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Synthetic methodologies for C-C and C-N bond formation involving alkyl radicals

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par

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Abstract

C-C and C-N bonds are some of the most common structures in molecules ranging from drugs to catalysts and to food additives. Many coupling reactions were developed to form these types of bonds with excellent selectivity and good performance. Still, the synthesis of some of those species either depends on traditional methods or requires expensive and rare reagents and catalysts. The use of precious metals in chemistry, and particularly in the industry, can make molecular synthesis expensive and energy-intensive since the extraction of those materials is costly. Moreover, in homogeneous catalysis, the recovery of metal-based catalysts is almost impossible, making these processes unsustainable for the future. Thus, the discovery of chemical reactions that don't involve precious materials is indispensable. This thesis concentrates on the development of two chemical transformations, one performing an sp^2-sp^3 radical reductive coupling, one performing a photocatalyzed alkyl amination, involving inexpensive reagents and catalysts.

The first chapter reviews the existing methodologies which use alkyl radicals to form carbon-carbon and carbon-nitrogen bonds. Alkyl radicals are formed from alkyl halides and pseudo-halides (Acids, esters, tosylates, etc.) via oxidation or reduction performed by metal or photoredox catalyst. The wide variety of available methodologies was illustrated, highlighting the advantages and weaknesses of each reaction.

The second chapter of this dissertation is devoted to the development of a new iron-based catalytic method to form stereoselectively Z-alkene boron species from the corresponding boron-alkyne. This novel stereoselective method opens a new way to obtain these types of molecules with cheap reagents, in high yields, with excellent stereoselectivity (Z:E ratio >10:1), and with good tolerance of functional group. The reaction is radical based, avoiding the problem of beta-hydride elimination, which usually occurs in ionic reactions involving metal centers. In order to prove the versatility of this method, the vinyl boron compound formed from this reaction was used for further functionalizations. The formal total synthesis of a 5-HT_{2c} receptor agonist was successfully performed, improving the overall yield of the process, and avoiding the use of expensive and polluting chemicals.

The third chapter of this thesis is concentrated on the development of a tandem photoredox/metal base catalyzed functionalization of anilines and imines with alkyl carboxylic esters. In this reaction, no late

transition metal is used, and the traditional metal-based photocatalyst is substituted with an inexpensive and more efficient organic dye. The alkylation of amines is a challenging topic in organic chemistry and classical nucleophilic substitution lacks selectivity and scope. Harvesting visible light with a photoredox catalyst opens the possibility to a radical pathway, making this coupling easy and with high tolerance for functional groups. In order to understand the catalytic cycle of the reaction, additional mechanistic studies were conducted, leading to some insight on how this reaction works.

Résumé

Les liaisons C-C et C-N sont entre les structures les plus courantes dans les molécules allant des médicaments aux catalyseurs et aux additifs alimentaires. De nombreuses réactions de couplage ont été développées pour former ces types de liaisons avec un' excellente sélectivité et des bonnes performances. Pourtant, la synthèse de certaine des ces espèces dépend de méthodes traditionnelles ou nécessite des réactifs et des catalyseurs coûteux et rares. L'utilisation des métaux précieux en chimie, et en particulier dans l'industrie, peut rendre la synthèse moléculaire coûteuse et consommatrice d'énergie car l'extraction des ces matériaux est coûteuse. De plus, en catalyse homogène, la récupération des catalyseurs à base des métaux est quasiment impossible, rendant ces procédés non durables pour l'avenir. Ainsi, la découverte de réactions chimiques n'impliquant pas de matériaux précieux est indispensable. Cette thèse se concentre sur le développement de deux transformations chimiques, l'une réalisant un couplage réducteur de radicaux sp2-sp3, l'autre réalisant une alkyl amination photocatalysée, impliquant des réactifs et des catalyseurs peu coûteux.

Le premier chapitre passe en revue les méthodologies existantes qui utilisent des radicaux alkyles pour former des liaisons carbone-carbone et carbone-azote. Les radicaux alkyle sont formés à partir d'halogénures d'alkyle et de pseudo-halogénures (acides, esters, tosylates, etc.) par oxydation ou réduction réalisée par un catalyseur métallique ou photorédox. La grande variété de méthodologies disponibles a été illustrée, mettant en évidence les avantages et les faiblesses de chaque réaction.

Le deuxième chapitre de cette thèse est consacré au développement d'une nouvelle méthode catalytique à base de fer pour former de manière stéréosélective des espèces de Z-alcène bore à partir du bore-alcyne correspondant. Cette nouvelle méthode stéréosélective ouvre une nouvelle voie pour obtenir ces types de molécules avec des réactifs bon marché, avec des rendements élevés, avec une excellente stéréosélectivité (rapport Z: E> 10: 1), et avec une bonne tolérance de groupe fonctionnel. La réaction est basée sur les radicaux, évitant le problème de l'élimination des bêta-hydrures, qui se produit généralement dans les réactions ioniques impliquant des centres métalliques. Afin de prouver la polyvalence de cette méthode, le composé vinyl-bore formé à partir de cette réaction a été utilisé pour d'autres fonctionnalisations. La synthèse totale formelle d'un

agoniste du récepteur 5-HT2c a été réalisée avec succès, améliorant le rendement global du procédé et évitant l'utilisation de produits chimiques coûteux et polluants.

Le troisième chapitre de cette thèse se concentre sur le développement d'une fonctionnalisation catalysée en tandem photorédox / base métallique d'anilines et d'imines avec des esters alkylcarboxyliques. Dans cette réaction, aucun métal de transition tardif n'est utilisé, et le photocatalyseur traditionnel à base de métal est remplacé par un colorant organique peu coûteux et plus efficace. L'alkylation des amines est un sujet difficile en chimie organique et la substitution nucléophile classique manque de sélectivité et de portée. La récolte de la lumière visible avec un catalyseur photoredox ouvre la possibilité d'une voie radicale, rendant ce couplage facile et avec une tolérance élevée pour les groupes fonctionnels. Afin de comprendre le cycle catalytique de la réaction, des études mécanistiques supplémentaires ont été menées, ce qui a permis de mieux comprendre le fonctionnement de cette réaction.

Riassunto

I legami C-C e C-N sono alcune delle strutture più comuni nelle molecole che vanno dai farmaci ai catalizzatori e agli additivi alimentari. Per formare questi tipi di legami, sono state sviluppate molte reazioni che danno eccellente selettività e ottime rese. Tuttavia, la sintesi di alcune di queste specie dipende da metodi tradizionali e richiede reagenti e catalizzatori costosi e rari. L'uso di metalli preziosi in chimica, e in particolare nell'industria, può rendere la produzione di prodotti chimici costosa e ad alta richiesta energetica poiché l'estrazione di quei materiali è laboriosa. Inoltre, nella catalisi omogenea, il recupero dei catalizzatori metallici è quasi impossibile, rendendo questi processi insostenibili per il futuro. Pertanto, la scoperta di reazioni chimiche che non coinvolgono materiali preziosi è indispensabile. Questa tesi si concentra sullo sviluppo di due nuove metodologie, una che esegue un accoppiamento riduttivo radicale sp2-sp3, l'altra che esegue un'amminazione alchilica fotocatalizzata, che coinvolge reagenti e catalizzatori economici.

Il primo capitolo esamina le metodologie esistenti che utilizzano i radicali alchilici per formare legami carbonio-carbonio e carbonio-azoto. I radicali alchilici sono formati da alogenuri alchilici e pseudo-alogenuri (acidi, esteri, tosilati, ecc.) tramite ossidazione o riduzione eseguita dal catalizzatore metallico o fotoredox. È stata illustrata l'ampia varietà di metodologie disponibili, evidenziando i vantaggi e i punti deboli di ciascuna reazione.

Il secondo capitolo di questa dissertazione è dedicato allo sviluppo di un nuovo metodo catalitico a base di ferro per formare stereoselettivamente Z-boro alcheni dal corrispondente boro-alchino. Questo nuovo metodo stereoselettivo apre una nuova via per ottenere questi tipi di molecole con reagenti economici, ad alte rese, con eccellente stereoselettività (rapporto Z: E> 10: 1) e con buona tolleranza di molti gruppi funzionali. La reazione è radicalica, evitando il problema della beta eliminazione dell'idrogeno, che di solito si verifica nelle reazioni ioniche che coinvolgono catalizzatori con metalli di transizione. Per dimostrare la versatilità di questo metodo, il composto boro-alchene formato da questa reazione è stato utilizzato per ulteriori funzionalizzazioni. La sintesi formale di un agonista del recettore 5-HT2c è stata eseguita con successo, migliorando la resa complessiva del processo ed evitando l'uso di sostanze chimiche costose e inquinanti.

Il terzo capitolo di questa tesi è concentrato sullo sviluppo di una funzionalizzazione di aniline e immine con esteri alchil carbossilici catalizzata da un tandem fotoredox/catalizzatore metallico. In questa reazione, non viene utilizzato alcun metallo di transizione pesante e il tradizionale fotocatalizzatore a base di metallo viene sostituito con un catalizzatore organico economico e più efficiente. L'alchilazione delle ammine è un argomento impegnativo in chimica organica e la classica sostituzione nucleofila classica manca di selettività e portata. L'utilizzo della luce visibile con un catalizzatore fotoredox apre la possibilità a un percorso radicale, rendendo questo accoppiamento facile e con un'elevata tolleranza per i gruppi funzionali. Al fine di comprendere il ciclo catalitico della reazione, sono stati condotti ulteriori studi meccanicistici, che hanno portato ad alcune informazioni su come questa reazione possa funzionare.

Abstrakt

C-C- und C-N-Bindungen sind einige der häufigsten Strukturen in Molekülen, die von Arzneimitteln über Katalysatoren bis hin zu Lebensmittelzusatzstoffen reichen. Viele Kupplungsreaktionen wurden entwickelt, um diese Arten von Bindungen mit ausgezeichneter Selektivität und guter Leistung zu bilden. Die Synthese einiger dieser Spezies hängt jedoch entweder von traditionellen Methoden ab oder erfordert teure und seltene Reagenzien und Katalysatoren. Die Verwendung von Edelmetallen in der Chemie und insbesondere in der Industrie kann die molekulare Synthese teuer und energieintensiv machen, da die Extraktion dieser Materialien kostspielig ist. Darüber hinaus ist bei der homogenen Katalyse die Rückgewinnung von Katalysatoren auf Metallbasis nahezu unmöglich, was diese Prozesse für die Zukunft nicht nachhaltig macht. Daher ist die Entdeckung chemischer Reaktionen, an denen keine wertvollen Materialien beteiligt sind, unverzichtbar. Diese Arbeit konzentriert sich auf die Entwicklung von zwei chemischen Umwandlungen, von denen eine radikalreduzierende sp2-sp3-Kupplung und eine photokatalysierte Alkylaminierung mit kostengünstigen Reagenzien und Katalysatoren.

Das erste Kapitel befasst sich mit den bestehenden Methoden, bei denen Alkylradikale zur Bildung von Kohlenstoff-Kohlenstoff- und Kohlenstoff-Stickstoff-Bindungen verwendet werden. Alkylradikale werden aus Alkylhalogeniden und Pseudohalogeniden (Säuren, Estern, Tosylaten usw.) durch Oxidation oder Reduktion durch Metall- oder Photoredoxkatalysator gebildet. Die Vielzahl der verfügbaren Methoden wurde veranschaulicht, wobei die Vor- und Nachteile jeder Reaktion hervorgehoben wurden.

Das zweite Kapitel dieser Dissertation befasst sich mit der Entwicklung einer neuen katalytischen Methode auf Eisenbasis zur Bildung stereoselektiver Z-Alken-Borspezies aus dem entsprechenden Bor-Alkin. Diese neuartige stereoselektive Methode eröffnet einen neuen Weg, um diese Arten von Molekülen mit billigen Reagenzien in hohen Ausbeuten, mit ausgezeichneter Stereoselektivität (Z: E-Verhältnis> 10: 1) und mit guter Toleranz gegenüber funktionellen Gruppen zu erhalten. Die Reaktion basiert auf Radikalen und vermeidet das Problem der Beta-Hydrid-Eliminierung, die normalerweise bei ionischen Reaktionen mit Metallzentren auftritt. Um die Vielseitigkeit dieses Verfahrens zu beweisen, wurde die aus dieser Reaktion gebildete

Vinylborverbindung für weitere Funktionalisierungen verwendet. Die formale Totalsynthese eines 5-HT2c-Rezeptoragonisten wurde erfolgreich durchgeführt, wodurch die Gesamtausbeute des Verfahrens verbessert und die Verwendung teurer und umweltschädlicher Chemikalien vermieden wurde.

Das dritte Kapitel dieser Arbeit konzentriert sich auf die Entwicklung einer Tandem-Photoredox / Metallbase-katalysierten Funktionalisierung von Anilinen und Iminen mit Alkylcarbonsäureestern. Bei dieser Reaktion wird kein spätes Übergangsmetall verwendet, und der herkömmliche Photokatalysator auf Metallbasis wird durch einen kostengünstigen und effizienteren organischen Farbstoff ersetzt. Die Alkylierung von Aminen ist ein herausforderndes Thema in der organischen Chemie, und der klassischen nukleophilen Substitution mangelt es an Selektivität und Umfang. Die Ernte von sichtbarem Licht mit einem Photoredoxkatalysator eröffnet die Möglichkeit eines Radikalwegs, wodurch diese Kupplung einfach und mit hoher Toleranz für funktionelle Gruppen erfolgt. Um den Katalysezyklus der Reaktion zu verstehen, wurden zusätzliche mechanistische Studien durchgeführt, die zu Einsichten über die Funktionsweise dieser Reaktion führten.

List of Symbols and Abbreviations

˚**C** Celsius

Ac acetyl

acac acetylacetonate

Ad adamantanyl

Ar aryl

BINOL 1,1’-Bi-2-naphthol

Bn benzyl

Boc tert-butyloxycarbonyl

bpy 2,2'-bipyridyl

Bu butyl, n-butyl

cat. catalyst

cm^{-1} wavenumber

Cp Cyclopentadienyl

Cy cyclohexyl

d.r. diastereomeric ratio

DABCO 1,4-diazabicyclo[2.2.2]octane

DBU 1,8-diazabicyclo(5.4.0)undec-7-ene

DCE 1,2-dichloroethane

DCM dichloromethane

DFT density-functional theory

diglyme bis(2-methoxyethyl) ether

DMA N,N-dimethylacetamide

DME 1,2-dimethoxyethane

DMF N,N-dimethylformamide

DMSO dimethylsulfoxide

dppe 1,2-bis(diphenylphosphino)ethane

dppf 1,1′-bis(diphenylphosphino)ferrocene

dtbpy 4,4'-di-tert-butyl-2,2'-dipyridyl

equiv. equivalent

ESI electrospray Ionization

ET energy transfer

Et ethyl

EWG electron-withdrawing group

g gram

GC gas chromatography

GC/MS gas chromatography/mass spectrometry

h hour

HOMO Highest occupied molecular orbital

HRMS high-resolution mass spectrometry

LED light-emitting diode

L_n Ligand

LUMO lowest unoccupied molecular orbital

m- meta

m meter

M molar

m multiplet

Me methyl

Mes 2,4,6-trimethylphenyl

mg miligram

MHz megahertz

min. minute

mL mililiter

MLCT Metal to ligand charge transfer

NHPI N−(acyloxy)phthalimides

NMP N-methylpyrrolidone

NMR Nuclear Magnetic Resonance

Nu nucleophile

o- ortho

p- para

PC photocatalyst

Ph Phenyl

phen 1,10-phenanthroline

ppy phenylpyridine

Pr propyl

Py pyridine

R carbon chain

RT room temperature

SCE saturated calomel electrode

SET single electron transfer

T temperature

t triplet

tBu ter-butyl

td triplet of doublet

Tf trifluoromethanesulfonyl

THF tetrahydrofuran

TLC Thin-layer chromatography

tmeda tetramethylethylendiamine

TMS trimethylsilyl

Tol tolyl

δ chemical shift

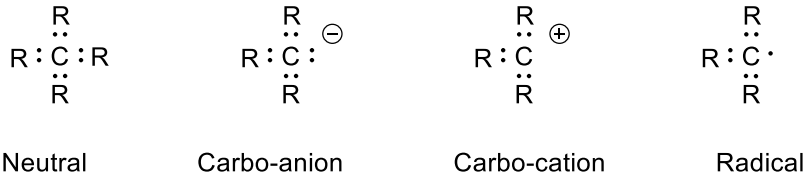
Table of contents

1. C-C and C-N coupling via alkyl radical

1.1 The use of carbon radical in organic synthesis

A carbon atom in an organic molecule can be neutral or charged. A usual stable carbon atom is neutral, this means that each of the four electrons of the outer shell are coupled and involved in a covalent bond with other atoms. If this situation is perturbed the carbon can lose or acquire an electron becoming a carbo-cation or carbo-anion. The large majority of organic chemistry reactions are based on the use of one of these two unstable and reactive carbon species to form new bonds (Scheme 1.1).

However, also another reactive species, usually understudied, exists: the radical.[1] A radical is formed when there is a homolytic dissociation of a chemical bond. This leaves the carbon atom with no formal charge but, since it is no more surrounded by 8 electrons in the outer shell, it is a very reactive and unstable species (Scheme 1.1).



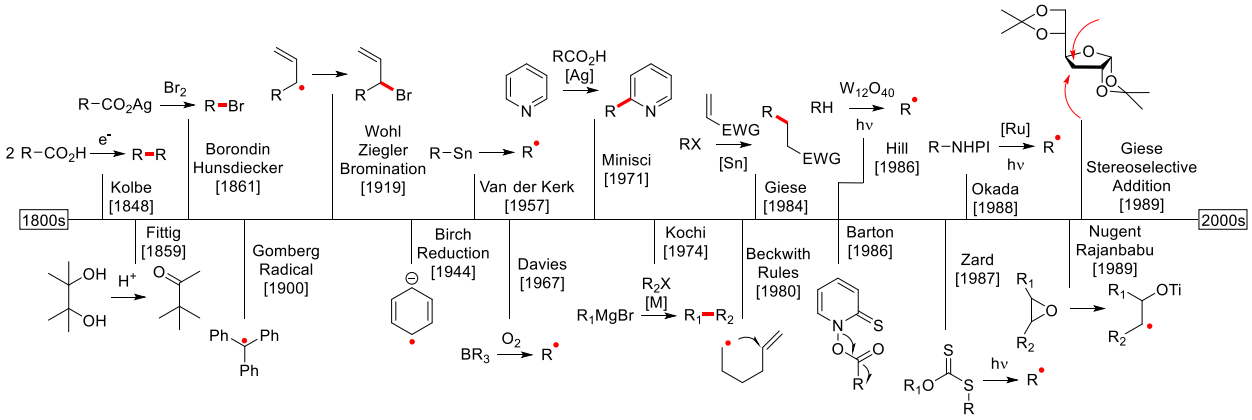
Scheme 1.1. A carbon atom in an organic molecule in its neutral form, as a carbo-anion, as a carbo-cation, and as a radical.

The first radical reaction was reported in 1848 by Kolbe, with a decarboxylative electrolysis that gave as product the C-C coupling of two acids. The reaction had poor selectivity with the formation of the homocoupling products (Scheme 1.2).[2,3] Later Fittig reported a pinacol rearrangement in acid ambient with a supposed radical pathway.[4] Borondin and Hunsdiecker discovered the decarboxylation of carboxylic silver salts to form halides.[5–7] The Wohl-Ziegler bromination is an early and useful tool for allylic and benzylic bromination, even with some uncertainties on the mechanism.[8–10]

It is necessary to wait until 1900 to have the first described radical. Gomberg was able to isolate as stable triphenyl radical from 1-chloro, triphenylmethane.[11] In 1944, Birch opens a completely new dimension on aromatic compound chemistry with one of the most famous radical reaction.[12–14] Van der Kerk developed a tin

promoted radical substitution, taking the lead on the vast tin-promoted radical chemistry.[15,16] In the late '60s Davies contributed with an oxidative homolysis of boronic species promoted by U.V. light.[17,18] Minisci heterocycle C-H activation gave a useful tool for heterocycle functionalization.[19–21] With the advent of palladium C-C coupling chemistry, Kochi developed a variation of Kumada coupling without the use the precious metal proposing a radical mechanism.[22]

In the '80s, Giese contributed a lot in tin radical chemistry, firstly with his tin mediated reductive coupling.[23–25] Tin free versions were developed recently.[26,27] Beckwith set important rules for radical cyclizations.[28]



Scheme 1.2. Timeline of the major discoveries in carbon radical chemistry from the 1800s to the 2000s.

An important milestone was set by Barton's decarboxylative hydrogenation[29,30] and decarboxylative halogenation.[31] A few years later Hasebe and Tsuchiya improved the methodology adding decarboxylation via oxime.[32] In the late '80s, the use of U.V. light to form alkyl radical gained popularity. Hill did C-H activation of substituted carbons exciting polyoxotungstates with light,[33] while Zard's xanthate decomposition photomediated, successfully formed alkyl radicals.[34] The use of visible light was made possible with Okada decarboxylation of NHPI esters using an organic photocatalyst.[35,36] Nugent and RajanBabu expanded radical chemistry also on epoxides.[37–39]

The late '80s until the beginning of the new millennium was a prolific period for enantioselective radical chemistry. Giese's contribution to enantioselective radical additions is surely very important.[40] He also contributed for the use of silicon, instead of tin as a radical mediator.[41] Other important contributions were

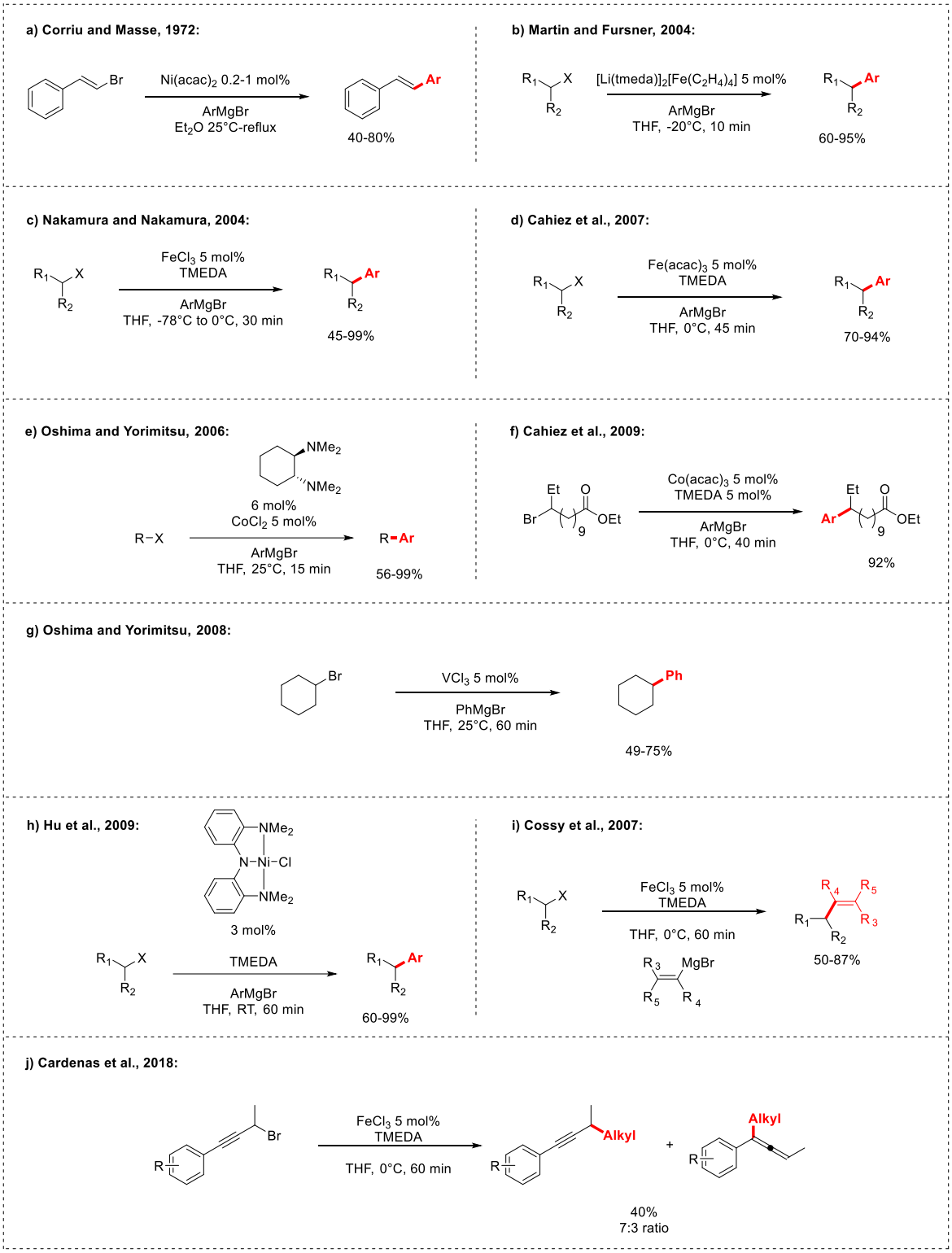
made with more specific studies on radical selectivity such as acylamides as asymmetric inductors for radical stereoselectivity.[42–45]

1.2 C-C bond formation via alkyl radicals from alkyl halides

1.2.1 Radical formation via metal catalysis

Alkyl halides are an optimal source of alkyl radicals. The bond between the halogen atom (usually bromine or iodine) and carbon is weak and easily reduced by transition metals. One of the most common partners of a carbon halide to perform C-C coupling is a Grignard reagent, both aryl and alkyl.

The first attempts were made in order to improve the palladium-based Kumada coupling, which usually gives the formation of an sp^2-sp^3 bond. [46,47] The substitution of palladium with less noble metals gave good results (Scheme 1.3, a). For example, the use of low valent iron as a catalyst for an alkyl halide-aryl Grignard cross-coupling by Martin and Fursner (Scheme 1.3, b).[48] Similar parallel studies were performed by Nakamura and Nakamura using $FeCl_3$ and organic base additives to obtain a similar result regarding scope and yields (Scheme 1.3, c).[49] Cahiez et al. developed the same cross-coupling using $Fe(acac)_3$ and TMEDA as catalyst (Scheme 1.3, d). In this case, a hypothesis of mechanism was made, involving a Fe^0/Fe^{II} cycle with the presence of a formal free alkyl radical, but no further experiments were performed to prove it.[50]



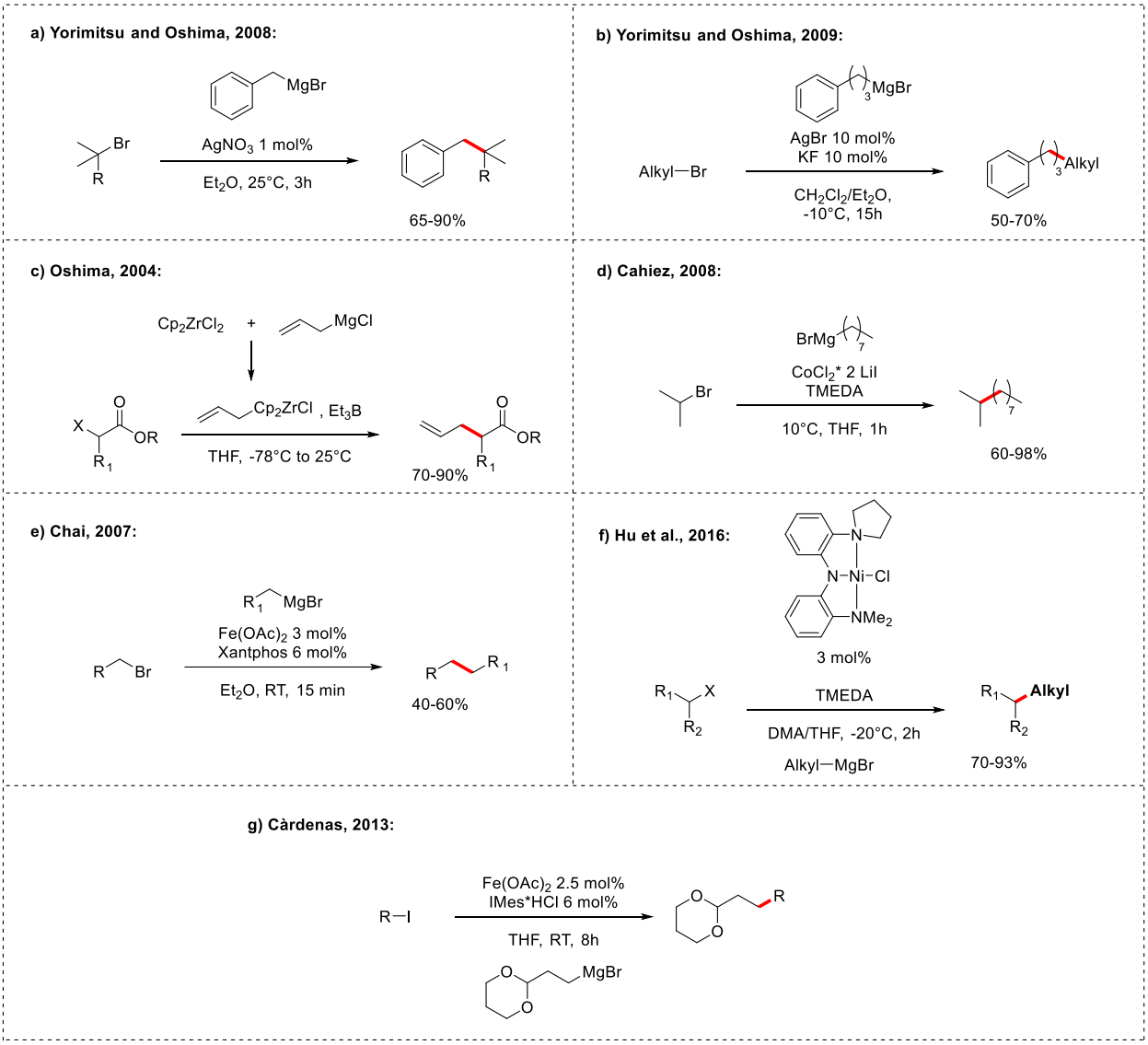
Scheme 1.3. Sp^2-sp^3 C-C radical coupling using light transition metals as catalysts.

In addition, other transition metals were used to perform the Kumada coupling. Cobalt Chloride diamine complex was a good candidate even if it did not work with tertiary halides (Scheme 1.3, e).[51] Chaiez used $Co(acac)_3$ and TMEDA successfully functionalizing different aryl Grignards, but also in this case substitution with tertiary halides were unsuccessful (Scheme 1.3, f).[52] Similar results were also obtained with vanadium (Scheme 1.3, g),[53] and Nickel-metal complexes (Scheme 1.3, h).[54,55]

The coupling of unactivated primary and secondary halides with non-aryl Grignards is more challenging. Cossy reported a radical coupling of unactivated secondary and primary alkyl halides (iodine and bromine) with vinyl Grignards (Scheme 1.3, i).[56] This method is successful for many halides, but the presence of different side products is reported. The homocoupling of the halide and its β-hydride elimination are the two most common side products that are inborn in this specific reaction. Similar problems were reported independently.[57]

Propargylic halides were are used to couple with aliphatic Grignards, but with a quite poor selectivity between the alkyne and the allenic product (Scheme 1.3, j).[58]

Sp^3-sp^3 coupling is surely a more complex challenge. The use of an unactivated alkyl halide and an alkyl Grignard leads to a multitude of possible side reactions. If in the case of aryl Grignard - alkyl halide coupling the side products were mainly formed by the alkyl halide (β-hydride elimination and homocoupling), in this case, byproducts are formed also by the alkyl Grignard, that undergoes to the same problems of β-hydride elimination and homocoupling once the alkyl chain is bonded to the catalyst metal center.[59] Anyway, some methods of sp^3-sp^3 coupling were successful, like the silver catalyzed coupling, developed by Oshima, between primary, secondary, and tertiary alkyl halides and benzylic Grignards (Scheme 1.4, a).[60] The method was subsequently expanded for linear alkyl Grignards (Scheme 1.4, b).[61] Oshima also developed a method for the coupling of allyl Grignard and α-halogenated carbonyl compounds mediate via a zirconocene-olefin complex (Scheme 1.4, c).[62]



Scheme 1.4. Sp^3-sp^3 C-C radical coupling using light transition metals as catalysts.

Cahiez developed a procedure for the coupling of primary and secondary alkyl halides with $CoCl_2$ as the catalyst (Scheme 1.4, d).[63] The Chai group reported a similar method using a surprisingly low percentage of iron acetate (II) as catalyst (Scheme 1.4, e). The method works well only with primary halides.[59]

In more recent years more extensive and complete methods were reported. Hu et al. developed a second-generation "nikamine" catalyst able to perform the coupling between primary and secondary halides and alkyl Grignards, with a great tolerance for functional groups (Scheme 1.4, f).[55] Càrdenas reported an example of sp^3-sp^3 coupling using an iron salt with an NHC ligand (Scheme 1.4, g).[64]

1.2.2 Radical formation via photocatalysis

Another innovative and easy way to harvest alkyl radicals is by using visible light. This would avoid the use of dangerous and polluting radical activators, like the tin-based ones. Not many organic molecules though can absorb visible light due to their simple and non-conjugated structure. Thus, to use this environmentally friendly and cheap source of energy, the use of metal photocatalyst and organic dyes is necessary.

These classes of compounds are known to absorb visible light. Thus, the catalyst reaches an excited state. This means that one electron on the outer shell of the molecule/metal center (HOMO) jumps on a higher empty orbital (LUMO) leaving behind a hole in the previous orbital.[65]

In order to explain better how a photoredox catalysts work, we can take the example of the most famous of all: $[Ru^{II}(bpy)_3]^{2+}$. When $[Ru^{II}(bpy)_3]^{2+}$ is excited by a photon, the molecule moves one electron from the metal center to one of the ligands. This is called metal to ligand charge transfer (MLCT). Thus, the molecule will become $[Ru^{III}(bpy^{\bullet-})(bpy)_2]^{2+*}$. This allows the formation of a triplet state, which makes more difficult the relaxation of the molecule to the ground state, thus prolonging the lifetime of the excited state. When the lifetime of the excited state is long enough (from hundreds of ns to few μs), it is possible to use the photocatalysts in chemical reactions, since the longer lifetime permits intermolecular interactions.[66]

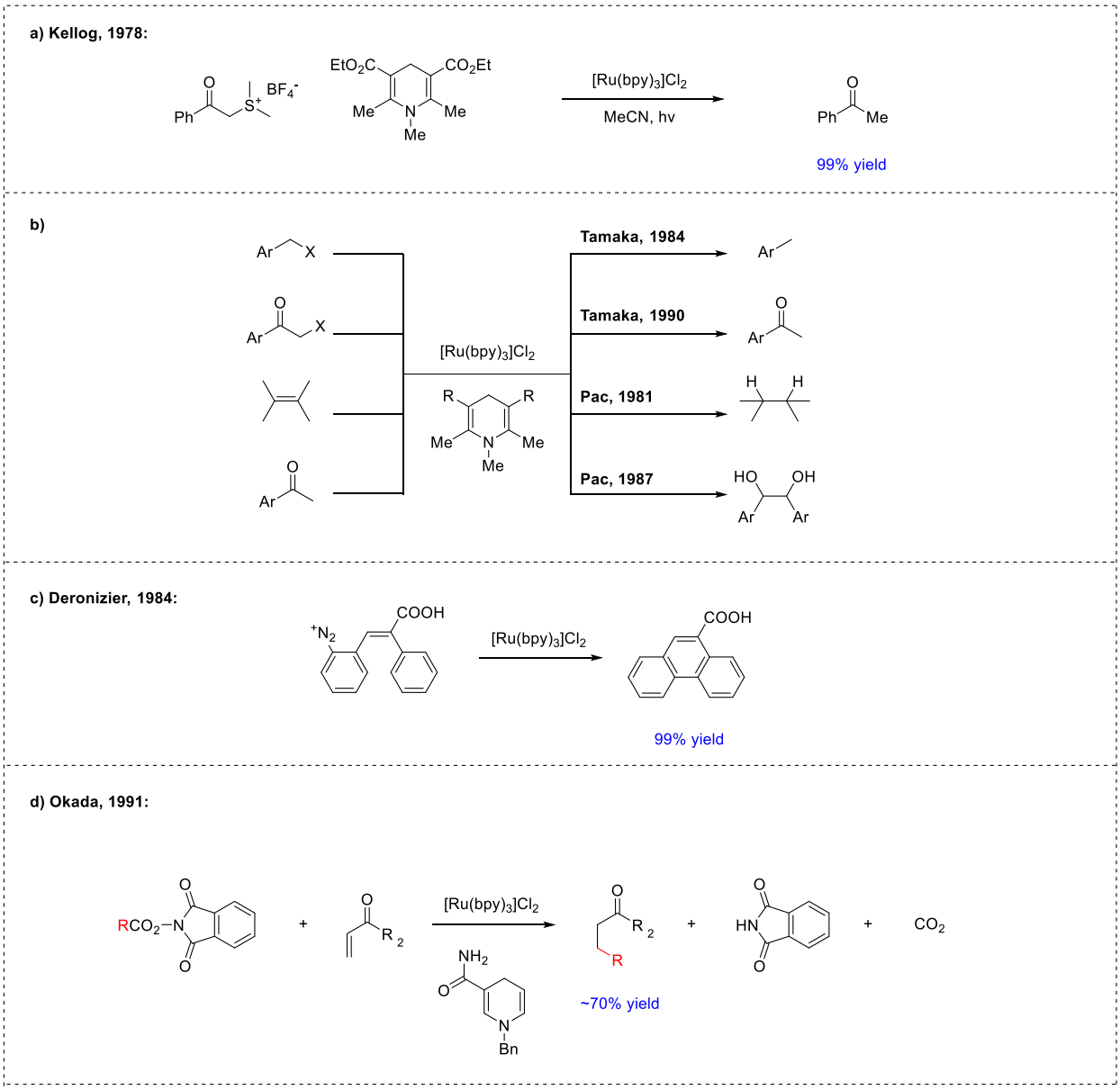
The usual excited state of a photocatalyst is both more oxidant and more reductive than the ground state, in fact, the unstable electronic nature of an excited state makes it easy both to lose or to gain one electron.

Moreover, the photocatalyst can return to a ground state in different ways. The first, and less interesting, is a non-radiative way. In this case, the photocatalyst's excited state rapidly goes back to the ground state dispersing the energy via vibration. This method of relaxation is always unproductive and, if a chemical species prefers this method of relaxation, it is not possible to use it as photocatalyst. The second method of relaxation is via energy transfer. The photocatalyst's excited state, in some circumstances, can pass the energy to a different molecular species. For this to happen, usually the photocatalyst and the molecule need to have an orbital overlap. The last method is the electron transfer. The photocatalyst's excited state gives or receives an electron from another chemical species going to a relaxed oxidized or reduced version of the initial

photocatalyst. This last method of relaxation is the one that is most often used to explain the mechanism of photocatalytic reactions.

Photoredox catalysts were already used a few decades ago to perform different reaction such as water splitting, CO_2 reduction or as components of solar panels.[67–70] The first molecular transformation performed by a photocatalyst and visible light was published by Kellog in 1978. The reaction was a photoinduced reduction of sulfonium ions using N-substituted dihydropyridine as reducing agent and $[Ru^{II}(bpy)_3]^{2+}$ as the catalyst to obtain the corresponding alkane and thioether (Scheme 1.5, a).[71,72]

The N-substituted dihydropyridine - $[Ru^{II}(bpy)_3]^{2+}$ system was later found to work in a wide variety of reductions. Such as benzylic halides[73,74] and phenacyl halides[75] (by Tanaka and co-workers), olefins[76–78] and aromatic carbonyl compounds (Scheme 1.5, b).[79]



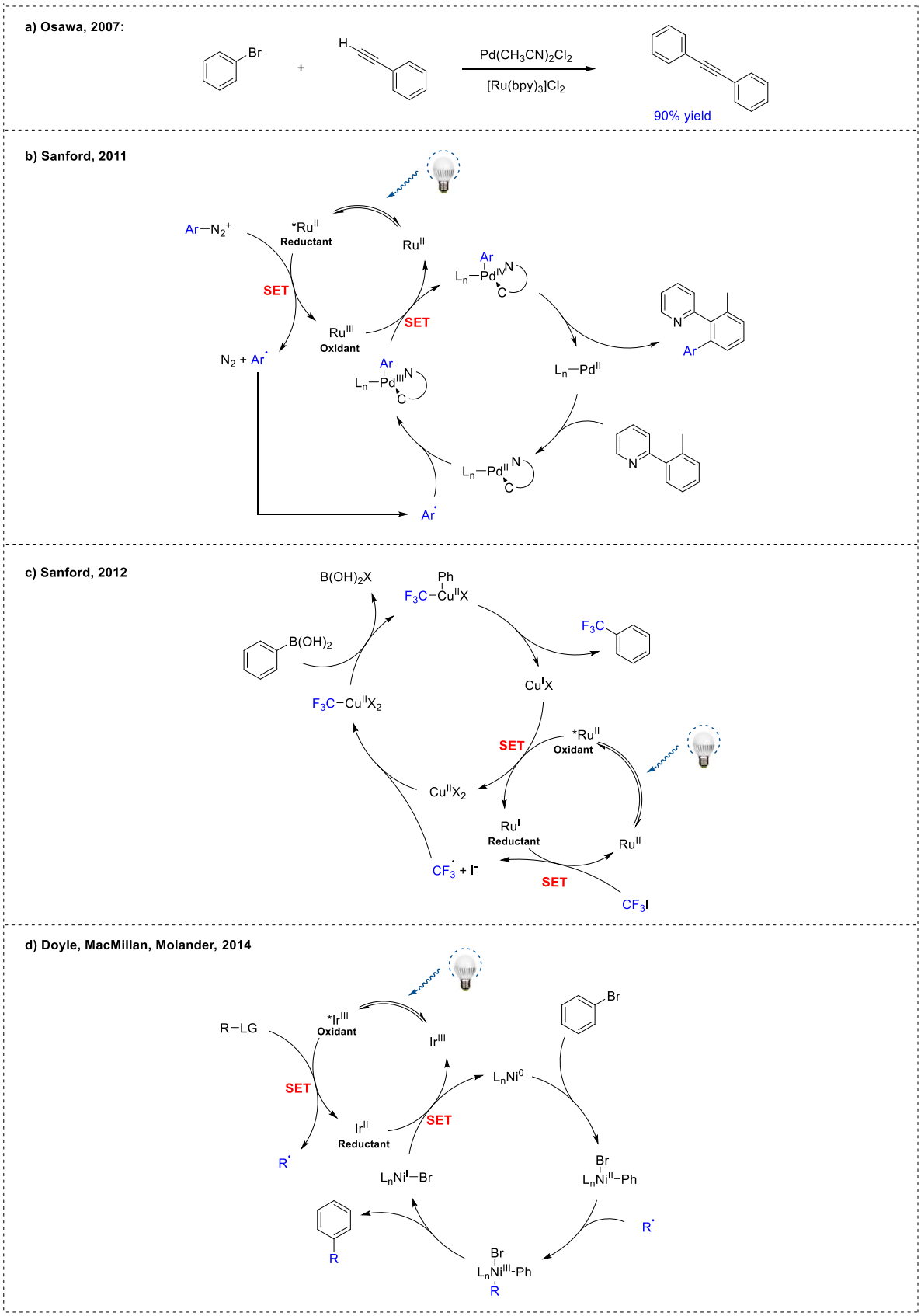
Scheme 1.5. Early uses of photocatalysis in organic synthesis.

In 1984 the first oxidative reaction with a photocatalyst was reported by Deronzier with a cyclization of a diazonium salt of benzophenone. In order to close the catalytic cycle of $[Ru^{II}(bpy)_3]^{2+}$, the oxidation of benzylic alcohol to aldehyde was used.[80] Shortly after the first redox neutral reaction was reported with a Pschorr reaction performed with a photocatalyst. The advantage of a redox neutral reaction was that no sacrificial oxidant or reducing agent was needed, reducing the waste and the complexity of the reaction system (Scheme 1.5, c).[81,82]

In 1991 Okada and coworkers discovered that the carboxylic esters of N(hydroxyl)phthalimide could be an effective source of alkyl radicals (Scheme 1.5, d). With a reduction performed by the photocatalyst, the ester fragments in CO_2, phthalimide (after protonation), and an alkyl radical. In this work, the radical was intercepted by a Michael acceptor.[36]

The main advantage of the use of a photocatalyst it is surely the possibility to have a strong oxidant/reductant in the solution (the excited state of the photocatalyst) without needing strong reaction conditions to obtain that. Often solely metal catalyze reaction needs to pass high energy transition states that make the reaction incompatible with sensitive functional groups.

In the last two decades, the use of a photocatalyst paired with a metal-based catalytic cycle was studied and many different new methodologies were discovered. The first example was reported by Osawa in 2007.[83] A Sonogashira C-C coupling performed in presence of $[Ru^{II}(bpy)_3]^{2+}$ and palladium (Scheme 1.6, a). The authors supposed that the ruthenium photocatalyst was able to substitute the usual copper salt used in the classical reaction,[84] but no hypothesis on the mechanism was made. In order to have a description of the mechanism of the reaction, to understand better the role that the photocatalyst was playing, the report from Stanford on his C-H arylation using diazonium salts can be of help.[85,86] The authors proposed mechanism, sees $[Ru^{II}(bpy)_3]^{2+}$ used in two parts of the catalytic cycle (Scheme 1.6, b). After excitation of the photocatalyst via visible light to Ru^{II}*, it reduces the diazonium salt, producing nitrogen gas and the aryl radical. The palladium catalyst, already coordinated to the aryl pyridine, captures the free aryl radical previously formed, becoming Pd^{III}. The reduction of the diazonium salt leaves Ru^{III}, which is a good oxidant, which can perform a direct SET (single electron transfer) to form Pd^{IV}. The palladium then, with a reductive elimination, forms the desired product.



Scheme 1.6. Tandem photocatalysis/transition metal catalysis radical C-C couplings.

A similar synthetic strategy was introduced by Sanford in 2012 combining a photocatalyst and a copper-based catalyst to perform trifluoromethylation of aryl boronic species.[87] In fact, it was previously demonstrated by MacMillan that $[Ru^{II}(bpy)_3]^{2+}$ was able to produce trifluoromethyl radicals from CF_3I under mild conditions.[88,89] In the reaction by Sanford, the photocatalyst is used both for the formation of trifluoromethyl radicals and for the oxidation of the copper complex (Scheme 1.6, c).

The formation of a C-C bond via this dual photocatalyst/metal-based catalyst system was further expanded by Doyle and Macmillan,[90] and Molander[91] independently introducing a nickel-photocatalyst based sp^3-sp^2 C-C coupling. Doyle and MacMillan developed a coupling of α-carbonyl sp^3 carbons with aryl halides, while Molander reported an sp^3-sp^2 Suzuki-Miyamura coupling. Even if the two reactions differ in the substrates used, the reported mechanism is very similar and can be summarized in one figure (Scheme 1.6, d). In this case, the iridium based photocatalyst is used in a reductive quenching cycle, in opposition with the one described above, with the oxidation of the radical precursor first, and the reduction of Ni^I to Ni^0 after.

1.2 C-N bond formation via alkyl radicals

C-N bond formation is a useful tool in organic synthesis since many natural products and drugs have secondary and tertiary amines in their structure.[92] The most logical method to functionalize amines is a direct S_N2 nucleophilic substitution between a primary or secondary amine and a halide in the presence of a base. This method goes under the name of Hofmann alkylation.[93] Even if this procedure is very simple, is not often used in organic synthesis due to its lack of selectivity. In fact, it is almost impossible to avoid over alkylation, and the formation of a mixture of secondary, tertiary, and even quaternary amines is inevitable.

Some late transition metal-catalyzed alternatives were developed, such as the Buchwald-Hartwig palladium C-N coupling.[94,95] Only a few years later Buchwald introduced a new nickel catalyzed method, that has the advantage of working without an expensive metal.[96] Nickel II COD (cyclooctadiene) was used as the catalyst, the reaction temperature was 70 to 100°C and a base was needed. The paper reported a wide scope, using aryl

chloride as reagent (not possible with the classic Buchwald-Hartwig amination). The use of aryl bromides was also reported, but reduced aryl sub-product was recovered.

Examples with milder conditions, air-stable Ni precatalysts,[97] and coupling with non-aromatic amines[98–102] were later reported by Yang and Fort.

Amination with electrophiles was not limited to aryl halides, in fact, an early report from Yang demonstrated the possibility of coupling aliphatic and aromatic amines with aryl tosylates.[103] The tosyl group acts as pseudohalide, allowing an oxidative insertion on Ni^0 in the aryl-tosyl bond.

The use of pseudohalides to perform a metal-catalyzed amination expanded the synthetic power of this transformation. In the last decade, in fact, many other options as amine coupling partner were discovered. Coupling with aryl phosphates,[104] sulfamates and carbamates,[105–108] methyl ethers,[109,110] and aryl pivalates[111] made this reaction a potent tool in organic chemistry.

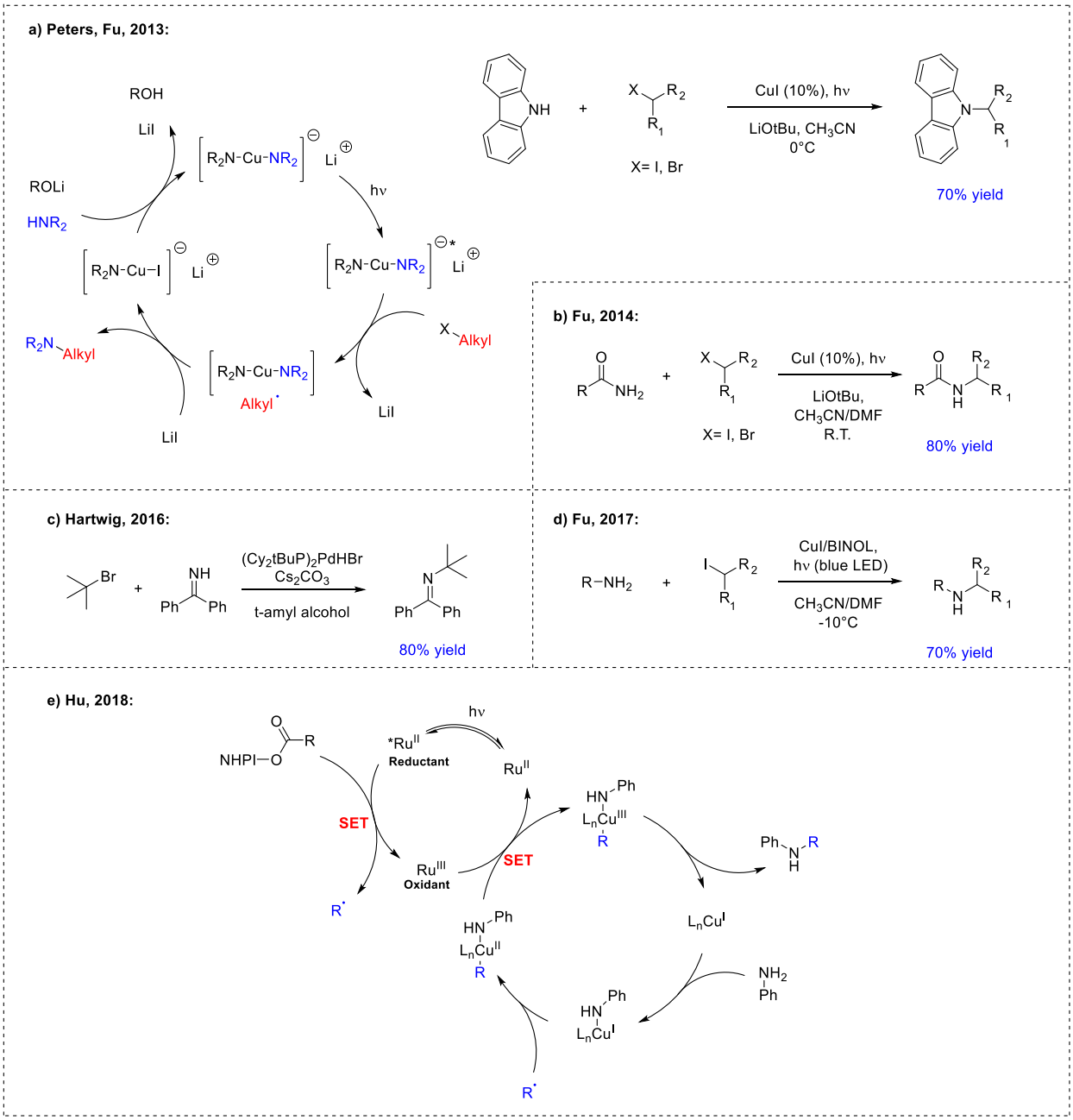
Amination becomes a challenge when aliphatic halides or pseudohalides are used. In this case, the use of traditional Buchwald-Hartwig or Ullmann coupling is ineffective due to the β-hydride elimination from metal-alkyl intermediates. Very sparse examples are present in the literature reporting this type of coupling performed by the sole metal catalyst, and they all have very limited scope.[112–117] To overcome these problems, different groups worked on a light/metal catalyst radical pathway, which overcome the β-hydride elimination problem.

Fu and Peters reported the first example of this method, performing an Ullmann coupling between an aryl halide and amines.[118] Even if in this work the N-alkylation is not performed, the reaction mechanism does not involve an oxidative addition of the metal into the C-X bond, but a single electron transfer (SET) between the excited Cu-amino complex and the halide. This innovative work showed the possibility of avoiding β-hydride elimination. In fact, soon after, the Fu group reported a coupling of carbazole with various aliphatic iodine halides.[119] The proposed mechanism starts with the coordination of the deprotonated carbazole to the copper complex (Scheme 1.7, a). Upon irradiation, the copper amino complex goes into an excited state, which can reduce the aliphatic halide, forming an alkyl radical. The radical coordinates to the copper that undergoes

reductive elimination forming the desired product. Notably, this copper-mediated C(sp^3)-carbazole cross-coupling was soon after reported in an asymmetric version, using visible light.[120]

Fu and Peter later reported a photoinduced coupling between alkyl halides (iodine and bromine) and amides and carbamates (Scheme 1.7, b).[121,122] The described mechanism is similar to the one described above, but the scope is limited to only secondary halides.

In 2016 Hartwig and coworkers developed a radical coupling between secondary and tertiary halides and benzophenone imine.[123] The latter is a synthetic equivalent of ammonia and can release a primary amine and benzophenone upon acidic hydrolysis (Scheme 1.7, c). The scope is limited to secondary and tertiary halides with good yields. The authors proposed that the process could start with the SET reduction of the alkyl halide by the Pd^0 complex. Even if the full mechanism is still unclear, on how the Pd^I complex could be involved in the C-N bond formation, evidence of the radical nature of the mechanism was displayed. Radical clock experiments and the incorporation of a THF molecule in the final product, when the reaction was performed in that solvent, are clear proof.



Scheme 1.7. Photomediated radical C-N coupling.

In 2017 Fu and Peters described a Cu-catalyzed N-alkylation of amines induced by visible light (Scheme 1.7, d).[124] This permitted the reaction to work in milder conditions.

Alkyl halides are not the only source of radicals. Fu and Peters developed a decarboxylative amination of NHPI esters.[125] The product of this reaction is the recombination of the alkyl radical formed by the reduction of the ester with the phthalimide.

The same concept was then used to form alkyl radical by Hu and coworkers to develop a tandem photocatalytic/metal-catalyzed C-N coupling.[126] The method comprehends the synthesis of substituted anilines with a wide scope of primary and secondary alkyl moieties. The proposed mechanism involved a dual catalytic cycle (Scheme 1.7, e); the ruthenium-based photocatalyst undergoes an oxidative quenching reducing the NHPI ester. The copper catalyst, after coordination with aniline, can coordinate the alkyl radical formed after decomposition of the NHPI ester radical anion. The Cu complex then is oxidized by the highly oxidative Ru^{III} species, regenerating the photocatalyst. Thus, the copper complex undergoes reductive elimination, forming the product.

1.3 Conclusions

Late transition metal catalysis became, in recent times, an indispensable tool in organic chemistry. The majority of C-C or C-heteroatom coupling can be performed successfully with late transition metal catalysis and many of these methodologies are broadly used in the industry.

The main problem of late transition metals is their rarity on earth's crust. Palladium, platinum, ruthenium, and iridium are some of the most expensive and rare metals, and it is usually difficult to recover them when they are used as homogeneous catalysts. So, the development of alternative methods using cheaper and more abundant elements is very important for the sustainability of future chemical processes.

The use of light transition metals, such as copper, iron, and nickel opens the route to the development of new chemical reactions, where it is possible to take advantage of some of the metal characteristics to repeat results obtained with late transition metal catalysis and achieve new results.

In this work, we developed novel methodologies to achieve C-C and C-N couplings. Light transition metals and organic photocatalyst were studied and employed to perform these reactions. The aim of these projects is to develop new methodologies that allow to use cheap reagents and catalysts to synthetise complex molecules, being able to tolerate many functional groups, making these method appealing to use in synthetic organic chemistry.

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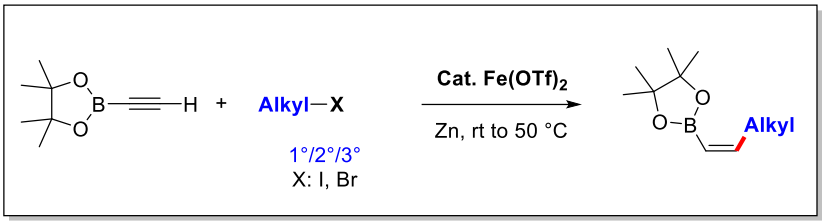
2. Z-Selective synthesis of vinyl boronates through Fe-catalyzed alkyl radical addition[a]



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2.1 Introduction

Z-Selective synthesis of 1,2-disubstituted alkenes is an important yet challenging task in organic synthesis.[1,2] Because the boronate group can be readily transformed into many common functional groups,[3] Z-olefins might be conveniently accessed from Z-vinyl boronates. While hydroborylation of terminal alkynes is an efficient method to synthesize vinyl boronates, it typically leads to E-isomers due to the syn addition mechanism (Figure 2.1a).[4–11] There are until now only three reports of Z-selective hydroboration of terminal alkynes, with limited scope for alkyl alkynes.[12–15] Here, an alternative approach to the synthesis of Z-vinyl boronates is described. This approach is based on Fe-catalyzed stereoselective addition of an alkyl radical, generated from an easily accessible alkyl halide under reductive conditions, to ethynylboronic acid pinacol ester (**1a**, Figure 2.1b)

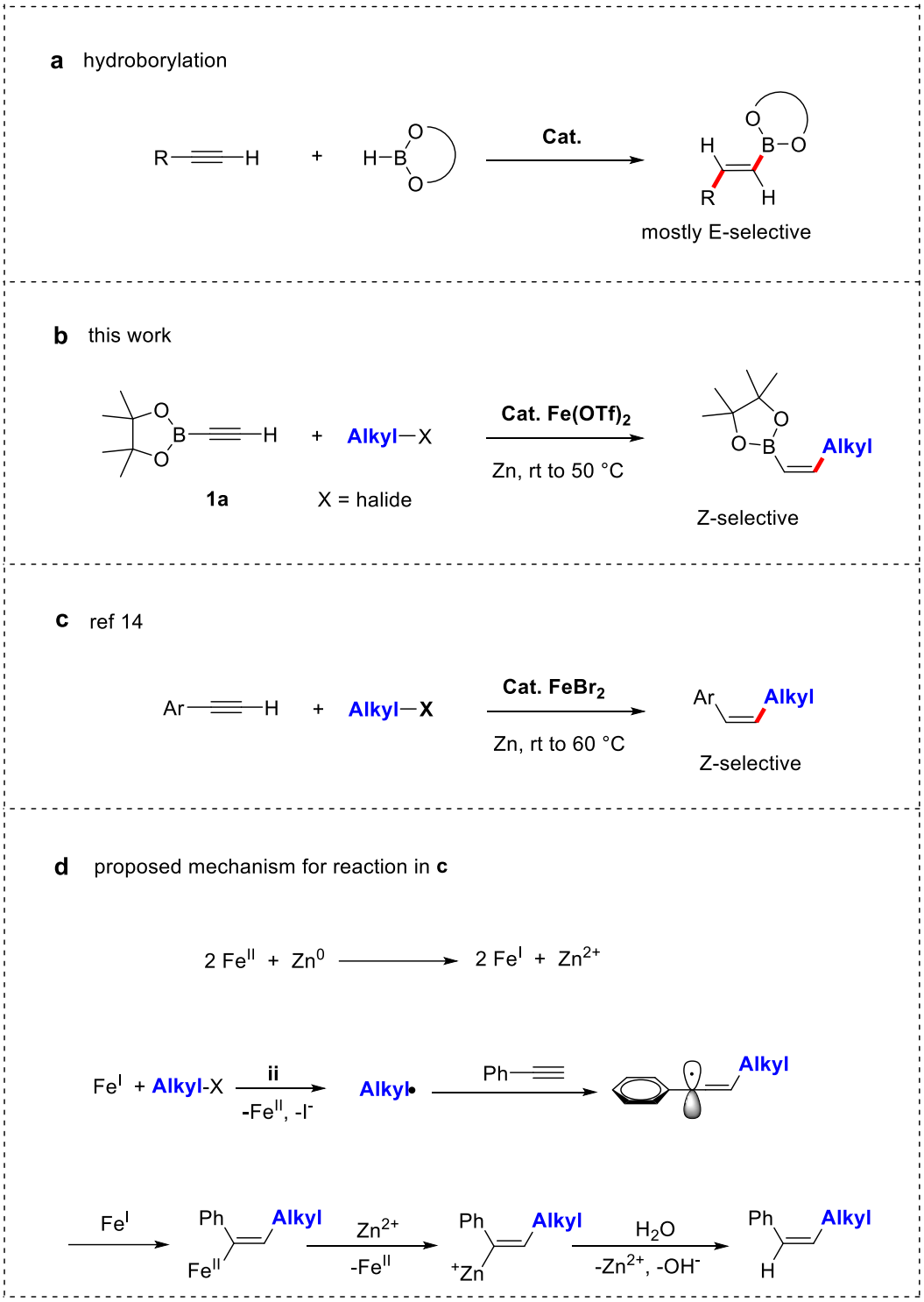
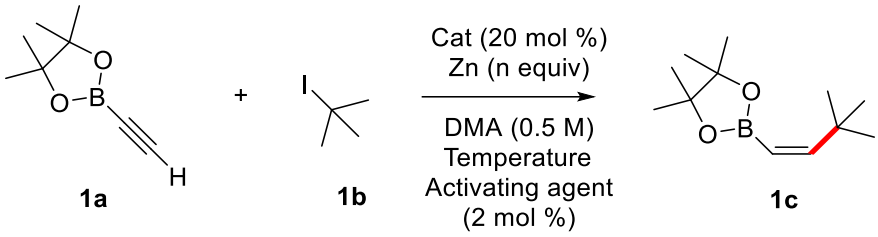


Figure 2.1. (a) Hydroborylation of alkyne to give vinyl boronates; (b) Synthesis of Z-vinyl boronates by Fe-catalyzed alkyl radical addition to **1a**; (c) Synthesis of Z-styrenes by Fe-catalyzed alkyl radical addition to aryl alkynes; (1d) The proposed mechanism for the reaction in c.

The approach is built upon a previous work developed by Hu and co-workers,[16–18] which showed that an alkyl radical was generated through the reaction of an alkyl halide with an Fe(I) species, produced by reduction of an Fe(II) catalyst with Zn (Figure 2.1c and 2.1d). The alkyl radical could be trapped by a terminal aryl alkyne to form a vinyl radical stabilized by an aryl group. Recombination of the vinyl radical with Fe(I) gave an Fe(II) vinyl intermediate. This step was stereoselective and favored a cis-arrangement of the aryl and alkyl groups. Transmatallation of the Fe(II) vinyl intermediate to Zn(II), followed by protonation, yielded the cis-alkene. In this chemistry, the aryl substituent of the alkyne was essential. Replacement of the aryl group by another electron-withdrawing group such as keto, ester, nitrile, or amide led to no formation of alkene. Here we show that the boronic acid pinacol ester group (Bpin) can serve the same function of an aryl group in stabilizing the vinyl radical. An important advantage of the Bpin group over an aryl group is that the former could be readily converted to numerous other functional groups, making this method of Z-alkene synthesis truly general.

2.2 Results and discussions

The reaction of **1a** with tert-butyl iodide (**1b**) was chosen as the test reaction (Table 2.1). At first, the conditions previously developed for the reductive coupling of ethynylbenzene with **1b**, that is, 1 equiv **1a**, 3 equiv of **1b**, 20 mol% of $FeBr_2$, 3 equiv of Zn metal, and 2 mol% of I_2 activator, DMA as solvent, 80°C, were employed (Table 2.1, entry 1). To our delight, a yield of 48% and a Z:E selectivity of 92:8 was obtained. Other metal salts such as $CuBr_2$, NiI_2, and CoI_2 were tested as catalysts. NiI_2 gave no yield, while $CuBr_2$ and CoI_2 gave lower yields but similar Z:E selectivity (Table 2.1, entries 2-4). FeI_2 had a similar efficiency to $FeBr_2$, but $Fe(OTf)_2$ (OTf = Triflate) gave a much higher yield of 82% when the reaction was conducted at 50°C (Table 2.1, entries 5-6). Unfortunately the Z:E selectivity dropped to 6:1. Replacement of the I_2 activator by TMS-I (TMS = tetramethyl silyl) led to a yield of 95% and a Z:E selectivity of 44:1 (Table 2.1, entry 7). When the loading of $Fe(OTf)_2$ was decreased to 10 mol%, the yield dropped to 42% (Table 2.1, entry 8). When the loading of Zn was decreased to 2 or 1 eq., the yields also dropped significantly (Table 2.1, entries 9-10).



entry	cat.	n	a.a.	temp. (°C)	yield (%)	Z:E[b]
1	$FeBr_2$	3	I_2	80	48	12:1
2	$CuBr_2$	3	I_2	80	33	13:1
3	NiI_2	3	I_2	80	0	n.d.
4	CoI_2	3	I_2	80	22	16:1
5	FeI_2	3	I_2	80	53	12:1
6	$Fe(OTf)_2$	3	I_2	50	82	6:1
7	$Fe(OTf)_2$	3	TMS-I	50	95	44:1
8	$Fe(OTf)_2$[c]	3	TMS-I	50	42	53:1
9	$Fe(OTf)_2$	1	TMS-I	50	2	n.d.
10	$Fe(OTf)_2$	2	TMS-I	50	47	130:1

Table 2.1. Optimization of conditions for the reaction of 2a with 2b. General conditions: Alkynyl Boronate Ester (0.5 mmol), terbutyl iodide (1.5 mmol), under N_2, in DMA (1 mL),. A.A. = Activating agent; Temp. = temperature; n.d. = not determined. [b]According to quantification by GC analysis. [c]10 mol% loading of catalyst.

The optimized conditions in Table 2.1 (entry 7) were applied for the coupling of **1a** with various tertiary and secondary alkyl iodides, yielding the corresponding Z-alkenes (Figure 2.2). Tert-butyl (**1c**), 1-adamantyl (**2b**), and tert-pentyl (**2c**) groups were added in high yields. Secondary alkyl groups such as 2-octyl (**2d**), cyclohexyl (**2e**), cyclooctyl (**2f**), 2-butyl (**2g**), 1-tert-butyl-4-cyclohexyl (**2h**) were added in good yields and selectivity as well. Addition of 2-propylbenzene (**2i**) and an ester-functionalized group (**2j**), on the other hand, had modest yields of about 40%. Alkyl bromides were then tested as substrates, but lower yields were obtained compared with alkyl iodides (e.g., for **2a**, **2c**, **2d**, **2f**, **2k**). The difference in stereoselectivity of some of the entry (**2f, 2k**)

between the iodine and the bromine is mainly due to instrument errors, since the reaction was performed in small scale. Cyclohexyl chloride was also tested, but no coupling was found.

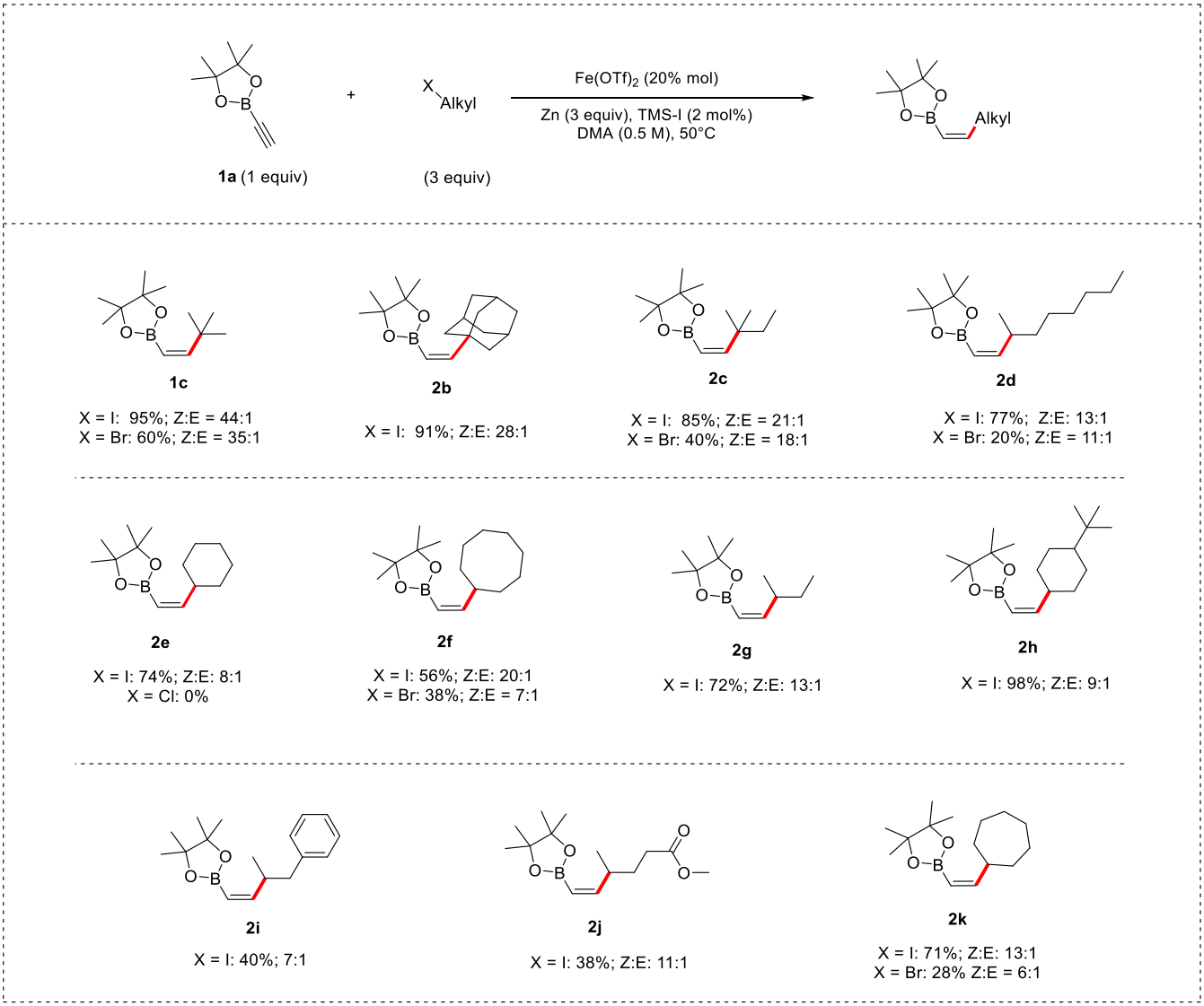
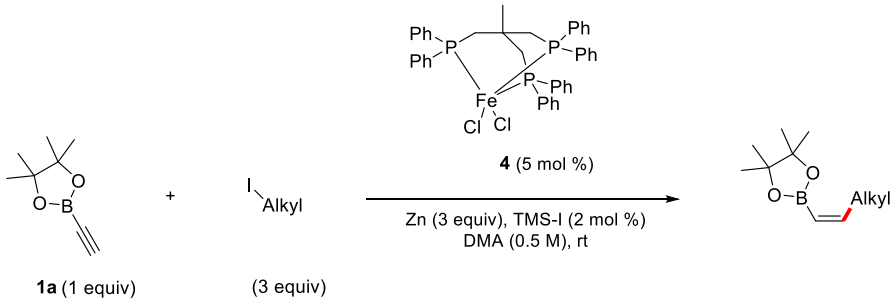
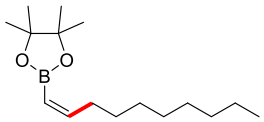


Figure 2.2. Scope of the coupling of 1 with tertiary and secondary alkyl halides. *Z:E* ratio calculated via ^{1}H NMR after purification.

When the same conditions were applied for the coupling of **1a** with primary alkyl iodides, very low yields were obtained. Upon further optimization, complex **4** was found to be a better catalyst than $Fe(OTf)_2$ (Figure 3). A new set of conditions were also identified: 1 equiv **1a**, 3 equiv of **1b**, 5 mol% of **4**, 3 equiv of Zn metal,

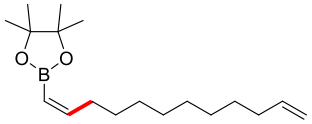
and 2 mol% of I_2 activator, DMA as solvent, room temperature (rt). The scope of this coupling was however limited. While for addition of n-octyl (**3a**) and dec-1-ene (**3b**) groups, the yields were good, the addition of other alkyl groups (**3c**-**3g**) had yields in the range of 20-35%. The use of halides with other functional groups gave non satisfactory results. The lower nucleophilicity of primary alkyl radicals compared to secondary and tertiary radicals might be the origin of the decreased efficiency of the reactions with primary alkyl iodides.





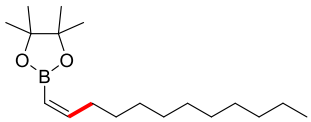
3a

Yield 77%
Selectivity Z:E: 10:1



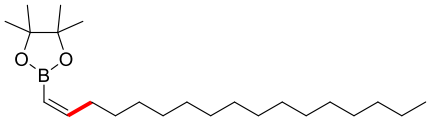
3b

Yield: 61%
Selecetivity Z:E: 10:1



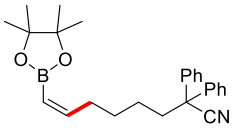
3c

Yield: 35%
Selectivity Z:E: 13:1



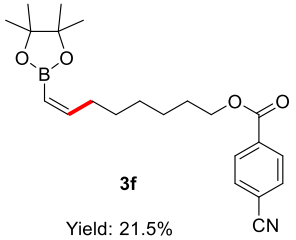
3d

Yield: 31%
Selectivity Z:E: 9:1



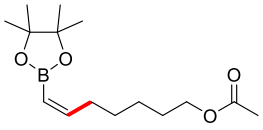
3e

Yield: 34%
Selectivity Z:E: 10:1



3f

Yield: 21.5%
Selectivity Z:E: 8:1



3g

Yield: 25.3%
Selectivity Z:E: 11:1

Figure 2.3. Scope studies for primary aliphatic halides. *Z:E* ratio calculated via ^{1}H NMR after purification.

The Z-vinyl boronate products obtained above could be converted to Z-alkenes bearing various functional groups by transformation of the Bpin group. For example, Pd-catalyzed Suzuki coupling of **2e** with ethyl 2-bromobenzoate gave **4a** in a 60% yield, bromination of **2b** with $CuBr_2$ gave **4b** in an 85% yield, and Cu-catalyzed azidation of **2b** with NaN_3 gave **4c** in an 86% yield (Figure 2.4).

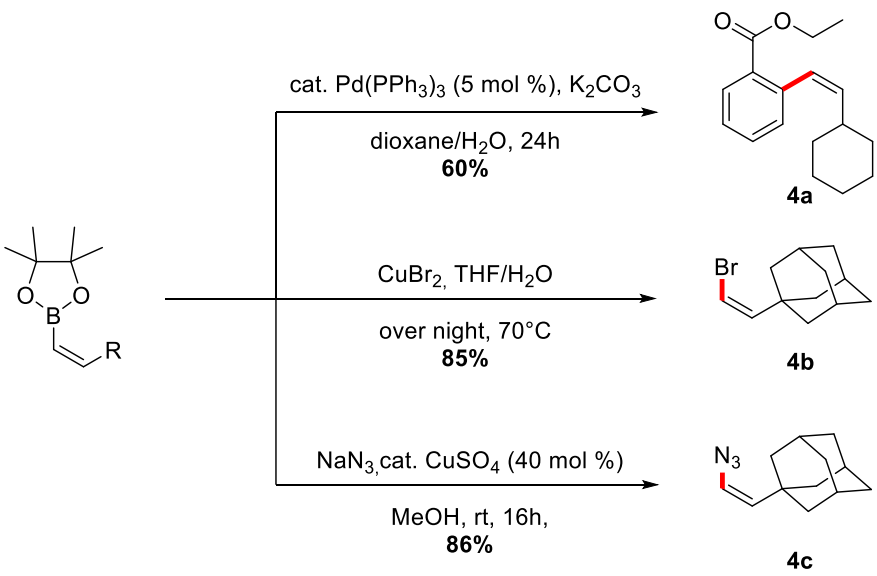


Figure 2.4. Further transformations of Z-vinyl boronates.

The Fe-catalyzed Z-alkene synthesis was then applied for the formal total synthesis of (Z)-7-chloro-6-{[5-(2-cyclohexyl-vinyl)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**5a**, Figure 2.5). This compound was reported as a 5-HT_{2c} receptor agonist, which might lead to treatment of various neurological disorders.[19] The key intermediate to **5a** was a Z-alkene **5b**, which could be produced by Pd-catalyzed heterogeneous hydrogenation of 1,2-disubstituted alkyne **5c**, but in a low yield (Figure 2.5a). The latter was obtained by Pd-catalyzed Sonogashira coupling of ethynylcyclohexane with the corresponding pyridinyl bromide **5d**. In our synthesis, the nitrile group in the commercially available reagent **5d** was reduced by $NaBH_4$

in the presence of $NiCl_2 \cdot 6H_2O$ (10 mol%) followed by protection with BOC_2O to give **5e** in a yield of 57% (Figure 2.5b). Pd-catalyzed Suzuki coupling of **5e** with **2e**, assembled by the Fe-catalyzed coupling of **1a** with cyclohexyl iodide, gave the alkylated Z-olefin **5f** in a yield of 72% (Figure 2.5b). Removal of the Boc group by TFA (TFA = Trifluoroacetic acid) gave the key intermediate **5b** in a quantitative yield (Figure 2.5b). In previous route a terminal alkyl alkyne was needed while in the present route an alkyl iodide is used. For many of the secondary alkyl groups shown in Figure 2.2, alkyl iodides are easily accessible. Thus, our synthetic route can be advantageous for obtaining certain alkylated derivatives of **5a**. Additionally, the stereoselective step in our synthesis has a higher yield than that in the previous route.

