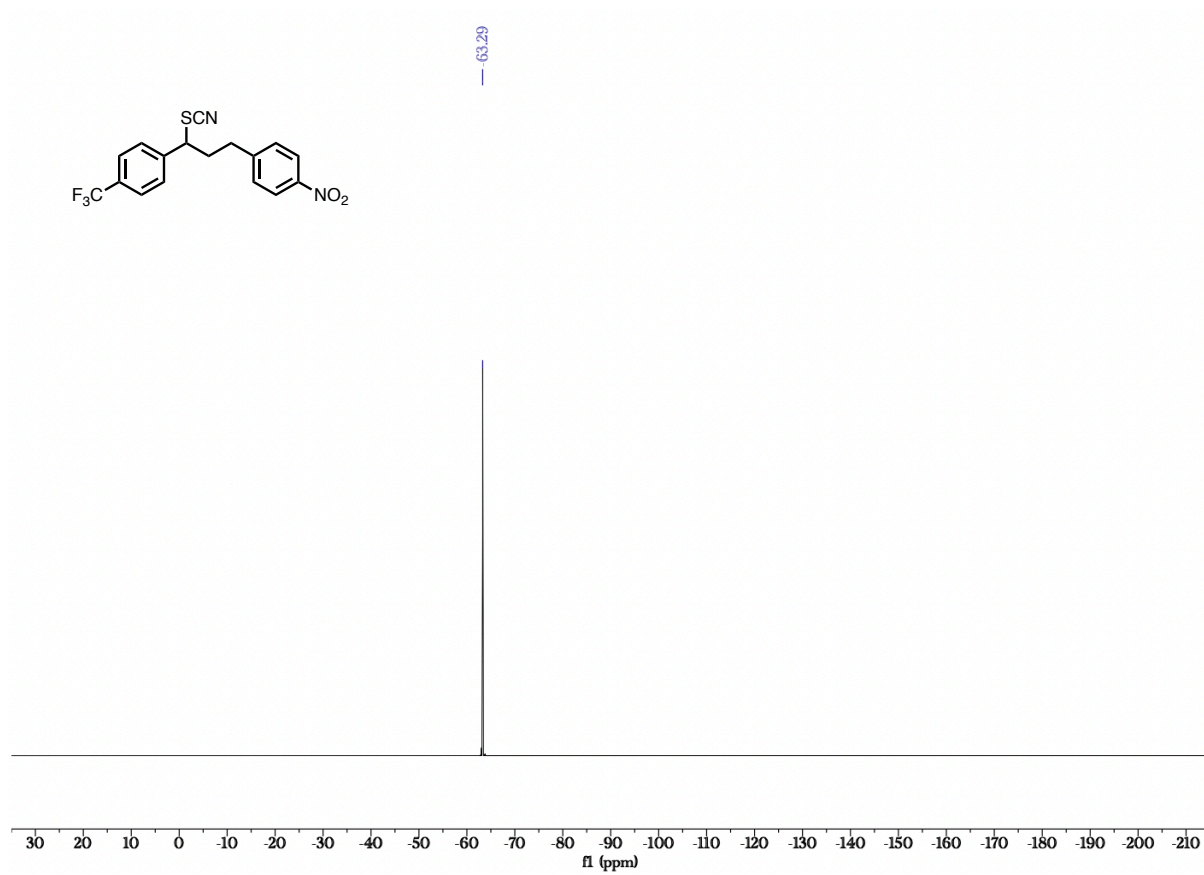
The compound **6t** was synthesized following the general procedure using 6-phenyl-2,7-dioxabicyclo[3.2.0]hept-3-ene (87.0 mg, 0.5 mmol, 1.0 equiv) and tosyl chloride (95.0 mg, 0.5

mmol, 1.0 equiv). After the reaction completion, the crude mixture was purified by flash column chromatography on silica (hexanes : EtOAc) to yield 63% of **6t** (98.31 mg, 0.315 mmol) as a clear oil. ¹H NMR (400 MHz, CDCl₃): 8.12 (d, 2H), 7.62 (t, 1H), 7.50-7.45 (m, 4H), 7.37-7.34 (m, 1H), 7.33-7.28 (m, 2H), 7.17 (d, 1H), 6.65 (d, 1H), 5.21 (s, 1H), 2.38 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): 171.55, 144.74, 143.38, 142.77, 134.71, 133.92, 132.57, 130.35, 130.25, 129.41, 129.37, 129.33, 129.02, 128.72, 128.64, 117.77, 111.49, 77.48, 77.16, 76.84, 68.96, 21.77. HRMS (ESI) m/z calculated for C₁₈H₁₆O₃S [M+Na]⁺ 335.0717 found 335.0713. IR (neat, cm⁻¹): 2918, 2851, 1699, 1599, 1319, 1148, 1084, 1025, 730, 704.

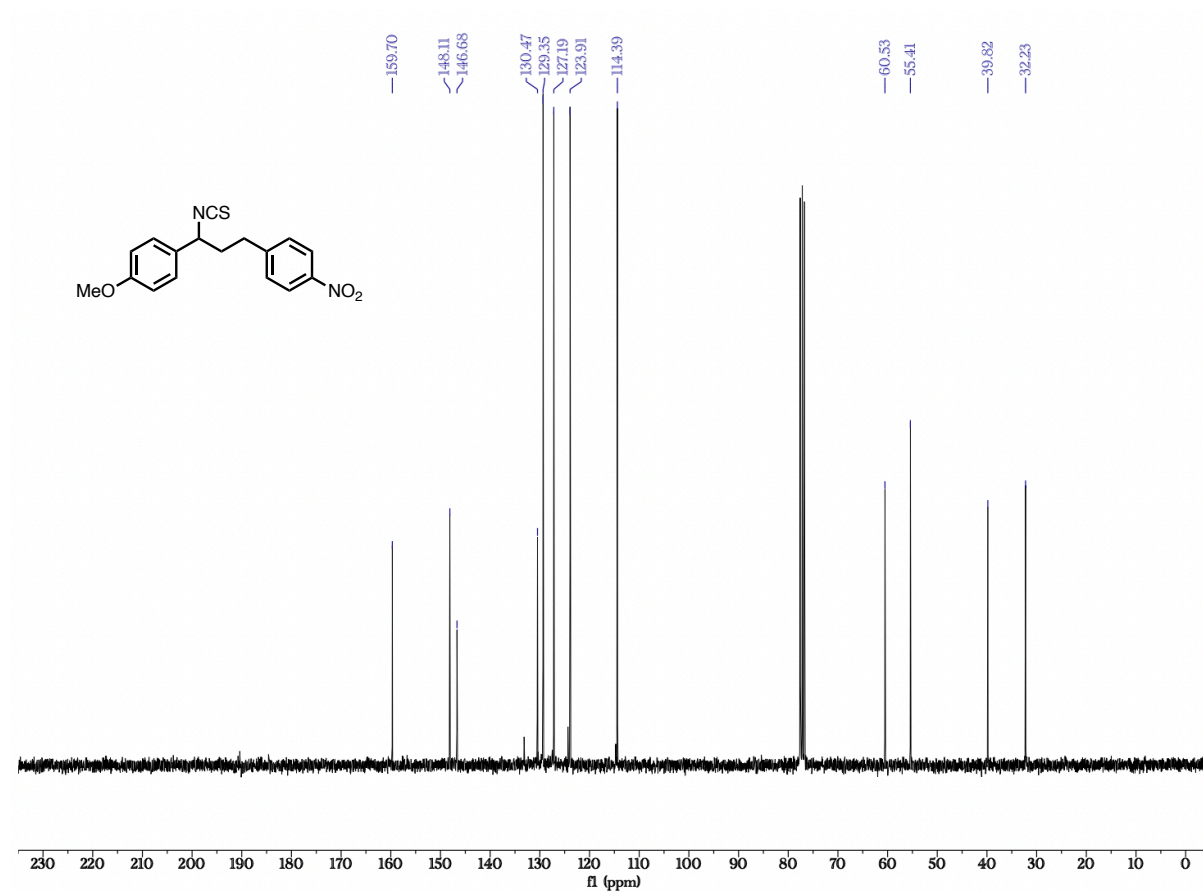
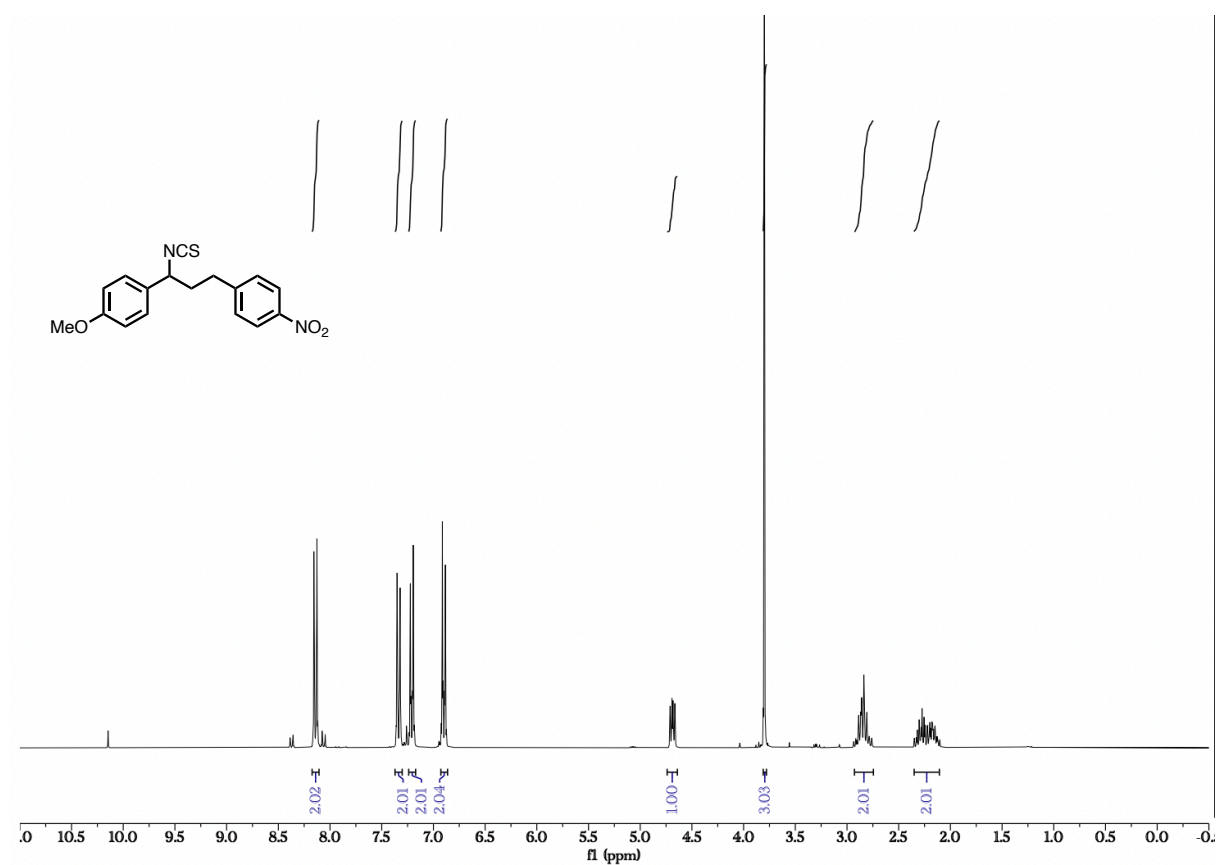
Copies of NMR spectra of Chapter 2:

1-nitro-4-(3-thiocyanato-3-(4-(trifluoromethyl)phenyl)propyl)benzene (3aa)

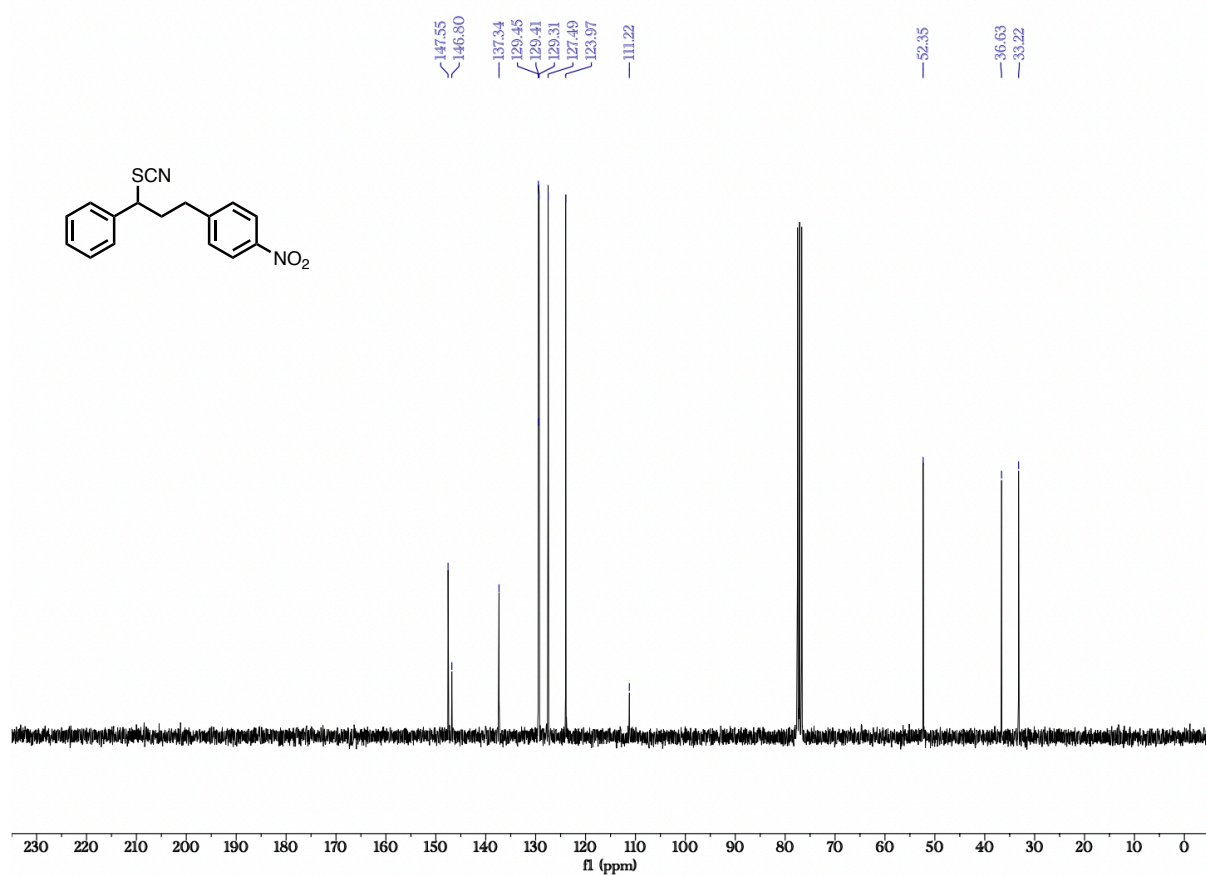
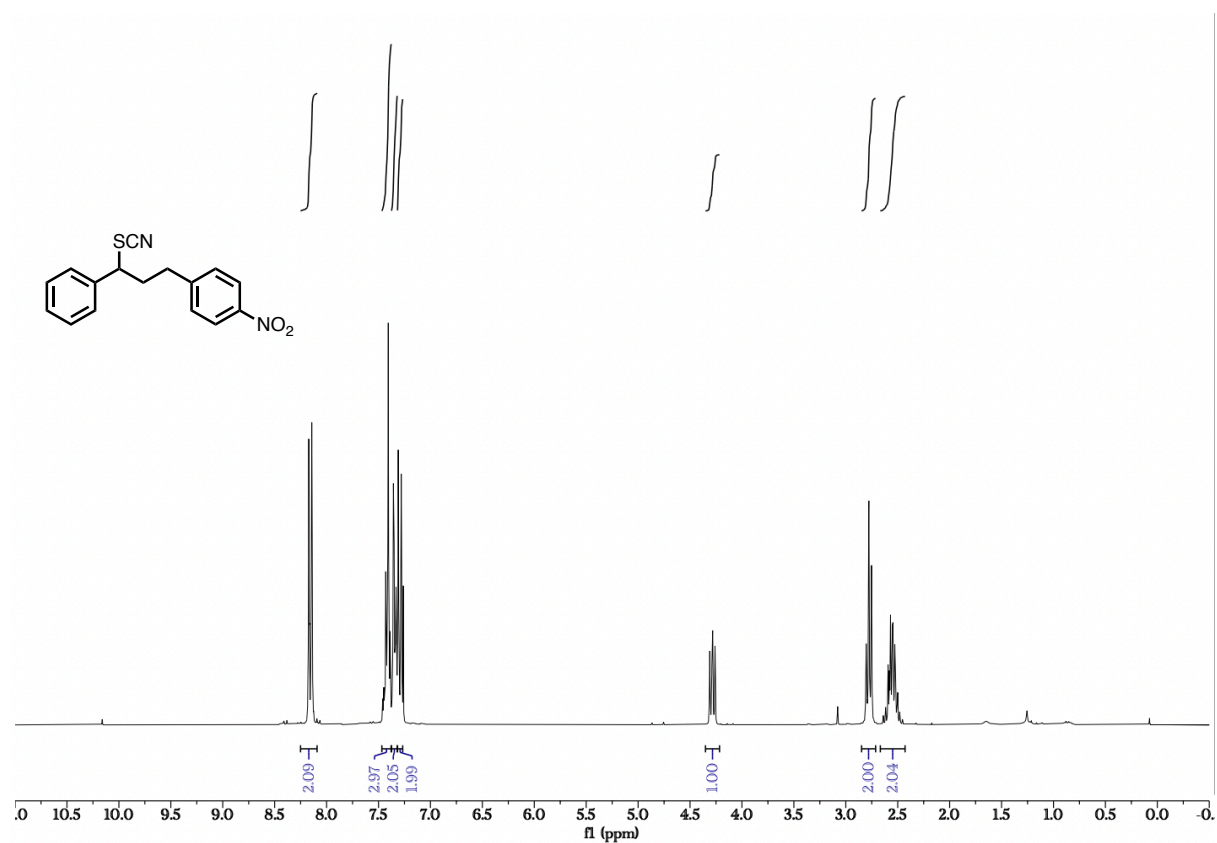




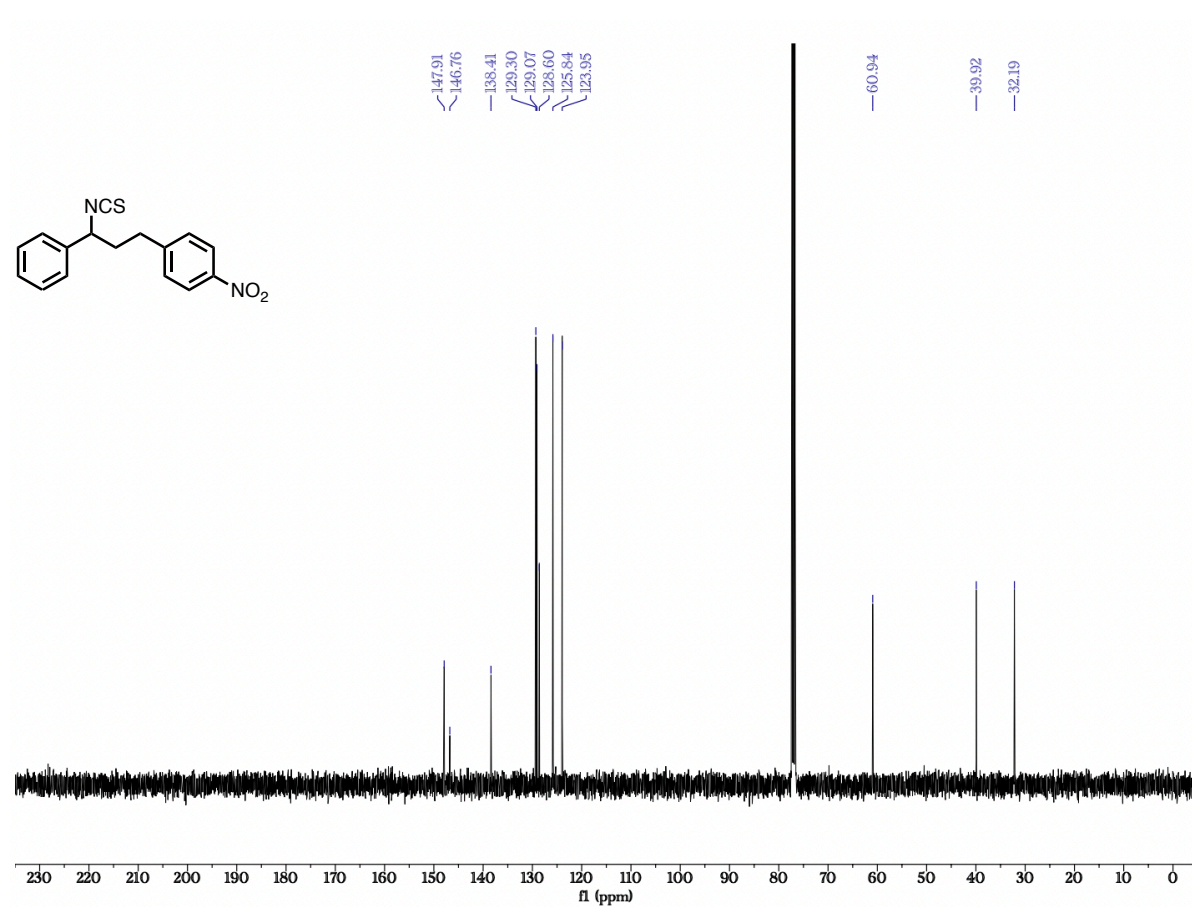
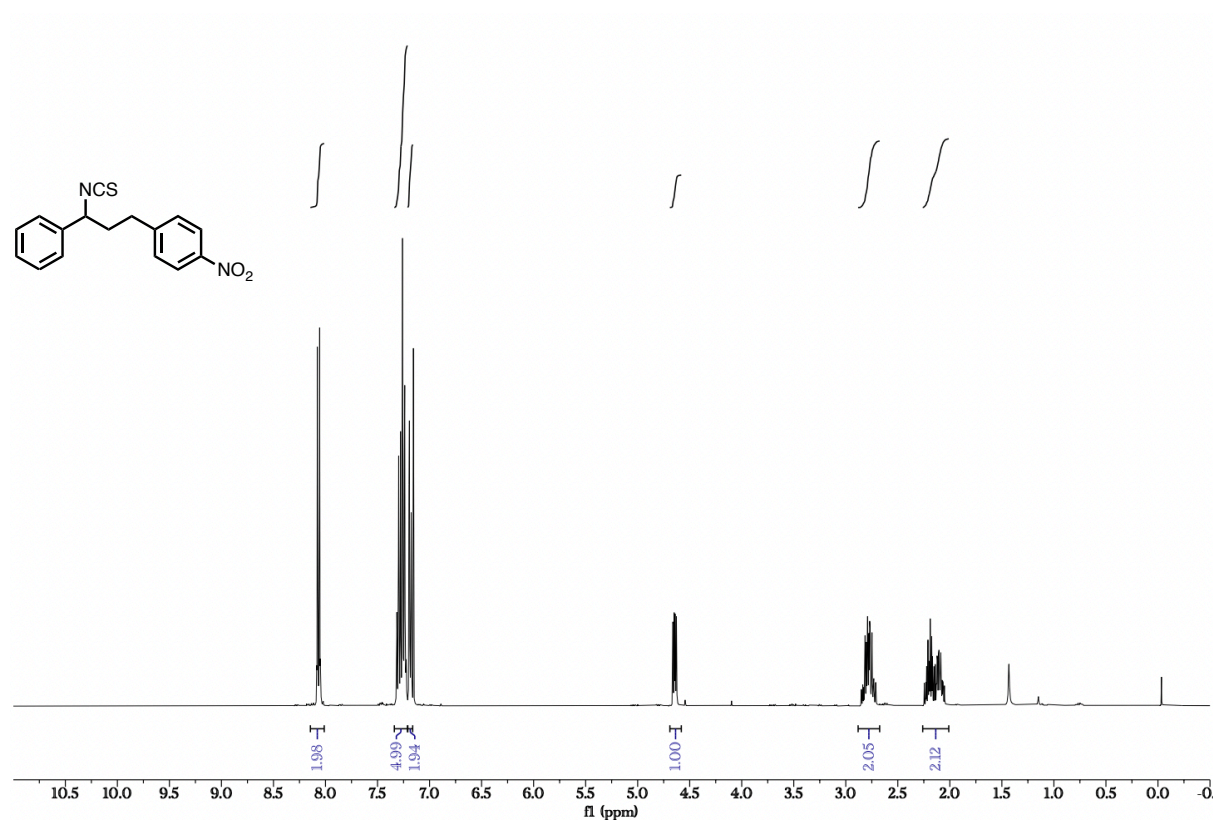
1-(3-isothiocyanato-3-(4-methoxyphenyl)propyl)-4-nitrobenzene (3ab')



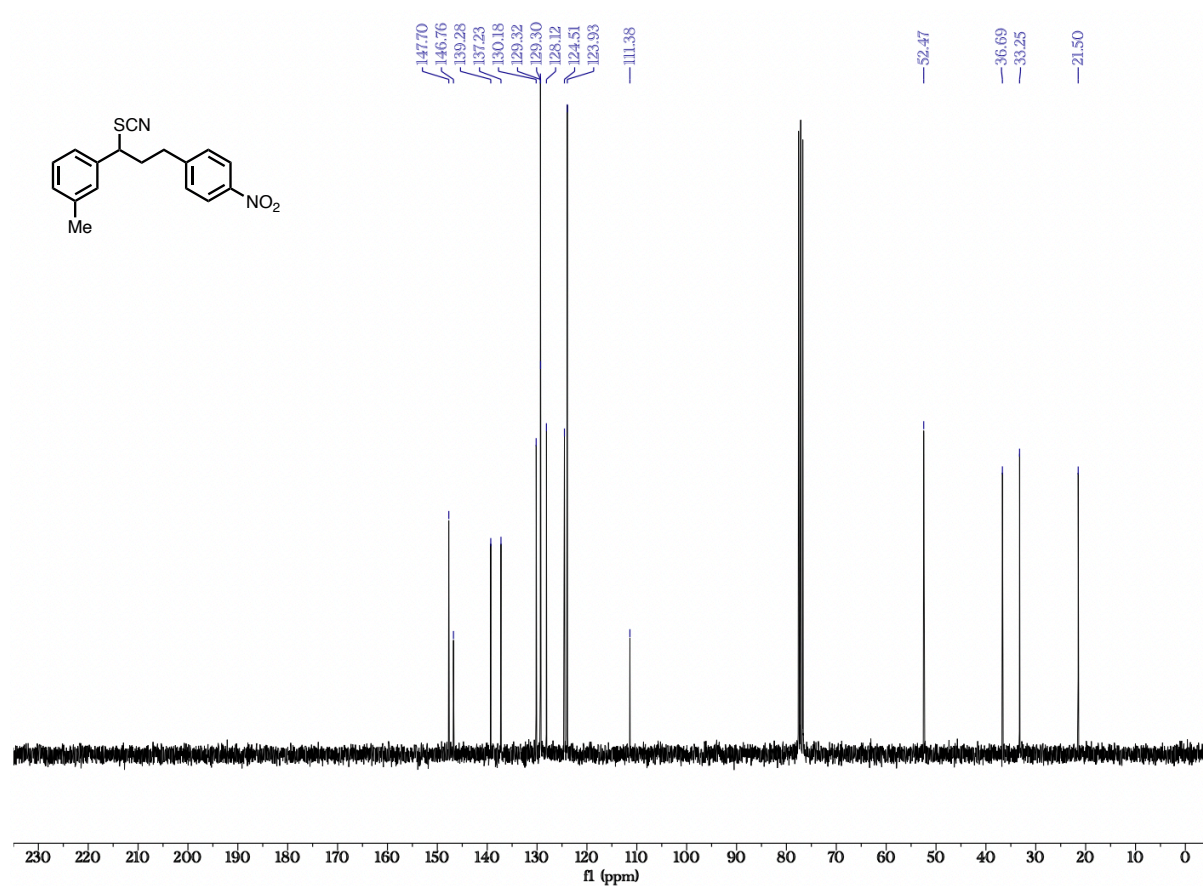
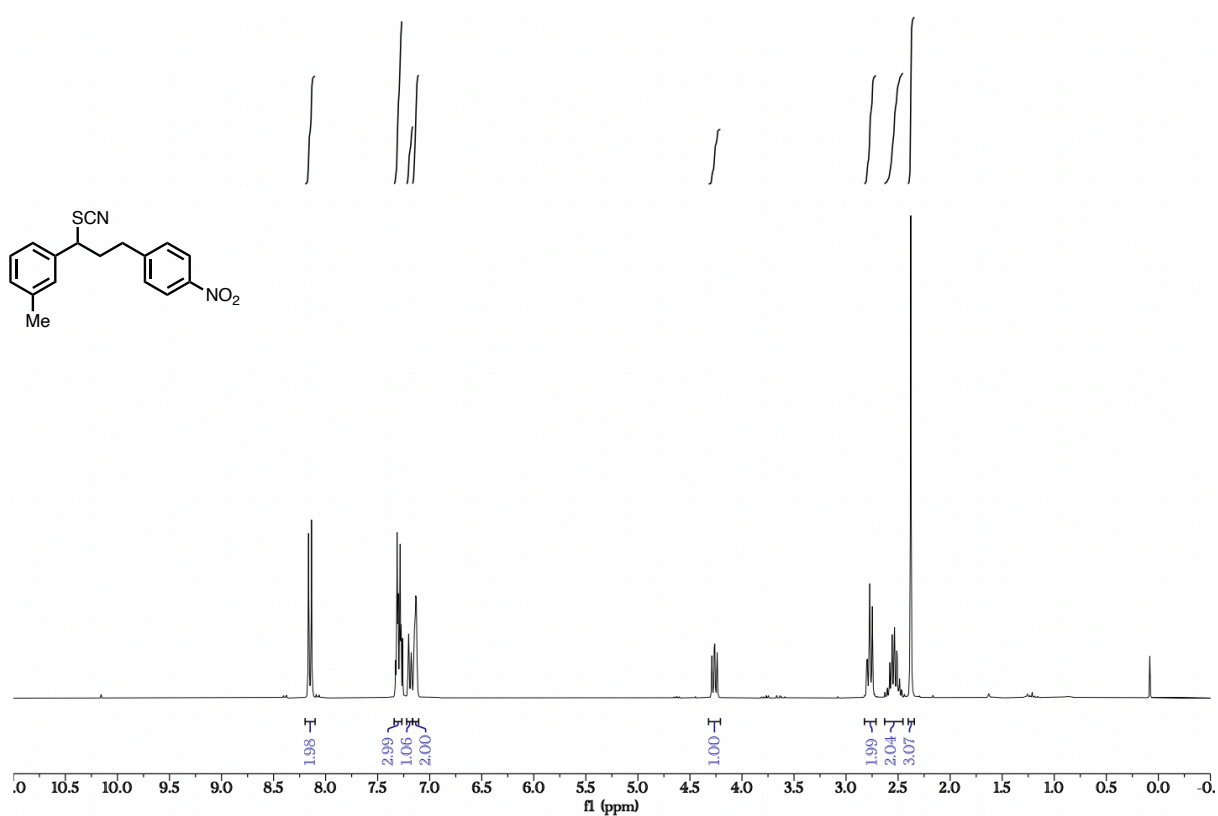
1-nitro-4-(3-phenyl-3-thiocyanatopropyl)benzene (3ac)



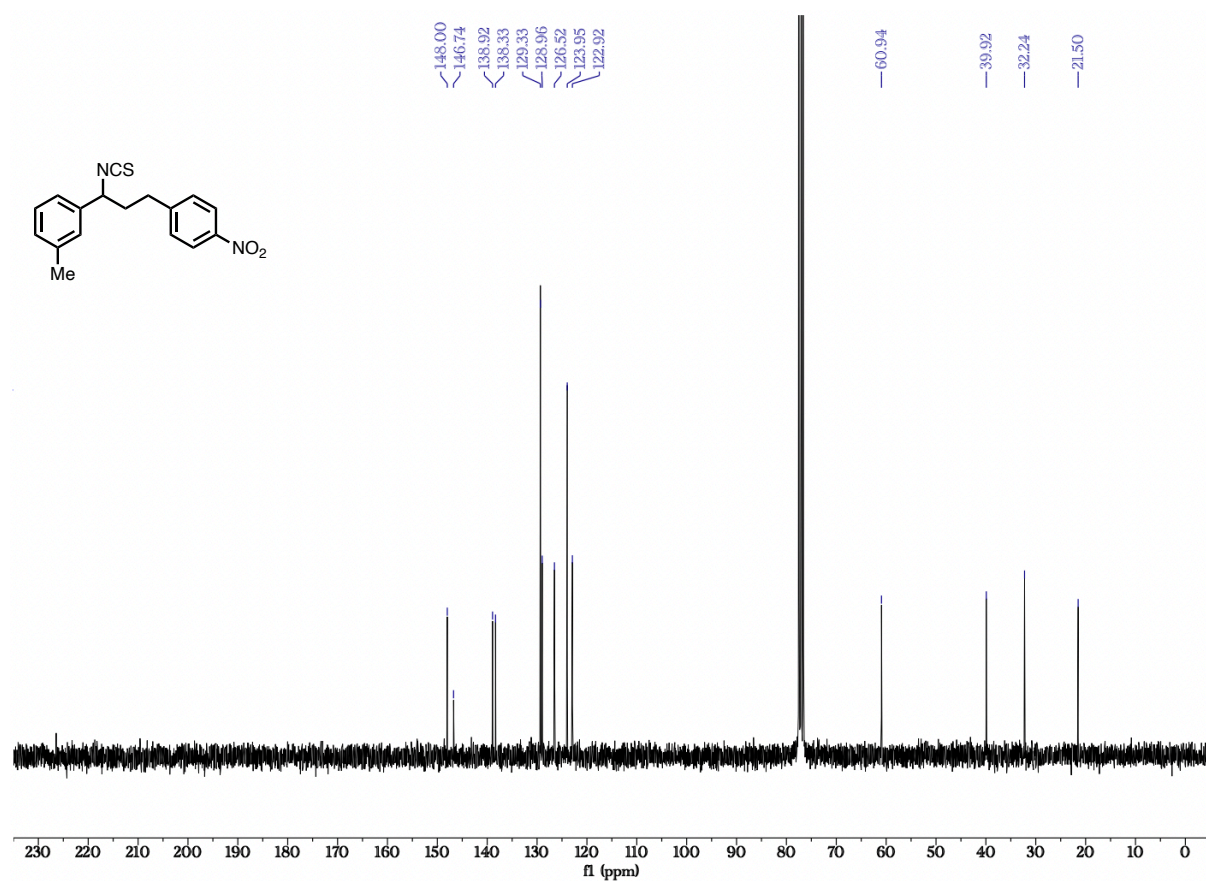
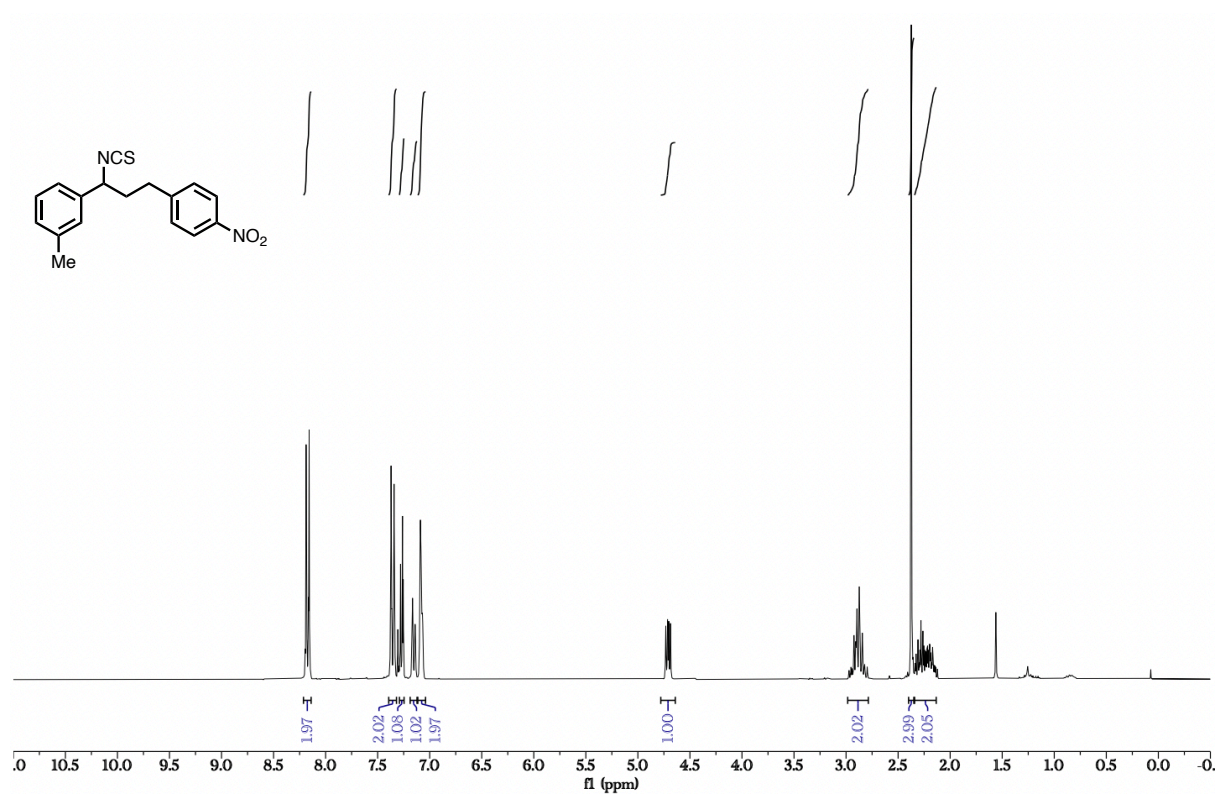
1-(3-isothiocyanato-3-phenylpropyl)-4-nitrobenzene (3ac')



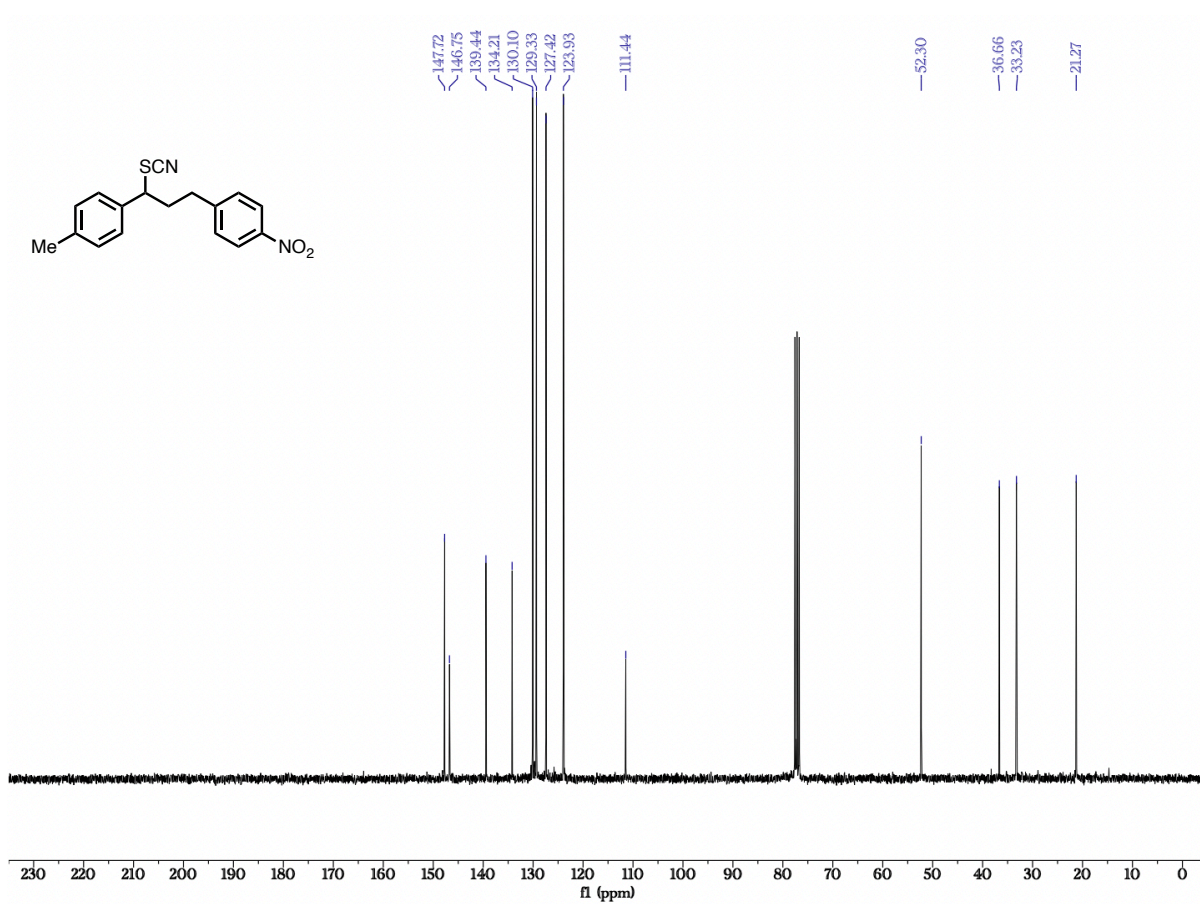
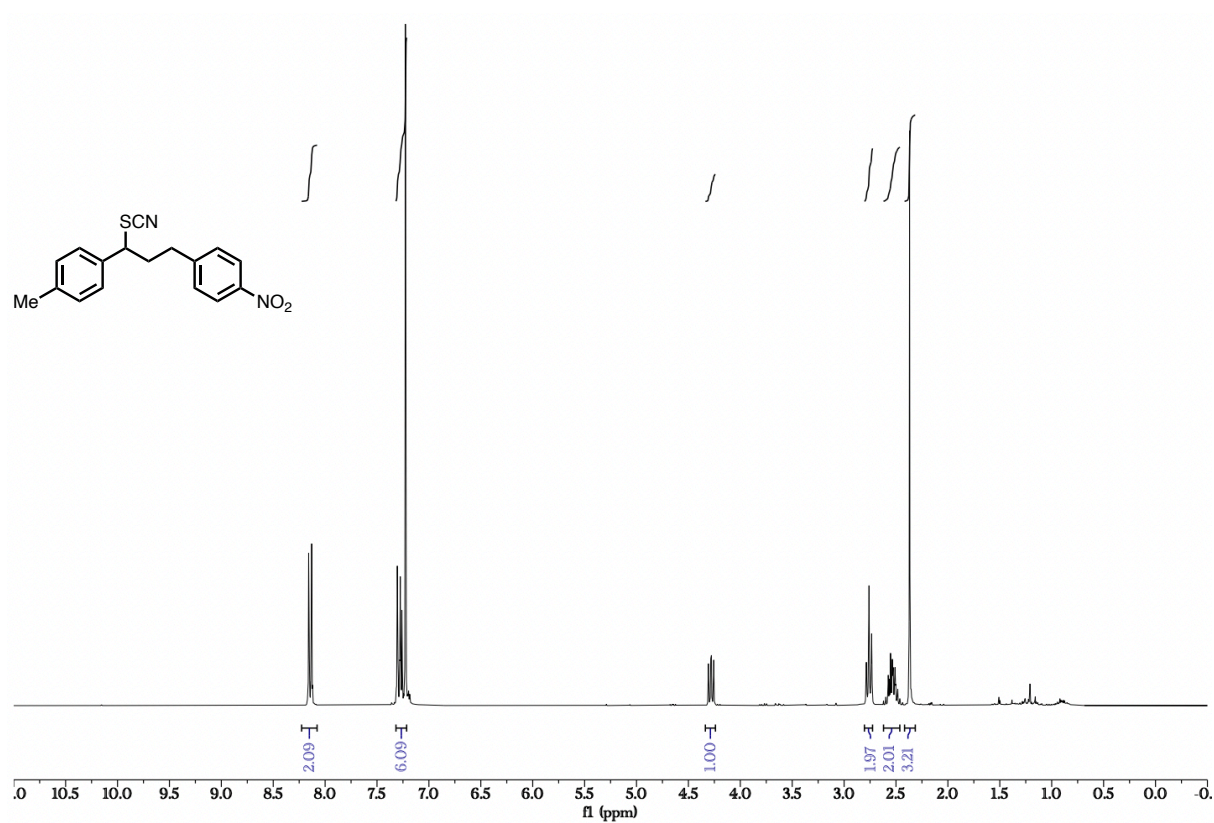
1-methyl-3-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3ad)



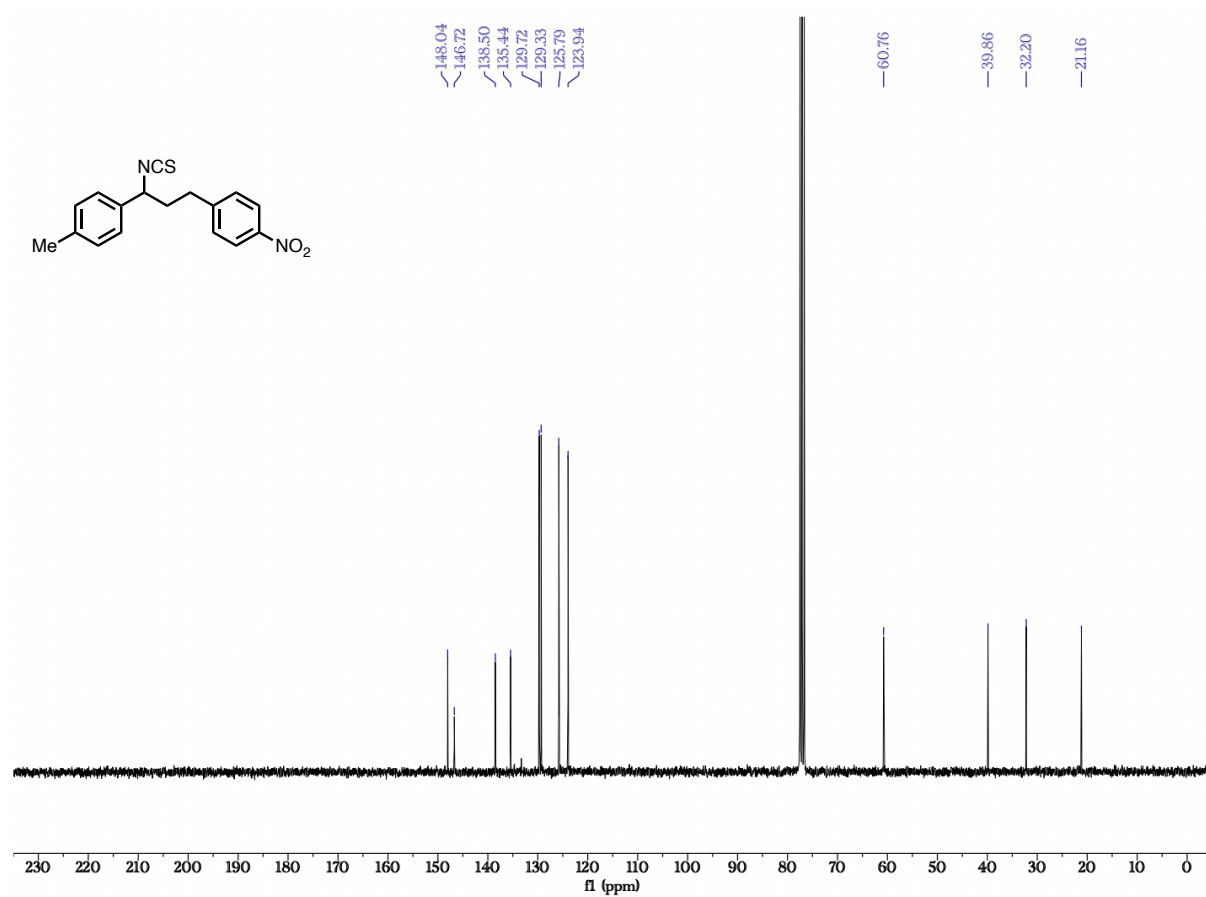
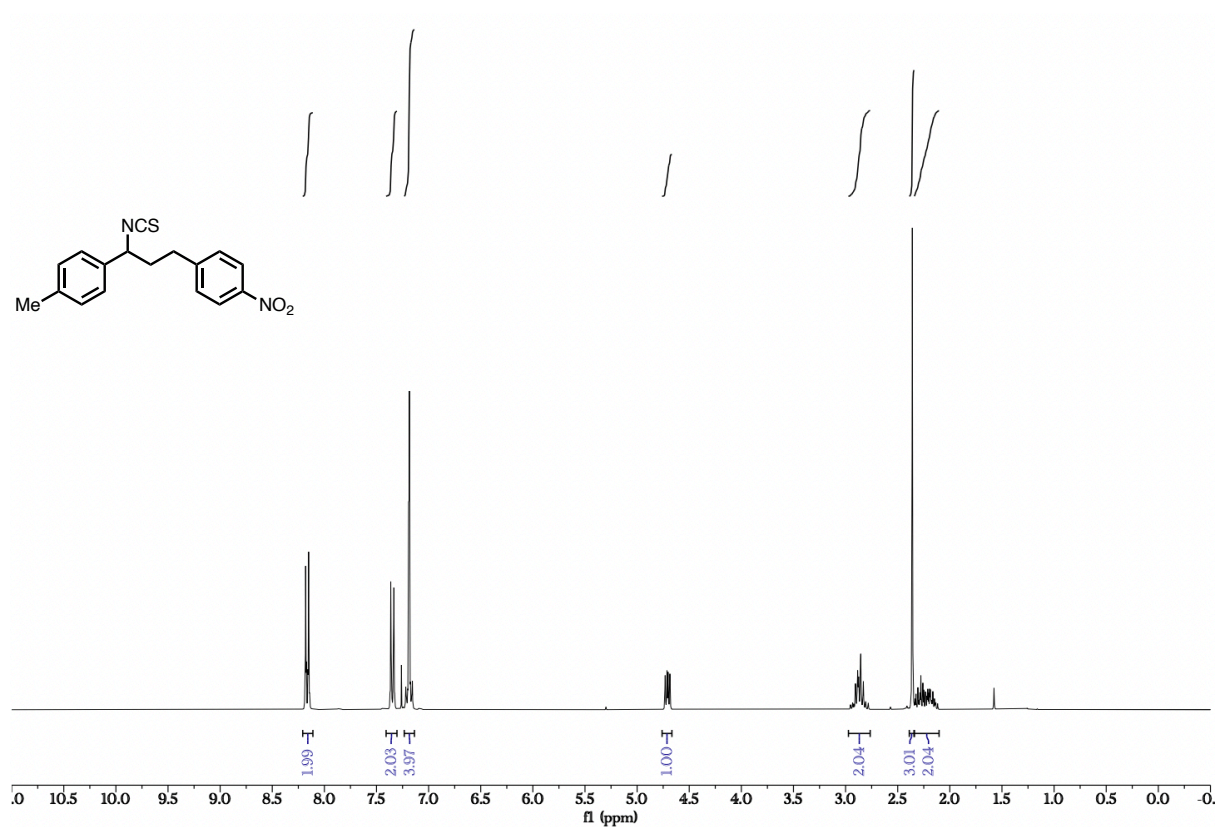
1-(1-isothiocyanato-3-(4-nitrophenyl)propyl)-3-methylbenzene (3ad')



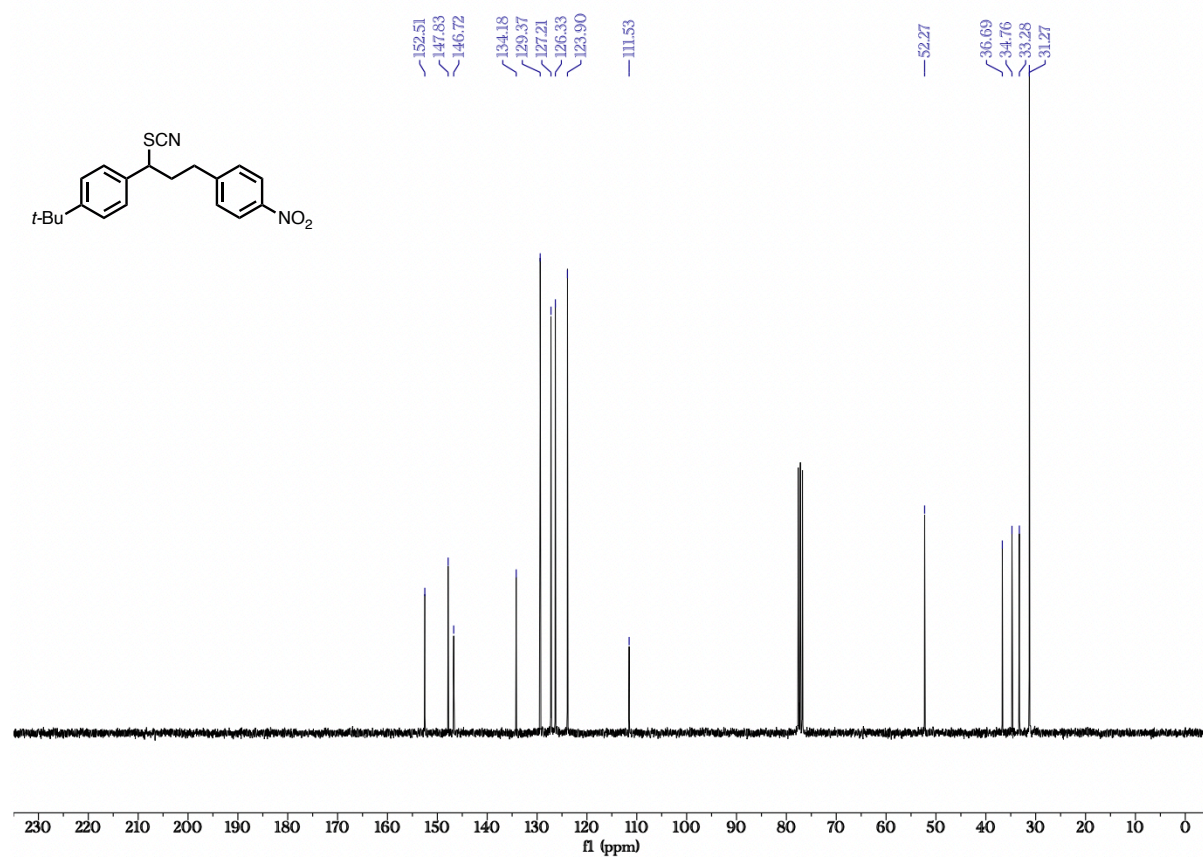
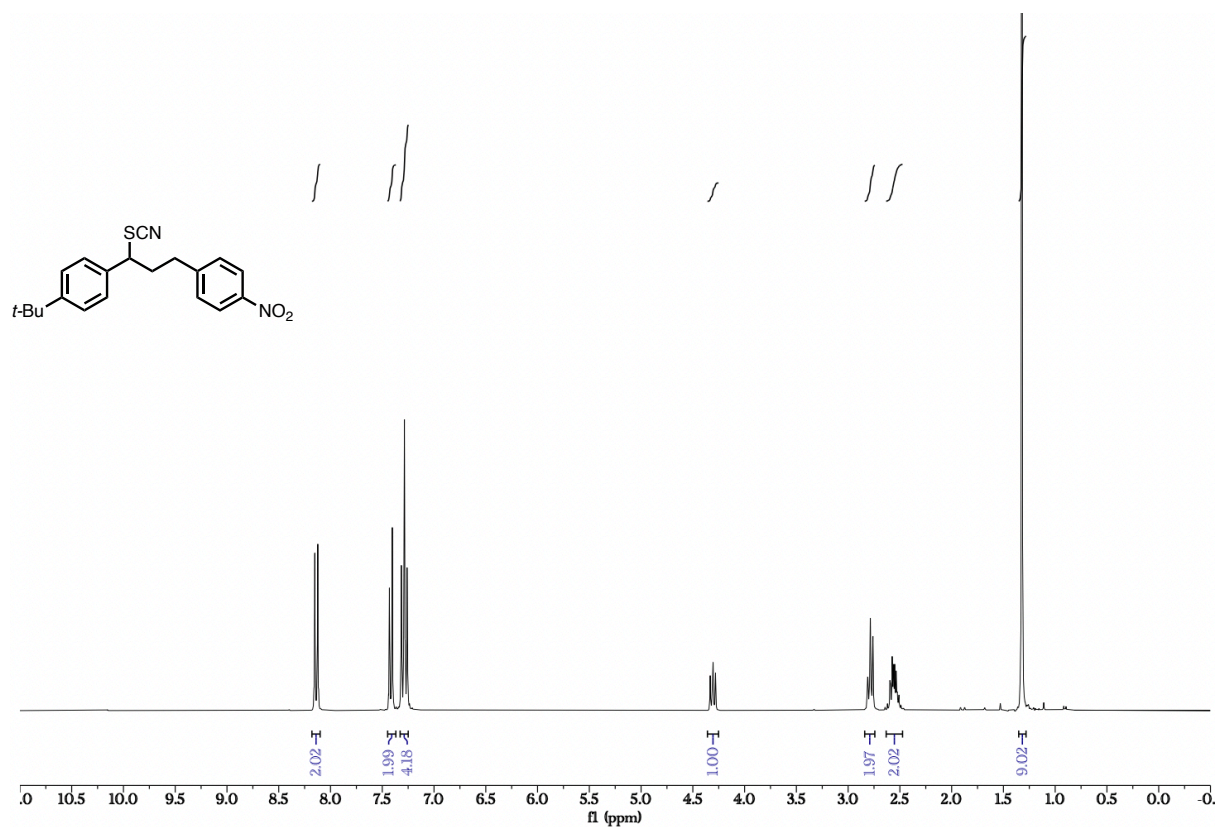
1-methyl-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3ae)



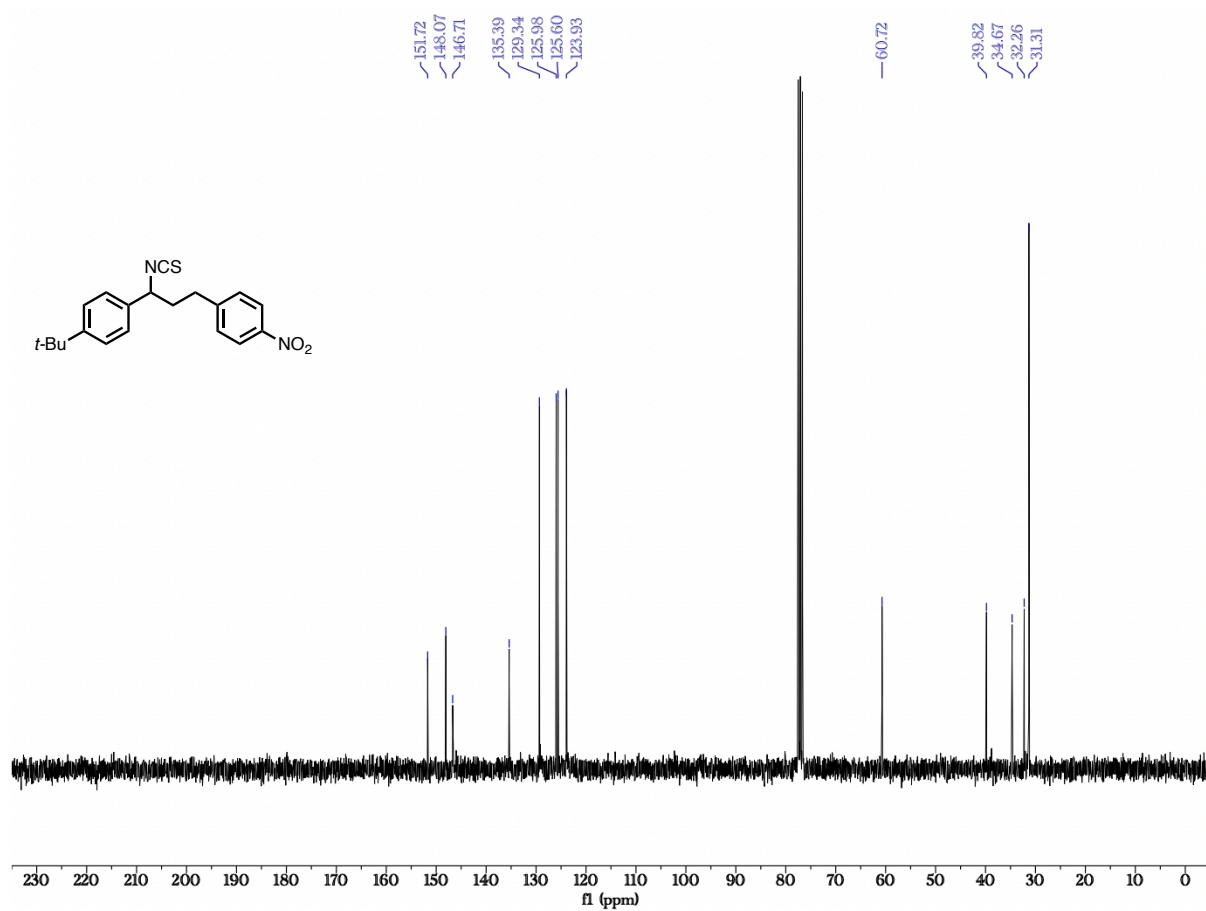
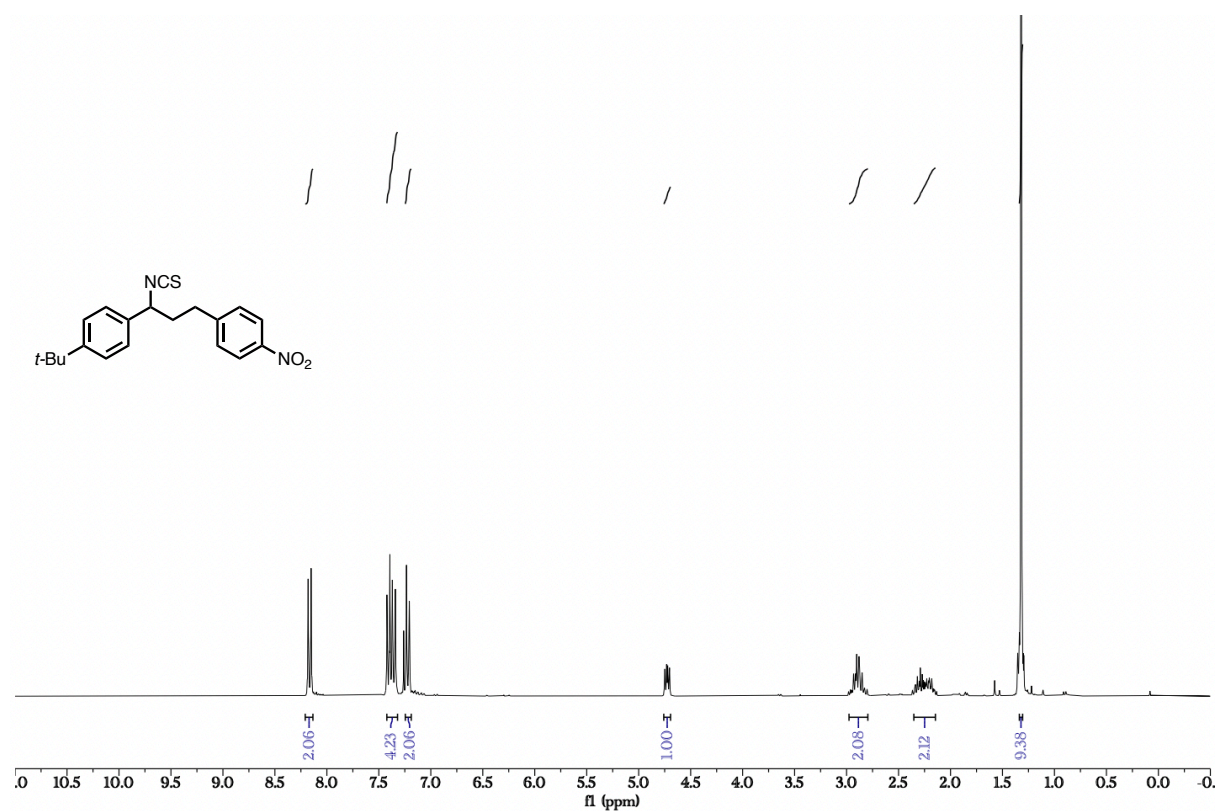
1-(1-isothiocyanato-3-(4-nitrophenyl)propyl)-4-methylbenzene (3ae')



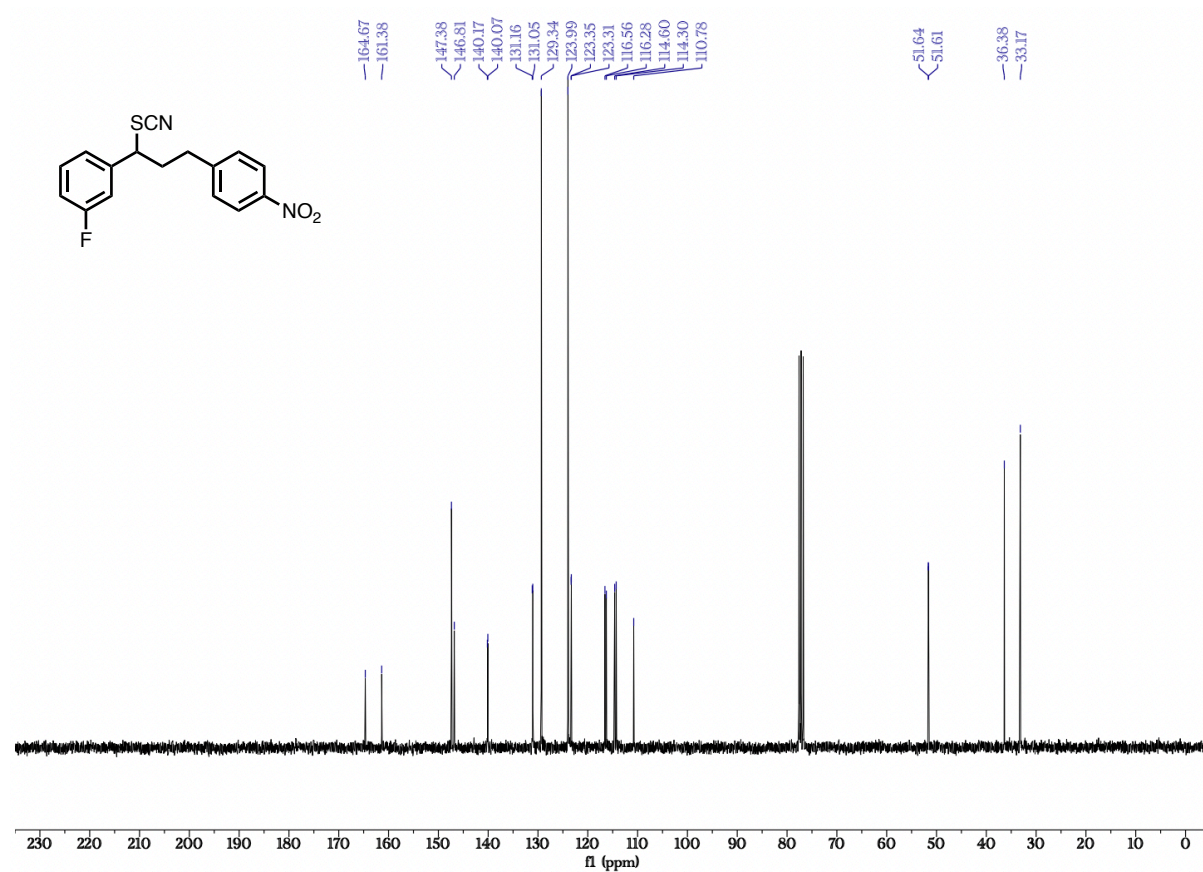
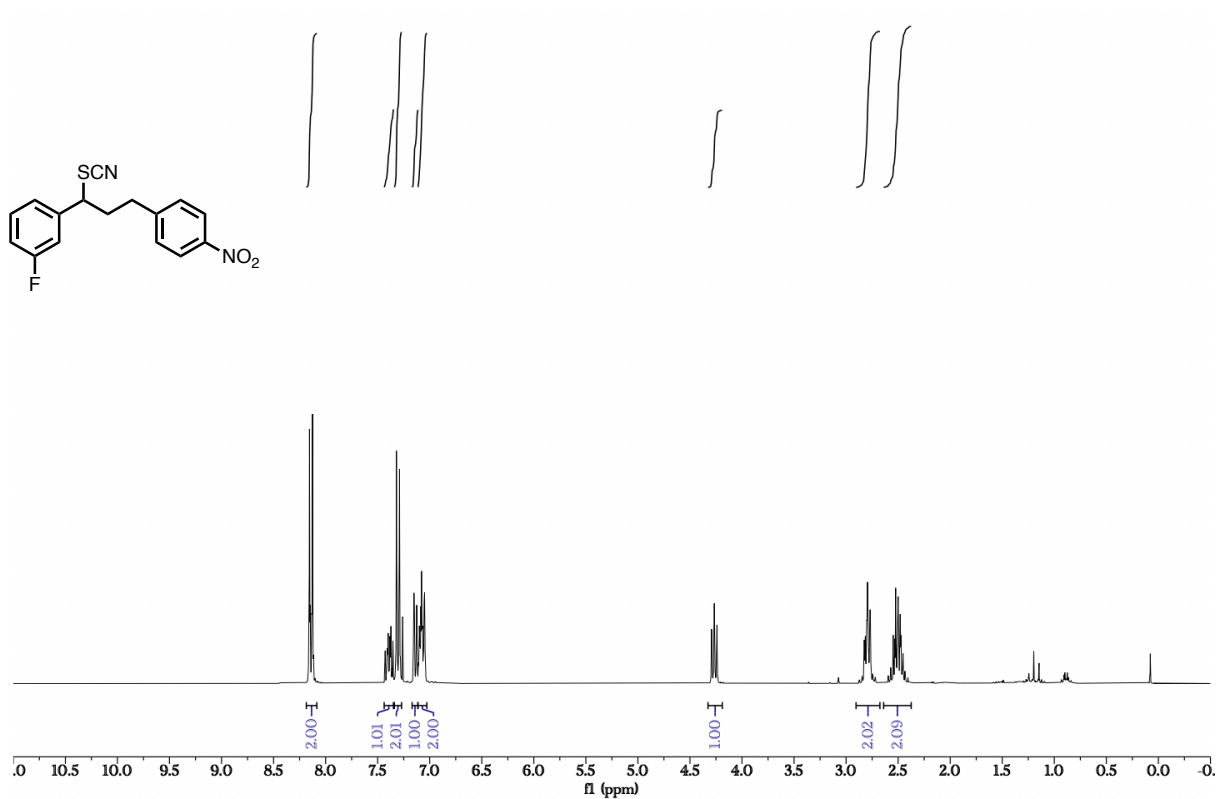
1-(*tert*-butyl)-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3af)

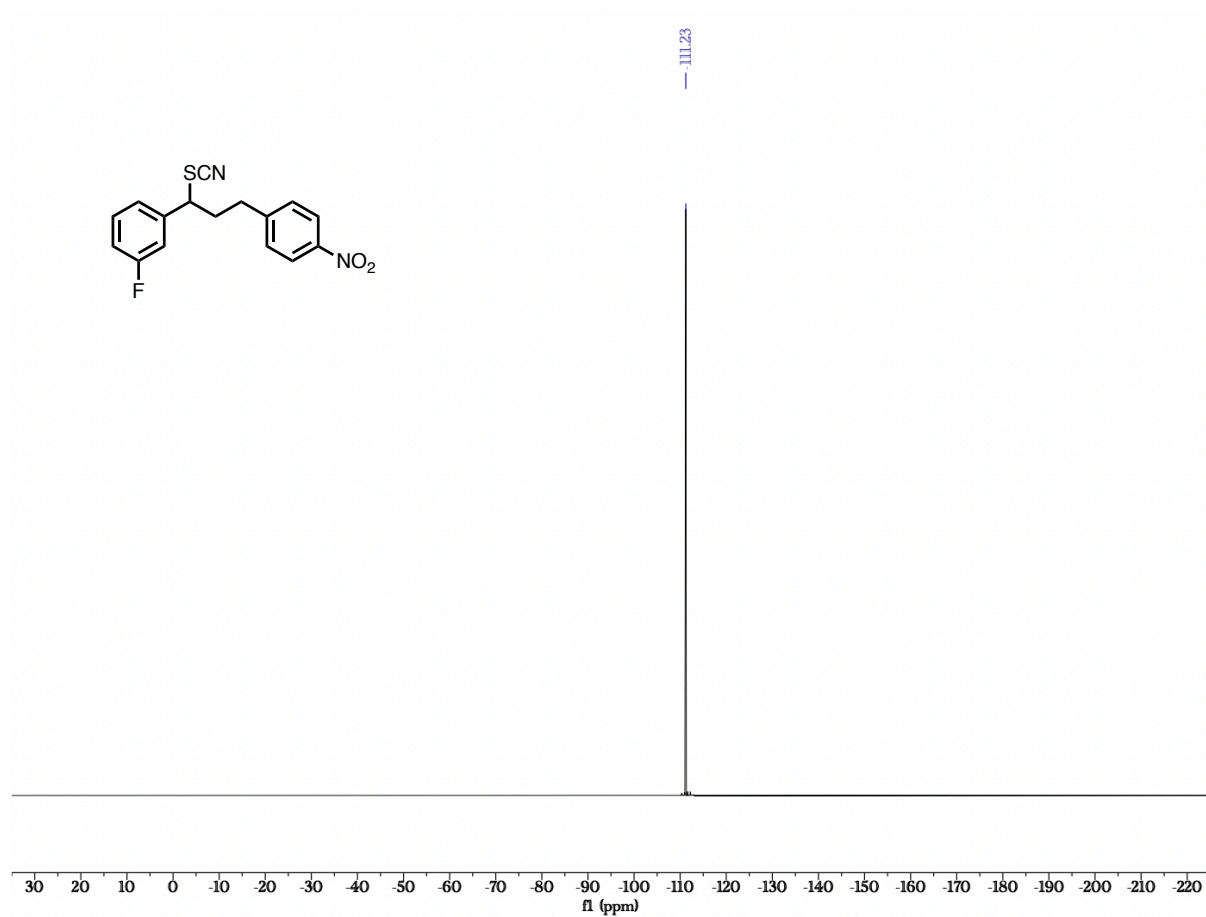


1-(*tert*-butyl)-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (3af')

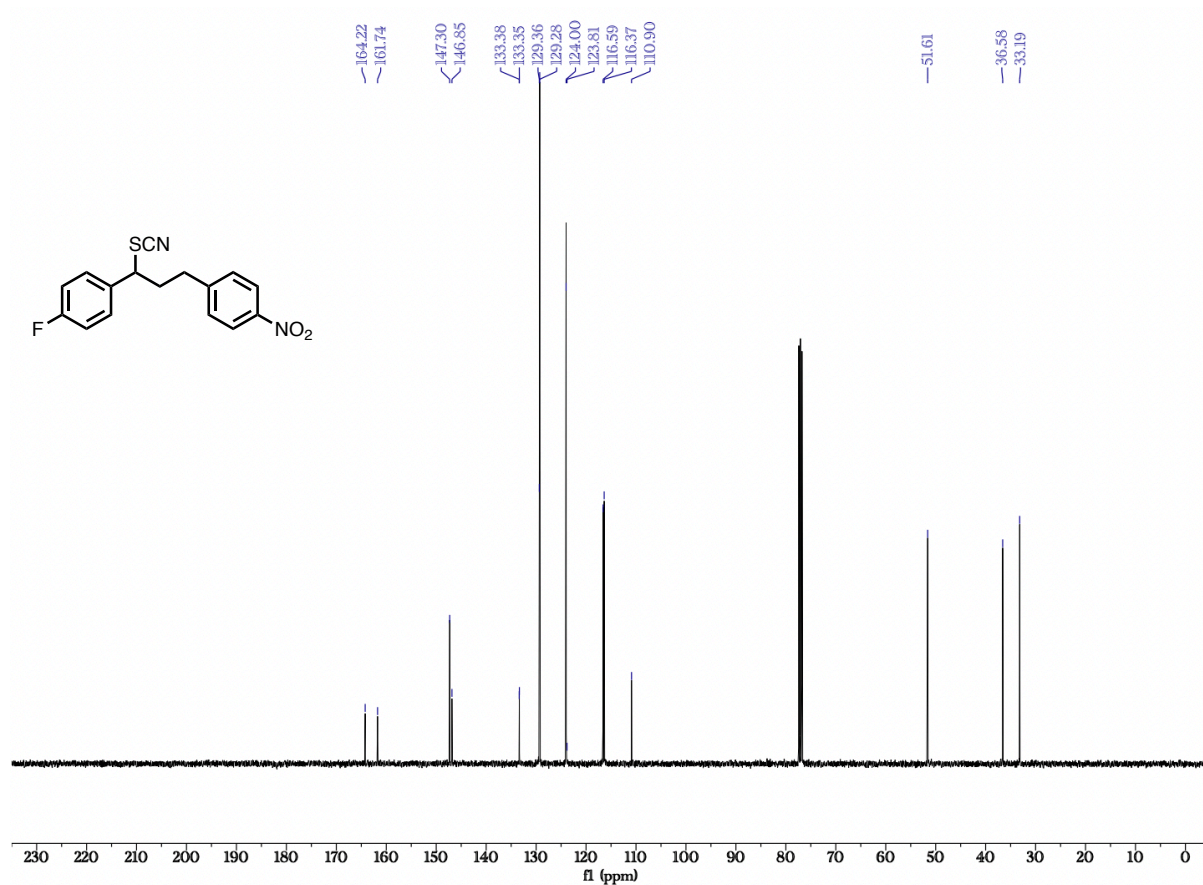
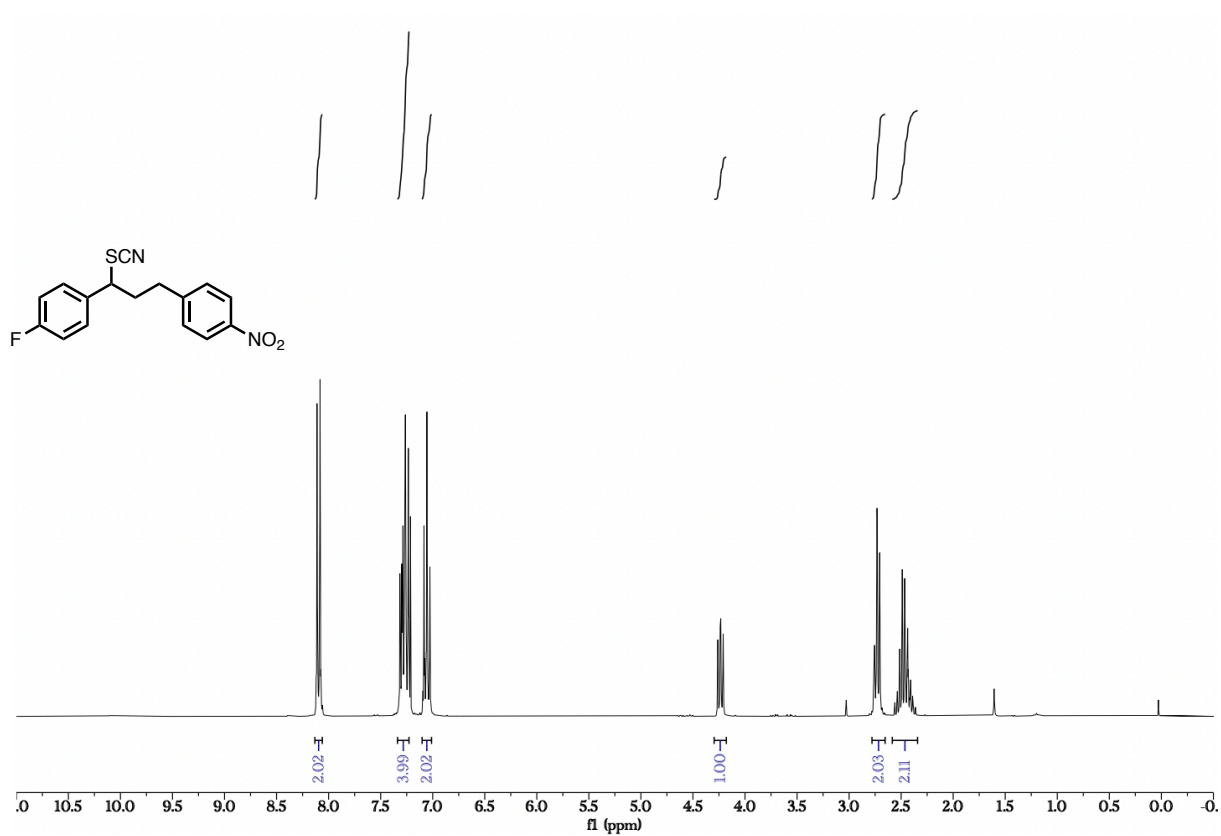


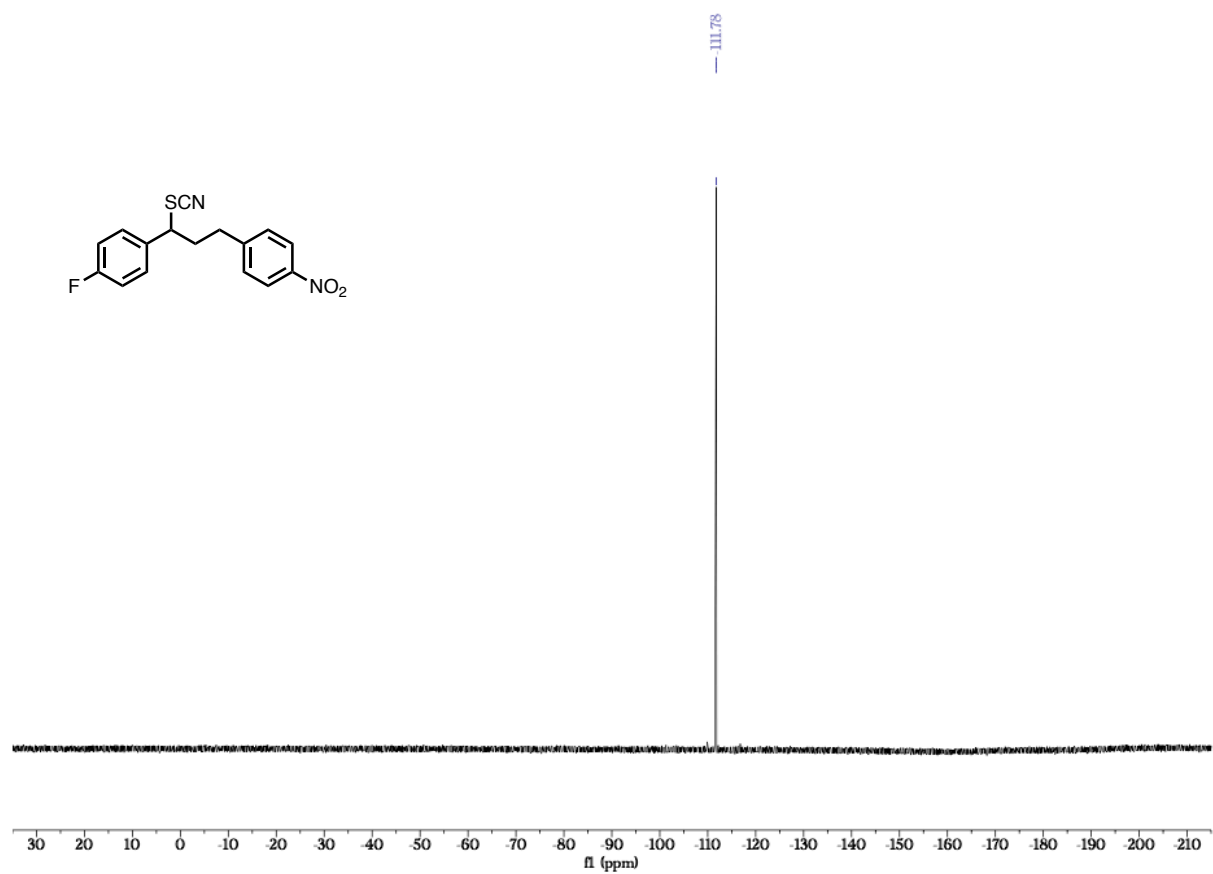
1-fluoro-3-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3ag)



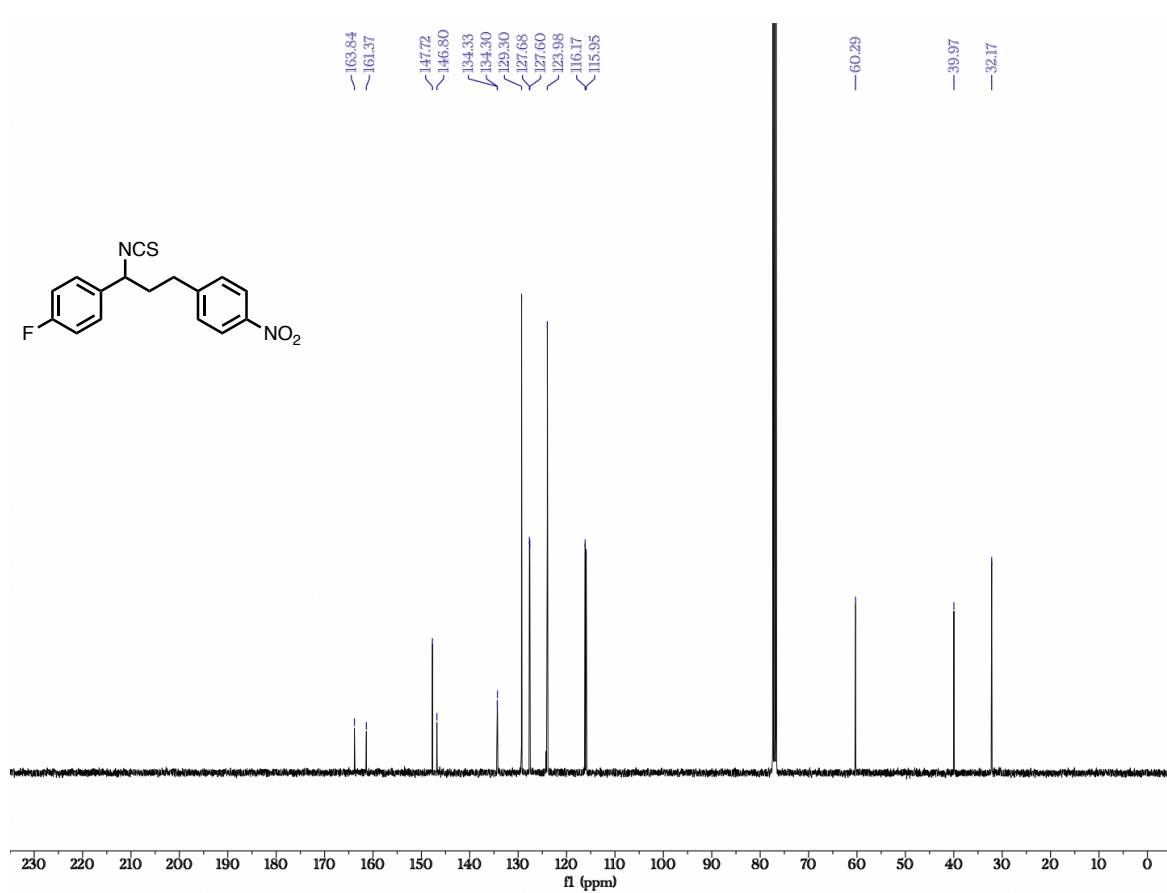
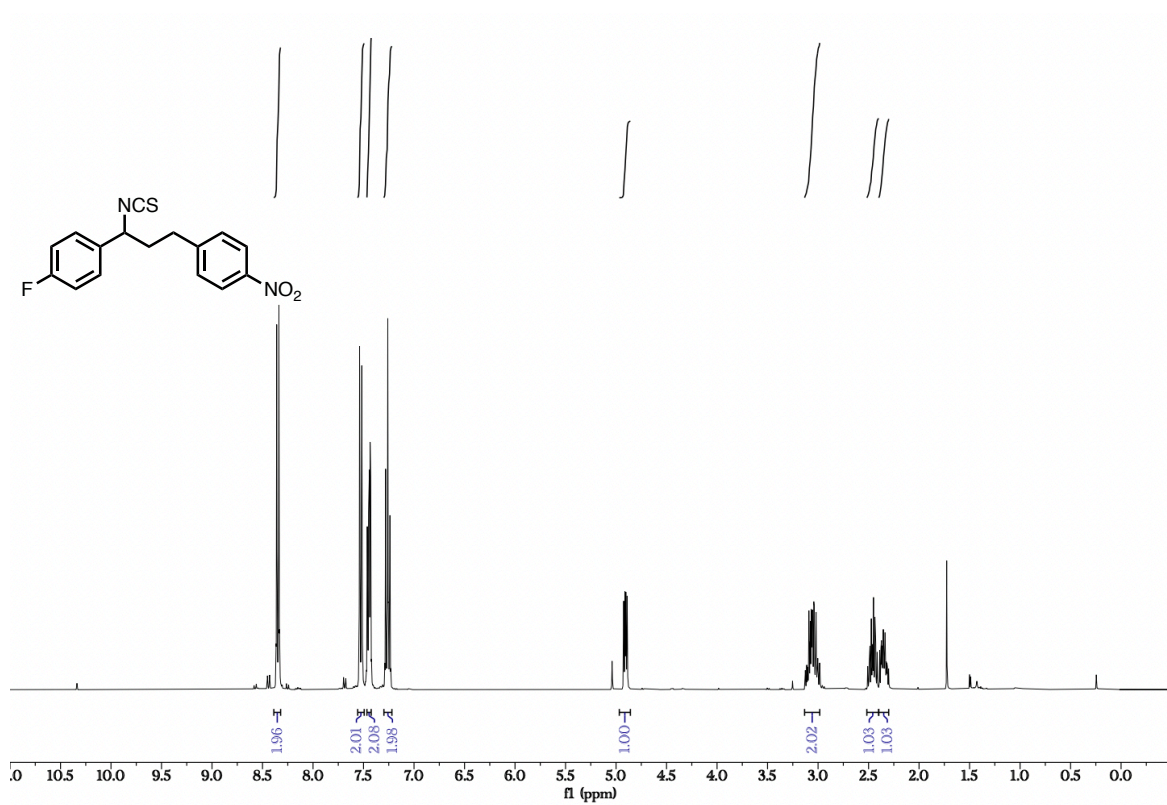


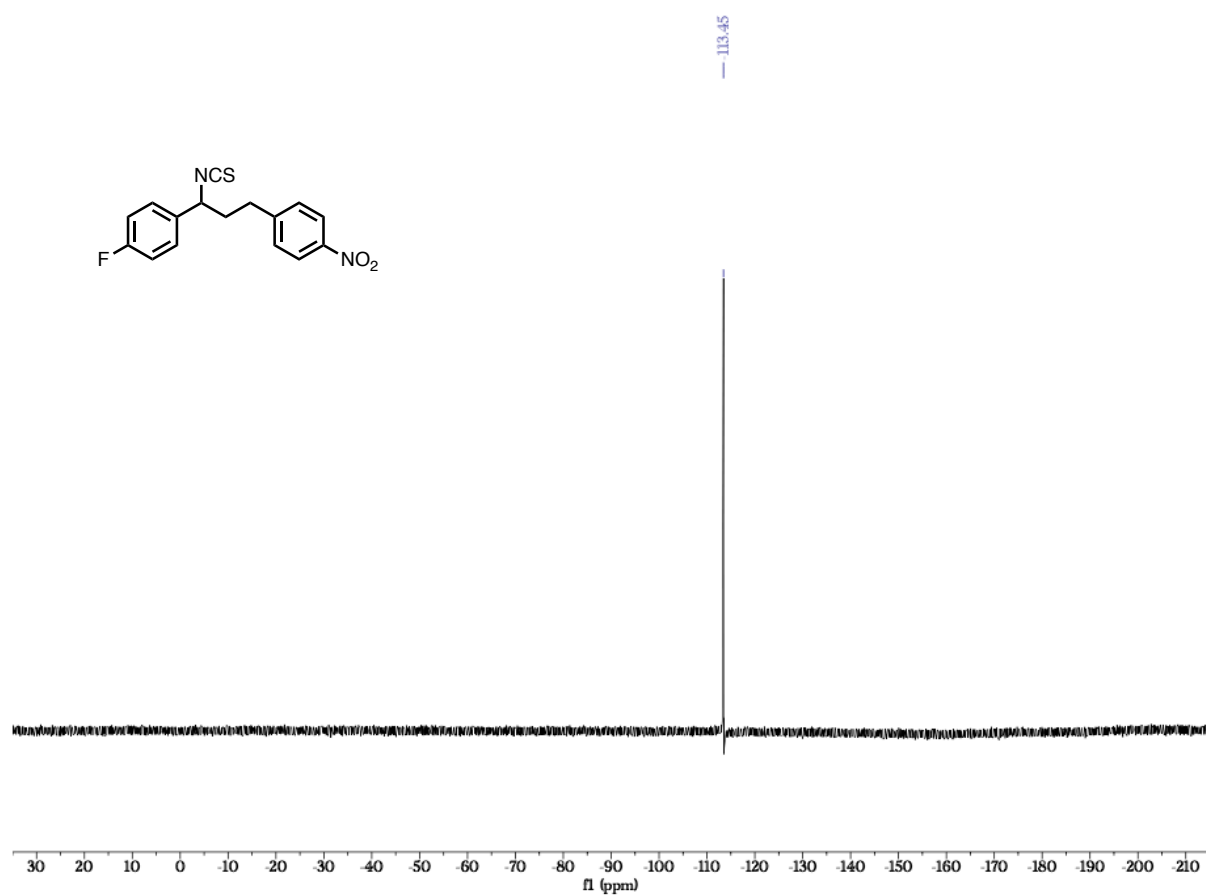
1-fluoro-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3ah)