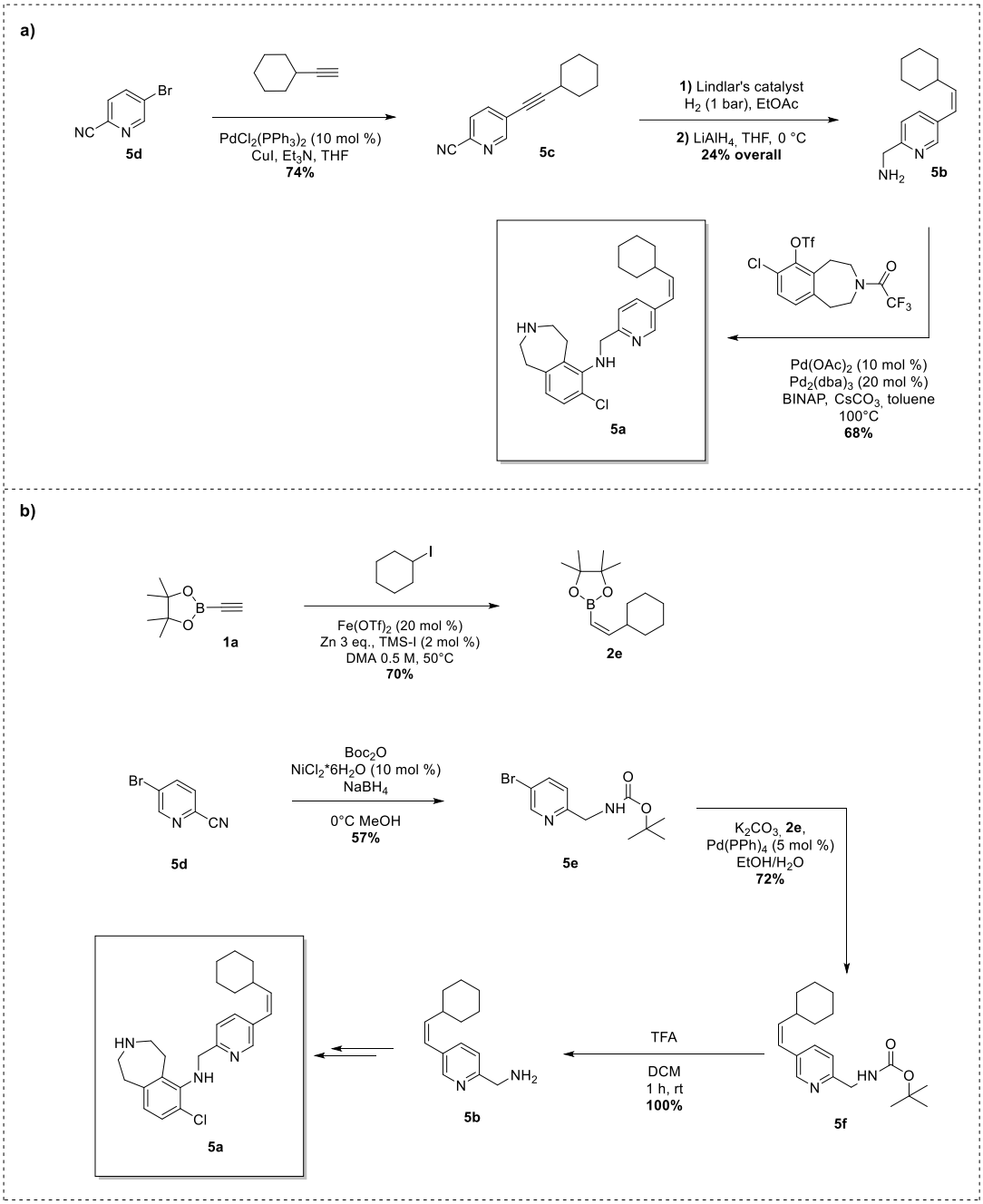


Figure 2.5. Total synthesis of (Z)-7-chloro-6-{[5-(2-cyclohexyl-vinyl)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1H-benzo[d]azepine. (a) Previous route (ref 19); (b) This work

2.3 Conclusions

In summary, Fe-catalyzed reductive coupling of ethynylboronic acid pinacol ester with alkyl halides has been developed for the stereoselective synthesis of Z-vinyl boronates. A simple salt, $Fe(OTf)_2$, could be used for the coupling of secondary and tertiary alkyl halides, particularly alkyl iodides, with good yields and high Z-selectivity. The coupling of primary alkyl halides has a limited scope, even when using a defined Fe complex (**4**) as catalyst. The Z-vinyl boronates could be converted to other Z-alkenes by transformation of the Bpin group. The method was applied for a formal total synthesis of a 5-HT_{2c} receptor agonist (**5a**).

2.4 Experimental section

General Information

NMR spectra were recorded on a 400 MHz instrument at ambient temperature in $CDCl_3$ or CD_2Cl_2 as solvent. ^1H NMR chemical shifts (δ, ppm) were measured relative to tetramethylsilane (TMS) signal in $CDCl_3$ (0.00 ppm) unless otherwise stated. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR chemical shifts (δ, ppm) are reported relative to $CDCl_3$ signal (77.16 ppm) unless otherwise stated.

Unless otherwise noted, all chemicals were commercially available and were used as received without further purifications. Solvents were purified using a two-column solid-state purification system and transferred to glove box without exposure to air by the aid of a Straus flask. Zn powder (<10μ, 98%+) was purchased from Aldrich. Anhydrous dimethylacetamide (DMA) (99.8% purity) was commercially purchased and stored under nitrogen. Iron(II) triflate ($FeOTf_2$, 98% purity) was purchased from Aldrich or Acros. All the diastereomeric ratios are calculated via ^1H NMR analysis after purification of the compounds.

Analysis of the stereoselectivity of compound 2h

Compound **2h** was recovered, after purification, as a mixture of different isomers. (Figure 2.6).

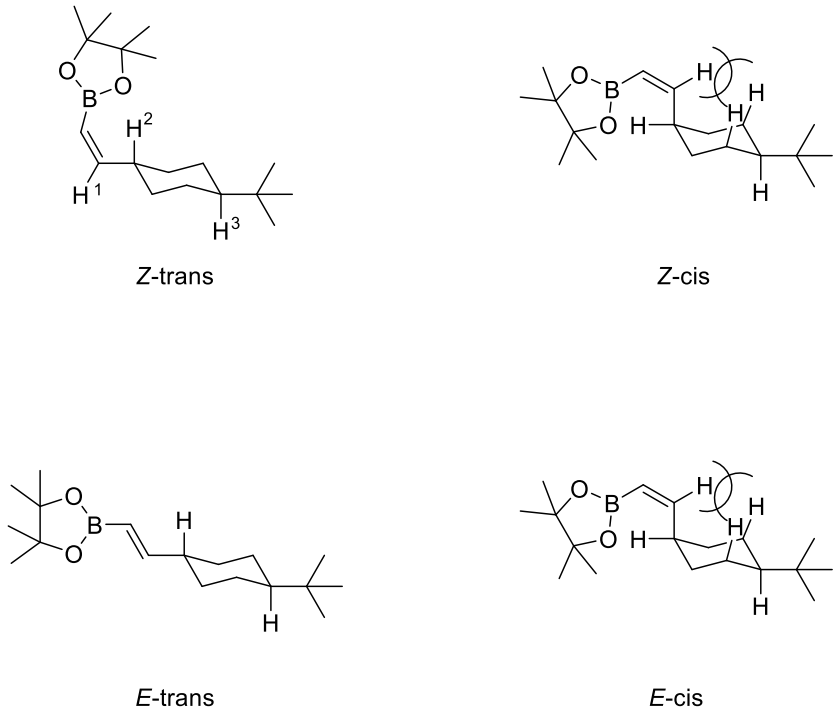


Figure 2.6. different possible isomers of compound **2h**.

From ^{1}H NMR analysis it was possible to know the *E*/*Z* ratio of the double bond. In order to understand the ratio between *Z*-trans and *Z*-cis, the two major isomers, a COSY-NMR analysis was necessary (Figure 2.7).

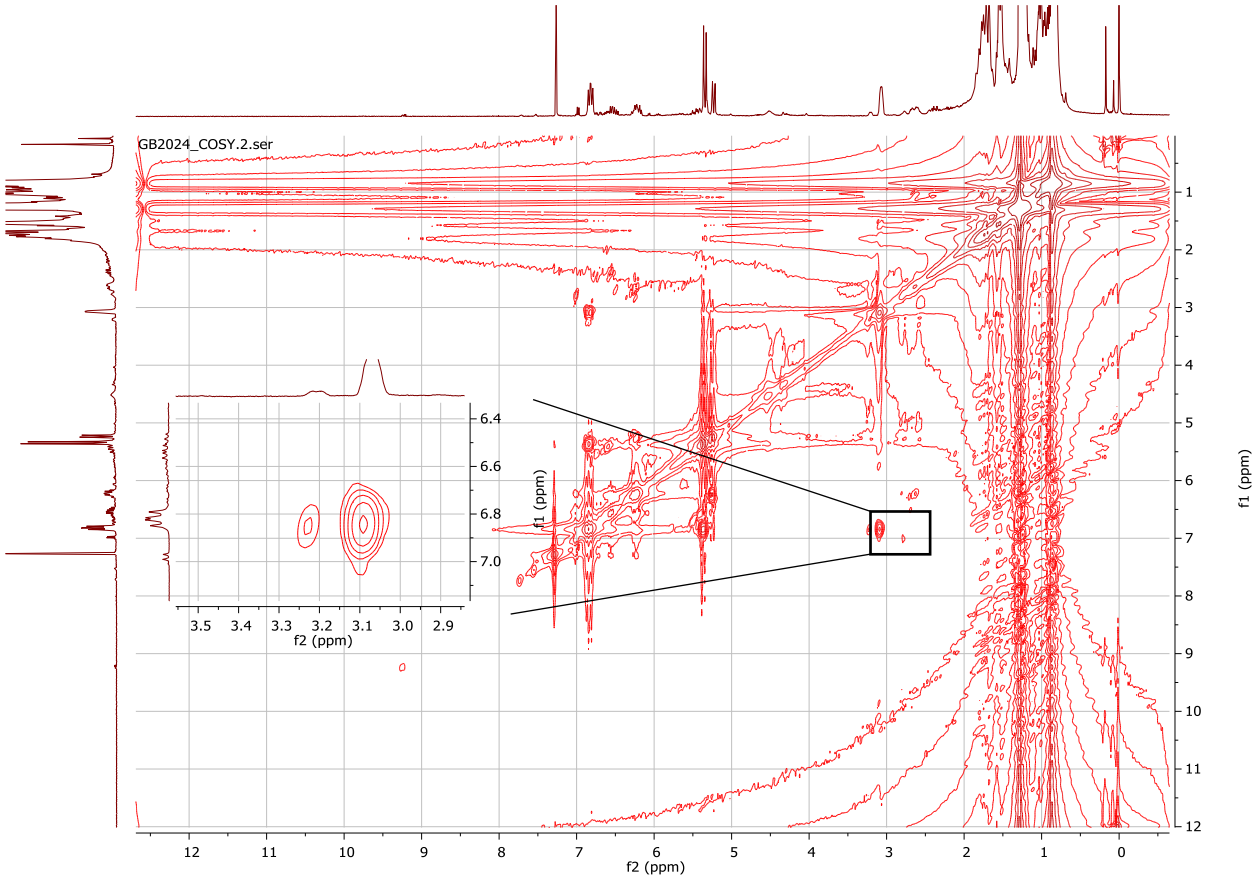


Figure 2.7. COSY analysis of molecule **2h**.

At 3.07 ppm (Figure 2.7), it is possible to see the signal of the vinyl hydrogen (**H2**, Figure 2.6) that has a correlation with the signal of the sp^2 hydrogen of the double bond (**H1**, Figure 2.6). In addition, another peak at 3.20 ppm, with an integral ratio of 1:14, also correlates with the same peak of the double bond. Thus, it is possible to state that these two peaks belong to the *Z*-trans and *Z*-cis isomers. In order to distinguish the two, it is possible to compare the separation between the signal of the CH adjacent to the t-Bu group (**H3**, Figure 2.7) and **H2**.[20] Unfortunately, in this case, the signal from **H3** overlaps with the other signals of the cyclohexyl moiety. Nevertheless, previous literature reports of similar cases demonstrated that a hydrogen on a cyclohexyl ring is more shielded if it is in axial position.[21,22] Consequently, we can assume the more downfield-shifted signal to belong to an axial hydrogen. Therefore, the major product of the reaction is the *Z*-trans isomer.

The stereoselectivity of this reaction is most likely achieved during the addition of the alkyl radical to the boron alkyne. In fact, compound *E*-cis and *Z*-cis both have steric interactions between the double bond and

the hydrogens of the cyclohexyl ring (Figure 2.6). So, the reductive insertion of the radical will be preferred on the other side, leading to the formation of the *Z*-trans product as major isomer.

Experimental protocols

General procedure for the reaction with tertiary and secondary alkyl halides (General procedure A)

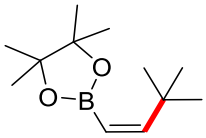
Zinc powder (25.5 mg, 0.39 mmol) was put in a 10 mL dry vial equipped with a stirring bar inside the glovebox. DMA (0.25 mL, 0.5 M) and TMSI (0.52 mg 0.0026 mmol) were added to this vial. The mixture was vigorously shaked until the disappearance of the white fume. $FeOTf_2$ (9.2 mg, 20 mol%), ethynyl boronic pinacolester (20 mg, 0.13 mmol) and the alkyl halide (0.39 mmol) were added. The vial was then sealed and its content was allowed to stir overnight (16-20 h) at 50°C. The mixture was quenched with water. *n*-Dodecane (29.5 µL, 0.13 mmol) was added as an internal standard, and the mixture was extracted into ca. 4 mL of ethyl acetate. The organic layer was analyzed by GC-MS. It was then dried over sodium sulfate and the solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography (ethyl acetate/hexanes).

General procedure for the reaction with primary alkyl halides (General procedure B)

Zinc powder (25.5 mg, 0.39 mmol) was put in a 10 mL dry vial equipped with a stirring bar inside the glovebox. DMA (0.25 mL, 0.5 M) and TMSI (0.52 mg 0.0026 mmol) were added to this vial. The mixture was vigorously shaked until the disappearance of the white fume. The iron complex **4** (5 mol%), ethynyl boronic pinacolester (20 mg, 0.13 mmol) and the alkyl halide (0.39 mmol) were added. The vial was then sealed and its content was allowed to stir overnight (16-20 h) at 50°C. The mixture was quenched with water. *n*-Dodecane (29.5 µL, 0.13 mmol) was added as an internal standard, and the mixture was extracted into ca. 4 mL of ethyl acetate. The organic layer was analyzed by GC-MS. It was then dried over sodium sulfate and

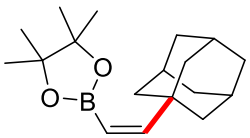
the solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography (ethyl acetate/hexanes).

Synthesis of (Z)-2-(3,3-dimethylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1c)



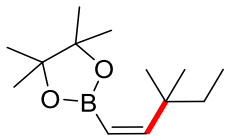
The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (25.9mg, 95%, Z:E: 44:1). ^{1}H NMR and ^{13}C NMR data were consistent with literature.[13]

Synthesis of 2-((Z)-2-((-adamantan-1-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2b)



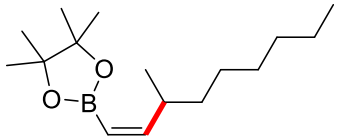
The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (34.1mg, 91%, Z:E: 28:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.07 (d, J = 15.1 Hz, 1H), 5.19 (d, J = 15.1 Hz, 1H), 1.99 (d, J = 4.3 Hz, 3H), 1.72 (dd, J = 11.9, 4.3 Hz, 12H), 1.31 (s, 12H). ^{13}C NMR (101 MHz, Chloroform-d) δ 159.44, 83.35, 41.96, 36.79, 28.55, 24.83. HRMS (APPI/LTQ-Orbitrap) m/z: [M]+ Calcd for C18H29BO2+ 288.2255; Found 288.2253.

Synthesis of (Z)-2-(3,3-dimethylpent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2c)



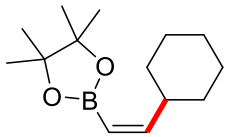
The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (11.7mg, 40%, Z:E: 18:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.19 (d, J = 15.0 Hz, 1H), 5.27 (d, J = 15.1 Hz, 1H), 1.40 (q, J = 7.5 Hz, 2H), 1.30 (s, 12H), 1.07 (s, 3H), 0.84 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 158.57, 83.27, 38.23, 35.60, 26.96, 24.81, 8.97. ^{11}B NMR (128 MHz, Chloroform-d) δ 30.76. HRMS (APPI/LTQ-Orbitrap) m/z: [M + H]+ Calcd for C13H26BO2+ 225.2020; Found 225.2025.

Synthesis of (Z)-4,4,5,5-tetramethyl-2-(3-methylnon-1-en-1-yl)-1,3,2-dioxaborolane (2d)



The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (26.6mg, 77%, Z:E: 13:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.15 (dd, J = 13.5, 9.8 Hz, 1H), 5.26 (d, J = 13.5 Hz, 1H), 2.90 (td, J = 6.7, 3.4 Hz, 1H), 1.27 (p, J = 4.3 Hz, 25H), 0.96 (d, J = 6.6 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.15, 82.67, 37.21, 35.96, 31.90, 29.34, 27.27, 24.87, 24.72, 22.69, 21.22, 14.10. HRMS (APPI/LTQ-Orbitrap) m/z: [M]+ Calcd for C16H31BO2+ 266.2412; Found 266.2412.

Synthesis of (Z)-2-(2-cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2e)

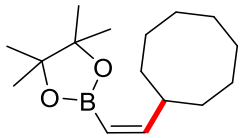


The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (22.7mg, 74%, Z:E: 8:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.27 (dd, J = 13.5, 9.3 Hz, 1H), 5.24 (dd, J = 13.6, 0.9 Hz, 1H), 2.73 (dtd, J = 14.1, 11.3, 10.7, 3.6 Hz, 1H), 1.84 – 1.53 (m, 8H), 1.28 (d, J = 1.3 Hz, 12H). ^{13}C NMR (101 MHz, Chloroform-d) δ 160.59, 82.74, 40.59, 33.33, 26.02, 25.76, 24.81. HRMS (APPI/LTQ-Orbitrap) m/z: [M]+ Calcd for C14H25BO2+ 236.1942; Found 236.1941.

Synthesis of (Z)-2-(2-cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2e) gram scale

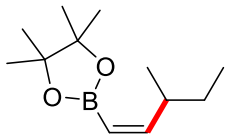
Zinc powder (941.96 mg, 14.4 mmol) was put in a 10 mL dry vial equipped with a stirring bar inside the glovebox. DMA (9.2 mL, 0.5 M) and TMSI (19.19 mg 0.095 mmol) were added to this vial. The mixture was vigorously shaked until the disappearance of the white fume. $FeOTf_2$ (339.8 mg, 20 mol%), ethynyl boronic pinacolester (1 g, 4.8 mmol) and the alkyl halide (3.028 g, 14.4 mmol) were added. The vial was then sealed and its content was allowed to stir overnight (16-20 h) at 50°C. The mixture was quenched with water. The mixture was extracted with ethyl acetate, the combined organic layers were dried over sodium sulfate and the solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography (ethyl acetate/hexanes 1:9) Off white oil (793.4mg, 70%, Z:E: 8:1) .

Synthesis of (Z)-2-(2-cyclooctylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2f)



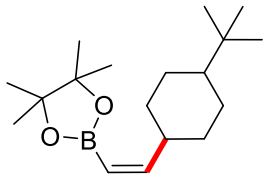
The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (19.2mg, 56%, Z:E: 20:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.34 (d, J = 3.6 Hz, 1H), 5.17 (d, J = 13.3 Hz, 1H), 3.07 (qt, J = 9.6, 3.4 Hz, 1H), 1.72 – 1.47 (m, 14H), 1.28 (s, 12H). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.92, 82.72, 39.32, 33.18, 26.76, 25.38, 24.88. ^{11}B NMR (128 MHz, Chloroform-d) δ 29.91. HRMS (APPI/LTQ-Orbitrap) m/z: [M]+ Calcd for C16H29BO2+ 264.2255; Found 264.2255.

Synthesis of (Z)-4,4,5,5-tetramethyl-2-(3-methylpent-1-en-1-yl)-1,3,2-dioxaborolane (2g)



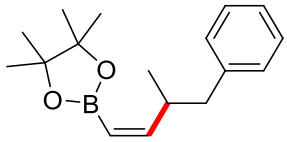
The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (19.7mg, 72%, Z:E: 13:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.13 (dd, J = 13.5, 9.8 Hz, 1H), 5.27 (d, J = 13.5 Hz, 1H), 2.80 (tt, J = 9.0, 6.1 Hz, 1H), 1.33 – 1.20 (m, 12H), 0.95 (d, J = 6.6 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 160.71, 82.71, 37.68, 29.96, 24.89, 24.70, 20.92, 11.78. ^{11}B NMR (128 MHz, Chloroform-d) δ 29.96. HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]+ Calcd for C12H24BO2+ 211.1864; Found 211.1864.

Synthesis of (Z)-2-(2-(4-(tert-butyl)cyclohexyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2h)



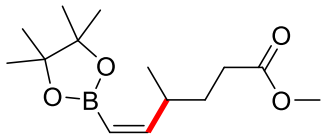
The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (37.2mg, 98%, Z:E: 9:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.83 (dd, J = 13.7, 9.4 Hz, 1H), 5.36 (d, J = 13.6 Hz, 1H), 1.88 – 1.62 (m, 6H), 1.61 – 1.53 (m, 4H), 1.28 (d, J = 2.7 Hz, 12H), 0.86 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 158.28, 82.71, 48.36, 34.59, 32.49, 27.51, 24.80, 22.14, 14.11. ^{11}B NMR (128 MHz, Chloroform-d) δ 29.61. HRMS (APPI/LTQ-Orbitrap) m/z: [M + H]+ Calcd for C18H34BO2+ 293.2646; Found 293.2648.

Synthesis of (Z)-4,4,5,5-tetramethyl-2-(3-methyl-4-phenylbut-1-en-1-yl)-1,3,2-dioxaborolane (2i)



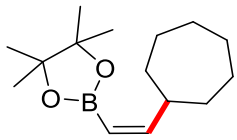
The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (14.1mg, 40%, Z:E: 7:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.32 – 7.17 (m, 5H), 6.28 (dd, J = 13.5, 9.6 Hz, 1H), 5.29 (d, J = 13.4 Hz, 1H), 3.31 (dq, J = 9.6, 6.9 Hz, 1H), 2.61 (ddd, J = 61.7, 13.3, 7.2 Hz, 2H), 1.27 (d, J = 2.2 Hz, 11H), 0.98 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 160.16, 140.77, 129.32, 127.96, 125.64, 82.79, 43.82, 37.80, 24.86, 20.19. ^{11}B NMR (128 MHz, Chloroform-d) δ 29.89. HRMS (APPI/LTQ-Orbitrap) m/z: [M]+ Calcd for C17H25BO2+ 272.1942; Found 272.1951.

Synthesis of methyl (S,Z)-4-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-enoate (2j)



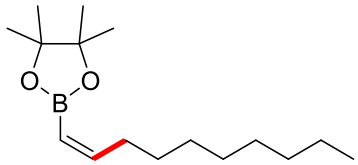
The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 8:2). Off white oil (13.24mg, 38%, Z:E: 11:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.11 (dd, J = 13.5, 10.0 Hz, 1H), 5.33 (d, J = 13.5 Hz, 1H), 4.32 (dd, J = 8.2, 4.6 Hz, 2H), 3.66 (s, 3H), 3.02 – 2.85 (m, 1H), 2.30 (t, J = 7.9 Hz, 2H), 1.82 – 1.64 (m, 2H), 1.27 (s, 12H), 1.01 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 174.41, 159.30, 130.90, 128.82, 82.87, 51.38, 35.87, 32.23, 31.93, 24.87, 24.75, 21.16. ^{11}B NMR (128 MHz, Chloroform-d) δ 29.93. HRMS (APPI/LTQ-Orbitrap) m/z: [M + H]+ Calcd for C14H26BO4+ 269.1919; Found 269.1917.

Synthesis of (Z)-2-(2-cycloheptylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2k)



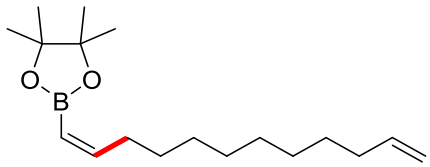
The synthesis was done following the general procedure A. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (23.0mg, 70.8%, Z:E: 13:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.36 (dd, J = 13.4, 9.7 Hz, 1H), 5.18 (d, J = 13.4 Hz, 1H), 2.92 (tq, J = 9.8, 5.0, 3.8 Hz, 1H), 1.77 – 1.40 (m, 7H), 1.28 (s, 17H). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.28, 82.72, 41.93, 35.12, 28.60, 26.58, 24.83. ^{11}B NMR (128 MHz, Chloroform-d) δ 29.67. HRMS (APPI/LTQ-Orbitrap) m/z: [M + H]+ Calcd for C15H28BO2+ 251.2177; Found 251.2178.

Synthesis of (Z)-2-(dec-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3a)



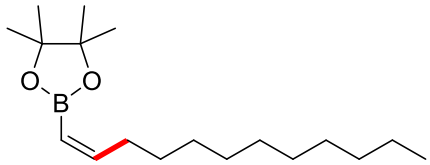
The synthesis was done following the general procedure B. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (26.6mg, 77%, Z:E: 10:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.46 (dt, J = 15.0, 7.8 Hz, 1H), 5.35 (d, J = 13.5 Hz, 1H), 2.41 (q, J = 7.3 Hz, 2H), 1.28 (d, J = 8.7 Hz, 24H), 0.90 (d, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 155.28, 82.76, 32.20, 31.93, 29.71, 29.47, 29.41, 29.29, 29.08, 24.84, 24.02, 22.70, 14.12. ^{11}B NMR (128 MHz, Chloroform-d) δ 34.43, 29.93. HRMS m/z: [M + H]+ Calcd for C16H32BO2+ 267.2490; Found 267.2485.

Synthesis of (Z)-2-(dodeca-1,11-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3b)



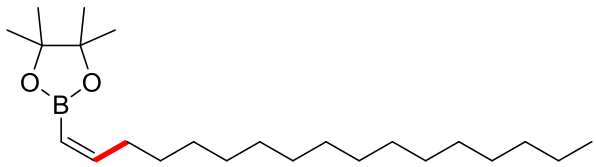
The synthesis was done following the general procedure B. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (23.2mg, 61%, Z:E: 10:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.44 (dt, J = 14.2, 7.3 Hz, 1H), 5.82 (ddt, J = 16.9, 10.1, 6.7 Hz, 1H), 5.33 (dt, J = 13.4, 1.4 Hz, 1H), 5.04 – 4.89 (m, 2H), 2.04 (qd, J = 7.6, 3.8 Hz, 2H), 1.45 – 1.20 (m, 27H). ^{13}C NMR (101 MHz, Chloroform-d) δ 155.21, 139.22, 114.05, 82.79, 33.83, 32.39, 29.40, 29.34, 29.13, 28.95, 24.81, 23.98. ^{11}B NMR (128 MHz, Chloroform-d) δ 34.52, 29.97. HRMS (APPI/LTQ-Orbitrap) m/z: [M]+ Calcd for $C_{18}H_{33}BO_2$+ 292.2568; Found 292.2573.

Synthesis of (Z)-2-(dodec-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3c)



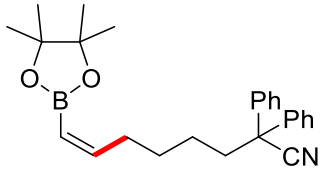
The synthesis was done following the general procedure B. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (13.4mg, 35%, Z:E: 13:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.45 (dt, J = 14.3, 7.5 Hz, 1H), 5.34 (dt, J = 13.5, 1.4 Hz, 1H), 2.41 (qd, J = 7.3, 1.4 Hz, 2H), 1.28 (d, J = 3.8 Hz, 28H), 0.90 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 155.28, 82.76, 32.20, 31.93, 29.66, 29.63, 29.48, 29.45, 29.37, 29.07, 24.84, 24.81, 22.69, 14.12. ^{11}B NMR (128 MHz, Chloroform-d) δ 30.02. HRMS (APPI/LTQ-Orbitrap) m/z: [M + H]+ Calcd for C18H36BO2+ 295.2803; Found 295.2798.

Synthesis of (Z)-2-(heptadec-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3d)



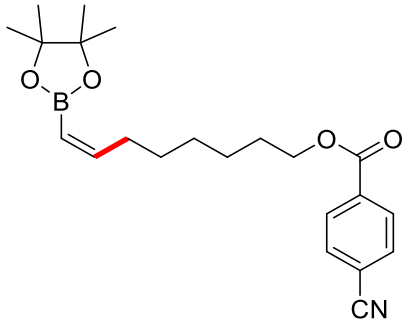
The synthesis was done following the general procedure B. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (14.7mg, 31%, Z:E: 9:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.45 (dt, J = 14.2, 7.5 Hz, 1H), 5.35 (dd, J = 13.5, 1.5 Hz, 1H), 2.49 – 2.35 (m, 2H), 1.29 (q, J = 6.2, 4.9 Hz, 38H), 0.90 (t, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 155.29, 82.76, 43.93, 32.45, 32.20, 31.94, 29.71, 29.67, 29.47, 29.43, 29.37, 29.18, 29.08, 24.84, 24.82, 22.70, 14.12. ^{11}B NMR (128 MHz, Chloroform-d) δ 34.55, 30.04. HRMS (APPI/LTQ-Orbitrap) m/z: [M + H]+ Calcd for C24H48BO2+ 379.3742; Found 379.3735.

Synthesis of (Z)-2,2-diphenyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-7-enenitrile (3e)



The synthesis was done following the general procedure B. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 8:2). Off white oil (31.8mg, 61%, Z:E: 10:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.47 – 7.24 (m, 10H), 6.39 (dt, J = 14.2, 7.5 Hz, 1H), 5.35 (d, J = 13.5 Hz, 1H), 2.48 – 2.33 (m, 7H), 1.68 – 1.43 (m, 9H), 1.25 (s, 12H). ^{13}C NMR (101 MHz, Chloroform-d) δ 154.26, 140.38, 128.94, 128.80, 128.56, 128.35, 127.96, 127.76, 126.88, 126.83, 82.84, 51.80, 39.46, 31.63, 29.27, 24.83. ^{11}B NMR (128 MHz, Chloroform-d) δ 29.95. HRMS (APPI/LTQ-Orbitrap) m/z: [M + H]+ Calcd for C26H33BNO2+ 402.2599; Found 402.2599.

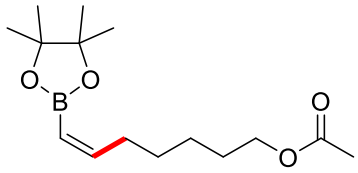
Synthesis of (Z)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-7-en-1-yl 4-cyanobenzoate (3f)



The synthesis was done following the general procedure B. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 8:2). Off white oil (10.7mg, 21.5%, Z:E: 8:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.21 – 8.10 (m, 2H), 7.77 (dd, J = 8.4, 1.8 Hz, 2H), 6.44 (dt, J = 14.2, 7.4 Hz, 1H), 5.36 (dt, J = 13.5, 1.3 Hz, 1H), 4.42 – 4.33 (m, 2H), 2.49 – 2.38 (m, 2H), 1.80 (p, J = 7.2, 6.8 Hz, 4H), 1.54 – 1.37 (m, 10H), 1.28 (s, 14H). ^{13}C NMR (101 MHz, Chloroform-d) δ 154.79, 134.32, 132.20,

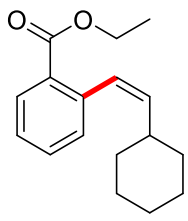
130.06, 118.02, 116.29, 82.81, 65.98, 32.03, 29.26, 28.63, 28.55, 25.79, 24.85. ^{11}B NMR (128 MHz, Chloroform-d) δ 29.99. HRMS (APPI/LTQ-Orbitrap) m/z: [M + K]+ Calcd for $C_{22}H_{30}BNO_4K$+ 422.1899; Found 422.1833.

Synthesis of (Z)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-1-yl acetate (3g)



The synthesis was done following the general procedure B. The crude residue was purified via column chromatography over silica gel (hexanes:ethyl acetate 9:1). Off white oil (9.28mg, 25.3%, Z:E: 11:1). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.43 (dt, J = 14.2, 7.4 Hz, 1H), 5.36 (dt, J = 13.5, 1.3 Hz, 1H), 4.07 (t, J = 6.8 Hz, 2H), 2.42 (qd, J = 7.2, 1.3 Hz, 2H), 2.06 (d, J = 1.9 Hz, 3H), 1.71 – 1.57 (m, 4H), 1.27 (d, J = 9.1 Hz, 15H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.20, 154.65, 82.81, 64.59, 31.90, 29.40, 29.21, 28.94, 28.60, 28.34, 25.89, 25.24, 24.83, 21.01. ^{11}B NMR (128 MHz, Chloroform-d) δ 33.68, 29.93. HRMS (APPI/LTQ-Orbitrap) m/z: [M]+ Calcd for C15H27BO4+ 282.1997; Found 282.2792.

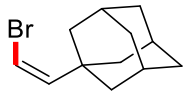
Synthesis of ethyl (Z)-2-(2-cyclohexylvinyl)benzoate (4a)



To a solution of ethyl 2-bromobenzoate (64.6 mg, 0.282 mmol) and potassium carbonate (116.92 mg, 0.84 6mmol) in degassed dioxane/water (1.6 mL, 1/1 ratio) was added molecule **3a** (100 mg, 0.423 mmol) and tetrakis(triphenylphosphine)palladium(0) (16.34 mg, 0.0142 mmol) at room temperature. Then the mixture was heated to 95°C for 1 hour. After quenching with water, the mixture was extracted with ethyl acetate and concentrated, obtaining the crude product, which was purified by chromatography (hexanes/ethyl acetate

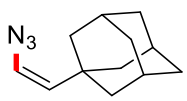
4:1) to afford a pure compound **5** as a off yellow liquid (56.3 mg, yield: 60%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.94 (dd, J = 7.8, 1.4 Hz, 1H), 7.47 (dd, J = 7.6, 1.4 Hz, 1H), 7.36 – 7.26 (m, 2H), 6.75 (d, J = 11.6 Hz, 1H), 5.54 (t, J = 10.9 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.36 – 2.17 (m, 1H), 1.77 – 1.60 (m, 7H), 1.39 (t, J = 7.1 Hz, 3H), 1.33 – 1.27 (m, 3H), 1.18 (d, J = 7.4 Hz, 5H). ^{13}C NMR (101 MHz, Chloroform-d) δ 167.39, 139.37, 137.77, 131.41, 130.54, 130.15, 126.81, 126.50, 60.80, 36.87, 33.24, 25.99, 25.62, 14.29. HRMS (ESI/QTOF) m/z: [M + Na]+ Calcd for C17H22NaO2+ 281.1512; Found 281.1515.

Synthesis of 1-((Z)-2-bromovinyl)adamantine (4b)



Molecule **3b** (100 mg, 0.35 mmol) was dissolved in 4 mL of diethyl ether and cooled to -20°C. A solution of Br_2 (55.9 mg, 0.35 mmol) in DCM (0.35 mL) was added dropwise over 15 minutes, then the mixture was stirred for additional 15 minutes. A solution of NaOMe (44 mg, 0.77 mmol) in MeOH (0.26 mL) was added and after 30 minutes the reaction was quenched with benzoic acid (20 equiv.) in DCM (3.4 mL). Purification by flash chromatography (hexanes/ethyl acetate from 0% to 20% of EA). Colorless liquid (71.7mg, yield 85%). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.10 (d, J = 13.7 Hz, 1H), 5.93 (d, J = 13.7 Hz, 1H), 2.02 (t, J = 3.1 Hz, 3H), 1.79 – 1.60 (m, 10H). 13C NMR (101 MHz, Chloroform-d) δ 148.73, 102.44, 41.61, 37.71, 36.62, 28.20. HRMS (APPI/LTQ-Orbitrap) m/z: [M]+ Calcd for C12H17+ 161.1330; Found 161.1322.

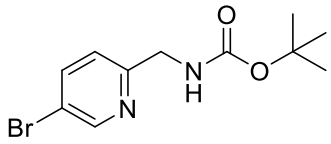
Synthesis of 1-((Z)-2-azidovinyl)adamantine (4c)



Molecule **3b** (100 mg, 0.35 mmol), NaN_3 (34 mg, 0.53 mmol) and $CuSO_4$ (33.5 mg, 0.21 mmol) were dissolved in 3 mL of MeOH and stirred at room temperature for one night. The mixture is then concentrate under reduced pressure, dissolved in DCM and washed with water and brine. The residue is dried with

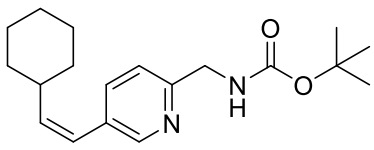
anhydrous sodium sulfate, concentrated and purified by flash chromatography to obtain a white solid (61 mg, 85.8%). ^{1}H NMR (400 MHz, Chloroform-d) δ 5.97 (d, J = 8.5 Hz, 1H), 4.56 (d, J = 8.5 Hz, 1H), 2.05 – 1.90 (m, 3H), 1.79 – 1.57 (m, 10H), 1.45 – 1.17 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 130.22, 123.05, 42.14, 36.77, 34.88, 28.60. HRMS (APPI/LTQ-Orbitrap) m/z: [M]+ Calcd for C12H17N+ 175.1356; Found 175.1355.

Synthesis of tert-butyl ((5-bromopyridin-2-yl)methyl)carbamate (5e)



5-bromopicolinonitrile (5 g, 27 mmol), $NiCl_2{*}6H_2O$ (10 mol%), $BocO_2$ (2 equiv.) and methanol (100 mL) were put in a flask which was then cooled to 0°C. Sodium boron hydride (7 equiv.) was then added portion-wise over 2h. After one additional hour of stirring at 15°C, the mixture was poured into ice-water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography giving the desired product as a white solid (4.46g, yield:57.2%). ^{1}H NMR (400 MHz, Methanol-d4) δ 8.57 (d, J = 2.4 Hz, 1H), 7.97 (dd, J = 8.4, 2.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 4.32 (s, 2H), 3.33 (dt, J = 3.3, 1.7 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, Methanol-d4) δ 157.82, 157.07, 149.40, 139.66, 122.47, 118.55, 79.15, 44.72, 27.34. Melting point: 92-94 °C.

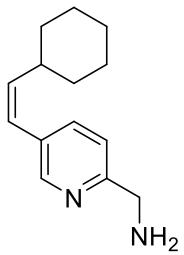
Synthesis of tert-butyl (Z)-((5-(2-cyclohexylvinyl)pyridin-2-yl)methyl)carbamate (5f)



To a solution of **13** (30.44 mg, 0.106 mmol) and potassium carbonate (49.2 mg, 0.356 mmol) in degassed 1,2-dimethoxyethane/ethanol/water (0.8 mL, 1/0.5/1 ratio) was added molecule **3a** (50 mg, 0.212 mmol) and

tetrakis(triphenylphosphine)palladium(0) (34.78 mg, 0.142 mmol) at room temperature. Then the mixture was heated to 95°C for 1 hour. After quenching with water, the mixture was extracted with ethyl acetate and concentrated, obtaining the crude product, which was purified by chromatography (hexanes/ethyl acetate 4:1) to afford a pure compound **14** as a colorless liquid (48.1 mg, yield: 72%). ^{1}H NMR (CDCl3, 400 MHz): δ 8.45 (1H, s), 7.53 (1H, d), 7.24 (1H, d), 6.24 (1H, d), 5.62 (1H, t), 4.44 (2H, d), 2.48 (1H, m), 1.69 (5H, m), 1.46 (9H, s), 1.21 (6H, m), 5.53-5.61 (1H,bs). ^{13}C NMR (101 MHz, Chloroform-d) δ 156.00, 155.21, 148.88, 141.15, 136.42, 132.16, 122.94, 121.13, 79.48, 45.58, 37.09, 33.10, 29.70, 28.42, 25.91, 25.56. HRMS (APPI/LTQ-Orbitrap) m/z: [M + H]+ Calcd for C19H29N2O2+ 317.2224; Found 317.2222.

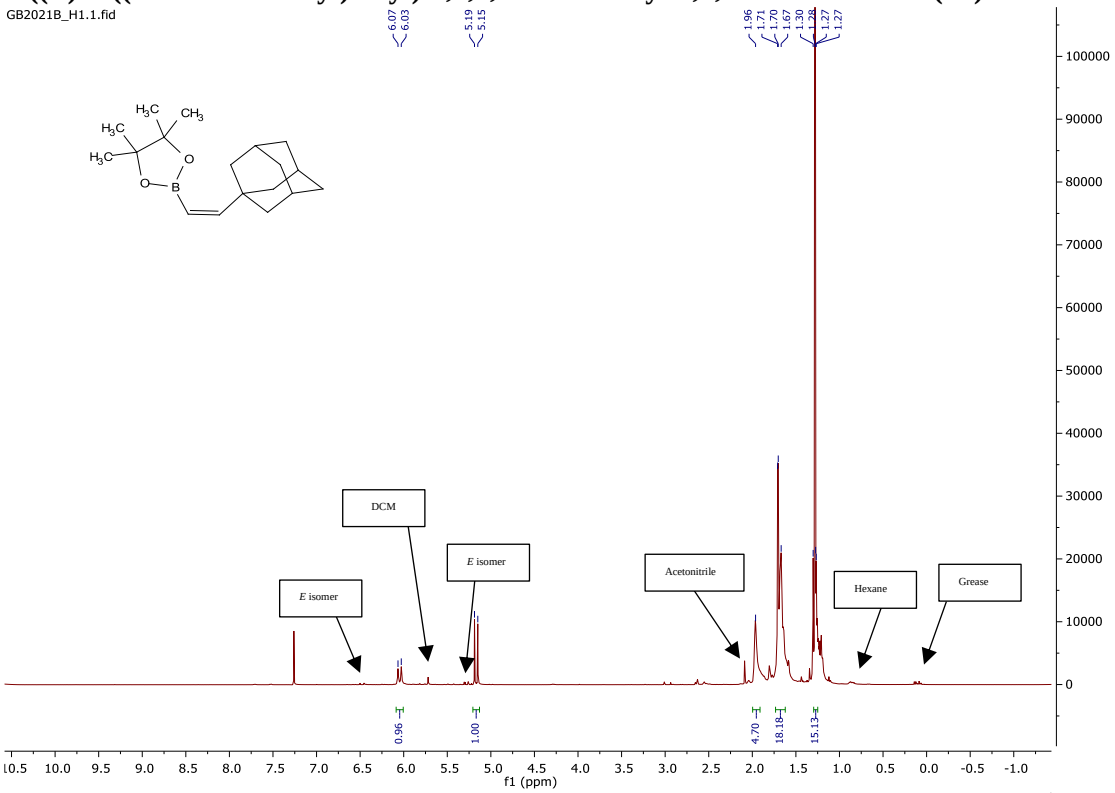
Synthesis of (Z)-(5-(2-cyclohexylvinyl)pyridin-2-yl)methanamine (5b)

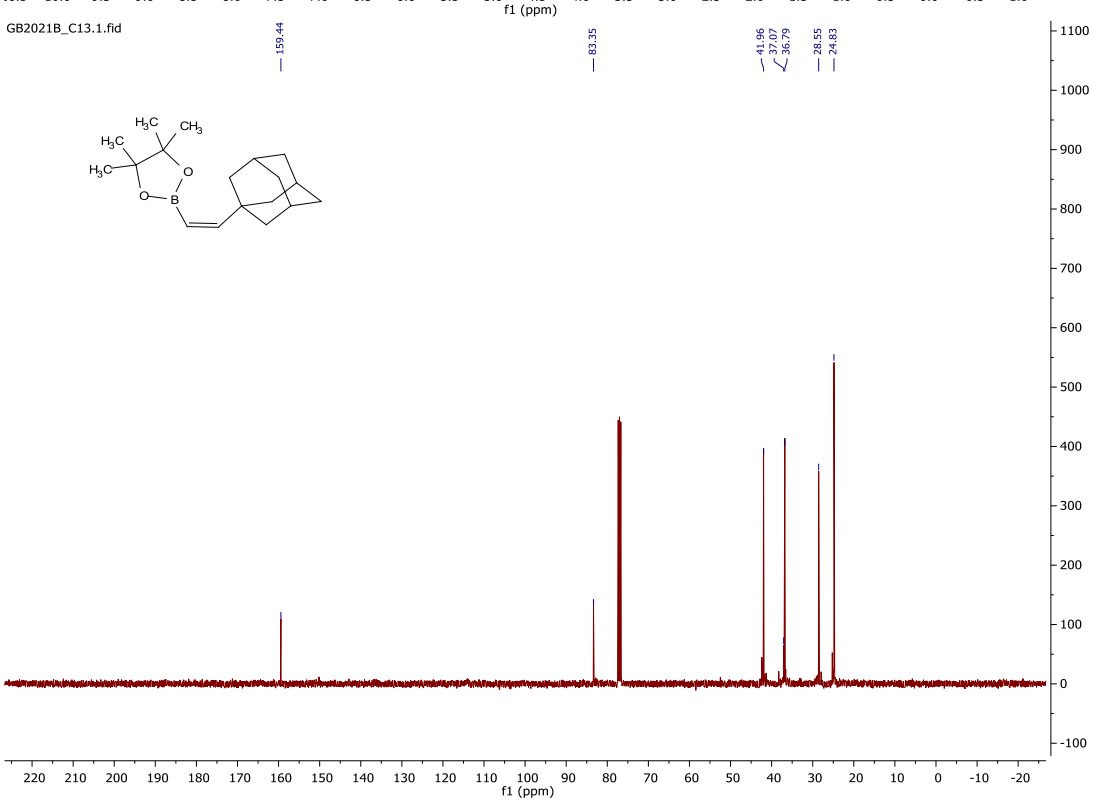


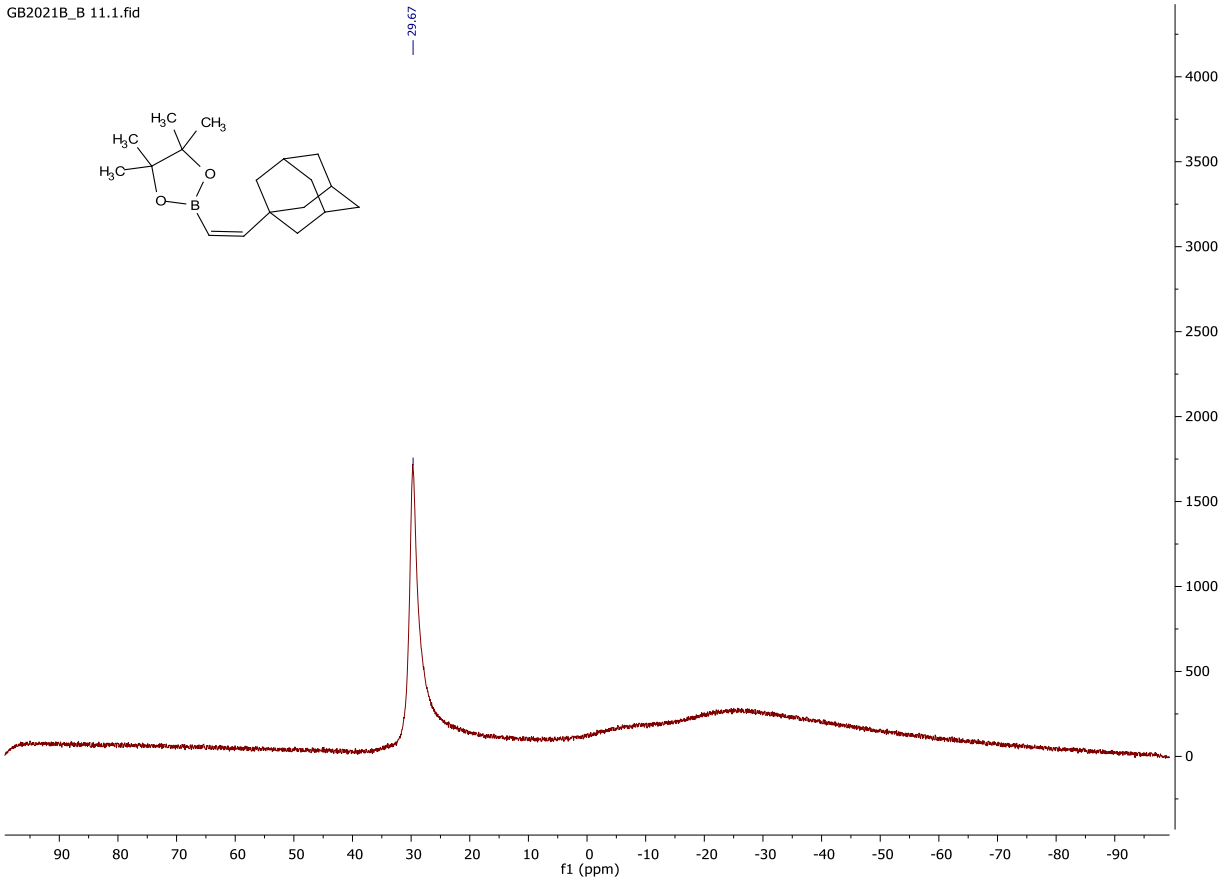
A solution of **14** (150 mg, 0.5 mmol) in DCM (5 mL) and trifluoroacetic acid (4 mL) was stirred for 45 minutes at room temperature, after which the solvent was evaporated. Ethyl ether (10 mL) was added, and the solvent was evaporated again. The residue was dissolved in DCM (20 mL), washed with saturated aqueous of sodium bicarbonate, dried with anhydrous sodium sulfate, and the solvent was evaporated to give product **9** in a quantitative yield as a green liquid (100 mg, quantitative yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.47 (s, 1H), 7.53 (dd, J = 8.0, 2.1 Hz, 1H), 7.31 – 7.22 (m, 1H), 6.25 (d, J = 11.7 Hz, 1H), 5.61 (dd, J = 11.7, 10.2 Hz, 1H), 4.00 (s, 2H), 2.49 (tdd, J = 10.7, 7.3, 3.2 Hz, 1H), 2.02 (d, J = 21.9 Hz, 2H), 1.78 – 1.63 (m, 5H), 1.36 – 1.11 (m, 5H). ^{13}C NMR (101 MHz, Chloroform-d) δ 159.39, 149.00, 140.97, 136.39, 131.86, 123.05, 120.80, 37.09, 33.11, 29.70, 25.91, 25.57. HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for C14H21N2+ 217.1699; Found 217.1701.

2.5 NMR spectra

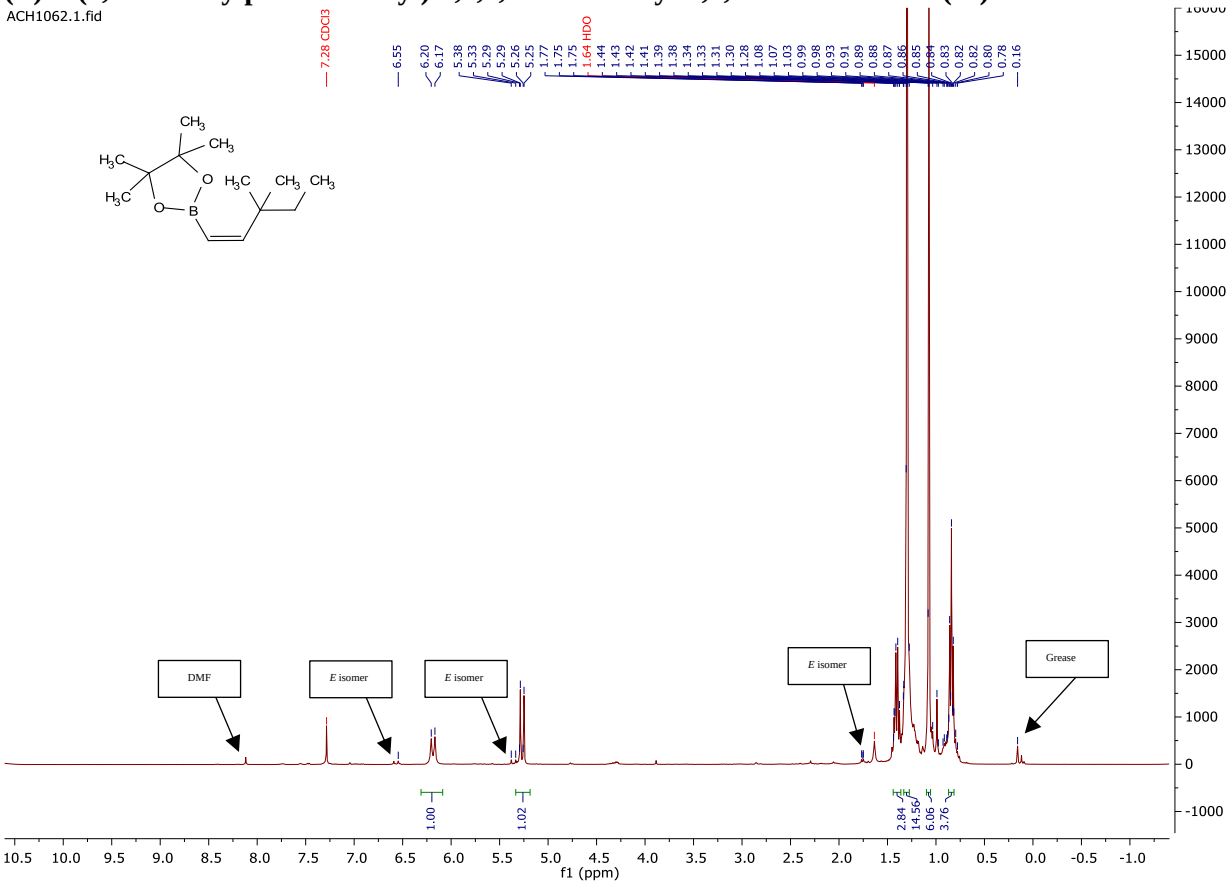
2-((Z)-2-((-adamantan-1-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2b)

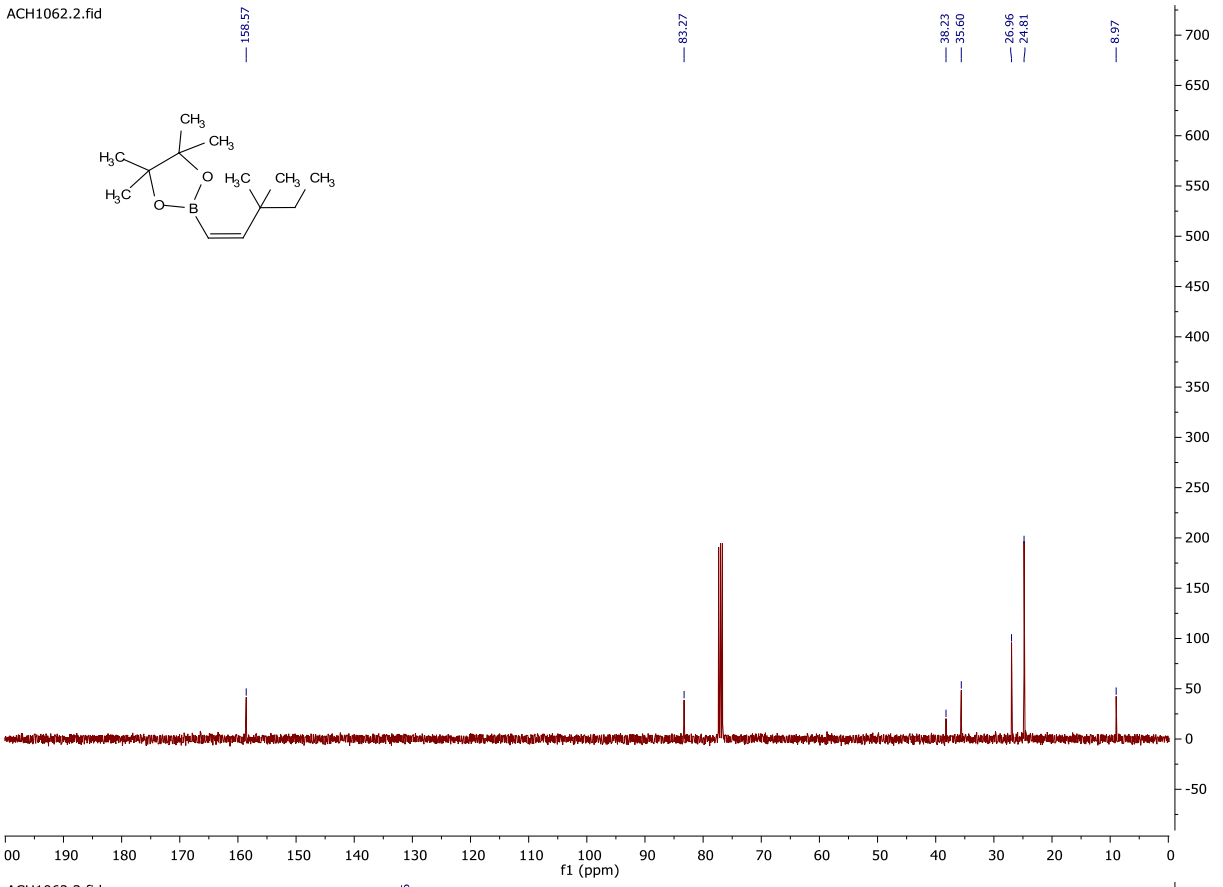






(Z)-2-(3,3-dimethylpent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2c)

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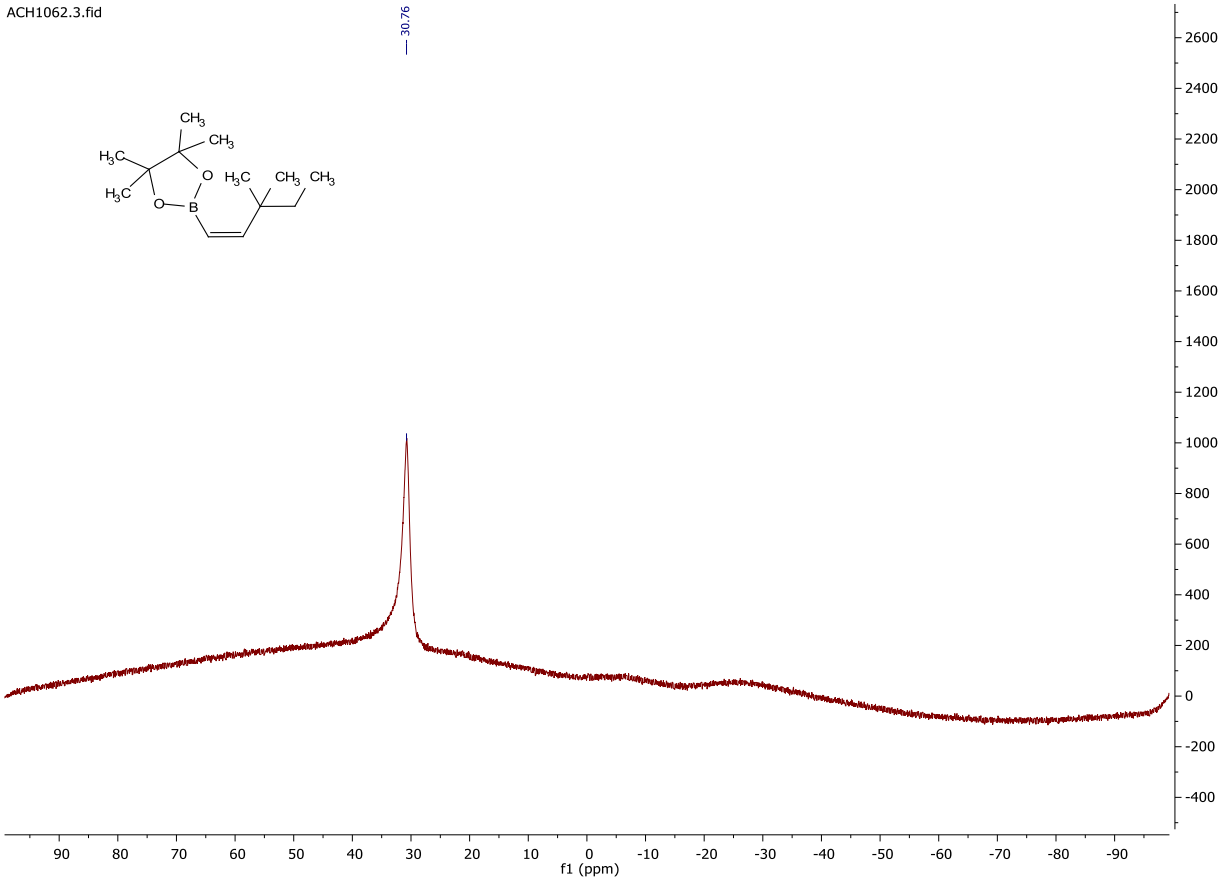
8.97
f1 (ppm)


ACH1062.3.fid
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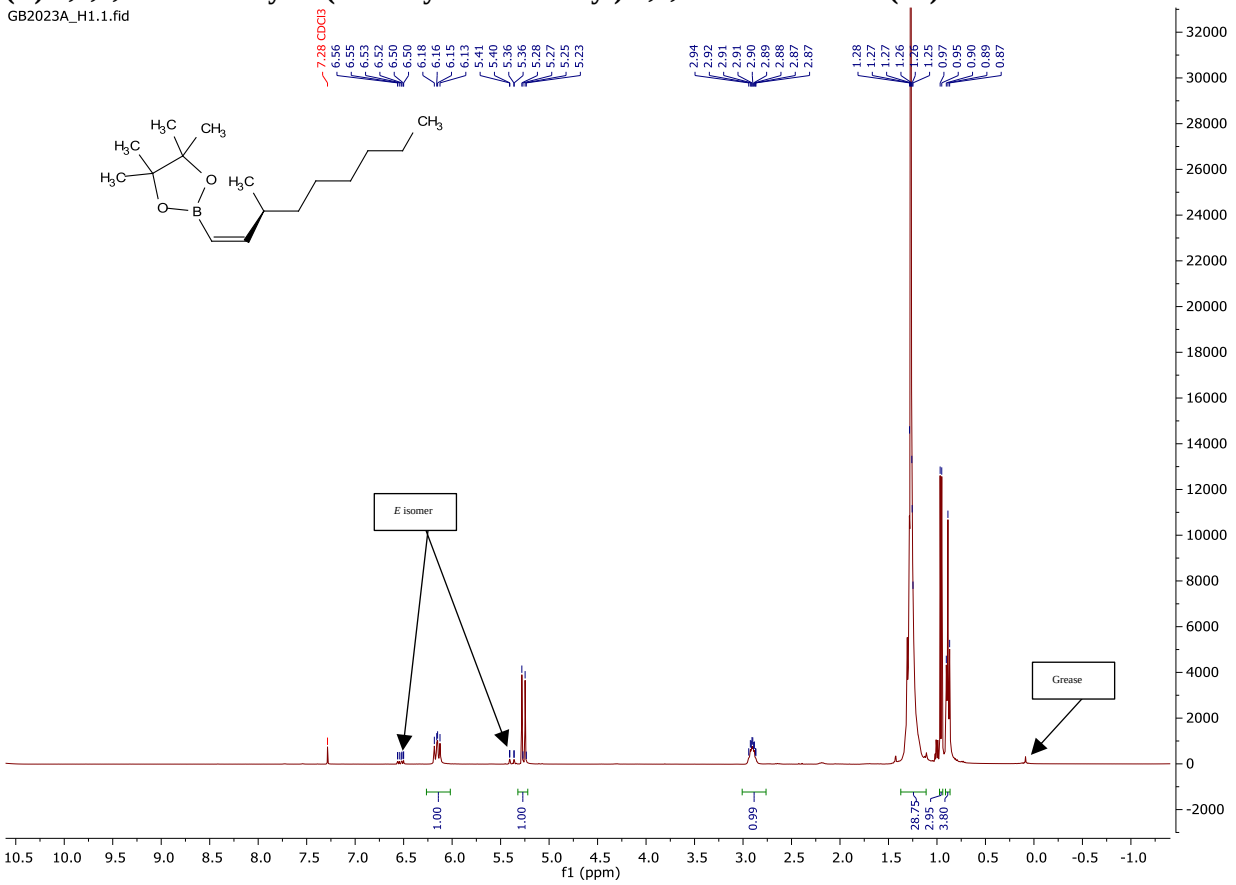
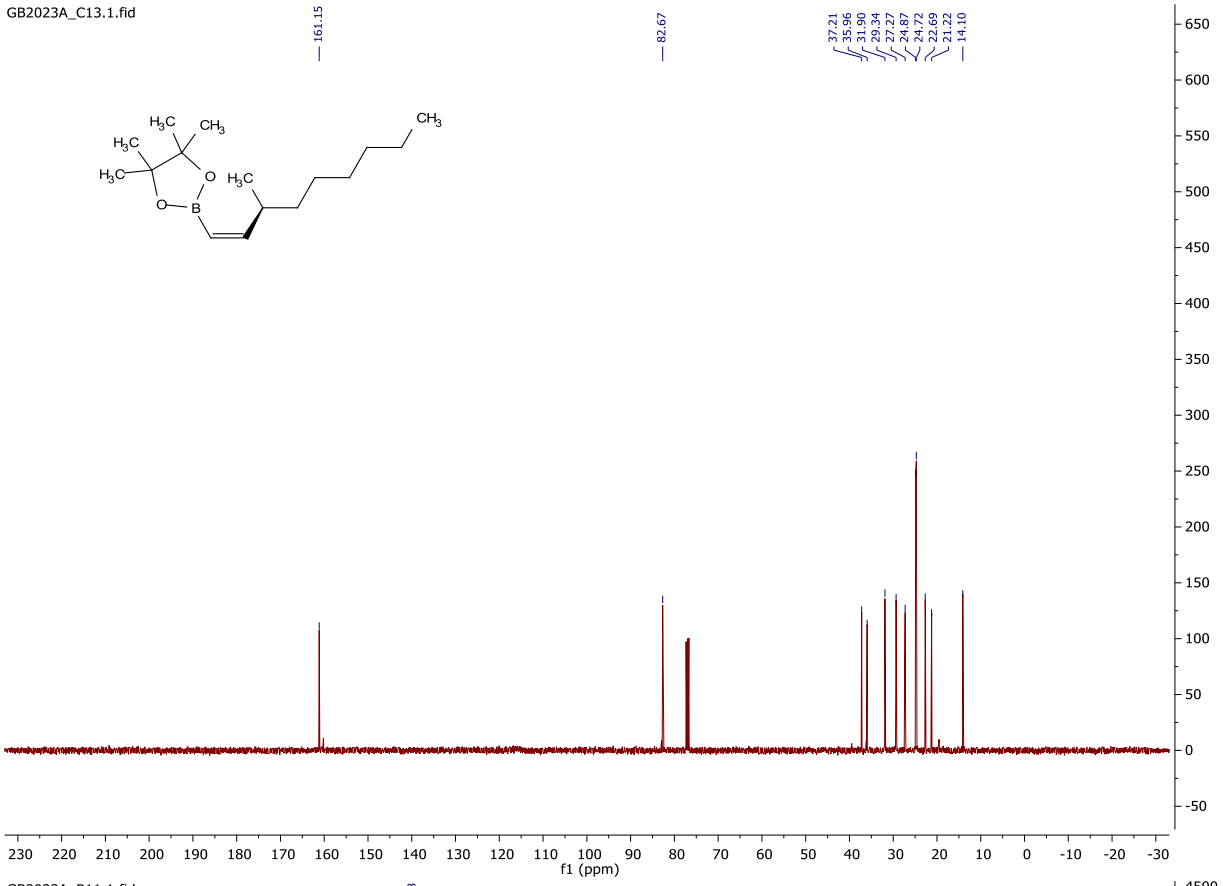
f1 (ppm)

(Z)-4,4,5,5-tetramethyl-2-(3-methylnon-1-en-1-yl)-1,3,2-dioxaborolane (2d)

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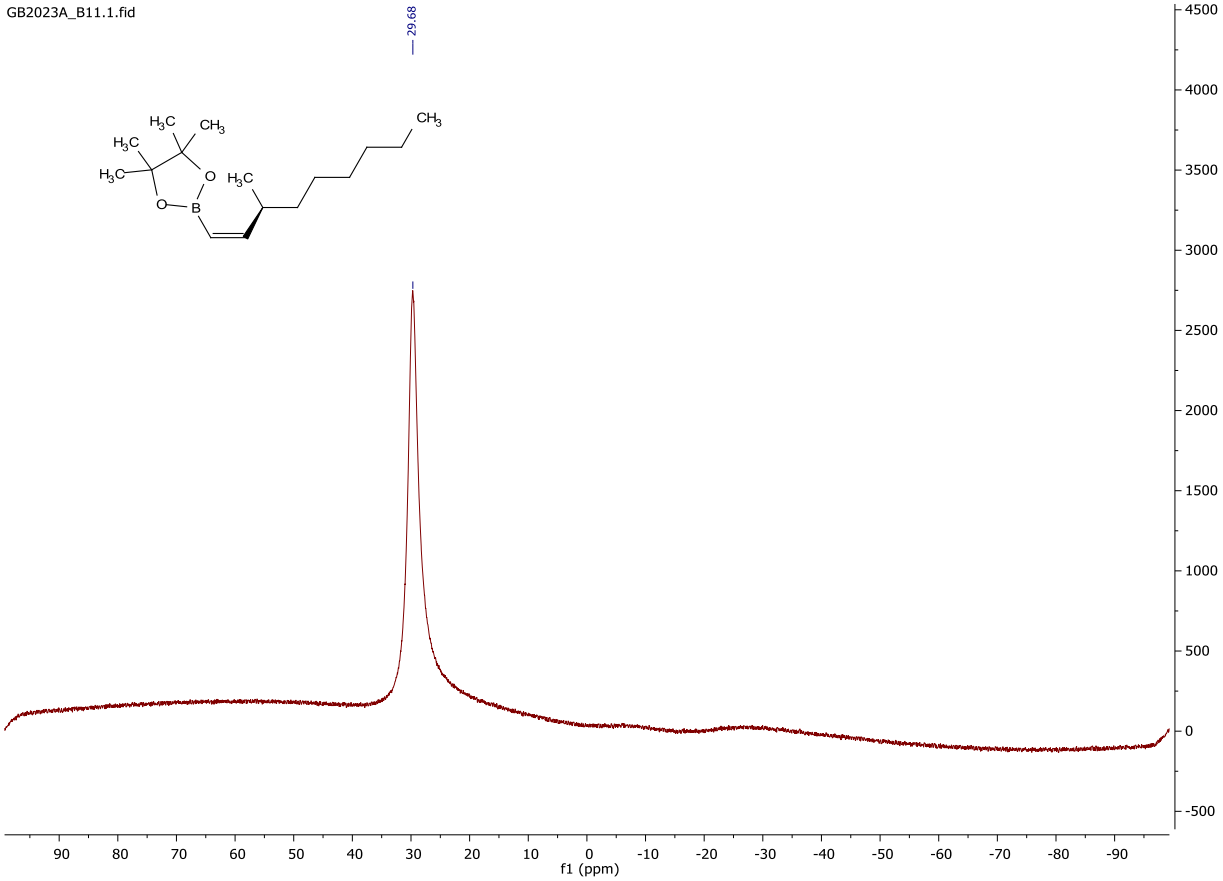
14.10
f1 (ppm)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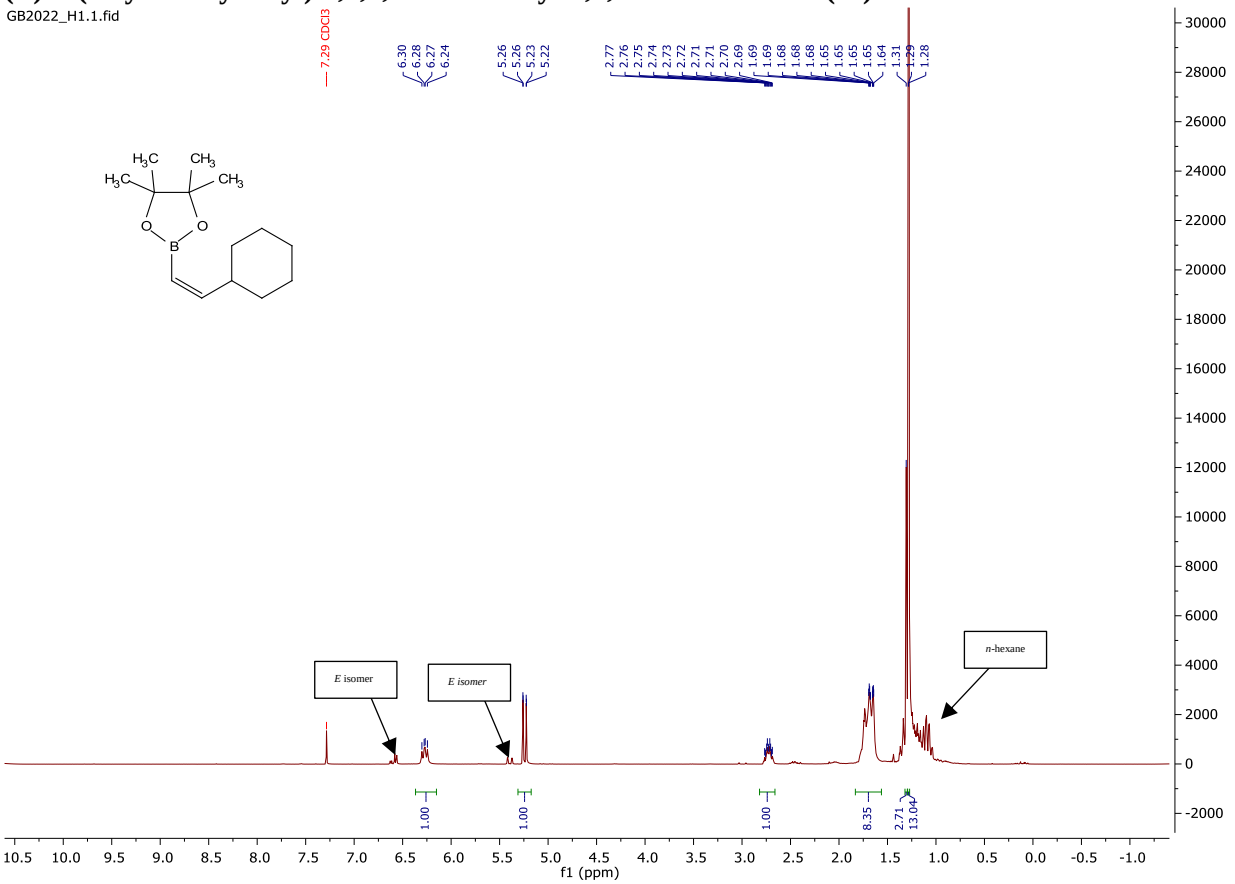
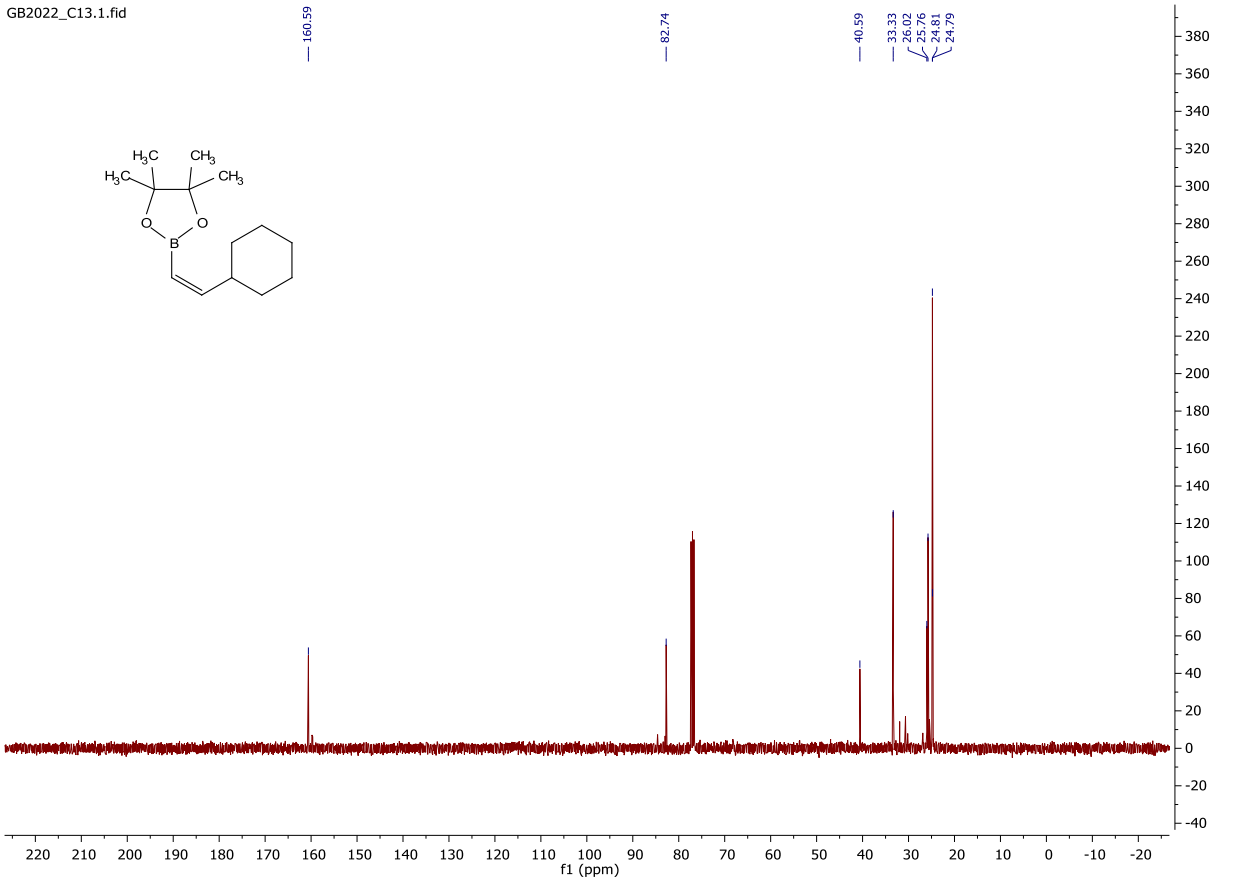
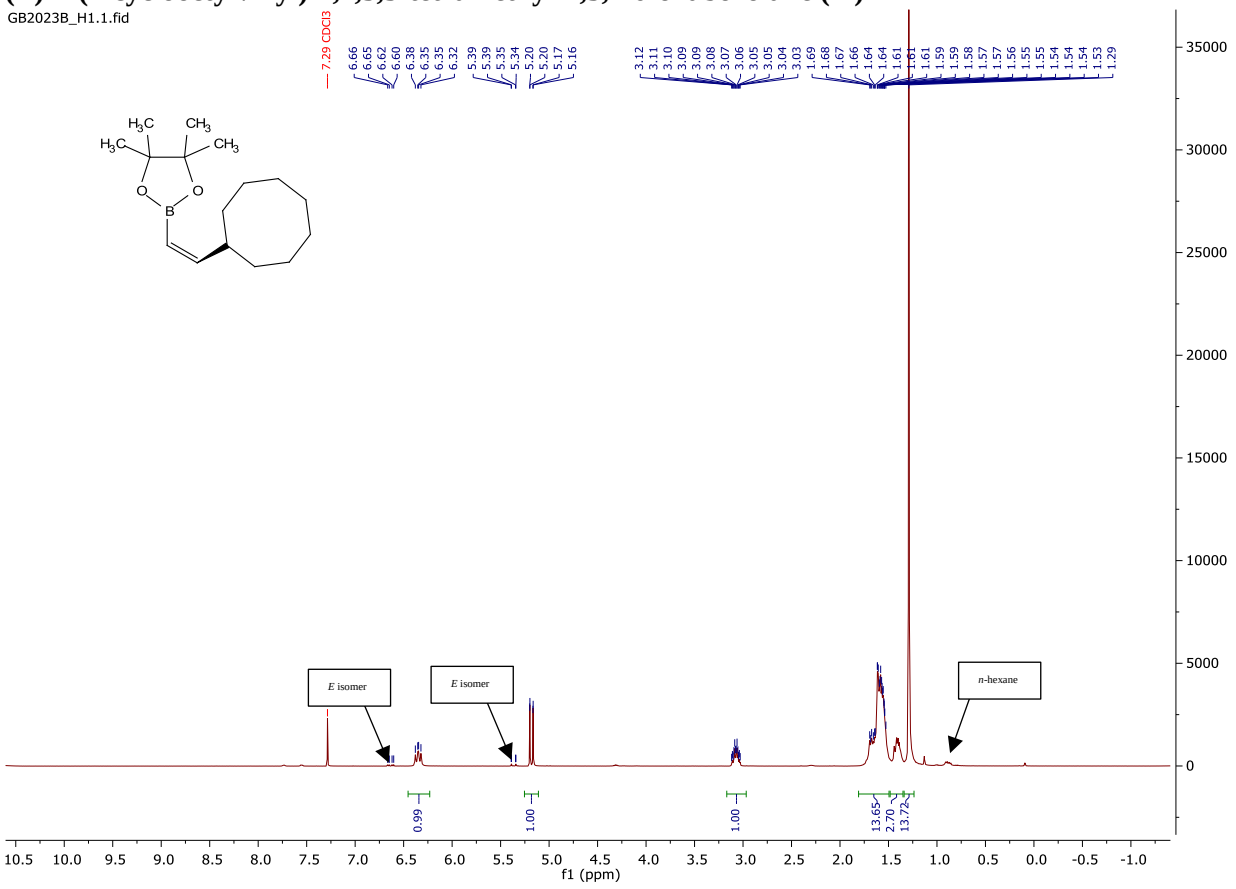
f1 (ppm)

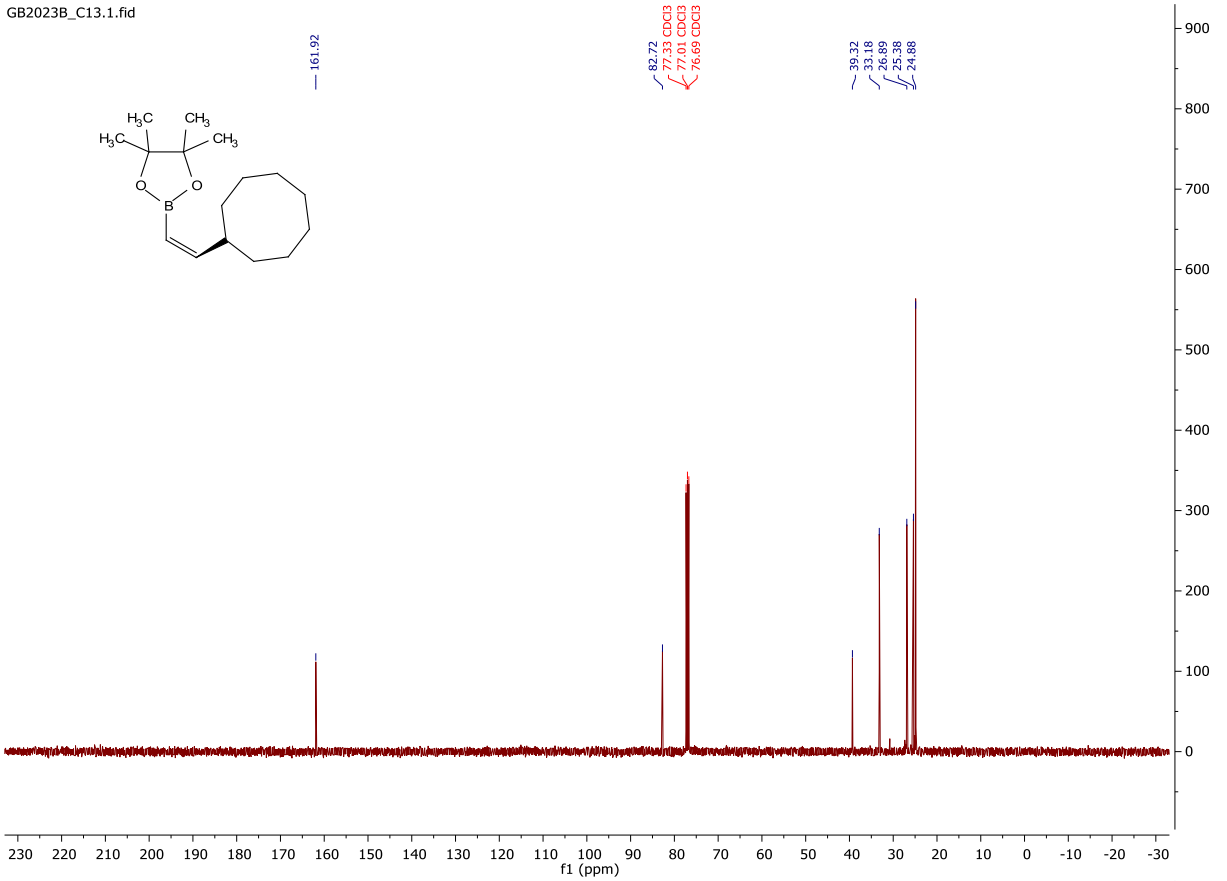
(Z)-2-(2-cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2e)





(Z)-2-(2-cyclooctylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2f)

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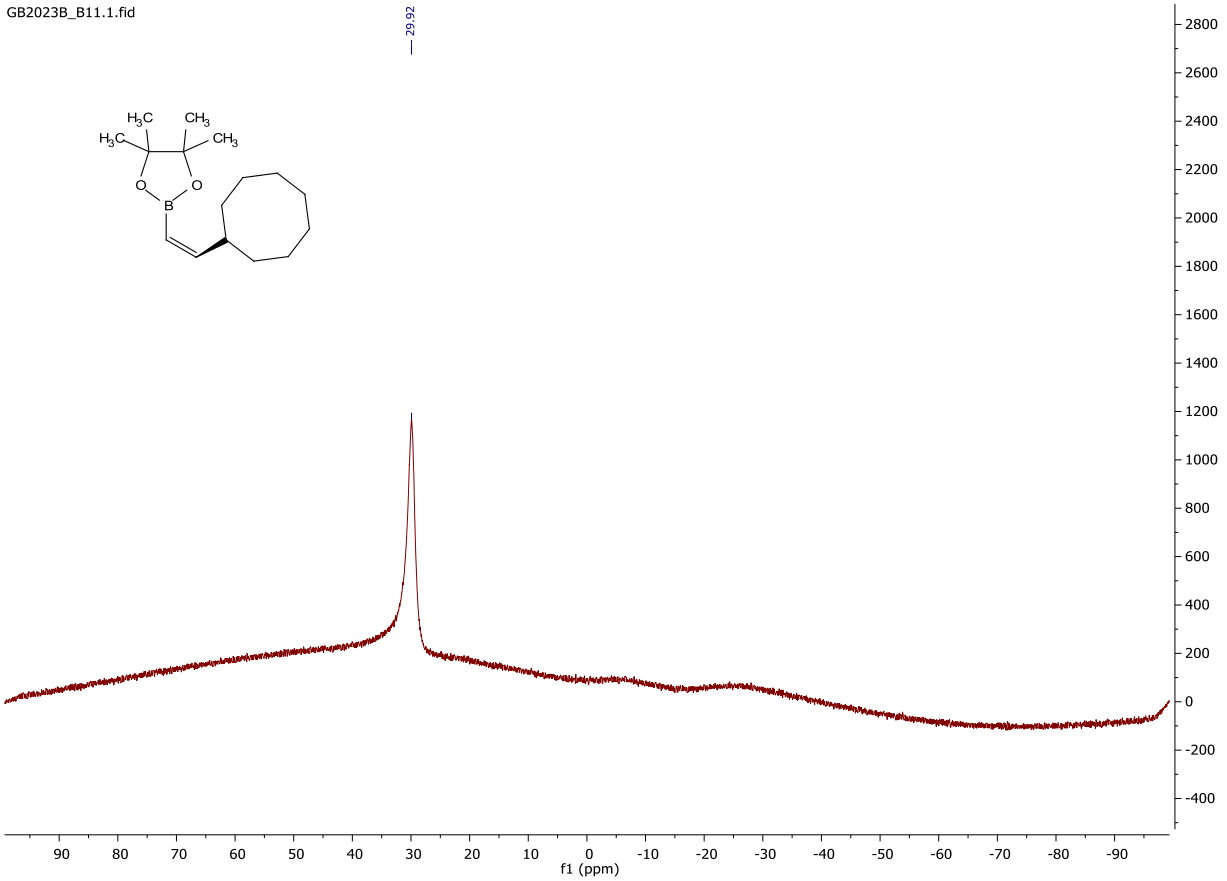
77.33 CDCl3
77.01 CDCl3
76.69 CDCl3
39.32
33.18
26.89
25.38
24.88
f1 (ppm)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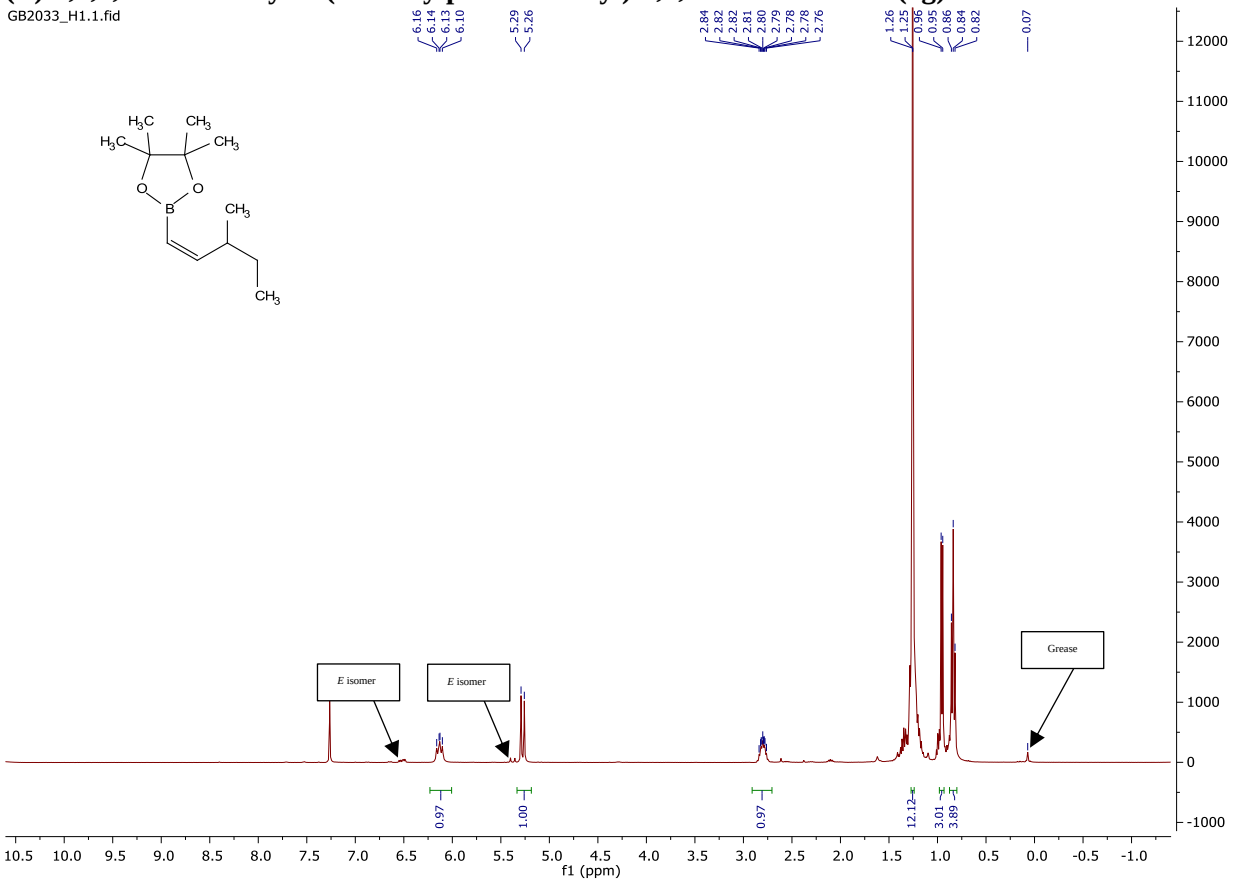
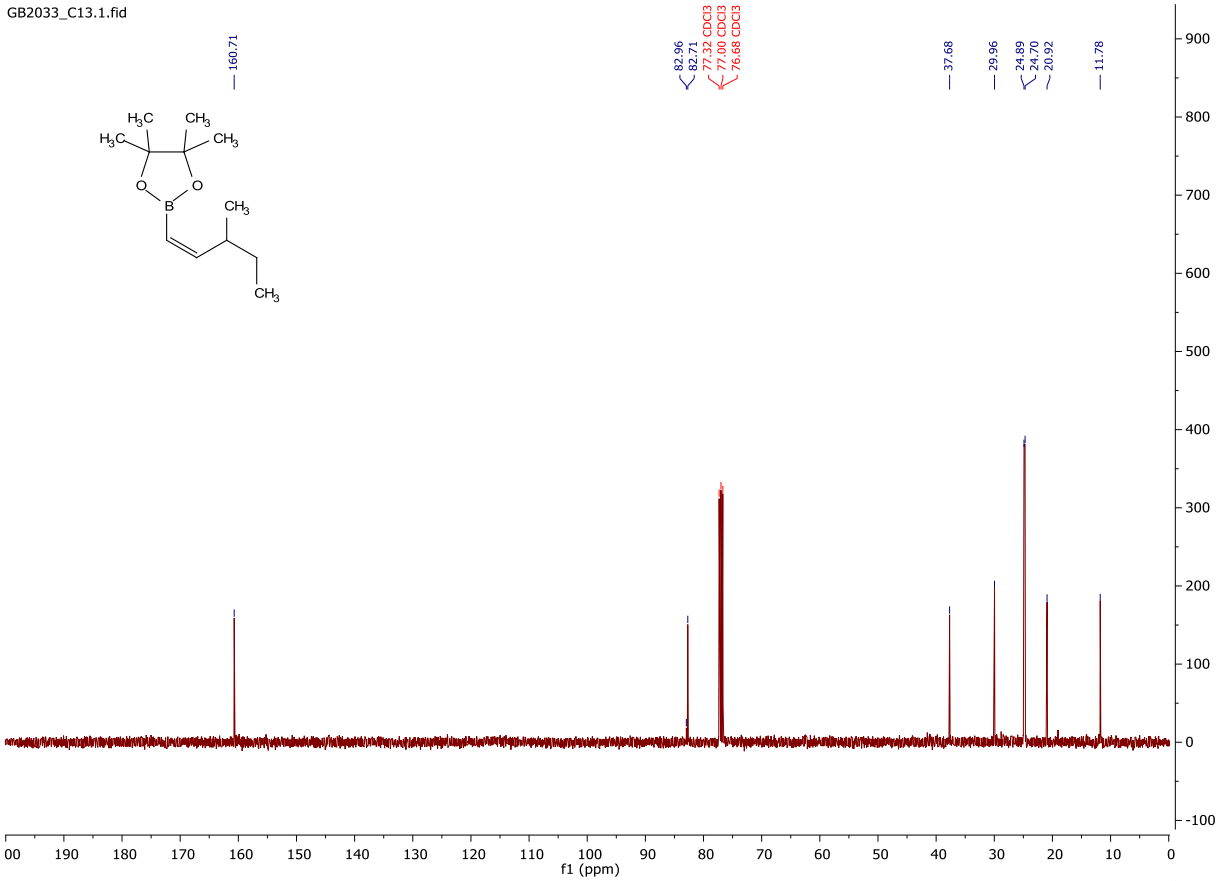
f1 (ppm)

(Z)-4,4,5,5-tetramethyl-2-(3-methylpent-1-en-1-yl)-1,3,2-dioxaborolane (2g)

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24.70
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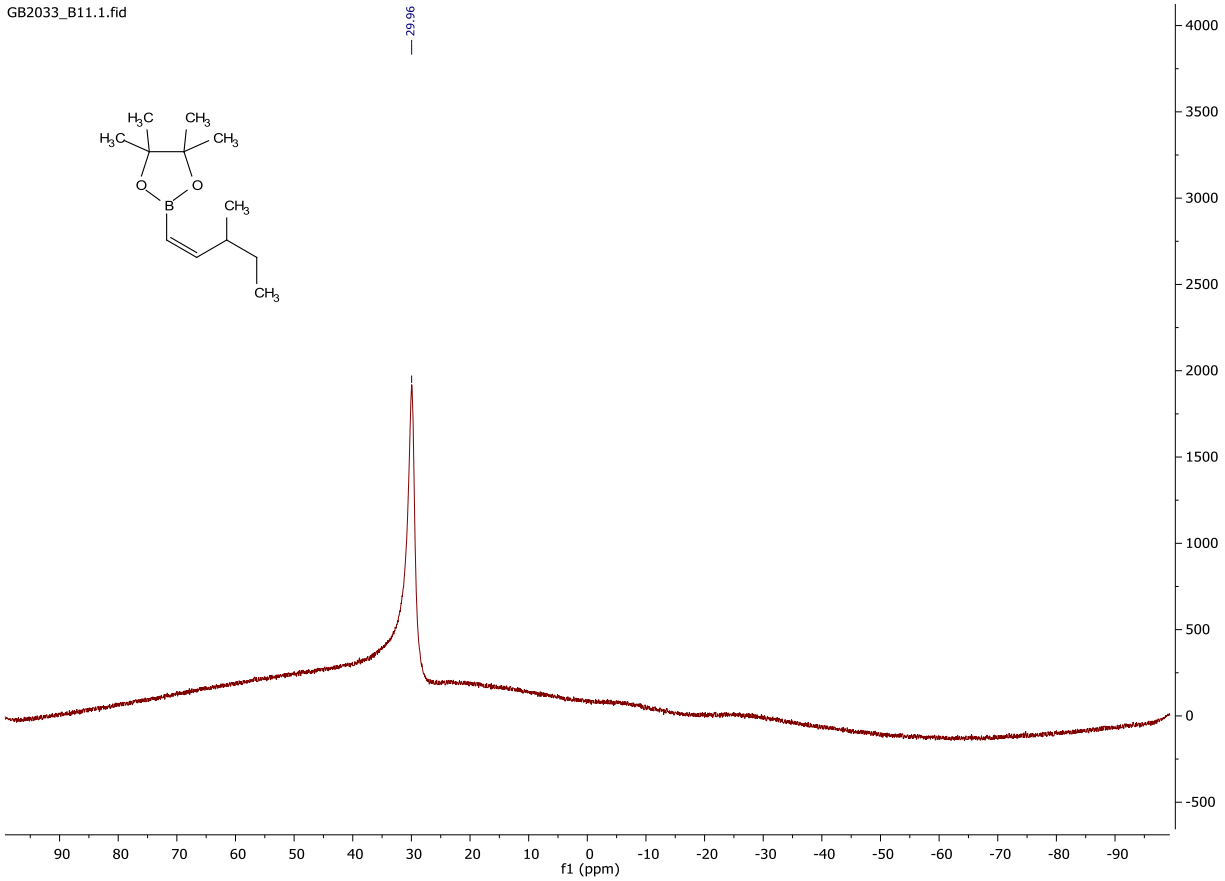
11.78
f1 (ppm)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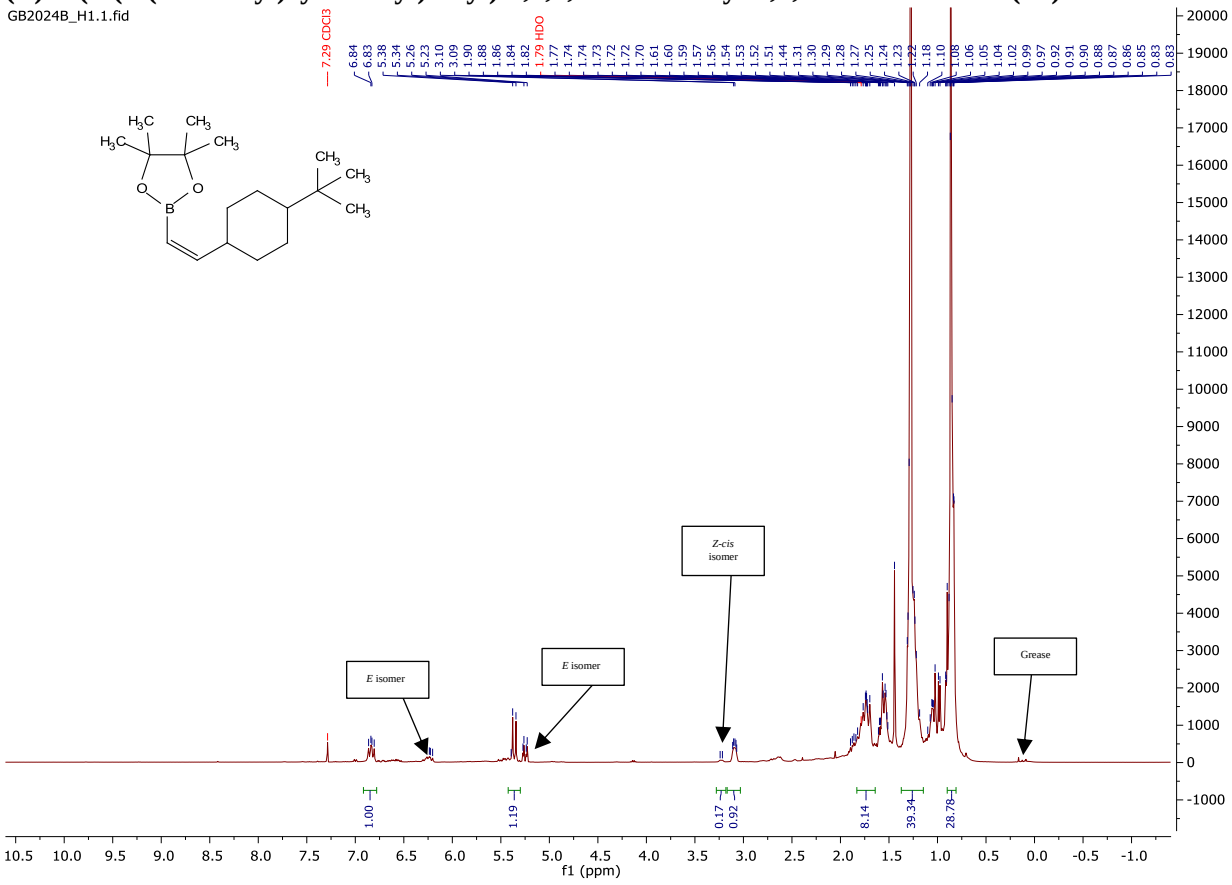
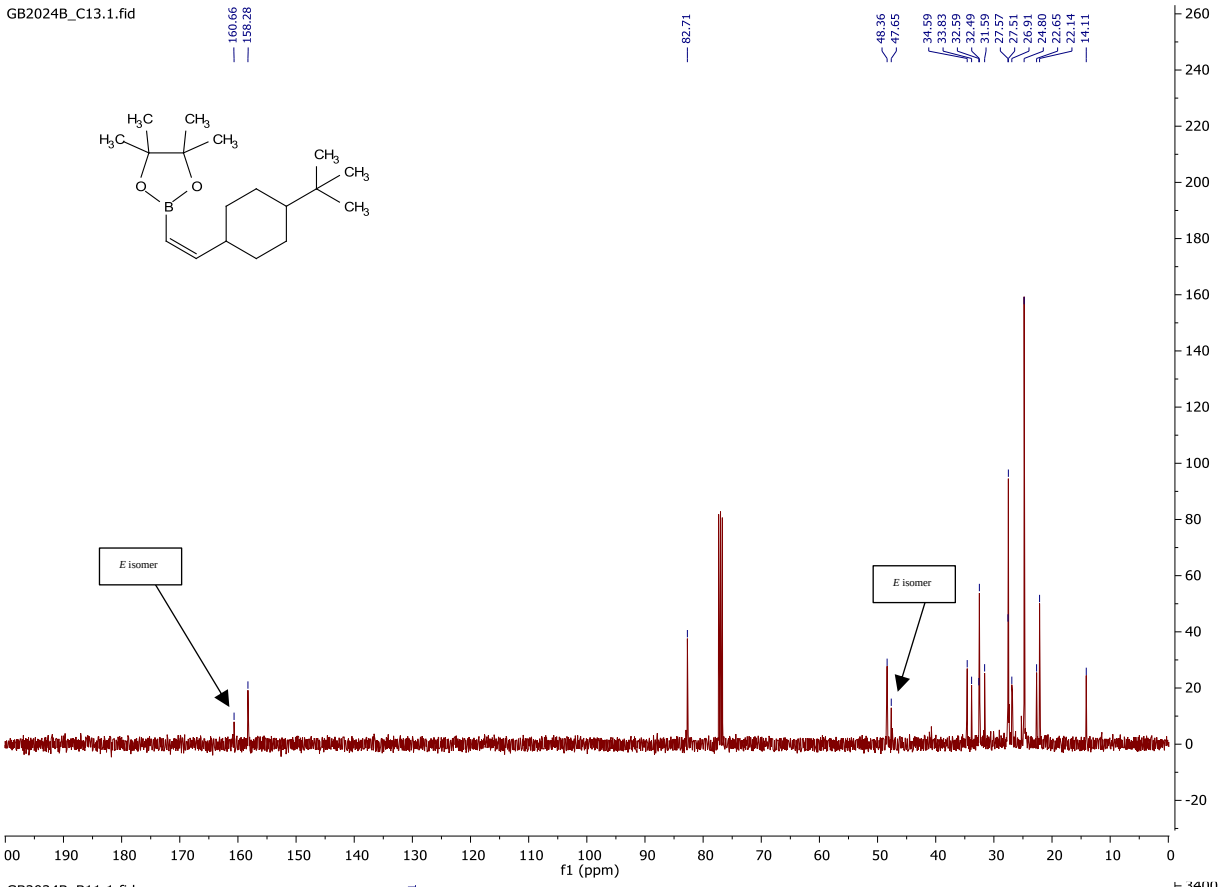
29.96
f1 (ppm)

(Z)-2-(2-(4-(tert-butyl)cyclohexyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2h)

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33.83
32.59
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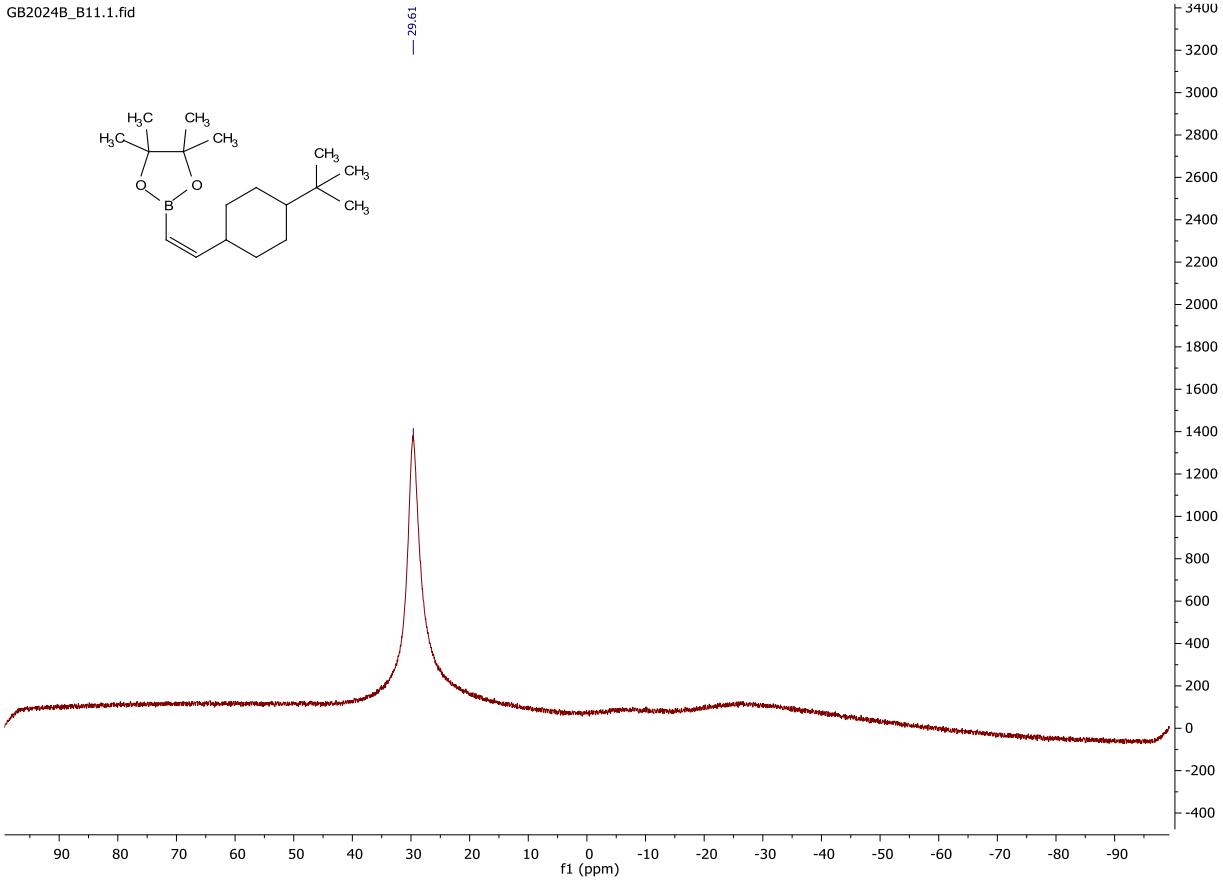
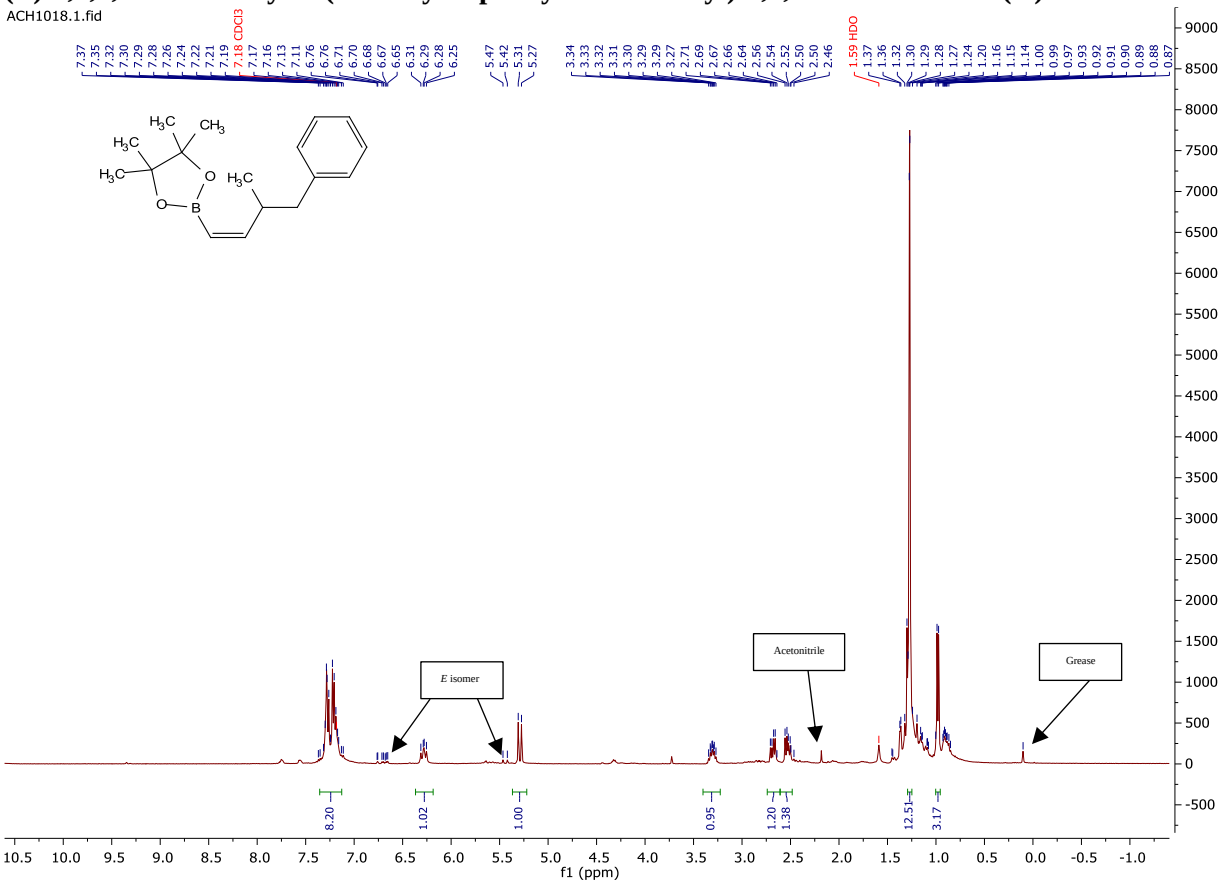
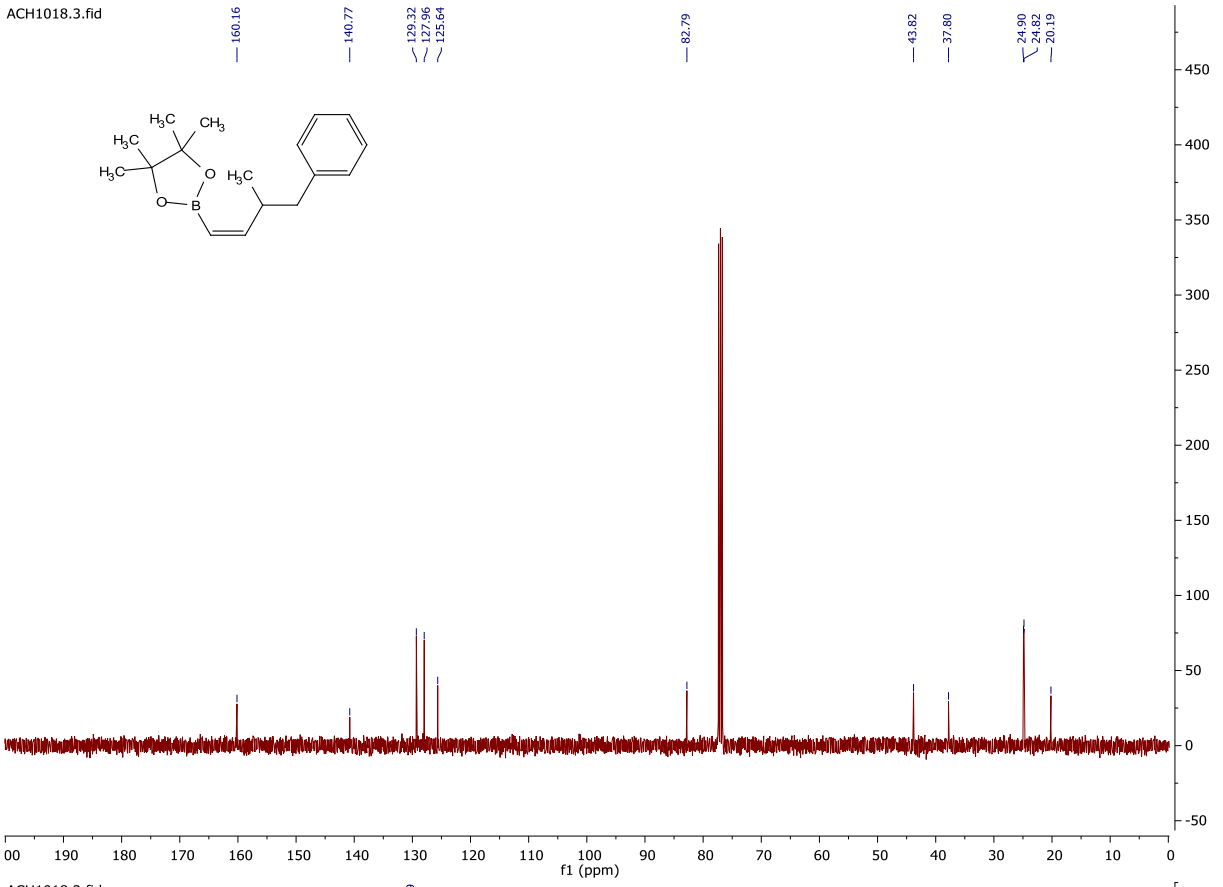
27.51
26.91
24.80
22.65
22.14
14.11
E isomer
E isomer
f1 (ppm)


GB2024B_B11.1.fid
29.61
f1 (ppm)

(Z)-4,4,5,5-tetramethyl-2-(3-methyl-4-phenylbut-1-en-1-yl)-1,3,2-dioxaborolane (2i)

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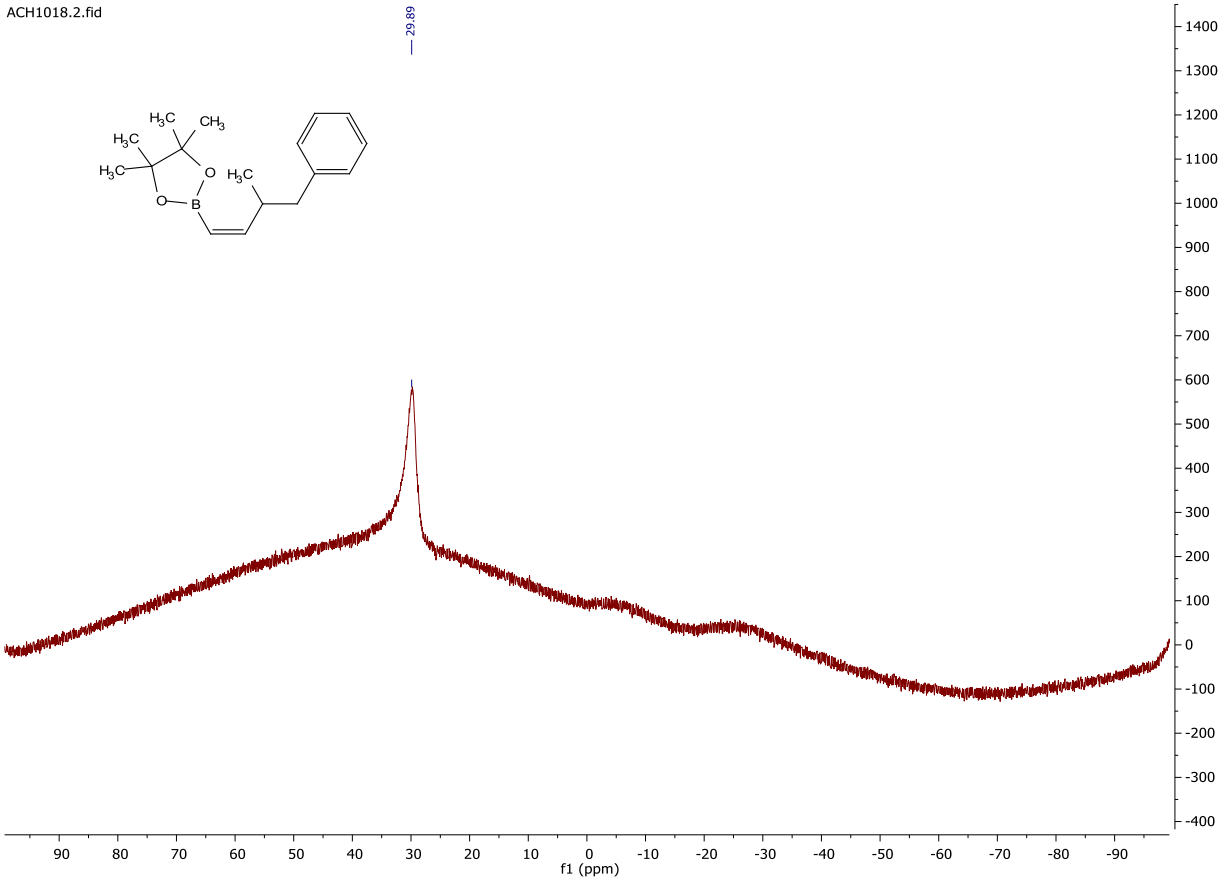
24.82
20.19
f1 (ppm)


ACH1018.2.fid
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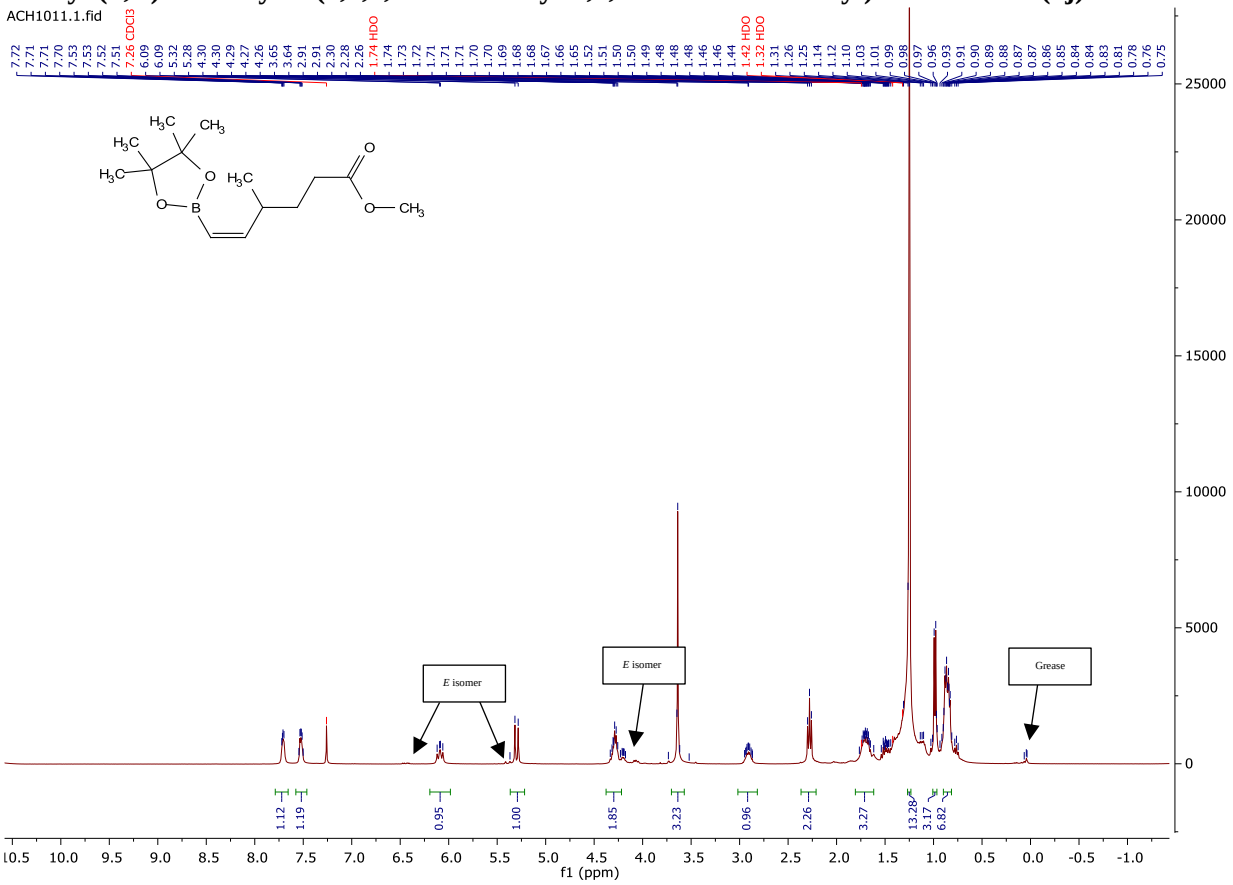
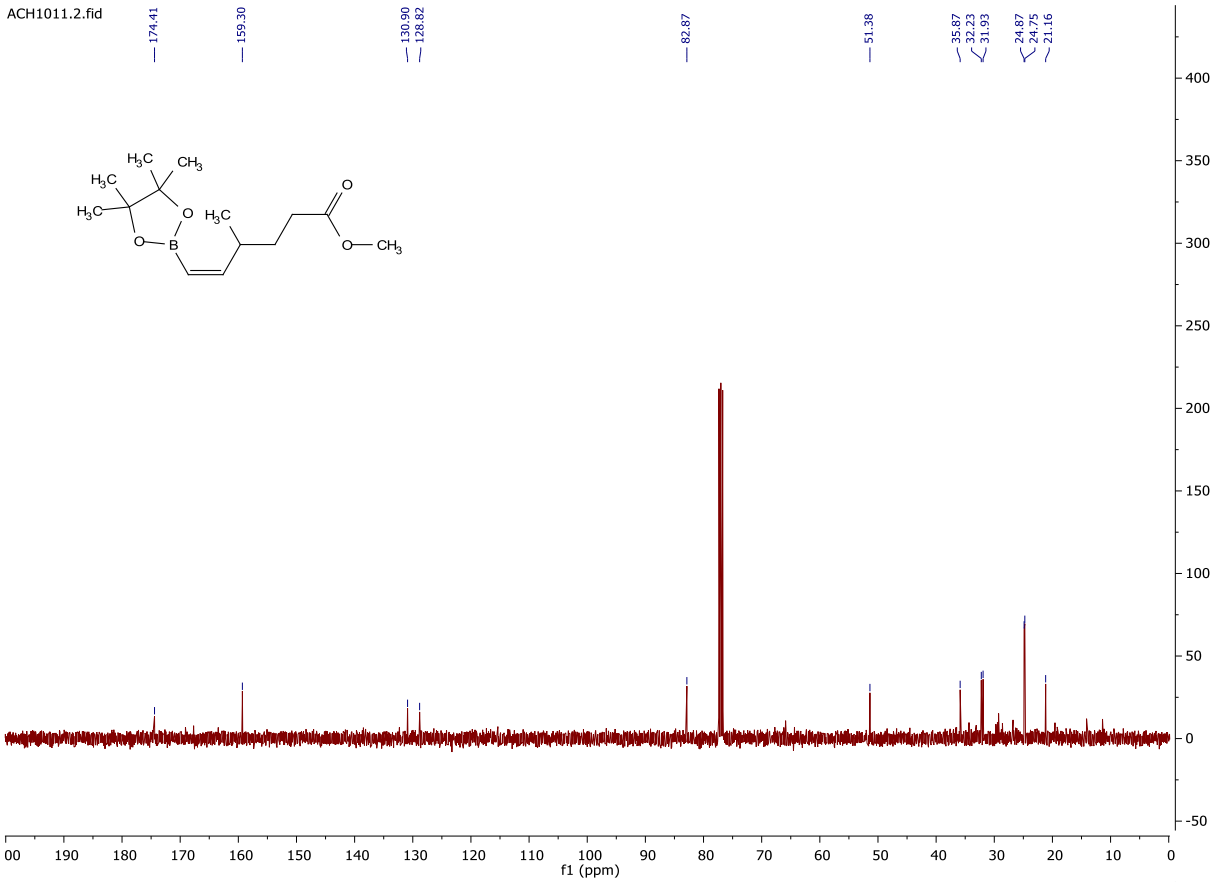
f1 (ppm)

methyl (S,Z)-4-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-enoate (2j)

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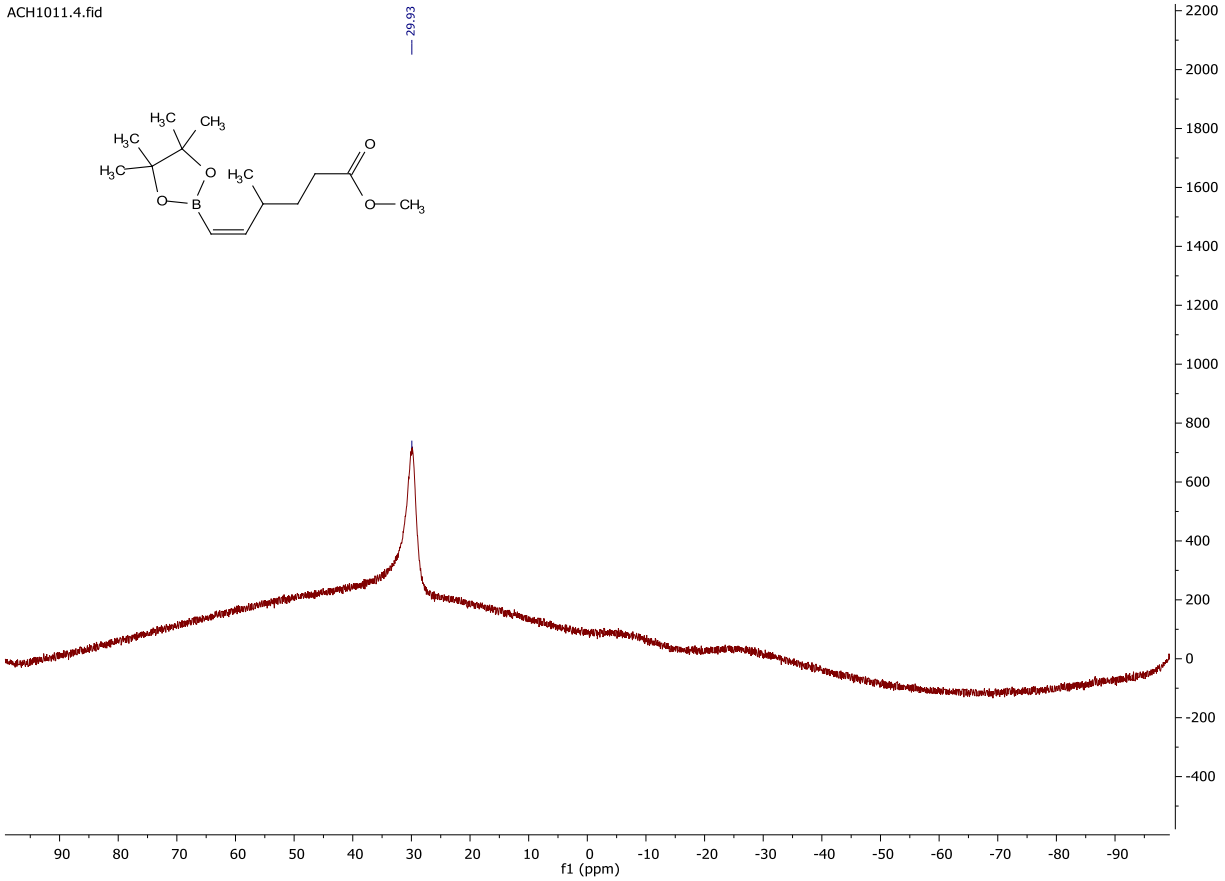
24.75
21.16
f1 (ppm)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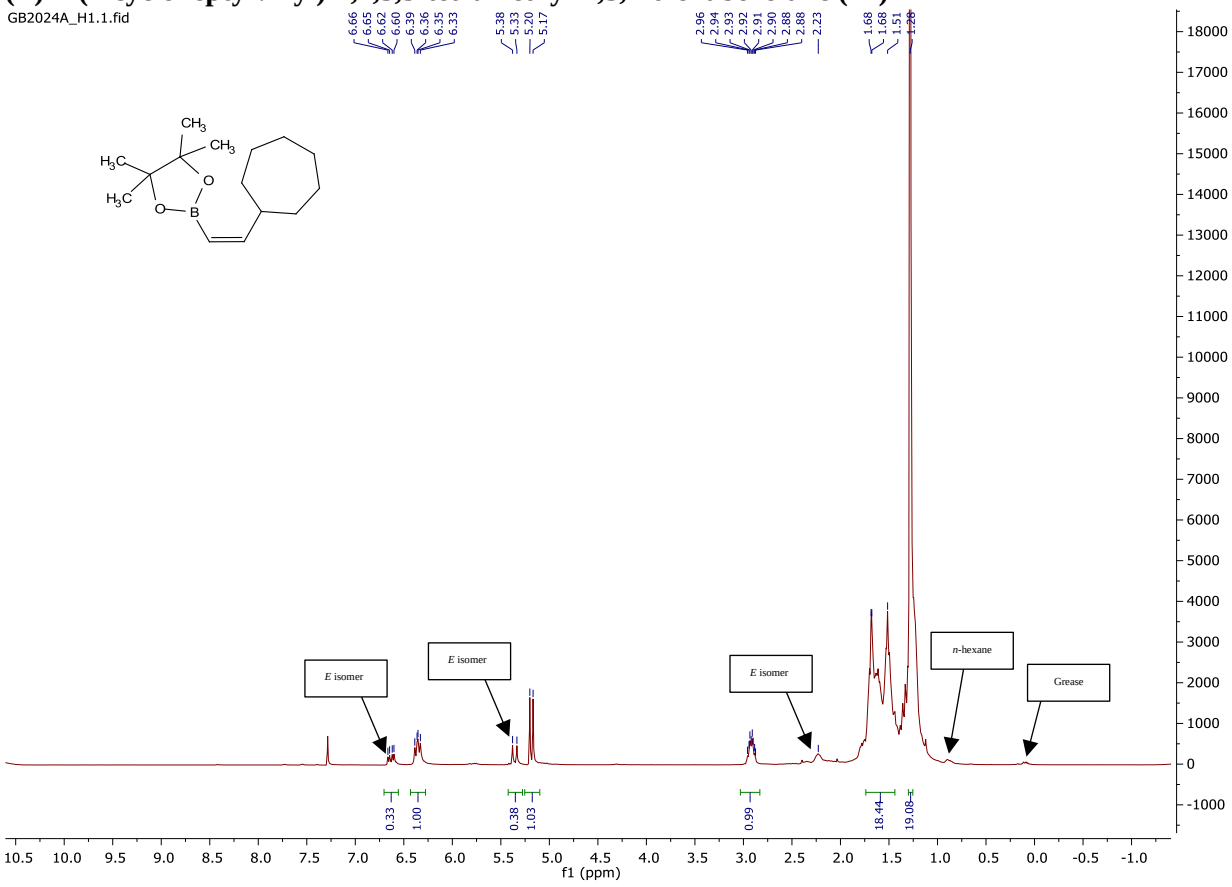
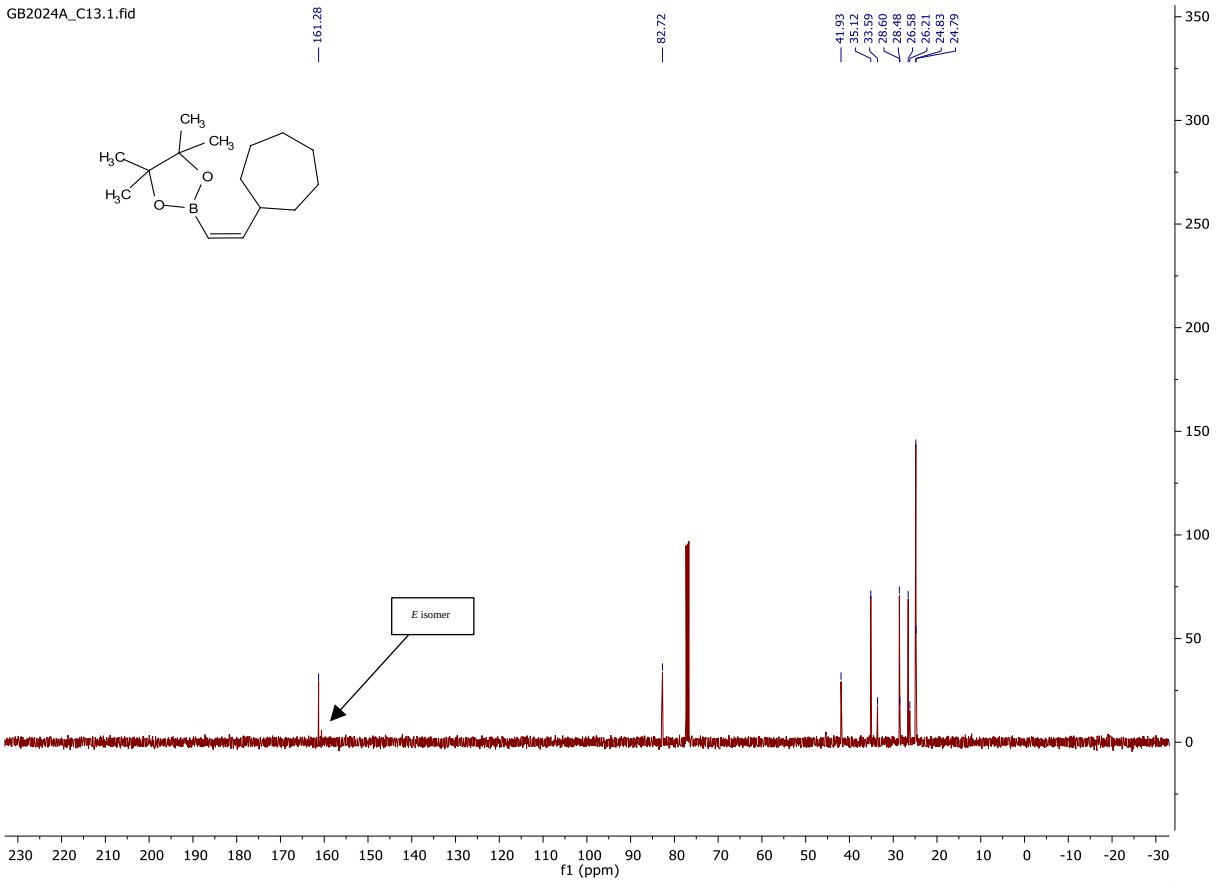
f1 (ppm)

(Z)-2-(2-cycloheptylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2k)




GB2024A_C13.1.fid
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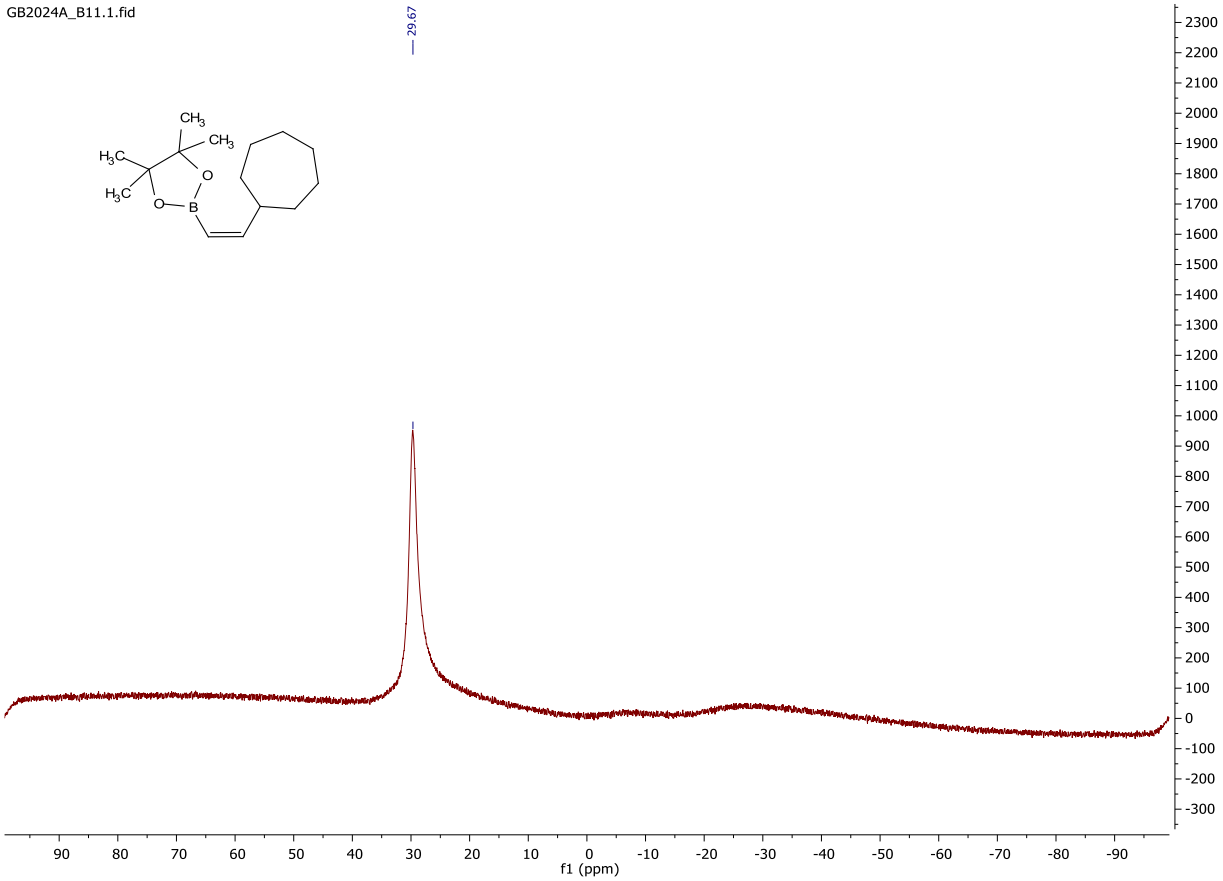
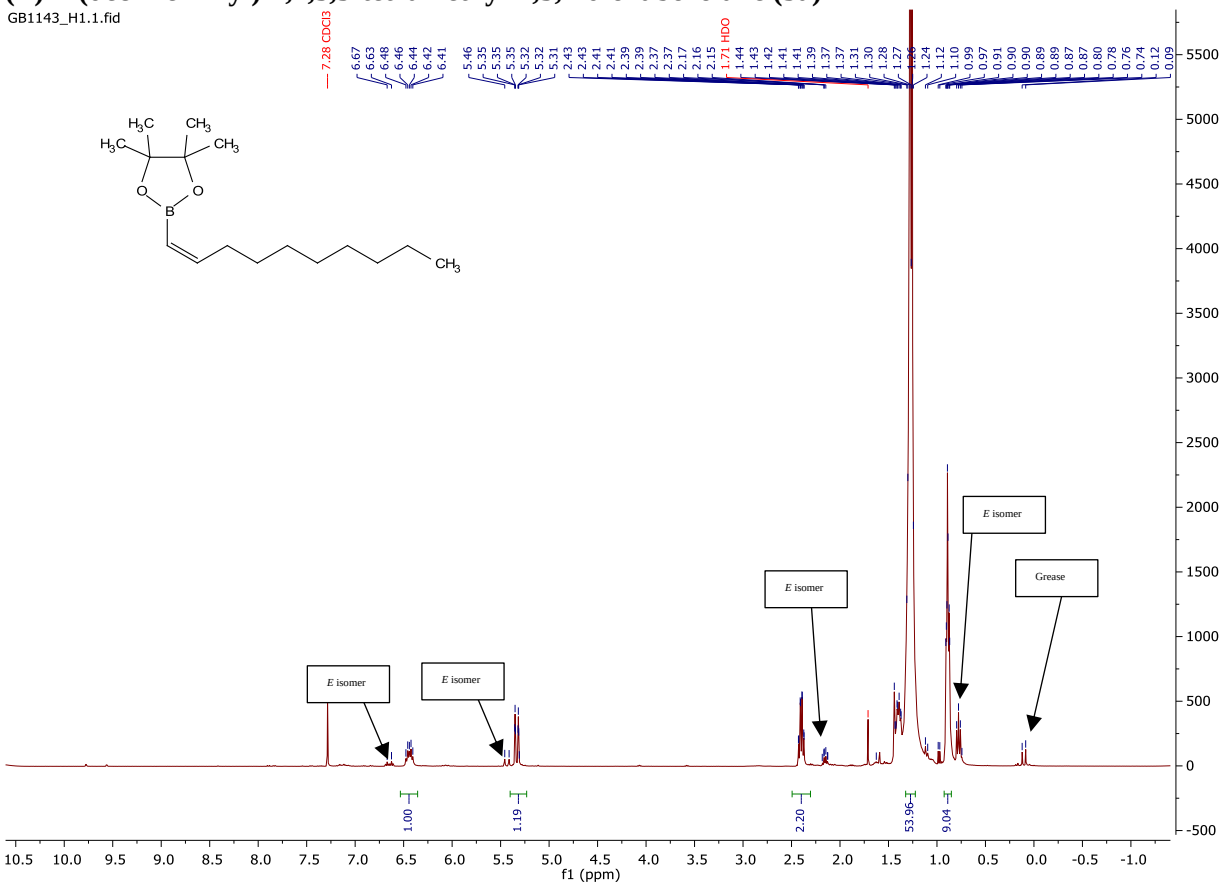
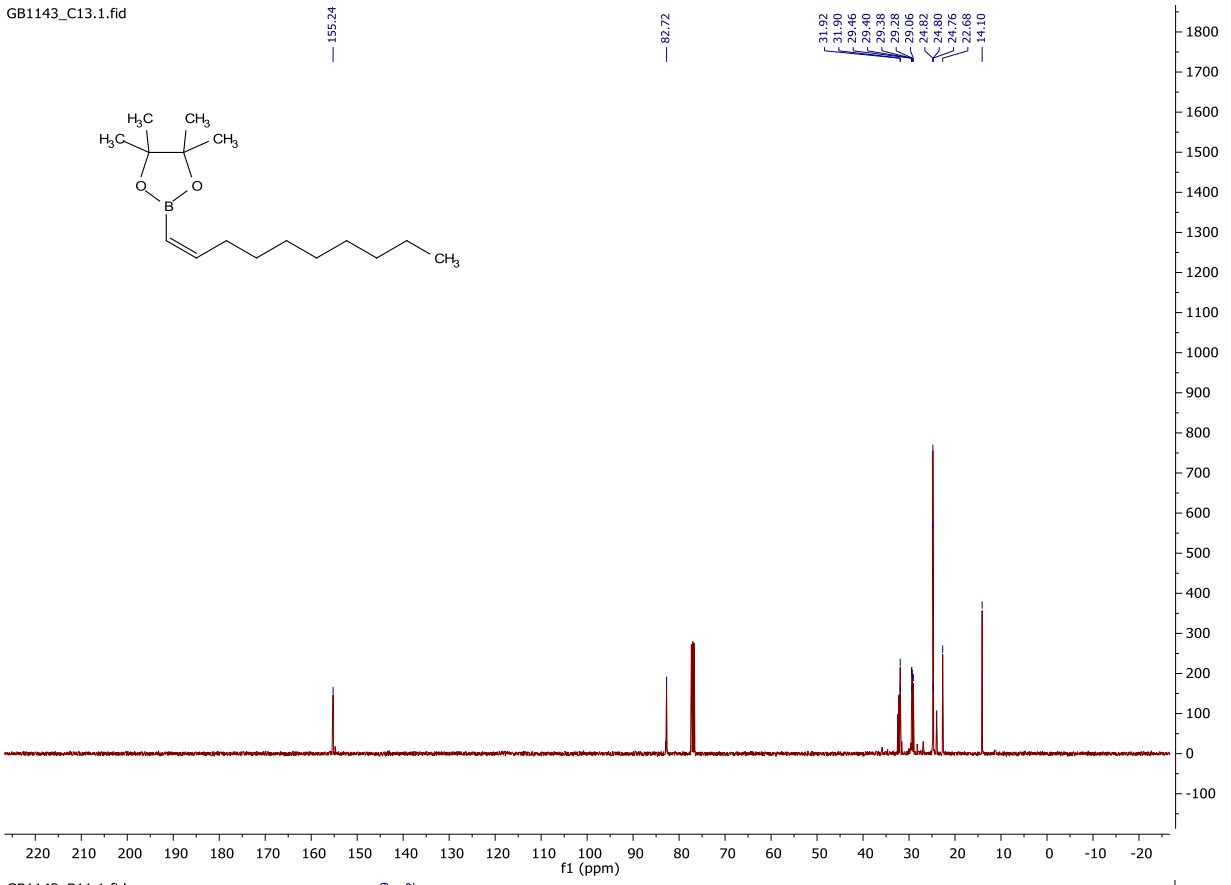
24.79
E isomer
f1 (ppm)


GB2024A_B11.1.fid
29.67
f1 (ppm)

(Z)-2-(dec-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3a)

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155.24
82.72
31.92
31.90
29.46
29.40
29.38
29.28
29.06
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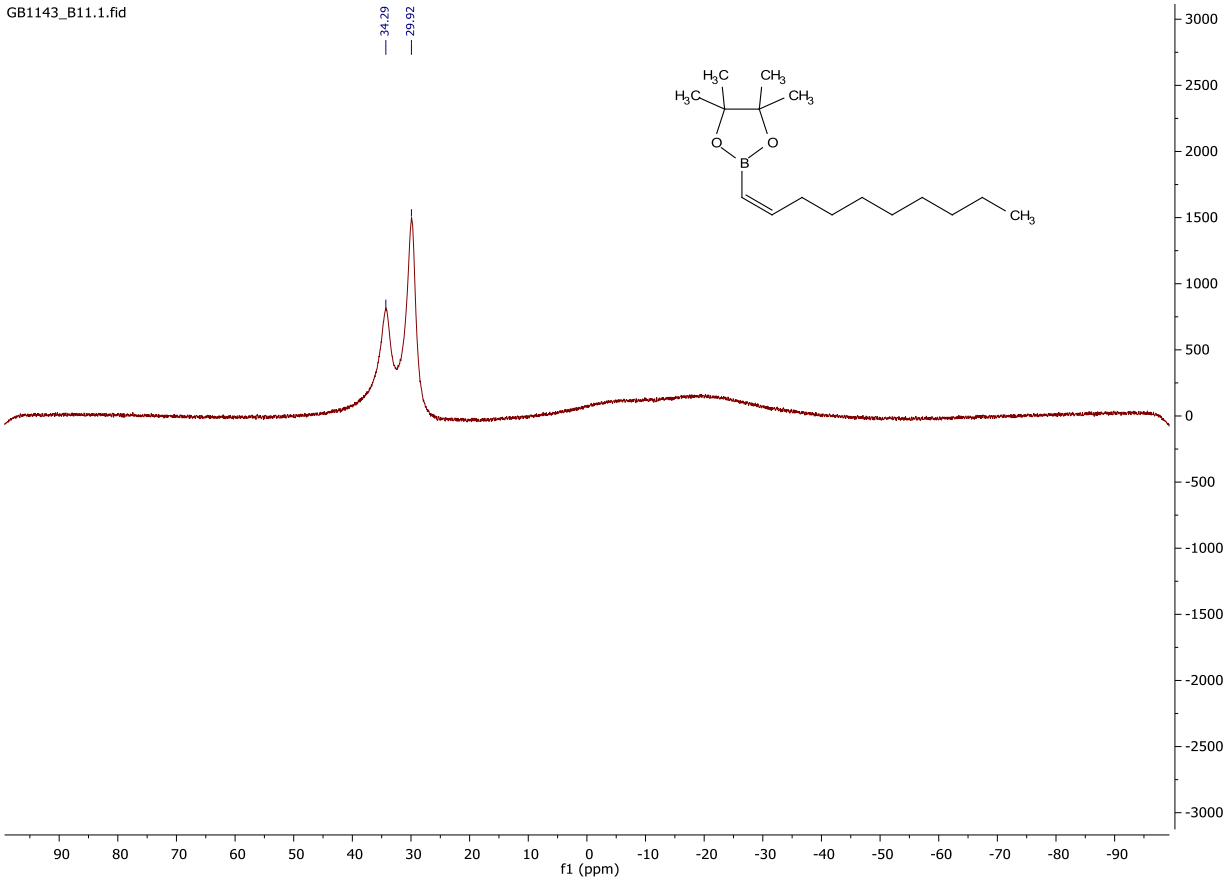
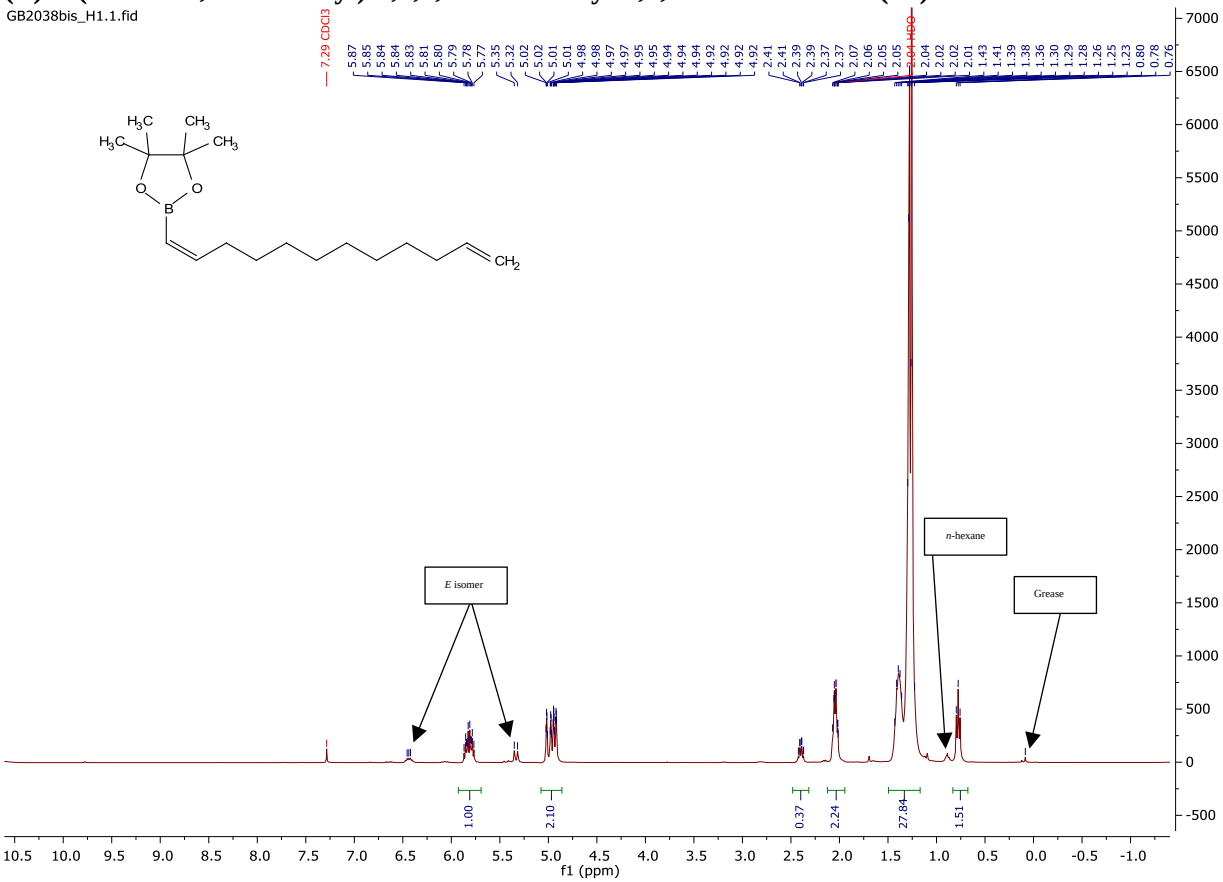
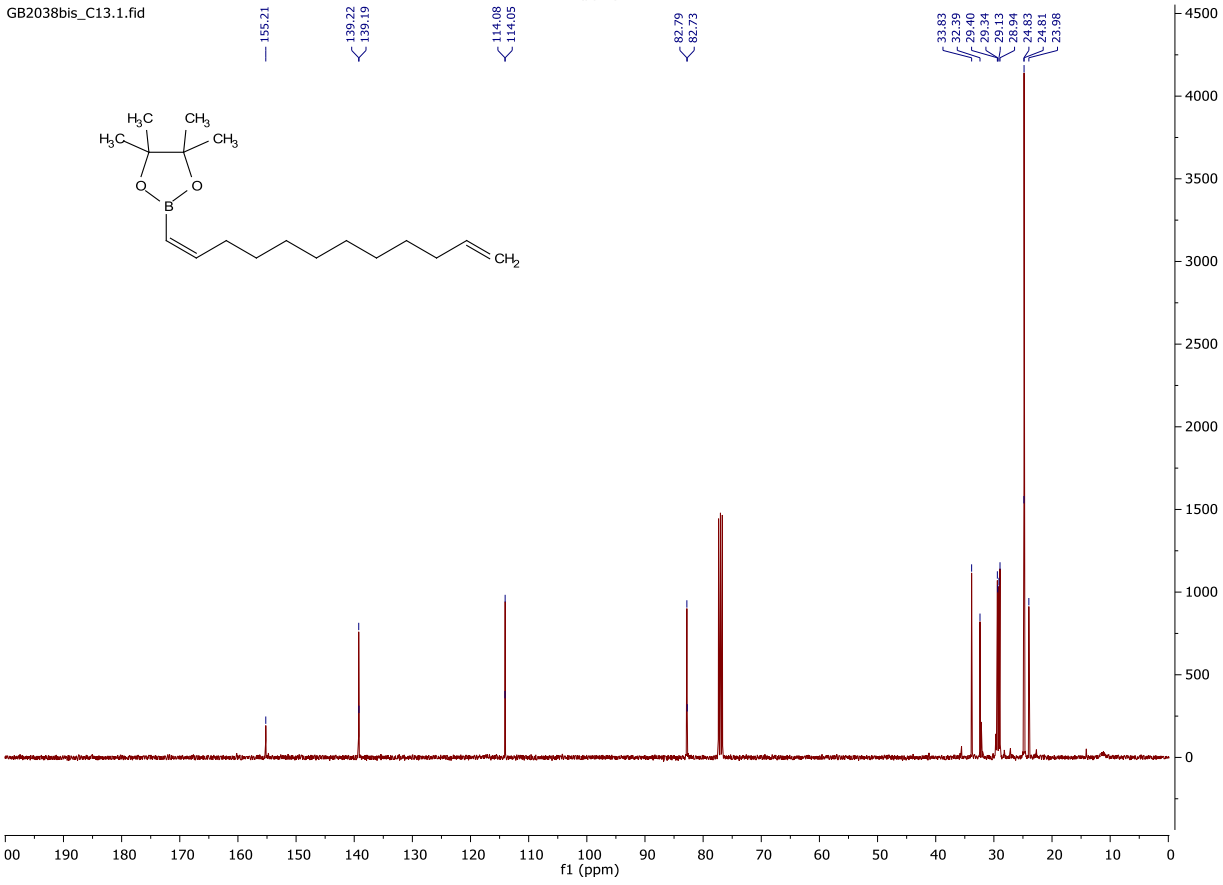
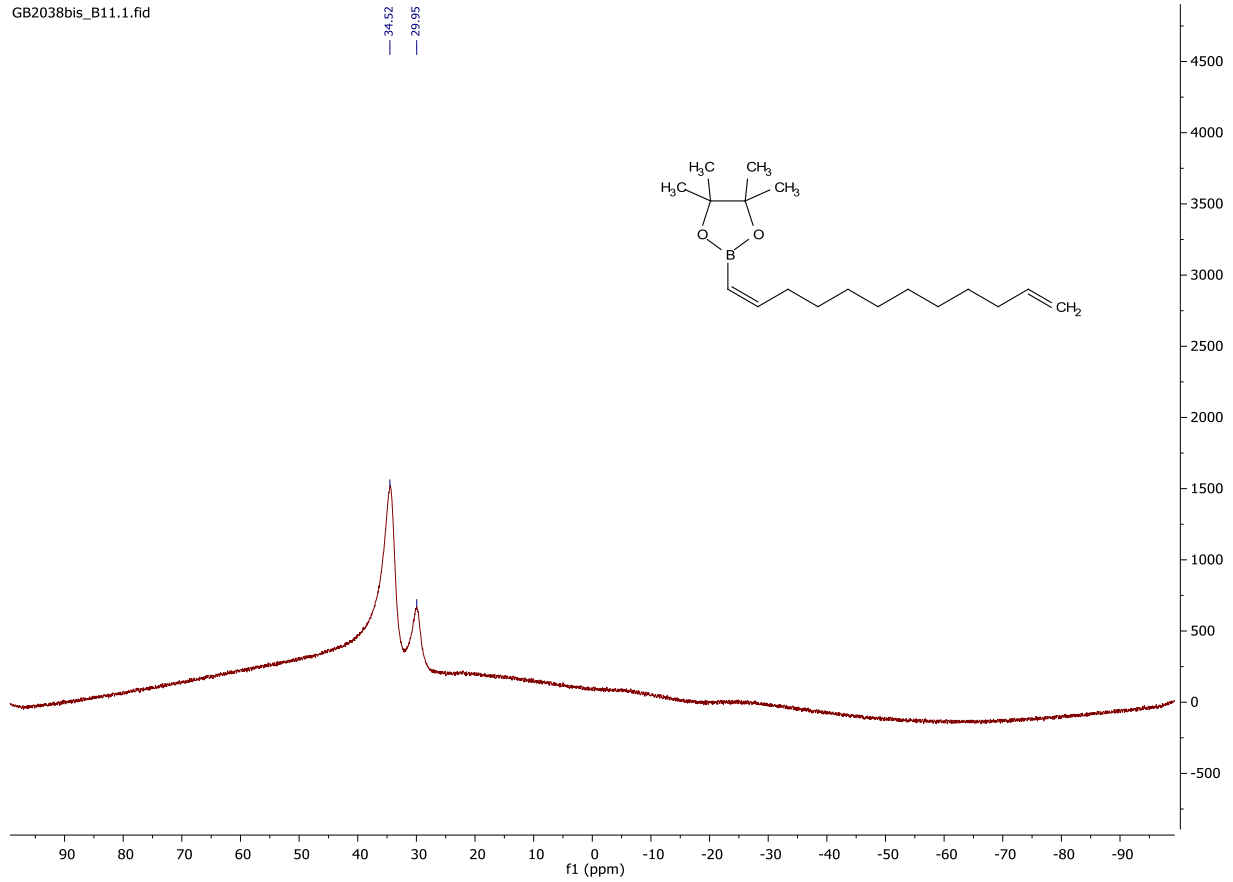
24.80
24.76
22.68
14.10
f1 (ppm)