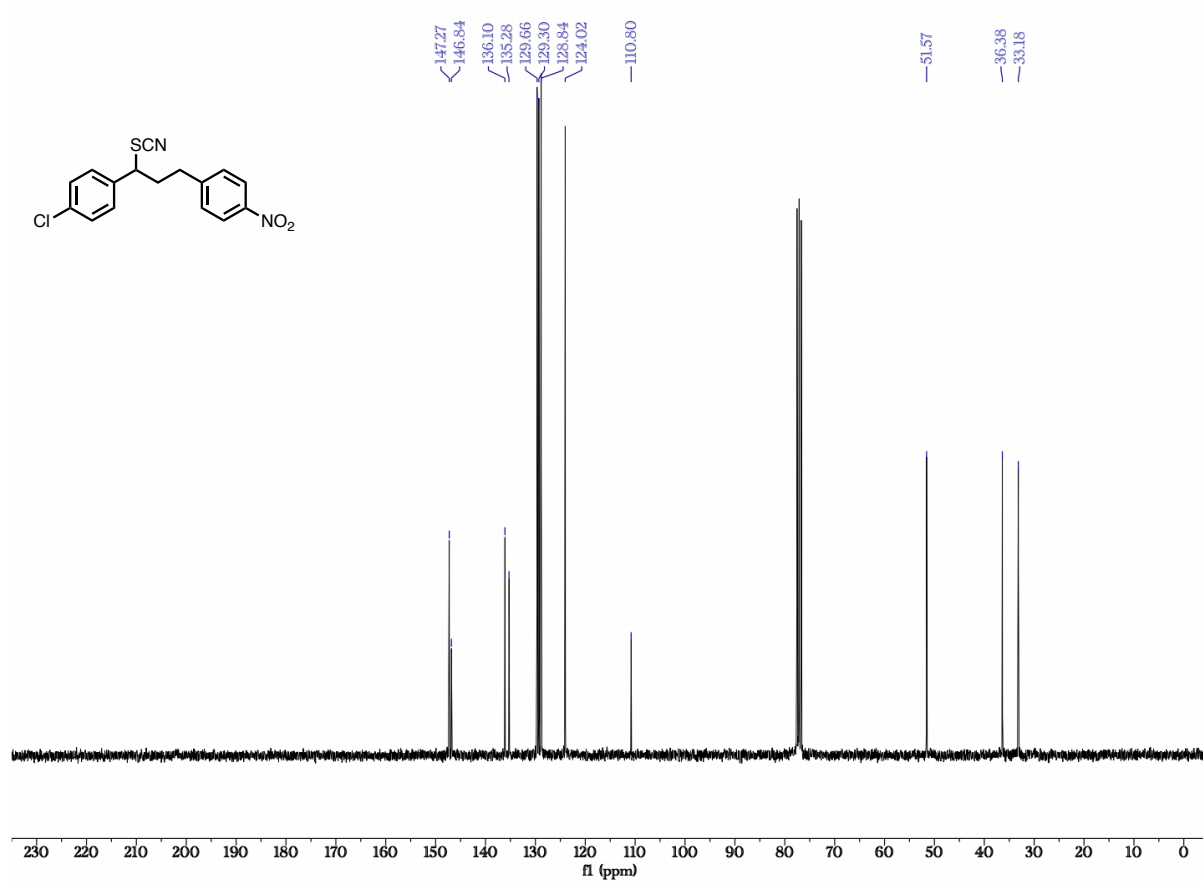
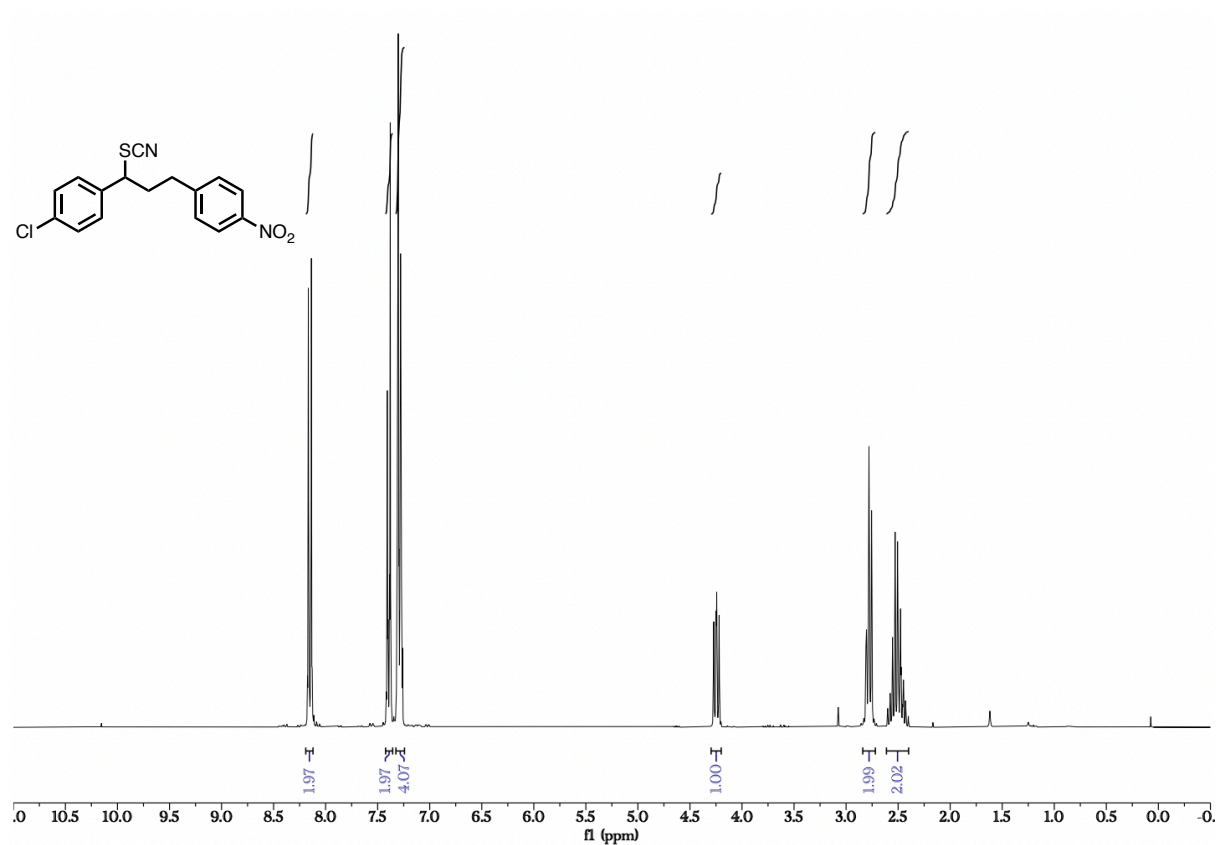


1-fluoro-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (3ah')

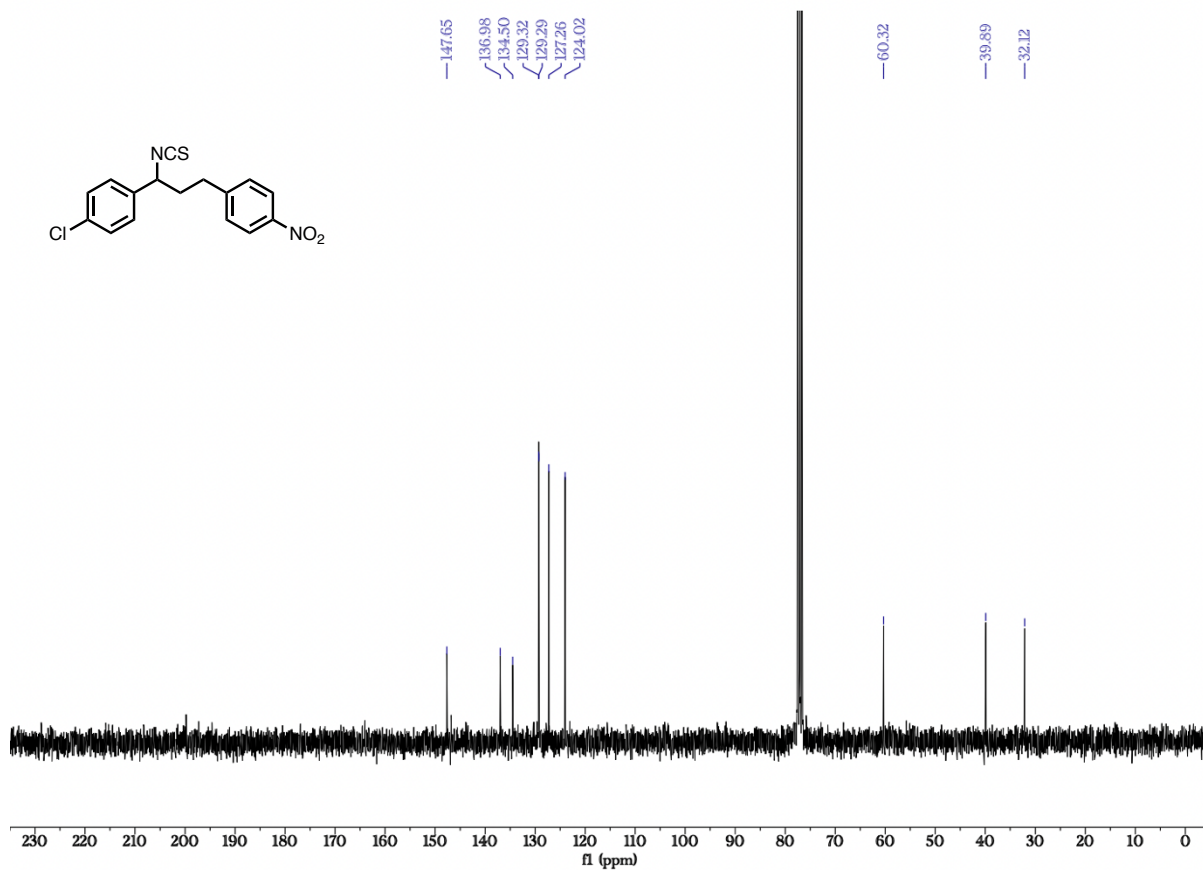
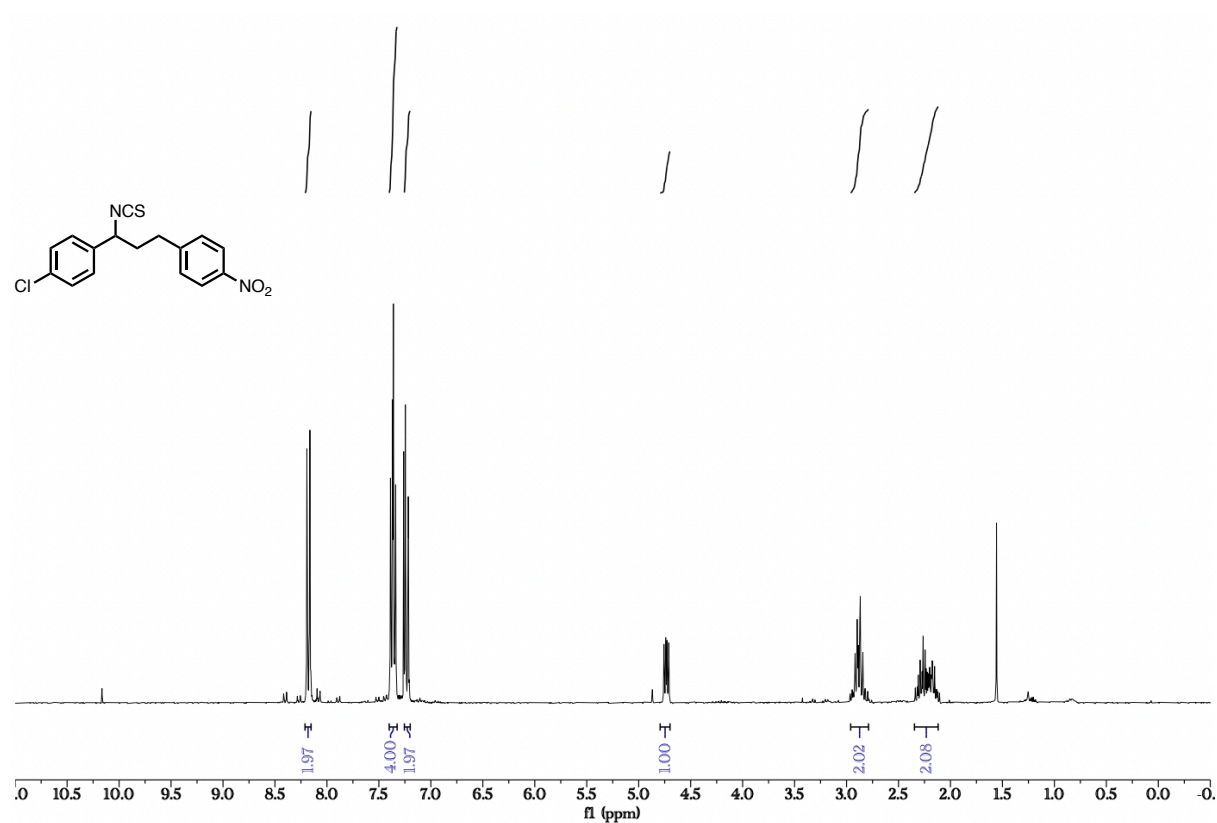




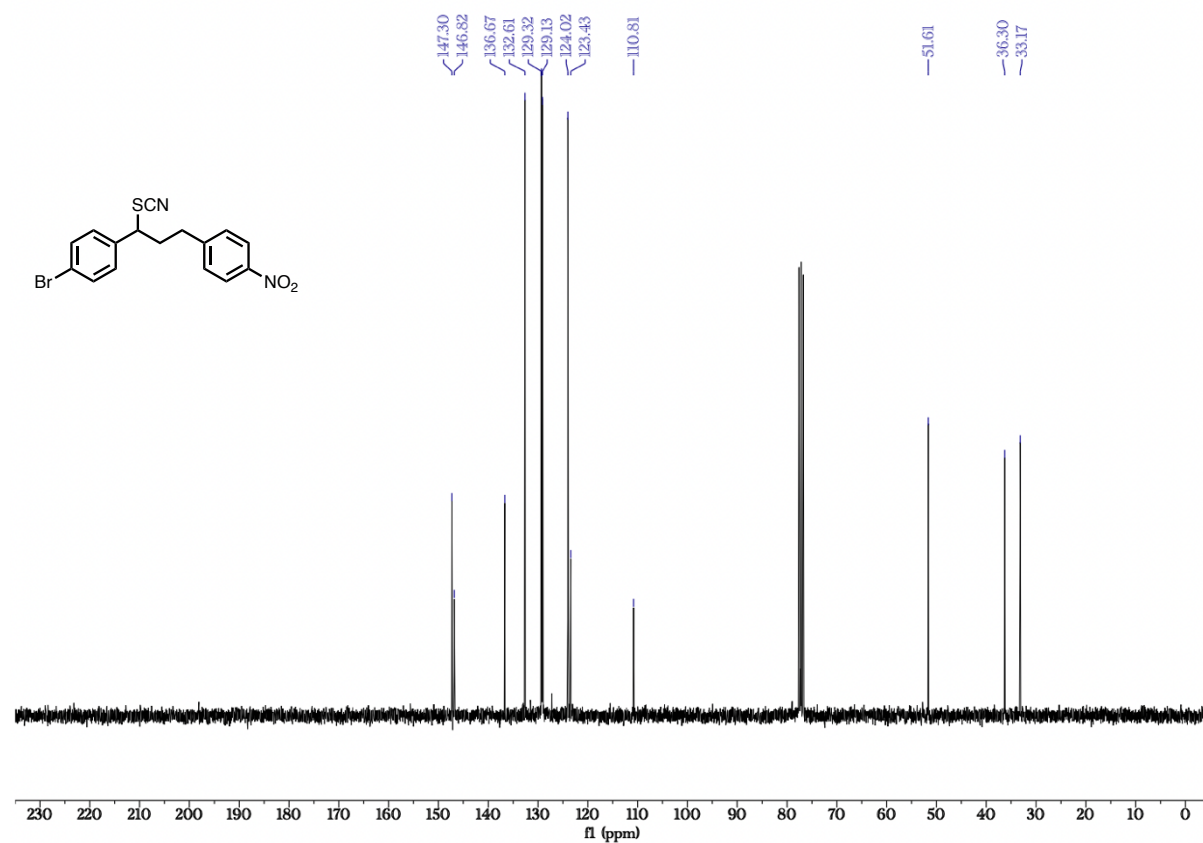
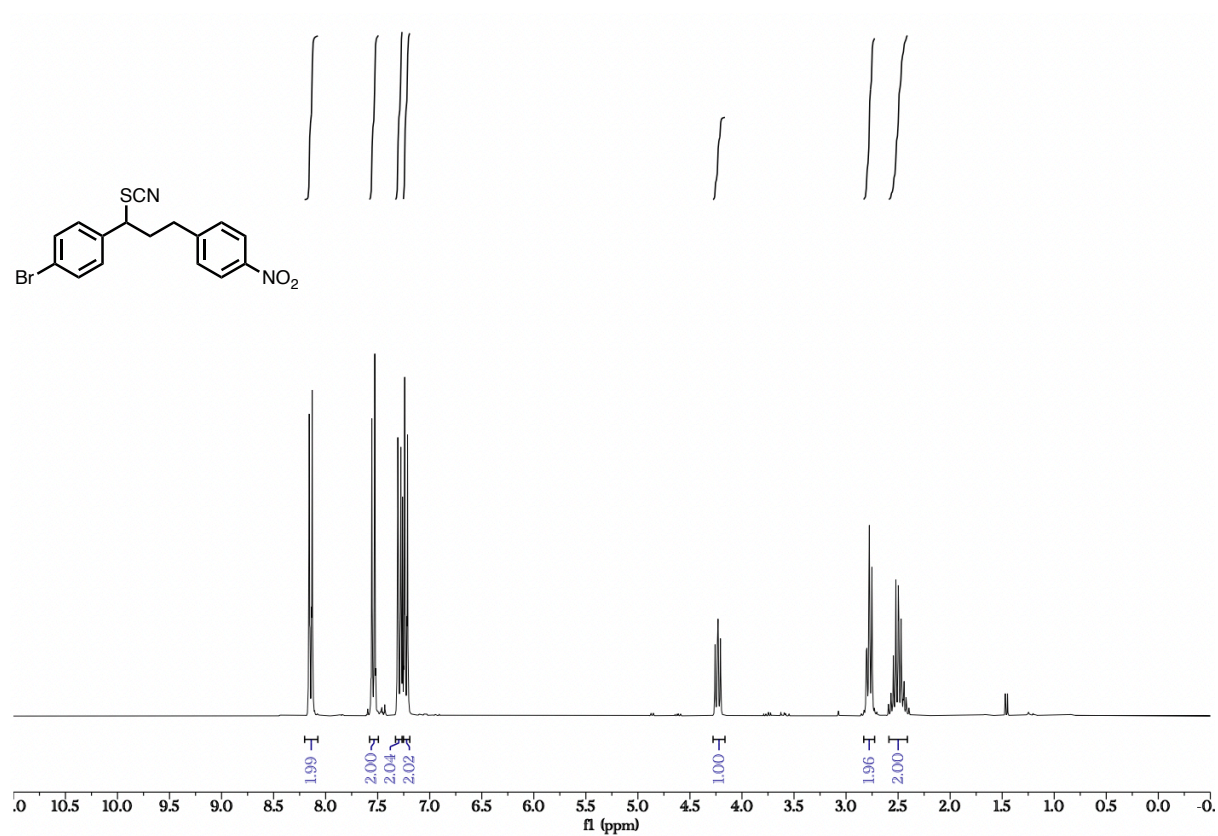
1-chloro-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3ai)



1-chloro-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (3ai')

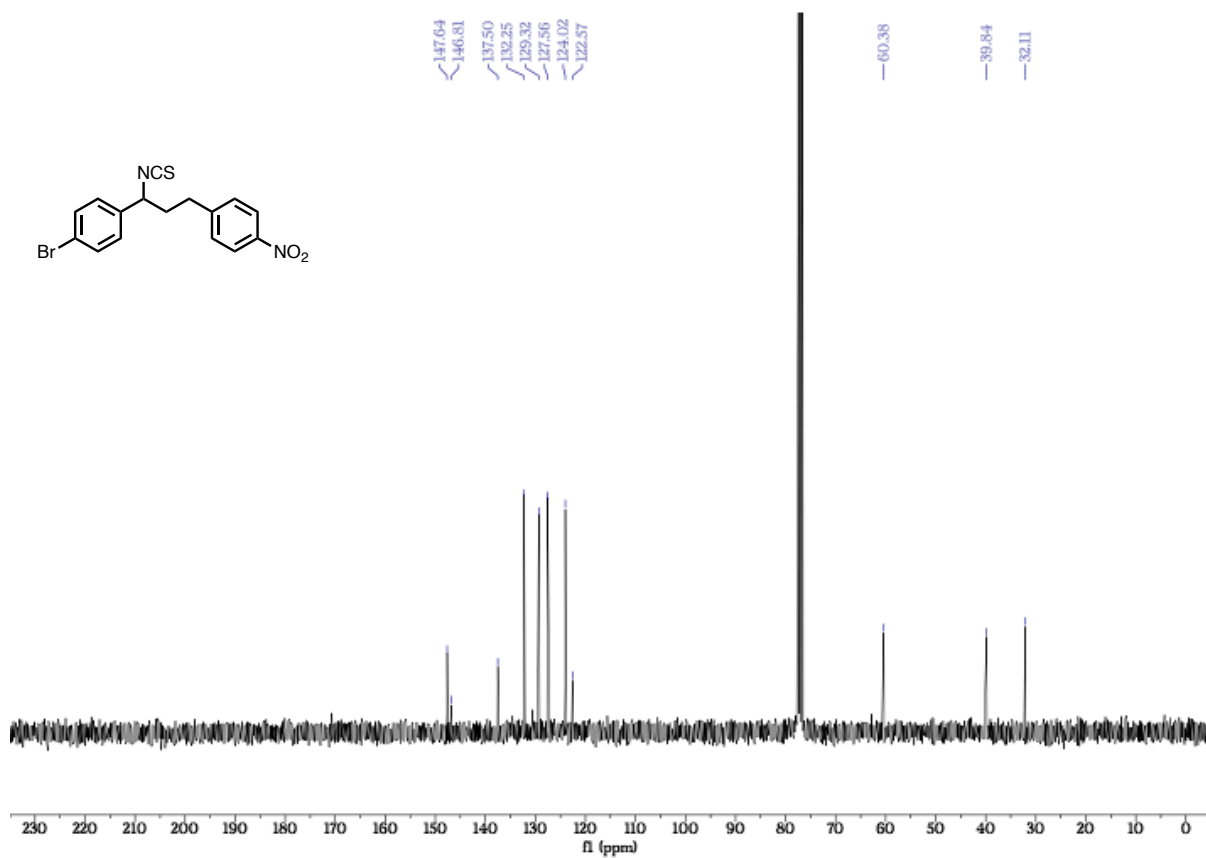


1-bromo-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3aj)

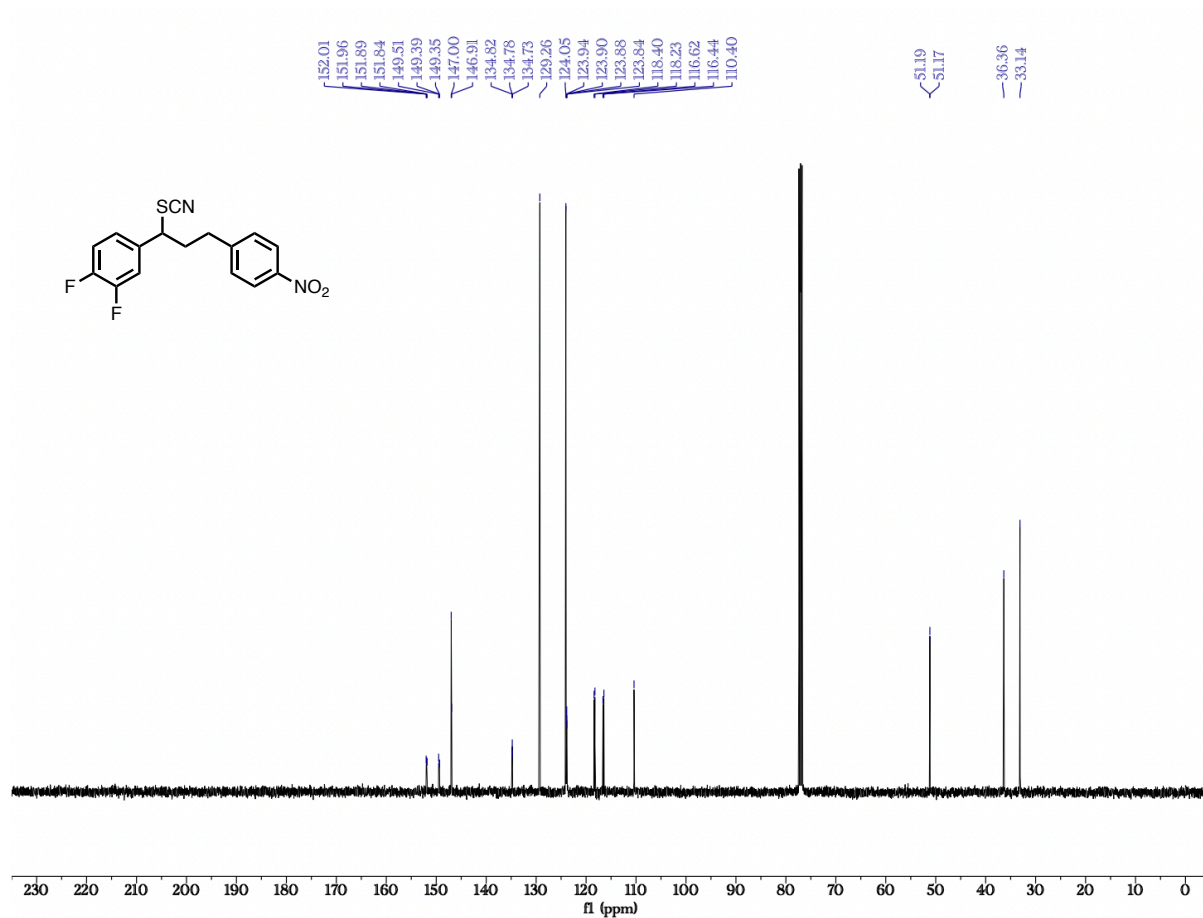
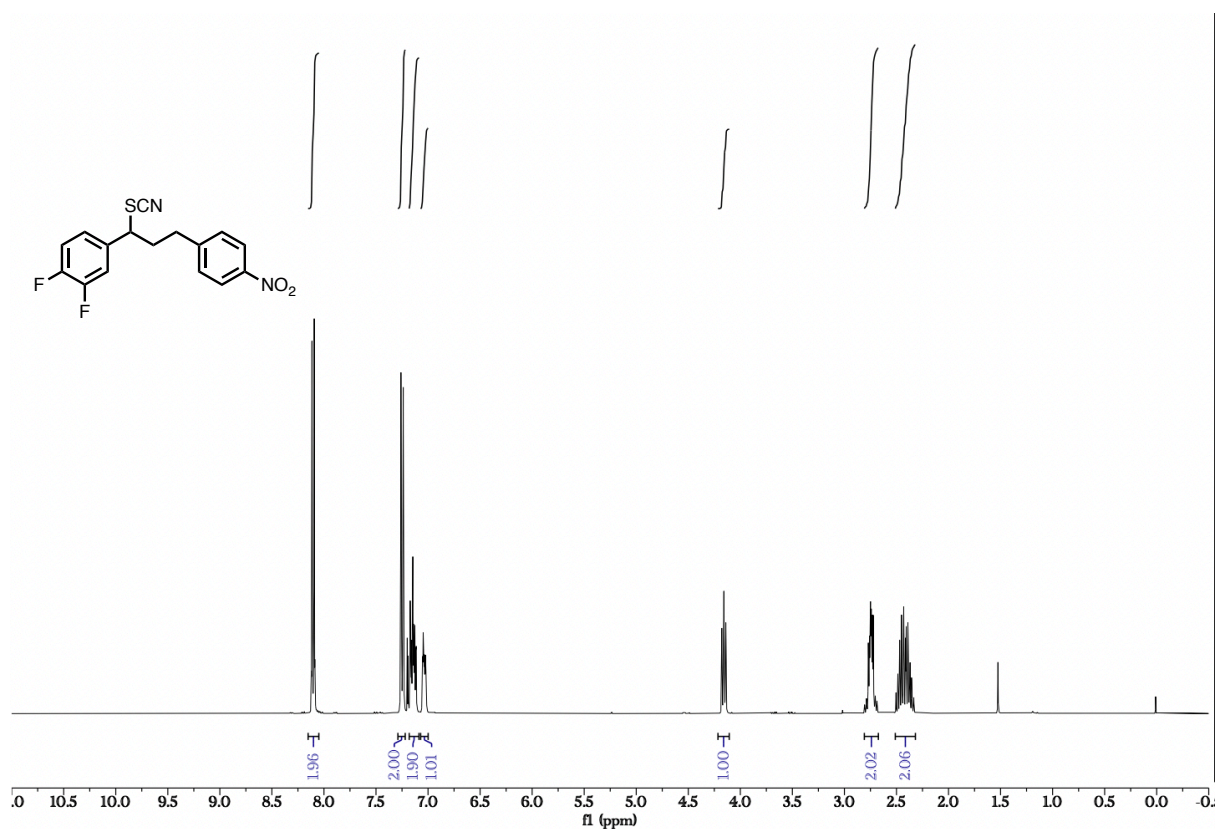


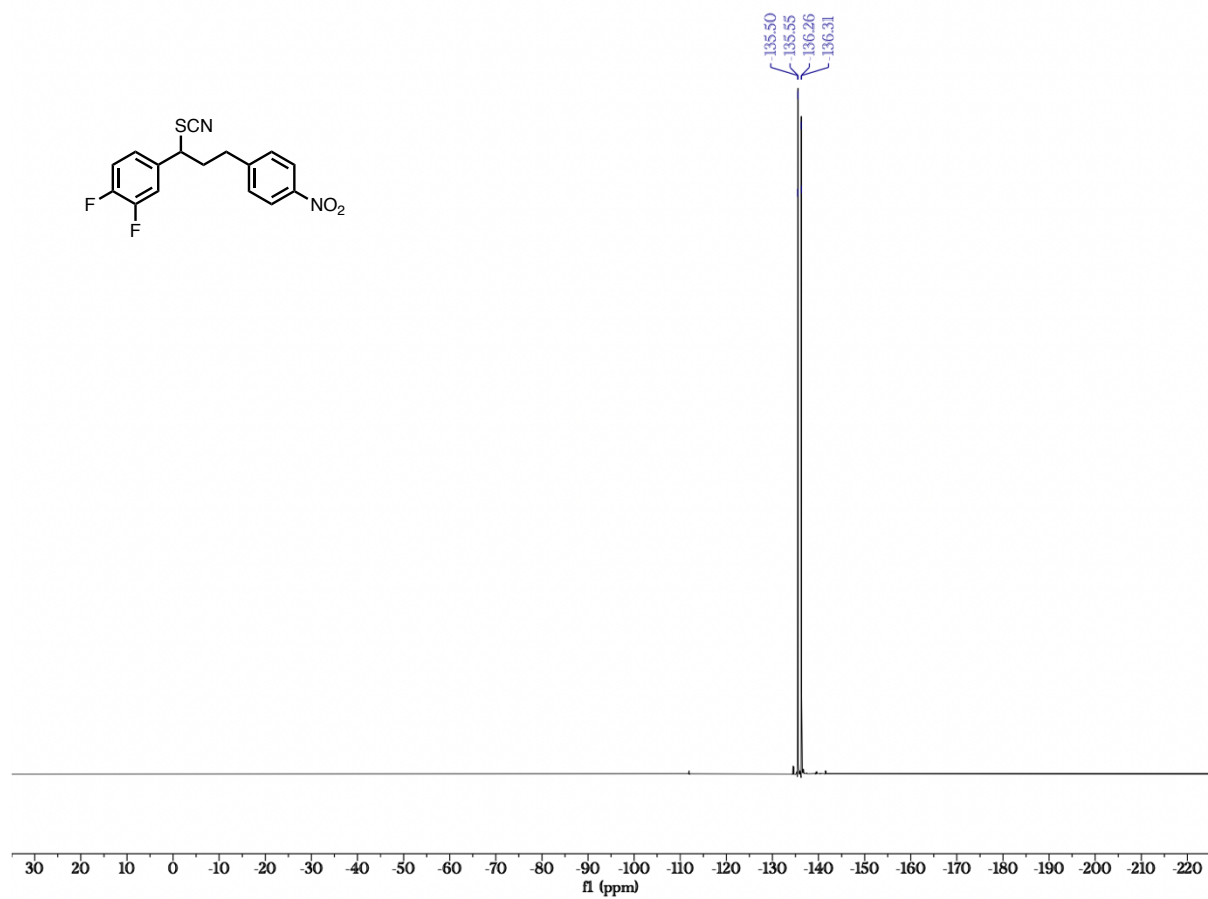
O=[N+]([O-])c1ccc(cc1)CC(C(=O)N)Cc2ccc(Br)cc2

1.00
2.04
2.07

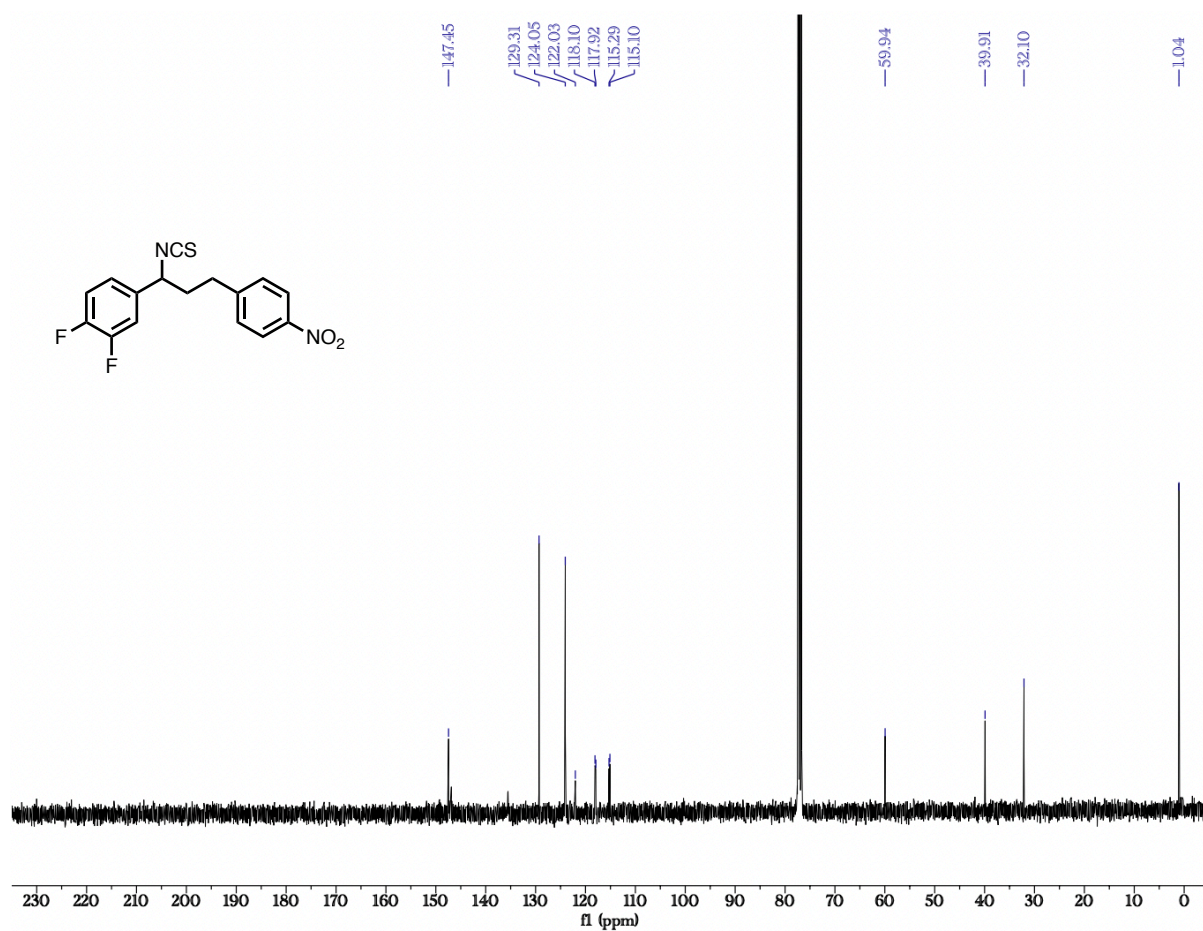
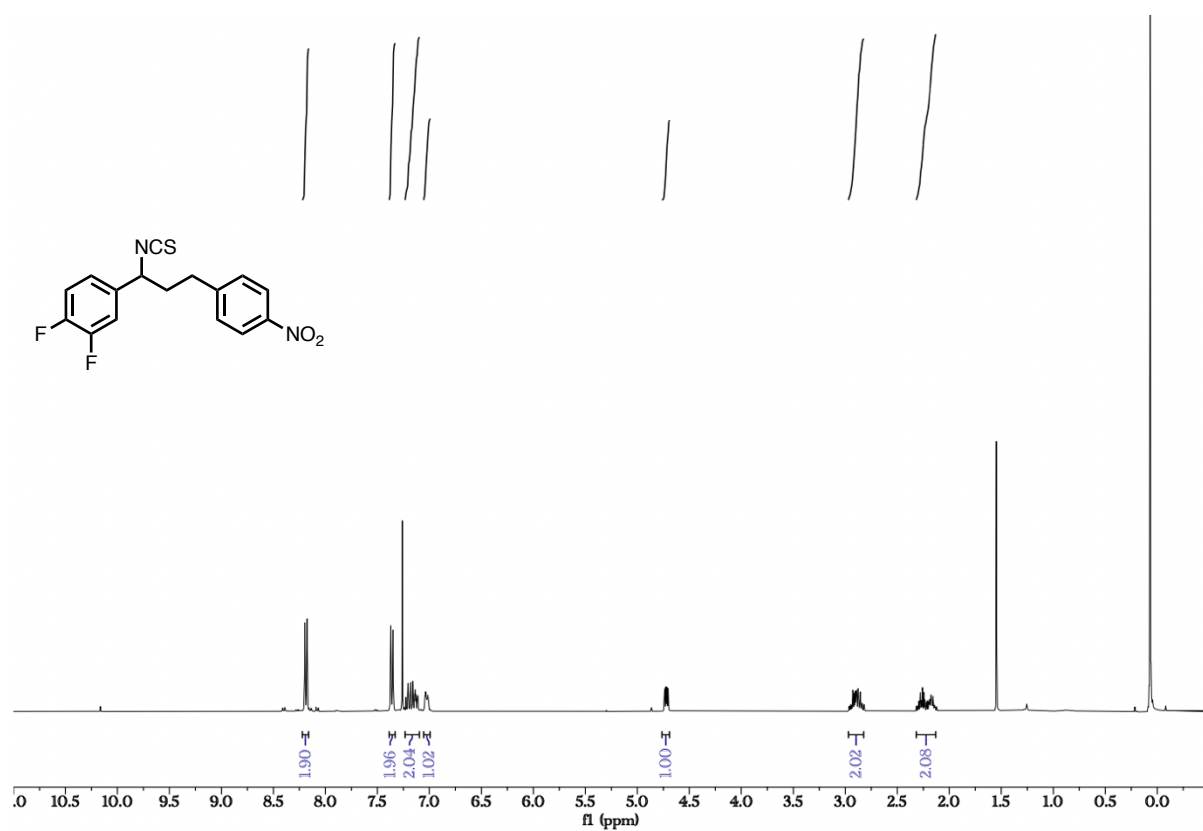


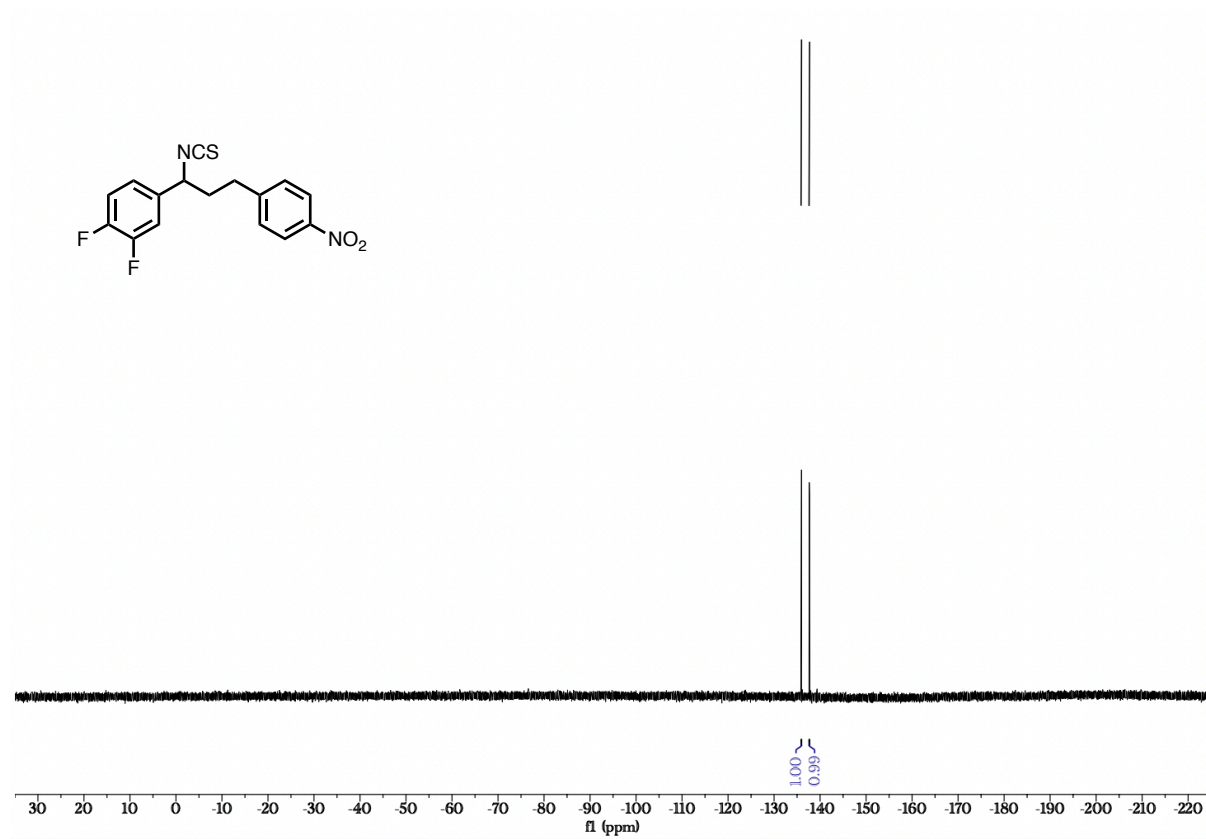
1,2-difluoro-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3ak)



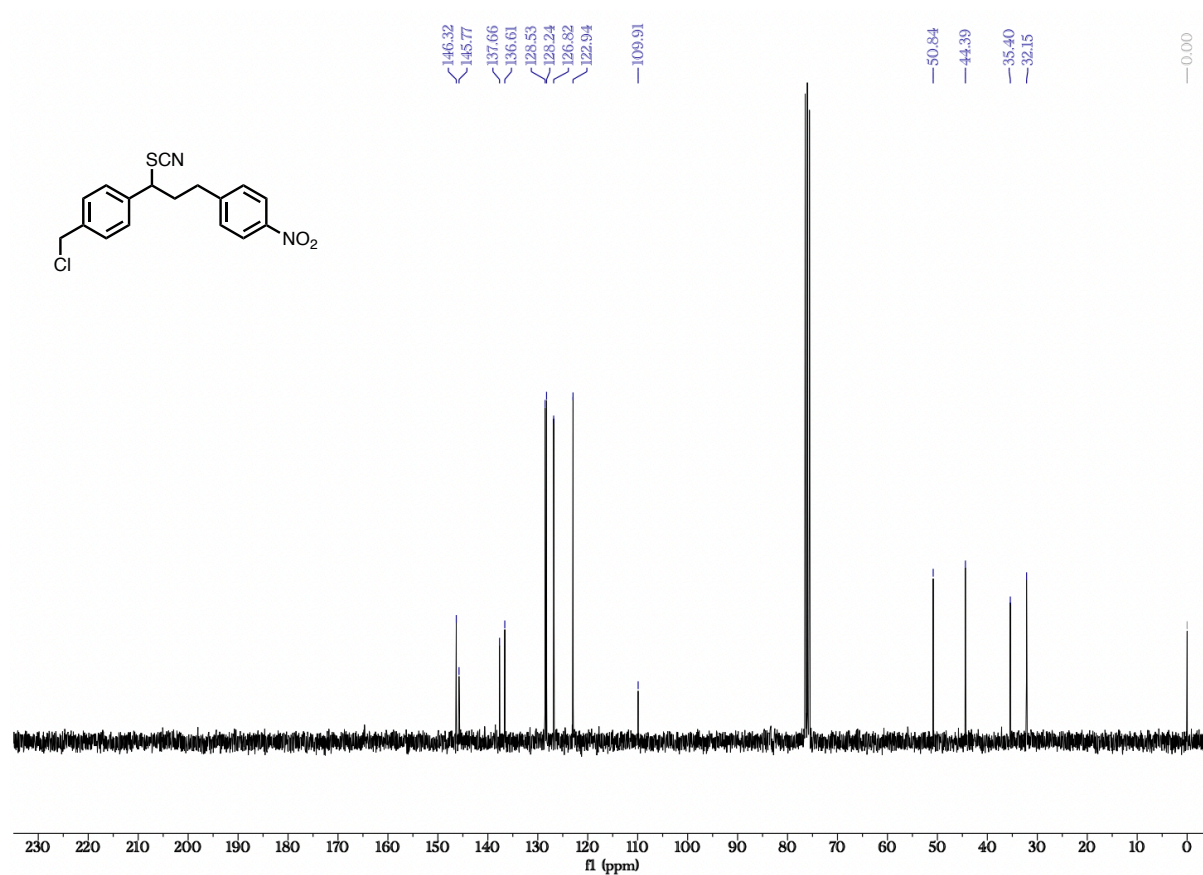
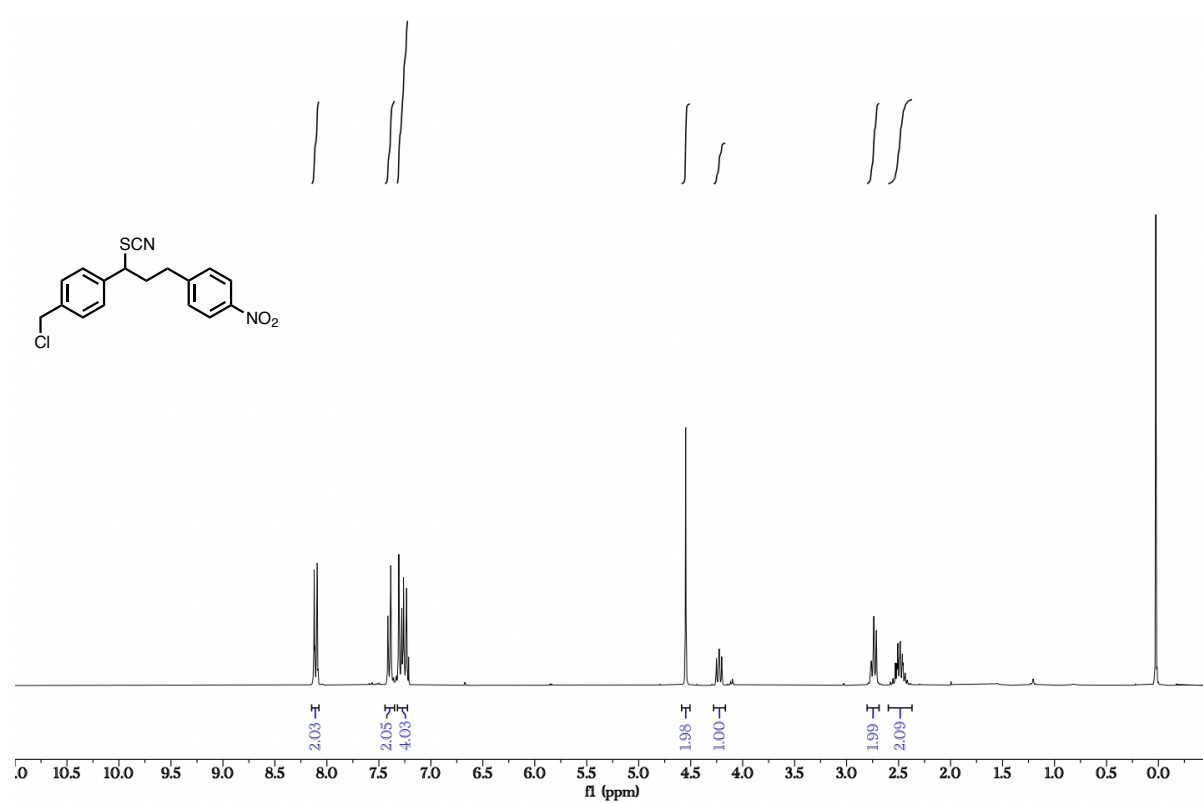


1,2-difluoro-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (3ak')

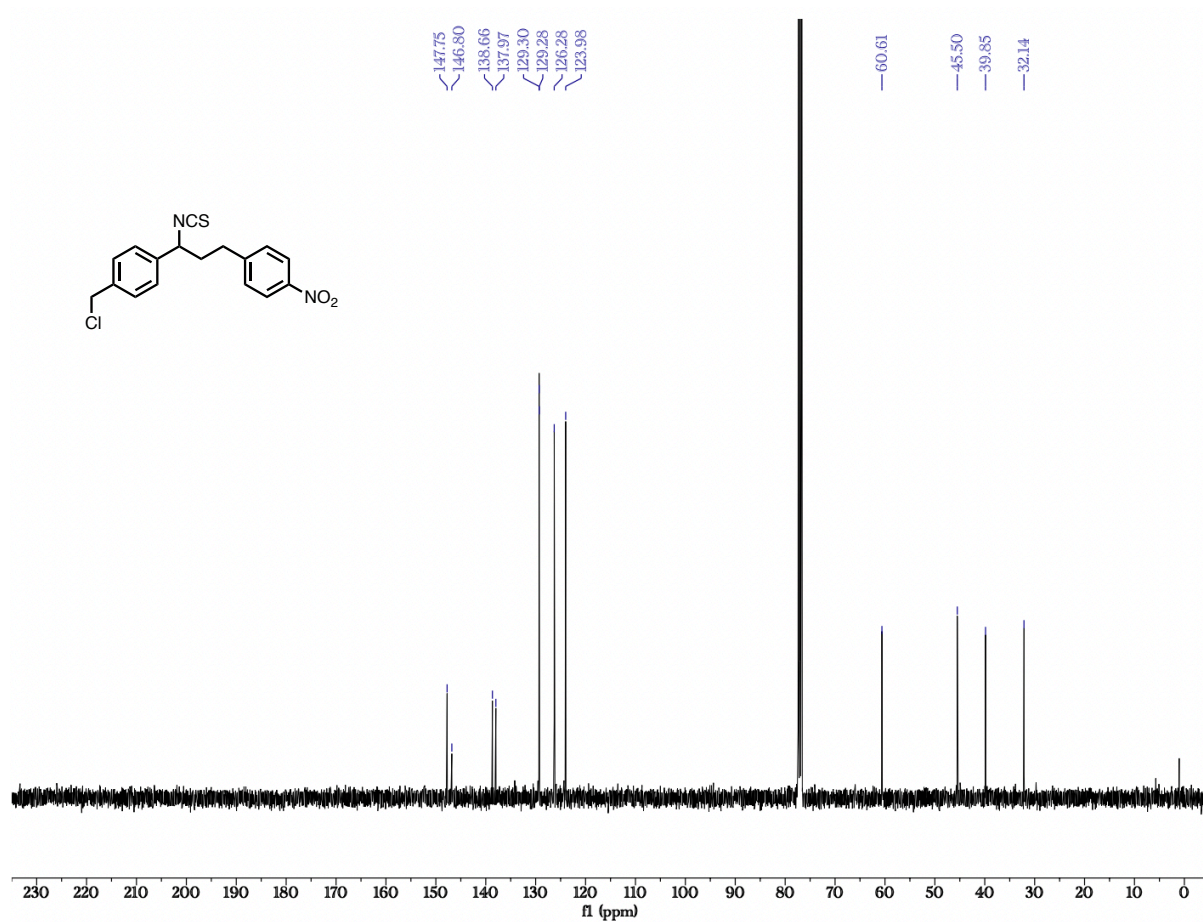
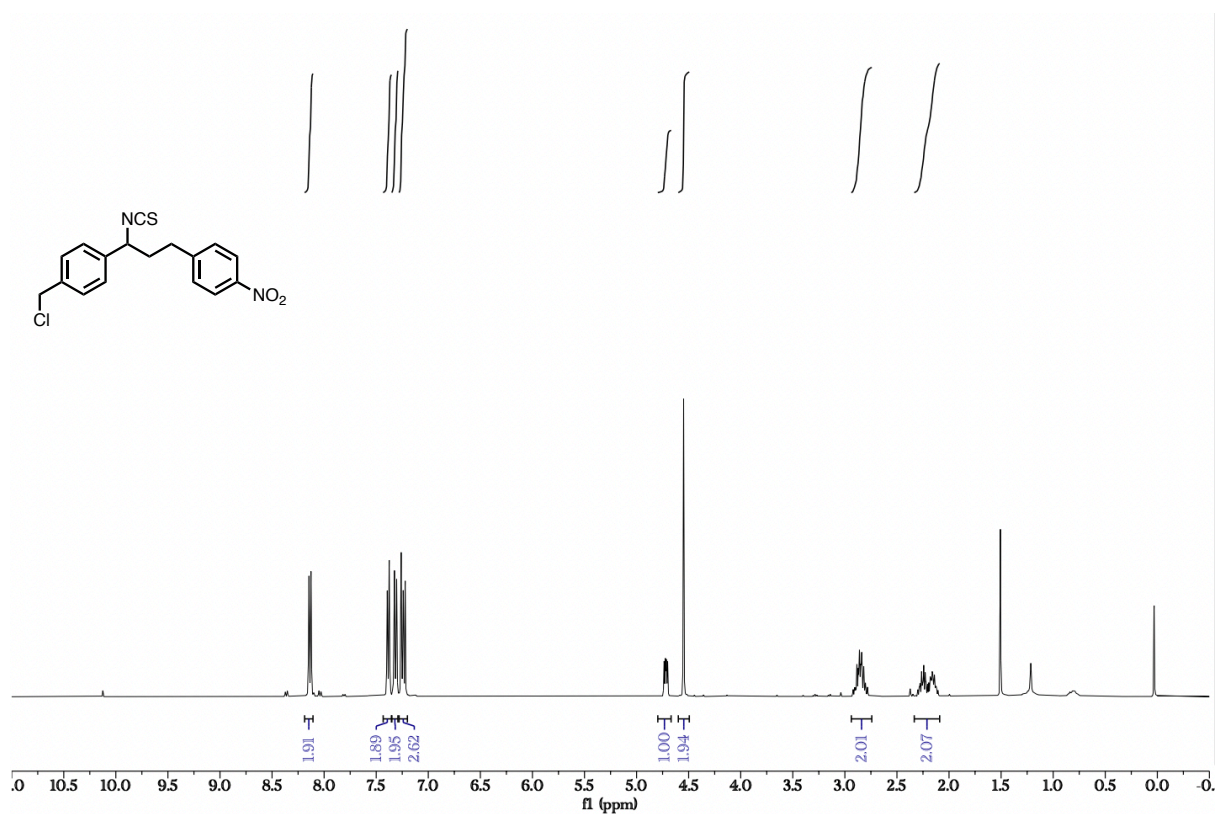




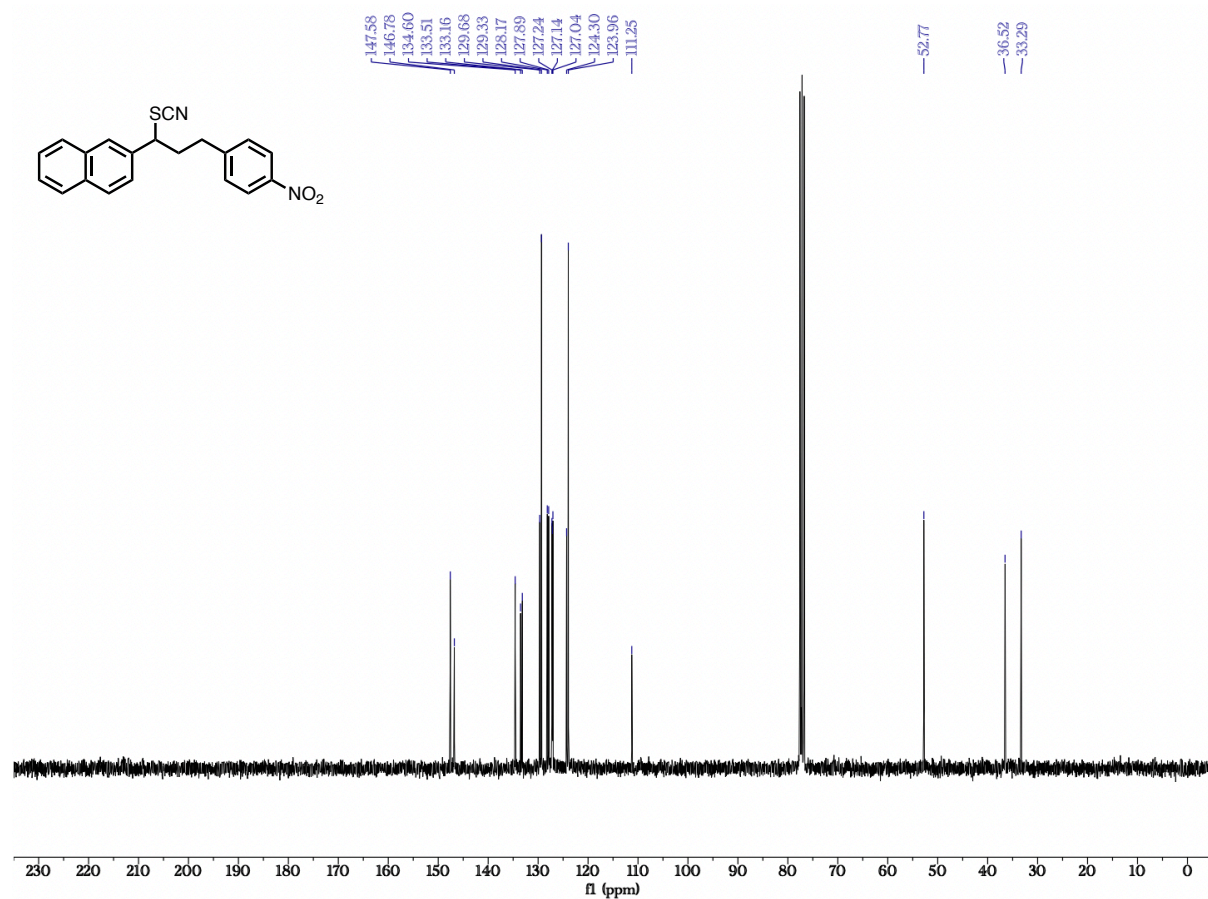
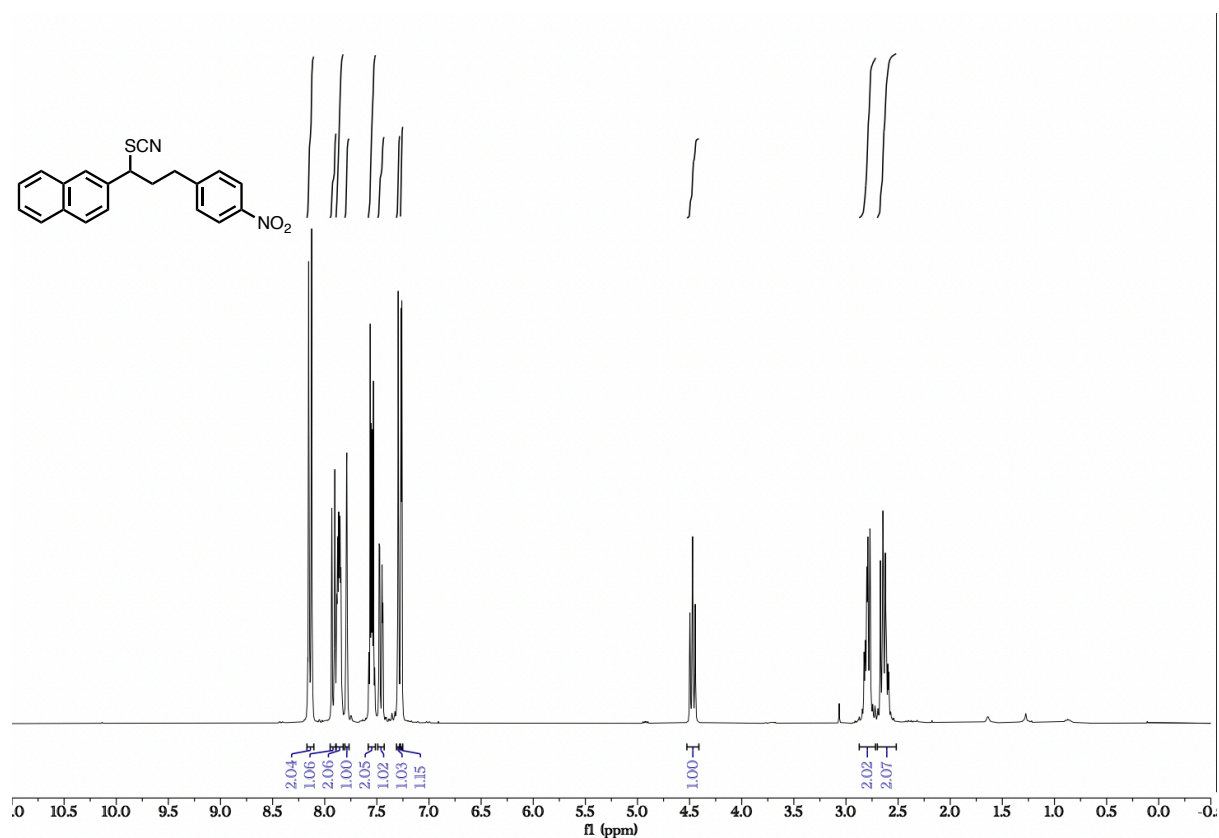
1-(chloromethyl)-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3al)



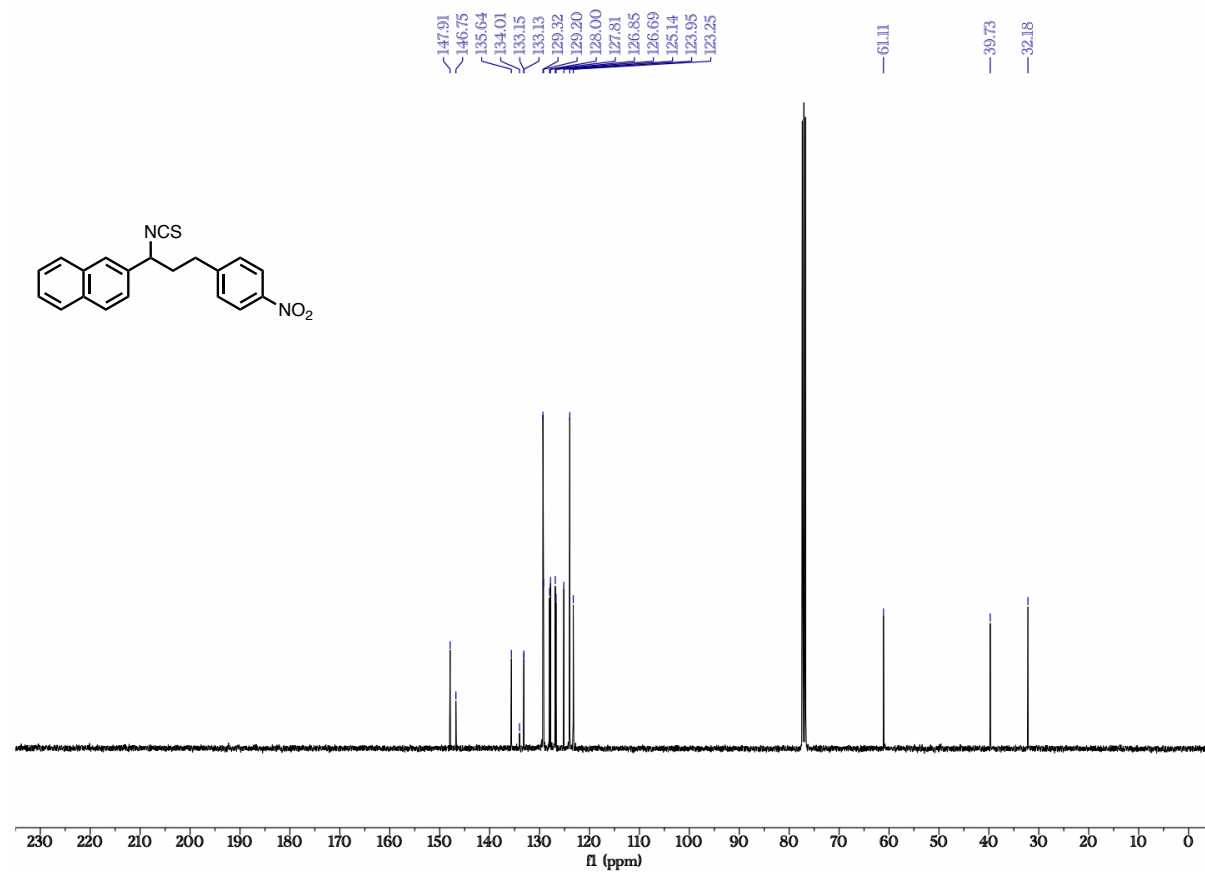
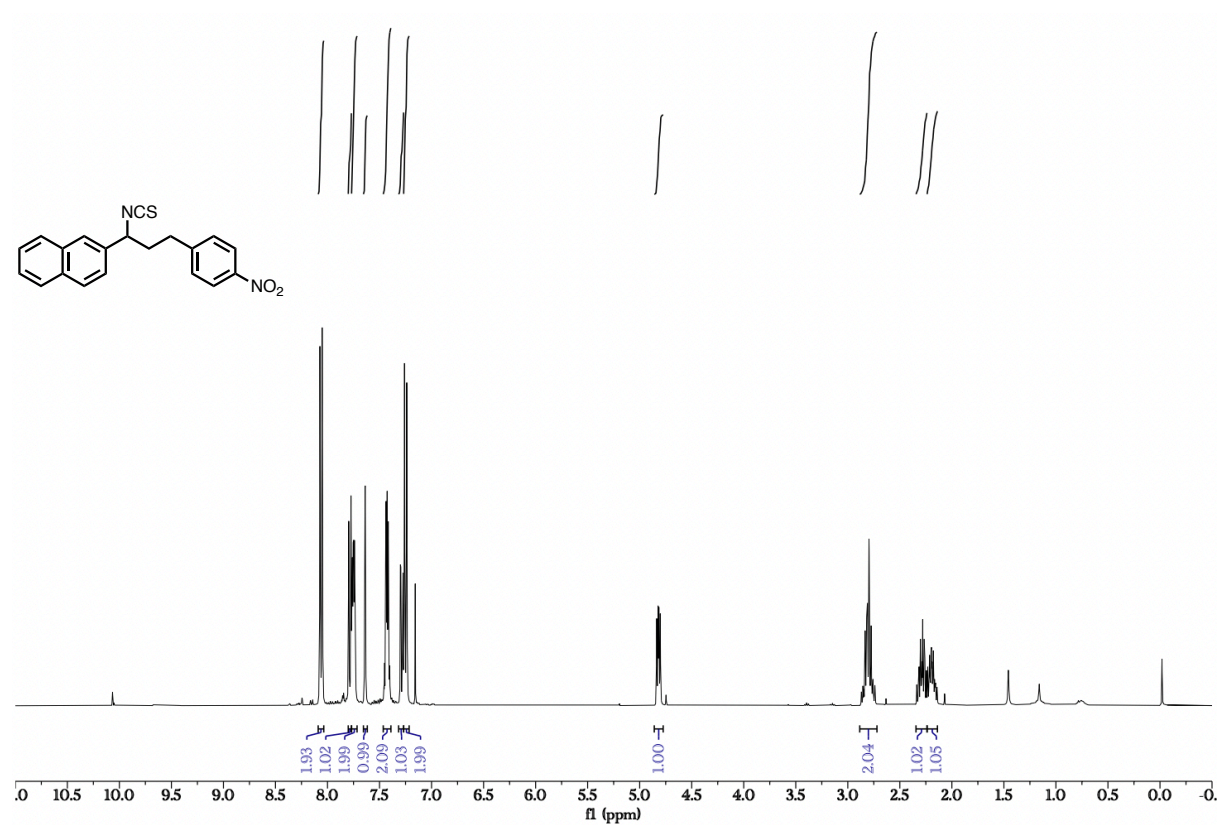
1-(chloromethyl)-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (3a')



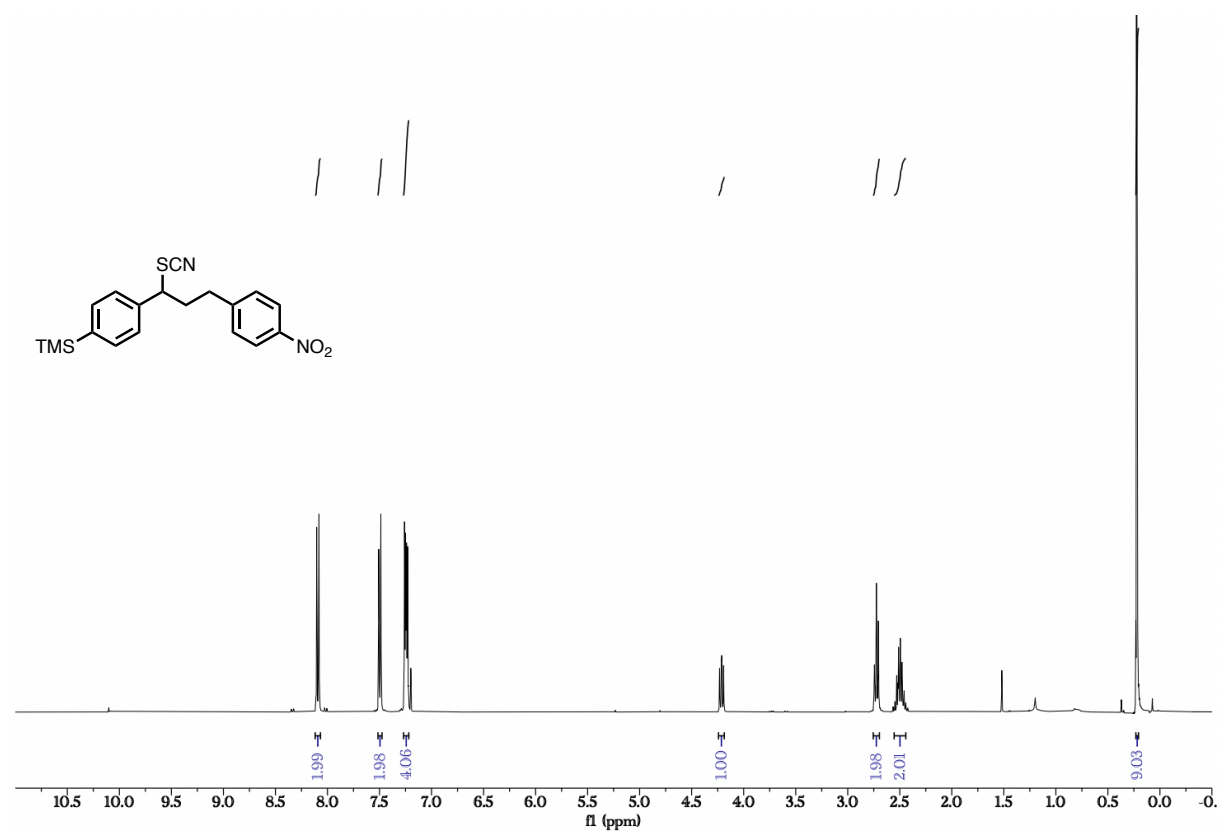
2-(3-(4-nitrophenyl)-1-thiocyanatopropyl)naphthalene (3am)



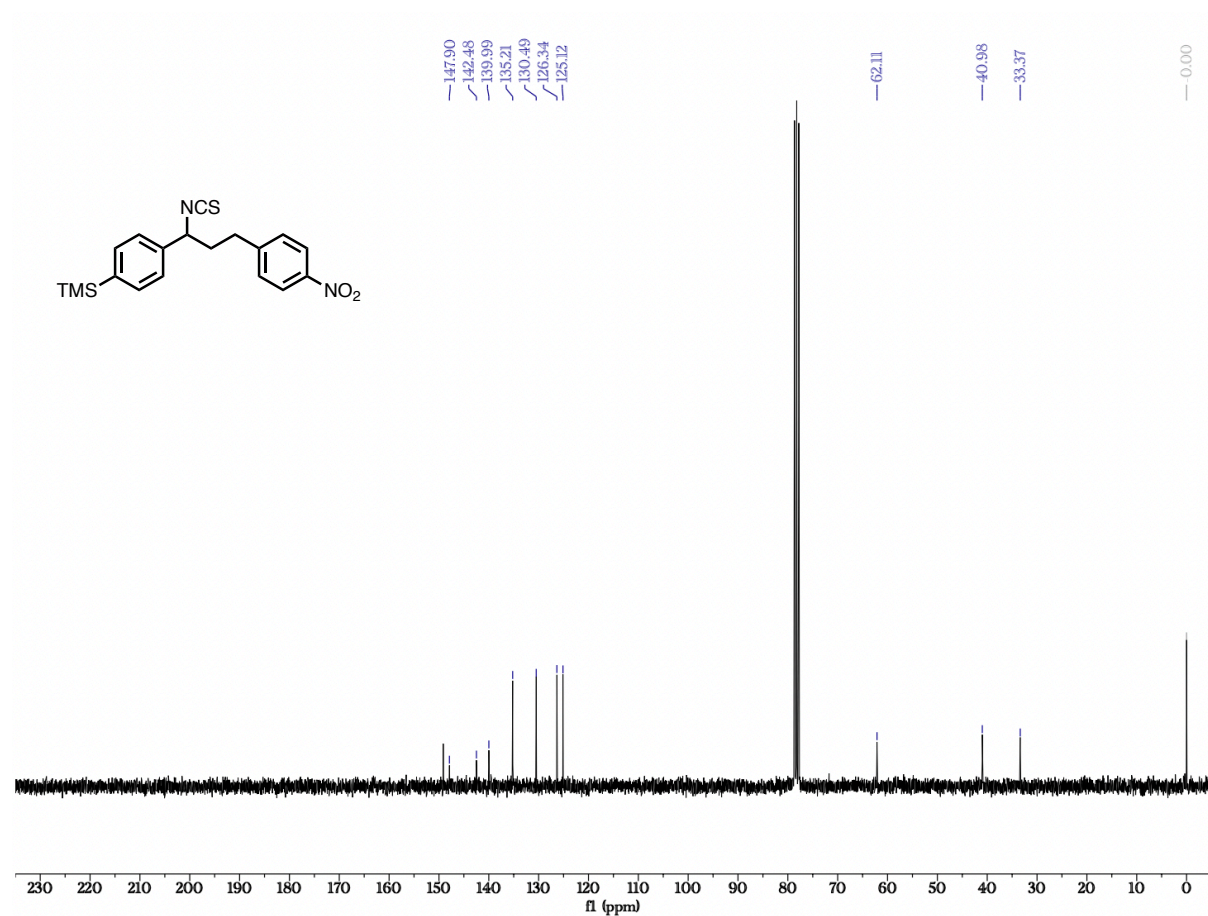
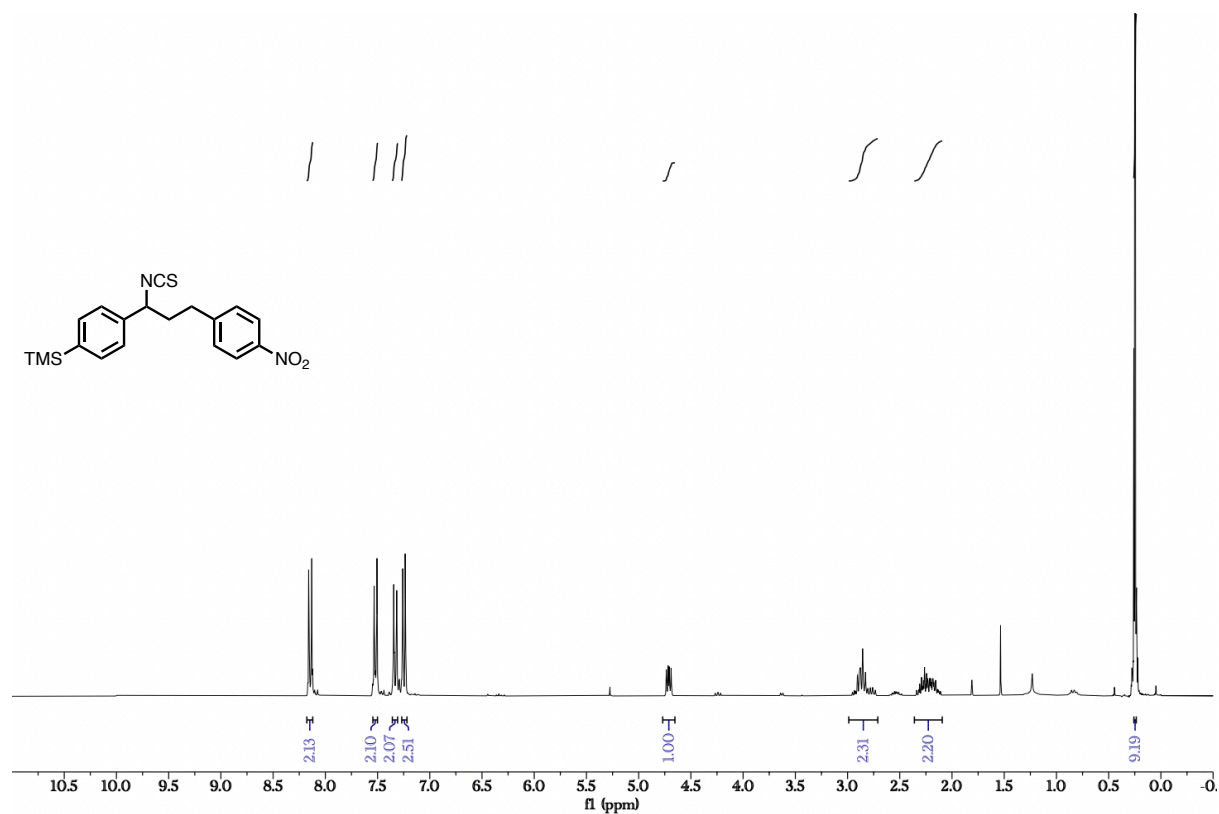
2-(1-isothiocyanato-3-(4-nitrophenyl)propyl)naphthalene (3am')



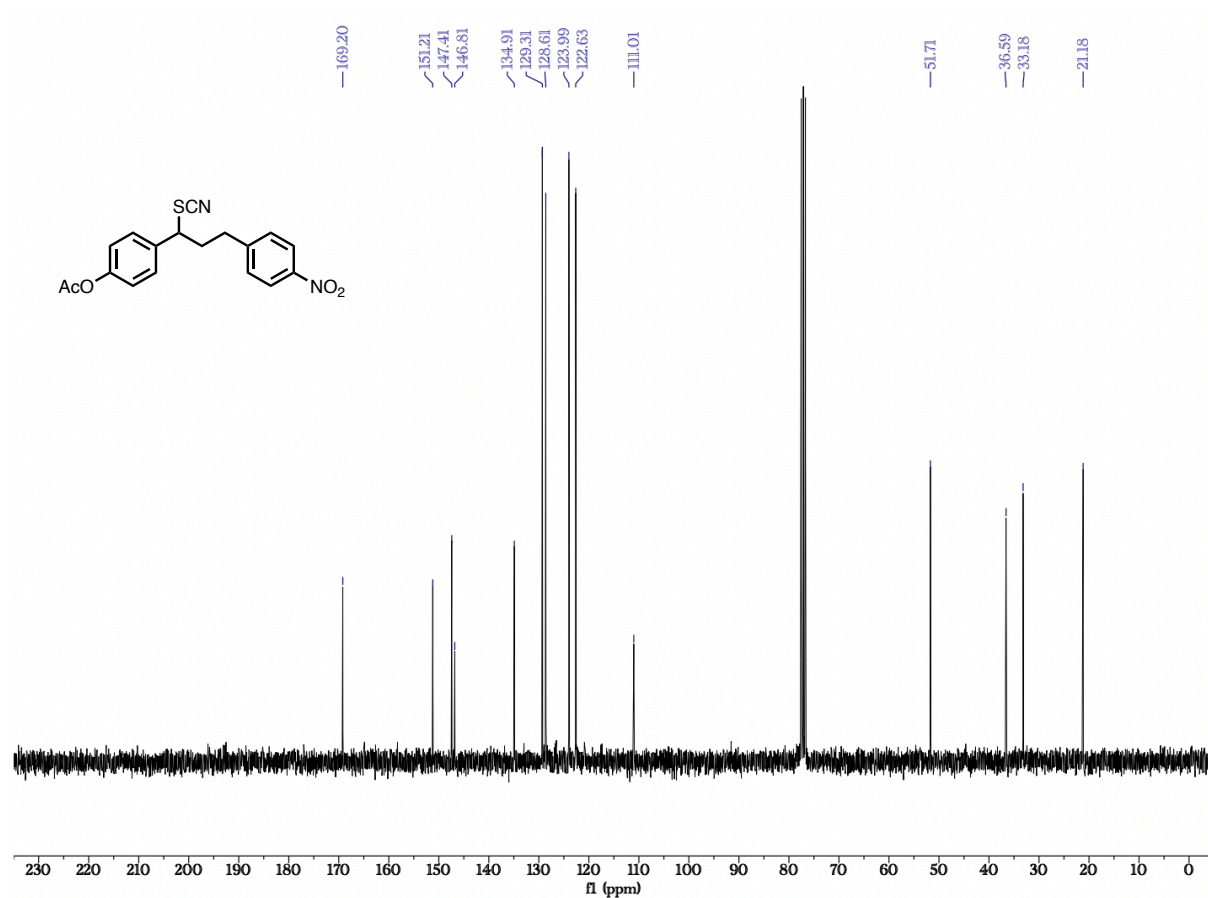
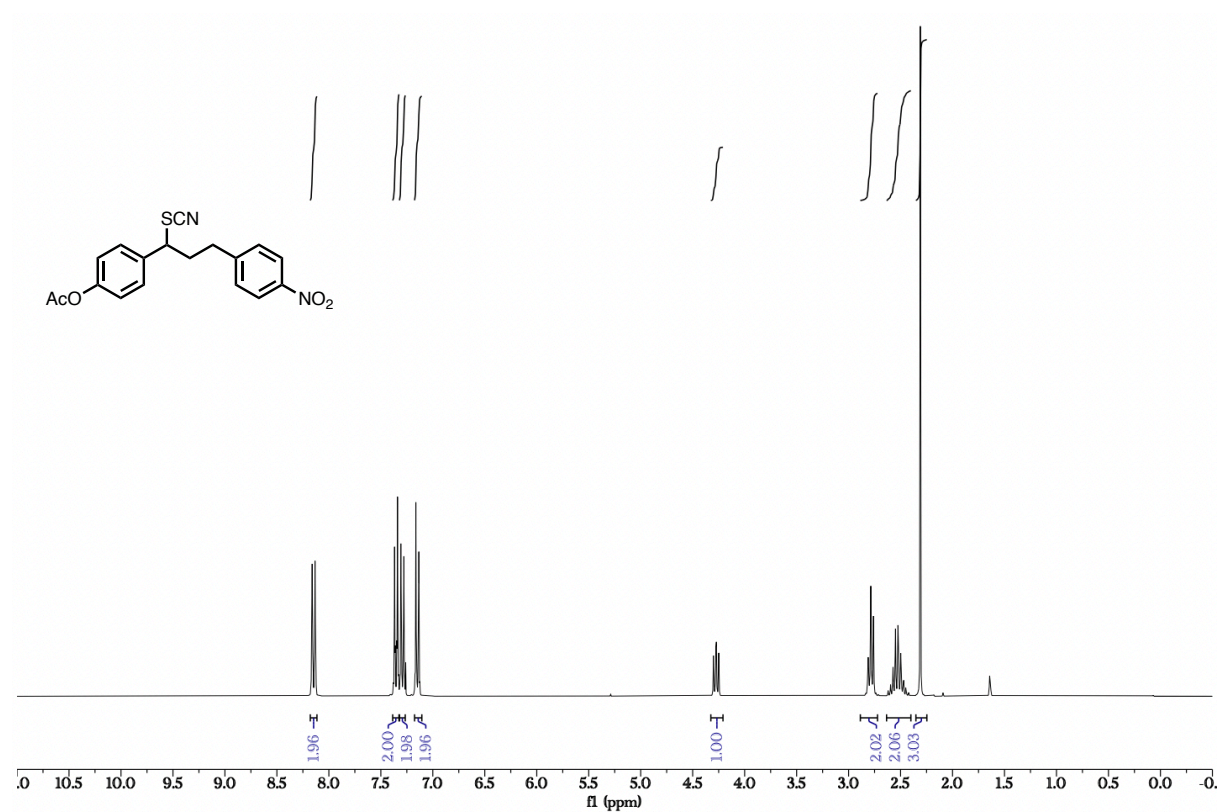
trimethyl(4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)phenyl)silane (3an)



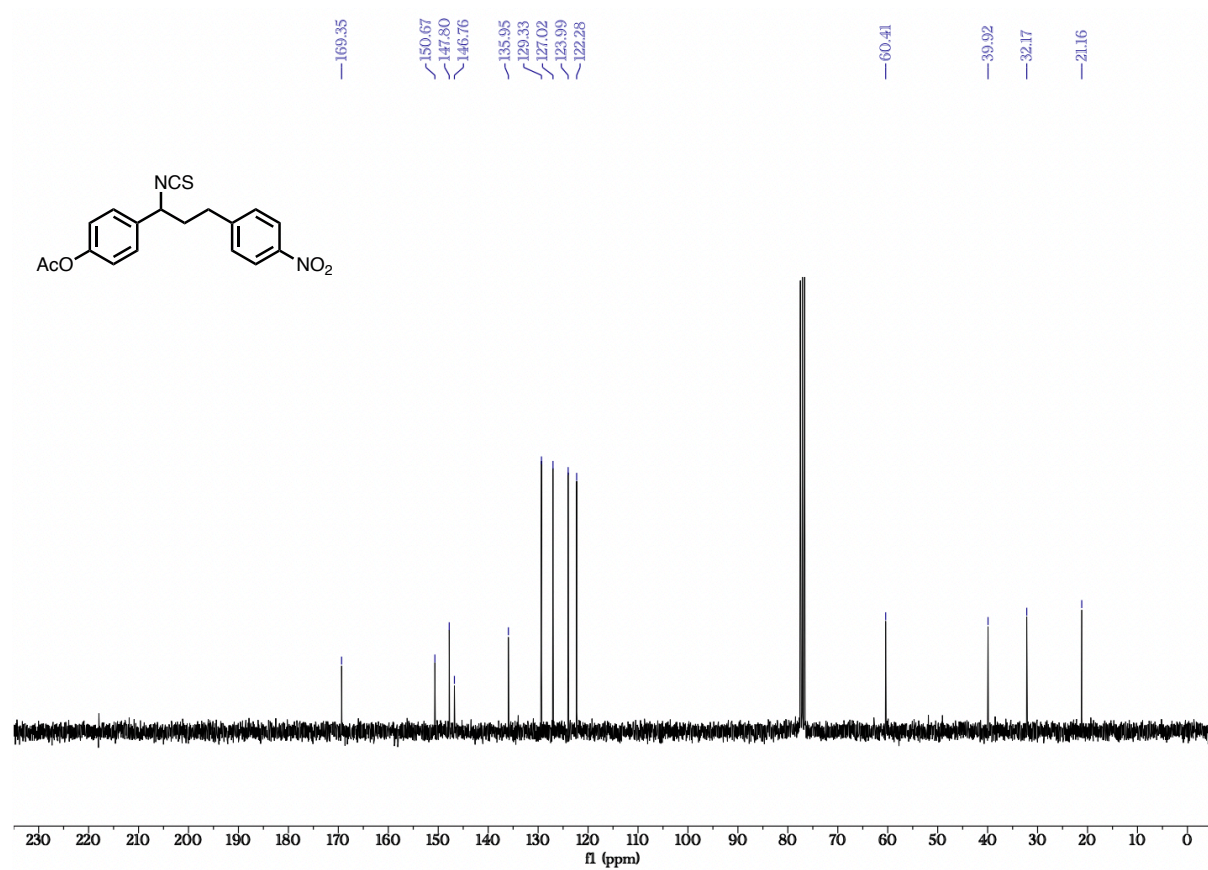
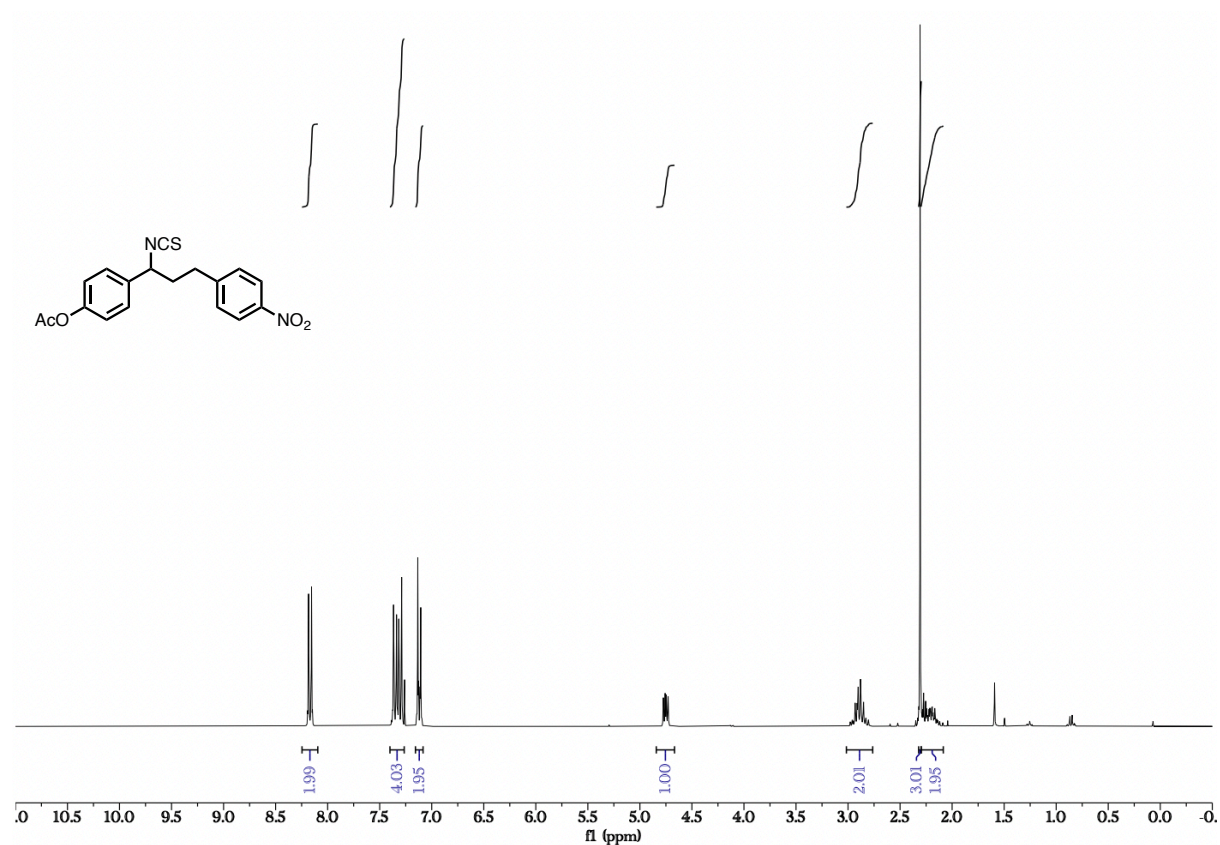
(4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)phenyl)trimethylsilane (3an')



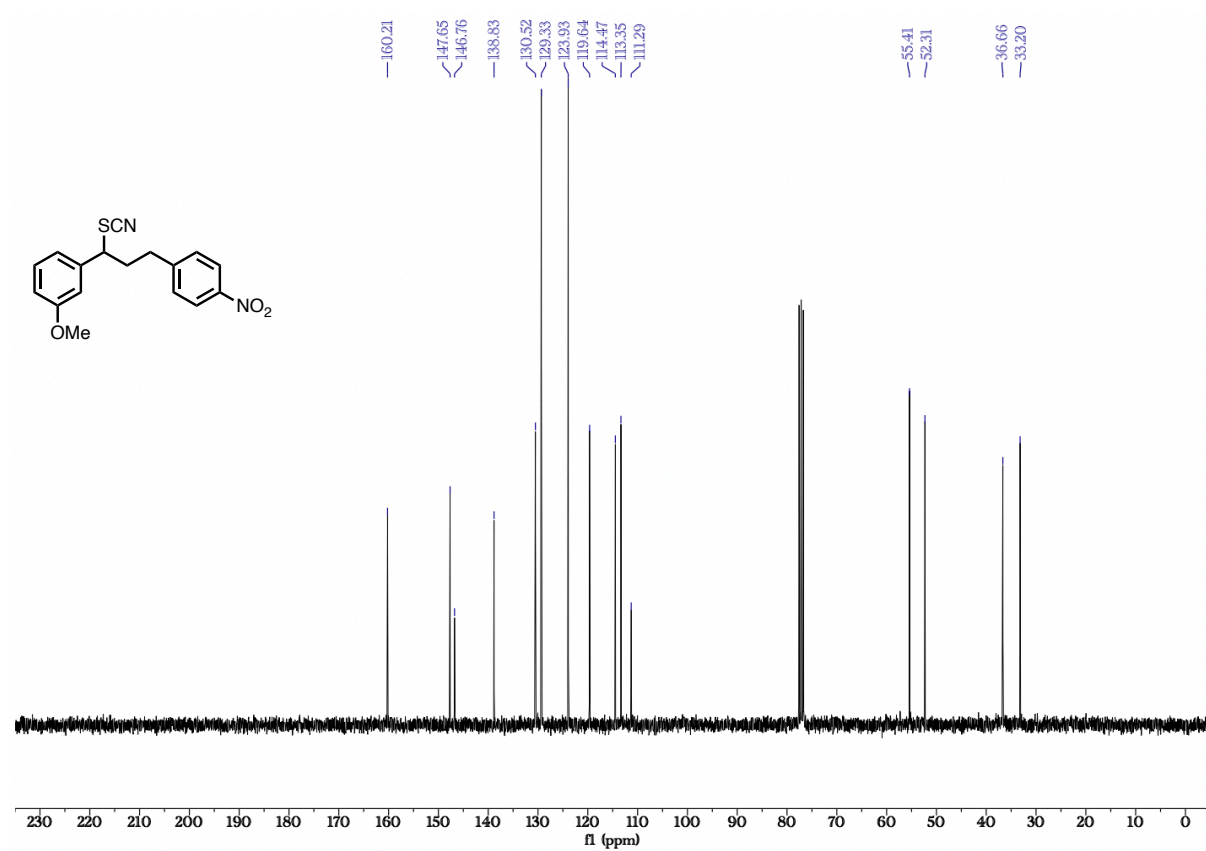
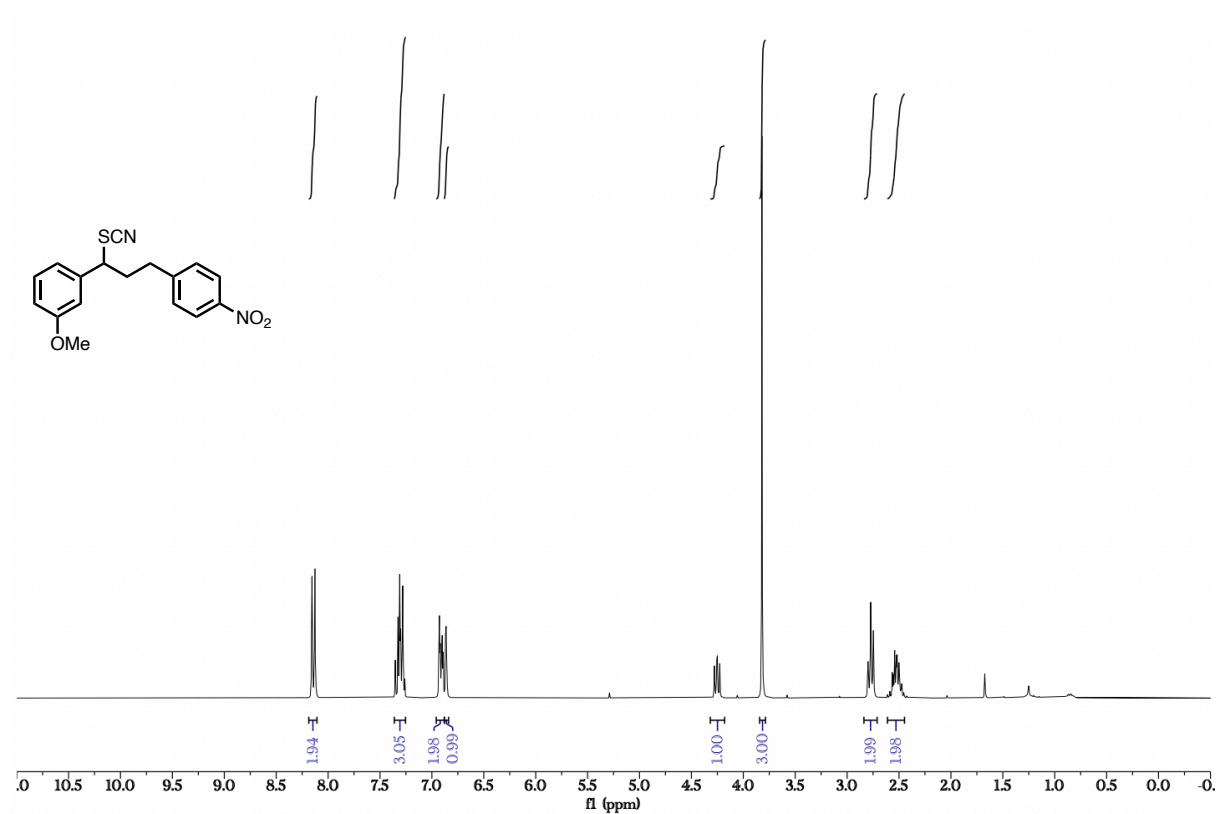
4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)phenyl acetate (3ao)



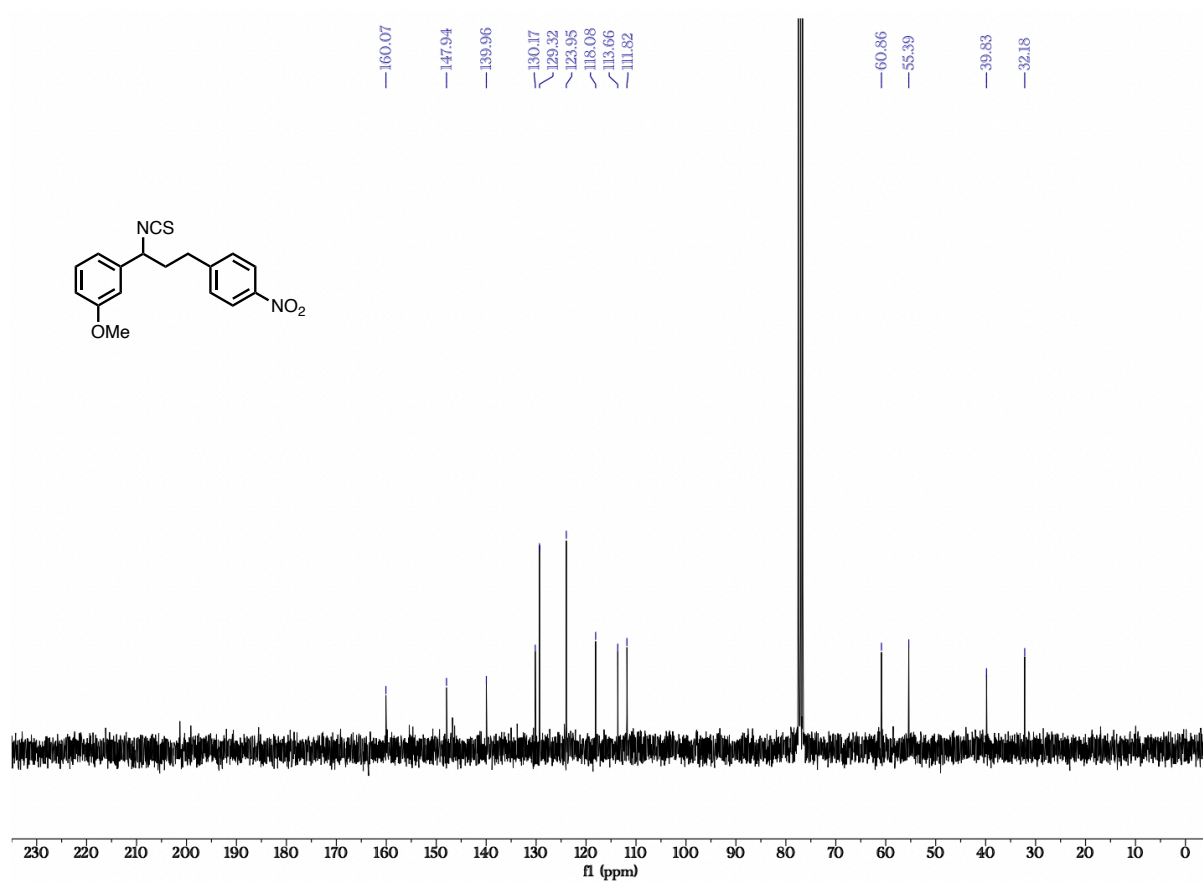
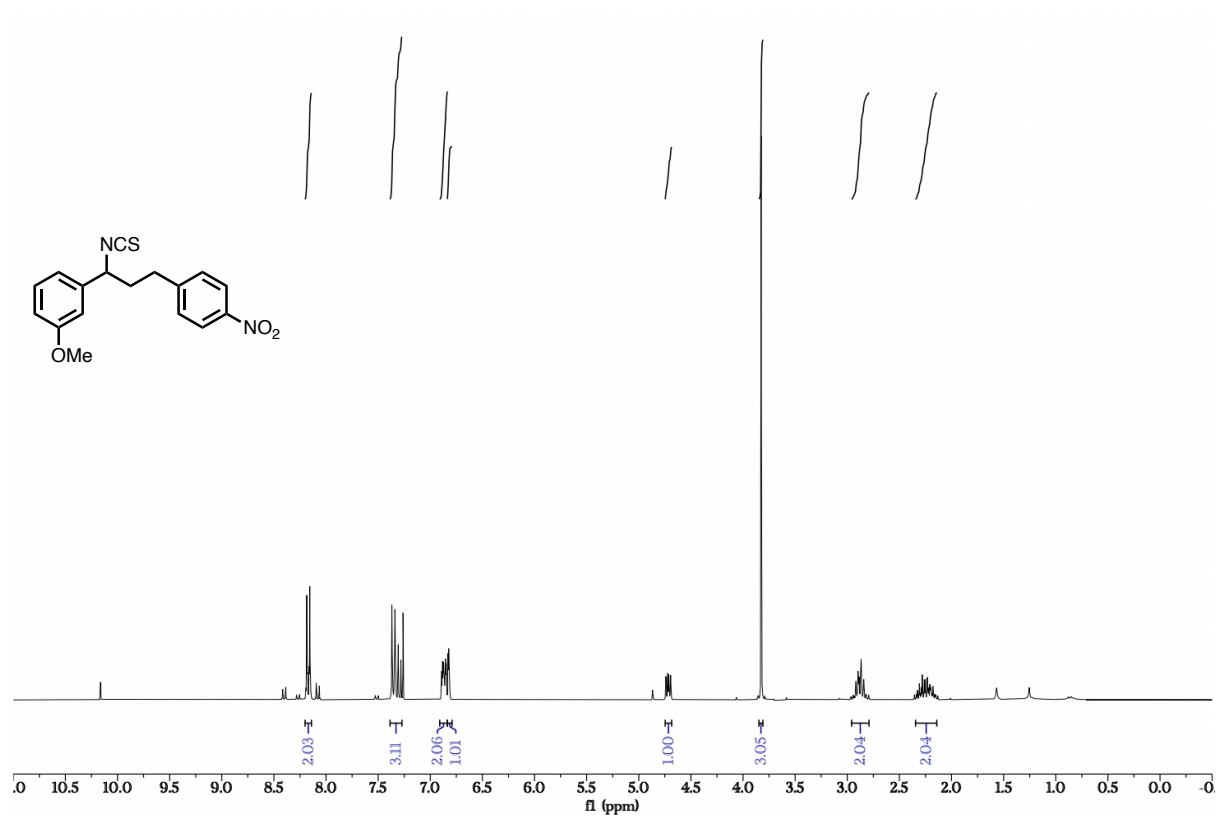
4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)phenyl acetate (3ao')



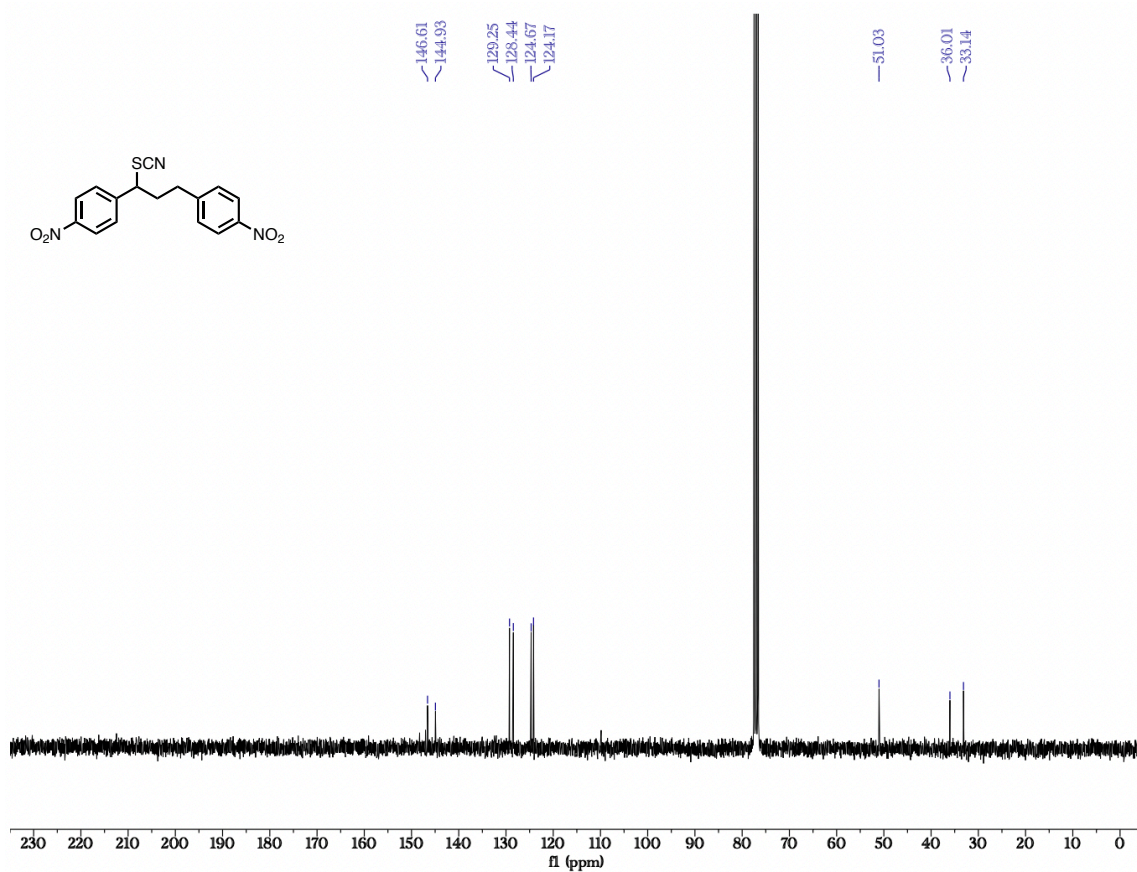
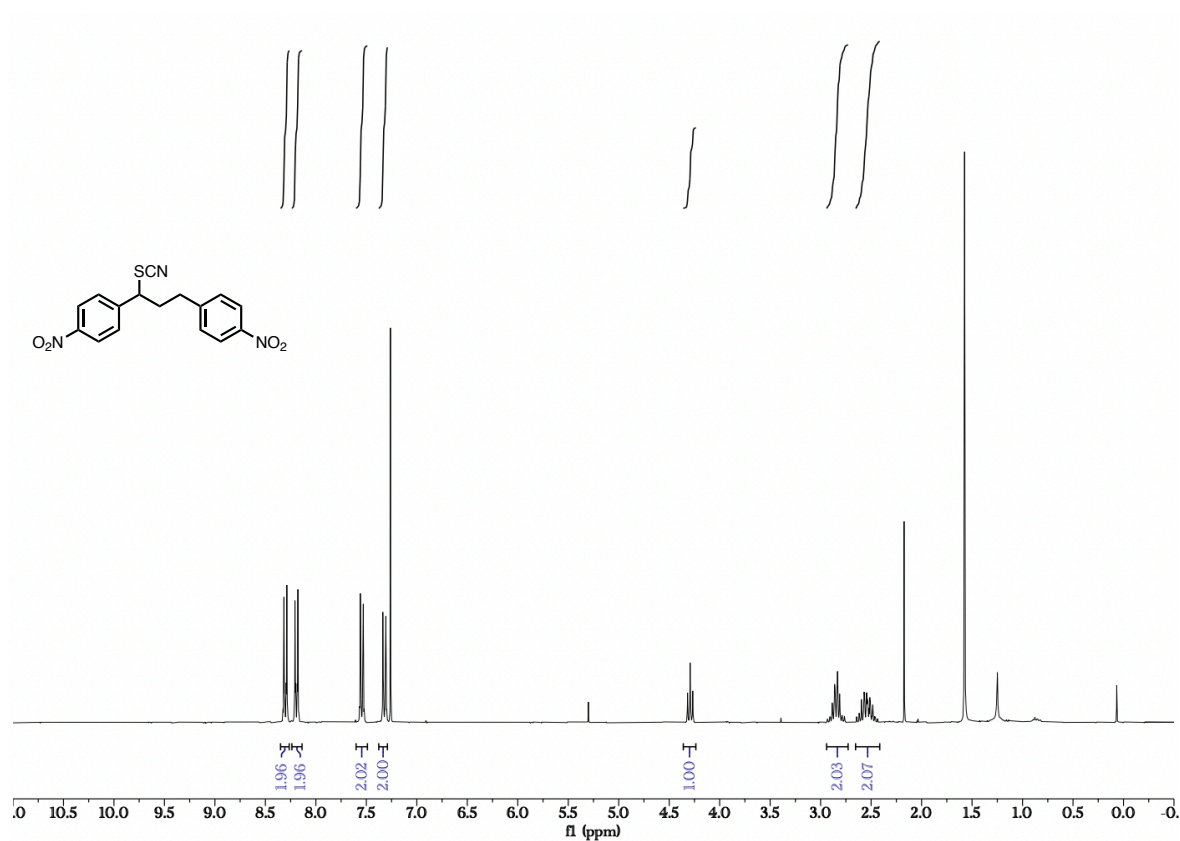
1-methoxy-3-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3ap)



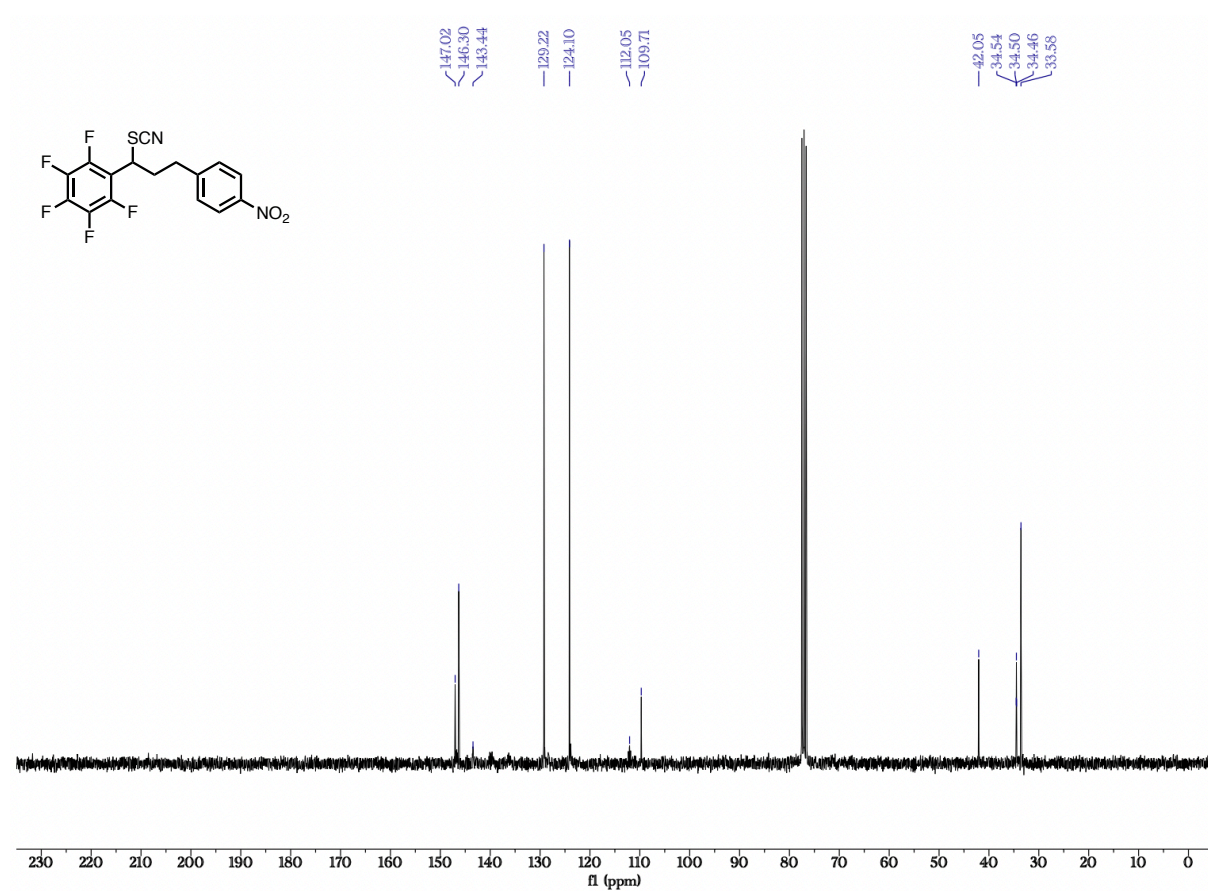
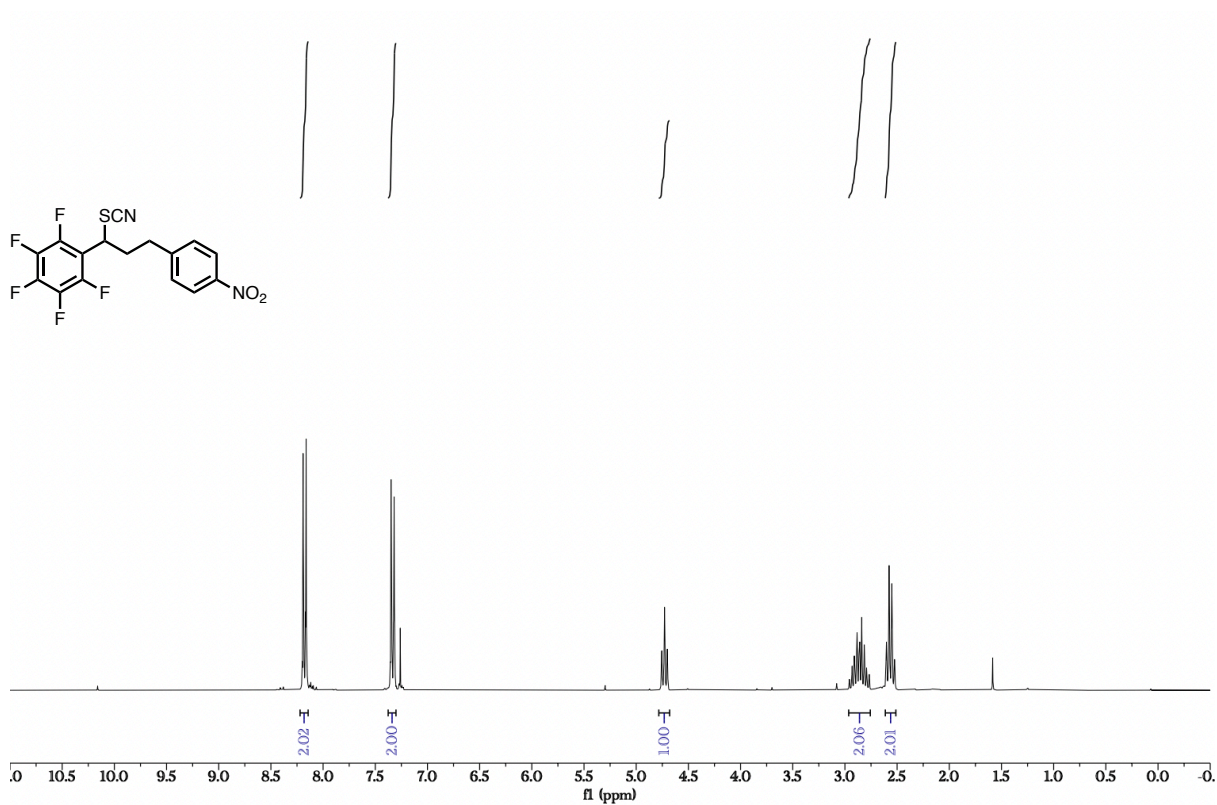
1-(1-isothiocyanato-3-(4-nitrophenyl)propyl)-3-methoxybenzene (3ap')

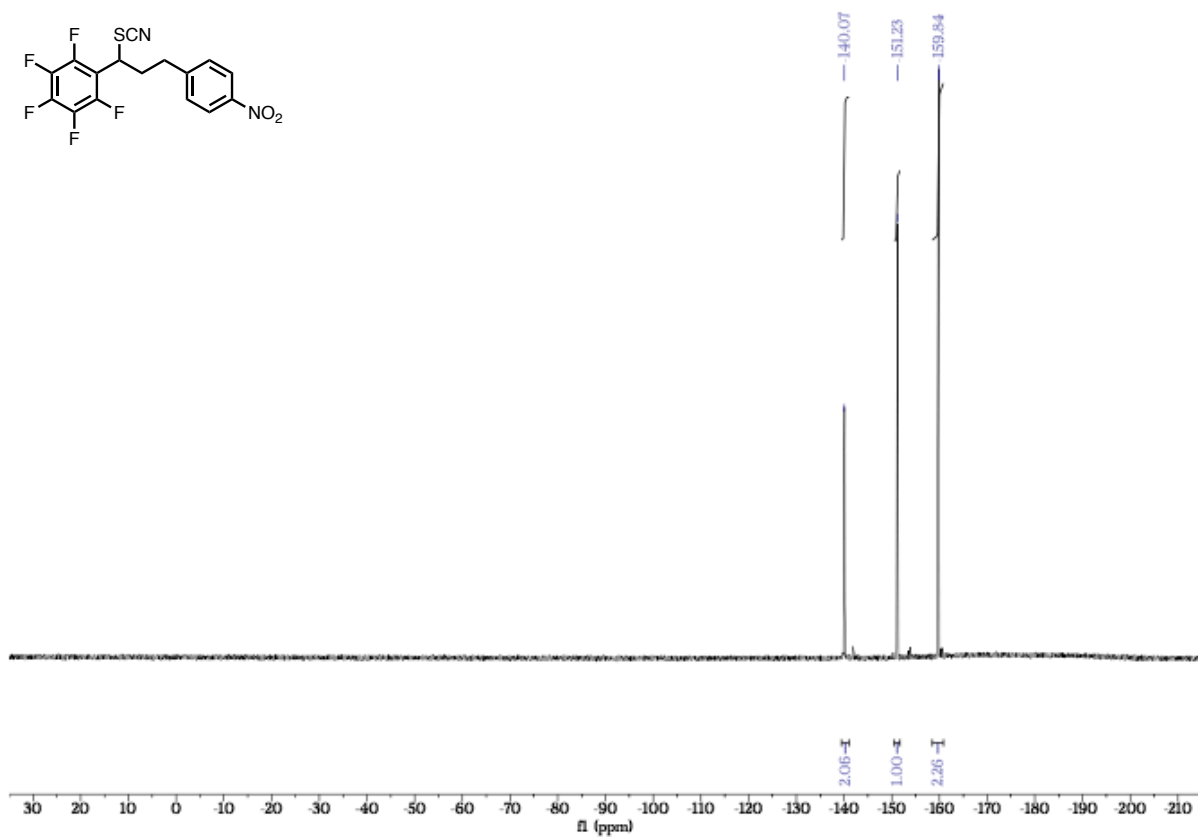
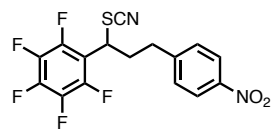


4,4'-(1-isothiocyanatopropane-1,3-diyl)bis(nitrobenzene) (3aq)

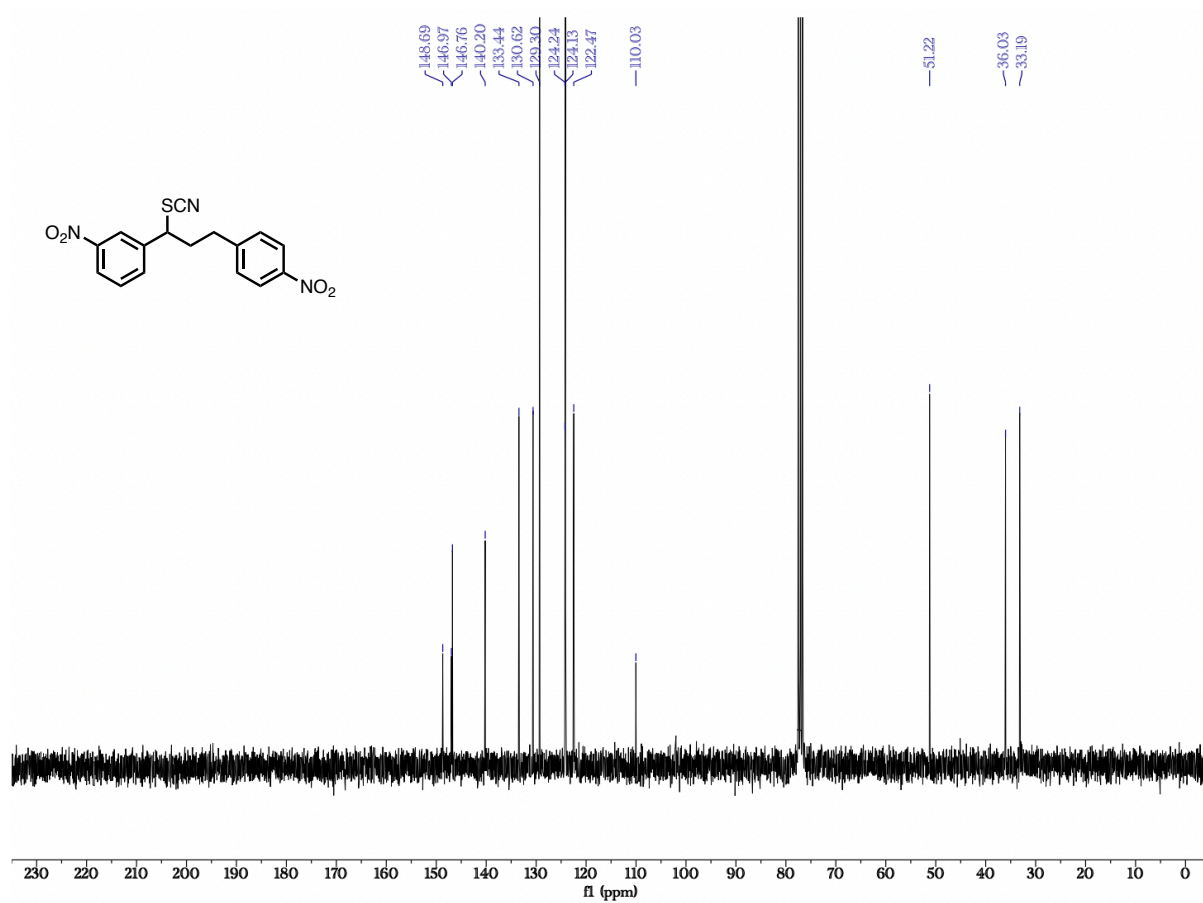
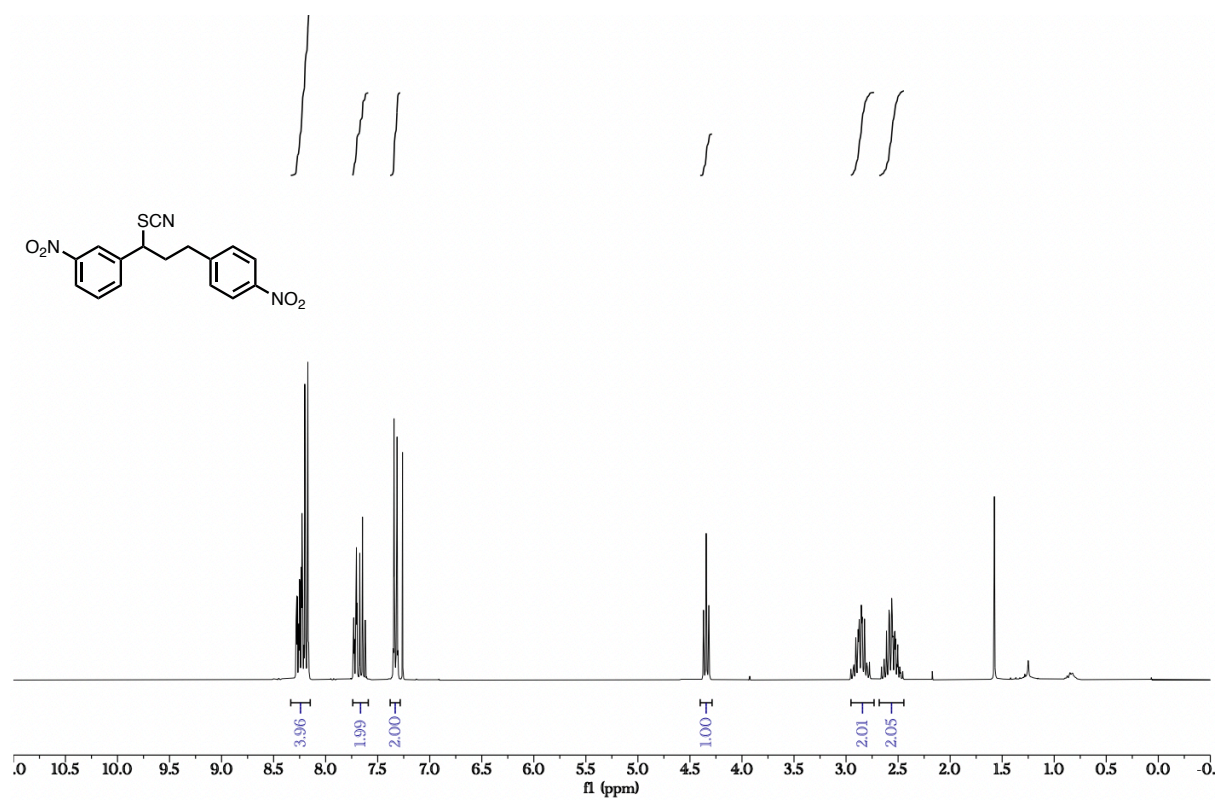


1,2,3,4,5-pentafluoro-6-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3ar)

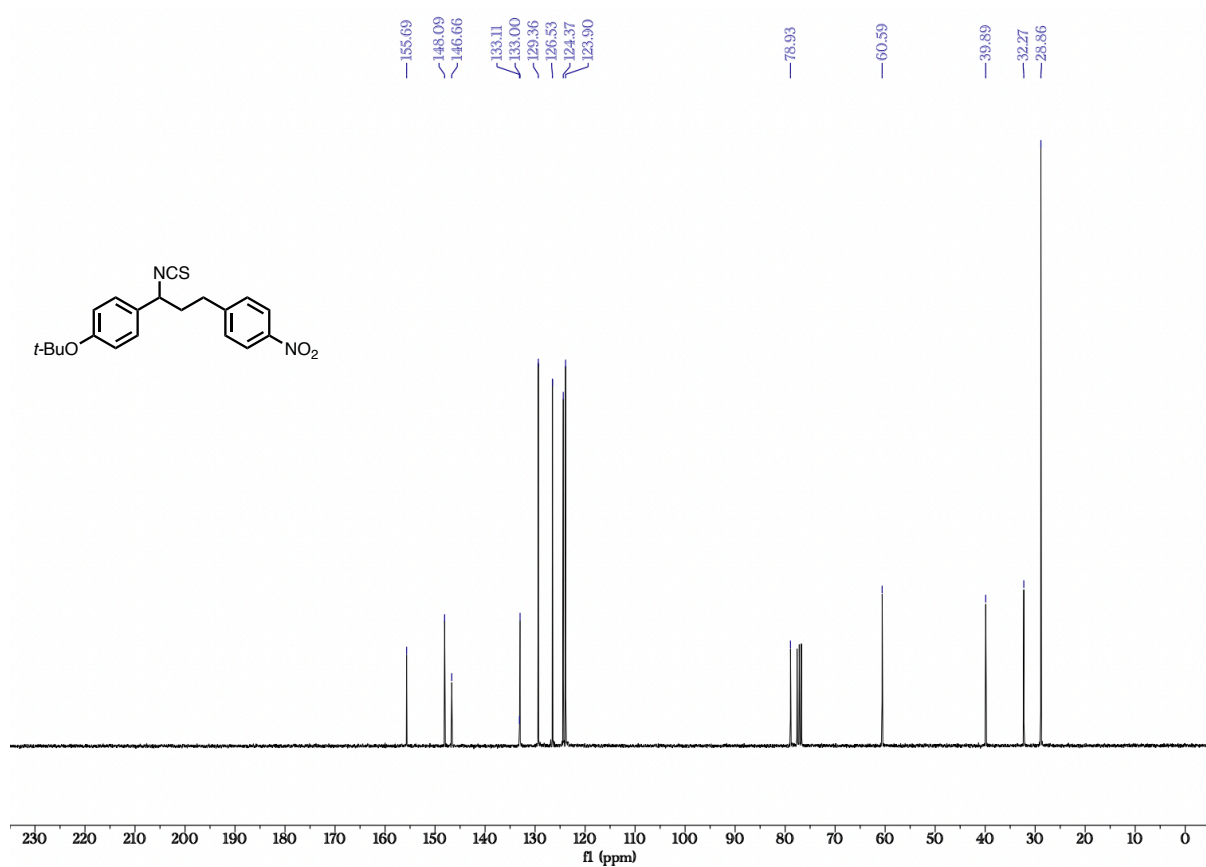
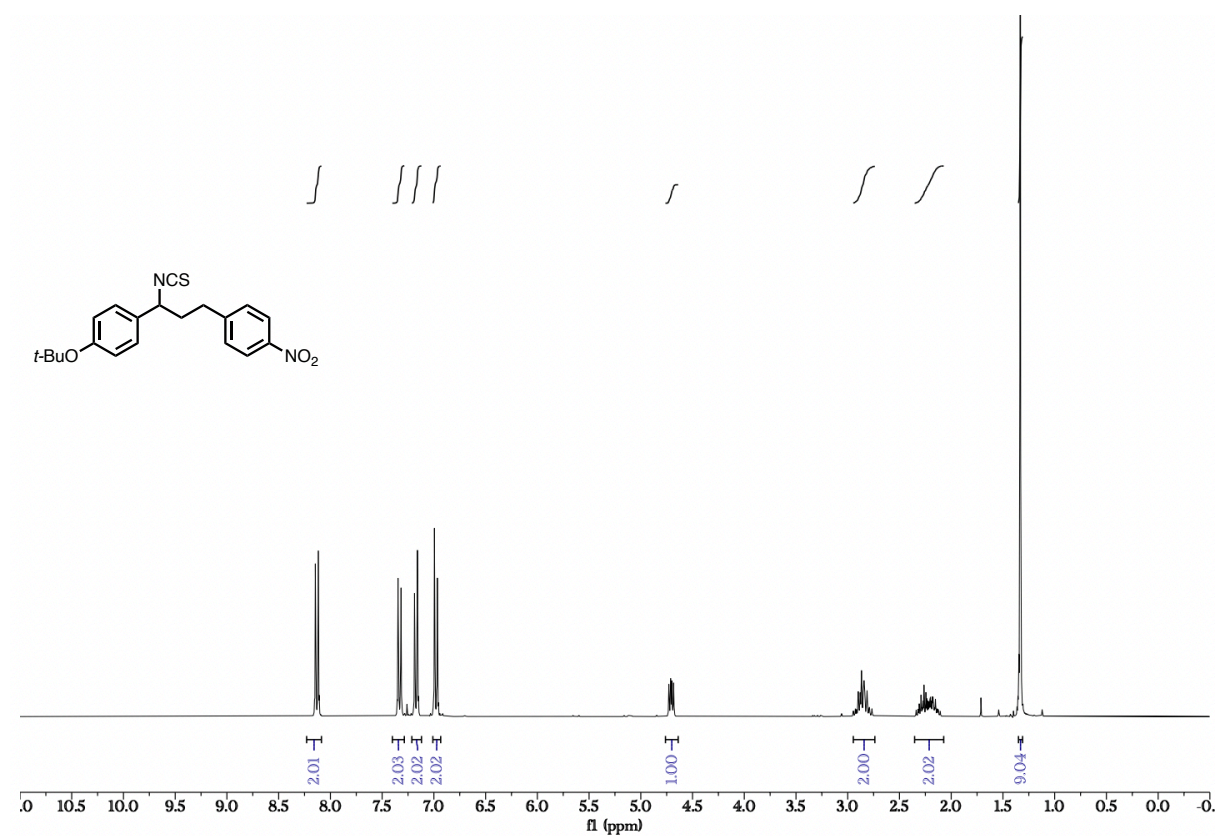




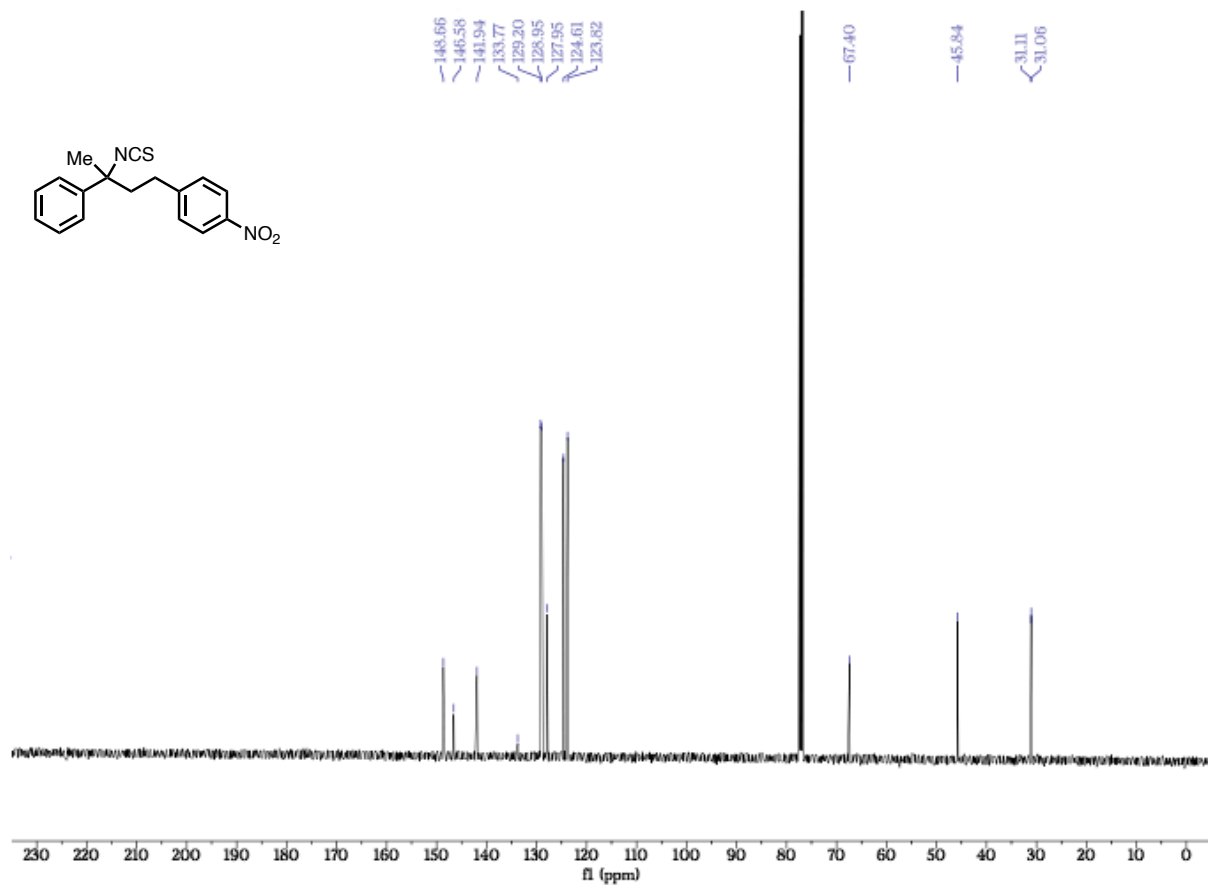
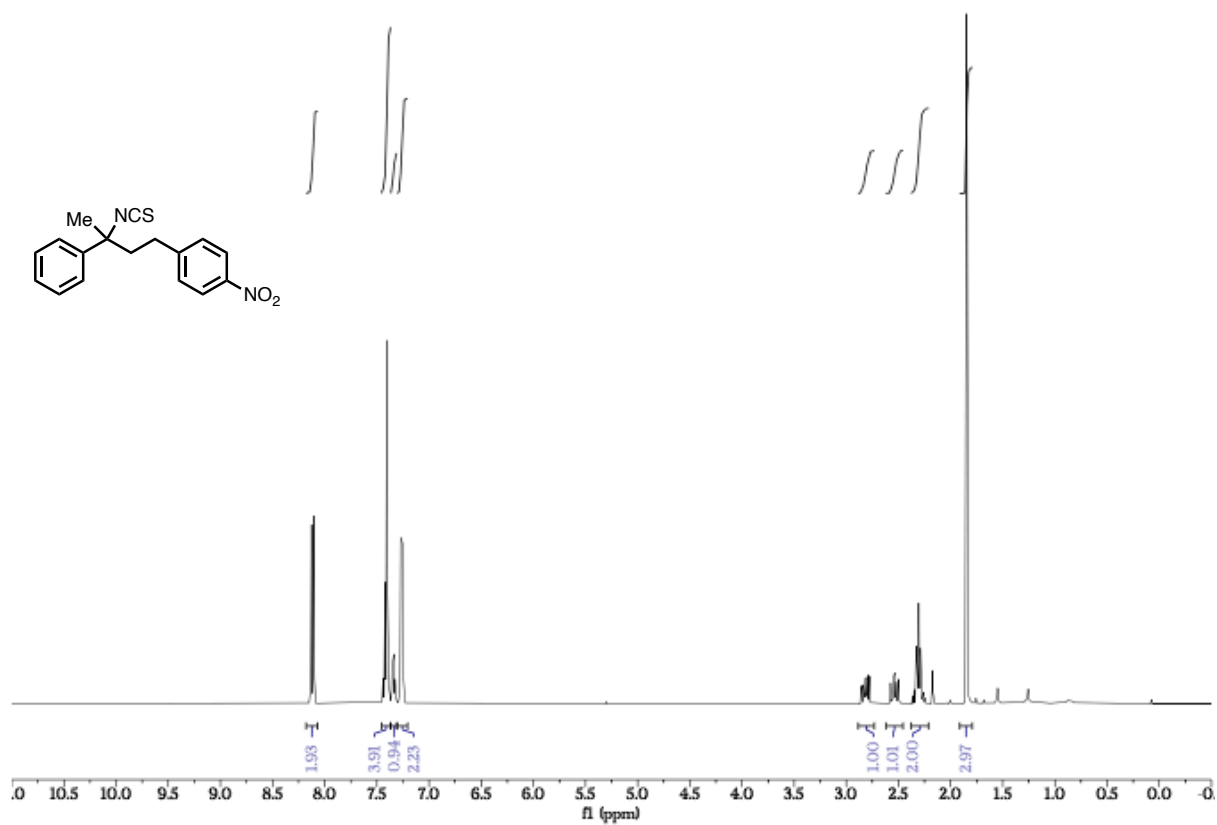
1-nitro-3-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3as)



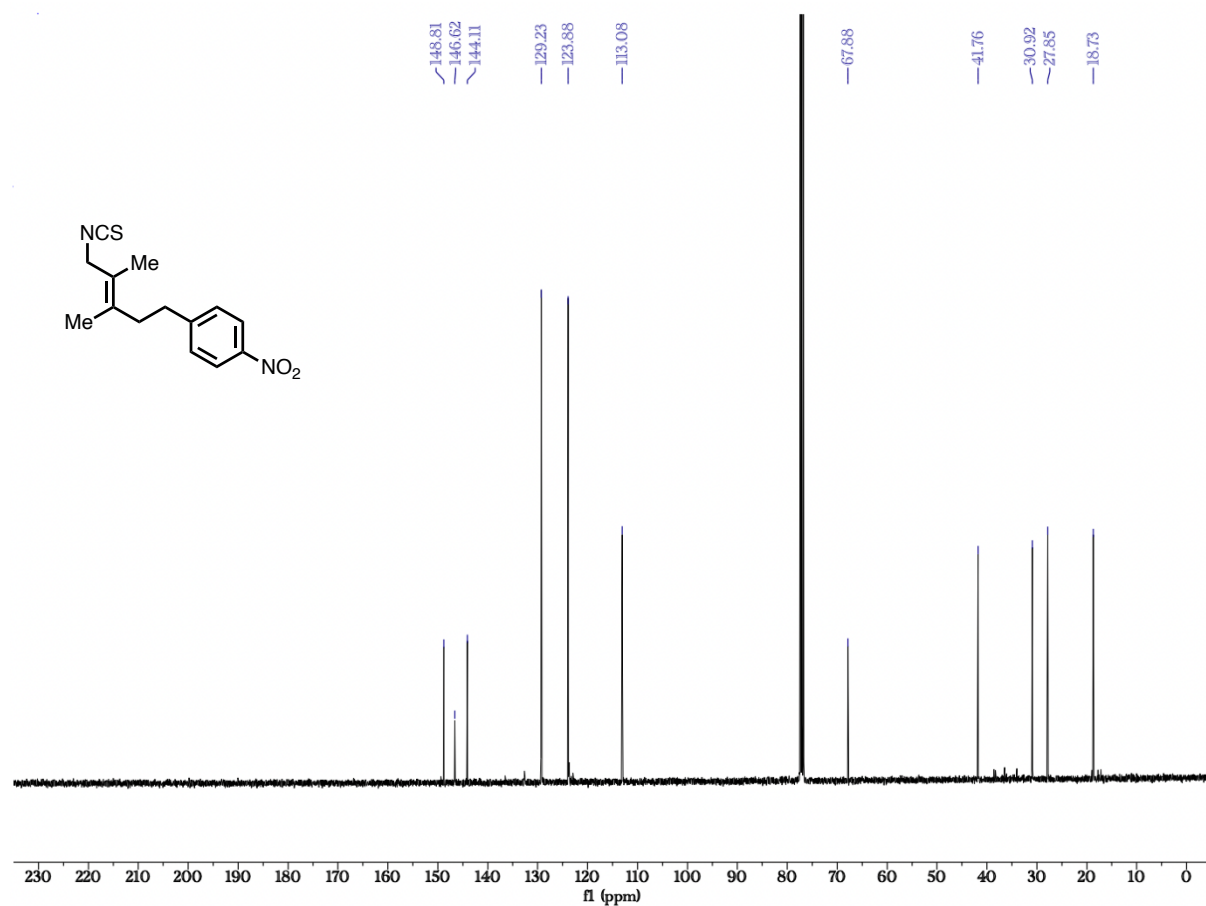
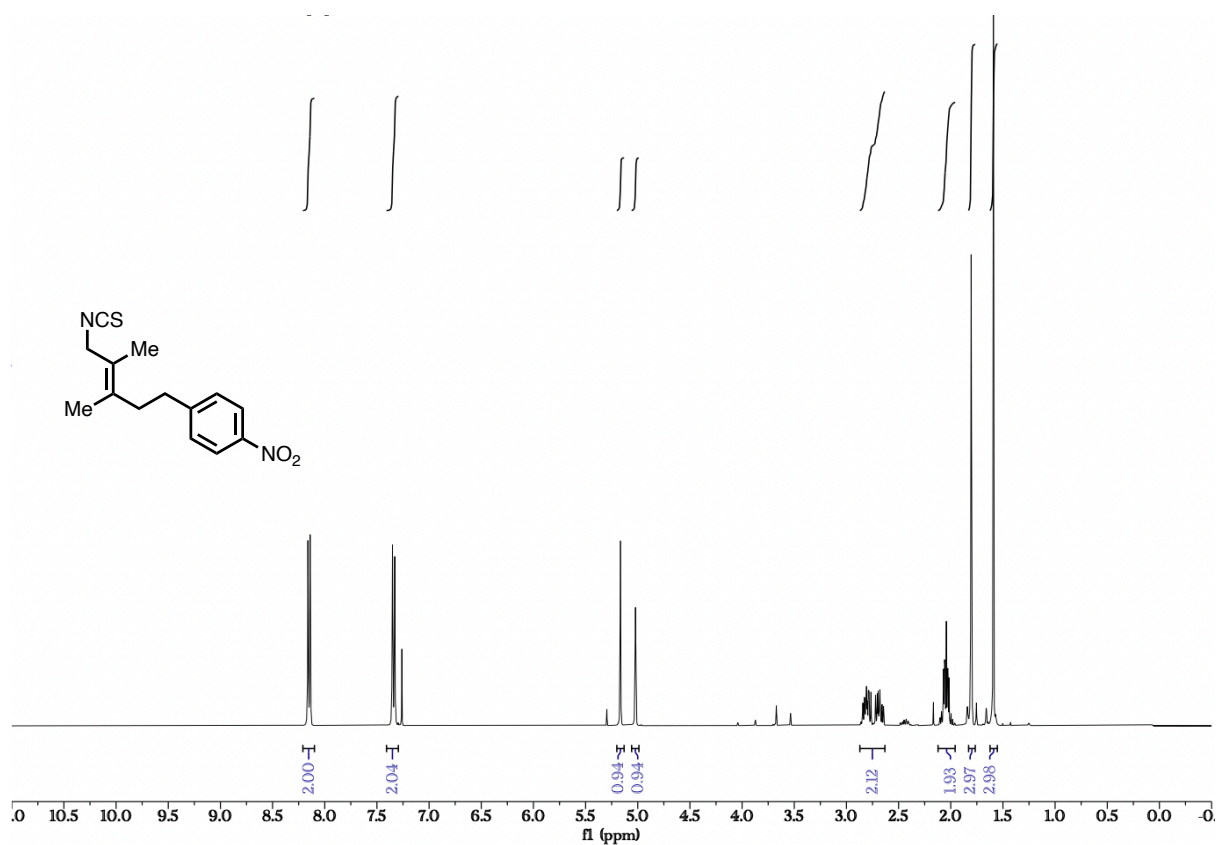
1-(*tert*-butoxy)-4-(1-isothiocyanato-3-(4-nitrophenyl)propyl)benzene (3at')



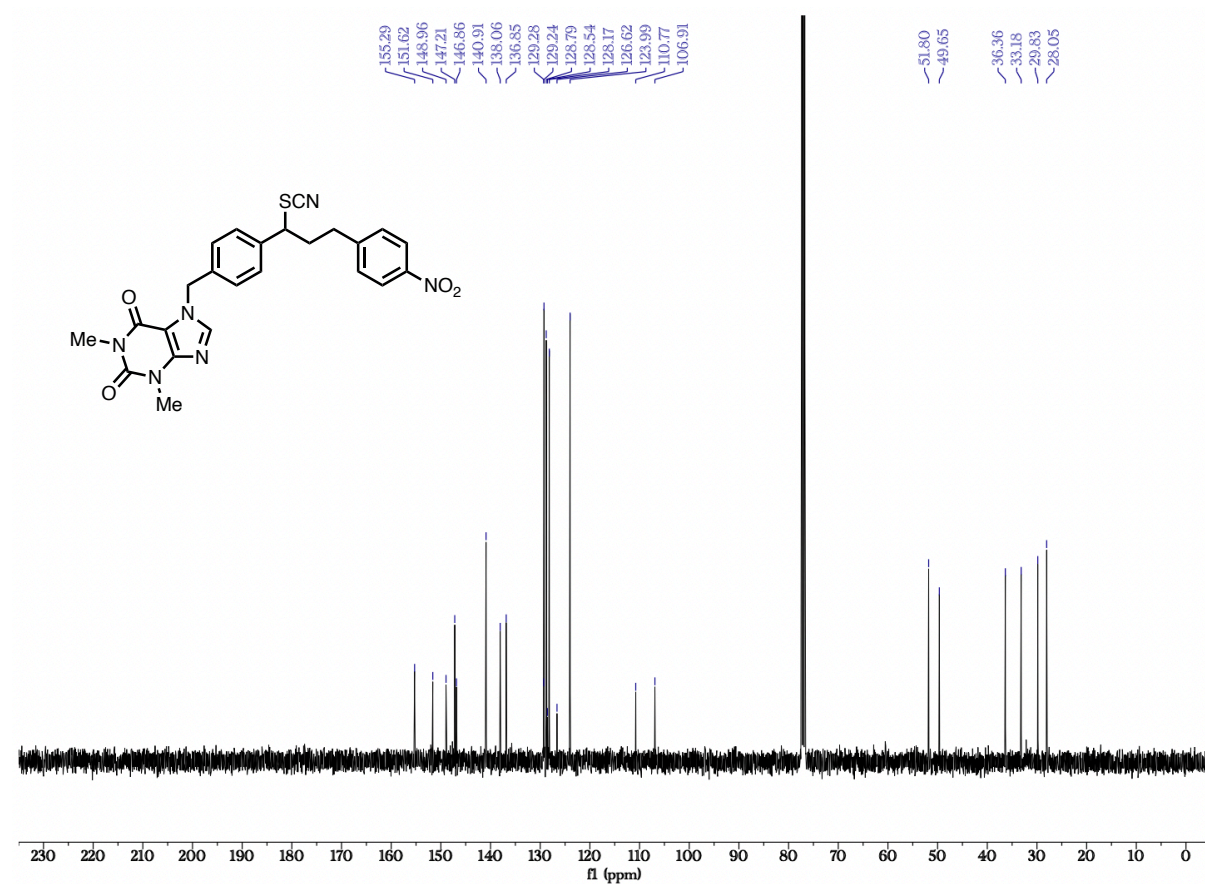
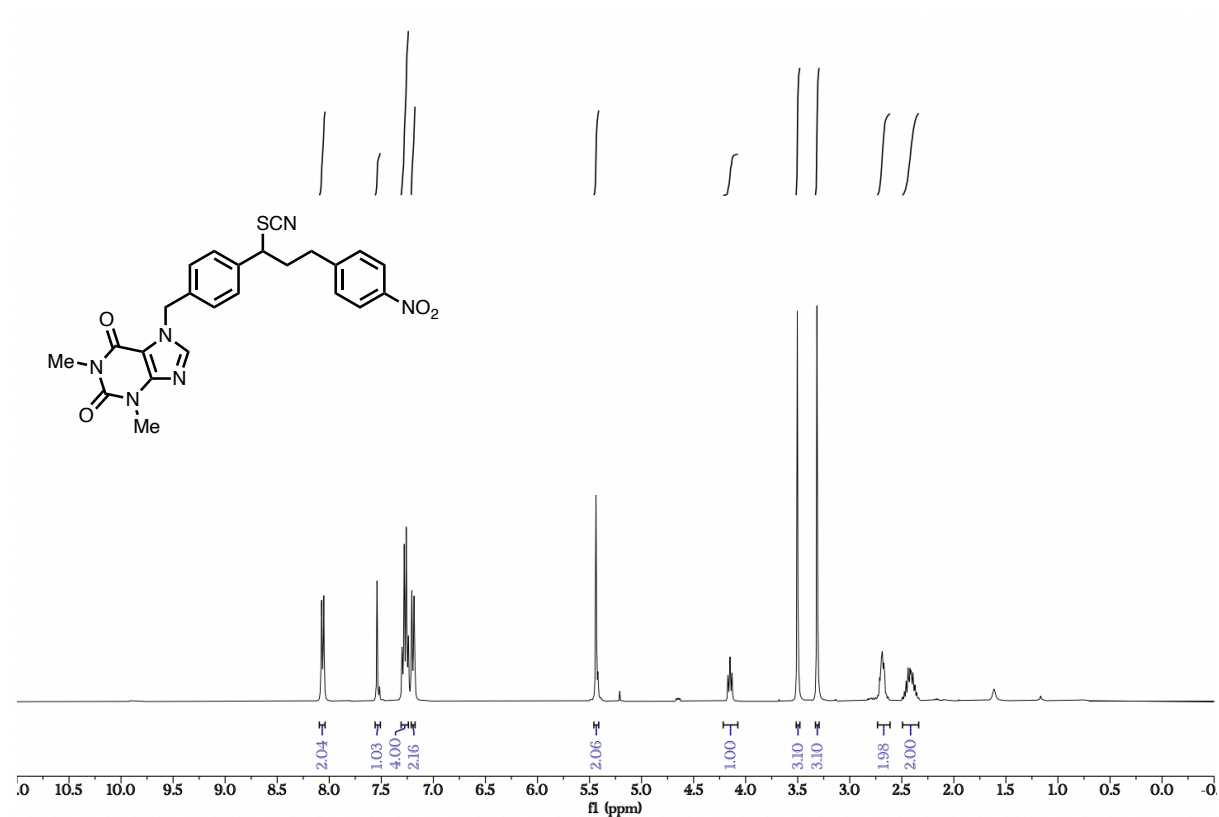
1-(3-isothiocyanato-3-phenylbutyl)-4-nitrobenzene (3au')



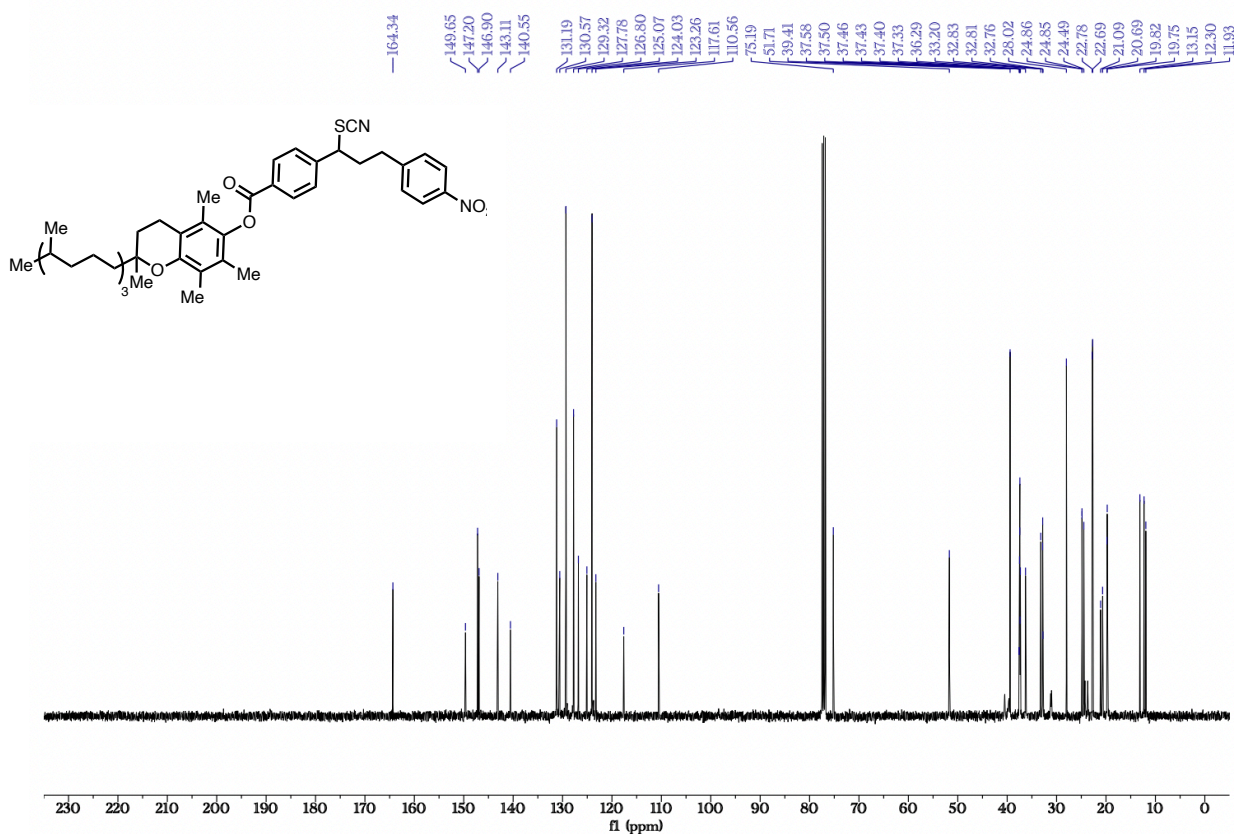
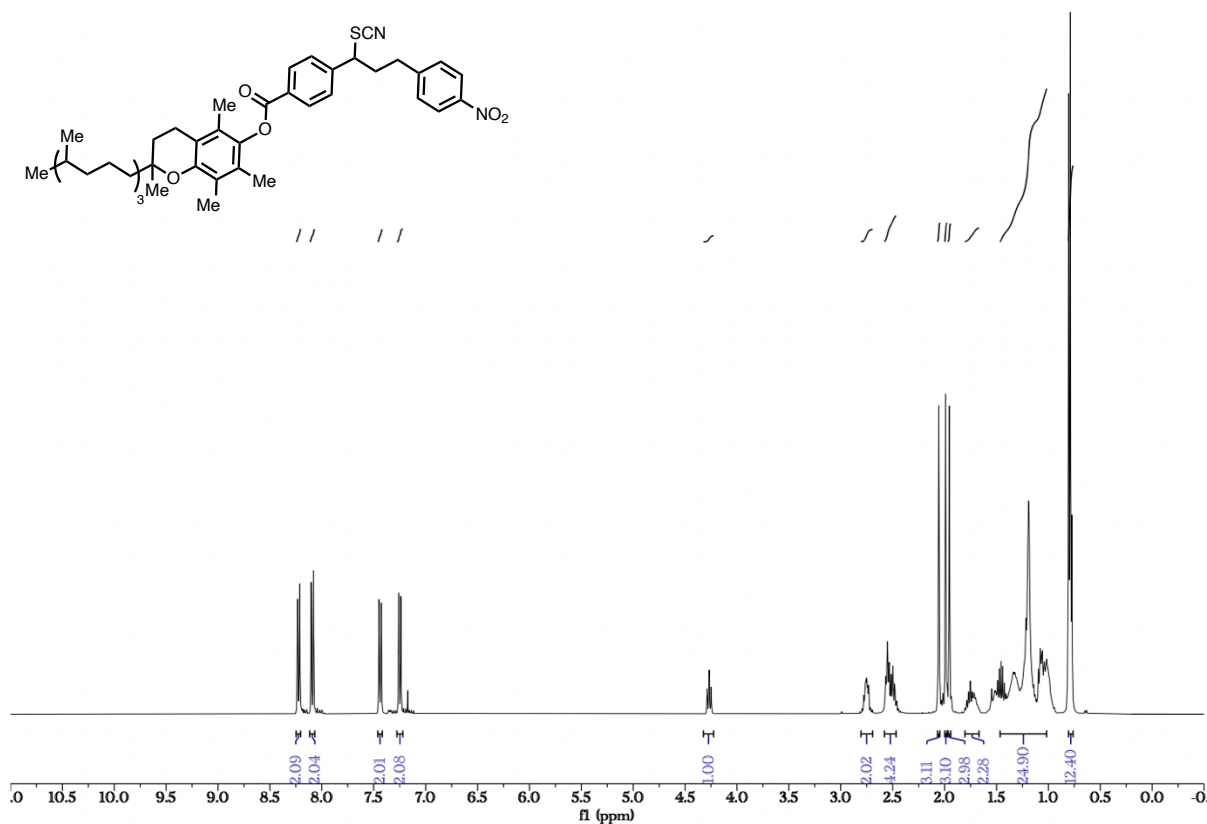
1-(5-isothiocyanato-3,4-dimethylpent-3-en-1-yl)-4-nitrobenzene (3av')



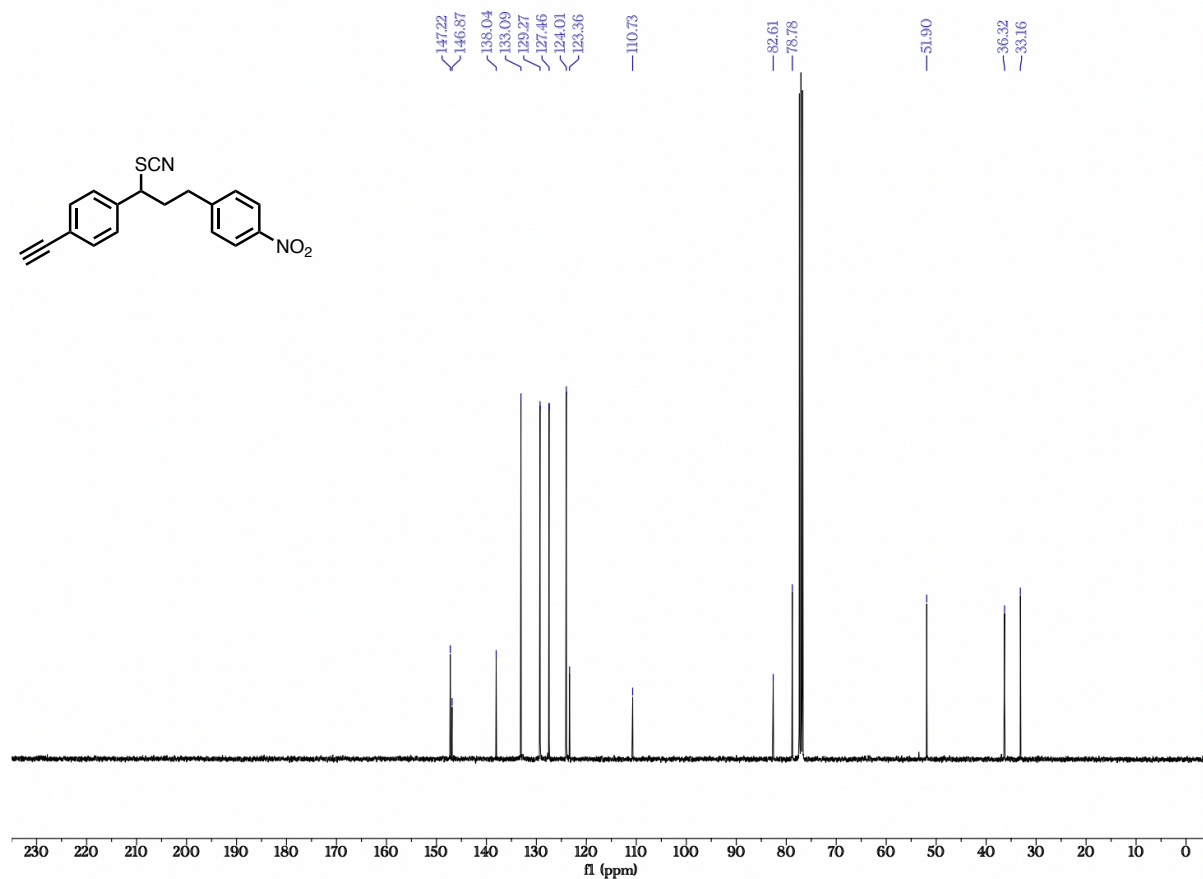
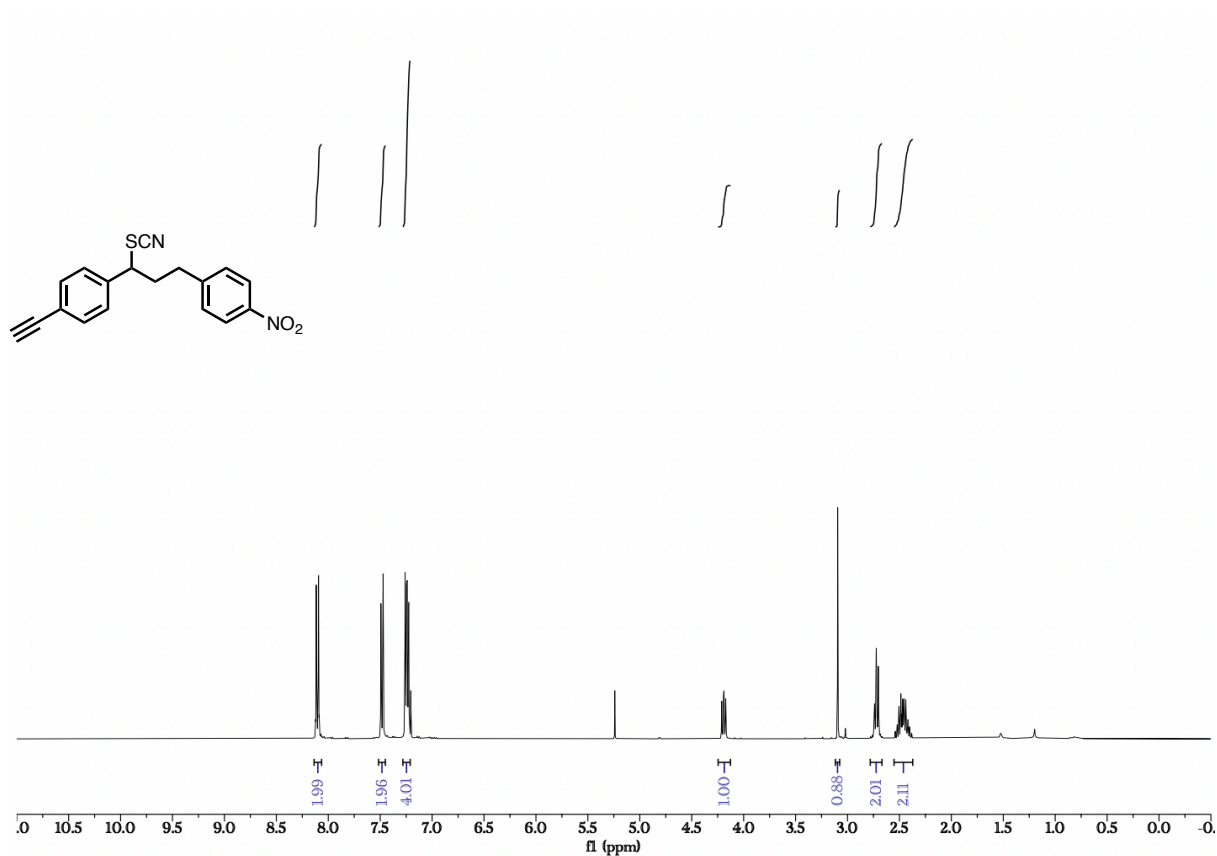
1,3-dimethyl-7-(4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzyl)-3,7-dihydro-1H-purine-2,6-dione (3aw)



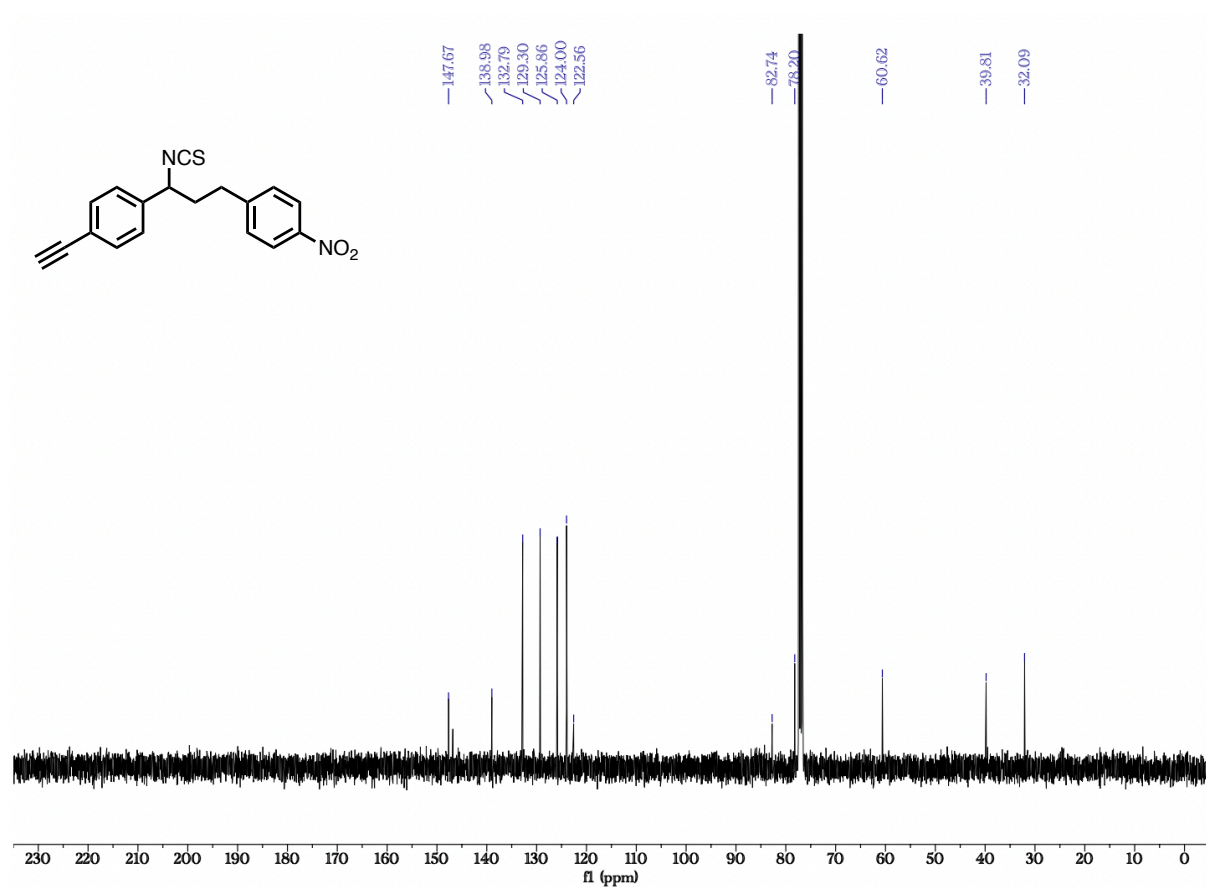
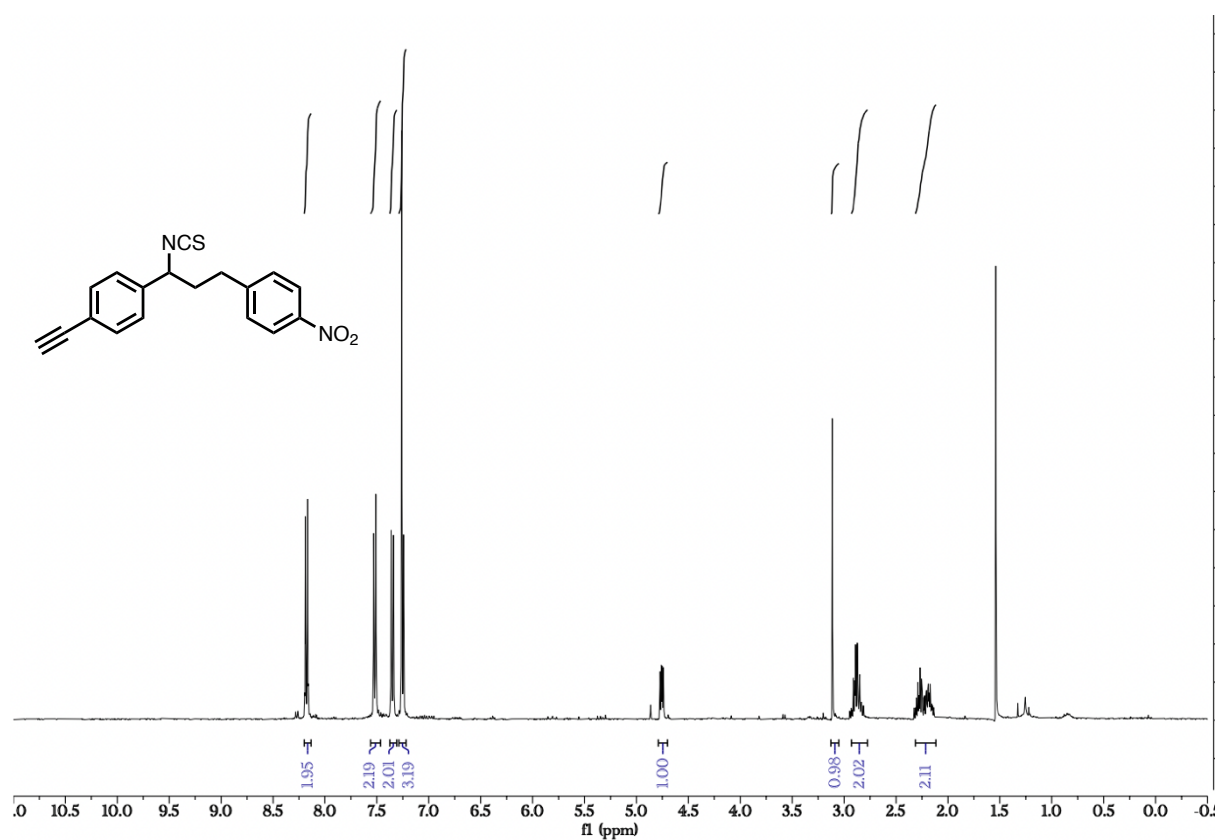
2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl 4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzoate (3ax)



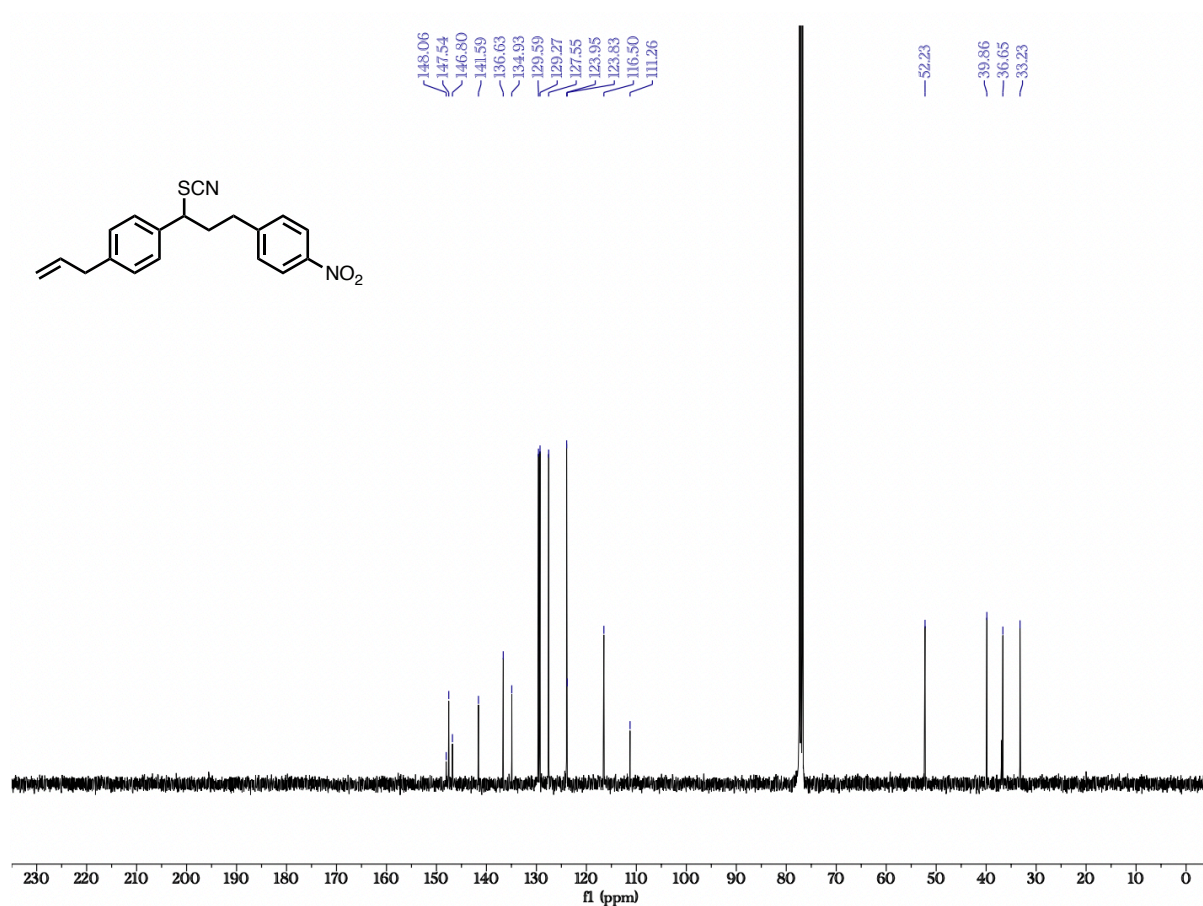
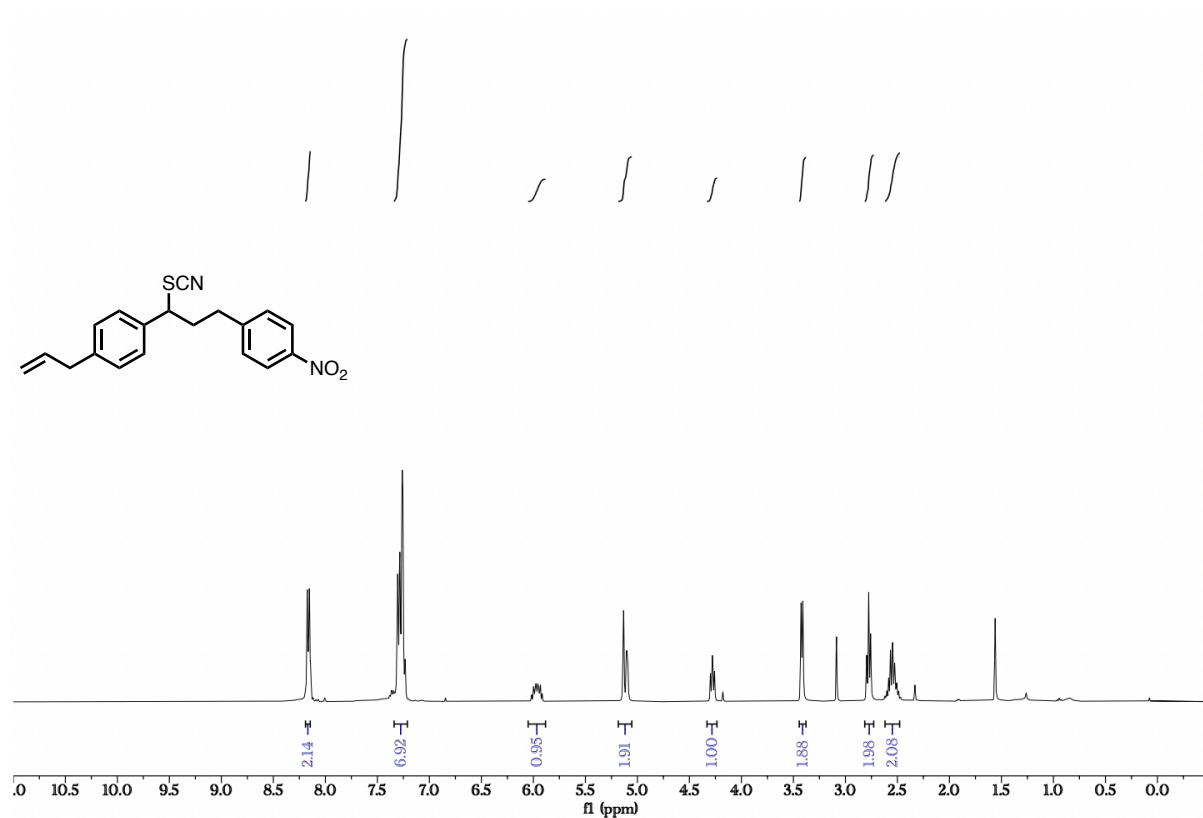
1-ethynyl-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3ay)



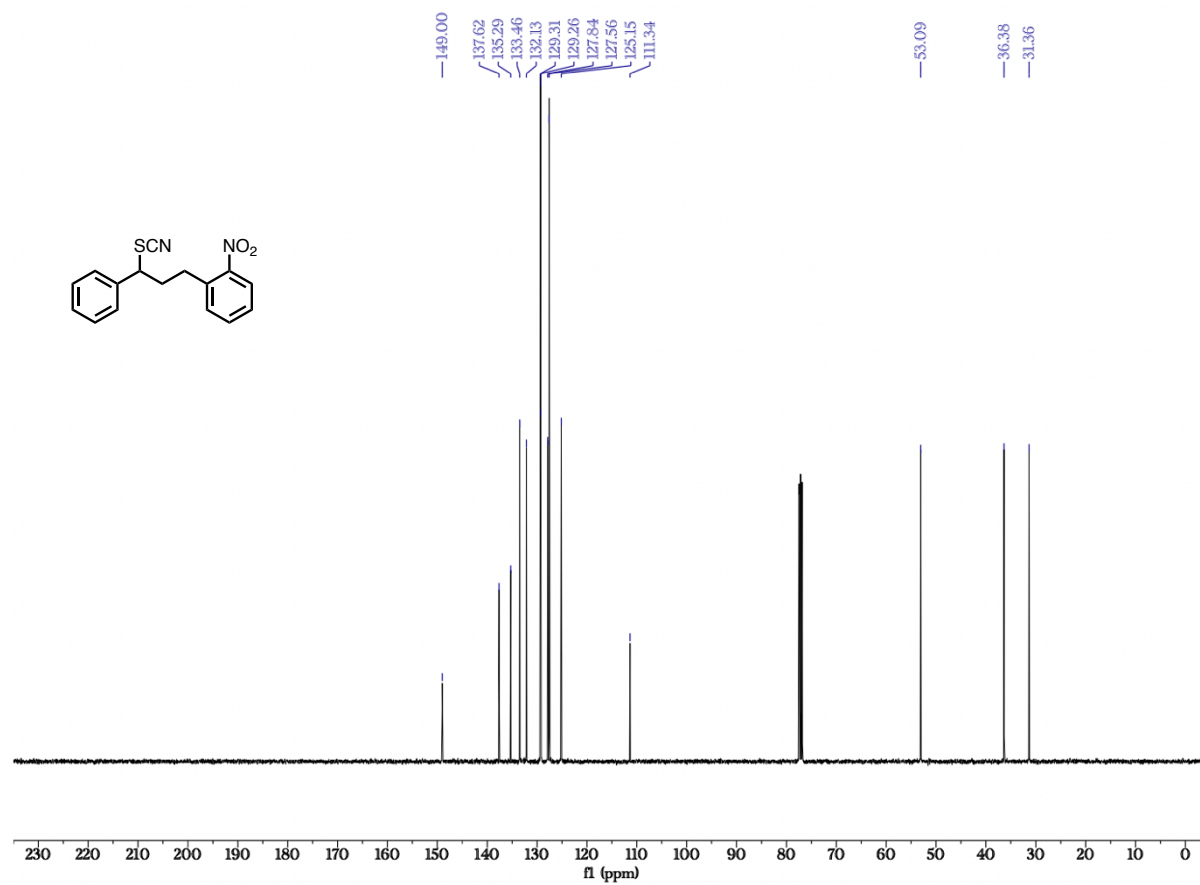
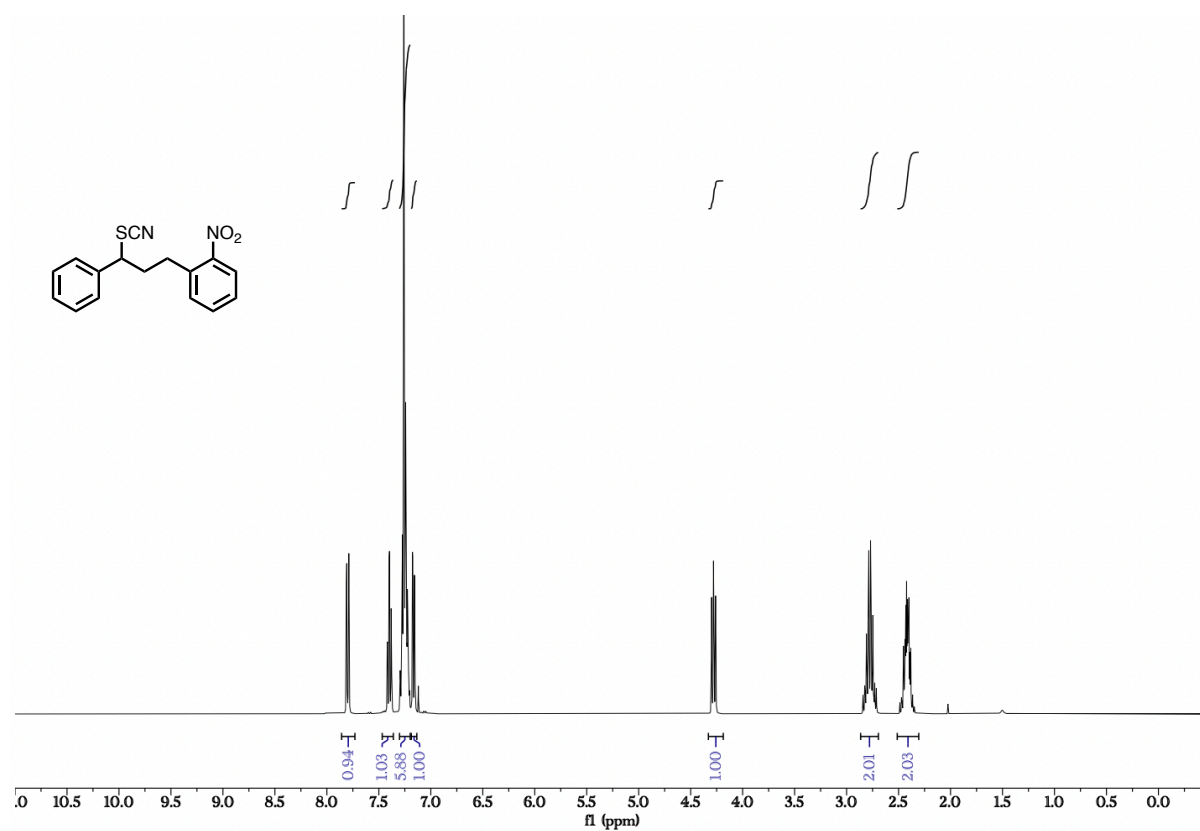
1-ethynyl-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3ay'



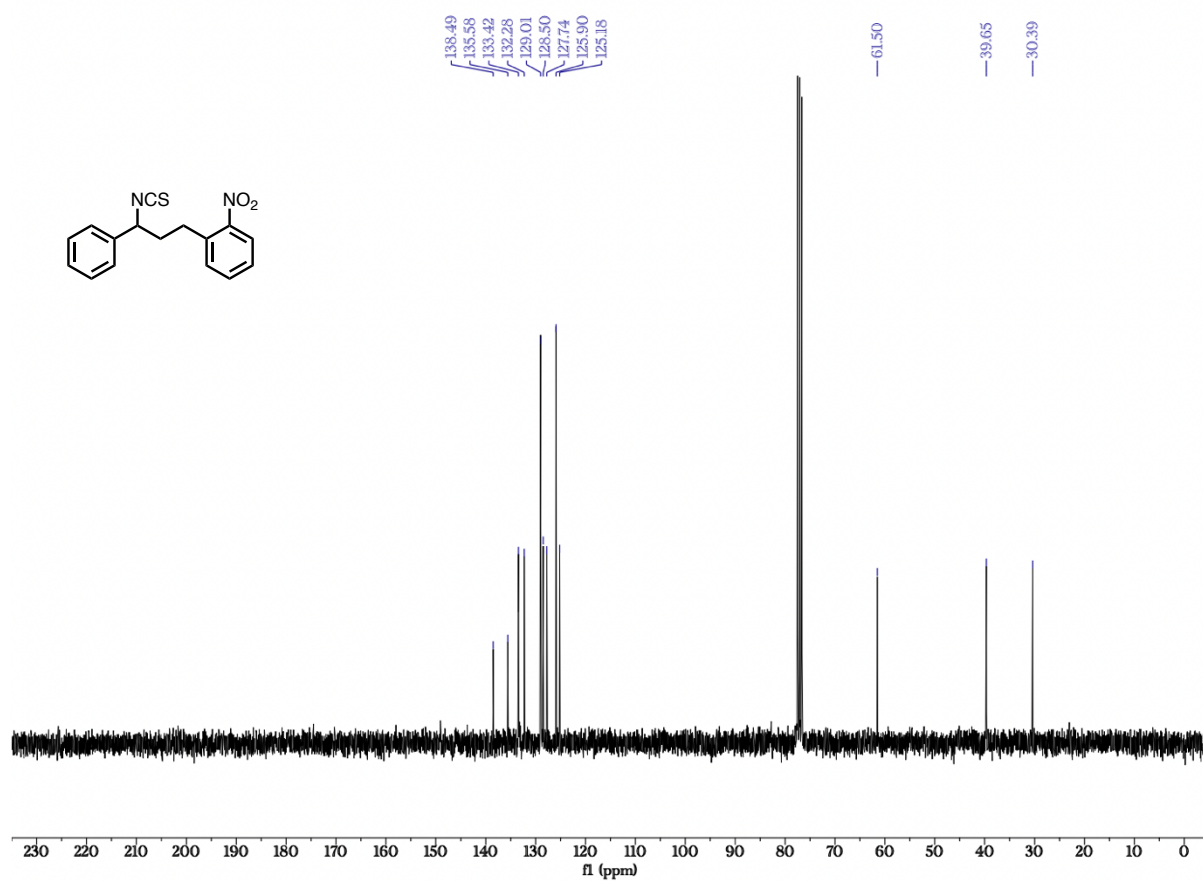
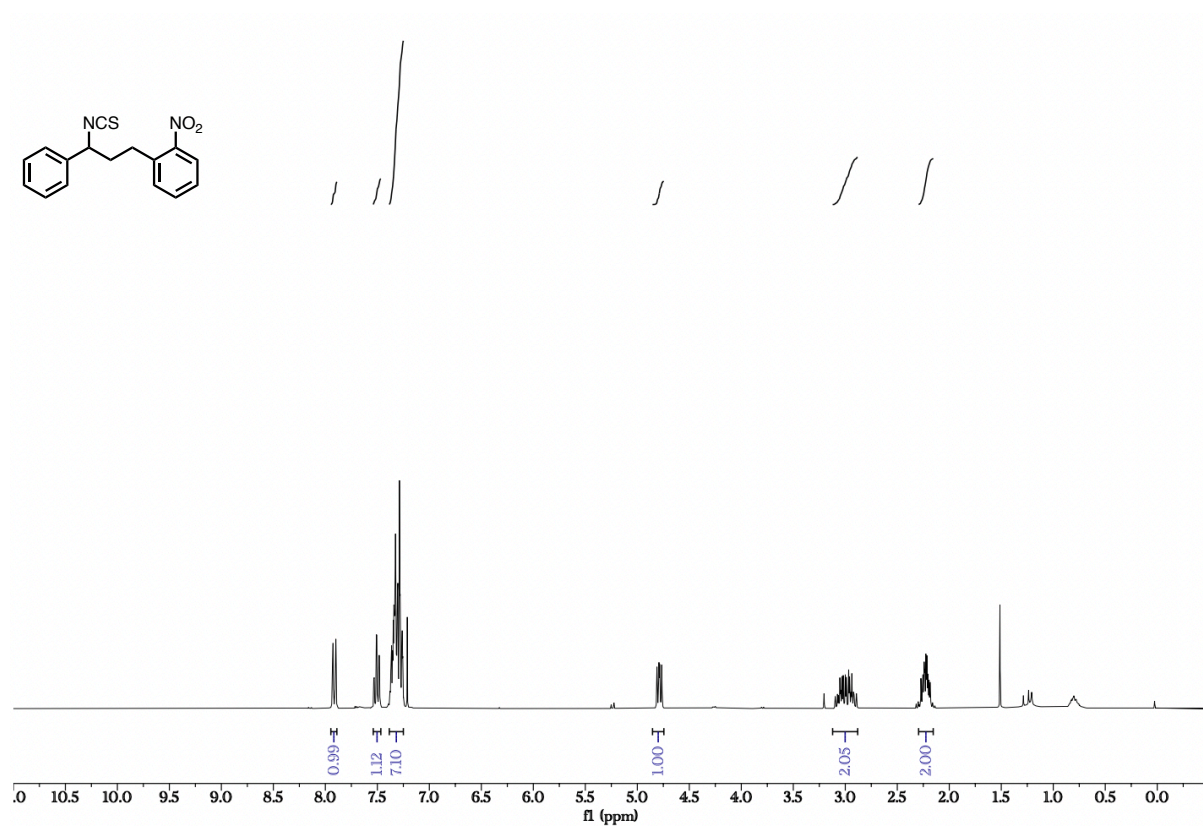
1-allyl-4-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3az)