GB1143_B11.1.fid
34.29
29.92
f1 (ppm)

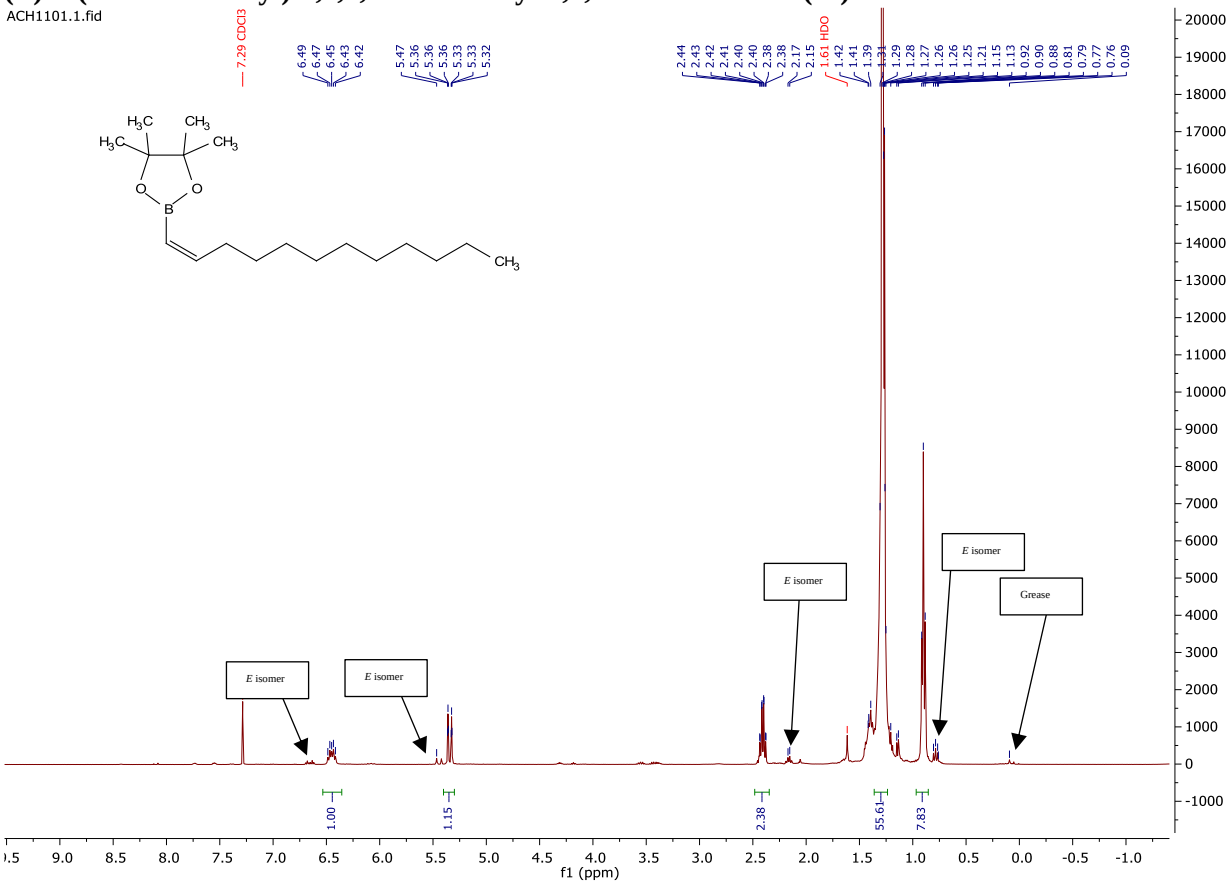
(Z)-2-(dodeca-1,11-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3b)

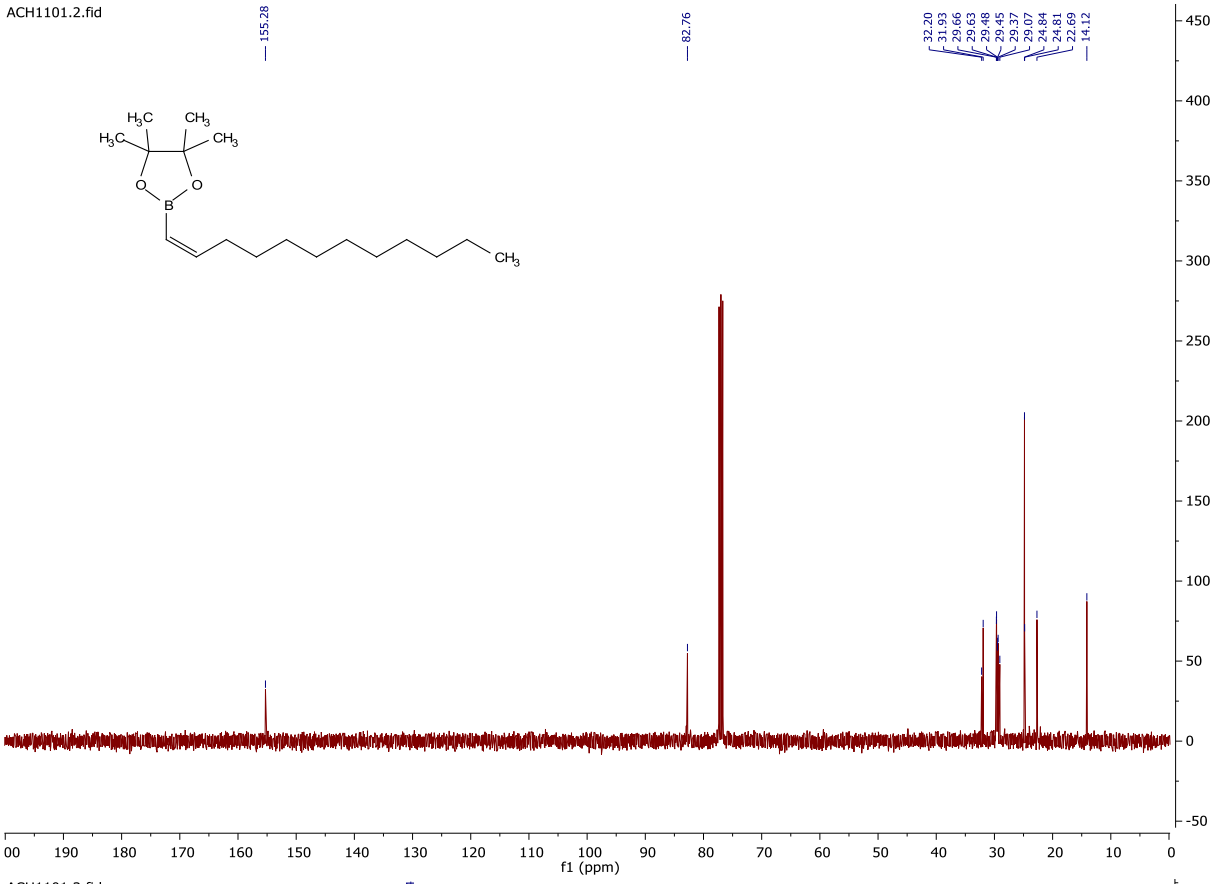






(Z)-2-(dodec-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3c)

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82.76
32.20
31.93
29.66
29.63
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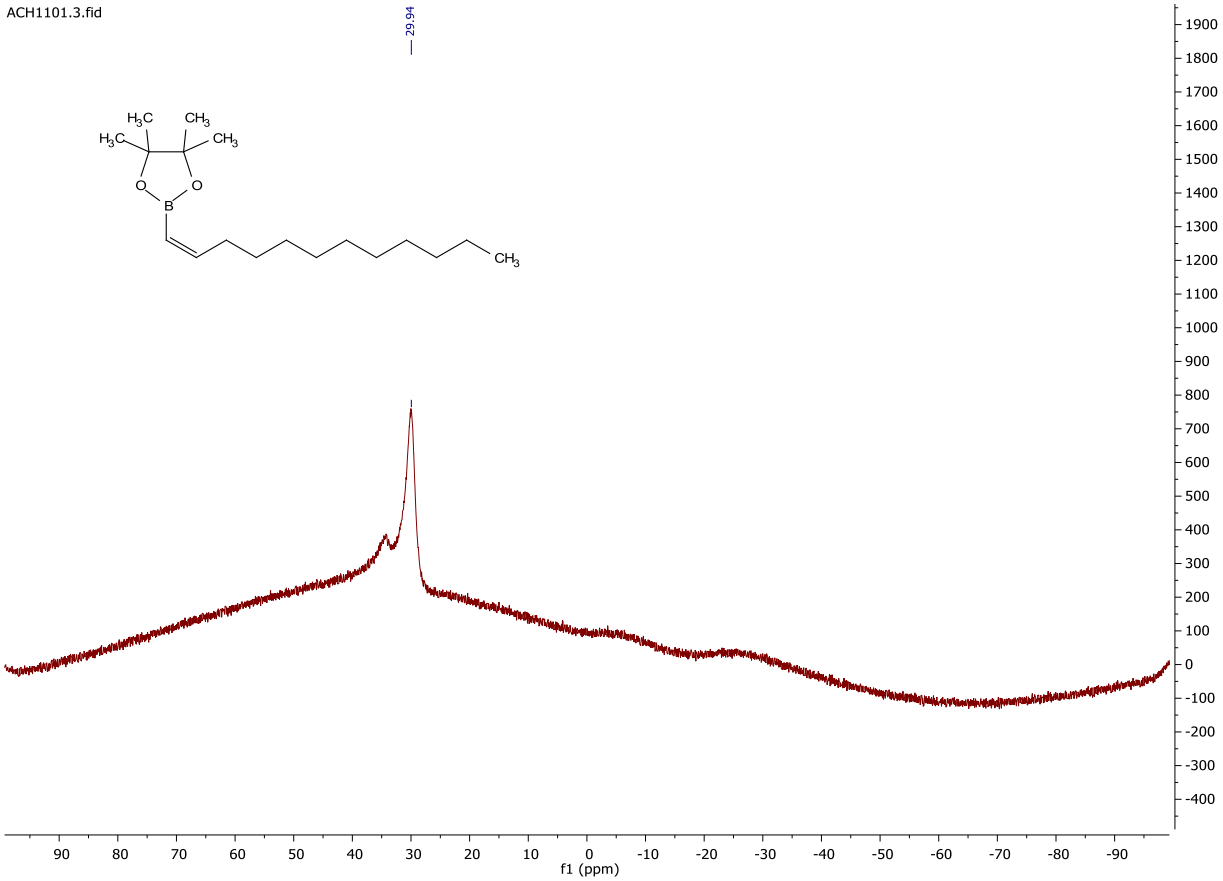
29.45
29.37
29.07
24.84
24.81
22.69
14.12
f1 (ppm)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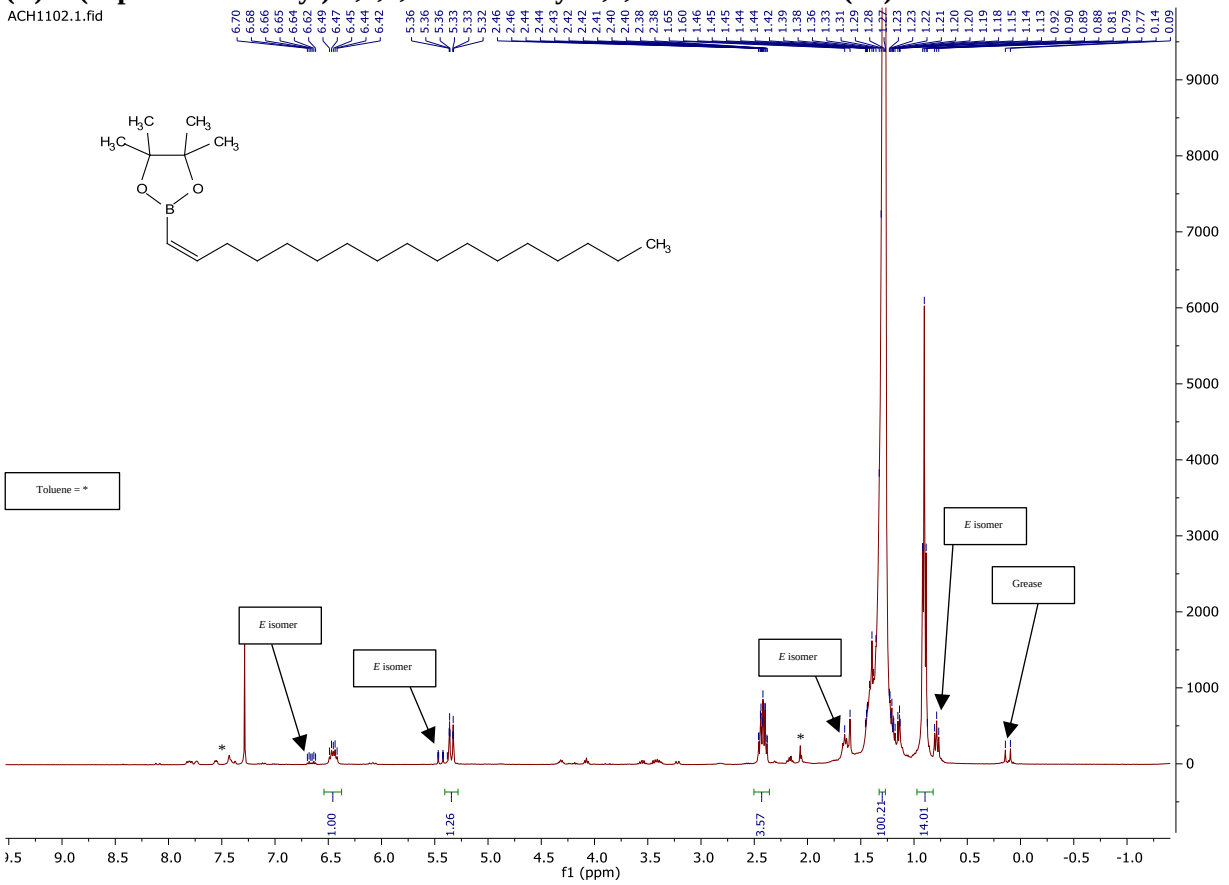
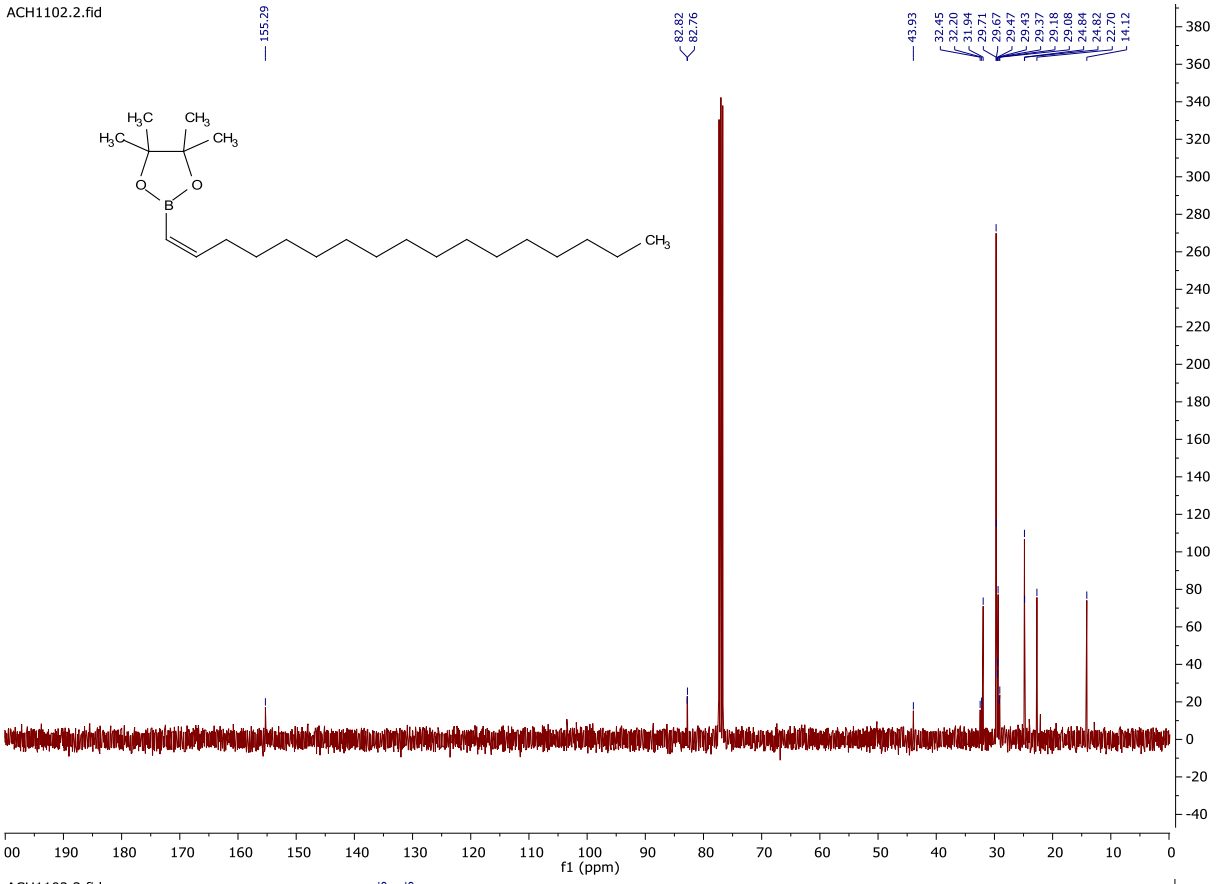
29.94
f1 (ppm)

(Z)-2-(heptadec-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3d)

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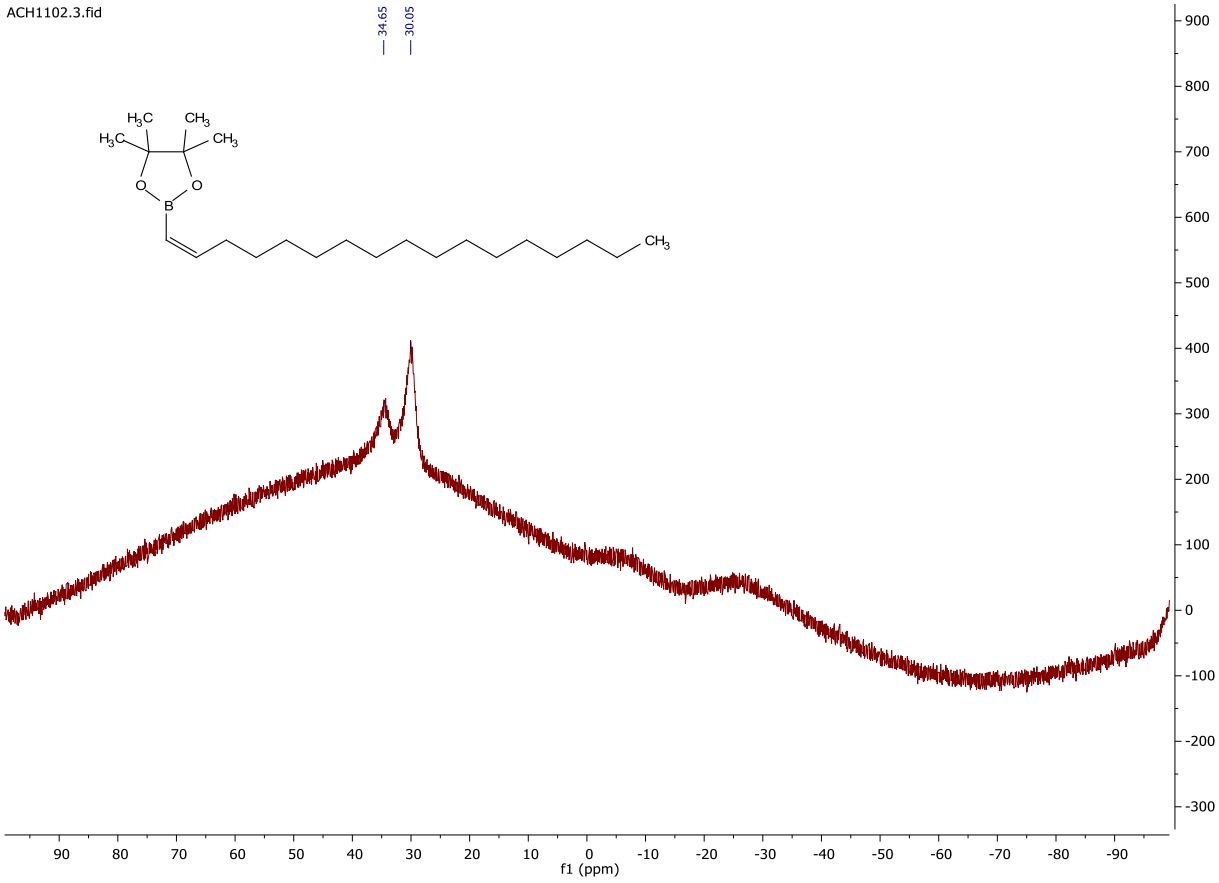
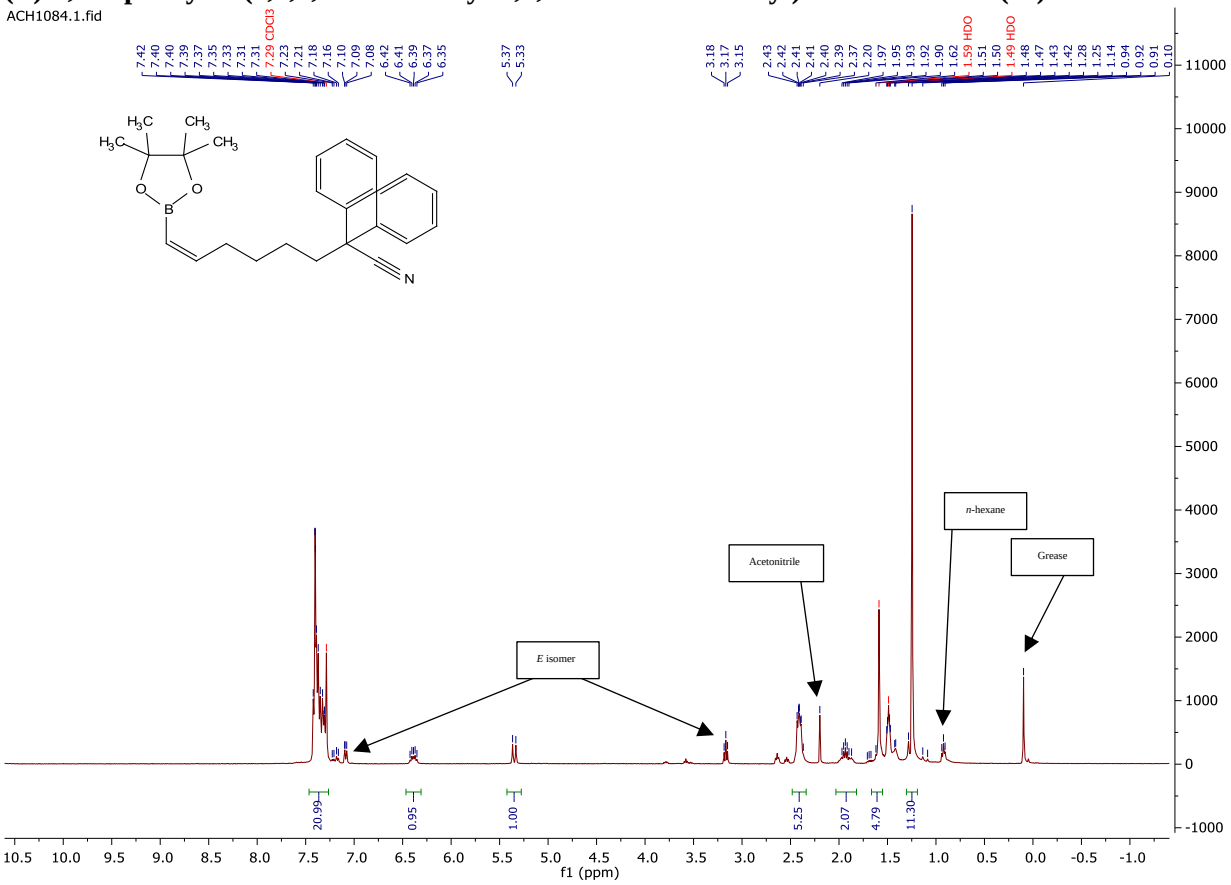
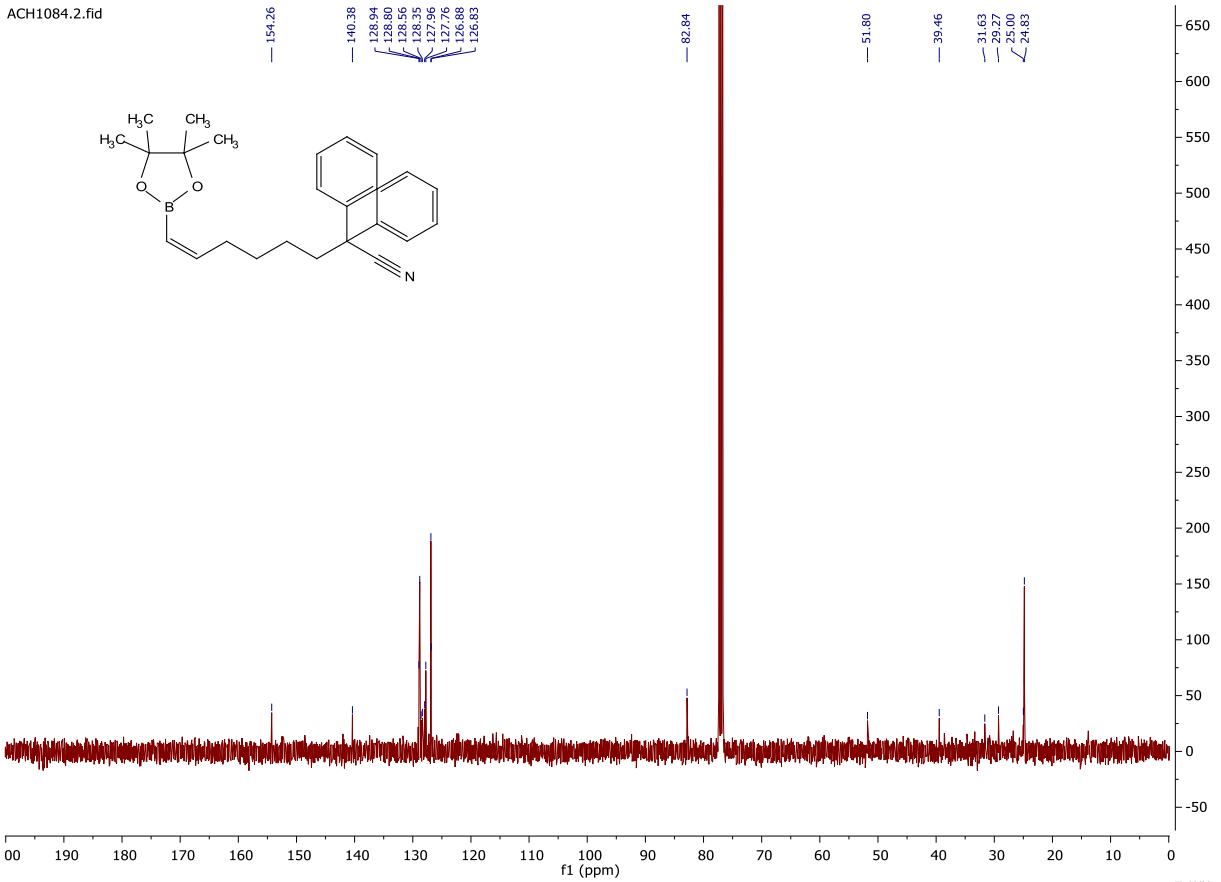
82.82
82.76
43.93
32.45
32.20
31.94
29.71
29.67
29.47
29.43
29.37
29.18
29.08
24.84
24.82
22.70
14.12
f1 (ppm)


ACH1102.3.fid
34.65
30.05
f1 (ppm)

(Z)-2,2-diphenyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-7-enenitrile (3e)

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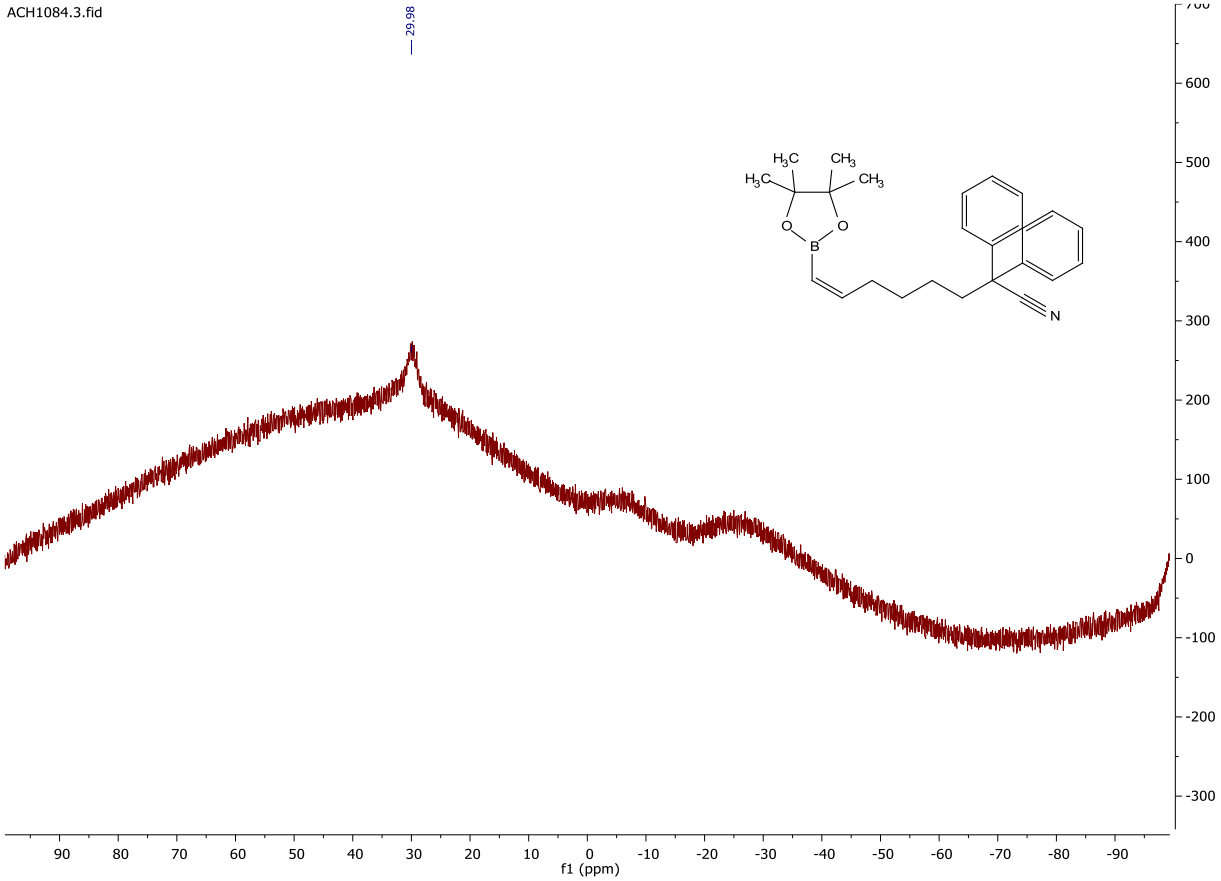
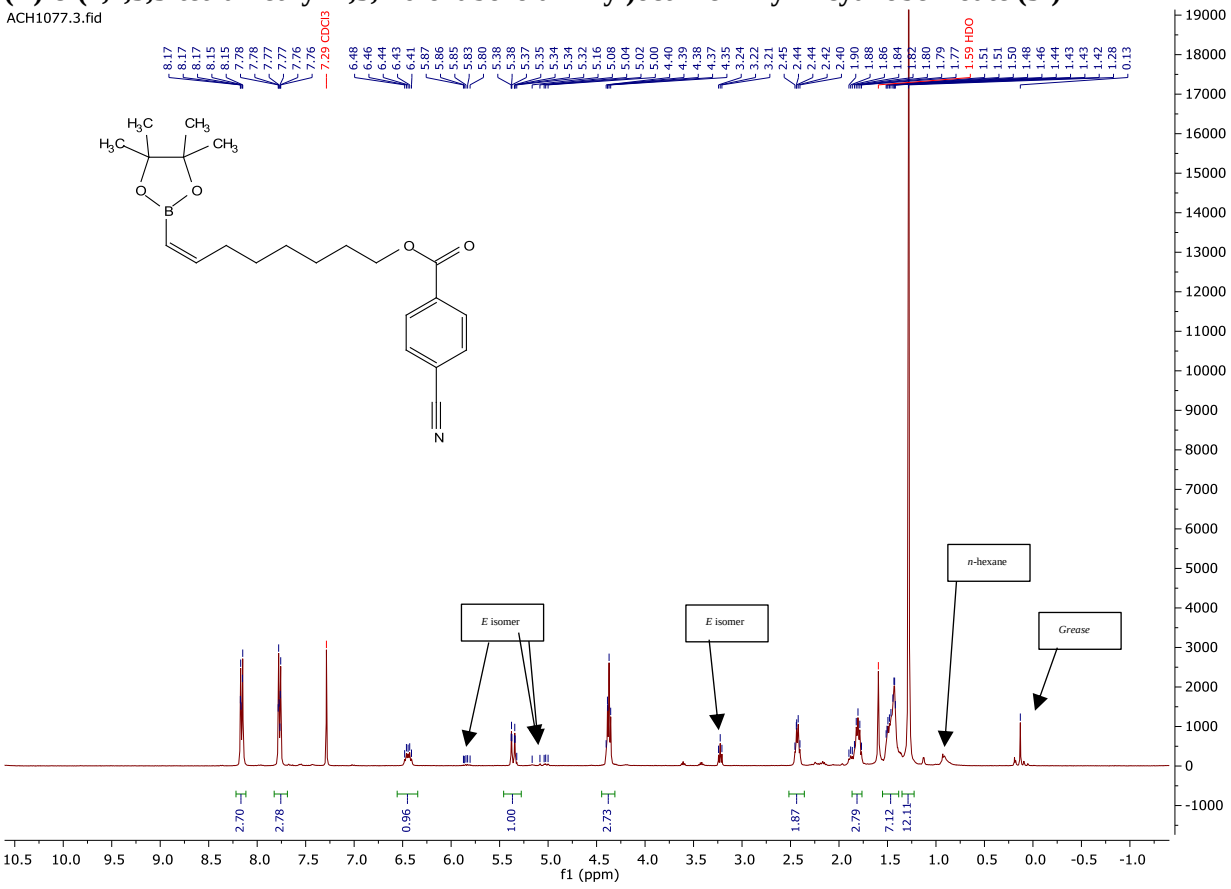
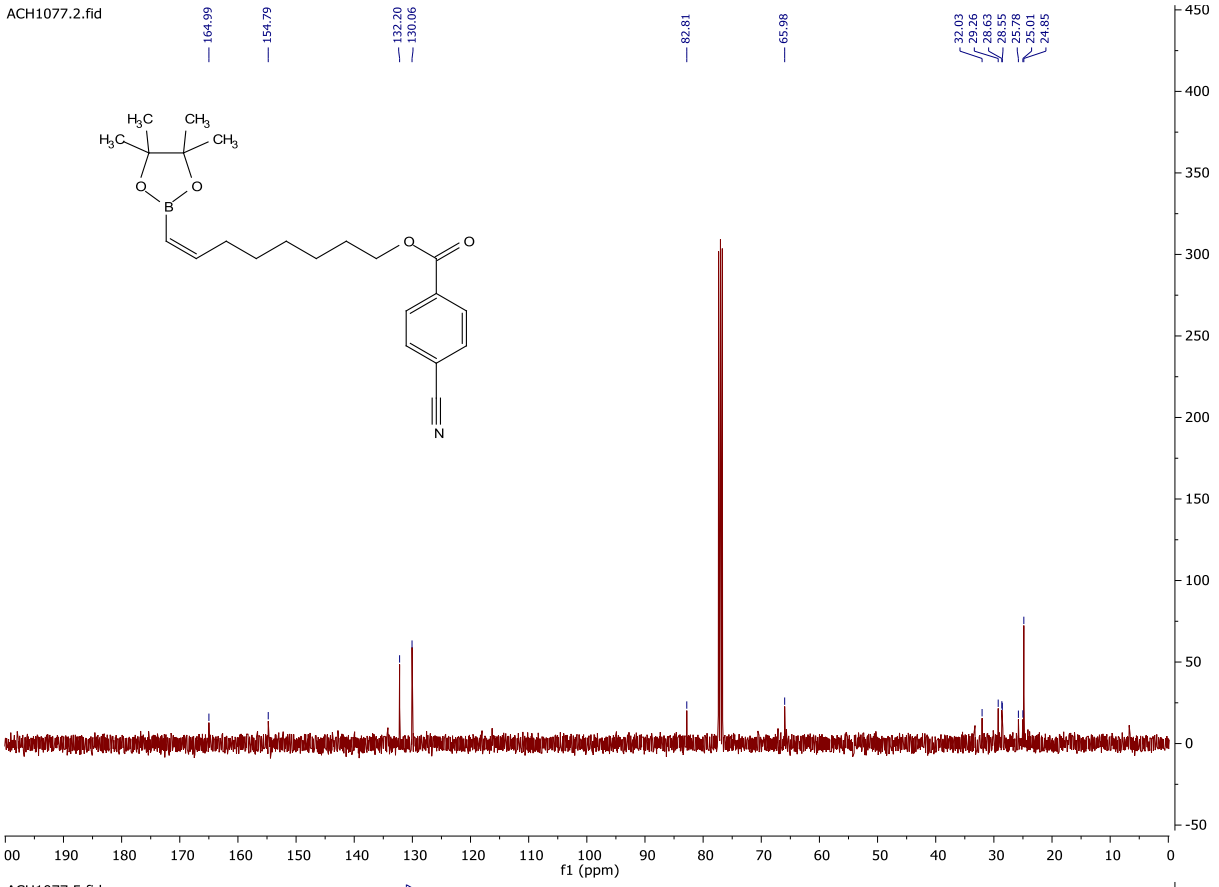
140.38
128.94
128.80
128.56
128.35
127.96
127.76
126.88
126.83
82.84
51.80
39.46
31.63
29.27
25.00
24.83
H3C
CH3
H3C
CH3
O
O
B
N
f1 (ppm)


ACH1084.3.fid
29.98
H3C
CH3
H3C
CH3
O
O
B
N
f1 (ppm)

(Z)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-7-en-1-yl 4-cyanobenzoate (3f)




ACH1077.2.fid
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154.79
132.20
130.06
82.81
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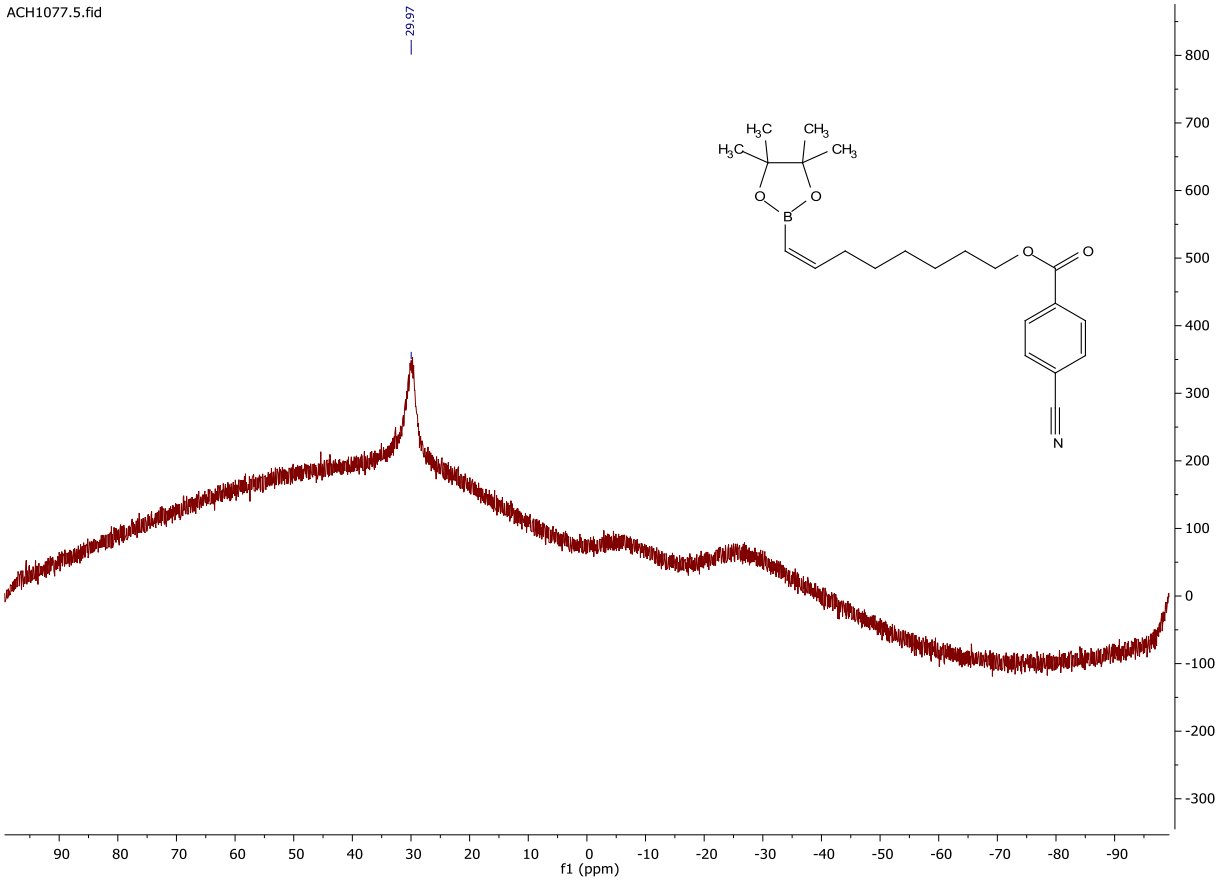
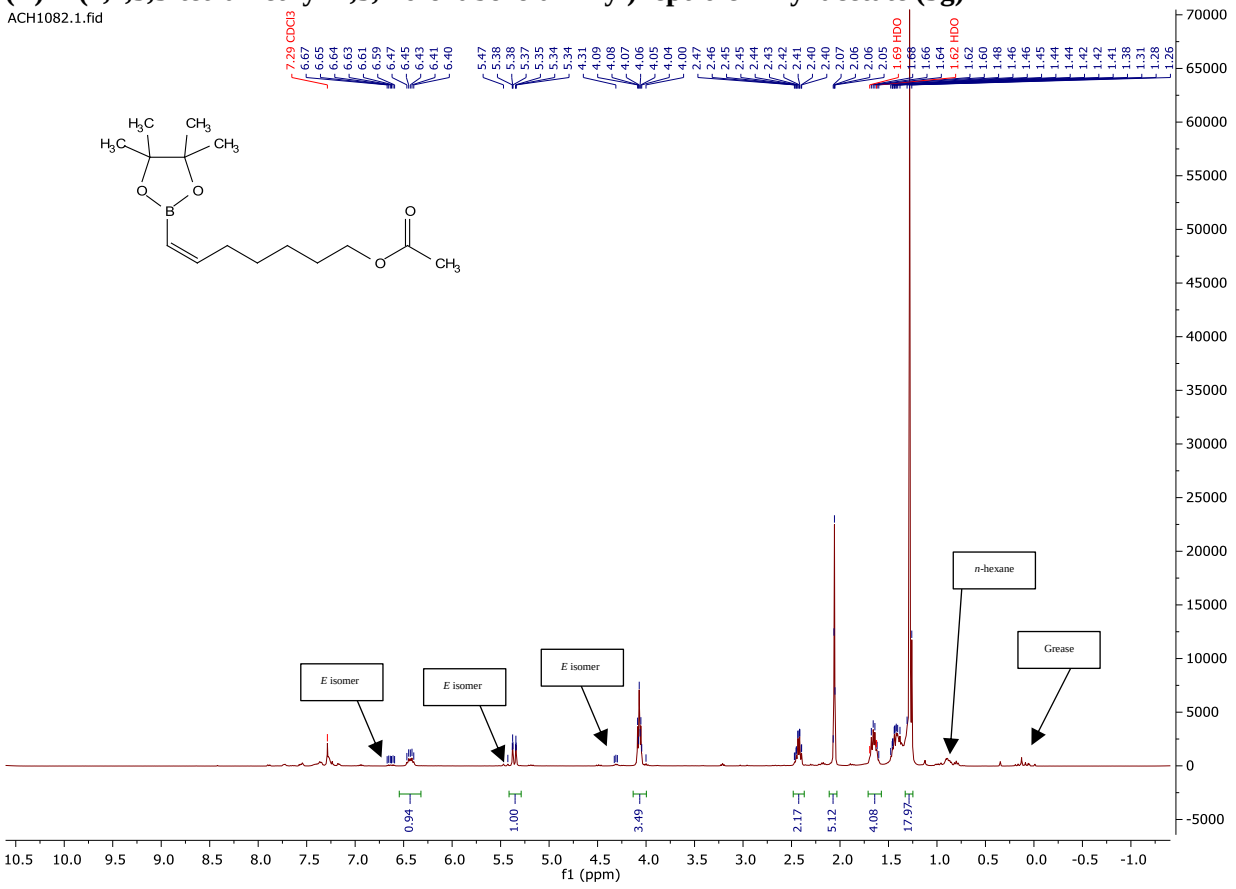
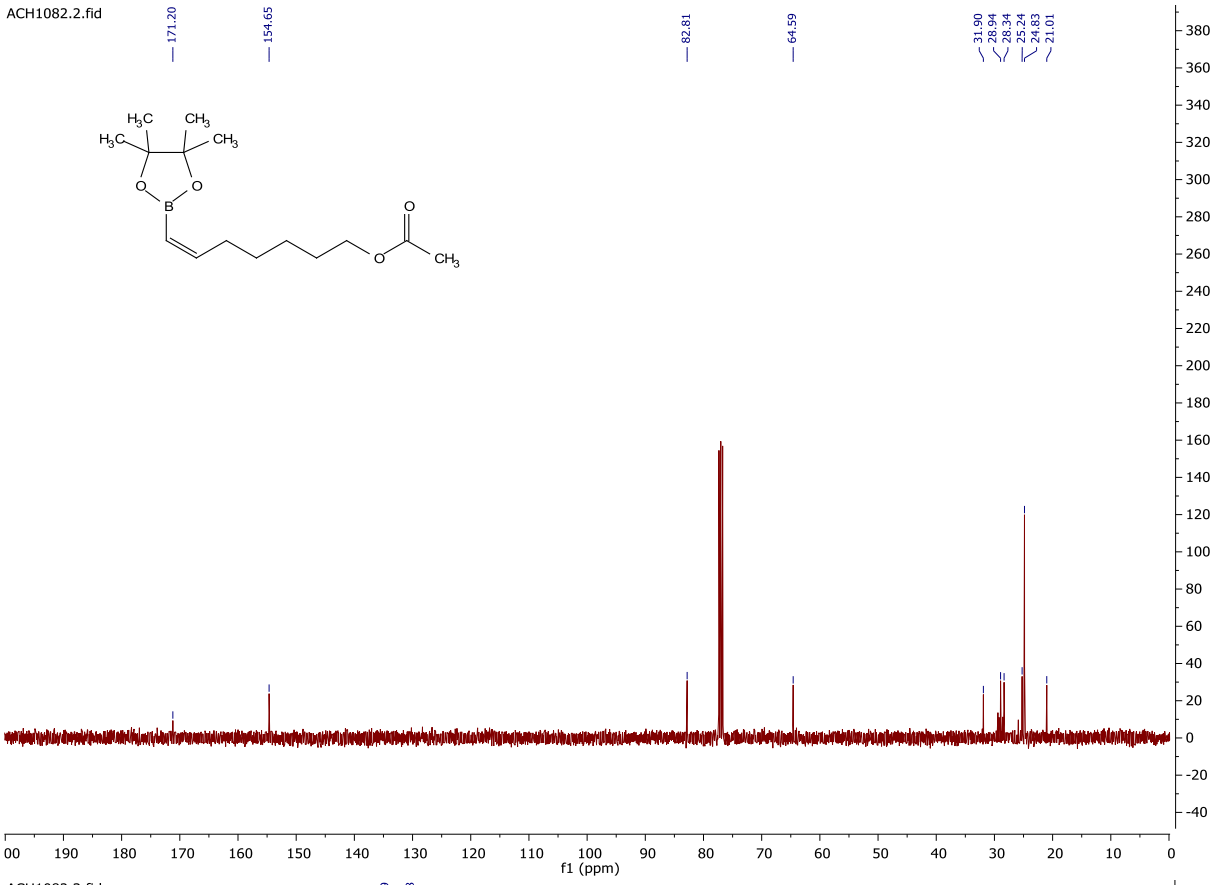
29.26
28.63
28.55
25.78
25.01
24.85
f1 (ppm)


ACH1077.5.fid
29.97
f1 (ppm)

(Z)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-1-yl acetate (3g)

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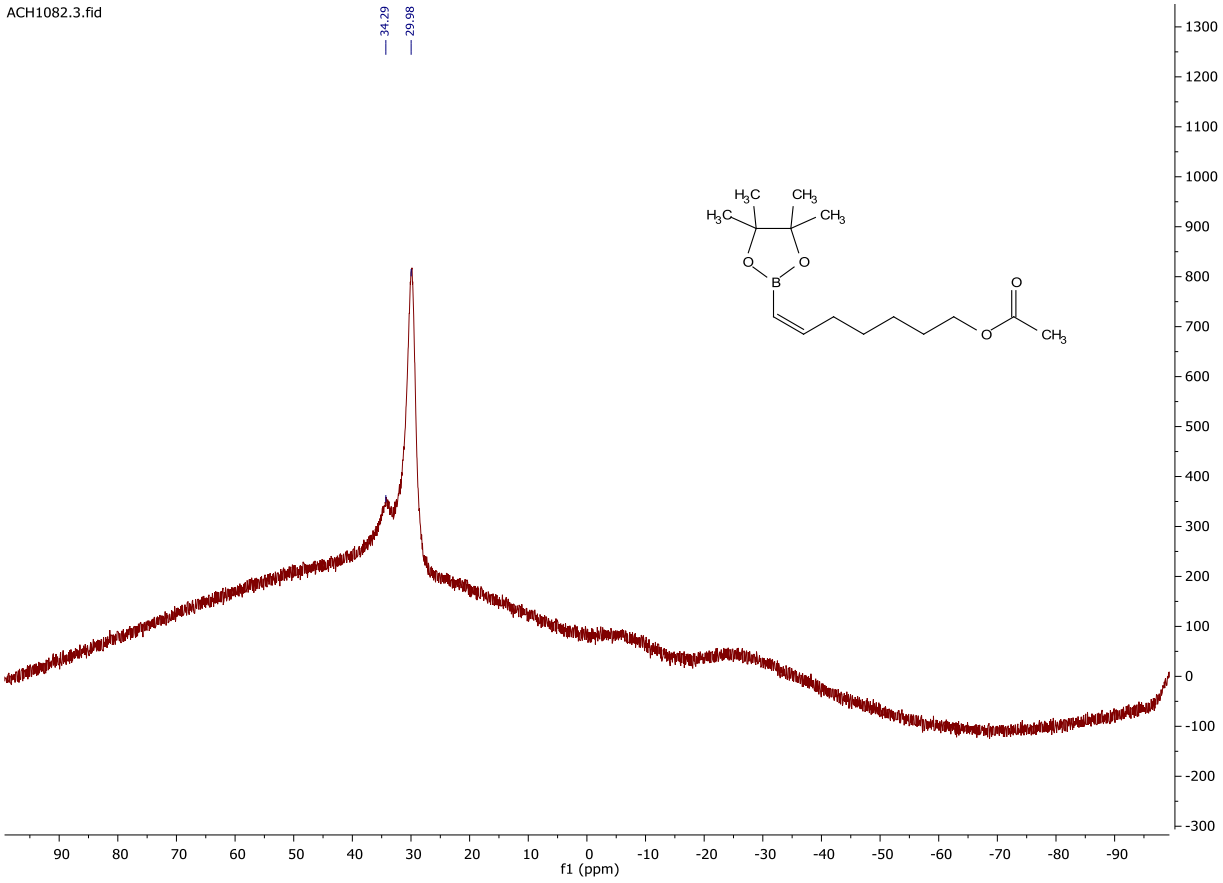
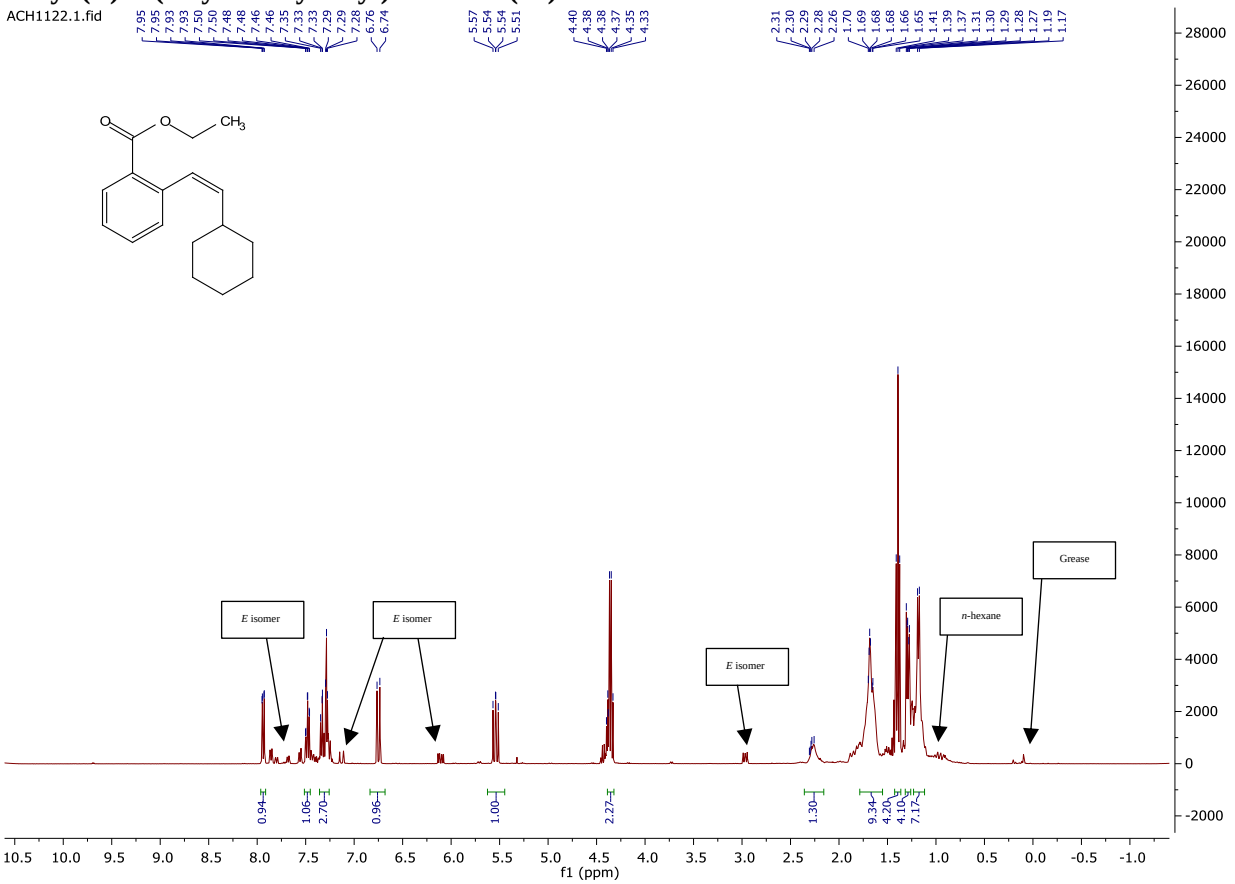
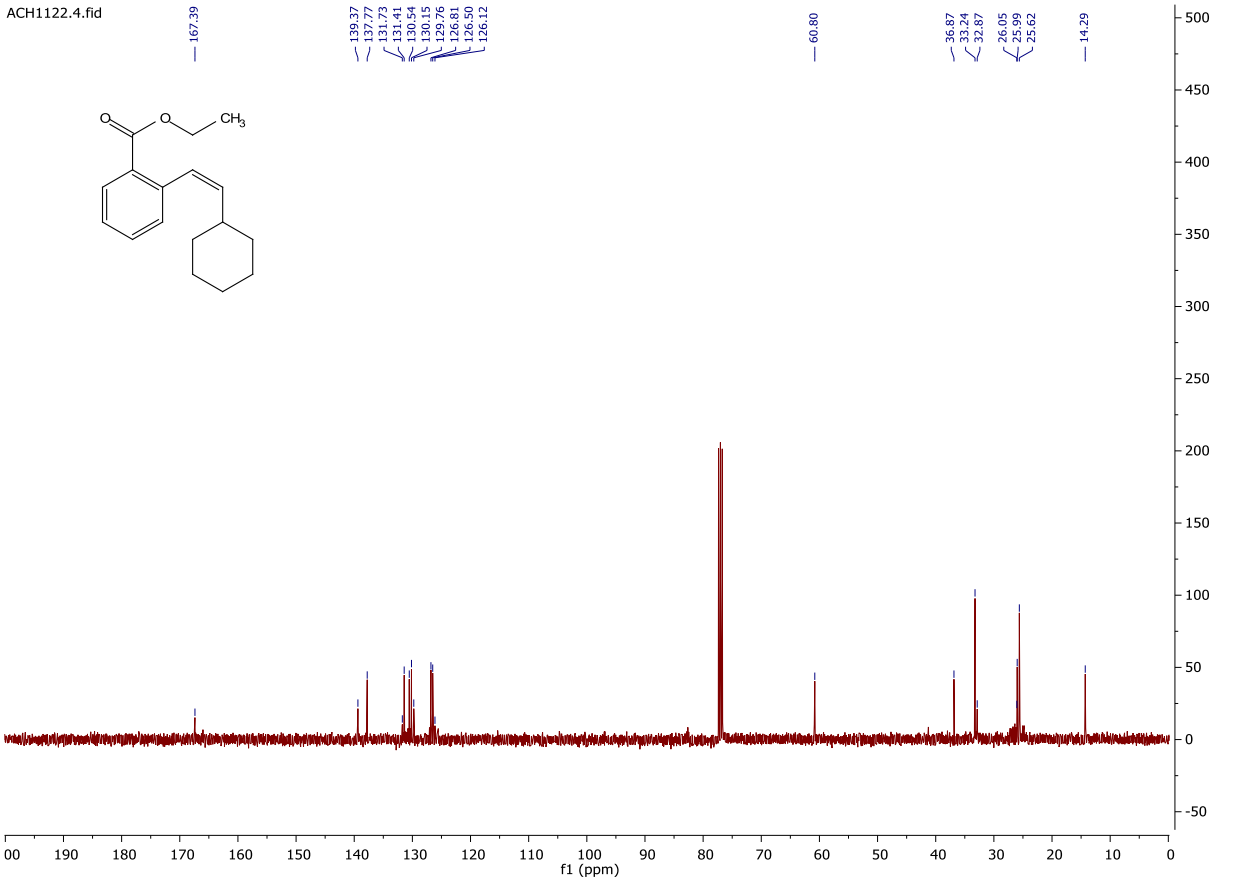
82.81
64.59
31.90
28.94
28.34
25.24
24.83
21.01
f1 (ppm)

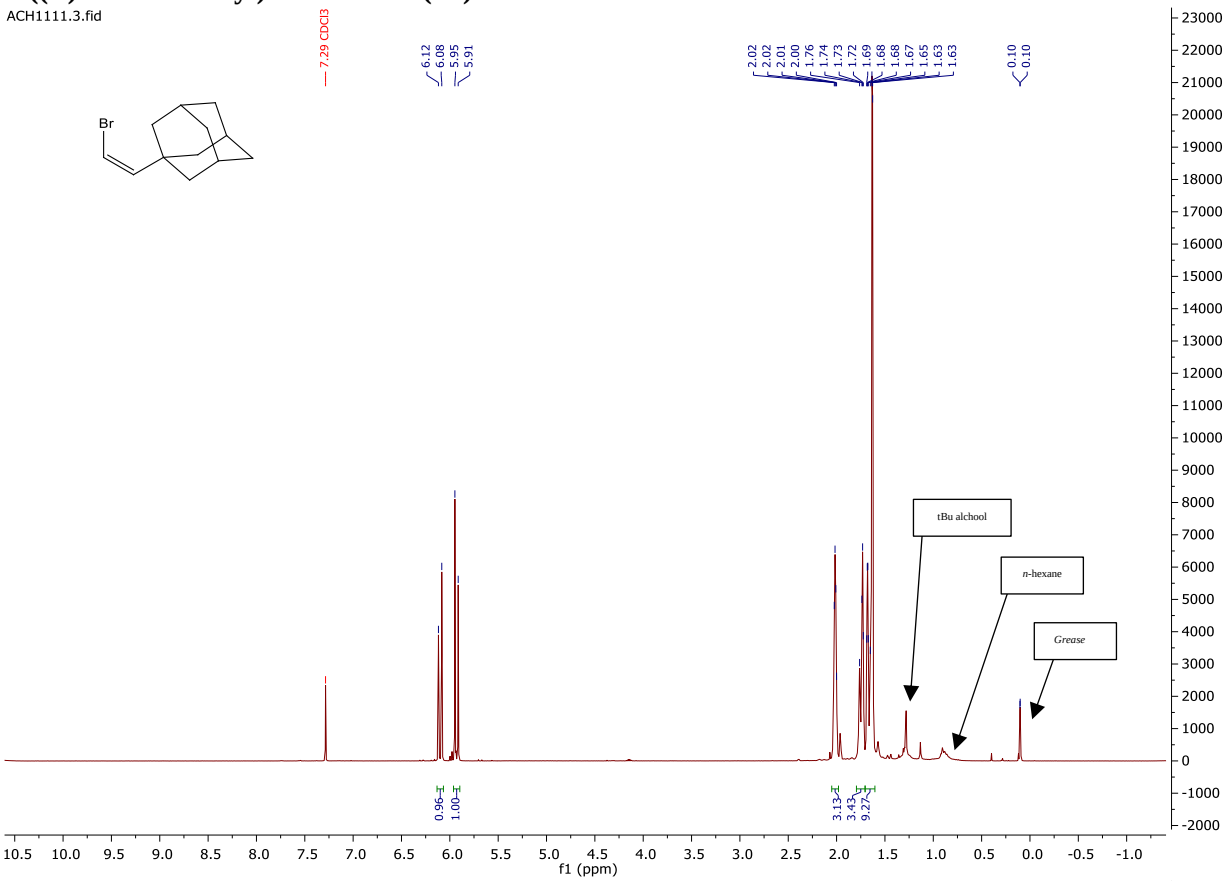

ACH1082.3.fid
34.29
29.98
f1 (ppm)

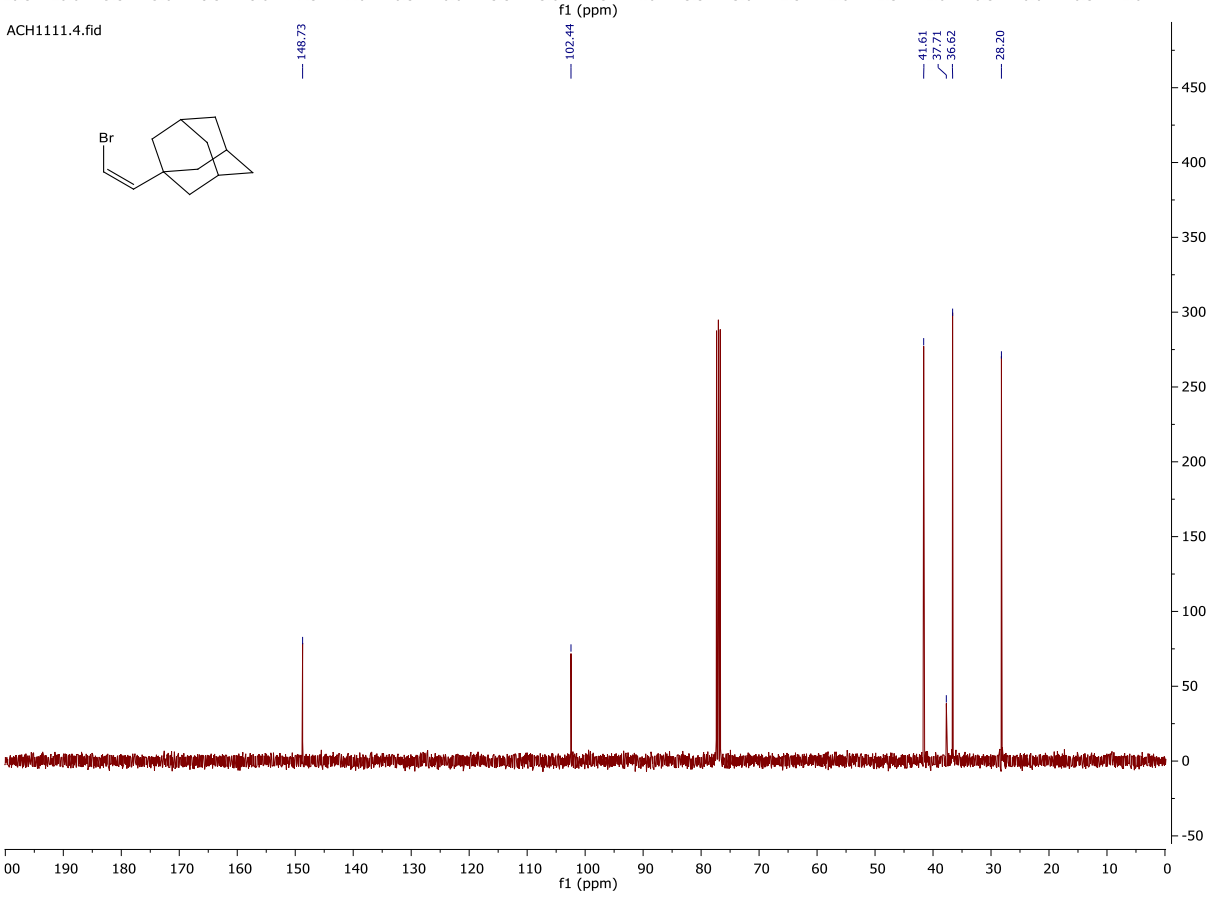
ethyl (Z)-2-(2-cyclohexylvinyl)benzoate (4a)



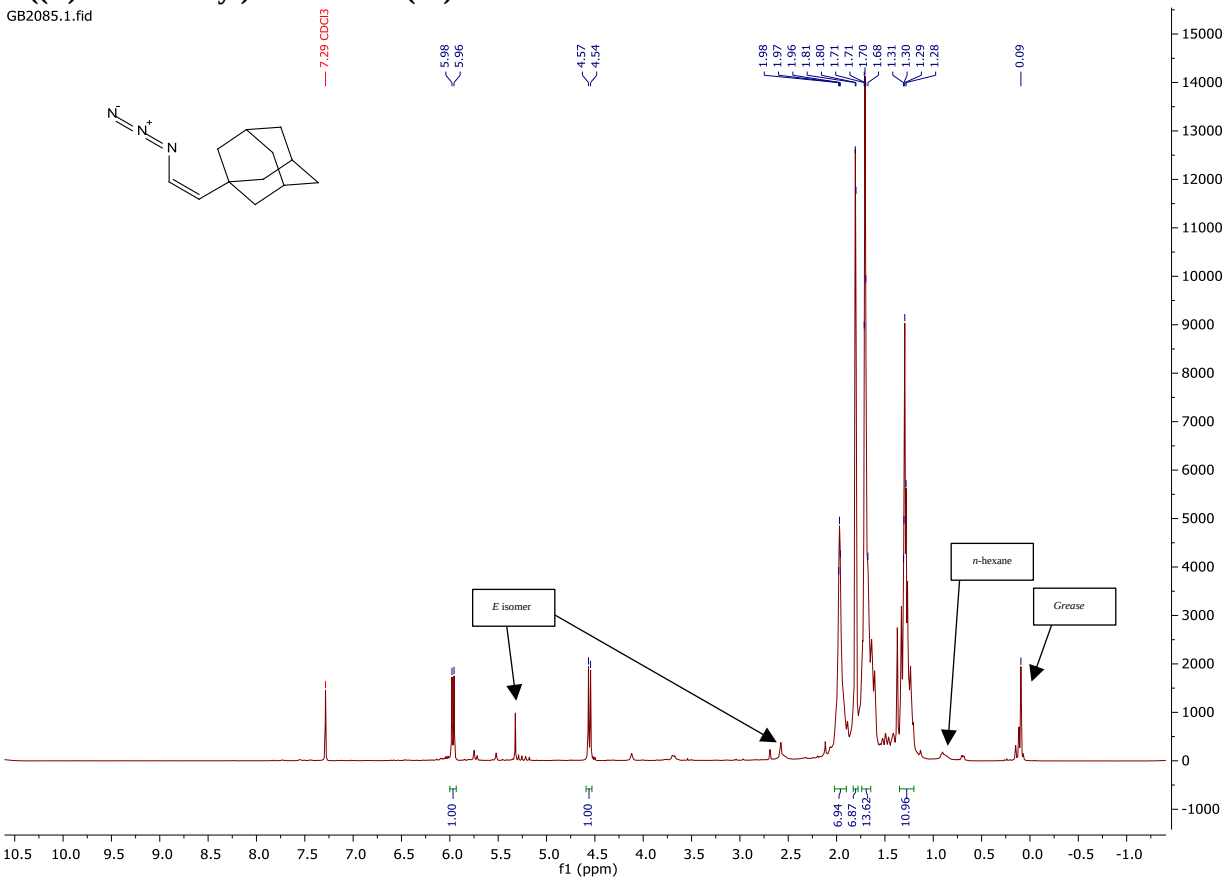


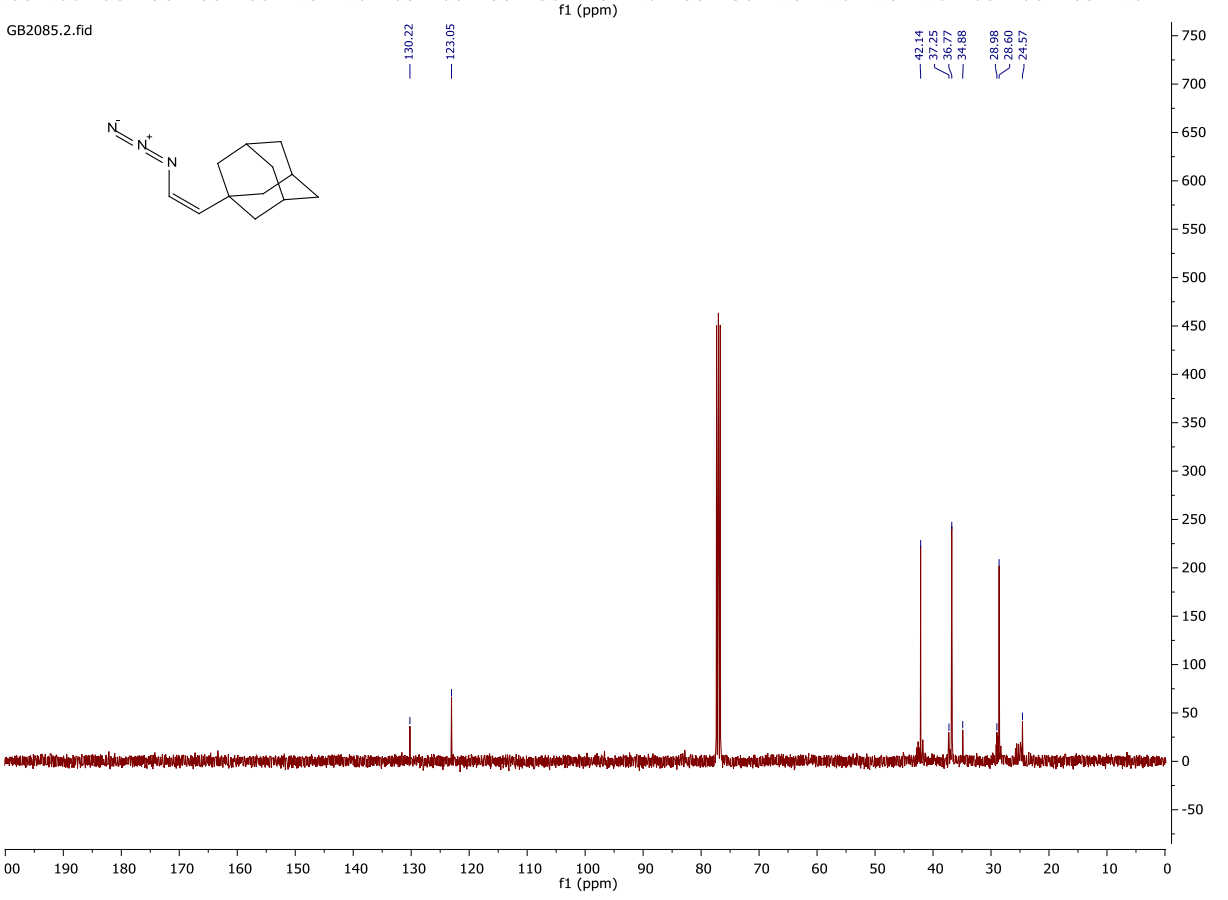
1-((Z)-2-bromovinyl)adamantine (4b)



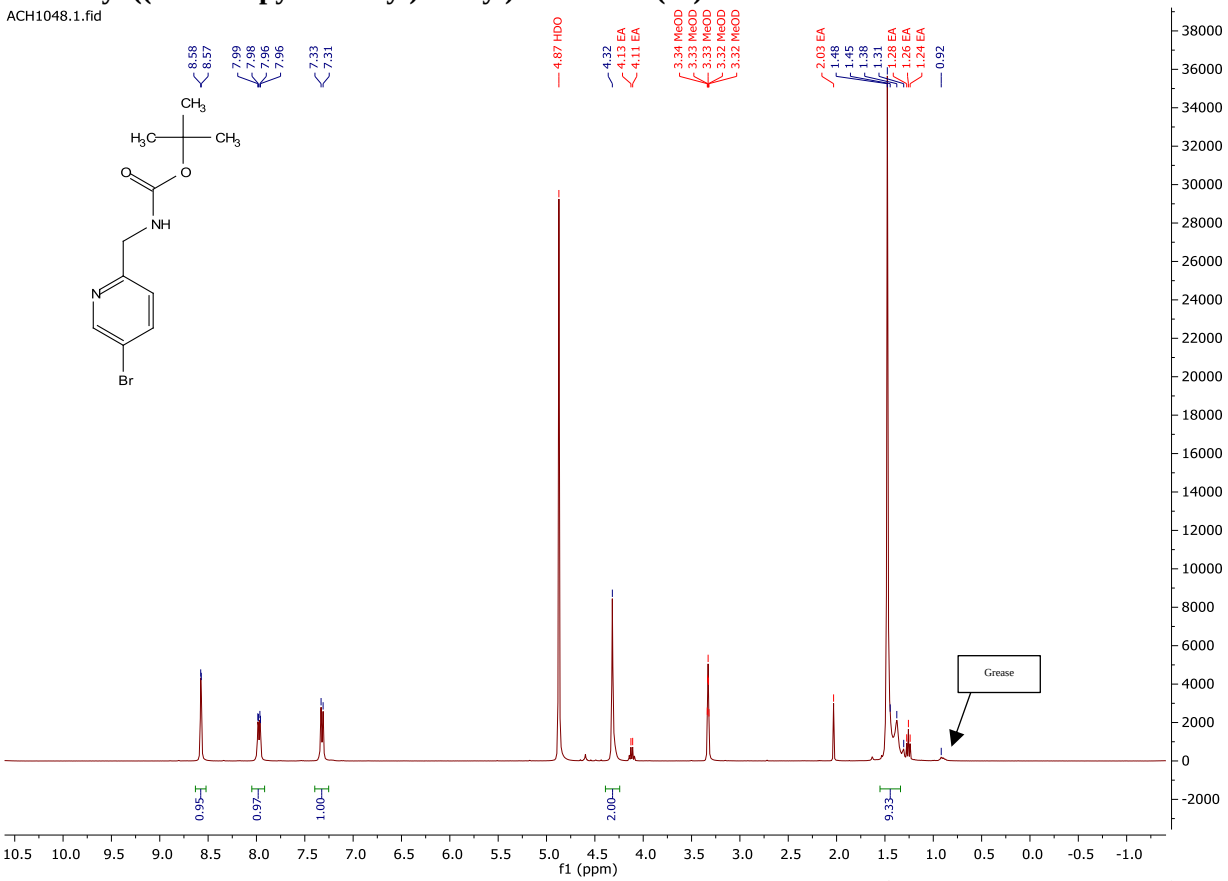


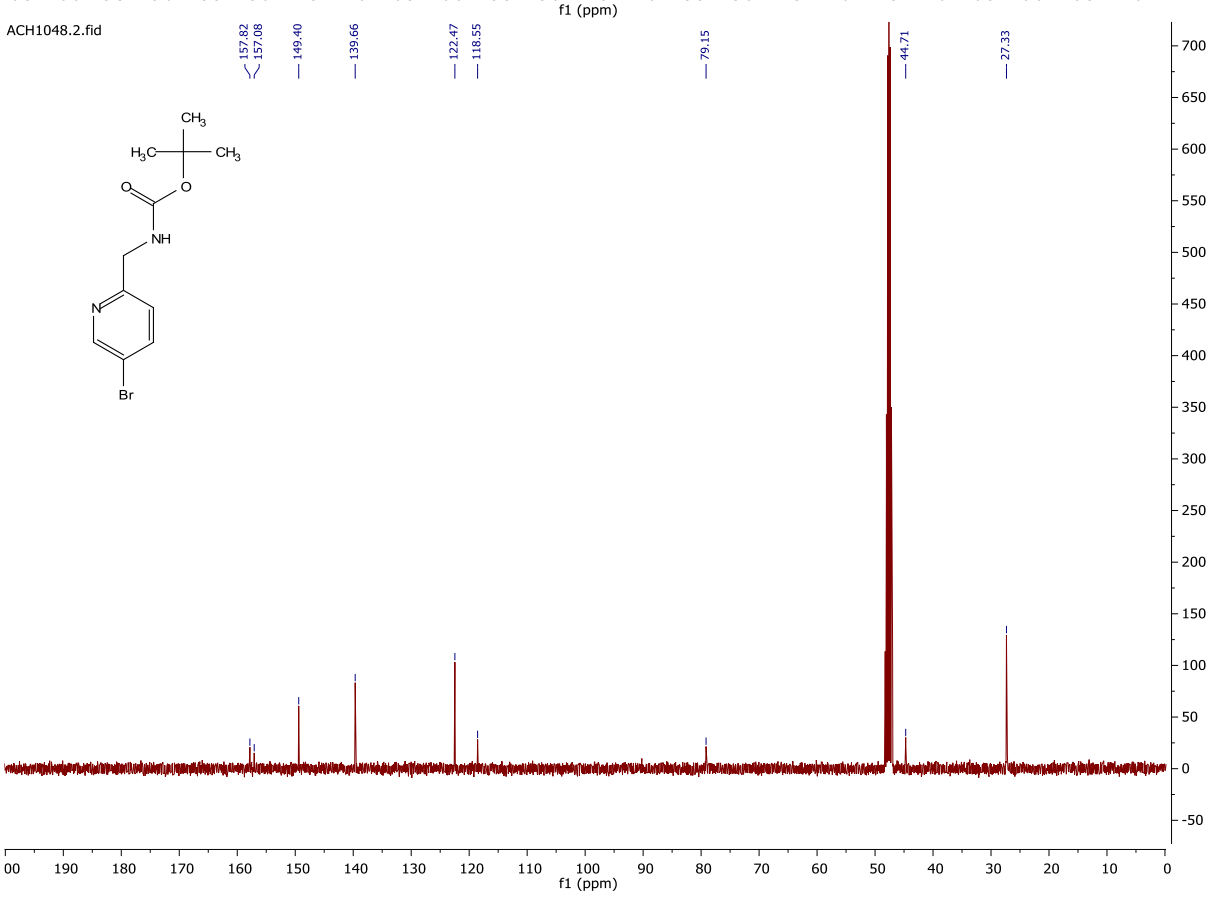
1-((Z)-2-azidovinyl)adamantine (4c)