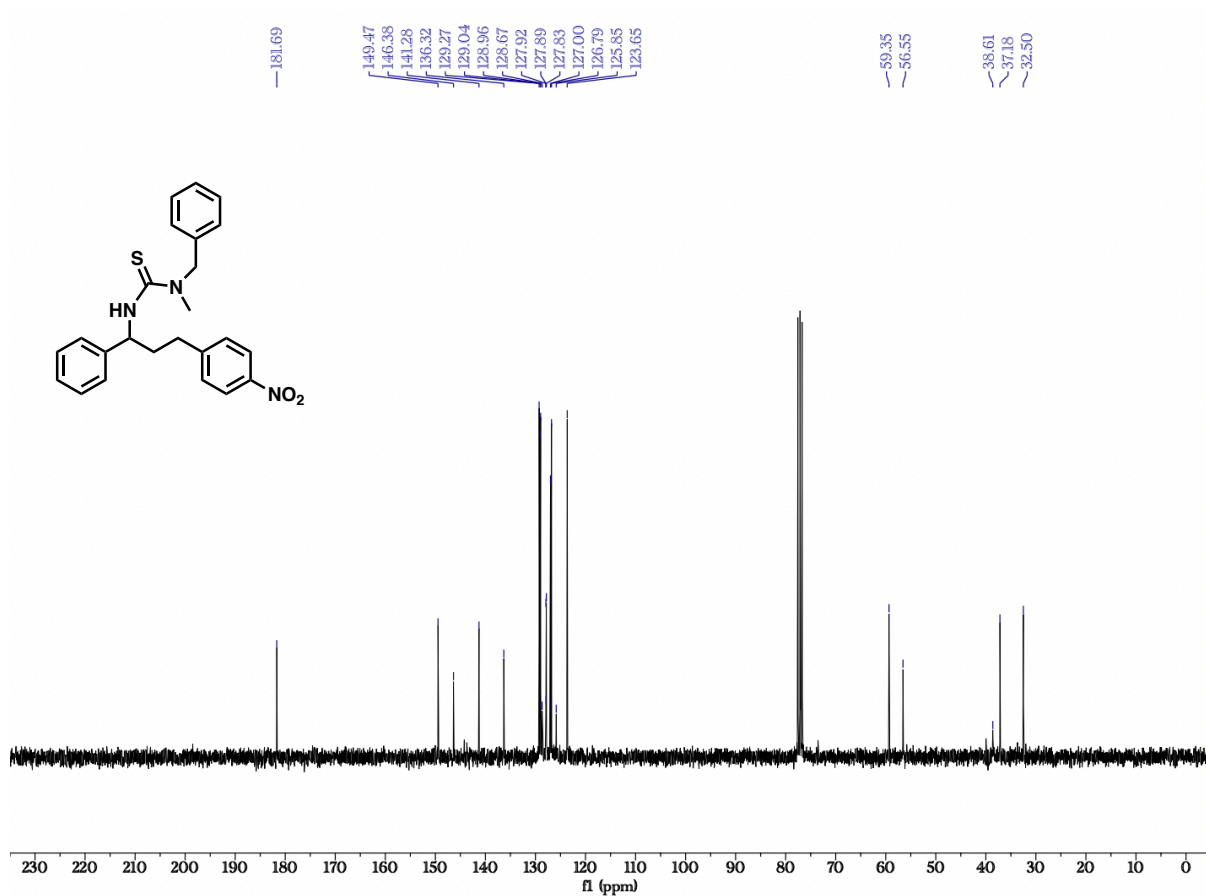
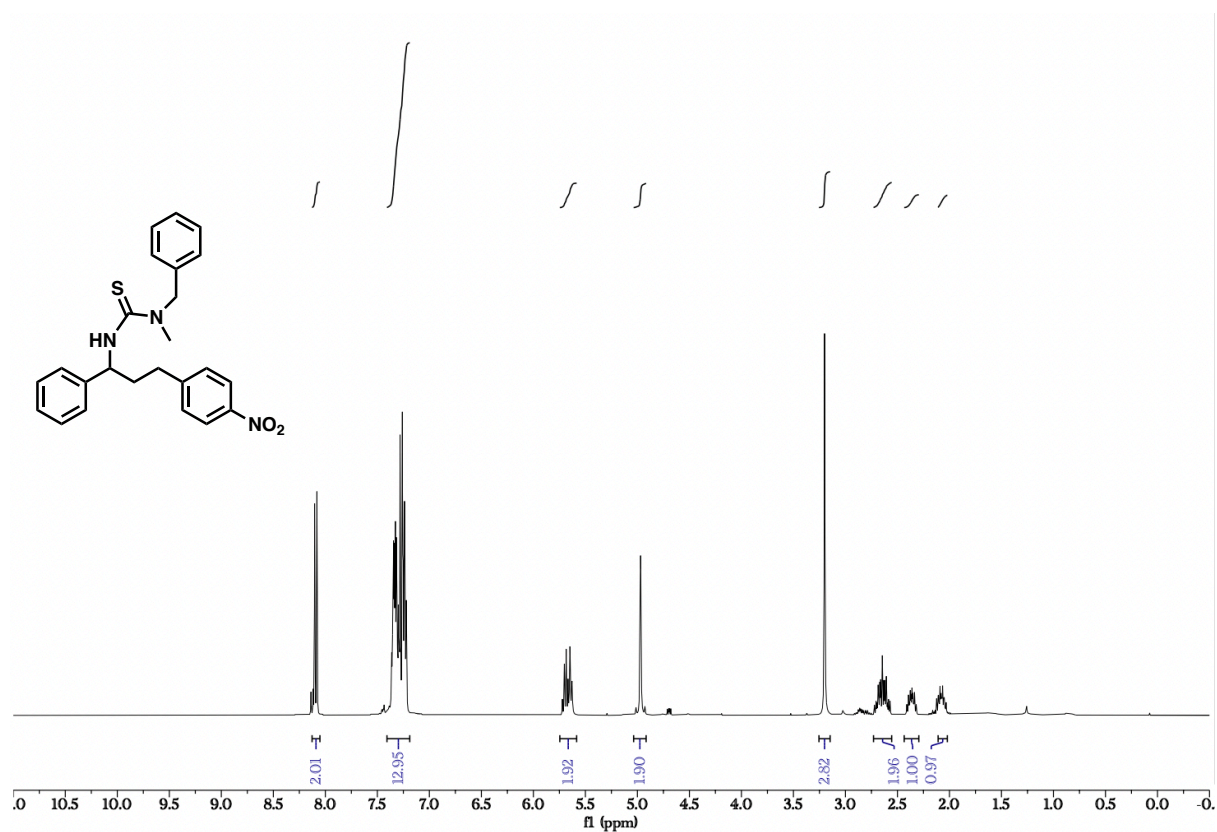
1-nitro-2-(3-phenyl-3-thiocyanatopropyl)benzene (3bc)



1-(3-isothiocyanato-3-phenylpropyl)-2-nitrobenzene (3bc')



1-benzyl-1-methyl-3-(3-(4-nitrophenyl)-1-phenylpropyl)thiourea (4a)



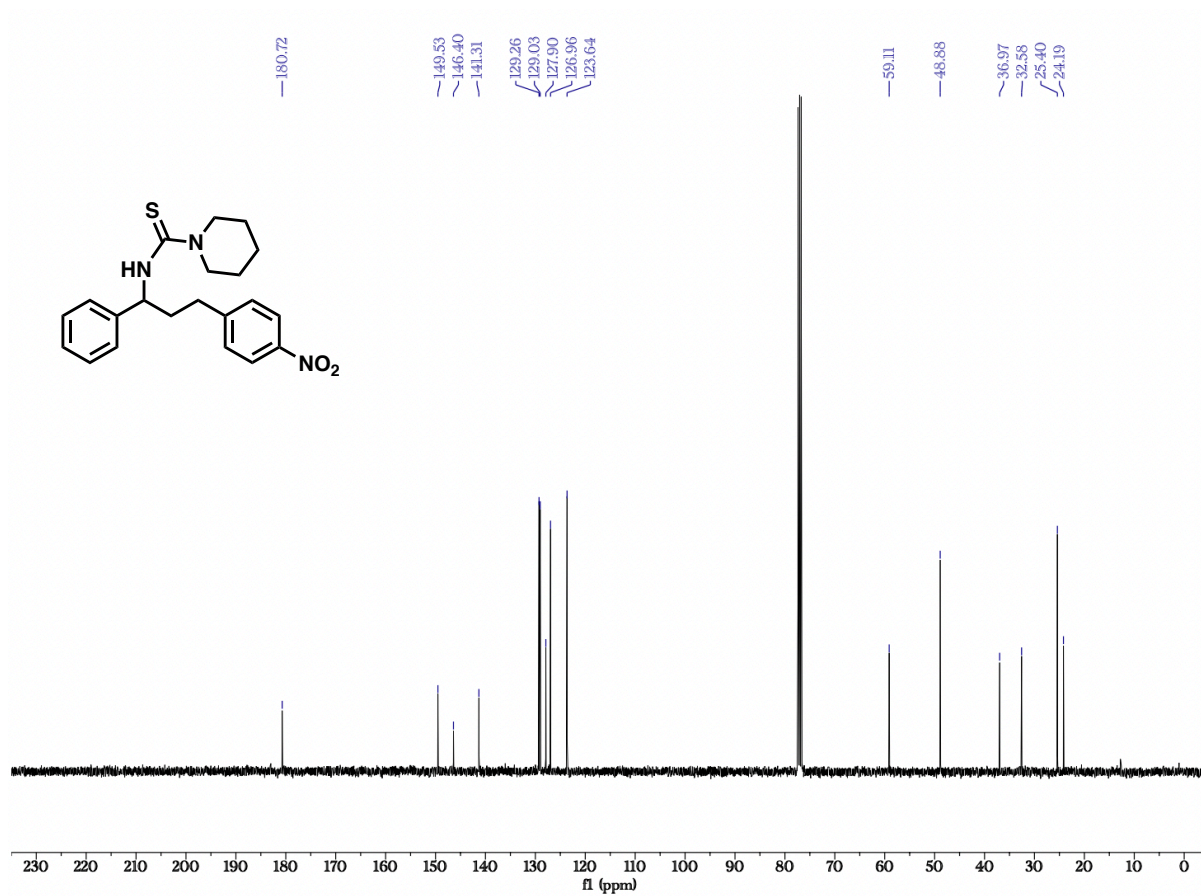
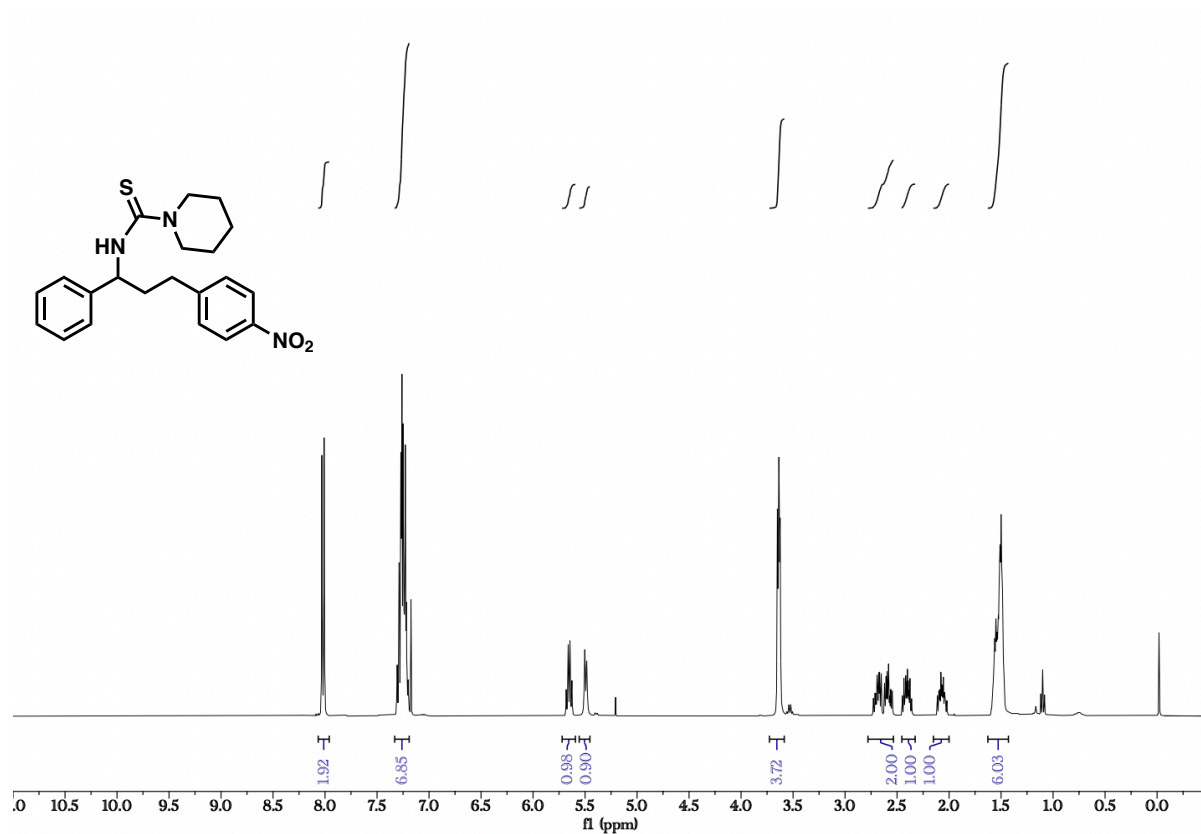
Chemical structure: CC(C1=CC=CC=C1)C(=S)N2CCOCC2C3=CC=C(C=C3)[N+](=O)[O-]

¹H NMR spectrum (ppm):

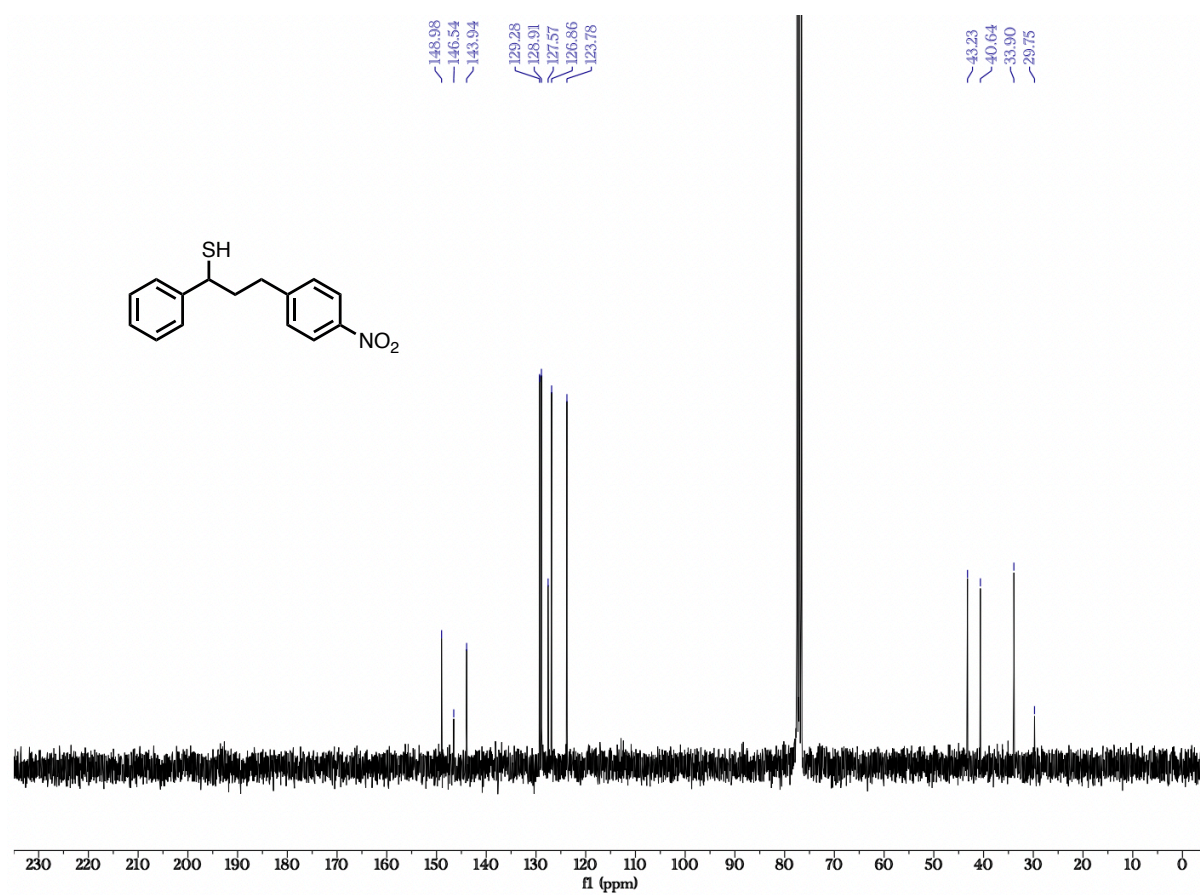
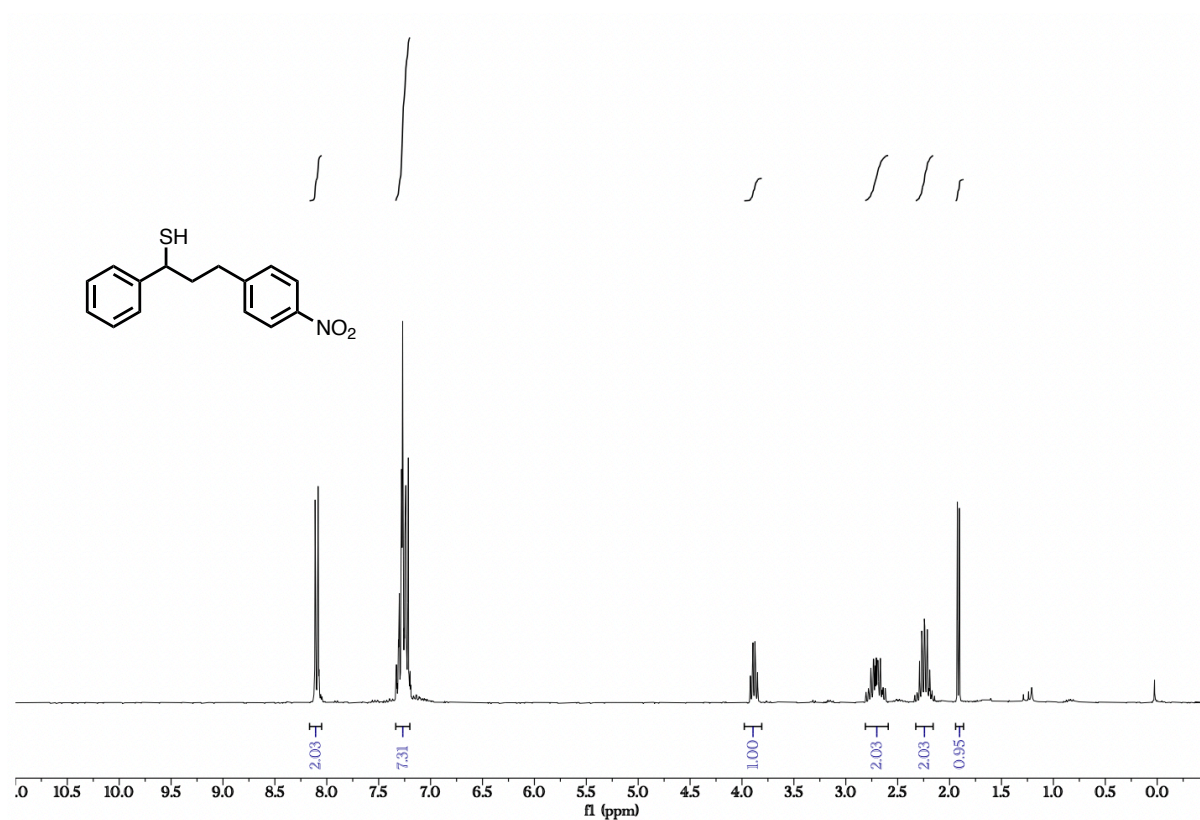
- 8.09 (s, 1H, integration 1.89)
- 7.24-7.34 (m, 6H, integration 6.74)
- 5.54 (s, 2H, integration 1.90)
- 3.54 (s, 4H, integration 7.74)
- 2.54 (m, 1H, integration 0.97)
- 2.44 (m, 1H, integration 1.00)
- 2.34 (m, 1H, integration 1.01)
- 2.14 (m, 1H, integration 1.00)



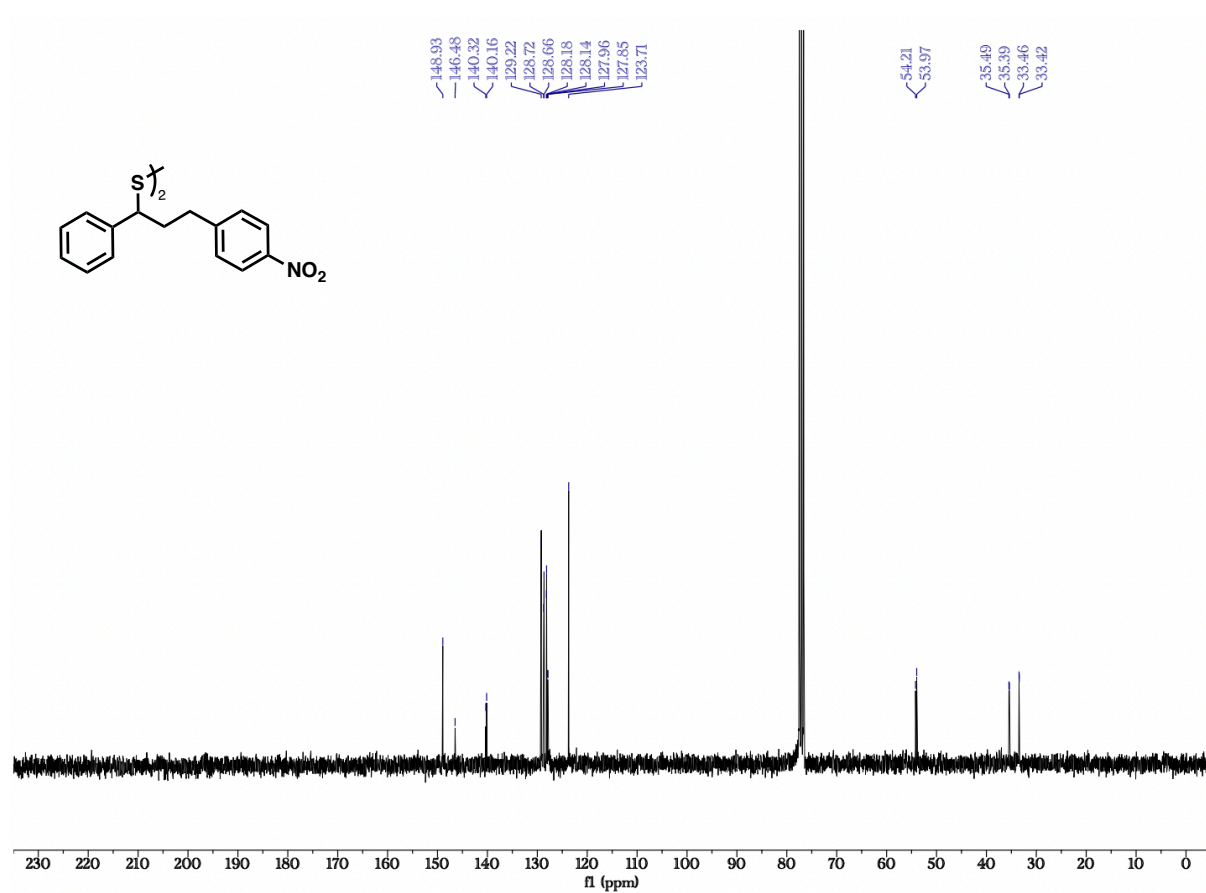
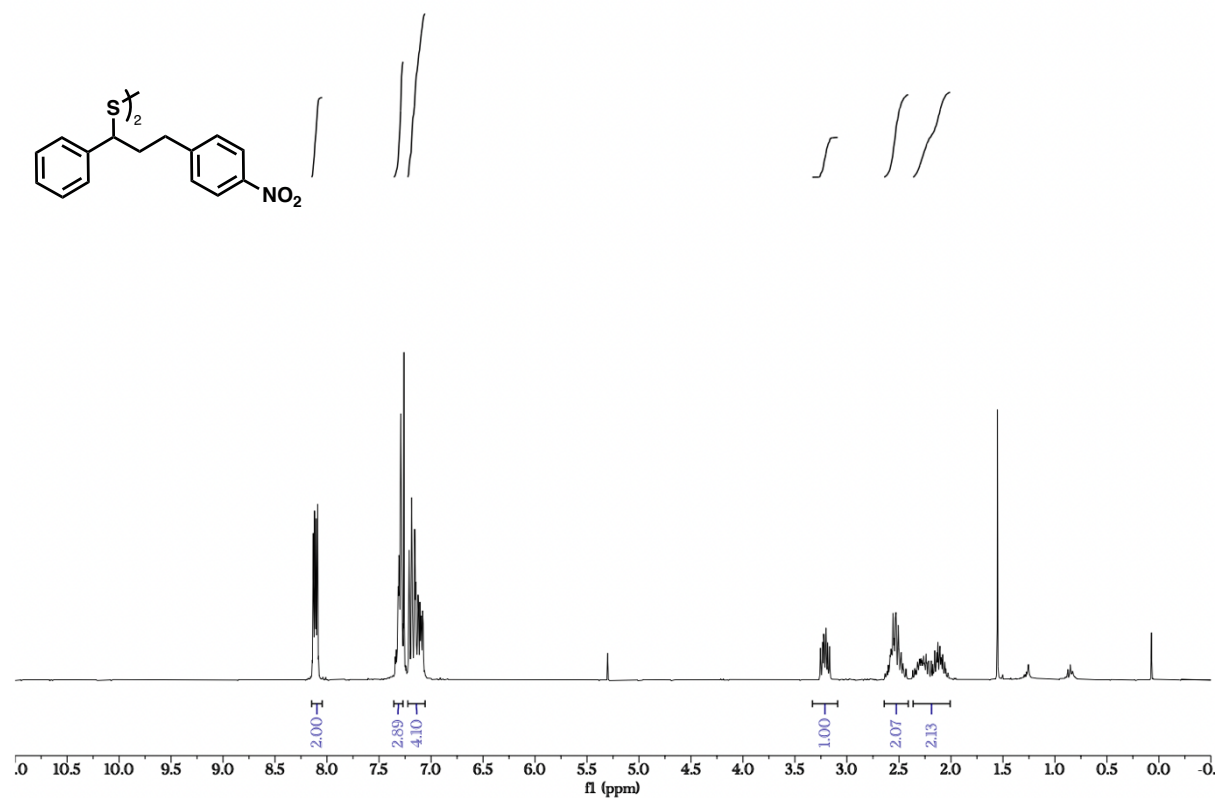
***N*-(3-(4-nitrophenyl)-1-phenylpropyl)piperidine-1-carbothioamide (4c)**



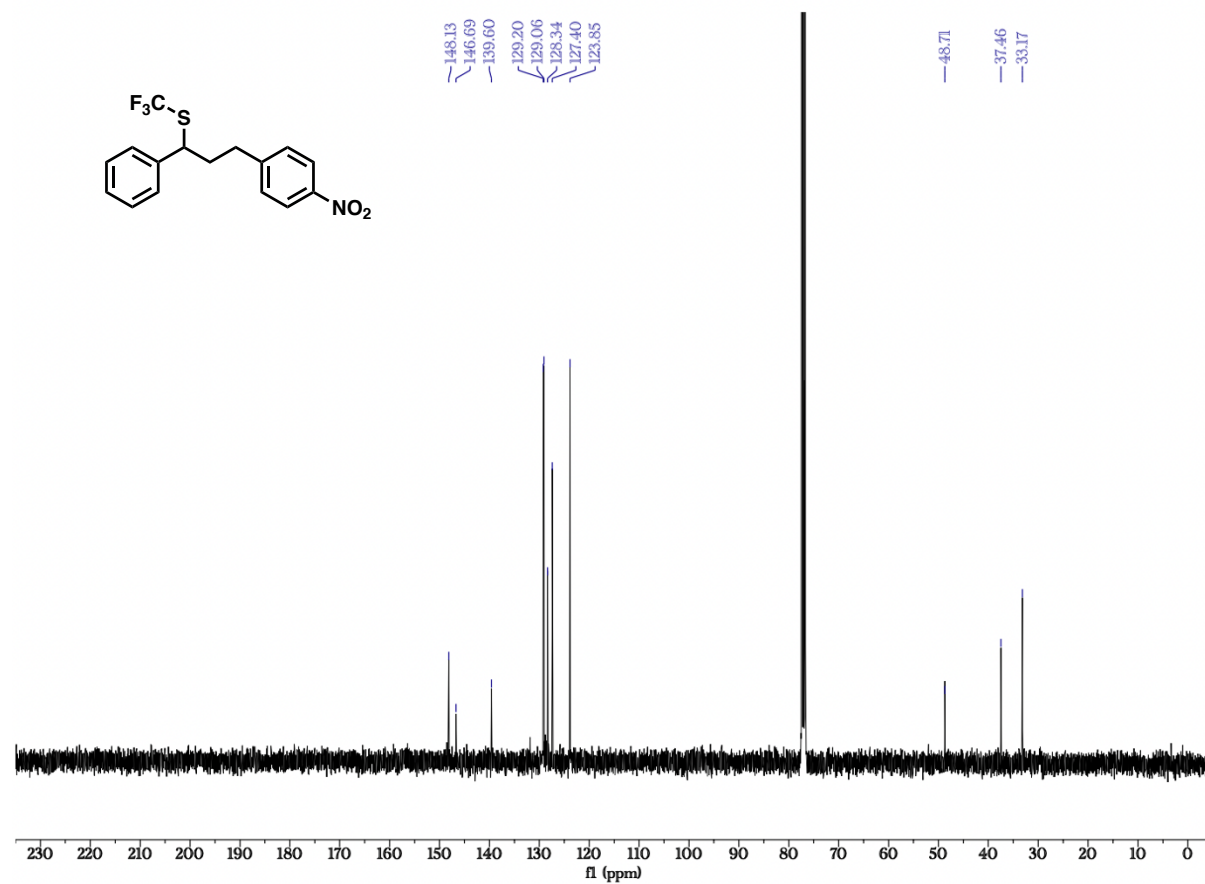
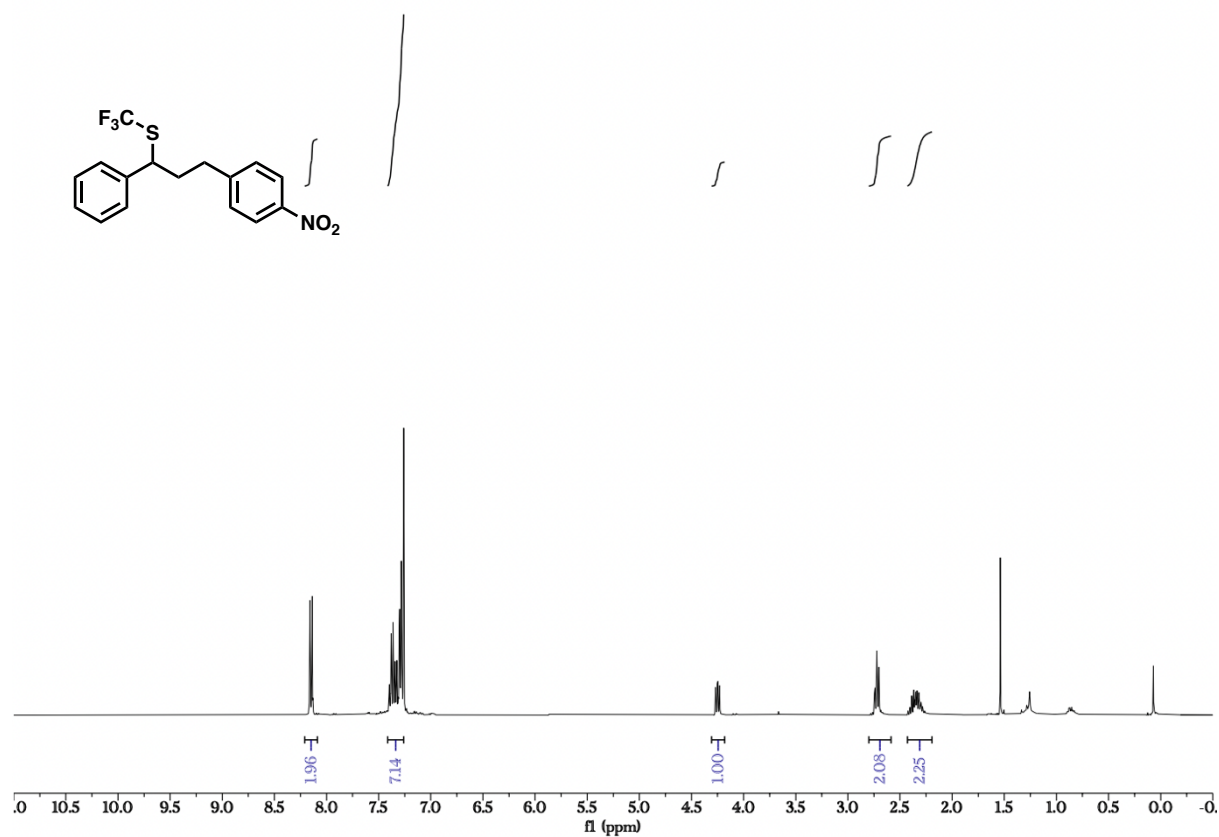
3-(4-nitrophenyl)-1-phenylpropane-1-thiol (5a)

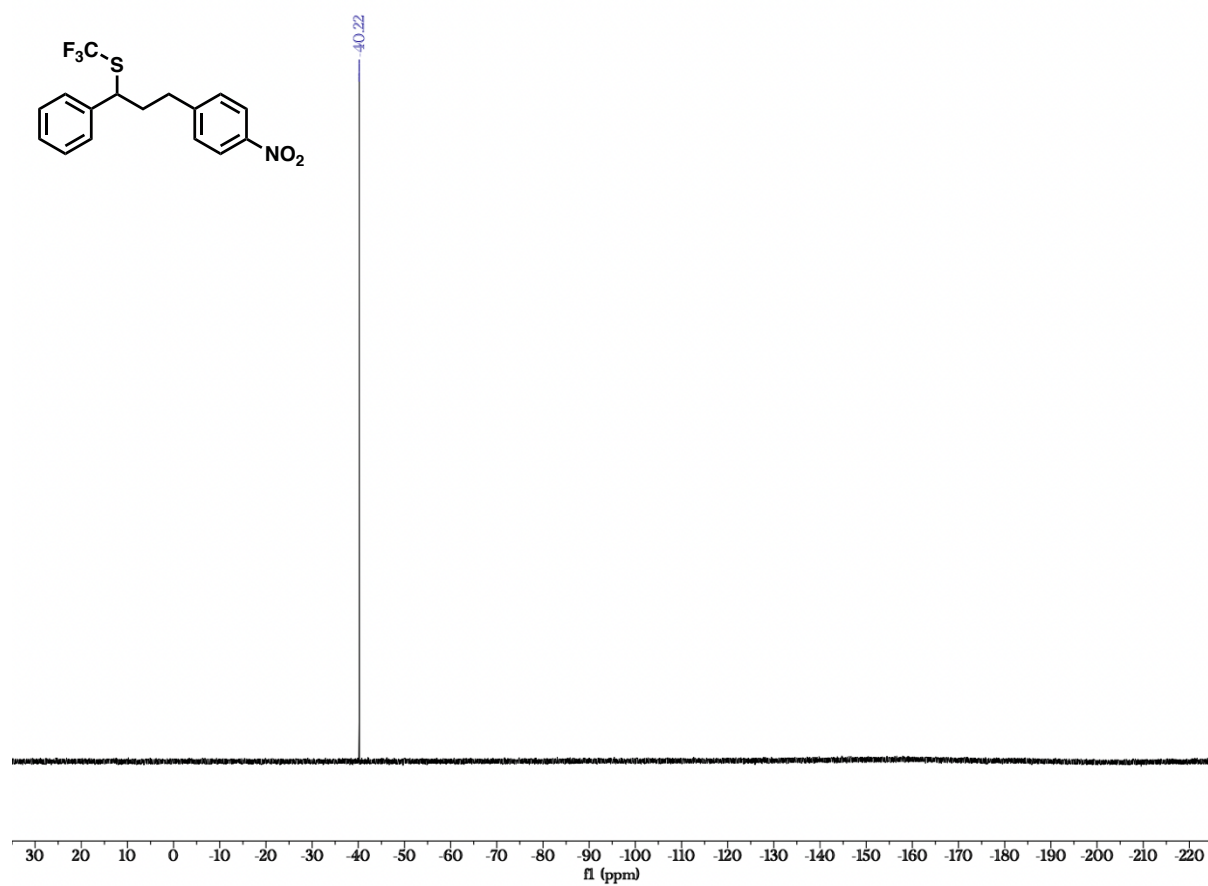


1,2-bis(3-(4-nitrophenyl)-1-phenylpropyl)disulfane (5b)



(3-(4-nitrophenyl)-1-phenylpropyl)(trifluoromethyl)sulfane (5c)





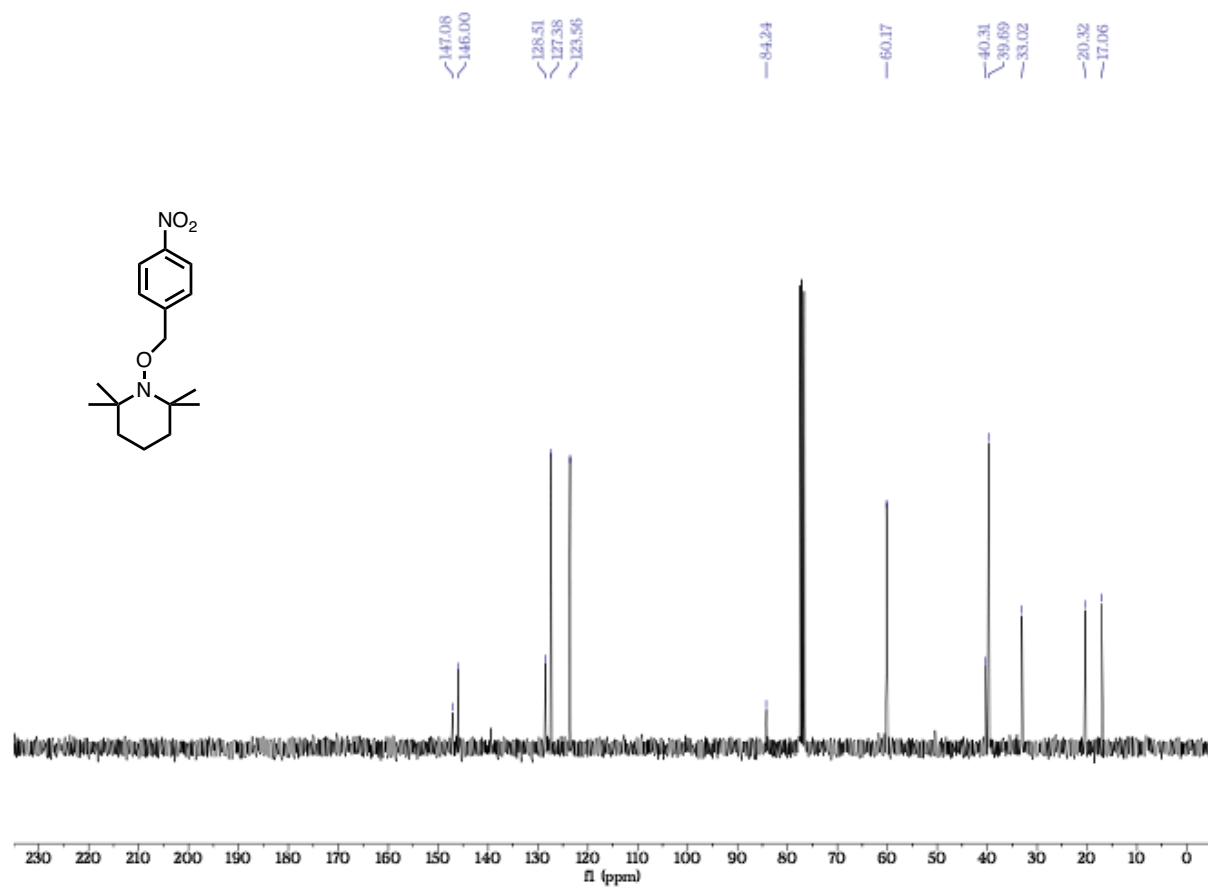
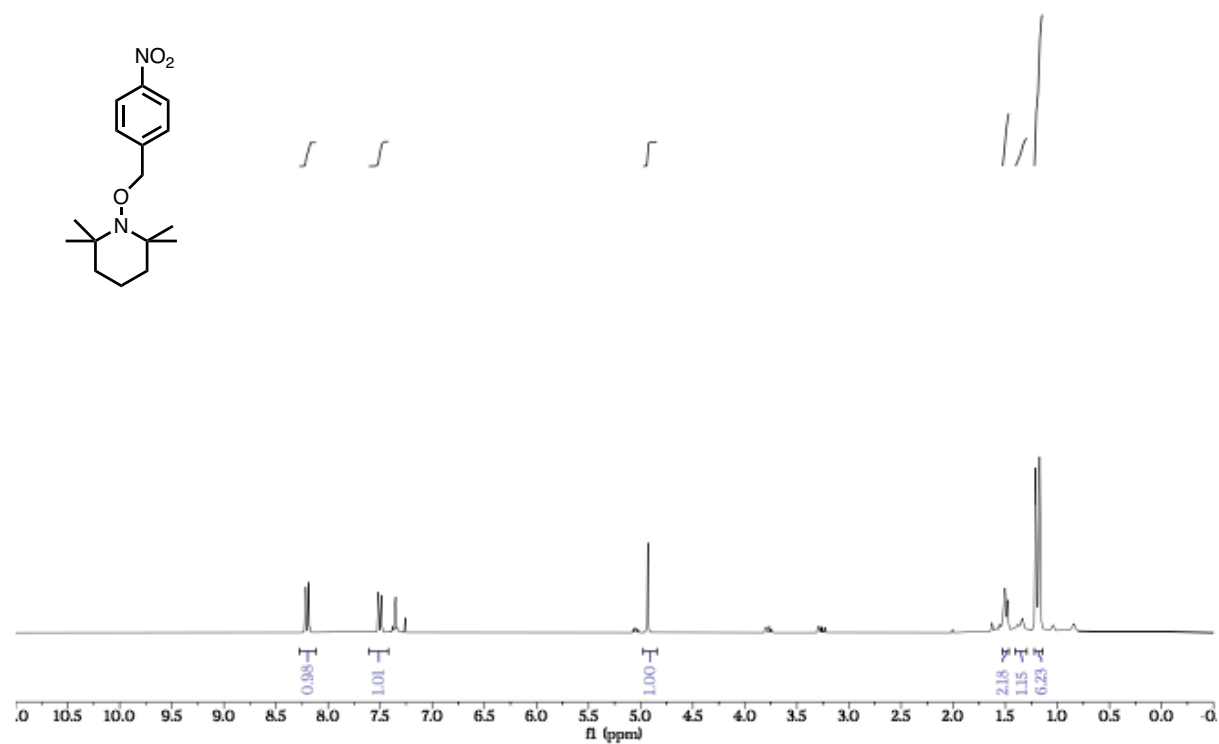
Chemical structure of 1-(4-aminophenyl)-2-phenylethane-1-ol: Nc1ccc(cc1)CC(O)c2ccccc2

¹H NMR spectrum (400 MHz, DMSO-d₆) showing peaks and integration values:

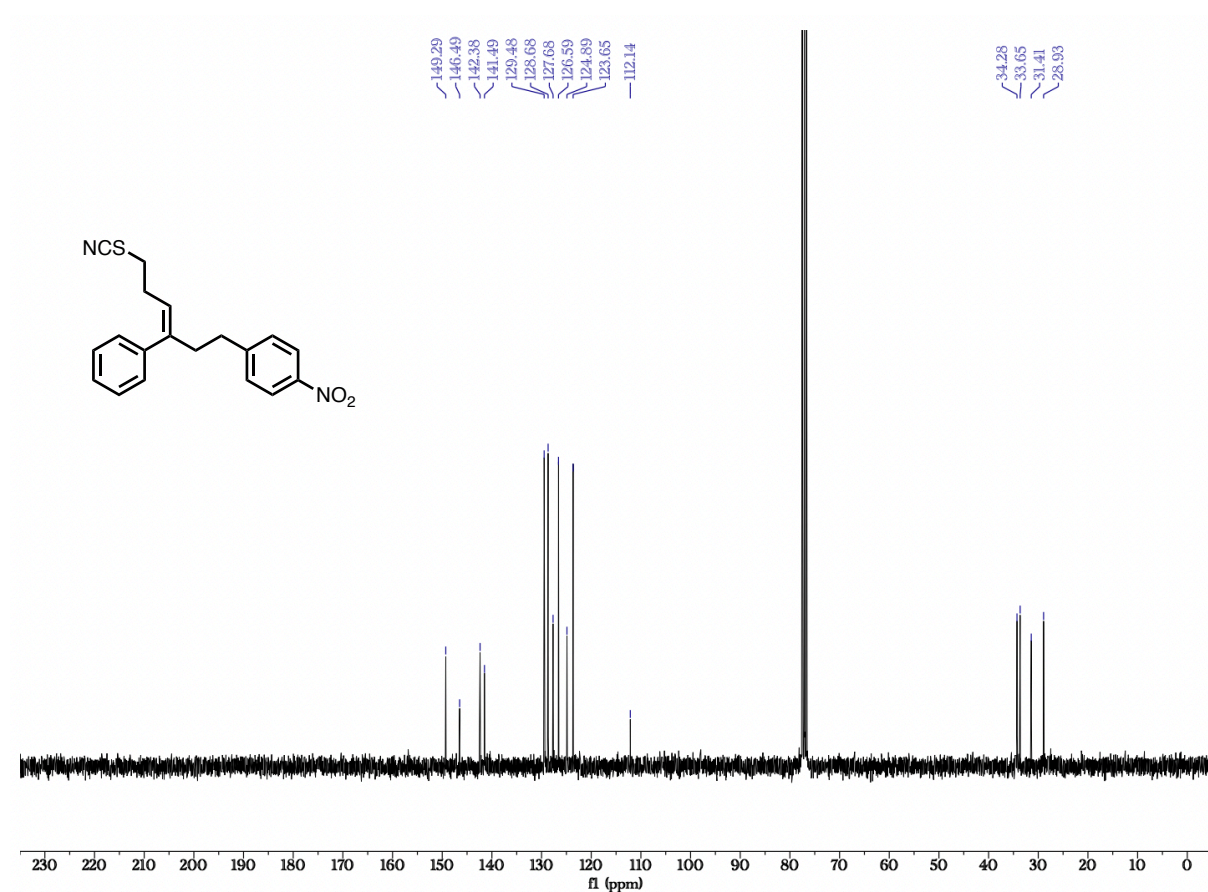
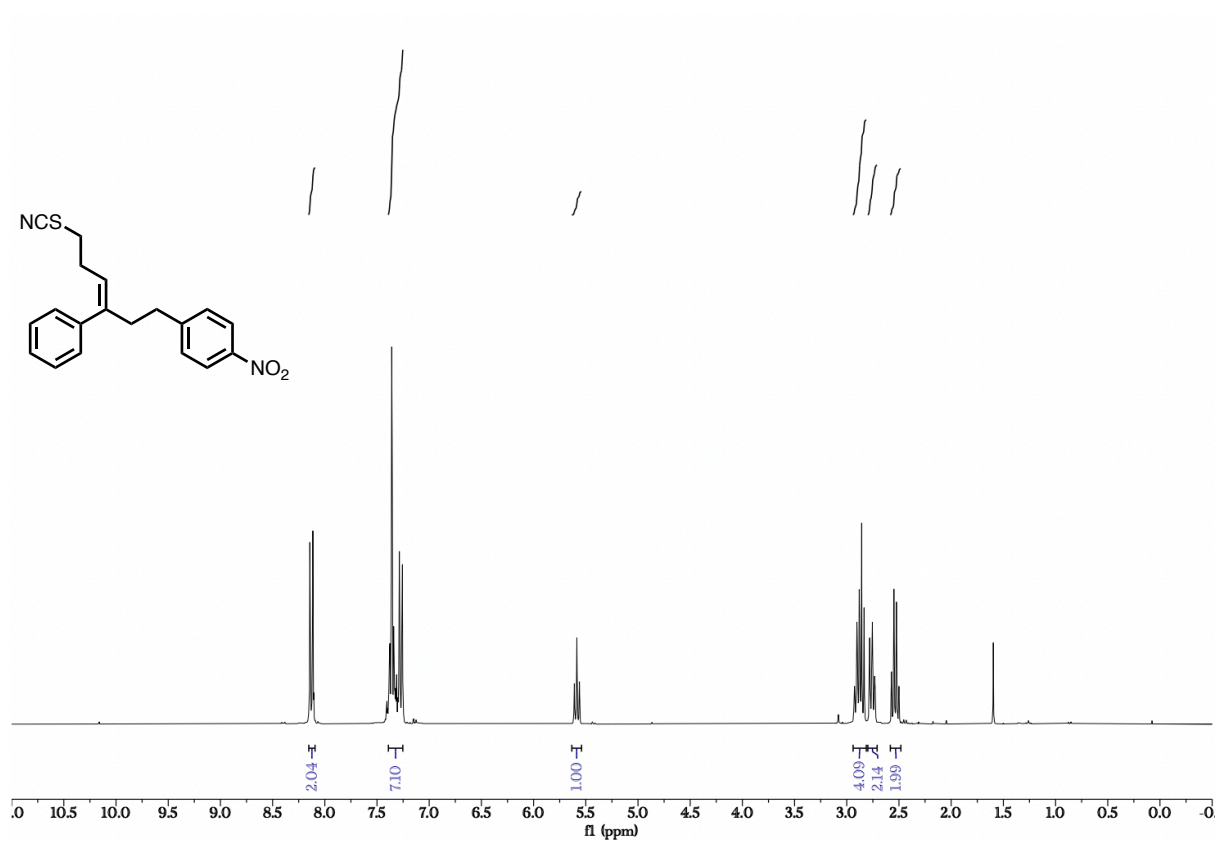
- Aromatic region (6.5-7.5 ppm):
 - Peak at ~7.2 ppm: Integration 2.01
 - Peak at ~7.1 ppm: Integration 3.00
 - Peak at ~7.0 ppm: Integration 1.80
 - Peak at ~6.7 ppm: Integration 1.83
- Aliphatic region (2.0-3.5 ppm):
 - Peak at ~3.5 ppm: Integration 2.03
 - Peak at ~2.6 ppm: Integration 2.08
 - Peak at ~2.5 ppm: Integration 1.96
 - Peak at ~2.1 ppm: Integration 2.00



2,2,6,6-tetramethyl-1-((4-nitrobenzyl)oxy)piperidine (6)

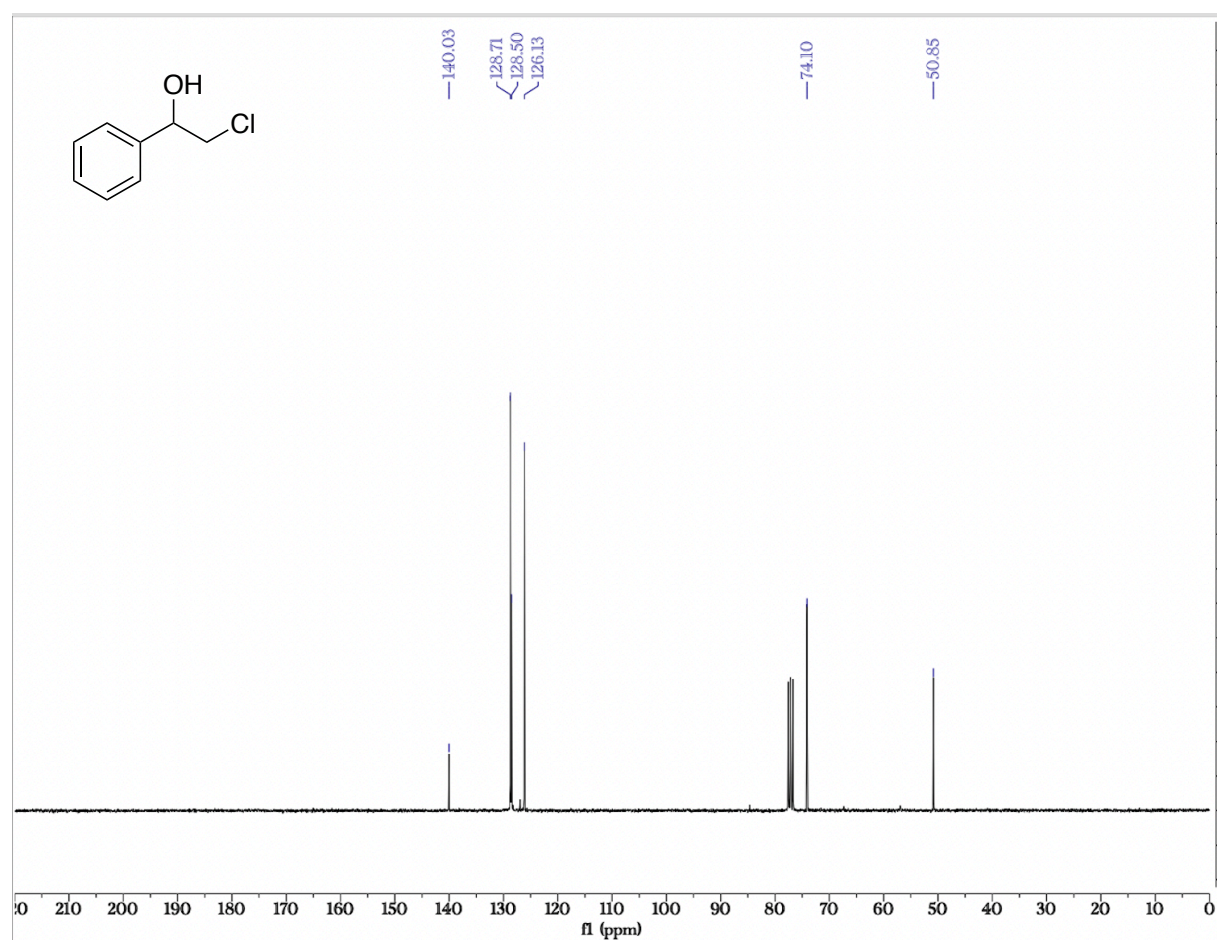
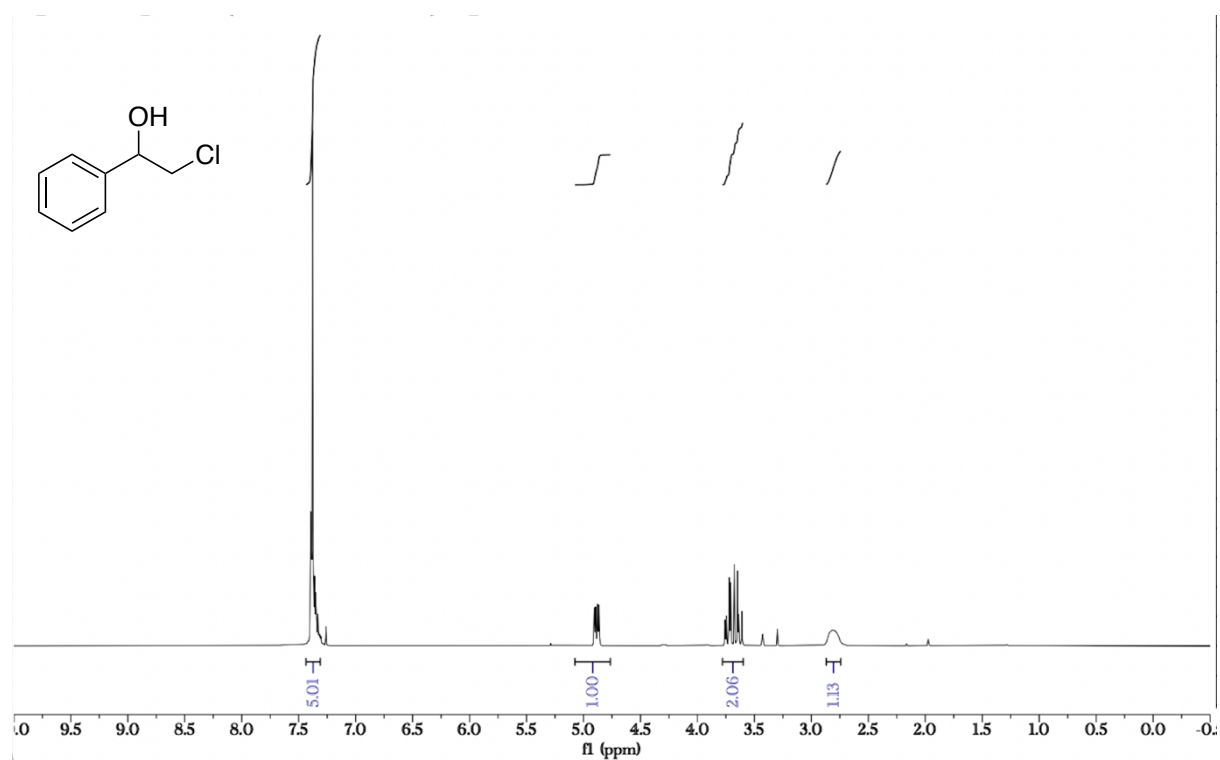


1-nitro-4-(3-phenyl-6-thiocyanatohex-3-en-1-yl)benzene (8)

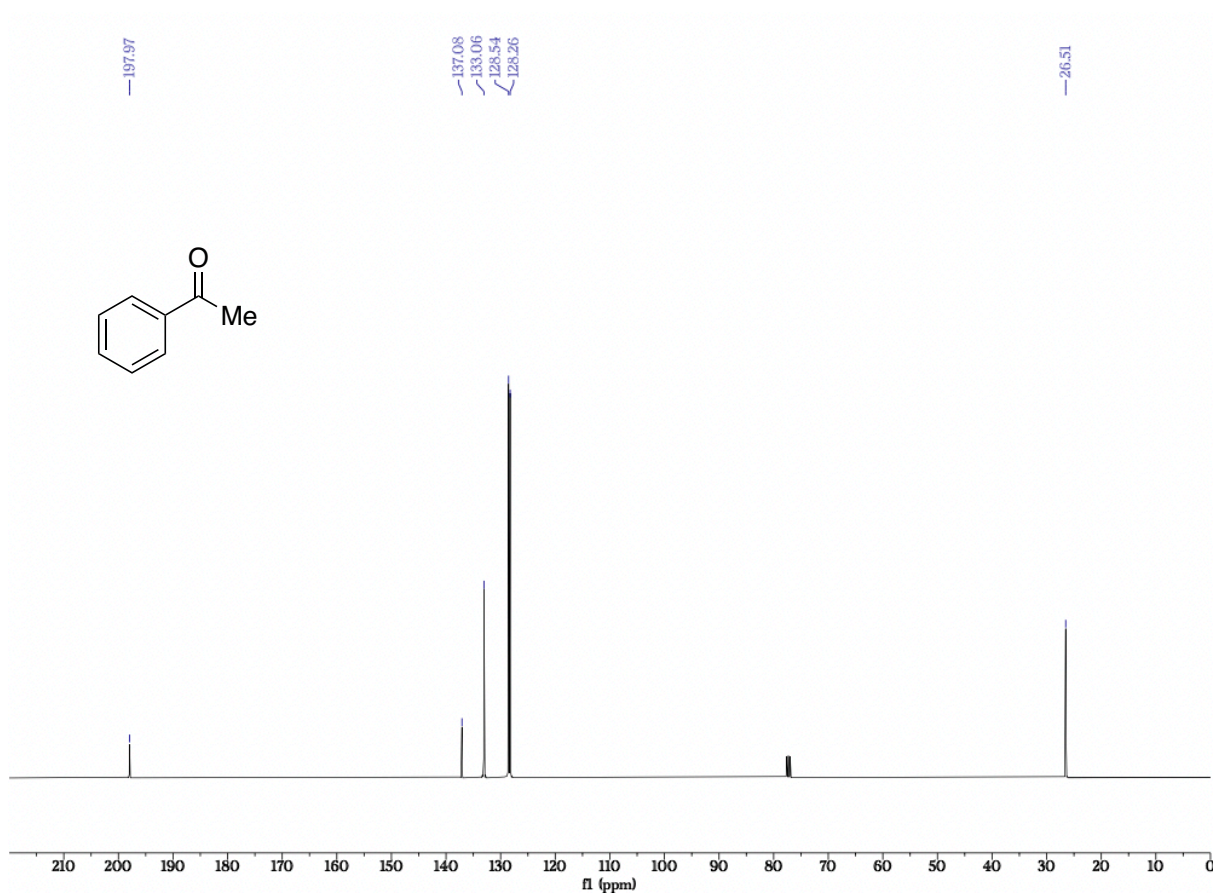
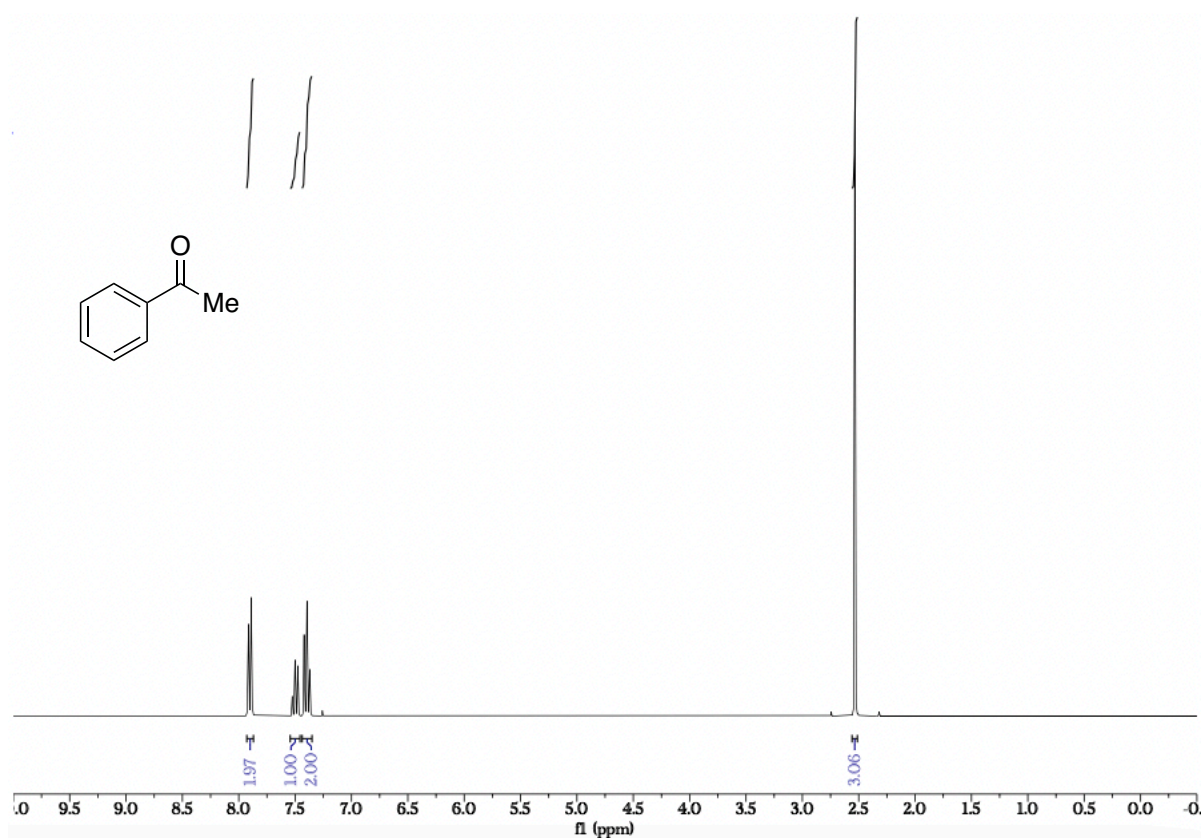


Copies of NMR spectra of Chapter 3:

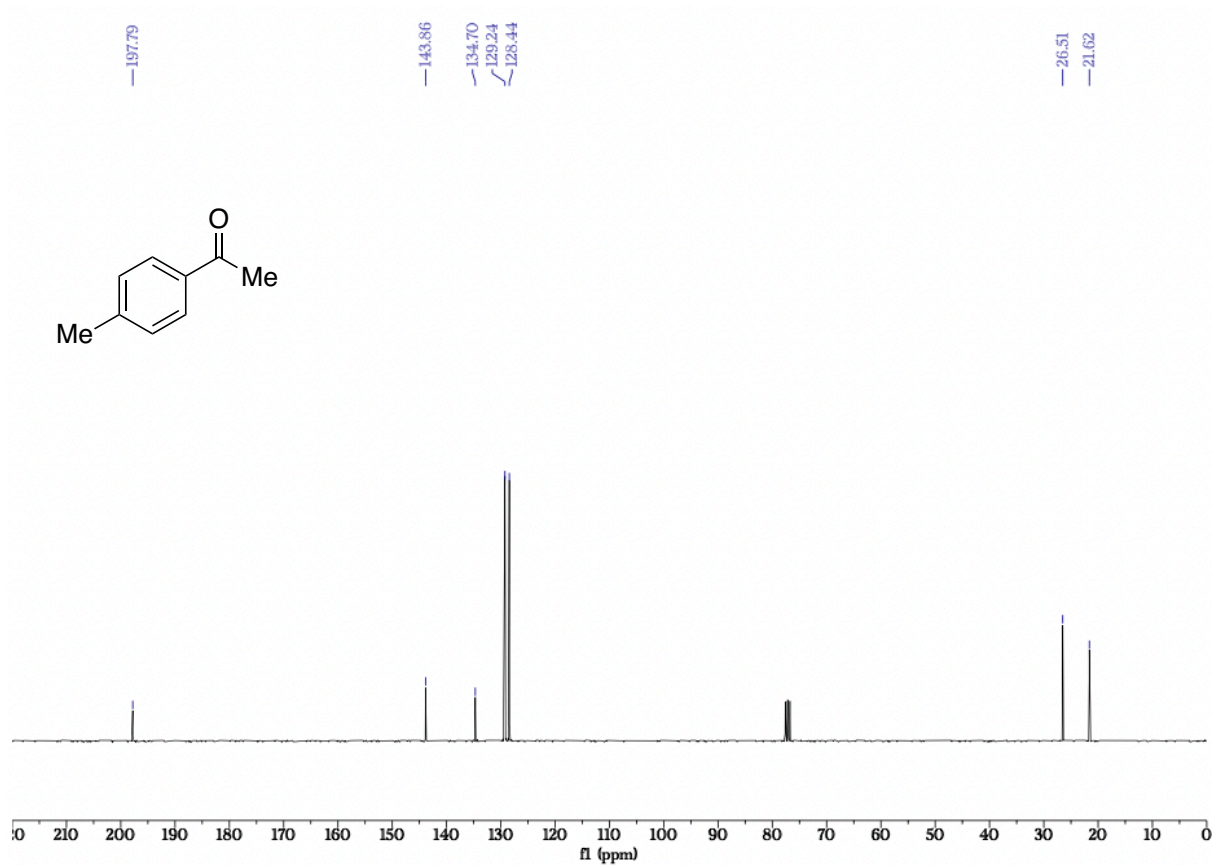
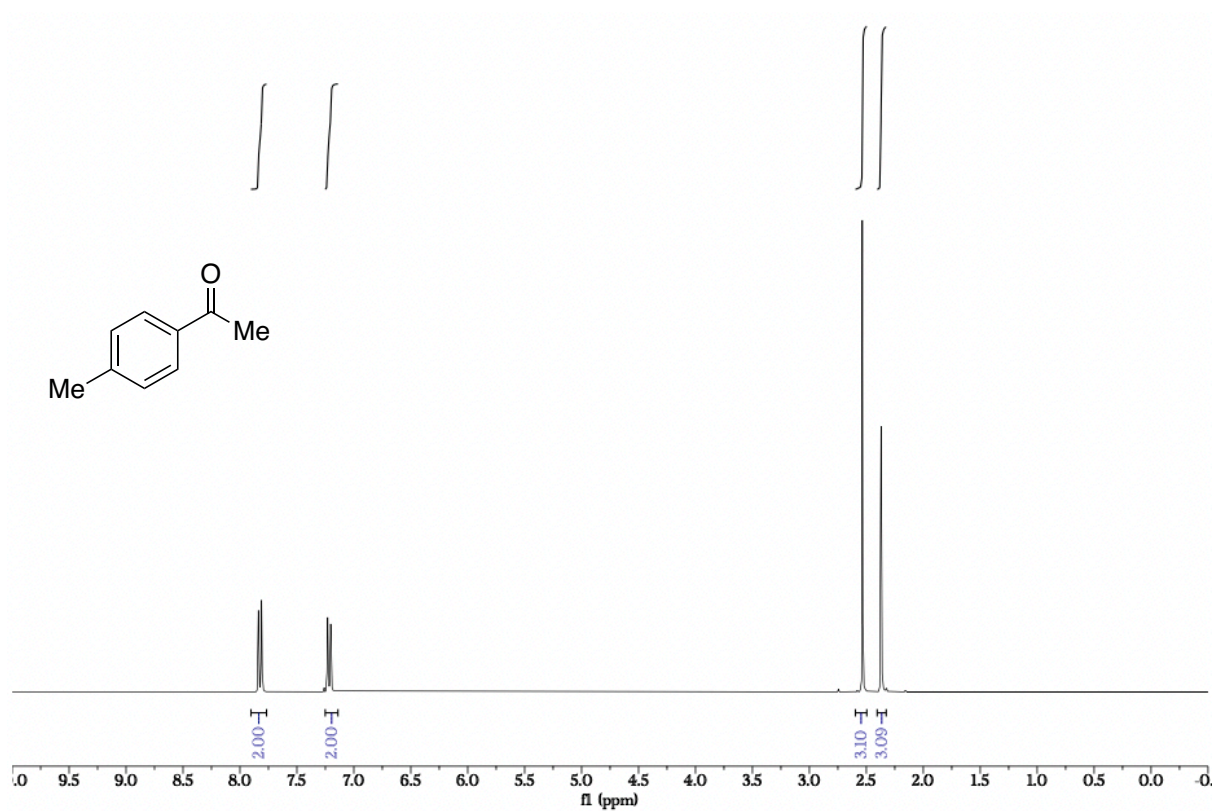
2-chloro-1-phenylethan-1-ol (IIa)



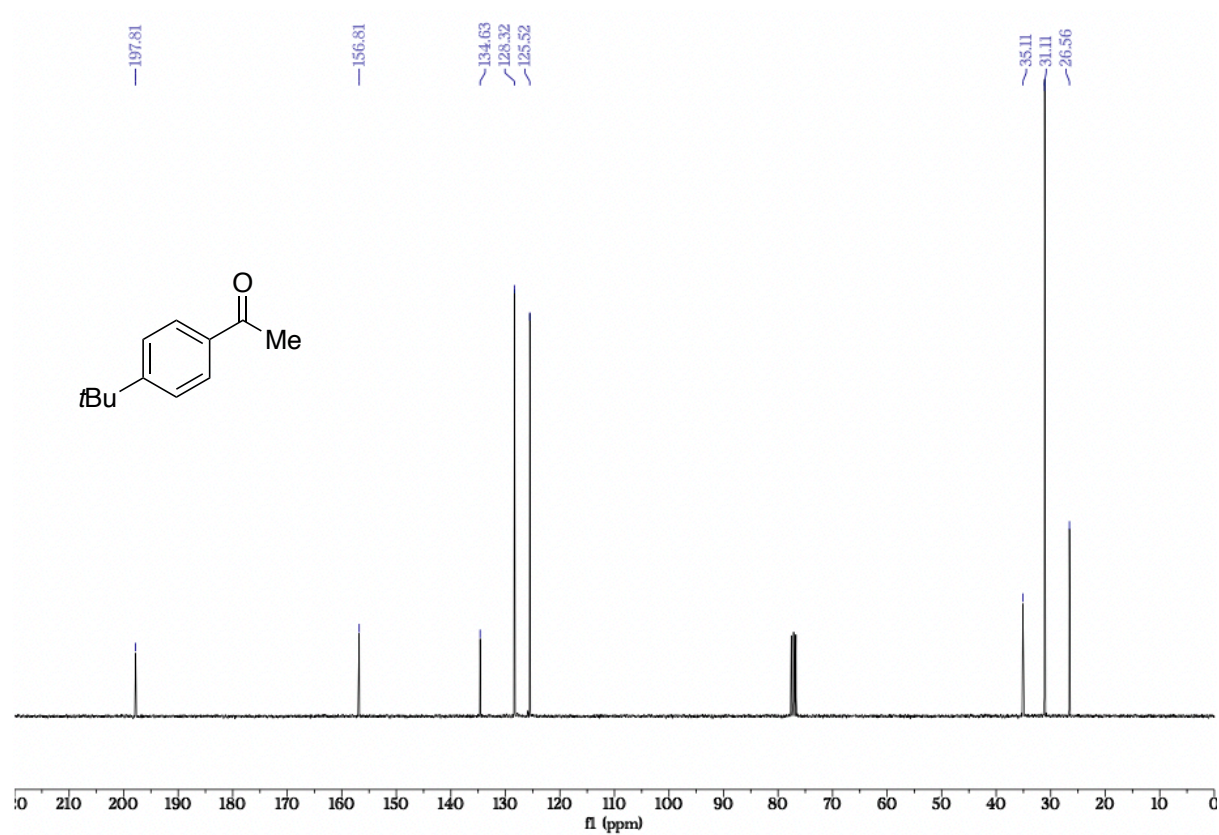
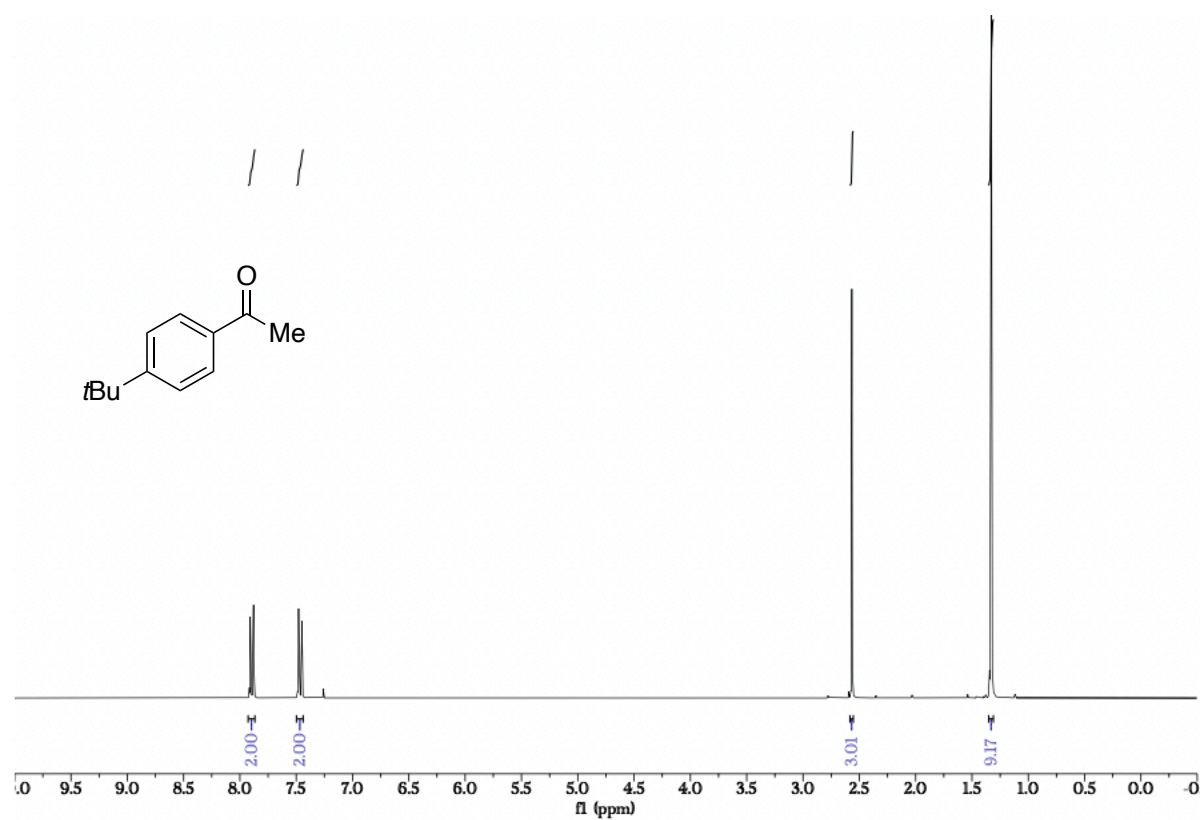
Acetophenone (2a):



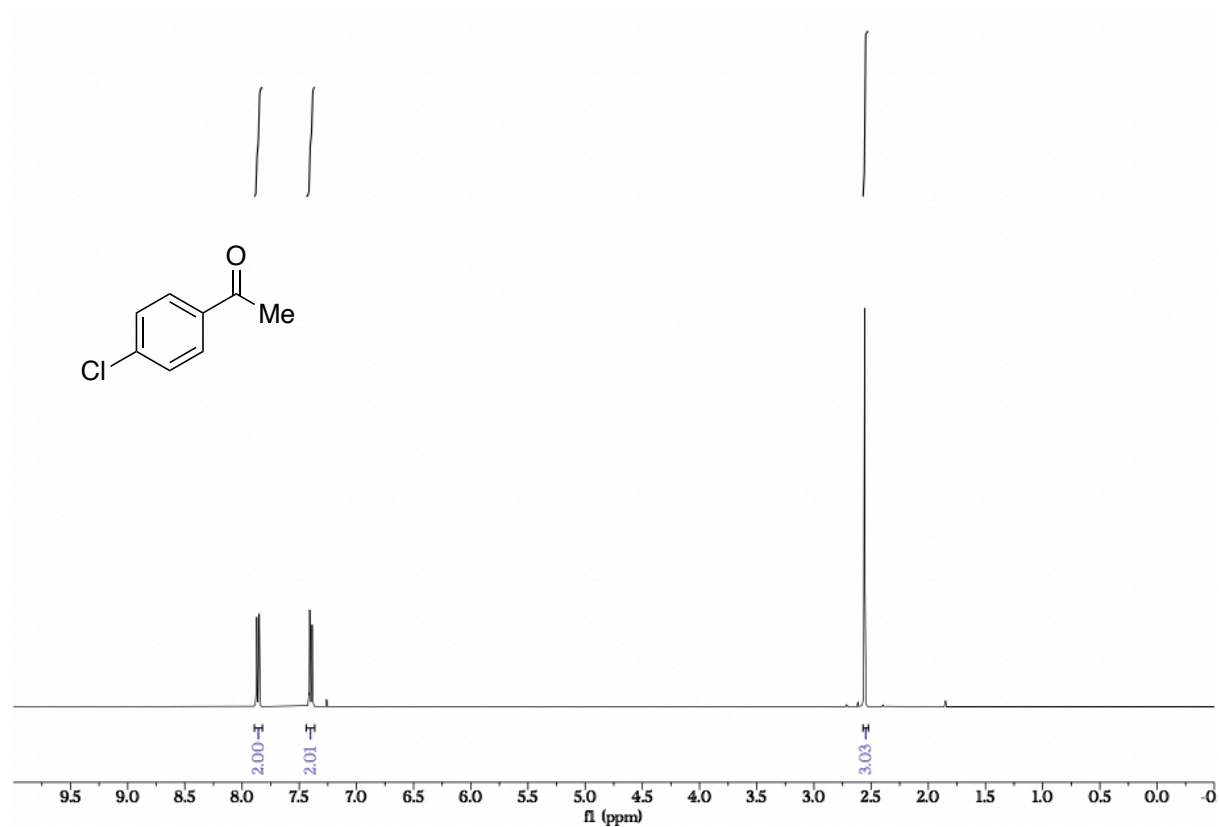
1-(*p*-tolyl)ethan-1-one (2b):



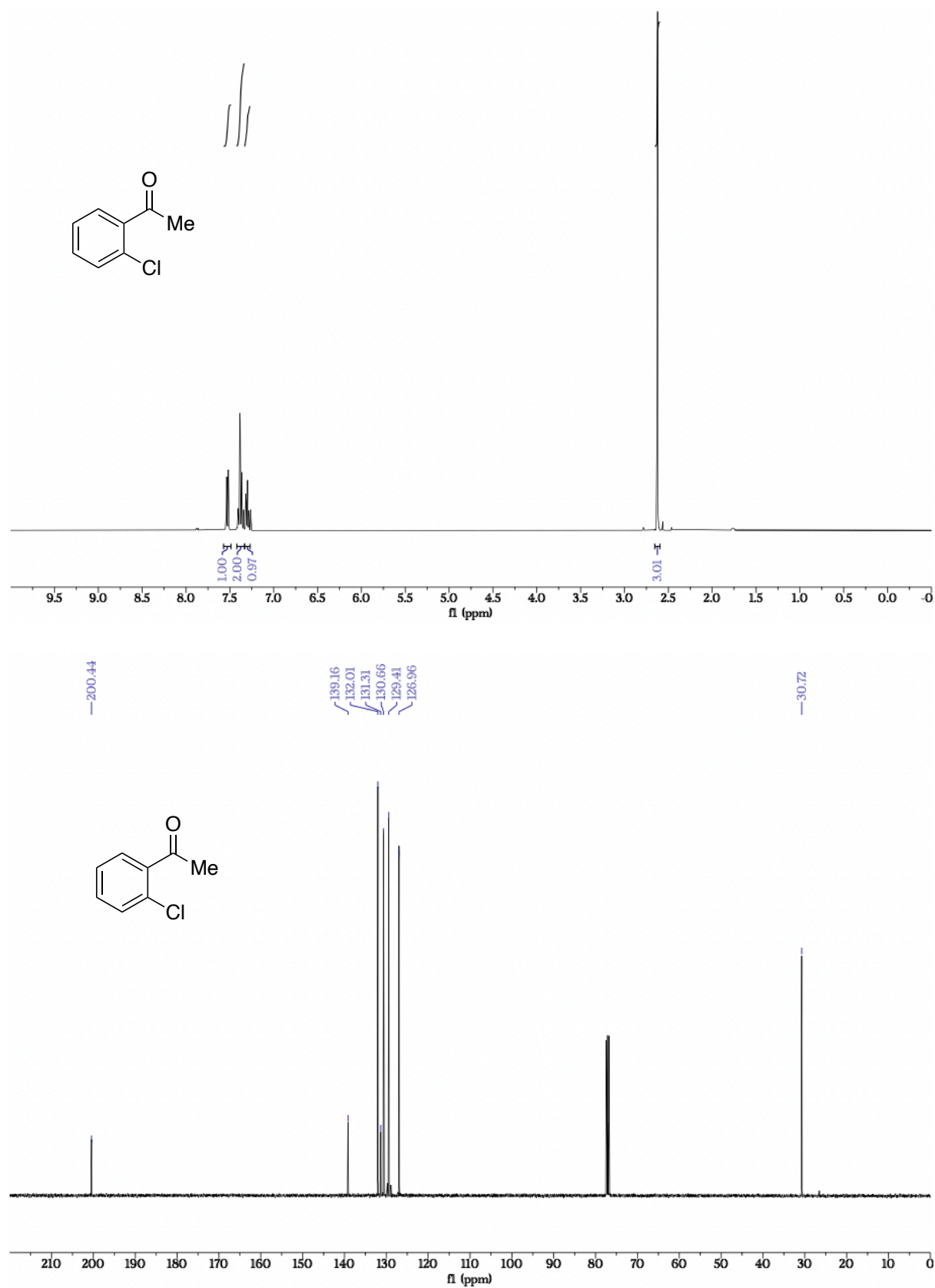
1-(4-(*tert*-butyl)phenyl)ethan-1-one (2c):



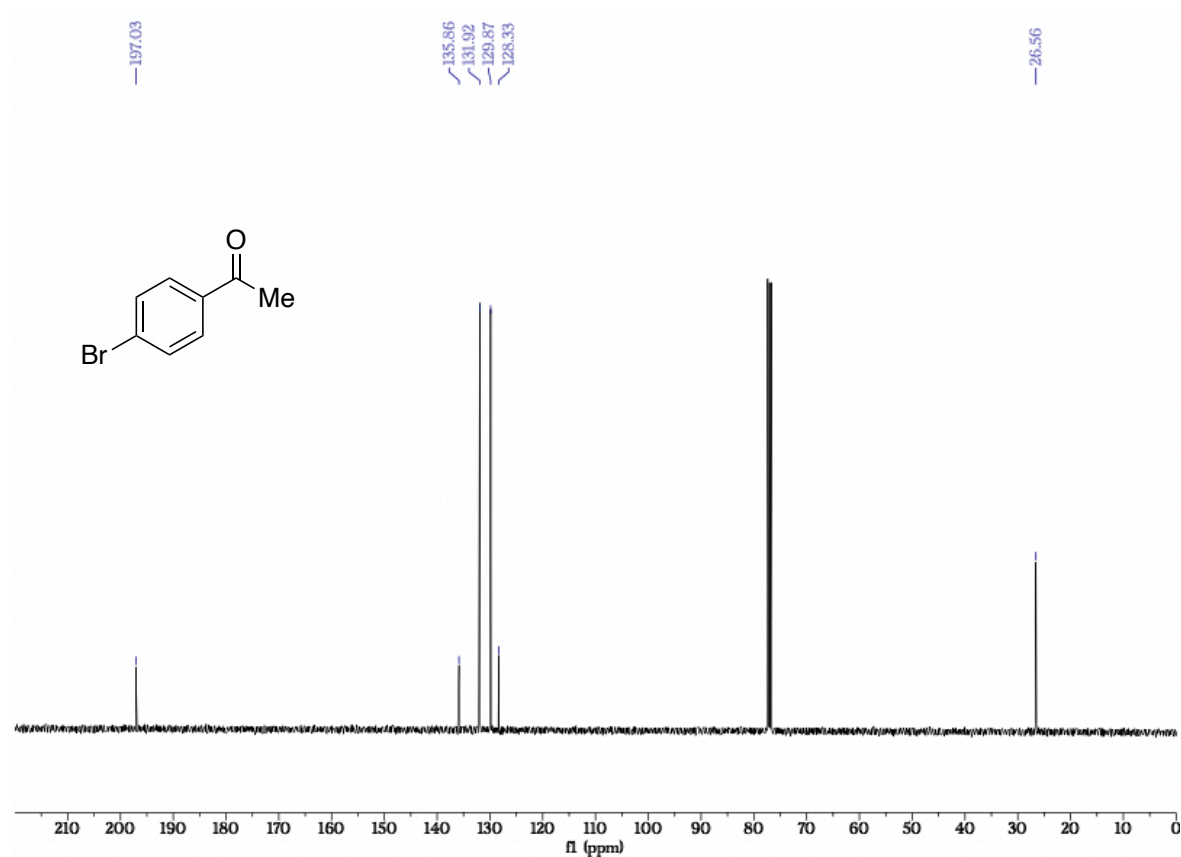
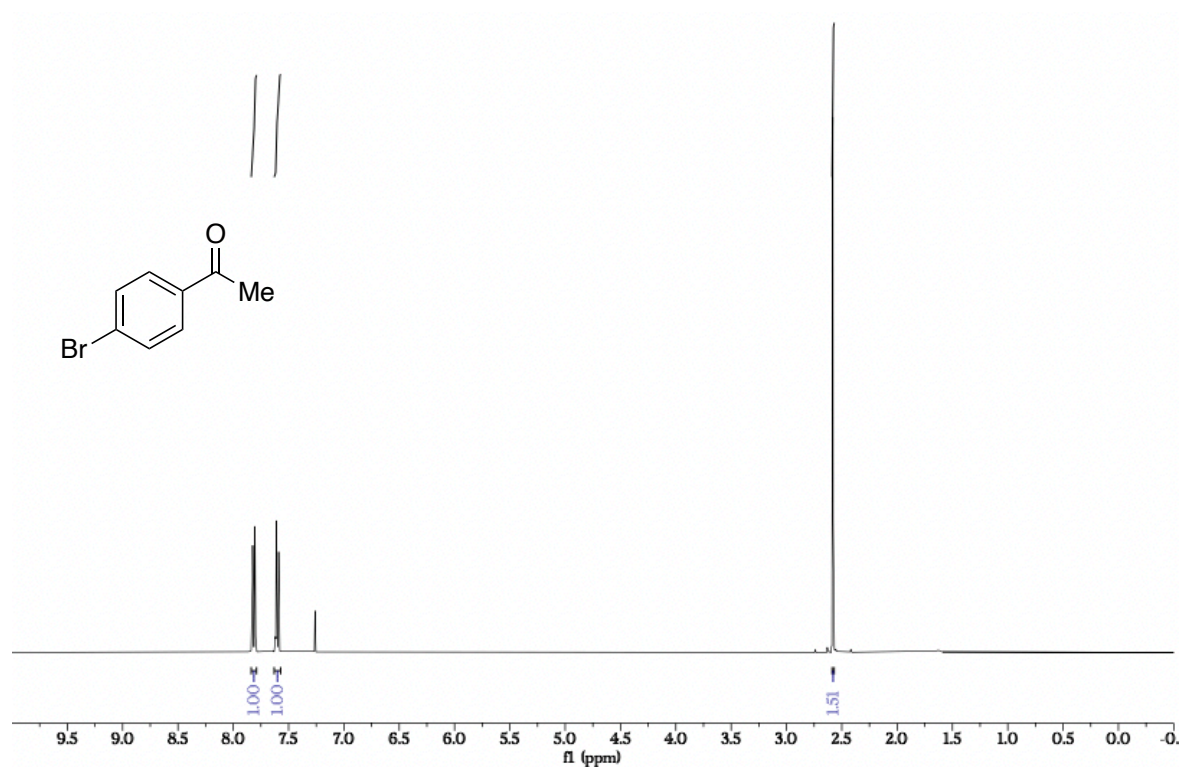
1-(4-chlorophenyl)ethan-1-one (2d):



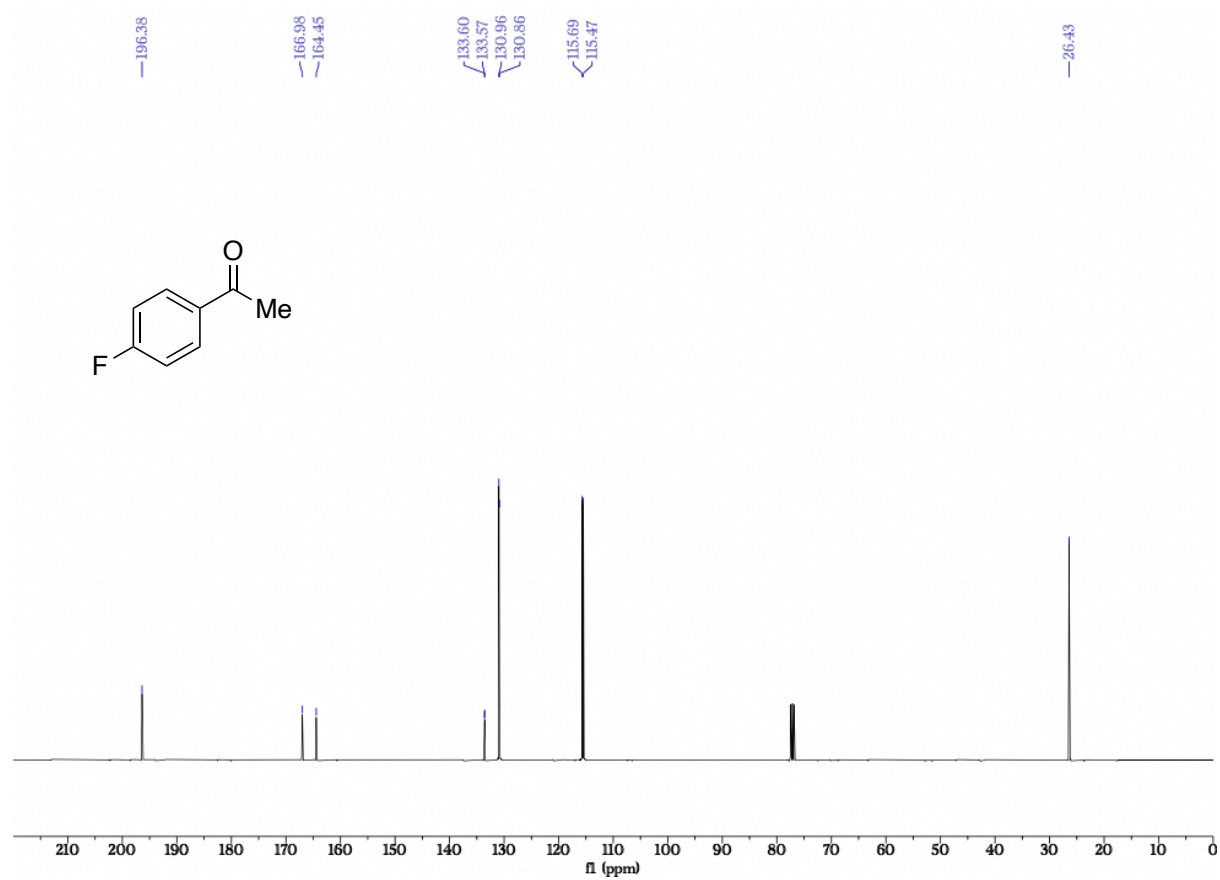
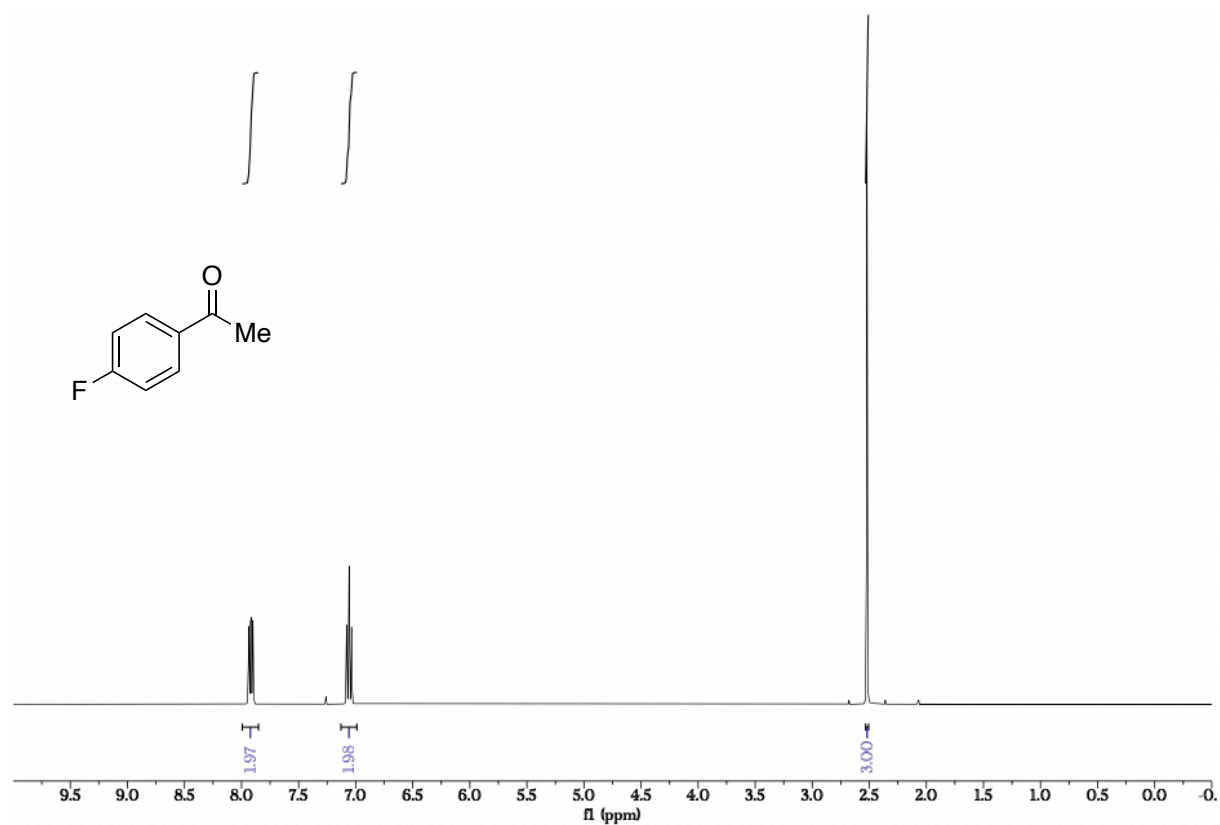
1-(2-chlorophenyl)ethan-1-one (2e):

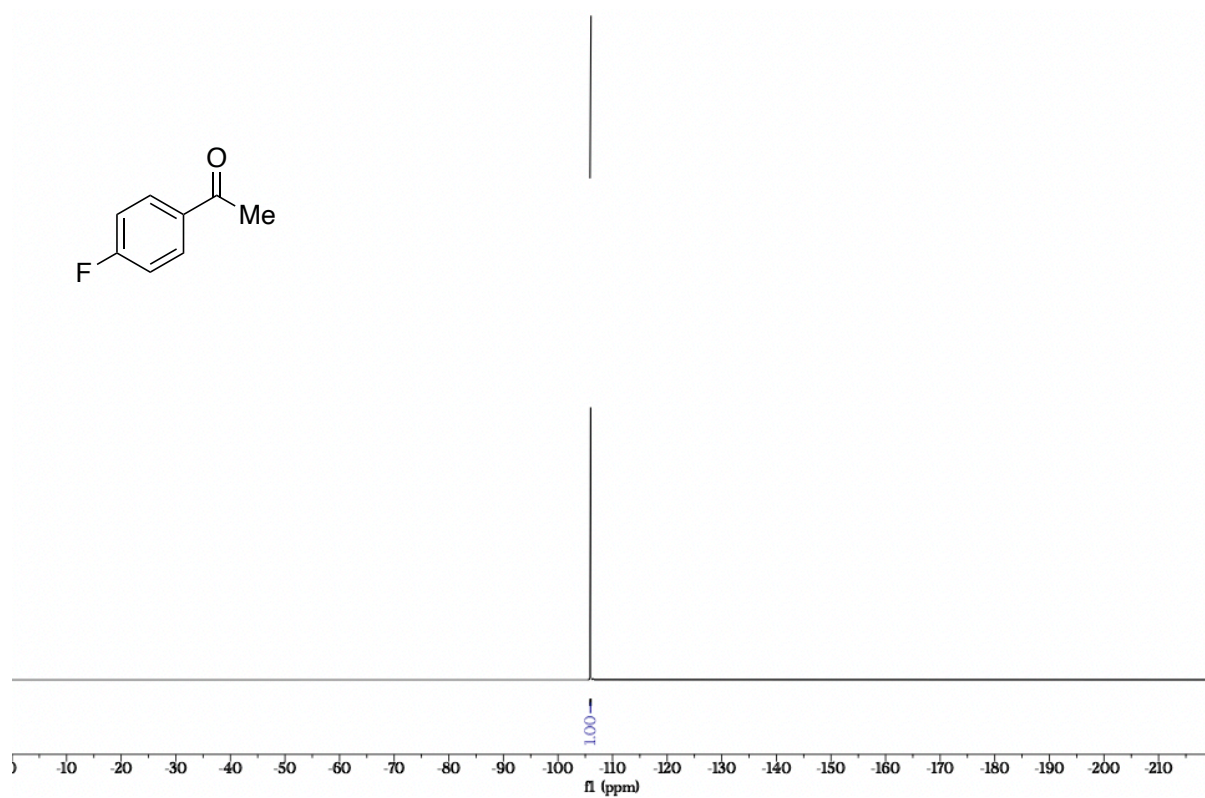


1-(4-bromophenyl)ethan-1-one (2f):

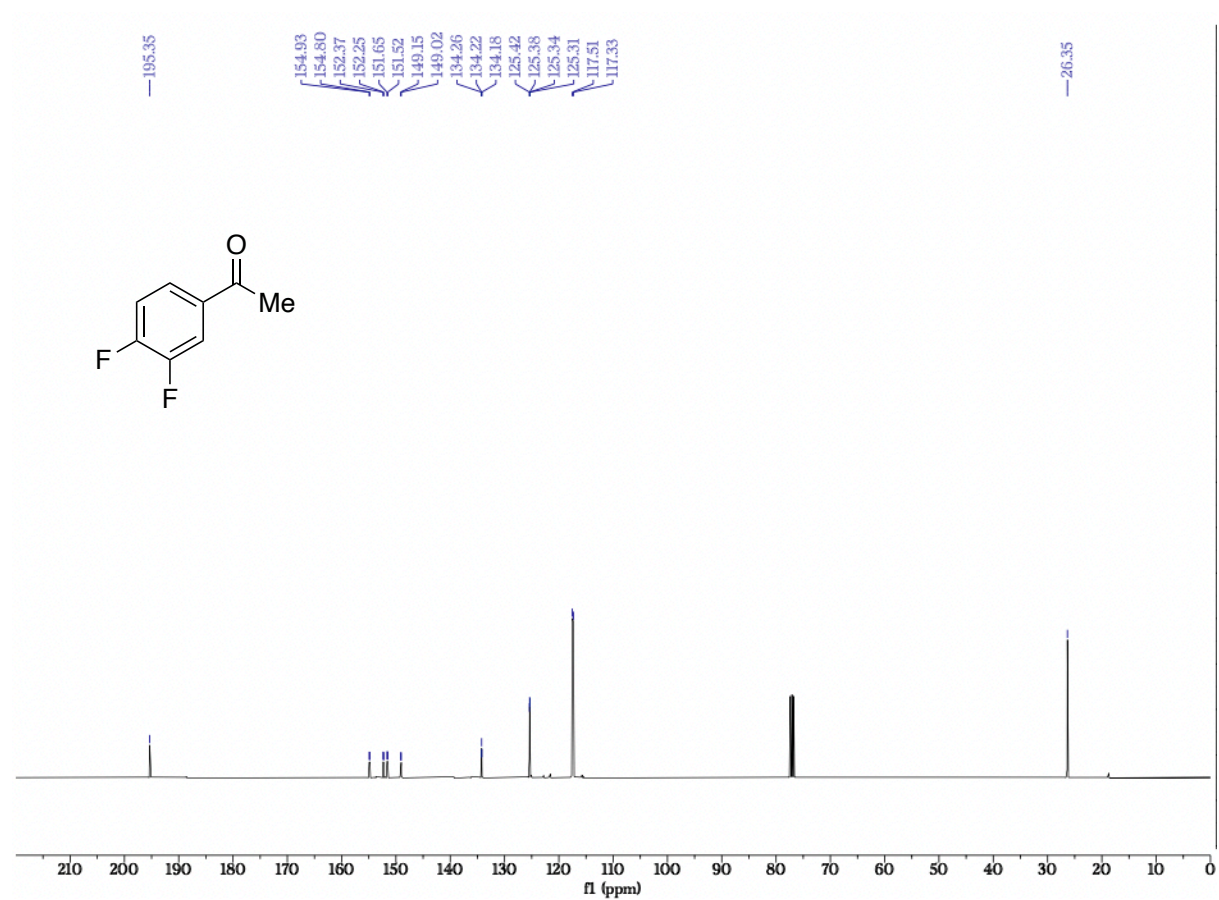
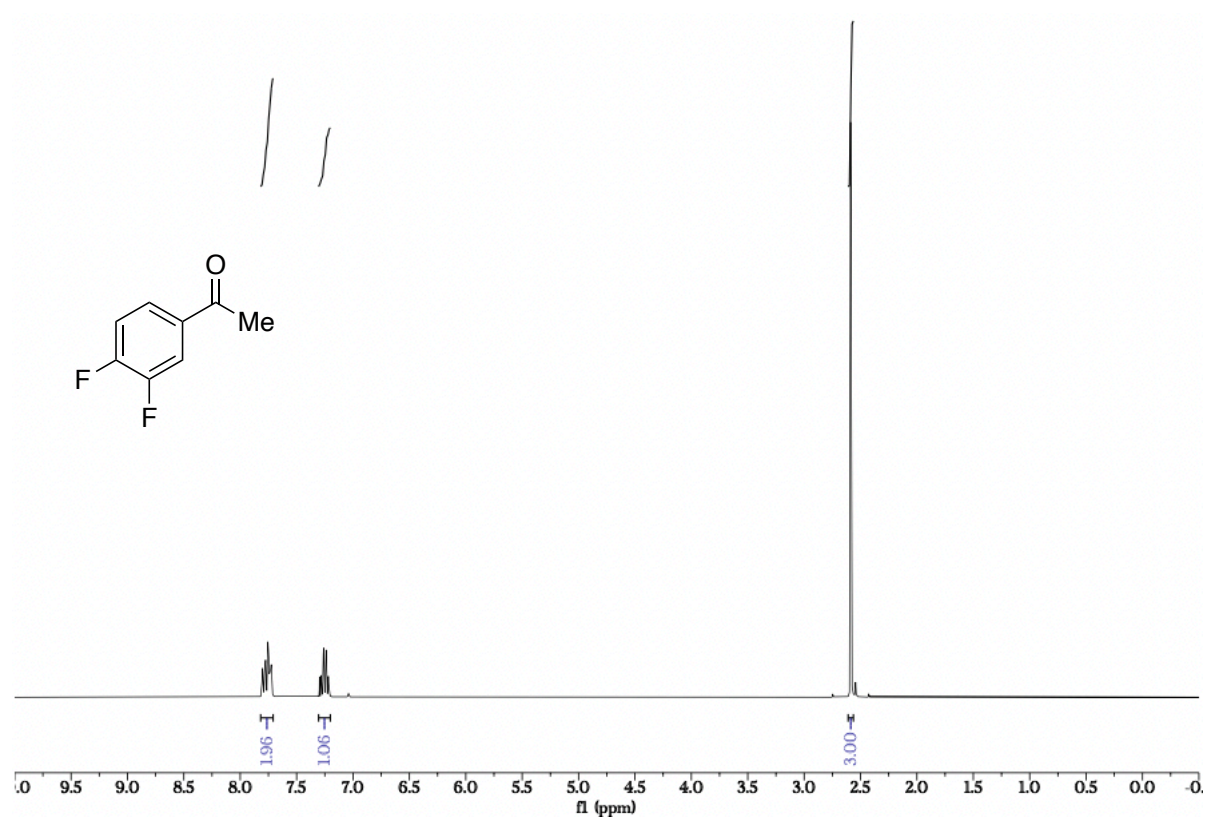


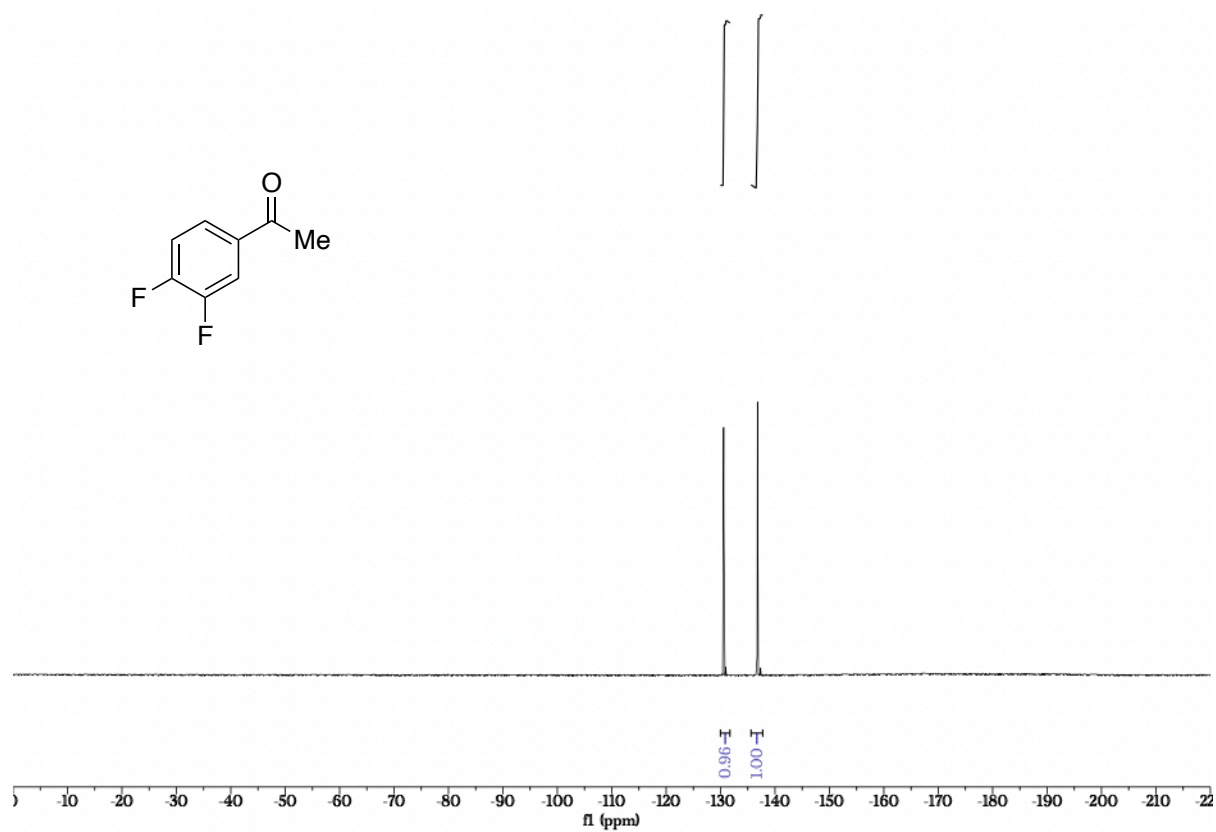
1-(4-fluorophenyl)ethan-1-one (2g):



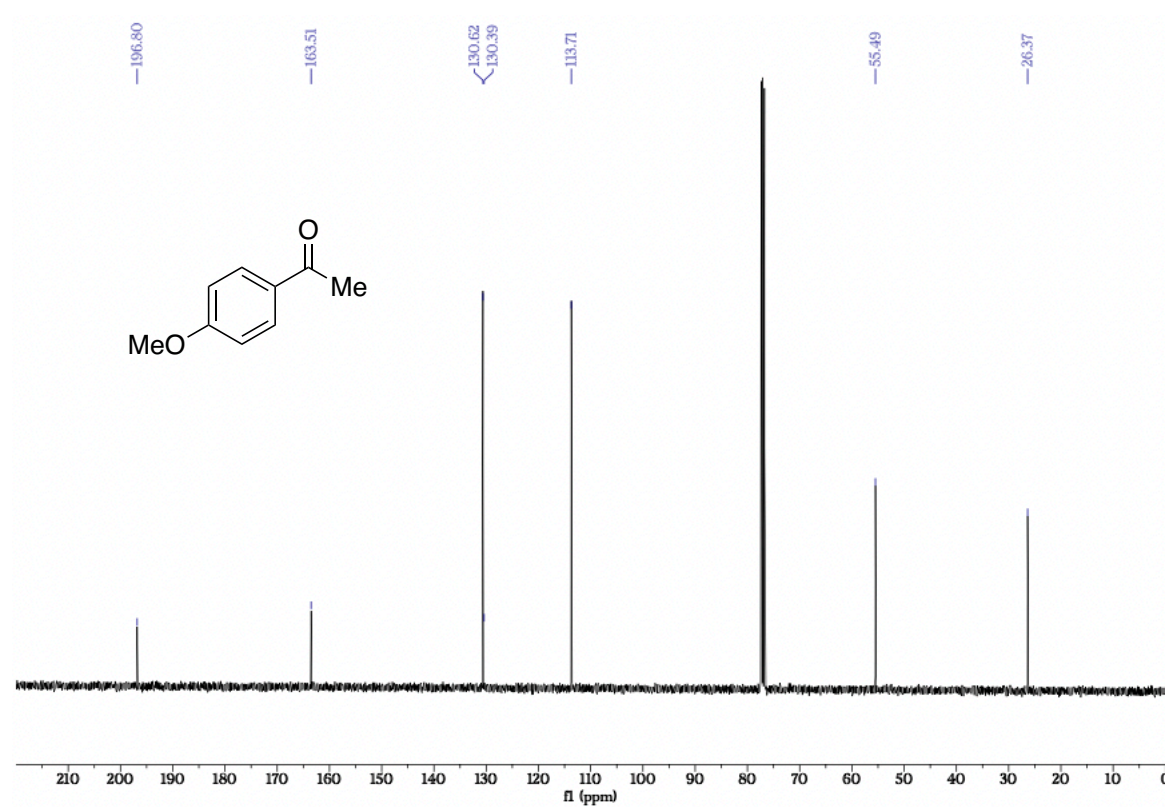
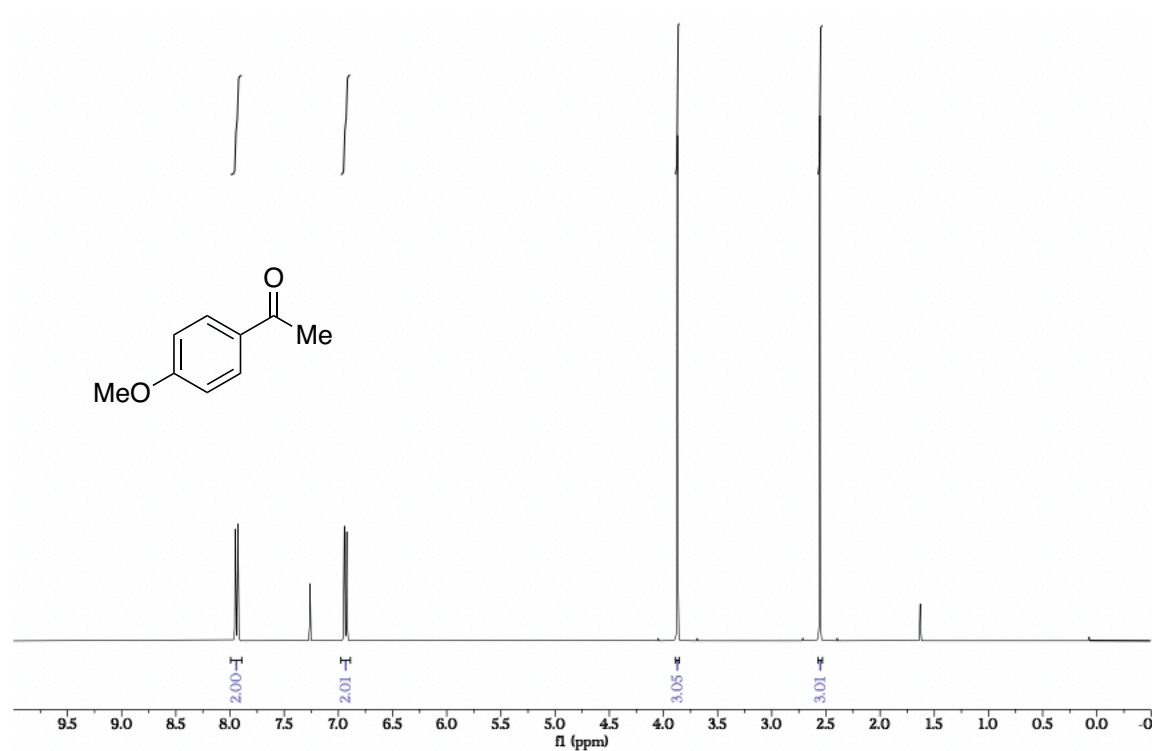


1-(3,4-difluorophenyl)ethan-1-one (2h):

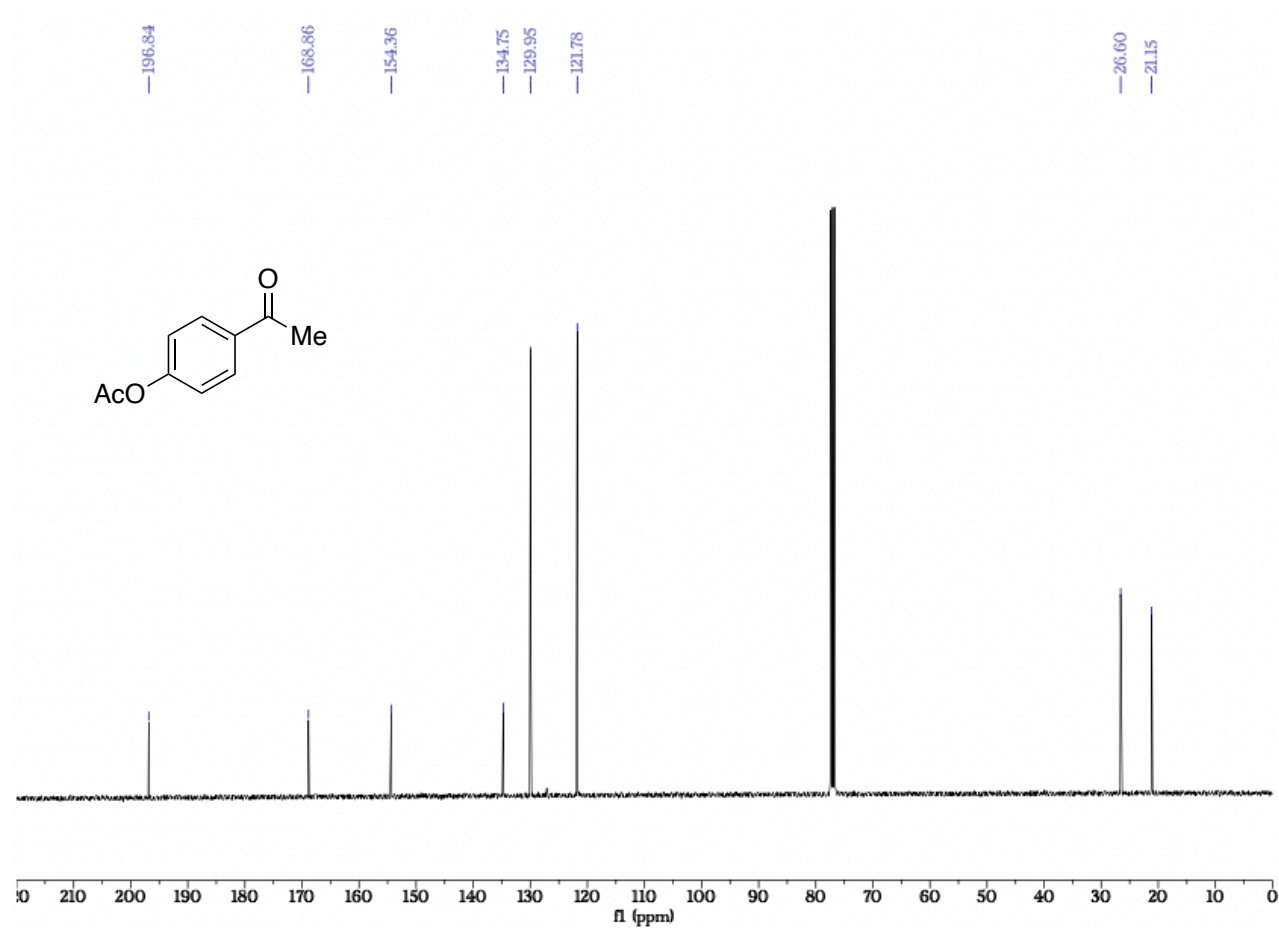
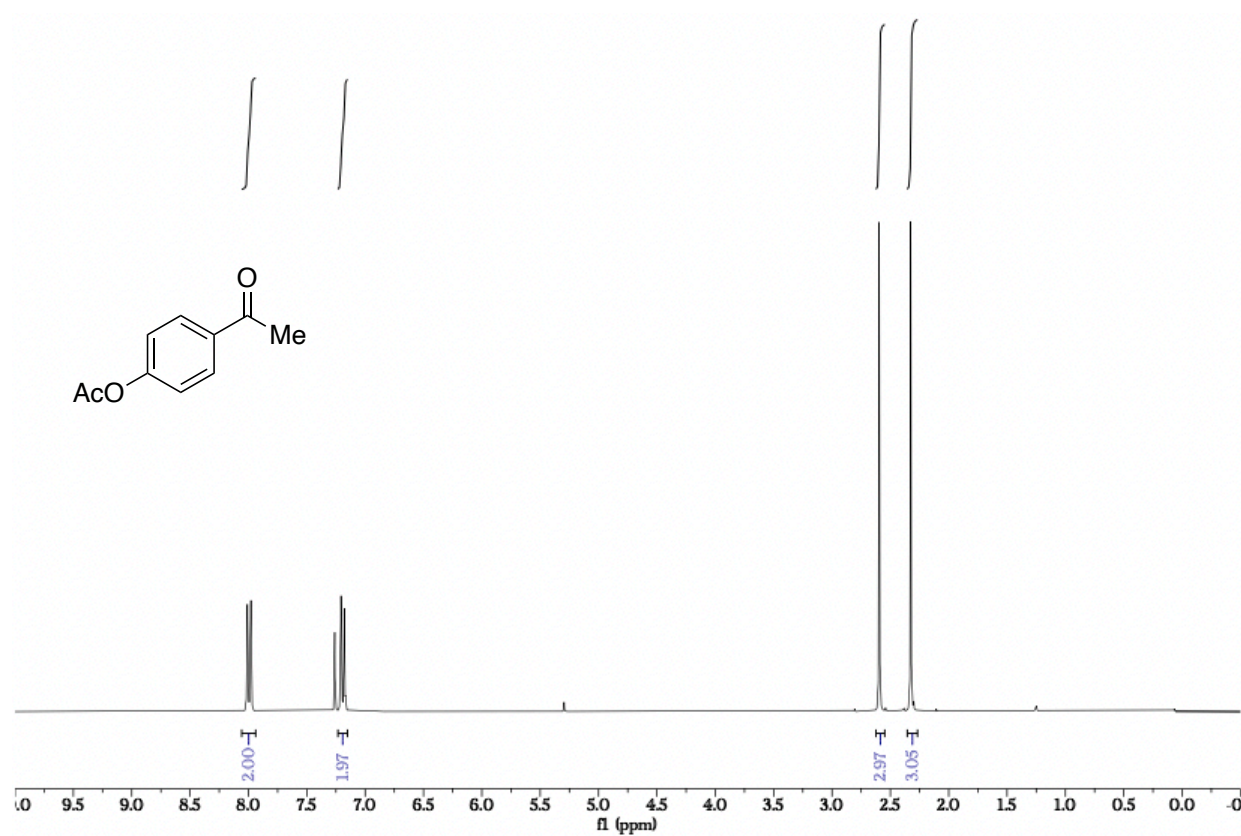




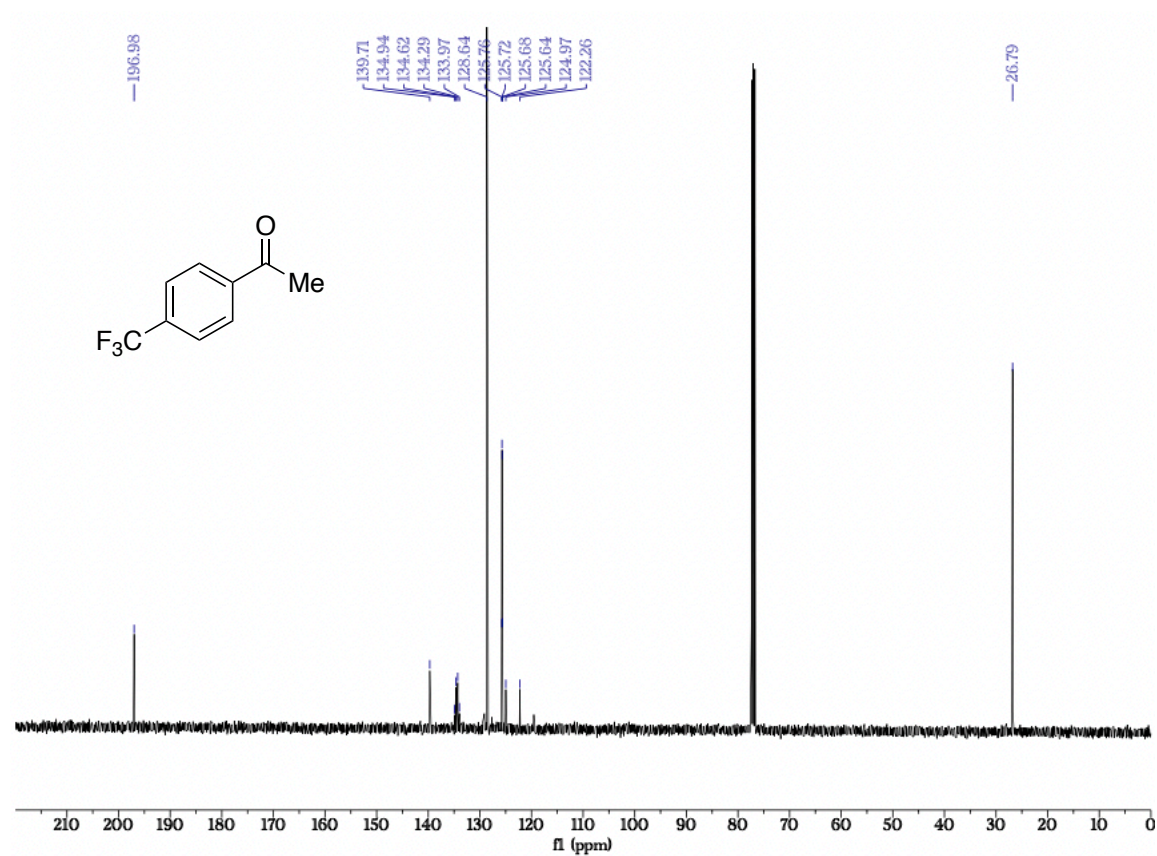
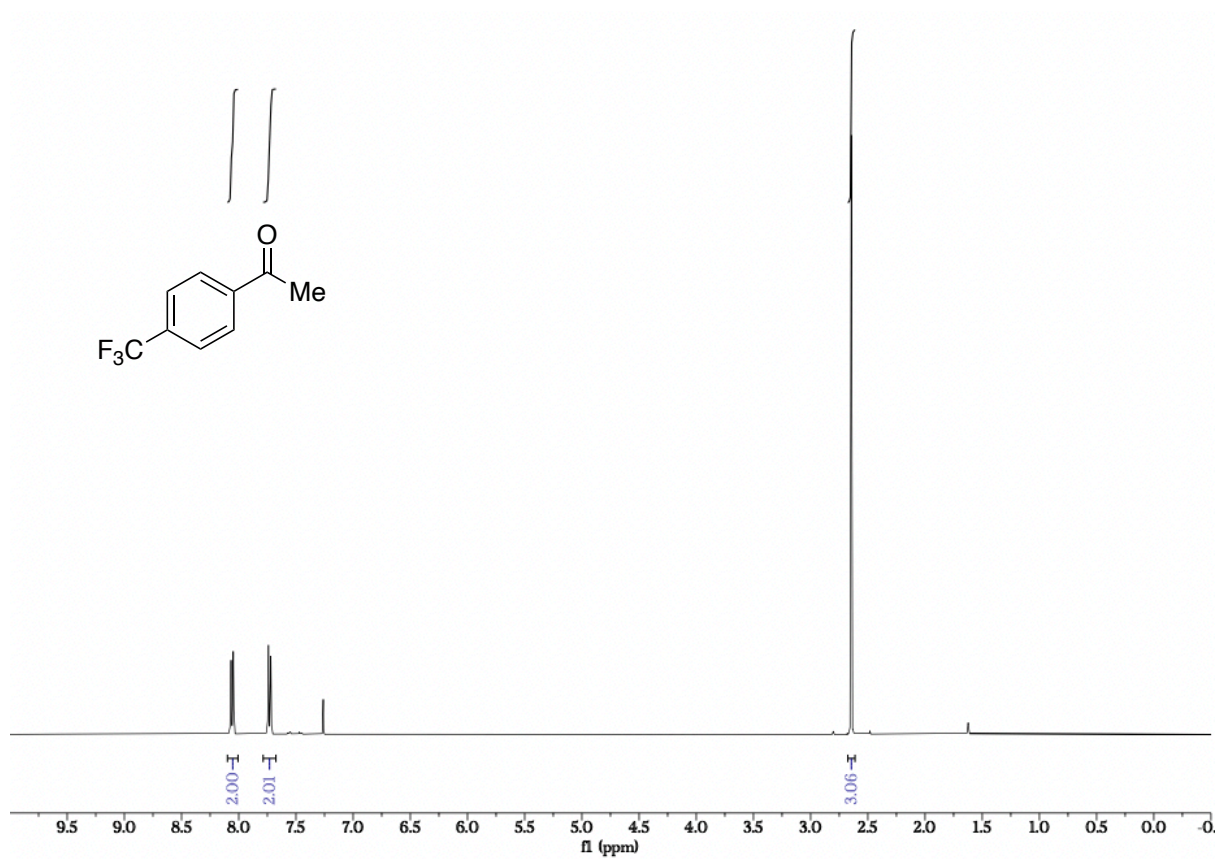
1-(4-methoxyphenyl)ethan-1-one (2i):

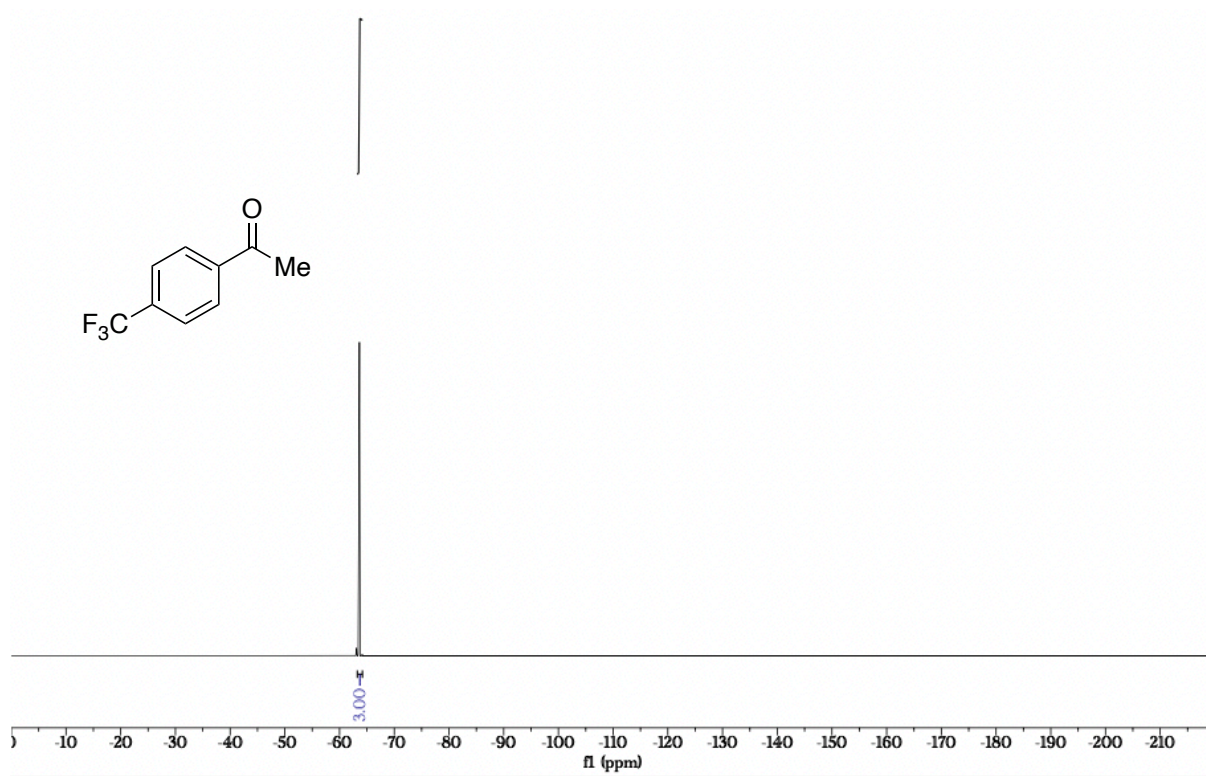


4-acetylphenyl acetate (2j):

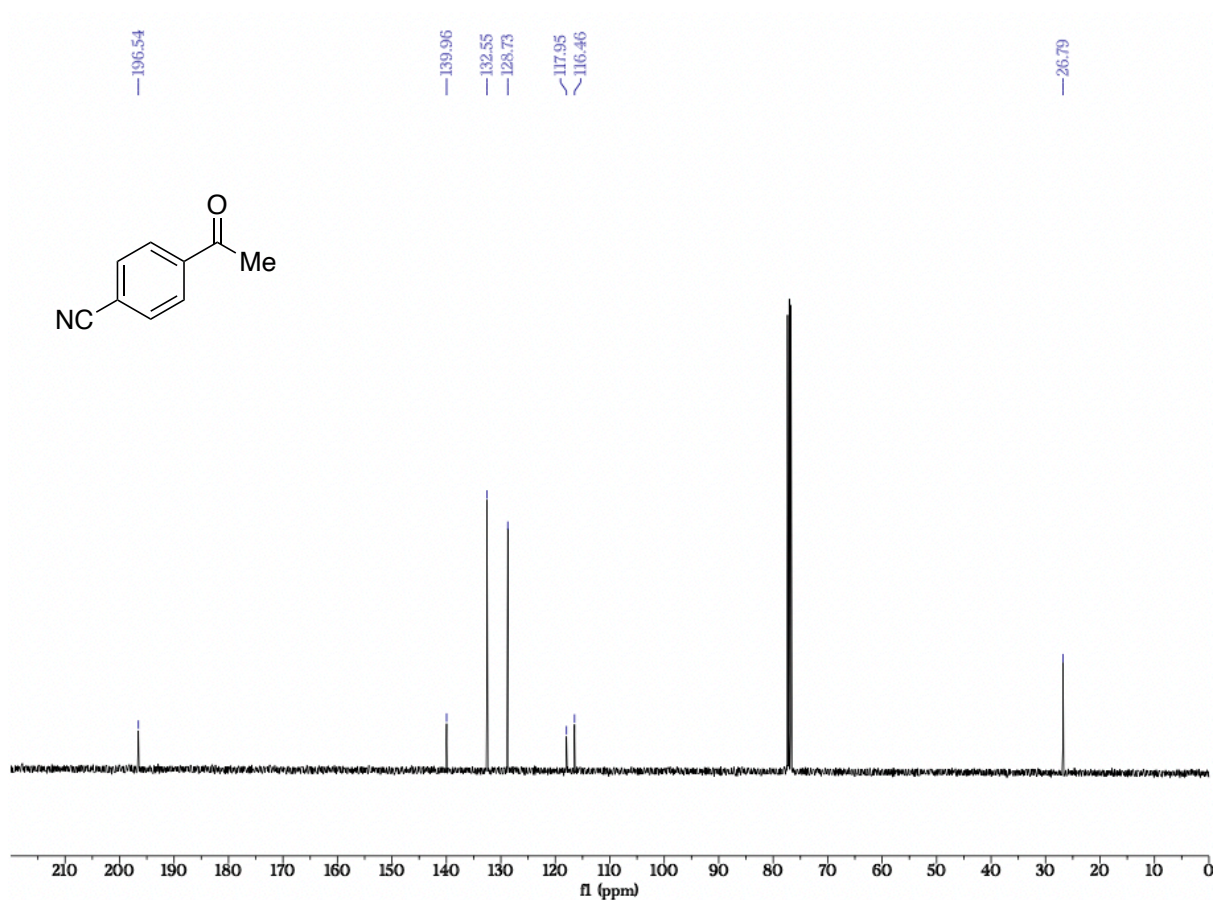
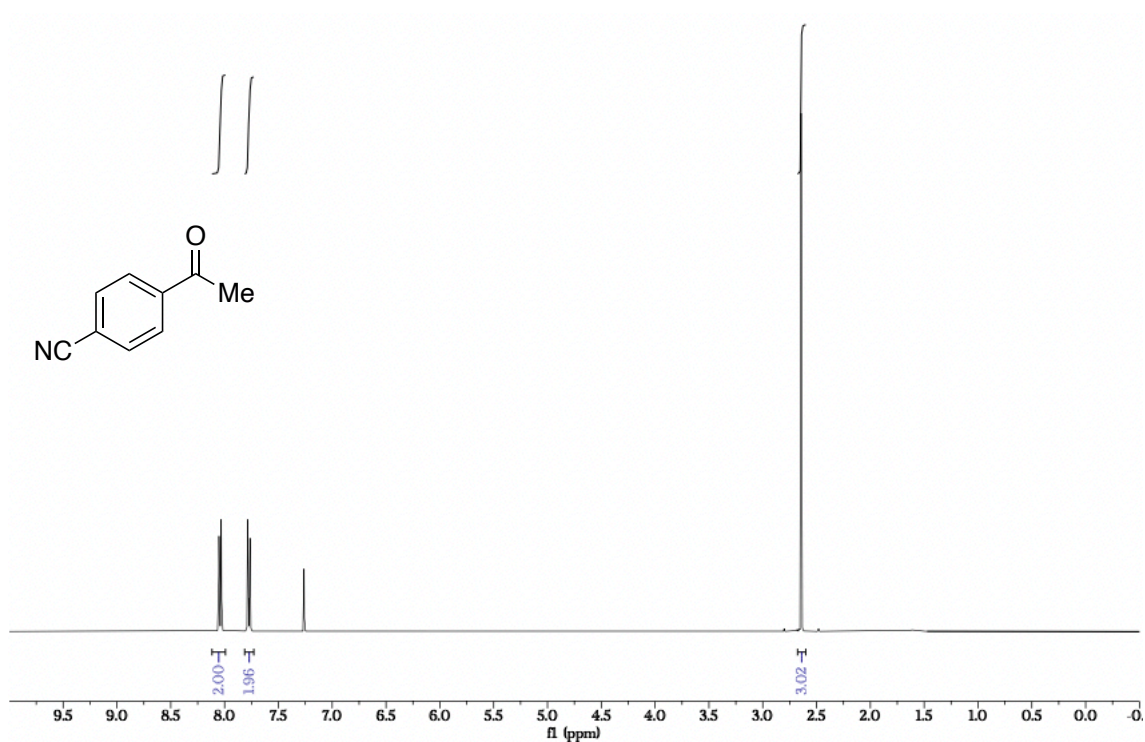


1-(4-(trifluoromethyl)phenyl)ethan-1-one (2k):

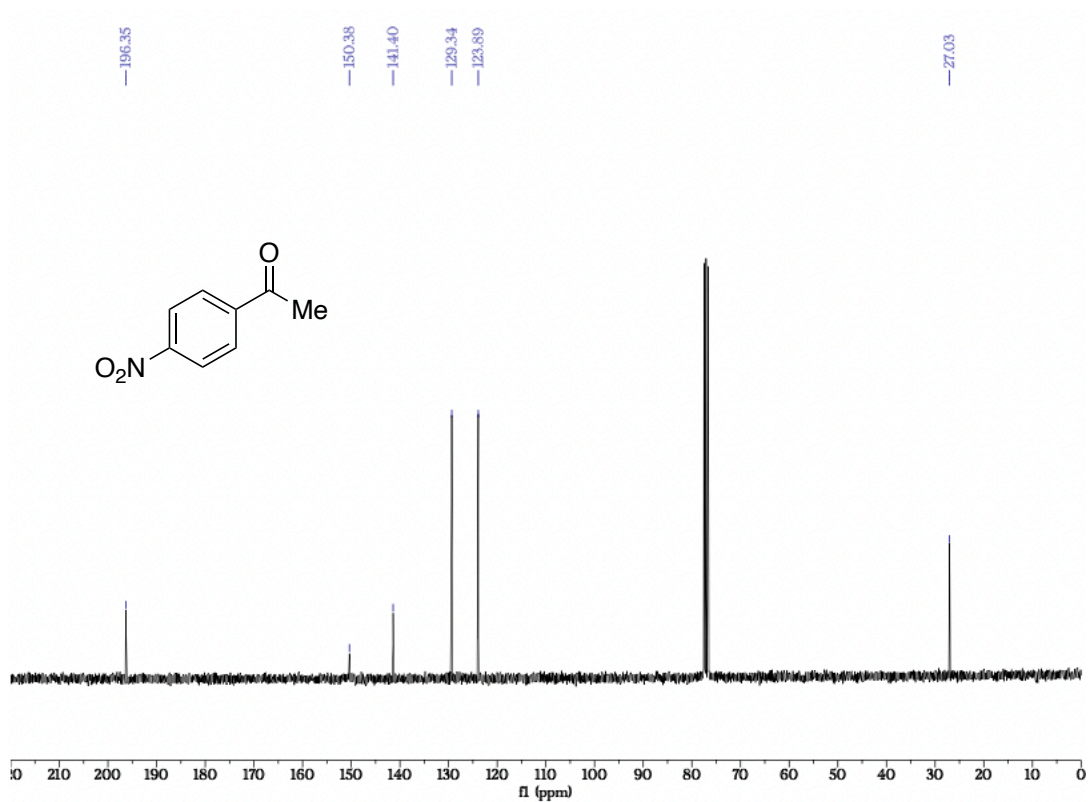




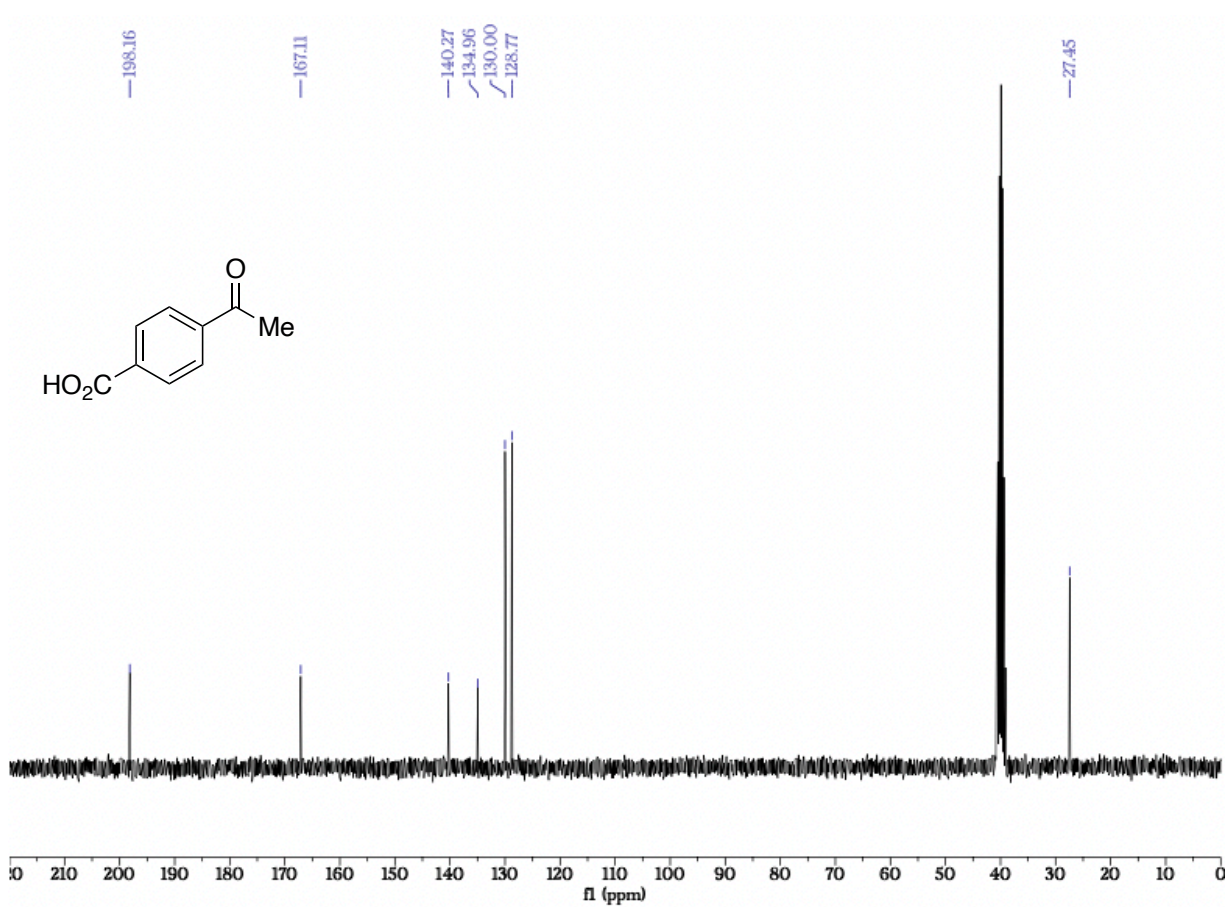
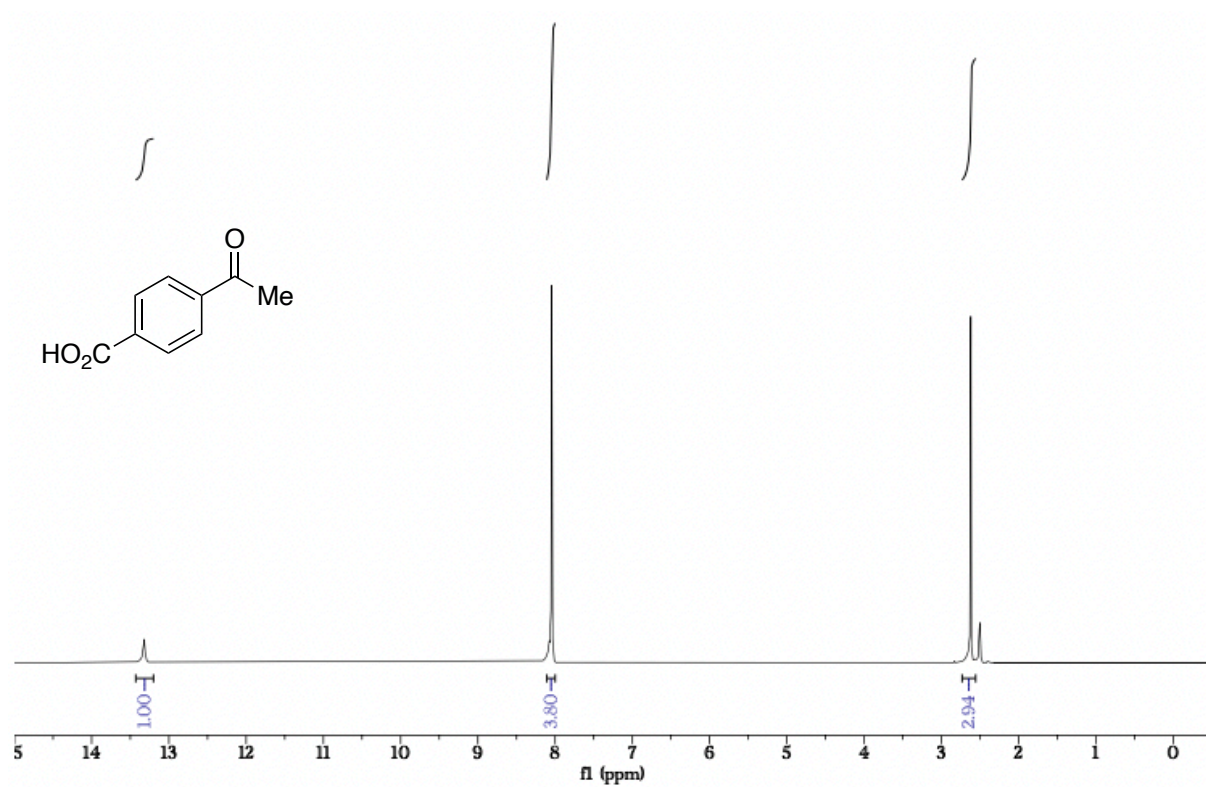
4-acetylbenzonitrile (2l):



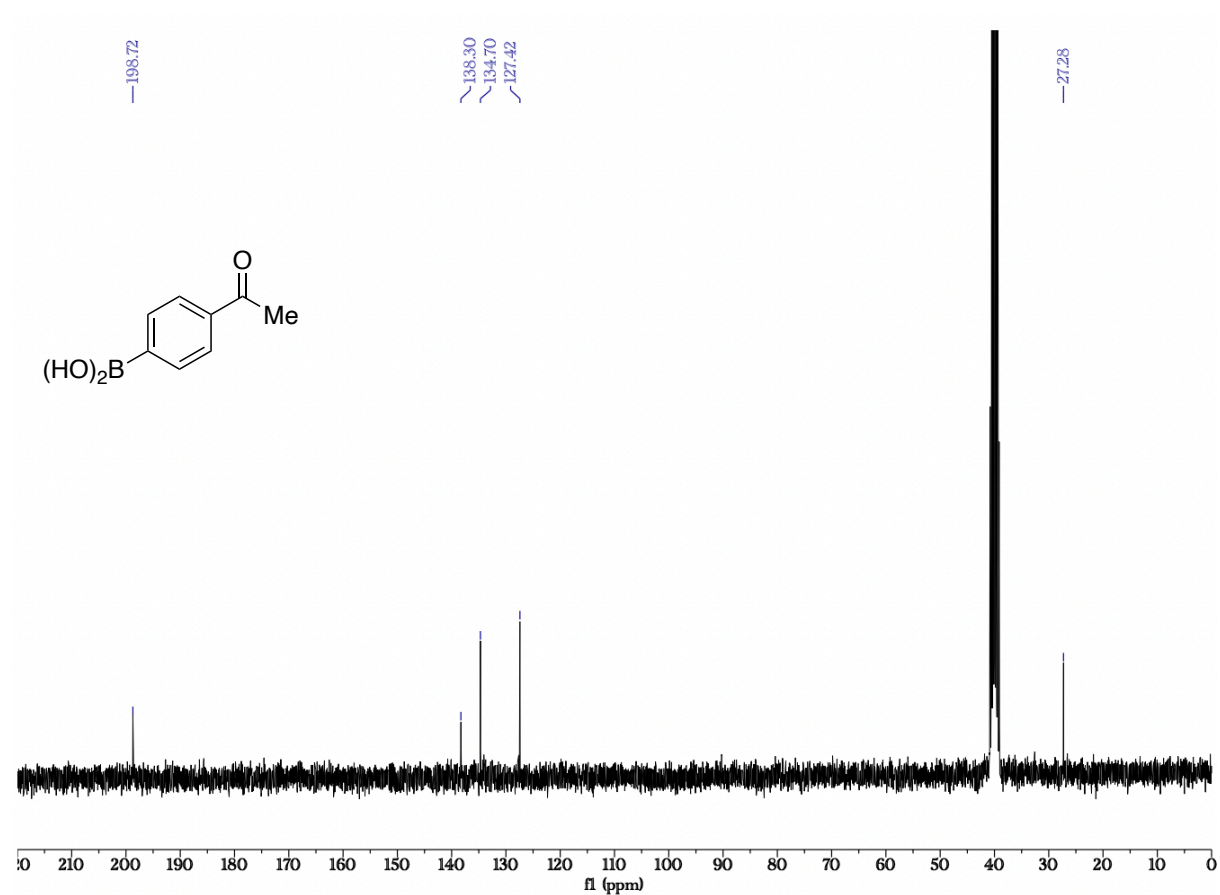
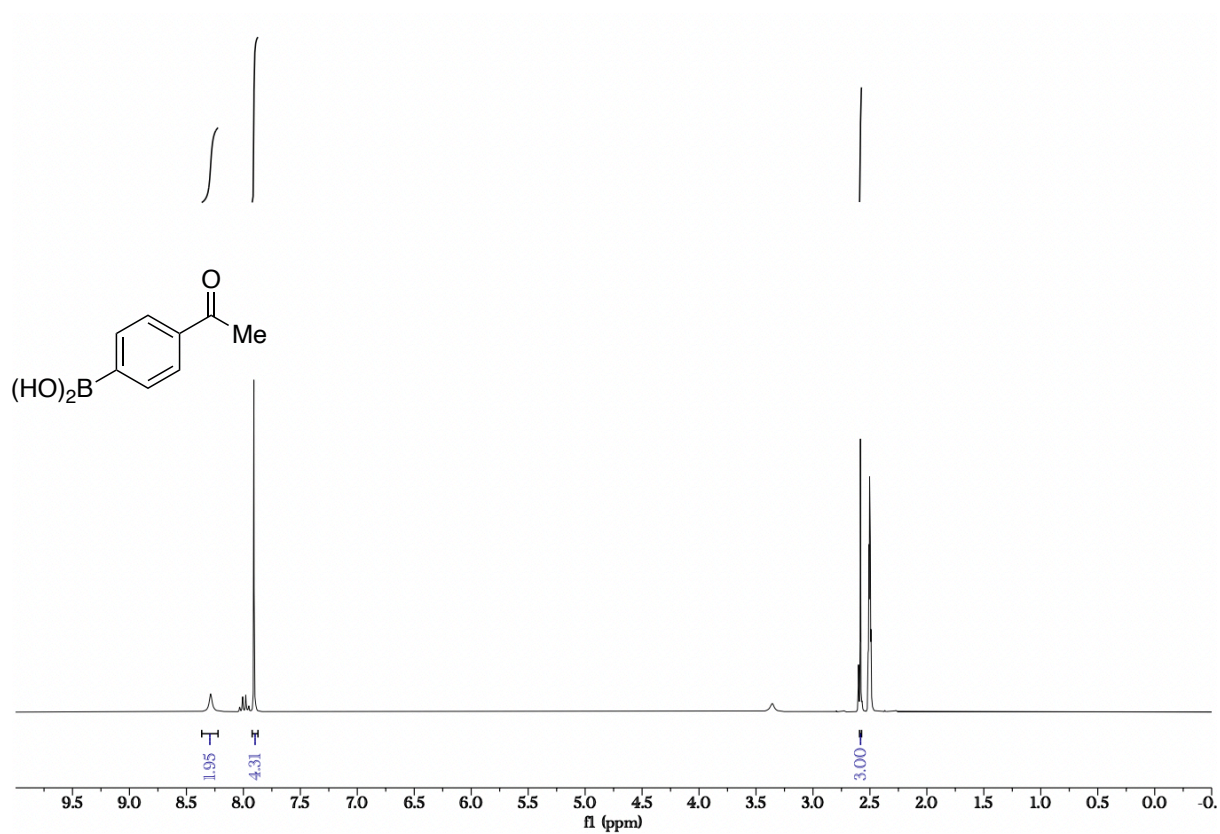
1-(4-nitrophenyl)ethan-1-one (2m):



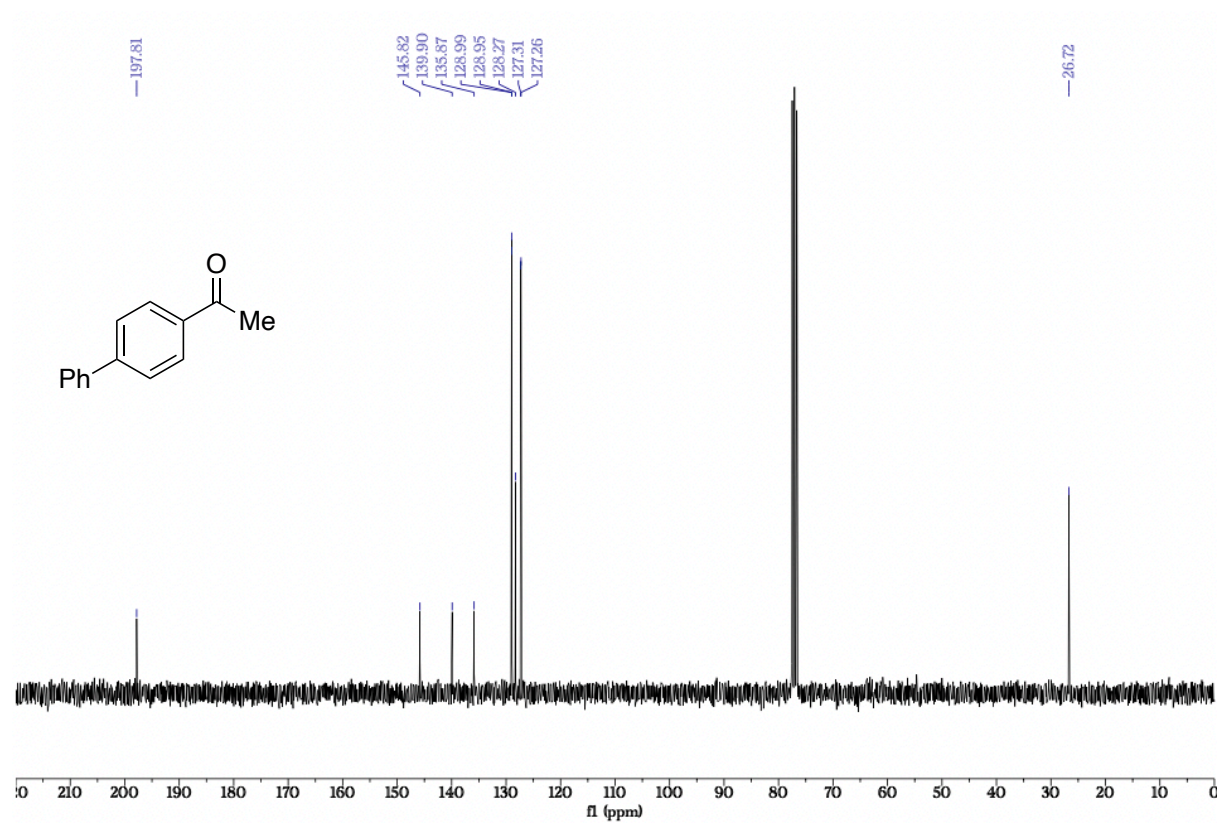
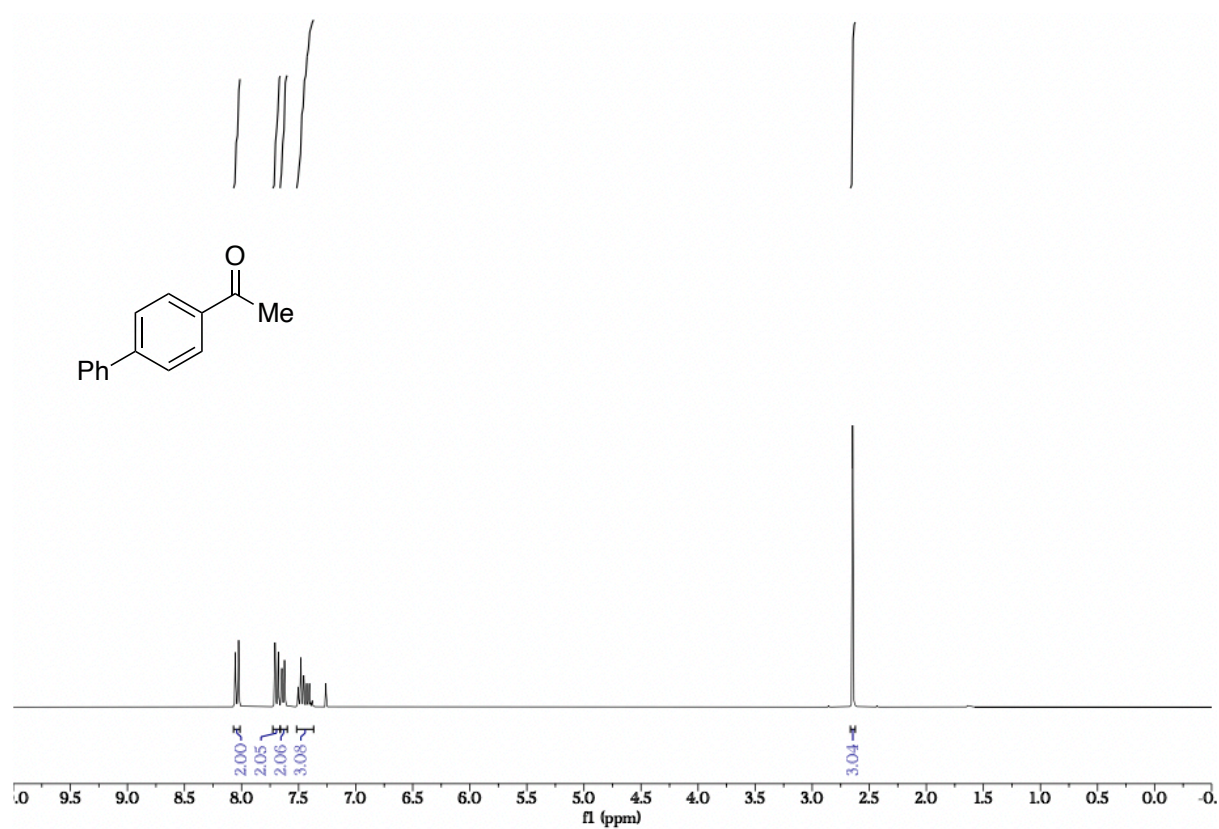
4-acetylbenzoic acid (2n):



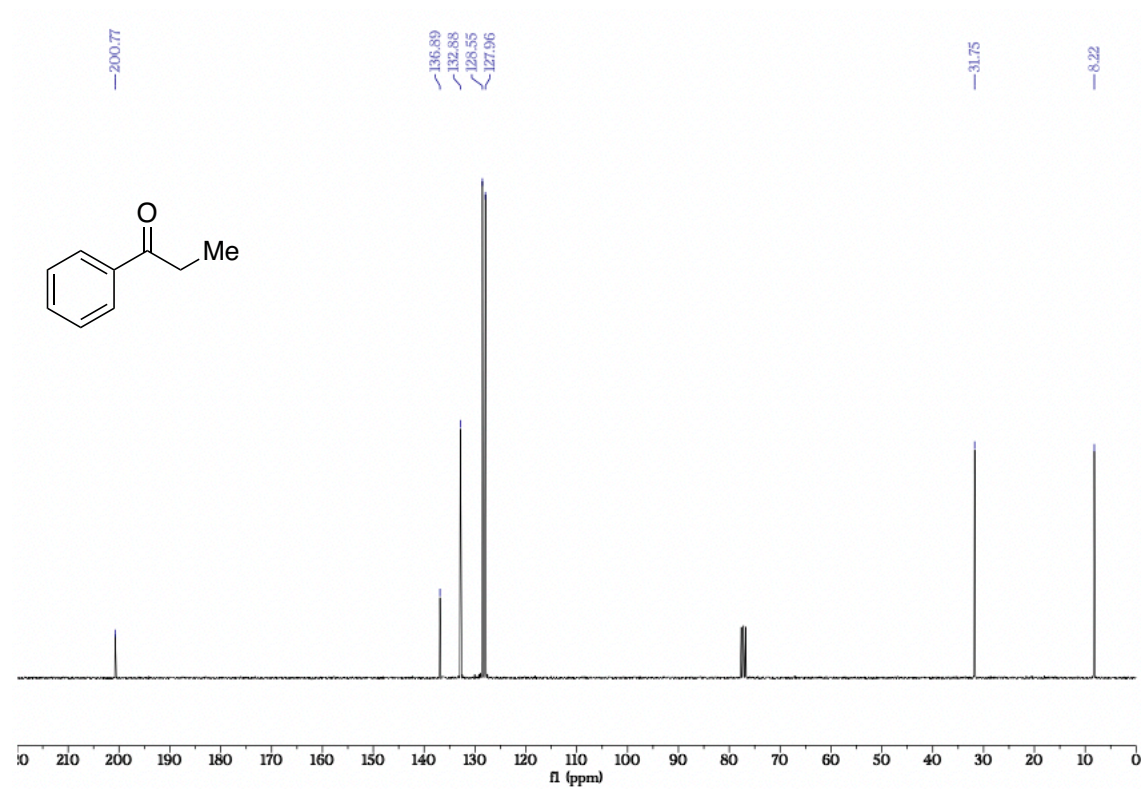
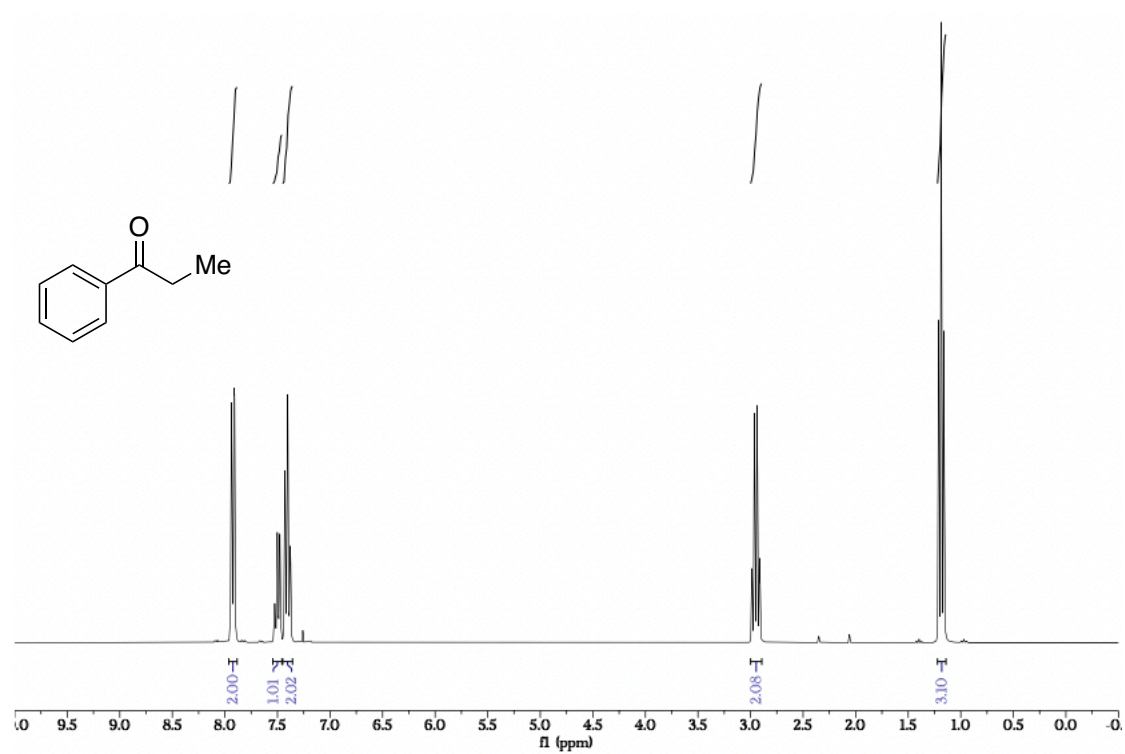
(4-acetylphenyl)boronic acid (2o):



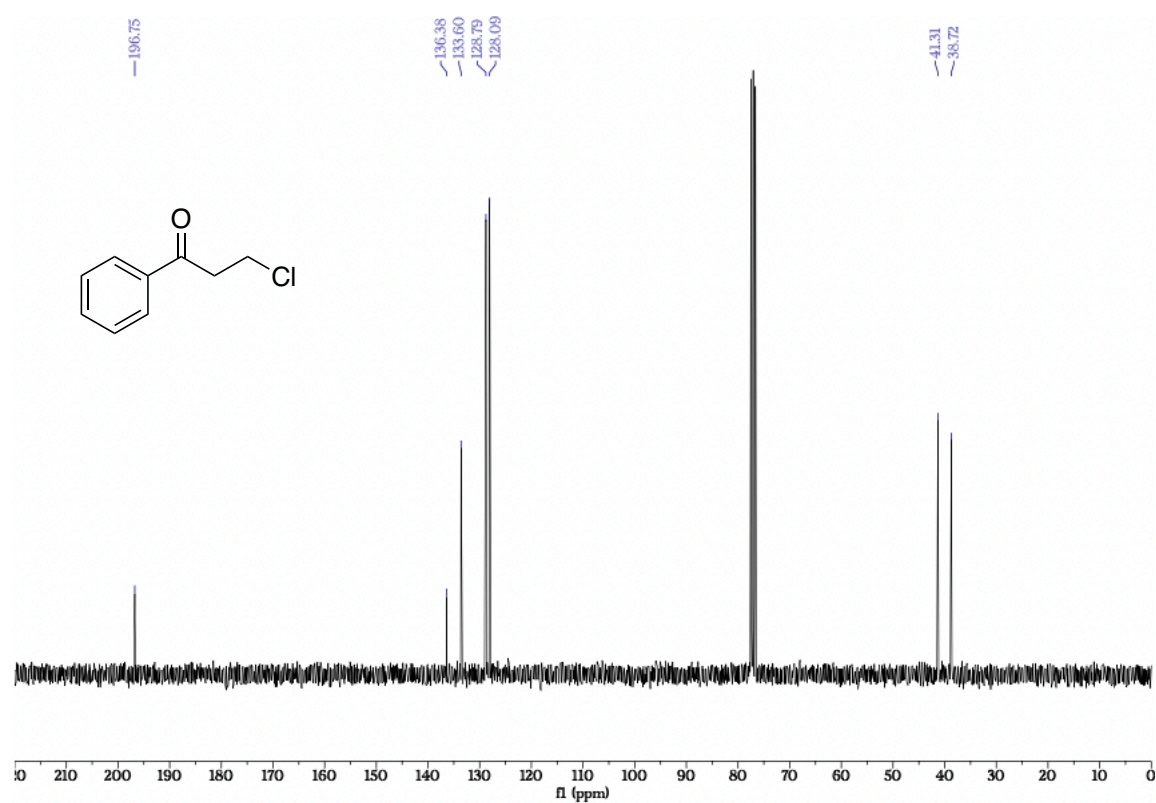
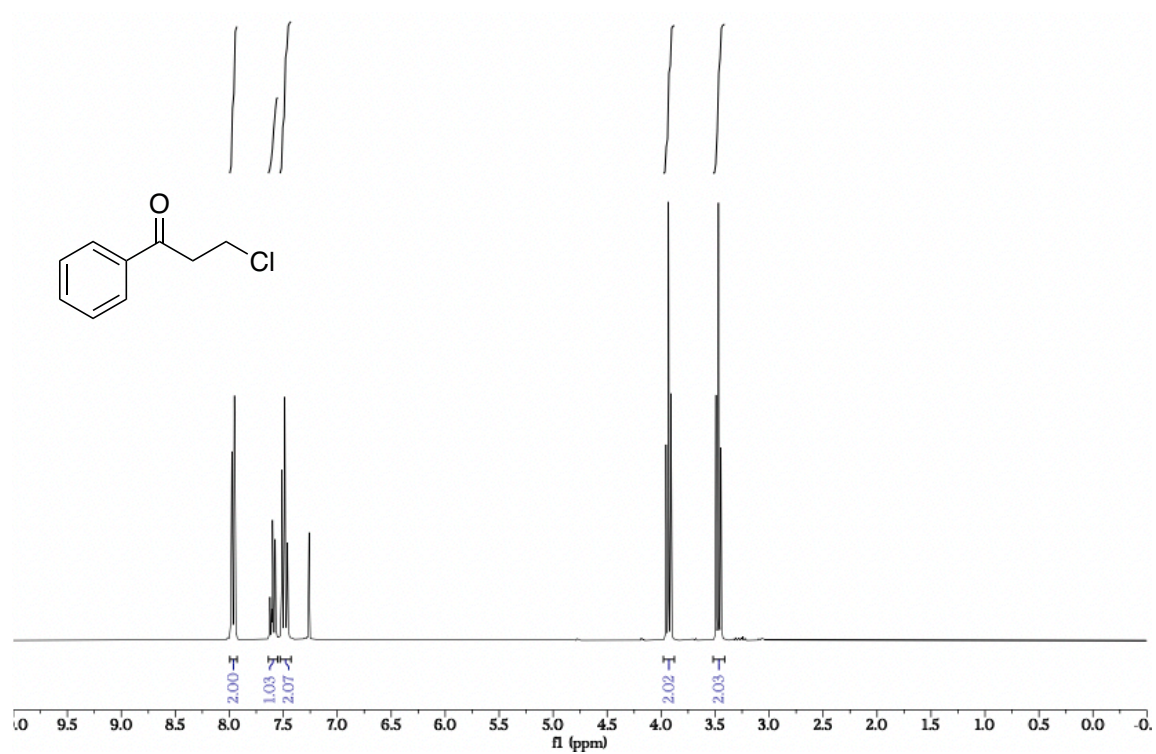
1-([1,1'-biphenyl]-4-yl)ethan-1-one (2p):



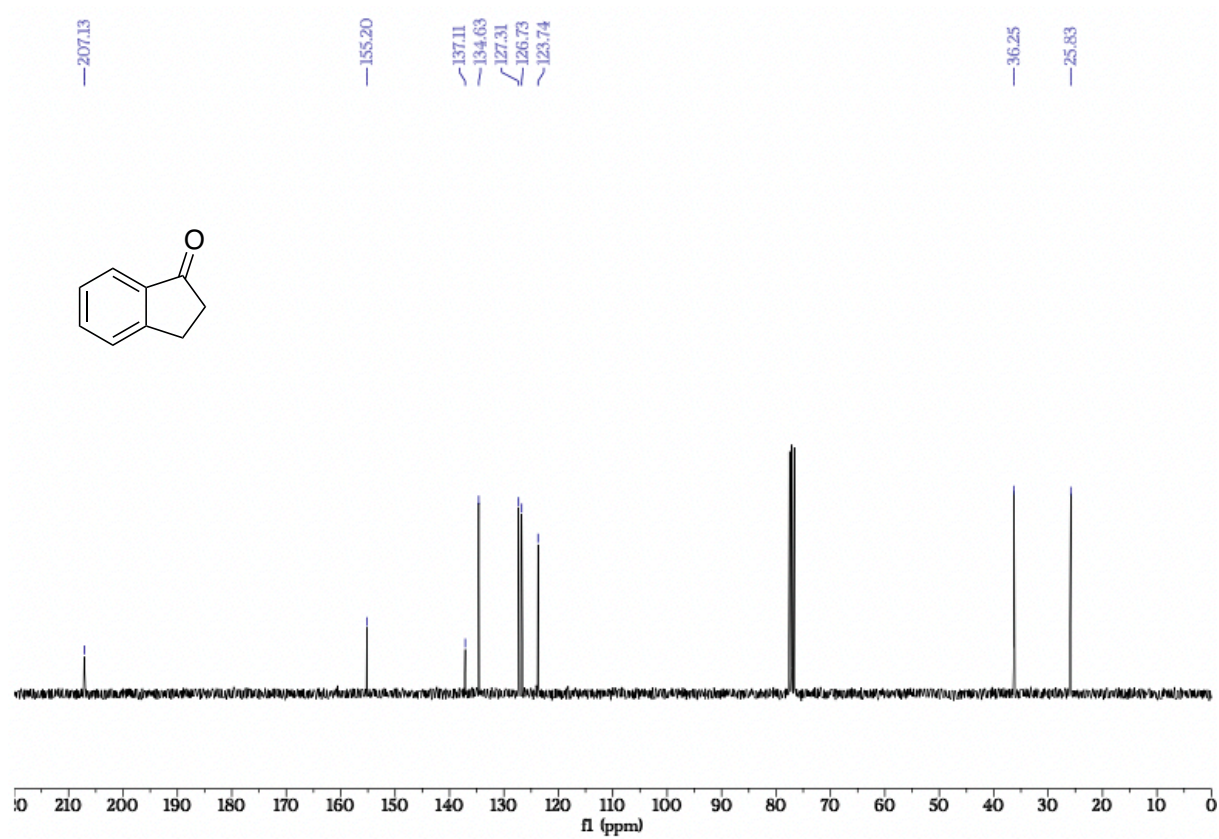
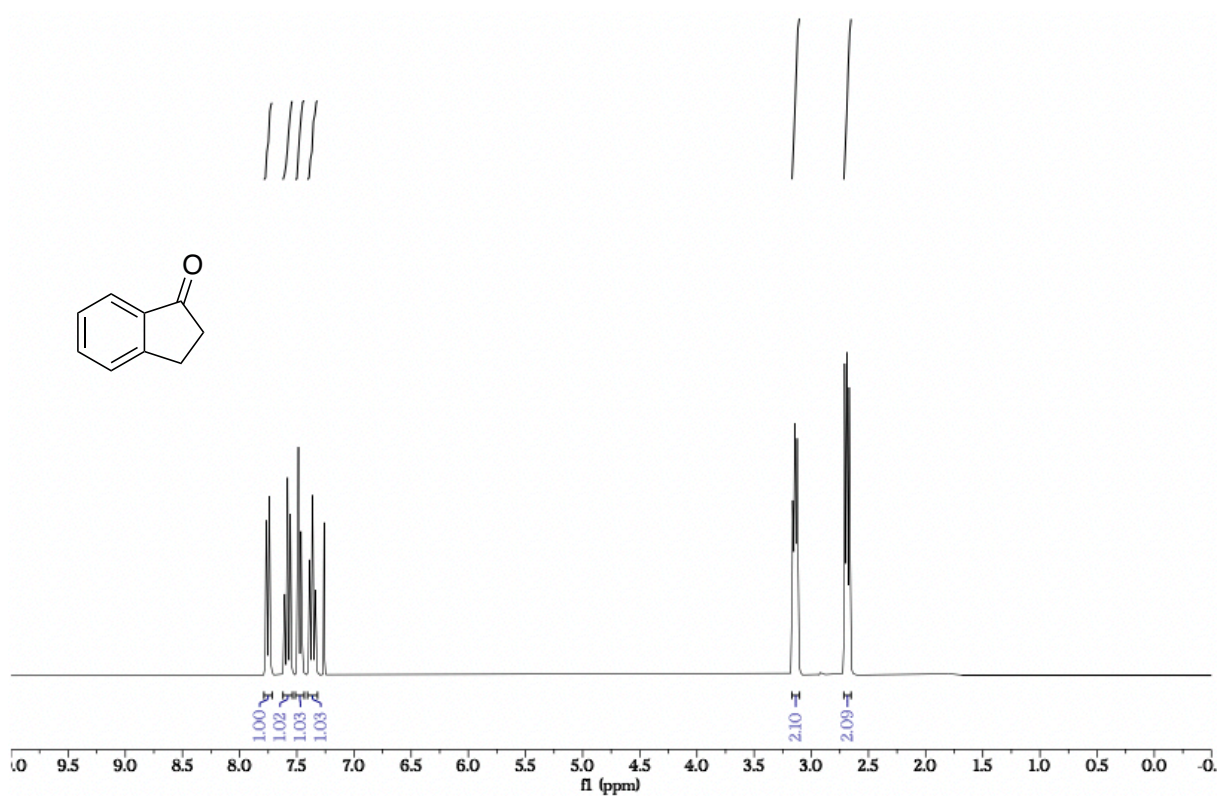
Propiophenone (2q):



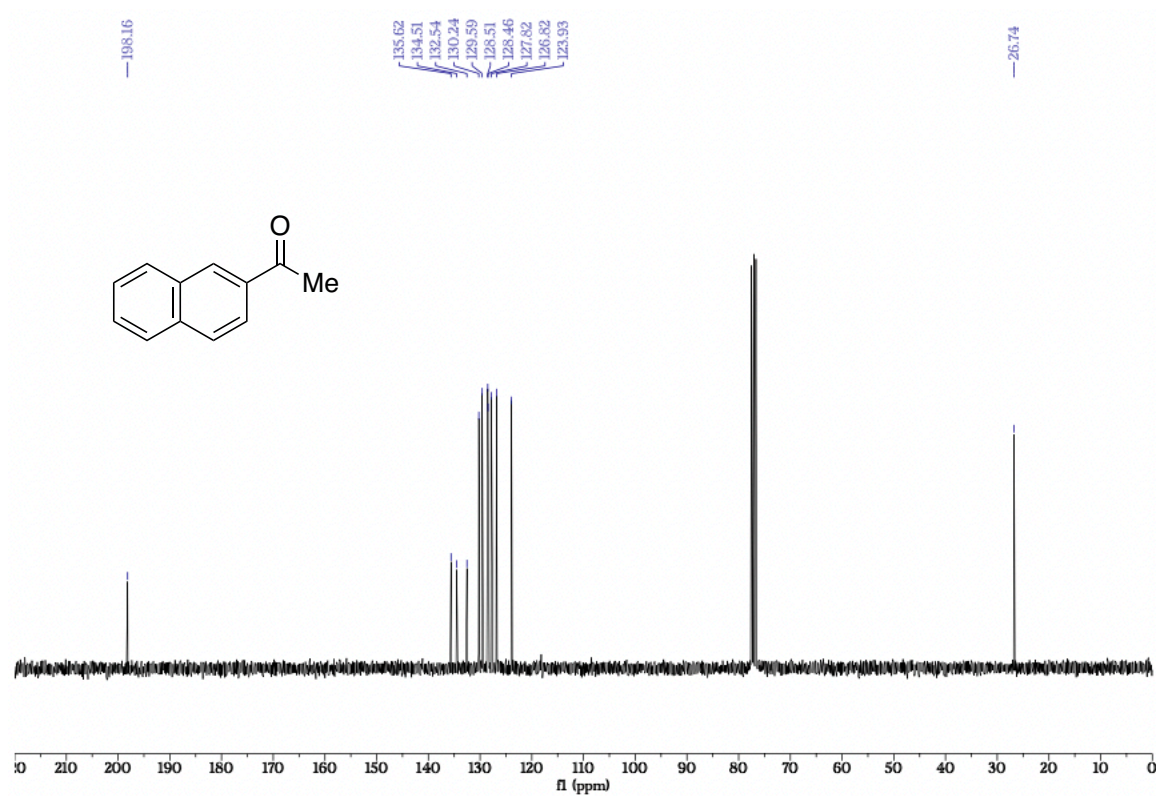
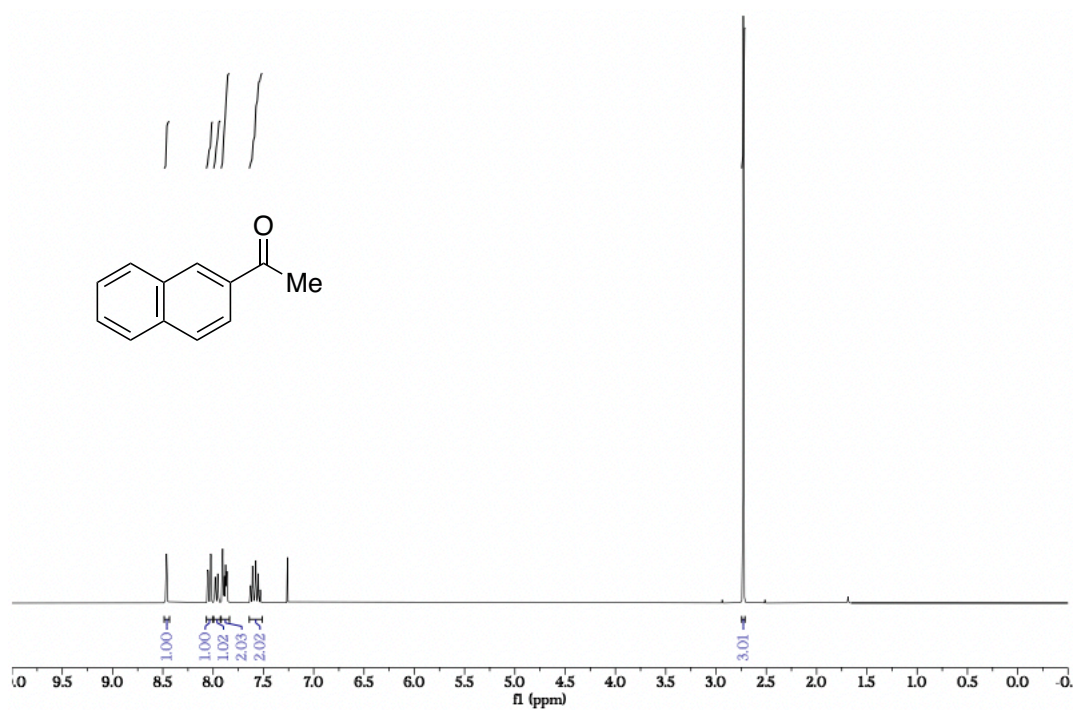
3-chloro-1-phenylpropan-1-one (2r):



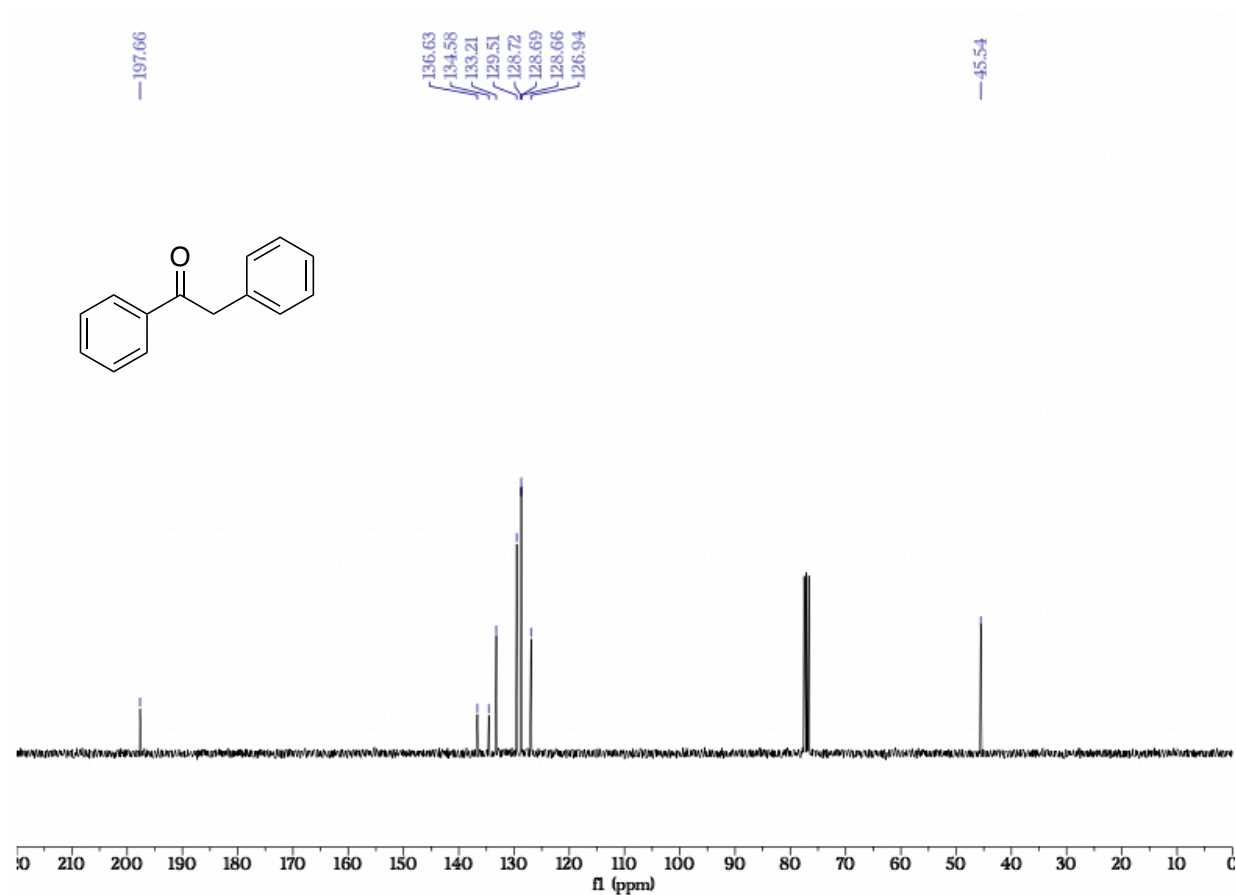
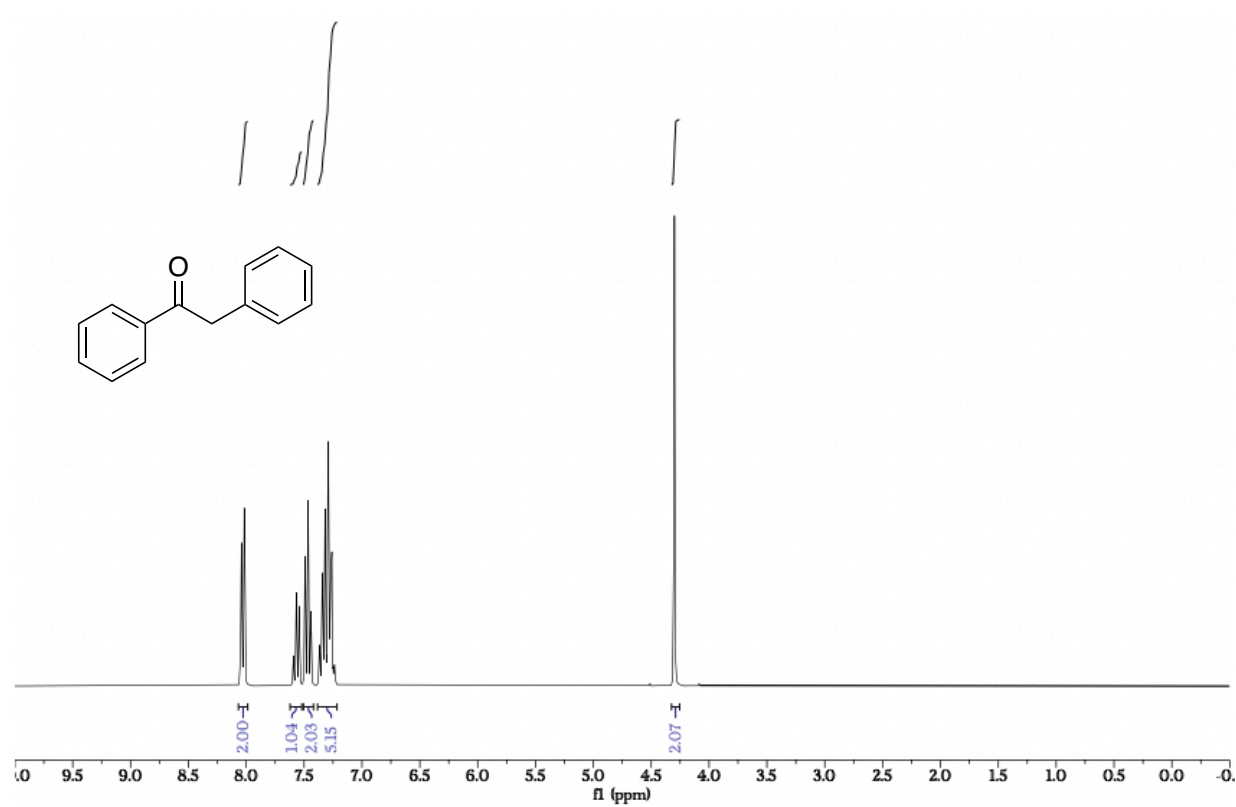
2,3-dihydro-1*H*-inden-1-one (2s):