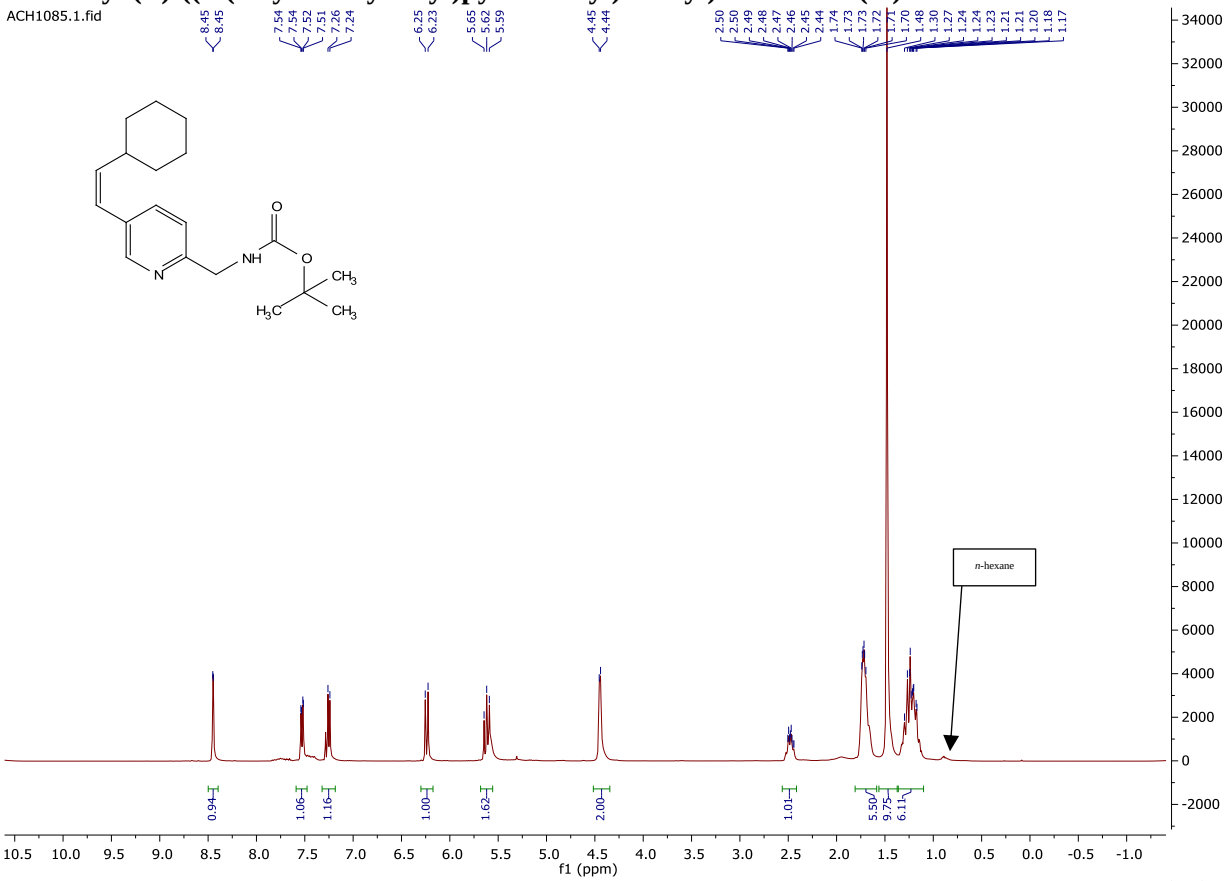


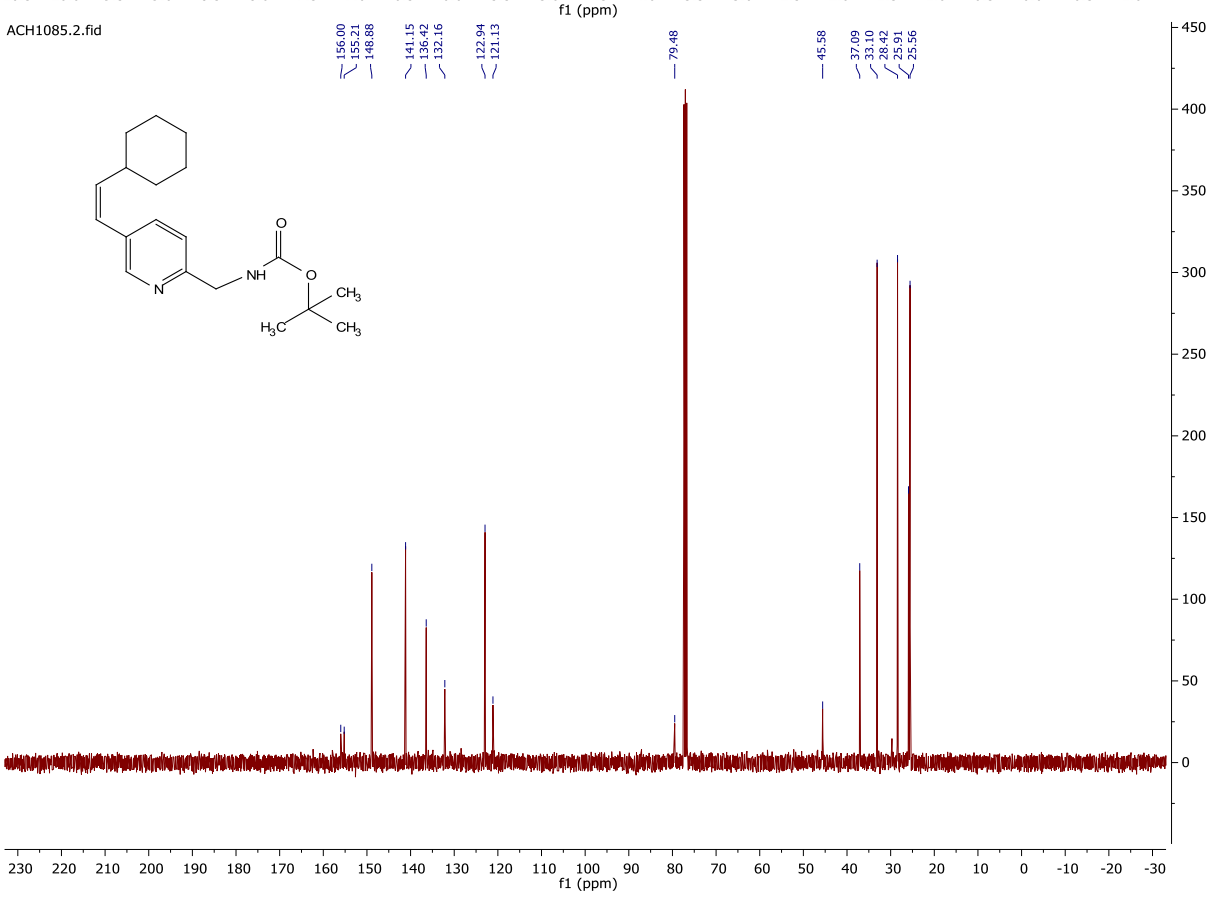
tert-butyl ((5-bromopyridin-2-yl)methyl)carbamate (5e)



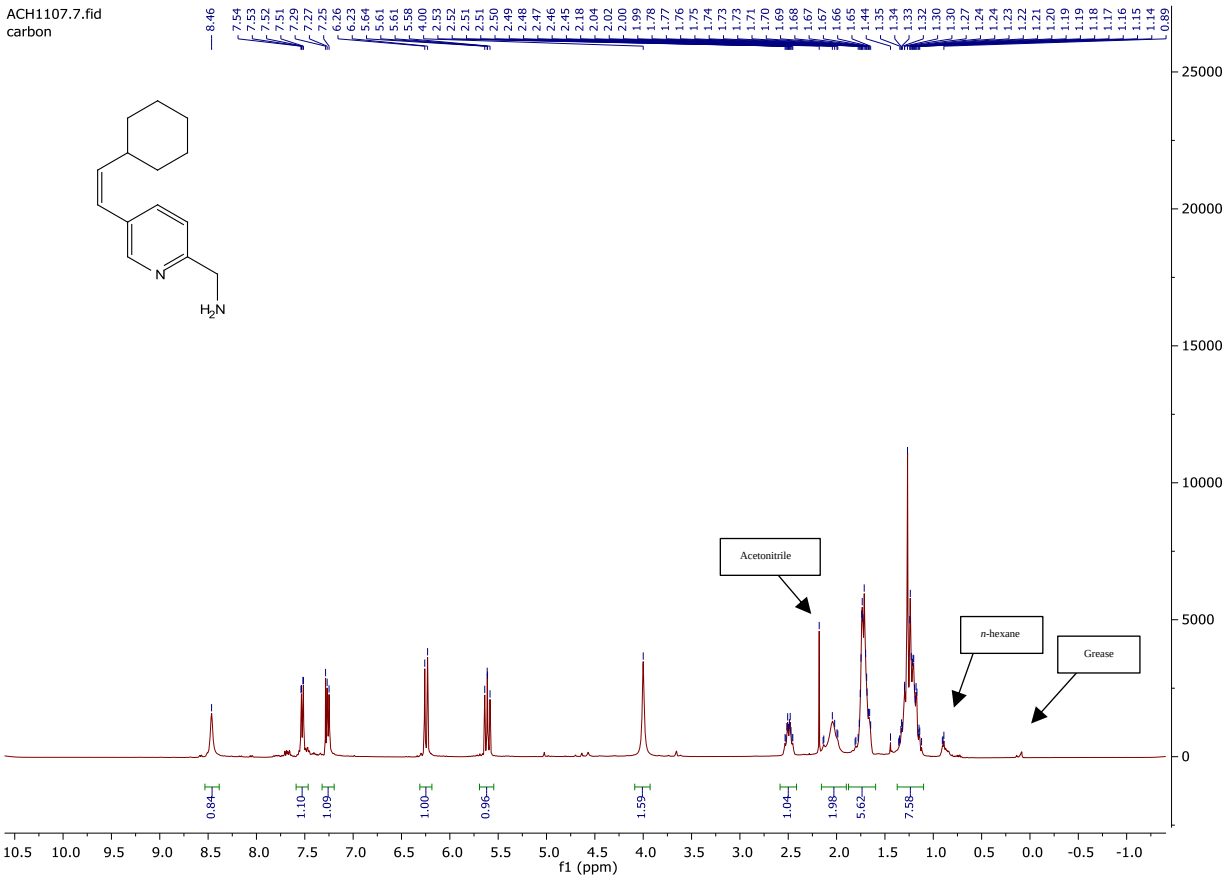


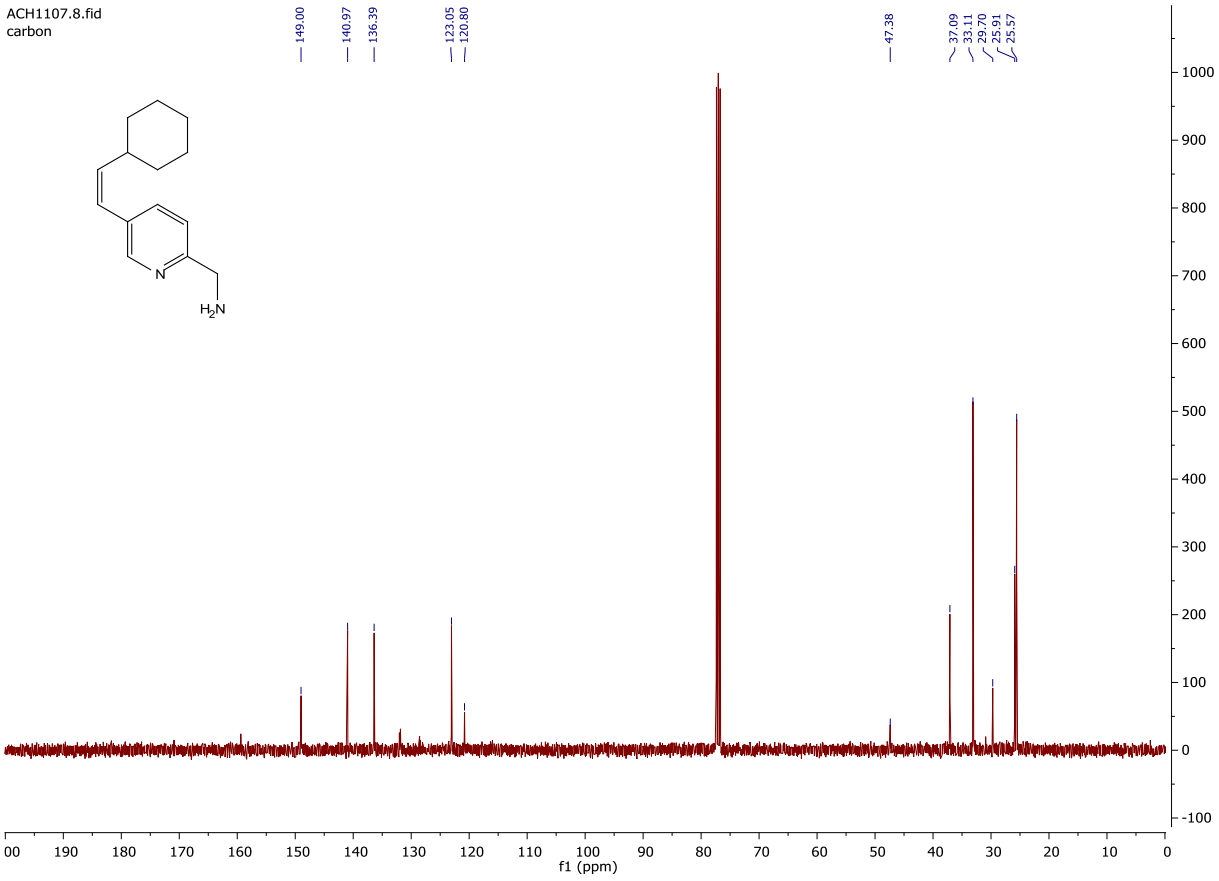
tert-butyl (Z)-((5-(2-cyclohexylvinyl)pyridin-2-yl)methyl)carbamate (5f)





(Z)-(5-(2-cyclohexylvinyl)pyridin-2-yl)methanamine **(5b)**





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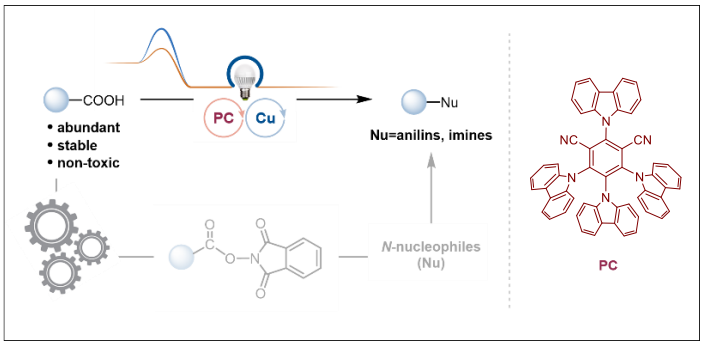
3. Tandem photoredox and copper-catalyzed decarboxylative C(sp3)-N coupling of anilines and imines using an organic photocatalyst[a]



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3.1 Introduction

Alkyl amines are an important class of organic molecules with wide applications in materials and medicines.[1–4] C(sp^3)-N coupling is potentially an efficient method to streamline the synthesis of alkyl amines, complementing traditional methods such as reductive amination,[5–7] direct *N*-alkylation,[8,9] the Curtius rearrangement,[10] and the Mitsunobu reaction.[11] However, C(sp^3)-N coupling remains challenging due to difficulty in C(sp^3)-N reductive elimination as well as side reactions such as β-H elimination. Hu group and others recently developed photoredox catalysis to effect decarboxylative C(sp^3)-N coupling (Figure 3.1, a-b).[12–18] This approach employs readily available alkyl carboxylic acids as starting reagents, activating them via either N-hydroxyphtalimide esters (NHPI) (Figure 3.1, a), or hyperiodide intermediates (Figure 3.1, b), and resulting in wide substrate scope. However, the photocatalysts were all based on precious metals such as Ru and Ir. Herein we report a method for decarboxylative C(sp^3)-N coupling using an organic photoredox catalyst in tandem with a Cu coupling catalyst (Figure 3.1, c). The organic photocatalyst enabled the coupling of both aniline and imines, an improvement over precious photocatalysts which worked for only one type of N coupling partners.[13–15]

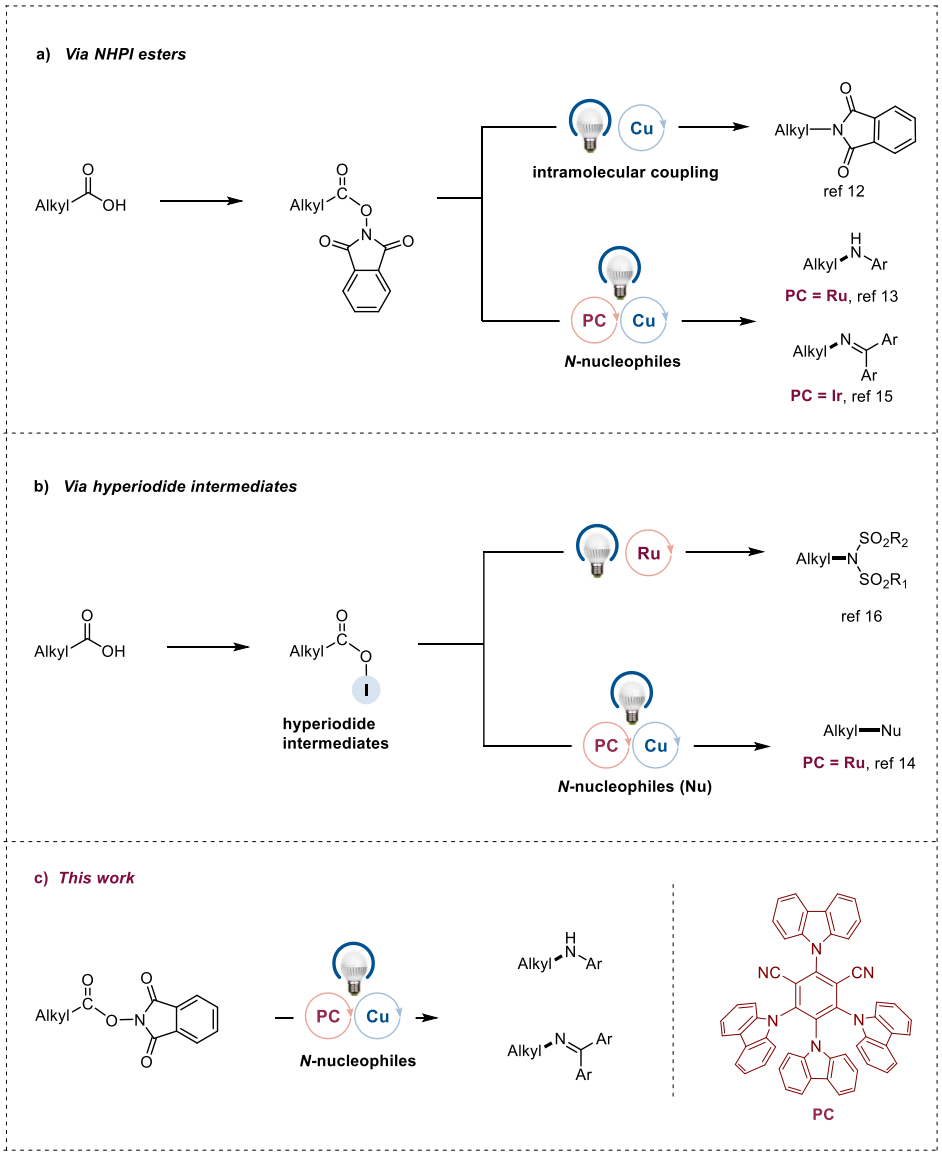
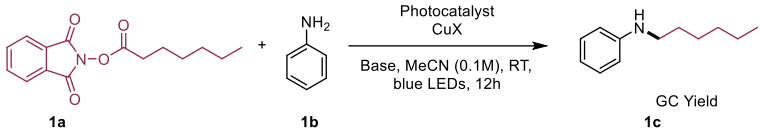


Figure 3.1. Photoredox-based decarboxylative C(sp3)-N coupling. (a) Via NHPI esters; (b) Via hyperiodide intermediates. (c) This work, using an organic photocatalyst.

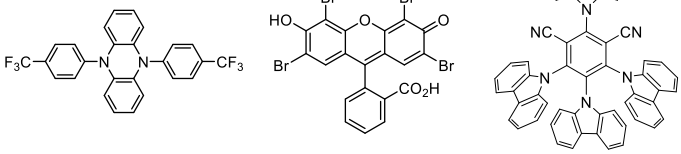
3.2 Results and discussion

3.2.1 Coupling with anilines

A representative C(sp^3)-N coupling of heptanoic acid NHPI ester **1a** with aniline **1b** was chosen as the test reaction for optimization. Conditions previously applied for the analogous coupling using $Ru(bpy)_3(PF_6)_2$ as photocatalyst were first applied.[13] When the commercially available organophotocatalyst, 5,10-bis(4-(trifluoromethyl)phenyl)-5,10-dihydrophenazine **1d** was used (10 mol %), together with 20 mol % of CuBr and 5 equiv of triethylamine (Table 3.1, entry 1), the reaction occurred (0.1 M acetonitrile, at room temperature, under the irradiation of blue LEDs, overnight) to give **1c** in a yield of 28%. Decreasing the loading of photocatalyst to 1% gave a similar yield (Table 3.1, entry 2). Replacing CuBr with CuCl increased the yield to 34% (Table 3.1, entry 3).



1a 1b 1c



1d 1e 1f

Entry	Photocatalyst	Base 1eq.	Solvent 0.1M	GC Yield[a]
1	**1d** 10%	CuBr 20%	Et3N 5 eq.	28%
2	**1d** 1%	CuBr 20%	Et3N 5 eq.	29%
3	**1d** 5%	CuCl 20%	Et3N 5 eq.	34%
4	**1d** 5%	CuCl 5%	Et3N 5 eq.	18%
5	4CzIPN 1%	CuCl 20%	Et3N 5 eq.	56%
6	Eosin Y 1%	CuCl 20%	Et3N 5 eq.	n.d.
7	4CzIPN 1%	CuCl 20%	Lutidine 5 eq.	n.d.
8	4CzIPN 1%	CuCl 20%	DIPEA 5 eq.	n.d.
9	4CzIPN 1%	CuCl 20%	DIPEA 5 eq.	20%
10	4CzIPN 1%	CuCl 20%	Et3N 1 eq.	66%
11	4CzIPN 1% (No light)	CuCl 20%	Et3N 1 eq.	n.d.
12	/	CuCl 20%	Et3N 1 eq.	n.d.

Table 3.1. Optimization for decarboxylative amination. General condition: NHPI ester (0.5 mmol), aniline (0.25 mmol), MeCN (2.5 mL), under N_2; yields calculated via GC with an internal standard. DIPEA = diisopropylamine; N.d. = not detected.

Decreasing the loading of CuCl to 5 mol % decreases the yield to 18% (Table 3.1, entry 4). While Eosin Y (**1e**) (1 mol%) gave no yield, 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (4CzIPN) [19–26] (**1f**) gave a yield of 56%. Decarboxylative activation of NHPI esters using **1f** was previously reported.[27,28] Many other photocatalyst were tested, using O-anisidine (**1g**) instead of aniline as test reaction (Table 3.2). The reaction conducted with a more electron-rich aniline gave us higher yields in all cases, making it easier to understand which catalyst performed the best. Ruthenium photocatalyst performed well (70% GC yield), but both variations of 4CzIPN and 4DPAIPN (**1h**) did better. Eventually, also with O-anisidine, the best results were obtained with 4CzIPN (**1f**). This catalyst can be easily synthesized from inexpensive precursors and requires no chromatographic purification. Several organic and inorganic bases were screened as bases, but only triethylamine and N,N-Diisopropylethylamine (DIPEA) were effective (Table 3.1, entries 1-5, 9, 10).

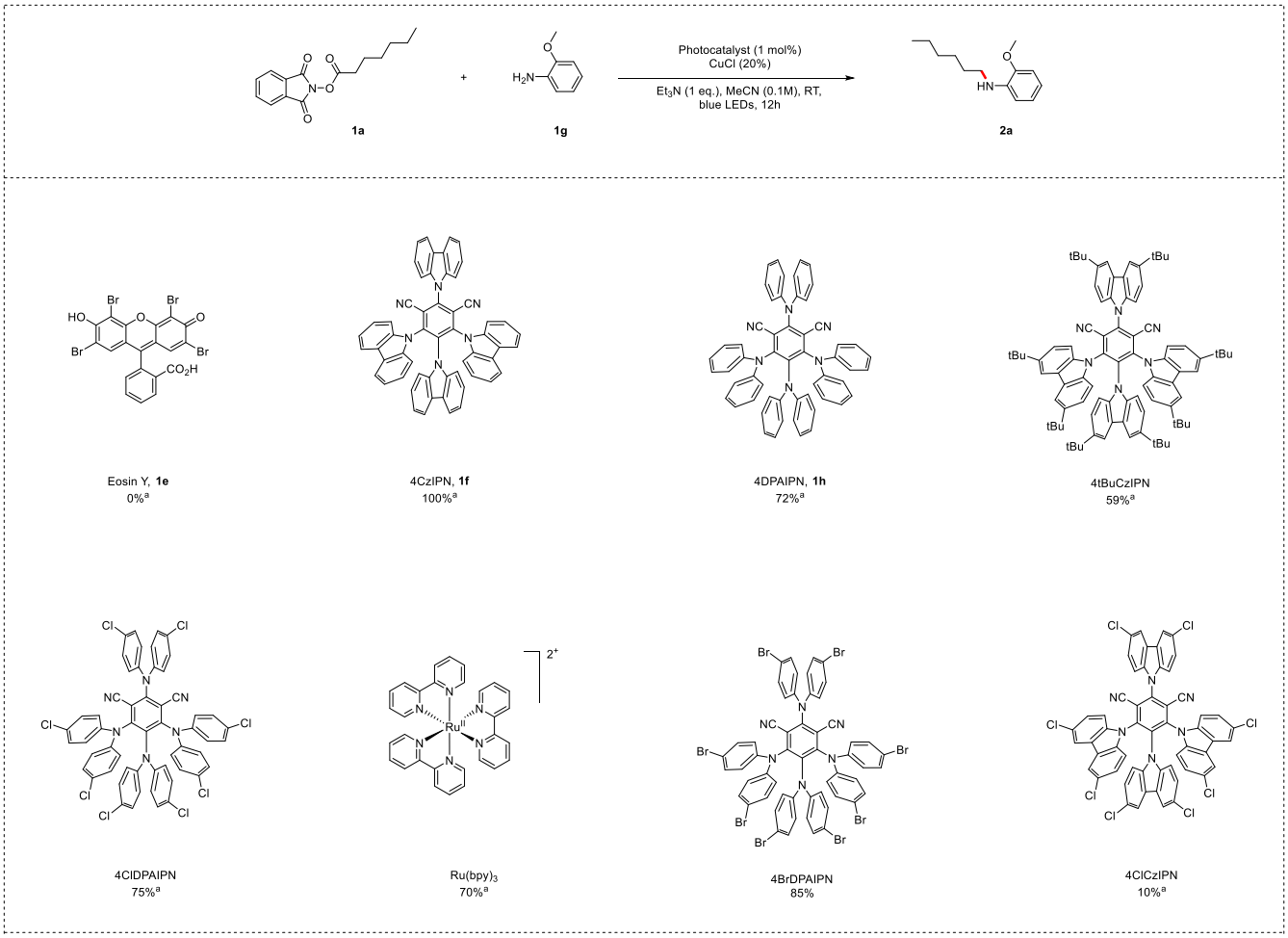


Table 3.2. Optimization of the photocatalyst for decarboxylative amination. General condition: NHPI ester (0.5 mmol), O-Anisidine (0.25 mmol), MeCN (2.5 mL), under N_2; [a]Corrected GC yields using n-dodecane as internal standard

Finally, the optimized conditions were: 1 mol % of **1f**, 20 mol % of CuCl, 1 equiv of triethylamine, in 0.1 M of acetonitrile at room temperature for 12h under the irradiation of blue LEDs. The yield of **1c** under these conditions was 66% (Table 3.1, entry 10). Control experiments showed that no coupling occurred when there was no light, or no photocatalyst (Table 3.1, entries 11-12).

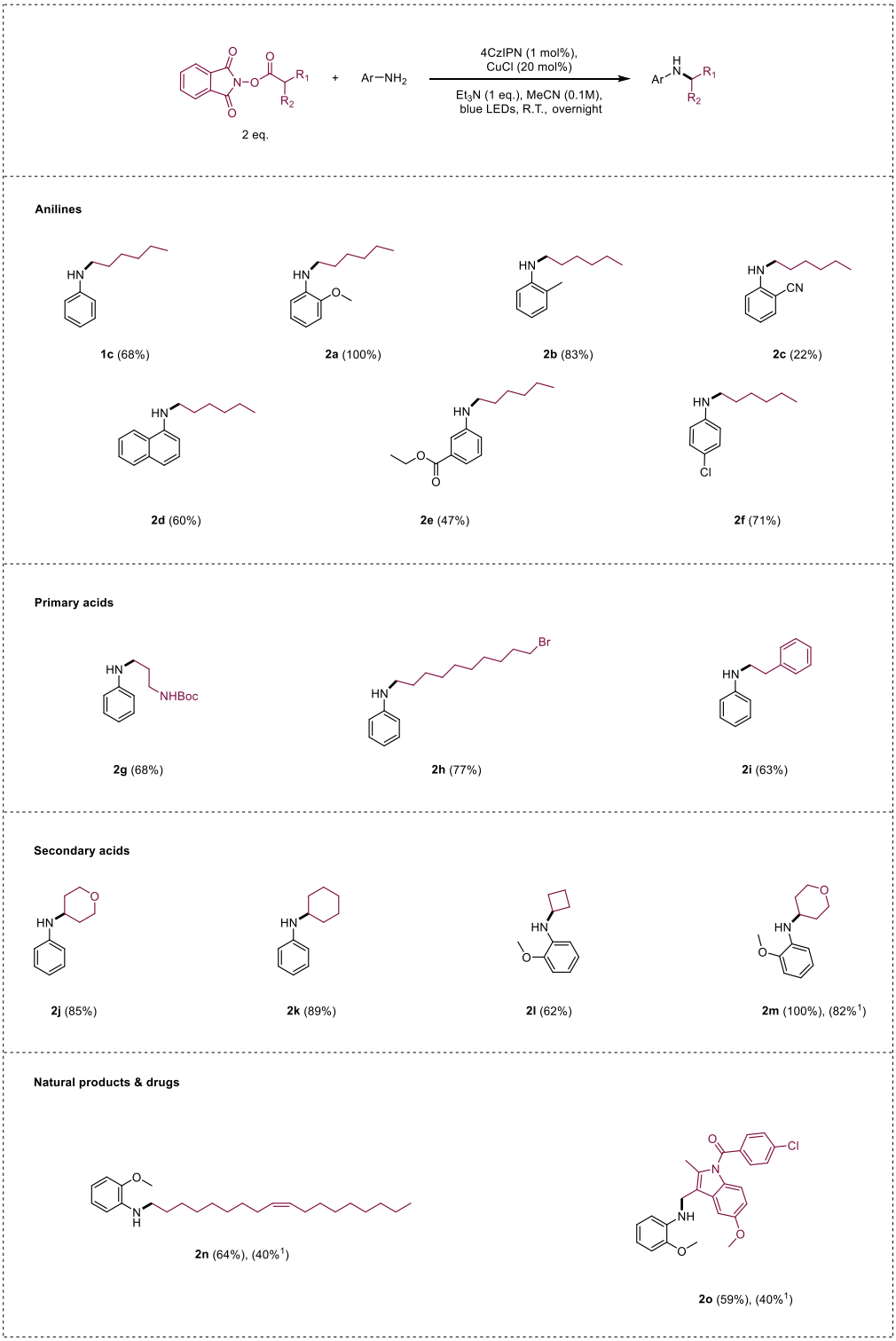
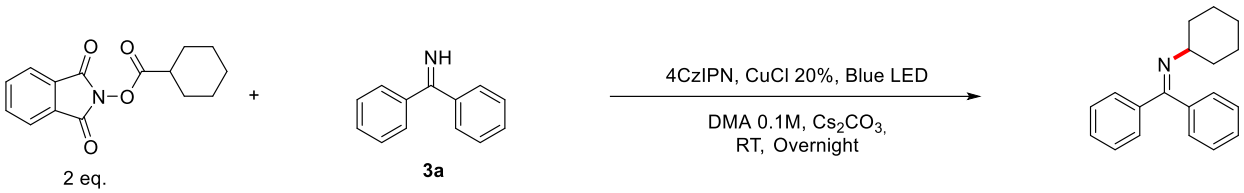


Figure 3.2. Scope of decarboxylative C(sp^3)-N coupling of anilines. Isolated yields were reported. [1]Yields using a Ru photocatalyst as previously reported.[13]

These optimized conditions in Table 3.1 were applied to explore the scope of the coupling (Figure 3.2). The coupling worked well with different types of anilines (**1c**, **2a**-**2f**). *Ortho*- (**2a**-**2c**), *meta*- (**2e**), and *para*-substitution (**2f**) in the anilines were tolerated. High yields (> 80%) were obtained with electron-rich anilines (**2a**, **2b**, **2d**). Yields dropped when electron-poor anilines were used (**2c**, **2e, 2f**). Coupling with electron-poor heterocycles, such as aminopyridine and aminoquinolines, was unsuccessful. Both primary (**1c**, **2g**-**2i**, **2n**) and secondary (**2j**-**2m**) alkyl carboxylic acid derivatives could be used as coupling partners. The coupling of tertiary alkyl carboxylic acid derivatives, as well as alkyl amines, was unsuccessful. Coupling was also unsuccessful if one of the partners bears a non-protected protic group (e.g., free alcohols and amines). The coupling had high functional group tolerance, as aryl-Cl (**2f**), ester (**2e**), nitrile (**2c**), NHBoc (**2g**), alkyl-Br (**2h**) groups were compatible. Moreover, the coupling of NHPI esters derived from natural fatty acid (**2n**) and indometacin (**2o**) gave good yields, demonstrating the utility of the method for late-stage functionalization. Note that the yields using 4CzIPN as the photocatalyst were often higher than using $Ru(bpy)_3(PF_6)_2$ as the photocatalyst (e.g., **2m**, **2n**, **2o**).[13]

3.2.2 *Coupling with imines*

Benzophenone imine and its derivatives are useful ammonia equivalents, which allow rapid and selective synthesis of masked primary amines.[23] We previously reported that the conditions for the decarboxylative coupling of NHPI esters with anilines were not efficient for the analogous coupling of NHPI esters with imines, which provided access to alkylated primary amines upon hydrolysis of coupling products.[15] A change of photocatalyst from $Ru(bpy)_3(PF_6)_2$ to Ir-$[(dtbbpy)(ppy)_2]PF_6$ was necessary for the latter coupling. To our delight, we found that the same organic photocatalyst **1f** catalyzed the coupling of NHPI esters with both anilines and imines. For the latter coupling, further optimization of conditions was necessary (Table 3.3). Applying the same conditions used for the coupling with amines (Table 3.3, entry 1) only traces of the product were detected. The change of solvent and base from acetonitrile to DMA and from Et_3N to Cs_2CO_3 gave a yield of 66% (Table 3.3, entry 3). The absence of a base or the use of a very strong base was unsuccessful (Table 3.3, entry 6, 7).



Entry	Photocatalyst	Base 1eq.	Solvent 0.1M	GC Yield[a]
1	4CzIPN 1%	Et_3N	Acetonitrile	Trace
2	4CzIPN 1%	Et_3N	DMA	Trace
3	4CzIPN 1%	Cs_2CO_3	DMA	66%
4	4CzIPN 1%	Rb_2CO_3	DMA	57%
5	4CzIPN 1%	K_2CO_3	DMA	42%
6	4CzIPN 1%	KOtBu	DMA	0%
7	4CzIPN 1%	No base	DMA	0%
8	4CzIPN 1%	K_3PO_4	DMA	45%
9	4CzIPN 1%	Cs_2CO_3 Ball Mill[b]	DMA	85%
10	4CzIPN 1%	Cs_2CO_3 Ball Mill[b]	THF	73%
11	4CzIPN 1%	Cs_2CO_3 Ball Mill[b]	DMF	80%
12	4CzIPN 1%	Cs_2CO_3 Ball Mill[b]	Toluene	12%
13	4CzIPN 1%	Cs_2CO_3 Ball Mill[b]	DCM	Trace
14	4CzIPN 1%, no light	Cs_2CO_3 Ball Mill[b]	DMA	n.d.
15	No catalyst, no light	Cs_2CO_3 Ball Mill[b]	DMA	n.d.

Table 3.3. Optimization for decarboxylative imination. [a]Corrected GC yields using n-dodecane as internal standard; [b]Anhydrous Cs_2CO_3 was ball milled for one minute at 350rpm in order to reduce the mash of the powder and enhance the surface contact during the reaction.

Since cesium carbonate is mostly insoluble in DMA, the mesh of the powder affected significantly the yield of the reaction. Thus a refinement of the mesh size, through ball milling the powder for 1 minute at 350rpm with a steel ball, and the use of it in the reaction mixture, gave a yield of 85% (Table 3.3, entry 9). The control experiment showed that no reaction occurred in the absence of light or photocatalyst (Table 3.3, entry 14, 15).

We were able to use benzophenone imine (**3a**) as the imine partner. In the previous protocol using an Iridium photocatalyst, **3a** was a poor coupling partner, and 3,3'-bis-(trifluoromethyl)benzophenone imine had to be used. **3a** is a better imine partner than 3,3'-bis-(trifluoromethyl)benzophenone imine as it is less costly and even commercially available. The optimized conditions for the coupling with **1c** were: 1 mol % of 4CzIPN (**1f**), 20 mol % of CuCl, 1 equiv. of Cs_2CO_3 ball milled, in 0.1 M DMA at room temperature overnight under blue LEDs light (Table 3.3, entry 9).

The conditions for the coupling of imines worked with primary, secondary, and tertiary alkyl NHPI esters (**3b-3l**, Figure 3.3), although the coupling of some tertiary substrates had modest yields (**3j** and **3k**). Coupling of NHPI esters derived from a complex natural product (**3m**), a fatty acid (**3n**), and a drug (**3o**) was also successful. Hydrolysis of the coupling product **3o** gave the corresponding primary amine derivative with negligible loss of yield (**3p**). Overall, the coupling was compatible with many functional groups, including ketones (**3m**), esters (**3b**), amides (**3o**, **3p**), halogen groups (**3e**, **3o**), olefins (**3n**), ethers (**3o**), protected amines (**3d**) and acetals (**3i**). A 1 mmol scale synthesis of **3e** was achieved in 51% yield.

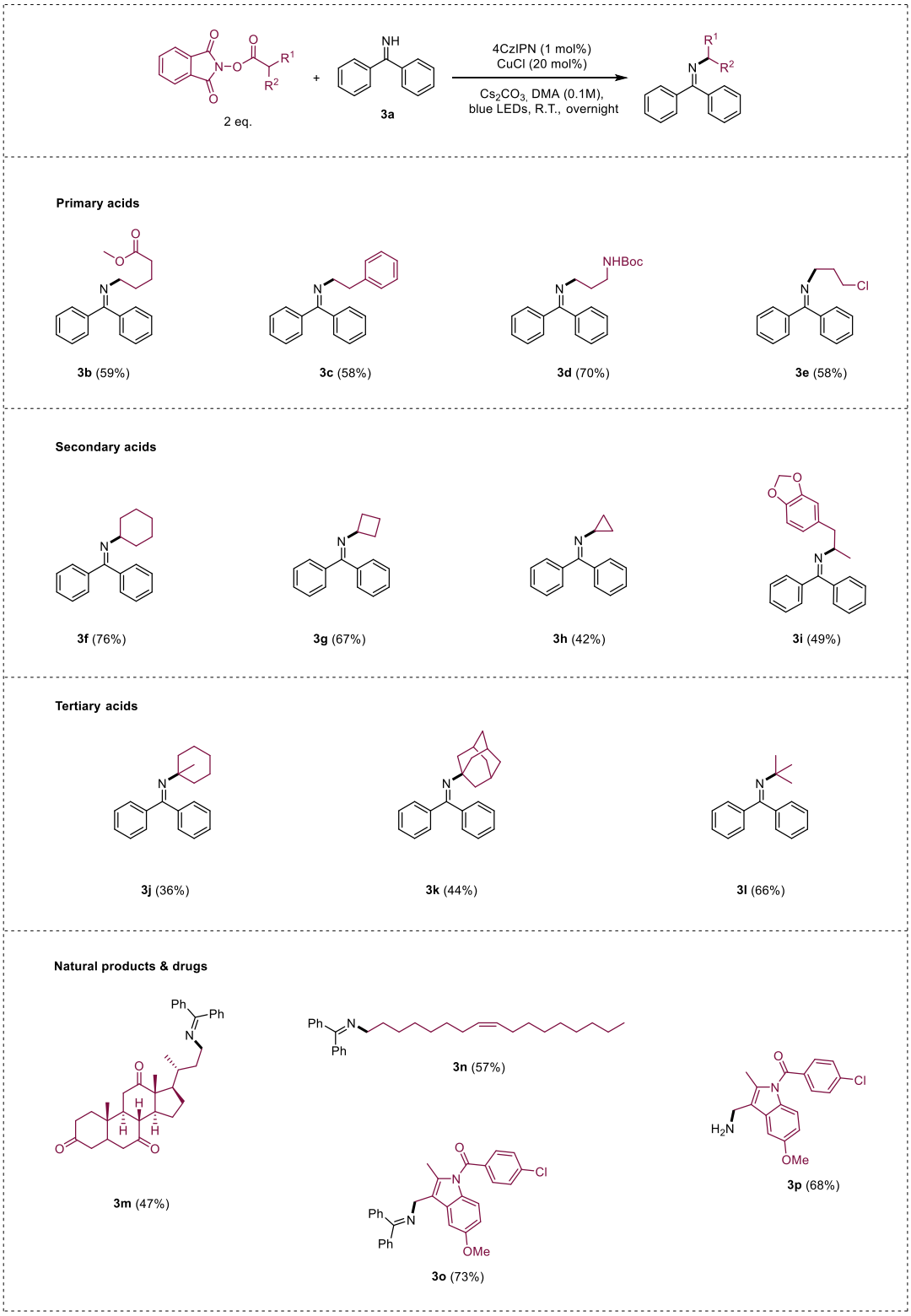


Figure 3.3. Scope of decarboxylative C(sp^3)-N coupling of imines. General optimized conditions: NHPI ester (0.5 mmol), benzophenone imine (0.25 mmol), 4CzIPN (1 mol %), CuCl (20 mol %), DMA (2.5 mL), Cs_2CO_3 (0.5 mmol), under N_2, blue LEDs, overnight. 3o was deprotected with 1M HCl in methanol for 1 hour to obtain 3p.

3.2.3 Mechanistic study

Fluorescence quenching experiments were conducted to probe the reaction mechanism. Aniline, CuCl, and TEA, but not the NHPI ester (**1a**), could quench the fluorescence of 4CzIPN (Figure 3.4). Because CuCl might bind to TEA, aniline, and **1a**, fluorescence quenching was monitored for a binary mixture of CuCl with another reaction component (Figures 3.5-3.7). The quenching was nearly identical with CuCl alone and with a 1:5 mixture of CuCl:**1a** (Figure 3.5), further excluding the quenching of the excited photocatalyst by NHPI ester or its potential Cu complex. The mixtures of Cu:aniline were less efficient than the sum of the two components alone to quench the fluorescence of 4CzIPN (Figure 3.6). This result suggested the formation of Cu-aniline species that have distinct quenching properties from its individual components. For the mixtures of Cu:TEA, varying the ratios of the two components resulted in only small and non-linear changes in the quenching rates (Figure 3.7). This result suggested the formation of Cu-TEA species, which is a poor quencher, showing a distinct quenching effect compared to Ir-based photocatalyst.[29,30] Together these results suggested that due to binding to aniline or TEA or both, there was no free CuCl available as a quencher in the solution. Both aniline and TEA (in a free or Cu-coordinated form) could engage in reductive quenching of the excited state of 4CzIPN. The coupling was successful only in the presence of TEA or DIPEA, but not with other bases, suggesting that TEA served more than a simple base. The quantum yield of the coupling was estimated to be 5.4%. This low quantum yield would be consistent with the scenario that the dominant reductive quenching of the photocatalyst in the reaction was by aniline, but this quenching was non-productive probably because it was reversible. The productive quenching was via the oxidation of TEA.

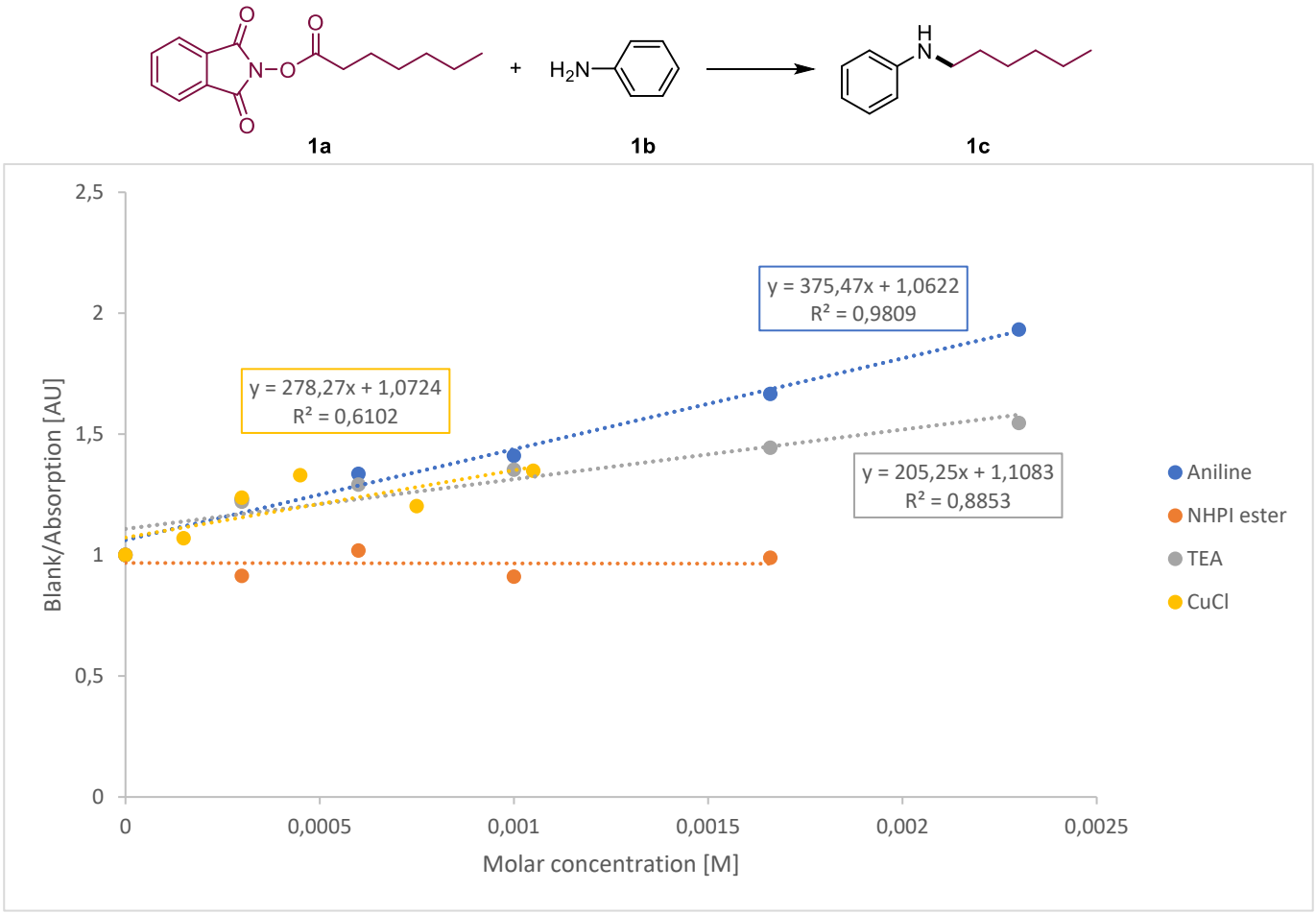


Figure 3.4. Stern-Volmer plots of fluorescence quenching of 4CzIPN by aniline, NHPI ester (1a), TEA, or CuCl.

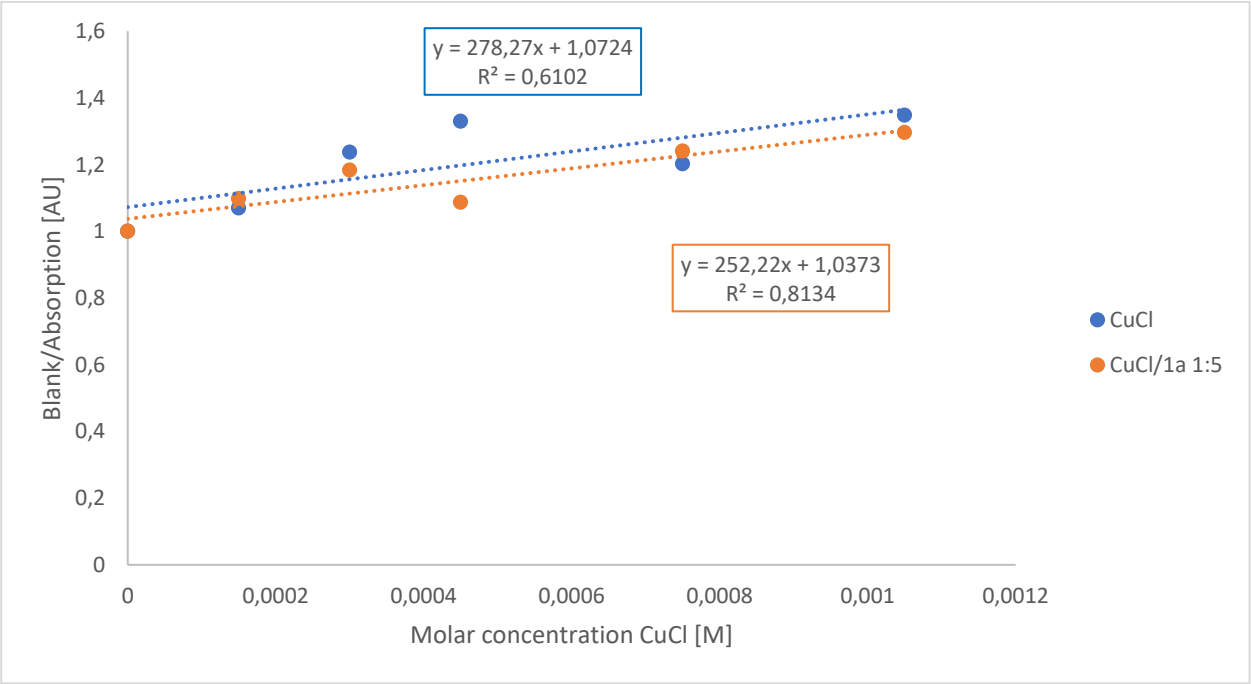


Figure 3.5. Stern-Volmer plots of fluorescence quenching of 4CzIPN by a mixture of CuCl and NHPI ester **1a** as well as CuCl alone.

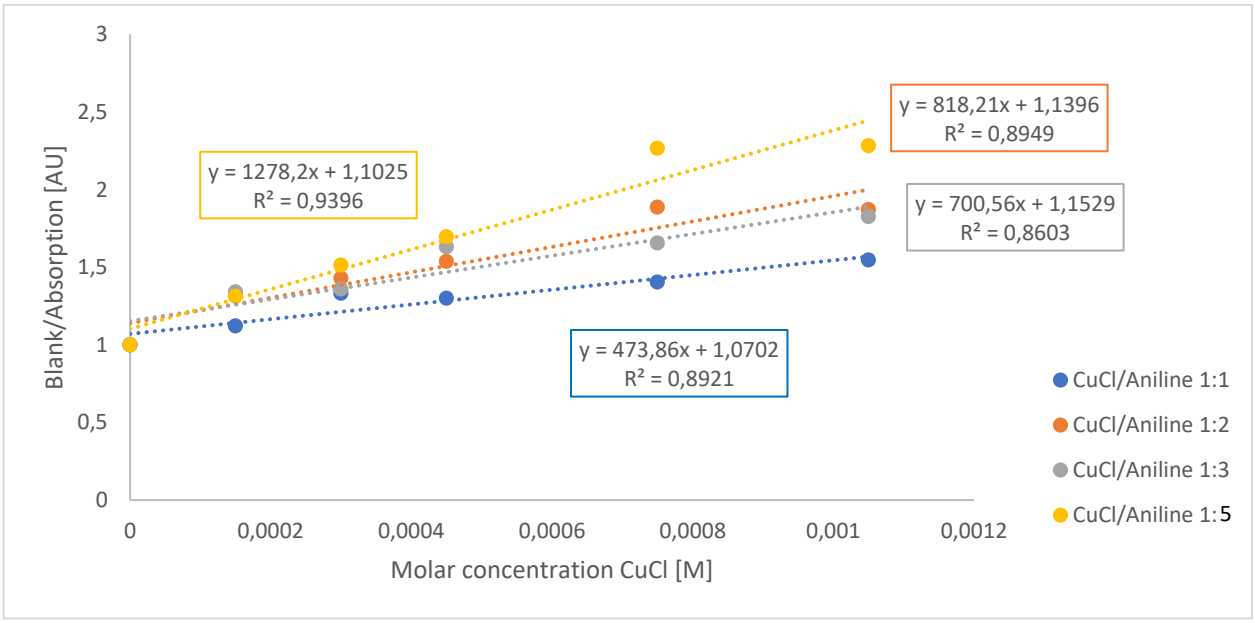


Figure 3.6. Stern-Volmer plots of fluorescence quenching of 4CzIPN by a mixture of CuCl and aniline. Increasing the ratios of aniline:Cu leads to an increase in quenching. But the quenching increase is not consistent with a non-bonded situation where the total quenching should be the sum of the individual quenchers. This result suggests the formation of a CuCl-aniline complex that has a quenching power lower than the two species combined.

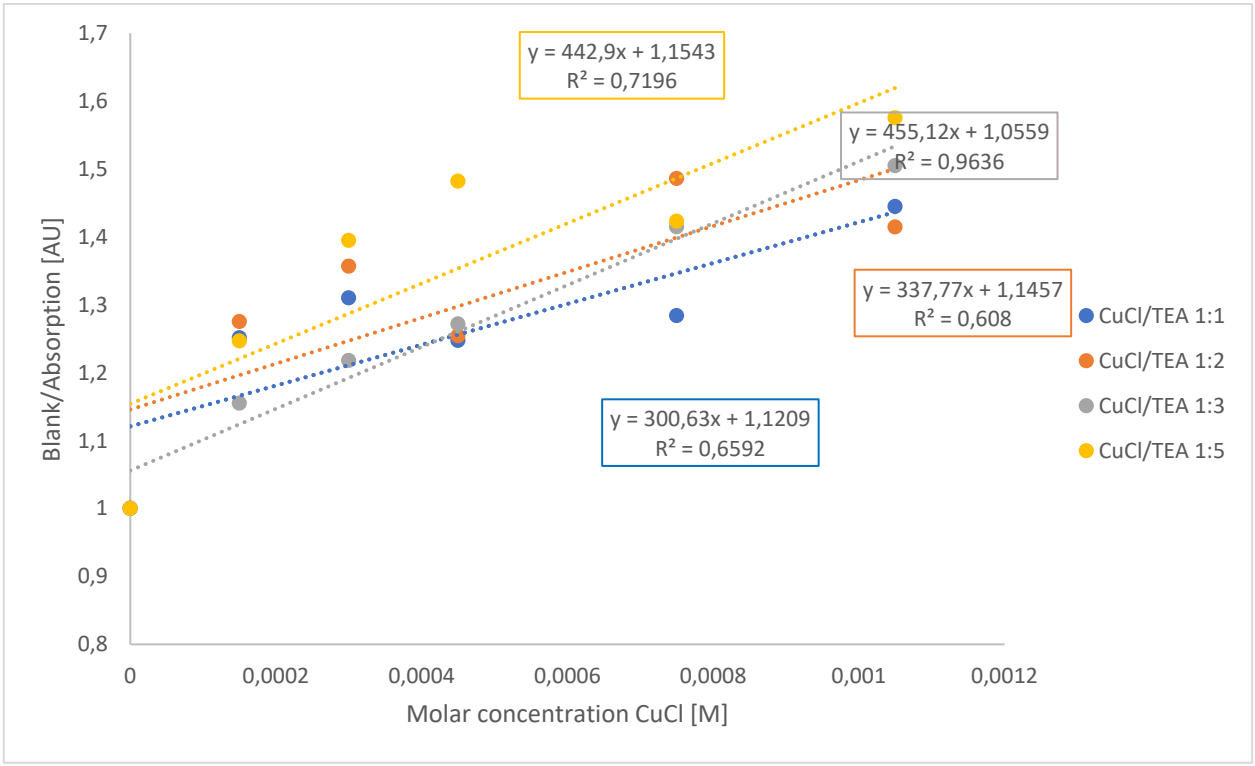


Figure 3.7. Stern-Volmer plots of fluorescence quenching of 4CzIPN by a mixture of CuCl and TEA. The slope does not increase in a significant way when the ratios pass from 1:1 to 1:5. This result indicates a formation of a CuCl-TEA complex that probably does not quench the photocatalyst at all. In this case, the errors in the collected data were quite large. The linear fitting of the data is very poor. These observations could be due to the formation of various complexes in equilibrium.

Based on the data and considerations above, we propose the following mechanism (Figure 3.8). Light excitation of 4CzIPN formed an excited 4CzIPN*, which was reductively quenched by TEA to form 4CzIPN^{-} and a TEA radical cation. Reduction of an NHPI ester by 4CzIPN^{-} regenerates the photocatalyst 4CzIPN and yields an NHPI ester radical anion. The latter quickly releases CO_2, a phthalimide anion, and an alkyl radical. Hydrogen atom transfer between a Cu^{I}-aniline species (**A**) with the TEA radical cation yields a protonated TEA cation and a Cu^{II}-anilido complex (**B**). The latter traps the alkyl radical to give a Cu^{III}-anilido species (**C**), which after C-N reductive elimination, delivers the coupling product and regenerates a Cu^{I} species (**D**) that can now bind aniline again.

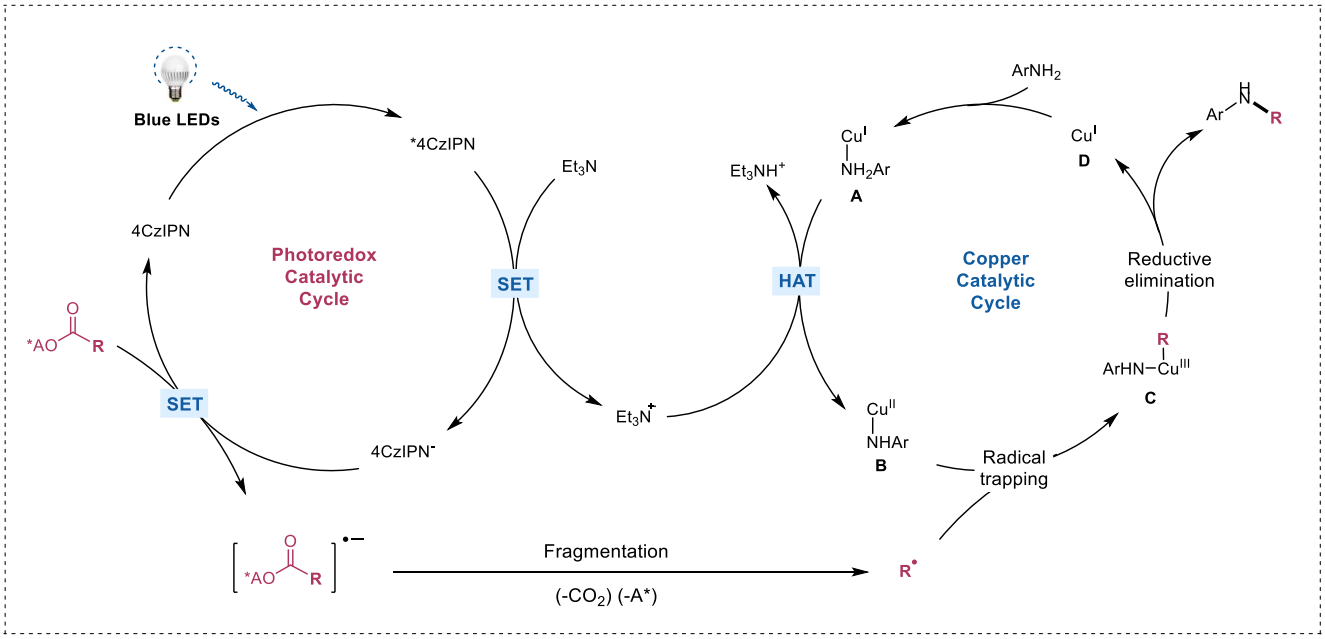


Figure 3.8. Proposed mechanism for decarboxylative C-N coupling with anilines

DIPEA and TEA were the only two bases that, during the initial screening, made the reaction successful. Since other bases, stronger, weaker, or with similar pKa were also tried, with scares results, this suggests that the role of these amines in the catalytic cycle is not a mere acid-base reaction. Both DIPEA and TEA have a low oxidation potential, so they can also act as reductive quenchers. For example, the PC's excited state can oxidize TEA to form a TEA radical cation **9a** (Figure 3.9). **9a** is capable of hydrogen atom abstraction.[31] Such an abstraction could be on a Cu(I) aniline complex to form a Cu(II) analide. Alternatively, **9a** can abstract a hydrogen atom from TEA to give radical **9b**.[32] **9b** then can abstract a hydrogen atom from a Cu(I) aniline complex to form a Cu(II) analide.[32–36] **9b** could also reduce Cu(I) yielding an iminium salt and Cu metal, which would terminate the reaction. [37]

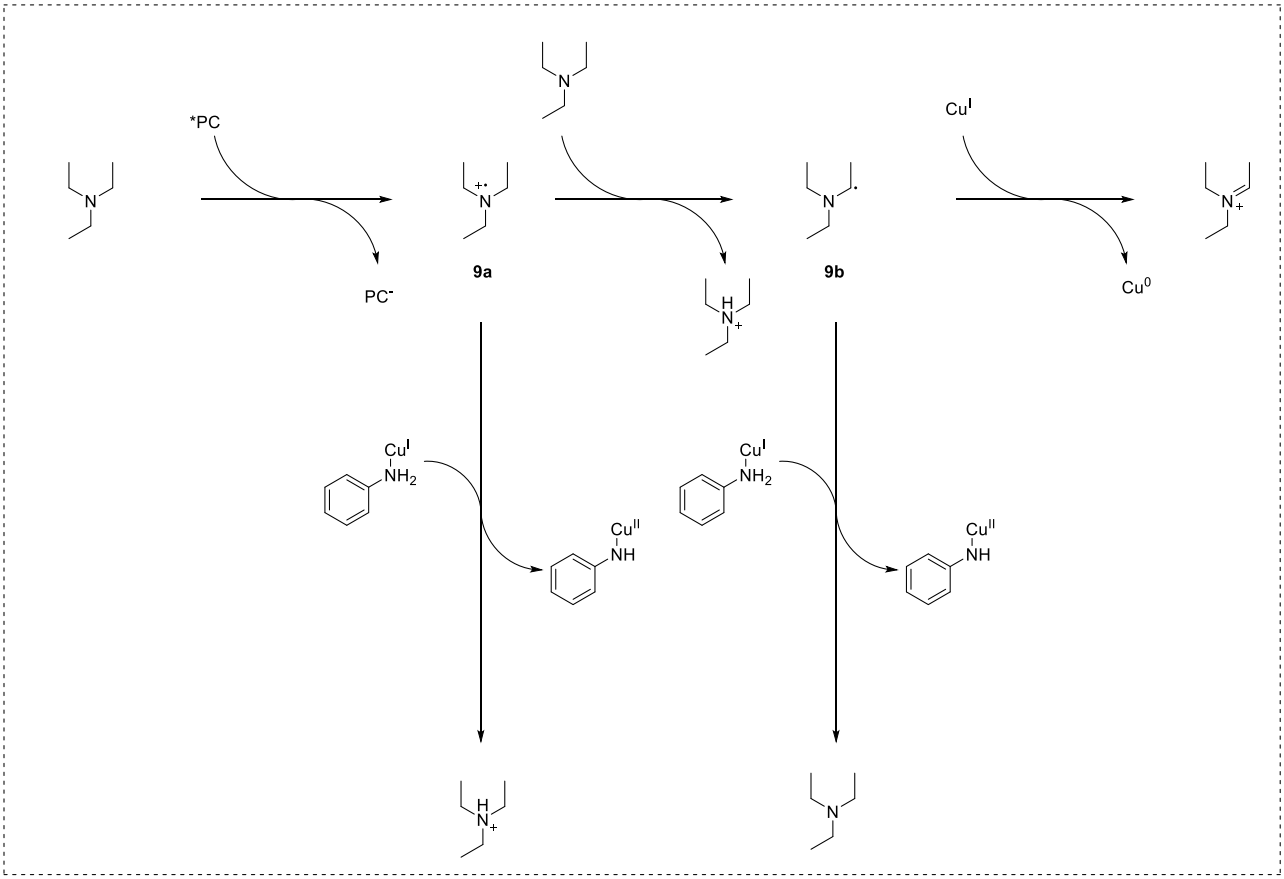


Figure 3.9. Possible reaction pathways of TEA.

The above mechanism (Figure 3.8) is different from that of the analogous coupling using $Ru(bpy)_3(PF_6)_2$ as the photocatalyst. The difference might originate from the redox potentials of the excited state of the photocatalysts. 4CzIPN* ($E_{1/2}$ 4CzIPN*/4CzIPN$^-$ = +1.35 V vs SCE)[19,20,23] is a more potent electron acceptor (oxidant) than $Ru(bpy)_3(PF_6)_2$* (E1/2 *Ru^{II}/Ru^{I} = +0.77 V vs SCE).[38] Thus, unlike $Ru(bpy)_3(PF_6)_2$*, 4CzIPN* can oxidize triethylamine leading to a reductive quenching process. This reactivity differs from that of Ru-based photoredox catalysis, which involved an oxidative quenching pathway.[13]

3.3 Conclusion

In summary, we have developed tandem photoredox and Cu catalysis for decarboxylative C(sp^3)-N coupling of anilines and imines using an inexpensive and easy to make organic photocatalyst.[23] The method can be applied for the synthesis of a broad range of alkylated primary and secondary amines. The organic photocatalyst not only broadens the scope of the coupling compared to previously reported Ru or Ir photocatalyst but also operates via a different mechanism. This work further demonstrates the potential of organic photoredox catalysts.

3.4 Experimental section

General Analytical Information

Nuclear Magnetic Resonance spectra were recorded on a Bruker Avance 400 MHz instruments at ambient temperature. All ^{1}H NMR spectra were measured in part per million (ppm) relative to the signals of tetramethylsilane (TMS, 0.00 ppm) added into the deuterated chloroform ($CDCl_3$, 7.26 ppm) unless otherwise stated.[39] Data for ^{1}H NMR were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, and br = broad signal), coupling constants, and integration. All ^{13}C NMR spectra were reported in ppm relative to $CDCl_3$ (77.16 ppm) unless otherwise stated, and were obtained with complete ^{1}H decoupling. All GC analyses were performed on a Perkin-Elmer Clarus 400 GC system with a FID detector. All GC-MS analyses were performed on an Agilent Technologies 7890A GC system equipped with a 5975C MS detector. High-resolution mass spectra (HRMS) by electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), and atmospheric pressure photoionization (APPI) method were performed at the EPFL ISIC Mass Spectroscopy Service.

General Manipulation Considerations

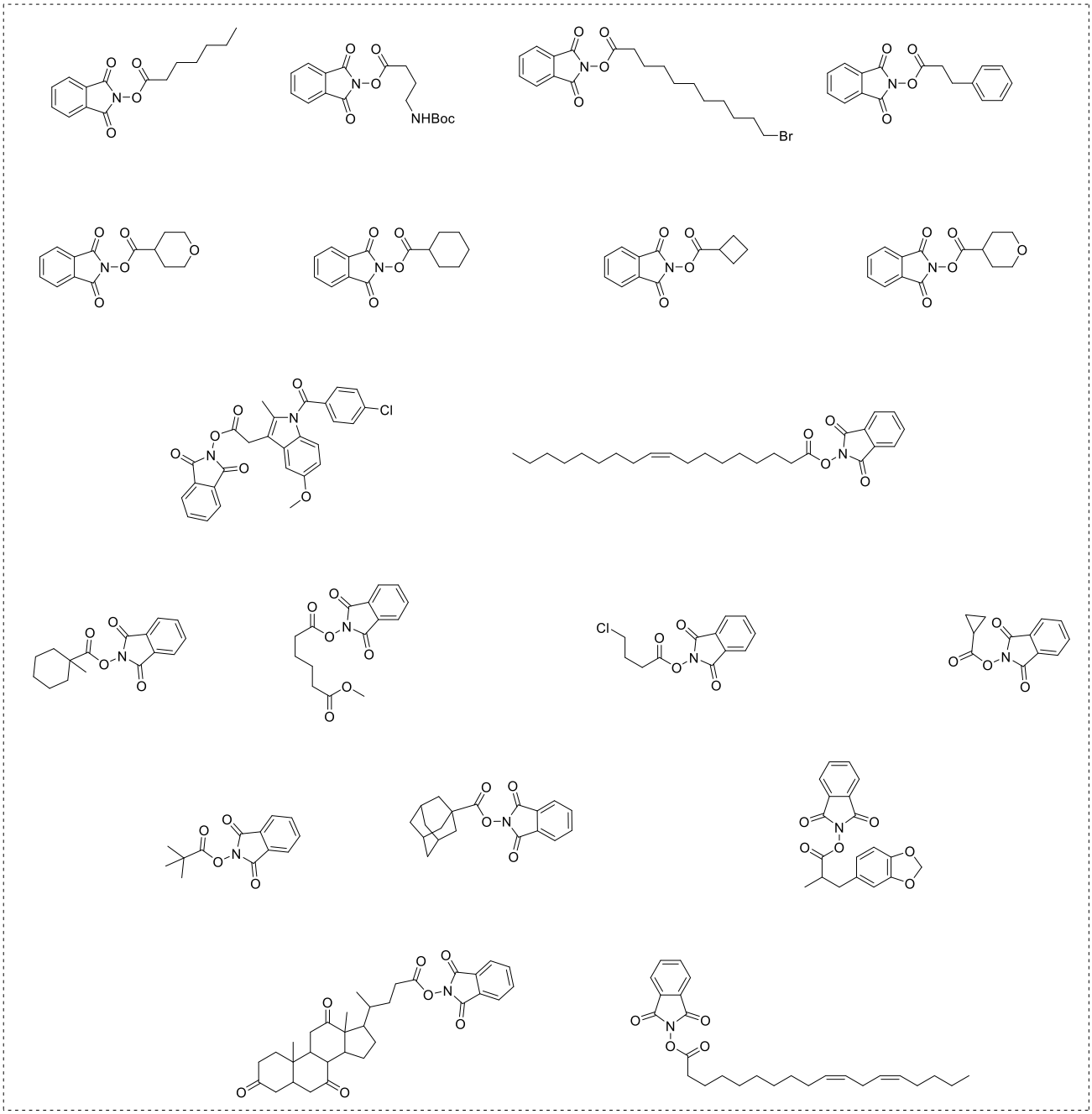
All manipulations for the decarboxylative C(sp^3)-N cross-coupling via tandem photoredox and copper-catalyzed reactions were set up in a 15 mL Teflon-screw capped test tubes (unless otherwise noted) under an inert nitrogen (N_2) atmosphere using glove-box techniques. The test tubes were then sealed with airtight electrical tapes and the reaction mixtures were stirred under the irradiation of blue LEDs with a fan cooling down the temperature (approximately room temperature). Blue LEDs were purchased from Kessil Co., Ltd. (40 W max., product No. A160WE). Table fan was purchased from Galaxus Co., Ltd. (35 W max.). Flash

column chromatography was performed using silica gel columns on an Isolera LC from Biotage. Notably, in the case of the imino compounds, the silica gel used for the purification of amine products were pre-neutralized with 5% triethylamine in hexanes solution prior to the usage, in order to minimize the product loss. The eluents for column chromatography were presented as ratios of solvent volumes. Yields reported in the publication are of isolated materials unless otherwise noted.

General procedure for the synthesis of NHPI esters (General Procedure A)

A round-bottom flask was charged with carboxylic acid (if solid, 1.0 equiv), nucleophile (N-hydroxyphthalimide, 1.0 equiv) and DMAP (0.1 equiv.). Dichloromethane (DCM) was added (0.2 M-0.5 M) and the mixture was stirred vigorously. Alternatively, carboxylic acid (if liquid, 1.0 equiv.) was added via syringe. N,N'-Diisopropylcarbodiimide (DIC) (1.1 equiv.) was then added dropwise via syringe and the mixture was allowed to stir until the carboxylic acid or the N-hydroxyphthalimide was fully consumed (determined by TLC). Typical reaction times were between 0.5 h and 12 h. Afterwards, the mixture was filtered over Celite and rinsed with additional CH_2Cl_2. The solvent was removed under reduced pressure, and purified by column chromatography to give the corresponding NHPI esters. Most NHPI esters are solid, which could be recrystallized (precipitation from a supersaturated solution of ethyl acetate adding hexanes) after column chromatography. Unless otherwise stated, NHPI esters were prepared following the General Procedure A.

The preparation and spectral data of the following NHPI esters have been reported.[40–42]



General procedure for visible-light-mediated decarboxylative amination of aniline (General procedure B)

An oven-dried 15 mL re-sealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was sequentially charged with NHPI ester (2 equiv.), 4CzIPN (**1f**) (1 mol%), CuBr (20 mol%), MeCN (0.1 M), aniline (1 equiv), Et_3N (1 equiv) in the glove box. The vial was sealed with a screw cap and removed from the glove box. Then the vial was placed 3 cm away from two blue LEDs, one facing the other horizontally, and irradiated under fan cooling (maintain the temperature at room temperature) overnight (see Fig. S1 for illustration). After the reaction, the resulting dark brown or orange reaction mixture was acidified with saturated NH_4Cl solution (~1 mL) and then neutralized with saturated $NaHCO_3$ solution (~1.5 mL). The crude product in the aqueous fraction was extracted with EtOAc (~10 mL). The aqueous fraction was further washed with EtOAc (3 x ~5 mL). The combined organic fractions were concentrated in vacuo with the aid of a rotary evaporator. The crude product residue was purified by flash chromatography using a solvent mixture (EtOAc, hexanes) as an eluent to afford the purified product.

General procedure for visible-light-mediated decarboxylative amination of benzophenone imines (General Procedure C)

An oven-dried 15 mL re-sealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was sequentially charged with NHPI ester (2 equiv.), 4CzIPN (**1f**) (1 mol%), CuBr (20 mol%), Cs_2CO_3 (2 equiv.), DMA (0.1 M), benzophenone imine (1 equiv) in the glove box. The vial was sealed with a screw cap and removed from the glove box. Then the vial was placed 3 cm away from two blue LEDs, one facing the other horizontally, and irradiated under fan cooling (maintain the temperature at room temperature) overnight. After the reaction, the resulting dark brown or orange reaction mixture was dried under reduced pressure. The crude product was dissolved in ethyl acetate and Et_3N was added (~1 mL). Silica was then added and the suspension

was dried under reduced pressure. The silica was dry loaded of a column. The crude product residue was purified by flash chromatography using a solvent mixture (EtOAc, hexanes 5% Et_3N) as an eluent to afford the purified product.

Quantum Yield

In a quartz cuvette equipped with a re-sealable screw cap, NHPI ester (**1a**) (0.6 mmol, 165.18 mg), CuCl (20 mol%, 6 mg), 4CzIPN (**1f**) (1 mol%, 2.4 mg), CD_3CN (3 mL), Et_3N (0.3 mmol, 42 µL) and aniline (0.3 mmol, 27.4 µL) were added under inert atmosphere. As light source, a fluorometer was used, with a beam of light set on 420 ±14 nm. The Blanck was calculated using a quartz cuvette filled with the same solvent and a 1 cm diameter photodiode. The power of the beam was 14 mW. The reaction was then put in front of the beam and no light passage was recorded by the photodiode. It is assumed that all the light emitted by the fluorometer is absorbed by the reaction. The reaction was stirred for 3 hours. Trimethoxybenzene was added as an internal standard and the yield was calculated via NMR.