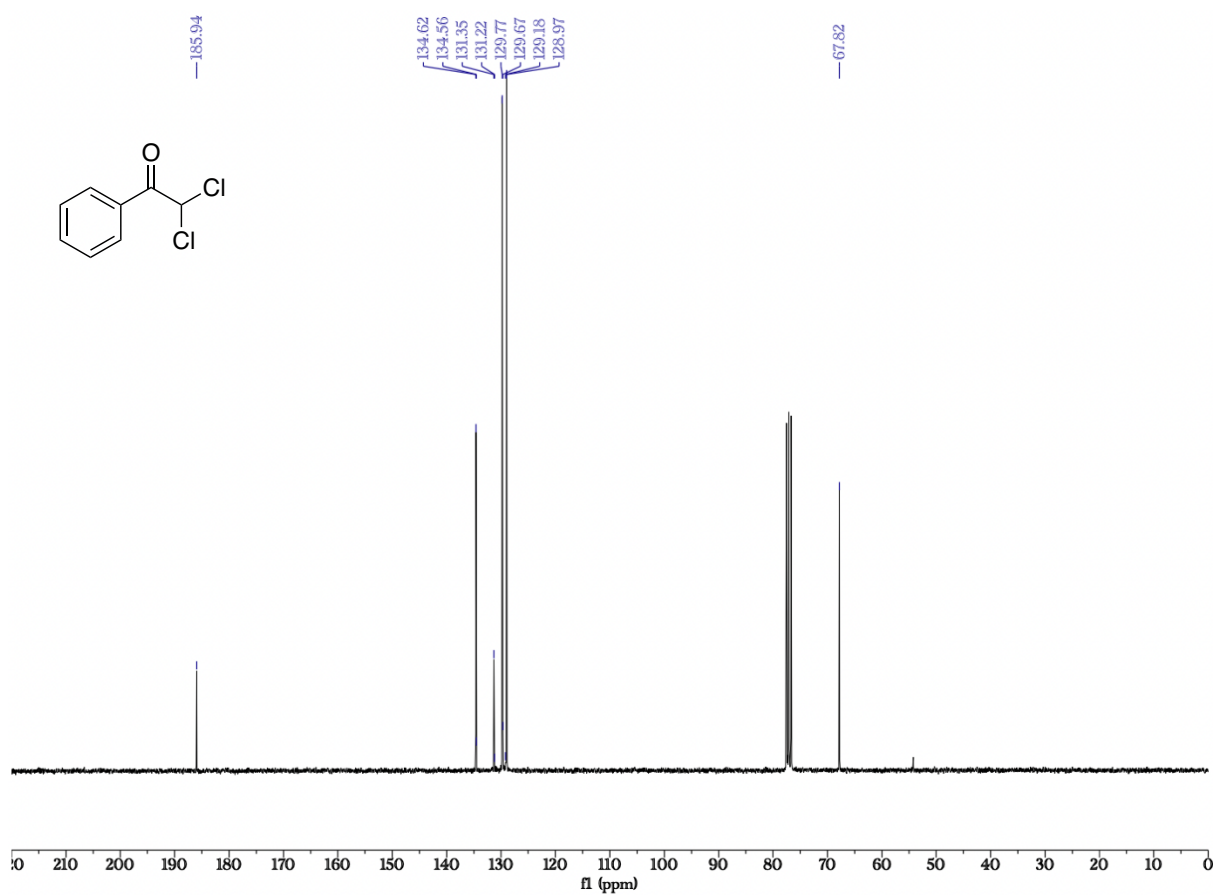
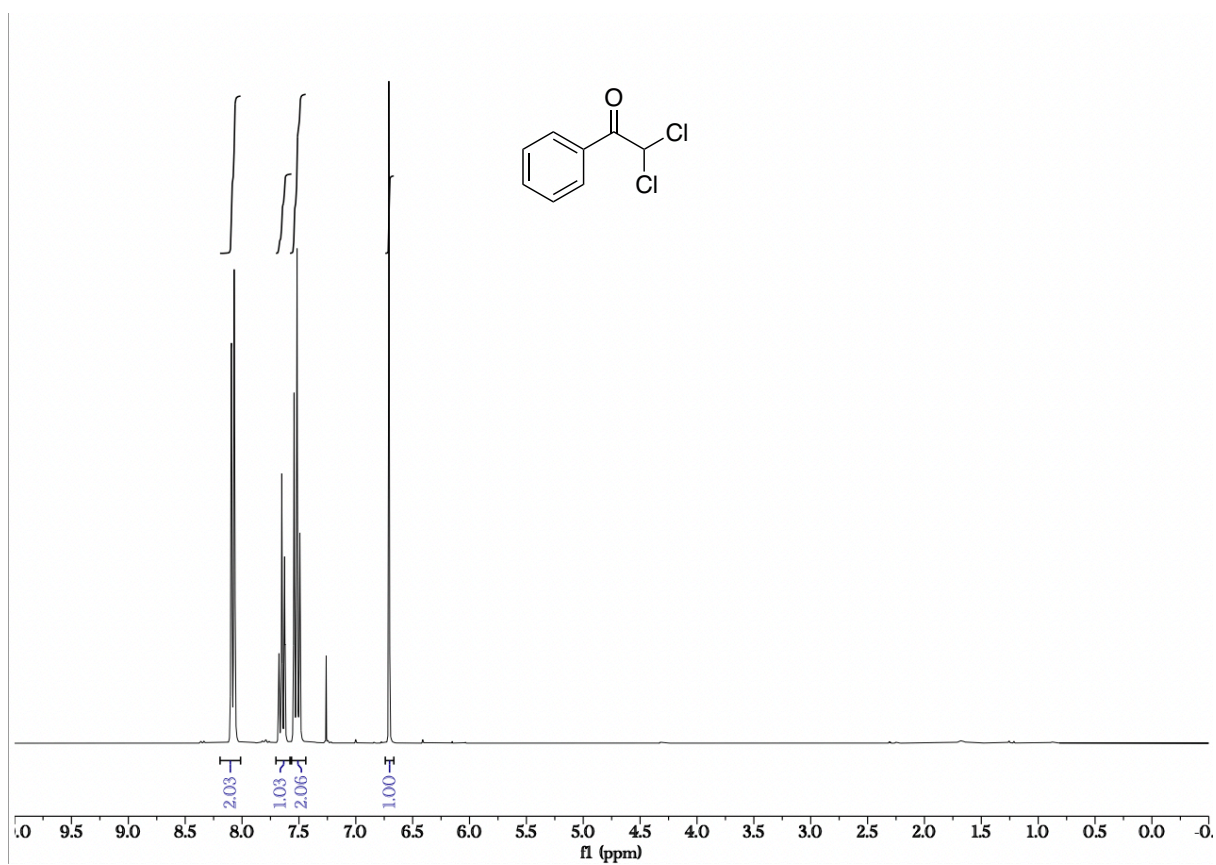
1-(naphthalen-2-yl)ethan-1-one (2t):



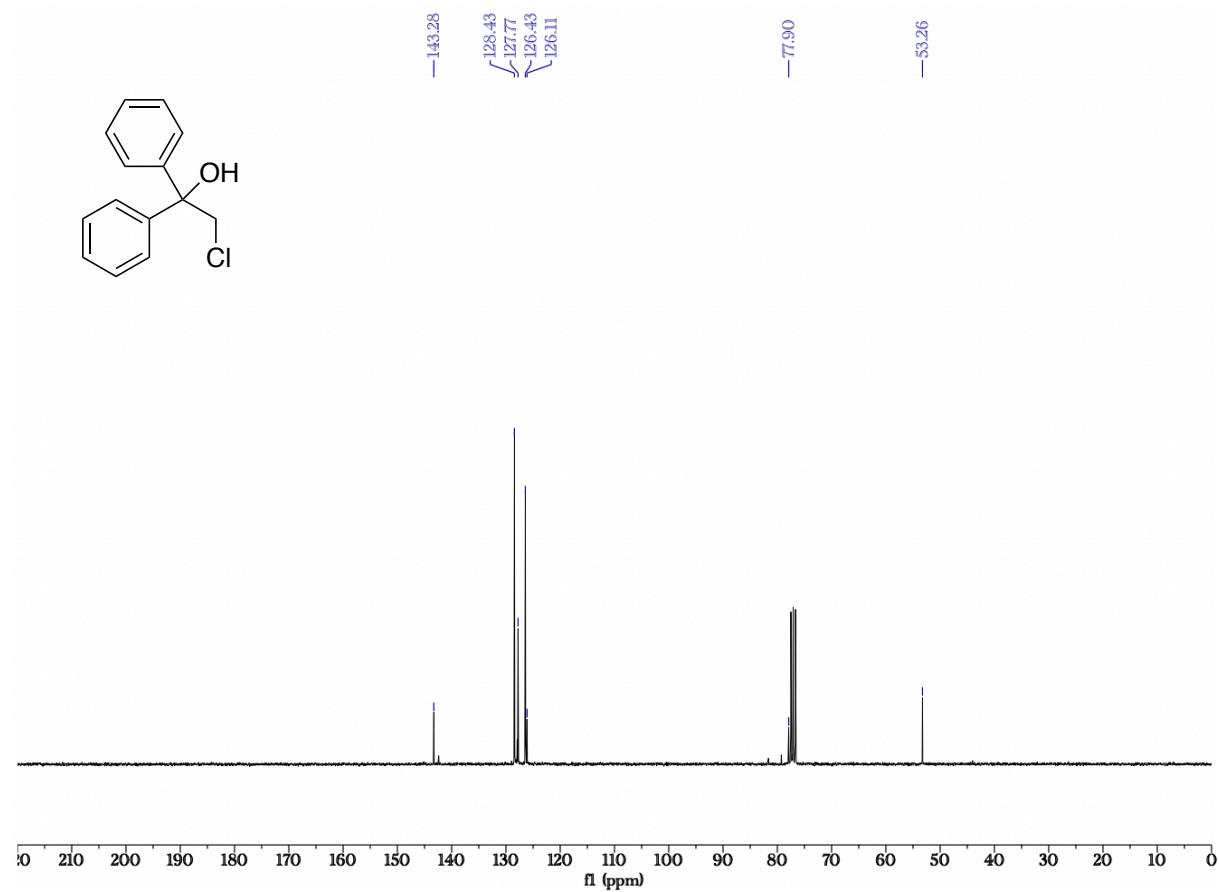
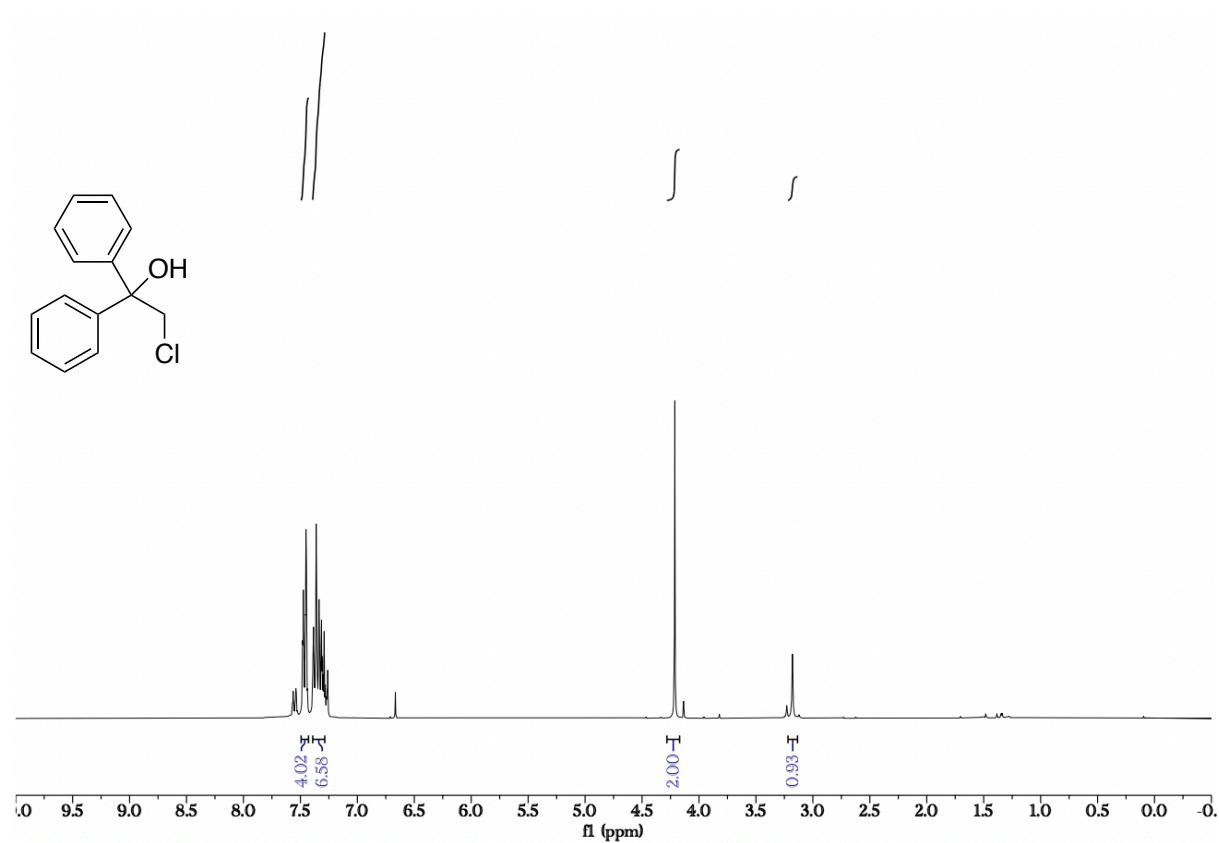
1,2-diphenylethan-1-one (2u):



2,2-dichloro-1-phenylethan-1-one (2v)

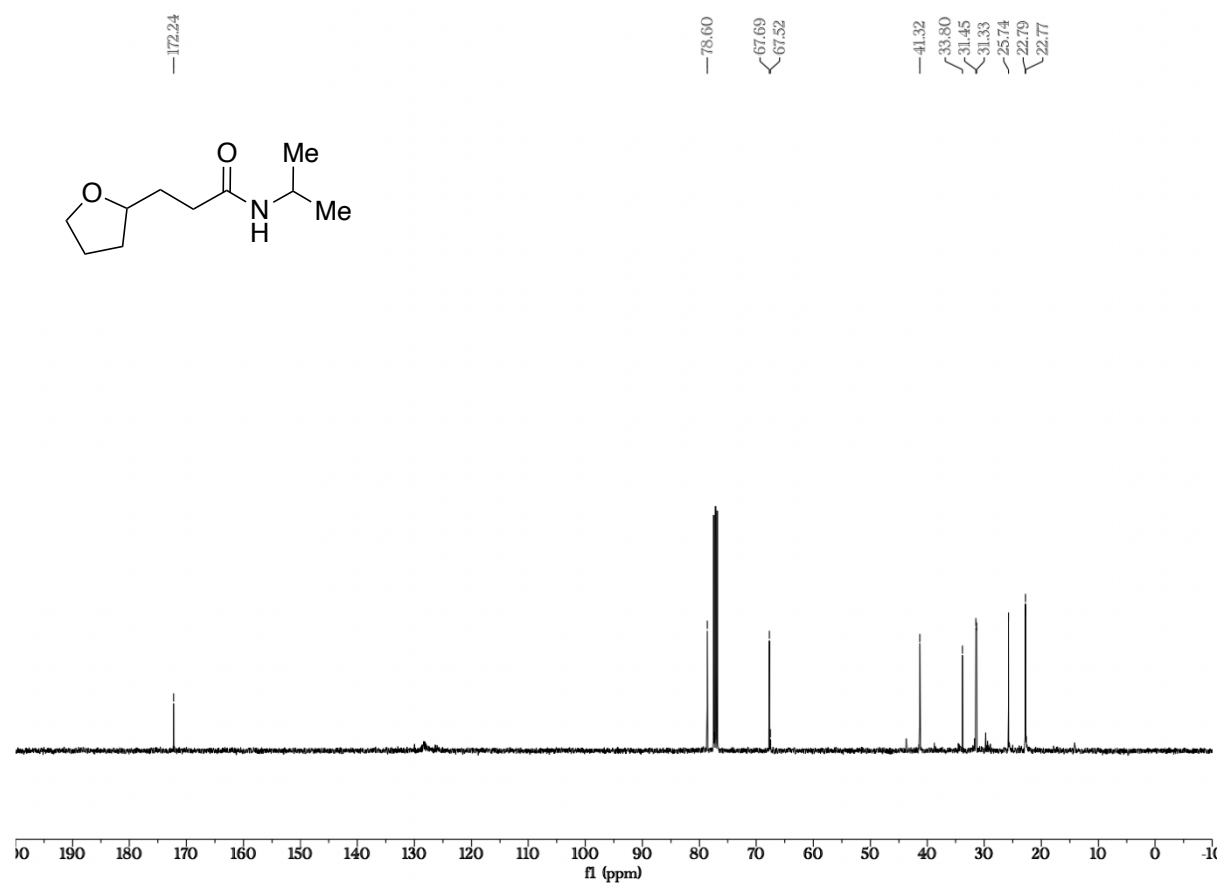
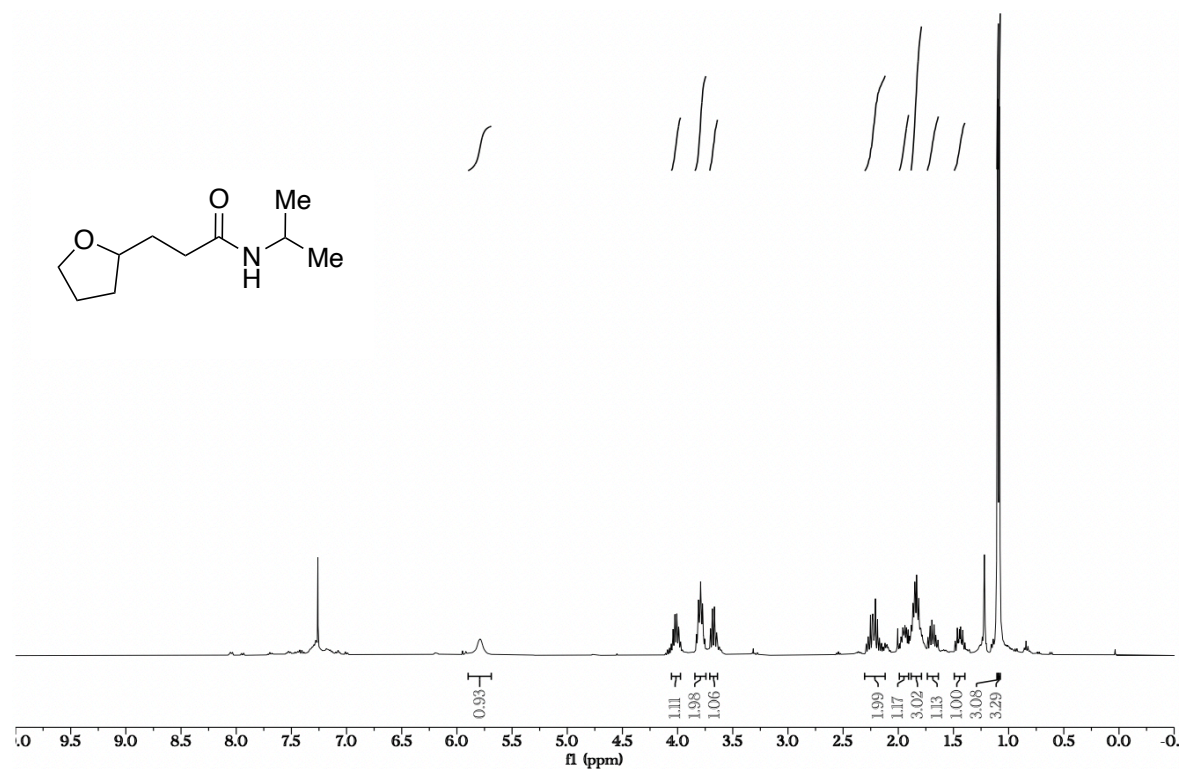


2-chloro-1,1-diphenylethan-1-ol (2w):

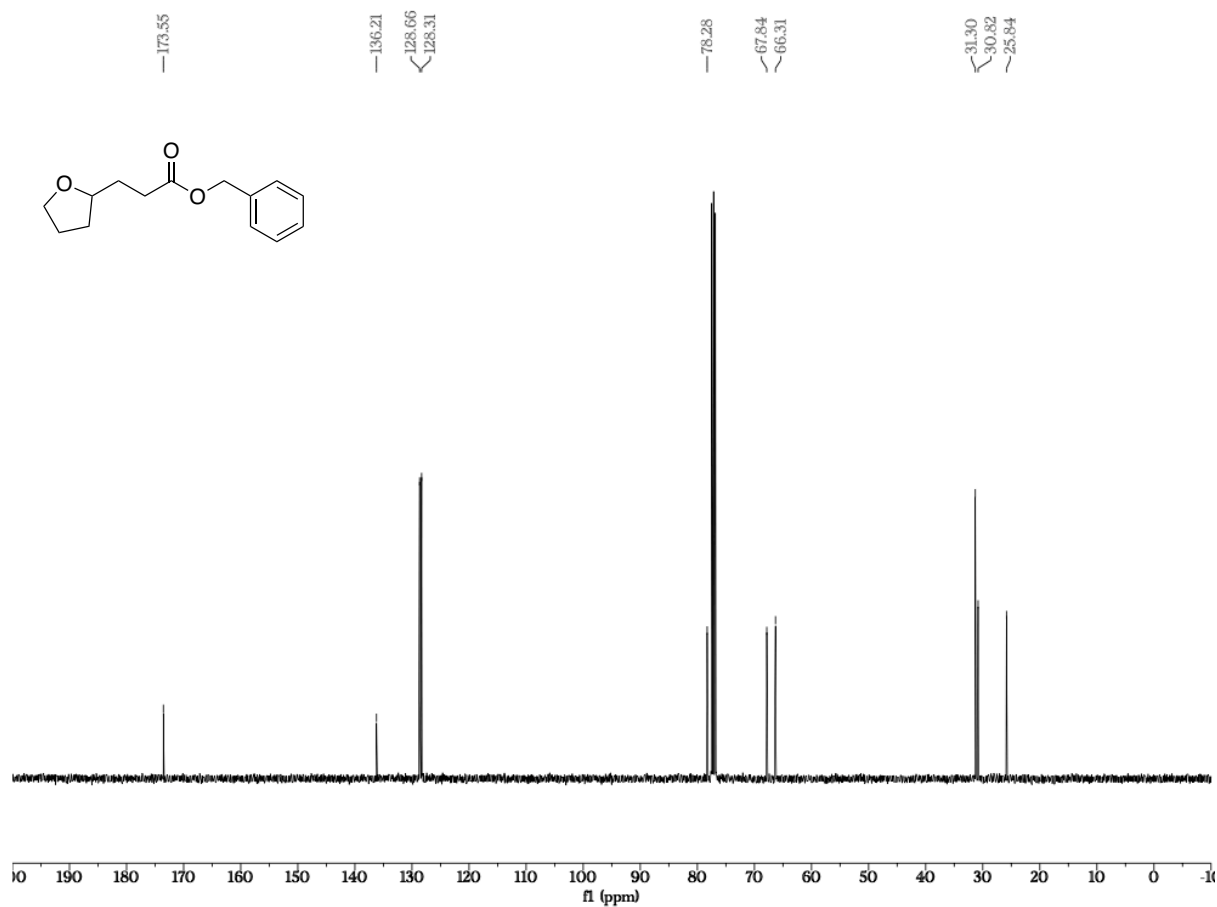
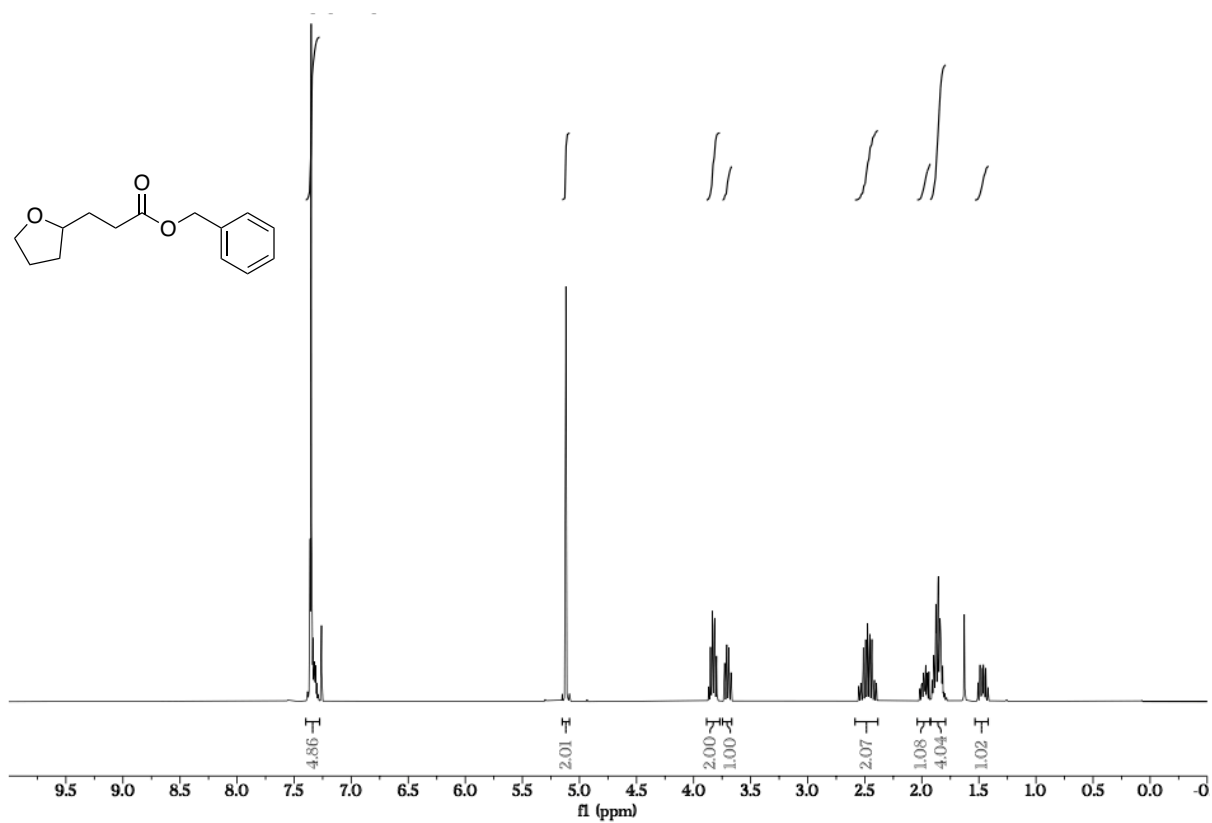


Copies of NMR spectra in chapter 4:

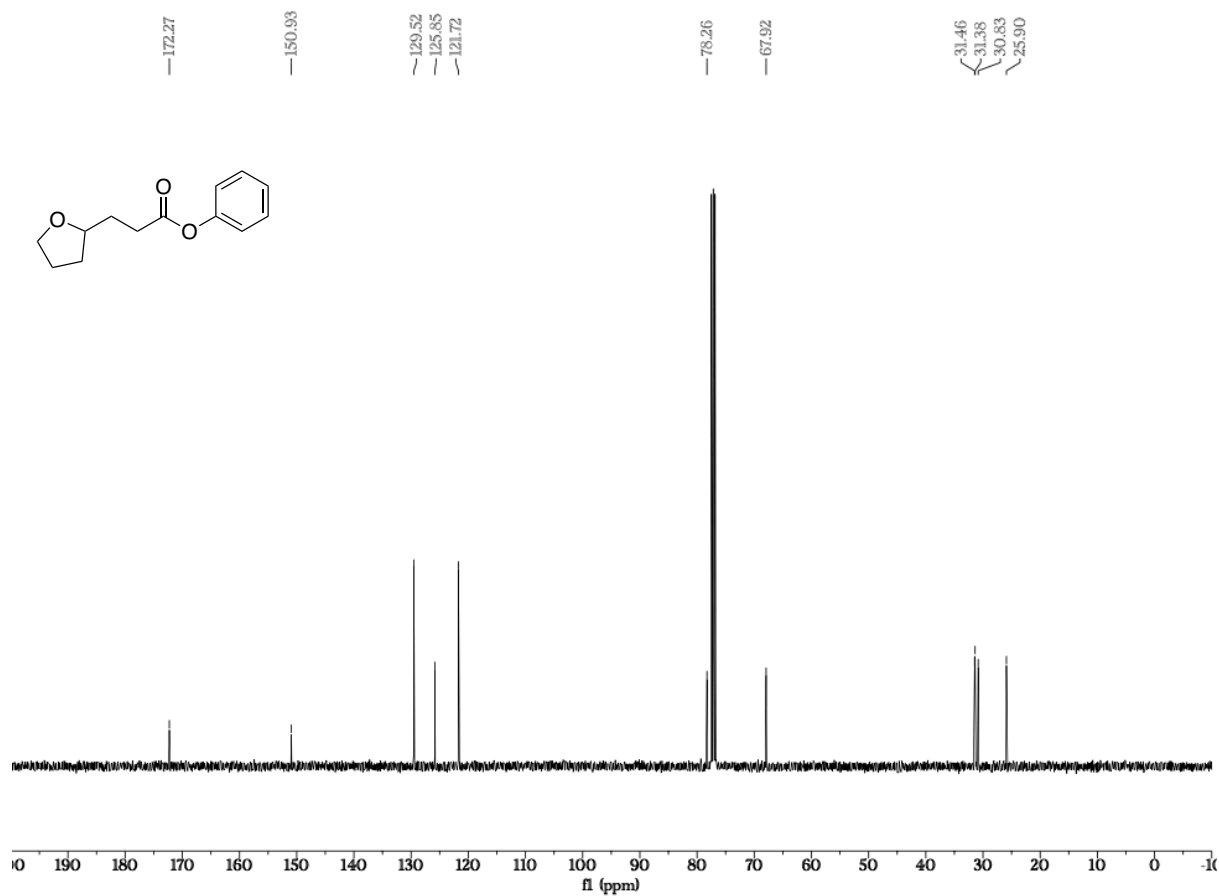
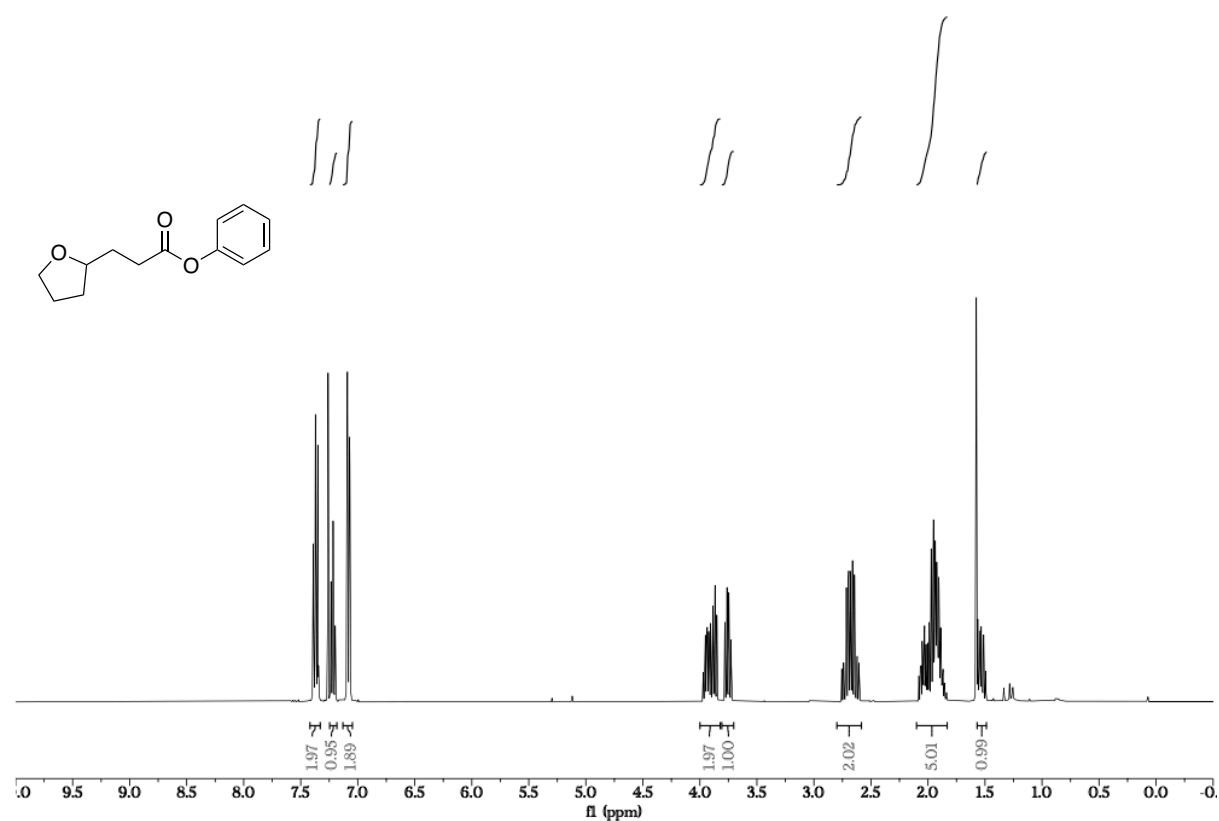
N-isopropyl-3-(tetrahydrofuran-2-yl)propanamide (3c)



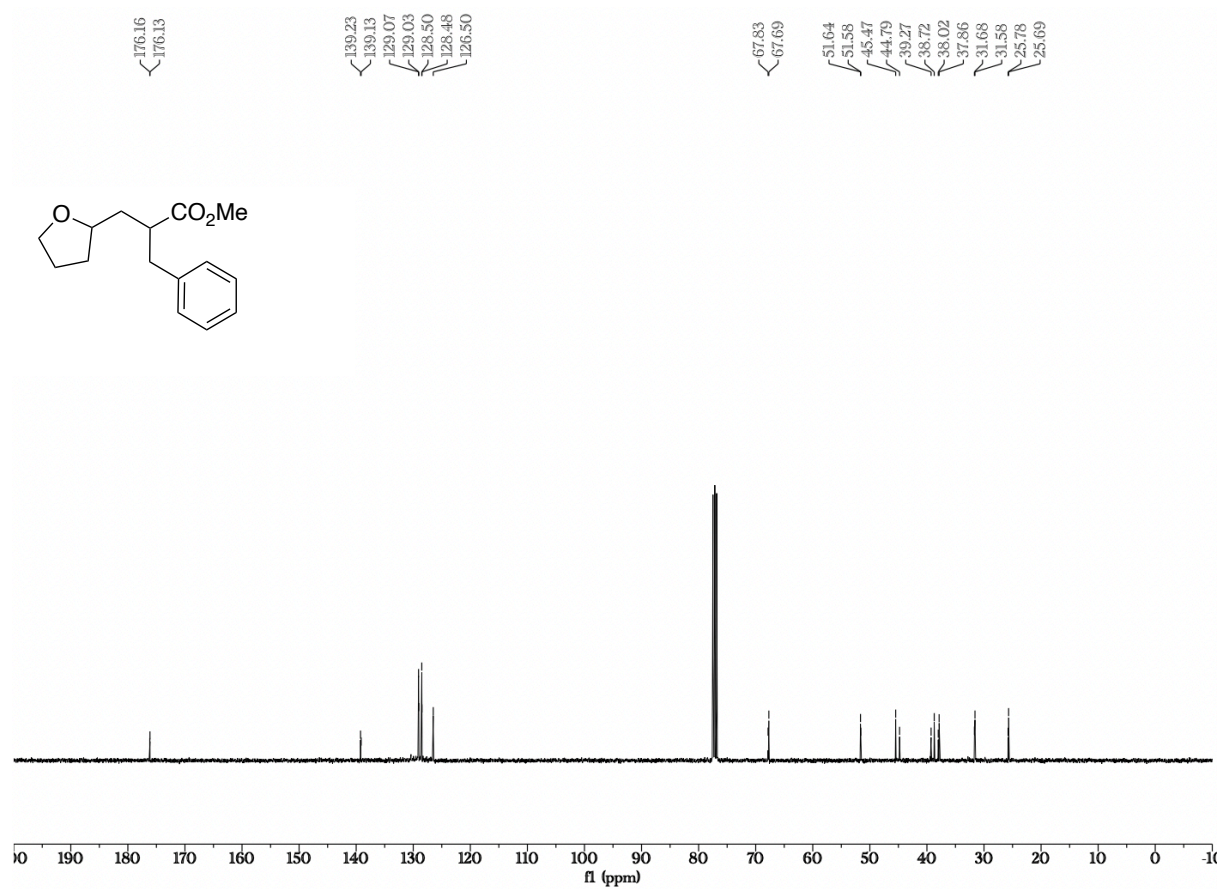
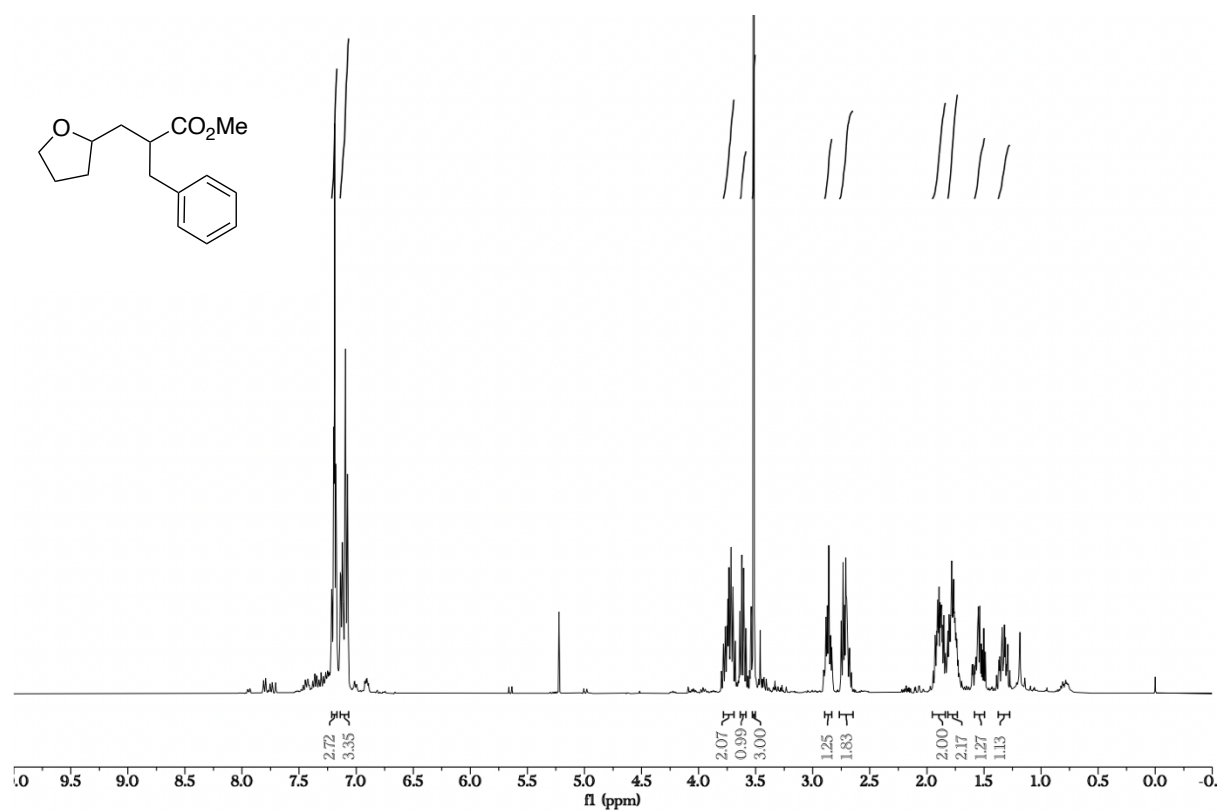
Benzyl 3-(tetrahydrofuran-2-yl)propanoate (3d)



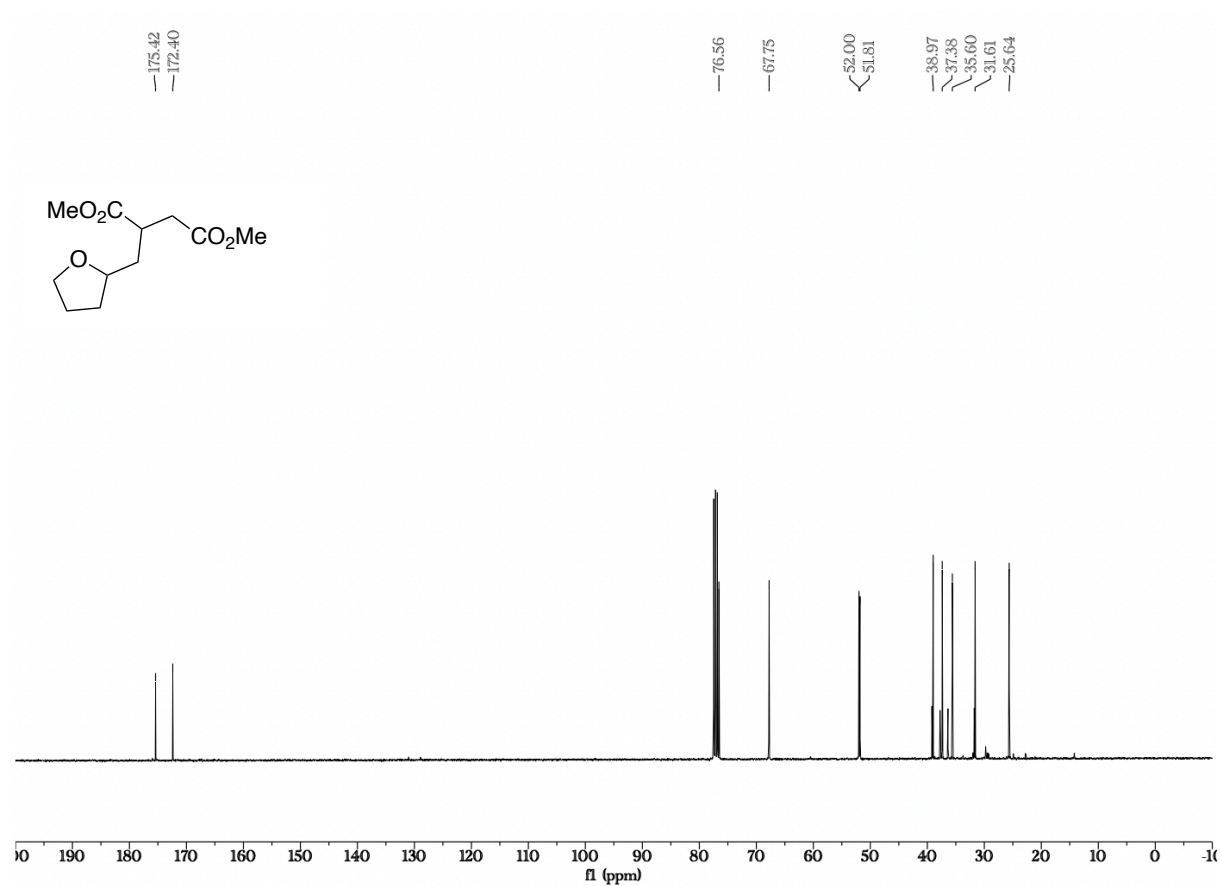
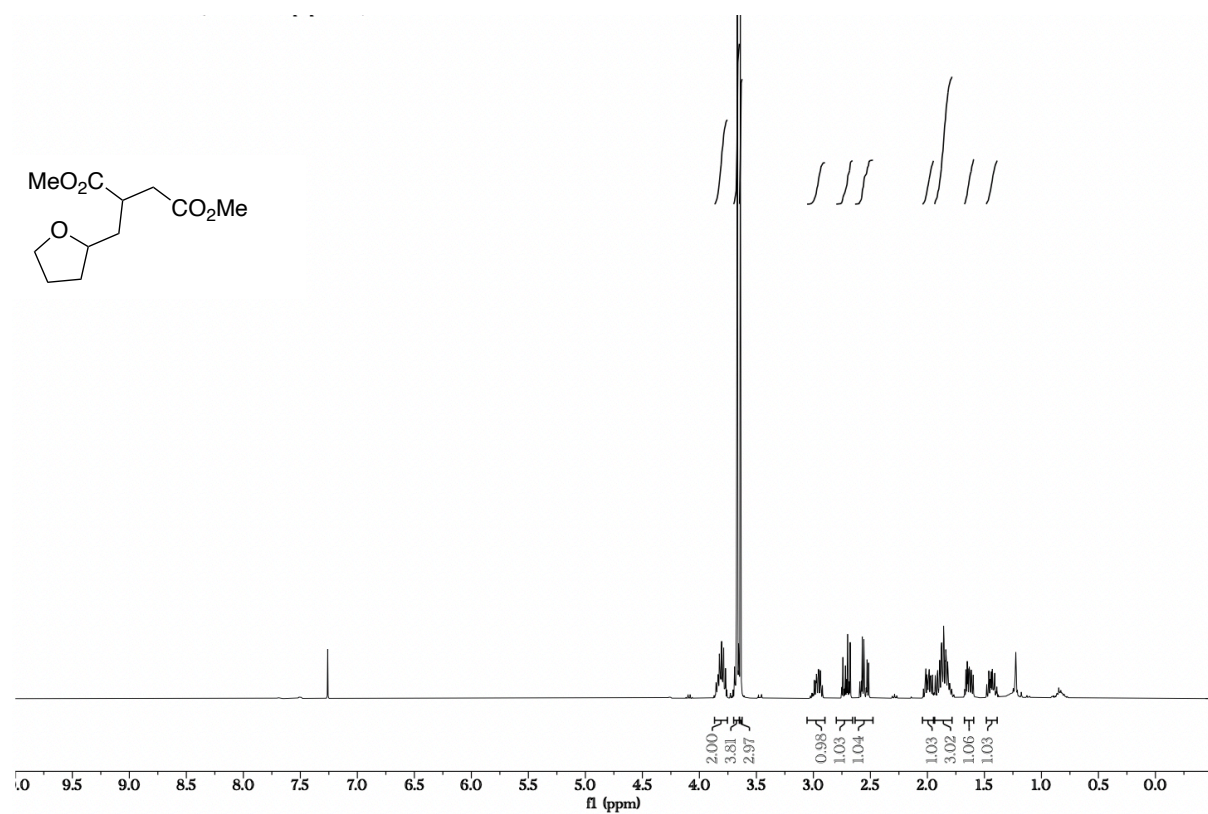
Phenyl 3-(tetrahydrofuran-2-yl)propanoate (3e)



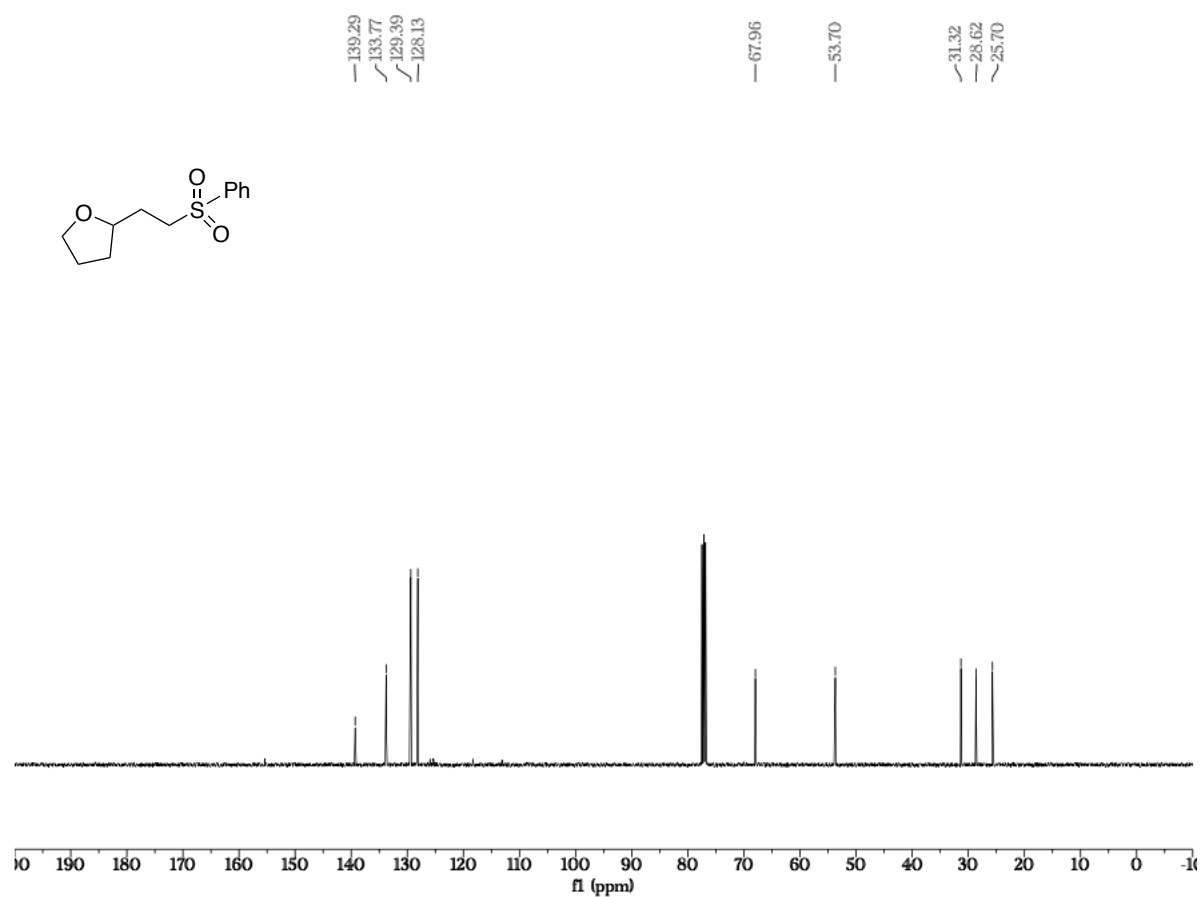
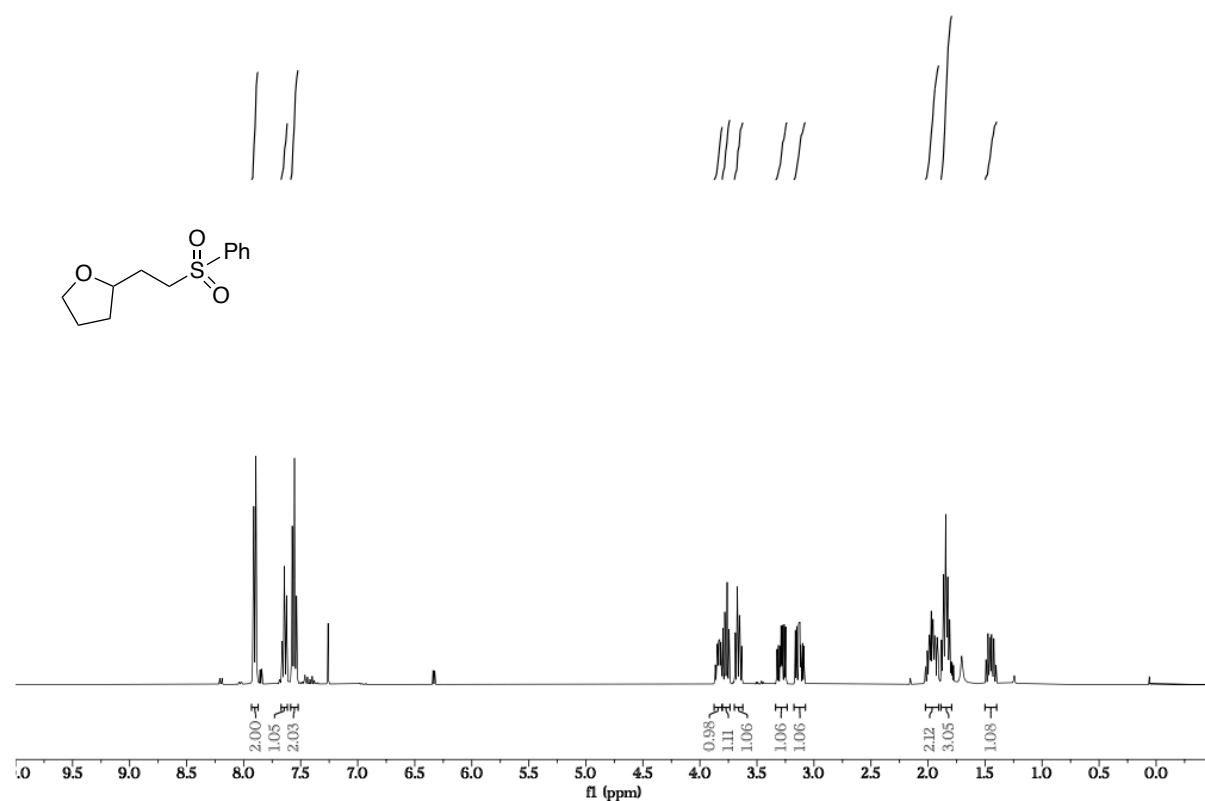
Methyl 2-benzyl-3-(tetrahydrofuran-2-yl)propanoate (3f)



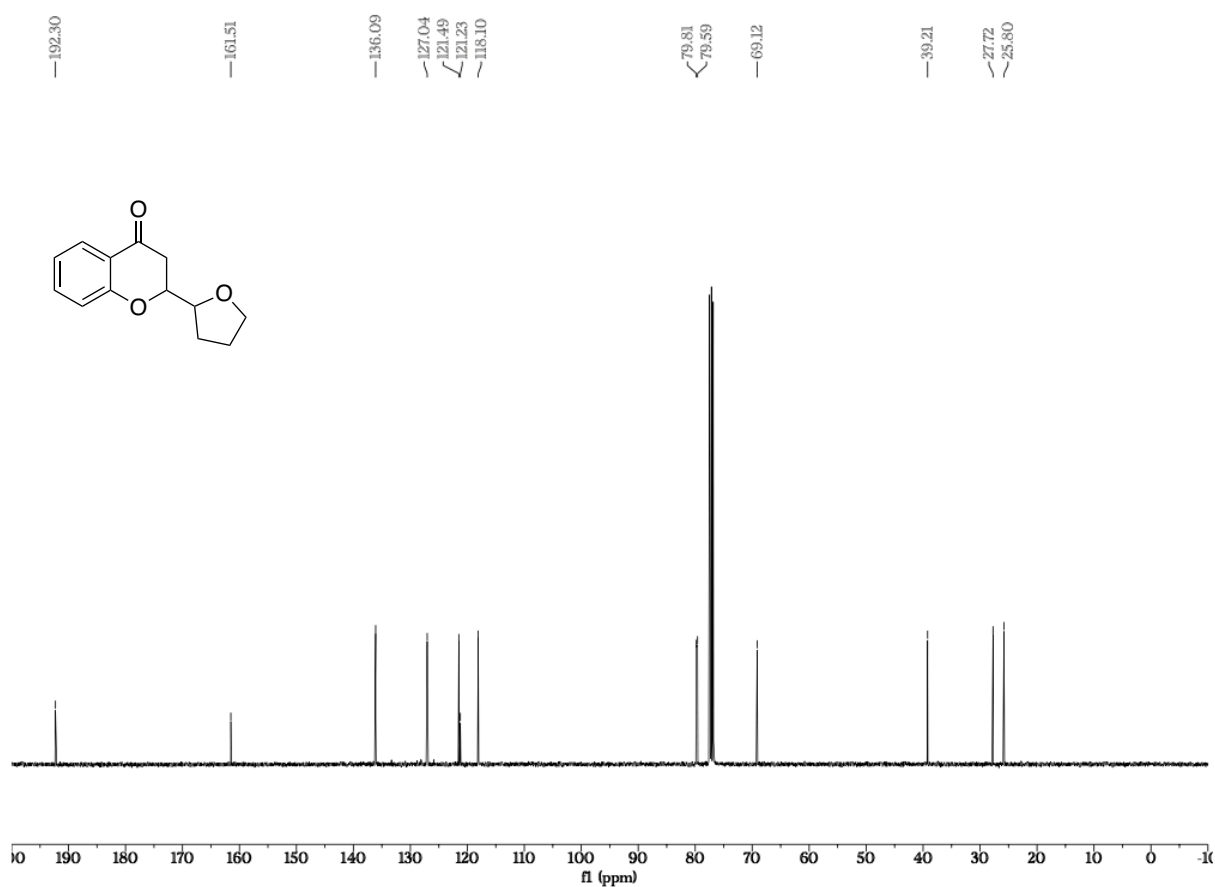
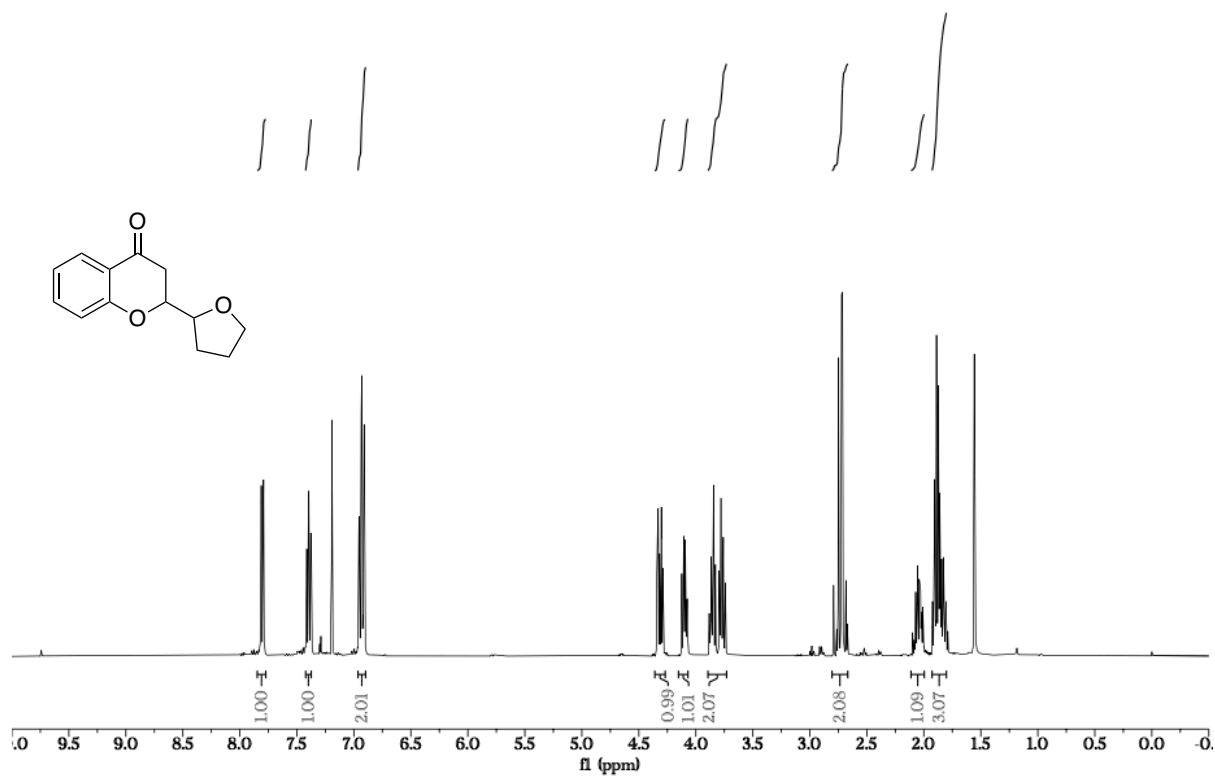
Dimethyl 2-((tetrahydrofuran-2-yl)methyl)succinate (3g)



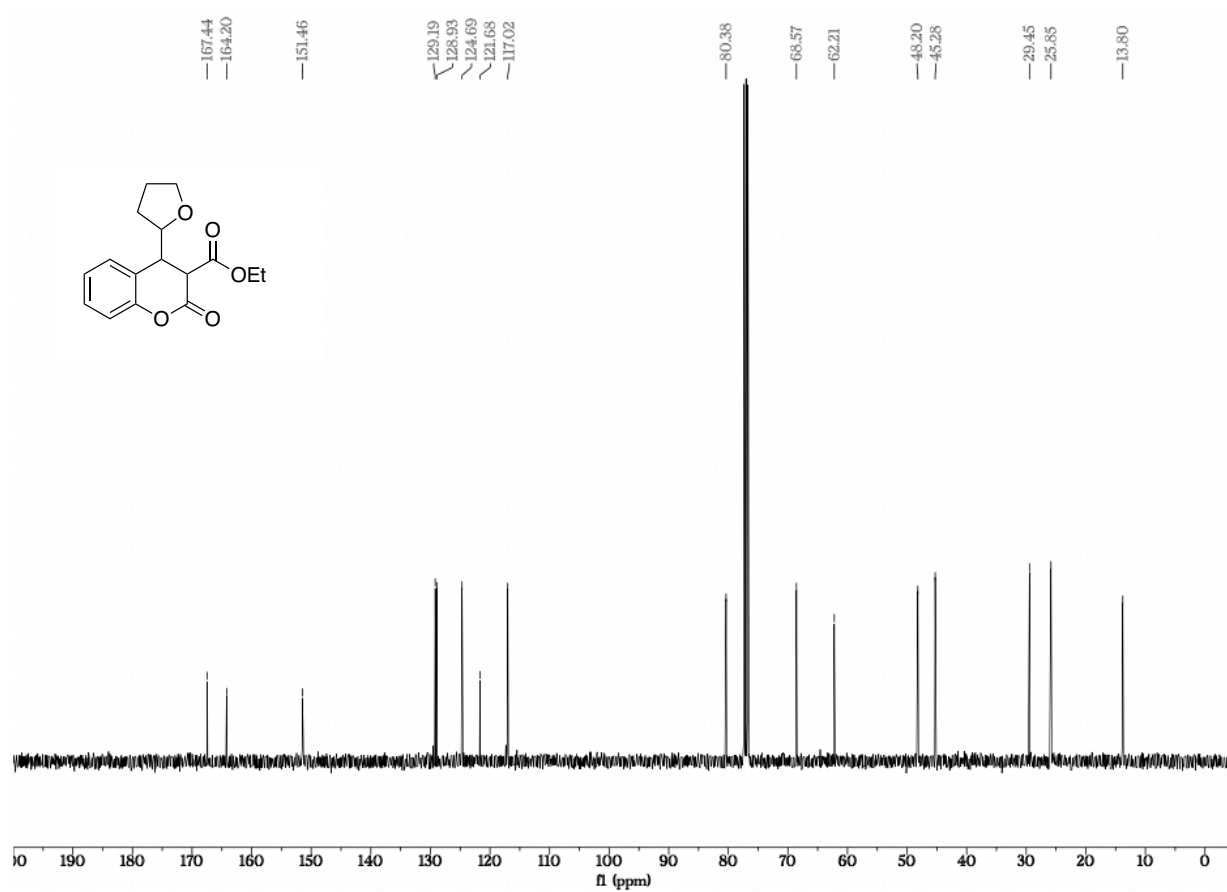
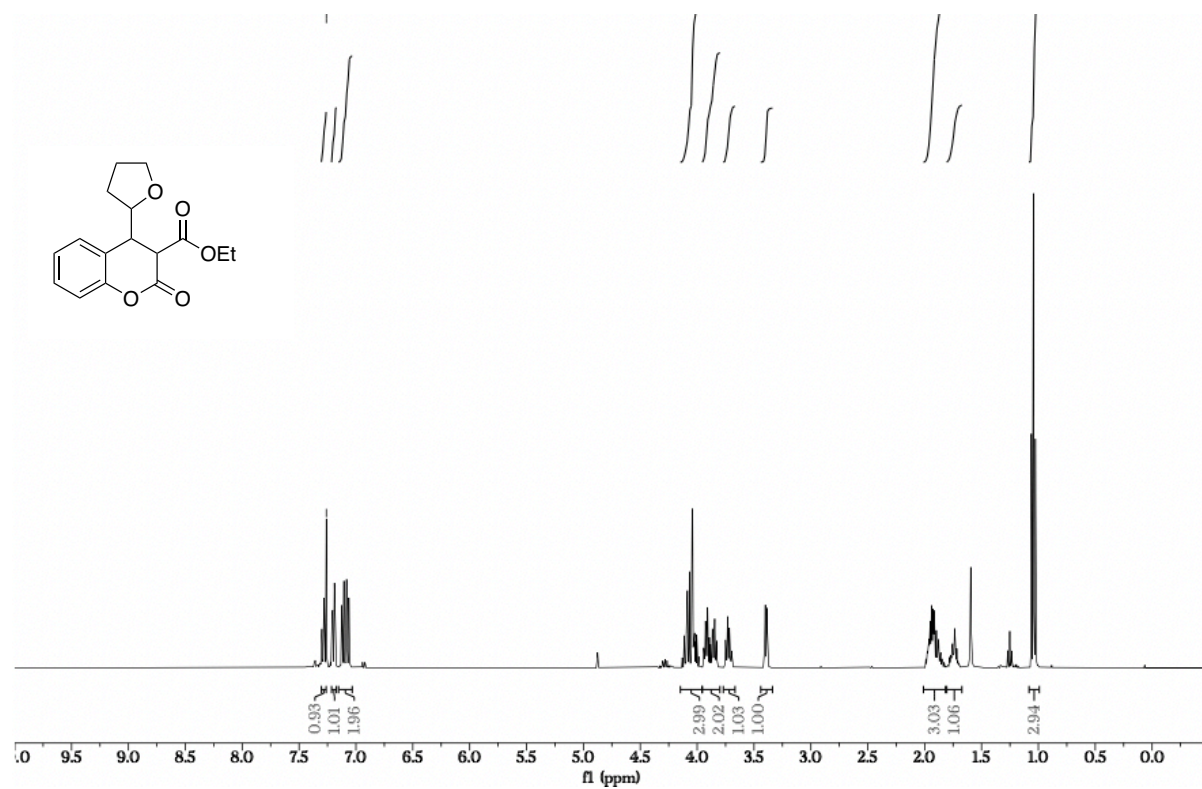
2-(2-(Phenylsulfonyl)ethyl)tetrahydrofuran (3h)



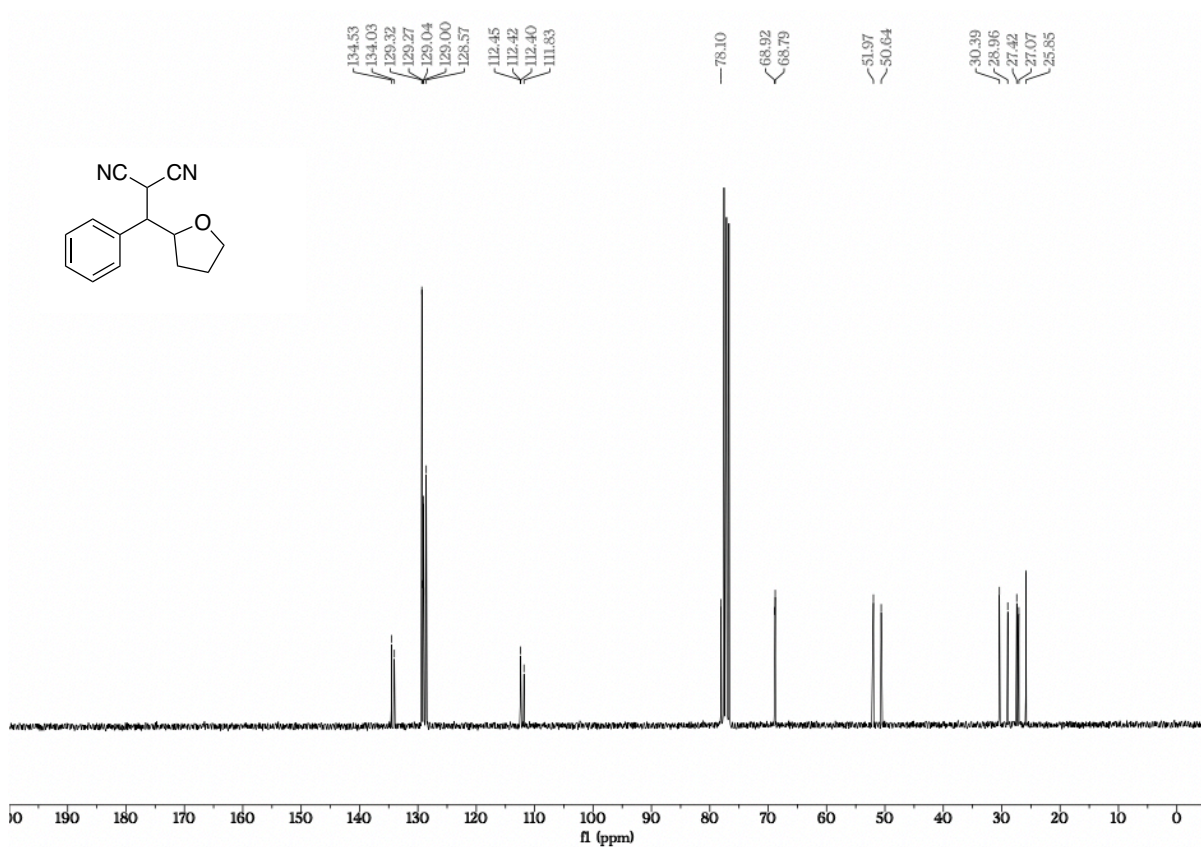
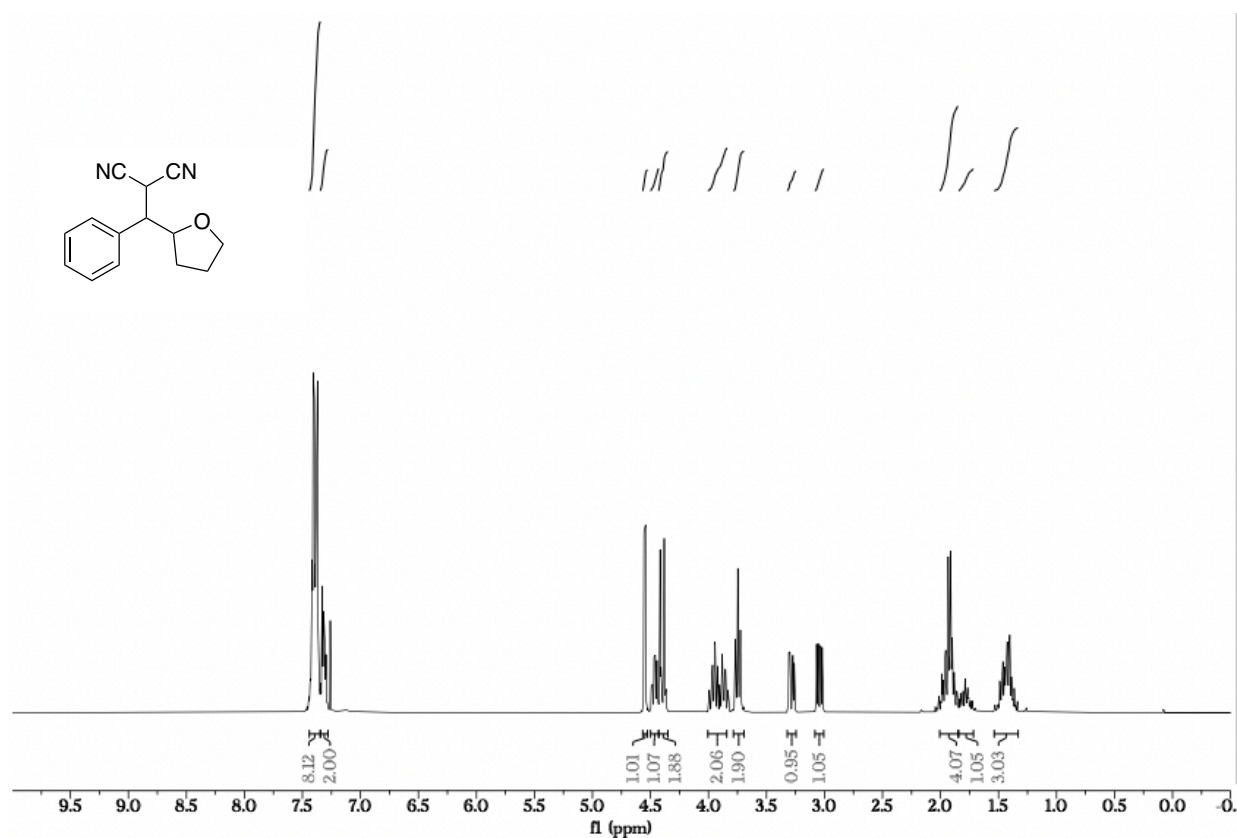
2-(Tetrahydrofuran-2-yl)chroman-4-one (3i)

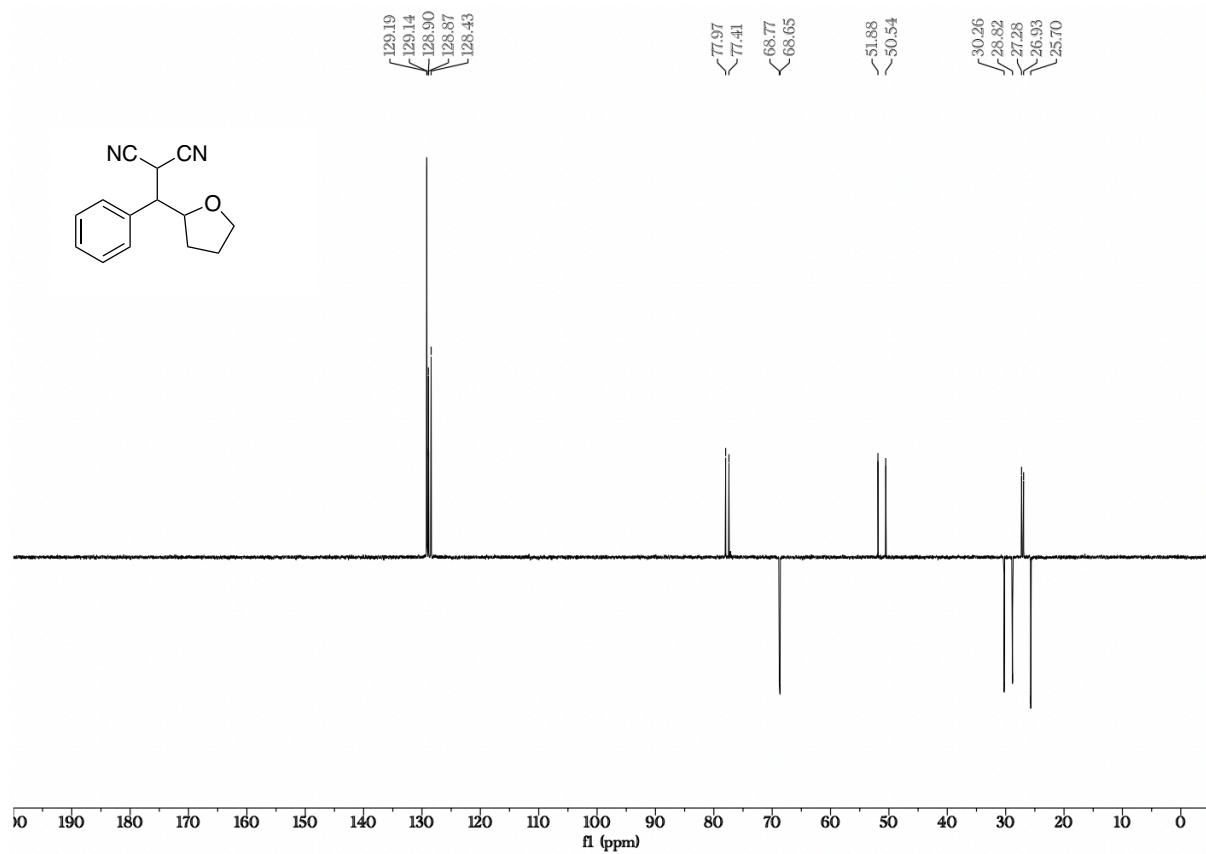


Ethyl 2-oxo-4-(tetrahydrofuran-2-yl)chromane-3-carboxylate (3j)

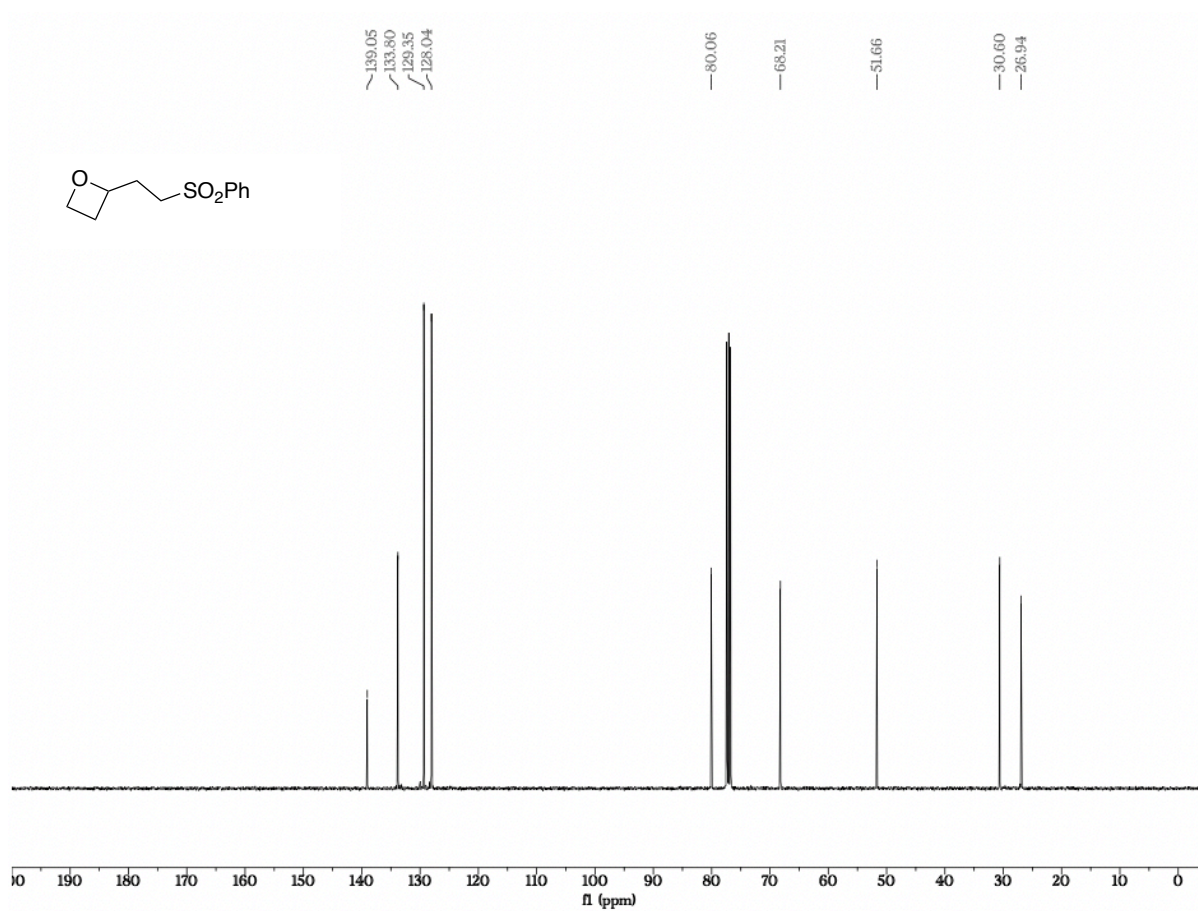
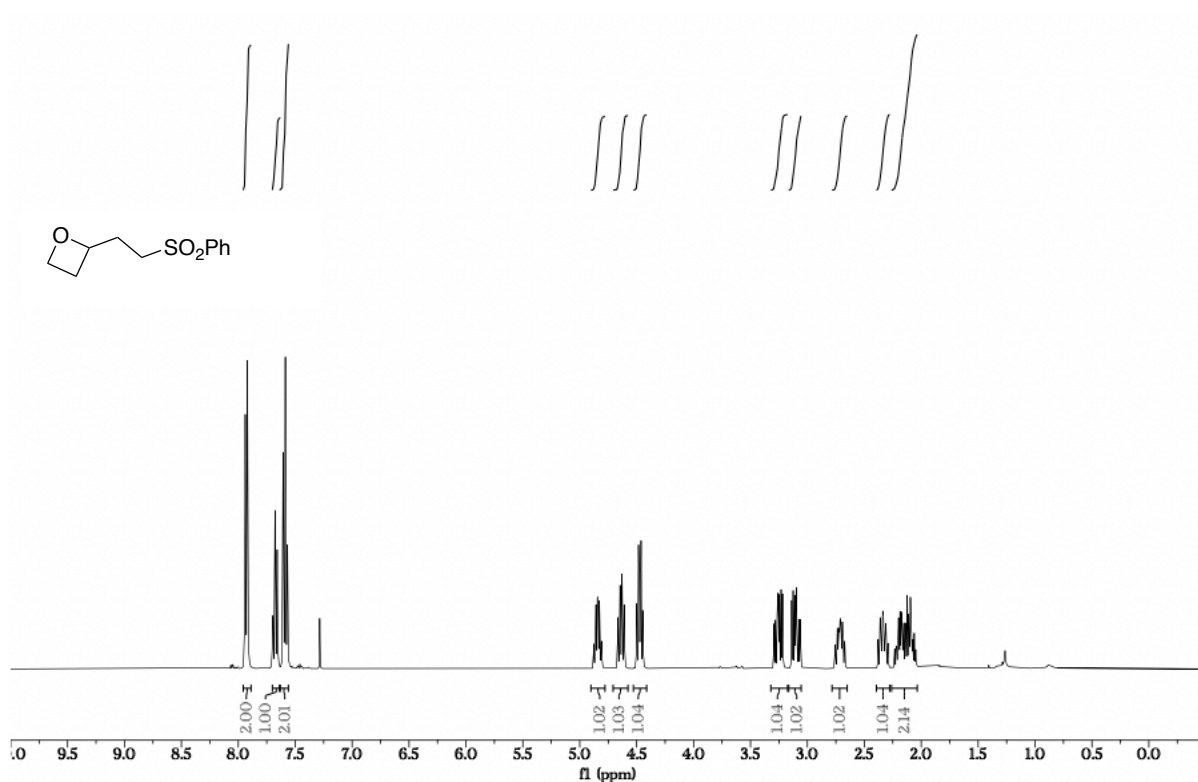


2-(Phenyl(tetrahydrofuran-2-yl)methyl)malononitrile (3k)

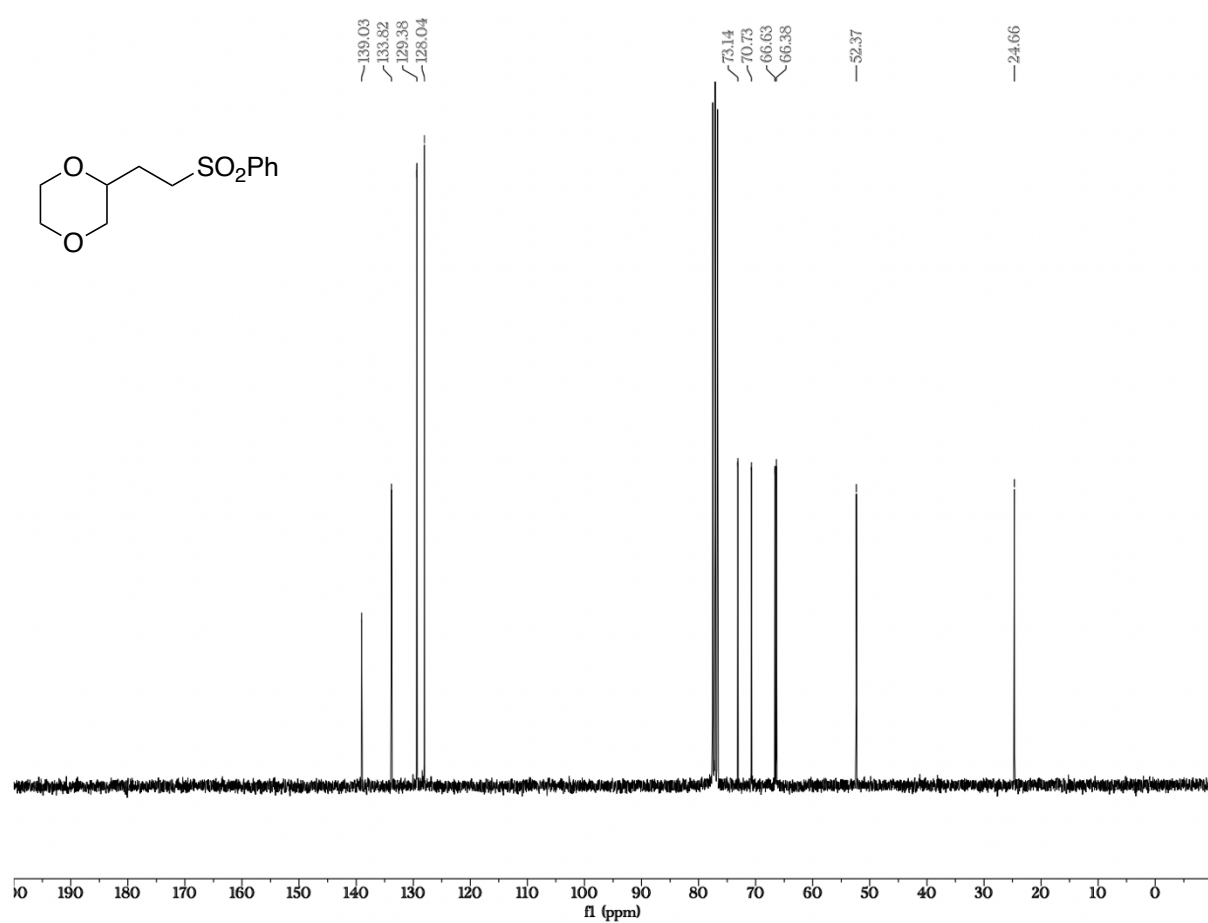
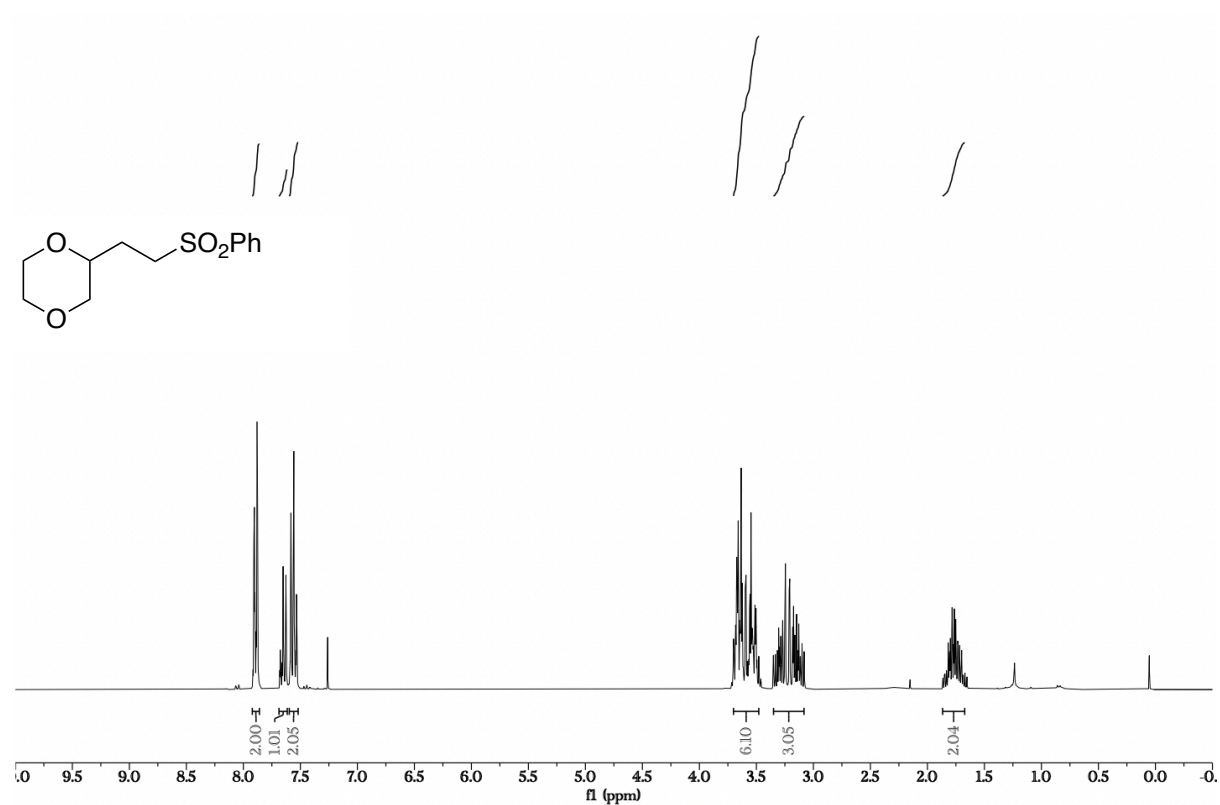




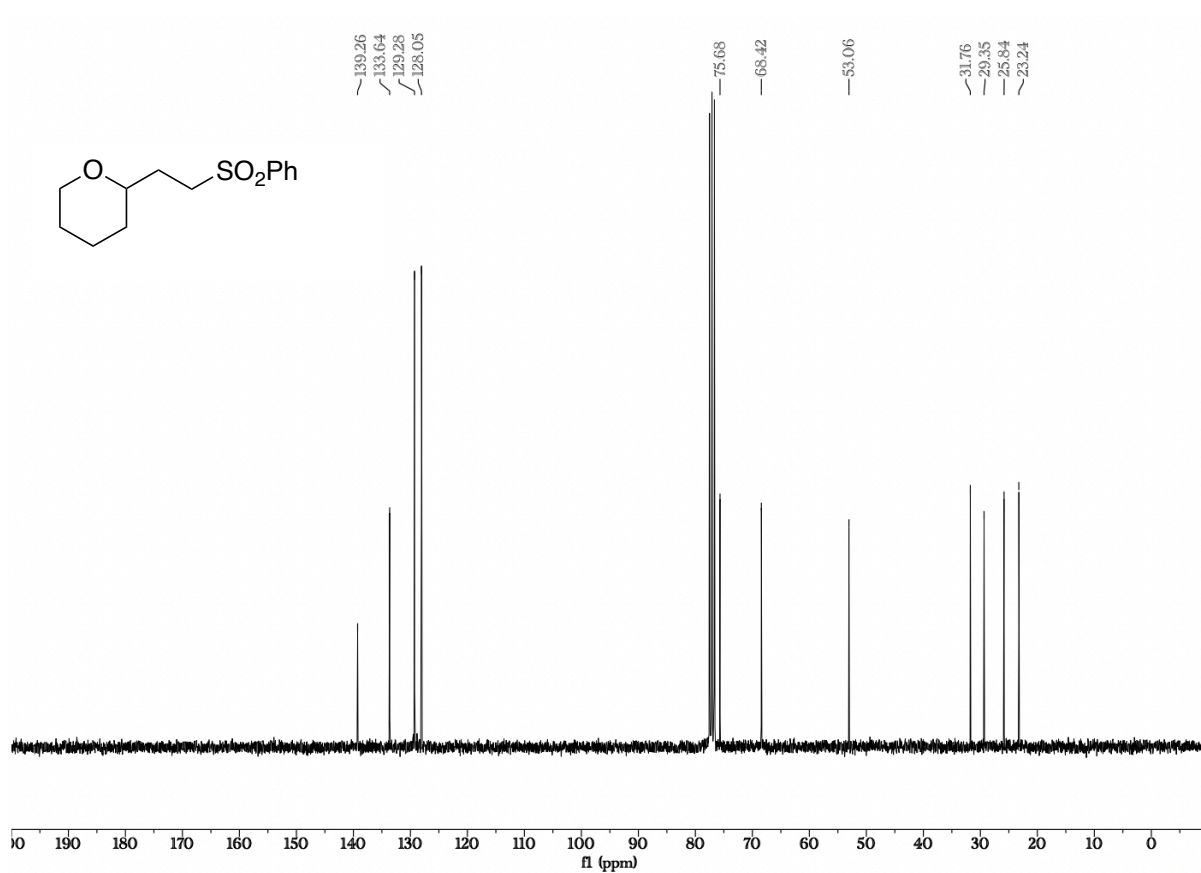
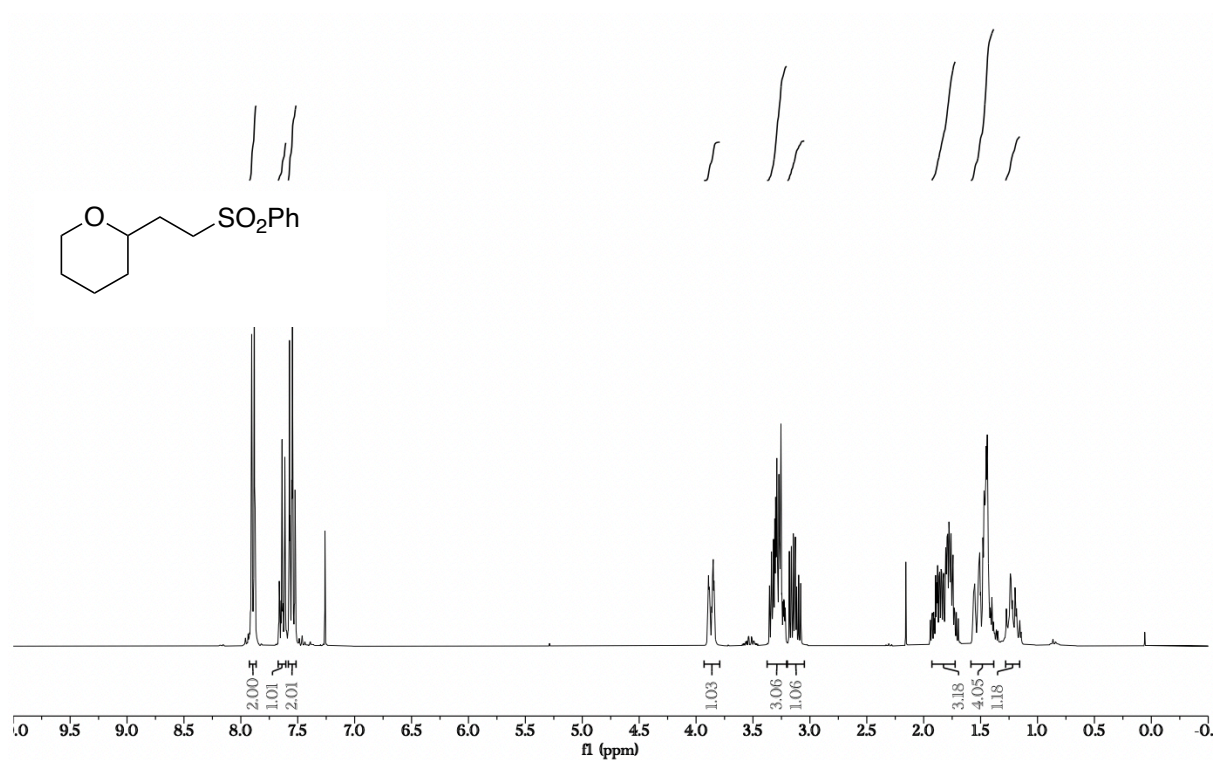
2-(2-(Phenylsulfonyl)ethyl)oxetane (3l)



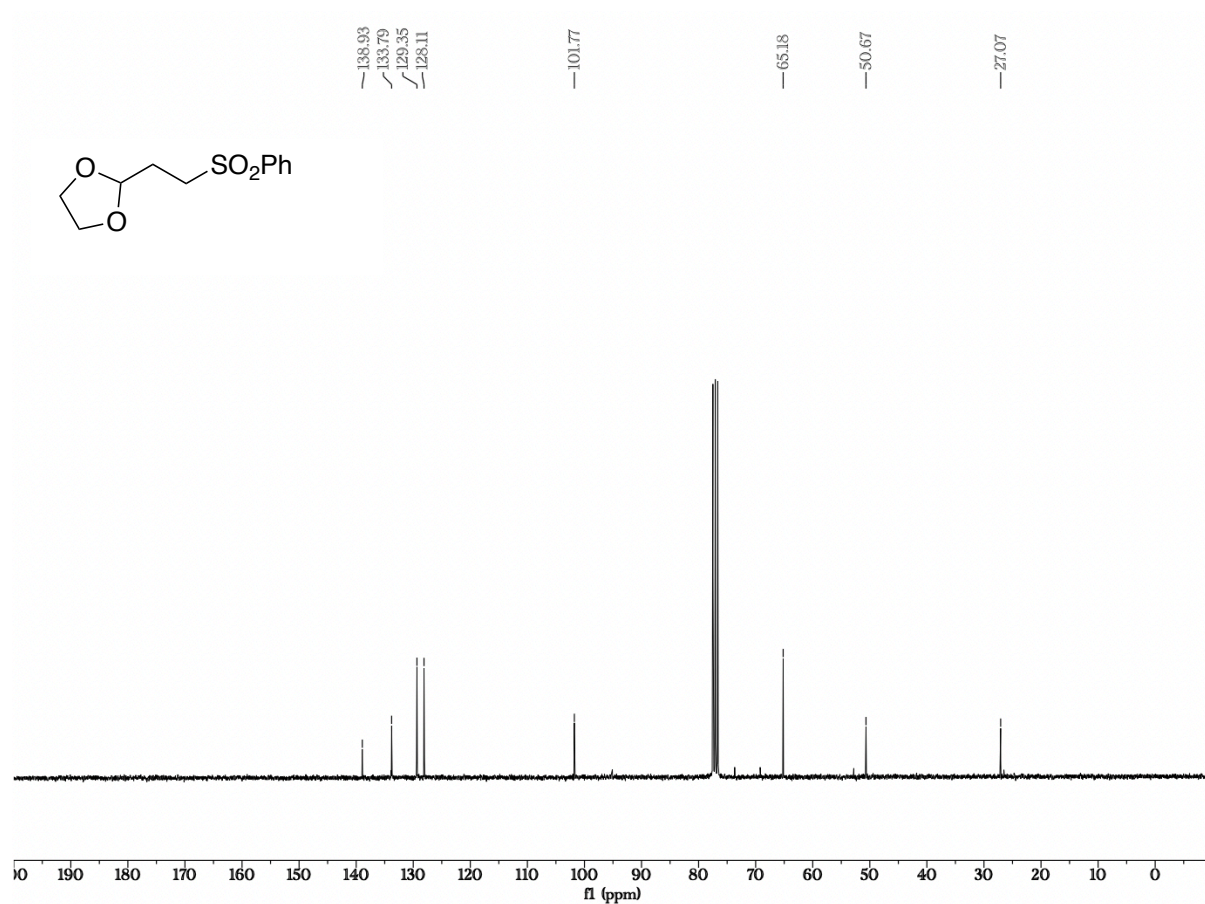
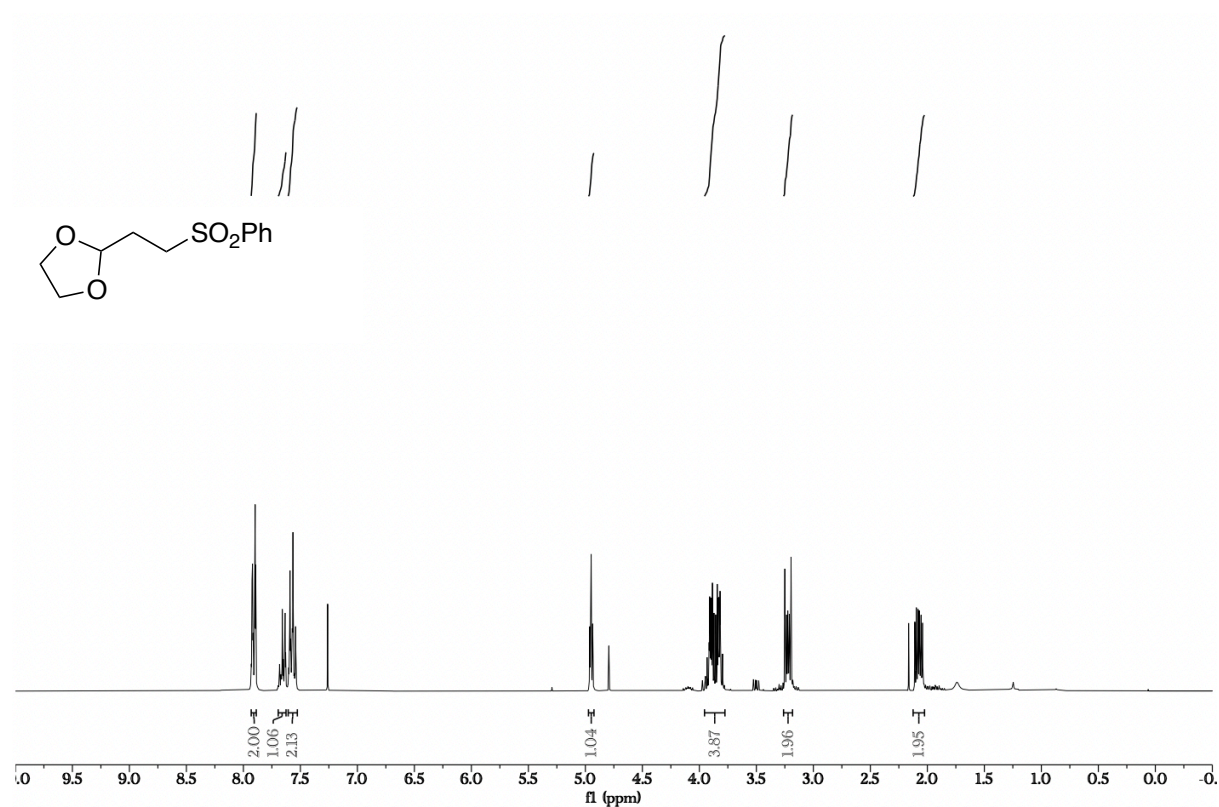
2-(2-(Phenylsulfonyl)ethyl)-1,4-dioxane (3m)



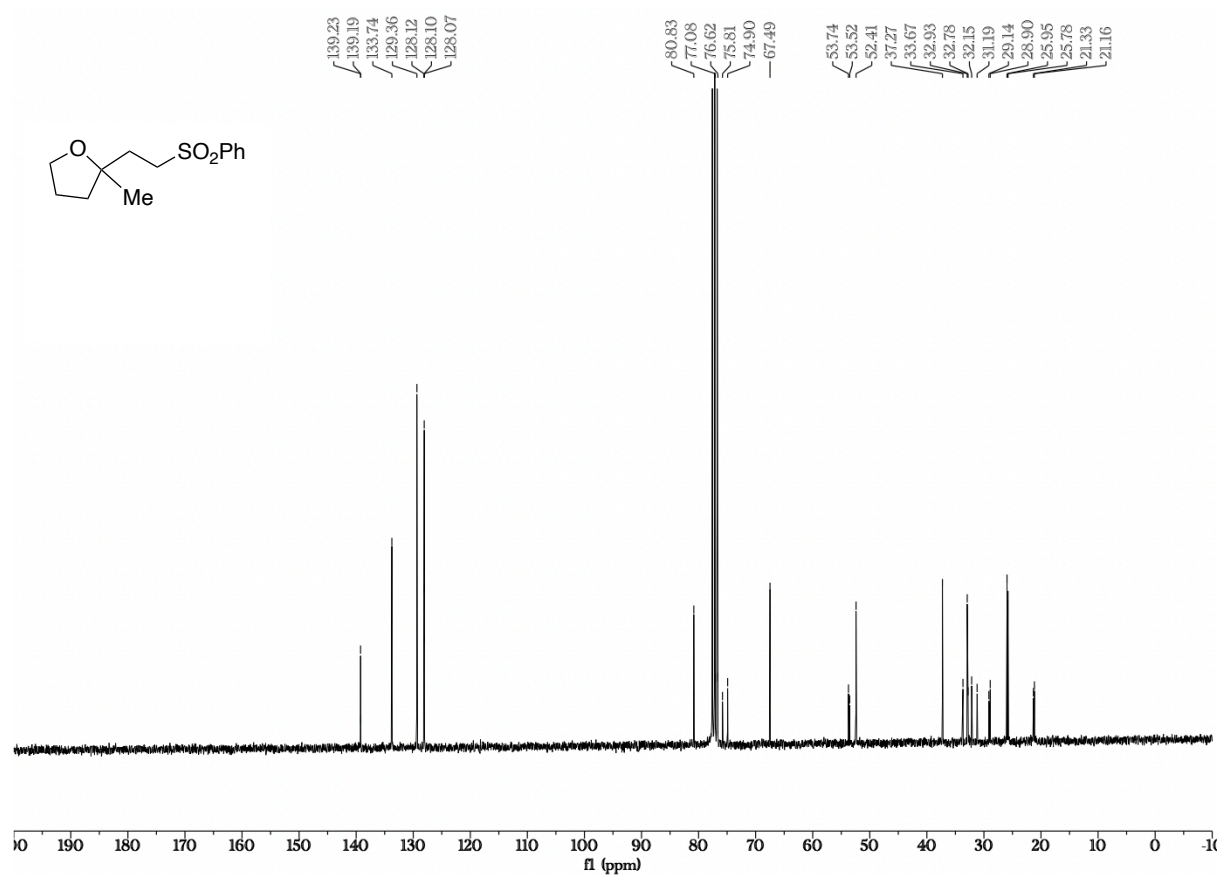
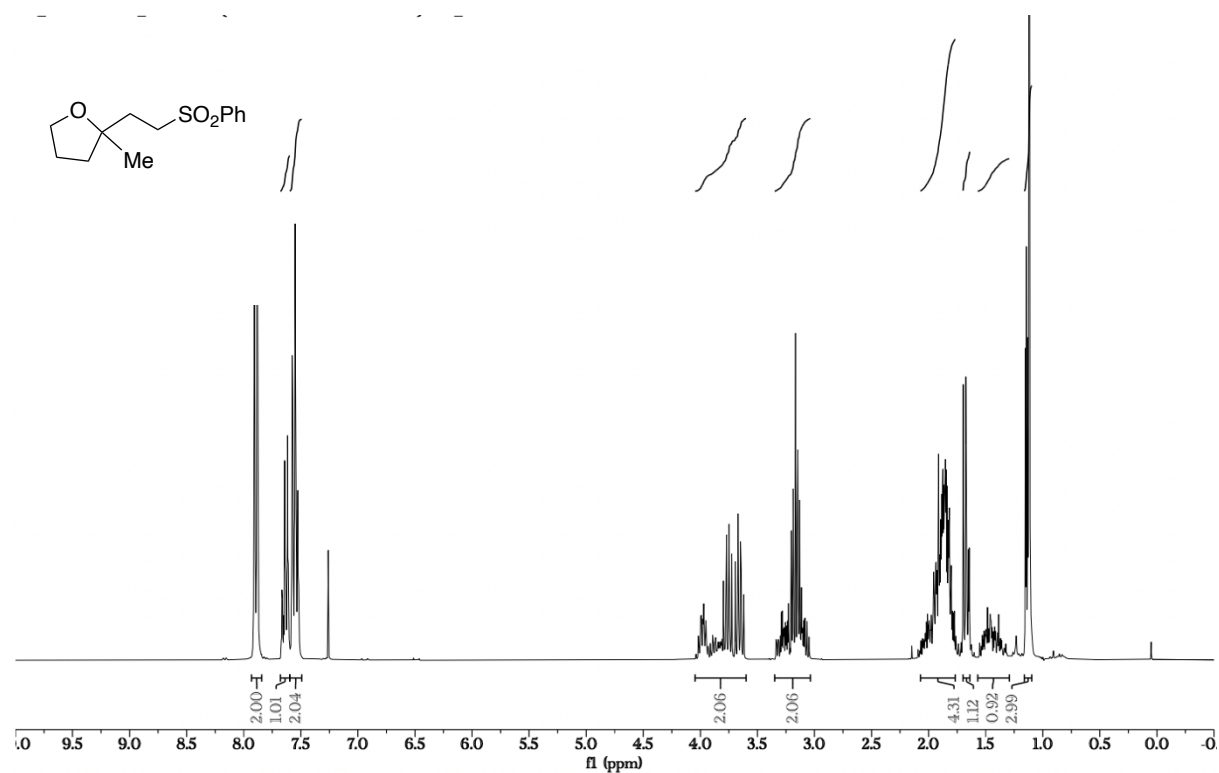
2-(2-(Phenylsulfonyl)ethyl)tetrahydro-2H-pyran (3n)

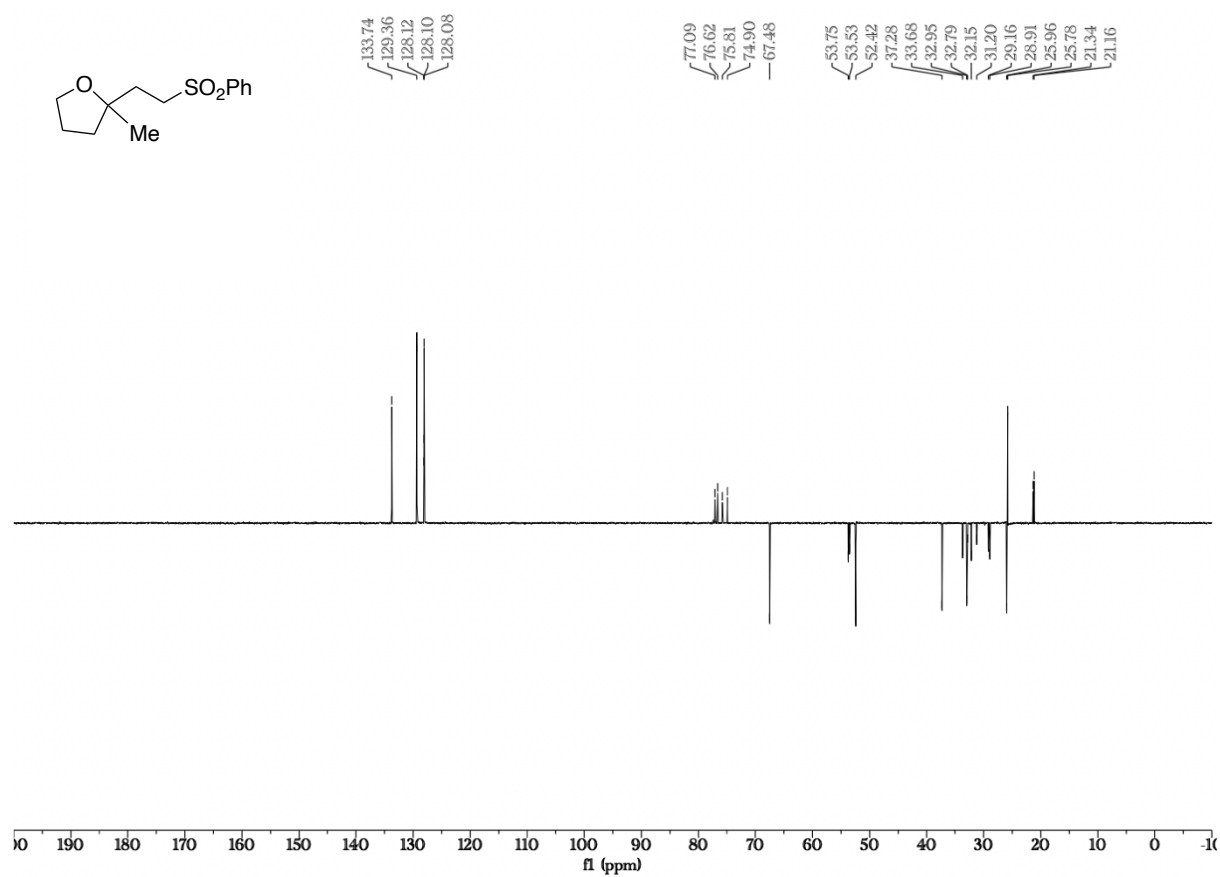


2-(2-(Phenylsulfonyl)ethyl)-1,3-dioxolane (3o)

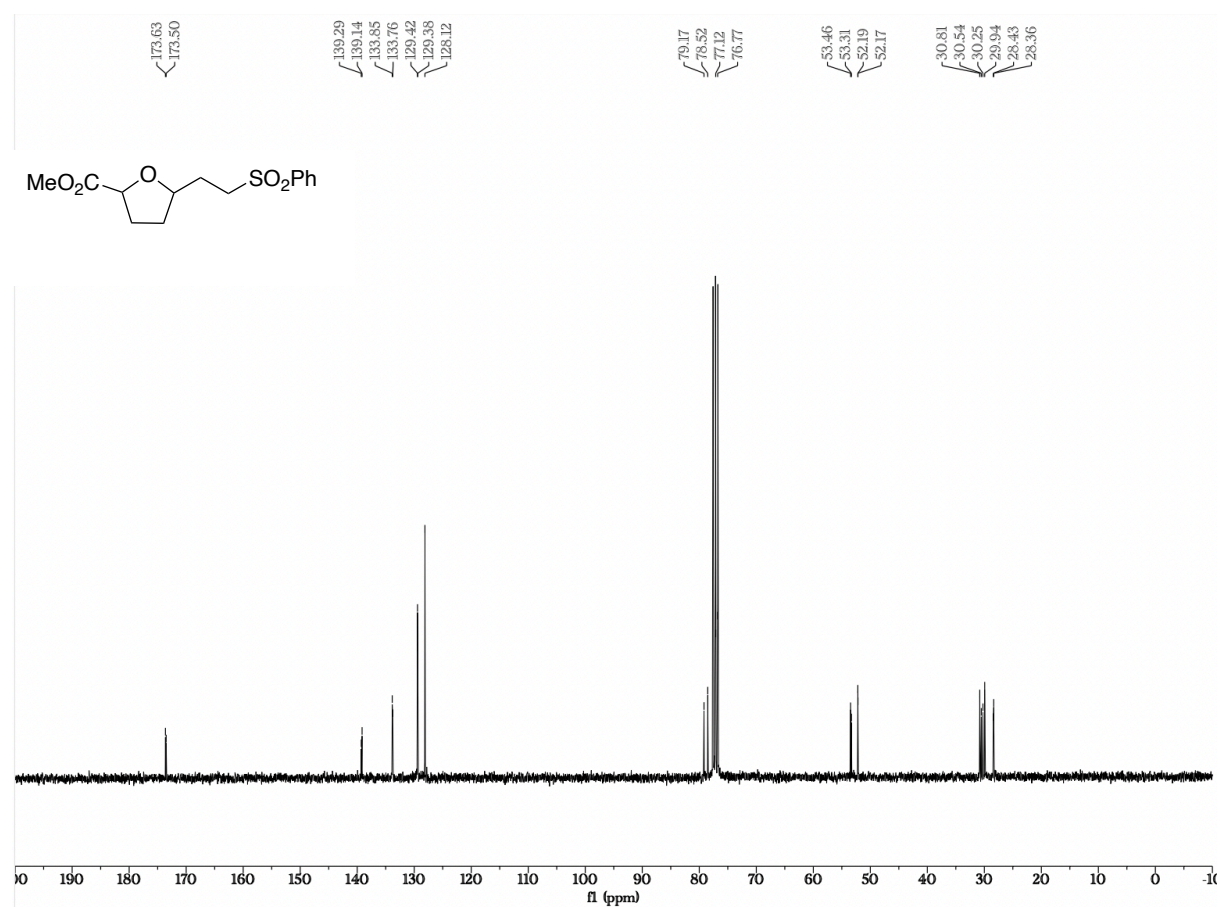
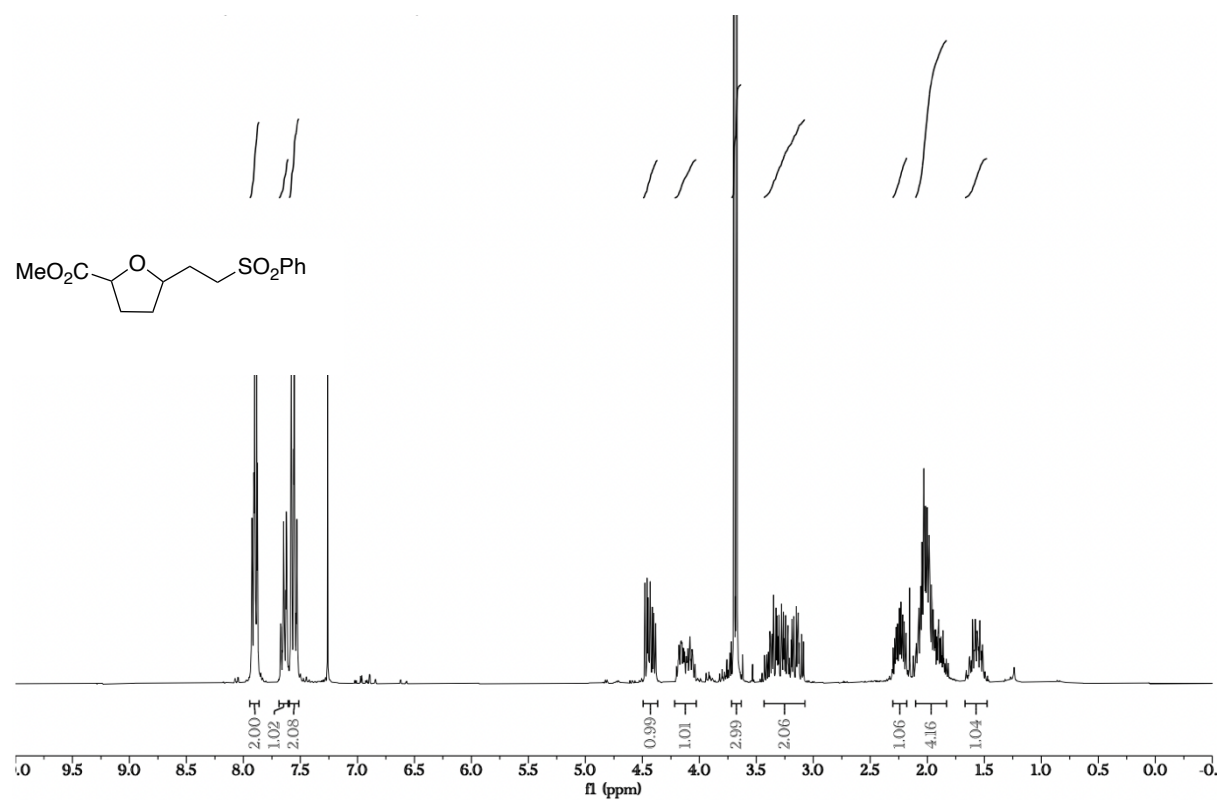


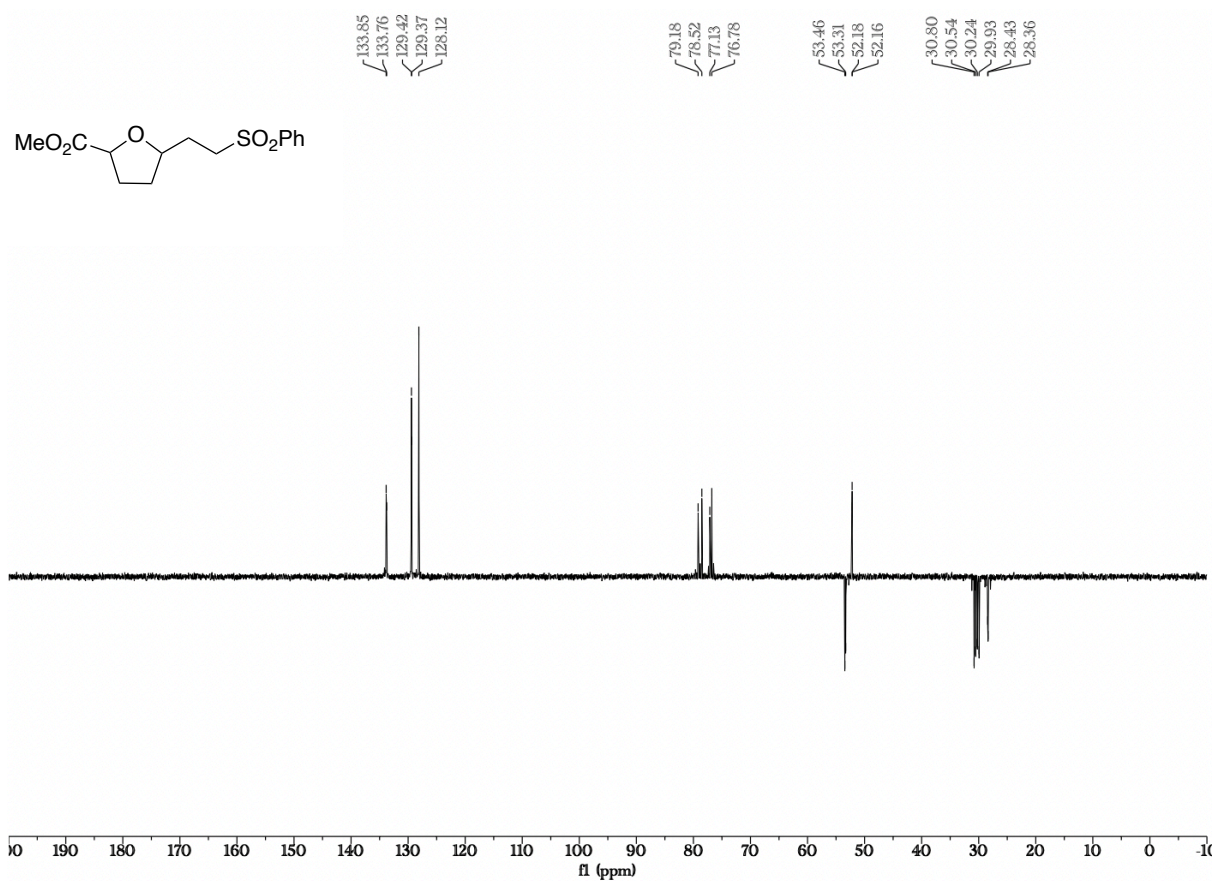
2-Methyl-2-(2-(phenylsulfonyl)ethyl)tetrahydrofuran (3p)



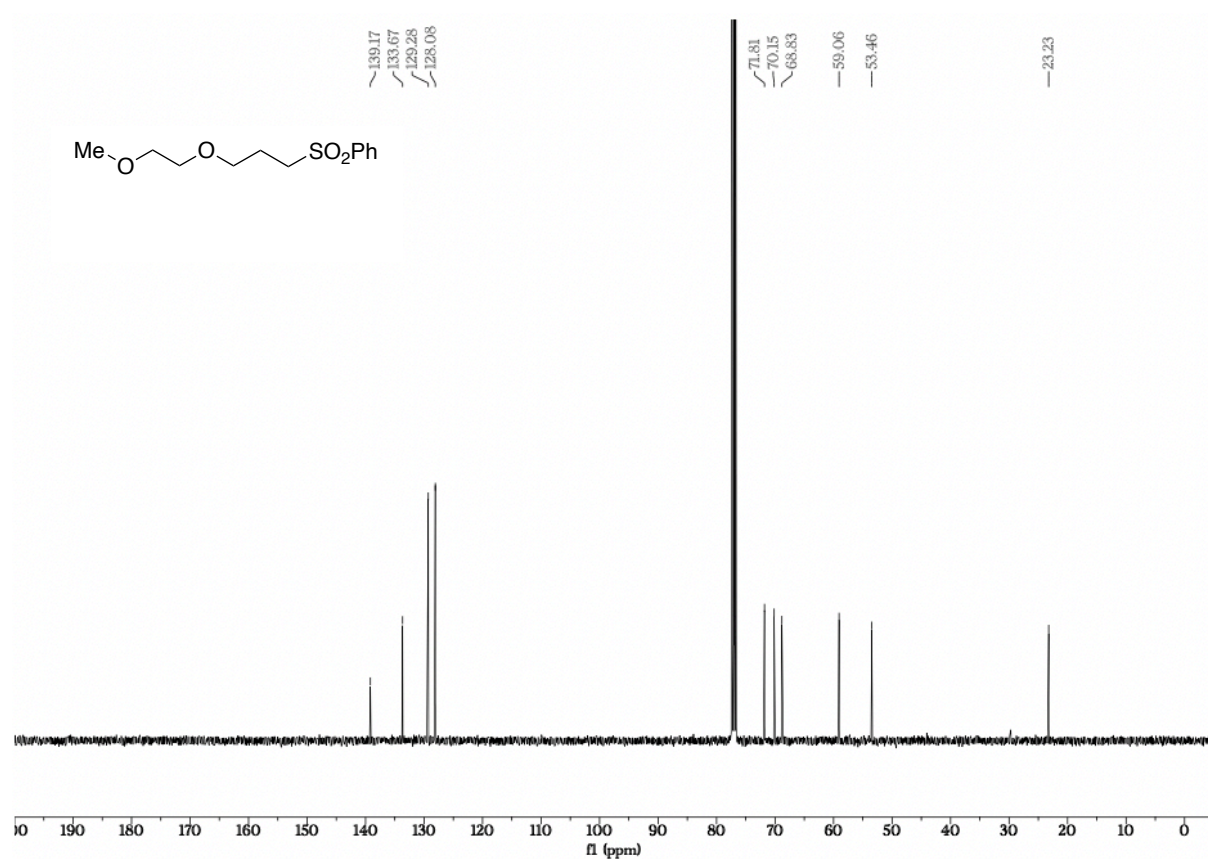
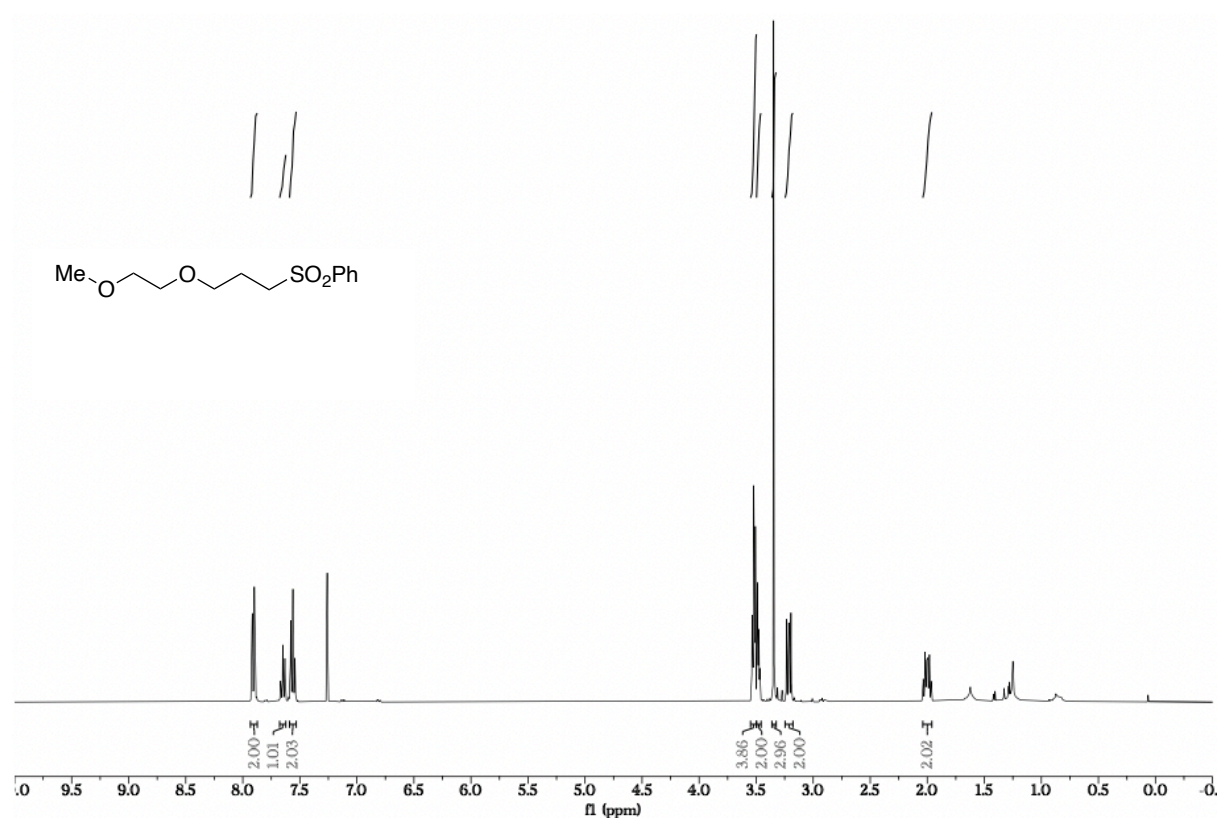


Methyl 5-(2-(phenylsulfonyl)ethyl)tetrahydrofuran-2-carboxylate (3q)

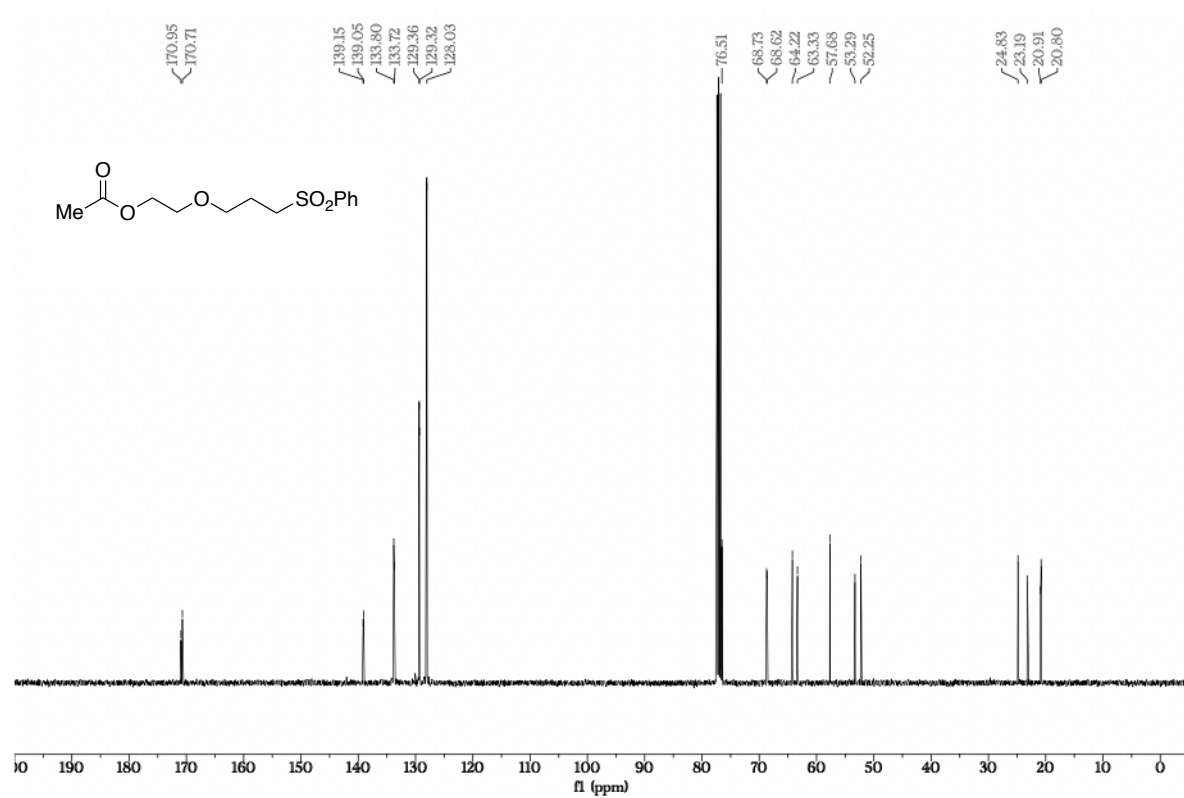
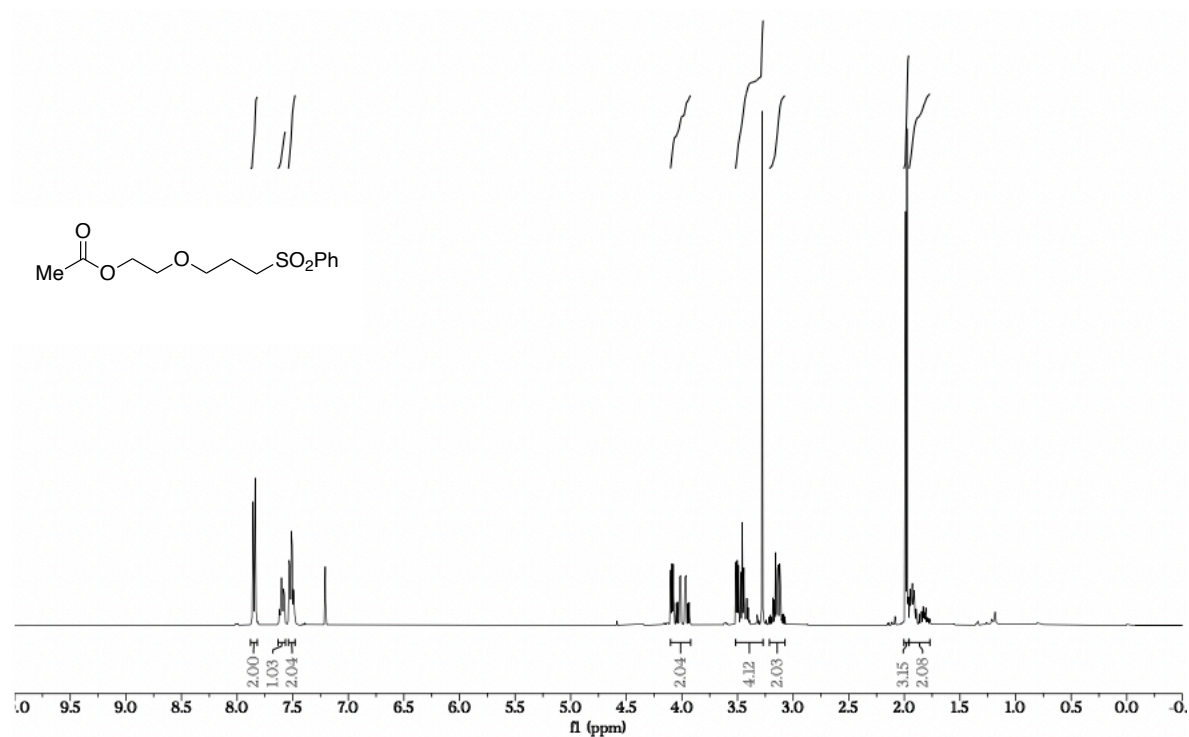


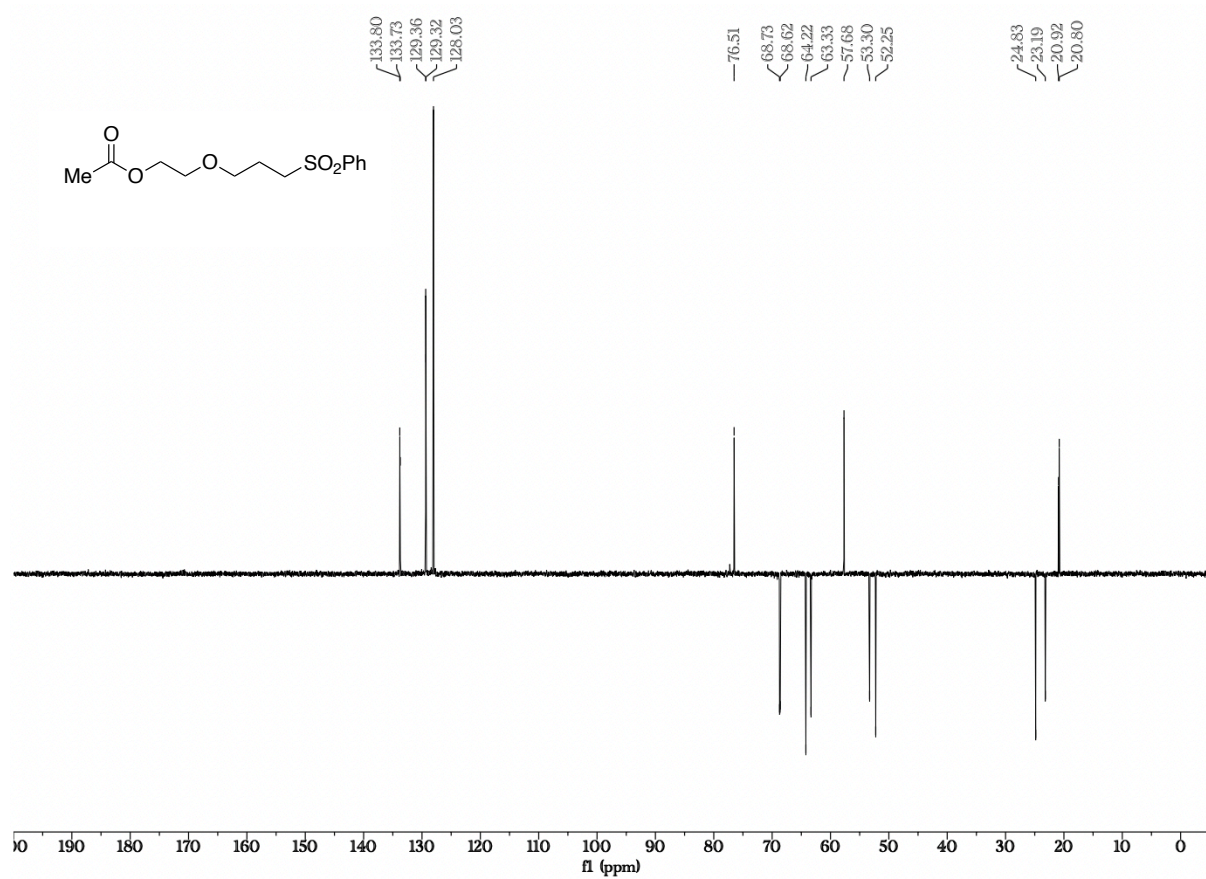


((3-(2-Methoxyethoxy)propyl)sulfonyl)benzene (3r)

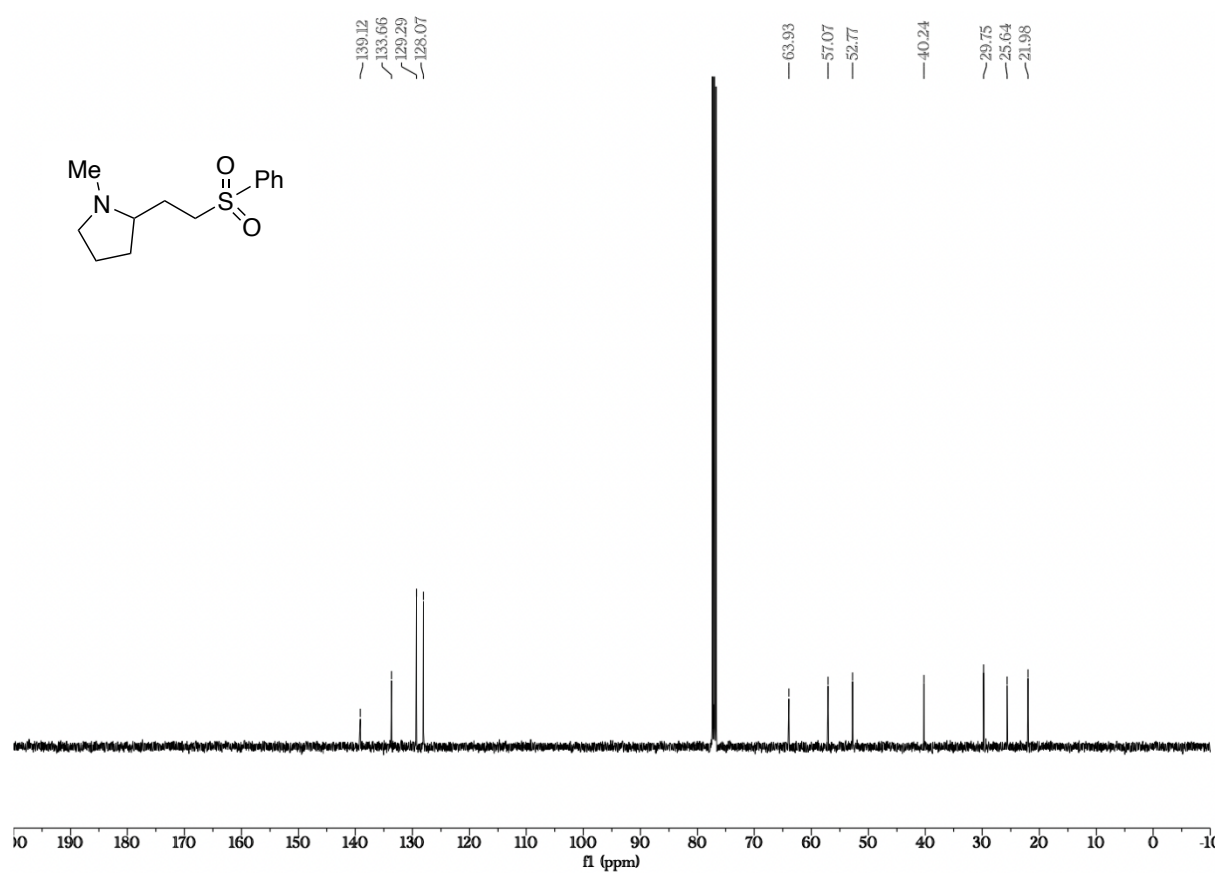
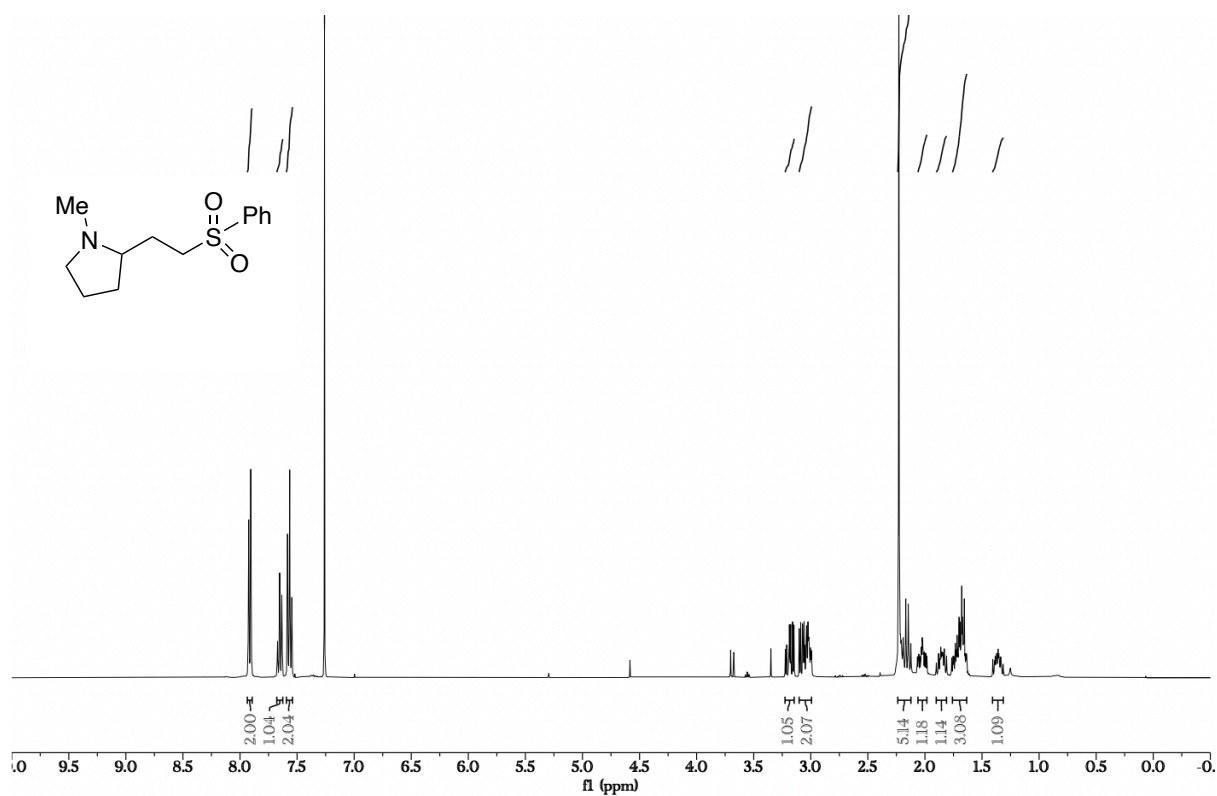


2-(3-(Phenylsulfonyl)propoxy)ethyl acetate (3s)

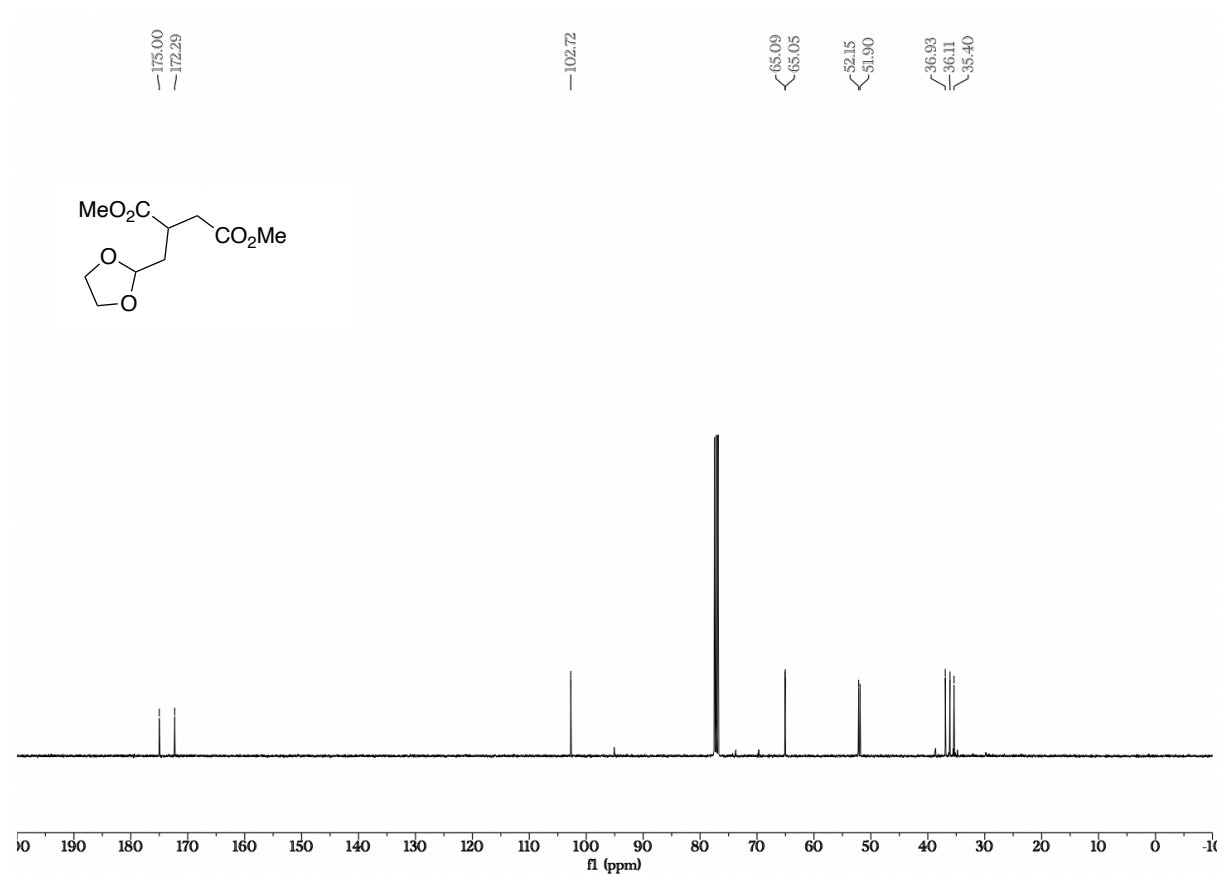
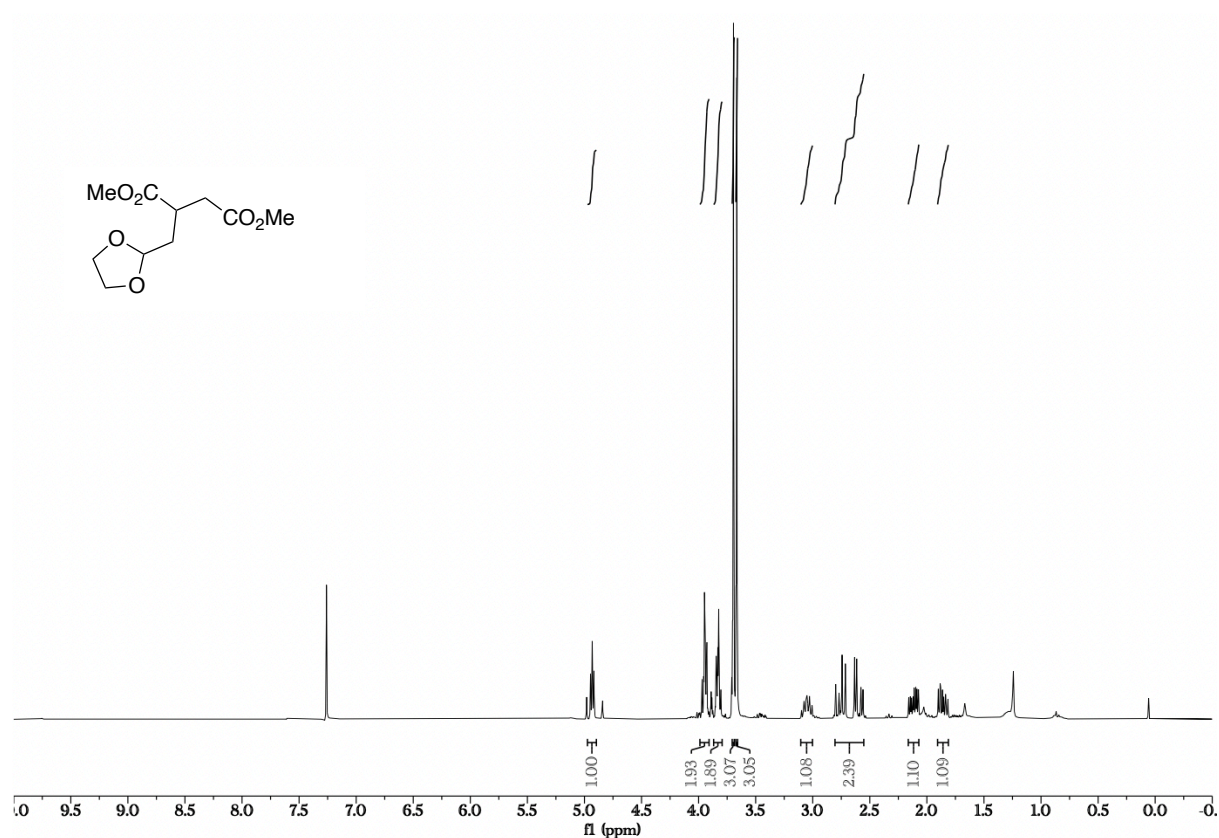




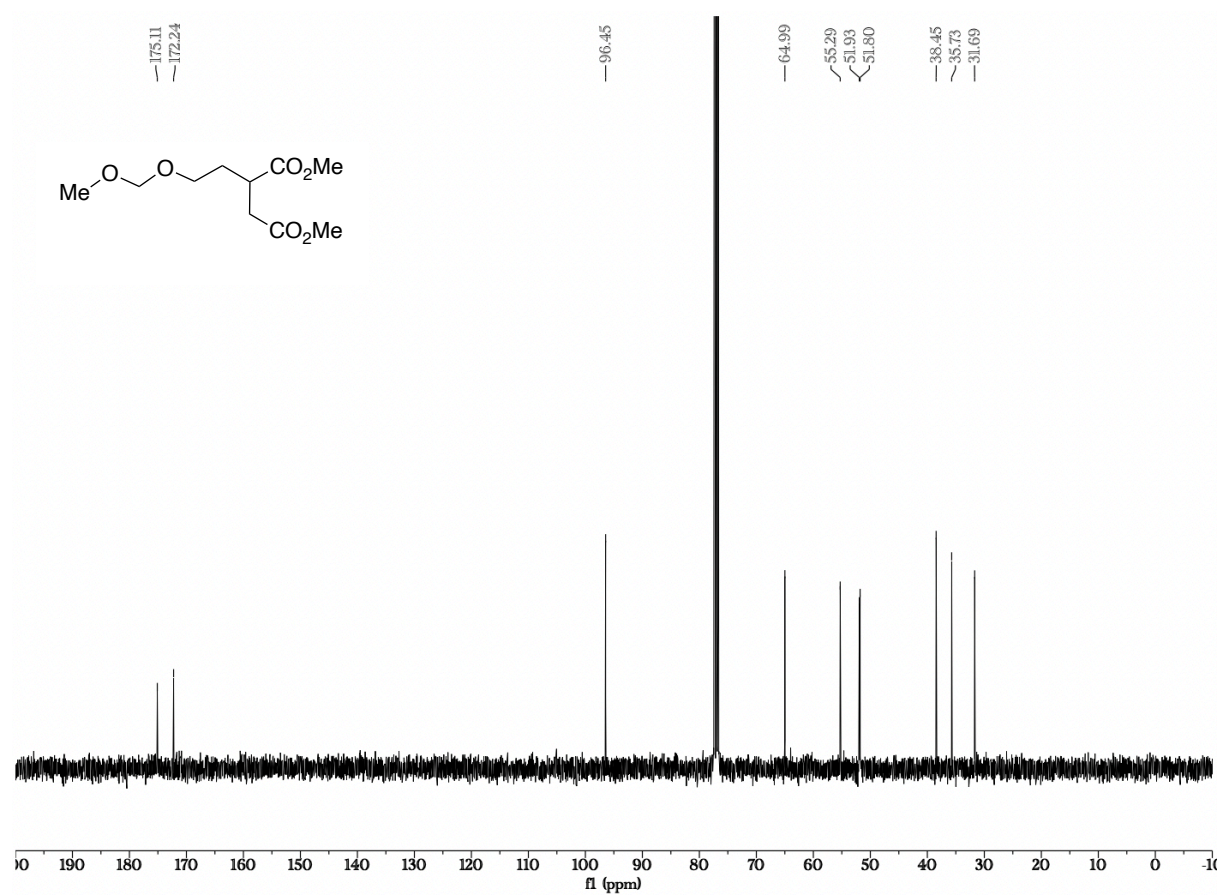
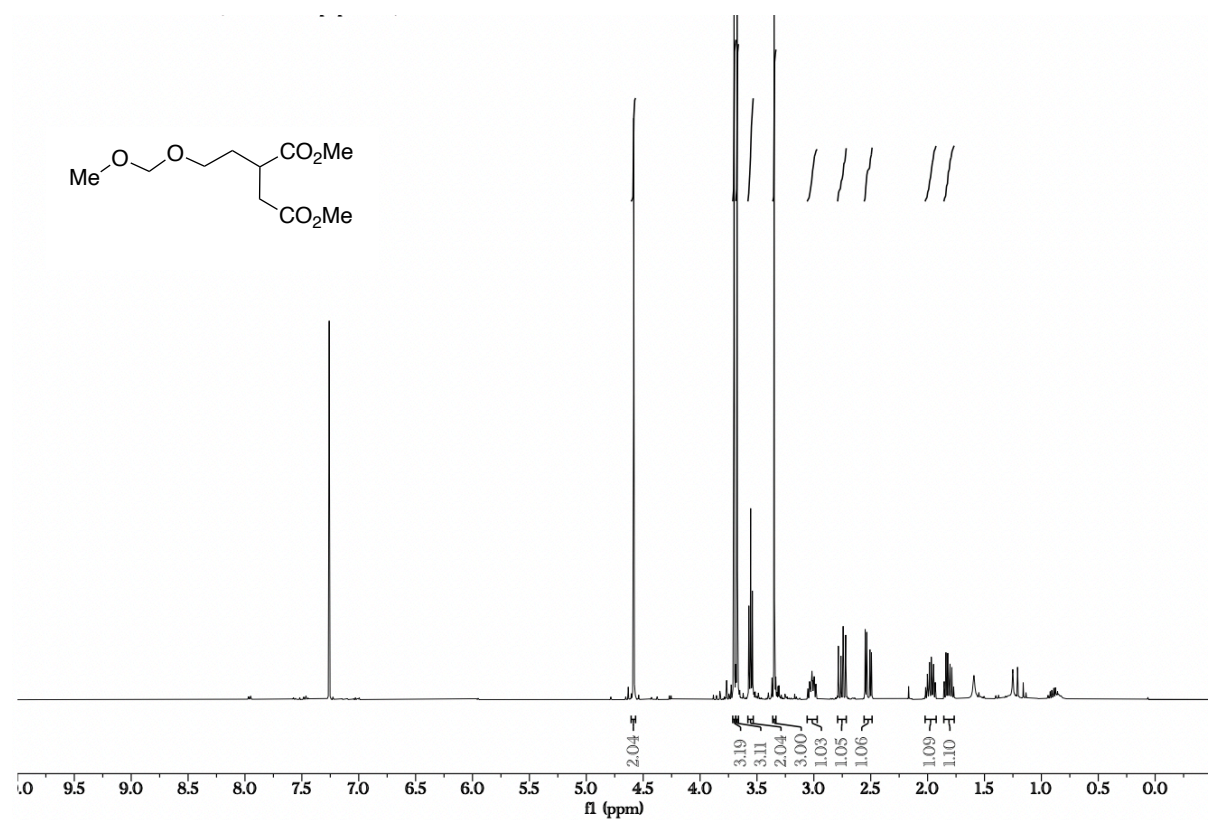
1-Methyl-2-(2-(phenylsulfonyl)ethyl)pyrrolidine (3t)



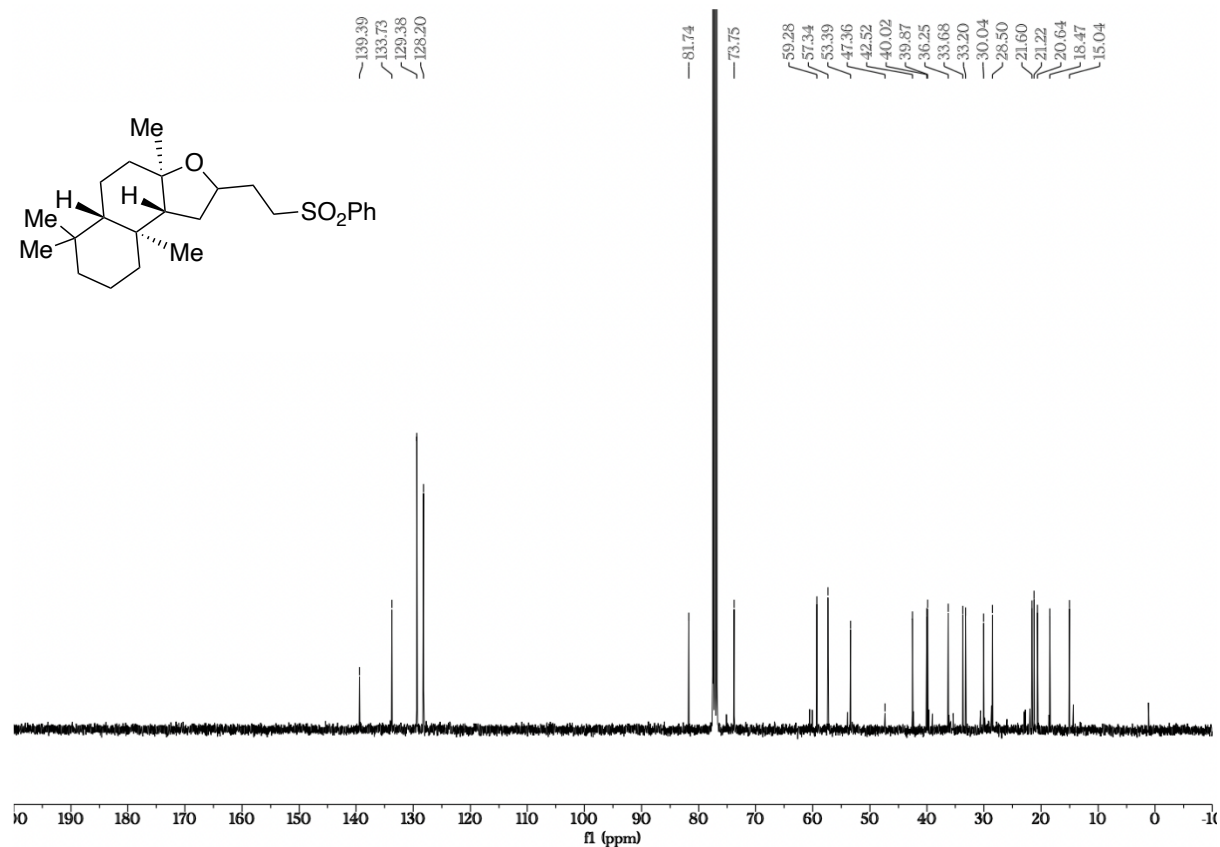
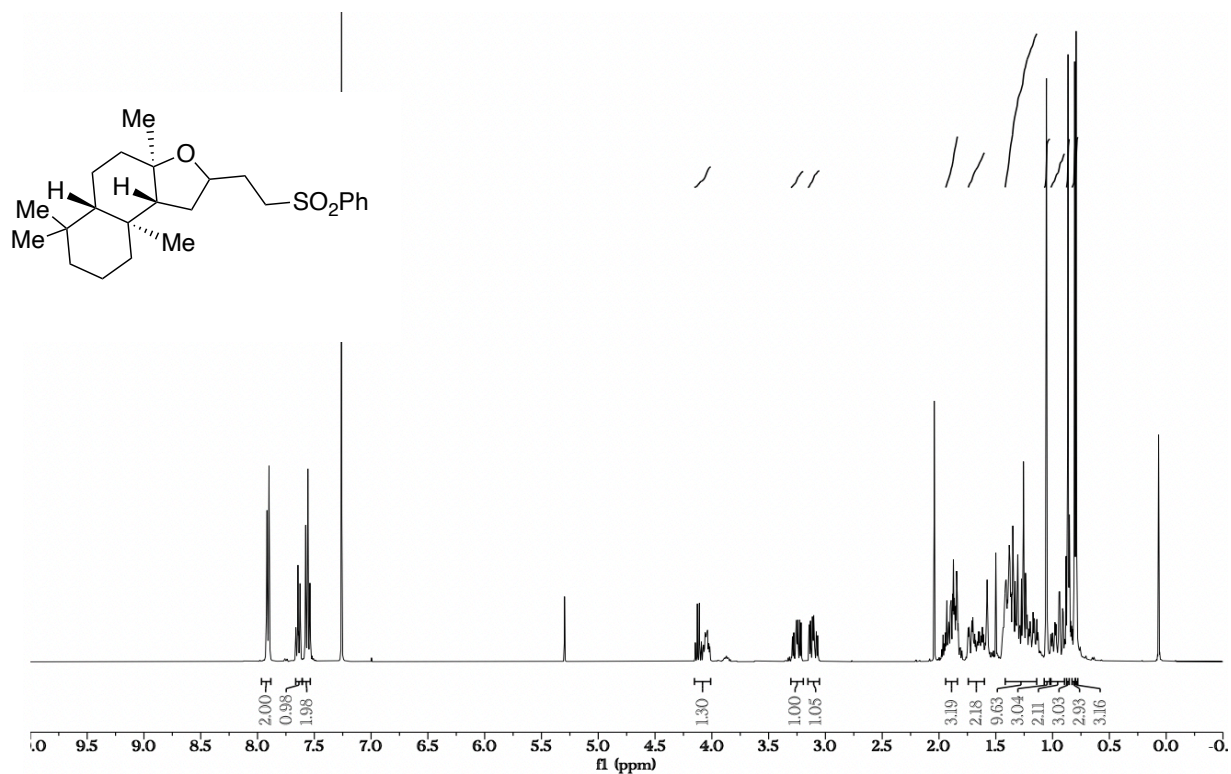
Dimethyl 2-((1,3-dioxolan-2-yl)methyl)succinate (3u)



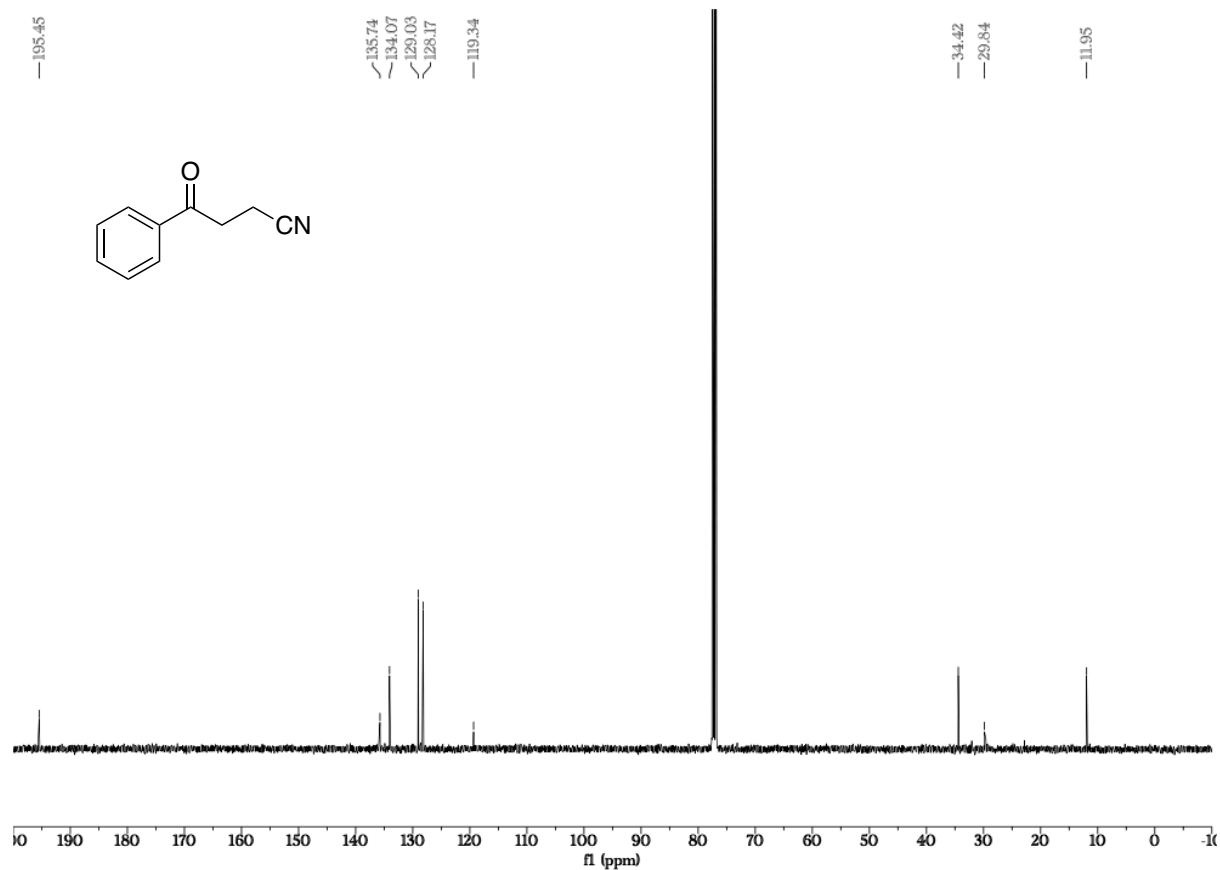
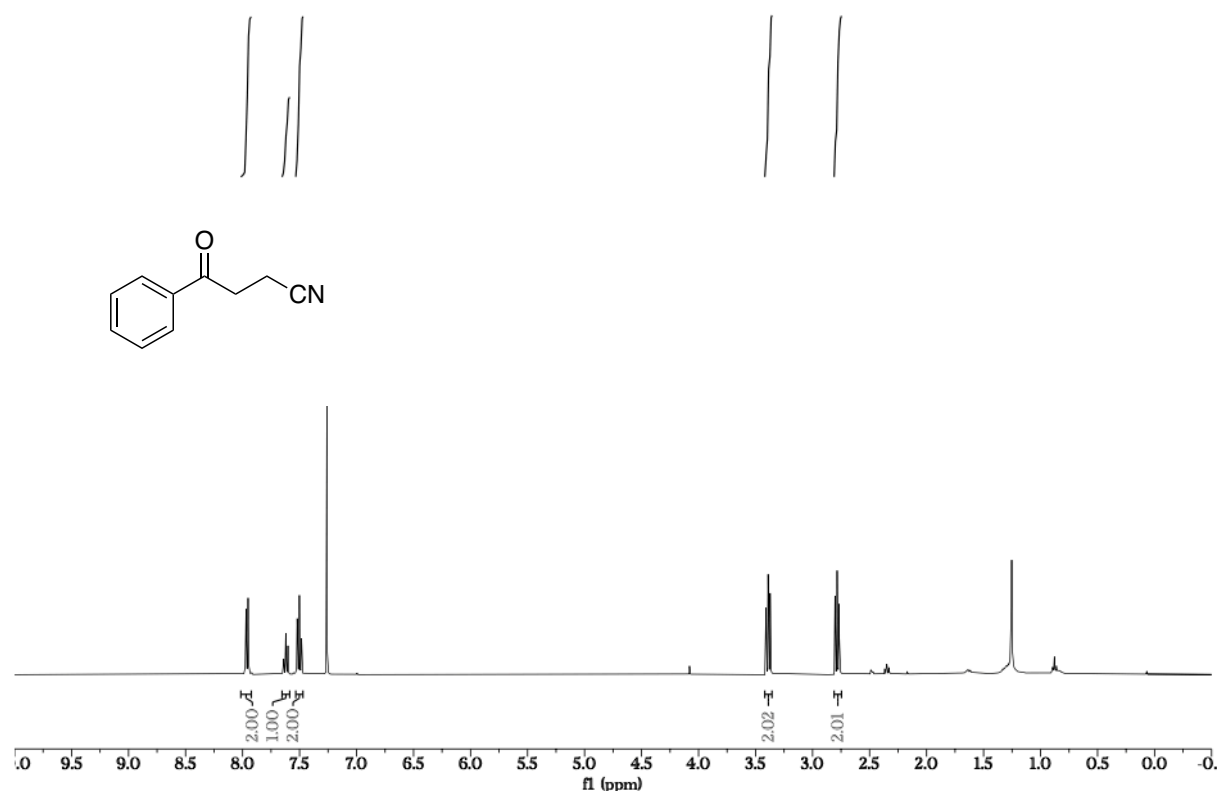
Dimethyl 2-(2-(methoxymethoxy)ethyl)succinate (3v)



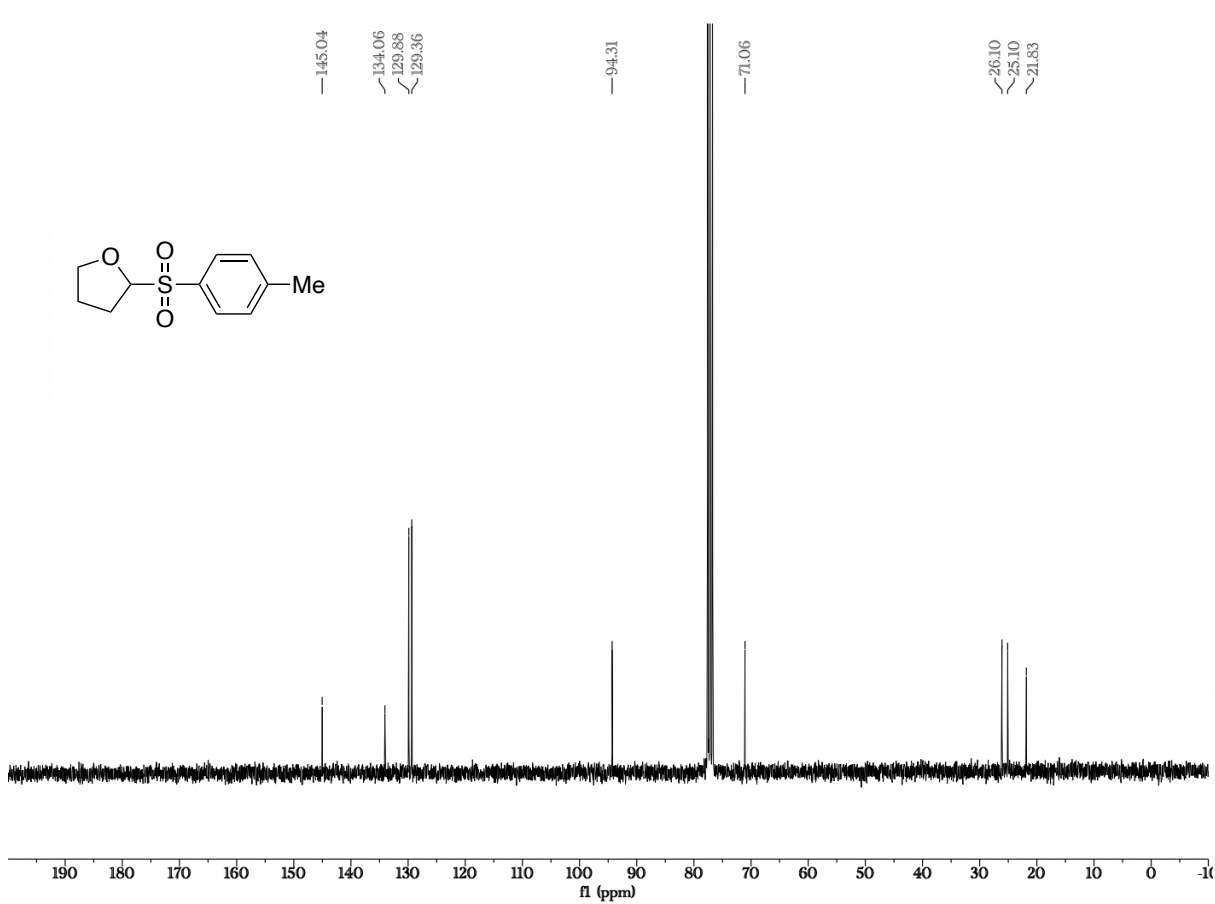
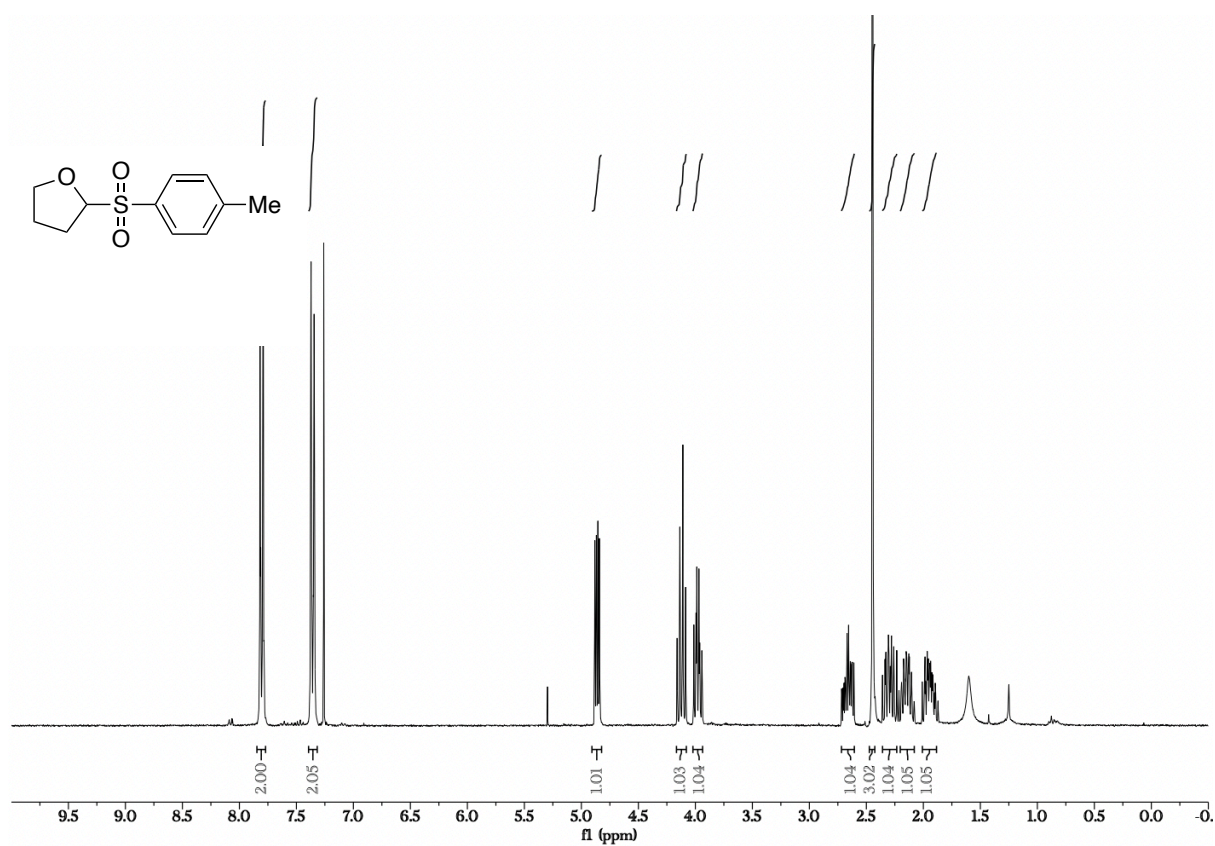
(3a*R*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-tetramethyl-2-(2-(phenylsulfonyl)ethyl)dodecahydronaphtho[2,1-*b*]furan (3w)



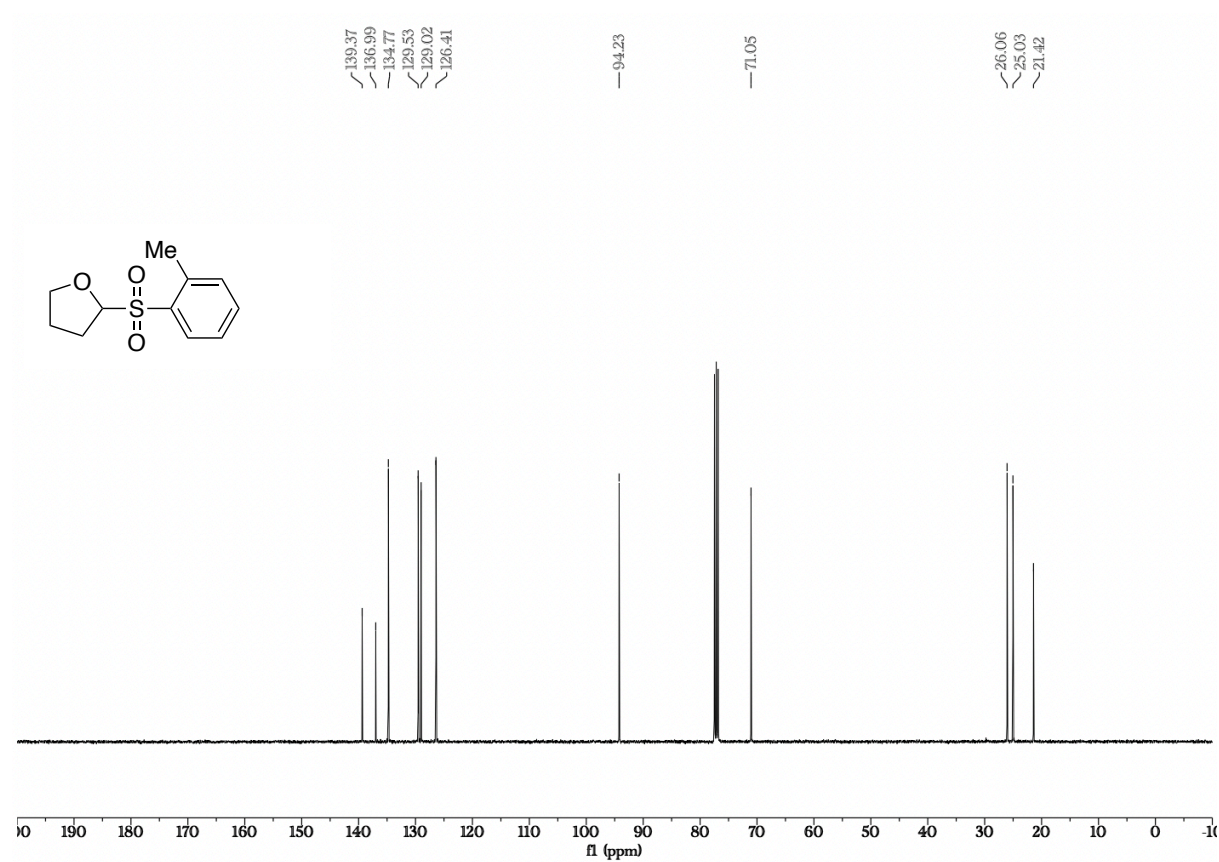
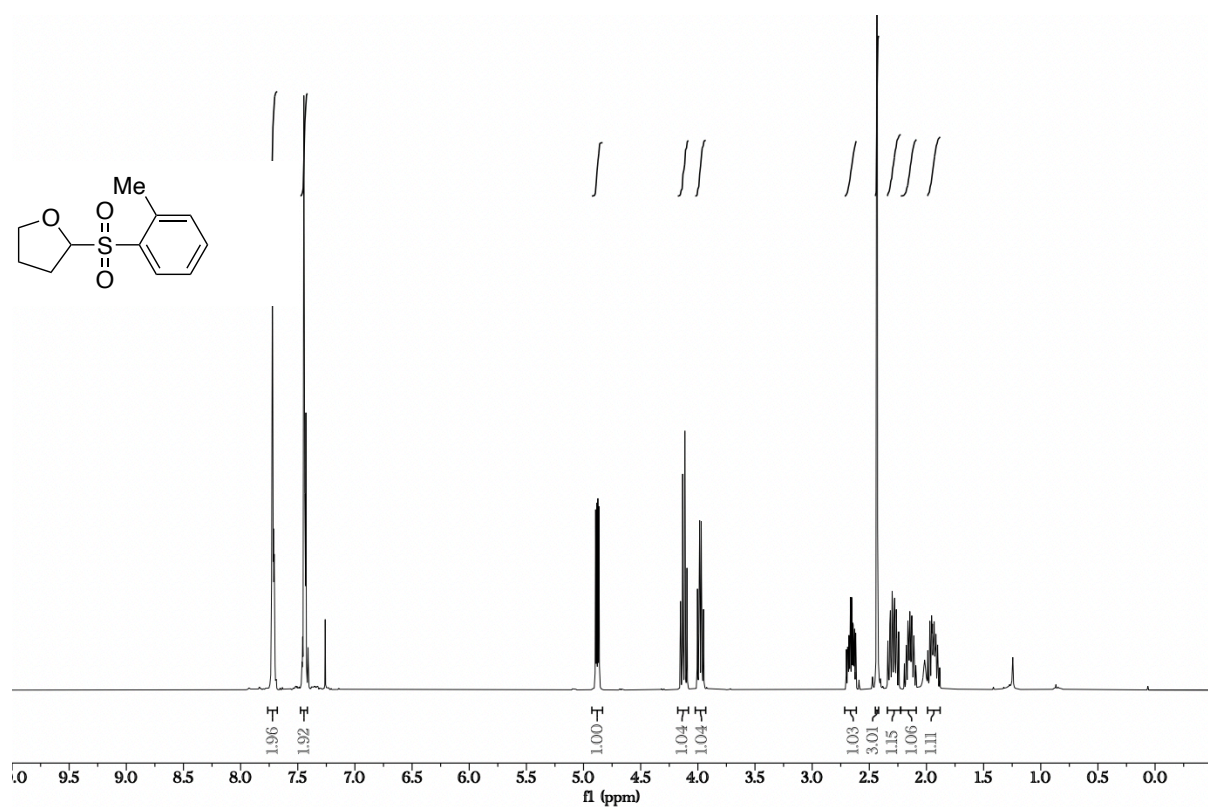
4-Oxo-4-phenylbutanenitrile (4)



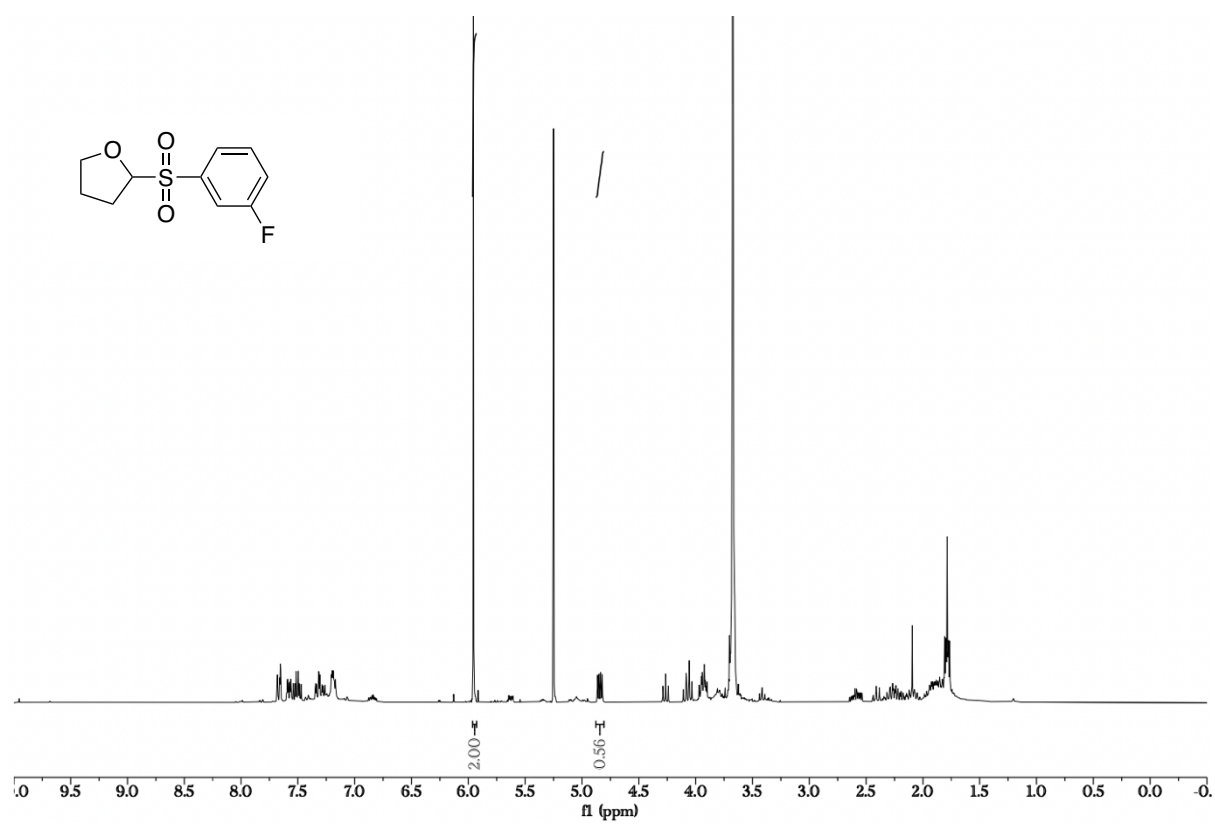
2-tosyltetrahydrofuran (6a)