In order to calculate the quantum yield, literature procedures were followed.[43,44]

Quantum yield: 5.4%

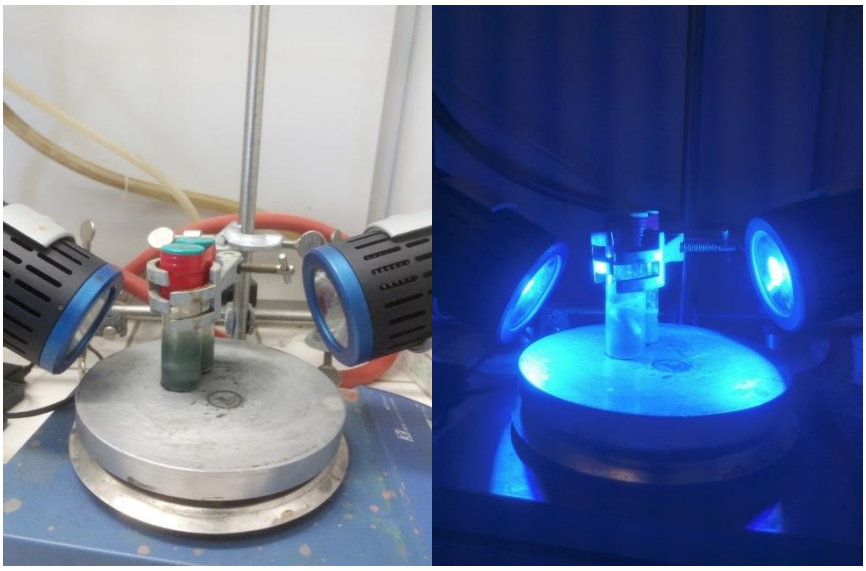
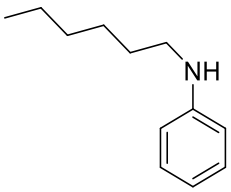


Figure 3.10. The general setup for the decarboxylative coupling.

N-hexylaniline (1c)



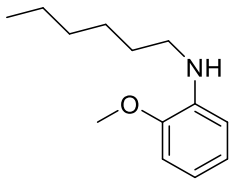
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 60 mg (0.34 mmol) (68%) of the title compound **1c** as a transparent oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.21 (t, J = 7.7 Hz, 2H), 6.73 (t, J = 7.3 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 3.64 (s, 1H), 3.14 (t, J = 7.1 Hz, 2H), 1.66 (p, J = 7.2 Hz, 2H), 1.49 – 1.34 (m, 5H), 0.99 – 0.92 (m, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 148.5, 129.2, 117.0, 112.7, 44.0, 31.6, 29.5, 26.8, 22.6, 14.0.

Spectral data match those previously reported.[45]

N-hexyl-2-methoxyaniline (2a)



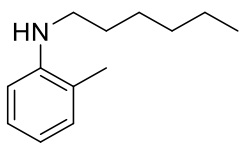
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 103.5 mg (0.5 mmol) (100%) of the title compound **2a** as a transparent oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 6.91 (t, J = 7.7 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.74 – 6.60 (m, 2H), 4.21 (bs, 1H), 3.88 (d, J = 2.2 Hz, 3H), 3.16 (td, J = 7.2, 2.0 Hz, 2H), 1.92 – 1.59 (m, 2H), 1.57 – 1.20 (m, 8H), 1.05 – 0.87 (m, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 146.7, 138.5, 121.3, 116.0, 109.7, 109.3, 55.3, 43.7, 31.7, 29.5, 26.9, 22.6, 14.0.

Spectral data match those previously reported.[46]

N-hexyl-2-methylaniline (2b)



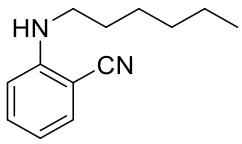
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 79 mg (0.41 mmol) (83%) of the title compound **2b** as an off-yellow oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.17 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.3 Hz, 1H), 6.73 – 6.61 (m, 2H), 3.50 (s, 1H), 3.19 (t, J = 7.3 Hz, 2H), 2.17 (s, 3H), 1.71 (p, J = 7.3 Hz, 2H), 1.46 (d, J = 7.4 Hz, 2H), 1.38 (d, J = 4.5 Hz, 4H), 0.98 – 0.92 (m, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 146.3, 130.0, 127.1, 121.6, 116.6, 109.6, 44.0, 31.6, 29.6, 26.9, 22.6, 17.4, 14.0.

Spectral data match those previously reported.[47]

2-(hexylamino)benzonitrile (2c)

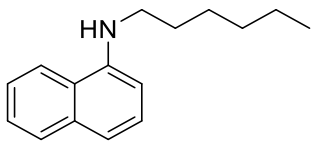


Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 21.6 mg (0.1 mmol) (22%) of the title compound **2c** as a transparent oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.40 (s, 2H), 6.68 (d, J = 8.1 Hz, 2H), 4.54 (bs, 1H), 3.21 (q, J = 6.9 Hz, 2H), 1.82 – 1.63 (m, 2H), 1.33 (d, J = 17.3 Hz, 6H), 0.92 (d, J = 6.9 Hz, 3H).

Spectral data match those previously reported.[48]

N-hexylnaphthalen-1-amine (2d)



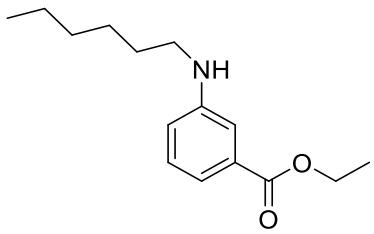
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 68 mg (0.3 mmol) (60%) of the title compound **2d** as a brown oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.84 (dd, J = 7.0, 2.8 Hz, 2H), 7.54 – 7.44 (m, 2H), 7.40 (td, J = 7.9, 2.1 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 6.66 (d, J = 7.4 Hz, 1H), 4.34 (s, 1H), 3.32 (t, J = 6.9 Hz, 2H), 1.82 (p, J = 7.0 Hz, 2H), 1.58 – 1.50 (m, 2H), 1.47 – 1.38 (m, 3H), 0.98 (q, J = 4.7 Hz, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 143.6, 134.3, 128.6, 126.7, 125.6, 124.5, 123.3, 119.8, 117.0, 104.1, 44.2, 31.7, 29.4, 27.1, 22.7, 14.1.

Spectral data match those previously reported.[49]

Ethyl 3-(hexylamino)benzoate (2e)



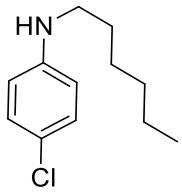
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 58 mg (0.23 mmol) (47%) of the title compound **2e** as a transparent oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.43 – 7.37 (m, 1H), 7.31 (t, J = 2.0 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 6.81 (ddd, J = 8.1, 2.6, 1.0 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.30 – 3.96 (bs, 1H), 3.17 (t, J = 7.1 Hz, 2H), 1.65 (p, J = 7.1 Hz, 2H), 1.47 – 1.31 (m, 6H), 0.96 – 0.88 (m, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 167.0, 148.1, 131.4, 129.0, 118.4, 117.2, 113.5, 60.8, 44.1, 31.6, 29.3, 26.8, 22.6, 14.3, 14.0.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{24}NO_2^+$ 250.1802; Found 250.1800

4-chloro-N-hexylaniline (2f)



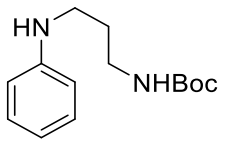
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 74.6 mg (0.35 mmol) (71%) of the title compound **2f** as a yellowish oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.14 (d, J = 8.3 Hz, 2H), 6.54 (d, J = 8.2 Hz, 2H), 3.74 (bs, J = 33.2 Hz, 1H), 3.09 (d, J = 7.4 Hz, 2H), 1.63 (p, J = 7.3 Hz, 2H), 1.47 – 1.24 (m, 7H), 0.92 (d, J = 7.0 Hz, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 147.0, 129.0, 121.6, 113.7, 44.1, 31.6, 29.4, 26.8, 22.6, 14.0.

Spectral data match those previously reported.[50]

Tert-butyl (3-(phenylamino)propyl)carbamate (2g)



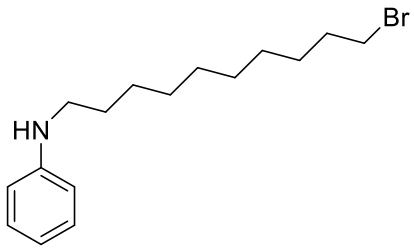
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 170.9 mg (0.34 mmol) (68%) of the title compound **2g** as a transparent oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.24 – 7.14 (m, 2H), 6.73 (t, J = 7.5 Hz, 1H), 6.66 (d, J = 8.0 Hz, 2H), 4.71 (s, 1H), 3.24 (dt, J = 21.4, 6.9 Hz, 4H), 1.89 – 1.73 (m, 2H), 1.48 (s, 9H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 168.1, 156.2, 148.0, 134.2, 132.7, 129.2, 123.5, 117.4, 113.0, 41.1, 38.1, 29.6, 28.4.

Spectral data match those previously reported.[51]

N-(10-bromodecyl)aniline (2h)



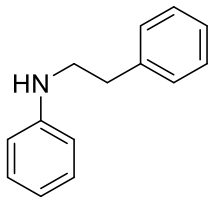
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 117 mg (0.39 mmol) (77%) of the title compound **2h** as a transparent oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.24 – 7.16 (m, 2H), 6.73 (t, J = 7.4 Hz, 1H), 6.65 (d, J = 7.9 Hz, 2H), 3.43 (dd, J = 6.9, 2.1 Hz, 2H), 3.13 (t, J = 7.2 Hz, 2H), 1.88 (p, J = 7.1 Hz, 2H), 1.65 (p, J = 7.3 Hz, 2H), 1.51 – 1.24 (m, 12H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 148.2, 129.2, 117.3, 112.8, 44.1, 34.0, 32.8, 29.5, 29.4, 29.3, 29.3, 28.7, 28.1, 27.1.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{27}BrN^+$ 312.1321; Found 312.1307

N-phenethylaniline (2i)



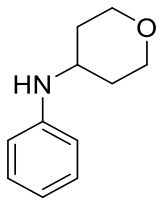
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 62 mg (0.31 mmol) (63%) of the title compound **2i** as a transparent oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.35 (t, J = 7.4 Hz, 2H), 7.31 – 7.18 (m, 5H), 6.75 (t, J = 7.4 Hz, 1H), 6.67 (d, J = 8.0 Hz, 2H), 3.44 (t, J = 7.1 Hz, 2H), 2.96 (t, J = 7.1 Hz, 2H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 147.9, 139.2, 129.3, 128.8, 128.6, 126.4, 117.5, 113.0, 45.1, 35.5.

Spectral data match those previously reported.[52]

N-phenyltetrahydro-2H-pyran-4-amine (2j)



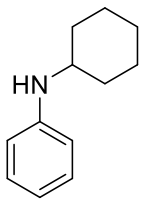
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 53 mg (0.43 mmol) (85%) of the title compound **2j** as a transparent oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.20 (t, J = 7.7 Hz, 2H), 6.73 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 8.0 Hz, 2H), 4.07 – 3.98 (m, 2H), 3.54 (ddd, J = 11.4, 9.3, 2.3 Hz, 3H), 2.07 (ddd, J = 12.8, 4.5, 2.3 Hz, 2H), 1.58 – 1.44 (m, 2H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 146.7, 134.2, 129.3, 123.5, 117.5, 113.3, 66.9, 49.1, 33.6.

Spectral data match those previously reported.[53]

N-cyclohexylaniline (2k)



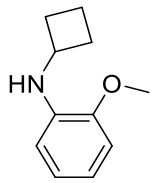
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 78 mg (0.45 mmol) (89%) of the title compound **2k** as a transparent oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.22 – 7.13 (m, 2H), 6.70 (t, J = 7.5 Hz, 1H), 6.64 (d, J = 7.9 Hz, 2H), 3.28 (td, J = 10.2, 6.4 Hz, 1H), 2.15 – 2.05 (m, 2H), 1.85 – 1.63 (m, 4H), 1.48 – 1.11 (m, 4H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 129.2, 117.1, 113.4, 51.9, 33.4, 29.7, 25.9, 25.0.

Spectral data match those previously reported.[54]

N-cyclobutyl-2-methoxyaniline (2l)



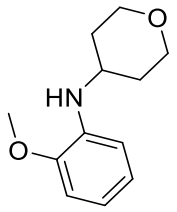
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 45 mg (0.31 mmol) (62%) of the title compound **2l** as a transparent oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 6.92 – 6.85 (m, 1H), 6.83 – 6.77 (m, 1H), 6.73 – 6.67 (m, 1H), 6.58 – 6.52 (m, 1H), 4.37 (bs, 1H), 3.96 (t, J = 7.6 Hz, 1H), 3.88 (d, J = 2.2 Hz, 3H), 2.54 – 2.42 (m, 2H), 1.87 (tdd, J = 19.6, 17.5, 9.2, 4.2 Hz, 4H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 146.7, 137.1, 121.2, 116.4, 110.3, 109.4, 55.3, 48.7, 31.2, 15.3.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{16}NO^+$ 178.1226; Found 178.1224

N-(2-methoxyphenyl)tetrahydro-2H-pyran-4-amine (2m)



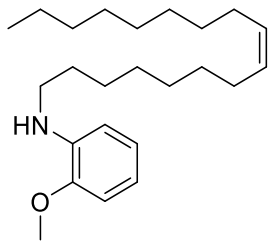
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 103 mg (0.5 mmol) (100%) of the title compound **2m** as an off-yellow oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 6.90 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.75 – 6.65 (m, 2H), 4.26 (s, 1H), 4.04 (dd, *J* = 12.1, 3.3 Hz, 2H), 3.88 (d, *J* = 2.2 Hz, 3H), 3.56 (t, *J* = 11.4 Hz, 3H), 2.15 – 2.04 (m, 2H), 1.64 – 1.49 (m, 2H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 146.9, 136.5, 121.2, 116.5, 110.4, 109.7, 66.9, 55.4, 48.8, 33.5, 29.7.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{18}NO_2^+$ 208.1332; Found 208.1331.

(Z)-N-(heptadec-8-en-1-yl)-2-methoxyaniline (2n)



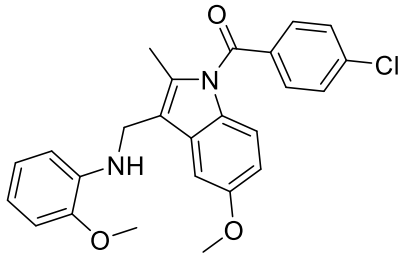
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 113.9 mg (0.32 mmol) (64%) of the title compound **2n** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 6.91 (t, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.73 – 6.60 (m, 2H), 5.40 (h, *J* = 2.2 Hz, 2H), 4.20 (s, 1H), 3.88 (d, *J* = 2.1 Hz, 3H), 3.16 (t, *J* = 7.2 Hz, 2H), 2.07 (q, *J* = 6.9, 6.4 Hz, 4H), 1.77 – 1.66 (m, 2H), 1.43 – 1.23 (m, 26H), 0.93 (t, *J* = 6.6 Hz, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 146.7, 138.5, 130.0, 129.7, 121.3, 116.0, 109.7, 109.3, 55.3, 43.7, 31.9, 29.8, 29.7, 29.5, 29.5, 29.4, 29.3, 29.2, 27.2, 22.7, 14.1.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{42}NO^+$ 360.3261; Found 360.3257

(4-chlorophenyl)(5-methoxy-3-(((2-methoxyphenyl)amino)methyl)-2-methyl-1H-indol-1-yl)methanone (2o)



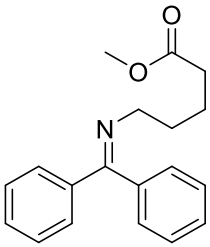
Following the General Procedure B with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (8:2) as an eluent to afford 127.6 mg (0.3 mmol) (59%) of the title compound **2o** as an off-yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 – 7.66 (m, 2H), 7.56 – 7.48 (m, 2H), 7.06 (d, *J* = 2.3 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.96 – 6.86 (m, 2H), 6.81 (dt, *J* = 15.2, 7.9 Hz, 2H), 6.71 (dt, *J* = 9.1, 2.3 Hz, 1H), 4.40 (s, 1H), 3.83 (d, *J* = 2.1 Hz, 6H), 2.45 (d, *J* = 2.0 Hz, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 168.4, 156.1, 147.1, 139.4, 136.2, 133.9, 131.2, 130.9, 130.4, 129.1, 121.3, 114.9, 111.9, 109.5, 101.2, 55.7, 55.3, 38.5, 13.3.

HRMS: (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]+ Calcd for C25H24ClN2O3+ 435.1470; Found 435.1449.

Methyl 5-((diphenylmethylene)amino)pentanoate (3b)



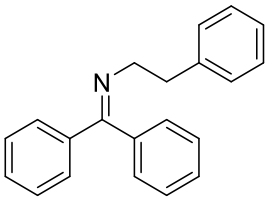
Following the General Procedure C with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (9:1) as an eluent to afford 86.8 mg (0.3 mmol) (59%) of the title compound **3b** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.65 – 7.60 (m, 2H), 7.52 – 7.43 (m, 3H), 7.40 – 7.31 (m, 3H), 7.20 – 7.15 (m, 2H), 3.67 (s, 3H), 3.41 (t, *J* = 6.4 Hz, 2H), 2.39 – 2.28 (m, 2H), 1.80 – 1.65 (m, 4H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 174.1, 168.2, 139.9, 136.9, 129.9, 128.5, 128.3, 128.0, 127.8, 53.3, 51.5, 33.9, 30.7, 23.0.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}NO_2^+$ 296.1645; Found 296.1648.

N-phenethyl-1,1-diphenylmethanimine (3c)



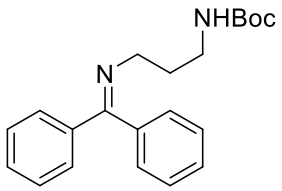
Following the General Procedure C with the corresponding NHPI ester (0.5 mmol) and aniline (0.25 mmol). The crude product was purified by LC hexanes with 5% TEA as an eluent to afford 41 mg (0.15 mmol) (58%) of the title compound **3c** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.65 – 7.58 (m, 2H), 7.45 – 7.31 (m, 3H), 7.31 – 7.12 (m, 3H), 6.99 (dd, *J* = 6.5, 2.9 Hz, 2H), 3.67 (t, *J* = 7.4 Hz, 2H), 3.03 (t, *J* = 7.5 Hz, 2H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 140.4, 139.9, 136.8, 129.9, 129.0, 128.4, 128.3, 128.2, 128.0, 127.7, 125.9, 55.6, 37.7.

Spectral data match those previously reported.[55]

Tert-butyl (3-((diphenylmethylene)amino)propyl)carbamate (3d)



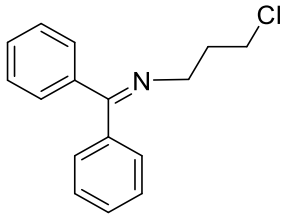
Following the General Procedure C with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (7:3) as an eluent to afford 117 mg (0.35 mmol) (70%) of the title compound **3d** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.63 – 7.59 (m, 3H), 7.51 – 7.41 (m, 3H), 7.40 – 7.32 (m, 2H), 7.18 (dd, *J* = 7.8, 1.7 Hz, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.31 (d, *J* = 6.8 Hz, 2H), 1.94 – 1.79 (m, 2H), 1.46 (s, 9H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 168.6, 156.0, 139.5, 134.2, 130.3, 130.1, 128.6, 128.4, 128.3, 128.1, 127.7, 123.5, 52.3, 39.9, 30.8, 28.5.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{27}N_2O_2^+$ 339.2067; Found 339.2073.

N-(3-chloropropyl)-1,1-diphenylmethanimine (3e)



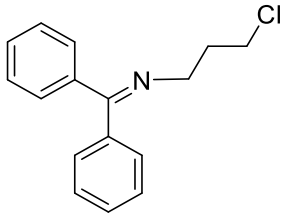
Following the General Procedure C with the corresponding NHPI ester (0.5 mmol) and aniline (0.25 mmol). The crude product was purified by LC hexanes with 5% TEA as an eluent to afford 37.2 mg (0.15 mmol) (58%) of the title compound **3e** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.66 – 7.61 (m, 2H), 7.55 – 7.44 (m, 3H), 7.37 (ddd, *J* = 14.6, 7.9, 6.2 Hz, 3H), 7.23 – 7.16 (m, 2H), 3.72 (t, *J* = 6.6 Hz, 2H), 3.51 (t, *J* = 6.4 Hz, 2H), 2.17 (p, *J* = 6.5 Hz, 2H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 130.1, 130.0, 128.5, 128.4, 128.3, 128.1, 127.7, 50.5, 43.2, 34.1.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{17}ClN^+$ 258.1044; Found 258.1049.

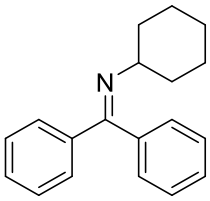
N-(3-chloropropyl)-1,1-diphenylmethanimine, 1mmol scale (3e)



Following the General Procedure C with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes with 5% TEA as an eluent to afford 65.5 mg (0.25 mmol) (51%) of the title compound **3e** as a colorless oil.

Spectral data match those described above.

N-cyclohexyl-1,1-diphenylmethanimine (3f)



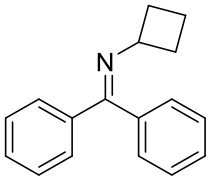
Following the General Procedure C with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (95:5) as an eluent to afford 100.4 mg (0.38 mmol) (76%) of the title compound **3f** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.4 Hz, 3H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.34 (q, *J* = 8.1, 7.3 Hz, 3H), 7.19 (d, *J* = 6.9 Hz, 2H), 3.25 (p, *J* = 7.4 Hz, 1H), 1.84 – 1.72 (m, 3H), 1.64 (dt, *J* = 8.2, 5.1 Hz, 5H), 1.35 – 1.26 (m, 2H), 1.26 – 1.13 (m, 2H), 0.91 (q, *J* = 5.5, 4.6 Hz, 1H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 165.57, 140.43, 137.55 (d, *J* = 15.0 Hz), 132.4, 130.1, 129.6, 128.4, 128.3, 128.1, 128.0, 127.7, 61.4, 34.0, 26.9, 25.7, 24.4.

Spectral data match those previously reported.[56]

N-cyclobutyl-1,1-diphenylmethanimine (3g)



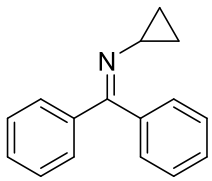
Following the General Procedure C with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (95:5) as an eluent to afford 78.9 mg (0.34 mmol) (67%) of the title compound **3g** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 6.9 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 3H), 7.36 (tt, *J* = 7.9, 3.9 Hz, 3H), 7.15 (dt, *J* = 7.2, 2.2 Hz, 2H), 4.03 (p, *J* = 7.8 Hz, 1H), 2.30 (q, *J* = 9.1, 8.6 Hz, 2H), 2.11 (tt, *J* = 11.2, 6.9 Hz, 2H), 1.93 – 1.81 (m, 1H), 1.69 (q, *J* = 10.0, 9.6 Hz, 1H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 166.6, 140.0, 137.6, 132.4, 130.1, 129.8, 128.4, 128.3, 128.3, 128.0, 127.9, 57.2, 31.5, 16.1.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}N^+$ 236.1434; Found 236.1438.

N-cyclopropyl-1,1-diphenylmethanimine (3h)



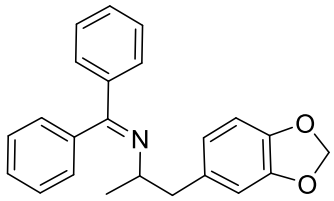
Following the General Procedure C with the corresponding NHPI ester (0.5 mmol) and aniline (0.25 mmol). The crude product was purified by LC hexanes with 5% TEA as an eluent to afford 23 mg (0.1 mmol) (42%) of the title compound **3h** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.60 – 7.53 (m, 2H), 7.52 – 7.41 (m, 3H), 7.37 – 7.30 (m, 5H), 2.91 (tt, *J* = 6.8, 3.4 Hz, 1H), 1.05 (p, *J* = 4.2 Hz, 2H), 0.89 – 0.81 (m, 2H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 129.4, 128.5, 128.4, 128.0, 36.0, 10.0.

Spectral data match those previously reported.[57]

N-(1-(benzo[d][1,3]dioxol-5-yl)propan-2-yl)-1,1-diphenylmethanimine (3i)



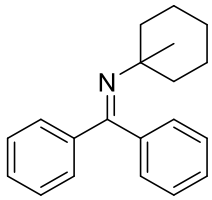
Following the General Procedure C with the corresponding NHPI ester (0.5 mmol) and aniline (0.25 mmol). The crude product was purified by LC hexanes with 5% TEA as an eluent to afford 42 mg (0.12 mmol) (49%) of the title compound **3i** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.87 – 7.82 (m, 1H), 7.65 – 7.47 (m, 4H), 7.41 – 7.32 (m, 5H), 6.88 – 6.45 (m, 3H), 5.91 (q, *J* = 1.4 Hz, 2H), 3.67 – 3.52 (m, 1H), 2.90 – 2.66 (m, 2H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.84 (dd, *J* = 9.6, 6.6 Hz, 1H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 133.7, 132.4, 130.1, 129.7, 128.3, 128.3, 128.2, 128.0, 127.5, 122.5, 110.0, 107.9, 100.6, 59.6, 44.5, 22.0.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}NO_2^+$ 344.1645; Found 344.1652.

N-(1-methylcyclohexyl)-1,1-diphenylmethanimine (3j)



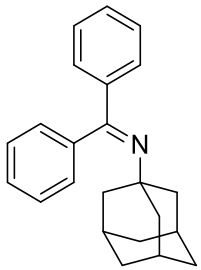
Following the General Procedure C with the corresponding NHPI ester (0.5 mmol) and aniline (0.25 mmol). The crude product was purified by LC hexanes with 5% TEA as an eluent to afford 25 mg (0.1 mmol) (36%) of the title compound **3j** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.62 – 7.56 (m, 2H), 7.43 – 7.37 (m, 3H), 7.36 – 7.27 (m, 3H), 7.26 – 7.20 (m, 2H), 1.81 – 1.50 (m, 5H), 1.45 (dq, *J* = 13.7, 4.4 Hz, 2H), 1.37 – 1.22 (m, 5H), 1.08 (s, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 163.6, 142.3, 129.3, 128.1, 128.0, 127.9, 127.8, 127.8, 58.6, 40.4, 26.1, 22.9.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}N^+$ 278.1903; Found 278.1904.

N-(adamantan-1-yl)-1,1-diphenylmethanimine (3k)



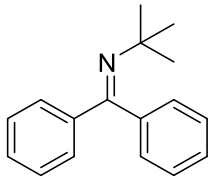
Following the General Procedure C with the corresponding NHPI ester (0.5 mmol) and aniline (0.25 mmol). The crude product was purified by LC hexanes with 5% TEA as an eluent to afford 35 mg (0.11 mmol) (44%) of the title compound **3k** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.59 – 7.54 (m, 2H), 7.42 – 7.38 (m, 3H), 7.34 – 7.27 (m, 3H), 7.24 – 7.19 (m, 2H), 1.99 (t, *J* = 3.3 Hz, 3H), 1.76 (d, *J* = 2.9 Hz, 6H), 1.65 – 1.52 (m, 6H), 1.28 (s, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 129.2, 128.3, 128.0, 127.8, 127.8, 127.7, 58.0, 44.2, 36.4, 29.8.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{26}N^+$ 316.2060; Found 316.2064.

N-tert-butyl-1,1-diphenylmethanimine (3l)



Following the General Procedure C with the corresponding NHPI ester (1 mmol) and aniline (0.5 mmol). The crude product was purified by LC hexanes / EtOAc (98:2) as an eluent to afford 78 mg (0.33 mmol) (66%) of the title compound **3l** as a colorless oil.

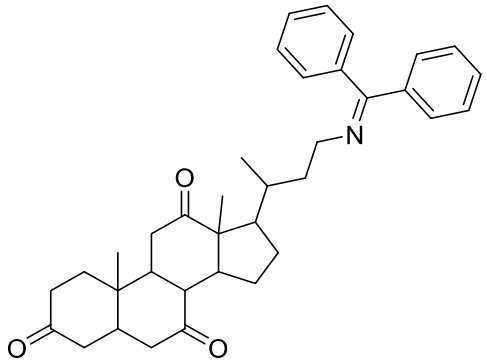
^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.88 – 7.82 (m, 2H), 7.60 (ddd, *J* = 15.3, 7.8, 2.0 Hz, 3H), 7.52 (td, *J* = 7.7, 7.2, 4.0 Hz, 2H), 7.45 – 7.40 (m, 3H), 7.38 – 7.28 (m, 3H), 7.26 – 7.21 (m, 2H), 1.27 – 1.15 (m, 9H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 196.8, 163.6, 142.1, 139.9, 137.6, 132.4, 130.1, 129.3, 128.5, 128.3, 128.1, 127.9, 127.8, 127.8, 57.0, 31.6.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}N^+$ 238.1590; Found 238.1595.

Spectral data match those previously reported**.**[56]

17-(4-((diphenylmethylene)amino)butan-2-yl)-10,13-dimethyldodecahydro-3H-cyclopenta[a]phenanthrene-3,7,12(2H,4H)-trione (3m)



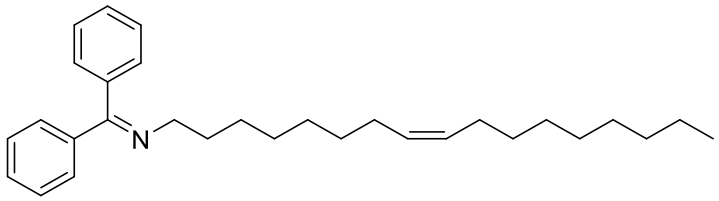
Following the General Procedure C with the corresponding NHPI ester (0.5 mmol) and aniline (0.25 mmol). The crude product was purified by LC hexanes with 5% TEA 20% ethyl acetate as an eluent to afford 63 mg (0.12 mmol) (47%) of the title compound **3m** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.65 – 7.57 (m, 2H), 7.51 – 7.42 (m, 3H), 7.40 – 7.31 (m, 3H), 7.22 – 7.15 (m, 2H), 4.03 (s, 3H), 3.86 (dp, *J* = 7.8, 6.4 Hz, 3H), 3.57 – 3.30 (m, 2H), 3.08 – 2.79 (m, 6H), 2.44 – 2.20 (m, 7H), 2.09 – 1.94 (m, 3H), 1.92 – 1.83 (m, 2H), 1.41 (s, 3H), 1.16 (d, *J* = 6.5 Hz, 20H), 0.78 (d, *J* = 6.3 Hz, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 129.7, 128.4, 128.3, 128.3, 128.0, 127.8, 56.9, 51.7, 51.7, 49.0, 46.9, 46.0, 45.6, 45.0, 42.8, 42.2, 38.7, 36.9, 36.5, 36.0, 35.3, 34.4, 27.7, 25.2, 23.5, 21.9, 19.1, 11.9.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{44}NO_3^+$ 538.3316; Found 538.3315.

(Z)-N-(heptadec-8-en-1-yl)-1,1-diphenylmethanimine (3n)



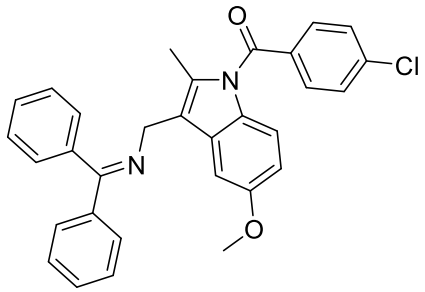
Following the General Procedure C with the corresponding NHPI ester (0.5 mmol) and aniline (0.25 mmol). The crude product was purified by LC hexanes with 5% TEA as an eluent to afford 118.6 mg (0.14 mmol) (57%) of the title compound **3n** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.65 – 7.60 (m, 2H), 7.55 – 7.43 (m, 3H), 7.41 – 7.31 (m, 2H), 7.22 – 7.16 (m, 2H), 5.45 – 5.30 (m, 1H), 3.39 (t, *J* = 7.1 Hz, 2H), 2.03 (qt, *J* = 6.4, 3.4 Hz, 4H), 1.40 – 1.23 (m, 25H), 0.99 – 0.83 (m, 4H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 132.4, 130.1, 129.9, 129.9, 128.4, 128.3, 128.0, 127.9, 31.9, 31.2, 29.8, 29.5, 29.4, 29.3, 29.3, 27.5, 27.2, 22.7, 14.1.

HRMS: (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{44}N^+$ 418.3468; Found 418.3463.

(4-chlorophenyl)(3-(((diphenylmethylene)amino)methyl)-5-methoxy-2-methyl-1H-indol-1-yl)methanone (3o)



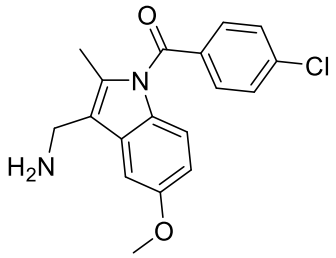
Following the General Procedure C with the corresponding NHPI ester (0.5 mmol) and aniline (0.25 mmol). The crude product was purified by LC hexanes with 5% TEA 10% ethyl acetate as an eluent to afford 92.32 mg (0.18 mmol) (73%) of the title compound **3o** as a colorless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.58 (d, *J* = 8.5 Hz, 2H), 7.47 – 7.41 (m, 3H), 7.40 – 7.37 (m, 3H), 7.33 (d, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H), 6.63 (dd, *J* = 9.0, 2.6 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 2H), 2.05 (s, 3H).

^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 183.0, 168.1, 164.7, 156.0, 139.2, 136.2, 131.0, 130.9, 129.3, 129.1, 128.1, 114.8, 111.9, 111.7, 101.1, 55.7, 34.0, 13.1.

HRMS: (APPI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{26}ClN_2O_2^+$ 493.1677; Found 493.1664.

(3-(aminomethyl)-5-methoxy-2-methyl-1H-indol-1-yl)(4-chlorophenyl)methanone (3p)



Following the General Procedure C with the corresponding NHPI ester (2 mmol) and aniline (1 mmol). The crude product was purified by LC hexanes with 5% TEA 10% ethyl acetate as an eluent. The imine was dissolved in methanol (7.5 mL) and 0.75 mL of HCl 1M was added dropwise. After 1 hour 12.5 mL of diethyl ether were added and the suspension was filtered and washed with additional ether. The solvent was evaporated under reduced pressure. 5 mL of ether and 5 mL of water were added. The organic layer was separated and the water was washed with additional ether. The combined organic layers were dried on anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The solid was dissolved in the minimum quantity of DCM and 20 mL of hexanes at 0°C were added. The precipitate is collected and washed with more hexane to afford 224 mg (0.68 mmol) (68%) of the title compound **3p** as a white solid.

^{1}H NMR: ($CDCl_3$, 400 MHz)δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.73 (dd, *J* = 9.0, 2.5 Hz, 1H), 5.60 (bs, *J* = 18.0 Hz, 1H), 5.36 (bs, 1H), 3.86 (s, 3H), 3.68 (s, 2H), 2.44 (s, 3H).

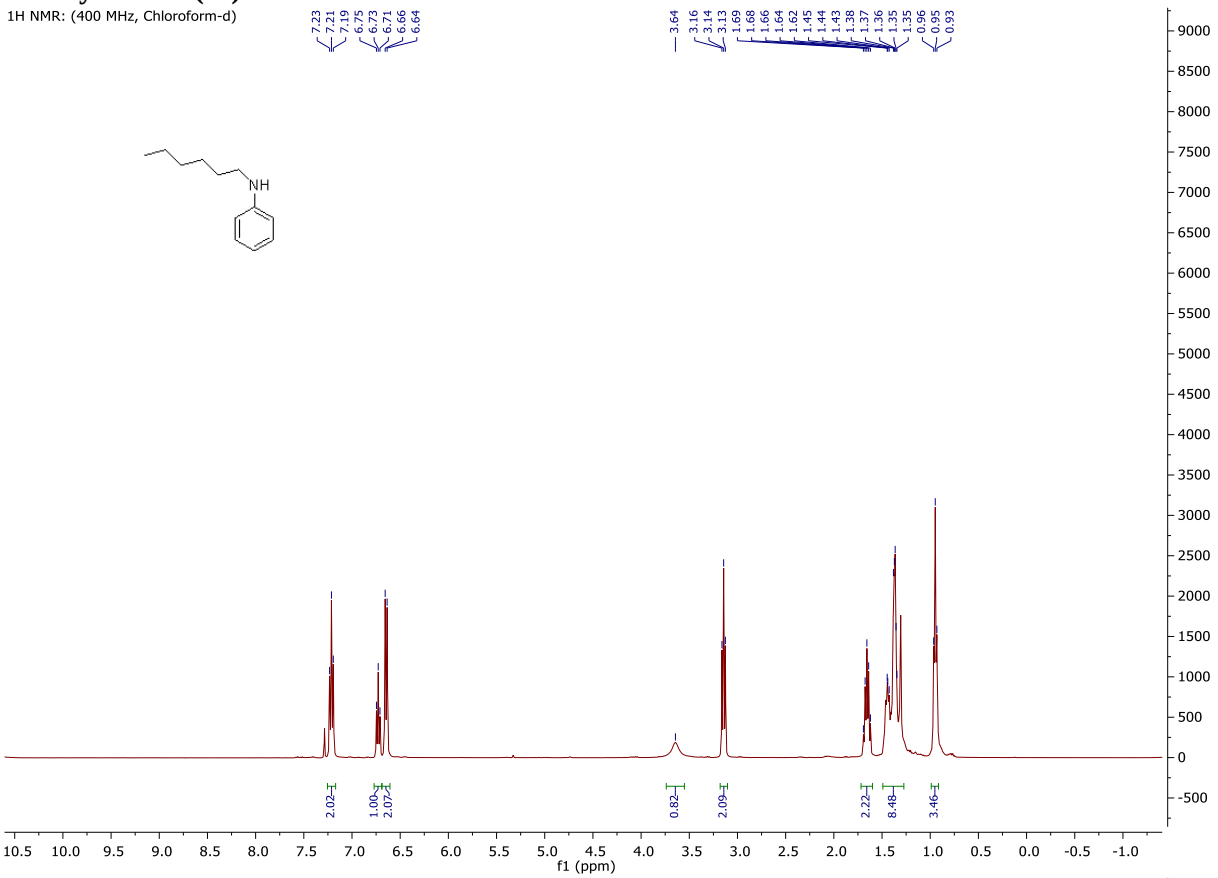
^{13}C {^{1}H} NMR: ($CDCl_3$, 101 MHz) δ 172.3, 156.3, 139.6, 131.2, 129.3, 115.1, 113.0, 112.3, 100.8, 55.8, 31.8, 13.2.

Spectral data match those previously reported.[58]

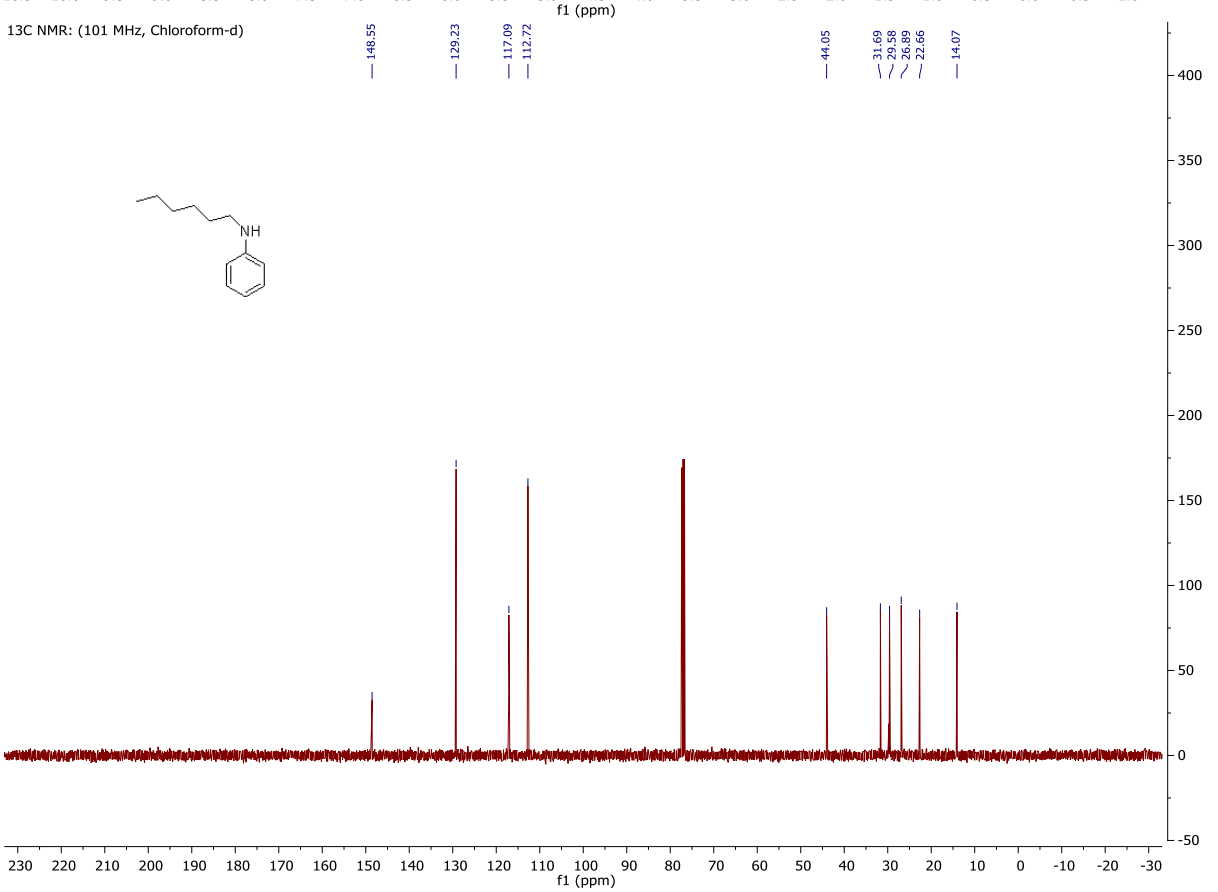
3.5 NMR Spectra

N-hexylaniline (1c)

1H NMR: (400 MHz, Chloroform-d)

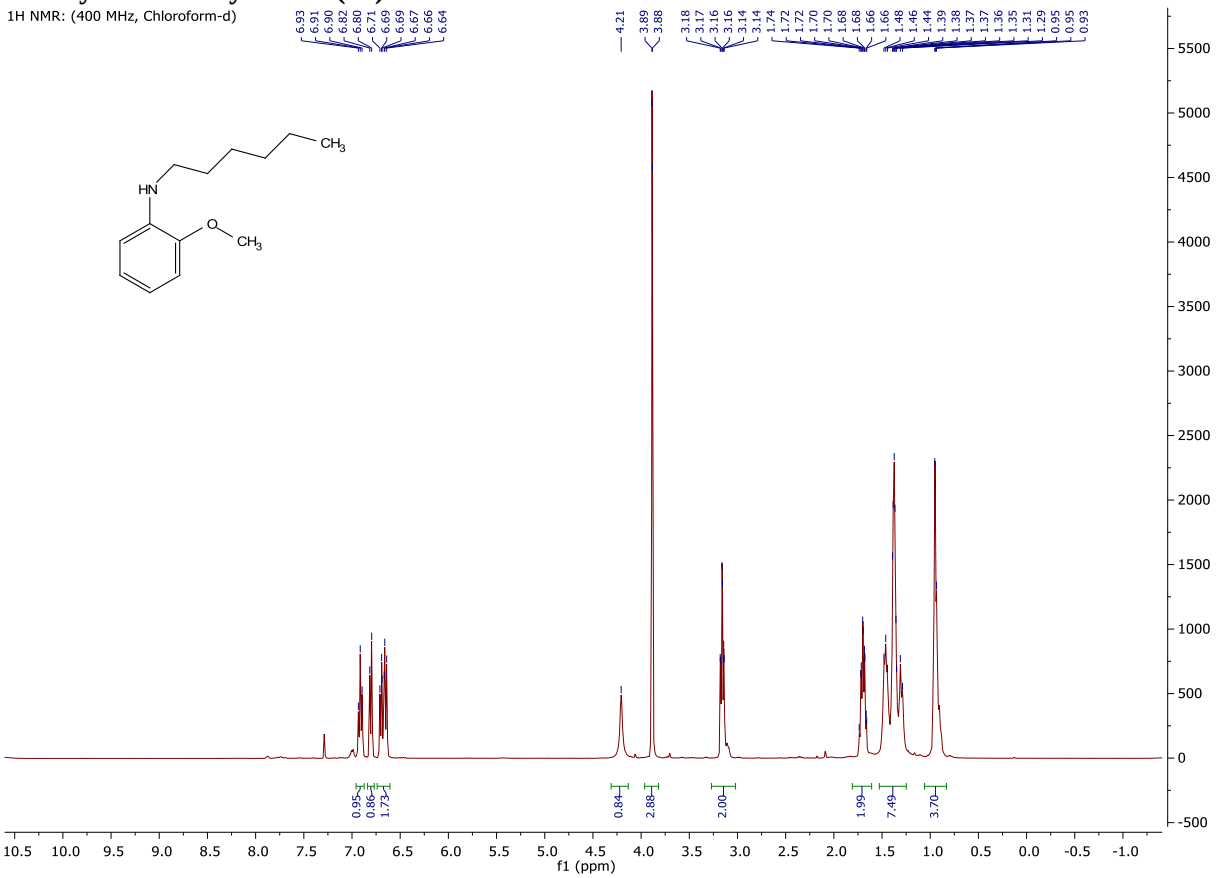


13C NMR: (101 MHz, Chloroform-d)

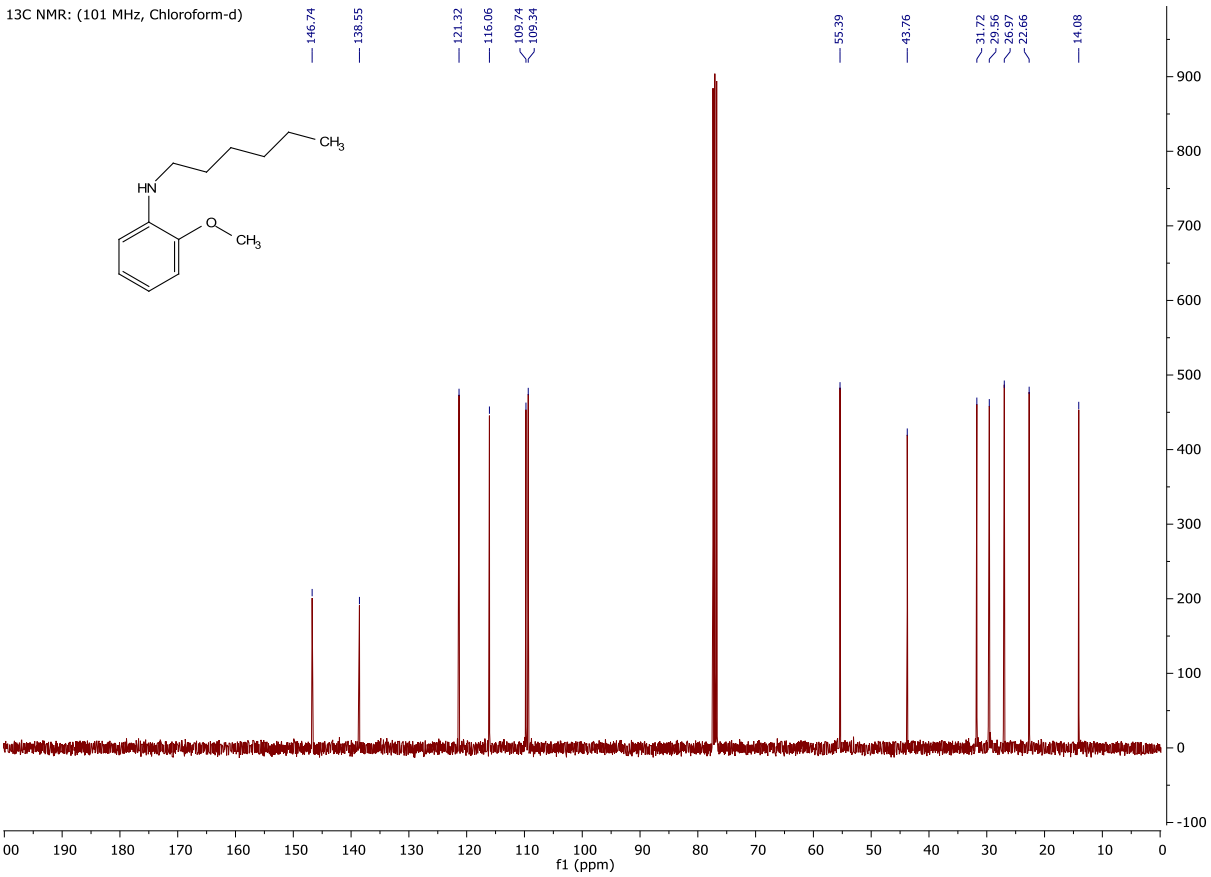


N-hexyl-2-methoxyaniline (2a)

1H NMR: (400 MHz, Chloroform-d)

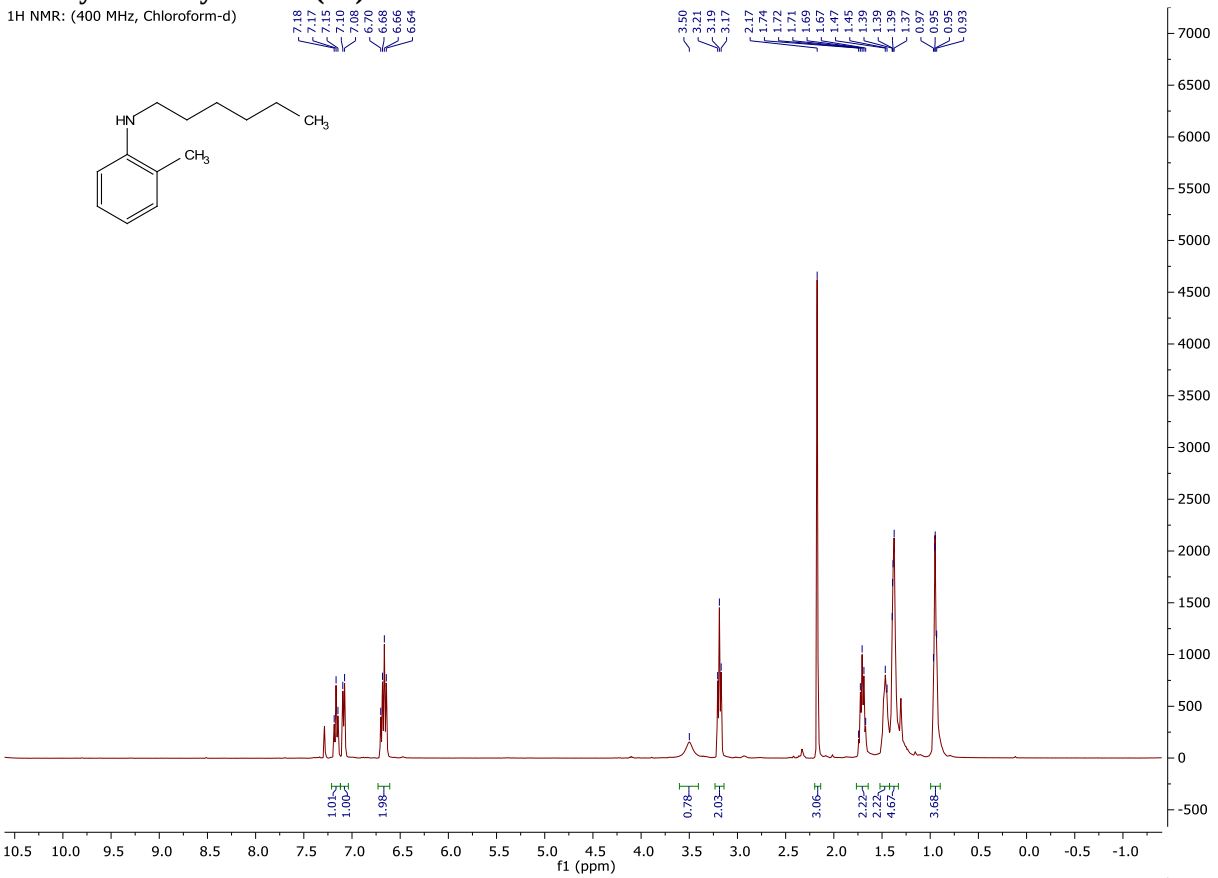


13C NMR: (101 MHz, Chloroform-d)

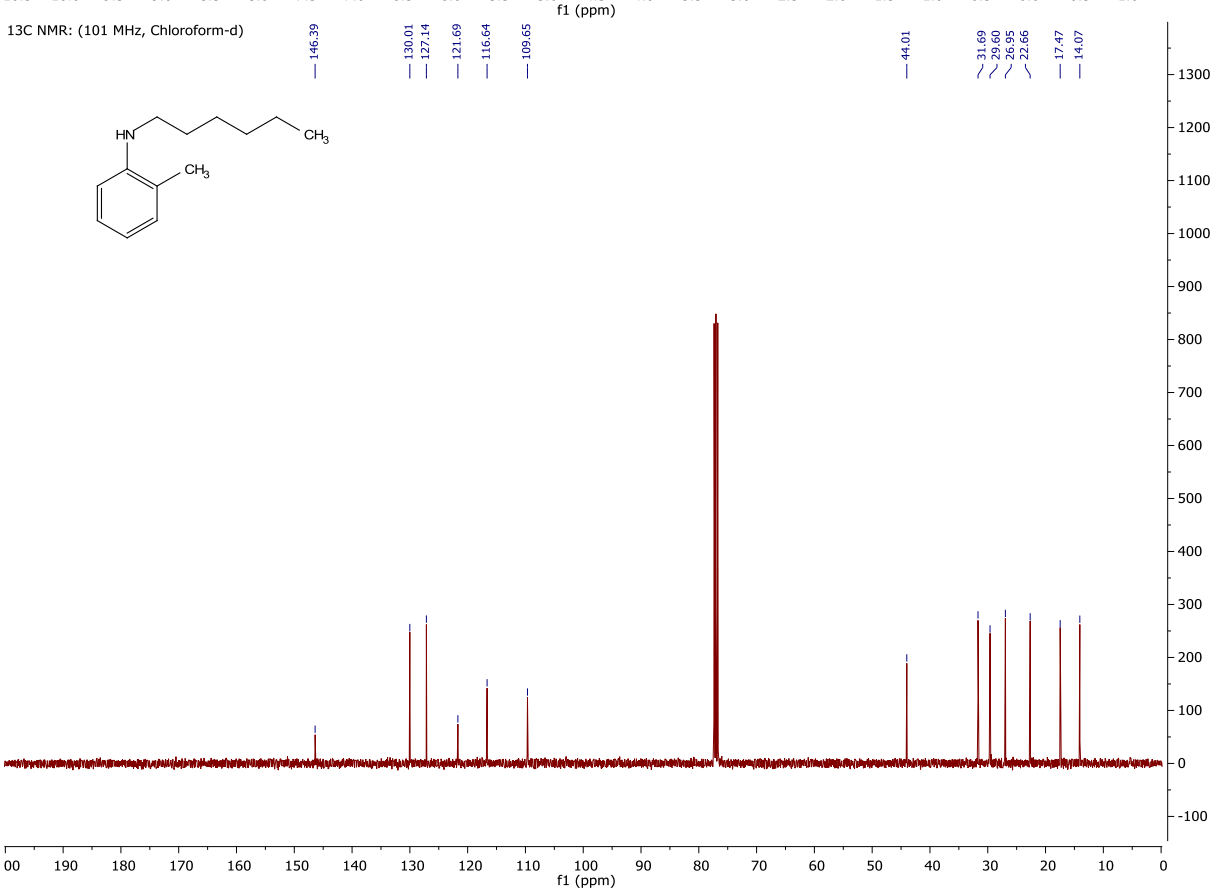


N-hexyl-2-methylaniline (2b)

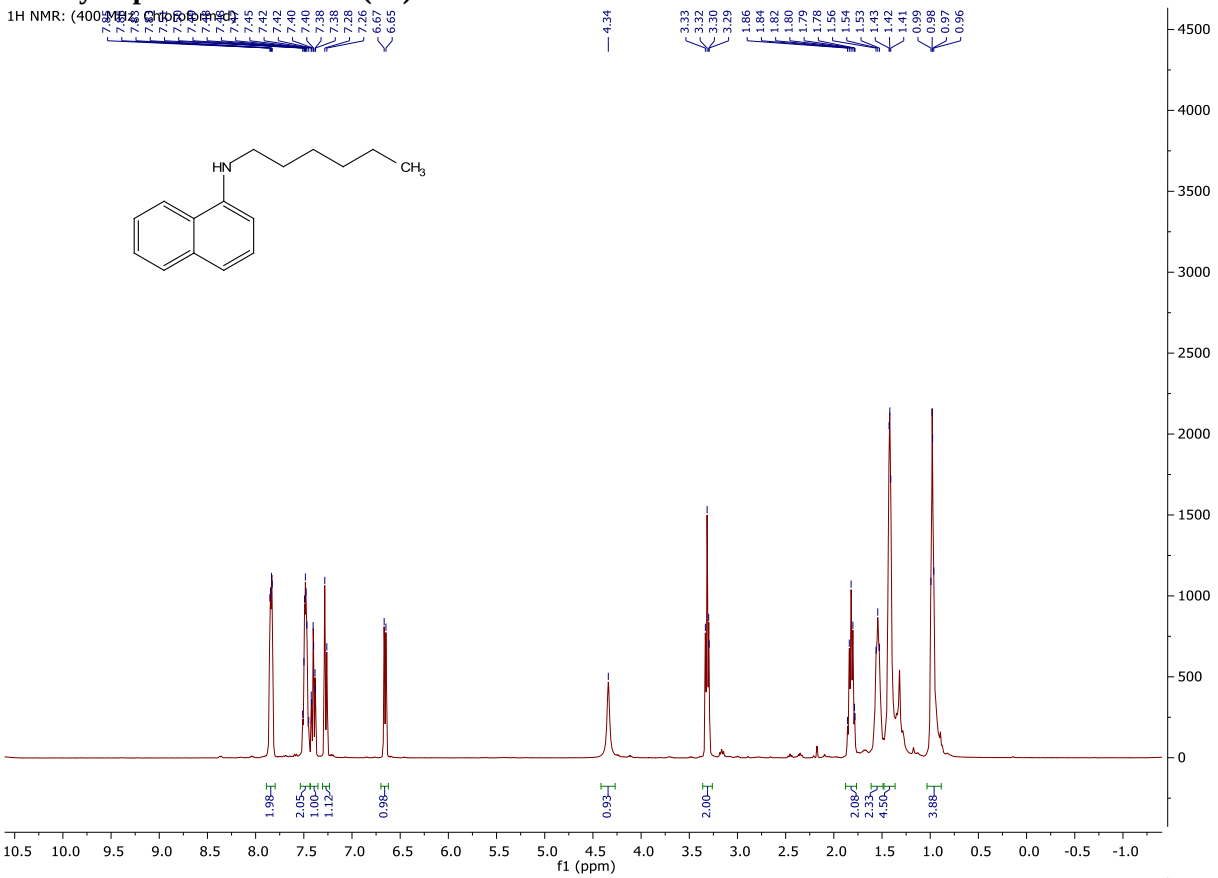
1H NMR: (400 MHz, Chloroform-d)

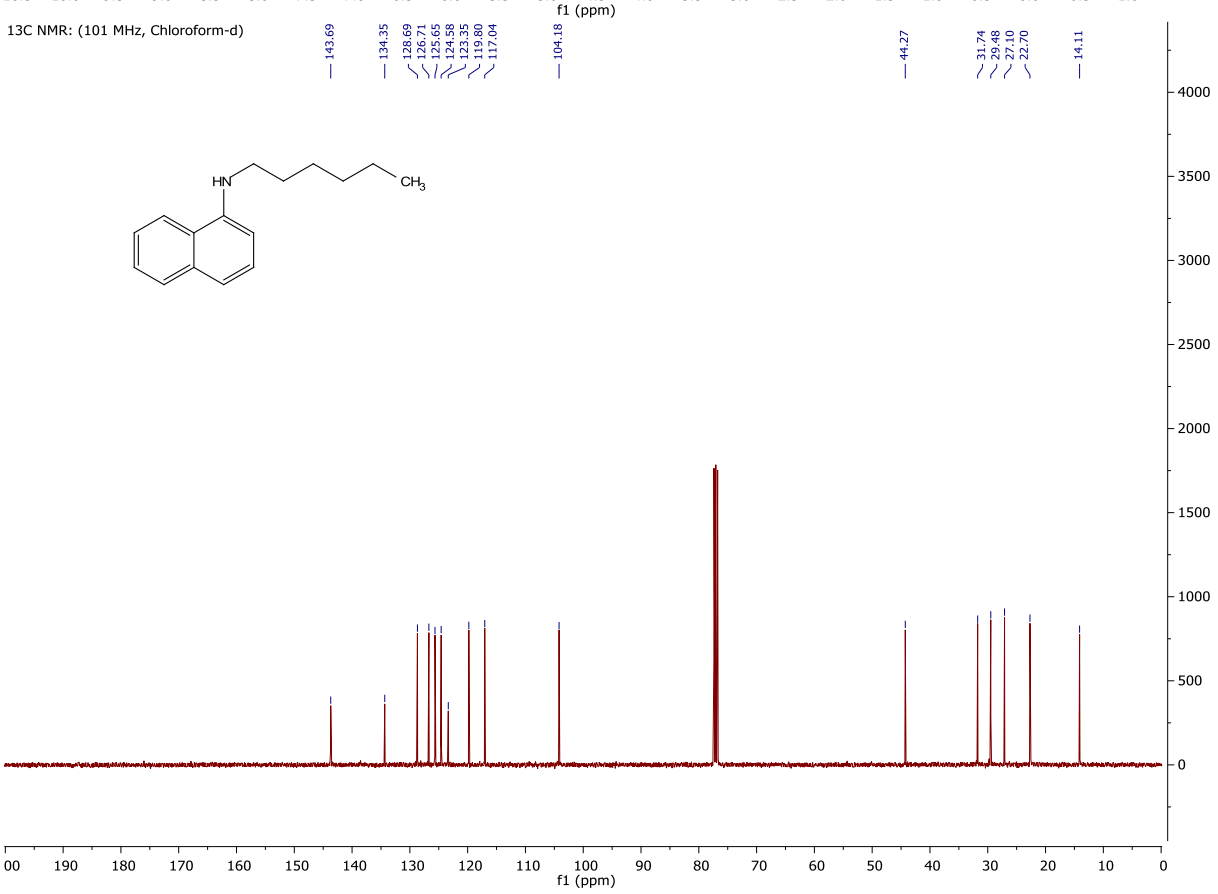


13C NMR: (101 MHz, Chloroform-d)

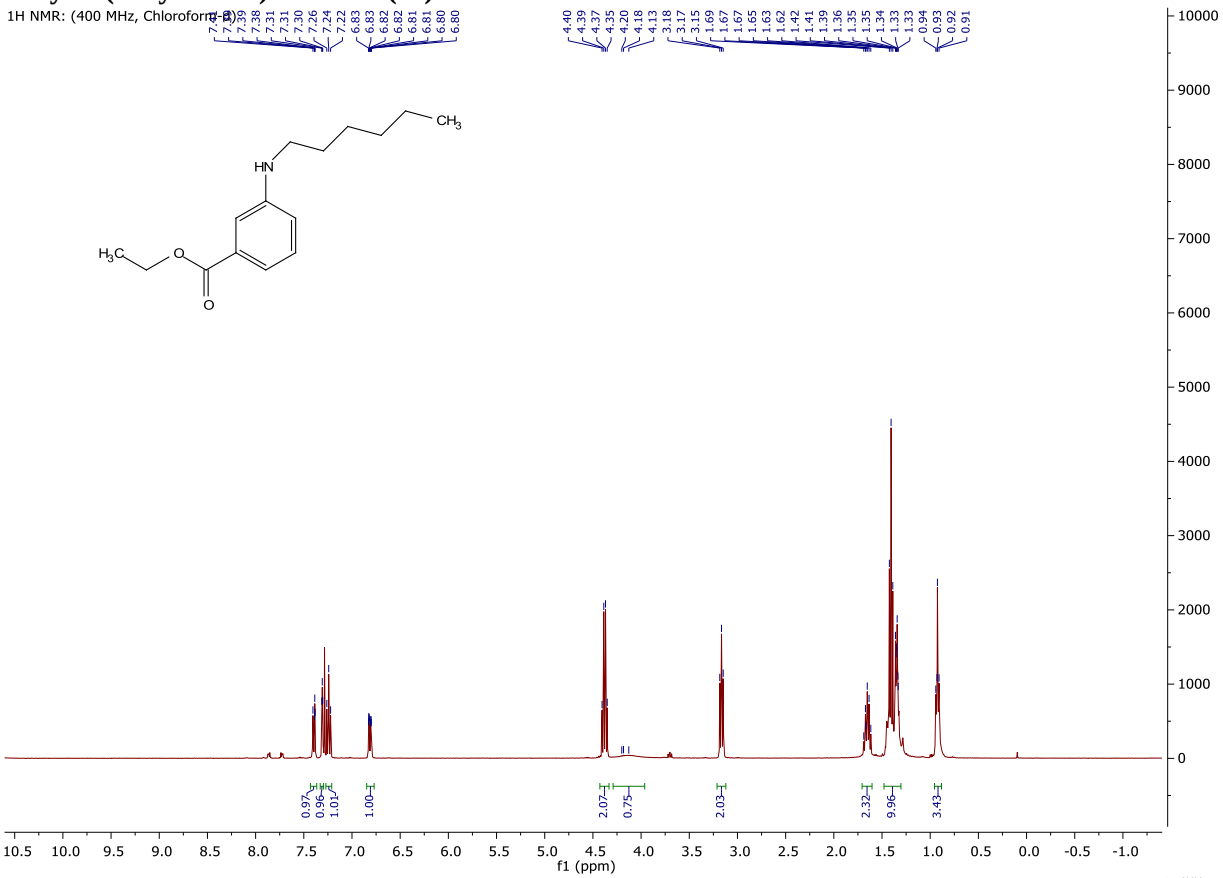


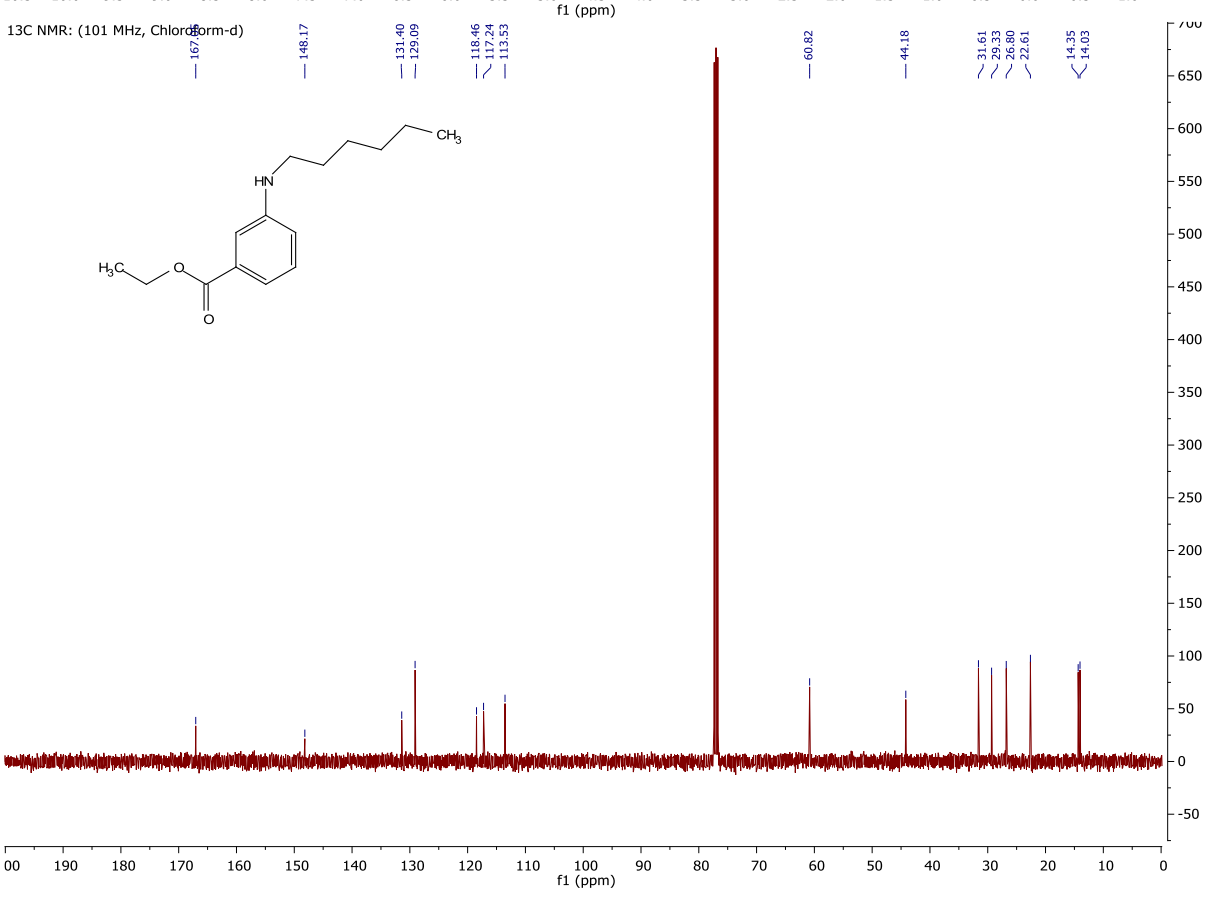
N-hexylnaphthalen-1-amine (2d)



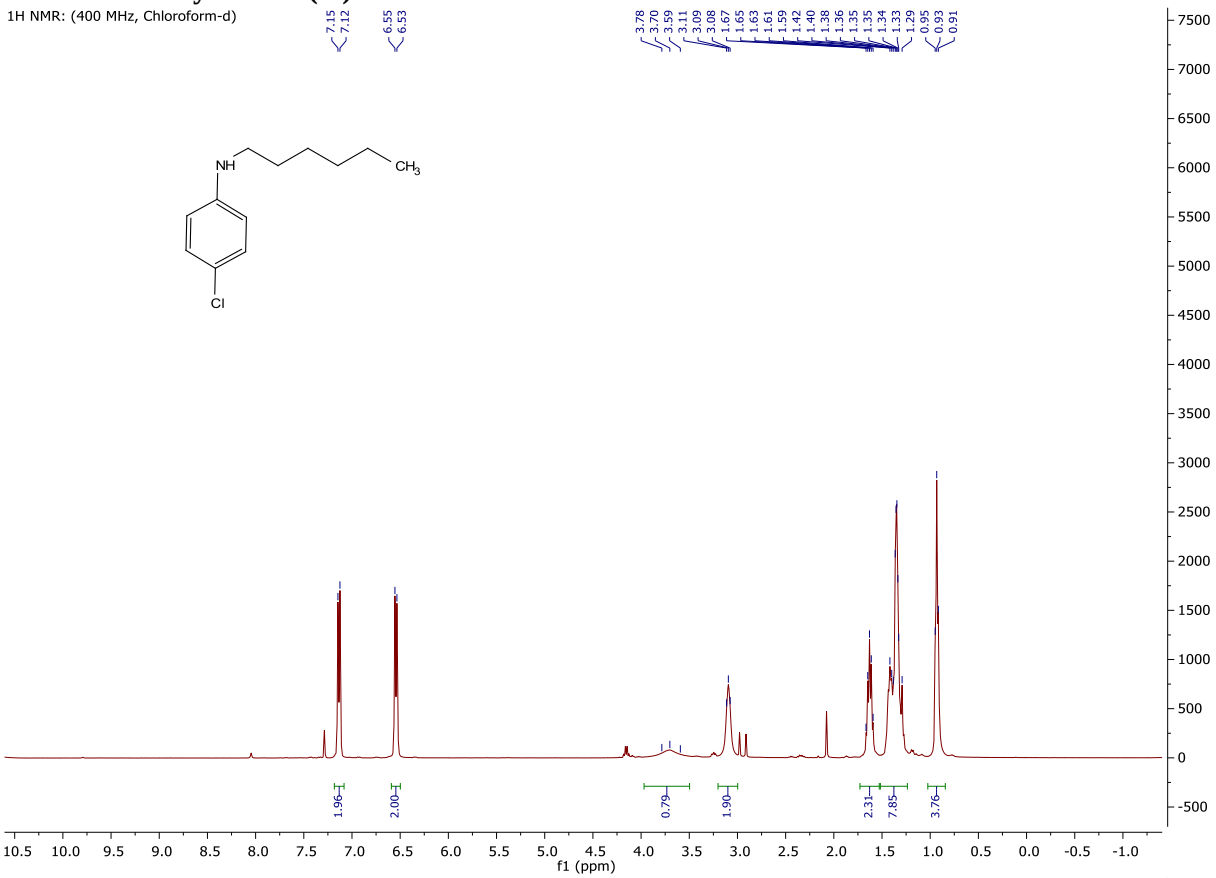


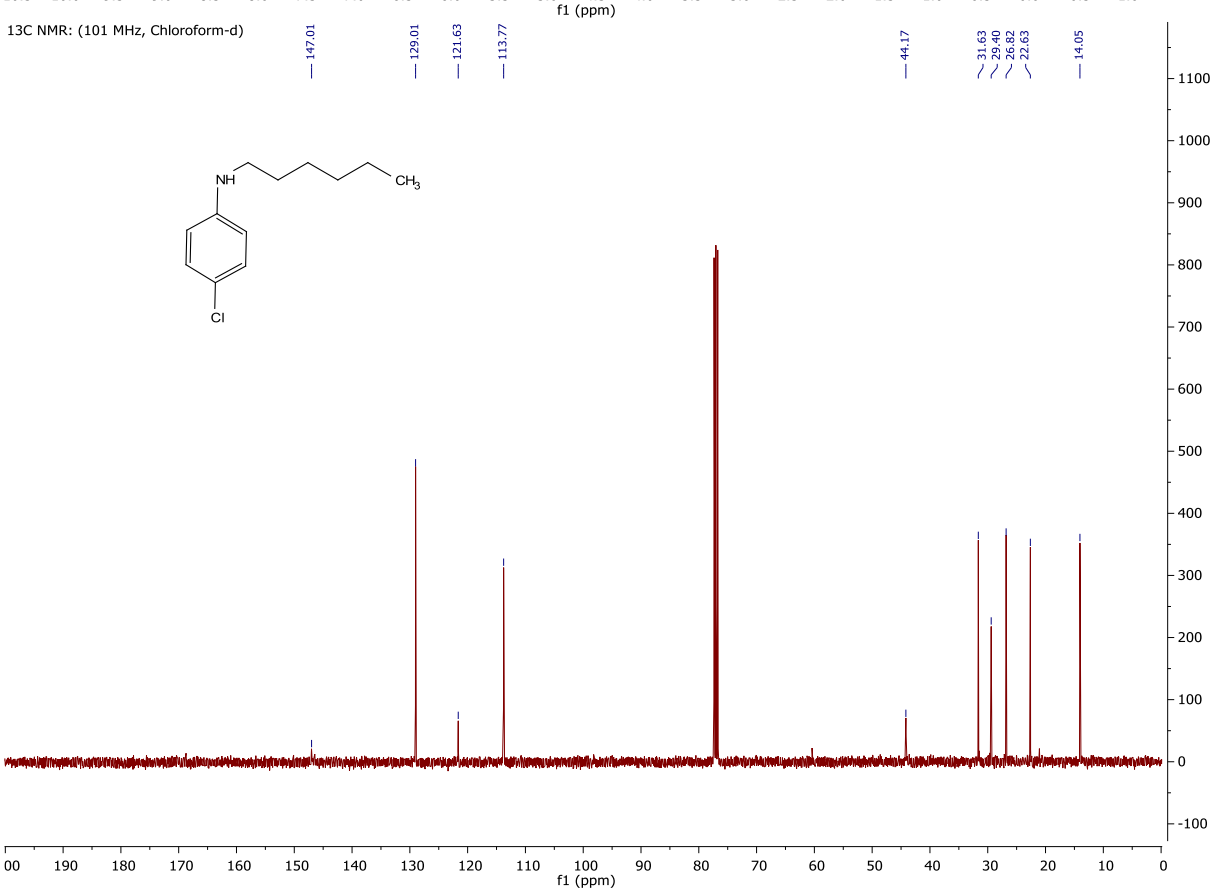
Ethyl 3-(hexylamino)benzoate (2e)



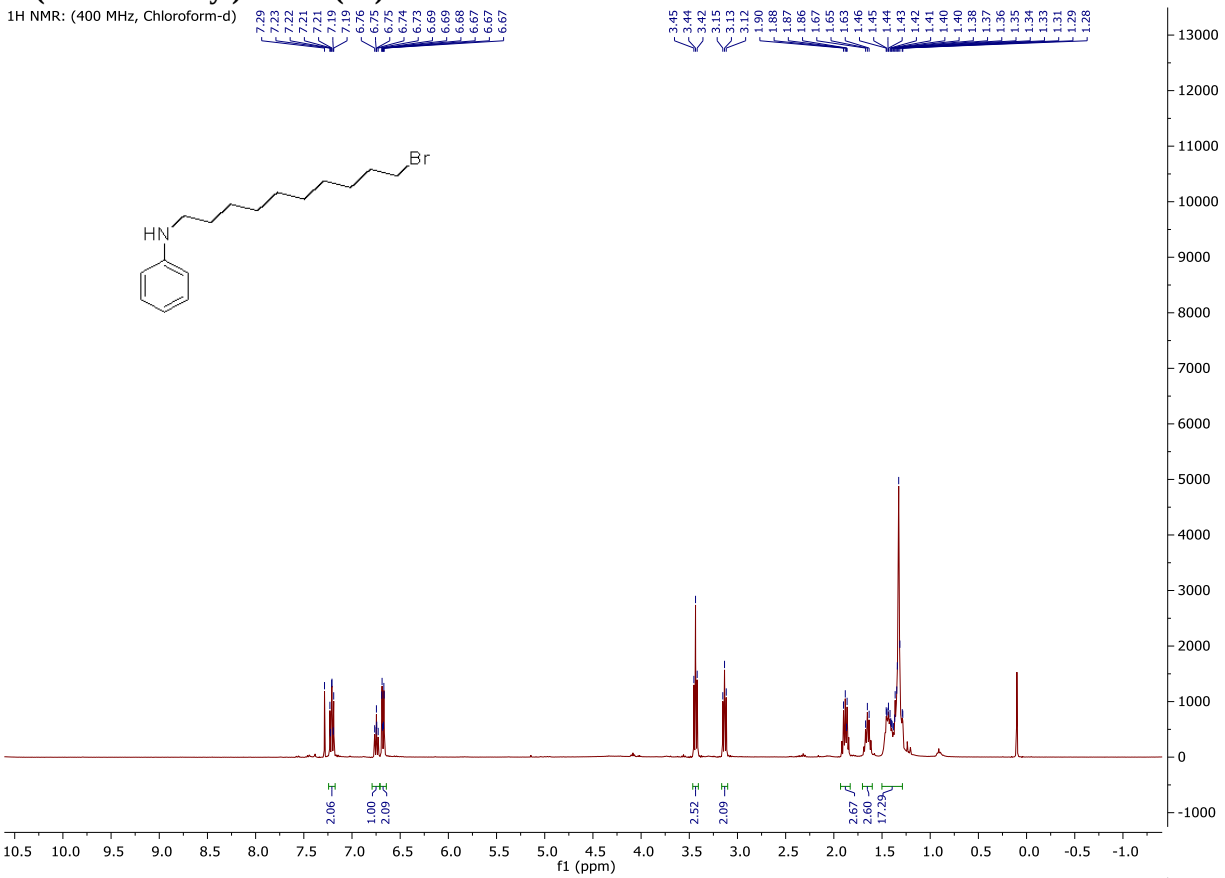


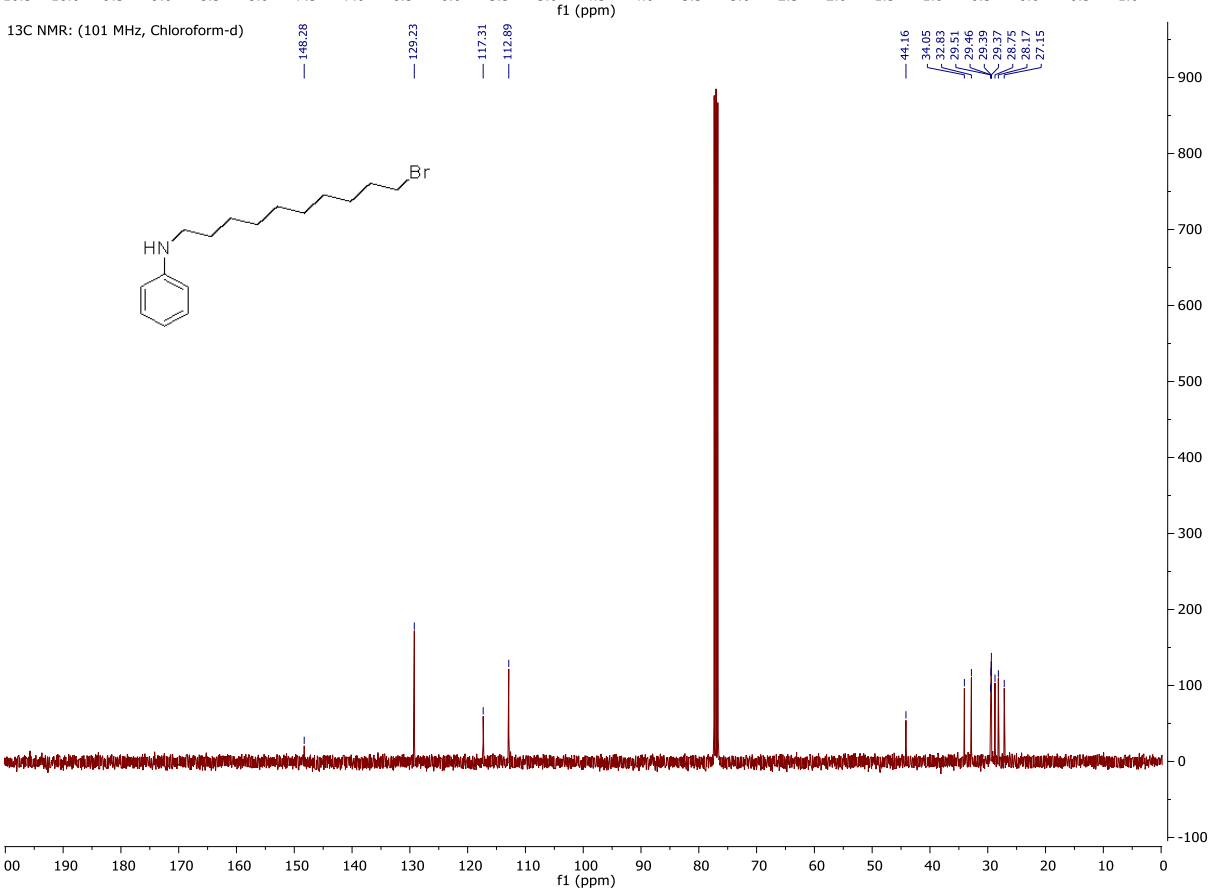
4-chloro-N-hexylaniline (2f)