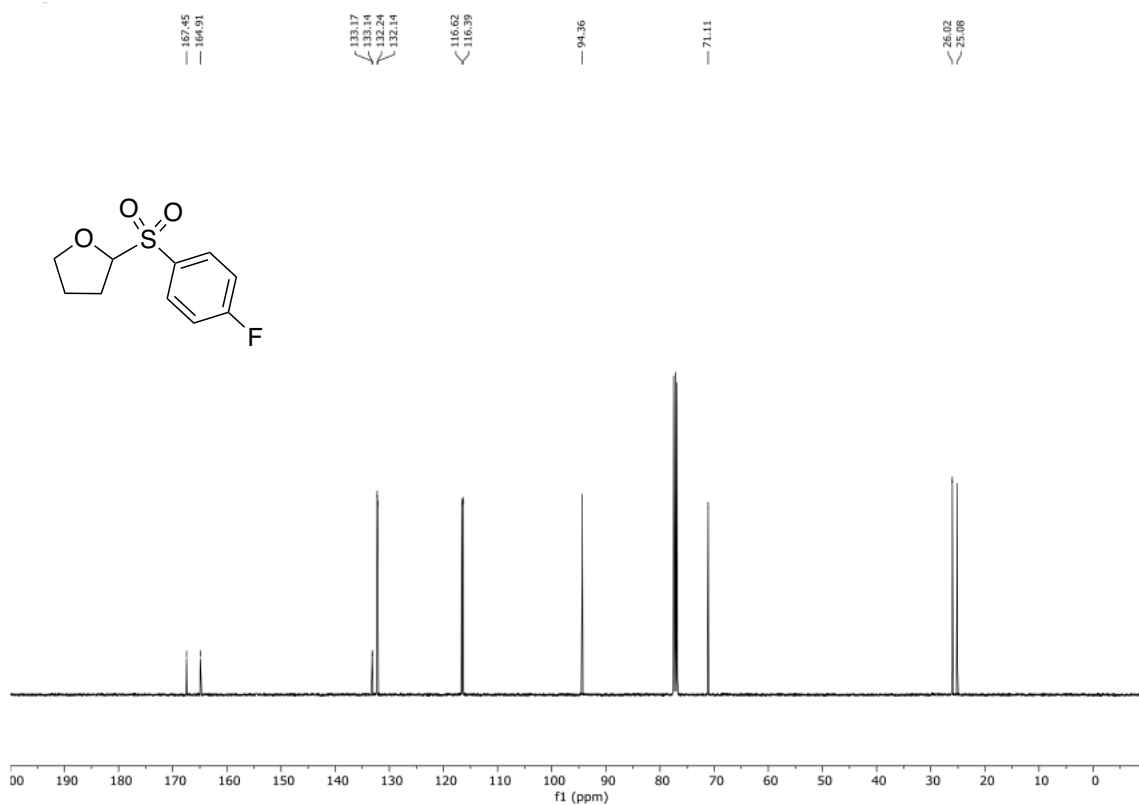
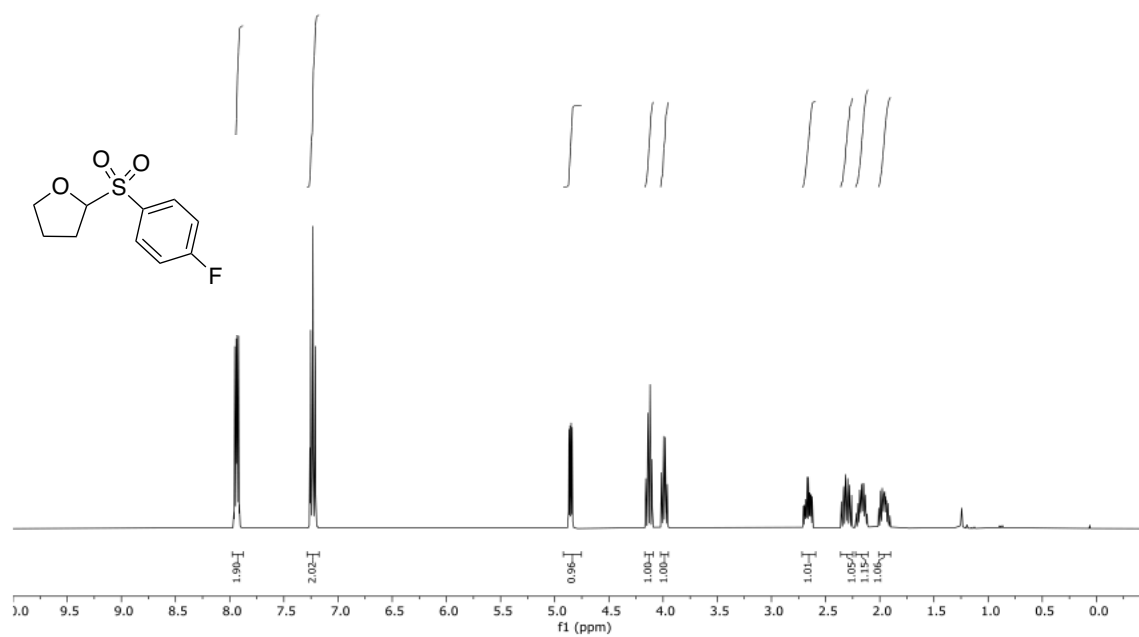
2-(*o*-tolylsulfonyl)tetrahydrofuran (6b)



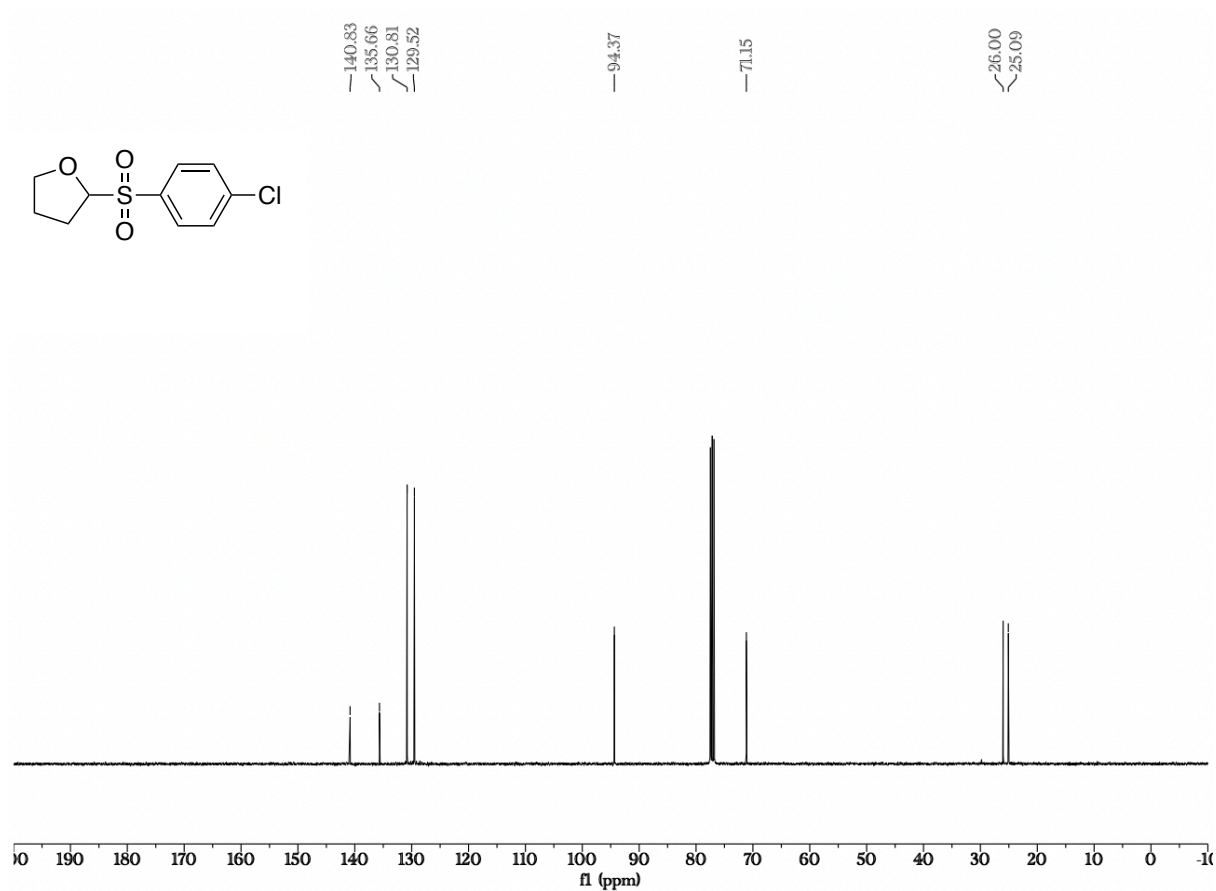
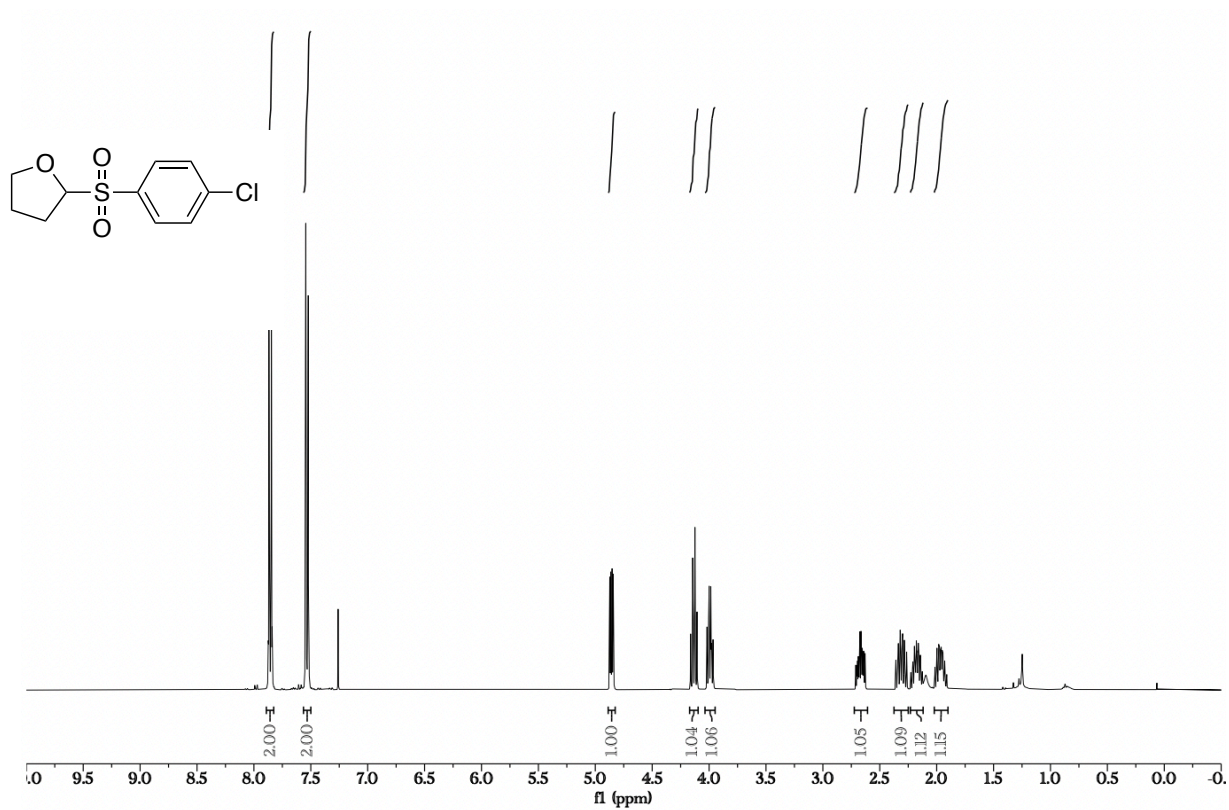
2-((3-fluorophenyl)sulfonyl)tetrahydrofuran (6c) – crude mixture



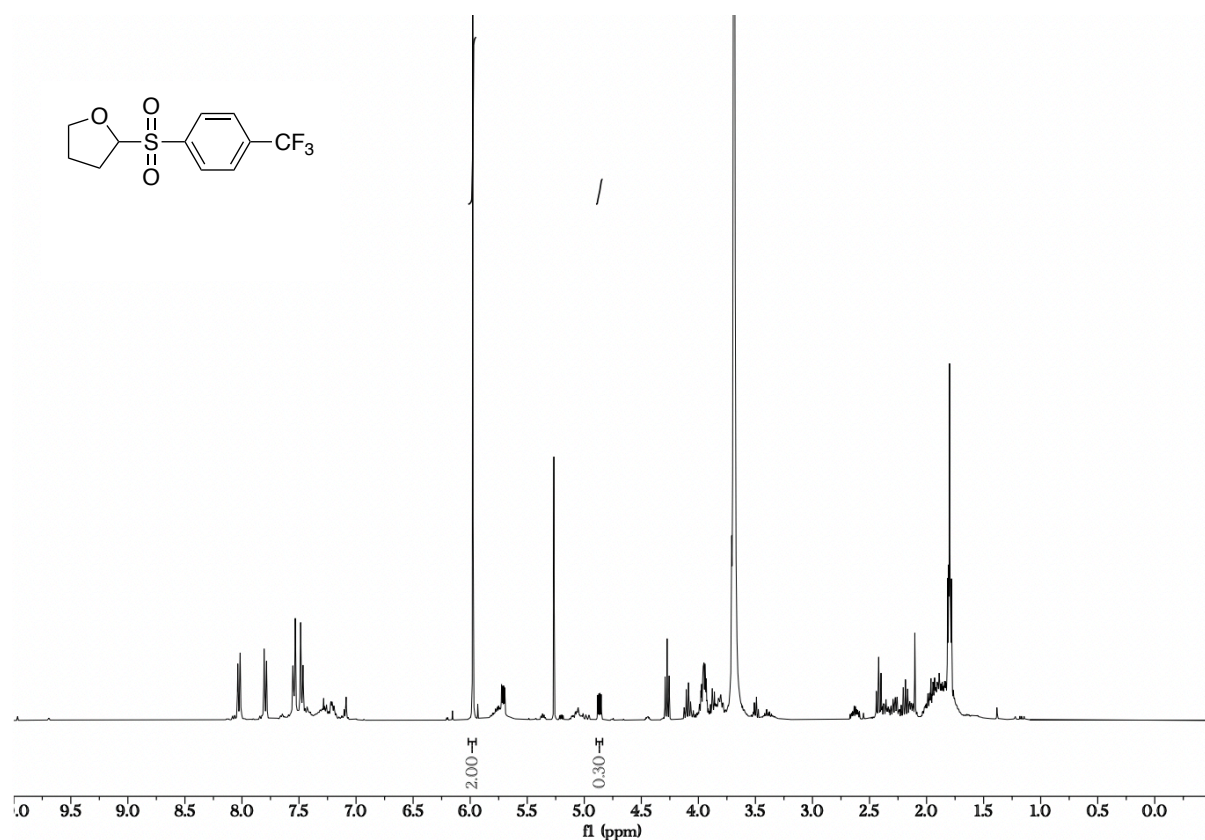
2-((4-fluorophenyl)sulfonyl)tetrahydrofuran (6d)



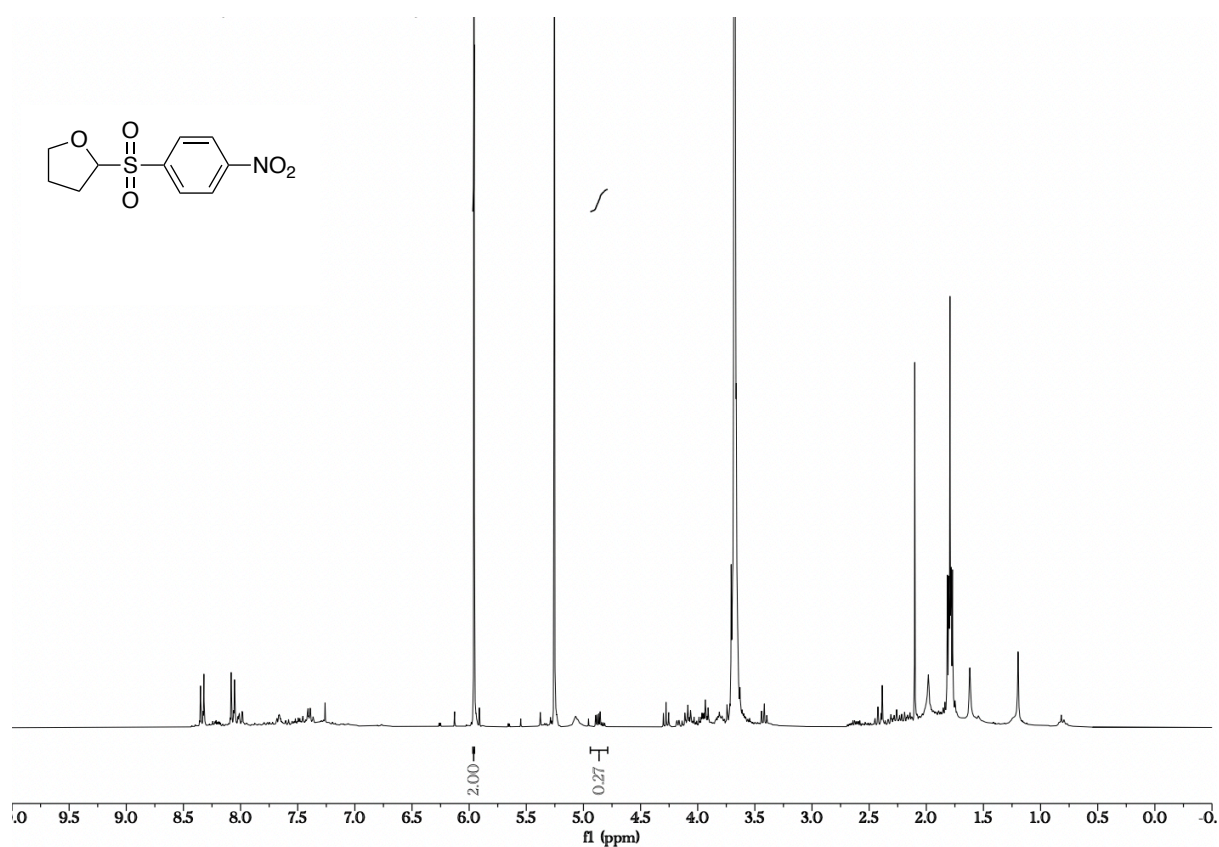
2-((4-chlorophenyl)sulfonyl)tetrahydrofuran (6e)



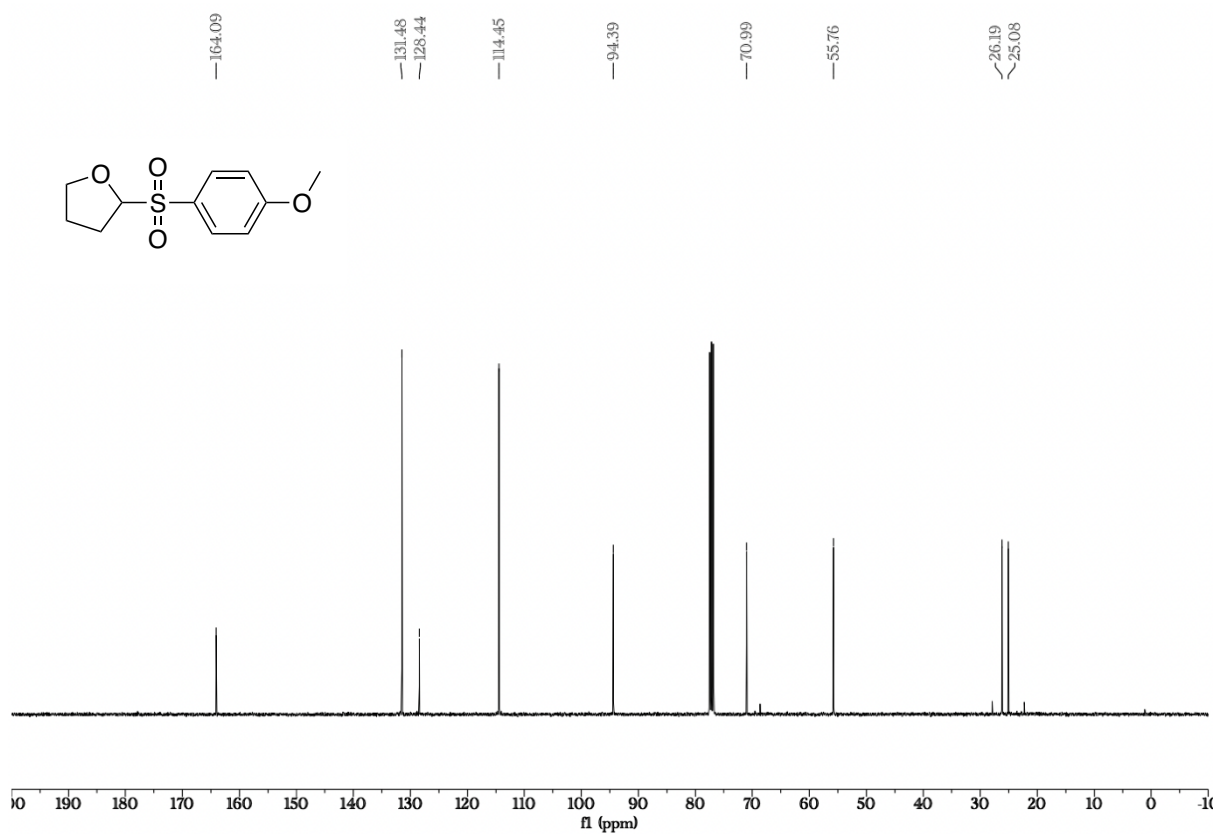
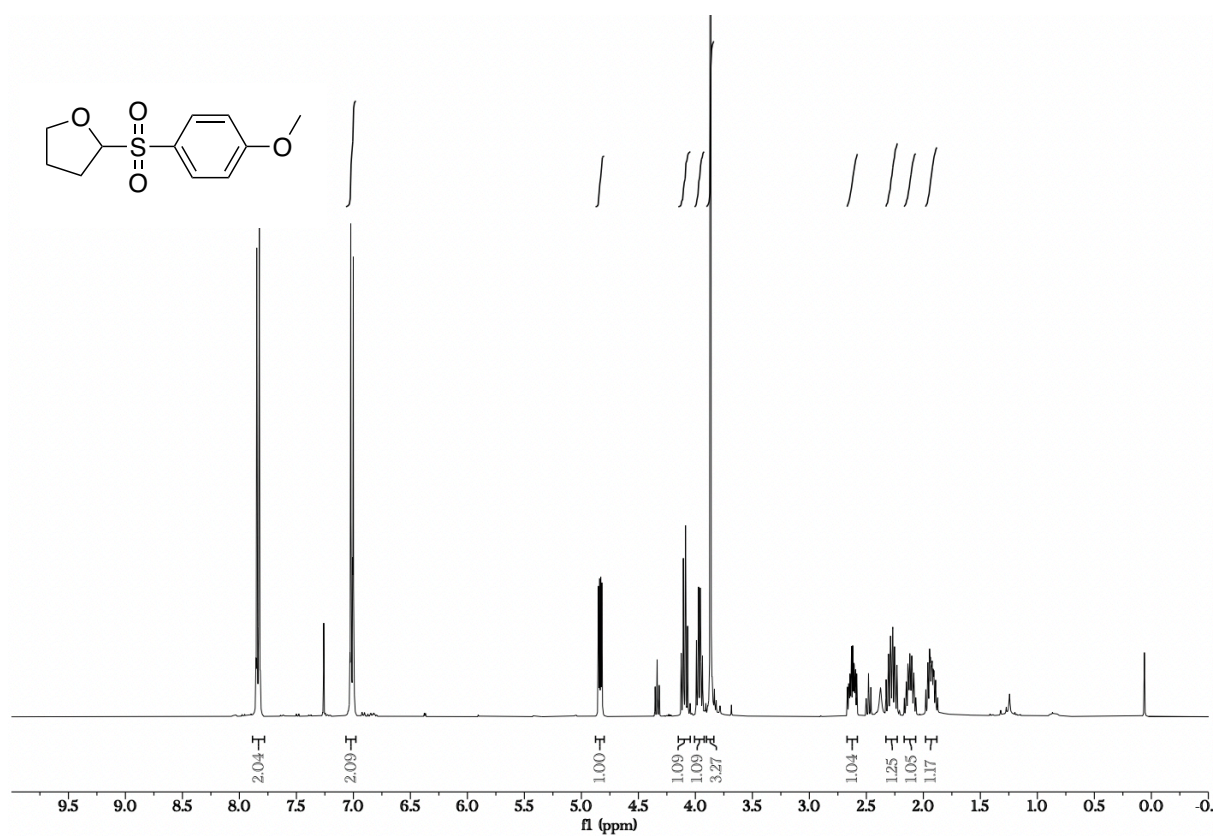
2-((4-(trifluoromethyl)phenyl)sulfonyl)tetrahydrofuran (6f) – crude mixture



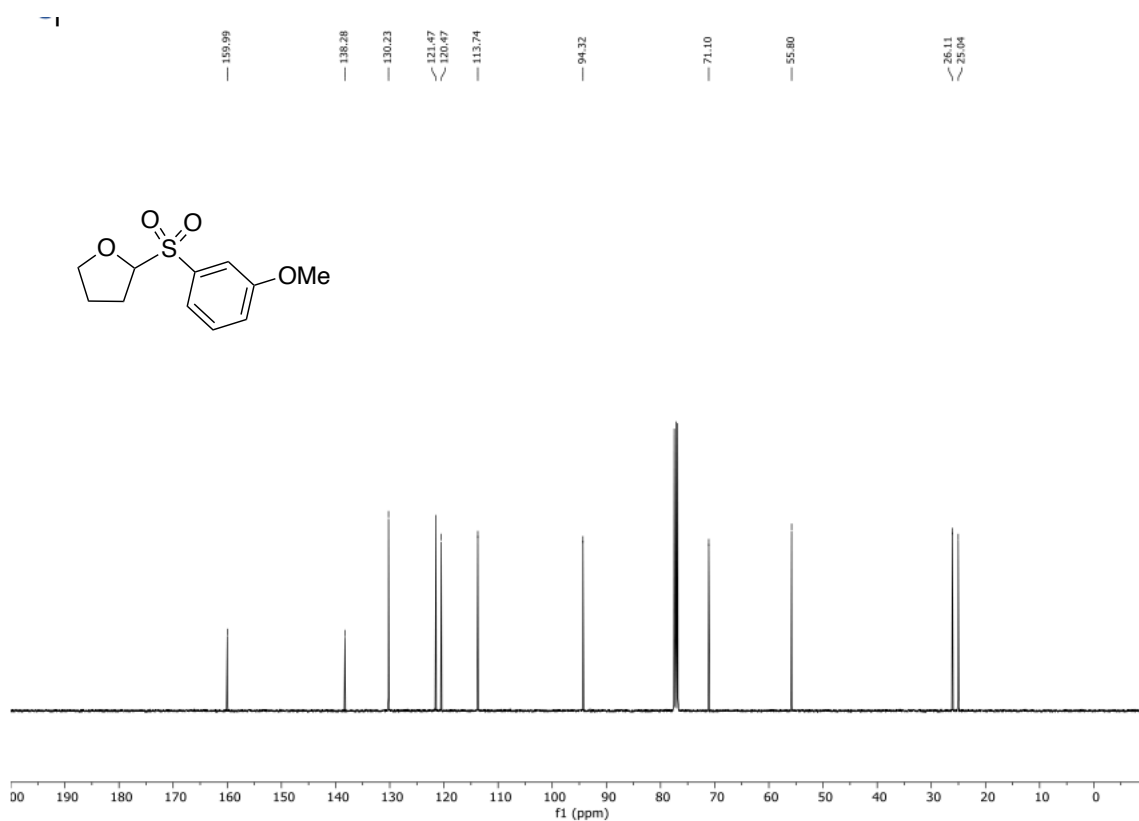
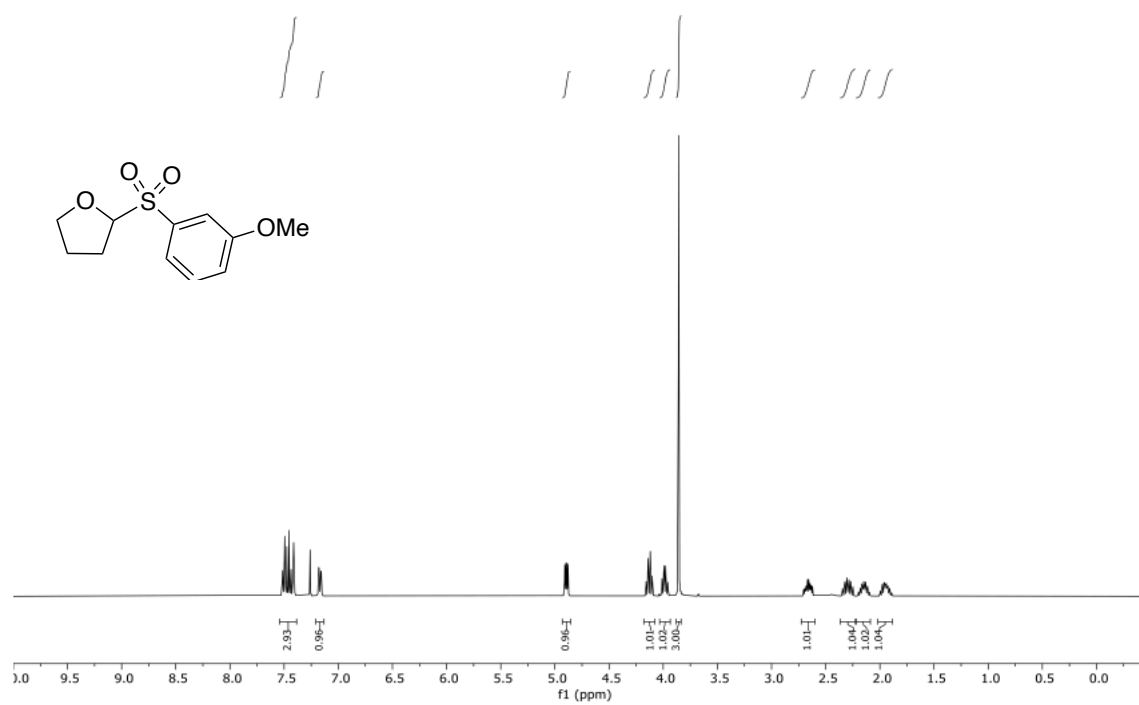
2-((4-nitrophenyl)sulfonyl)tetrahydrofuran (6g) – crude mixture



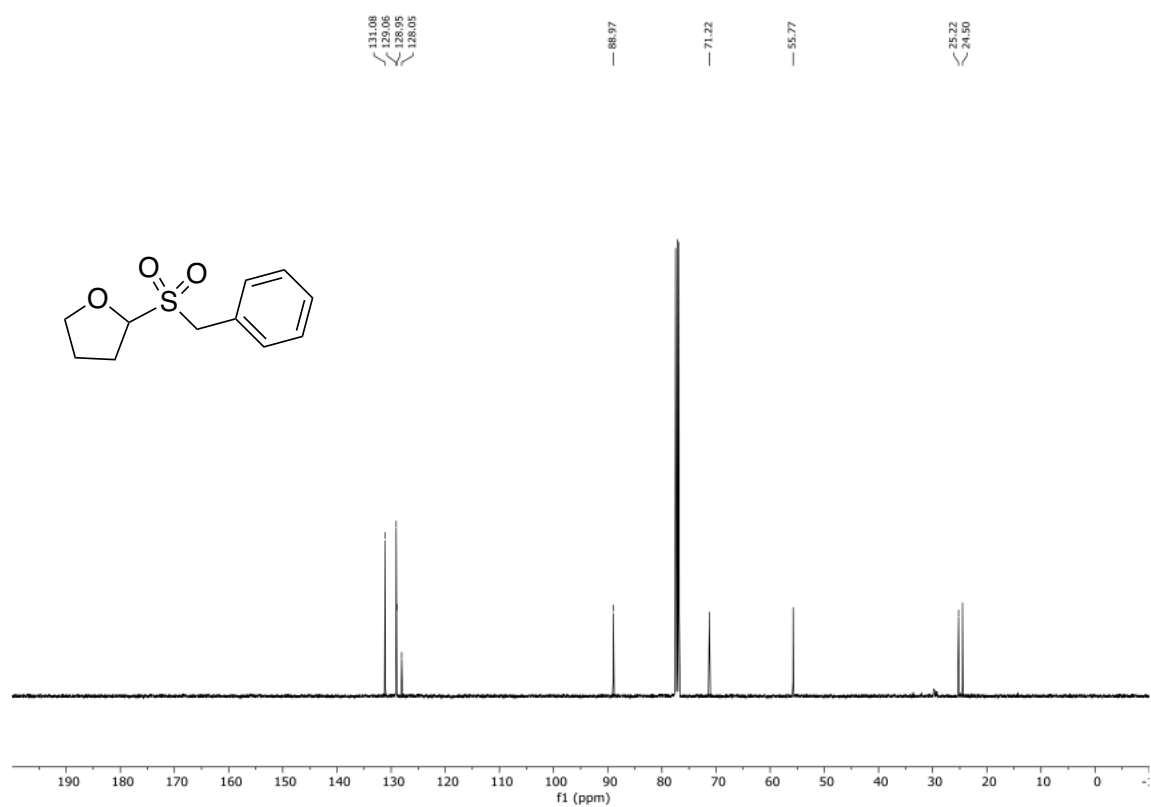
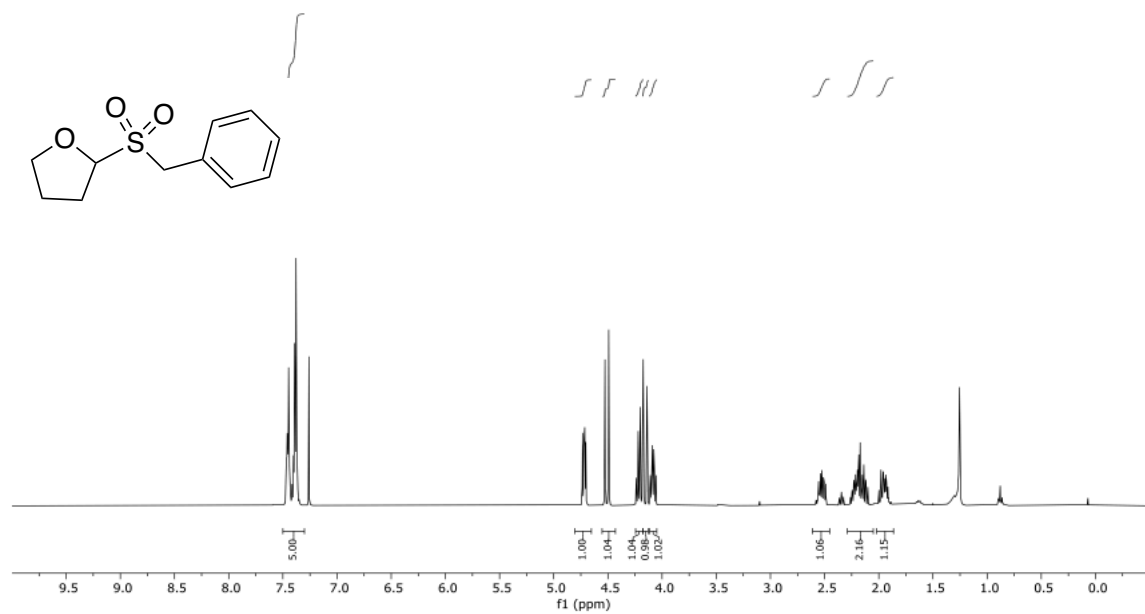
2-((4-methoxyphenyl)sulfonyl)tetrahydrofuran (6h)



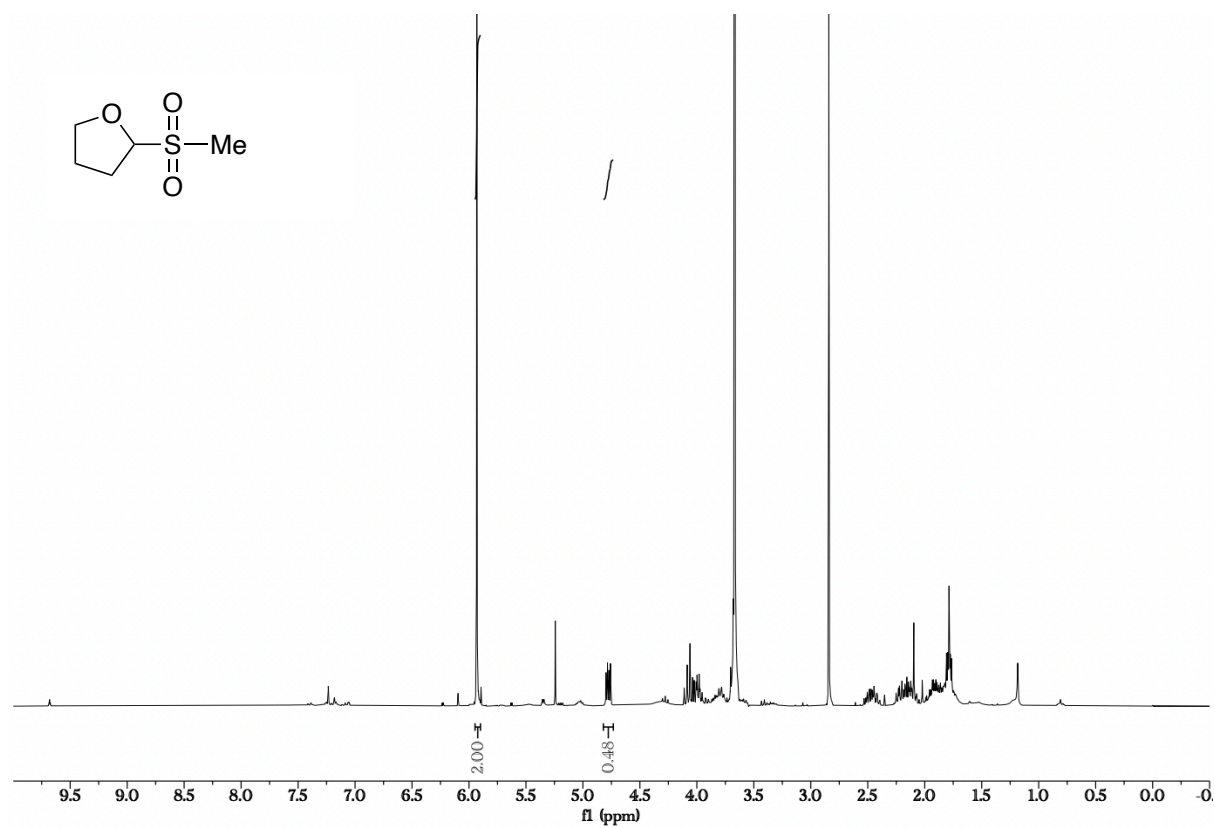
2-((3-methoxyphenyl)sulfonyl)tetrahydrofuran (6i)



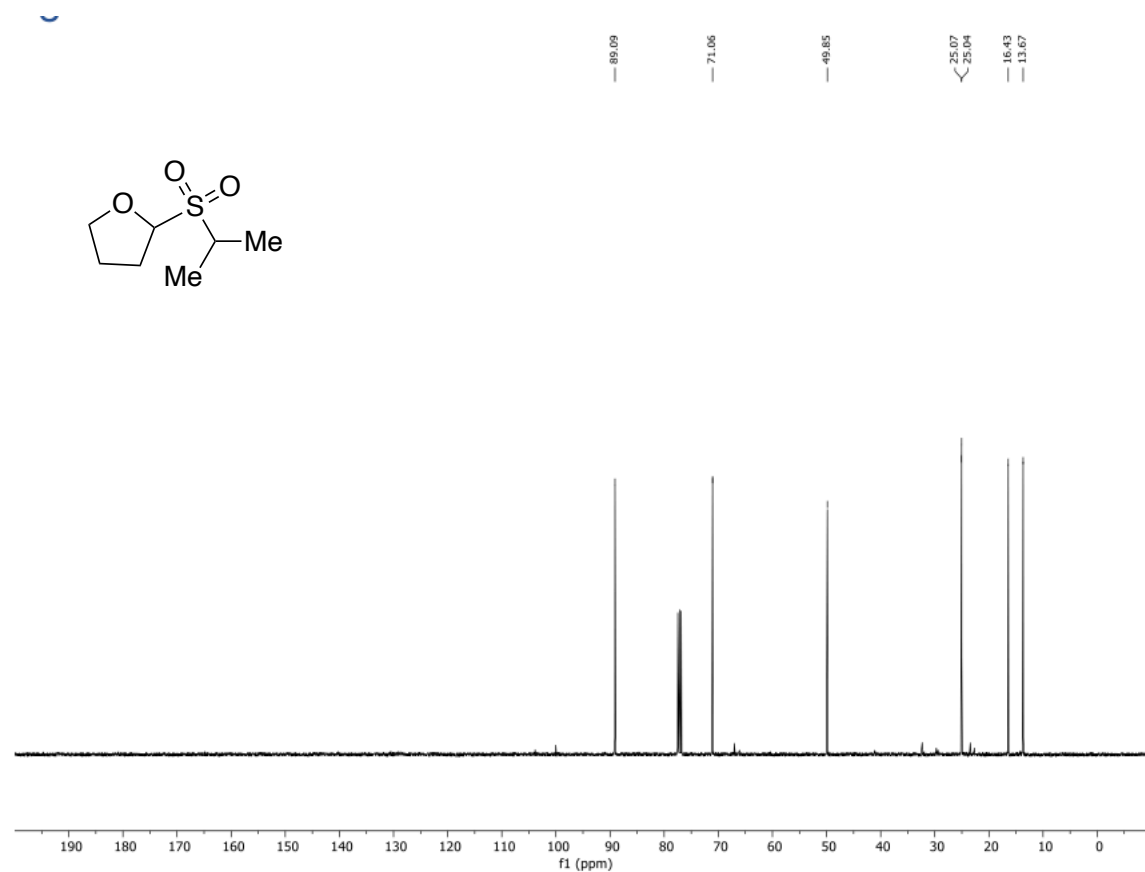
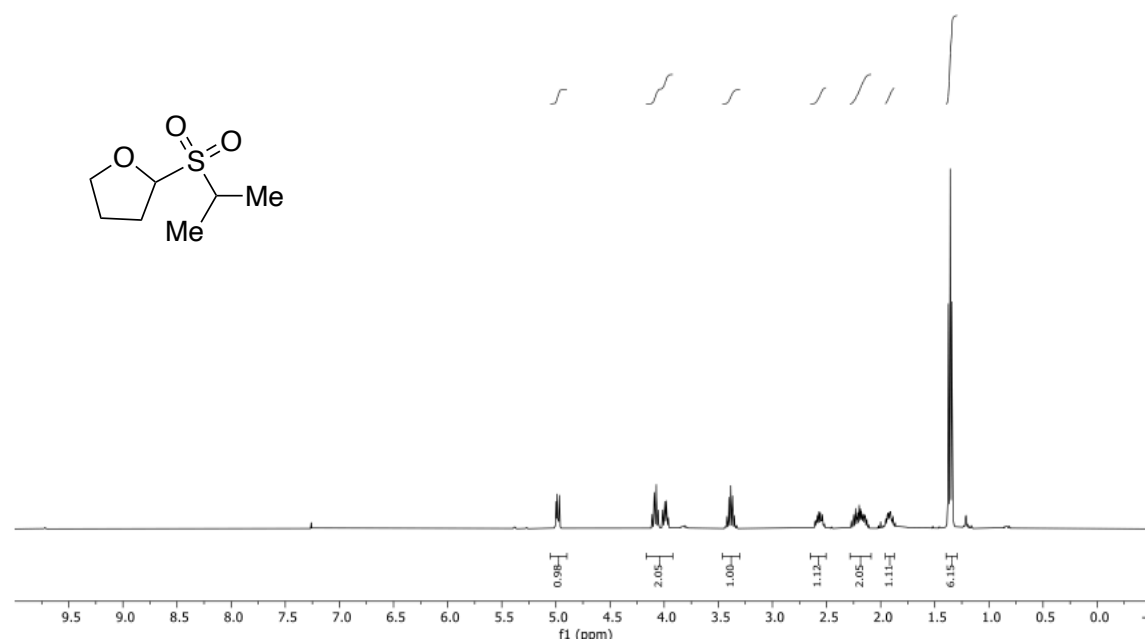
2-(benzylsulfonyl)tetrahydrofuran (6j)



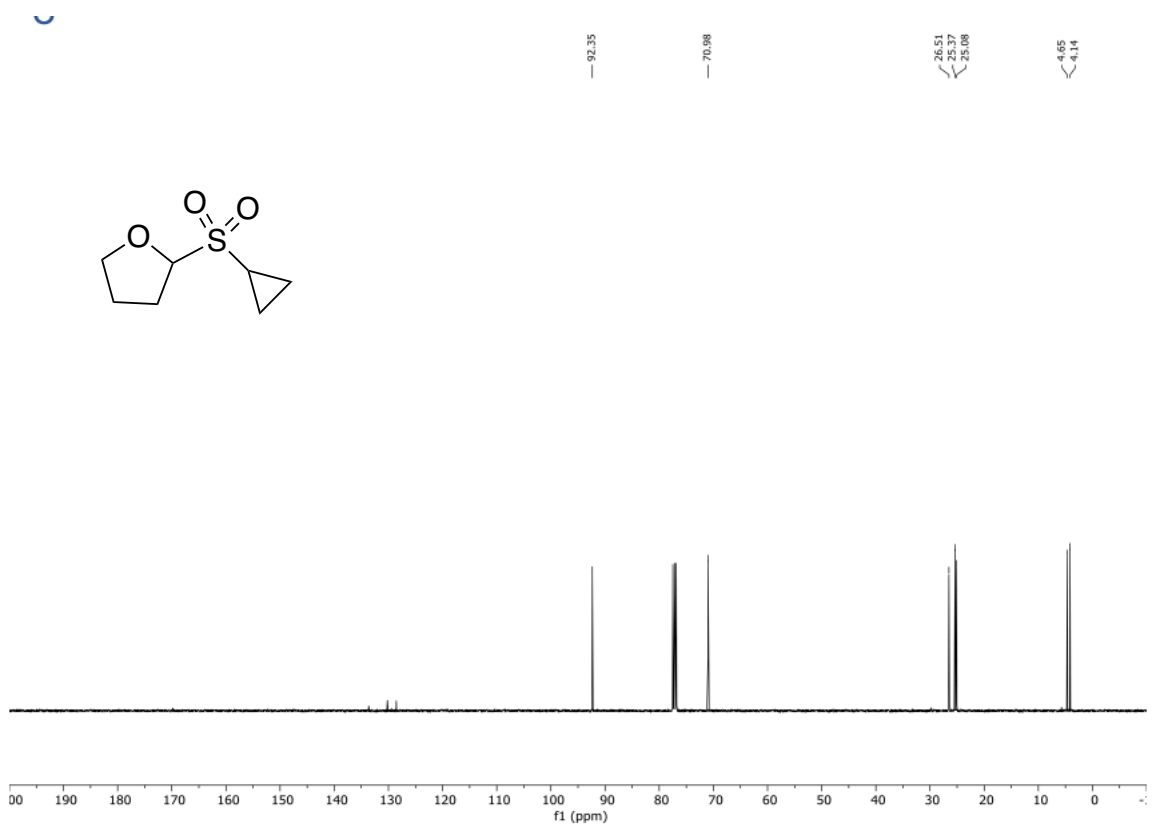
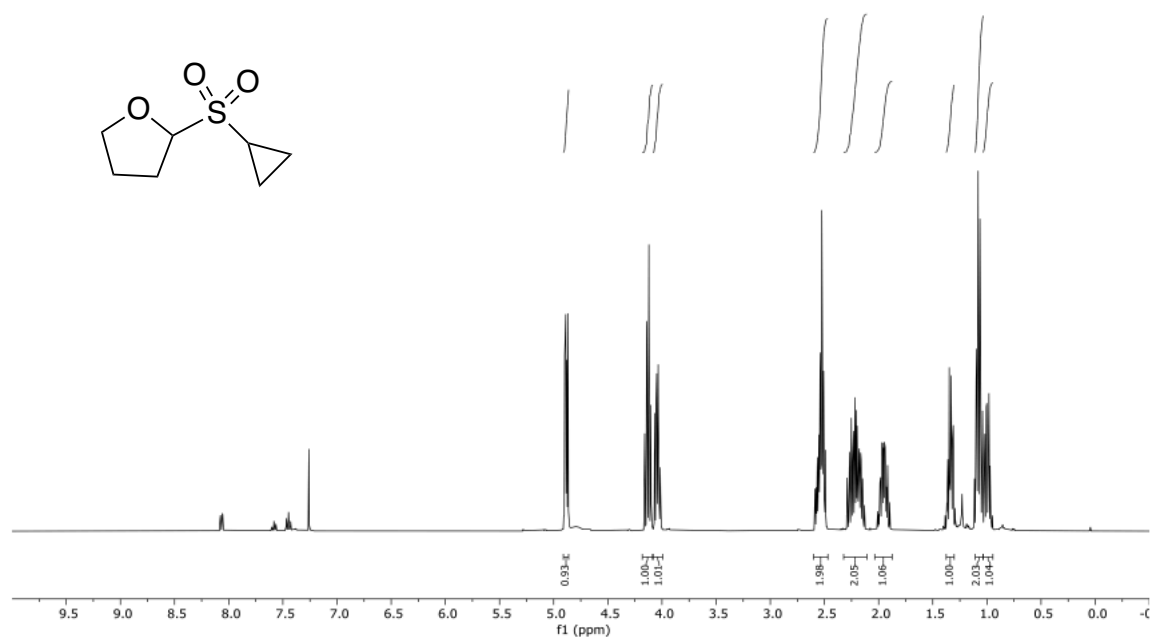
2-(methylsulfonyl)tetrahydrofuran (6k) – crude mixture



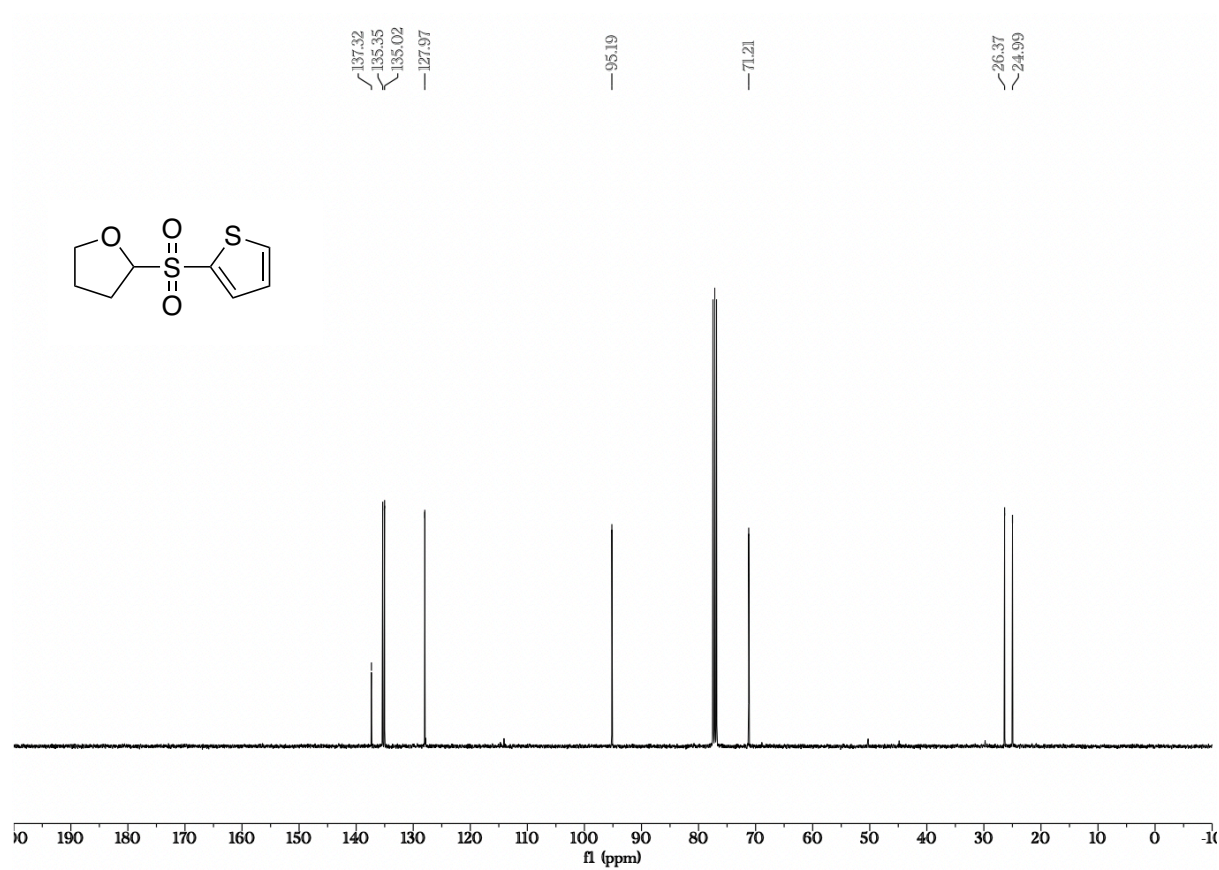
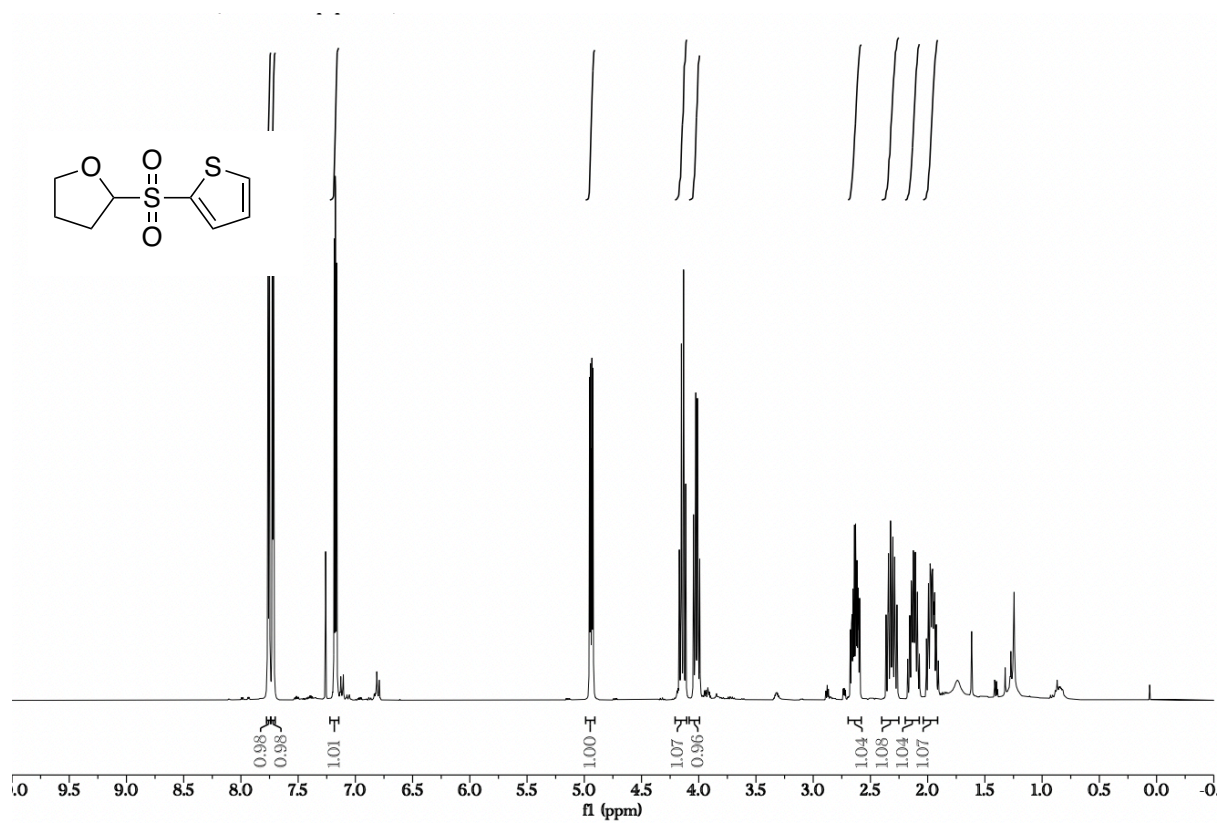
2-(isopropylsulfonyl)tetrahydrofuran (6l)



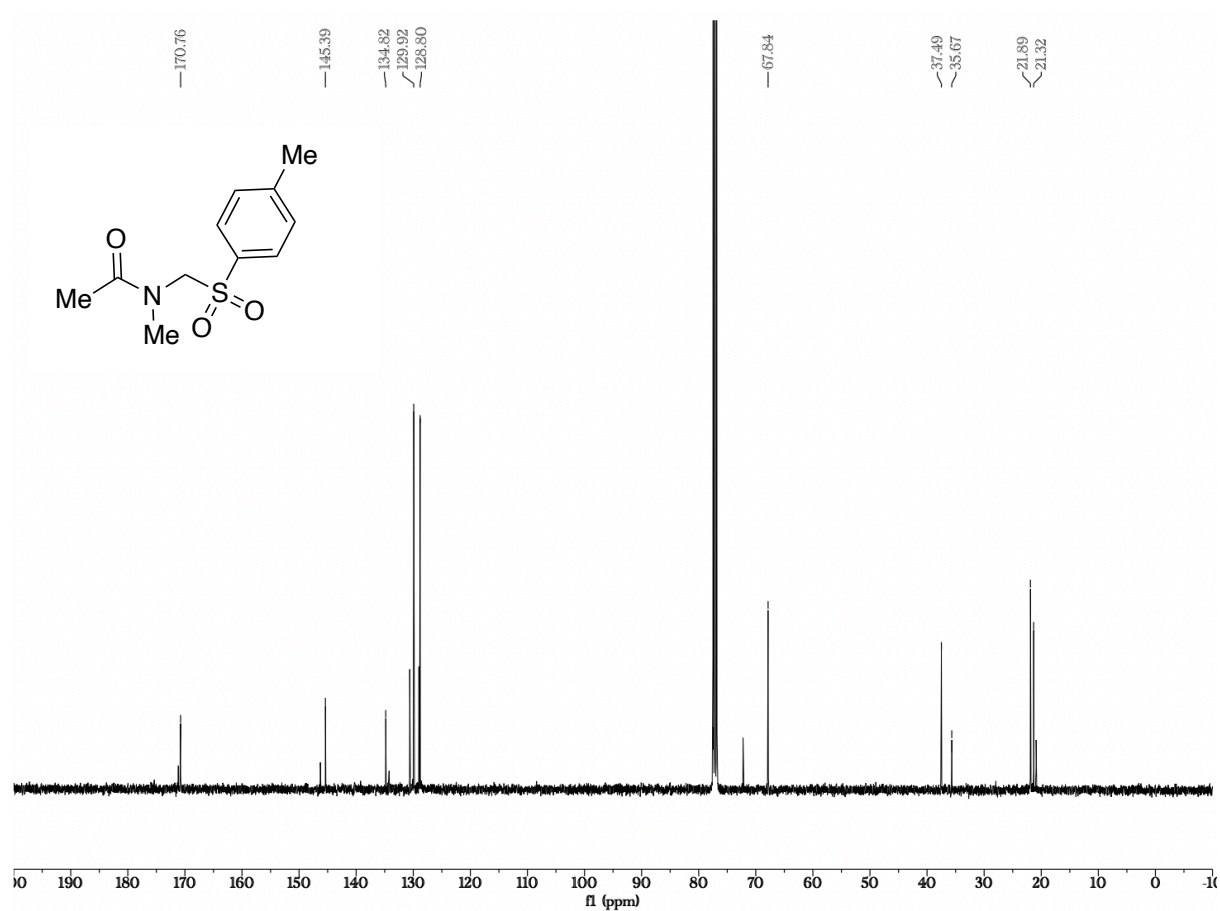
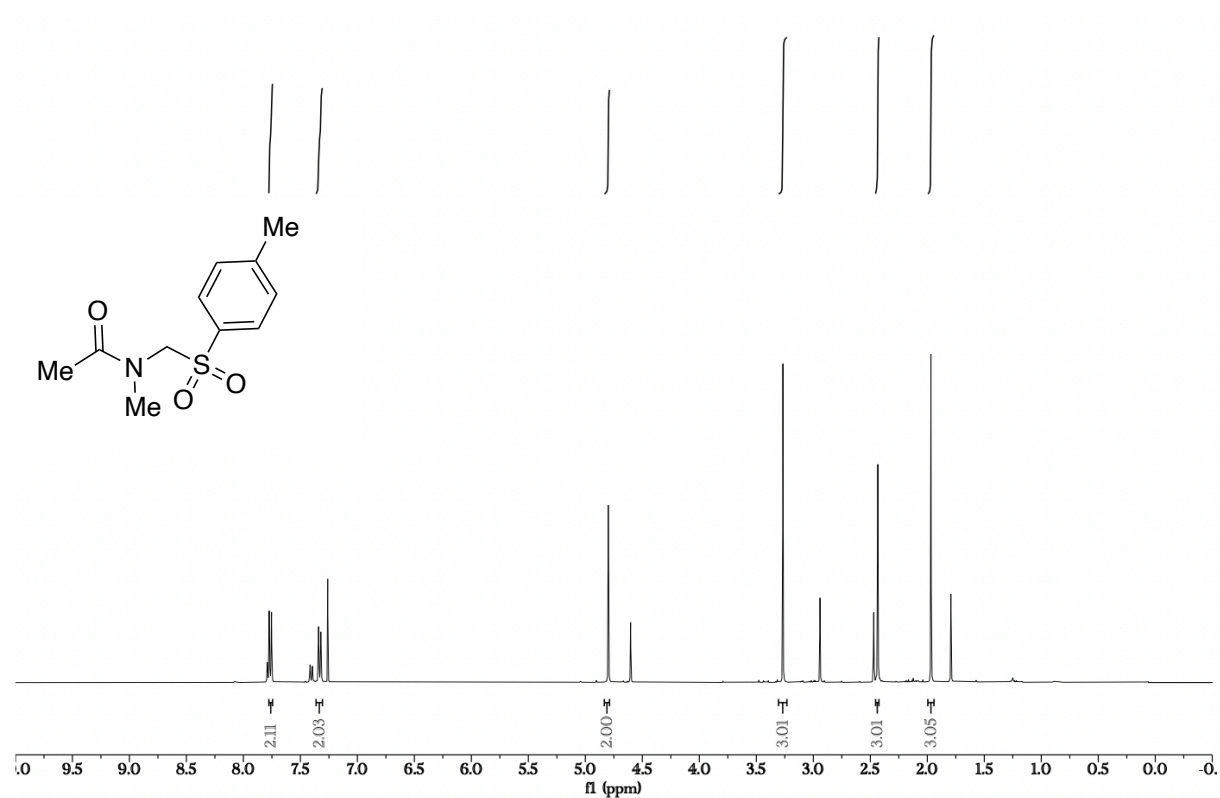
2-(cyclopropylsulfonyl)tetrahydrofuran (6m)



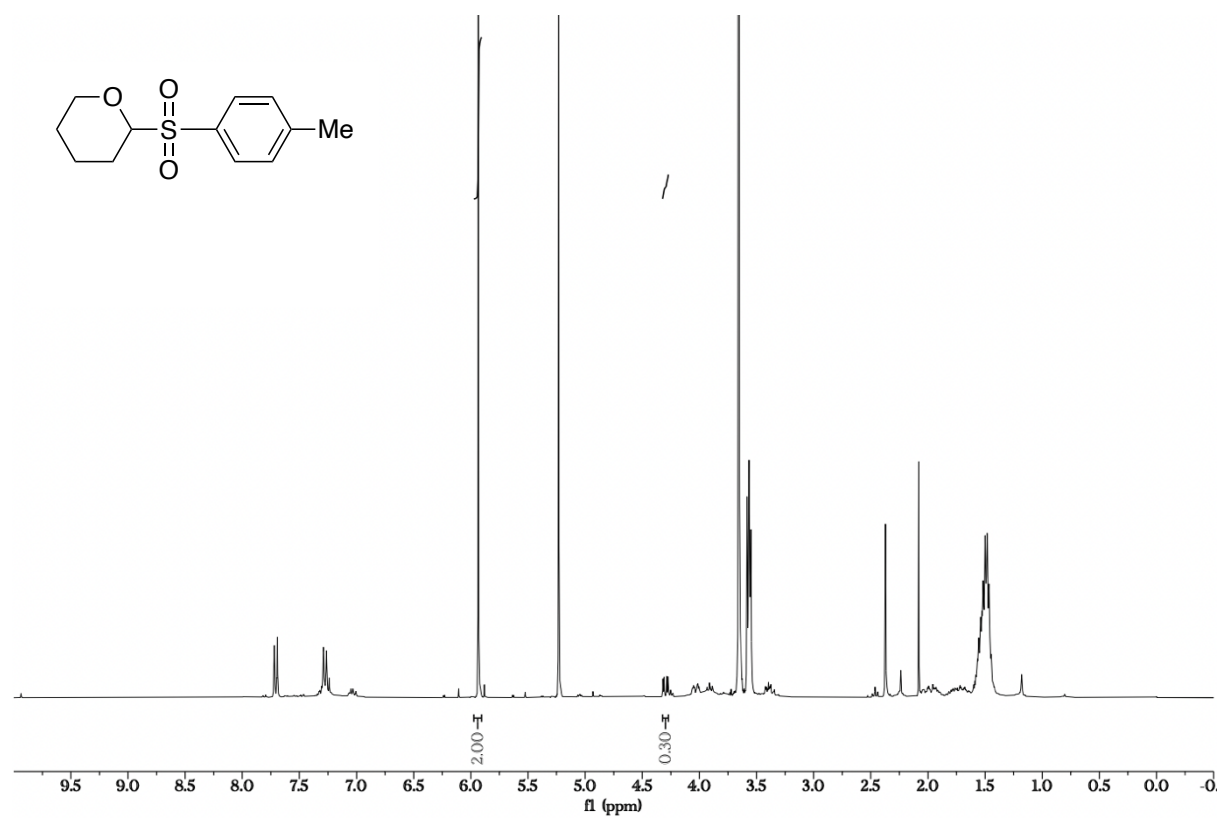
2-(thiophen-2-ylsulfonyl)tetrahydrofuran (6n)



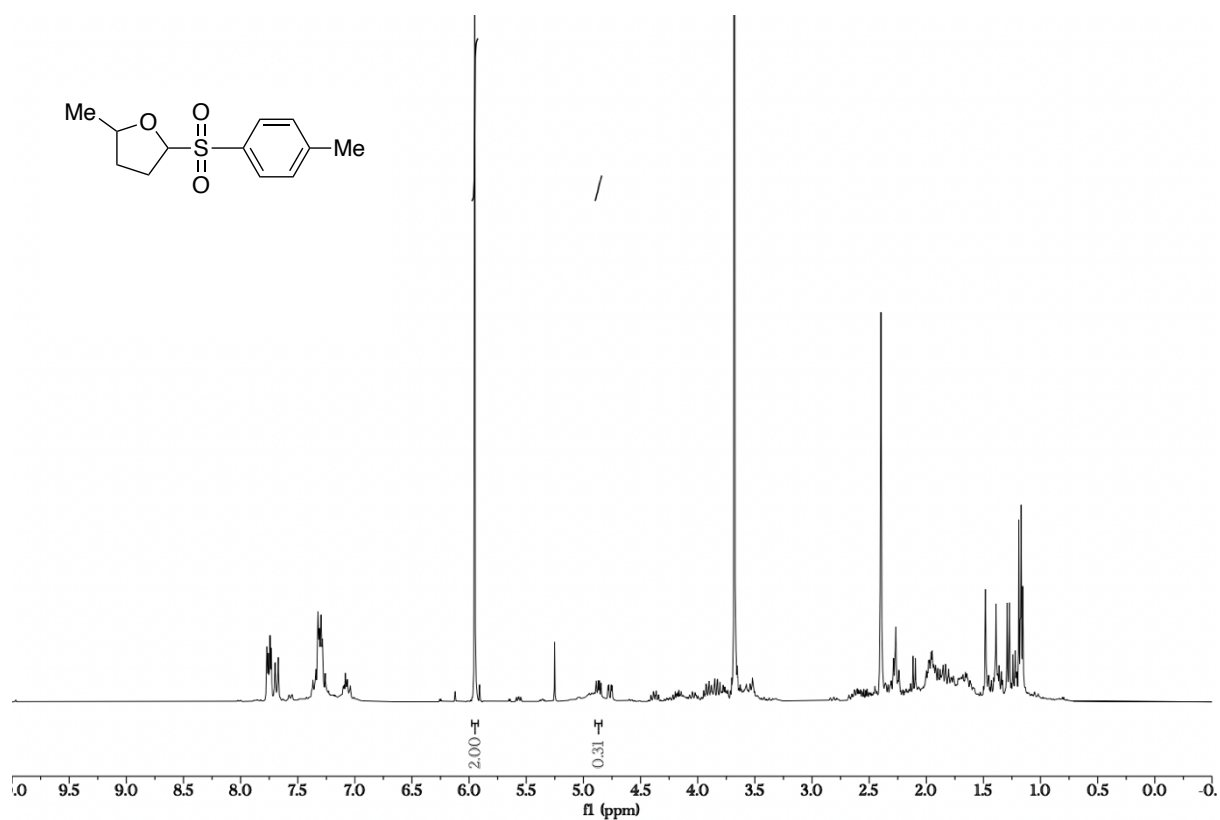
N-methyl-N-(tosylmethyl)acetamide (6o)



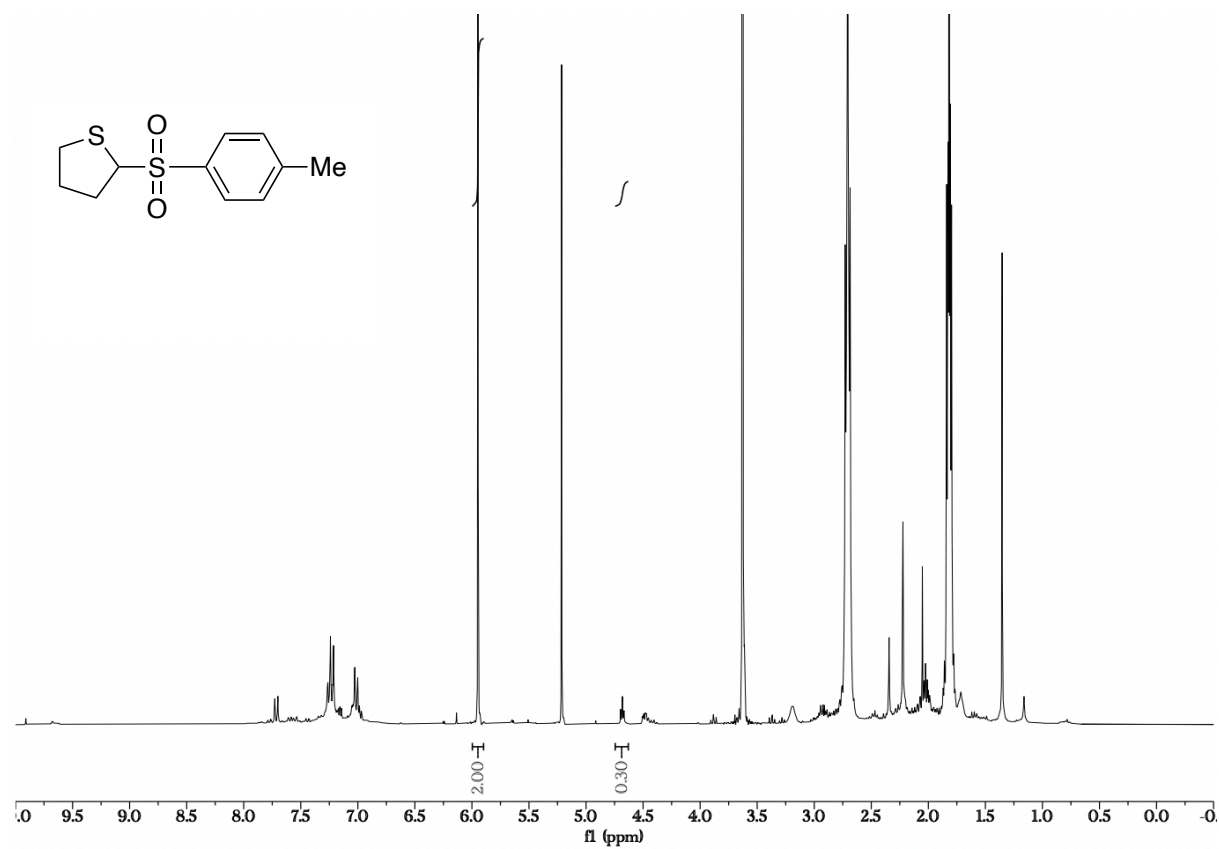
2-tosyltetrahydro-2H-pyran (6p) – crude mixture



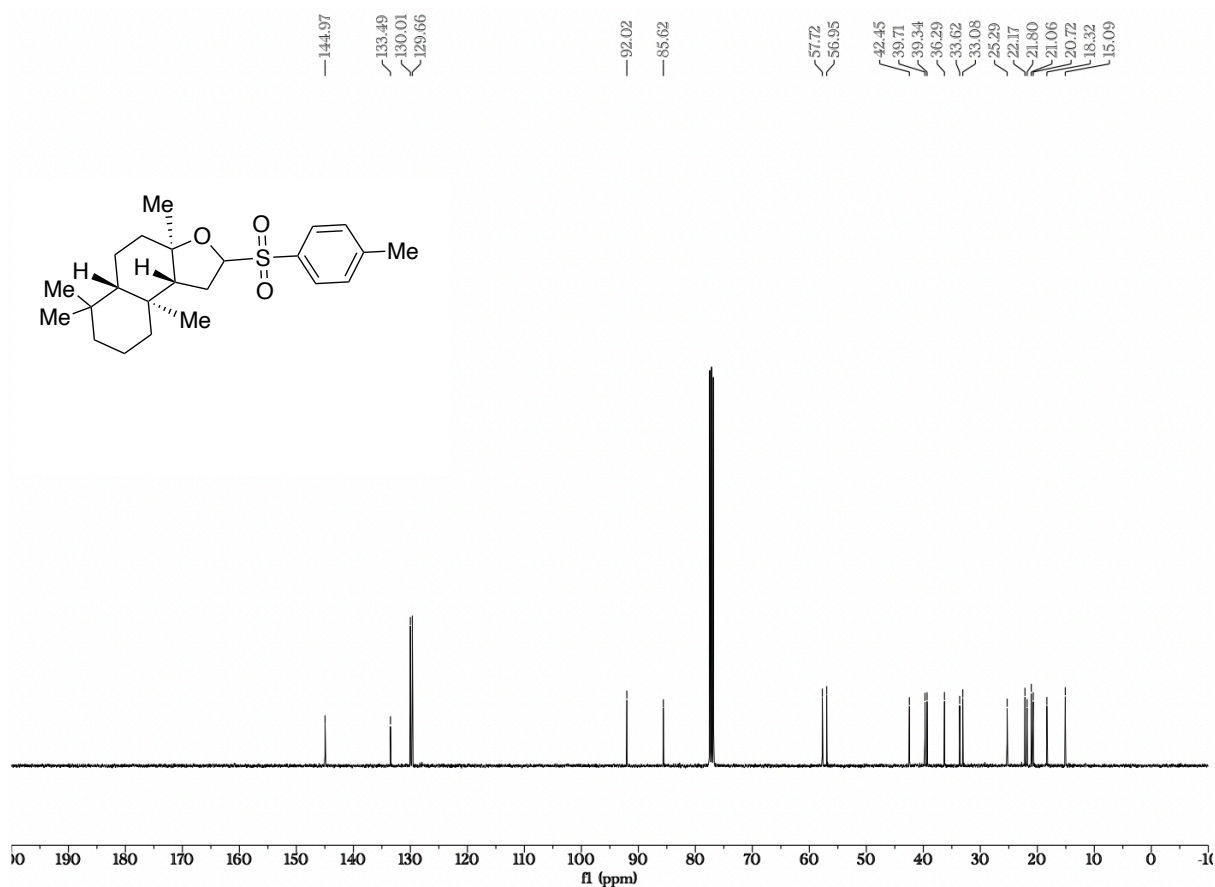
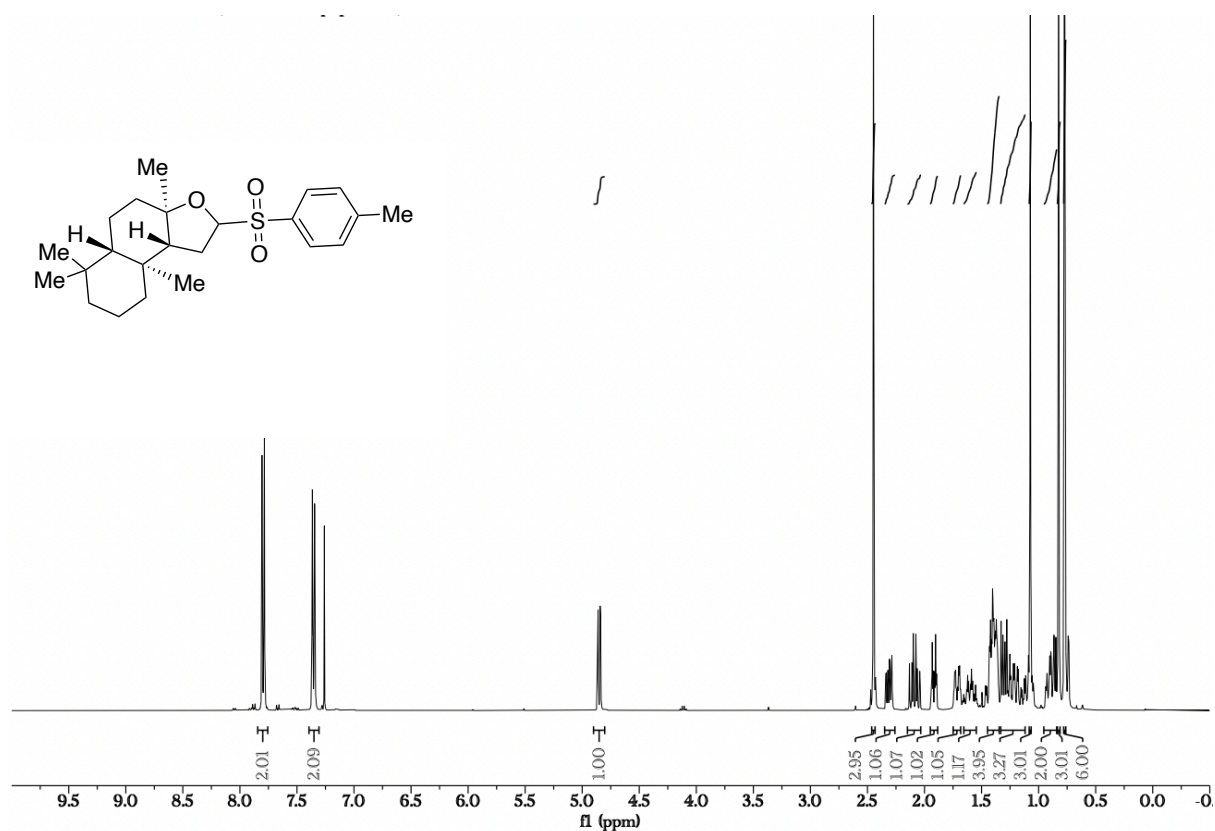
2-methyl-5-tosyltetrahydrofuran (6q) – crude mixture



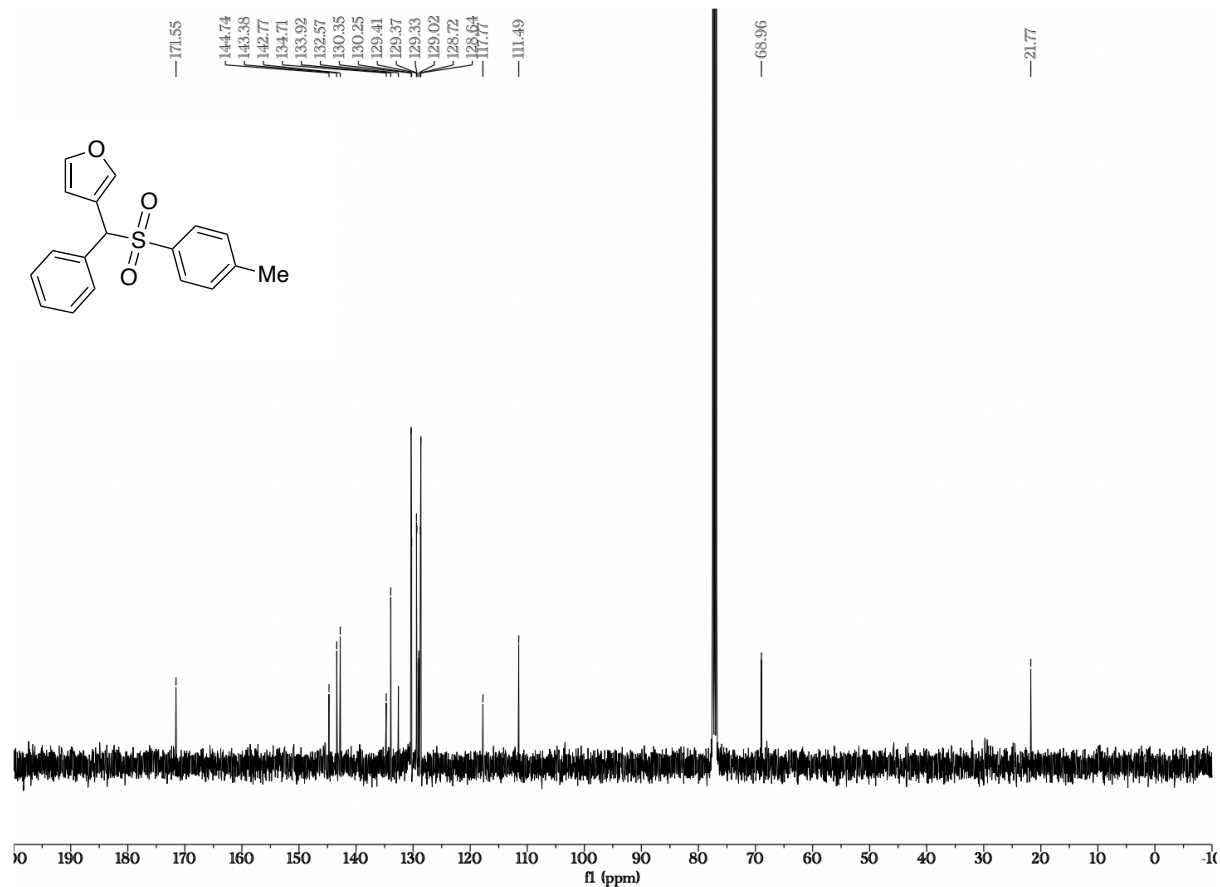
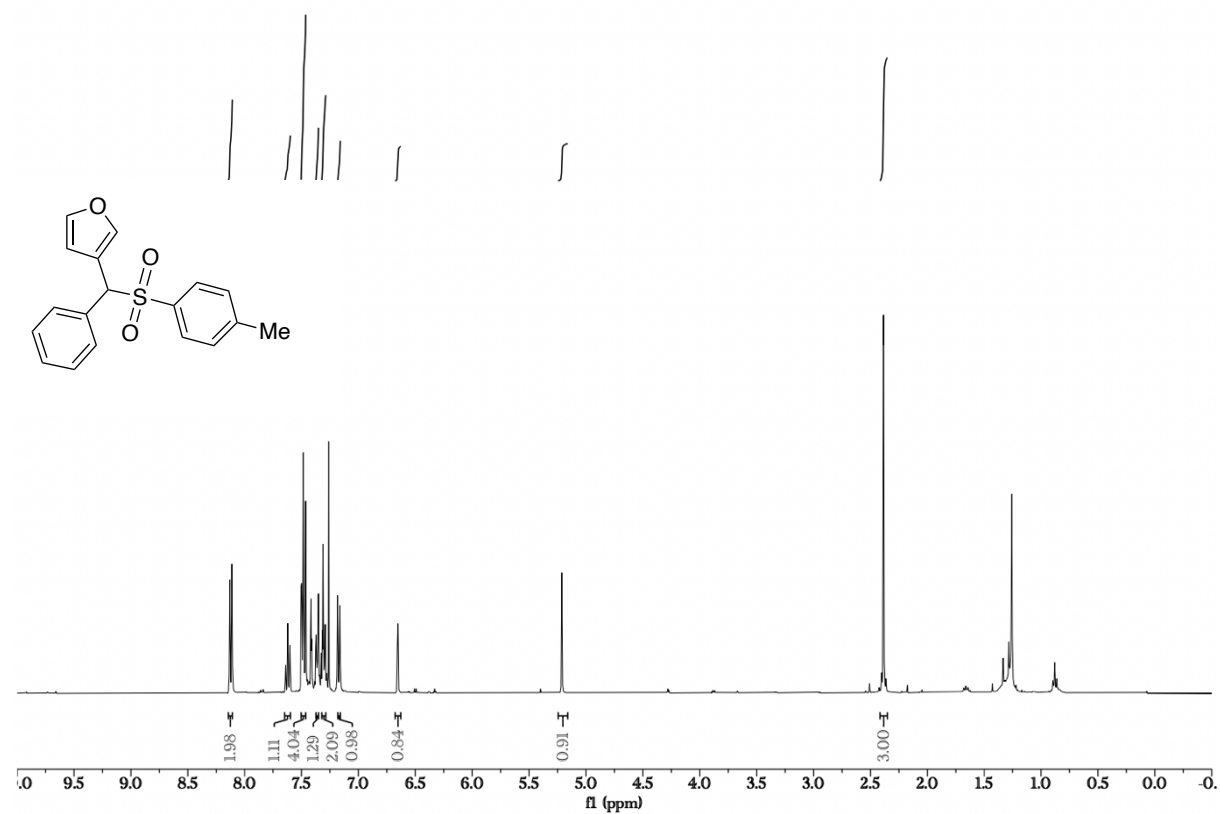
2-tosyltetrahydrothiophene (6r) – crude mixture



(3a*R*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-tetramethyl-2-tosyldodecahydronaphtho[2,1-*b*]furan (6s)

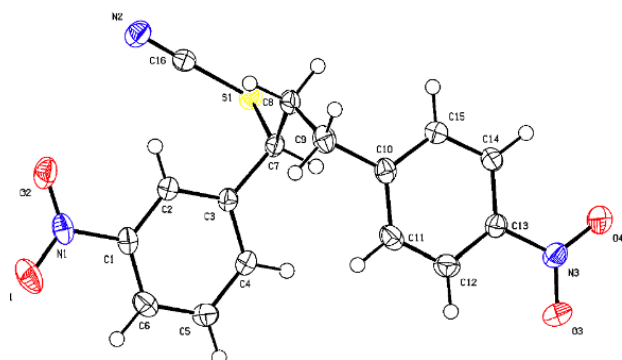


3-(phenyl(tosyl)methyl)furan (6t)



Crystallographic data:

1-nitro-3-(3-(4-nitrophenyl)-1-thiocyanatopropyl)benzene (3as):



Bond precision: C-C = 0.0021 Å

Wavelength=1.54184

Cell: a=7.2702 (2) b=8.4702 (3) c=14.3028 (2)
alpha=100.218 (2) beta=98.646 (2) gamma=113.519 (3)
Temperature: 123 K

	Calculated	Reported
Volume	770.56 (4)	770.56 (4)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C16 H13 N3 O4 S	C16 H13 N3 O4 S
Sum formula	C16 H13 N3 O4 S	C16 H13 N3 O4 S
Mr	343.35	343.35
Dx, g cm ⁻³	1.480	1.480
Z	2	2
Mu (mm ⁻¹)	2.116	2.116
F000	356.0	356.0
F000'	357.77	
h, k, lmax	9, 10, 17	9, 10, 17
Nref	3131	3024
Tmin, Tmax	0.837, 0.900	0.694, 1.000
Tmin'	0.683	

Correction method= # Reported T Limits: Tmin=0.694 Tmax=1.000
AbsCorr = GAUSSIAN

Data completeness= 0.966

Theta(max)= 74.201

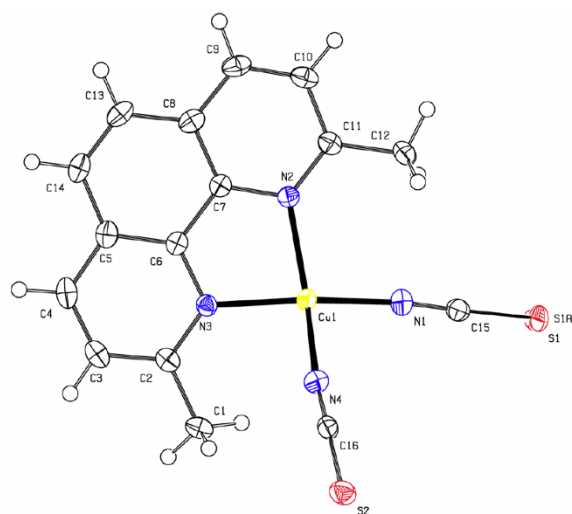
R(reflections)= 0.0374 (2749)

wR2(reflections)=
0.1068 (3024)

S = 1.048

Npar= 217

Cu(dmp)(NCS)₂:



Bond precision: C-C = 0.0036 Å

Wavelength=1.54184

Cell: a=8.8992(6) b=8.9294(7) c=10.6352(6)
 alpha=82.005(5) beta=88.941(5) gamma=66.762(7)

Temperature: 123 K

	Calculated	Reported
Volume	768.40(10)	768.40(10)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C16 H12 Cu N4 S2	C16 H12 Cu N4 S2
Sum formula	C16 H12 Cu N4 S2	C16 H12 Cu N4 S2
Mr	387.97	387.96
Dx, g cm ⁻³	1.677	1.677
Z	2	2
Mu (mm ⁻¹)	4.567	4.567
F000	394.0	394.0
F000'	392.15	
h,k,lmax	11,11,13	10,11,13
Nref	3062	2972
Tmin,Tmax	0.830,0.856	0.819,1.000
Tmin'	0.420	

Correction method= # Reported T Limits: Tmin=0.819 Tmax=1.000
 AbsCorr = GAUSSIAN

Data completeness= 0.971

Theta(max)= 73.016

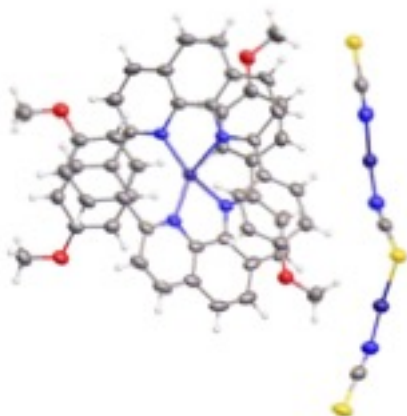
R(reflections)= 0.0316(2661)

wR2(reflections)= 0.0850(2972)

S = 1.044

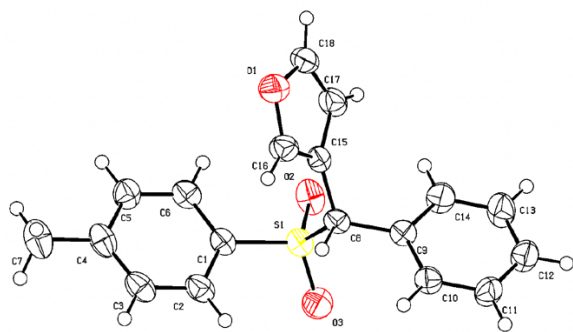
Npar= 220

[Cu(dap)₂][Cu₂(NCS)₃]:



Bond precision:	C-C = 0.0050 Å	Wavelength=1.54184	
Cell:	a=7.5452 (2)	b=33.3472 (6)	c=38.4904 (7)
	alpha=90	beta=90	gamma=90
Temperature:	123 K		
	Calculated	Reported	
Volume	9684.6 (4)	9684.6 (4)	
Space group	P b c a	P b c a	
Hall group	-P 2ac 2ab	-P 2ac 2ab	
Moiety formula	C3 Cu2 N3 S3, C52 H40 Cu N4 O4	C52 H40 Cu N4 O4, C3 Cu2 N3 S3	
Sum formula	C55 H40 Cu3 N7 O4 S3	C55 H40 Cu3 N7 O4 S3	
Mr	1149.77	1149.74	
Dx, g cm-3	1.577	1.577	
Z	8	8	
Mu (mm-1)	3.198	3.198	
F000	4688.0	4688.0	
F000'	4659.21		
h,k,lmax	9, 41, 47	9, 40, 47	
Nref	9542	9224	
Tmin,Tmax	0.825, 0.938	0.823, 1.000	
Tmin'	0.660		
Correction method= # Reported T Limits: Tmin=0.823 Tmax=1.000			
AbsCorr = GAUSSIAN			
Data completeness=	0.967	Theta(max)= 72.058	
R(reflections)=	0.0462 (6821)	wR2(reflections)=	
		0.1291 (9224)	
S =	1.038	Npar= 653	

3-(phenyl(tosyl)methyl)furan (6t):



Bond precision: C-C = 0.0049 Å

Wavelength=1.54184

Cell: a=17.8893 (5)

b=5.6039 (2)

c=15.4841 (4)

alpha=90

beta=90

gamma=90

Temperature: 123 K

	Calculated	Reported
Volume	1552.28 (8)	1552.28 (8)
Space group	P c a 21	P c a 21
Hall group	P 2c -2ac	P 2c -2ac
Moiety formula	C18 H16 O3 S	C18 H16 O3 S
Sum formula	C18 H16 O3 S	C18 H16 O3 S
Mr	312.37	312.37
Dx, g cm ⁻³	1.337	1.337
Z	4	4
Mu (mm ⁻¹)	1.935	1.935
F000	656.0	656.0
F000'	659.17	
h, k, lmax	22, 7, 19	22, 6, 19
Nref	3199 [1663]	3011
Tmin, Tmax	0.890, 0.944	0.806, 1.000
Tmin'	0.778	

Correction method= # Reported T Limits: Tmin=0.806 Tmax=1.000

AbsCorr = GAUSSIAN

Data completeness= 1.81/0.94

Theta(max)= 75.228

R(reflections)= 0.0354 (2783)

wR2(reflections)=
0.0951 (3011)

S = 1.066

Npar= 200

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Appendix:

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- Y. Abderrazak, O. Reiser, Copper Photocatalyzed Divergent Access to Organic Thio- and Isothiocyanates. *ACS Catal.* **2024**, 4847–4855. DOI: 10.1021/acscatal.4c00565
- Y. Abderrazak, A. Chinchole, O. Reiser, Palladium-free Oxidation using Copper as a site-selective sequential photooxidant-photoreductant, *Catalysis science & technology*, 2024. DOI: 10.1039/d4cy00590b
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Declaration:

Herewith I declare that this present thesis is a presentation of my original work prepared single-handed. Wherever contributions from other are involved all of them are clearly marked with reference to literature, license, and acknowledgment of collaborative research.

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