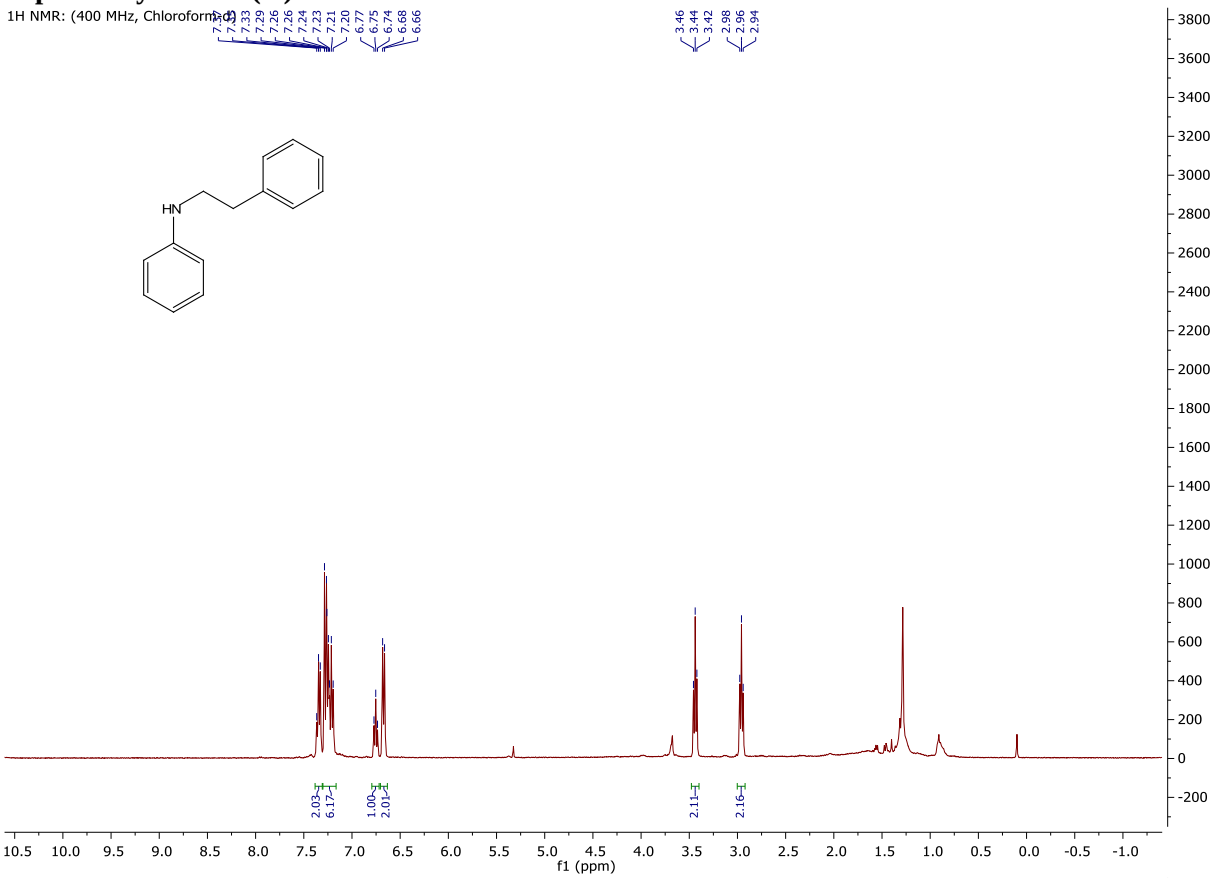


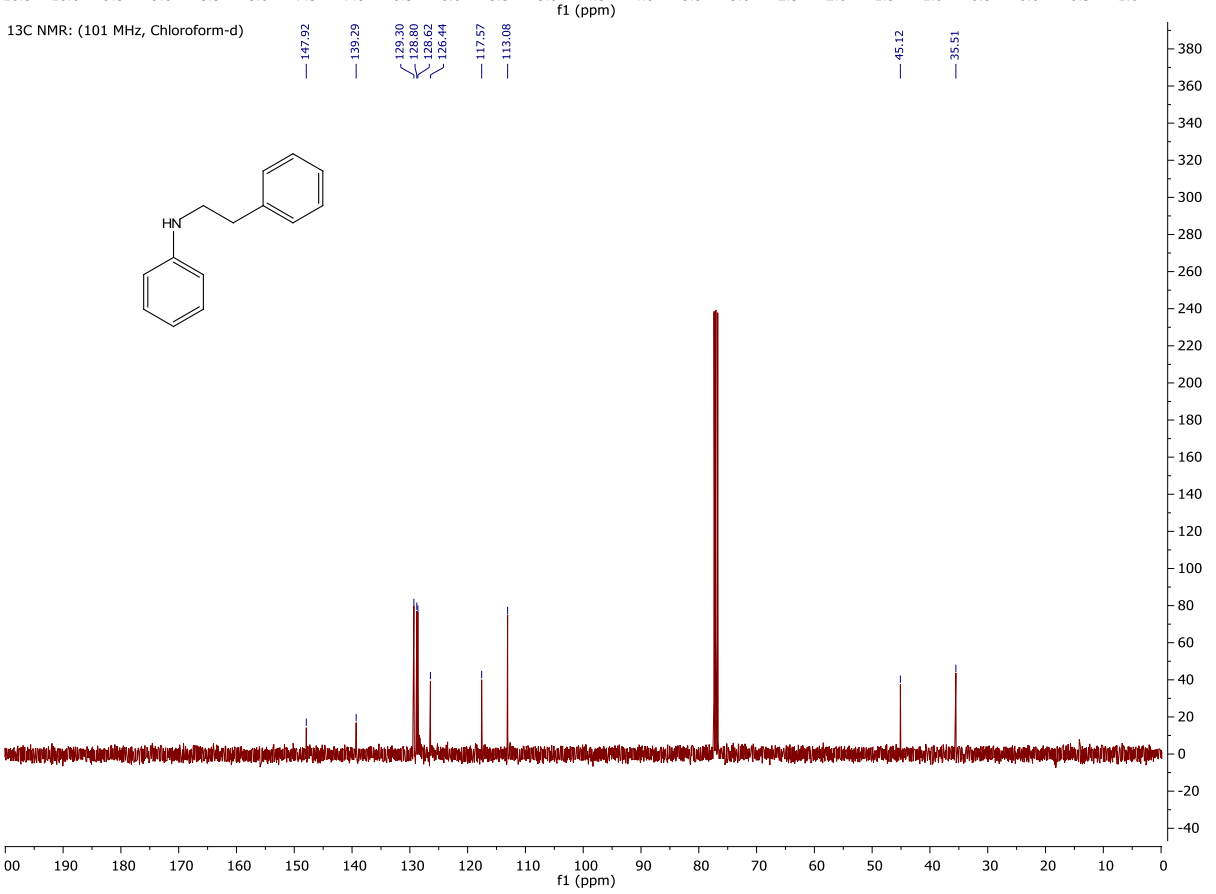
N-(10-bromodecyl)aniline (2h)



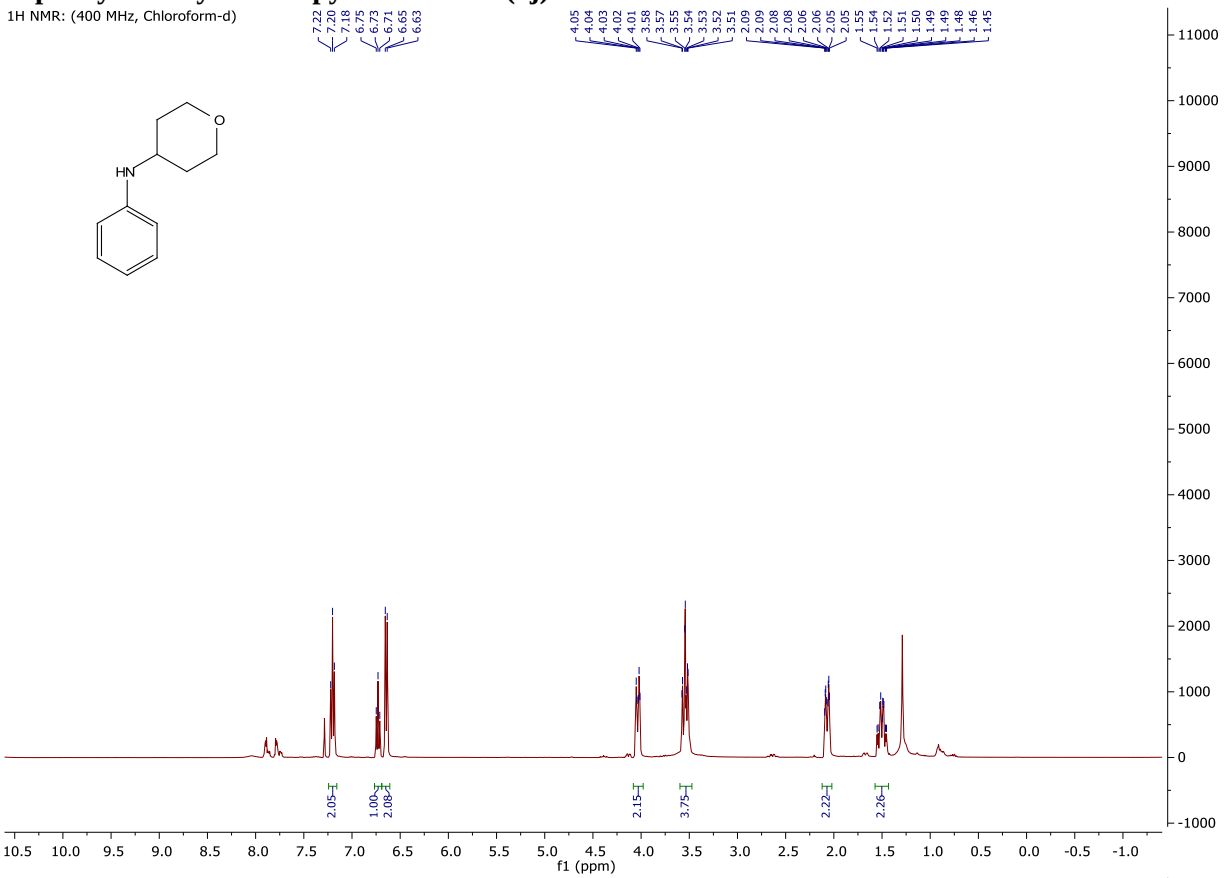


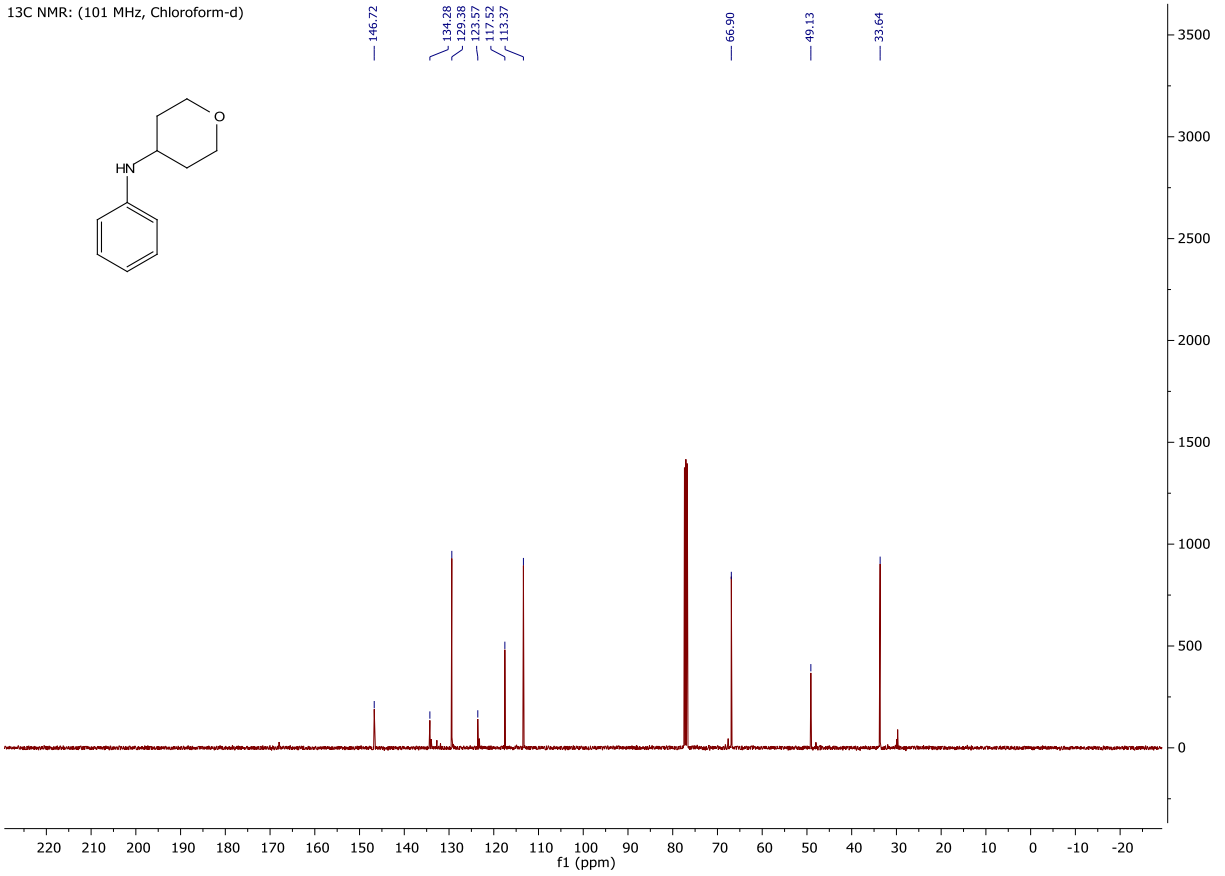
N-phenethylaniline (2i)



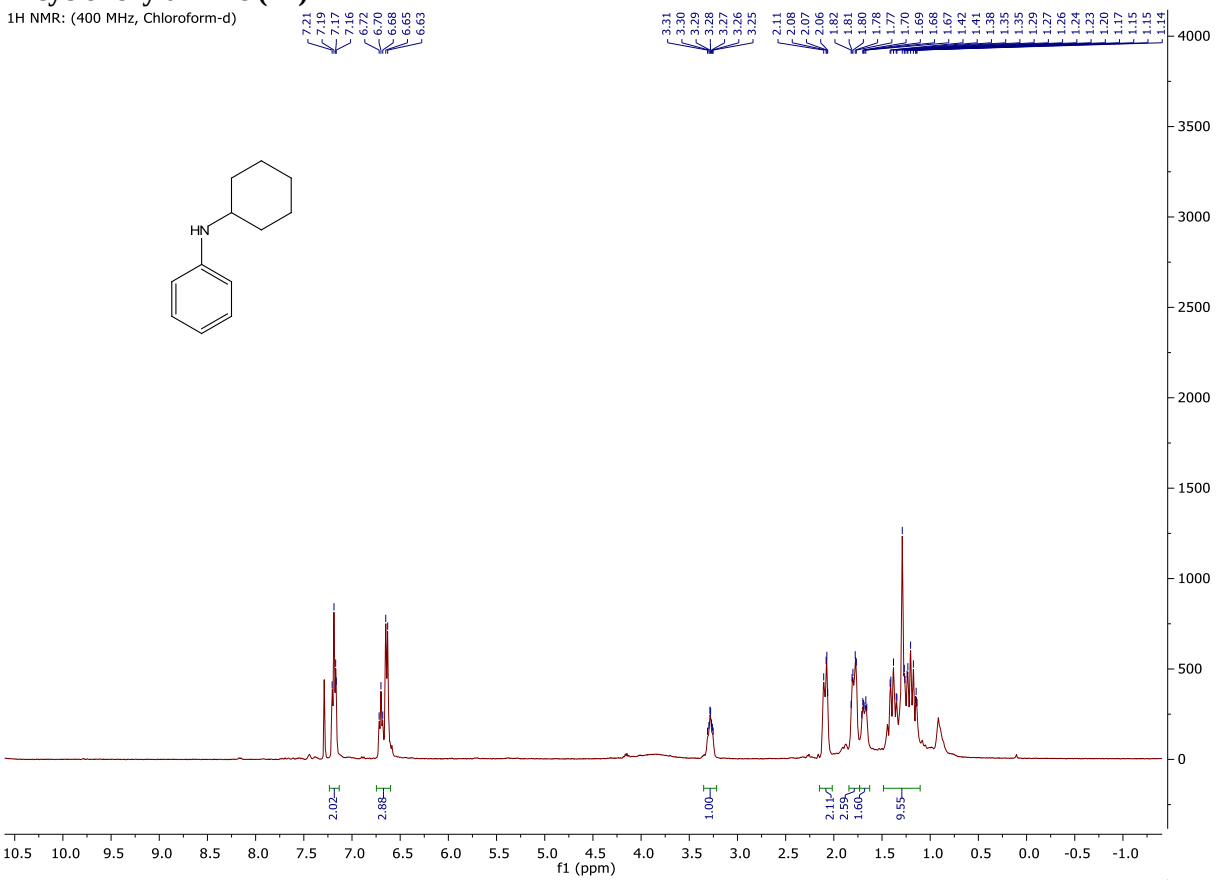


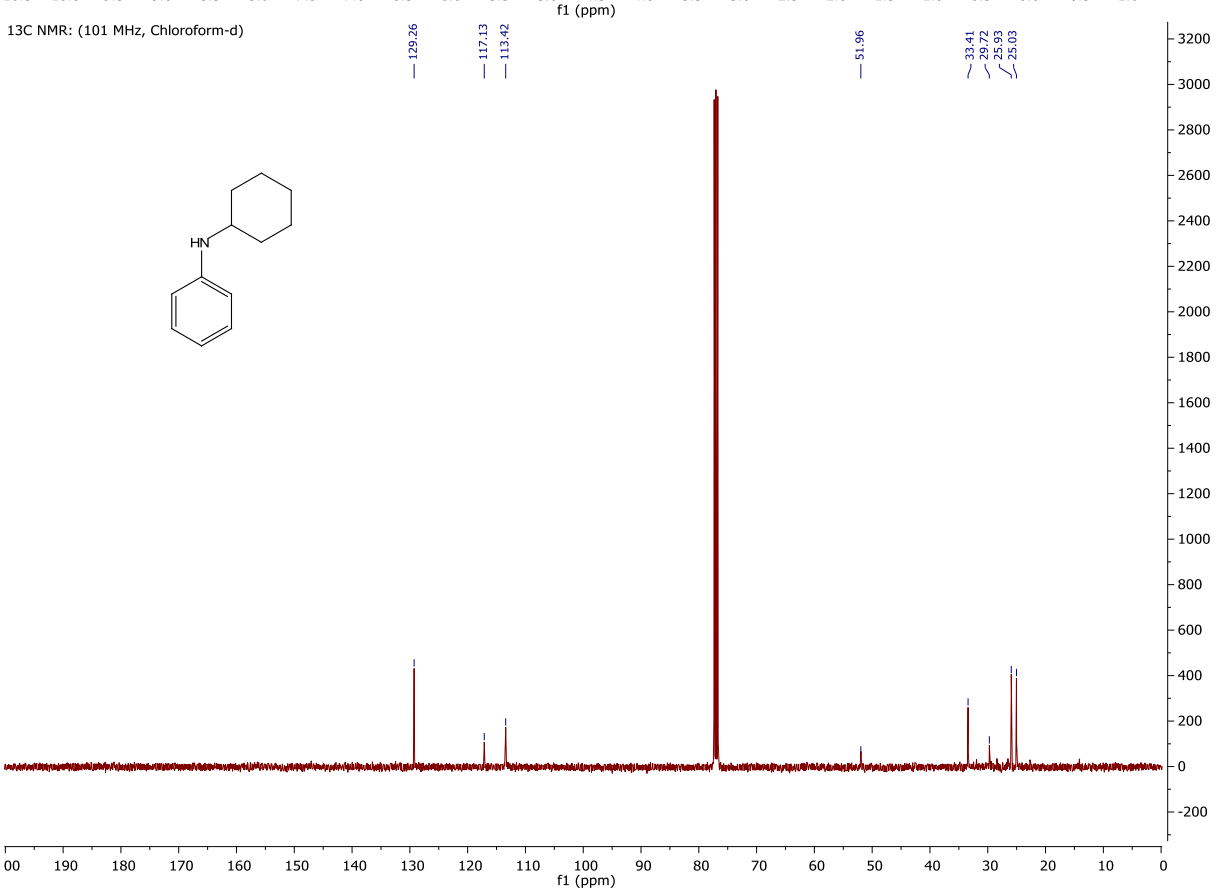
N-phenyltetrahydro-2H-pyran-4-amine (2j)



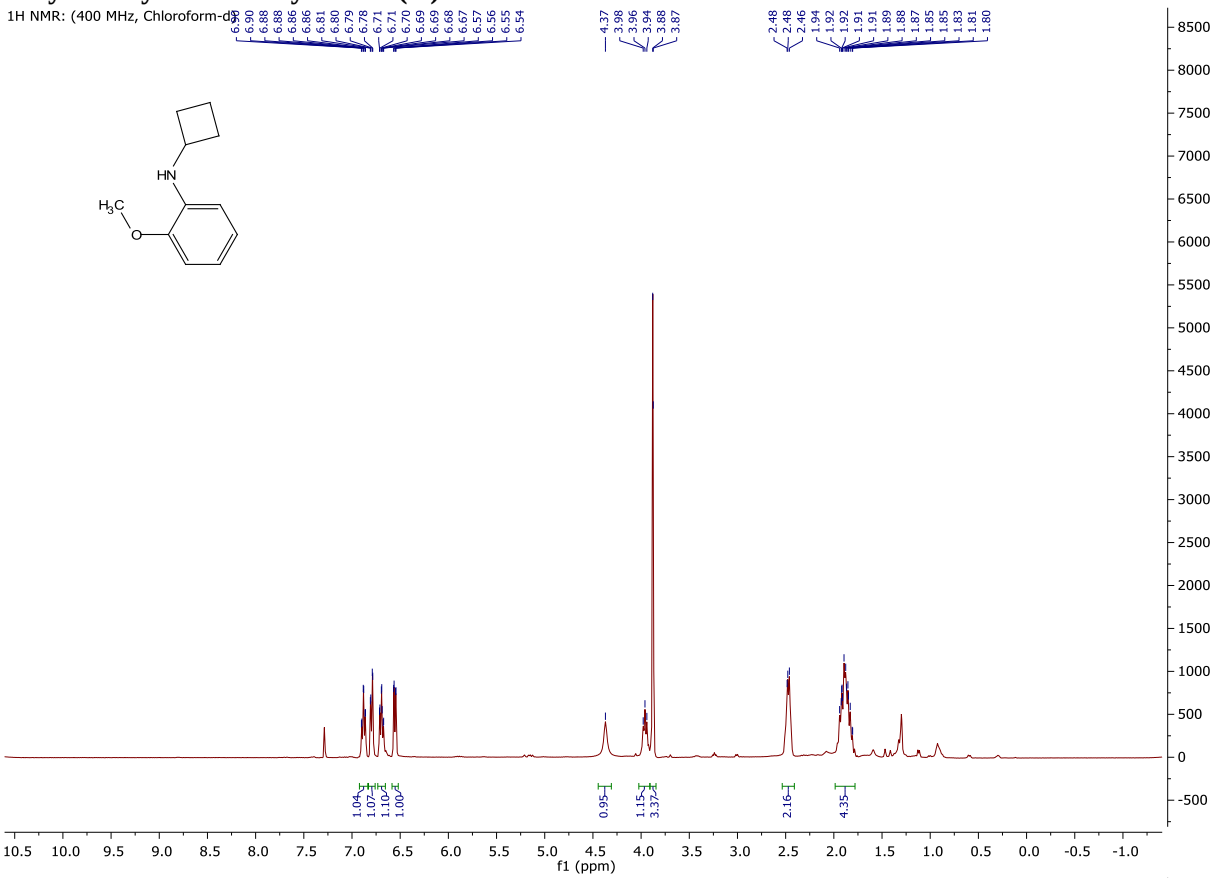


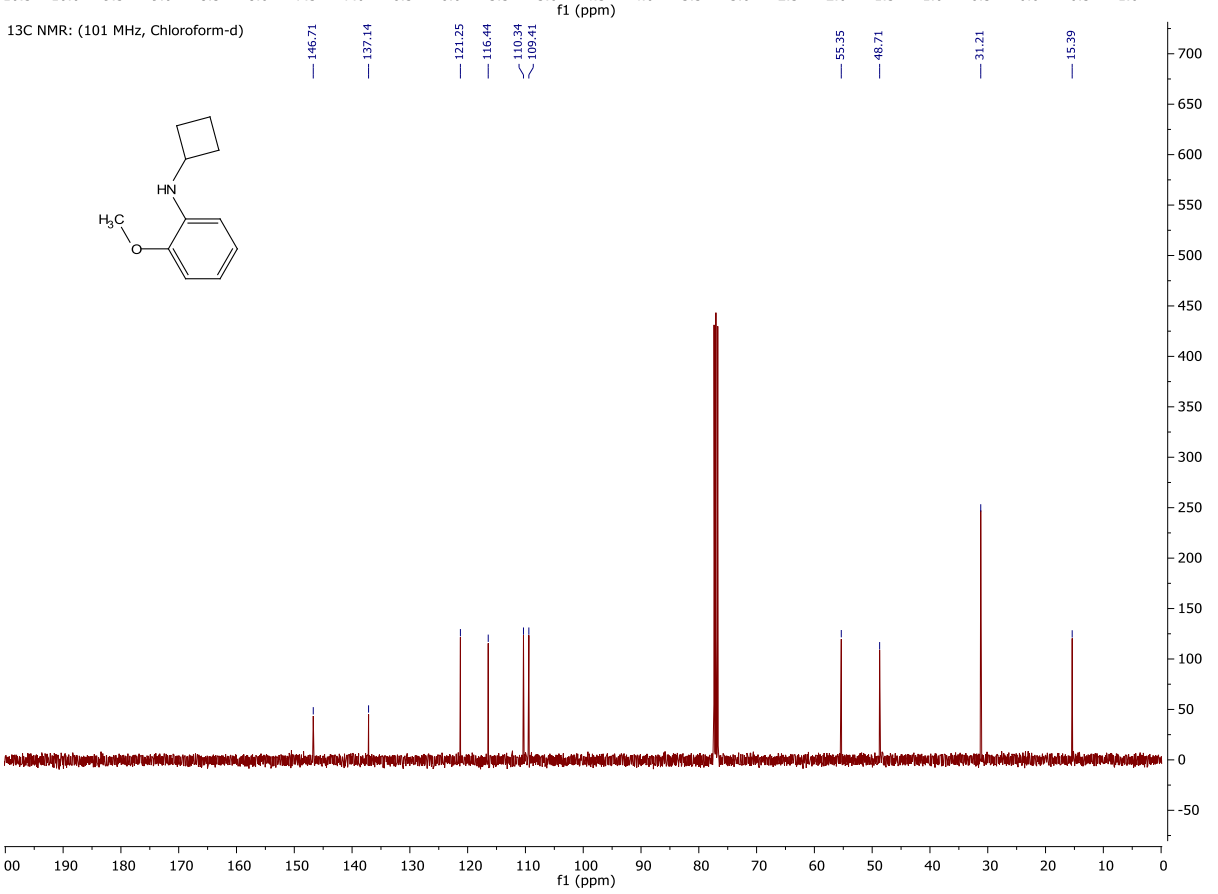
N-cyclohexylaniline (2k)



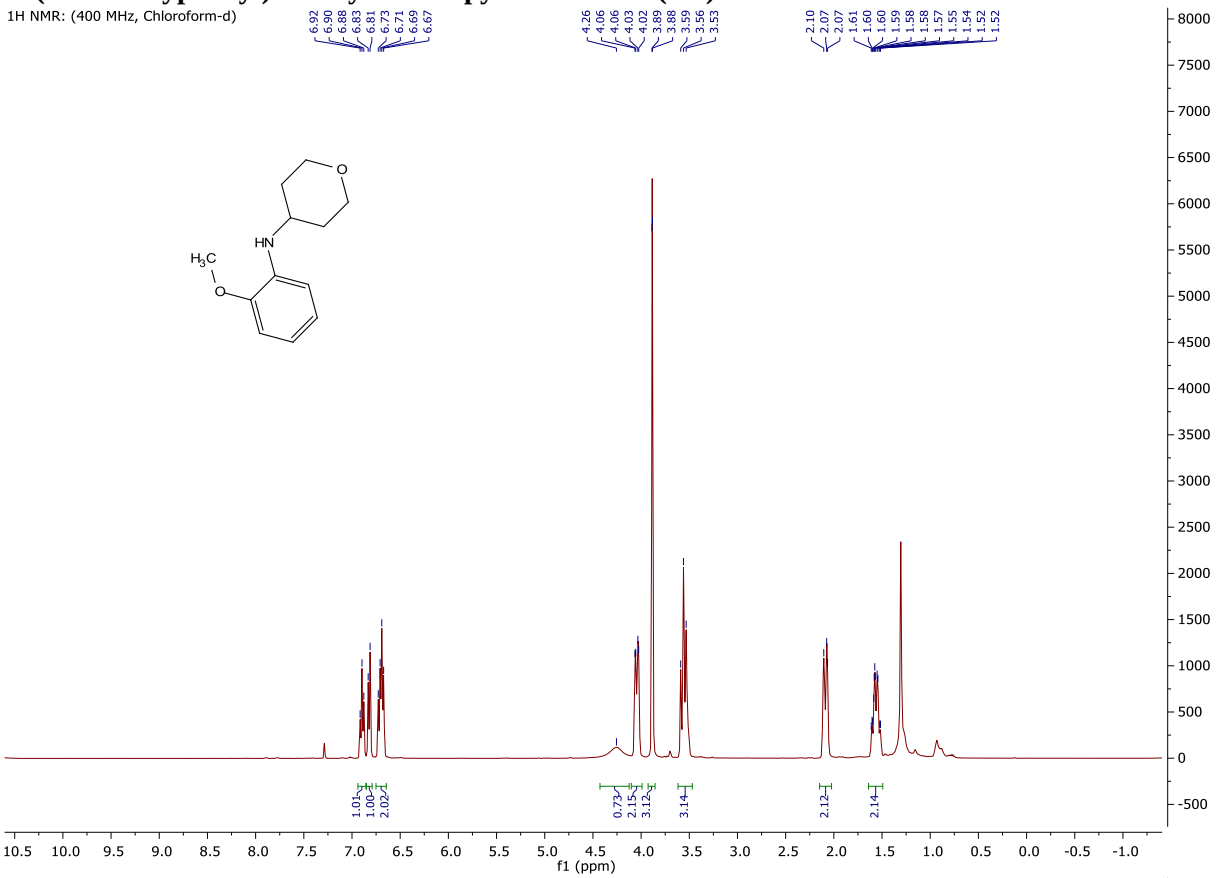


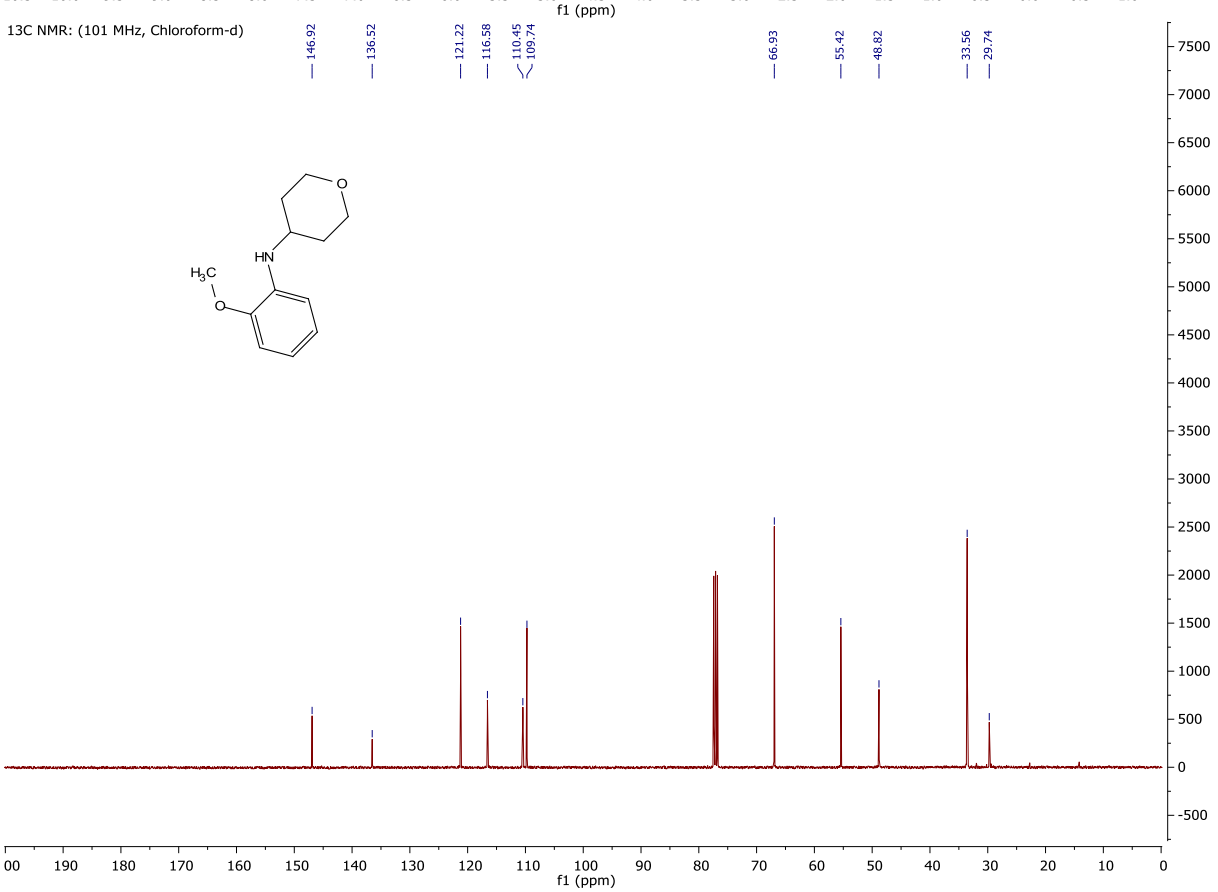
N-cyclobutyl-2-methoxyaniline (2l)



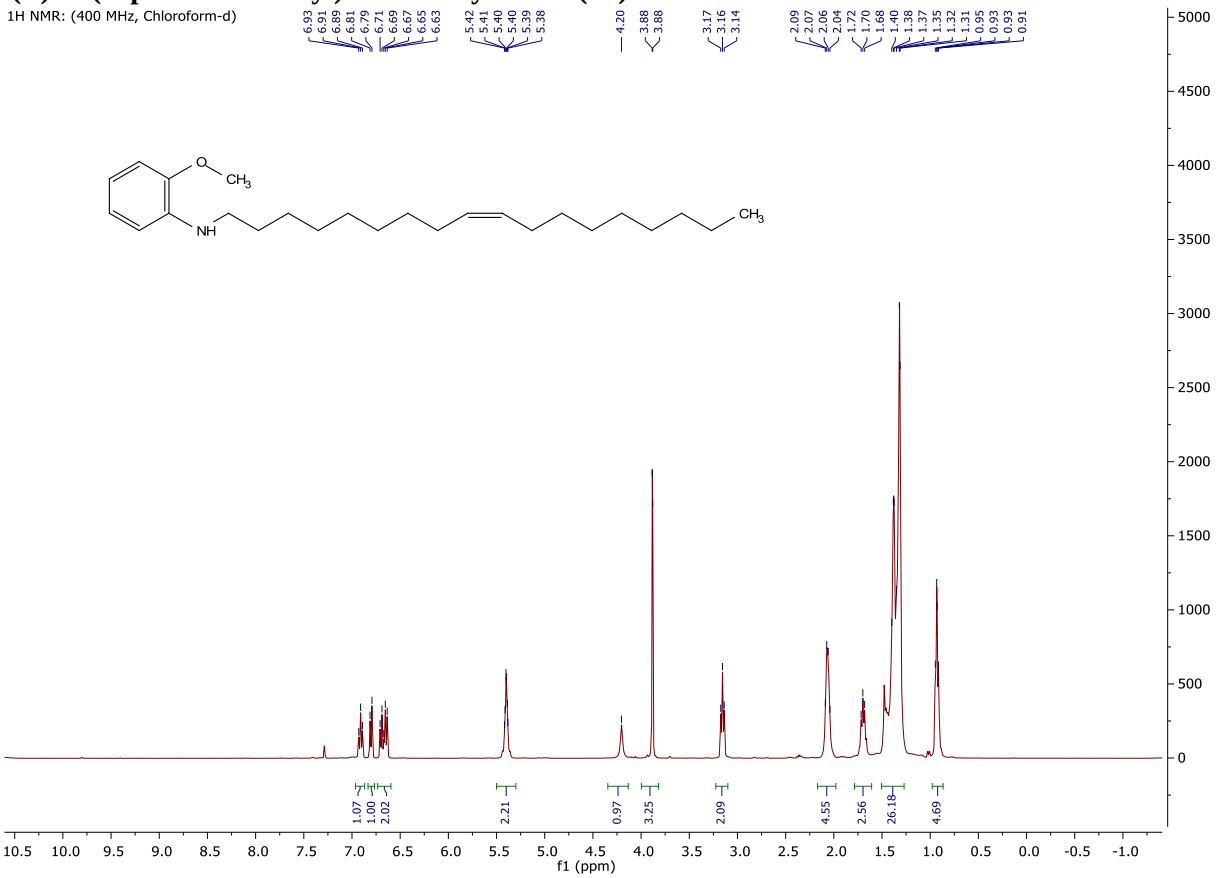


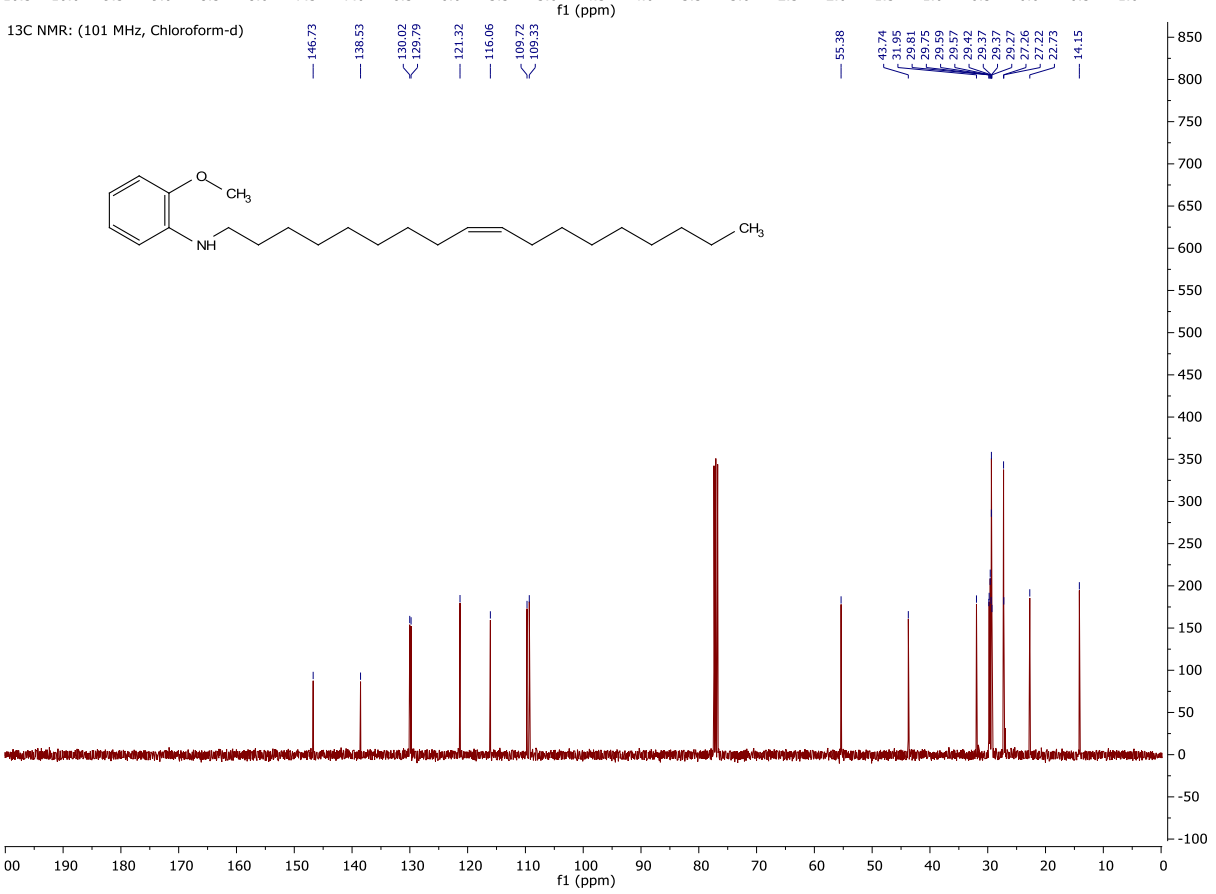
N-(2-methoxyphenyl)tetrahydro-2H-pyran-4-amine (2m)



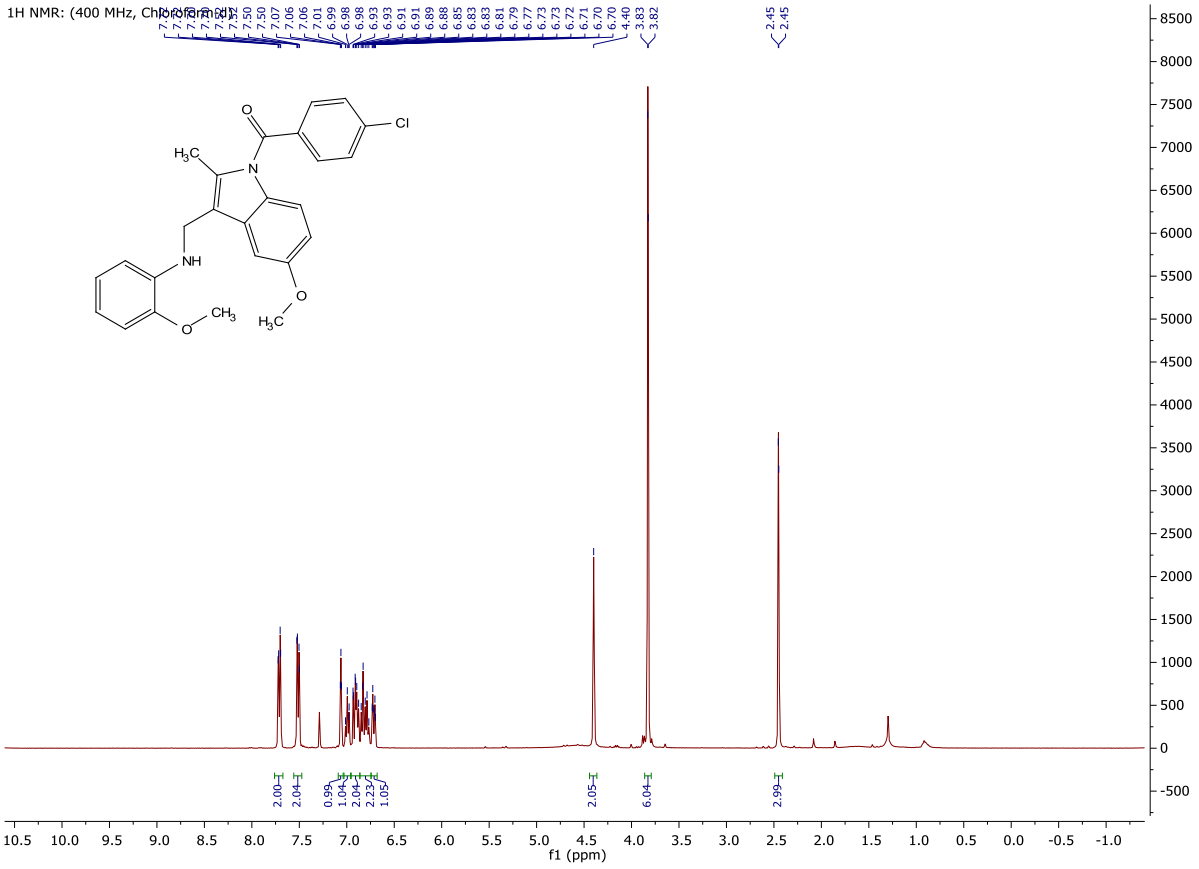


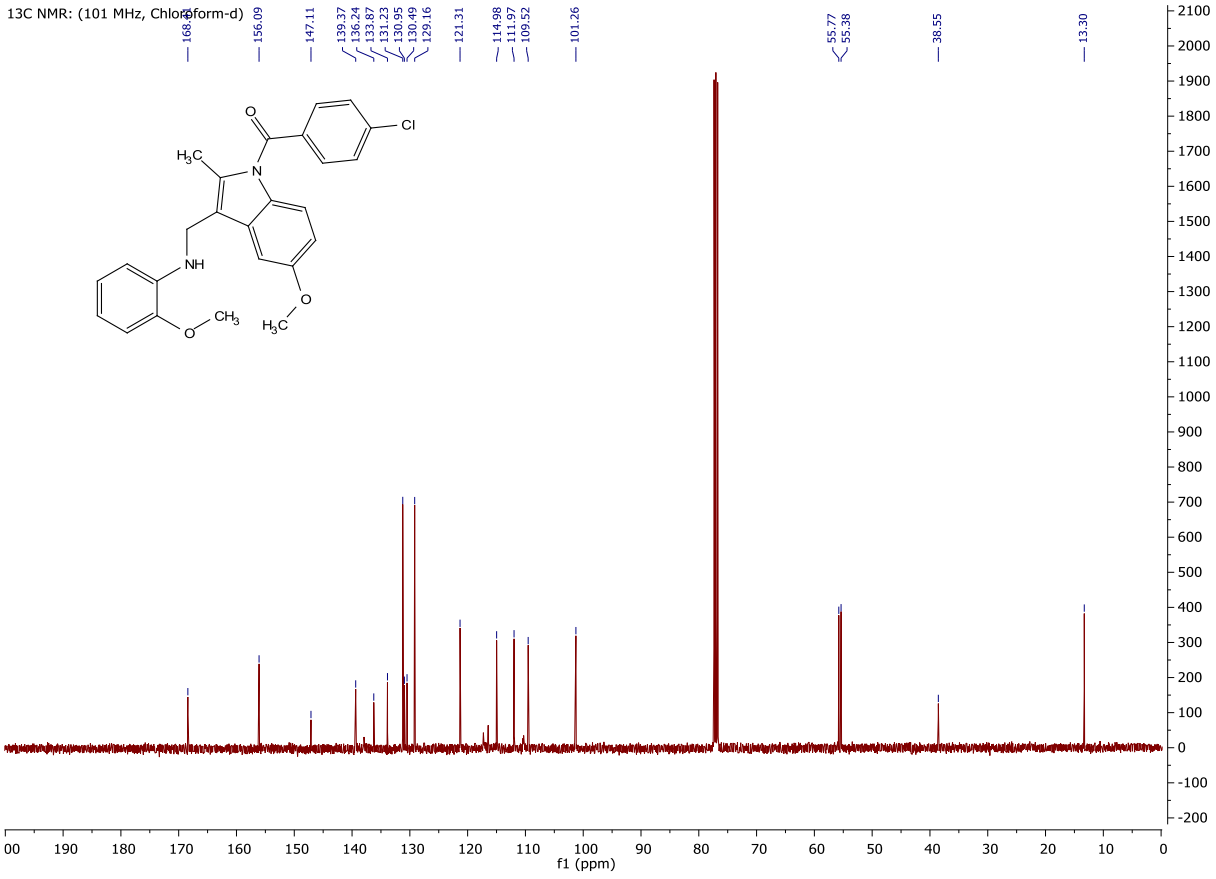
(Z)-N-(heptadec-8-en-1-yl)-2-methoxyaniline (2n)



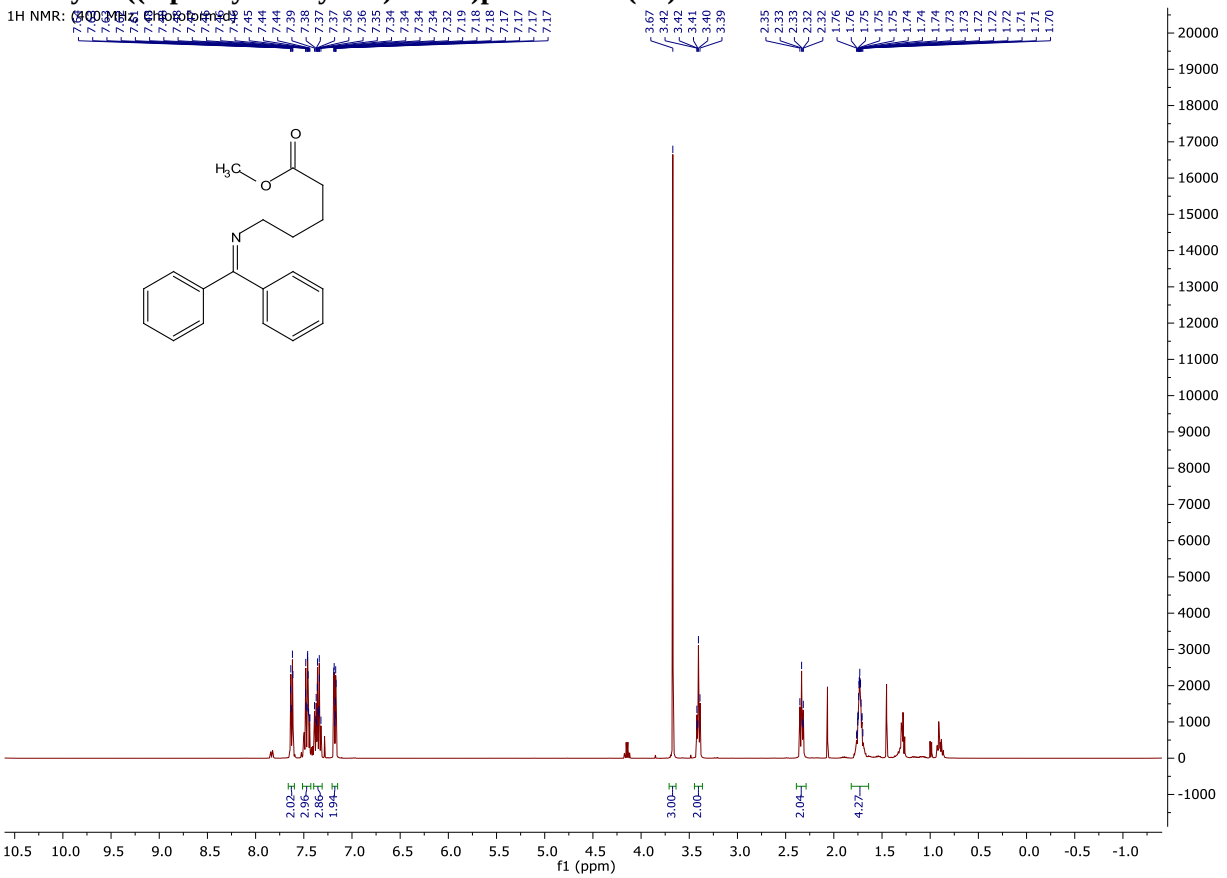


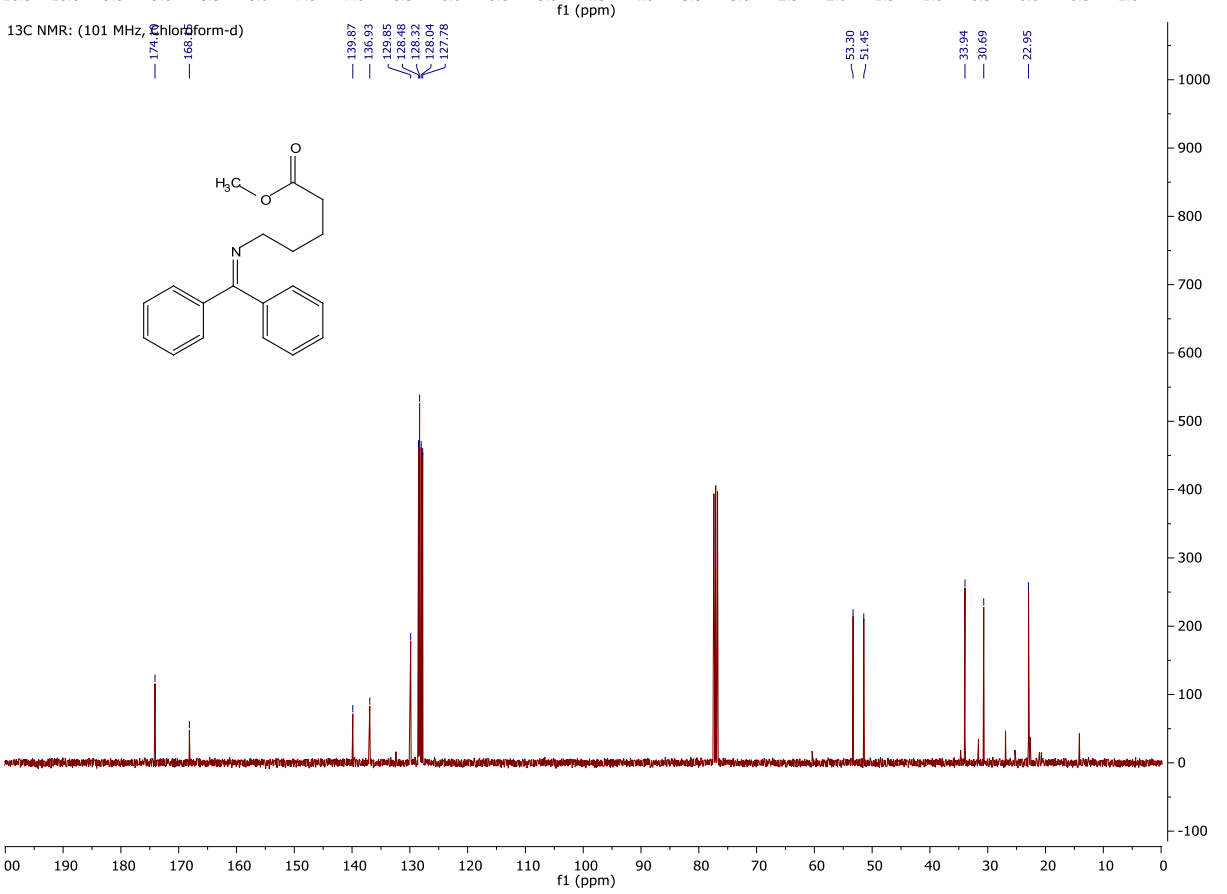
(4-chlorophenyl)(5-methoxy-3-(((2-methoxyphenyl)amino)methyl)-2-methyl-1H-indol-1-yl)methanone (2o)



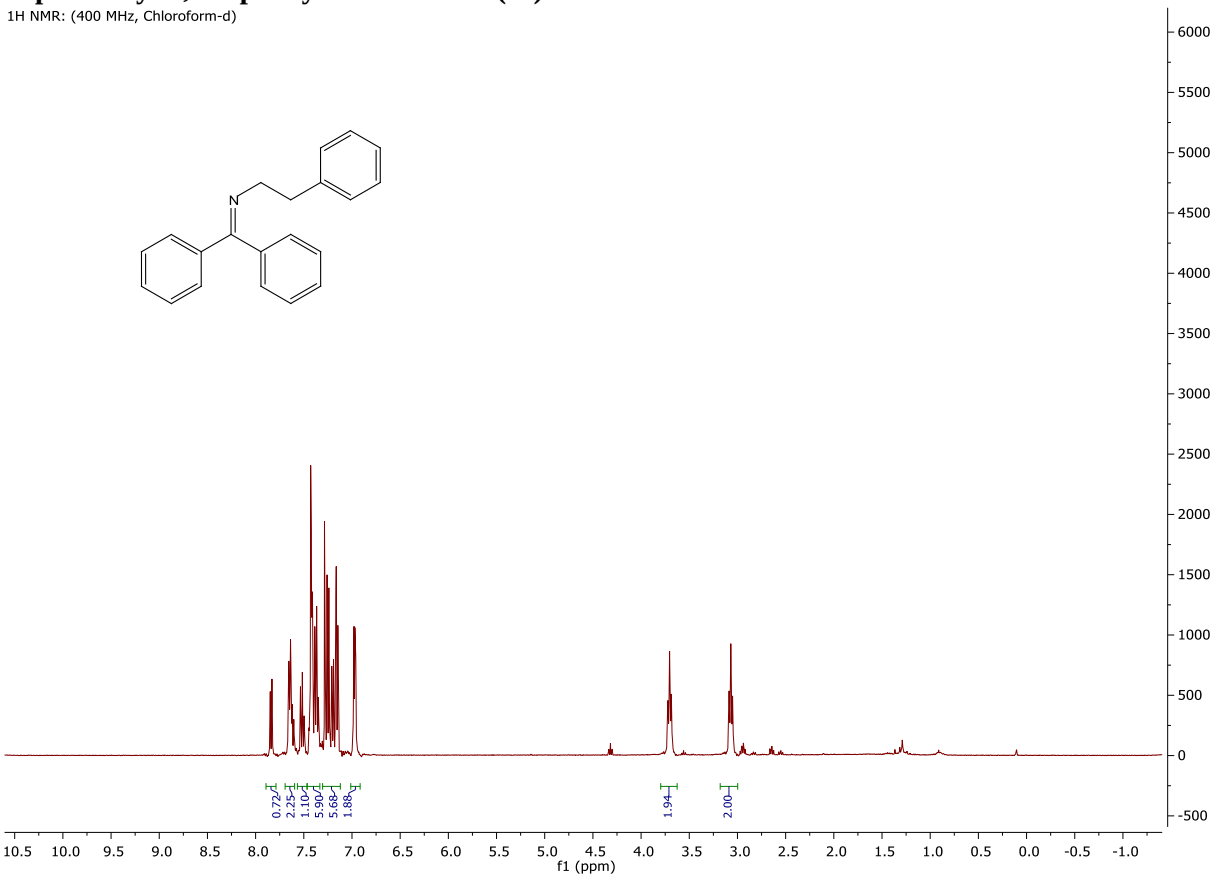

13C NMR: (101 MHz, Chloroform-d)
168.82
156.09
147.11
139.37
136.24
133.87
131.23
130.95
130.49
129.16
121.31
114.98
111.97
109.52
101.26
55.77
55.38
38.55
13.30
O
Cl
H3C
N
NH
O
CH3
O
H3C
f1 (ppm)

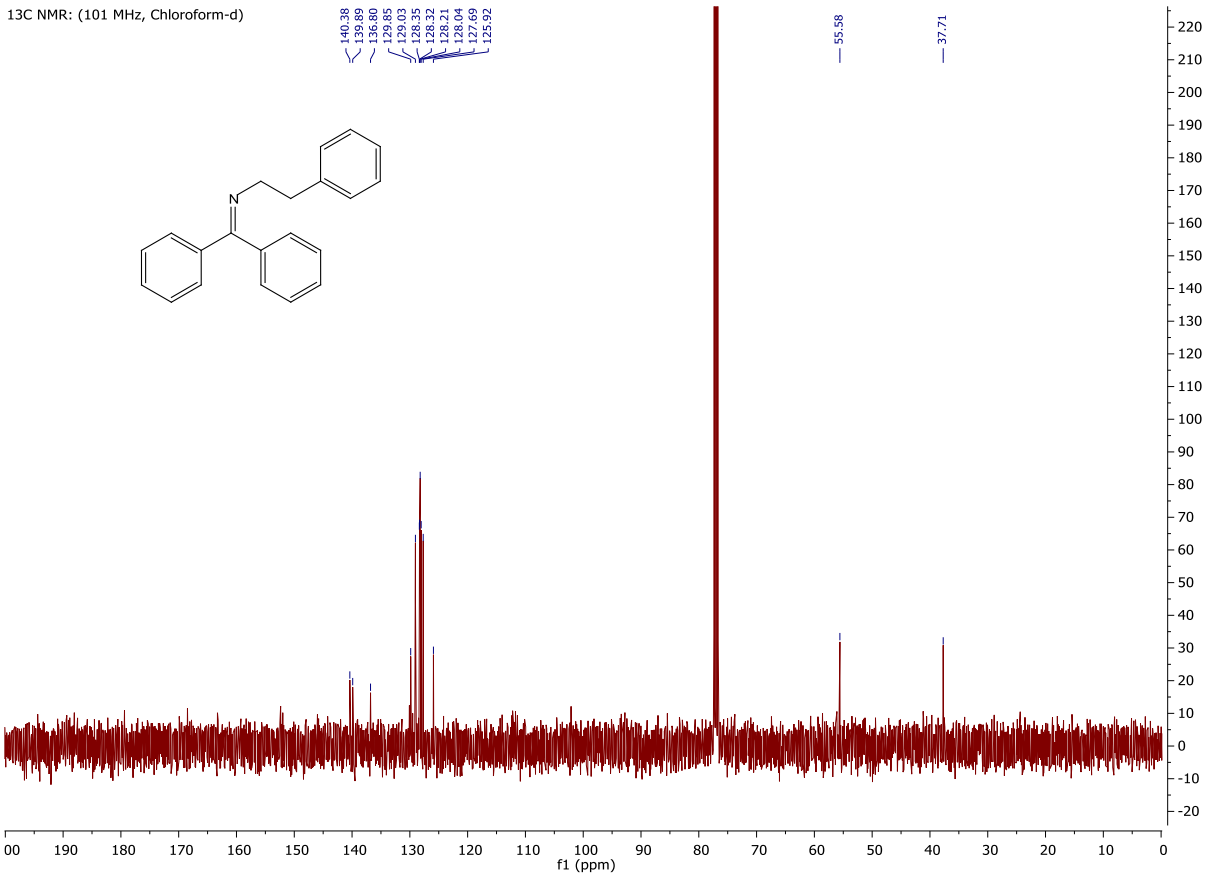
Methyl 5-((diphenylmethylene)amino)pentanoate (3b)



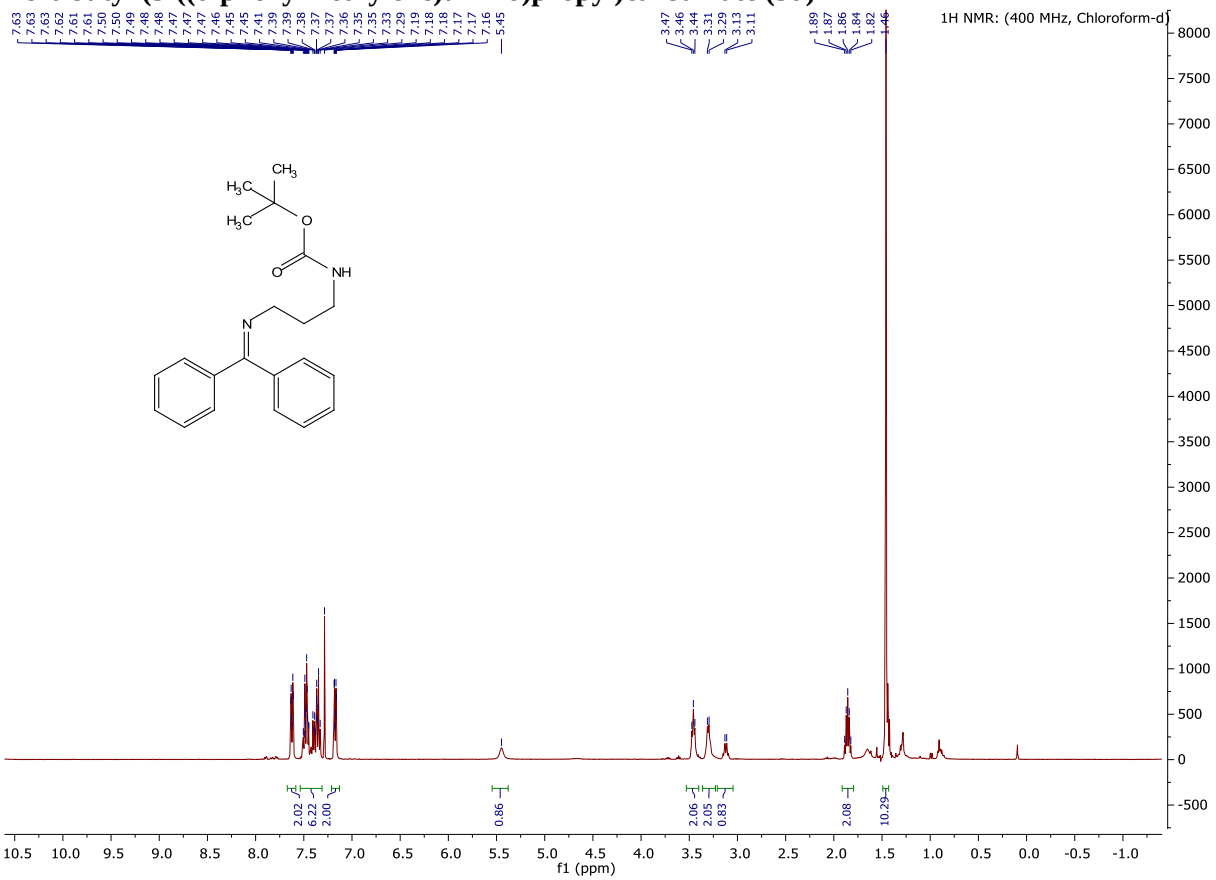


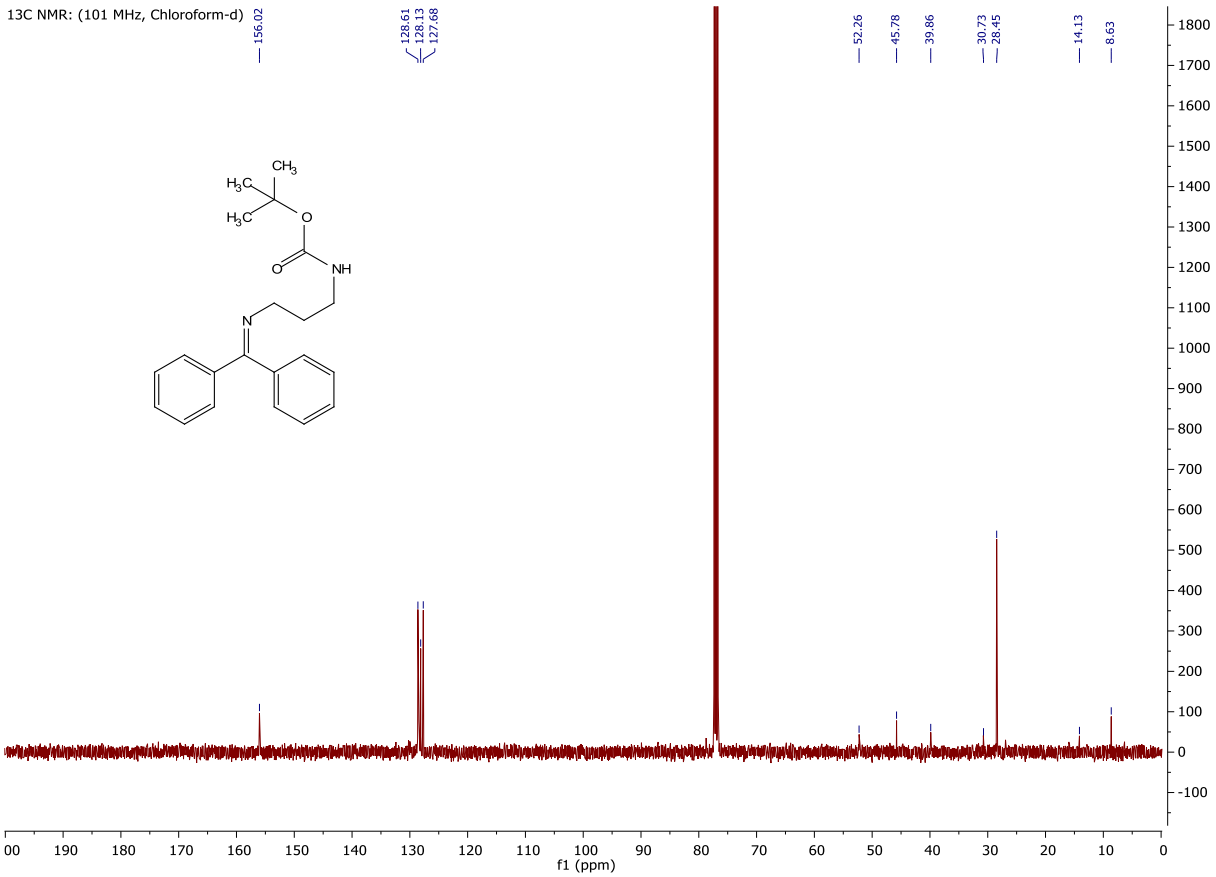
N-phenethyl-1,1-diphenylmethanimine (3c)



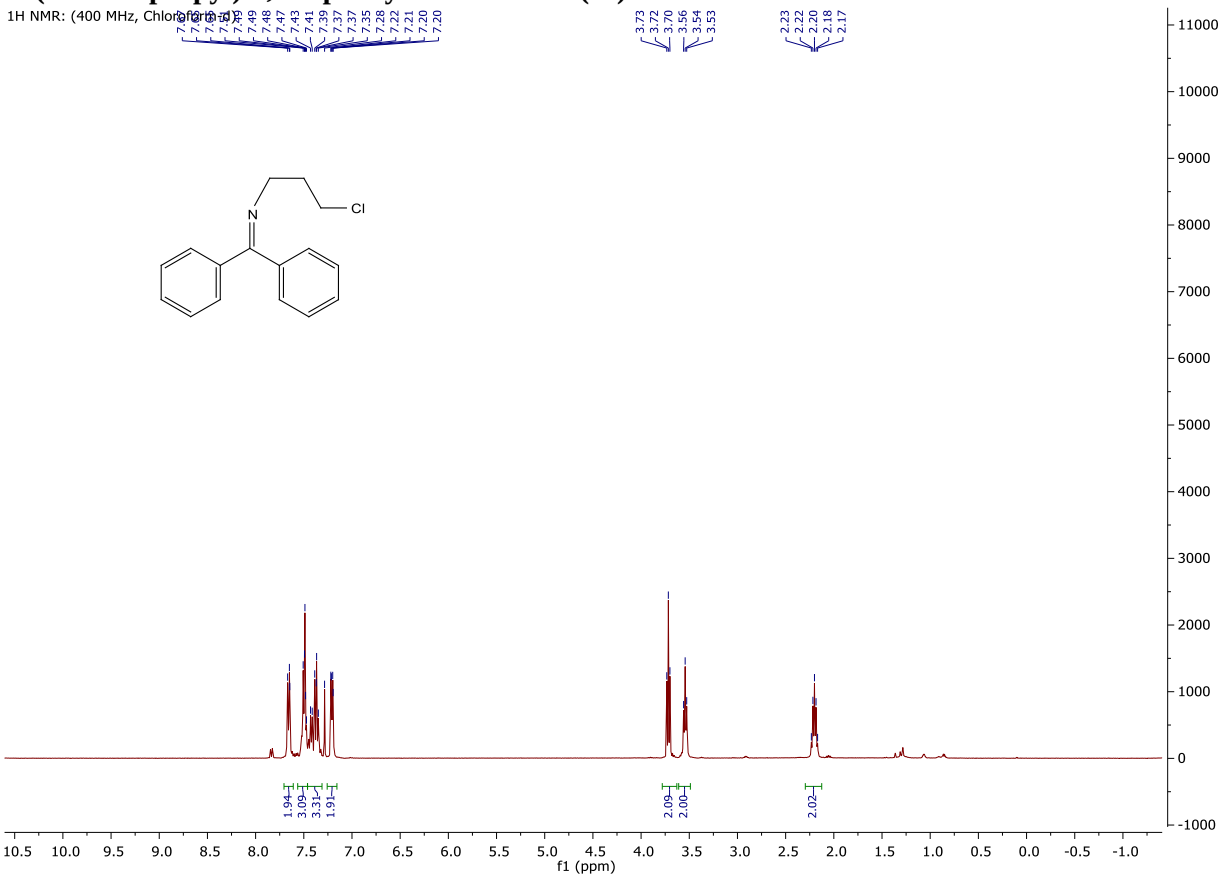


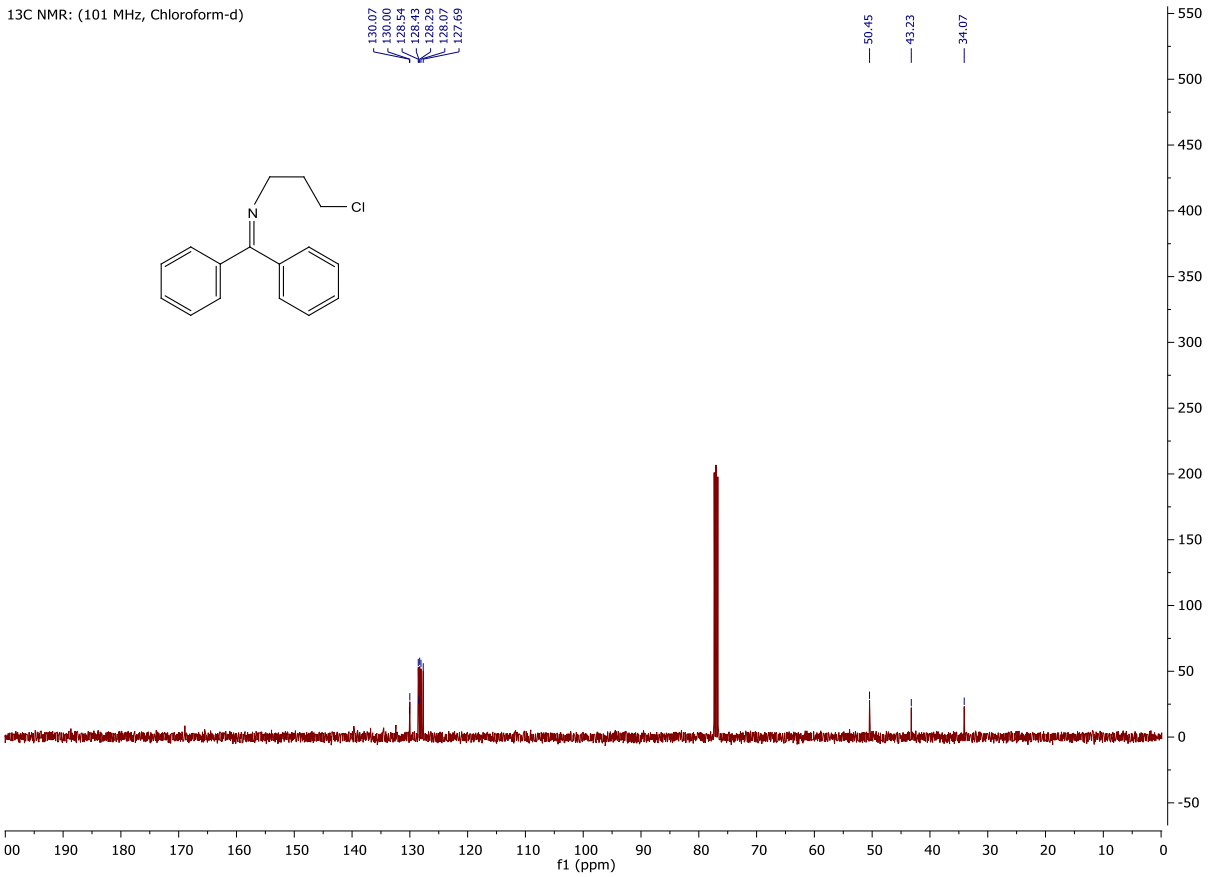
Tert-butyl (3-((diphenylmethylene)amino)propyl)carbamate (3d)



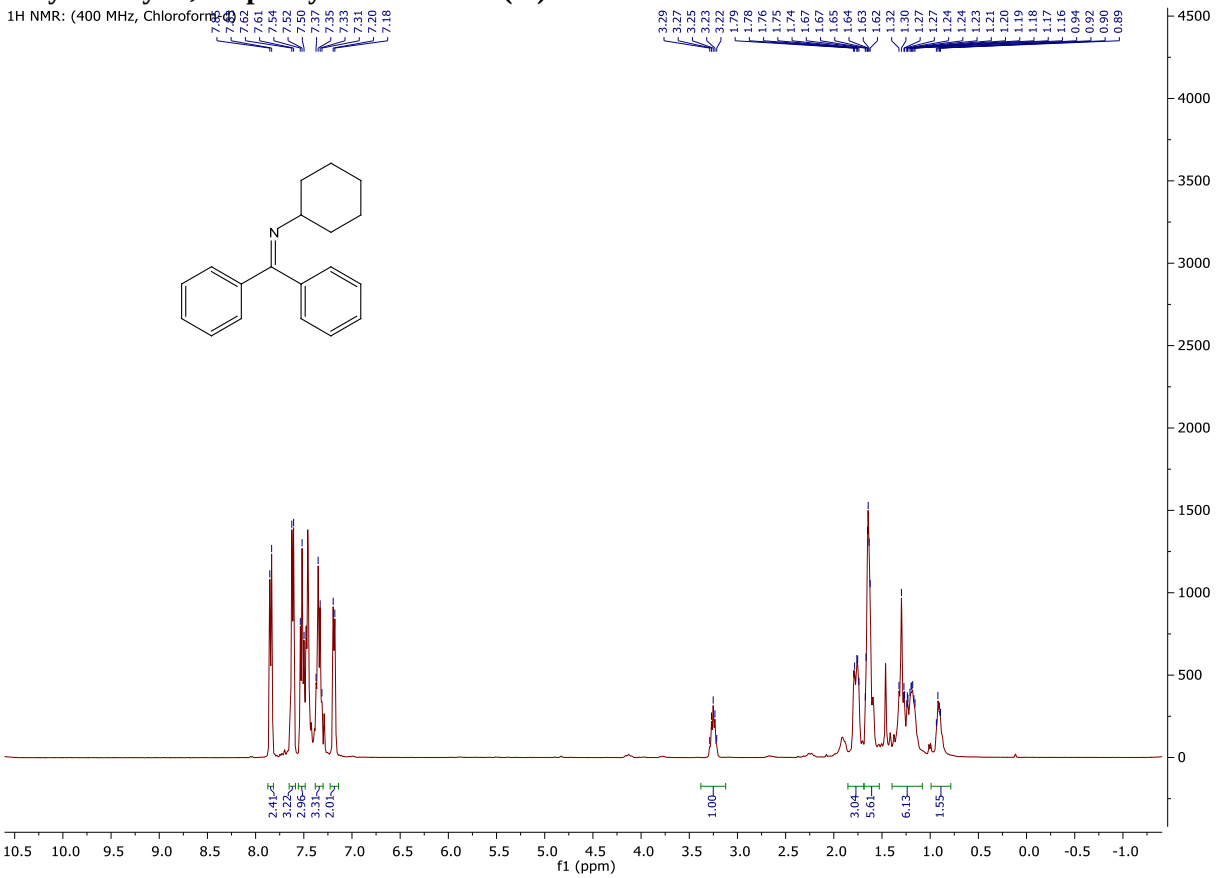


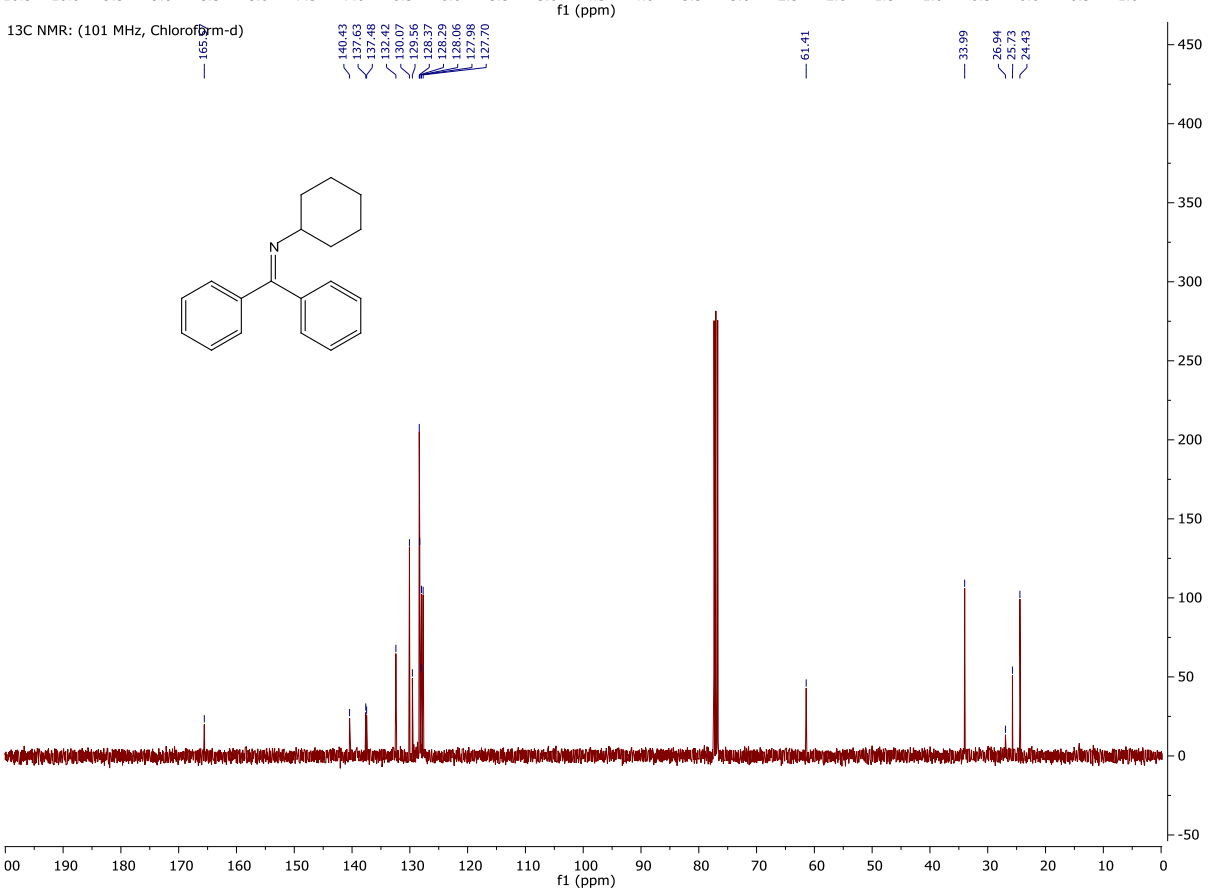
N-(3-chloropropyl)-1,1-diphenylmethanimine (3e)



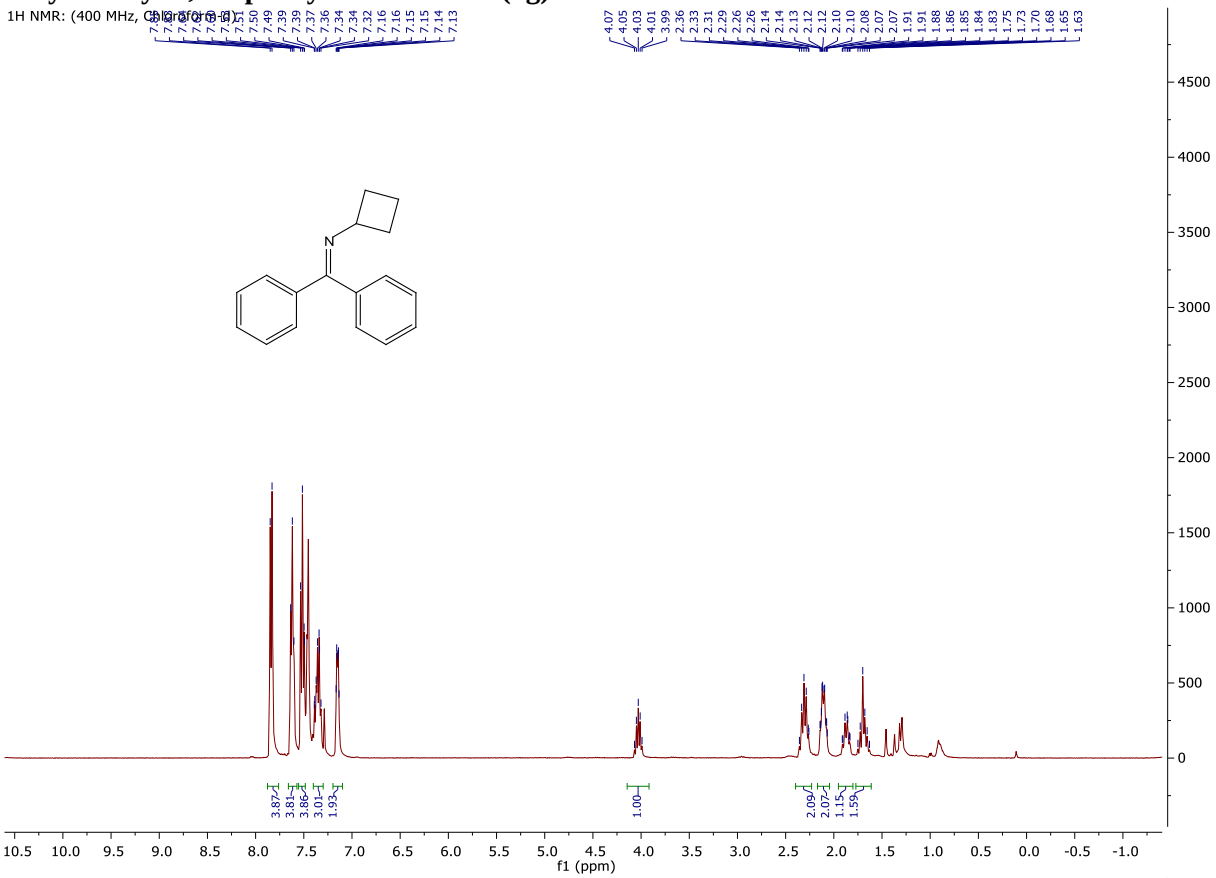


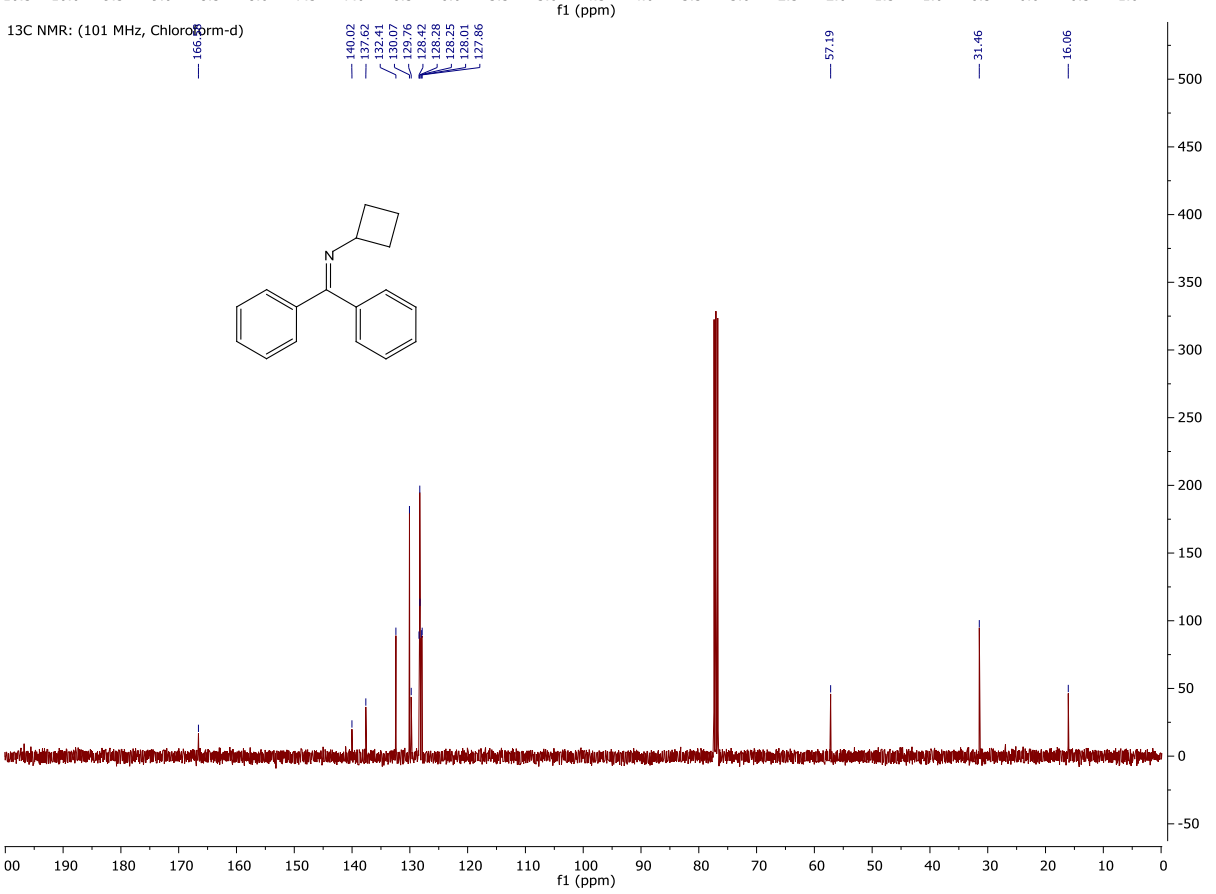
N-cyclohexyl-1,1-diphenylmethanimine (3f)



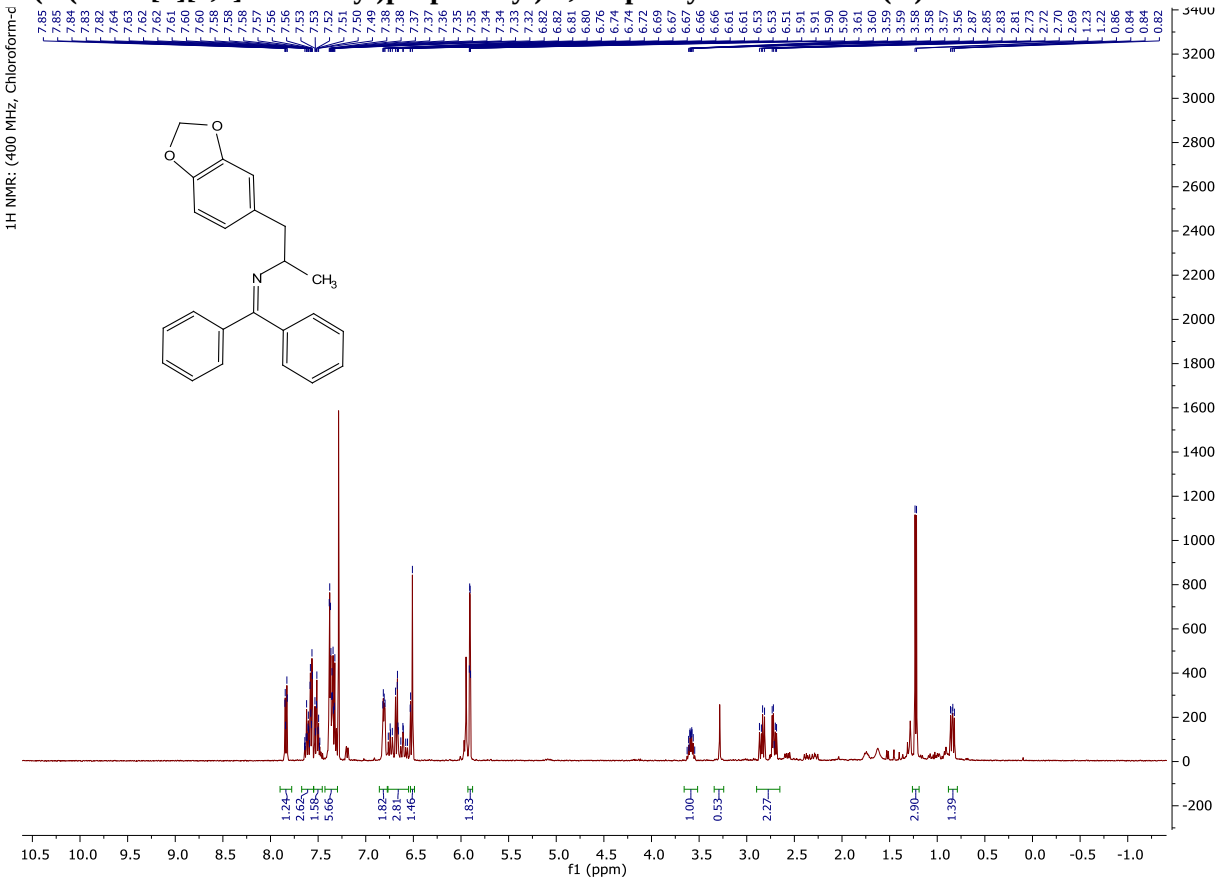


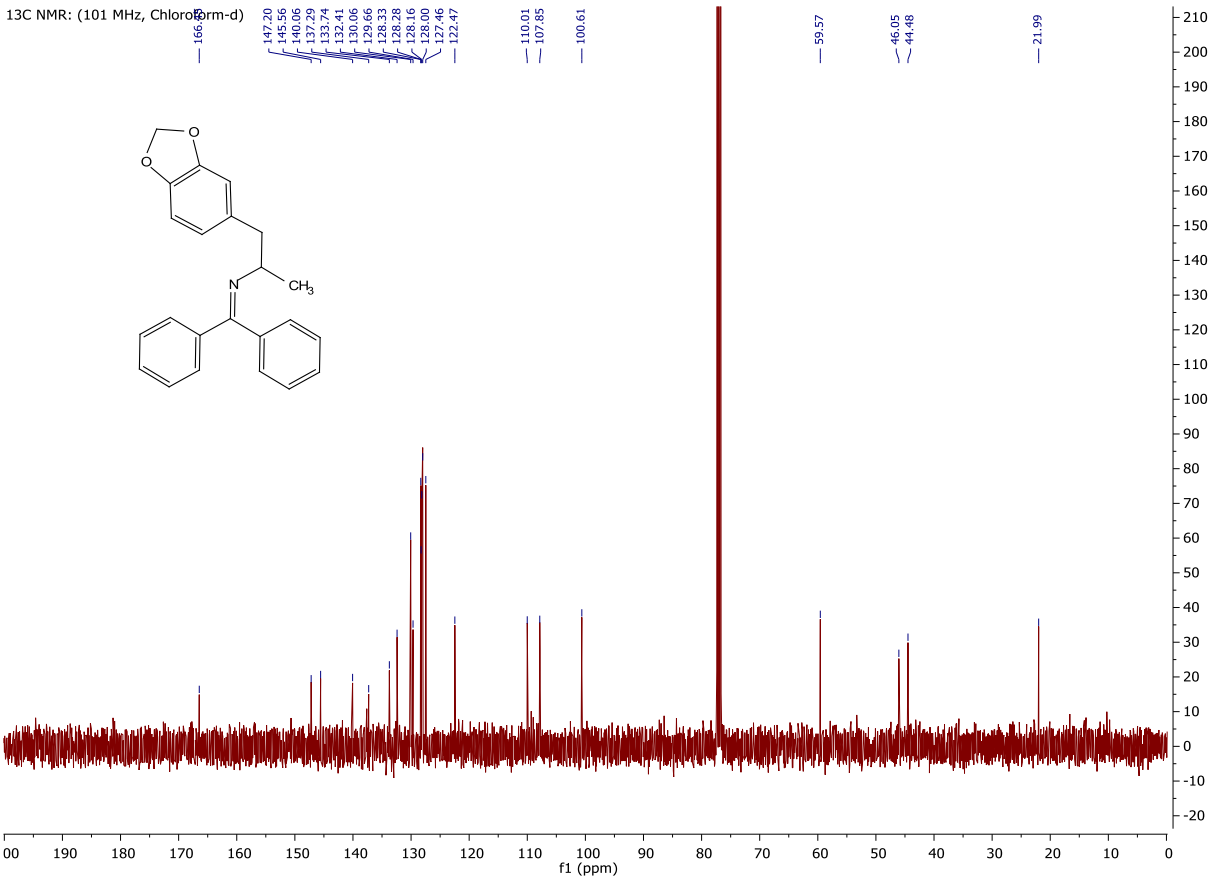
N-cyclobutyl-1,1-diphenylmethanimine (3g)





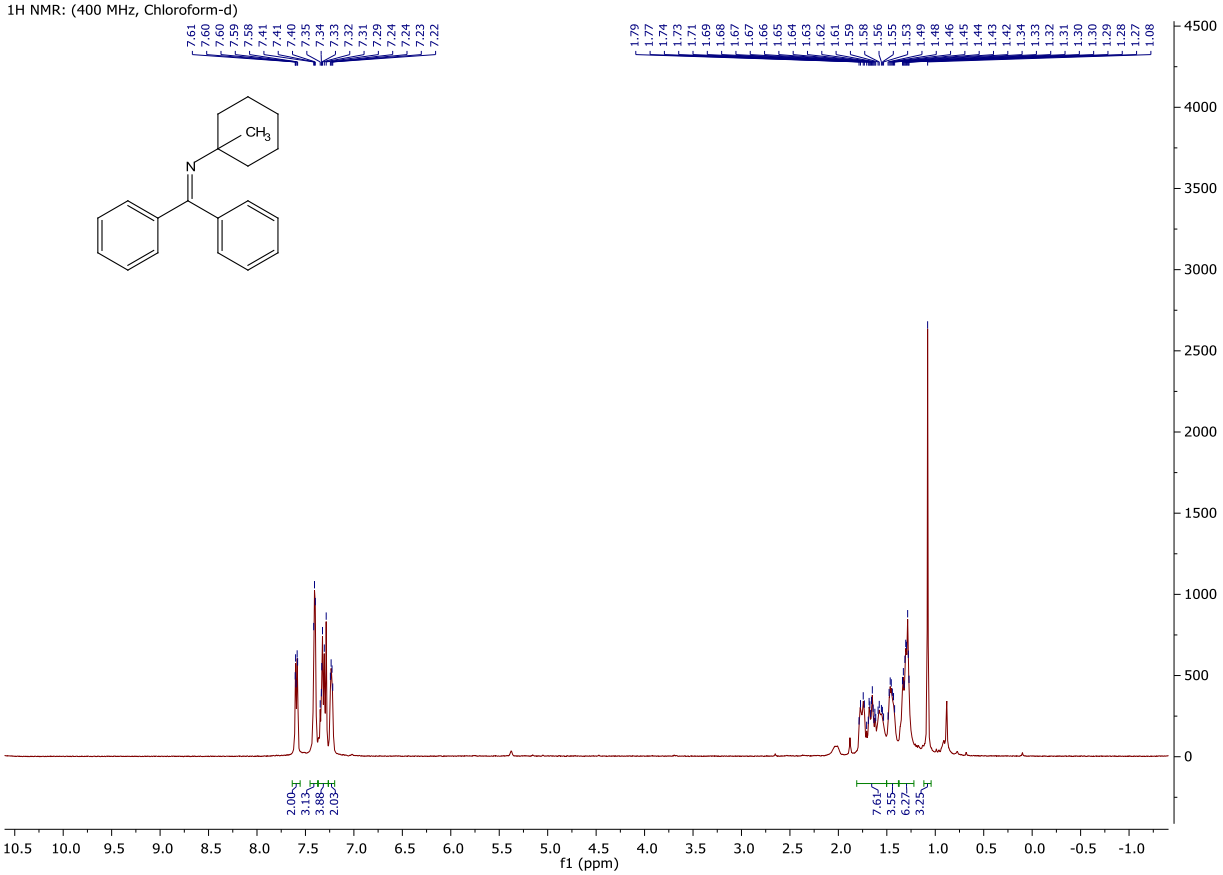
N-(1-(benzo[d][1,3]dioxol-5-yl)propan-2-yl)-1,1-diphenylmethanimine (3i)



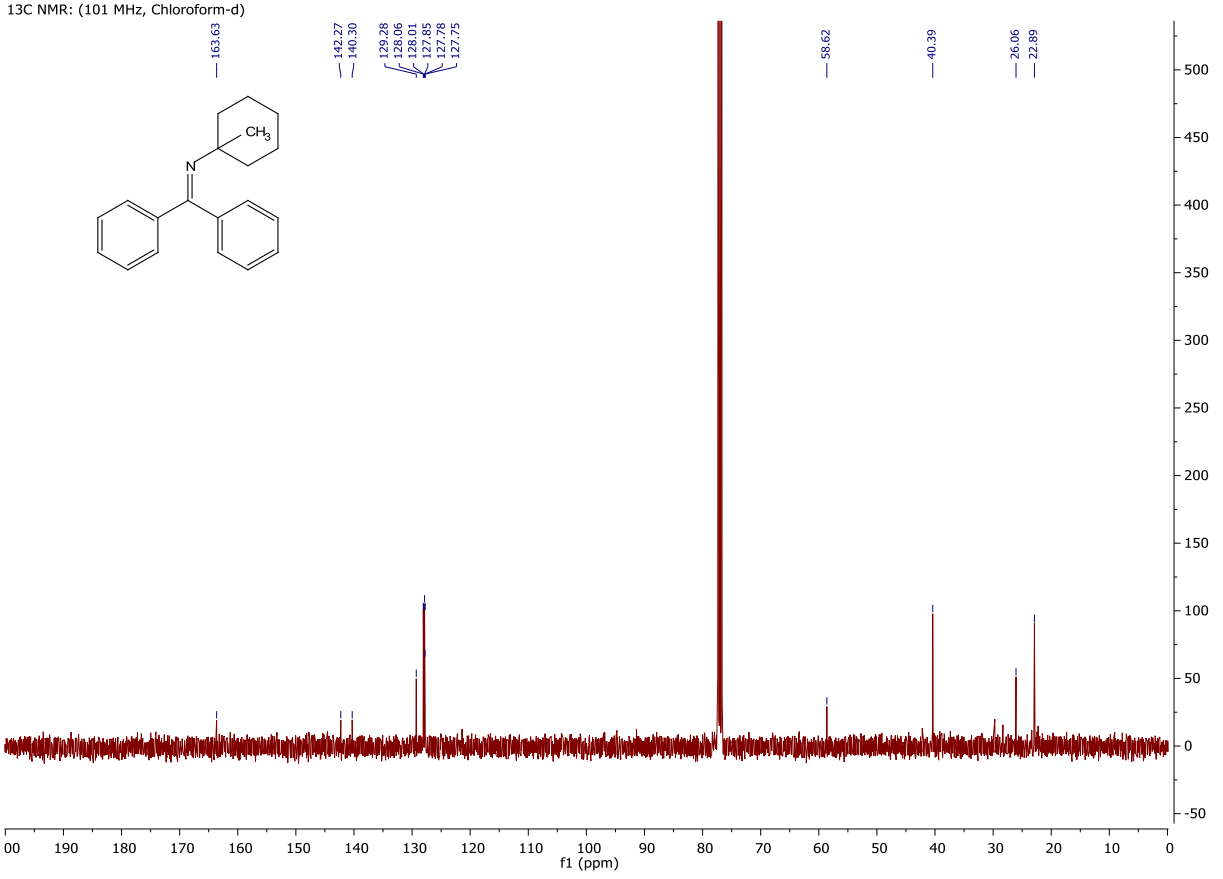


N-(1-methylcyclohexyl)-1,1-diphenylmethanimine (3j)

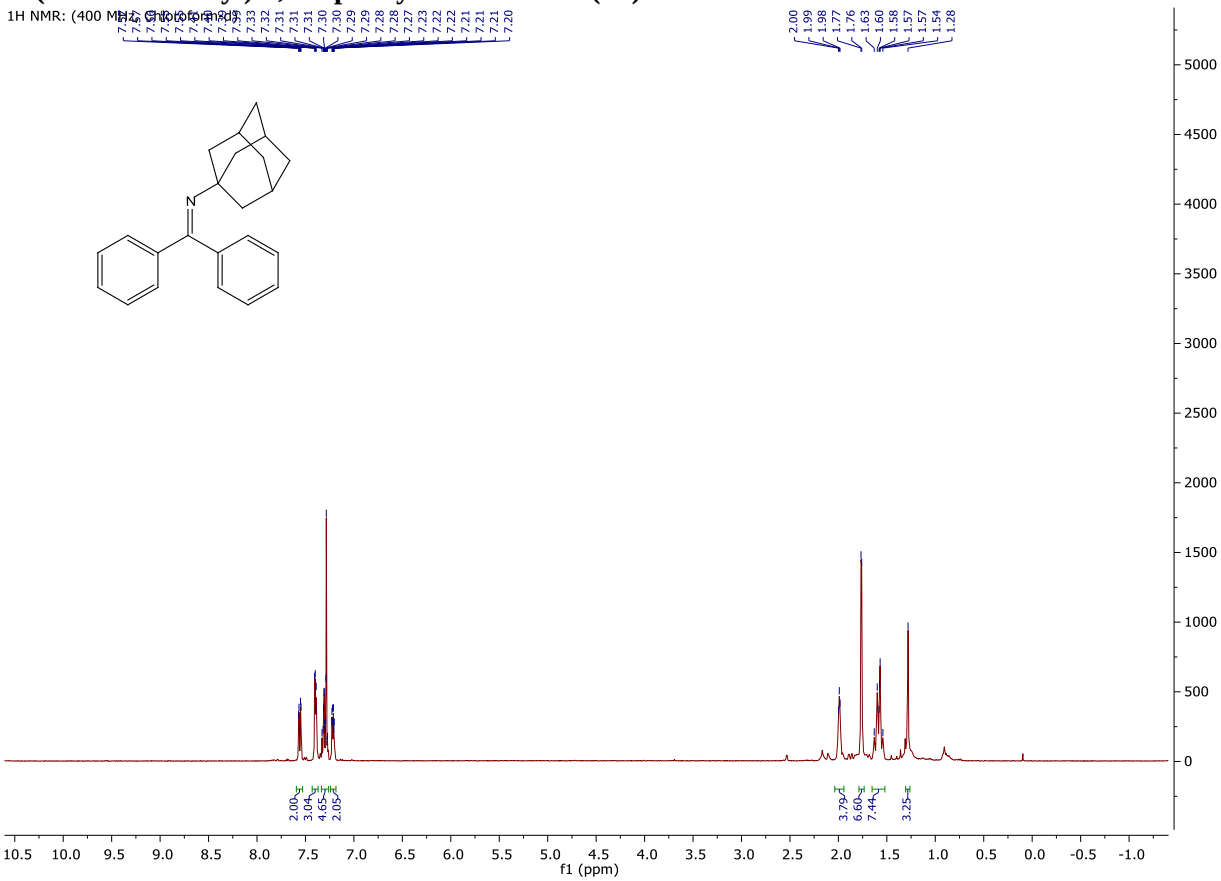
1H NMR: (400 MHz, Chloroform-d)

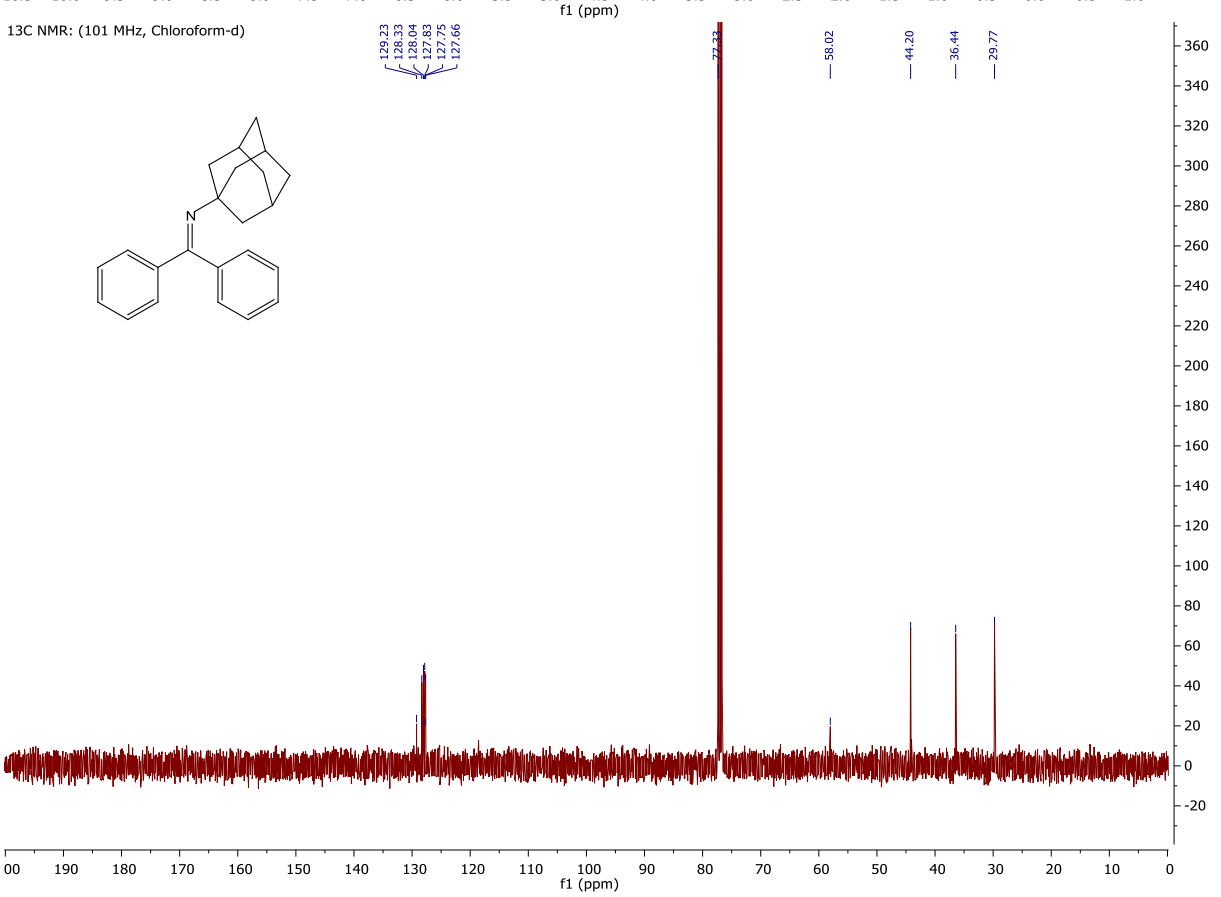


13C NMR: (101 MHz, Chloroform-d)



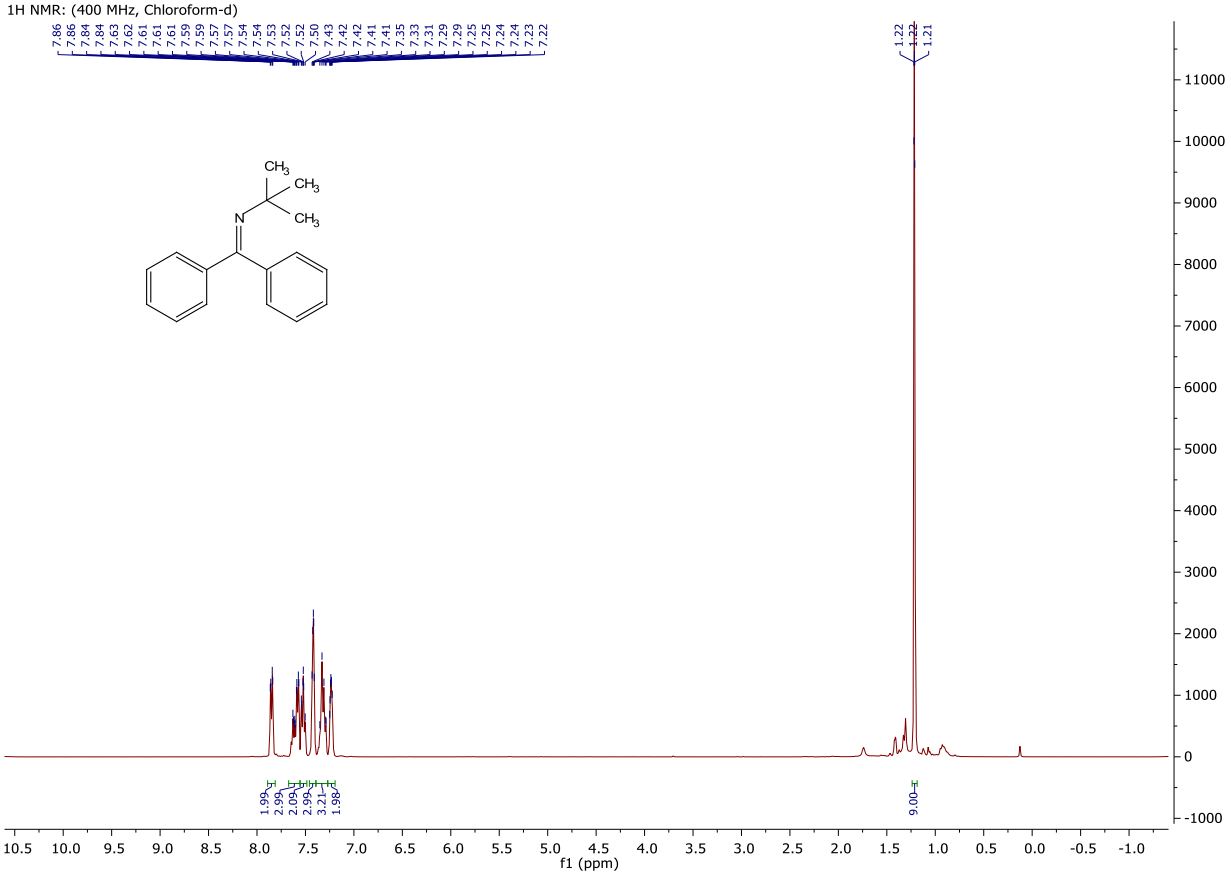
N-(adamantan-1-yl)-1,1-diphenylmethanimine (3k)



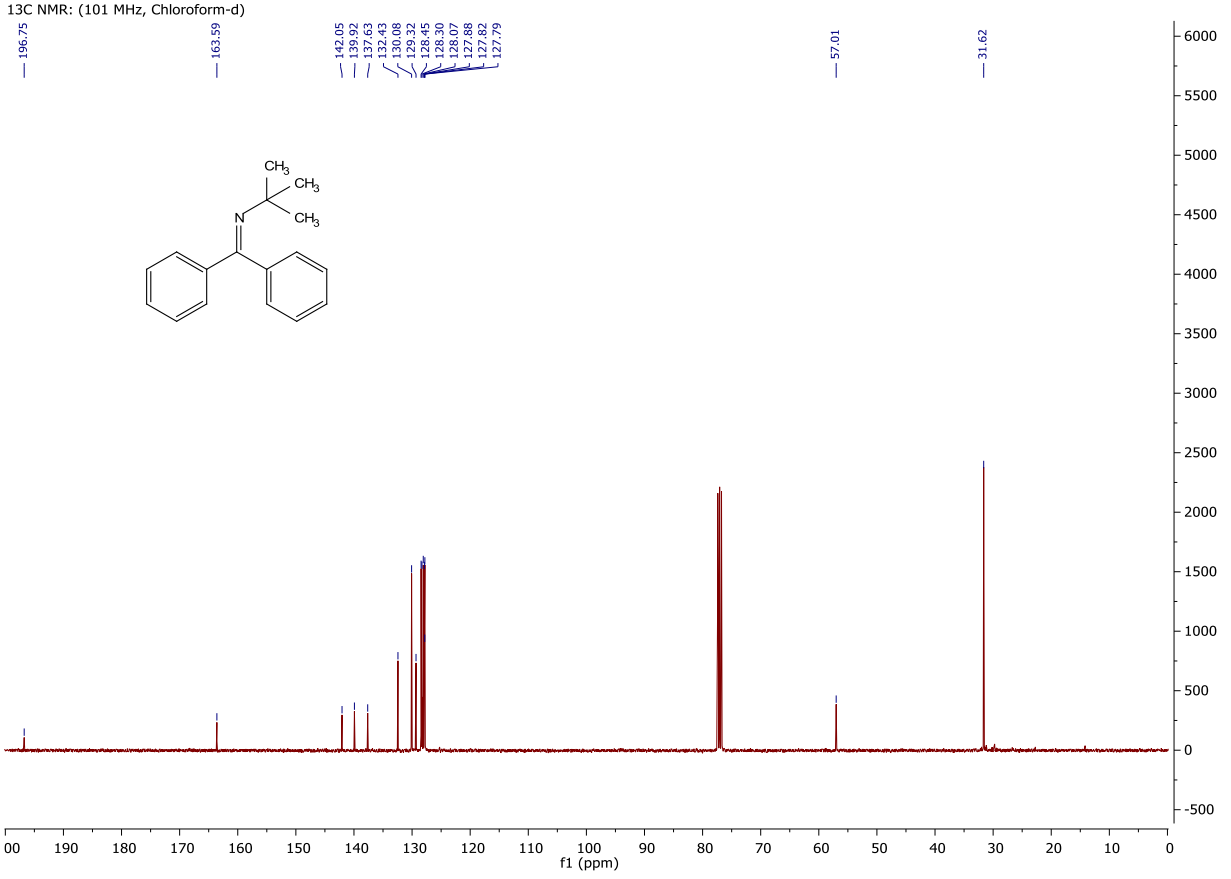


N-tert-butyl-1,1-diphenylmethanimine (3l)

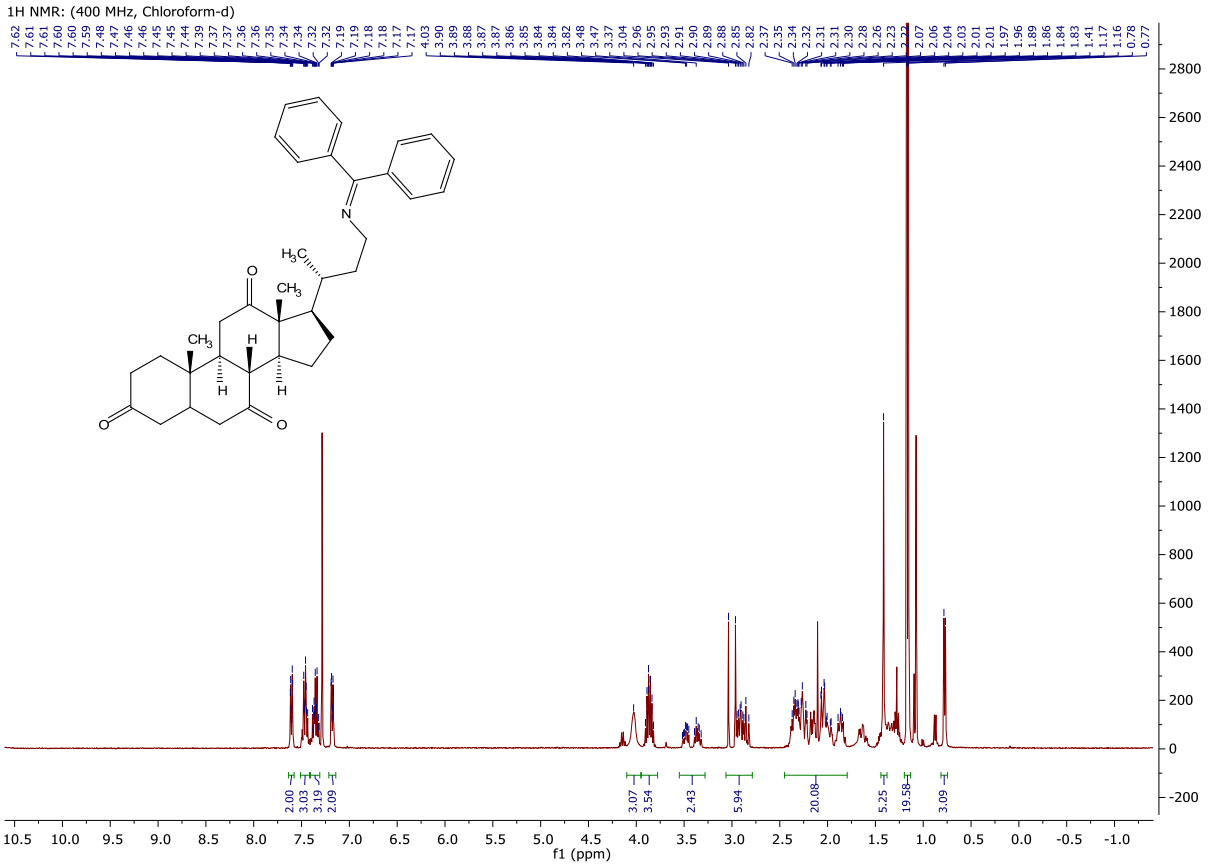
1H NMR: (400 MHz, Chloroform-d)

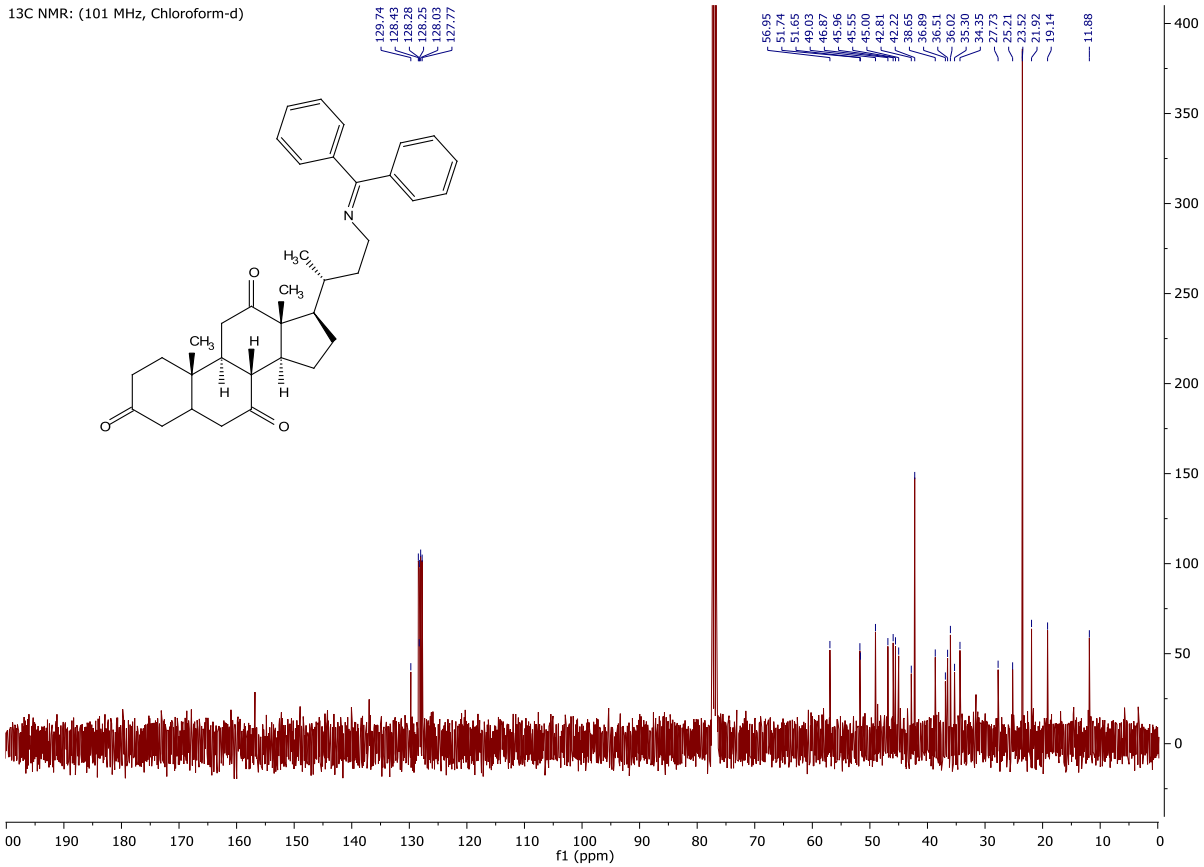


13C NMR: (101 MHz, Chloroform-d)

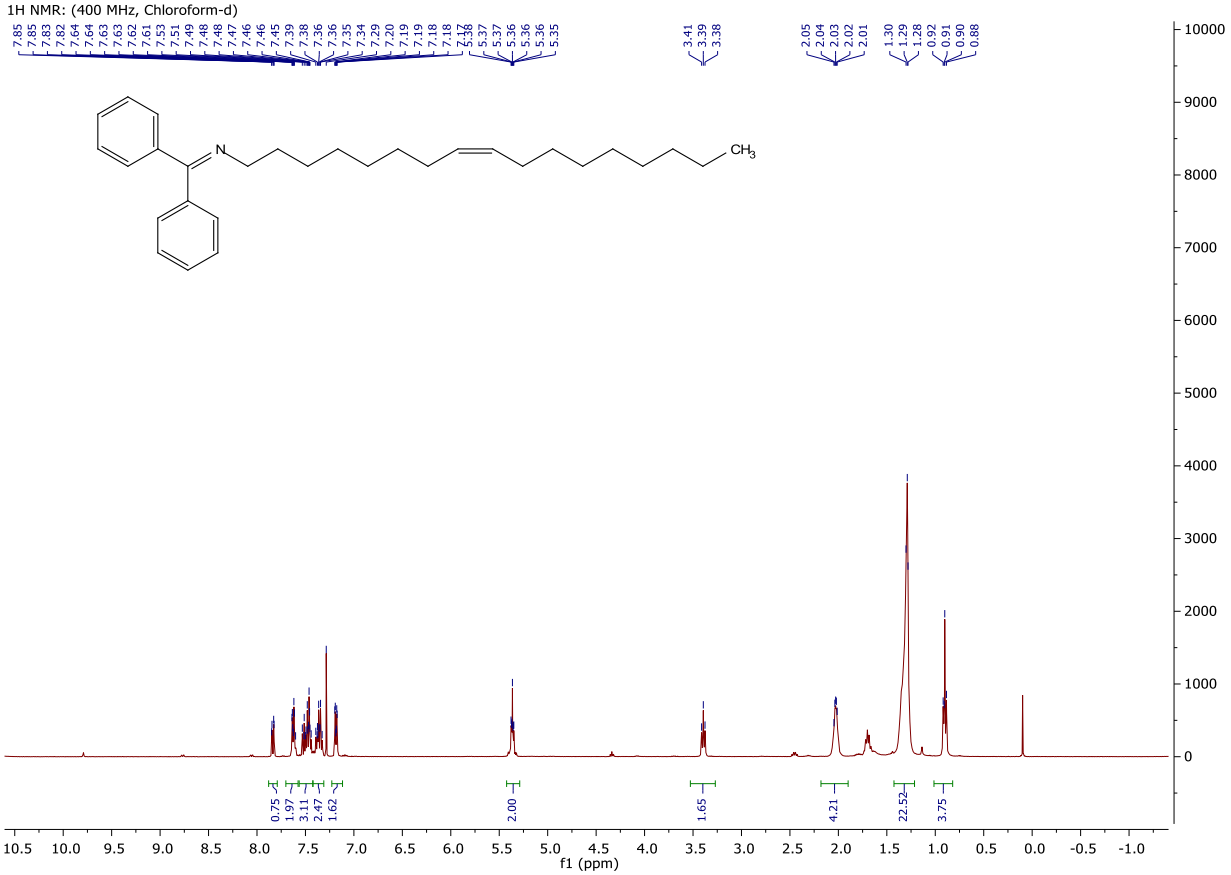


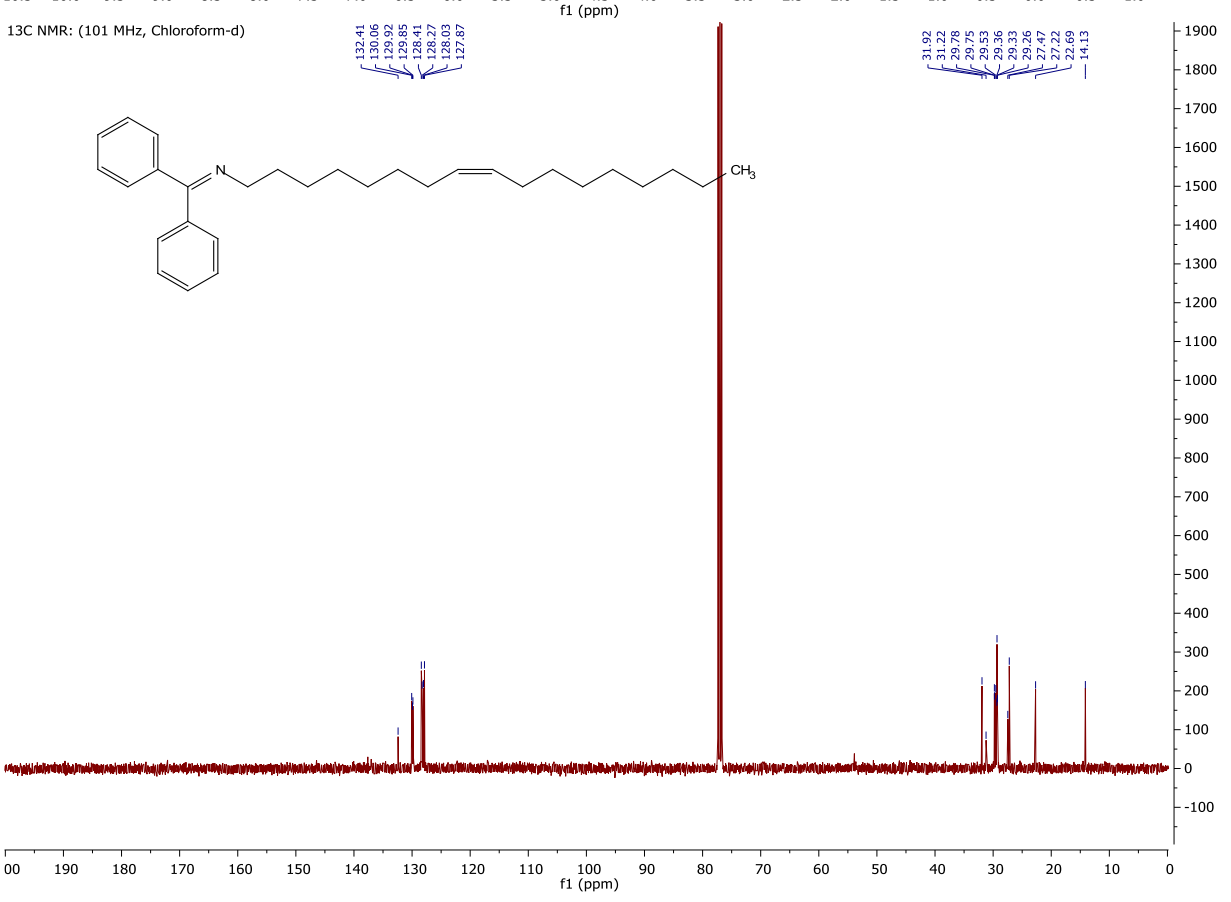
17-(4-((diphenylmethylene)amino)butan-2-yl)-10,13-dimethyldodecahydro-3H-cyclopenta[a]phenanthrene-3,7,12(2H,4H)-trione (3m)



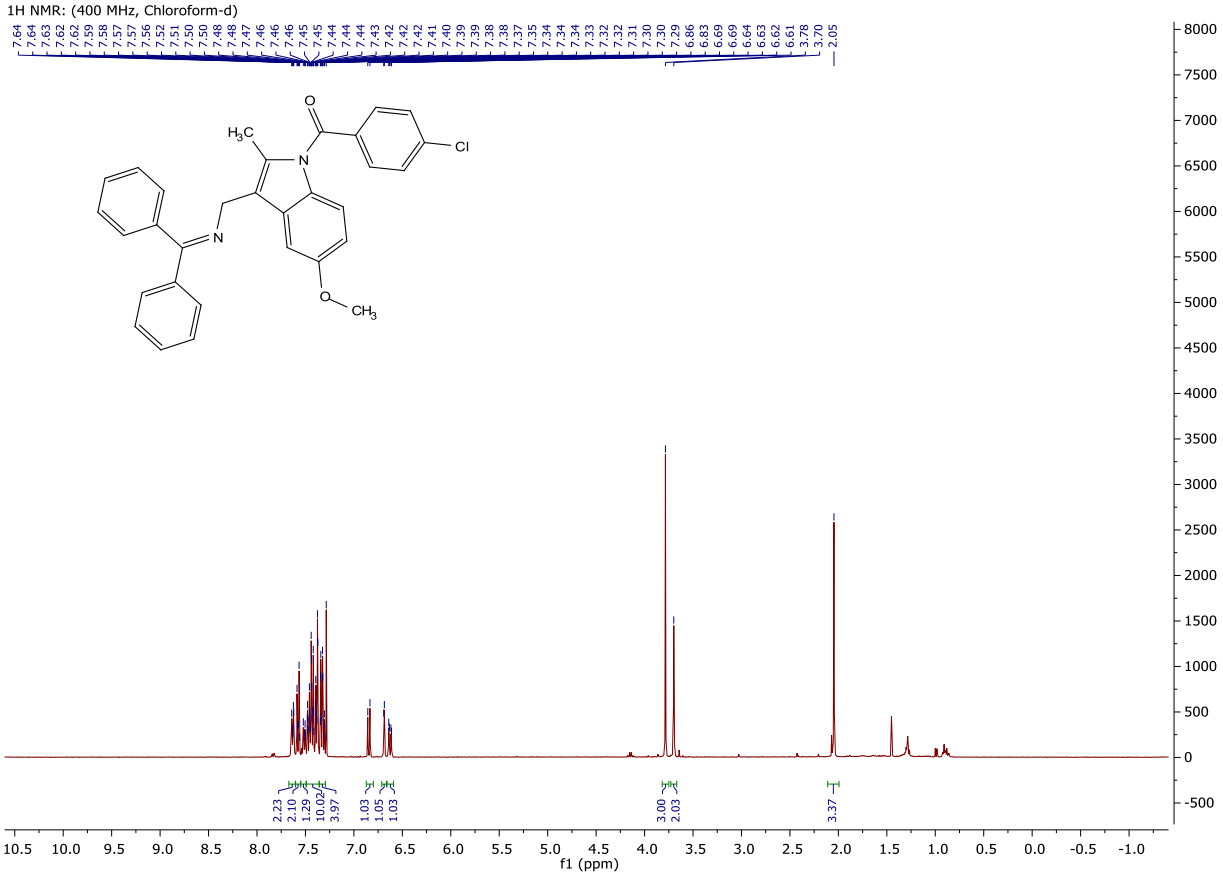

13C NMR: (101 MHz, Chloroform-d)
129.74
128.43
128.28
128.25
128.03
127.77
56.95
51.74
51.65
49.03
46.87
45.96
45.55
45.00
42.81
42.22
38.65
36.89
36.51
36.02
35.30
34.35
27.73
25.21
23.52
21.92
19.14
11.88
N
O
O
O
CH3
CH3
H3C
H
H
H
400
350
300
250
200
150
100
50
0
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

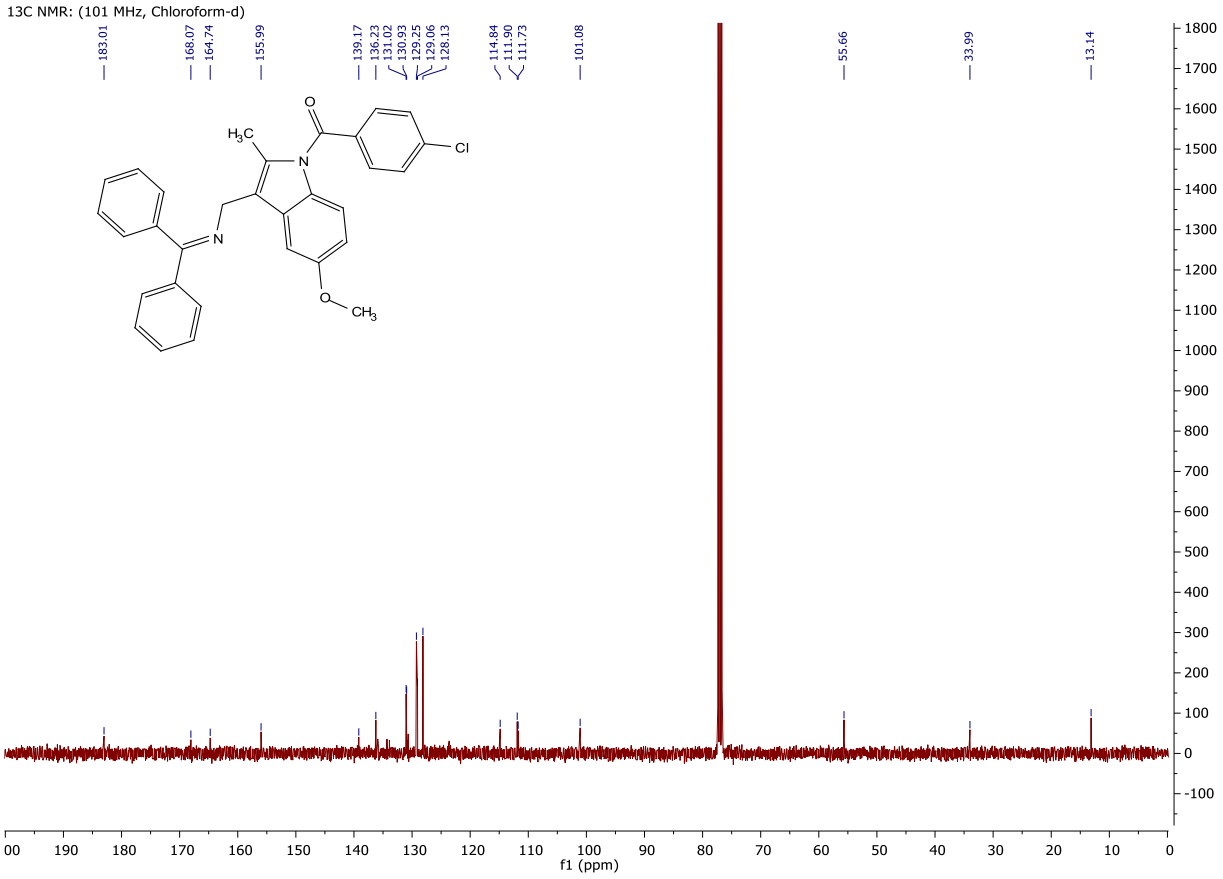
(Z)-N-(heptadec-8-en-1-yl)-1,1-diphenylmethanimine (3n)



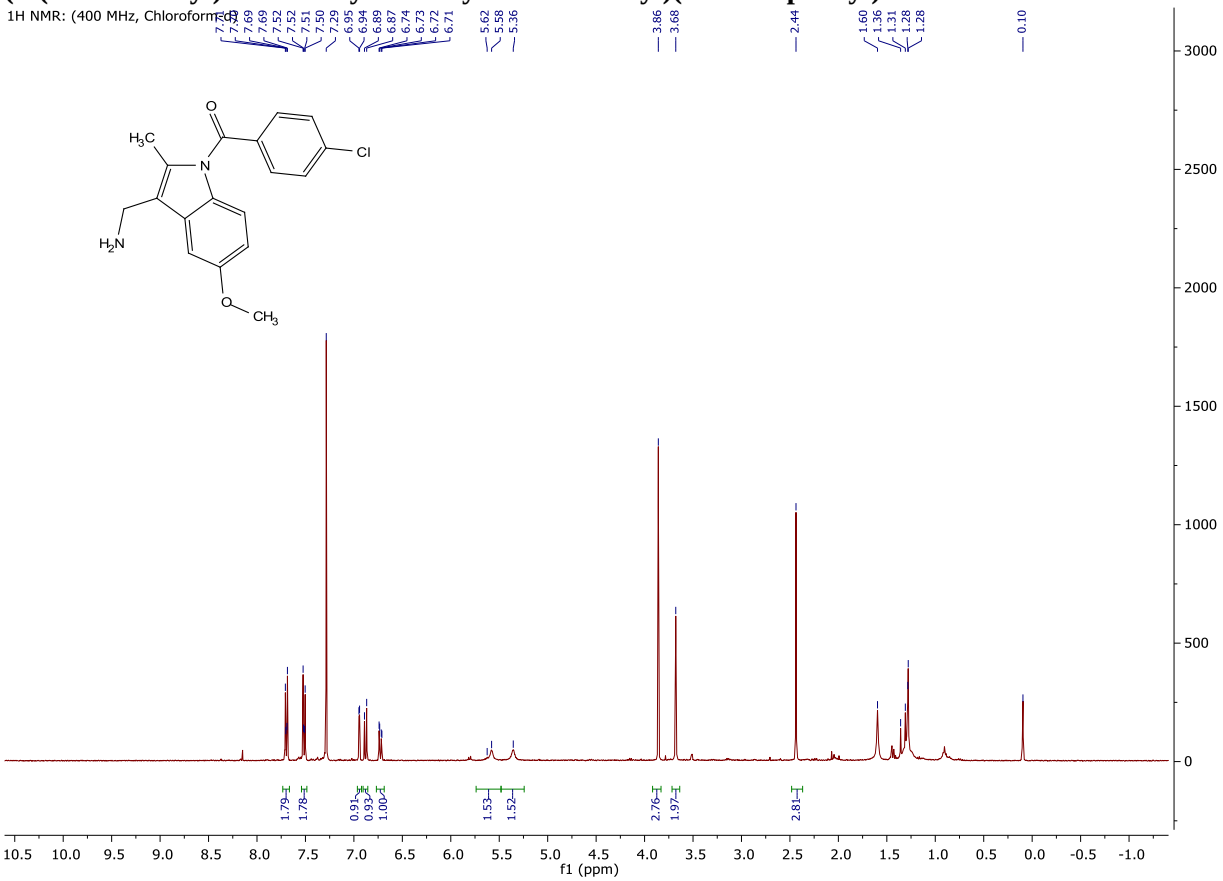


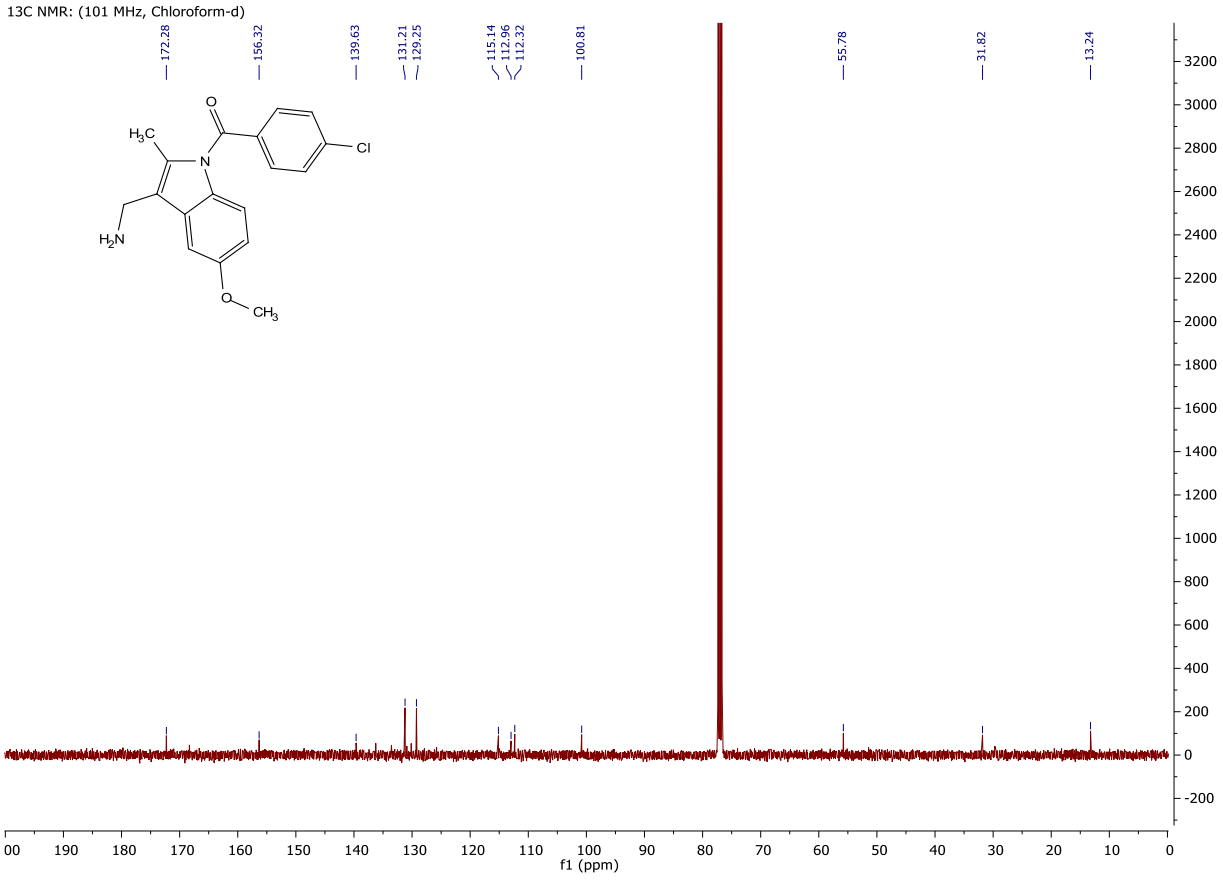
(4-chlorophenyl)(3-(((diphenylmethylene)amino)methyl)-5-methoxy-2-methyl-1H-indol-1-yl)methanone (3o)




13C NMR: (101 MHz, Chloroform-d)
183.01
168.07
164.74
155.99
139.17
136.23
131.02
130.93
129.25
129.06
128.13
114.84
111.90
111.73
101.08
55.66
33.99
13.14
f1 (ppm)

(3-(aminomethyl)-5-methoxy-2-methyl-1H-indol-1-yl)(4-chlorophenyl)methanone **(3p)**





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4. Conclusion and outlook

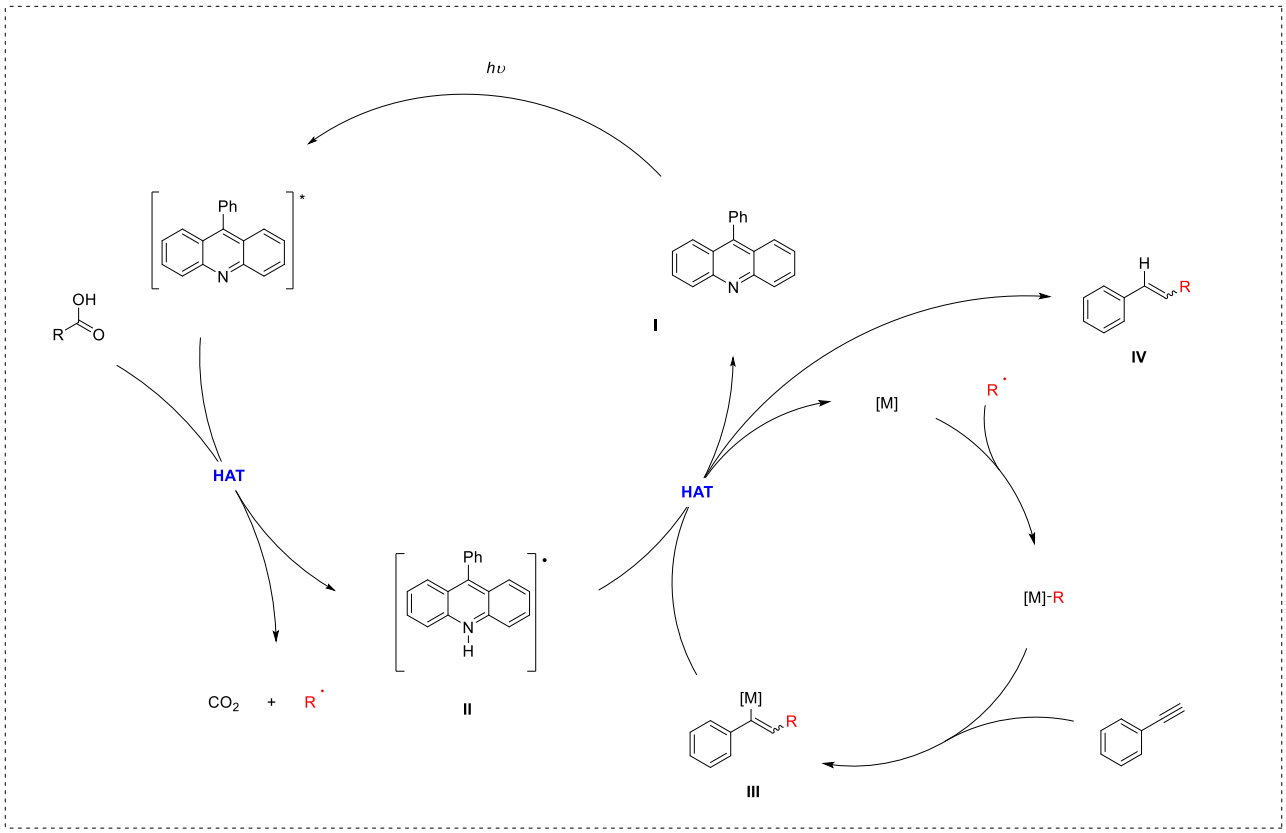
In this thesis were successfully reported methodologies for carbon-carbon and carbon-nitrogen coupling. The reactions, even if they use two different methods of catalysis, have the formation of an alkyl radical from a halide or an ester as starting point. Alkyl radicals based reactions are becoming more and more a useful tool to build organic bonds. Since they are completely different from traditional ionic chemistry, they can perform better in many cases.[1] with classical Pd catalyzed C-C coupling it is very easy to perform the reaction with aromatic halides to form sp^2-sp^2 bonds, but when an alkyl halide is used, the reaction becomes very inefficient and it is difficult to avoid side products formation.[2] Radical pathway instead can avoid the metal coordination of the alkyl radical species forming easily products that were difficult to synthesize before.

New methods for the formation of alkyl radicals from all sorts of halides and pseudo-halides is surely a very promising starting point for new chemistry.[3–10] In chapter one was shown how versatile this reactive species can be, but surely there is more room for new discoveries in this field.

The substitution of Ruthenium based photocatalyst with a cheaper and greener organic dye resulted successful (as reported in chapter 3). 4CzIPN was found to be a formidable photocatalyst, easy to excite with visible light, and capable of catalyzing both amination and imination coupling with alkyl esters. This reaction type has great potential and it could be used in the future for other types of coupling. For example, after the formation of the alkyl radical, the coupling partner could be changed to any nucleophile. The reaction could form ethers, thioethers, C-C bonds, and others. Since some initial mechanistic studies were conducted, we know that the tuning of the photocatalyst may be necessary. Fortunately, 4CzIPN is not a one-of-a-kind compound. Waser and coworkers reported modifications of the initial structure of this photocatalyst, demonstrating that, easily changing portions of the molecule, it was possible to tune the redox potentials of the photocatalyst.[11] Thus, with this possibility of tuning the redox potentials, it would be possible to develop more C-heteroatom couplings.

The family of organic dyes is not limited to 4CzIPN and derivates. Recent literature continues to report new methods to produce alkyl radicals in innovative ways. A recent publication reported a decarboxylative coupling of a carboxylic ester with an aniline.[12] The reaction was catalyzed by a phenyl-acridine derivate that is able, under visible light irradiation, to oxidize the carboxylic acid. The alkyl radical thus formed couples with aniline

with the help of a copper complex. Unfortunately, to equilibrate the redox balance of this reaction, the addition of a stoichiometric amount of oxidant (di-ter-butyl peroxide) was needed. This fact makes the reaction less appealing to be performed since the poor atom economy and the presence of peroxide in the solution that lowers the tolerance of functional groups.



Scheme 4.1. Proposed reaction pathway for the decarboxylative reductive coupling between free carboxylic acids and alkynes.

In order to resolve this problem and produce a redox neutral reaction cycle, it would be possible to couple the net oxidizing radical formation phenyl-acridine/carboxylic acid with a reductive partner. For example the reductive coupling of an alkyne (phenyl alkyne, boronic alkyne). In this case, the theoretical catalytic cycle would be as follow (Scheme 4.1). The phenyl-acridine photocatalyst **I** get excited by visible light irradiation, and can perform a hydrogen atom extraction on the carboxylic acid, the latter decomposes, forming an alkyl radical and CO_2 and a protonated radical phenyl acridine **II**. With the help of a metal catalyst, the radical couples with the alkyne forming a metal-alkene species **III**. Finally, acridine (**II**) performs HAT (hydrogen

atom transfer) forming the product **IV**, acridine, and the initial metal catalyst. This reaction could lead to a reductive coupling of alkyne with carboxylic acids, with very little waste (loss of CO_2), and without using any late transition metals, nor for the photoredox or for the metal-based catalysis part.

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5. Curriculum vitae

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EDUCATION

Swiss Federal Institute of Technology, Lausanne (EPFL) 2016-present

Doctor of Science in Chemistry

- Focus on methodological chemistry and reaction discovery

University of Pavia 2014-2016

Master of Science in Organic Chemistry, Summa cum Laude (top 5%)

University of Pavia 2011-2014

Bachelor of Science in Chemistry

CORE EXPERIENCE

Laboratory of Inorganic Synthesis and Catalysis, EPFL (2016-Present)

"Synthetic methodologies for C-C and C-N bond formation involving alkyl radicals" (PhD Thesis)

- Development of new catalytic methods to form carbon-carbon or carbon-heteroatom bonds using lightweight transition metal complexes as well as organo-photocatalyst. These innovative reactions lead to more efficient synthetic pathways. Their mild conditions permit to add reactive functional groups in a late stage of the synthesis, giving a useful tool to synthetic chemists. Moreover, the substitution of rare metals with cheaper alternatives could lead to a future use in industry.

- All projects were conducted under minimal supervision, with the responsibility of coordinating people with different expertise and the managing of a lab technician. The results were presented to superiors and peers on regular basis in a multicultural environment to have exchange of opinions and ideas.
- Responsible for training new members on usage of multiple laboratory equipment.
- Responsible for sourcing management of laboratory machinery (up to 10.000 CHF) with direct contact with the suppliers.
- Responsible for the supply of consumables for different machines for all the group (20+ people) up to 5000 CHF.

University of Pavia, Laboratory of Extraction and Total Synthesis, MSc (2015-2016)

Investigation of the total synthesis of Okamurallene, a natural bioactive tetrahydrofuranoid molecule. The project consisted in the development of a synthetic strategy and its practical application in the lab, trying to overcome the challenges of this complicated multistep synthesis. Due to the complexity of the molecule, many of the theorized synthetic strategies were not successful and other pathways had to be developed, giving the possibility to explore many chemical reactions and laboratory techniques.

TECHNICAL SKILLS

Project management

Managing different projects autonomously, with tight deadlines.

Project management from the initial idea to the end, ability in communication with stakeholders to achieve the set goals.

Ability to present results in a clear manner and write complete reports and scientific publications.

Excellent team player both with colleagues and external collaborators to achieve the results.

Analysis of complex data and ability to organize large amount of information in a clear manner.

Ability to communicate and work in a multicultural environment, learning and understanding differences.

Teaching at bachelor's and master's level in practical laboratory and theoretical courses

Laboratory techniques

Multistep synthesis of organic molecules and precursors.

Setup of air/moisture/light sensitive reactions both in the hood (Schlenk line) and in the glove box.

Purification of compounds via column (silica, reverse phase, alumina), distillation, recrystallization, preparative TLC, liquid chromatography, etc.

Handling of different reaction sizes, from few milligrams to tens of grams.

Synthesis and handling of ligands and complexes of various transition metals.

Ability to plan a successful optimization pathway to improve reaction conditions and obtain higher yields.

Laboratory Instruments

UV spectroscopy, IR spectroscopy, Fluorometer, NMR, HPLC, GC, GC/MS, Mass spectrometry, Solvent system (purification and drying of solvents) use and maintenance, Glove box use and maintenance.

Computer skills

Microsoft Office, Chemdraw, Mestrenova.

LANGUAGES	**English:** Fluent **Italian:** Mother language **French:** Intermediate **German:** Beginner
OTHERS	Half marathon runner Engadiner skimarathon finisher Outdoor enthusiast (climbing, hiking, ski mountaineering) Free time photographer
PERSONAL INFORMATION	27 years old, married, Swiss driver's license (Type A and B)
PUBLICATION AND AWARDS	– *Org. Lett.* **2019**, 21, 2, 490, 493. https://doi.org/10.1021/acs.orglett.8b03772 – *Org. Lett.* **2020,** 14, 5412–5416 https://doi.org/10.1021/acs.orglett.0c01769 – Other publications in progress – Scholarship for top class students 2016